2

Stereochemistry, Conformation, and Stereoselectivity

Introduction

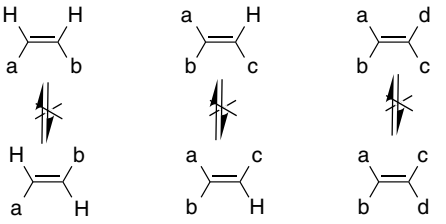
In the discussion of the structural features of carbon compounds in the Chapter 1, we emphasized some fundamental principles of molecular geometry. Except in strained rings, sp^3 carbon is nearly tetrahedral in shape. Double bonds involving sp^2 carbon are trigonal and planar and have a large barrier to rotation. The *sp* hybridization, e.g., in alkynes, leads to a linear (digonal) geometry. *Stereochemistry* in its broadest sense describes how the atoms of a molecule are arranged in three-dimensional space. In particular, *stereoisomers* are molecules that have identical connectivity (constitution) but differ in three-dimensional structure. Stereoisomers differ from one another in *configuration* at one or more atoms. *Conformations* are the various shapes that are available to molecules by single-bond rotations and other changes that do not involve bond breaking. Usually, conformational processes have relatively low energy requirements. The stereochemical features of a molecule, both configuration and conformation, can influence its reactivity. After discussing configuration and conformation, we consider *stereoselectivity*, the preference of a reaction for a particular stereoisomeric product.

2.1. Configuration

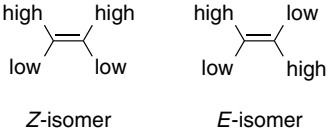
2.1.1. Configuration at Double Bonds

The sp^2 hybridization in the carbon atoms in a double bond and the resulting π bond favor a planar arrangement of the two carbon atoms and the four immediate

ligand atoms. When the substituents at the two carbons are nonidentical, two structurally distinct molecules exist.

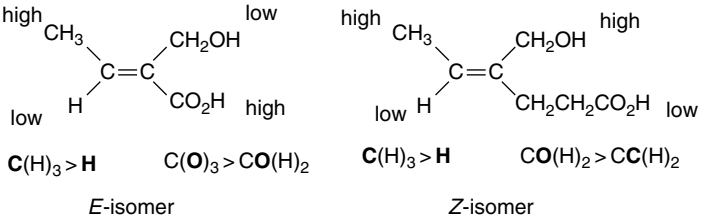


Owing to the high barrier to rotation in most alkenes (> 50 kcal/mol), these structures are not easily interconverted and the compounds exist as two isomers (stereoisomers) having different physical and chemical properties. There are two common ways of naming such compounds. If there is only one substituent at each carbon, the compounds can be called *cis* and *trans*. The isomer with both substituents on the same side of the double bond is the *cis* isomer, whereas the one with substituents on opposite sides is the *trans* isomer. If there is more than one substituent at either carbon, these designations can become ambiguous. There is an unambiguous system that can be applied to all compounds, no matter how many or how complex the substituents might be: the isomers are designated *Z* (for together) or *E* (for opposite). This system is based on the *Cahn-Ingold-Prelog priority rules*, which assign priority in the order of decreasing atomic number. If two substituent atoms have the same atomic number (e.g., two carbon substituents), the atomic numbers of successive atoms in the groups are compared until a difference is found. Multiple bonds, such as in a carbonyl group, are counted as two (or three for a triple bond) atoms. It is the *first difference* that determines priority. When priority has been assigned, the isomer with the higher-priority groups at each carbon on the same side of the double bond is called the *Z*-isomer. The isomer with the higher-priority substituents on opposite sides is the *E*-isomer.

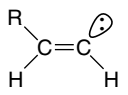


Z-isomer *E*-isomer

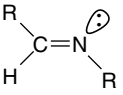
Example 2.1



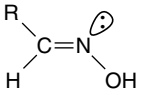
Certain atoms have an unshared electron pair rather than a substituent. Electron pairs are assigned the lowest priority in the Cahn-Ingold-Prelog convention, so assignment the *Z*- or *E*-configuration to compounds such as imines and oximes follows the same rules with R or H >:.



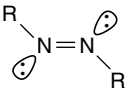
E-vinyl anion



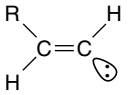
E-imine



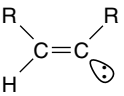
E-oxime



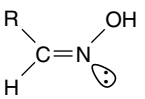
E-azo



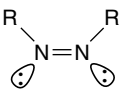
Z-vinyl anion



Z-imine



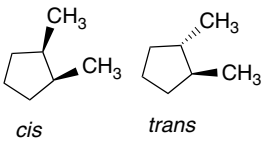
Z-oxime



Z-azo

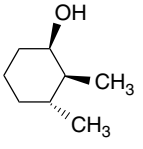
2.1.2. Configuration of Cyclic Compounds

Just as substituents can be on the same or opposite side of a double bond, they can be on the same or opposite side in cyclic compounds. The two arrangements are different *configurations* and cannot be interchanged without breaking and reforming at least one bond. Here the terms *cis* (for the same side) and *trans* (for the opposite side) are unambiguous and have been adopted as the designation of configuration. The stereochemistry is specified *relative to the group that takes precedence in the naming of the molecule*, as illustrated for 2,3-dimethylcyclohexanol.

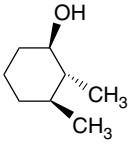


cis *trans*

stereoisomers of
1,2-dimethylcyclopentane

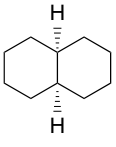


cis,trans-2,3-dimethyl-
cyclohexanol

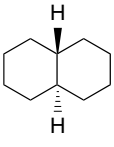


trans,cis-2,3-dimethyl-
cyclohexanol

Stereoisomers also arise when two rings share a common bond. In the *cis* isomer both branches of the fused ring are on the same side. In the *trans* isomer they are on opposite sides.



cis-decalin
cis-decahydronaphthalene



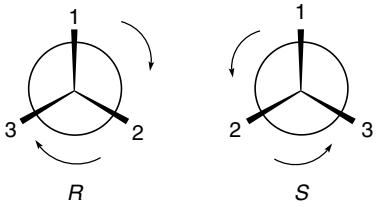
trans-decalin
trans-decahydronaphthalene

2.1.3. Configuration at Tetrahedral Atoms

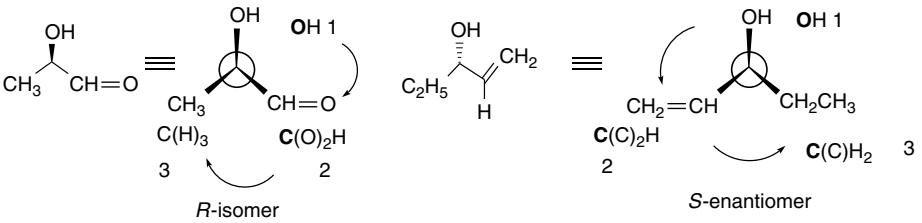
Carbon and other atoms with sp^3 hybridization have approximately tetrahedral geometry. With the exception of small deviations in bond angles, each of the substituents is in a geometrically equivalent position. Nevertheless, there is an important stereochemical feature associated with tetrahedral centers. If all four substituents are different, they can be arranged in two different ways. The two different arrangements are mirror images of one another, but they cannot be superimposed.

Any object that cannot be superimposed on its mirror image is called *chiral*, that is, it has the property of being right-handed or left-handed. Molecules (or other objects) that are not chiral are described as being *achiral*, which is the opposite of chiral. Tetrahedral atoms with four nonidentical substituents, then, give rise to two stereoisomers. Such atoms are called *stereogenic centers*, sometimes shortened to *stereocenters*. An older term applied specifically to carbon is *asymmetric carbon*.

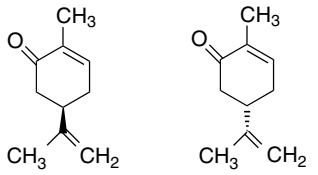
The chirality (or handedness) at stereogenic centers is specified by application of the Cahn-Ingold-Prelog priority rules, as described for double bonds. The four nonidentical ligand atoms are assigned a decreasing priority $1 > 2 > 3 > 4$. The molecule is then viewed opposite from the lowest-priority group, that is, the group is placed behind the stereocenter and away from the viewer. Two arrangements are possible for the other three substituents. The groups can decrease in priority in either a clockwise or a counterclockwise direction. The clockwise direction configuration is assigned *R* (for *rectus*) and the counterclockwise direction is assigned *S* (for *sinistre*).



Example 2.2



The two nonsuperimposable mirror image molecules are called an *enantiomeric pair* and each is the *enantiomer* of the other. The separated enantiomers have identical properties with respect to achiral environments. They have the same solubility, physical, and spectroscopic properties and the same chemical reactivity toward achiral reagents. However, they have different properties in chiral environments. The enantiomers react at different rates toward chiral reagents and respond differently to chiral catalysts. Usually enantiomers cause differing physiological responses, since biological receptors are chiral. For example, the odor of the *R*- (spearmint oil) and *S*- (caraway seed oil) enantiomers of carvone are quite different.



(R)-Carvone *(S)*-Carvone

The activity of enantiomeric forms of pharmaceuticals is often distinctly different.

Enantiomers also differ in a specific physical property, namely the rotation of plane polarized light. The two enantiomers rotate the light in equal, but opposite directions. The property of rotating plane polarized light is called *optical activity*, and the magnitude of rotation can be measured by instruments called polarimeters. The observed rotation, known as α, depends on the conditions of measurement, including concentration, path length, solvent, and the wavelength of the light used. The rotation that is characteristic of an enantiomer is called the *specific rotation* and is symbolized by $[\alpha]_{589}$, where the subscript designates the wavelength of the light. The observed rotation α at any wavelength is related to $[\alpha]_\lambda$ by the equation

$$[\alpha]_\lambda = \frac{100\alpha}{cl} \tag{2.1}$$

where c is the concentration in g/100 mL and l is the path length in decimeters.

Depending on how it was obtained, a sample of a chiral compound can contain only one enantiomer or it can be a mixture of both. Enantiomerically pure materials are referred to as *homochiral* or *enantiopure*. The 1:1 mixture of enantiomers has zero net rotation (because the rotations caused by the two enantiomers precisely cancel each other) and is called a *racemic mixture* or *racemate*. A racemic mixture has its own characteristic properties in the solid state. It differs in melting point and solubility from the pure enantiomers, owing to the fact that the racemic mixture can adopt a different crystalline structure from that of the pure enantiomers. For example, Figure 2.1 shows the differing intermolecular hydrogen-bonding and crystal-packing arrangements in (+/−) and (−) 2,5-diazabicyclo[2.2.2]octa-3,6-dione.[1]

The composition of a mixture of enantiomers is given by the *enantiomeric excess*, abbreviated e.e, which is the percentage excess of the major enantiomer over the minor enantiomer:

$$\text{e.e.} = \%\ \text{Major} - \%\ \text{Minor} \tag{2.2}$$

[1] M.-J. Birenne, J. Gabard, M. Leclercq, J.-M. Lehn, M. Cesario, C. Pascard, M. Cheve, and G. Dutruc-Rosset, *Tetrahedron Lett.*, **35**, 8157 (1994).

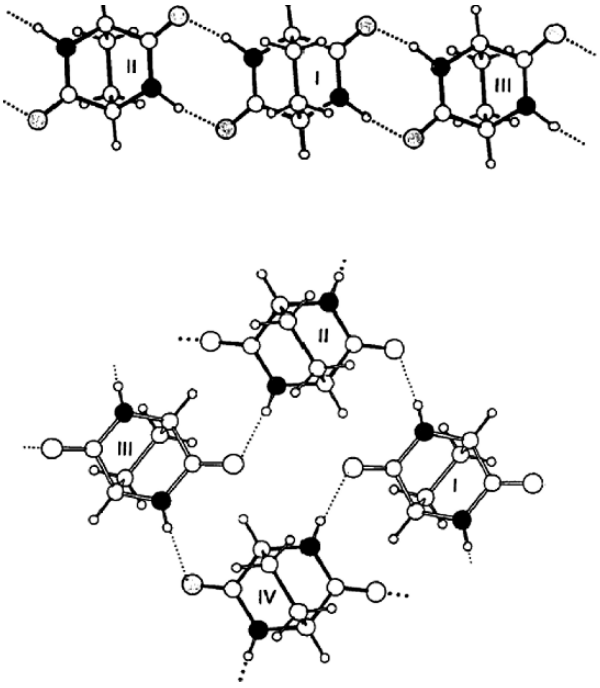


Fig. 2.1. Alternative hydrogen-bonding and crystal-packing arrangements for racemic (top) and (−) (bottom) forms of 2,5-diazabicyclo[2.2.2]octane-3,6-dione. Reproduced from *Tetrahedron Lett.*, **35**, 8157 (1994), by permission of Elsevier.

