

Stereochemistry, Conformation, and Stereoselectivity

Introduction

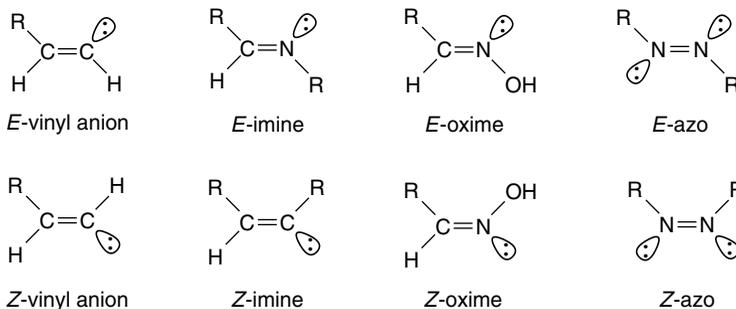
In the discussion of the structural features of carbon compounds in the Chapter 1, we emphasized some fundamental principles of molecular geometry. Except in strained rings, sp^3 carbon is nearly tetrahedral in shape. Double bonds involving sp^2 carbon are trigonal and planar and have a large barrier 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

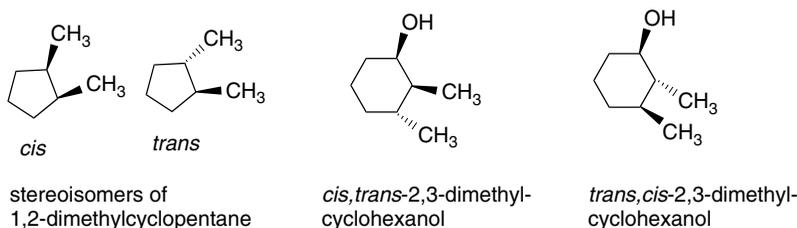
The sp^2 hybridization in the carbon atoms in a double bond and the resulting π bond favor a planar arrangement of the two carbon atoms and the four immediate

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 >:

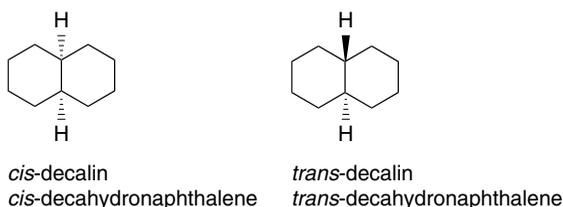


2.1.2. Configuration of Cyclic Compounds

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.

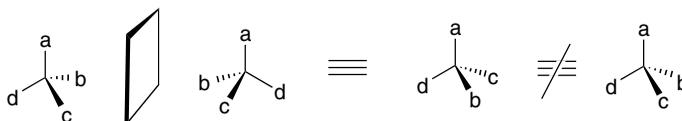


Stereoisomers also arise when two rings share a common bond. In the *cis* isomer both branches of the fused ring are on the same side. In the *trans* isomer they are on opposite sides.



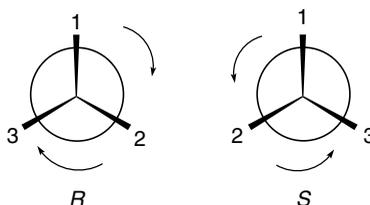
2.1.3. Configuration at Tetrahedral Atoms

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.

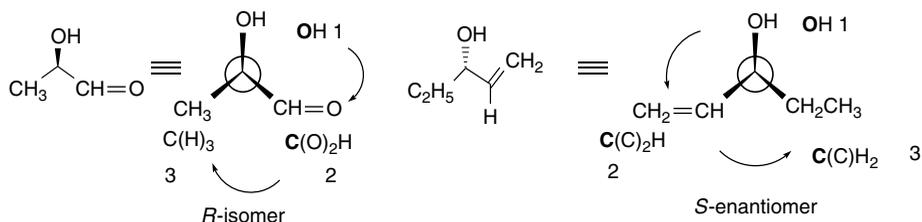


Any object that cannot be superimposed on its mirror image is called *chiral*, that is, it has the property of being right-handed or left-handed. Molecules (or other objects) that are not chiral are described as being *achiral*, which is the opposite of chiral. Tetrahedral atoms with four nonidentical 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*.

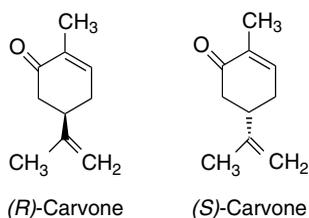
The chirality (or handedness) at stereogenic centers is specified by application of the Cahn-Ingold-Prelog priority rules, as described for double bonds. The four nonidentical ligand atoms are assigned a decreasing priority $1 > 2 > 3 > 4$. The molecule is then viewed opposite from the lowest-priority 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.



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

$$[\alpha]_{\lambda} = \frac{100\alpha}{cl} \quad (2.1)$$

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:

$$\text{e.e.} = \% \text{ Major} - \% \text{ Minor} \quad (2.2)$$

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).

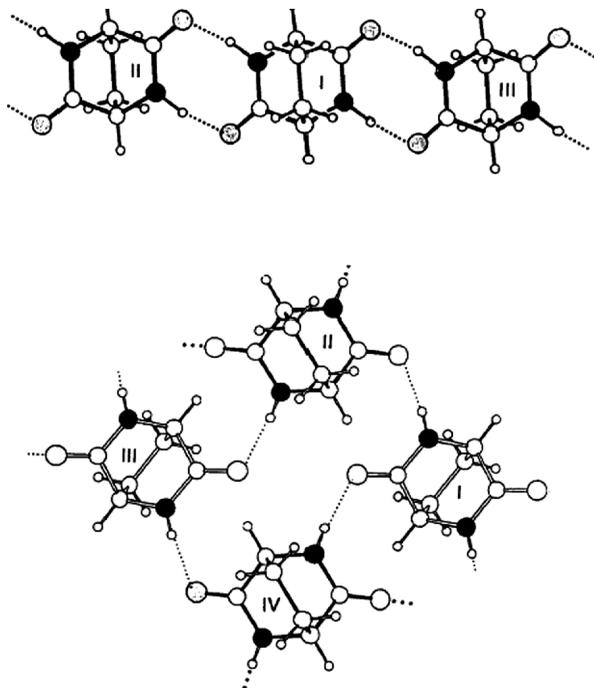


Fig. 2.1. Alternative hydrogen-bonding and crystal-packing arrangements for racemic (top) and (-) (bottom) forms of 2,5-diazabicyclo[2.2.2]octane-3,6-dione. Reproduced from *Tetrahedron Lett.*, **35**, 8157 (1994), by permission of Elsevier.

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

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

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) \times $[\alpha]_{\lambda}$. If $[\alpha]_{\lambda}$ is known, measurement of α allows the optical purity and enantiomeric excess to be determined:

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

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:

$$\theta = 3330(\epsilon_L - \epsilon_R) \quad (2.5)$$

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

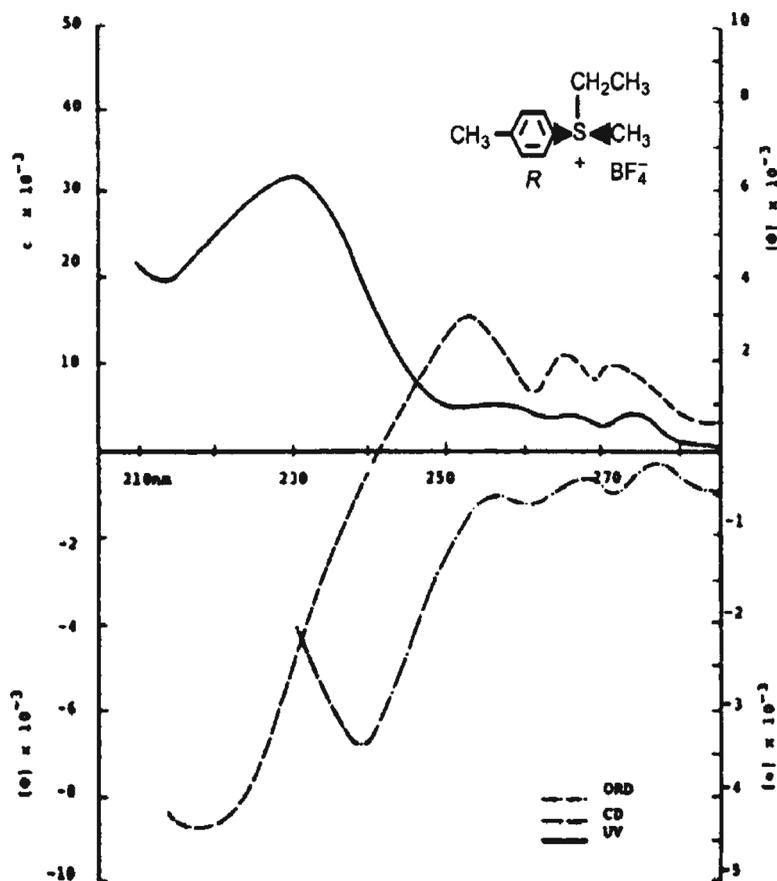


Fig. 2.2. UV absorption, ORD, and CD curves of (*R*)-ethyl methyl *p*-tolyl sulfonium tetrafluoroborate. Reproduced from *J. Org. Chem.*, **41**, 3099 (1976), by permission of the American Chemical Society.

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).

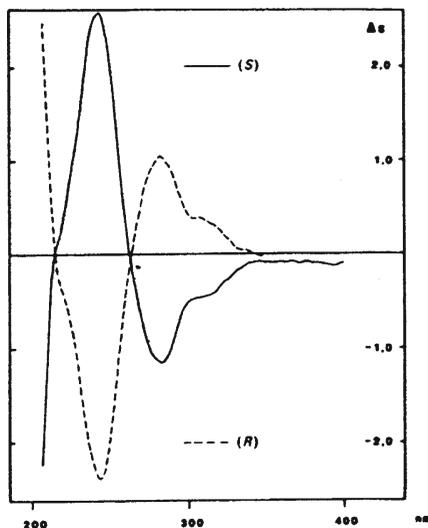


Fig. 2.3. CD spectra of (*S*)- and (*R*)-2-amino-1-phenyl-1-propanone hydrochloride. Reproduced from *Helv. Chim. Acta*, **69**, 1498 (1986), by permission of Wiley-VCH.

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

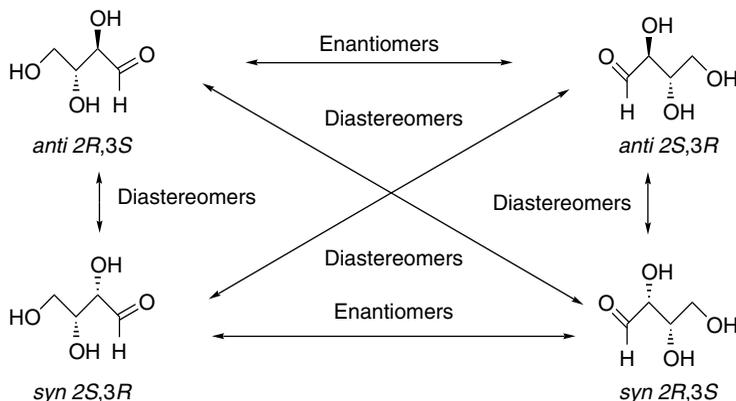
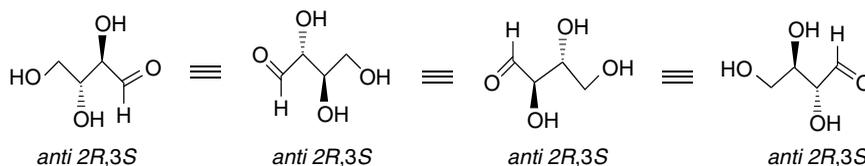


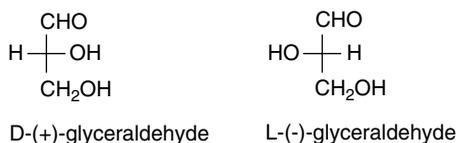
Fig. 2.4. Extended chain representation of all stereoisomers of 2,3,4-trihydroxybutanal.

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-2R,3R* and *syn-2R,3S* 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-2R,3S* stereoisomer.



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.



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

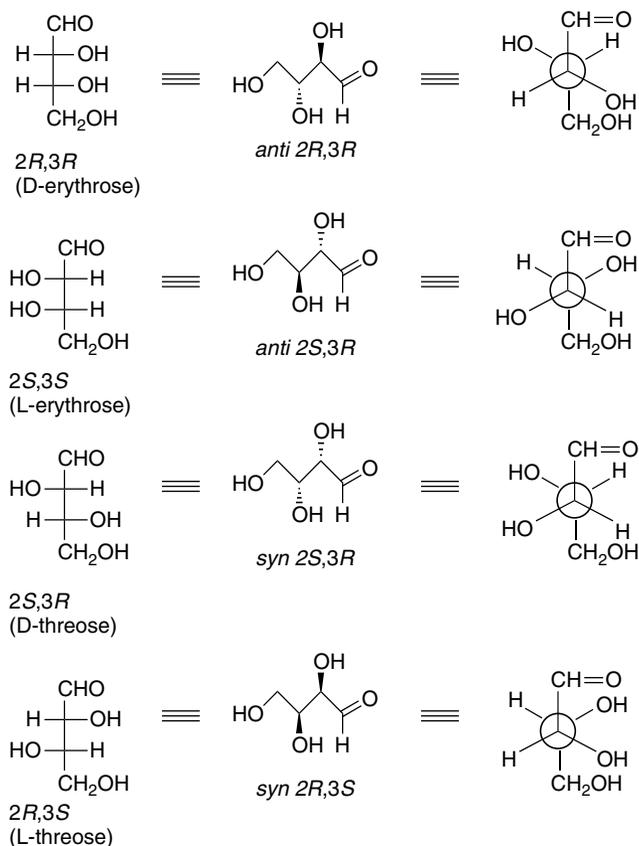


Fig. 2.5. Fischer, extended, and Newman projection representations of the stereoisomers of 2,3,4-trihydroxybutanal.

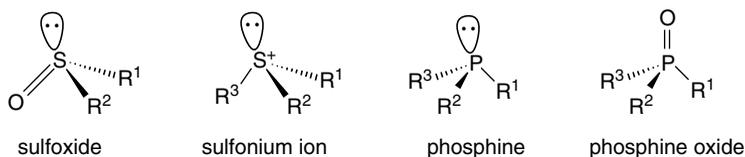
by *Newman projection formulas*. Figure 2.5 shows 2,3,4-trihydroxybutanal (now also with its carbohydrate names, erythrose and threose) as Fischer projection formulas as well as extended and Newman representations.

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.)

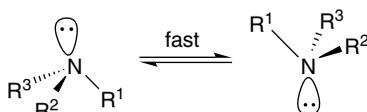
2.1.5. Other Types of Stereogenic Centers

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

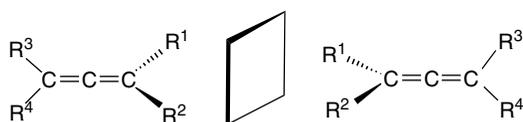
so evident are the cases of *trivalent* sulfur and phosphorus compounds, including sulfonium salts, sulfoxides, and phosphines. The heteroatom in these structures is approximately tetrahedral, with an electron pair occupying one of the tetrahedral positions. Because there is a relatively high energy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



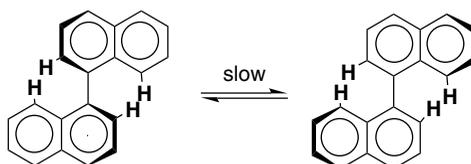
Trivalent nitrogen compounds are also approximately tetrahedral in shape. In this case, however, the barrier to inversion is small and the compounds cannot be separated as pure enantiomers at normal temperatures.



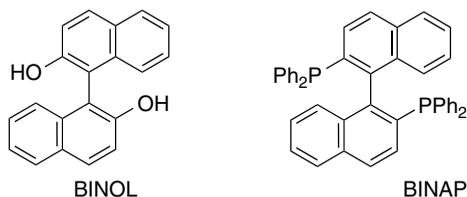
Allenes (see p. 6 for a discussion of bonding in allenes) can be chiral. An allene having nonidentical substituents at both sp^2 carbons gives nonsuperimposable mirror images.



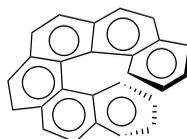
Molecules with shapes analogous to screws are also chiral, since they can be right-handed or left-handed. There are several kinds of molecules in which steric factors impose a screwlike shape. A very important case is 1, 1'-binaphthyl compounds. Steric interactions between the 2 and 8' hydrogens prevent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



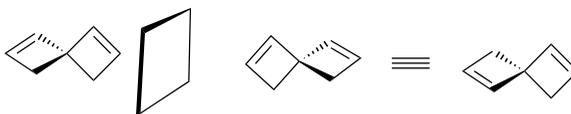
A particularly important example is the 2, 2'-diol, which is called BINOL. Another important type includes 1, 1'-binaphthyl diphosphines, such as BINAP.⁵ BINOL and BINAP are useful chiral ligands in organometallic compounds that serve as catalysts for hydrogenations and other reactions. In Section 2.5.1.1,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



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



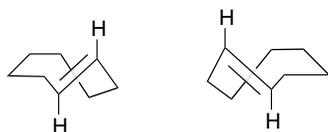
The *E*-cycloalkenes are also chiral. *E*-cyclooctene is a good example. Examination of the structures below using molecular models demonstrates that the two mirror images cannot be superimposed.

⁵. A. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990).

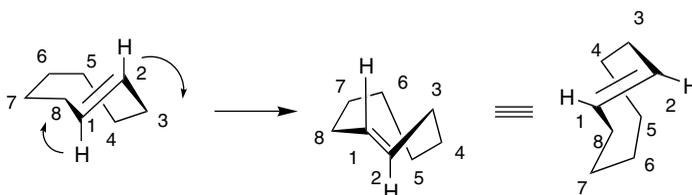
⁶. M. S. Newman and D. Lednicer, *J. Am. Chem. Soc.*, **78**, 4765 (1956).

⁷. R. H. Martin and M. J. Marchant, *Tetrahedron*, **30**, 347 (1974).

⁸. L. A. Hulshof, M. A. McKerverve, and H. Wynberg, *J. Am. Chem. Soc.*, **96**, 3906 (1974).

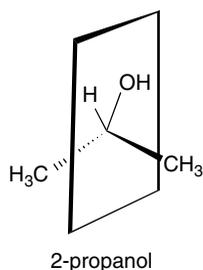


E-cyclooctene is subject to thermal racemization. The molecular motion allows the double bond to slip through the ring, giving the enantiomer. The larger and more flexible the ring, the easier the process. The rates of racemization have been measured for *E*-cyclooctene, *E*-cyclononene, and *E*-cyclododecene. 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*-cyclododecene racemizes immediately on release from the chiral platinum complex used for its preparation.⁹



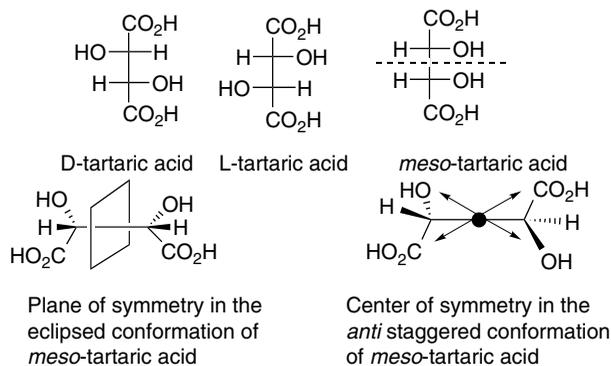
2.1.6. The Relationship between Chirality and Symmetry

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.

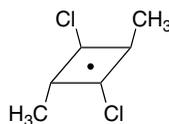


⁹ A. C. Cope and B. A. Pawson, *J. Am. Chem. Soc.*, **87**, 3649 (1965); A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *J. Am. Chem. Soc.*, **87**, 3644 (1965).

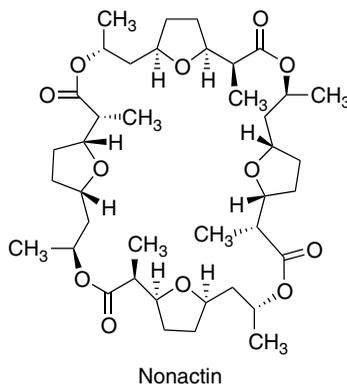
More elaborate molecules can also have a plane of symmetry. For example, there are only three stereoisomers of tartaric acid (2,3-dihydroxybutanedioic acid). Two of these are chiral but the third is achiral. In the achiral stereoisomer, the substituents are located with respect to each other in such 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.



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.

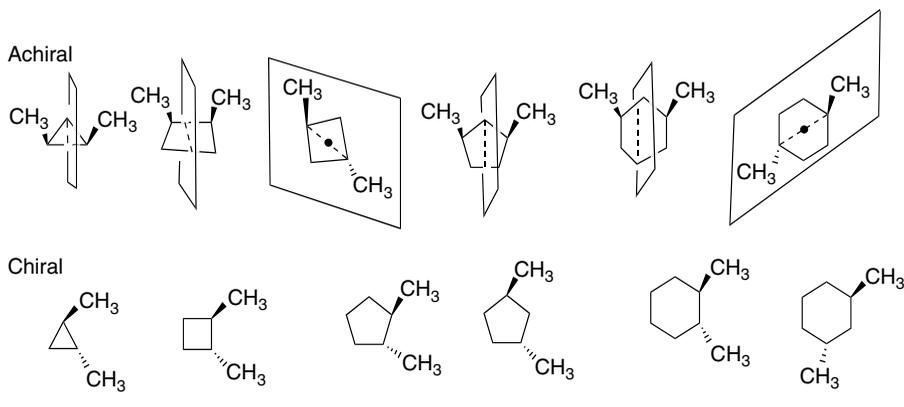


Another very striking example is the antibiotic nonactin. Work out problem 2.15 to establish the nature of the of symmetry in nonactin.



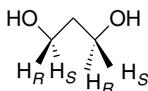
Various di- and polysubstituted cyclic compounds provide other examples of molecules having planes of symmetry. Since chirality depends on *configuration*, not *conformation*, cyclic molecules can be represented as planar structures to facilitate recognition of symmetry elements. These planar structures 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

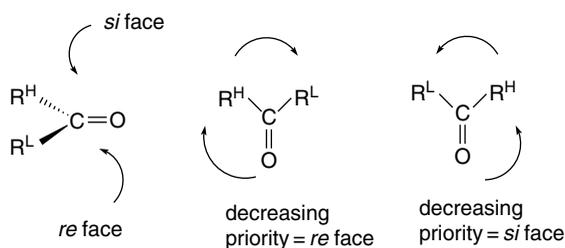


2.1.7. Configuration at Prochiral Centers

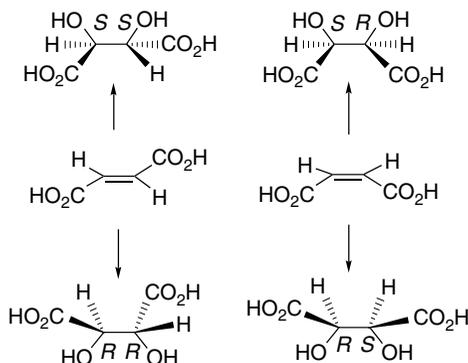
Prochiral centers have two identical ligands, such as two hydrogens, and are achiral. In many situations, however, these identical ligands are *topologically nonequivalent* or *heterotopic*. This occurs when the other two substituents are different. If either of the identical groups is replaced by a 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

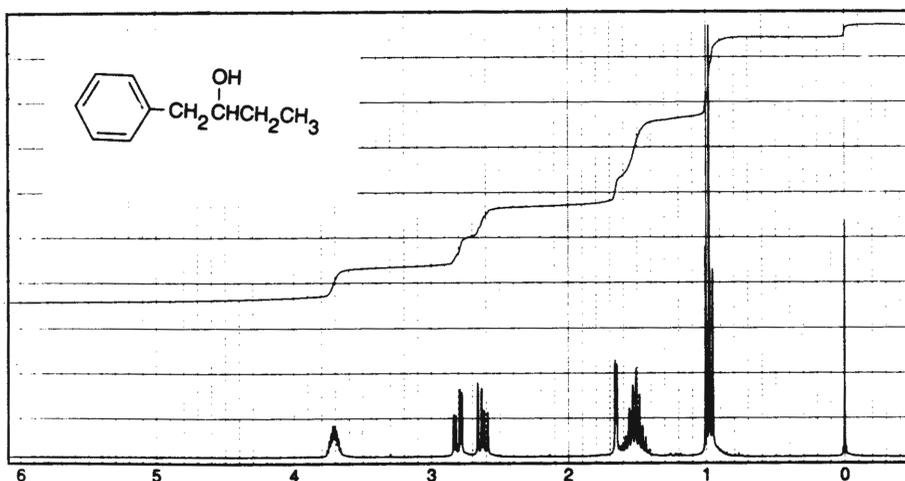
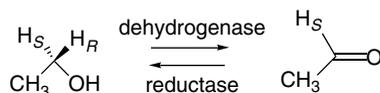


Fig. 2.6. NMR spectrum of 1-phenyl-2-butanol showing the diastereotopic nature of C(1) protons. Reproduced from *Aldrich Library of ^{13}C and ^1H NMR Spectra*, Vol. 2, 1993, p. 386.

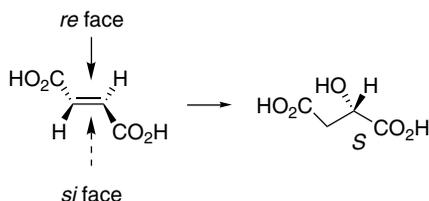
Figure 2.6. The C(1) CH_2 group appears as a quartet near 2.8 ppm with further coupling to the C(2) proton. The C(1) hydrogens are diastereotopic. The C(3) hydrogens are also diastereotopic, but their nonidentity is not obvious in the multiplet at about 1.6 ppm.

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.



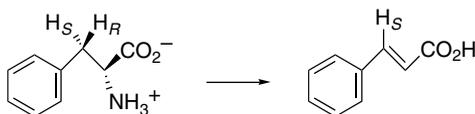
Conversely, *reductases* selectively reduce acetaldehyde from the *re* face.

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.

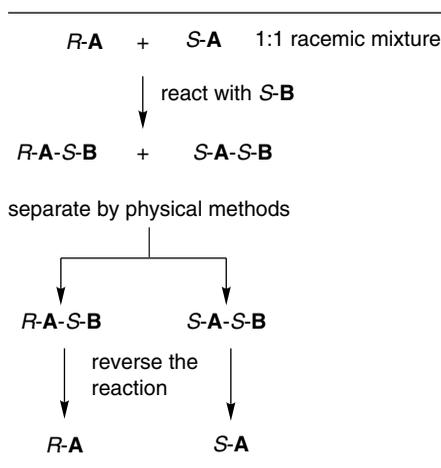


2.1.8. Resolution—The Separation of Enantiomers

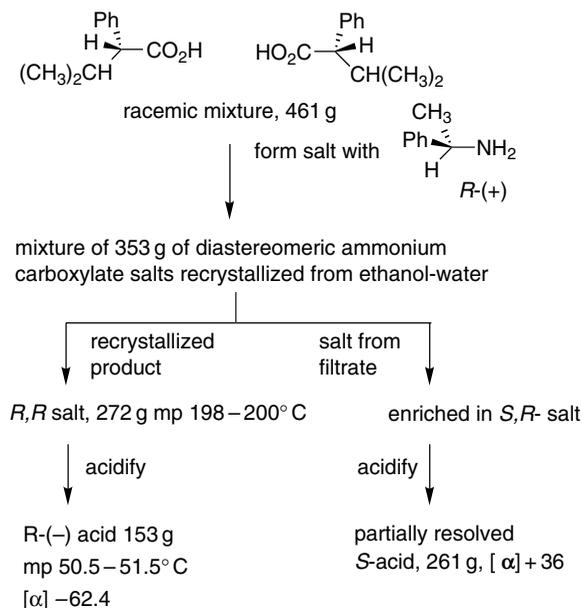
Since all living cells and organisms involve reactions of enantiomerically pure materials such as carbohydrates, proteins, and DNA, most naturally occurring chiral compounds exist in enantiomerically pure form. Chemical reactions, however, often produce racemic mixtures. This is *always* the case if 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.

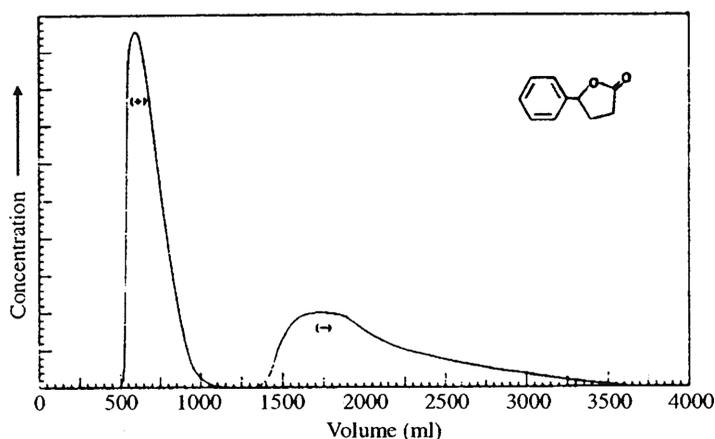
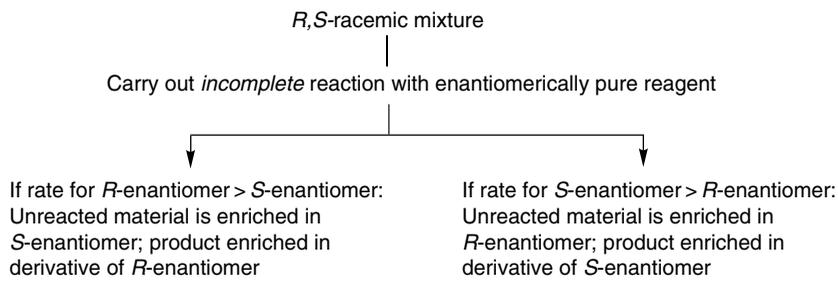


Fig. 2.7. Preparative chromatographic resolution of 5 g of γ -phenyl- γ -butyrolactone on 480 g of cellulose triacetate (column 5 cm \times 60 cm). Reproduced from *Helv. Chim. Acta*, **70**, 1569 (1987), by permission of Wiley-VCH.