Alternatively, e.e. can be expressed in terms of the mole fraction of each enantiomer:

$$\text{e.e.} = (\text{Mole fraction}_{\text{major}} - \text{Mole fraction}_{\text{minor}}) \times 100 \tag{2.3}$$

The *optical purity*, an older term, is numerically identical. It represents the observed rotation, relative to the rotation of the pure enantiomer. Since the two enantiomers cancel each other out, the observed rotation is the product of (% Major − % Minor) × $[\alpha]_\lambda$. If $[\alpha]_\lambda$ is known, measurement of α allows the optical purity and enantiomeric excess to be determined:

$$\text{e.e.} = \frac{\alpha_{\text{obs}} \times 100}{[\alpha]_\lambda} \tag{2.4}$$

There are several other ways of measuring e.e., including NMR spectroscopy, chromatography, and capillary electrophoresis (see Topic 2.1).

Measurement of rotation as a function of wavelength is useful in structural studies aimed at determining the configuration of a chiral molecule. This technique is called *optical rotatory dispersion* (ORD),[2] and the resulting plot of rotation against wavelength is called an ORD curve. The shape of the ORD curve is determined by the

[2] P. Crabbe, *Top. Stereochem.* **1**, 93 (1967); C. Djerassi, *Optical Rotatory Dispersion,* McGraw-Hill, New York, 1960; P. Crabbe, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden Day, San Francisco, 1965; E. Charney, *The Molecular Basis of Optical Activity. Optical Rotatory Dispersion and Circular Dichroism*, Wiley, New York, 1979.

configuration of the molecule and its absorption spectrum. In many cases, the ORD curve can be used to determine the configuration of a molecule by comparison with similar molecules of known configuration. Figure 2.2 shows the UV, ORD, and CD spectra of an enantiomerically pure sulfonium ion salt.[3]

Chiral substances also show differential absorption of circularly polarized light. This is called *circular dichroism* (CD) and is quantitatively expressed as the molecular ellipticity θ, where ε_L and ε_R are the extinction coefficients of left and right circularly polarized light:

$$\theta = 3330(\varepsilon_L - \varepsilon_R) \tag{2.5}$$

Molecular ellipticity is analogous to specific rotation in that two enantiomers have exactly opposite values at every wavelength. Two enantiomers also show CD spectra having opposite signs. A compound with several absorption bands may show both positive and negative bands. Figure 2.3 illustrates the CD curves for both enantiomers of 2-amino-1-phenyl-1-propanone.[4]

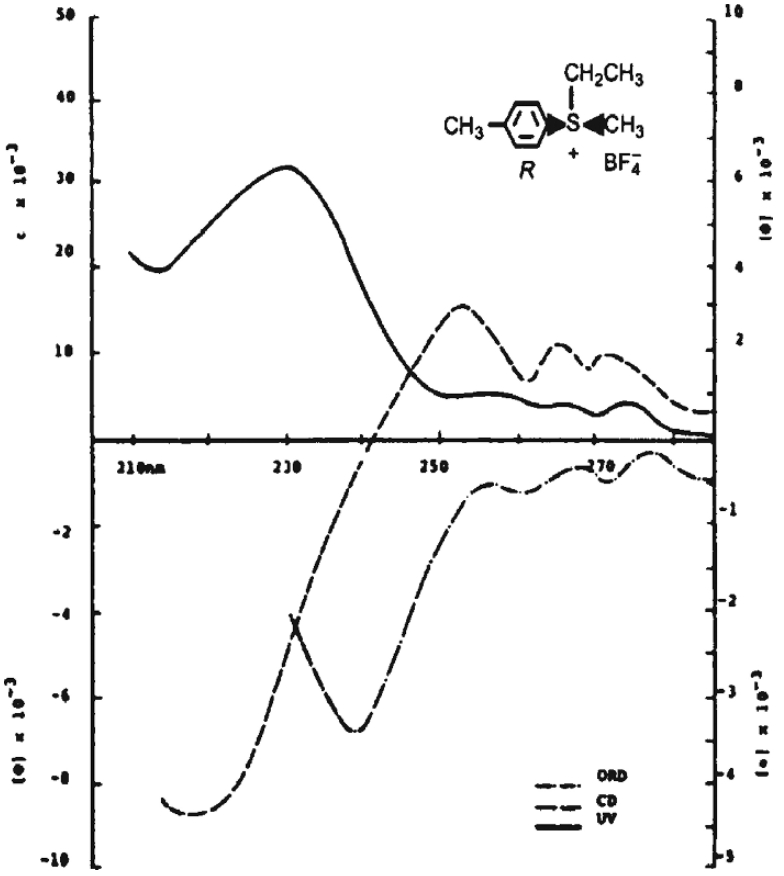


Fig. 2.2. UV absorption, ORD, and CD curves of (*R*)-ethyl methyl *p*-tolyl sulfonium tetrafluoroborate. Reproduced from *J. Org. Chem.*, **41**, 3099 (1976), by permission of the American Chemical Society.

3. K. K. Andersen, R. L. Caret, and D. L. Ladd, *J. Org. Chem.*, **41**, 3096 (1976).
4. J.-P. Wolf and H. Pfander, *Helv. Chim. Acta*, **69**, 1498 (1986).

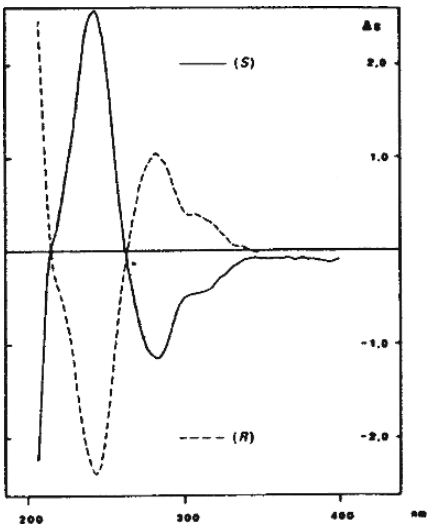


Fig. 2.3. CD spectra of (*S*)- and (*R*)-2-amino-1-phenyl-1-propanone hydrochloride. Reproduced from *Helv. Chim. Acta*, **69**, 1498 (1986), by permission of Wiley-VCH.

2.1.4. Molecules with Multiple Stereogenic Centers

Molecules can have several stereogenic centers, including double bonds with *Z* or *E* configurations and asymmetrically substituted tetrahedral atoms. The maximum number of stereoisomers that can be generated from *n* stereogenic centers is 2^n. There are several ways of representing molecules with multiple stereogenic centers. At the present time, the most common method in organic chemistry is to depict the molecule in an extended conformation with the longest chain aligned horizontally. The substituents then point in or out and up or down at each tetrahedral site of substitution, as represented by wedged and dashed bonds. The four possible stereoisomers of 2,3,4-trihydroxybutanal are shown in this way in Figure 2.4. The configuration at each center is specified as *R* or *S*. The isomers can also be characterized as *syn* or *anti*. Two

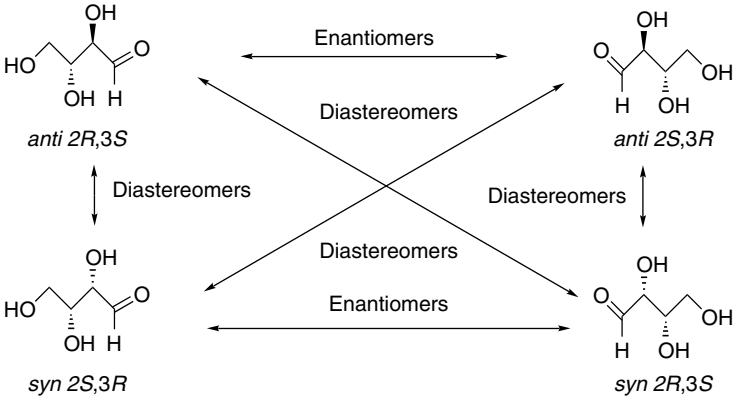
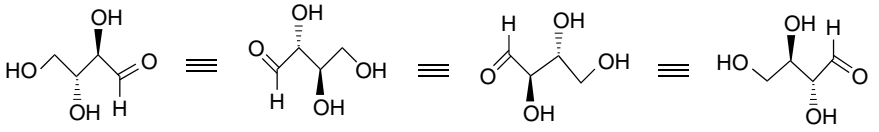


Fig. 2.4. Extended chain representation of all stereoisomers of 2,3,4-trihydroxybutanal.

adjacent substituents pointed in the same direction (in or out) are *syn*, whereas those pointed in opposite directions are *anti*.

For molecules with more than one stereogenic center, the *enantiomeric pair must have the opposite configuration at each center*. The two enantiomeric relationships are shown in Figure 2.4. There are four other pairings that do not fulfill this requirement, but the structures are still stereoisomeric. Molecules that are stereoisomeric but are not enantiomeric are called *diastereomers*, and four of these relationships are pointed out in Figure 2.4. Molecules that are diastereomeric have the same *constitution* (connectivity) but differ in *configuration* at one or more of the stereogenic centers. The positions in two diastereomers that have different configurations are called *epimeric*. For example, the *anti*-2*R*,3*R* and *syn*-2*R*,3*S* stereoisomers have the same configuration at C(2), but are epimeric at C(3). There is nothing unique about the way in which the molecules in Figure 2.4 are positioned, except for the conventional depiction of the extended chain horizontally. For example, the three other representations below also depict the *anti*-2*R*,3*S* stereoisomer.



anti 2*R*,3*S* *anti* 2*R*,3*S* *anti* 2*R*,3*S* *anti* 2*R*,3*S*

Another means of representing molecules with several stereocenters is by *Fischer projection formulas*. The main chain of the molecule is aligned vertically, with (by convention) the most oxidized end of the chain at the top. The substituents that are shown horizontally project toward the viewer. Thus the vertical carbon-carbon bonds point away from the viewer at all carbon atoms. Fischer projection formulas represent a *completely eclipsed conformation* of the vertical chain. Because the horizontal bonds project from the plane of the paper, any reorientation of the structures must not change this feature. *Fischer projection formulas may be reoriented only in the plane of the paper*. Fischer projection formulas use an alternative system for specifying chirality. The chirality of the highest-numbered chiral center (the one most distant from the oxidized terminus, that is, the one closest to the bottom in the conventional orientation), is specified as D or L, depending on whether it is like the D- or L-enantiomer of glyceraldehyde, which is the reference compound. In the conventional orientation, D-substituents are to the right and L-substituents are to the left.

D-(+)-glyceraldehyde L-(-)-glyceraldehyde

The *relative configuration* of adjacent substituents in a Fischer projection formula are designated *erythro* if they are on the same side and *threo* if they are on the opposite side. The stereochemistry of adjacent stereocenters can also be usefully represented

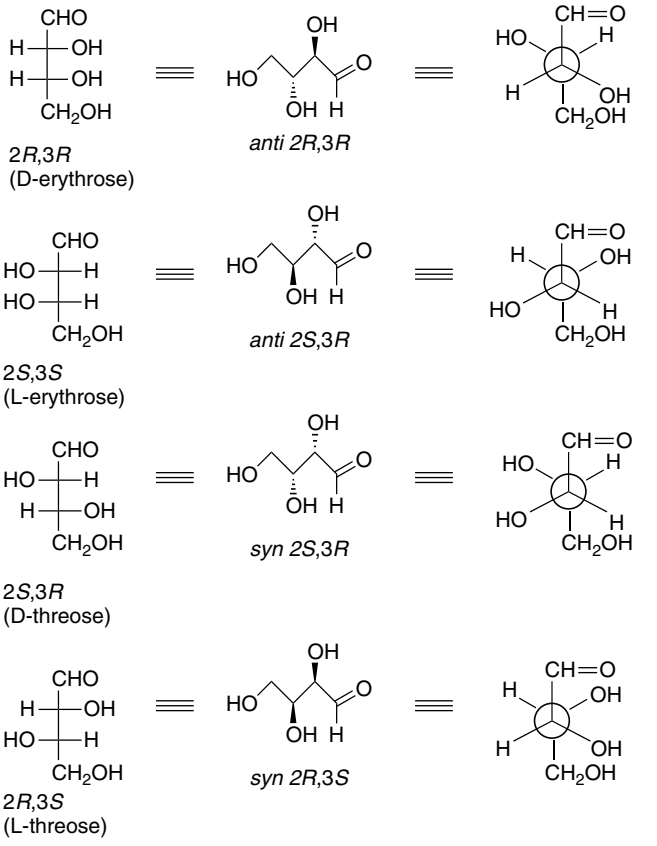


Fig. 2.5. Fischer, extended, and Newman projection representations of the stereoisomers of 2,3,4-trihydroxybutanal.

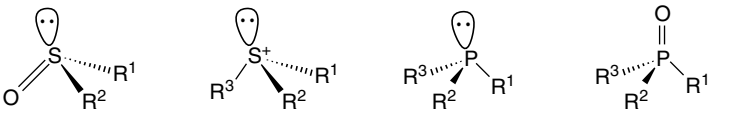
by *Newman projection formulas*. Figure 2.5 shows 2,3,4-trihydroxybutanal (now also with its carbohydrate names, erythrose and threose) as Fischer projection formulas as well as extended and Newman representations.

Because the Fischer projection formulas represent an eclipsed conformation of the carbon chain, the relative orientation of two adjacent substituents is opposite from the extended staggered representation. Adjacent substituents that are *anti* in an extended representation are on the same side of a Fischer projection formula, whereas adjacent substituents that are *syn* in an extended representation are on opposite sides in a Fischer projection. As with extended representations, an enantiomeric pair represented by Fischer projection formulas has the opposite configuration at *all stereogenic centers* (depicted as left or right.)