Scheme 2.4. Conceptual Basis of Kinetic Resolution

CHAPTER 2

Stereochemistry,
Conformation,
and Stereoselectivity



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.

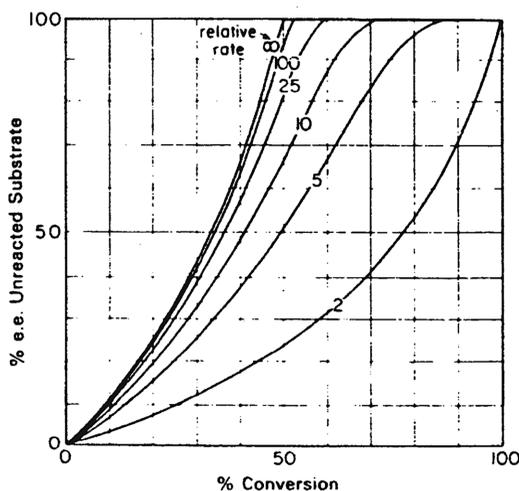


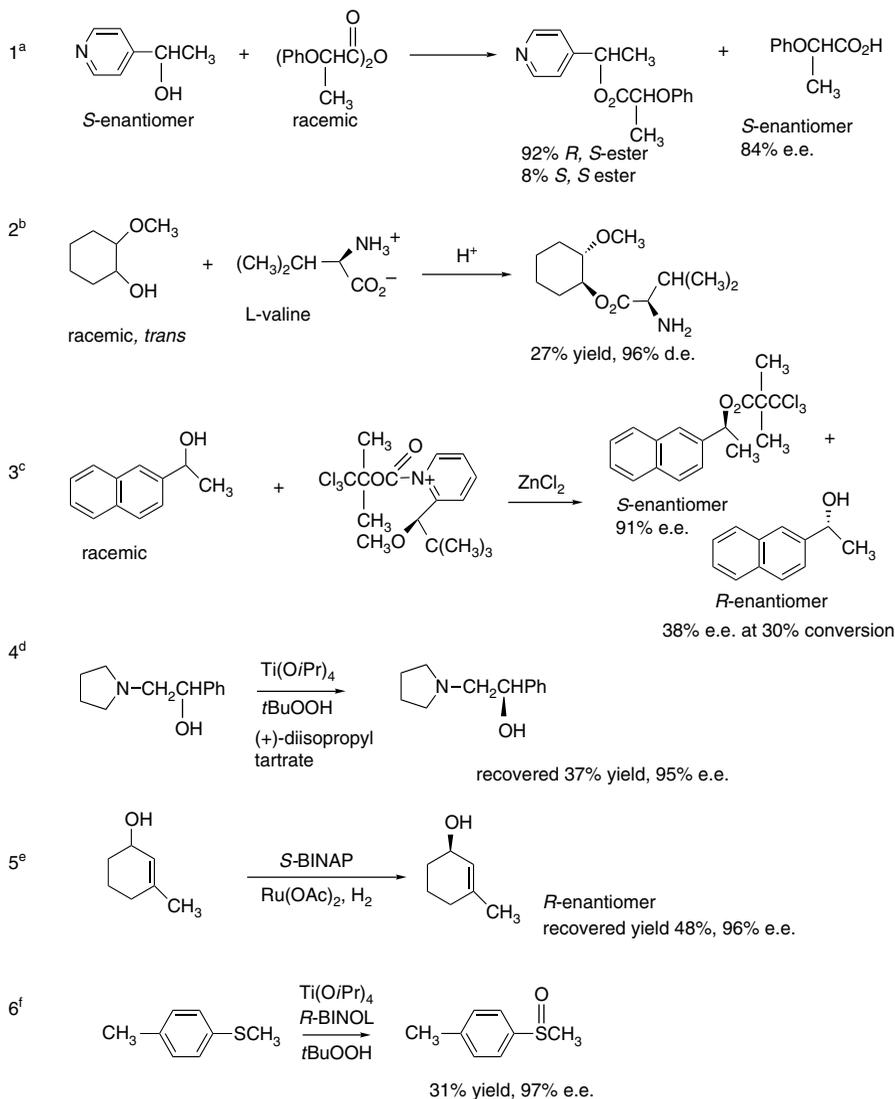
Fig. 2.8. Dependence of enantiomeric excess on relative rate of reaction and extent of conversion with a chiral reagent in kinetic resolution. Reproduced from *J. Am. Chem. Soc.*, **103**, 6237 (1981), by permission of the American Chemical Society.

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 1 to 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. Kitamura, 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

$$v_R = k_R[R]/K_R \text{ and } v_S = k_S[S]/K_S \quad (2.6)$$

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

$$E = \frac{k_S/K_S}{k_R/K_R} \quad (2.7)$$

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).

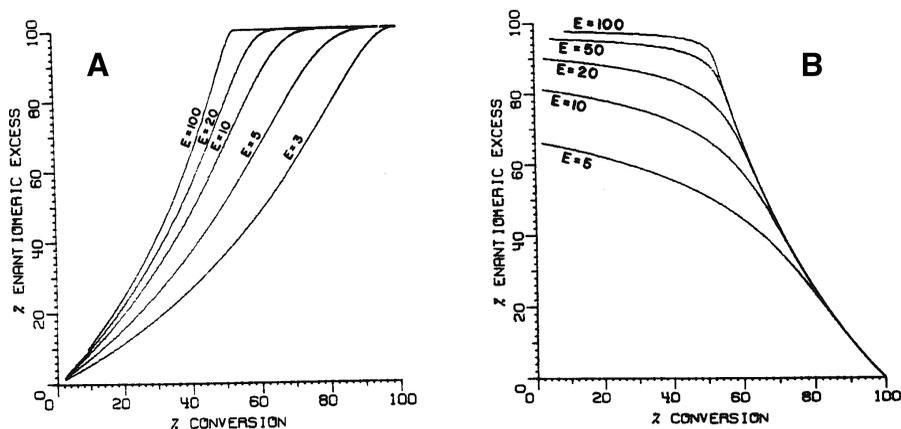
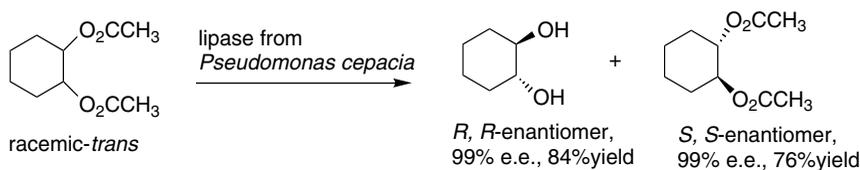
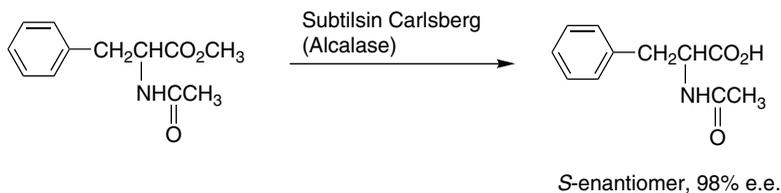


Fig. 2.9. Plots of enantiomeric excess as a function of extent of conversion for various values of E : (A) unreacted starting material; (B) product. Reproduced from *J. Am. Chem. Soc.*, **104**, 7294 (1982), by permission of the American Chemical Society.

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.



Ref. 13



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).

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

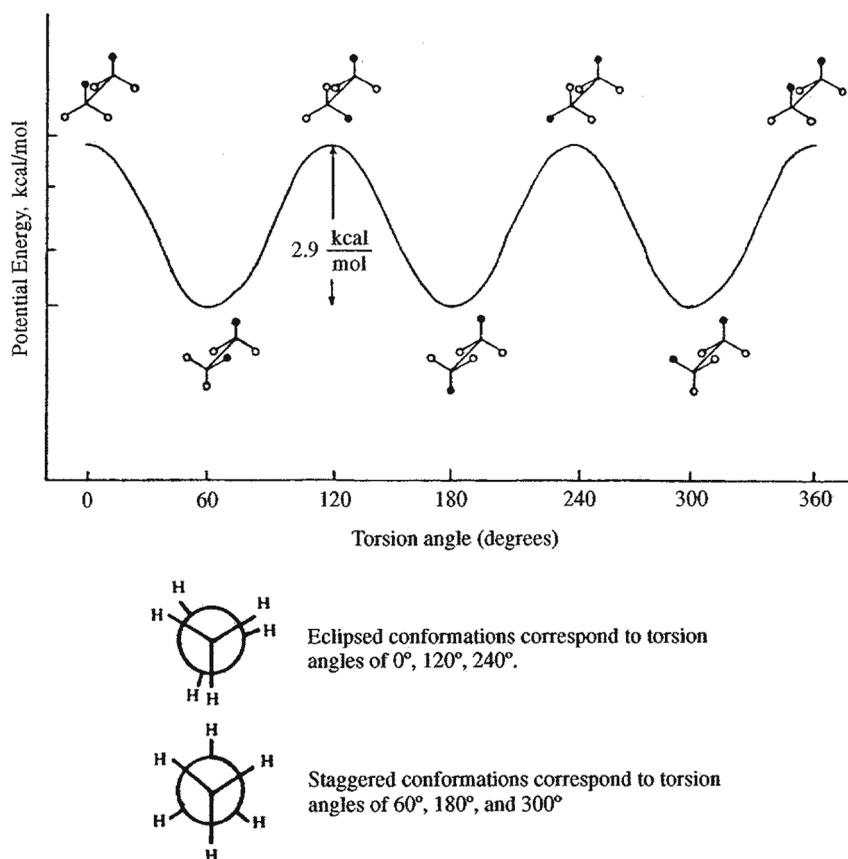
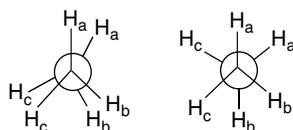
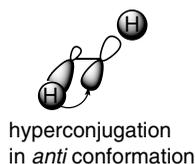


Fig. 2.10. Potential energy as a function of torsion angle for ethane.

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



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).

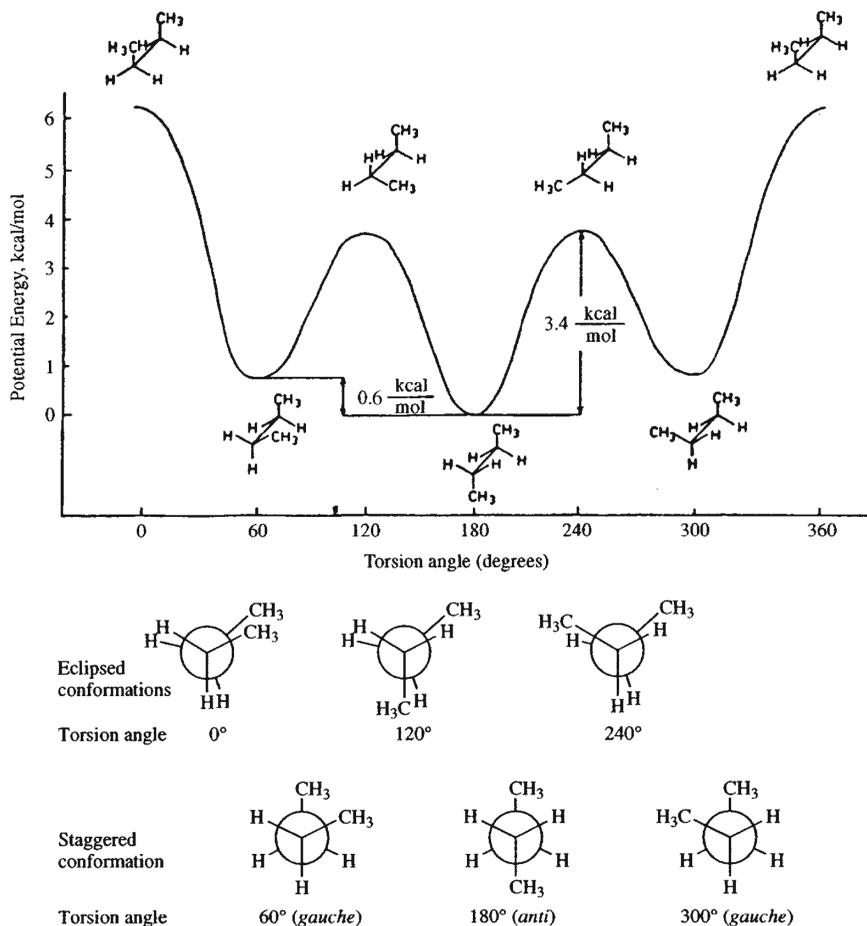


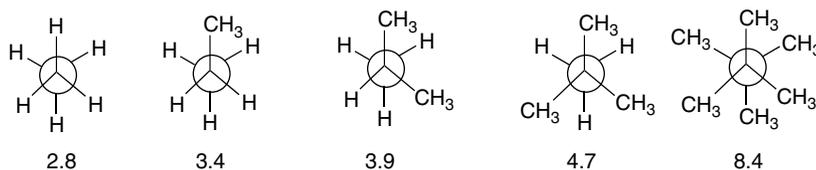
Fig. 2.11. Potential energy diagram for rotation about the C(2)–C(3) bond in *n*-butane.

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

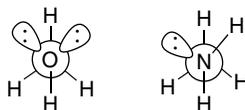
The conformation of other simple hydrocarbons can be interpreted by extensions of the principles illustrated in the analysis of rotational barriers in ethane and *n*-butane. The staggered conformations correspond to torsional minima and the eclipsed conformations to torsional maxima. Of the staggered 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.



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 → 2.0 → 1.1) in proportion to the number of anti H–H arrangements (3 → 2 → 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 Cycloalkenes*, 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. Badenhop 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 $\text{CH}_3 - \text{X}^a$

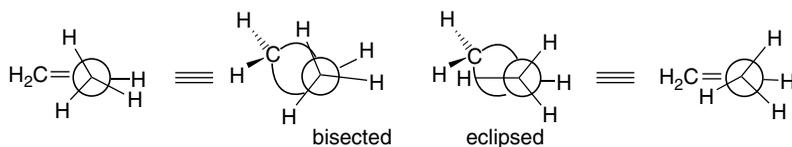
Alkanes ^a	Barrier (kcal/mol)	Heteroatom compounds	Barrier (kcal/mol)
$\text{CH}_3 - \text{CH}_3$	2.9	$\text{CH}_3 - \text{NH}_2^c$	2.0
$\text{CH}_3 - \text{CH}_2\text{CH}_3$	3.4	$\text{CH}_3 - \text{NHCH}_3^c$	3.0
$\text{CH}_3 - \text{CH}(\text{CH}_3)_2$	3.9	$\text{CH}_3 - \text{N}(\text{CH}_3)_2^c$	4.4
$\text{CH}_3 - \text{C}(\text{CH}_3)_3$	4.7	$\text{CH}_3 - \text{OH}^d$	1.1
$(\text{CH}_3)_3\text{C} - \text{C}(\text{CH}_3)_3$	8.4 ^b	$\text{CH}_3 - \text{OCH}_3^d$	4.6

a. Taken from the compilation of J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968).

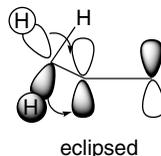
b. Footnote 9, J. E. Andersen, A. de Meijere, S. I. Kozhushkov, L. Lunazzi, and A. Mazzanti, *J. Org. Chem.*, **68**, 8494 (2003).

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 $\sigma - \pi^*$ interactions. The major effect is a transfer of electron density from the methyl $\sigma \text{ C-H}$ bonds to the empty π^* orbital.

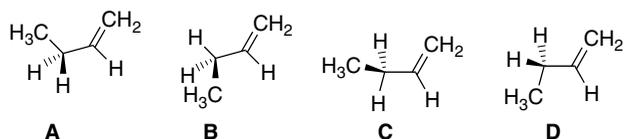


Computational approaches can provide an indication of the magnitude of the interaction. A “block-localized” wave function calculation estimates a stabilization of about 5.4 kcal/mol at the 6-31G** level.²⁴ The computation also shows a shortening of the C(2)–C(3) single bond as the result of the $\sigma - \pi^*$ 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(3d,2p) level of computation, the $\text{CH}_3 - \text{C} =$ 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).

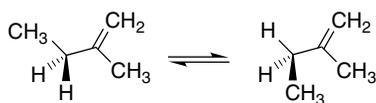
²⁵ T. Kundu, L. Goodman, and J. Leszczynski, *J. Chem. Phys.*, **103**, 1523 (1995).

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

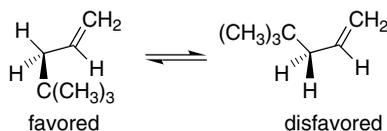


Conformations **A** and **B** are of the eclipsed type, whereas **C** and **D** are bisected. It has been determined by microwave spectroscopy that the eclipsed conformations are more stable than the bisected ones and that **B** is about 0.15 kcal more stable than **A**.²⁶ MO calculations at the HF/6-31G* 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++(3df,3pd) 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).

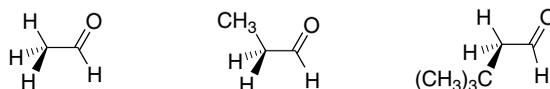
³⁰ R. W. Hoffmann, *Chem. Rev.*, **89**, 1841 (1989).

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 (3df,2p) 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.

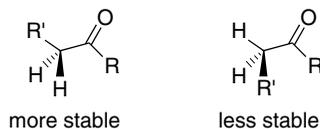
ΔV_{nn}	-10.621
ΔV_{ee}	-5.492
ΔV_{ne}	+18.260
Δt	-0.938
Δ total	+1.209

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.



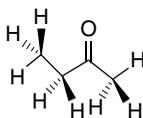
³¹ I. Kleiner, J. T. Hougen, R. D. Suenram, F. J. Lovas, and M. Godefroid *J. Mol. Spectros.*, 153, 578 (1992); S. P. Belov, M. Y. Tretyakov, I. Kleiner, and J. T. Hougen, *J. Mol. Spectros.*, 160, 61 (1993).

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

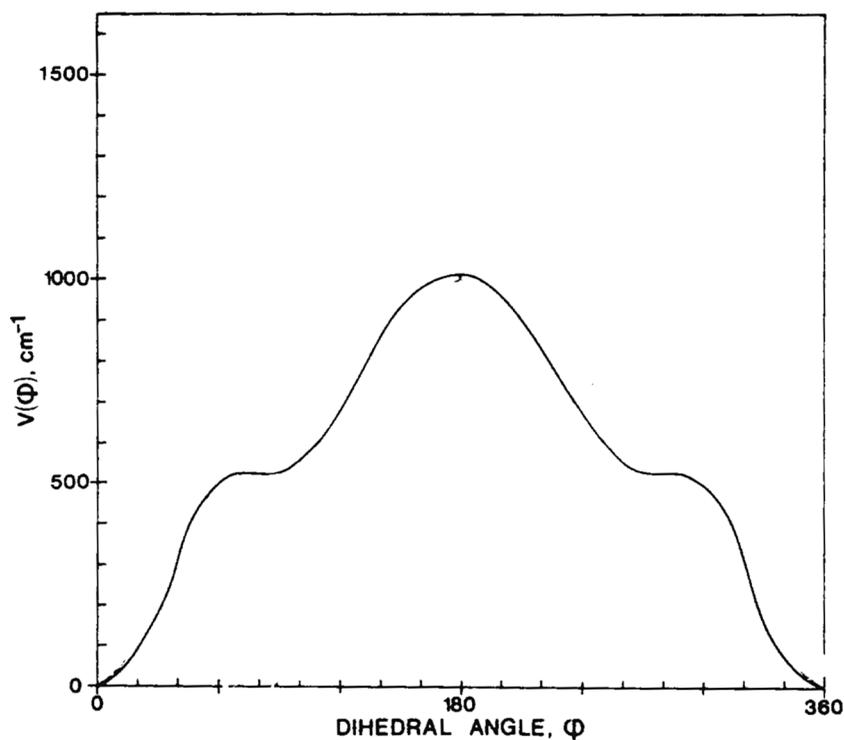
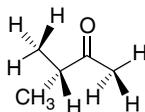


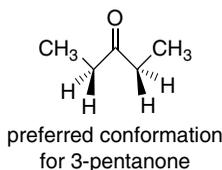
Fig. 2.12. Calculated potential energy diagram (HF/6-31G) for rotation about C(2)–C(3) bond of 2-butanone. Reproduced from *Can. J. Chem.* **69**, 1827 (1991), by permission of the National Research Council Press.

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).

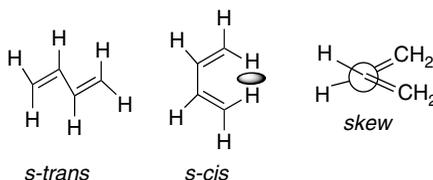


Moreover, electron diffraction studies of 3-pentanone indicate the methyl-eclipsed conformation shown below to be the most stable rotamer.³⁷



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.



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).

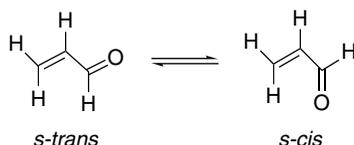
³⁸ A. Almendingen, O. Bastiansen, and M. Traetteburg, *Acta Chem. Scand.*, **12**, 1221 (1958); K. K. Kuchitsu, T. Fukuyama, and Y. Morino, *J. Mol. Struct.*, **1**, 643 (1967); R. L. Lipnick and E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **95**, 6370 (1973).

³⁹ K. B. Wiberg and R. E. Rosenberg, *J. Am. Chem. Soc.*, **112**, 1509 (1990).

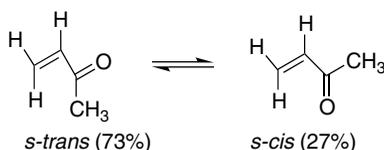
⁴⁰ A. J. P. Devaquet, R. E. Townshend, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 4068 (1976); K. B. Wiberg, P. R. Rablen, and M. Marquez, *J. Am. Chem. Soc.*, **114**, 8654 (1992); M. Head-Gordon and J. A. Pople, *J. Phys. Chem.*, **97**, 1147 (1993).

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

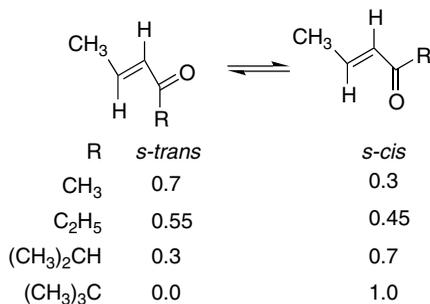
The case of α,β -unsaturated carbonyl compounds is analogous to that of 1,3-dienes, in that conjugation favors coplanarity of the $C=C-C=O$ system. The rotamers that are important are the *s-trans* and *s-cis* conformations. Microwave data indicate that the *s-trans* form is the only conformation present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



The equilibrium distribution of *s-trans* and *s-cis* conformations of substituted α,β -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.



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



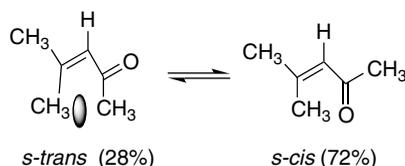
An unfavorable methyl-methyl interaction destabilizes the *s-trans* conformation of 4-methylpent-3-en-2-one (mesityl oxide) relative to the *s-cis* conformation, and the equilibrium favors the *s-cis* form.

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).

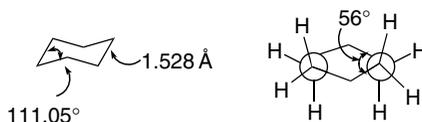
⁴³ G. Montaudo, V. Librando, S. Caccamese, and P. Maravigna, *J. Am. Chem. Soc.*, **95**, 6365 (1973).

⁴⁴ A. Bienvenue, *J. Am. Chem. Soc.*, **95**, 7345 (1973).



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 \AA , the C–H bonds are 1.119 \AA , and the C–C–C angles are 111.05° .⁴⁵

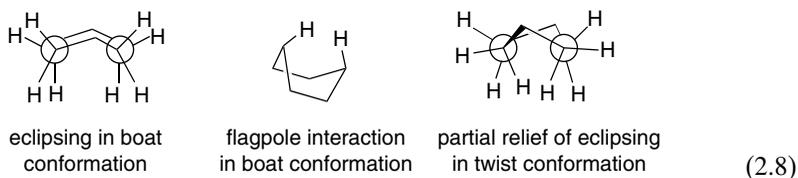


Two nonchair conformations of cyclohexane that have normal bond angles and bond lengths are the *twist* and the *boat*,⁴⁶ both of which are less stable than the chair. A direct measurement of the chair-twist energy difference has been made using low-temperature IR spectroscopy.⁴⁷ The chair was determined 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).



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 strain, 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

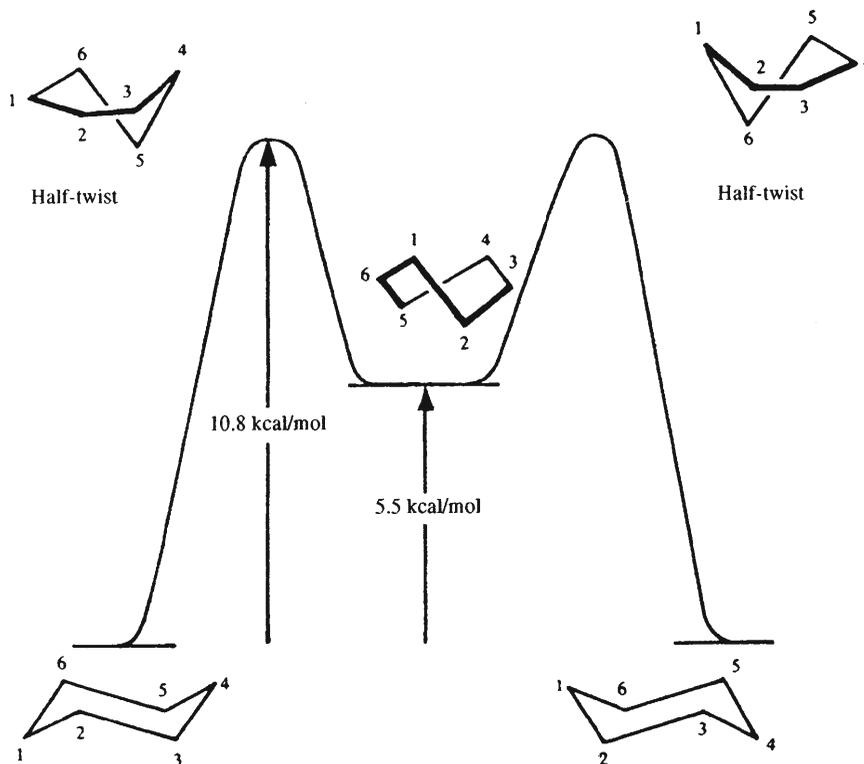


Fig. 2.13. Energy diagram for ring inversion of cyclohexane.

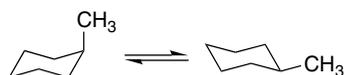
⁴⁸ F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **89**, 760 (1967).

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 (1977).

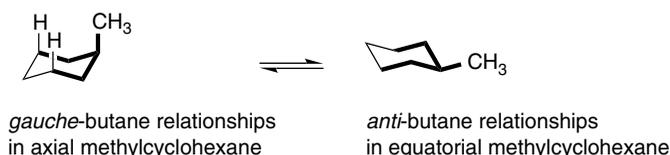
⁵⁰ N. Leventis, S. B. Hanna, and C. Sotiriou-Leventis, *J. Chem. Educ.* **74**, 813 (1997); R. R. Sauers, *J. Chem. Educ.* **77**, 332 (2000).

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*.



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.

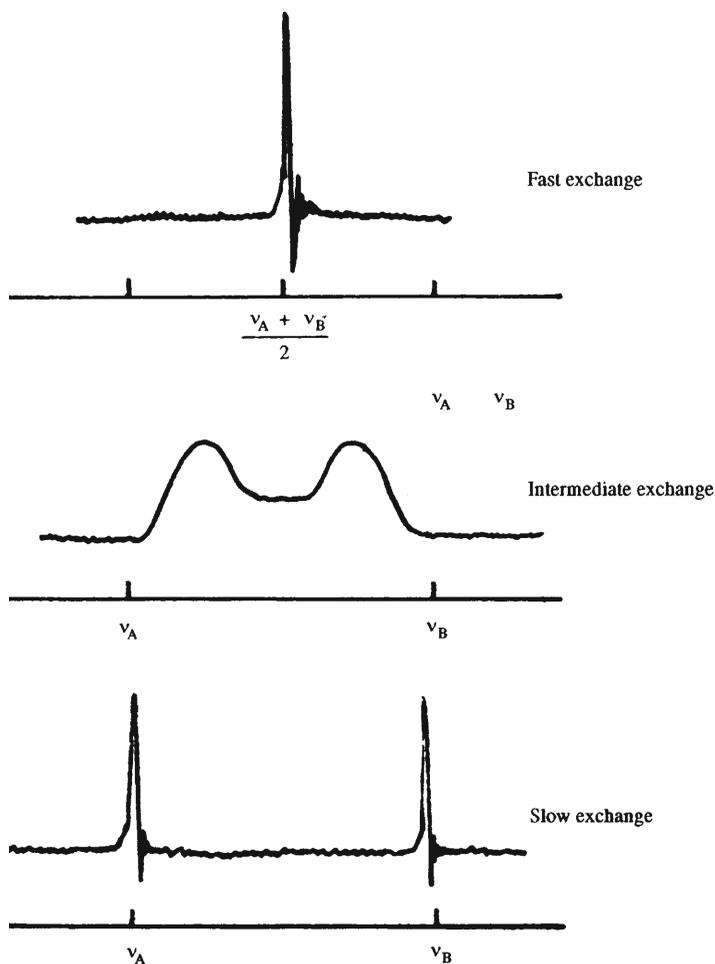


Fig. 2.14. Appearance of NMR spectra for system undergoing site exchange at various rates.

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).

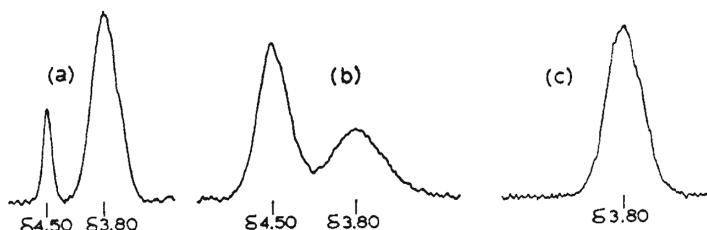


Fig. 2.15. 60-MHz ^1H -NMR spectrum for the C(1)H in chlorocyclohexane: (a) axial-equatorial equilibrium at -115°C ; (b) axial-enriched mixture at -150°C ; (c) pure equatorial conformer at -150°C . Reproduced from *J. Am. Chem. Soc.*, **91**, 3223 (1969), by permission of the American Chemical Society.

Crystallization of chlorocyclohexane at low temperature provided crystals containing only the equatorial isomer. When the solid is dissolved at -150°C , the NMR spectrum of the solution exhibits only the signal characteristic of the equatorial conformer. When the solution is warmed to -115° , the conformational equilibrium is reestablished. The appearance of the 60-MHz spectrum of the H-C-Cl hydrogen is shown in Figure 2.15.

The free-energy difference between conformers is referred to as the *conformational free energy*. For substituted cyclohexanes it is conventional to specify the value of $-\Delta G_c$ for the equilibrium:



As ΔG_c is negative when the equatorial conformation is more stable than the axial, the value of $-\Delta G_c$ is positive for groups that favor the equatorial position. The larger the $-\Delta G_c$, the greater the preference for the equatorial position.

The case of iodocyclohexane provides an example of the use of NMR spectroscopy to determine the conformational equilibrium constant and the value of $-\Delta G_c$. At -80°C , the NMR shows two distinct peaks in the area of the CHI signal as shown in Figure 2.16.⁵³ The multiplet at higher field is a triplet of triplets with coupling constants of 3.5 and 12 Hz. This pattern is characteristic of a hydrogen in an axial position with two axial-axial couplings and two axial-equatorial couplings. The broader peak at lower field is characteristic of a proton at an equatorial position and reflects the four equatorial-equatorial couplings of such a proton. The relative area of the two peaks is 3.4:1 in favor of the conformer with the axial hydrogen. This corresponds to a $-\Delta G_c$ value of 0.47 kcal/mol for the iodo substituent.

Another method for measuring conformational free energies involves establishing an equilibrium between diastereomers differing only in the orientation of the designated substituent group. The equilibrium constant can then be determined and used to calculate the free-energy difference between the isomers. For example, *cis*- and *trans*-*t*-butylcyclohexanol can be equilibrated using a nickel catalyst in refluxing benzene to give a mixture containing 28% *cis*-4-*t*-butylcyclohexanol and 72% *trans*-*t*-butylcyclohexanol.⁵⁴

⁵³ F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Am. Chem. Soc.*, **91**, 334 (1969).

⁵⁴ E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.*, **87**, 5031 (1965).

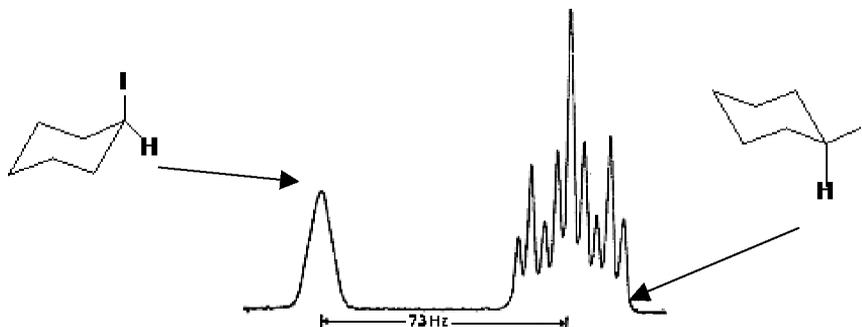
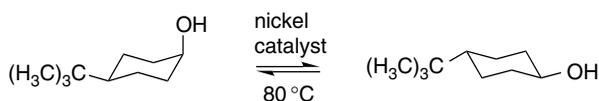


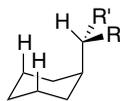
Fig. 2.16. NMR spectrum of iodocyclohexane at -80°C . Only the low field CHI signal is shown (100 MHz). Reproduced from *J. Am. Chem. Soc.*, **91**, 344 (1969), by permission of the American Chemical Society.



Assuming that only conformations that have the *t*-butyl group equatorial are significant, the free-energy change for the equilibration is equal to the free-energy difference between an axial and equatorial hydroxy group. The equilibrium constant leads to a value of $-\Delta G_c = 0.7\text{kcal/mol}$ for the hydroxy substituent. This approach also assumes that the *t*-butyl group does not distort the ring or interact directly with the hydroxy group.

There are several other methods available for determining conformational free energies.⁵⁵ Values for many substituents in addition to those listed in Table 2.2 have been compiled.⁵⁶

The methyl, ethyl, and isopropyl groups have similar conformational energies, with isopropyl being only slightly greater than methyl and ethyl. The similar values for the three substituents reflects the fact that rotation about the bond between the substituent and the ring allows each group to adopt a conformation that minimizes the effect of the additional methyl substituent in the ethyl and isopropyl groups.



methyl: R, R' = H
 ethyl R = H, R' = CH₃
i-propyl R, R' = CH₃

A *t*-butyl substituent in the axial orientation experiences a strong van der Waals repulsion with the *syn*-axial hydrogens that cannot be relieved by rotation about the bond to the ring. As a result, the $-\Delta G_c$ value for *t*-butyl group is much larger than for the other alkyl groups. A value of about 5 kcal/mol has been calculated by *molecular*

⁵⁵ F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, **3**, 139 (1971).

⁵⁶ E. L. Eliel, S. H. Wilen, and L. N. Mander *Stereochemistry of Organic Compounds*, Wiley, New York, 1993, pp. 696–697.

Table 2.2. Conformational Free Energies ($-\Delta G_c$) for Some Substituent Groups^a

Substituent	$-\Delta G_c$	Substituent	$-\Delta G_c$
F	0.26 ^b	C ₆ H ₅	2.9 ^c
Cl	0.53 ^b	CN	0.2 ^b
I	0.47 ^b	CH ₃ CO ₂	0.71 ^b
CH ₃	1.8 ^c	HO ₂ C	1.35 ^d
CH ₃ CH ₂	1.8 ^c	C ₂ H ₅ O ₂ C	1.1–1.2 ^d
(CH ₃) ₂ CH	2.1 ^c	HO (aprotic solvent)	0.52 ^d
(CH ₃) ₃ C	> 4.7 ^d	HO (protic solvent)	0.87 ^d
CH ₂ =CH	1.7 ^e	CH ₃ O	0.60 ^d
HC≡C	0.5 ^f	O ₂ N	1.16 ^b

a. For a more extensive compilation see E. L. Eliel, S. H. Wilen, and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1993, pp. 696–697.

b. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, **3**, 140 (1971).

c. N. L. Allinger and L. A. Freiburg, *J. Org. Chem.*, **31**, 804 (1966).

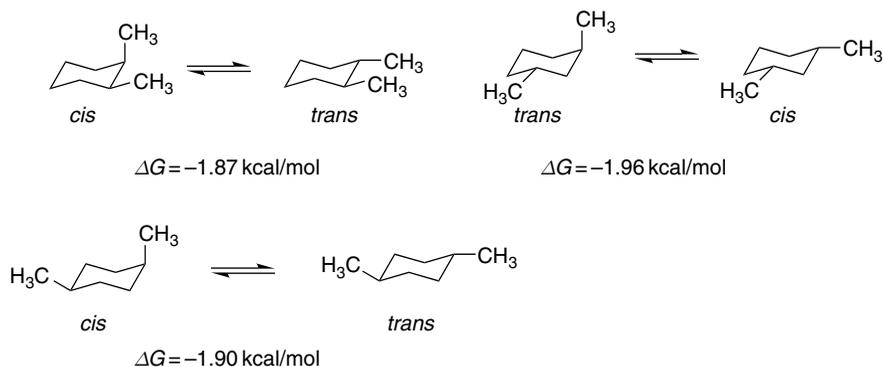
d. J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).

e. E. L. Eliel and M. Manoharan, *J. Org. Chem.*, **46**, 1959 (1981).

mechanics.⁵⁷ Experimental attempts to measure the $-\Delta G_c$ value for *t*-butyl have provided only a lower limit, because very little of the axial conformation is present and the energy difference is similar to that between the chair and twist forms of the cyclohexane ring.

The strong preference for a *t*-butyl group to occupy the equatorial position makes it a useful group for the study of *conformationally biased systems*. A *t*-butyl substituent ensures that the conformational equilibrium lies heavily to the side having the *t*-butyl group equatorial but does not stop the process of conformational inversion. It should be emphasized that “conformationally biased” is not synonymous with “conformationally locked.” Because ring inversion can still occur, it is incorrect to think of the systems being “locked” in a single conformation.

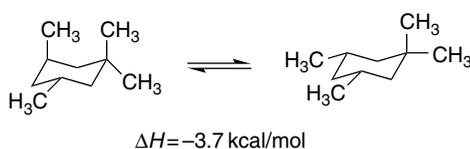
When two or more substituents are present on a cyclohexane ring, the interactions between the substituents must be included in the analysis. The dimethylcyclohexanes provide a case in which a straightforward interpretation is in good agreement with the experimental data. The ΔG of the equilibrium for the *cis* \rightleftharpoons *trans* isomerization is given for 1,2-, 1,3-, and 1,4-dimethylcyclohexane.⁴⁹



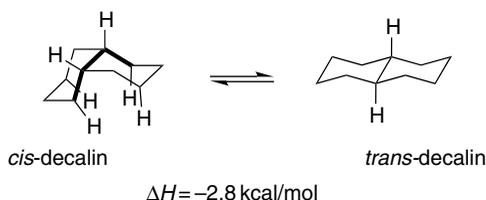
⁵⁷ N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. VanCatledge, *J. Am. Chem. Soc.*, **90**, 1199 (1968); B. van de Graf, J. M. A. Baas, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **97**, 268 (1978); J. M. A. Baas, A. van Veen, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **99**, 228 (1980); S. Antunez and E. Juaristi, *J. Org. Chem.*, **61**, 6465 (1996).

The more stable diastereomer in each case is the one in which both methyl groups are equatorial. The ΔG difference favoring the diequatorial isomer is about the same for each case (about 1.9 kcal/mol) and is very close to the $-\Delta G_c$ value of the methyl group (1.8 kcal/mol). This implies that there are no important interactions present that are not also present in methylcyclohexane. This is reasonable since in each case the axial methyl group interacts only with the 3,5-diaxial hydrogens, just as in methylcyclohexane. Moreover, both of the 1,2-dimethyl isomers have similar *gauche* interactions between the two methyl groups.

Conformations in which there is a 1,3-diaxial interaction between substituent groups *larger than hydrogen* are destabilized by van der Waals repulsion. Equilibration of *cis*- and *trans*-1,1,3,5-tetramethylcyclohexane, for example, results in a mixture favoring the *cis* isomer by 3.7 kcal/mol.⁵⁸ This provides a value for a 1,3-diaxial methyl-methyl interaction that is 1.9 kcal/mol higher than the 1,3-methyl-hydrogen interaction.



The decalin (decahydronaphthalene) ring provides another important system for the study of conformational effects in cyclohexane rings. Equilibration of the *cis* and *trans* isomers favors the *trans* isomer by about 2.8 kcal/mol. Note that this represents a change in configuration, not conformation. The energy difference can be analyzed by noting that the *cis* isomer has an inter-ring *gauche*-butane interaction that is not present in the *trans* isomer. There are also cross-ring interactions between the axial hydrogens on the concave surface of the molecule.

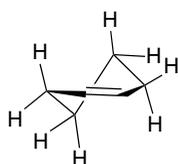


There is an important difference between the *cis*- and *trans*-decalin systems with respect to their conformational flexibility. Owing to the nature of its ring fusion, *trans*-decalin is incapable of chair-chair inversion; *cis*-decalin is conformationally mobile and undergoes ring inversion at a rate only slightly slower than cyclohexane ($\Delta G^\ddagger = 12.3\text{--}12.4 \text{ kcal/mol}$).⁵⁹ The *trans*-decalin system is a “conformationally locked” system and can be used to compare properties and reactivity of groups in axial or equatorial environments.

⁵⁸ N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961).

⁵⁹ F. R. Jensen and B. H. Beck, *Tetrahedron Lett.*, 4523 (1966); D. K. Dalling, D. M. Grant, and L. F. Johnson, *J. Am. Chem. Soc.*, **93**, 367 (1971); B. E. Mann, *J. Magn. Resonance*, **21**, 17 (1976).

The effect of introducing sp^2 -hybridized atoms into acyclic molecules was discussed in Section 2.2.1, and it was noted that torsional barriers in 1-alkenes and aldehydes are somewhat smaller than in alkanes. Similar effects are seen when sp^2 centers are incorporated into six-membered rings. Whereas the energy barrier for ring inversion in cyclohexane is 10.3 kcal/mol, it is reduced to 7.7 kcal/mol in methylenecyclohexane⁶⁰ and to 4.9 kcal/mol in cyclohexanone.⁶¹ The conformation of cyclohexene is described as a half-chair. Structural parameters determined on the basis of electron diffraction and microwave spectroscopy reveal that the double bond can be accommodated into the ring without serious distortion. The C(1)–C(2) bond length is 1.335 Å, and the C(1)–C(2)–C(3) bond angle is 123°. ⁶² The substituents at C(3) and C(6) are tilted from the usual axial and equatorial directions and are referred to as *pseudoaxial* and *pseudoequatorial*.



half-chair conformation
of cyclohexene

There have been both experimental and theoretical studies of the conformational process. According to NMR studies, the E_a for ring inversion is 5.3 kcal/mol.⁶³ An IR study gave a significantly higher barrier of about 10 kcal/mol.⁶⁴ A more recent theoretical study using both MO and DFT calculations found the barrier to be about 5.5–6.0 kcal/mol.⁶⁵ The preference for equatorial orientation of a methyl group in cyclohexene is less than in cyclohexane, because of the ring distortion and the removal of one 1,3-diaxial interaction. A value of 1 kcal/mol has been suggested for the $-\Delta G_c$ value for a methyl group in 4-methylcyclohexene.⁶⁶

Alkylidenecyclohexanes bearing alkyl groups of moderate size at C(2) tend to adopt the conformation with the alkyl group axial, in order to relieve unfavorable interactions with the alkylidene group. This results from van der Waals repulsion between the alkyl group in the equatorial position and *cis* substituents on the exocyclic

⁶⁰ J. T. Gerig, *J. Am. Chem. Soc.*, **90**, 1065 (1968).

⁶¹ F. R. Jensen and B. H. Beck, *J. Am. Chem. Soc.*, **90**, 1066 (1968).

⁶² J. F. Chiang and S. H. Bauer, *J. Am. Chem. Soc.*, **91**, 1898 (1969); L. H. Scharpen, J. E. Wollrab, and D. P. Ames, *J. Chem. Phys.*, **49**, 2368 (1968).

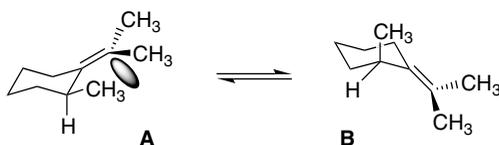
⁶³ F. A. L. Anet and M. Z. Haq, *J. Am. Chem. Soc.*, **87**, 3147 (1965).

⁶⁴ V. E. Rivera-Gaines, S. J. Leibowitz, and J. Laane, *J. Am. Chem. Soc.*, **113**, 9735 (1991).

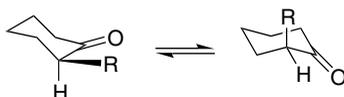
⁶⁵ S. V. Shishkina, O. V. Shiskin, and J. Leszczynski, *Chem. Phys. Lett.*, **354**, 428 (2002).

⁶⁶ B. Rickborn and S.-Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

double bond, and is an example of 1,3-allylic strain.⁶⁷ The repulsive energy is small for methylenecyclohexanes, but molecular mechanics calculations indicate that the axial conformation **B** is 2.6 kcal/mol more stable than **A** with an exocyclic isopropylidene group.⁶⁸



An alkyl group at C(2) of a cyclohexanone ring is more stable in the equatorial than in the axial orientation. The equatorial orientation is eclipsed with the carbonyl group and corresponds to the more stable conformation of open-chain ketones (see p. 148). This conformation also avoids 3,5-diaxial interactions with *syn*-diaxial hydrogens. Conformational free energies ($-\Delta G_c$) for 2-alkyl substituents in cyclohexanones have been determined by equilibration studies. The value for the methyl group is similar to cyclohexanes, whereas the values for ethyl and isopropyl are somewhat smaller. This is attributed to a compensating repulsive steric interaction with the carbonyl oxygen for the larger substituents.⁶⁹



The $-\Delta G_c$ of an alkyl group at C(3) of cyclohexanone is less than that of an alkyl group in cyclohexane because of reduced 1,3-diaxial interactions. A C(3) methyl group in cyclohexanone has a $-\Delta G_c$ of 1.3–1.4 kcal/mol.⁵⁴

2.2.3. Conformations of Carbocyclic Rings of Other Sizes

The most important structural features that influence the conformation and reactivity of cycloalkanes differ depending on whether small (cyclopropane and cyclobutane), common (cyclopentane, cyclohexane, and cycloheptane), medium (cyclooctane through cycloundecane), or large (cyclododecane and up) rings are

⁶⁷. F. Johnson, *Chem. Rev.* **68**, 375 (1968); R. W. Hoffmann, *Chem. Rev.*, **89**, 1841 (1989).

⁶⁸. N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968); P. W. Rabideau, ed., *The Conformational Analysis of Cyclohexenes, Cyclohexadiene and Related Hydroaromatic Compounds*, VCH Publishers, Weinheim, 1989.

⁶⁹. N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961); B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Interscience, New York, 1965, pp. 113–114.

Table 2.3. Strain Energies for Cycloalkanes^a

Cycloalkane	Strain energy (kcal/mol)
Cyclopropane	28.1 ^b
Cyclobutane	26.3
Cyclopentane	7.3
Cyclohexane	1.4
Cycloheptane	7.6
Cyclooctane	11.9
Cyclononane	15.5
Cyclodecane	16.4
Cyclododecane	11.8

a. Values taken from E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).

b. P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.*, **92**, 2377 (1970).

considered. The small rings are dominated by angle and torsional strain. The common rings are relatively unstrained and their conformations are most influenced by torsional factors. Medium rings exhibit conformational equilibria and chemical properties indicating that cross-ring van der Waals repulsions play an important role. Large rings become increasingly flexible and possess a large number of low-energy conformations. The combination of all types of strain for a given ring results in a total *strain energy* for that ring. Table 2.3 presents data on the strain energies of cycloalkanes up to cyclodecane.

The cyclopropane ring is planar and the question of conformation does not arise. The C–C bond lengths are slightly shorter than normal, at 1.50 Å, and the H–C–H angle of 115° C is opened somewhat from the tetrahedral angle.⁷⁰ These structural features and the relatively high reactivity of cyclopropane rings are explained by the concept of “bent bonds,” in which the electron density is displaced from the internuclear axis (see Topic 1.3).

Cyclobutane adopts a puckered conformation in which substituents can occupy axial-like or equatorial-like positions.⁷¹ 1,3-Disubstituted cyclobutanes show small energy preferences for the *cis* isomer, which places both substituents in equatorial-like positions.⁷² The energy differences and the barrier to inversion are both smaller than in cyclohexane.



There is minimal angle strain in cyclopentane, but considerable torsional strain is present. Cyclopentane is nonplanar and the two minimum energy geometries are the envelope and the half-chair.⁷³ In the envelope conformation, one carbon atom is

⁷⁰ O. Bastiansen, F. N. Fritsch, and K. Hedberg, *Acta Crystallogr.*, **17**, 538 (1964).

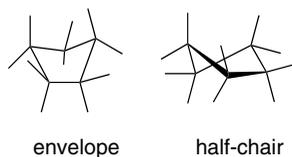
⁷¹ A. Almenningen, O. Bastiansen, and P. N. Skancke, *Acta Chem. Scand.*, **15**, 711 (1961).

⁷² (a) K. B. Wiberg and G. M. Lampman, *J. Am. Chem. Soc.*, **88**, 4429 (1966);

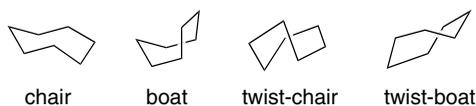
(b) N. L. Allinger and L. A. Tushaus, *J. Org. Chem.*, **30**, 1945 (1965).

⁷³ A. C. Legon, *Chem. Rev.*, **80**, 231 (1980); B. Fuchs, *Top. Stereochem.*, **10**, 1 (1978).

displaced from the plane of the other four. In the half-chair conformation, three carbons are coplanar, with one of the remaining two being above the plane and the other below. The planar portions of both conformations have torsional strain owing to C–H and C–C bond eclipsing. The energy differences between the conformers are small and there is rapid interconversion of conformers.⁷⁴ All of the carbon atoms move rapidly through planar and nonplanar positions, owing to a process called *pseudorotation*.



As ring size increases, there are progressively more conformations that have to be considered. For cycloheptane, four conformations have been calculated to be particularly stable.⁷⁵ NMR investigations indicate that the twist-chair is the most stable.⁷⁶ Various derivatives adopt mainly twist-chair conformations.⁷⁷ The individual twist-chair conformations interconvert rapidly by pseudorotation.⁷⁸ The most recent MM4 and CCSD/6-311++G** computations (see Section 2.3) indicate the following relative energies.⁷⁹ Figure 2.17 shows the conformations.



	MM4	CCSD/6-311++G**
Twist-chair	0	0
Chair	1.4	0.9
Boat	3.8	3.3
Twist-boat	3.5	3.3

Relative energy in kcal/mol

⁷⁴ W. J. Adams, H. J. Geise, and L. S. Bartell, *J. Am. Chem. Soc.*, **92**, 5013 (1970); J. B. Lambert, J. J. Papay, S. A. Khan, K. A. Kappauf, and E. S. Magyar, *J. Am. Chem. Soc.*, **96**, 6112 (1974).

⁷⁵ J. B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7036 (1967); D. F. Bocian and H. L. Strauss, *J. Am. Chem. Soc.*, **99**, 2866 (1977); P. M. Iavanov and E. Osawa, *J. Comput. Chem.*, **5**, 307 (1984).

⁷⁶ J. B. Hendrickson, R. K. Boeckman, Jr., J. D. Glickson, and E. Grunwald, *J. Am. Chem. Soc.*, **95**, 494 (1973).

⁷⁷ F. H. Allen, J. A. K. Howard, and N. A. Pitchard, *Acta Crystallog.*, **B49**, 910 (1993).

⁷⁸ D. F. Bocian, H. M. Pickett, T. C. Rounds, and H. L. Strauss, *J. Am. Chem. Soc.*, **97**, 687 (1975).

⁷⁹ K. B. Wiberg, *J. Org. Chem.*, **68**, 9322 (2003).

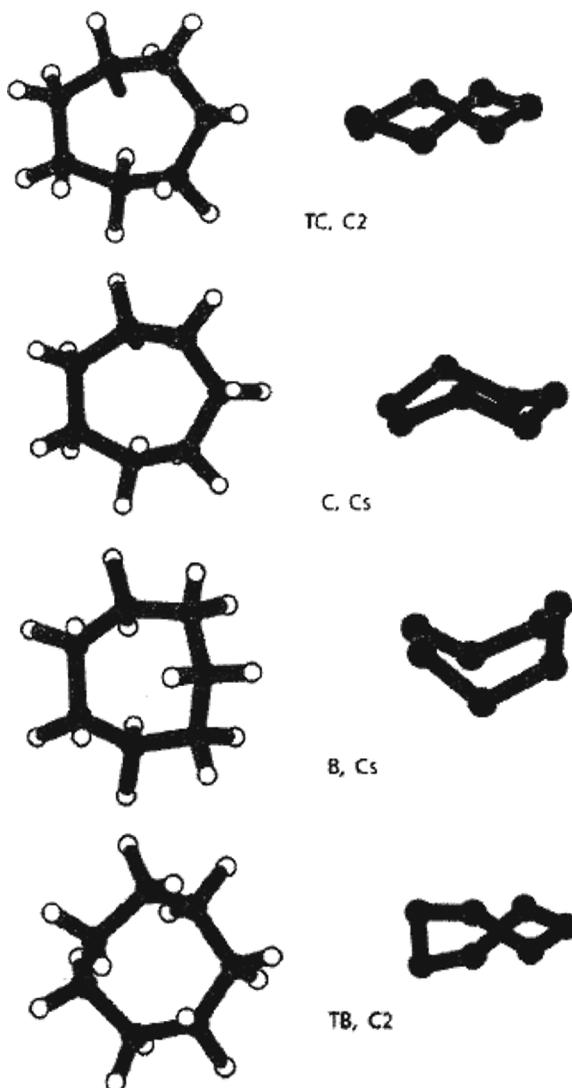


Fig. 2.17. The four most favorable conformations of cycloheptane. Reproduced from *J. Org. Chem.*, **68**, 9322 (2003), by permission of the American Chemical Society.

For cyclooctane, a total of 11 conformations have been suggested for consideration and their relative energies calculated. According to MM⁸⁰ and CCSDT/6-311++G**⁷⁹ computations, there are five other conformations that are energy minima, of which the boat-chair is calculated to be the most stable. This result is in agreement with analyses of the temperature dependence of the ¹⁹F NMR spectra of fluorocyclooctanes.⁸¹ The activation energy for interconversion of conformers is 5–8 kcal/mol.

⁸⁰. I. Kolossvary and W. C. Guida, *J. Am. Chem. Soc.*, **115**, 2107 (1993).

⁸¹. J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 1386 (1969); see also F. A. Anet and M. St. Jacques, *J. Am. Chem. Soc.*, **88**, 2585, 2586 (1966).

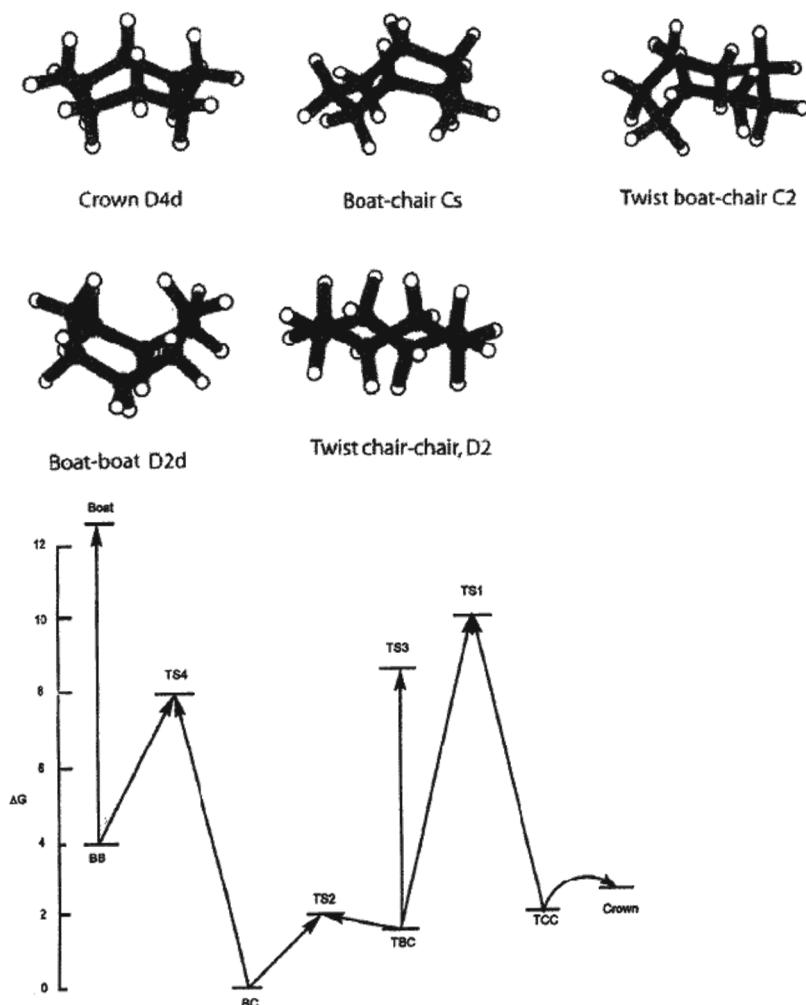


Fig. 2.18. Structures of the low-energy conformations of cyclooctane and the energy barriers separating them. Reproduced from *J. Org. Chem.*, **68**, 9322 (2003), by permission of the American Chemical Society.