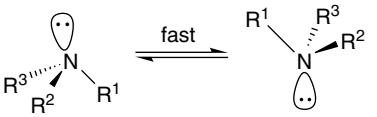
2.1.5. Other Types of Stereogenic Centers

Although asymmetrically substituted carbon atoms are by far the most common type of stereogenic center in organic compounds, several other kinds of stereogenic centers are encountered. Tetravalent nitrogen (ammonium) and phosphorus (phosphonium) ions are obvious extensions. Phosphine oxides are also tetrahedral and are chiral if all three substituents (in addition to the oxygen) are different. Not quite

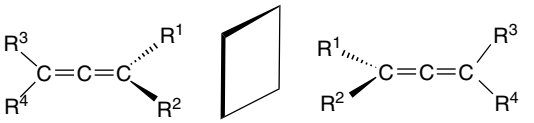
so evident are the cases of *trivalent* sulfur and phosphorus compounds, including sulfonium salts, sulfoxides, and phosphines. The heteroatom in these structures is approximately tetrahedral, with an electron pair occupying one of the tetrahedral positions. Because there is a relatively high energy barrier to inversion of these tetrahedral molecules, they can be obtained as pure enantiomers.



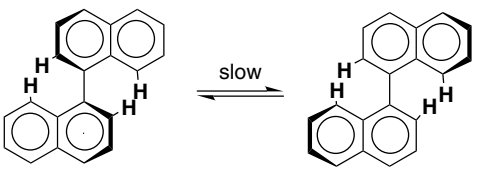
Trivalent nitrogen compounds are also approximately tetrahedral in shape. In this case, however, the barrier to inversion is small and the compounds cannot be separated as pure enantiomers at normal temperatures.



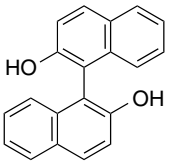
Allenes (see p. 6 for a discussion of bonding in allenes) can be chiral. An allene having nonidentical substituents at both sp^2 carbons gives nonsuperimposable mirror images.



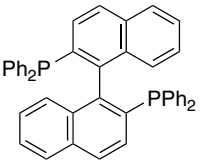
Molecules with shapes analogous to screws are also chiral, since they can be right-handed or left-handed. There are several kinds of molecules in which steric factors impose a screwlike shape. A very important case is 1, 1′-binaphthyl compounds. Steric interactions between the 2 and 8′ hydrogens prevent these molecules from being planar, and as a result, there are two nonsuperimposable mirror image forms.



A particularly important example is the 2, 2′-diol, which is called BINOL. Another important type includes 1, 1′-binaphthyl diphosphines, such as BINAP.[5] BINOL and BINAP are useful chiral ligands in organometallic compounds that serve as catalysts for hydrogenations and other reactions. In Section 2.5.1.1, we discuss how compounds such as BINOL and BINAP have been used to develop *enantioselective hydrogenation catalysts*.

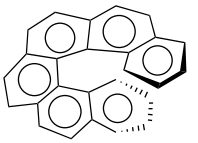


BINOL

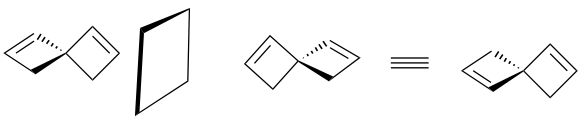


BINAP

A spectacular example of screw-shaped chirality is hexahelicene, in which the six fused benzene rings cannot be planar and give rise to right-handed and left-handed enantiomers. The specific rotation $[\alpha]_{589}$ is about 3700.[6] Hexahelicene can be racemized by heating. The increased molecular vibration allows the two terminal rings to slip past one another. The activation energy required is 36.2 kcal/mol.[7]

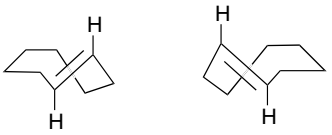


Many *spiro* compounds are chiral. In *spiro* structures, two rings share a common atom. If neither ring contains a plane of symmetry, *spiro* compounds are chiral. An example is *S*-(+)-*spiro*[3,3]hepta-1,5-diene.[8]

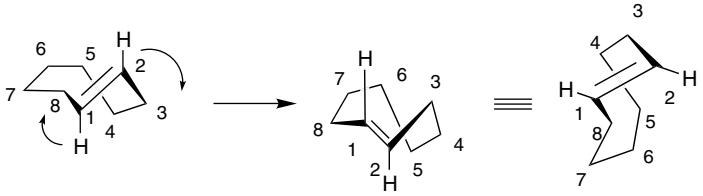


The *E*-cycloalkenes are also chiral. *E*-cyclooctene is a good example. Examination of the structures below using molecular models demonstrates that the two mirror images cannot be superimposed.

5. A. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990).
6. M. S. Newman and D. Lednicer, *J. Am. Chem. Soc.*, **78**, 4765 (1956).
7. R. H. Martin and M. J. Marchant, *Tetrahedron*, **30**, 347 (1974).
8. L. A. Hulshof, M. A. McKervey, and H. Wynberg, *J. Am. Chem. Soc.*, **96**, 3906 (1974).

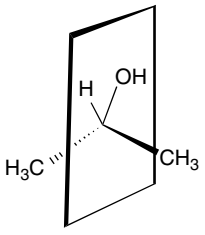


E-cyclooctene is subject to thermal racemization. The molecular motion allows the double bond to slip through the ring, giving the enantiomer. The larger and more flexible the ring, the easier the process. The rates of racemization have been measured for *E*-cyclooctene, *E*-cyclononene, and *E*-cyclodecene. For *E*-cyclooctene the half-life is 1 h at 183.9° C. The activation energy is 35.6 kcal/mol. *E*-cyclononene, racemizes much more rapidly. The half-life is 4 min at 0° C, with an activation energy of about 20 kcal/mol. *E*-cyclodecene racemizes immediately on release from the chiral platinum complex used for its preparation.[9]



2.1.6. The Relationship between Chirality and Symmetry

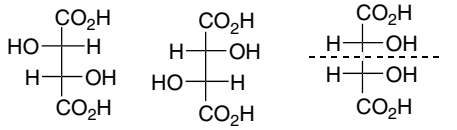
Molecules that possess certain elements of symmetry are not chiral, because the element of symmetry ensures that the mirror image forms are superimposable. The most common example is a *plane of symmetry*, which divides a molecule into two halves that have identical placement of substituents on both sides of the plane. A trivial example can be found at any tetrahedral atom with two identical substituents, as, for example, in 2-propanol. The plane subdivides the 2-H and 2-OH groups and the two methyl groups are identical.

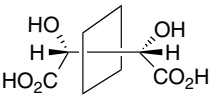


2-propanol

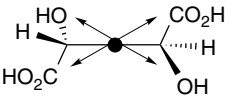
[9] A. C. Cope and B. A. Pawson, *J. Am. Chem. Soc.*, **87**, 3649 (1965); A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *J. Am. Chem. Soc.*, **87**, 3644 (1965).

More elaborate molecules can also have a plane of symmetry. For example, there are only three stereoisomers of tartaric acid (2,3-dihydroxybutanedioic acid). Two of these are chiral but the third is achiral. In the achiral stereoisomer, the substituents are located with respect to each other in such a way as to generate a plane of symmetry. Compounds that contain two or more stereogenic centers but have a plane of symmetry are called *meso forms*. Because they are achiral, they do not rotate plane polarized light. Note that the Fischer projection structure of *meso*-tartaric acid reveals the plane of symmetry.



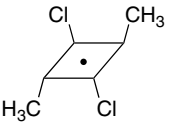


Plane of symmetry in the eclipsed conformation of *meso*-tartaric acid

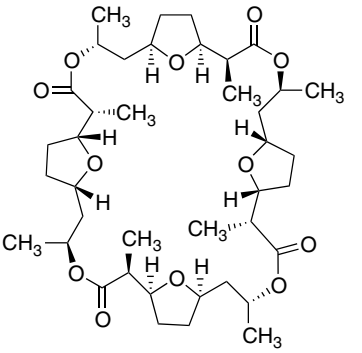


Center of symmetry in the *anti* staggered conformation of *meso*-tartaric acid

A less common element of symmetry is a *center of symmetry*, which is a point in a molecule through which a line oriented in any direction encounters the same environment (structure) when projected in the opposite direction. For example, *trans*, *trans, cis*-2,4-dichloro-1,3-dimethylcyclobutane has a center of symmetry, but no plane of symmetry. It is achiral.



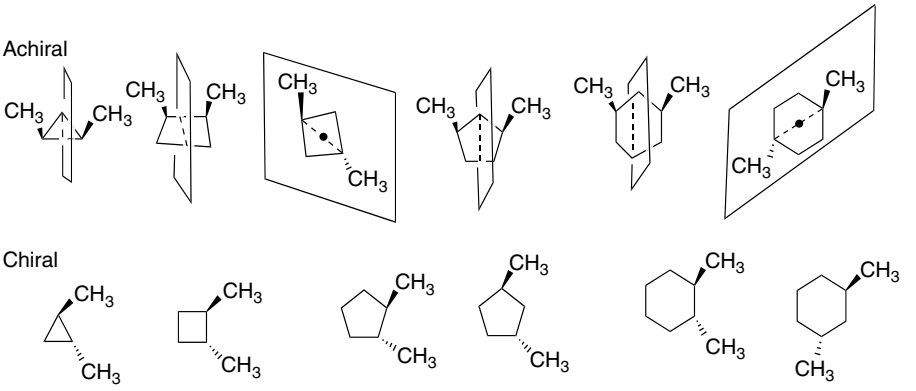
Another very striking example is the antibiotic nonactin. Work out problem 2.15 to establish the nature of the of symmetry in nonactin.



Nonactin

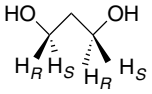
Various di- and polysubstituted cyclic compounds provide other examples of molecules having planes of symmetry. Since chirality depends on *configuration*, not *conformation*, cyclic molecules can be represented as planar structures to facilitate recognition of symmetry elements. These planar structures clearly convey the *cis* and *trans* relationships between substituents. Scheme 2.1 gives some examples of both chiral and achiral dimethylcycloalkanes. Note that in several of the compounds there is both a center and a plane of symmetry. Either element of symmetry ensures that the molecule is achiral.

Scheme 2.1. Chiral and Achiral Disubstituted Cycloalkanes

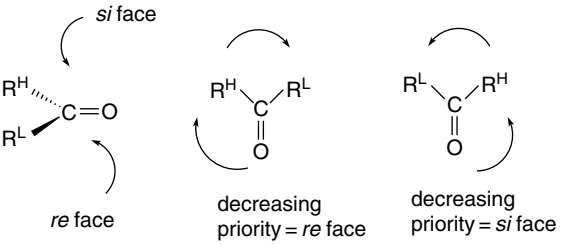


2.1.7. Configuration at Prochiral Centers

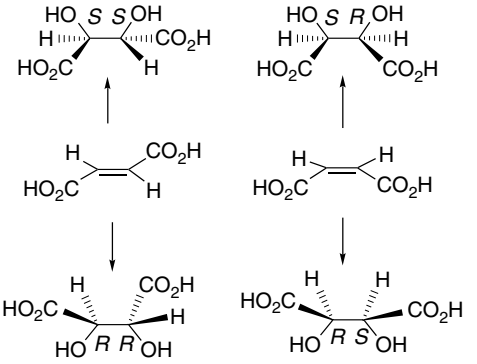
Prochiral centers have two identical ligands, such as two hydrogens, and are achiral. In many situations, however, these identical ligands are *topologically nonequivalent* or *heterotopic*. This occurs when the other two substituents are different. If either of the identical groups is replaced by a different ligand, a stereogenic center is created. The two positions are called *enantiotopic*. The position, which if assigned a higher priority, gives an *R* configuration is called pro-*R*. The position, which if assigned a higher priority, gives an *S* configuration is called pro-*S*. Propane-1,3-diol is an example of a prochiral molecule. The C(1) and C(3) positions are prochiral, but the C(2) is not, because its two hydroxymethyl ligands are identical.



Unsymmetrically substituted carbonyl groups are prochiral centers, since addition of a fourth ligand generates a stereogenic center. These are designated by determining the Cahn-Ingold-Prelog priority order. The carbonyl group is said to have an *re* face and an *si* face.



Achiral reagents do not distinguish between the two faces, but chiral reagents do and give unequal amounts of enantiomeric products. Other trigonal centers, including carbon-carbon double bonds, present two prochiral faces. For example, *E*- and *Z*-butenedioic acid (maleic and fumaric acid) generate different stereoisomers when subjected to *syn*-dihydroxylation. If the reagent that is used is chiral, the *E*-isomer will generate different amounts of the *R*,*R* and *S*,*S* products. The *S*,*R* and *R*,*S* forms generated from the *Z*-isomer are *meso* forms and will be achiral, even if they are formed using a chiral reagent.



The concept of heterotopic centers and faces can be extended to diastereotopic groups. If one of two equivalent ligands in a molecule is replaced by a test group, the ligands are diastereotopic when the resulting molecules are diastereomers. Similarly, if a transformation at opposite faces of a trigonal center generates two different diastereomers, the faces are diastereotopic. There is an important difference between enantiotopic and diastereotopic centers. Two identical ligands at enantiotopic centers are in *chemically equivalent environments*. They respond identically to probes, including chemical reagents, that are achiral. They respond differently to chiral probes, including chiral reagents. Diastereotopic centers are *topologically nonequivalent.* That is, their environments in the molecule are different and they respond differently to achiral, as well as to chiral probes and reagents. As a consequence of this nonequivalence, diastereotopic protons, as an example, have different chemical shifts and are distinguishable in NMR spectra. Enantiotopic protons do not show separate NMR signals. Two diastereotopic protons give rise to a more complex NMR pattern. Because of their chemical shift difference, they show a geminal coupling. An example of this effect can be seen in the proton NMR spectra of 1-phenyl-2-butanol, as shown in

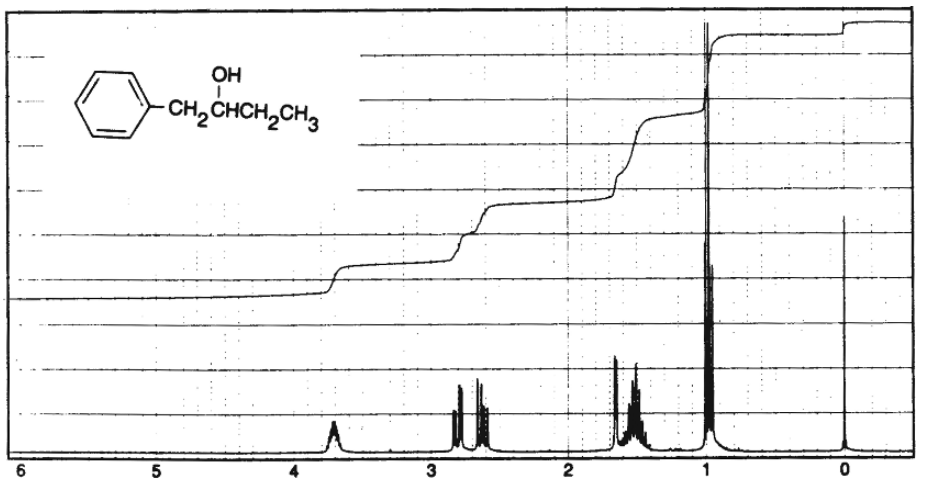
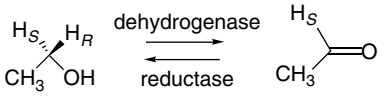


Fig. 2.6. NMR spectrum of 1-phenyl-2-butanol showing the diastereotopic nature of C(l) protons. Reproduced from *Aldrich Library of* ^{13} *C and* ^{1}*H NMR Spectra*, Vol. 2, 1993, p. 386.

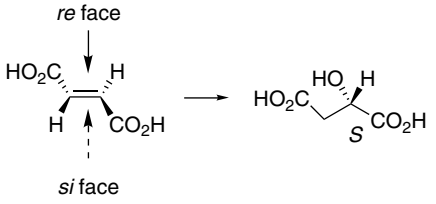
Figure 2.6. The C(1) CH_2 group appears as a quartet near 2.8 ppm with further coupling to the C(2) proton. The C(1) hydrogens are diastereotopic. The C(3) hydrogens are also diastereotopic, but their nonidentity is not obvious in the multiplet at about 1.6 ppm.

Because biological reactions involve chiral enzymes, enantiotopic groups and faces typically show different reactivity. For example, the two methylene hydrogens in ethanol are enantiotopic. Enzymes that oxidize ethanol, called *alcohol dehydrogenases*, selectively remove the pro-*R* hydrogen. This can be demonstrated by using a deuterated analog of ethanol in the reaction.



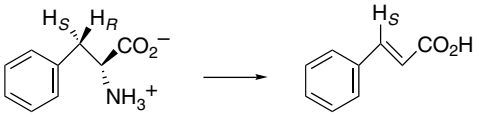
Conversely, *reductases* selectively reduce acetaldehyde from the *re* face.

Fumaric acid is converted to L-malic acid (*S*-2-hydroxybutanedioic acid) by the enzyme *fumarase*. The hydroxyl group is added stereospecifically from the *si* face of the double bond.



Enzymes also distinguish between diastereotopic groups and faces. For example, L-phenylalanine is converted to cinnamic acid by the enzyme *phenylalanine ammonia*

lyase. The reaction occurs by an *anti* elimination involving the amino group and the 3-*pro-R* hydrogen.

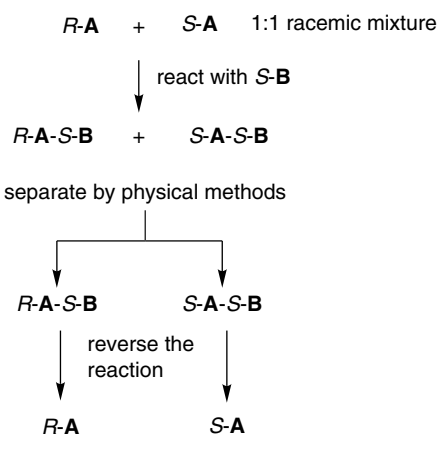


2.1.8. Resolution—The Separation of Enantiomers

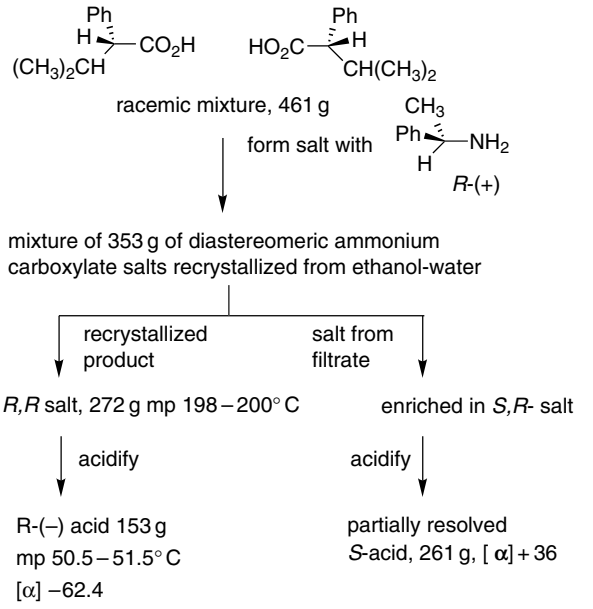
Since all living cells and organisms involve reactions of enantiomerically pure materials such as carbohydrates, proteins, and DNA, most naturally occurring chiral compounds exist in enantiomerically pure form. Chemical reactions, however, often produce racemic mixtures. This is *always* the case if only racemic and/or achiral reactants, reagents, catalysts, and solvents are used. The products of chemical reactions can be enantiomerically enriched or enantiopure only if chiral starting materials, reagents, catalysts or solvents are used. (See Section 2.5 for a discussion of enantioselective reactions.) Racemic mixtures can be separated into the two enantiomeric forms. The process of separating a racemic mixture into its enantiomers is called *resolution*, and it can be accomplished in several different ways.

Historically, the usual method was to use an existing enantiomerically pure compound, often a naturally occurring material, as a *resolving agent*. When a racemic mixture of **A** (*R*,*S*-**A**) reacts with a pure enantiomer (*S*-**B**), the two products are *diastereomeric*, namely *R*,*S*-**AB** and *S*,*S*-**AB**. As diastereomers have differing physical properties, they can be separated by such means as crystallization or chromatography. When the diastereomers have been separated, the original reaction can be reversed to obtain enantiomerically pure (or enriched) samples. The concept is summarized in Scheme 2.2. Scheme 2.3 describes an actual resolution.

Scheme 2.2. Conceptual Representation of Resolution through Separation of Diastereomeric Derivatives



Scheme 2.3. Resolution of 3-Methyl-2-Phenylbutanoic Acid[a]



* a. C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohahi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967).

Another means of resolution is to use a chiral material in a physical separation. Currently, many resolutions are done using medium- or high-pressure chromatography with chiral column-packing materials. Resolution by chromatography depends upon differential adsorption of the enantiomers by the chiral stationary phase. Differential adsorption occurs because of the different "fit" of the two enantiomers to the chiral adsorbent. Figure 2.7 shows such a separation. Topic 2.1 provides additional detail on several types of chiral stationary phases.

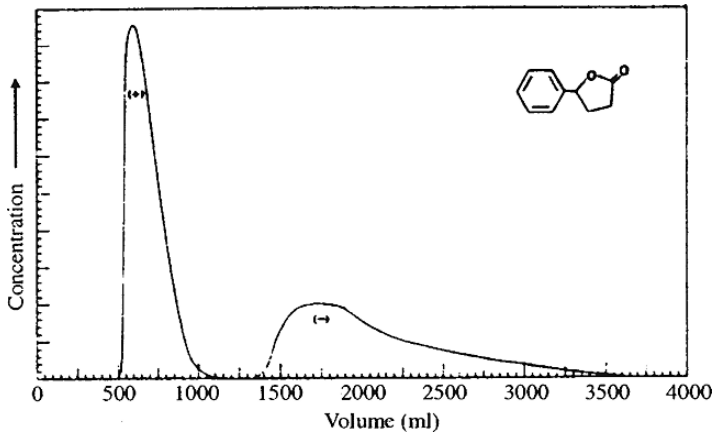


Fig. 2.7. Preparative chromatographic resolution of 5 g of γ-phenyl-γ-butyrolactone on 480 g of cellulose triacetate (column 5 cm × 60 cm). Reproduced from *Helv. Chim. Acta*, **70**, 1569 (1987), by permission of Wiley-VCH.

Scheme 2.4. Conceptual Basis of Kinetic Resolution

R,S-racemic mixture

↓

Carry out *incomplete* reaction with enantiomerically pure reagent

↓

If rate for *R*-enantiomer > *S*-enantiomer: Unreacted material is enriched in *S*-enantiomer; product enriched in derivative of *R*-enantiomer

If rate for *S*-enantiomer > *R*-enantiomer: Unreacted material is enriched in *R*-enantiomer; product enriched in derivative of *S*-enantiomer

Another means of resolution depends on the difference in rates of reaction of two enantiomers with a chiral reagent. The rates of reaction of each enantiomer with a single enantiomer of a chiral reagent are different because the transition structures and intermediates (*R*-substrate…*R*-reagent) and (*S*-substrate…*R*-reagent) are *diastereomeric*. *Kinetic resolution* is the term used to describe the separation of enantiomers on the basis of differential reaction rates with an enantiomerically pure reagent. Scheme 2.4 summarizes the conceptual basis of kinetic resolution.

Because the separation is based on differential rates of reaction, the degree of resolution that can be achieved depends on both the *magnitude of the rate difference and the extent of reaction*. The greater the difference in the two rates, the higher the enantiomeric purity of both the reacted and unreacted enantiomer. The extent of enantiomeric purity can be controlled by controlling the degree of conversion. As the extent of conversion increases, the enantiomeric purity of the *unreacted enantiomer increases*.[10] The relationship between the relative rate of reaction, extent of conversion, and enantiomeric purity of the unreacted enantiomer is shown graphically in Figure 2.8.