Figure 2.18 illustrates the low-energy conformations and the barriers separating them. The crown and twist-chair-twist conformations are quite similar.

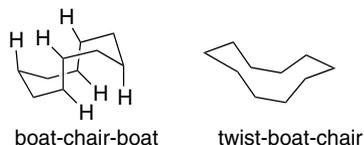
The number of conformations rapidly increases with ring size. For cyclodecane there are 18 conformers that are found as minima in MM3 calculations.⁸² The lowest four are within 1 kcal/mol of one another. Low-temperature NMR studies indicate that the boat-chair-boat is the lowest in energy,⁸³ and studies of cyclodecane derivatives by X-ray crystallography showed that the boat-chair-boat conformation is adopted in the solid state.⁸⁴ As was indicated in Table 2.3, cyclodecane is significantly more

⁸² N. Weinberg and S. Wolfe, *J. Am. Chem. Soc.*, **116**, 9860 (1994).

⁸³ D. M. Pawar, S. V. Smith, H. L. Mark, R. M. Odom, and E. A. Noe, *J. Am. Chem. Soc.*, **120**, 10715 (1998).

⁸⁴ J. D. Dunitz, in *Perspectives in Structural Chemistry*, Vol II, J. D. Dunitz and J. A. Ibers, eds., Wiley, New York, 1968, pp. 1–70.

strained than cyclohexane. Examination of the boat-chair-boat conformation reveals that the source of most of this strain is the close van der Waals contacts between two sets of three hydrogens on either side of the molecule, as indicated in the drawing below. Distortion of the molecule to twist forms relieves this interaction but introduces torsional strain.



The conformational possibilities for larger rings quickly become very large, but an interesting simplifying concept has emerged. The diamond lattice, which consists of a continuous array of chair cyclohexane rings, is the most stable arrangement for a large array of sp^3 carbon atoms. There are both theoretical and experimental results that show that complex polycyclic saturated hydrocarbons are most stable in diamond-type structures. Adamantane is a familiar example of this type of structure.



It might be anticipated that large flexible rings would adopt similar structures incorporating the chair cyclohexane conformation. Conformations for C_{10} through C_{24} cycloalkanes corresponding to diamond lattice sections have been identified by systematic topological analysis using models and molecular mechanics computations.⁸⁵ This type of relationship is illustrated in Figure 2.19 for cyclodecane. Molecular

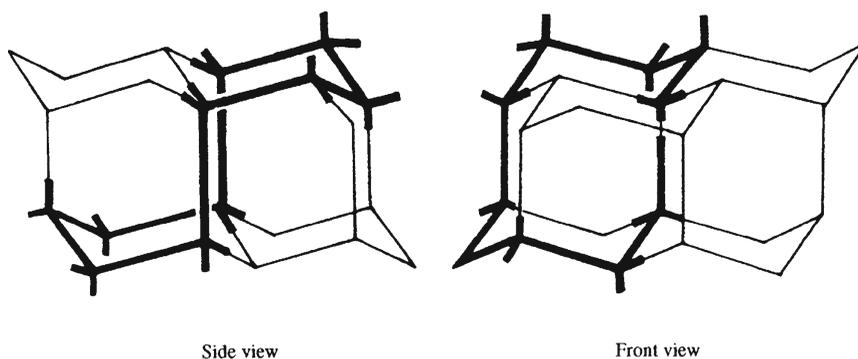


Fig. 2.19. Equivalent diamond lattice conformations of cyclodecane (boat-chair-boat).

⁸⁵ J. Dale, *J. Chem. Soc.*, 93 (1963); M. Saunders, *Tetrahedron*, **23**, 2105 (1967); J. Dale, *Top. Stereochem.*, **9**, 199 (1976).

mechanics computations indicate that this is indeed the minimum energy conformation for cyclododecane.^{80,86}

As the ring size increases, the number of possible conformations increases further so that many alternative diamond lattice conformations are available.⁸⁷

2.3. Molecular Mechanics

The analysis of molecular conformation can be systematically and quantitatively approached through molecular mechanics.⁸⁸ A molecule adopts the geometry that minimizes its total strain energy. The minimum energy geometry is strained (destabilized) to the extent that its structural parameters deviate from their ideal values. The energy for a particular kind of distortion is a function of the amount of distortion and the opposing force. The total strain energy is the sum of several contributions:

$$E_{\text{strain}} = E(r) + E(\theta) + E(\varphi) + E(d) \quad (2.9)$$

where $E(r)$ is the energy associated with stretching or compression of bonds, $E(\theta)$ is the energy of bond angle distortion, $E(\varphi)$ is the torsional strain, and $E(d)$ are the energy increments that result from nonbonded interactions between atoms.

Molecular mechanics calculations involve summation of the force fields for each type of strain. The original mathematical expressions for the force fields were derived from classical mechanical potential energy functions. The energy required to stretch a bond or to bend a bond angle increases as the square of the distortion:

$$\text{Bond stretching : } E(r) = 0.5k_r(r - r_0)^2 \quad (2.10)$$

where k_r , is the stretching force constant, r the bond length, and r_0 the normal bond length.

$$\text{Bond angle bending : } E(\theta) = 0.5k_\theta(\Delta\theta)^2 \quad (2.11)$$

where k_θ is the bending force constant and $\Delta\theta$ is the deviation of the bond angle from its normal value. The torsional strain is a sinusoidal function of the torsion angle. Torsional strain results from the barrier to rotation about single bonds, as described for ethane on p. 142–143. For molecules with a threefold barrier such as ethane, the form of the torsional barrier is:

$$E(\varphi) = 0.5V_0(1 + \cos 3\varphi) \quad (2.12)$$

where V_0 is the rotational energy barrier and φ is the torsional angle. For hydrocarbons, V_0 can be taken as being equal to the ethane barrier (2.9 kcal/mol).

Nonbonded interaction energies, which may be attractive or repulsive, are the most difficult contributions to evaluate. When two uncharged atoms approach each other, the interaction between them is very small at large distances, becomes slightly

⁸⁶. M. Saunders, *J. Comput. Chem.*, **12**, 645 (1991).

⁸⁷. M. Saunders, *J. Am. Chem. Soc.*, **109**, 3150 (1987); V. L. Shannon, H. L. Strauss, R. G. Snyder, C. A. Elliger, and W. L. Mattice, *J. Am. Chem. Soc.*, **111**, 1947 (1989); M. Saunders, K. N. Houk, Y. D. Wu, W. C. Still, M. Lipton, G. Chang, and W. C. Guida, *J. Am. Chem. Soc.*, **112**, 1419 (1990).

⁸⁸. For general reviews see: W. Gans, A. Amann, and J. C. A. Boeyens, *Fundamental Principles of Molecular Modeling*, Plenum Press, New York, 1996; A. K. Rappe and C. J. Casewitt, *Molecular Mechanics Across Chemistry*, University Science Books, Sausalito, CA, 1997; J. C. A. Boeyens and P. Comba, *Coordn. Chem. Rev.*, **212**, 3 (2001).

attractive as the separation approaches the sum of their van der Waals radii, but then becomes strongly repulsive as the separation becomes less than the sum of their van der Waal radii. The attractive interaction results from a mutual polarization of the electrons of the atoms. Such attractive forces are called *London forces* or *dispersion forces* and are relatively weak interactions. London forces vary inversely with the sixth power of internuclear distance and become negligible as internuclear separation increases. At distances smaller than the sum of the van der Waals radii, the much stronger electron-electron repulsive forces are dominant. Electrostatic forces must take into account bond dipoles and their orientation. Bond dipoles also have a polarizing effect on adjacent groups.⁸⁹

The separation of the total strain energy into component elements of bond length strain, bond angle strain, torsional strain, and nonbonded interactions is useful for analysis of structural and steric effects on equilibria and reactivity. Minimization of the total strain energy of a molecule, expressed by a parameterized equation for each of the force fields, can be accomplished by iterative computation. The quantitative application of molecular mechanics for calculation of minimum energy geometries, heats of formation, and strain energies has been developed to a high level of reliability. The method has been refined to the point that geometries of saturated hydrocarbons can be calculated to an accuracy of 0.005 Å in bond length and 1° in bond angle.⁹⁰ Similar accuracy can be obtained for unsaturated hydrocarbons⁹¹ and molecules with oxygen functional groups.⁹² Molecular mechanics calculations can also be applied to unstable reactive intermediates such as carbocations.⁹³

The molecular mechanics computations can be done using commercially available programs. The parameters used in the programs determine the range of applicability and reliability of the results. Several systems of parameters and equations for carrying out the calculations have been developed. The most frequently used methods in organic chemistry are those developed by N. L. Allinger and co-workers and is frequently referred to as MM (molecular mechanics) calculations.⁹⁴ The most recent version is called MM4.⁹⁵ The computations involve iterations to locate an energy minimum. Precautions must be taken to establish that a true (“global”) minimum, as opposed to a local minimum energy, has been achieved. This can be accomplished by using a number of different initial geometries and comparing the structures and energies of the minima that are located. In addition to comparing the relative energy of various conformations of an individual molecule, MM computations can be used to calculate total molecular energy (enthalpy of formation) to a high level of accuracy. Heats of formation for most hydrocarbons are accurate to ± 0.5 kcal/mol. This application of MM is discussed further in Section 3.1.2.4.

⁸⁹ L. Dosen-Micovic, D. Jeremic, and N. L. Allinger, *J. Am. Chem. Soc.*, **105**, 1716, 1723 (1983); B. Mannfors, K. Palmo, and S. Krimm, *J. Mol. Struct.*, **556**, 1 (2000).

⁹⁰ N. L. Allinger, Y. H. Yuh, and J.-H. Lii, *J. Am. Chem. Soc.*, **111**, 8551 (1989); N. L. Allinger, K. Chen, and J.-H. Lii, *J. Comput. Chem.*, **17**, 642 (1996).

⁹¹ N. Nevins, K. Chen, and N. L. Allinger, *J. Comput. Chem.*, **17**, 669 (1996); N. Nevins, J.-H. Lii, and N. L. Allinger, *J. Comput. Chem.*, **17**, 695 (1996); N. Nevins and N. L. Allinger, *J. Comput. Chem.*, **17**, 730 (1996).

⁹² C. H. Langley, J. H. Lii, and N. L. Allinger, *J. Comput. Chem.*, **22**, 1396, 1426, 1451 (2001).

⁹³ B. Reindl, T. Clark, and P. v. R. Schleyer, *J. Comput. Chem.*, **17**, 1406 (1996); B. Reindl and P. v. R. Schleyer, *J. Comput. Chem.*, **18**, 28 (1997); B. Reindl, T. Clark, and P. v. R. Schleyer, *J. Comput. Chem.*, **18**, 533 (1997); B. Reindl, T. Clark, and P. v. R. Schleyer, *J. Phys. Chem. A*, **102**, 8953 (1998).

⁹⁴ N. L. Allinger, Y. H. Yuh and J.-H. Lii, *J. Am. Chem. Soc.*, **111**, 8551 (1989).

⁹⁵ N. L. Allinger, K. S. Chen, and J. H. Lii, *J. Comput. Chem.*, **17**, 642 (1996).

Molecular mechanics can also be used in connection with MO or DFT calculations in computations on transition structures. Because transition structures have partial bonds that vary from case to case, no general set of parameters is applicable. One approach is to apply MO or DFT calculations to the reacting portion of the molecule to obtain structural information. This portion of the structure can then be incorporated into an MM computation involving the remainder of the molecule.⁹⁶ It is also possible to use several levels of computations. For example, high-level MO or DFT calculations can be applied to the reaction core, intermediate level calculations to the part of the system immediately adjacent to the reaction core, and MM calculations for the remainder of the molecule.⁹⁷ Two examples of these approaches are given in Section 2.5.4, where large catalytic molecules have been examined using combined approaches.

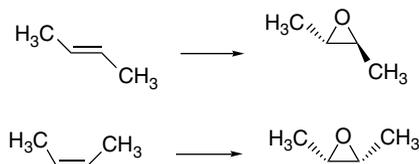
2.4. Stereoselective and Stereospecific Reactions

In this section we discuss relationships between reactivity and stereochemistry. Many reactions can produce two or more stereoisomeric products. If a reaction shows a preference for one of the stereoisomers, it is *stereoselective*. Throughout the sections on individual reactions in Parts A and B, we discuss the stereoselectivity associated with particular reactions. In this chapter, we use a few examples to illustrate the fundamental concepts of stereoselectivity.

Stereoselectivity is intimately related to the mechanism of the reaction. Some reactions are *stereospecific*, that is reactions in which *stereoisomeric reactants each provide stereoisomeric products*. For example, the S_N2 substitution reaction results in an inversion of the configuration. It is a stereospecific reaction. The *R*-reactant gives the *S*-product and the *S*-reactant gives the *R*-product (assuming the priority order remains unchanged).



As another example, epoxidation of *E*-2-butene gives *trans*-2,3-dimethyloxirane, whereas *Z*-2-butene gives *cis*-2,3-dimethyloxirane.



⁹⁶ J. E. Eksterowicz and K. N. Houk, *Chem. Rev.*, **93**, 2439 (1993); F. Maseras and K. Morokuma, *J. Comput. Chem.*, **16**, 1170 (1995).

⁹⁷ M. Svensson, S. Humbel, R. D. J. Froese, T. Matsubara, S. Sieber, and K. Morokuma, *J. Phys. Chem.*, **100**, 19357 (1996).

We discuss several examples to illustrate how reactant structure and mechanism can lead to stereoselectivity, including stereospecificity. We also consider *enantioselective* and *enantiospecific* reactions, which are reactions that favor one enantiomer of a reaction product.

2.4.1. Examples of Stereoselective Reactions

Scheme 2.6 gives some examples of the types of stereoselective reactions that are discussed. The first three examples in the scheme are catalytic hydrogenations. Usually such reactions favor *syn* addition of hydrogen from the less hindered face of the double bond; that is, both hydrogens are added to the same face of the π bond. The second entry illustrates another aspect of catalytic hydrogenation: the tendency of hydroxy groups to be *syn*-directive, that is, to favor addition from the same side that is occupied by the hydroxy group. These features are believed to be related to the interaction of the alkene with the catalytic surface during hydrogenation and are discussed further in Section 2.4.2.1. As can be seen from the variable degree of stereoselectivity in Entries 1 and 2, as well as the exception in Entry 3, *catalytic hydrogenation is not always highly stereoselective*.

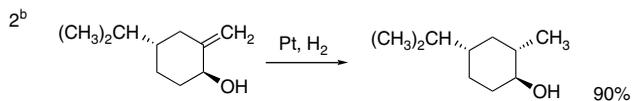
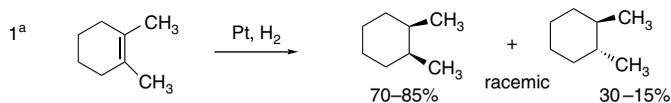
Entries 4 through 6 are examples of stereoselective reduction of cyclic ketones. Comparing entries 4 and 5 shows that stereoselectivity can be controlled by the choice of reagents. As we discuss further in Section 2.4.1.2, some hydride donors, e.g., NaBH_4 , approach from the axial direction to give equatorial alcohol. More bulky reducing agents favor the equatorial approach and give axial alcohol. Entry 6 illustrates the tendency of reagents to attack the norbornane ring from the *exo* direction. Entry 7 is an example of diastereoselective addition of a Grignard reagent adjacent to a stereocenter. This is an example of *1,2-asymmetric induction*, in which the configuration at the adjacent stereocenter establishes a preference for the direction of addition to the carbonyl group. This kind of reaction has been studied extensively and is discussed in Section 2.4.1.3. One of the issues that must be considered in this case is the conformation of the reactant. Although the preferred conformation of ring compounds is often evident, the flexibility of acyclic compounds introduces additional variables. Entry 8 is another example in which the configuration of the α -oxy substituent controls the direction of addition of hydride to the carbonyl group.

2.4.1.1. Substituent Directing Effects in Heterogeneous and Homogeneous Hydrogenation The hydrogenation of carbon-carbon double bonds is a very general reaction. Except for very sterically hindered cases, the reaction usually proceeds rapidly and cleanly. Hydrogenation can be carried out using either finely dispersed metal (heterogeneous) or soluble (homogeneous) metal complexes. The heterogeneous catalysts are transition metals, particularly platinum, palladium, rhodium, ruthenium, and nickel. The metals are used as finely dispersed solids or adsorbed on inert supports such as charcoal or alumina. Homogeneous catalysts are usually complexes of rhodium, ruthenium, or iridium. Phosphine ligands are common in these catalytic complexes. Depending upon the conditions and the catalyst, other functional groups may also be subject to catalytic hydrogenation, but for now we focus on double bonds.



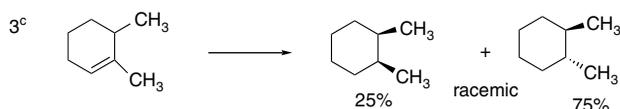
A. Catalytic Hydrogenation. (See section 2.4.1.1)

Unfunctionalized alkene usually reacts by preferential *syn* delivery of hydrogen from the less hindered face of the double bond. The degree of stereoselectivity is dependent on the reactant structure, catalysts and reaction conditions. Donor functional groups, particularly hydroxy and amino can be *syn* directive.



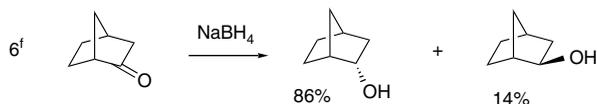
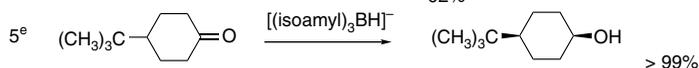
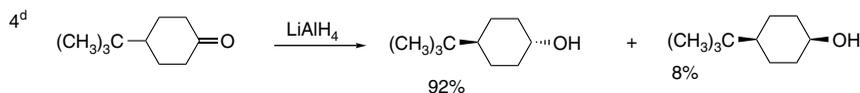
(The same article also sites other examples with low stereoselectivity.)

A representative exception.



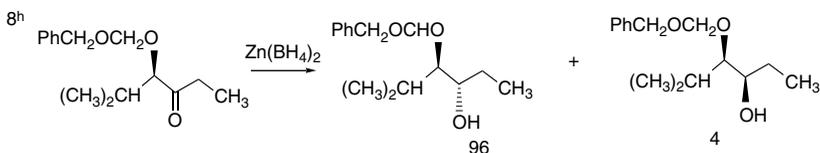
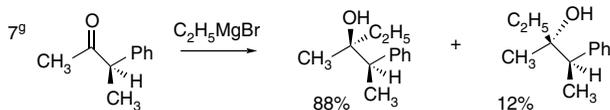
B. Hydride Reduction of Cyclic Ketones (see Section 2.4.1.2)

Unhindered cyclohexanones normally react with NaBH_4 and LiAlH_4 by preferential reagent approach from the axial direction forming mainly the equatorial alcohol. The presence of axial substituents or use of more sterically demanding reagents, such as alkylborohydrides leads to selective equatorial approach and formation of axial alcohols. Bicyclic ketones are generally reduced by hydride approach from the less hindered face of the carbonyl group.



C. Nucleophilic Addition to Acyclic Ketones (see Section 2.4.1.3)

Adjacent stereocenters influence the mode of addition of nucleophiles such as hydrides and organometallic reagents to acyclic ketones. The Felkin-Ahn transition state provides a predictive model that is general when steric effects are dominant. Other factors must be considered when polar or chelating substituents are present.



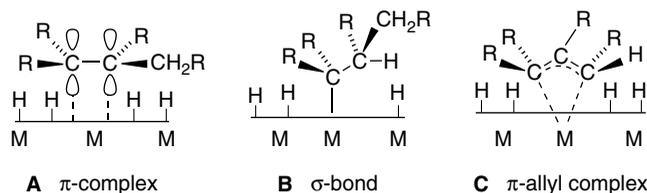
(Continued)

CHAPTER 2

Stereochemistry,
Conformation,
and Stereoselectivity

- a. C. A. Brown, *J. Am. Chem. Soc.*, **91**, 5901 (1969).
 b. M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).
 c. S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 6082, 6087 (1960).
 d. H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970).
 e. S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).
 f. H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).
 g. O. Arjona, R. Perez-Ossorio, A. Perez-Rubalcaba, and M. L. Quiroga, *J. Chem. Soc., Perkin Trans. 2*, 597 (1981);
 C. Alvarez-Ibarra, O. Arjona P. Perez-Ossorio, A. Perez-Rubalcaba, M. L. Quiroga, and M. J. Santemas, *J. Chem. Soc., Perkin Trans. 2*, 1645 (1983).
 h. G. J. McGarvey and M. Kimura, *J. Org. Chem.*, **47**, 5420 (1982).

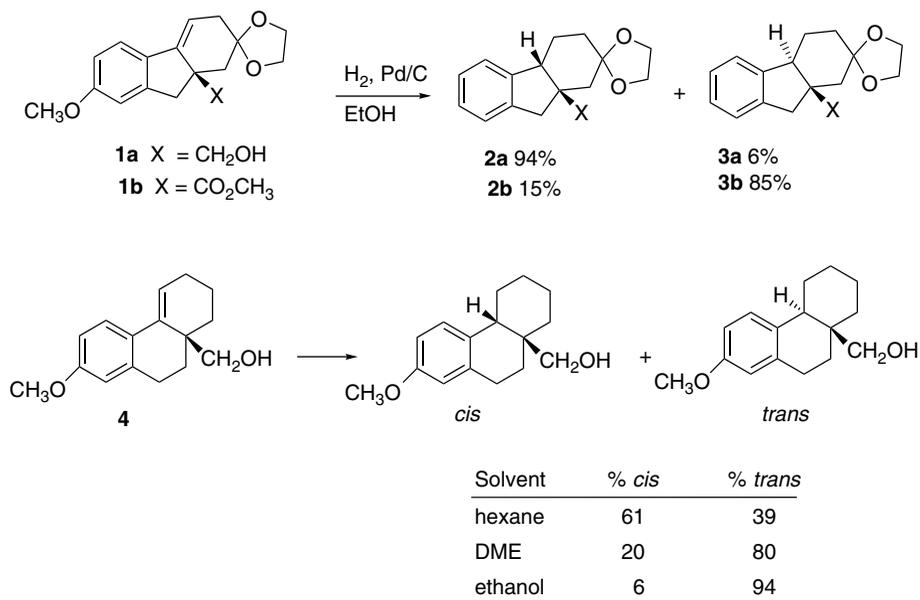
The mechanistic description of heterogeneous hydrogenation is somewhat vague, partly because the reactive sites on the metal surface are not as precisely described as small molecule reagents in solution. As understanding of the chemistry of homogeneous hydrogenation catalysts has developed, it has become possible to extrapolate those mechanistic concepts to heterogeneous catalysts. It is known that hydrogen is adsorbed onto the metal surface, forming metal-hydrogen bonds similar to those found in transition metal hydride complexes. Alkenes are also adsorbed on the catalyst surface and at least three types of intermediates have been implicated in hydrogenation. The initially formed intermediate is pictured as attached at both carbon atoms of the double bond by π -type bonding, as shown in **A**. The bonding involves the alkene π and π^* orbitals interacting with acceptor and donor orbitals of the metal. A hydrogen can be added to the adsorbed group, leading to **B**, which involves a carbon-metal σ bond. This species can react with another hydrogen to give the alkane. Alkanes have little affinity for the catalyst surface, so this reaction is effectively irreversible. A third intermediate species, shown as **C**, accounts for double-bond isomerization and the exchange of hydrogen that sometimes accompanies hydrogenation. This intermediate is equivalent to an allyl group bound to the metal surface by π bonds. It can be formed from adsorbed alkene by abstraction of an allylic hydrogen atom by the metal. Formation of the allyl species is reversible and can lead to alkene isomerization. Analogous reactions take place at single metal ions in homogeneous catalysis. A major uncertainty in heterogeneous catalysis is whether there are cooperative interactions involving several metal centers.



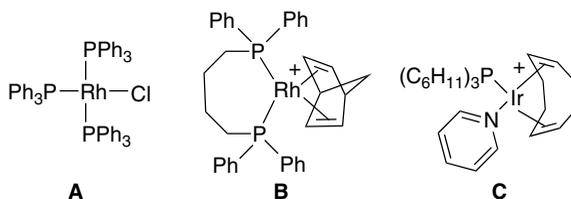
In most cases, both hydrogen atoms are added to the same side of the reactant (*syn* addition). If hydrogenation occurs by addition of hydrogen in two steps, as implied by the mechanism above, the intermediate must remain bonded to the metal surface in such a way that the stereochemical relationship is maintained. Adsorption to the catalyst surface normally involves the less sterically congested face of the double bond, and as a result, hydrogen is added from the less hindered face of the molecule. There are many cases of hydrogenations where hydrogen addition is not entirely *syn* and independent corroboration of the stereochemistry is normally necessary.

The facial stereoselectivity of hydrogenation is affected by the presence of polar functional groups that can influence the mode of adsorption to the catalyst surface. For

instance, there are many of examples where the presence of a hydroxy group results in the hydrogen being introduced from the same side of the molecule occupied by the hydroxy group. This *syn*-directive effect suggests that the hydroxy group interacts with the catalyst surface. This behavior can be illustrated with the alcohol **1a** and the ester **1b**.⁹⁸ Although the overall shapes of the two molecules are similar, the alcohol gives mainly the product with a *cis* ring juncture (**2a**), whereas the ester gives mainly a product with *trans* stereochemistry (**3b**). The stereoselectivity of hydroxy-directed hydrogenation is a function of solvent and catalyst as indicated for alcohol **4**.⁹⁹ The *cis* isomer is the main product in hexane. This result implies that the hydroxy group directs the molecule to the catalyst surface. In ethanol, the competing interaction of the solvent molecules evidently swamps out the directive effect of the hydroxymethyl group in **4** and the *trans* product is formed.



Substituent directive effects are also observed with soluble (homogeneous) hydrogenation catalysts. A number of transition metal complexes function as homogeneous hydrogenation catalysts. Three important examples are shown below.

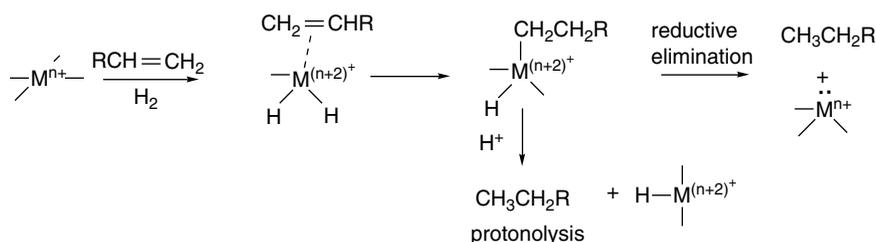


⁹⁸. H. W. Thompson, *J. Org. Chem.*, **36**, 2577 (1971).

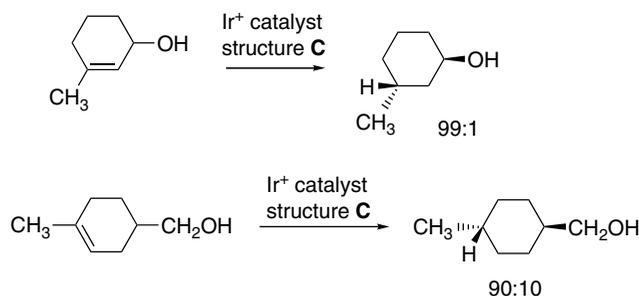
⁹⁹. H. W. Thompson, E. McPherson, and B. L. Lences, *J. Org. Chem.*, **41**, 2903 (1976).

Compound **A** is known as Wilkinson's catalyst and was one of the first of the homogeneous catalysts to be developed.¹⁰⁰ The cationic rhodium complex **B** is a useful catalyst for hydrogenations that involve a chelated structure between the reactant and the catalyst, such as allylic alcohols.¹⁰¹ The catalyst is activated by the hydrogenation of the norbornadiene ligand, which opens two binding sites at the catalytic metal. The iridium complex **C** (Crabtree catalyst) functions in a similar manner.¹⁰² The cyclooctadiene ligand is removed on exposure to hydrogen, providing two open positions. The Rh^+ and Ir^+ metal centers in these catalysts have eight electrons in their valence shells and are able to accommodate up to five additional donor pairs. We will encounter other examples of homogeneous catalysts in Section 2.5.1.1 when we discuss enantioselective hydrogenation.

The mechanism of homogeneous catalysis involves the same steps as heterogeneous catalysis. An initial π complex is formed with the reactant. Metal-hydride bonds then react with the complexed alkene to form a C–H bond and σ bond between the metal and alkyl group. There can be variation in the timing of formation of the M–H bonds. The metal carbon bond can be broken by either *reductive elimination* or *protonolysis*. Note that reductive elimination changes the metal oxidation state, whereas protonolysis does not. The catalytic cycle proceeds by addition of alkene and hydrogen.



As in heterogeneous hydrogenation, substituents can affect the stereoselectivity of the reduction by forming an additional bond to the metal center. This requires that there be sufficient ligand positions to accommodate binding by the substituent. Stereoselective hydrogenation based on substituent directive effects is particularly prevalent for cyclic compounds. The iridium catalyst $[\text{Ir}(\text{cod})_2\text{py}(\text{PCy}_3)]^+\text{PF}_6^-$ (structure **C** above) has been used frequently. Cyclohexenols and cyclohexenylmethanols exhibit good stereoselectivity, with delivery of the hydrogen *syn* to the hydroxy group.¹⁰³



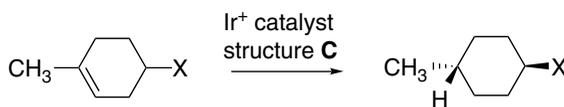
¹⁰⁰ J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

¹⁰¹ J. M. Brown, B. A. Chaloner, A. G. Kent, B. A. Murrer, P. N. Nicholson, D. Parker, and P. J. Sidebottom, *J. Organomet. Chem.*, **216**, 263 (1981); D. A. Evans and M. M. Morrissey, *J. Am. Chem. Soc.*, **106**, 3866 (1984).

¹⁰² R. H. Crabtree, H. Felkin, and G. E. Morris, *J. Organomet. Chem.*, **141**, 205 (1977).

¹⁰³ R. M. Crabtree and M. W. Davis, *J. Org. Chem.*, **51**, 2655 (1986).

In contrast to the results seen with heterogeneous catalysts, the methoxy, ester, and acetyl groups are also strongly directive in the 4-methylcyclohex-3-enyl system. The effect of amido substituents is greater than the ester substituent.¹⁰⁴ This result indicates that the carbonyl oxygen is a strong donor group toward the Ir⁺ catalyst, whereas carbonyl groups are not effective as directing groups with the heterogeneous catalysts.

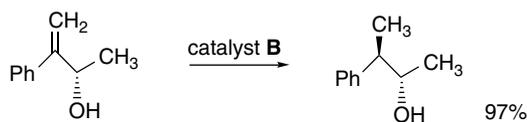


X	product yield %		ref.
	directed	nondirected	
-CO ₂ CH ₃	95	1.7	a
-COCH ₃	99.2	0.8	a
-OCH ₃	>99.9	0.1	a
-C(=O)-N	>99	<1	b
-CH ₂ CO ₂ CH ₃	50	50	b

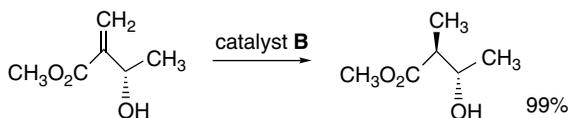
a. R. M. Crabtree and M.W. Davis, *J. Org. Chem.*, **51**, 2685 (1986).

b. A. G. Schultz and P. J. McCloskey, *J. Org. Chem.*, **50**, 5905(1985).

The flexibility of acyclic systems adds another element to the analysis of substituent directive effects. Some of the best examples of stereoselective reductions involve allylic alcohols and the rhodium catalyst **B**.



Ref. 105



Ref. 106

Stereoselectivity is also observed for homoallylic alcohols.



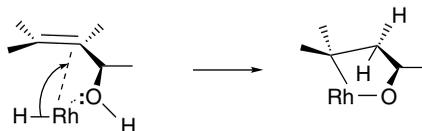
Ref. 105

¹⁰⁴. A. G. Schultz and P. J. McCloskey, *J. Org. Chem.*, **50**, 5905 (1985).

¹⁰⁵. J. M. Brown and R. G. Naik, *J. Chem. Soc. Chem. Commun.*, 348 (1982).

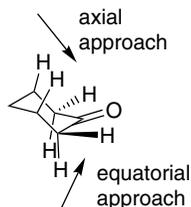
¹⁰⁶. J. M. Brown and I. Cutting, *J. Chem. Soc., Chem. Commun.*, 578 (1985).

The stereoselectivity for allylic and homoallylic alcohols is attributed to a chelated complex with delivery of the hydrogen *syn* with respect to the hydroxy group.¹⁰⁷



The general principles that emerge from these examples are the following: (1) The choice of catalyst must be appropriate. In particular, it must have sufficient exchangeable coordination sites to accommodate the directive group and still support the hydrogenation mechanism. (2) The structure of the reactant determines the nature of the coordination and the degree and direction of stereoselectivity. For cyclic systems, this usually results in *syn* delivery of hydrogen. For acyclic systems, the conformation of the coordinated reagent will control stereoselectivity. (3) In the examples cited above, the phosphine ligands were not explicitly considered, but their presence is crucial to the stability and reactivity of the metal center. When we consider enantioselective hydrogenation in Section 2.5.1.1, we will see that chiral phosphine ligands can also be used to establish a chiral environment at the metal center.

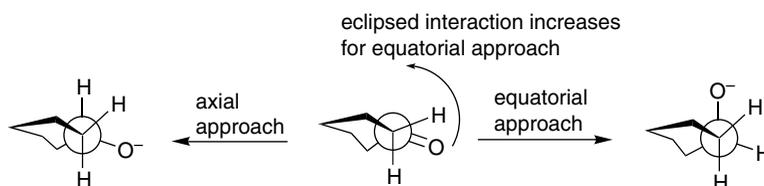
2.4.1.2. Hydride Reduction of Cyclic Ketones Section B of Scheme 2.6 gives some examples of hydride reduction of cyclic ketones. The stereoselectivity of nucleophilic additions to cyclic ketones has been studied extensively. The stereoselectivity in cyclohexanones is determined by the preference for approach of reactants from the axial or equatorial direction. The chair conformation of cyclohexanone places the carbonyl group in an unsymmetrical environment. The axial face has C(2, 6) – H_{eq} bonds that are nearly eclipsed with the C=O bond and the C(3,5)-diaxial hydrogens point toward the trajectory for reagent approach. In contrast, the equatorial face has axial C–H bonds at an angle of roughly 120° to the carbonyl plane. There is more steric bulk, including the 3,5-axial hydrogens, on the axial face. Remember also that the reagent interaction is with the LUMO and that the optimal trajectory is at an angle somewhat greater than 90° to the carbonyl plane.



It is observed that small nucleophiles prefer to approach the carbonyl group of cyclohexanone from the axial direction, even though this is a more sterically

¹⁰⁷ J. M. Brown, *Angew. Chem. Int. Ed. Engl.*, **26**, 190 (1987).

congested approach.¹⁰⁸ For example, NaBH_4 and LiAlH_4 deliver hydride by axial approach to form mainly the equatorial alcohol. How do the differences in the C–C bonds (on the axial side) as opposed to the C–H bonds (on the equatorial side) influence the stereoselectivity of cyclohexanone reduction? Torsional effects are believed to play a major role in the preference for axial approach. In the reactant conformation, the carbonyl group is almost eclipsed by the equatorial C(2) and C(6) C–H bonds. This torsional strain is relieved by axial attack, whereas equatorial approach increases strain because the oxygen atom must move through a fully eclipsed arrangement.¹⁰⁹



The stereoselectivity can be reversed by using more sterically demanding reagents. More bulky reducing agents usually approach the cyclohexanone carbonyl from the equatorial direction. This is called *steric approach control* and is the result of van der Waals repulsions with the 3,5-axial hydrogens. Alkylborohydride reagents are used instead of NaBH_4 , and alkoxy derivatives can be used in place of LiAlH_4 . The bulkier nucleophiles encounter the 3,5-axial hydrogens on the axial approach trajectory and therefore prefer the equatorial approach.¹¹⁰ A large amount of data has been accumulated on the stereoselectivity of reduction of cyclic ketones.¹¹¹ Table 2.4 compares the stereochemistry of reduction of several ketones by hydride donors of increasing steric bulk. The trends in the data illustrate the increasing importance of steric approach control as both the hydride reagent and the ketone become more highly substituted. For example, the axial methyl group in 3,3,5-trimethylcyclohexanone favors an equatorial approach. The alkyl-substituted borohydrides have especially high selectivity for the less hindered direction of approach.

The factors controlling the direction of reagent approach have also been studied in norbornan-2-ones. The stereochemistry of a number of reactions of the parent system and the 7,7-dimethyl derivative have been examined.¹¹² Some of the results are included in Table 2.4. These compounds reveal a reversal of the preferred direction of attack with the introduction of the 7,7-dimethyl substituents. In the parent system the *exo* direction of attack is preferred because the single CH_2 group at C(7) offers less steric resistance than the $-\text{CH}_2\text{CH}_2-$ unit on the *endo* side of the molecule. The *endo*

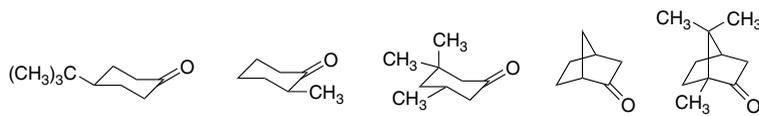
¹⁰⁸. B. W. Gung, *Tetrahedron*, **52**, 5263 (1996).

¹⁰⁹. M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968); Y. D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, **109**, 906, 908 (1987); Y. D. Wu, K. N. Houk, and M. N. Paddon-Row, *Angew. Chem. Int. Ed. Engl.*, **31**, 1019 (1992).

¹¹⁰. W. G. Dauben, G. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970); D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979); T. Wipke and P. Gund, *J. Am. Chem. Soc.*, **98**, 8107 (1976).

¹¹¹. D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979); D. C. Wigfield and D. J. Phelps, *J. Org. Chem.*, **41**, 2396 (1976).

¹¹². H. C. Brown, J. H. Kawakami, and K.-T. Liu *J. Am. Chem. Soc.*, **95**, 2209 (1973).

Table 2.4. Stereoselectivity of Hydride Reducing Agents toward Cyclic Ketones^a


Reductant	% equat.	% equat.	% equat.	% <i>exo</i>	% <i>endo</i>
NaBH ₄	20 ^b	25 ^c	58 ^c	86 ^d	86 ^d
LiAlH ₄	8	24	83	89	92
LiAl(OMe) ₃ H	9	69		98	99
LiAl(O- <i>t</i> -Bu) ₃ H	9 ^e	36 ^f	95	94 ^f	94 ^f
LiBH(<i>s</i> -Bu) ₃	93 ^g	98 ^g	99.8 ^g	99.6 ^g	99.6 ^g
LiBH(<i>siam</i>) ₃ ^h	> 99 ⁱ	> 99 ⁱ	> 99 ⁱ	NR ⁱ	

a. Except where noted otherwise, the data are those given by H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970). Data for many other cyclic ketones and reducing agents are given by A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962) and W. T. Wipke and P. Gund, *J. Am. Chem. Soc.*, **98**, 8107 (1976).

b. P. T. Lansbury and R. E. MacLeay, *J. Org. Chem.*, **28**, 1940 (1963).

c. B. Rickborn and W. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).

d. H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).

e. J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).

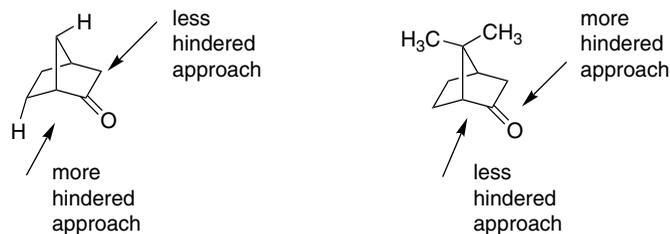
f. E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).

g. H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).

h. (*siam*) is an abbreviation for 1,2-dimethylpropyl.

i. S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).

hydrogens are in a relationship to the reaction site that is similar to the 1,3-diaxial interaction in a chair cyclohexane ring. When a *syn*-7-methyl group is present, the relative steric bulk of the two bridges is reversed.¹¹³

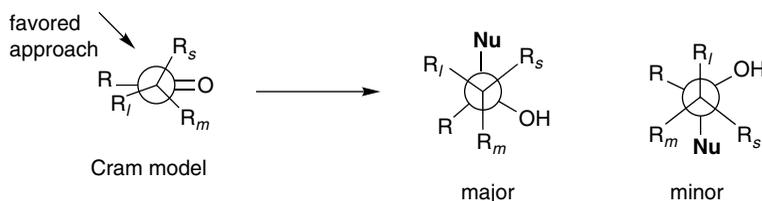


This relatively straightforward combination of torsional and steric effects as the source of stereoselectivity becomes more complicated when *polar* substituents are introduced into the picture. Polar effects are discussed in Topic 2.4.

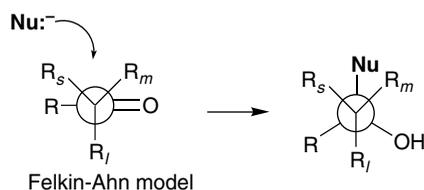
2.4.1.3. Stereoselective Nucleophilic Additions to Acyclic Carbonyl Groups The stereochemistry of nucleophilic addition to acyclic aldehydes and ketones is influenced by nearby substituents. A particularly important case occurs when there is a stereogenic center adjacent to the carbonyl group. As a result of the adjacent substituent, two diastereomers can be formed, depending on the direction of the approach of the nucleophile. The stereoselectivity of addition can be predicted on the basis of a conformational model of the TS. The addition reaction has been studied with several kinds

¹¹³ H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).

of nucleophiles; we use data from hydride addition and organometallic compounds in our discussion. The initial data were analyzed some time ago by D. J. Cram and co-workers,¹¹⁴ who observed that the *major* product was correctly predicted by a model in which the largest α group was eclipsed with the other carbonyl substituent. This empirical relationship became known as *Cram's rule*.



As chemists considered the origin of this diastereoselectivity, the reactant conformation that is considered to be the most important one has changed. The currently preferred *Felkin-Ahn model* places the largest substituent perpendicular to the carbonyl group.¹¹⁵ The major product results from the nucleophile approaching opposite to the largest substituent. This is the same product as predicted by the Cram model, although the interpretation is different.



The Felkin-Ahn model invokes a combination of steric and stereoelectronic effects to account for the observed stereoselectivity. An approach from the direction of the smallest substituent minimizes steric interaction with the groups R_l (largest group) and R_m (medium group). Another key idea is that the nucleophile approaches from above or below the carbonyl group on a trajectory that makes an angle of about 107° to the plane of the carbonyl group.¹¹⁶ This reflects the fact that the primary interaction of the approaching nucleophile is with the antibonding LUMO. However, it is also proposed that there is a stereoelectronic (hyperconjugation) effect, which involves the interaction between the approaching nucleophile and the LUMO of the carbonyl group. This orbital, which accepts the electrons of the incoming nucleophile, is stabilized when the R_l group is perpendicular to the plane of the carbonyl group.¹¹⁷ This conformation permits a stabilizing interaction between the developing bond to the nucleophile and the antibonding σ^* orbital associated with the $C-R_l$ bond. Because this is a $\sigma \rightarrow \sigma^*$ interaction, it should increase in importance with the electron-acceptor capacity of X.

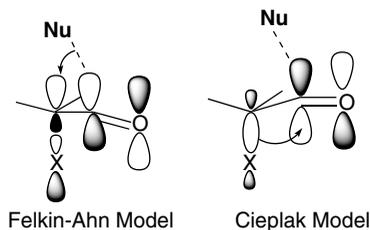
¹¹⁴ D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

¹¹⁵ M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 4199 (1968).

¹¹⁶ H. B. Burgi, J. D. Dunitz, and E. Shefter, *J. Am. Chem. Soc.*, **95**, 5065 (1973).

¹¹⁷ N. T. Ahn, *Top. Current Chem.*, **88**, 145 (1980).

The *Cieplak model* emphasizes an alternative interaction, between the σ orbital of the C–X bond and the antibonding orbital to the nucleophile.¹¹⁸ In this case, a better donor X should be the most stabilizing. Li and le Noble pointed out that *both of these hyperconjugative interactions will be present in the transition structure*.¹¹⁹ There is also general agreement that addition of reactive nucleophiles have *early transition states*, which would suggest that substituent effects might best be examined in the *reactant*.



One broad generalization is that when steric interactions are dominant the Felkin-Ahn model is predictive. Thus *steric approach control*, the idea that the approaching nucleophile will approach the carbonyl group from the least hindered direction, is the first guiding principle.¹²⁰

The TS model emphasizing steric effects must be elaborated when there is a polar substituent in the vicinity of the carbonyl group. At least three additional factors may then be involved. There are stereoelectronic effects associated with heteroatom substituents. Electronegative substituents such as halogen are assigned to the l position in the Felkin-Ahn TS on the basis of presumed stronger stereoelectronic interactions with the C=O bond. According to this analysis, the σ^* bond to the halogen stabilizes the TS. An *anti*-periplanar arrangement maximizes this interaction. It is likely that there are also electrostatic effects involved in controlling nucleophilic addition reactions, since compounds such as decalones,¹²¹ norbornan-7-ones,¹²² and adamantanones,¹²³ which have remote substituents that cannot directly interact with the reaction site, nevertheless influence the stereoselectivity. It remains a point for discussion as to whether these substituent effects are electrostatic in nature or are transmitted by hyperconjugation. (See Topic 2.4 for further discussion.)

It should also be emphasized that the *metal counterions* associated with the nucleophiles are active participants in carbonyl addition reactions. There are strong interactions between the carbonyl oxygen and the metal ions in the TSs and intermediates. This effect can be recognized, for example, in the reactivity of borohydrides, where the Li^+ , Ca^{2+} , and Zn^{2+} salts are more reactive than the standard NaBH_4 reagent because of the greater Lewis acid strength of these cations.

The examples just discussed pertain to substituents that are on the carbon adjacent to the carbonyl center and the stereoselectivity is referred to as 1,2-asymmetric

¹¹⁸ A. S. Cieplak, *J. Am. Chem. Soc.*, **103**, 4540 (1981).

¹¹⁹ H. Li and W. J. le Noble, *Recl. Trav. Chim. Pays-Bas*, **111**, 199 (1992).

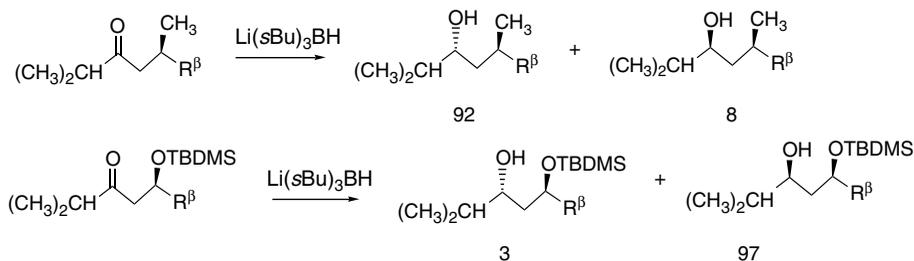
¹²⁰ W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965).

¹²¹ Y.-D. Wu, J. A. Tucker, and K. N. Houk, *J. Am. Chem. Soc.*, **113**, 5018 (1991).

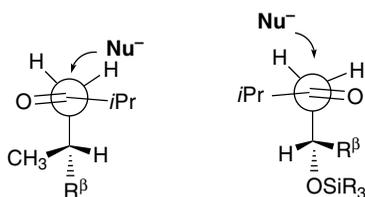
¹²² G. Mehta and F. A. Khan, *J. Am. Chem. Soc.*, **112**, 6140 (1990); H. Li, G. Mehta, S. Padma, and W. J. le Noble, *J. Org. Chem.*, **56**, 2006 (1991); G. Mehta, F. A. Khan, B. Ganguly, and J. Chandrasekhan, *J. Chem. Soc., Perkin Trans.*, **2**, 2275 (1994).

¹²³ C. K. Cheung, L. T. Tseng, M.-H. Lin, S. Srivastava, and W. J. le Noble, *J. Am. Chem. Soc.*, **108**, 1598 (1986); J. M. Hahn and W. J. le Noble, *J. Am. Chem. Soc.*, **114**, 1916 (1992).

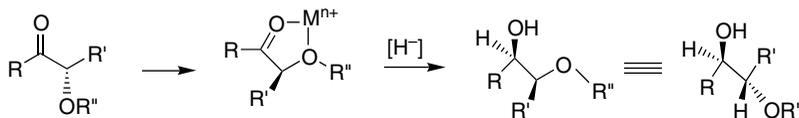
induction. More remote substituents can also affect the stereoselectivity of addition to the carbonyl group. For example, both β -methyl and β -siloxy substituents result in highly stereoselective reductions in ketones by trialkylborohydrides, but their directive effects are opposite.¹²⁴ This is a case of 1,3-asymmetric induction.



These results are attributed to alternative conformations of the reactant, with hydride attack being *anti* to the largest alkyl substituent in the methyl case and *anti* to the siloxy group in that case. The corresponding TSs are both of the Felkin-Ahn type in the sense that the large substituent is aligned perpendicularly with respect to the carbonyl group. In the methyl case, the favored TS minimizes the steric interaction of the isopropyl group with the β substituents. In the siloxy case, the favored TS has a stabilizing arrangement of the C=O and C–O dipoles and also avoids a steric interaction between the isopropyl group and R^β .



Another factor that affects stereoselectivity of carbonyl addition reactions is *chelation*.¹²⁵ If an α or β substituent can form a chelate with a metal ion involving the carbonyl oxygen, the stereoselectivity is usually governed by the chelated conformation. Complexation between a donor substituent, the carbonyl oxygen, and the Lewis acid can establish a preferred conformation for the reactant, which then controls reduction. Usually hydride is delivered from the less sterically hindered face of the chelate.



For example, α -hydroxy¹²⁶ and α -alkoxyketones¹²⁷ are reduced to *anti* 1,2-diols by $\text{Zn}(\text{BH}_4)_2$ via chelated TSs. This stereoselectivity is consistent with the preference for

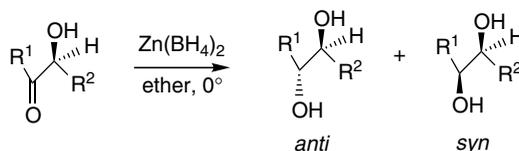
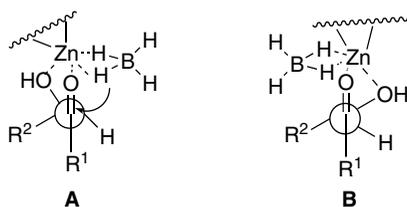
¹²⁴. D. A. Evans, M. J. Dart, and J. L. Duffy, *Tetrahedron Lett.*, **35**, 8541 (1994).

¹²⁵. D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1983).

¹²⁶. T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **24**, 2653 (1983).

¹²⁷. G. J. McGarvey and M. Kimura, *J. Org. Chem.*, **47**, 5420 (1982).

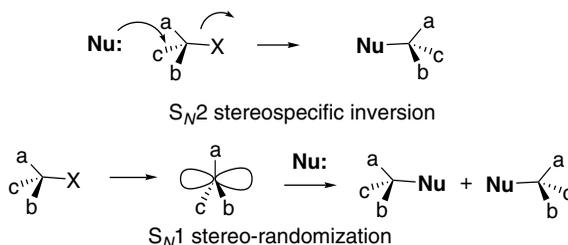
TS **A** over **B**. The stereoselectivity increases with the bulk of substituent R^2 . LiAlH_4 shows a similar trend, but with reduced selectivity.



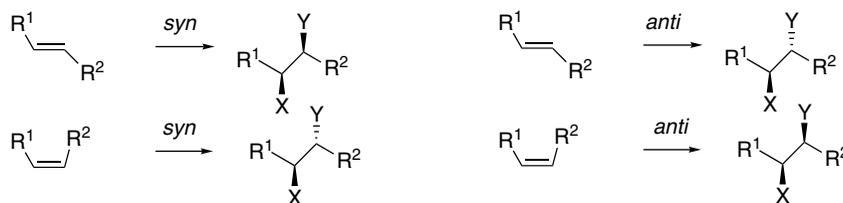
R^1	R^2	$\text{Zn}(\text{BH}_4)_2$ <i>anti</i> : <i>syn</i>	LiAlH_4 <i>anti</i> : <i>syn</i>
$n\text{-C}_5\text{H}_{11}$	CH_3	77:23	64:36
CH_3	$n\text{-C}_5\text{H}_{11}$	85:15	70:30
$i\text{-C}_3\text{H}_7$	CH_3	85:15	58:42
CH_3	$i\text{-C}_3\text{H}_7$	96:4	73:27
Ph	CH_3	98:2	87:13
CH_3	Ph	90:10	80:20

2.4.2. Examples of Stereospecific Reactions

In stereospecific reactions the configuration of the product is directly related to the configuration of the reactant and is determined by the reaction mechanism. Stereoisomeric reactants give different, usually stereoisomeric, products. The reaction mechanism determines the stereochemical relationship between the reactants and products. For any given reaction, stereospecificity may be lost or altered if there is a change in the mechanism. For example, the S_N2 reaction occurs with stereospecific inversion. However, when the mechanism shifts to S_N1 because of a change in reactants or reaction conditions, stereospecificity is lost.

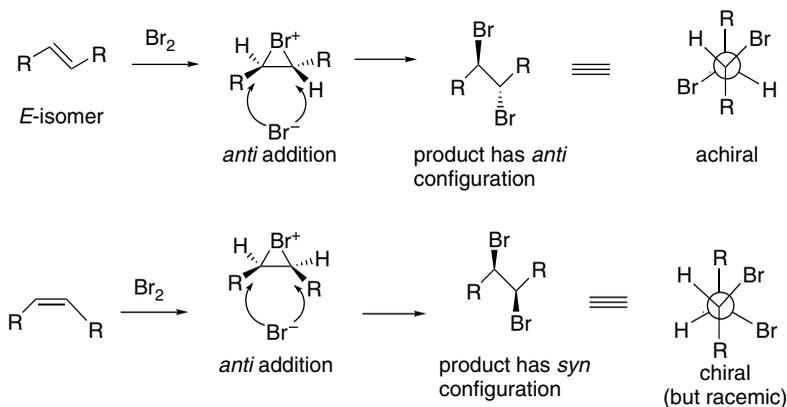


Another familiar and important example is *syn* and *anti* addition to double bonds. There are many examples of stereospecific reactions involving additions to carbon-carbon double bonds. Addition can be *anti* or *syn*, depending on the mechanism. If the mechanism specifies *syn* or *anti* addition, different products will be obtained from the *E*- and *Z*-isomers.

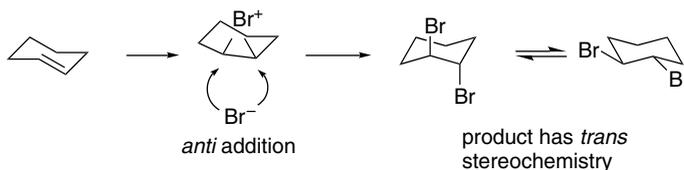


The examples in Scheme 2.7 include bromination, epoxidation and dihydroxylation, and hydroboration-oxidation of alkenes.

2.4.2.1. Bromination of Alkenes The bromination of substituted alkenes provides a number of examples of stereospecific reactions. These can be illustrated by considering the *Z*- and *E*-stereoisomers of disubstituted alkenes. The addition of bromine is usually stereospecifically *anti* for unconjugated disubstituted alkenes and therefore the *Z*- and *E*-alkenes lead to *diastereomeric products*. When both substituents on the alkene are identical, as in 2-butene, the product from the *Z*-alkene is chiral, whereas the product from the *E*-alkene is the achiral *meso* form (see p. 132).



The preference for *anti* addition is also evident from the formation of the *trans* product from cyclic alkenes.



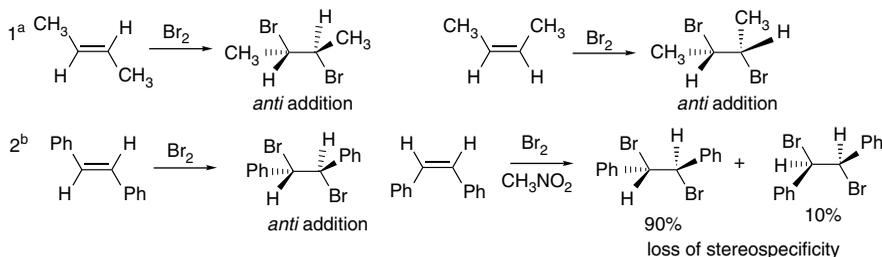
Scheme 2.7. Examples of Stereospecific Reactions

CHAPTER 2

Stereochemistry,
Conformation,
and Stereoselectivity

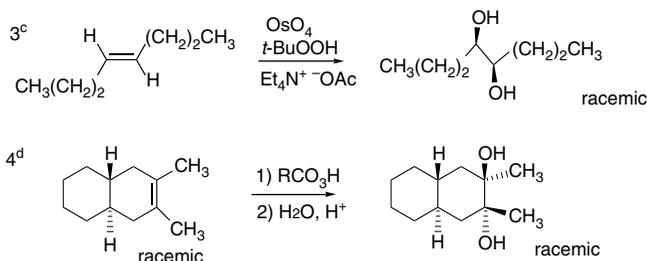
A. Bromination of Alkenes (see Section 2.4.2.1 for additional discussion)

Bromination of simple alkenes normally proceeds via a bromonium ion and is stereospecifically *anti*. Exceptions occur when the bromonium ion is in equilibrium with a corresponding carbocation.