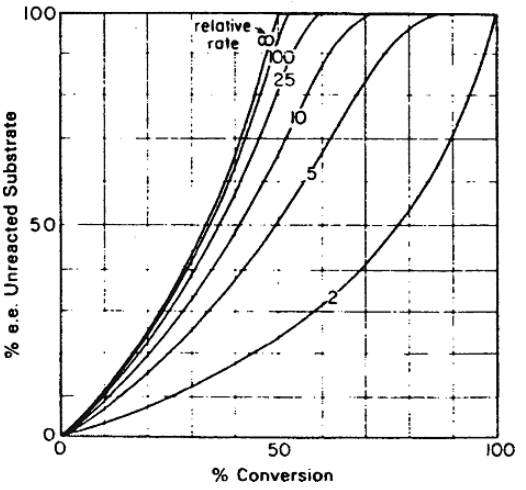


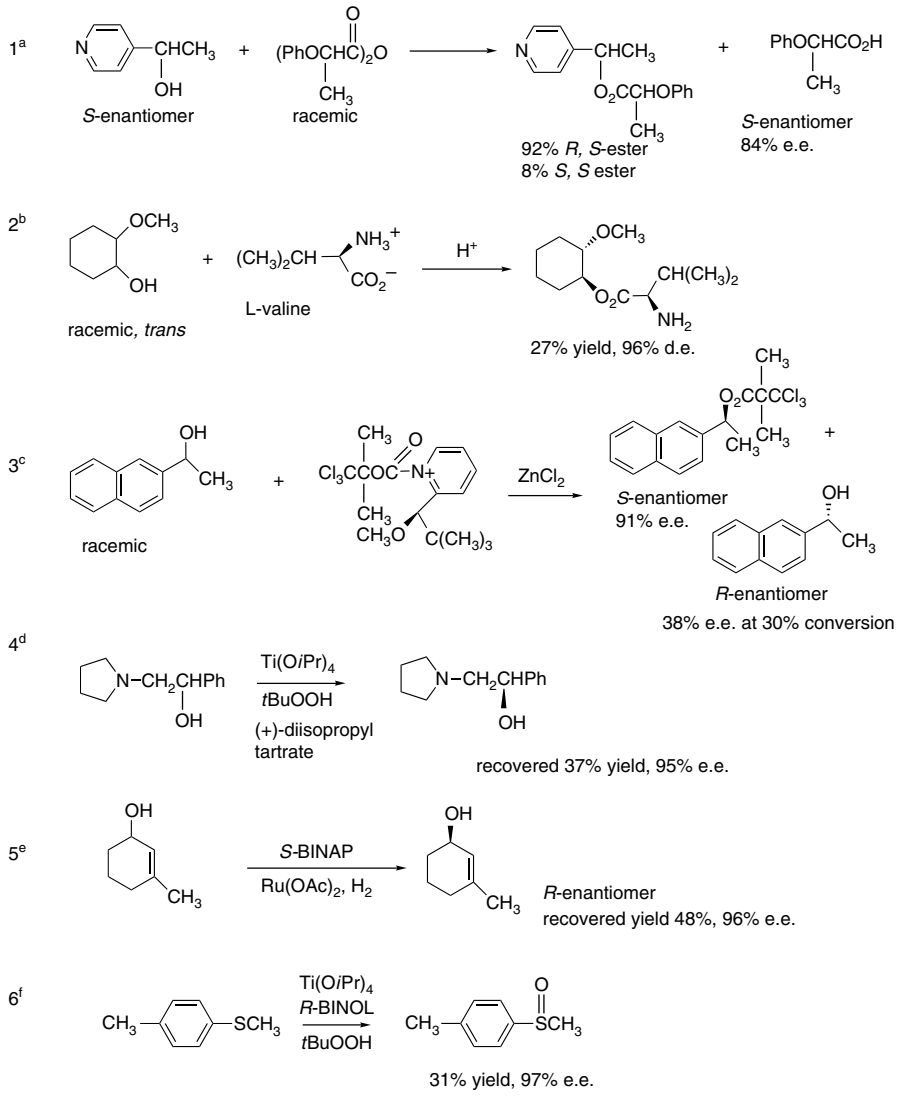
Fig. 2.8. Dependence of enantiomeric excess on relative rate of reaction and extent of conversion with a chiral reagent in kinetic resolution. Reproduced from *J. Am. Chem. Soc.*, **103**, 6237 (1981), by permission of the American Chemical Society.

[10] V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981).

Of course, the high conversion required for high enantiomeric purity when the relative reactivity difference is low has a serious drawback. The *yield of the unreacted substrate is low* if the overall conversion is high. Relative reactivity differences of < 10 can achieve high enantiomeric purity only at the expense of low yield.

Scheme 2.5 gives some specific examples of kinetic resolution procedures. Entries 1to 3 in Scheme 2.5 are acylation reactions in which esters are formed. Either the

Scheme 2.5. Examples of Kinetic Resolution



a. U. Salz and C. Rüchardt, *Chem. Ber.*, **117**, 3457 (1984).
b. P. Stead, H. Marley, M. Mahmoudian, G. Webb, D. Noble, Y. T. Ip, E. Piga, S. Roberts, and M. J. Dawson, *Tetrahedron: Asymmetry*, **7**, 2247 (1996).
c. E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, **118**, 1809 (1996).
d. S. Miyano, L. D. Lu, S. M. Viti, and K. B. Sharpless, *J. Org. Chem.*, **48**, 3608 (1983).
e. M. Kitmura, I. Kasahara, K. Manabe, R. Noyori, and H. Takaya, *J. Org. Chem.*, **53**, 708 (1988).
f. N. Komatsu, M. Hashizuma, T. Sugita, and S. Uemura, *J. Org. Chem.*, **58**, 7624 (1993).

alcohol or the acylation reagent is enantiopure. The enantioselectivity is a result of differential interactions in the TS (transition structure) and the reactions are carried to partial conversion to achieve kinetic resolution. These reactions presumably proceed via the typical addition-elimination mechanism for acylation (see Section 7.4) and do not have the benefit of any particular organizing center such as a metal ion. The observed enantioselectivities are quite high, and presumably depend primarily on steric differences in the diastereomeric TSs. Entries 4 and 5 involve enantioselective catalysts. Entry 4, is an oxidative cleavage that involves a complex of Ti(IV) with the chiral ligand, diisopropyl tartrate. It is sufficiently selective to achieve 95% e.e. at the point of about 67% completion. The other enantiomer is destroyed by the oxidation. Entry 5 uses a hydrogenation reaction with the chiral BINAP ligand (see p. 130 for structure). The *S*-enantiomer is preferentially hydrogenated and the *R*-enantiomer is obtained in high e.e. In both of these examples, the reactant coordinates to the metal center through the hydroxy group prior to reaction. The relatively high e.e. that is observed in each case reflects the high degree of order and discrimination provided by the chiral ligands at the metal center. Entry 6 is the oxidative formation of a sulfoxide, using BINOL (see p. 130) as a chiral ligand and again involves a metal center in a chiral environment. We discuss enantioselective catalysis further in Section 2.5.

Enzymes constitute a particularly important group of enantioselective catalysts,[11] as they are highly efficient and selective and can carry out a variety of transformations. Enzyme-catalyzed reactions can be used to resolve organic compounds. Because the enzymes are derived from L-amino acids, they are chiral and usually one enantiomer of a reactant (substrate) is much more reactive than the other. The interaction with each enantiomer is diastereomeric in comparison with the interaction of the enzyme with the other enantiomer. Since enzymatic catalysis is usually based on a specific fit to an "active site," the degree of selectivity between the two enantiomers is often very high. For enzymatic resolutions, the enantioselectivity can be formulated in terms of two reactants in competition for a single type of catalytic site.[12] Enzymatic reactions can be described by *Michaelis-Menten kinetics*, where the key parameters are the equilibrium constant for binding at the active site, K, and the rate constant, k, of the enzymatic reaction. The rates for the two enantiomers are given by

$$v_R = k_R[R]/K_R \text{ and } \nu_S = k_S[S]/K_S \tag{2.6}$$

In a resolution with the initial concentrations being equal, $[S] = [R]$ the enantiomeric selectivity ratio E is the relative rate given by

$$E = \frac{k_S/K_S}{k_R/K_R} \tag{2.7}$$

Figure 2.9 shows the relationship between the e.e. of unreacted material and product as a function of the extent of conversion and the value of E.

The most generally useful enzymes catalyze hydrolysis of esters and amides (esterases, lipases, peptidases, acylases) or interconvert alcohols with ketones and aldehydes (oxido-reductases). Purified enzymes can be used or the reaction can be done by incubating the reactant with an organism (e.g., a yeast) that produces an

[11] J. B. Jones, *Tetrahedron*, **42**, 3351 (1986); J. B. Jones, in *Asymmetric Synthesis*, J. D. Morrison, ed., Vol. 5, Academic Press, Chap. 9; G. M. Whitesides and C.-H. Wong, *Angew. Chem. Int. Ed. Engl.*, **24**, 617 (1985).

[12] C.-S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, **104**, 7294 (1982).

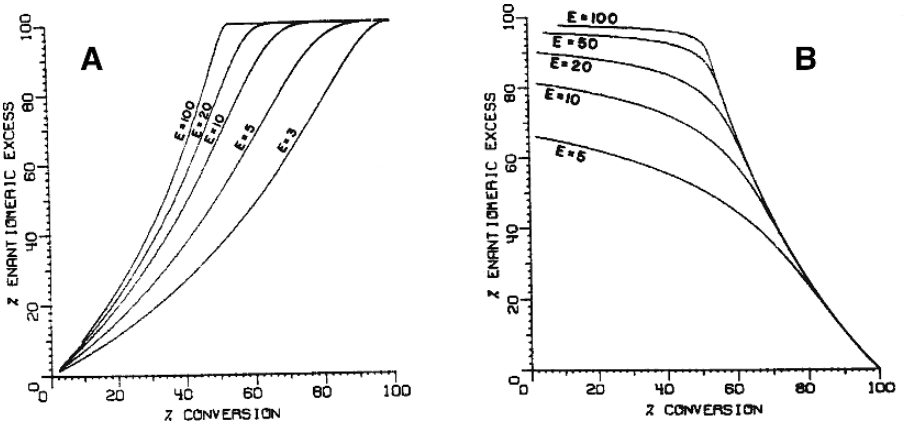
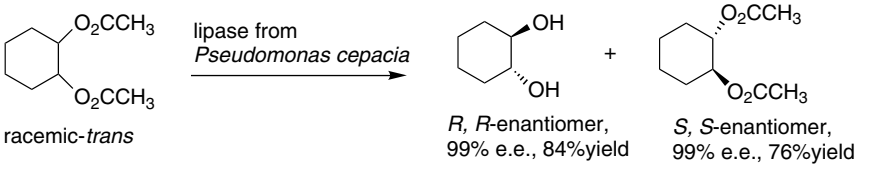


Fig. 2.9. Plots of enantiomeric excess as a function of extent of conversion for various values of E: (A) unreacted starting material; (B) product. Reproduced from *J. Am. Chem. Soc.*, **104**, 7294 (1982), by permission of the American Chemical Society.

appropriate enzyme during fermentation. Two examples are shown below. The main restriction on enzymatic resolution is the relatively limited range of reactions and substrates to which it is applicable. Enzymes usually have high substrate specificity, that is, they show optimal reactivity for compounds that are similar in structure to the natural substrate. Topic 2.2 gives further information about the application of enzymatic resolution.

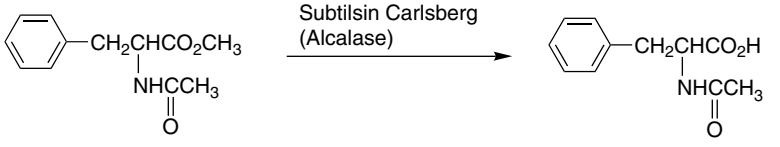


racemic-*trans*

R, R-enantiomer, 99% e.e., 84%yield

S, S-enantiomer, 99% e.e., 76%yield

Ref. 13



S-enantiomer, 98% e.e.

Ref. 14

13. G. Caron and R. J. Kazlauskas, *J. Org. Chem.*, **56**, 7251 (1991).
14. J. M. Roper and D. P. Bauer, *Synthesis*, 1041 (1983).

2.2. Conformation

The structural aspects of stereochemistry discussed in the previous section are the consequences of *configuration*, the geometric arrangement fixed by the chemical bonds within the molecule. Now, we want to look at another level of molecular structure, *conformation*. Conformations are the different shapes that a molecule can attain without breaking any covalent bonds. They differ from one another as the result of rotation at one or more single bond. The energy barrier for rotation of carbon-carbon single bonds is normally small, less than 5 kcal/mol, but processes that involve several coordinated rotations can have higher energy requirements. *Conformational analysis* is the process of relating conformation to the properties and reactivity of molecules.

2.2.1. Conformation of Acyclic Compounds

Ethane is a good molecule with which to begin. The two methyl groups in ethane can rotate with respect to one another. There are two unique conformations, called *staggered* and *eclipsed*. The eclipsed conformation represents the maximum energy and the staggered is the minimum. The difference between the two is 2.88 kcal/mol, as shown in Figure 2.10. As a result, any individual molecule is likely to be in the

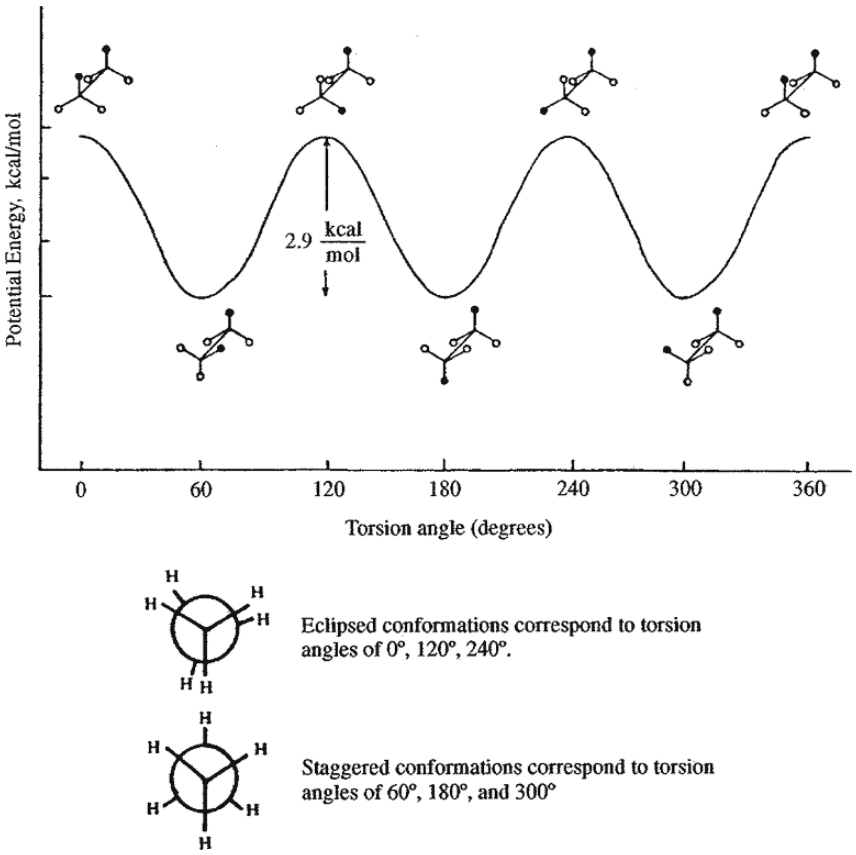
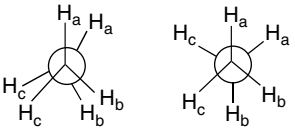
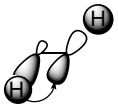


Fig. 2.10. Potential energy as a function of torsion angle for ethane.

staggered conformation at any given instant, but each molecule can rapidly traverse through the eclipsed conformation. The rate of rotation is about $6 \times 10^9\ s^{-1}$ at 25° C.