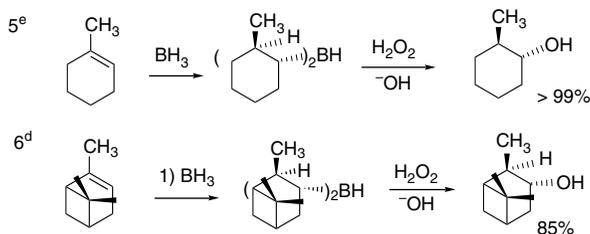
B. Dihydroxylation and Epoxidation-Hydrolysis of Alkenes (see Section 2.4.2.2 for additional discussion)

Dihydroxylation of alkenes can be carried out with *syn* stereospecificity using OsO_4 as the active oxidant. The reaction occurs by a cycloaddition mechanism. Epoxidation is also a stereospecific *syn* addition. Ring opening of epoxides by hydrolysis also leads to diols. This is usually an *anti* addition with inversion of configuration at the site of nucleophilic attack, leading to overall *anti* dihydroxylation.



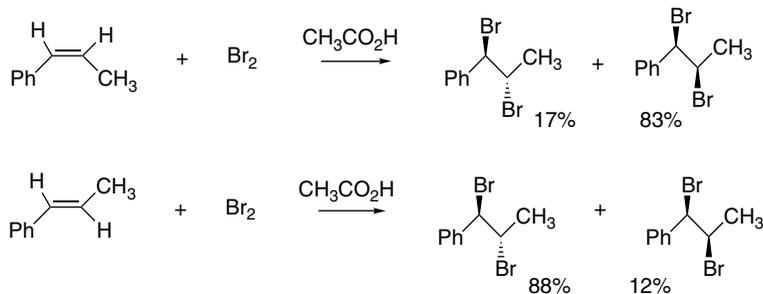
C. Hydroboration-Oxidation (see Section 2.4.2.3 for additional discussion)

Hydroboration-oxidation occurs by *syn* addition. The reagents are borane or an alkyl or dialkyl derivative, followed by oxidation, usually with H_2O_2 and OH^- . The oxidation occurs with *retention of configuration of the alkyl group*. The regioselectivity favors addition of the boron at the less-substituted carbon of the double bond. As a result, the reaction sequence provides a stereospecific *syn*, anti-Markovnikov hydration of alkenes.

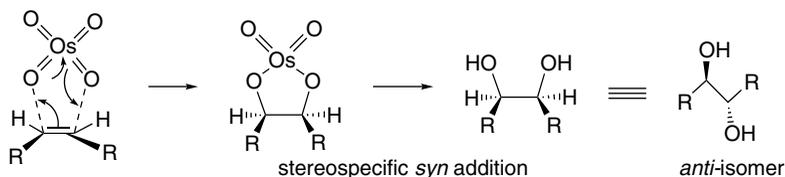


- a. J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1469, 1477 (1969).
 b. R. E. Buckles, J. M. Bader, and R. L. Thurmaier, *J. Org. Chem.*, **27**, 4523 (1962).
 c. K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, **43**, 2063 (1978).
 d. B. Rickborn and D. K. Murphy, *J. Org. Chem.*, **34**, 3209 (1969).
 e. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).
 f. G. Zweifel and H. C. Brown, *Org. Synth.*, **52**, 59 (1972).

The mechanism of bromination is discussed more fully in Section 5.3, but the fundamental cause of the stereospecificity is the involvement of the positively charged bromonium ion intermediate. The bromonium ion is opened by an *anti* approach of the bromide, leading to net *anti* addition. Entry 1 in Scheme 2.7 illustrates this behavior. Stereoisomeric products are obtained from the *E*- and *Z*-isomers, both as the result of *anti* addition. Stereospecificity is diminished or lost when the bromonium ion is not the *only intermediate in the reaction*. Entry 2 in Scheme 2.7 shows this behavior for *cis*-stilbene in nitromethane, where most of the product is the result of *syn* addition. The addition is *anti* in less polar solvents such as cyclohexane or carbon tetrachloride. The loss of *anti* stereospecificity is the result of a change in mechanism. The polar solvent permits formation of a carbocation intermediate. If the bromonium ion can open to a carbocation, a mixture of *syn* and *anti* products is formed. In the stilbene case, the more stable *anti* product is formed. Some loss of stereospecificity is also observed with 1-phenylpropene, where the phenyl group provides stabilization of an open carbocation intermediate.¹²⁸ Part of the product from both isomers is the result of *syn* addition.

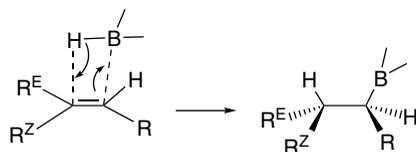
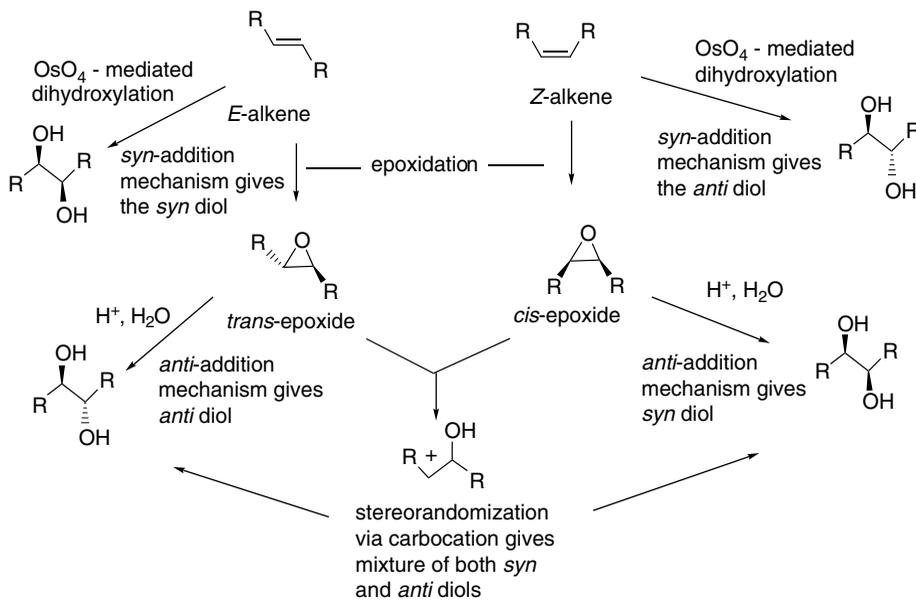


2.4.2.2. Epoxidation and Dihydroxylation of Alkenes There are several ways to convert alkenes to diols. Some of these methods proceed by *syn* addition, but others lead to *anti* addition. An important example of *syn* addition is osmium tetroxide-catalyzed dihydroxylation. This reaction is best carried out using a catalytic amount of OsO_4 , under conditions where it is reoxidized by a stoichiometric oxidant. Currently, the most common oxidants are *t*-butyl hydroperoxide, potassium ferricyanide, or an amine oxide. The two oxygens are added from the same side of the double bond. The key step in the reaction mechanism is a [3 + 2] cycloaddition that ensures the *syn* addition.

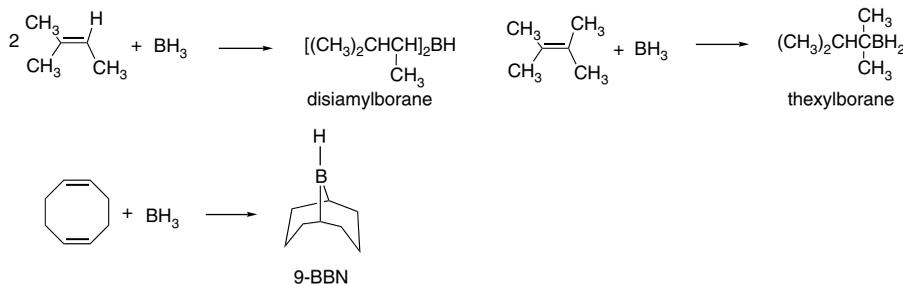


¹²⁸. R. C. Fahey and H.-J. Schneider, *J. Am. Chem. Soc.*, **90**, 4429 (1968).

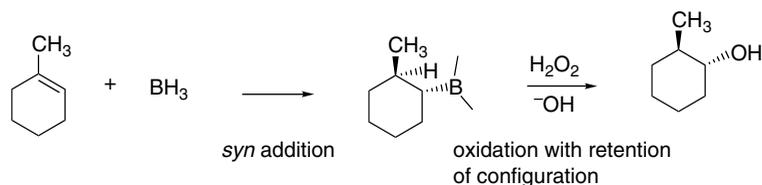
Scheme 2.8. Summary of Stereochemistry of Alkene Dihydroxylation by OsO₄-Catalysis and Epoxide Ring Opening



When the reaction is done with borane it is usually carried to the trialkylborane stage, but by controlling the stoichiometry the dialkyl or monoalkylborane can be obtained, especially from highly substituted alkenes such as 2-methyl-2-butene or 2,3-dimethylbutene. The resulting dialkyl and monoalkyl boranes are known as disiamylborane and thexylborane. Another useful dialkyl borane is 9-borabicyclo[3.3.1]nonane, known as 9-BBN.



When hydroboration is done in a synthetic context it is usually followed by a secondary reaction, most frequently oxidation by hydrogen peroxide and a base, which gives the corresponding alcohol *with retention of configuration*. The stereospecificity is very high. The regioselectivity is also usually excellent for the addition of the borane at the less substituted carbon of the double bond. This is illustrated in Entry 5 of Scheme 2.7, where 1-methylcyclohexene gives *trans*-2-methylcyclohexanol as a result of *syn* addition, followed by oxidation with retention of configuration. The stereospecificity is higher than 99% and none of the *cis* isomer is detected.



There is also an element of stereoselectivity associated with the hydroboration. The borane approaches from the less hindered face of the alkene. For 3-methylcyclohexene, a mixture of products is formed because the 3-methyl substituent has only weak influence on the regiochemistry and the steric approach. This stereoselectivity is accentuated by use of the larger dialkyl and alkyl boranes, as is illustrated by the data for 7,7-dimethylnorbornene in Table 2.5. All of the stereoselectivity and regioselectivity elements are illustrated by Entry 6 in Scheme 2.7. The boron adds at the less substituted end of the double bond and *anti* to the larger dimethyl bridge. Note that this forces the C(2) methyl into proximity of the larger bridge. After oxidation, the hydrogen and hydroxyl that were added are *syn*.

Each of the stereoselective reactions that were considered in Section 2.4 are discussed in more detail when the reaction is encountered in subsequent chapters. The key point for the present is that *reaction mechanism determines stereochemical outcome*. Knowledge about the mechanism allows the prediction of stereochemistry, and conversely, information about stereochemistry provides insight into the mechanism. As we consider additional reactions, we will explore other examples of the relationships between mechanism and stereochemistry.

Table 2.5. Stereoselectivity of Hydroboration

Reagent	3-Methylcyclohexene ^a				Norbornene ^b		7,7-Dimethyl-norbornene ^b	
	<i>cis</i> -2	<i>trans</i> -2	<i>cis</i> -3	<i>trans</i> -3 ^a	<i>exo</i>	<i>endo</i> ^b	<i>exo</i>	<i>endo</i> ^c
B ₂ H ₆	16	34	18	32	99.5	0.5	22	78
Disiamylborane	18	30	27	25	87	13		
9-BBN	0	20	40	40	99.5	0.5	3	97

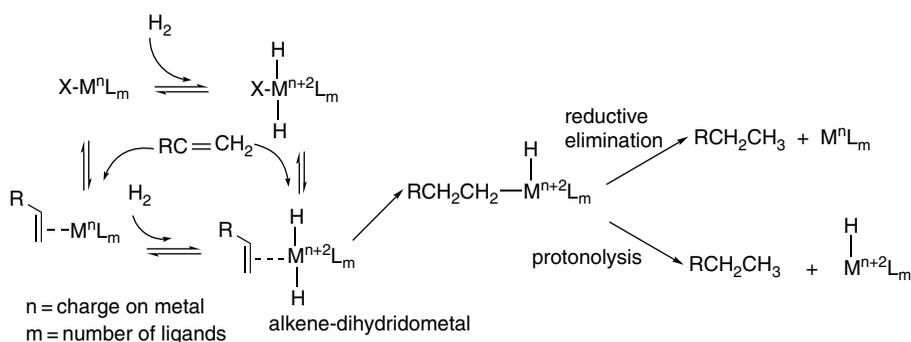
a. H. C. Brown, R. Liotta, and L. Brener, *J. Am. Chem. Soc.*, **99**, 3427 (1977).

b. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.*, **95**, 2209 (1973).

Enantioselective reactions are a particular case of stereoselective reactions that show a preference for one of a pair of enantiomers. As noted in Section 2.1.8, no reaction can produce an excess of one enantiomer unless there is at least one chiral component involved. *Enantiospecific reactions* are a special case of stereoselective reactions in which the mechanism ensures that the configuration of reactant, reagent, or catalyst determines that of the product. A simple example is S_N2 substitution, where the back-side displacement mechanism dictates inversion of configuration. In the next several subsections, we discuss examples of enantioselective and enantiospecific reactions.

2.5.1. Enantioselective Hydrogenation

Most catalytic hydrogenations are carried out under heterogeneous conditions using finely dispersed transition metals as catalysts. Such reactions take place on the catalyst surface (heterogeneous hydrogenation) and are not normally enantioselective, although they may be stereoselective (see Section 2.4.1.1). In addition, certain soluble transition metal complexes are active hydrogenation catalysts.¹³² Many of these catalysts include phosphine ligands, which serve both to provide a stable soluble complex and to adjust the reactivity of the metal center. Hydrogenation by homogeneous catalysts is believed to take place through a π complex of the unsaturated compound. The metals also react with molecular hydrogen and form metal hydrides. The addition of hydrogen to the metal can occur before or after complexation of the alkene. An alkylmetal intermediate is formed by transfer of hydrogen from the metal to the carbon. This intermediate can break down to alkane by reductive elimination or in some cases by reaction with a proton source.

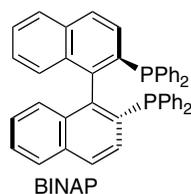


The process of homogeneous catalytic hydrogenation can be made enantioselective by establishing a chiral environment at the catalytic metal center. Most of the successful cases of enantioselective hydrogenation involve reactants having a potential

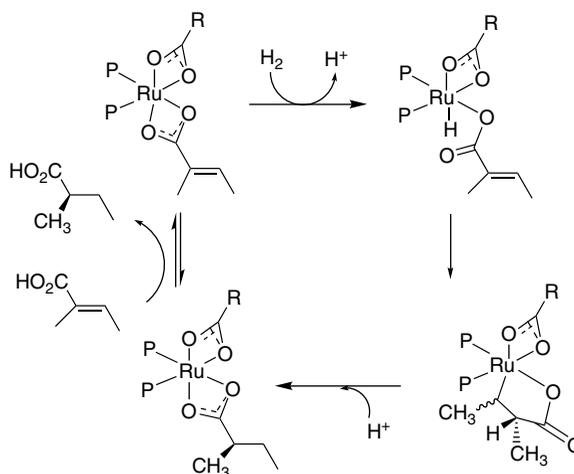
¹³² A. J. Birch and D. H. Williamson, *Org. Reactions*, **24**, 1 (1976); B. R. James, *Homogeneous Hydrogenation*, Wiley, New York, 1973; B. R. James, in *Comprehensive Organometallic Chemistry*, G. Wilkinson, F. G. A. Stone, and E. W. Abel, eds., Pergamon Press, Oxford, 1982, Vol. 8, Chap. 51; P. A. Chaloner, M. A. Esteruelas, F. Joo, L. A. Oro, *Homogeneous Hydrogenation*, Kluwer Academic, Dordrecht, 1994.

coordinating group. For example, α , β -unsaturated acids and esters, as well as allylic alcohols, are among the reactants that give good results. The reason for this is that the functional group can complex with the metal center, increasing the overall degree of structural organization. Scheme 2.9 provides some examples of enantioselective hydrogenations. Entries 1 and 2 involve acrylic acid derivatives with rhodium catalysts containing chiral phosphine ligands. Entry 3 involves an unsaturated diester. The reactants in Entries 4 and 5 are α -amido acrylic acids.

A number of chiral ligands have been explored in order to develop enantioselective hydrogenation catalysts.¹³³ Some of the most successful catalysts are derived from chiral 1, 1'-binaphthylidiphosphines such as BINAP.¹³⁴ These ligands are chiral by virtue of the sterically restricted rotation of the two naphthyl rings (see Section 2.1.5). Scheme 2.10 gives the structures and common names of some other important chiral diphosphine ligands.



α , β -Unsaturated acids can be reduced enantioselectively with ruthenium and rhodium catalysts having chiral phosphine ligands. The mechanism of such reactions using $\text{Ru}(\text{BINAP})(\text{O}_2\text{CCH}_3)_2$ is consistent with the idea that coordination of the carboxy group establishes the geometry at the metal ion.¹³⁵ The configuration of the product is established by the hydride transfer from ruthenium to the α -carbon that occurs on formation of the alkyl-metal intermediate. The second hydrogen is introduced by protonolysis.



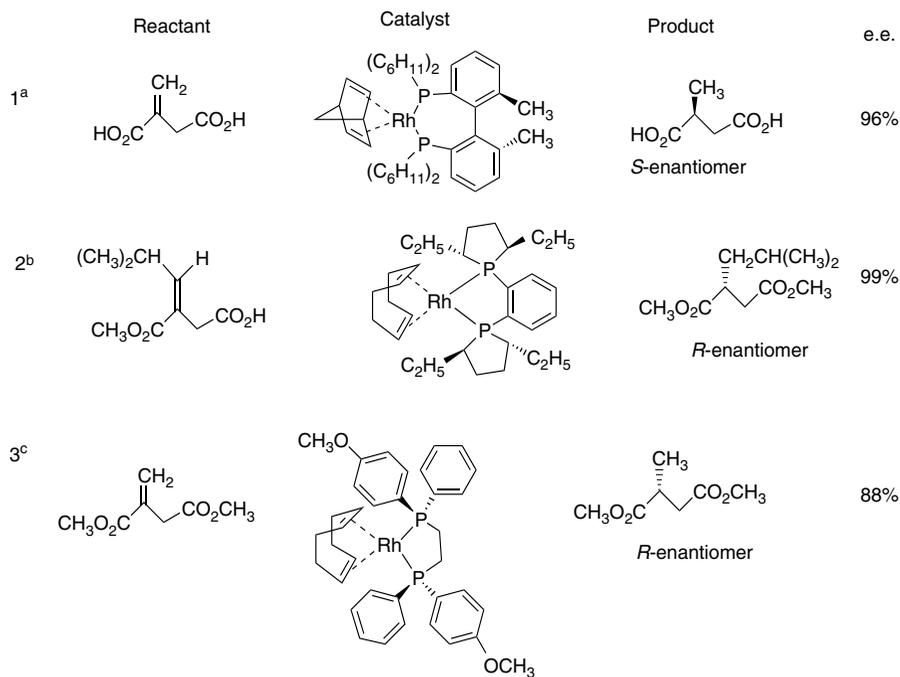
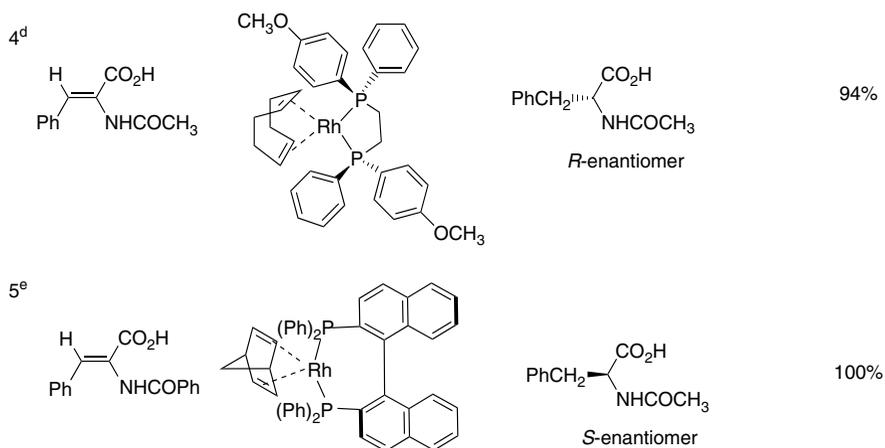
¹³³ B. Bosnich and M. D. Fryzuk, *Top.Stereochem.*, **12**, 119 (1981); W. S. Knowles, W. S. Chrisopfel, K. E. Koenig, and C. F. Hobbs, *Adv. Chem. Ser.*, **196**, 325 (1982); W. S. Knowles, *Acc. Chem. Res.*, **16**, 106 (1983).

¹³⁴ R. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990).

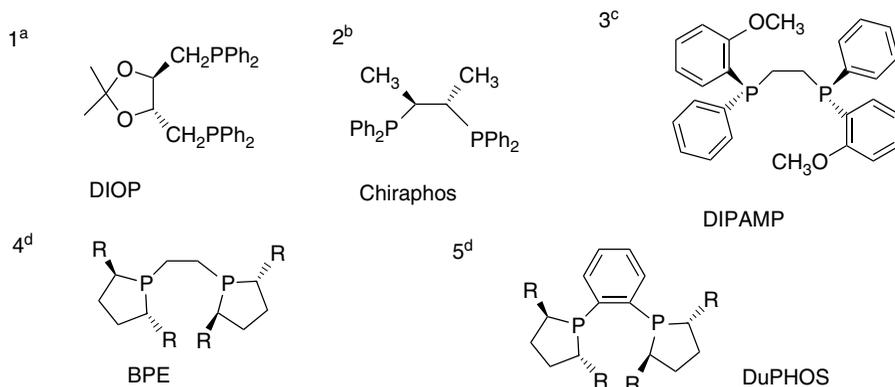
¹³⁵ M. T. Ashby and J. T. Halpern, *J. Am. Chem. Soc.*, **113**, 589 (1991).

A. Acrylic acid and esters.

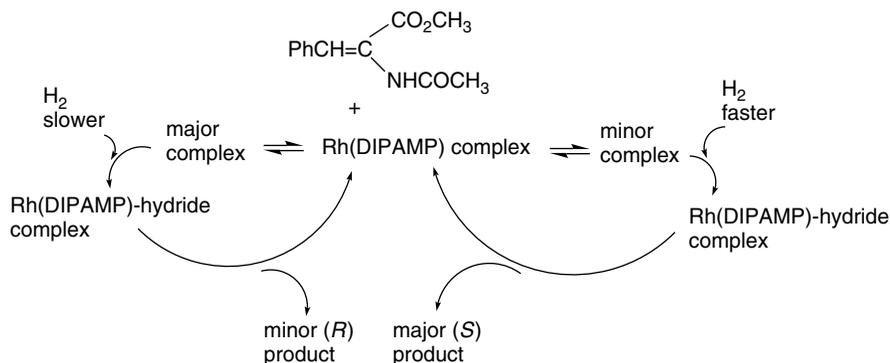
SECTION 2.5

Enantioselective
ReactionsB. α -Amidoacrylic acids.a. T. Chiba, A. Miyashita, H. Nohira, and H. Takaya, *Tetrahedron Lett.*, **32**, 4745 (1991).b. M. J. Burk, F. Bienewald, M. Harris, and A. Zanotti-Gerosa, *Angew. Chem. Int. Ed. Engl.*, **37**, 1931 (1998).c. W. C. Chrispfel and B. D. Vineyard, *J. Am. Chem. Soc.*, **101**, 4406 (1979).d. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **99**, 5946 (1977).e. A. Miyashita, H. Takaya, T. Souchi, and R. Noyori, *Tetrahedron*, **40**, 1245 (1984).

CHAPTER 2

Stereochemistry,
Conformation,
and Stereoselectivitya. H. B. Kagan and T.-P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972).b. M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **100**, 5491 (1978).c. W. S. Knowles, *Acc. Chem. Res.*, **16**, 106 (1983).d. M. J. Burk, J. E. Feaster, W. A. Nugent, and R. L. Harlow, *J. Am. Chem. Soc.*, **115**, 10125 (1993).

An especially important case is the enantioselective hydrogenation of α -amidoacrylic acids, which leads to α -aminoacids.¹³⁶ A particularly detailed study was carried out on the mechanism of reduction of methyl *Z*- α -acetamidocinnamate by a rhodium catalyst with the chiral diphosphine ligand DIPAMP.¹³⁷ It was concluded that the reactant can bind reversibly to the catalyst to give either of two complexes. Addition of hydrogen at rhodium then leads to a reactive rhodium hydride intermediate and eventually to product. Interestingly, the addition of hydrogen occurs most rapidly in the *minor isomeric complex* and the enantioselectivity is due to this kinetic preference. The major isomer evidently encounters greater steric repulsions if hydrogenation proceeds and is therefore less reactive.¹³⁸



¹³⁶ J. M. Brown, *Chem. Soc. Rev.*, **22**, 25 (1993). A. Pfaltz and J. M. Brown in *Stereoselective Synthesis*, G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schauman, eds., Thieme, New York, 1996, Part D, Sec. 2.5.1.2; U. Nagel and J. Albrecht, *Top. Catal.*, **5**, 3 (1998).

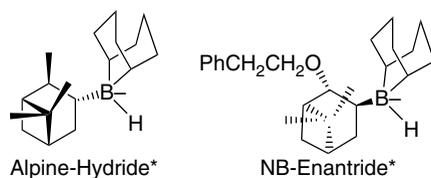
¹³⁷ C. R. Landis and J. Halpern, *J. Am. Chem. Soc.*, **109**, 1746 (1987).

¹³⁸ S. Feldgus and C. R. Landis, *J. Am. Chem. Soc.*, **122**, 12714 (2000).

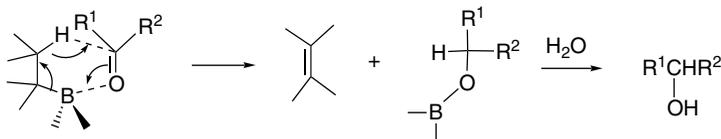
These examples illustrate the factors that are usually involved in successful enantioselective hydrogenation. The first requirement is that the metal center have the necessary reactivity toward both molecular hydrogen and the reactant alkene. The metal center must retain this reactivity in the presence of the chiral ligands. Furthermore, because most of the ligands are bidentate, there must be sufficient coordination sites to accommodate the ligand, as well as hydrogen and the reactant. In particular, there must be at least one remaining coordination site for the functional group. As we can see from the detailed mechanisms of the α -amido acrylates, the Rh center proceeds through a hexacoordinate dihydride intermediate to a pentacoordinate σ -alkyl intermediate. The reductive elimination frees two coordination sites (including the dissociation of the product). This coordinatively unsaturated complex can then proceed through the catalytic cycle by addition of reactant and hydrogen.

2.5.2. Enantioselective Reduction of Ketones

Hydride reducing agents convert ketones to secondary alcohols. Unsymmetrical ketones lead to chiral secondary alcohols. The common hydride reducing agents NaBH_4 and LiAlH_4 are achiral and can only produce racemic alcohol. Let us look at some cases where the reaction can be enantioselective. A number of alkylborohydride derivatives with chiral substituents have been prepared. These reagents are generally derived from naturally occurring terpenes.¹³⁹ Two examples of the alkylborohydride group have the trade names Alpine-Hydride[®] and NB-Enantride[®].¹⁴⁰ NB-Enantride achieves 76% e.e. in the reduction of 2-butanone.¹⁴¹



Trialkylboranes and dialkylchloroboranes are also useful for reduction of aldehydes and ketones.¹⁴² These reactions involve the coordination of the carbonyl oxygen to boron and transfer of a β -hydrogen through a cyclic TS.



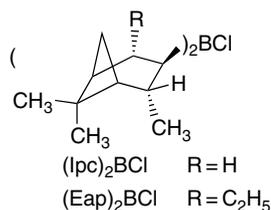
¹³⁹. M. M. Midland, *Chem. Rev.*, **89**, 1553 (1989).

¹⁴⁰. Alpine-Hydride and NB-Enantride are trade names of the Sigma Aldrich Corporation.

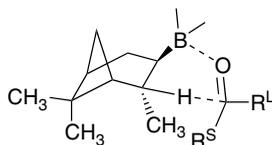
¹⁴¹. M. M. Midland, A. Kazubski, and R. E. Woodling, *J. Org. Chem.*, **56**, 1068 (1991).

¹⁴². M. M. Midland and S. A. Zderic, *J. Am. Chem. Soc.*, **104**, 525 (1982).

When the borane is chiral, these reactions can be enantioselective. The most highly developed of the chiral boranes are derived from α -pinene. The dialkylborane is known as diisopinocampheylborane, Ipc_2BH . Both enantiomers are available.¹⁴³ The corresponding *B*-alkyl and chloroborane derivatives act as enantioselective reductants toward ketones. For example the BBN derivative of isopinocampheylborane is enantioselective in the reduction of acetophenone.¹⁴⁴ The degree of enantioselectivity of alkylchloroboranes depends on the alkyl substituent, increasing from methyl (14% e.e. *S*), ethyl (33% e.e. *S*) through isopropyl (81% e.e. *S*), but then completely reversing with the *t*-butyl derivative (96% e.e. *R*).¹⁴⁵ Di-(isopinocampheyl)chloroborane,¹⁴⁶ $(\text{Ipc})_2\text{BCl}$, and *t*-butylisopinocampheylchloroborane¹⁴⁷ achieve high enantioselectivity for aryl and hindered dialkyl ketones. Diiso-2-ethylapopinocampheylchloroborane, $(\text{Eap})_2\text{BCl}$, shows good enantioselectivity toward an even wider range of ketones.¹⁴⁸



In most cases, the enantioselectivity can be predicted by a model that places the smaller carbonyl substituent toward the isopinocampheyl methyl group.¹⁴⁹



The origin of the enantioselectivity has been examined using semiempirical (AM1) computations.^{145c} The main differences in stability arise at the stage of formation of the borane-ketone complex, where the boron changes from sp^2 to sp^3 hybridization. The boron substituents introduce additional steric compressions. Table 2.6 gives some typical results for enantioselective reduction of ketones.

An even more efficient approach to enantioselective reduction of ketones is to use a chiral catalyst. One of the most successful is the oxazaborolidine **D**, which is

¹⁴³ H. C. Brown, P. K. Jadhav, and A. K. Mandal, *Tetrahedron*, **37**, 3547 (1981); H. C. Brown and P. K. Jadhav, in *Asymmetric Synthesis*, J. D. Morrison, ed., Academic Press, New York, 1983, Chap. 1.

¹⁴⁴ M. M. Midland, S. Greer, A. Tramontano, and S. A. Zderic, *J. Am. Chem. Soc.*, **101**, 2352 (1979).

¹⁴⁵ (a) M. M. Rogic, *J. Org. Chem.*, **61**, 1341 (1996); (b) M. M. Rogic, P. V. Ramachandran, H. Zinnen, L. D. Brown, and M. Zheng, *Tetrahedron: Asymmetry*, **8**, 1287 (1997); (c) M. M. Rogic, *J. Org. Chem.*, **65**, 6868 (2000).

¹⁴⁶ H. C. Brown, J. Chandrasekharan, and P. V. Ramachandran, *J. Am. Chem. Soc.*, **110**, 1539 (1988); M. Zhao, A. O. King, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *Tetrahedron Lett.*, **38**, 2641 (1997).

¹⁴⁷ H. C. Brown, M. Srebnik, and P. V. Ramachandran, *J. Org. Chem.*, **54**, 1577 (1989).

¹⁴⁸ H. C. Brown, P. V. Ramachandran, A. V. Teodorovic, and S. Swaminathan, *Tetrahedron Lett.*, **32**, 6691 (1991).

¹⁴⁹ M. M. Midland and J. L. McLoughlin, *J. Org. Chem.*, **49**, 1316 (1984).

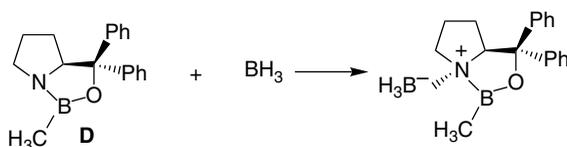
Table 2.6. Enantioselective Reduction of Ketones

Reagent	Ketone	% e.e.	Configuration
Alpine-Borane [ⓐ]	3-Methyl-2-butanone	62	S
NB-Enantride [ⓑ]	2-Octanone	79	S
Eapine-Hydride [ⓒ]	2-Octanone	78	S
(Ipc) ₂ BCl [ⓓ]	2-Acetylnaphthalene	94	S
(Ipc)(<i>t</i> -Bu)BCl [ⓔ]	Acetophenone	96	R
(Ipc) ₂ BCl [ⓕ]	2,2-Dimethylcyclohexanone	91	S
(Eap) ₂ BCl [ⓖ]	3-Methyl-2-butanone	95	R

NOTE: © Trademark of Sigma Aldrich Corporation.

- H. C. Brown and G. G. Pai, *J. Org. Chem.*, **50**, 1384 (1985).
- M. M. Midland and A. Kazubski, *J. Org. Chem.*, **47**, 2495 (1982).
- P. Ramachandran, R. Veeraghavan, H. C. Brown, and S. Swaminathan, *Tetrahedron: Asymmetry*, **1**, 433 (1990).
- M. Zhao, A. O. King, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *Tetrahedron Lett.*, **38**, 2641 (1997).
- H. C. Brown, M. Srebnik, and P. V. Ramachandran, *J. Org. Chem.*, **54**, 1577 (1989).
- H. C. Brown, J. Chandrasekharan, and P. V. Ramachandran, *J. Am. Chem. Soc.*, **110**, 1539 (1988).
- H. C. Brown, P. V. Ramachandran, A. V. Teodorovic, and S. Swaminathan, *Tetrahedron Lett.*, **32**, 6691 (1991).

derived from the amino acid proline.¹⁵⁰ The enantiomer is also available. An adduct of borane and **D** is the active reductant. This adduct can be prepared, stored, and used as a stoichiometric reagent, if so desired.¹⁵¹



A catalytic amount (5–20 mol %) of this reagent, along with additional BH₃ as the reductant, can reduce ketones such as acetophenone and pinacolone in > 95% e.e. There are experimental data indicating that the steric demand of the boron substituent influences enantioselectivity.¹⁵² The enantioselectivity and reactivity of these catalysts can be modified by changes in substituent groups to optimize selectivity toward a particular ketone.¹⁵³

Computational studies have explored the mechanism and origin of the enantioselectivity of these reactions. Based on semiempirical MO calculations (MNDO), it has

- E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987); E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed. Engl.*, **37**, 1987 (1998).
- D. J. Mahre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 2880 (1993).
- E. J. Corey and R. K. Bakshi, *Tetrahedron Lett.*, **31**, 611 (1990); T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts, and E. J. J. Grabowski, *J. Org. Chem.*, **56**, 763 (1991).
- A. W. Douglas, D. M. Tschaen, R. A. Reamer, and Y.-J. Shi, *Tetrahedron: Asymmetry*, **7**, 1303 (1996).

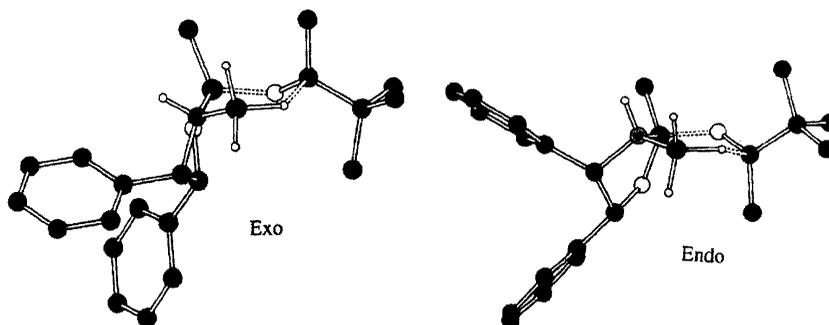
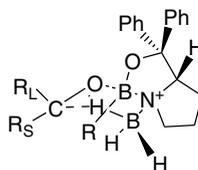
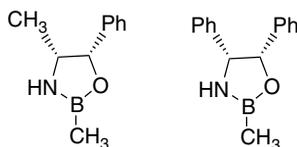


Fig. 2.20. Optimized (HF/3-21G) structures of the *exo* and *endo* transition states for reduction of *t*-butyl methyl ketone by a model catalyst. The *exo* structure is favored by 2.1 kcal, in accord with an experimental e.e of 88%. Reproduced from *J. Am. Chem. Soc.*, **116**, 8516 (1994), by permission of the American Chemical Society.

been suggested that the enantioselectivity in these reductions arises from a chair-like TS in which the governing steric interaction is the one with the alkyl substituent on boron.¹⁵⁴



There also have been ab initio studies of the transition structure using several model catalysts and calculations at the HF/3-21G, HF/6-31G(*d*), and MP2/6-31G(*d*) levels.¹⁵⁵ The enantioselectivity is attributed to the preference for an *exo* rather than an *endo* approach of the ketone, as shown in Figure 2.20.



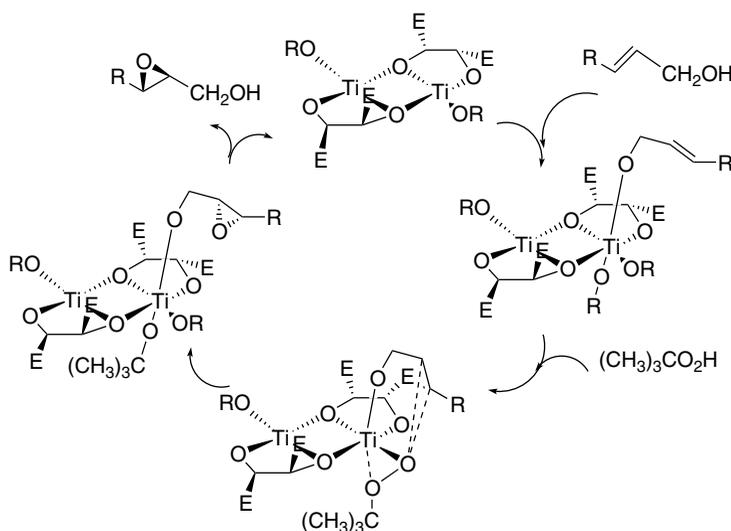
2.5.3. Enantioselective Epoxidation of Allylic Alcohols

Certain transition metal complexes catalyze oxidation of allylic alcohols to the corresponding epoxides. The most useful procedures involve *t*-butyl hydroperoxide as

¹⁵⁴ D. K. Jones, D. C. Liotta, I. Shinkai, and D. J. Mathre, *J. Org. Chem.*, **58**, 799 (1993); L. P. Linney, C. R. Self, and T. H. Williams, *J. Chem. Soc., Chem. Commun.* 1651 (1994).

¹⁵⁵ G. J. Quallich, J. F. Blake, and T. M. Woodall, *J. Am. Chem. Soc.*, **116**, 8516 (1994).

the stoichiometric oxidant in combination with titanium catalysts. When enantiomerically pure tartrate esters are included in the system, the reaction is highly enantioselective and is known as *Sharpless asymmetric epoxidation*.¹⁵⁶ Either the (+) or (–) tartrate ester can be used, so either enantiomer of the desired product can be obtained. The allylic hydroxyl group serves to coordinate the reactant to titanium. The mechanism involves exchange of the allylic alcohol and *t*-butyl hydroperoxide for another ligand at the titanium atom. In the TS an oxygen atom from the peroxide is transferred to the double bond.¹⁵⁷ The electrophilic metal polarizes the weak O–O bond of the hydroperoxide to effect the transfer of oxygen to the alkene π bond. Both kinetic data and consideration of the energetics of the monomeric and dimeric complexes suggest that the active catalyst is dimeric.¹⁵⁸



The orientation of the reactants is governed by the chirality of the tartrate ester.¹⁵⁹ The enantioselectivity can be predicted in terms of the model shown below.¹⁶⁰

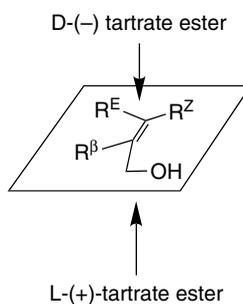
¹⁵⁶ R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, I. Ojima, ed., VCH Publishers, New York, 1993, pp. 103–158.

¹⁵⁷ M. G. Finn and K. B. Sharpless in *Asymmetric Synthesis*, Vol. 5, J. D. Morrison, ed., Academic Press, New York, 1985, Chap 8; B. H. McKee, T. H. Kalantar, and K. B. Sharpless, *J. Org. Chem.*, **56**, 6966 (1991); For an alternative description of the origin of enantioselectivity, see E. J. Corey, *J. Org. Chem.*, **55**, 1693 (1990).

¹⁵⁸ M. G. Finn and K. B. Sharpless, *J. Am. Chem. Soc.*, **113**, 113 (1991).

¹⁵⁹ V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981); K. B. Sharpless, S. S. Woodard, and M. G. Finn, *Pure Appl. Chem.*, **55**, 1823 (1983); M. G. Finn, and K. B. Sharpless, *J. Am. Chem. Soc.*, **113**, 113 (1996); B. H. McKee, T. H. Kalantar, and K. B. Sharpless, *J. Org. Chem.*, **56**, 6966 (1991).

¹⁶⁰ M. G. Finn and K. B. Sharpless in *Asymmetric Synthesis*, J. D. Morrison, ed., Vol 5, Academic Press, New York, 1985, Chap. 5.



There has been a DFT (BLYP/HW3) study of the TS and its relationship to the enantioselectivity of the reaction.¹⁶¹ The strategy used was to build up the model by successively adding components. First the titanium coordination sphere, including the allylic alcohol and peroxide group, was modeled (Figure 2.21a). The diol ligand and allylic alcohol were added to the coordination sphere (Figure 2.21b). Then the steric bulk associated with the hydroperoxide was added (Figure 2.21c). Finally the tartrate esters were added (using formyl groups as surrogates; Figure 2.21d). This led successively to TS models of increasingly detailed structure. The energies of the added components were minimized to identify the most stable structure at each step. The key features of the final TS model are the following: (1) The peroxide-titanium interaction has a spiro rather than planar arrangement in the TS for oxygen transfer. (2) The breaking O–O bond is nearly perpendicular to the plane of the C=C bond to meet the stereoelectronic requirement for electrophilic attack. (3) The orientation of the alkyl group of the peroxide plays a key role in the enantioselectivity, which is consistent with the experimental observation that less bulky hydroperoxides give much lower enantioselectivity. (4) This steric effect leads to an arrangement in which the C–O bond of the allylic alcohol bisects the O–Ti–O bonds in the favored TS. (5) The tartrate ester groups at the catalytically active titanium center are in equatorial positions and do not coordinate to titanium, which implies a conformation flip of the diolate ring as part of the activation process, since the ester groups are in axial positions in the dimeric catalyst. (6) This conformation of the tartrate ligands places one of the ester groups in a position that blocks one mode of approach and determines the enantioselectivity.

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

As with enantioselective hydrogenation, we see that several factors are involved in the high efficacy of the $Ti(OiPr)_4$ -tartrate epoxidation catalysts. The metal ion has two essential functions. One is the assembly of the reactants, the allylic alcohol, and the hydroperoxide. The second is its Lewis acid character, which assists in the rupture of the O–O bond in the coordinated peroxide. In addition to providing the reactive oxidant, the *t*-butyl hydroperoxide contributes to enantioselectivity through its steric bulk. Finally, the tartrate ligands establish a chiral environment that leads to a preference for one of the diastereomeric TSs and results in enantioselectivity.

¹⁶¹ Y.-D. Wu and D. K. W. Lai, *J. Am. Chem. Soc.*, **117**, 11327 (1995).

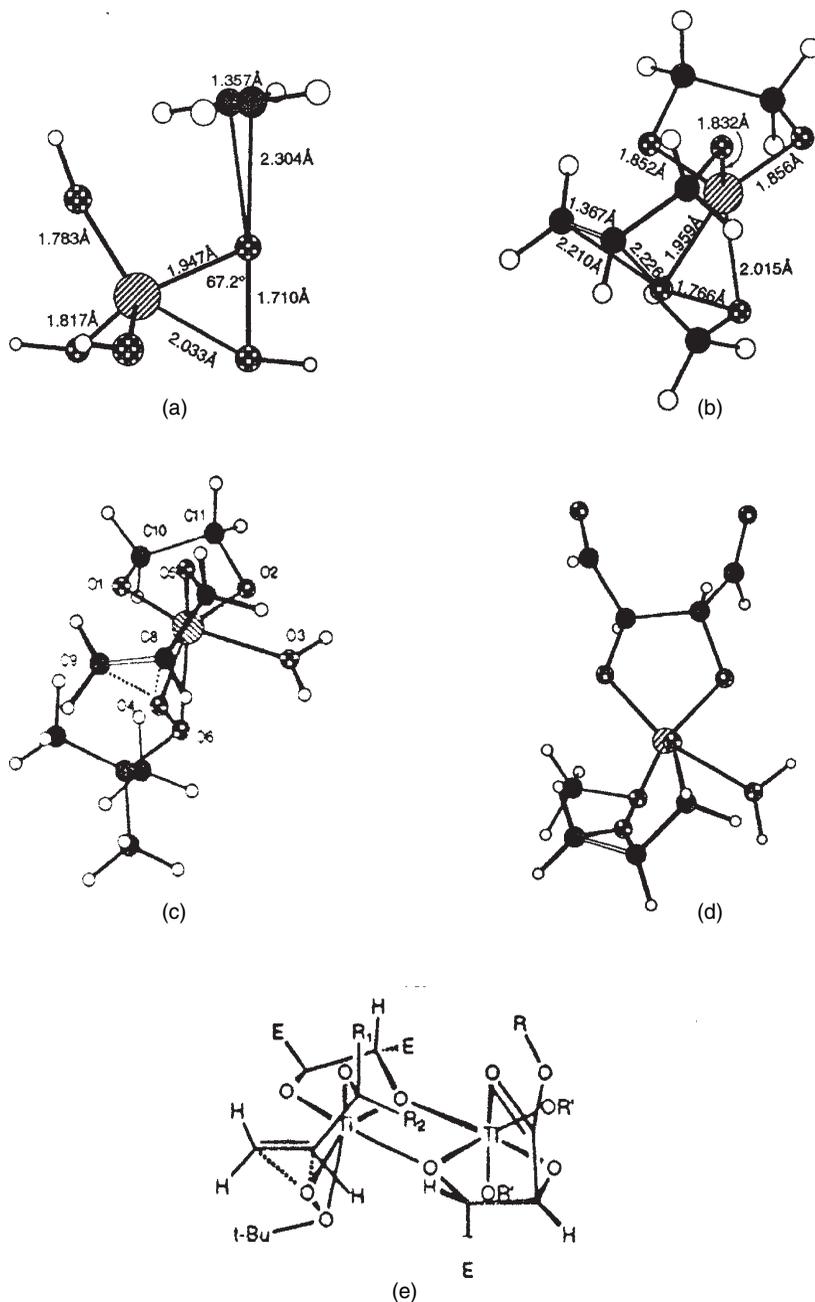
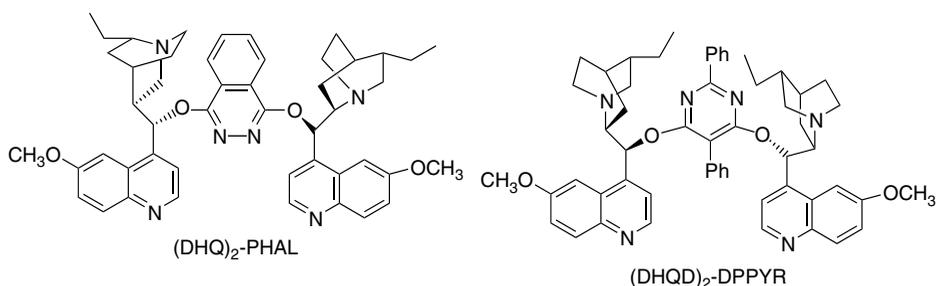


Fig. 2.21. Successive models of the transition structures for Sharpless epoxidation: (a) the hexacoordinate Ti core with hydroxide and hydroperoxide ligand and a coordinated alkene; (b) Ti with methylhydroperoxide, allyl alcohol, and ethanediol as ligands; (c) monomeric catalytic center incorporating *t*-butylhydroperoxide as oxidant; (d) monomeric catalytic center with formyl groups added; (e) representation of the active dimeric catalyst. Reproduced from *J. Am. Chem. Soc.*, **117**, 11327 (1995), by permission of the American Chemical Society.

2.5.4. Enantioselective Dihydroxylation of Alkenes

Osmium tetroxide is a stereospecific oxidant that produces diols from alkenes by a *syn*-addition.¹⁶² Currently, the reaction is carried out using a catalytic amount of OsO₄, with a stoichiometric oxidant such as *t*-butyl hydroperoxide,¹⁶³ potassium ferricyanide,¹⁶⁴ or morpholine-*N*-oxide.¹⁶⁵ Osmium tetroxide oxidations can be highly enantioselective in the presence of chiral ligands. The most highly developed ligands are derived from the cinchona alkaloids dihydroquinine (DHQ) and dihydroquinidine (DHQD).¹⁶⁶ The most effective ligands are dimeric derivatives of these alkaloids such as (DHQ)₂-PHAL and (DHQD)₂-DDPYR,¹⁶⁷ in which the alkaloid units are linked by heterocyclic ethers. These ligands not only induce high enantioselectivity, but they also *accelerate the reaction*.¹⁶⁸ Optimization of the reaction conditions permits rapid and predictable dihydroxylation of many types of alkenes.¹⁶⁹ The premixed catalysts are available commercially and are referred to by the trade names AD-mix™.



From extensive studies, a consensus has been reached about some aspects of the catalytic mechanism and enantioselectivity: (1) The amine ligands, in particular the quinuclidine nitrogen, are important in activating and stabilizing the osmium intermediate.¹⁷⁰ (2) From the kinetics of the reaction, it is also evident that the *binding of the*

¹⁶² M. Schroeder, *Chem. Rev.*, **80**, 187 (1980).

¹⁶³ K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98**, 1986 (1976); K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, **43**, 2063 (1978).

¹⁶⁴ M. Minato, K. Yamamoto and J. Tsuji, *J. Org. Chem.*, **55**, 766 (1990); K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, **57**, 2768 (1992); J. Eames, H. J. Mitchell, A. Nelson, P. O'Brien, S. Warren, and P. Wyatt, *Tetrahedron Lett.*, **36**, 1719 (1995).

¹⁶⁵ V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1973 (1976).

¹⁶⁶ H. C. Kolb, M. S. Van Nieuwenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994).

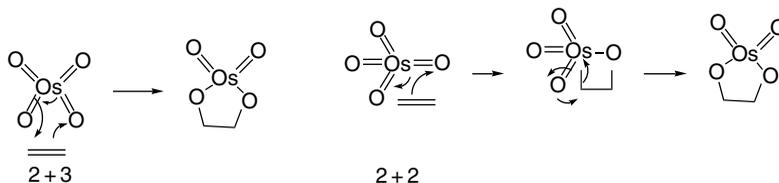
¹⁶⁷ G. A. Crispino, K.-S. Jeong, H. C. Kolb, Z.-M. Wang, D. Xu, and K. B. Sharpless, *J. Org. Chem.*, **58**, 3785 (1993); G. A. Crispino, A. Makita, Z.-M. Wang, and K. B. Sharpless, *Tetrahedron Lett.*, **35**, 543 (1994); K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H.-C. Kwong, K. Morikawa, Z. M. Wang, D. Xu, and X. L. Zhang, *J. Org. Chem.*, **57**, 2768 (1992); W. Amberg, Y. L. Bennani, R. K. Chadha, G. A. Crispino, W. D. Davis, J. Hartung, K. S. Jeong, Y. Ogino, T. Shibata, and K. B. Sharpless, *J. Org. Chem.*, **58**, 844 (1993); H. Becker, S. B. King, M. Taniguchi, K. P. M. Vanhessche, and K. B. Sharpless, *J. Org. Chem.*, **60**, 3940 (1995).

¹⁶⁸ P. G. Anderson and K. B. Sharpless, *J. Am. Chem. Soc.*, **115**, 7047 (1993).

¹⁶⁹ H.-L. Kwong, C. Sorato, Y. Ogino, H. Chen, and K. B. Sharpless, *Tetrahedron Lett.*, **31**, 2999 (1990); T. Gobel and K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.*, **32**, 1329 (1993).

¹⁷⁰ D. W. Nelson, A. Gypser, P. T. Ho, H. C. Kolb, T. Kondo, H.-L. Kwong, D. V. McGrath, A. E. Rubin, P.-O. Norrby, K. P. Gable, and K. B. Sharpless, *J. Am. Chem. Soc.*, **119**, 1840 (1997).

reactant is a distinct step in the mechanism and that there are *attractive interactions* between the catalyst ligands and the reactant.¹⁷¹ The ligands do not function only by steric exclusion, but contribute to the net stabilization of the TS. (3) The aromatic linker groups determine the size of the binding pocket; the ethyl groups on the quinuclidine ring have differing orientations in the DHQD and DHQD catalysts and are a more integral part of the pocket in the DHQD system. (4) The concerted [2+3]cycloaddition mechanism for the actual oxidation step is energetically preferable to an alternative two-step mechanism involving [2+2]cycloaddition.¹⁷²



Within these general terms, the interpretation and prediction of enantioselectivity depends on the binding of the particular reactant in the catalyst pocket. A wide range

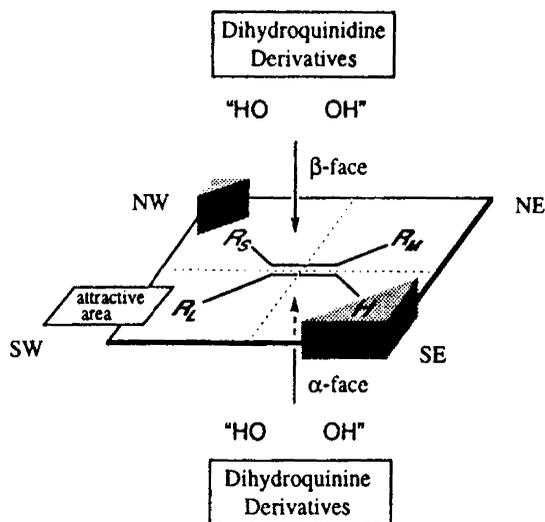


Fig. 2.22. Predictive schematic model for enantioselectivity of AD-mix dihydroxylation catalysts. Reproduced from *Chem. Rev.*, **94**, 2483 (1994), by permission of the American Chemical Society.

- ¹⁷¹. H. C. Kolb, M. S. Van Nieuwenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994); E. J. Corey and M. C. Noe, *J. Am. Chem. Soc.*, **118**, 319 (1996); E. J. Corey and M. C. Noe, *J. Am. Chem. Soc.*, **118**, 11038 (1996); P.-O. Norrby, H. Becker, and K. B. Sharpless, *J. Am. Chem. Soc.*, **118**, 35 (1996). H. C. Kolb, P. G. Andersson, and K. B. Sharpless, *J. Am. Chem. Soc.*, **116**, 1278 (1994); B. B. Lohray and V. Bhushan, *Tetrahedron Lett.*, **33**, 5113 (1992).
- ¹⁷². S. Dapprich, G. Ujaque, F. Maseras, A. Lledos, D. G. Musaev, and K. Morokuma, *J. Am. Chem. Soc.*, **118**, 11660 (1996); U. Pidun, C. Boehme, and G. Frenking, *Angew. Chem. Int. Ed. Engl.*, **35**, 2817 (1996); M. Torrent, L. Deng, M. Duran, M. Sola, and T. Ziegler, *Organometallics*, **16**, 13 (1997).

of reactants have been examined, and an empirical model for predicting orientation has been developed from the data.¹⁷³ This model is shown in Figure 2.22. Note that the DHQD and DHQ ligands have opposite enantioselectivity because they are of opposite absolute configuration.

There have been a several efforts aimed at theoretical modeling and analysis of the enantioselectivity of osmium-catalyzed dihydroxylation. The system is too large to be amenable to ab initio approaches, but combinations of quantum chemical (either MO or DFT) and molecular mechanics make the systems tractable. A hybrid investigation based on DFT (B3LYP/6-31G) computation and MM3 was applied to the (DHQD)₂PYDZ catalyst (PYDZ = 3, 5-pyridazinyl).¹⁷⁴ This study examined a number of possible orientations of styrene within the complex and computed their relative energy. The energies were obtained by combining DFT calculations on the reaction core of OsO₄ and the double bond, with MM3 calculations on the remainder of the molecule. Two orientations were found to be very close in energy and these were 2.5–10 kcal/mol more favorable than all the others examined. Both led to the observed enantioselectivity. The two preferred TS structures are shown in Figure 2.23.

Most of the differences in energy among the various orientations are due to differences in the MM portion of the calculation, pointing to nonbonded interactions as the primary determinant of the binding mode. Specifically, attractive interaction with quinoline ring A ($\pi - \pi$ stacking, 6.1 kcal/mol), quinoline ring B (2.3 kcal/mol), and a perpendicular binding interaction with the pyridazine ring (1.3 kcal/mol) offset the energy required to fit the reactant molecule to the catalytic site. This is consistent with the view that there is an *attractive interaction with the ligand system*.

Norrby, Houk, and co-workers approached the problem by deriving a molecular mechanics type of force field from quantum chemical calculations.¹⁷⁵ This model, too, suggests that there are two possible bonding arrangements and that either might be preferred, depending on the reactant structure. This model was able

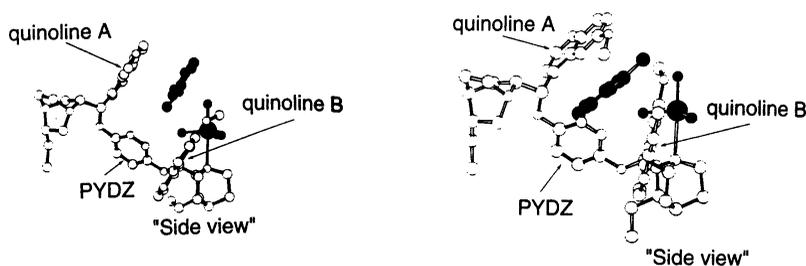


Fig. 2.23. Two most favored orientations of styrene for enantioselective dihydroxylation by (DHQD)₂PYDZ catalyst. The bridging structure is 3,5-pyridazinyl. Reproduced from *J. Am. Chem. Soc.*, **121**, 1317 (1999), by permission of the American Chemical Society.

¹⁷³ H. C. Kolb, P. G. Andersson, and K. B. Sharpless, *J. Am. Chem. Soc.*, **116**, 1278 (1994).

¹⁷⁴ G. Ujaque, F. Maseras, and A. Lledos, *J. Am. Chem. Soc.*, **121**, 1317 (1999).

¹⁷⁵ P.-O. Norrby, T. Rasmussen, J. Haller, T. Strassner, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 10186 (1999).