Shortly, we will learn that for some hydrocarbon molecules, van der Waals repulsions are a major factor in conformational preferences and energy barriers, but that is not the case for ethane. Careful analysis of the van der Waals radii show that the hydrogens do not come close enough to account for the barrier to rotation.[15] Furthermore, the barrier of just under 3 kcal is applicable to more highly substituted single bonds. The barrier becomes significantly larger only when additional steric components are added, so the barrier must be an intrinsic property of the bond and not directly dependent on substituent size. The barrier to rotation is called the *torsional barrier*. There are analogous (although smaller) barriers to rotation about C−N and C−O bonds. Topic 1.3 probes further into the origin of the torsional barrier in small molecules. The conclusion reached is that the main factor responsible for the torsional barrier is σ-σ* delocalization (hyperconjugation), which favors the staggered conformation.



hyperconjugation
in *anti* conformation

The interplay between the torsional barrier and nonbonded (van der Waals) interactions can be illustrated by examining the conformations of *n*-butane. The relationship between energy and the torsion angle for rotation about the C(2)−C(3) bond is presented in Figure 2.11. The potential energy diagram of *n*-butane resembles that of ethane in having three maxima and three minima, but differs in that one of the minima is lower than the other two and one of the maxima is of higher energy than the other two. The minima correspond to staggered conformations. Of these, the *anti* is lower in energy than the two *gauche* conformations. The energy difference between the *anti* and *gauche* conformations in *n*-butane is about 0.6 kcal/mol.[16] The maxima correspond to eclipsed conformations, with the highest-energy conformation being the one with the two methyl groups eclipsed with each other.

The rotational profile of *n*-butane can be understood as a superimposition of van der Waals repulsion on the ethane rotational energy profile. The two *gauche* conformations are raised in energy relative to the *anti* by an energy increment resulting from the van der Waals repulsion between the two methyl groups of 0.6 kcal/mol. The

15. E. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 599.
16. G. J. Szasz, N. Sheppard, and D. H. Rank, *J. Chem. Phys.*, **16**, 704 (1948); P. B. Woller and E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **94**, 5310 (1972).

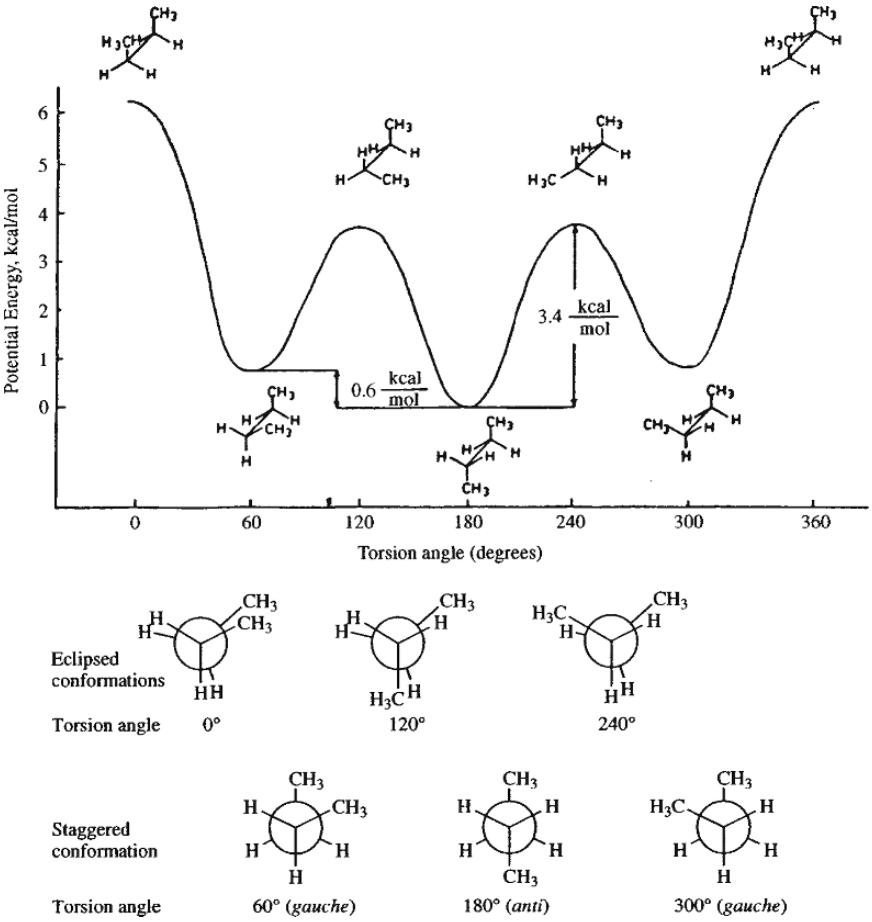


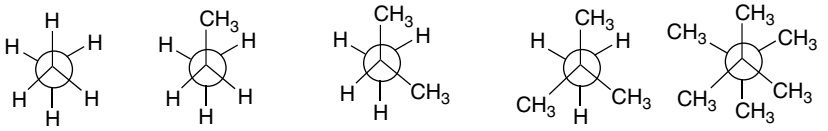
Fig. 2.11. Potential energy diagram for rotation about the C(2)−C(3) bond in *n*-butane.

eclipsed conformations all incorporate 2.8 kcal/mol of torsional strain relative to the staggered conformations, just as in ethane. The methyl-methyl eclipsed conformation is further strained by the van der Waals repulsion between the methyl groups. The van der Waals repulsion between methyl and hydrogen is smaller in the other eclipsed conformations. The methyl/methyl eclipsed barrier is not known precisely, but the range in experimental and theoretical values is between 4.0 and 6.6 kcal/mol, with the most recent values being at the low end of the range.[17]

The conformation of other simple hydrocarbons can be interpreted by extensions of the principles illustrated in the analysis of rotational barriers in ethane and *n*-butane. The staggered conformations correspond to torsional minima and the eclipsed conformations to torsional maxima. Of the staggered conformations, *anti* forms are more stable than *gauche*. Substitution of a methyl group for hydrogen on one of the carbon atoms produces an increase of 0.4–0.6 kcal/mol in the height of the rotational energy barrier. The barrier in ethane is 2.88 kcal/mol. In propane, the barrier is 3.4 kcal/mol, corresponding to an increase of 0.5 kcal/mol for methyl-hydrogen eclipsing. When

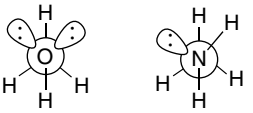
[17] N. L. Allinger, R. S. Grev, B. F. Yates, and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **112**, 114 (1990); W. A. Herrebout, B. J. van der Veken, A. Wang, and J. R. Durig, *J. Phys. Chem.*, **99**, 578 (1995).

two methyl-hydrogen eclipsing interactions occur, as in 2-methylpropane, the barrier is raised to 3.9 kcal/mol. The increase in going to 2,2-dimethylpropane, in which the barrier is 4.7 kcal/mol, is 1.8 kcal/mol for the total of three methyl-hydrogen eclipsing interactions. For 2,2,3,3-tetramethylbutane, in which there are three methyl-methyl interactions, the barrier is 8.4 kcal/mol. Rotational barriers in kcal/mol are shown below.



2.8 3.4 3.9 4.7 8.4

The magnitudes of the barriers to rotation of many small organic molecules have been measured.[18] The experimental techniques used to study rotational processes include microwave spectroscopy, electron diffraction, ultrasonic absorption, and infrared spectroscopy.[19] Some representative barriers are listed in Table 2.1. As with ethane, the barriers in methylamine and methanol appear to be dominated by *hyperconjugative stabilization* of the *anti* conformation. The barrier decreases ($2.9 \rightarrow 2.0 \rightarrow 1.1$) in proportion to the number of anti H–H arrangements ($3 \rightarrow 2 \rightarrow 1$). (See Topic 1.1 for further discussion.)[20]



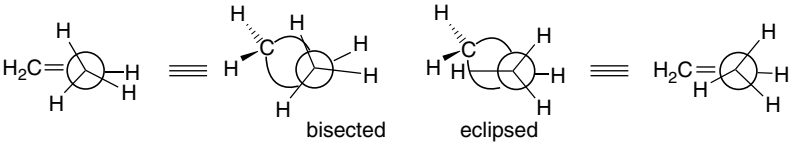
The conformation of simple alkenes can be considered by beginning with propene. There are two families of conformations available to terminal alkenes: *eclipsed* and *bisected* conformations, as shown below for propene. The eclipsed conformation is preferred by about 2 kcal/mol and represents a barrier to rotation of the methyl group.[21,22] A simple way to relate the propene rotational barrier to that of ethane is to regard the π bond as a "banana bond" (see p. 7). The bisected conformation of propene is then seen to correspond to the eclipsed conformation of ethane, while the more stable eclipsed conformation corresponds to the staggered conformation of ethane.[23]

18. For reviews, see (a) J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968); (b) J. E. Andersen, in *The Chemistry of Alkenes and Cycloalkens,* S. Patai and Z. Rappoport, eds., Wiley, Chichester, 1992, Chap. 3II. D.
19. Methods for determination of rotational barriers are discussed in Ref. 18a and by E. Wyn-Jones and R. A. Pethrick, *Top. Stereochem.*, **5**, 205 (1969).
20. J. K. Badenhoop and F. Weinhold, *Int. J. Quantum Chem.*, **72**, 269 (1999); V. Pophristic and L. Goodman, *J. Phys. Chem. A.*, **106**, 1642 (2002).
21. J. R. Durig, G. A. Guirgis, and S. Bell, *J. Phys. Chem.*, **93**, 3487 (1989).
22. Detailed analysis of the rotation shows that it is coupled with vibrational processes. L. Goodman, T. Kundu, and J. Leszczynski, *J. Phys. Chem.*, **100**, 2770 (1996).
23. K.-T. Lu, F. Weinhold, and J. C. Weisshaar, *J. Chem. Phys.*, **102**, 6787 (1995).

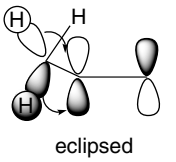
Table 2.1. Rotational Barriers of Compounds of Type CH_3-X[a]

Alkanes[a]	Barrier (kcal/mol)	Heteroatom compounds	Barrier (kcal/mol)
CH_3-CH_3	2.9	CH_3-NH_2[c]	2.0
$CH_3-CH_2CH_3$	3.4	CH_3-NHCH_3[c]	3.0
$CH_3-CH(CH_3)_2$	3.9	$CH_3-N(CH_3)_2$[c]	4.4
$CH_3-C(CH_3)_3$	4.7	CH_3-OH[d]	1.1
$(CH_3)_3C-C(CH_3)_3$	8.4[b]	CH_3-OCH_3[d]	4.6

a. Taken from the compilation of J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968).
b. Footnote 9, J. E. Andersen, A. de Meijere, S. I. Kozhushkov, L. Lunazzi, and A. Mazzanti, *J. Org. Chem.*, **68**, 8494 (2003).
c. M. L. Senent and Y. G. Meyers, *J. Chem. Phys.*, **105**, 2789 (1996).
d. V. Pophristic, L. Goodman, and N. Guchhait, *J. Phys. Chem. A*, **101**, 4290 (1997).



The conformation of propene is influenced by hyperconjugation. The methyl substituent has an overall stabilizing effect (2.7 kcal) on the double bond, as can be concluded from the less negative heat of hydrogenation compared to ethene (see Section 3.1.1). This stabilization arises from σ-π^* interactions. The major effect is a transfer of electron density from the methyl σ C−H bonds to the empty π^* orbital.

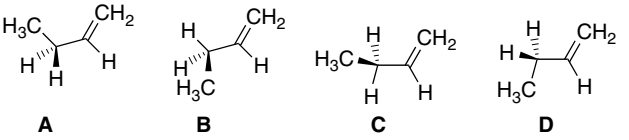


Computational approaches can provide an indication of the magnitude of the interaction. A "block-localized" wave function calculation estimates a stabilization of about 5.4 kcal/mol at the 6-31G** level.[24] The computation also shows a shortening of the C(2)−C(3) single bond as the result of the σ-π^* delocalization. Because the extent of hyperconjugation differs between the two unique conformers, this factor contributes to the energy difference between them. The energy difference between the eclipsed and bisected conformations has been broken into components, as described for ethane in Topic 1.3. The hyperconjugation component is the major factor. At the MP2/6-311(3*d*,2*p*) level of computation, the $CH_3-C=$ bond length is 1.4952 Å, versus 1.5042 Å in the staggered conformation. The corresponding difference in energy is the largest component of the energy barrier and results from adjustments in the bond length in response to the rotation.[25]

[24] The block-localized calculations are conceptually similar to NBO analysis (see Section 1.4.2) in that they compare a calculation in which the orbitals are strictly localized with the unrestricted calculation to estimate the effect of delocalization. Y. Mo and S. D. Peyerimhoff, *J. Chem. Phys.*, **109**, 1687 (1998).

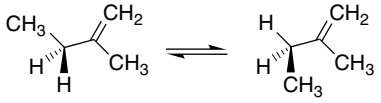
[25] T. Kundu, L. Goodman, and J. Leszczynksi, *J. Chem. Phys.*, **103**, 1523 (1995).

With more highly substituted terminal alkenes, additional conformations are available, as indicated for 1-butene.

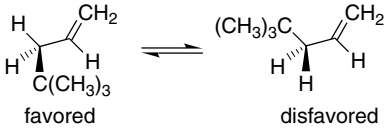


Conformations **A** and **B** are of the eclipsed type, whereas **C** and **D** are bisected. It has been determined by microwave spectroscopy that the eclipsed conformations are more stable than the bisected ones and that **B** is about 0.15 kcal more stable than **A**.[26] MO calculations at the HF/6-31G* level found relative energies of 0.00, −0.25, 1.75, and 1.74 kcal/mol, respectively, for **A**, **B**, **C**, and **D**.[27] More recently, experimental far-IR spectroscopy and MP2/6-31G++(3*df*,3*pd*) computations indicate a difference of about 0.2 kcal (favoring **B**).[28]

Further substitution can introduce van der Waals repulsions that influence conformational equilibria. For example, methyl substitution at C(2), as in 2-methyl-1-butene, introduces a methyl-methyl *gauche* interaction in the conformation analogous to **B**, with the result that in 2-methyl-1-butene the two eclipsed conformations are of approximately equal energy.[29]



Increasing the size of the group at C(3) increases the preference for the eclipsed conformation analogous to **B** at the expense of **A**. 4,4-Dimethyl-1-pentene exists mainly in the hydrogen-eclipsed conformation.



This interaction is an example of *1,3-allylic strain*.[30] This type of steric strain arises in eclipsed conformations when substituents on the double bond and the C(3) group, which are coplanar, are large enough to create a nonbonded repulsion. The conformation of alkenes is an important facet with regard to the stereoselectivity of addition

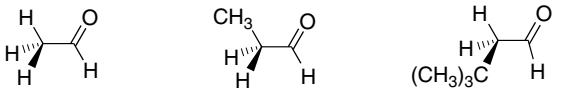
[26] S. Kondo, E. Hirota, and Y. Morino, *J. Mol. Spectrosc.*, **28**, 471 (1968).
[27] W. J. Hehre, J. A. Pople, and A. J. P. Devaquet, *J. Am. Chem. Soc.*, **98**, 664 (1976).
[28] S. Bell, B. R. Drew, G. A. Guirgis, and J. R. During, *J. Mol. Struct.*, **553**, 199 (2000).
[29] T. Shimanouchi, Y. Abe, and K. Kuchitsu, *J. Mol. Struct.*, **2**, 82 (1968).
[30] R. W. Hoffmann, *Chem. Rev.*, **89**, 1841 (1989).

reactions of alkenes. Allylic strain and other conformational factors contribute to the relative energy of competing TSs, and can lead to a preference for a particular stereoisomeric product.

The preferred conformations of carbonyl compounds, like 1-alkenes, are eclipsed rather than bisected, as shown below for ethanal and propanal. The barrier for methyl group rotation in ethanal is 1.17 kcal/mol.[31] Detailed analysis has indicated that small adjustments in molecular geometry, including σ-bond lengthening, must be taken into account to quantitatively analyze the barrier.[32] The total barrier can be dissected into nuclear-nuclear, electron-electron, nuclear-electron, and kinetic energy (Δt), as described in Topic 1.3 for ethane. MP2/6-311+G (3*df*,2*p*) calculations lead to the contributions tabulated below. The total barrier found by this computational approach is very close to the experimental value. Contributions to the ethanal energy barrier in kcal/mol are shown below.

ΔV_{nn}	−10.621
ΔV_{ee}	−5.492
ΔV_{ne}	+18.260
Δt	−0.938
Δ total	+1.209

In propanal, it is the methyl group, rather than the hydrogen, that is eclipsed with the carbonyl group in the most stable conformation. The difference in the two eclipsed conformations has been determined by microwave spectroscopy to be 0.9 kcal/mol.[33] A number of other aldehydes have been studied by NMR and found to have similar rotameric compositions.[34] When the alkyl substituent becomes too sterically demanding, the hydrogen-eclipsed conformation becomes more stable. This is the case with 3,3-dimethylbutanal.



preferred conformations for ethanal, propanal, and 3, 3-dimethylbutanal

Ketones also favor eclipsed conformations. The preference is for the rotamer in which the alkyl group, rather than a hydrogen, is eclipsed with the carbonyl group because this conformation allows the two alkyl groups to be *anti* rather than *gauche* with respect to the other carbonyl substituent.

more stable less stable

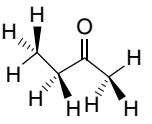
[31] I. Kleiner, J. T. Hougen, R. D. Suenram, F. J. Lovas, and M. Godefroid *J. Mol. Spectros.*, 153, 578 (1992); S. P. Belov, M. Y. Tretyakov, I. Kleiner, and J. T. Hougen, *J. Mol. Spectros.*, 160, 61 (1993).

[32] L. Goodman, T. Kundu, and J. Leszczynski, *J. Am. Chem. Soc.*, **117**, 2082 (1995).

[33] S. S. Butcher and E. B. Wilson, Jr., *J. Chem. Phys.*, **40**, 1671 (1964).

[34] G. J. Karabatsos and N. Hsi, *J. Am. Chem. Soc.*, **87**, 2864 (1965).

The conformational profile for 2-butanone has been developed from analysis of its infrared spectrum.[35] The dominant conformation is *anti* with a C(1)H and the C(4) methyl group eclipsed with the carbonyl.



The C(3)–C(4) rotational barrier is 2.48 kcal/mol, similar to the ethane barrier, while the C(1)–C(2) rotational barrier is 0.67 kcal/mol. Figure 2.12 shows the rotational potential energy diagram for 2-butanone as calculated at the HF/6-31G level. The preferred conformation of 3-methyl-2-butanone is similar.[36]

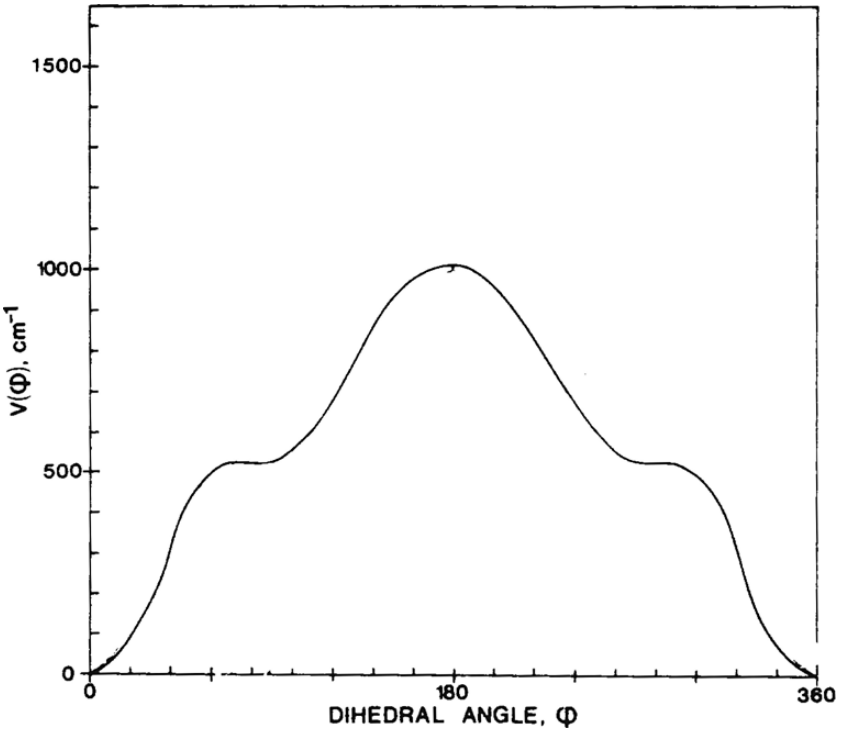
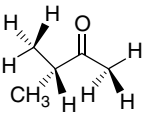
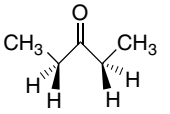


Fig. 2.12. Calculated potential energy diagram (HF/6-31G) for rotation about C(2)–C(3) bond of 2-butanone. Reproduced from *Can. J. Chem.* **69**, 1827 (1991), by permission of the National Research Council Press.

35. J. R. Durig, F. S. Feng, A. Y. Wang, and H. V. Phan, *Can. J. Chem.*, **69**, 1827 (1991).
36. T. Sakurai, M. Ishiyama, H. Takeuchi, K. Takeshita, K. Fukushi, and S. Konaka, *J. Mol. Struct.*, **213**, 245 (1989); J. R. Durig, S. Shen, C. Zeng, and G. A Guirgis, *Can. J. Anal. Sci. Spectrosc.* **48**, 106 (2003).



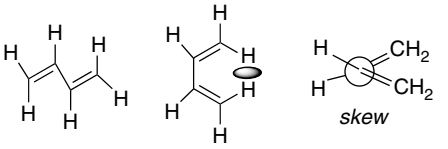
Moreover, electron diffraction studies of 3-pentanone indicate the methyl-eclipsed conformation shown below to be the most stable rotamer.[37]



preferred conformation for 3-pentanone

The pattern, then, is that methyl and unbranched alkyl groups prefer to be eclipsed with the carbonyl group.

1,3-Dienes adopt conformations in which the double bonds are coplanar, so as to permit optimum π-orbital overlap and electron delocalization. The two alternative planar conformations for 1,3-butadiene are referred to as *s-trans* and *s-cis*. In addition to the two planar conformations, there is a third conformation, referred to as the *skew* conformation, which is cisoid but not planar. Various types of structural studies have shown that the *s-trans* conformation is the most stable one for 1,3-butadiene.[38] A small amount of the skew conformation is also present in equilibrium with the major conformer.[39] The planar *s-cis* conformation incorporates a van der Waals repulsion between the hydrogens on C(1) and C(4), which is relieved in the skew conformation.



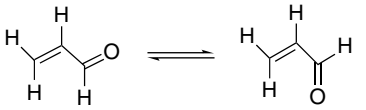
s-trans *s-cis* *skew*

The barrier for conversion of the skew conformation to the *s-trans* is 3.9 kcal/mol. The energy maximum presumably refers to the conformation in which the two π bonds are mutually perpendicular. The height of this barrier gives an approximation of the stabilization provided by conjugation in the planar *s-trans* conformation. Various MO calculations find the *s-trans* conformation to be 2–5 kcal/mol lower in energy than either the planar or skew cisoid conformations.[40] Most high-level MO calculations

37. C. Romers and J. E. G. Creutzberg, *Rec. Trav. Chim.*, **75**, 331 (1956).
38. A. Almenningen, O. Bastiansen, and M. Traetteburg, *Acta Chem. Scand.*, **12**, 1221 (1958); K. K. Kuchitsu, T. Fukuyama, and Y. Morino, *J. Mol. Struct.*, **1**, 643 (1967); R. L. Lipnick and E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **95**, 6370 (1973).
39. K. B. Wiberg and R. E. Rosenburg, *J. Am. Chem. Soc.*, **112**, 1509 (1990).
40. A. J. P. Devaquet, R. E. Townshend, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 4068 (1976); K. B. Wiberg, P. R. Rablen, and M. Marquez, *J. Am. Chem. Soc.*, **114**, 8654 (1992); M. Head-Gordon and J. A. Pople, *J. Phys. Chem.*, **97**, 1147 (1993).

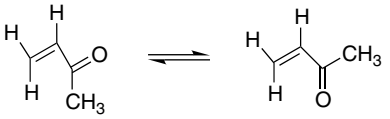
favor the skew conformation over the planar *s-cis*, but the energy differences found are quite small.[39,41]

The case of α,ß-unsaturated carbonyl compounds is analogous to that of 1,3-dienes, in that conjugation favors coplanarity of the C=C−C=O system. The rotamers that are important are the *s-trans* and *s-cis* conformations. Microwave data indicate that the *s-trans* form is the only conformation present in detectable amounts in 2-propenal (acrolein).[42]



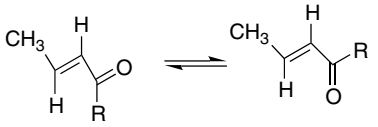
s-trans *s-cis*

The equilibrium distribution of *s-trans* and *s-cis* conformations of substituted α,ß-unsaturated ketones depends on the extent of van der Waals interaction between the C(1) and the C(4) substituents.[43] Methyl vinyl ketone has the minimal unfavorable van der Waals repulsions and exists predominantly as the *s-trans* conformer.



s-trans (73%) *s-cis* (27%)

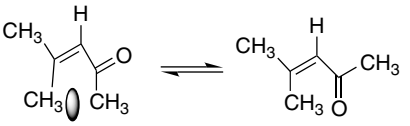
When larger alkyl groups are substituted for methyl, the ratio of the *s-cis* form progressively increases as the size of the alkyl group increases.[44]



R	*s-trans*	*s-cis*
CH_3	0.7	0.3
C_2H_5	0.55	0.45
$(CH_3)_2CH$	0.3	0.7
$(CH_3)_3C$	0.0	1.0

An unfavorable methyl-methyl interaction destabilizes the *s-trans* conformation of 4-methylpent-3-en-2-one (mesityl oxide) relative to the *s-cis* conformation, and the equilibrium favors the *s-cis* form.

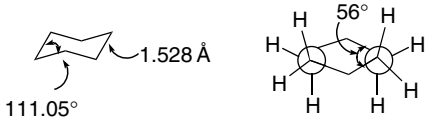
41. J. Breulet, T. J. Lee, and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **106**, 6250 (1984); D. Feller and E. R. Davidson, *Theor. Chim. Acta*, **68**, 57 (1985).
42. E. A. Cherniak and C. C. Costain, *J. Chem. Phys.* **45**, 104 (1966).
43. G. Montaudo, V. Librando, S. Caccamese, and P. Maravigna, *J. Am. Chem. Soc.*, **95**, 6365 (1973).
44. A. Bienvenue, *J. Am. Chem. Soc.*, **95**, 7345 (1973).



s-trans (28%) *s-cis* (72%)

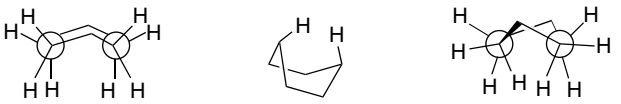
2.2.2. Conformations of Cyclohexane Derivatives

The conformational analysis of six-membered ring compounds is particularly well developed. Cyclohexane and its derivatives lend themselves to thorough analysis because they are characterized by a small number of energy minima. The most stable conformations are separated by barriers that are somewhat higher and more easily measured than rotational barriers in acyclic compounds or other ring systems. The most stable conformation of cyclohexane is the chair. Electron diffraction studies in the gas phase reveal a slight flattening of the chair, compared with the geometry obtained using tetrahedral molecular models. The torsion angles are 55.9°, compared with 60° for the "ideal" chair conformation, and the axial C−H bonds are not perfectly parallel, but are oriented outward by about 7°. The C−C bonds are 1.528 Å, the C−H bonds are 1.119 Å, and the C−C−C angles are 111.05°.[45]



Two nonchair conformations of cyclohexane that have normal bond angles and bond lengths are the *twist* and the *boat*,[46] both of which are less stable than the chair. A direct measurement of the chair-twist energy difference has been made using low-temperature IR spectroscopy.[47] The chair was determined to be 5.5 kcal/mol lower in energy than the twist. The twist and the boat conformations are more flexible than the chair, but are destabilized by torsional strain, as the bonds along the "sides" of the boat are eclipsed. In addition, the boat conformation is further destabilized by a van der Waals repulsion between the "flagpole" hydrogens. Both this van der Waals repulsion and the torsional strain are somewhat reduced in the twist conformation.

45. H. J. Geise, H. R. Buys, and F. C. Mijlhoff, *J. Mol. Struct.*, **9**, 447 (1971).
46. For a review of nonchair conformations of six-membered rings, see G. M. Kellie and F. G. Riddell, *Top. Stereochem.* **8**, 225 (1974).
47. M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.*, **97**, 3244 (1975).



eclipsing in boat conformation | flagpole interaction in boat conformation | partial relief of eclipsing in twist conformation (2.8)

Interconversion of chair forms is known as *conformational inversion*, and occurs by rotation about the carbon-carbon bonds. For cyclohexane, the first-order rate constant for ring inversion is 10^4–10^5 sec^{-1} at 27° C. The enthalpy of activation is 10.8 kcal/mol.[48] Calculation of the geometry of the transition state by *molecular mechanics* (see Section 2.3) suggests a half-twist form lying 12.0 kcal/mol above the chair. According to this analysis, the half-twist form incorporates 0.2 kcal/mol of strain from bond length deformation, 2.0 kcal/mol of bond angle strain, 4.4 kcal/mol of van der Waals stain, and 5.4 kcal/mol of torsional strain.[49] Figure 2.13 presents a two-dimensional energy diagram illustrating the process of conformational inversion in cyclohexane. The boat form is not shown in the diagram because the chair forms can interconvert without passing through the boat. The boat lies 1–2 kcal/mol above the twist conformation and is a transition state for interconversion of twist forms.[50]

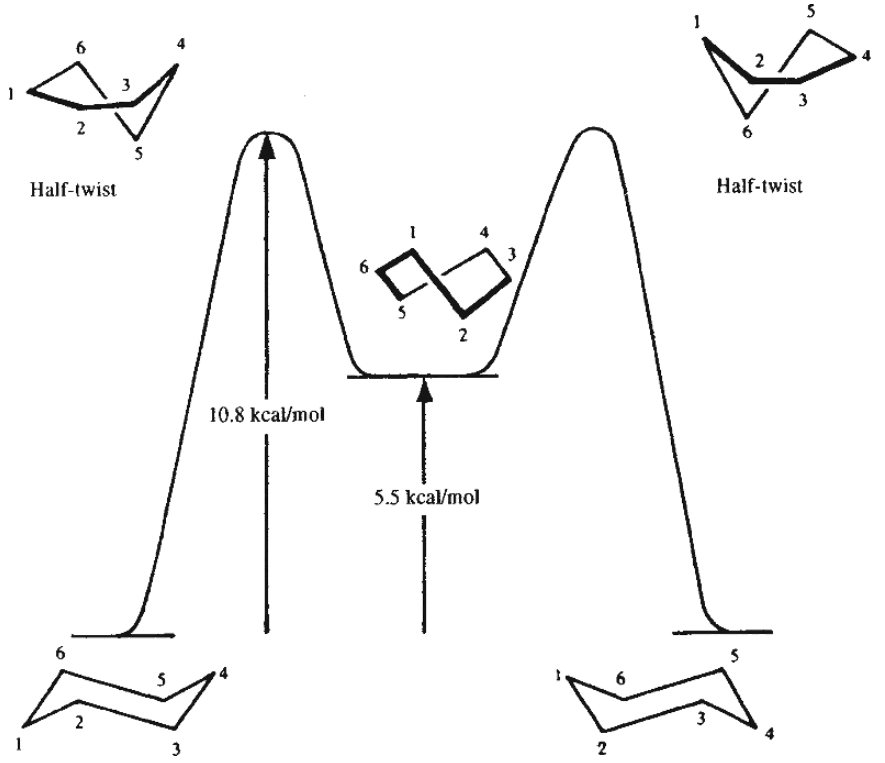
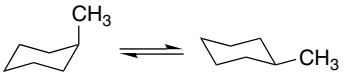


Fig. 2.13. Energy diagram for ring inversion of cyclohexane.

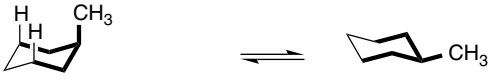
48. F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **89**, 760 (1967).
49. N. L. Allinger, M. A. Miller, F. A. van Catledge, and J. A. Hirsch, *J. Am. Chem. Soc*., **89**, 4345 (1967); N. L. Allinger, *J. Am Chem. Soc.*, **99**, 8127 (1997).
50. N. Leventis, S. B. Hanna, and C. Sotiriou-Leventis, *J. Chem. Educ.* **74**, 813 (1997); R. R. Sauers, *J. Chem. Educ*. **77**, 332 (2000).

Visual models, additional information and exercises on Cyclohexane Conformations can be found in the Digital Resource available at: Springer.com/carey-sundberg.

Substitution on a cyclohexane ring does not greatly affect the rate of conformational inversion, but does change the equilibrium distribution between alternative chair forms. All substituents that are axial in one chair conformation become equatorial on ring inversion, and vice versa. For methylcyclohexane, ΔG for the equilibrium is -1.8 kcal/mol, corresponding to a composition with 95% of the equatorial methyl conformation.



Two factors contribute to the preference for the equatorial conformation. The equatorial methyl conformation corresponds to an *anti* arrangement with respect to the C(2)–C(3) and C(6)–C(5) bonds, whereas the axial methyl group is in a *gauche* relationship to these bonds. We saw earlier that the *gauche* conformation of *n*-butane is 0.5–0.6 kcal/mol higher in energy than the *anti* conformation. In addition, there is a van der Waals repulsion between the axial methyl group and the axial hydrogens at C(3) and C(5). Interactions of this type are called *1,3-diaxial interactions*.



gauche-butane relationships in axial methylcyclohexane

anti-butane relationships in equatorial methylcyclohexane

Energy differences between conformations of substituted cyclohexanes can be measured by several methods, as can the kinetics of the ring inversion processes. NMR spectroscopy is especially valuable for both thermodynamic and kinetic studies.[51] Depending on the rate of the process, the difference in chemical shift between the two sites and the field strength of the spectrometer, the observed spectrum will be either a weighted average spectrum (rapid site exchange, $k > 10^5\,\text{sec}^{-1}$) or a superposition of the spectra of the two conformers reflecting the equilibrium composition (slow site exchange, $k < 10^3\,\text{sec}^{-1}$). At intermediate rates of exchange, broadened spectra are observed. Analysis of the temperature dependence of the spectra can provide the activation parameters for the conformational process. Figure 2.14 illustrates the change in appearance of a simple spectrum.

For substituted cyclohexanes, the slow-exchange condition is met at temperatures below about $-50°$ C. Data for the half-life for conformational equilibration of

[51] G. Binsch, *Top. Stereochem.* **3**, 97 (1968); F. G. Riddell, *Nucl. Magn. Reson.*, **12**, 246 (1983); J. Sandstrom, *Dynamic NMR Spectroscopy*, Academic Press, New York, 1982; J. L. Marshall, *Nuclear Magnetic Resonance*, Verlag Chemie, Deerfield Beach, FL, 1983; M. Oki, *Applications of Dynamic NMR to Organic Chemistry*, VCH Publishers, Deerfield Beach, FL, 1985; Y. Takeuchi and A. P. Marchand, eds., *Applications of NMR Spectroscopy in Stereochemistry and Conformational Analysis*, VCH Publishers, Deerfield Beach, FL, 1986.

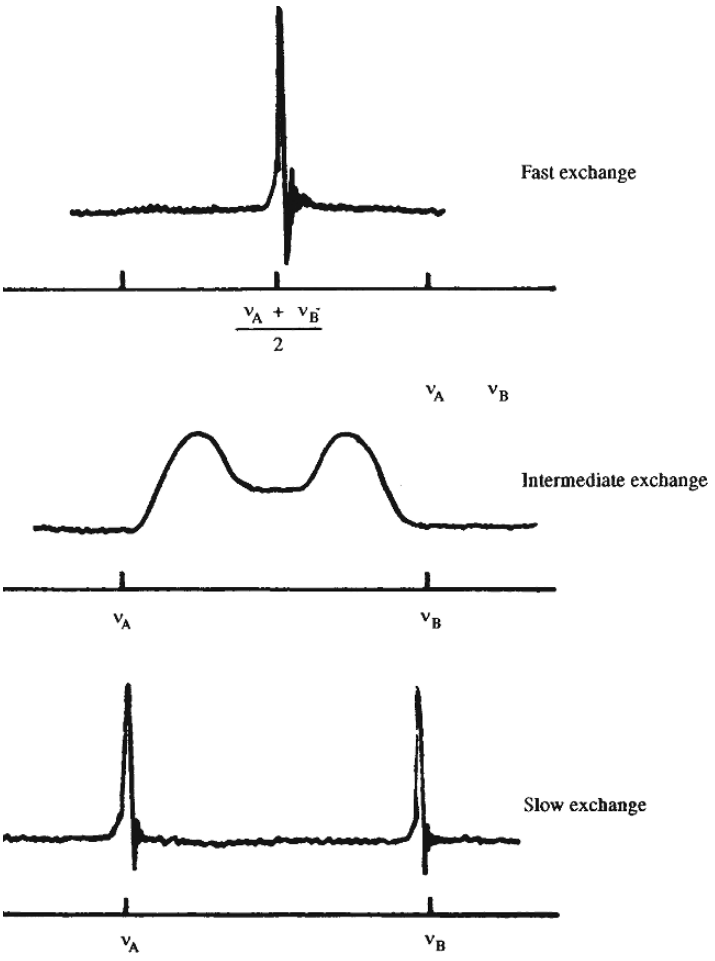


Fig. 2.14. Appearance of NMR spectra for system undergoing site exchange at various rates.

chlorocyclohexane as a function of temperature is shown below. From these data, it can be seen that conformationally pure solutions of equatorial chlorocyclohexane can be maintained at low temperature.[52]

Half-Life for Conformation Inversion for Chlorocyclohexane at Various Temperatures

Temperature (°C)	Half-Life
25	1.3×10^{-5} s
−60	2.5×10^{-2} s
−120	23 min
−160	22 yr

[52] F. R. Jensen and C. H. Bushweller, *J. Am. Chem. Soc.*, **91**, 3223 (1969).