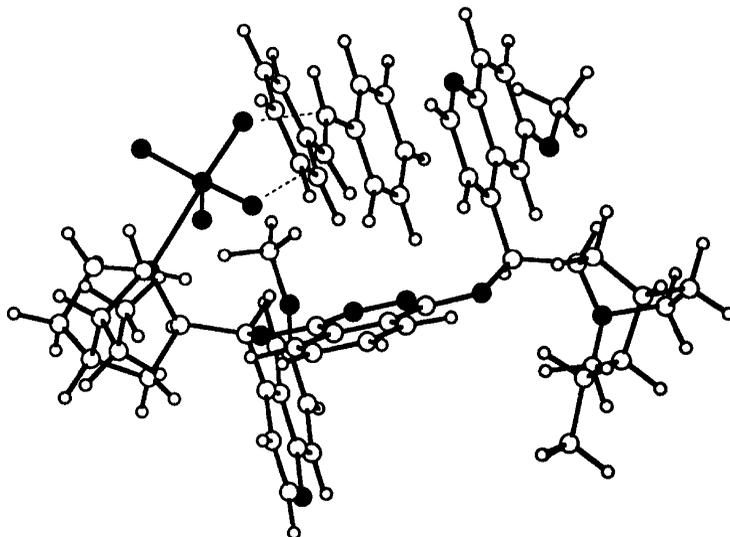


Fig. 2.24. Preferred orientation of stilbene with the (DHQD)₂PHAL catalyst. Reproduced from *J. Am. Chem. Soc.*, **121**, 10186 (1999), by permission of the American Chemical Society.

to predict the observed enantioselectivity for several styrene derivatives with the PHAL linker. Figure 2.24 shows the optimum TS for the reaction with stilbene. A noteworthy feature of this model is that it uses *both* the binding modes identified for styrene.

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

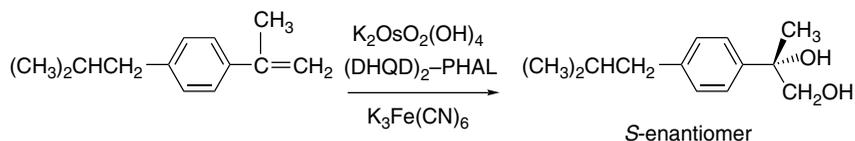
The cases we have considered involve aryl rings as the governing structural feature for enantioselectivity. The AD systems also show excellent enantioselectivity toward functionalized alkenes, especially allylic and homoallylic systems with oxygen substituents.¹⁷⁶ In these systems, another important structural variable comes into play, that is, the conformation of the allylic substituent and its possible interaction with the reaction site.¹⁷⁷

The asymmetric dihydroxylation has been applied in many synthetic sequences and is discussed further in Part B, Chapter 12. For example the dihydroxylation was the starting point for enantioselective synthesis of *S*-ibuprofen and a similar route was used to prepare *S*-naproxen, which contains a methoxynaphthalene ring.¹⁷⁸ Ibuprofen and naproxen are examples of the NSAID class of analgesic and anti-inflammatory agents.

¹⁷⁶ J. K. Cha and N. S. Kim, *Chem. Rev.*, **95**, 1761 (1995); For additional recent example see: A. Bayer and J. S. Svendsen, *Eur. J. Org. Chem.*, 1769 (2001); L. F. Tietze and J. Grolitzer, *Synthesis*, 877 (1997).

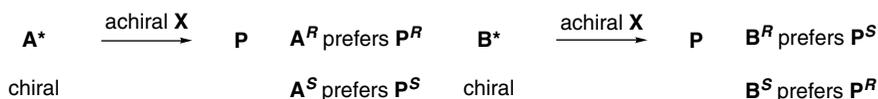
¹⁷⁷ E. Vedejs, W. H. Dent, III, D. M. Gapinski, and C. K. McClure, *J. Am. Chem. Soc.*, **109**, 5437 (1987).

¹⁷⁸ H. Ishibashi, M. Maeki, J. Yagi, M. Ohba, and T. Kanai, *Tetrahedron*, **55**, 6075 (1999).

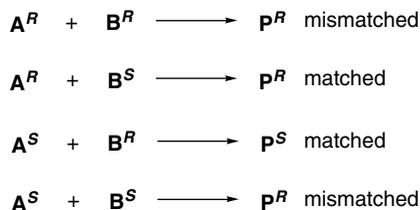


2.6. Double Stereodifferentiation: Reinforcing and Competing Stereoselectivity

Up to this point, we have considered cases in which there is a single major influence on the stereo- or enantioselectivity of a reaction. We saw examples of reactant control of facial selectivity, such as 1,2- and 1,3-asymmetric induction in carbonyl addition reactions. In the preceding section, we considered several examples in which the chirality of the catalyst controls the stereochemistry of achiral reagents. Now let us consider cases where there may be two or more independent influences on stereoselectivity, known as *double stereodifferentiation*.¹⁷⁹ For example, if a reaction were to occur between two carbonyl compounds, each having an α -stereocenter, one carbonyl compound would have an inherent preference for *R* or *S* product. The other would have also have an inherent preference. These preferences would be expressed even toward achiral reagents.



If \mathbf{A}^* and \mathbf{B}^* were then to react with one another to create a product with a new chiral center, there would be a two (enantiomeric) matched pairs and two (enantiomeric) mismatched pairs.



In the matched cases the preference of one compound is reinforced by the other. In the mismatched case, they are competing. The concept of matched and mismatched TSs

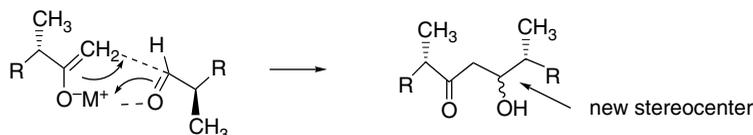
¹⁷⁹ C. H. Heathcock and C. T. White, *J. Am. Chem. Soc.*, **101**, 7076 (1979); S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem. Int. Ed. Engl.*, **24**, 1 (1985).

can be expressed in terms of the free-energy differences resulting from the individual preferences $\Delta\Delta G^*_1$ and $\Delta\Delta G^*_2$ plus any incremental change resulting from the combination ΔG^*_{12} .

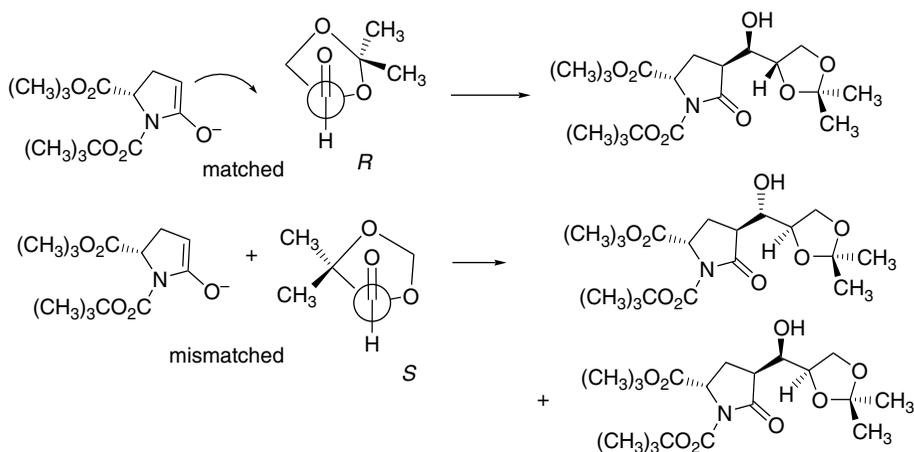
$$\Delta G^*_{\text{matched}} = \Delta\Delta G^*_1 + \Delta\Delta G^*_2 + \Delta G^*_{12}$$

$$\Delta G^*_{\text{mismatched}} = \Delta\Delta G^*_1 - \Delta\Delta G^*_2 + \Delta G^*_{12}$$

An example of such a situation is an aldol addition reaction in which one carbonyl compound acts as the nucleophile and the other as the electrophile.

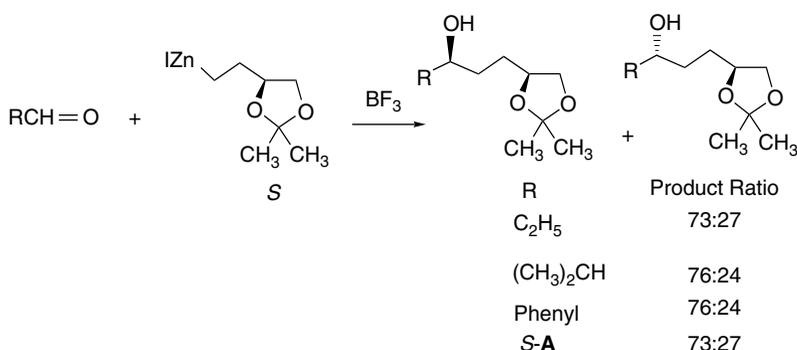


In fact, this case has been extensively studied and we consider it in more detail in Part B, Chapter 2. An example is the condensation of the enolate of a derivative of pyroglutamic acid and a protected form of glyceraldehyde. In the case of the (*R*)-aldehyde a single enantiomer is formed, whereas with the (*S*)-aldehyde a 1:1 mixture of two diastereomers is formed, along with a small amount of a third diastereomer.¹⁸⁰ The facial preference of the enolate is determined by the steric effect of the *t*-butoxycarbonyl group, whereas in the aldehyde the Felkin-Ahn TS prefers an approach *anti* to the α -oxygen.

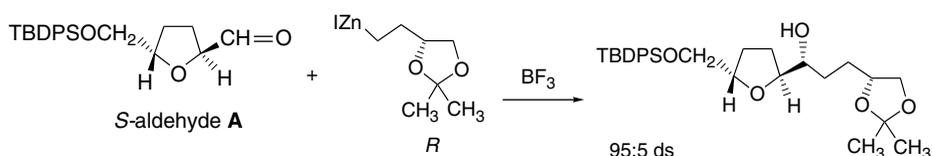


Another example involves addition of an organozinc reagent to a tetrahydrofuran aldehyde. With achiral aldehydes, only a small preference for formation of one enantiomer is seen.

¹⁸⁰ P. B. Hitchcock, B. A. Starkmann, and D. W. Young, *Tetrahedron Lett.*, **42**, 2381 (2001).

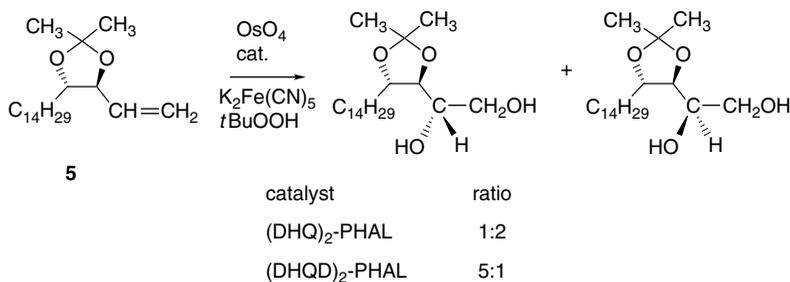


When a chiral aldehyde is used, the matched combination gives a 95:5 stereoselectivity.¹⁸¹



In this case, it is the stereocenter in the aldehyde that has the dominant influence on the diastereoselectivity.

In the analysis of multiple stereochemical influences, it is useful to classify the stereoselectivity as *substrate (reactant) controlled* or *reagent controlled*. For example, in the dihydroxylation of the chiral alkene **5**, the product is determined primarily by the choice of hydroxylation catalyst, although there is some improvement in the diastereoselectivity with one pair.¹⁸² This is a case of *reagent-controlled* stereoselection.

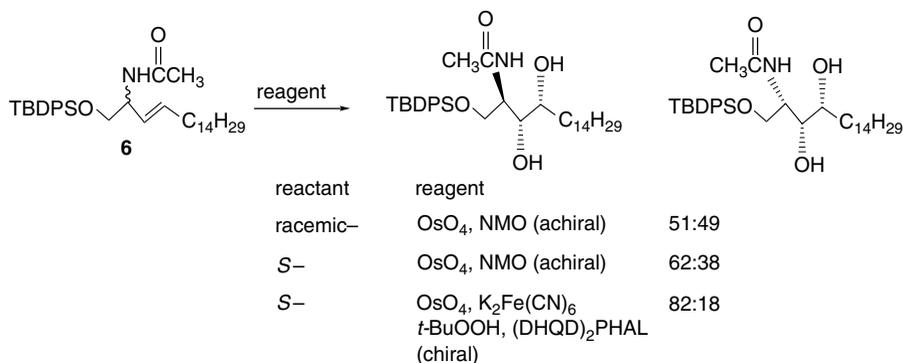


Similarly with the internal alkene **6**, the use of racemic reactant and achiral catalyst gives racemic product. Use of enantiopure *reactant* causes a modest degree of diastereoselectivity to arise from the stereocenter in the reactant. However, when a chiral catalyst is used this is reinforced by the *reagent-control*.¹⁸³

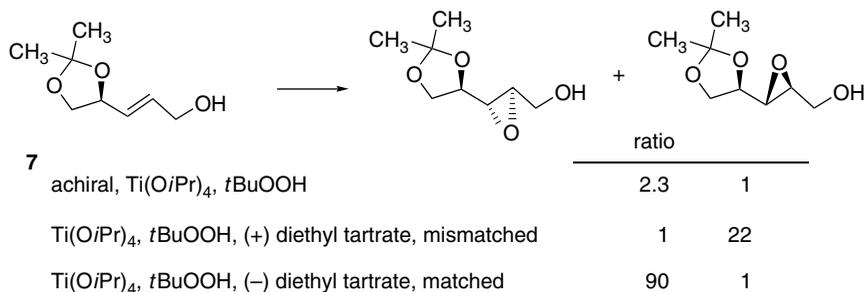
¹⁸¹ U. Koert, H. Wagner, and U. Pindun, *Chem. Ber.*, **127**, 1447 (1994).

¹⁸² R. A. Fernandes and P. Kumar, *Tetrahedron Lett.*, **41**, 10309 (2001).

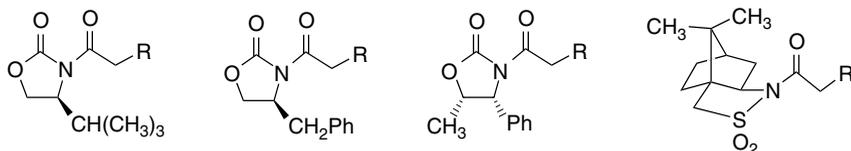
¹⁸³ C. Martin, W. Prunck, M. Bortolussi, and R. Bloch, *Tetrahedron: Asymmetry*, **11**, 1585 (2000).



Another example of reagent control can be found in the Sharpless epoxidation of **7**. With achiral reagents in the absence of a tartrate ligand, there is weak stereoselection. The tartrate-based catalysts control the enantioselectivity, although there is a noticeable difference between the matched and mismatched pairs.



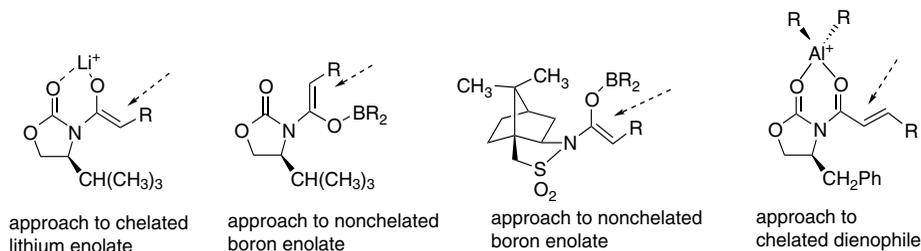
An important strategy for achieving *substrate control* is the use of *chiral auxiliaries*, which are structures incorporated into reactants for the purpose of influencing the stereochemistry. Two of the most widely used systems are oxazolidinones¹⁸⁴ derived from amino acids and sultams¹⁸⁵ derived from camphorsulfonic acid. These groups are most often used as carboxylic acid amides. They can control facial stereoselectivity in reactions such as enolate alkylation, aldol addition, and Diels-Alder cycloadditions, among others. The substituents on the chiral auxiliary determine the preferred direction of approach.



¹⁸⁴. D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, **96**, 835 (1996).

¹⁸⁵. W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990).

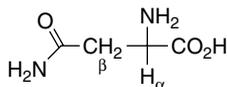
Depending upon the particular system, there may or may not be chelation between a metal cation or Lewis acid and the auxiliary. A change from a chelated to a nonchelated structure can lead to a change in the direction of approach. The configuration at the α -carbon can be controlled in this way. We will see many examples of the implementation of this strategy in subsequent chapters.



Topic 2.1. Analysis and Separation of Enantiomeric Mixtures

2.1.1. Chiral Shift Reagents and Chiral Solvating Agents

There are several techniques for determination of the enantiomeric purity of a chiral compound. As discussed in Section 2.1.3, the measured rotation can provide this information if the specific rotation $[\alpha]$ is known. However, polarimetry is not very sensitive, especially if $[\alpha]$ is relatively low. Several other methods for determining enantiomeric purity have been developed. One of the most frequently used in organic chemistry involves NMR spectroscopy with *chiral shift reagents*, which are complexes of a lanthanide metal and a chiral ligand. The reagents also have labile ligand positions that can accommodate the substance being analyzed. The lanthanides have strong affinity for oxygen and nitrogen functional groups that act as Lewis bases. The lanthanides also have the property of inducing large chemical shifts without excessive broadening of the lines.¹⁸⁶ Shift reagents can be used with both ^1H and ^{13}C NMR spectra. For small organic molecules the most frequently used shift reagents are $\text{Eu}[\text{tfc}]_3$ and $\text{Eu}[\text{nfc}]_3$ (see Scheme 2.11).¹⁸⁷ The scheme also shows some chiral shift reagents that have proven successful for analysis of amino acids and oligopeptides. Figure 2.25 shows a comparison of the NMR spectrum of asparagine with and without the chiral shift reagent.

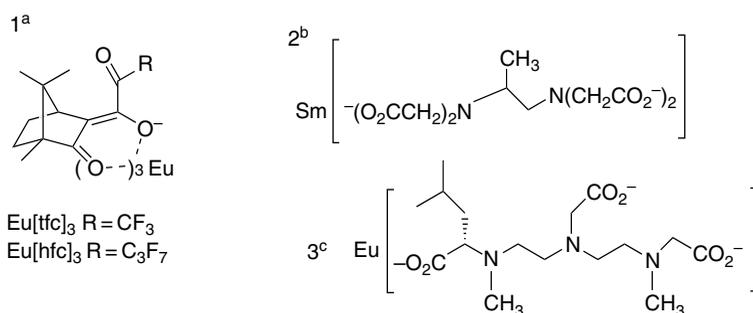


There are also several reagents that can be used to derivatize alcohols, amines, or carboxylic acids to give diastereomeric compounds. The diastereomers then give distinct NMR spectra that can be used to determine the enantiomeric ratio. Typically these compounds have at least an aryl substituent, which leads to strong shifts of signals owing to the anisotropic shielding of aromatic rings. Examples of such compounds are given in Scheme 2.12.

¹⁸⁶ D. Parker, *Chem. Rev.*, **91**, 1441 (1991); R. Rothchild, *Enantiomer*, **5**, 457 (2000).

¹⁸⁷ H. L. Goering, J. N. Eikenberry, G. S. Koerner, and C. J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).

Scheme 2.11. Chiral Shift Reagents



- a. H. L. Goering, J. Eikenberry, G. Koerner, and C. J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).
 b. A. Inamoto, K. Ogasawara, K. Omata, K. Kabuto, and Y. Sasaki, *Org. Lett.*, **2**, 3543 (2000).
 c. M. Watanabe, T. Hasegawa, H. Miyake, and Y. Kojima, *Chem. Lett.*, **4** (2001).

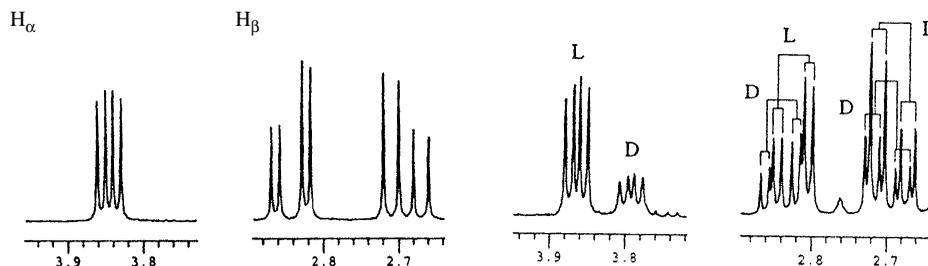
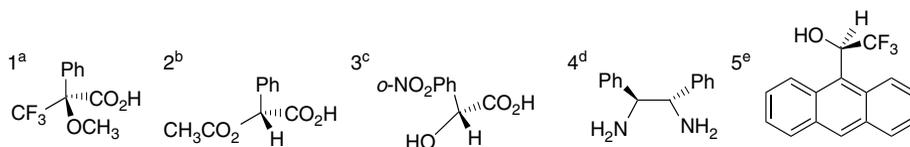


Fig. 2.25. NMR spectrum of 1:2 D:L asparagine mixture with NMR chiral shift reagent: (a) without shift reagent; (b) with shift reagent. Reproduced from *Org. Lett.*, **2**, 3543 (2000), by permission of the American Chemical Society.

Scheme 2.12. Chiral Derivatizing and Solvating Agents



- a. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
 b. D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 83 (1983).
 c. M. A. Haiza, A. Sanyal, and J. K. Snyder, *Chirality*, **9**, 556 (1997).
 d. R. Fulwood and D. Parker, *Tetrahedron: Asymmetry*, **3**, 25 (1992); R. Fulwood and D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 57 (1994).
 e. W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **91**, 5150 (1969); W. H. Pirkle and D. J. Hoover, *Top. Stereochem.*, **13**, 263 (1982).

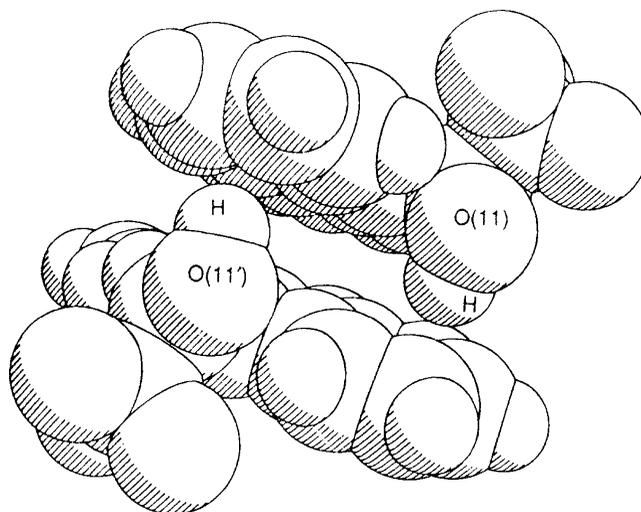


Fig. 2.26. Space-filling model of crystallographic structure of *S*-enantiomer 2,2,2-trifluoro-1-(9-anthryl)ethanol showing hydrogen bonding to the A-ring of anthracene. Reproduced from *J. Chem. Soc., Chem. Commun.*, 765 (1991), by permission of the Royal Society of Chemistry.

Chemical shifts sufficient for analysis can sometimes be achieved without the need for covalent bonding. If solvation is strong enough, the chiral additive induces sufficiently different chemical shifts in the two enantiomeric complexes to permit analysis. One such compound is called the *Pirkle alcohol* (Entry 5 in Scheme 2.12).¹⁸⁸ The structurally important features of this compound are the trifluoroethanol group, which provides a strong hydrogen bond acceptor, and the anthracene ring, which generates anisotropic shielding. In some cases, there may also be π - π stacking interactions. The structure of the compound has been determined in both the crystalline state and solution. Figure 2.26 shows an intermolecular hydrogen bond between the hydroxyl group and the anthracene ring for the *S*-enantiomer.¹⁸⁹

Various amines and amides that can serve as hydrogen bond donors are used as chiral solvating agents for carboxylic acids and alcohols. One example is 1,2-diphenylethane-1,2-diamine (Entry 4 in Scheme 2.12).¹⁹⁰ The alkaloid quinine also shows enantioselective solvation with certain alcohols.¹⁹¹ It is also possible to design molecules to act as chiral receptors, such as structure **8**, which incorporates a binding environment for the carboxylic acid group and gives good NMR resolution of chiral and prochiral carboxylic acids.¹⁹²

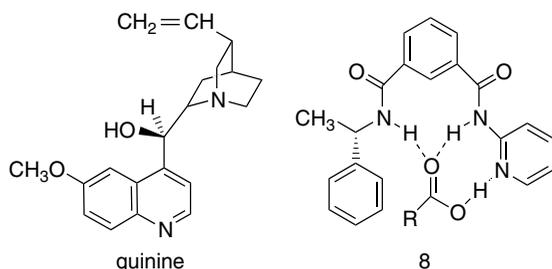
¹⁸⁸ W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **91**, 5150 (1969); W. H. Pirkle and D. J. Hoover, *Top. Stereochem.*, **13**, 263 (1982).

¹⁸⁹ H. S. Rzepa, M. L. Webb, A. M. Z. Slawin, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 765 (1991); M. L. Webb and H. S. Rzepa, *Chirality*, **6**, 245 (1994).

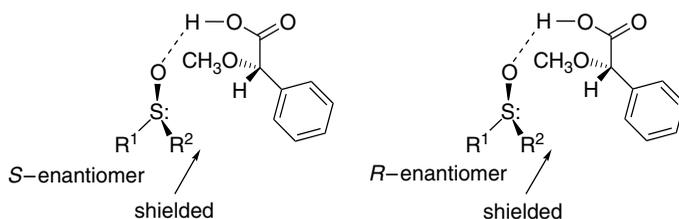
¹⁹⁰ R. Fulwood and D. Parker, *Tetrahedron: Asymmetry*, **3**, 25 (1992); R. Fulwood and D. Parker, *J. Chem. Soc., Perkin Trans.*, **2**, 57 (1994); S. E. Yoo and S. I. Kim, *Bull. Kor. Chem. Soc.*, **17**, 673 (1996).

¹⁹¹ C. Rosini, G. Uccello-Barretta, D. Pini, C. Abete, and P. Salvadori, *J. Org. Chem.*, **53**, 4579 (1988).

¹⁹² T. Stork and G. Helmchen, *Rec. Trav. Chim. Pays-Bas*, **114**, 253 (1995).



Sulfoxides form hydrogen-bonded complexes with α-methoxyphenylacetic acid, which results in differential shielding of the two substituents.¹⁹³



T.2.1.2 Separation of Enantiomers

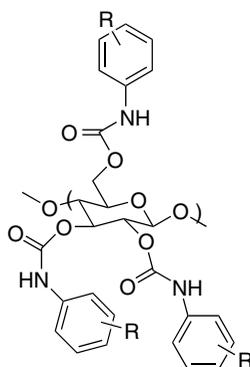
The classical method for separating enantiomers is to form diastereomeric compounds using a stoichiometric amount of a *resolving agent*. This method was described in Section 2.1.8. In this section, we discuss methods of resolution based on physical separations, including chromatography with chiral packing materials and capillary electrophoresis.

T.2.1.2.1. Separation by Chromatography. Chromatography is an important means of separating enantiomers on both an analytical and preparative scale. These separations are based on use of a *chiral stationary phase* (CSP). Chromatographic separations result from differential interactions of the enantiomers with the solid column packing material. The differential adsorption arises from the diastereomeric nature of the interaction between the enantiomers and the CSP. Hydrogen bonding and aromatic π - π interactions often contribute to the binding.

One important type of chiral packing material is derivatized polysaccharides, which provide a chiral lattice, but separation is improved by the addition of structural features that enhance selectivity. One group of compounds includes aroyl esters and carbamates, which are called Chiralcels (also spelled Chiracel)¹⁹⁴; two of the most important examples are the 4-methylbenzoyl ester, called Chiralcel OJ, and the 3,5-dimethylphenyl carbamate, called Chiralcel OD. There is a related series of materials derived from amylose rather than cellulose, which have the trade name Chiralpak.

¹⁹³. P. H. Buist, D. Marecak, H. L. Holland, and F. M. Brown, *Tetrahedron: Asymmetry*, **6**, 7 (1995).

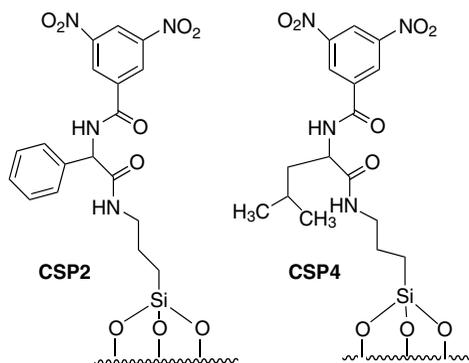
¹⁹⁴. Y. Okamoto and E. Yashima, *Angew. Chem.*, **37**, 1021 (1998).



repeating unit for *tris*-carbamoyl
derivatives of cellulose

Related materials can be prepared in which the polysaccharides are linked to a silica support by covalently bound tether groups. For example, silica derivatized by 3-aminopropyl groups can be linked to polysaccharides using diisocyanates.¹⁹⁵ These materials seem to adopt organized structural patterns on the surface, and this factor is believed to contribute to their resolving power. The precise structural basis of the chiral recognition and discrimination of derivatized polysaccharides has not been elucidated, but it appears that in addition to polar interactions, π - π stacking is important for aromatic compounds.¹⁹⁶

Other types of CSPs, known as *brush type*, have been constructed synthetically. A chiral structure, usually an amide, is linked to silica by a tether molecule. This approach has the potential for design of the chiral recognition elements. The ability to synthetically manipulate the structures also permits investigation of the role of specific structural elements in chiral selectivity. Several synthetic CSPs were developed by W. H. Pirkle and co-workers at the University of Illinois. An important example is the 3,5-dinitrobenzoyl (3,5-DNB) derivative of *R*-phenylglycine, which is attached to silica by aminopropyl tethers (**CSP 2**). The 3,5-DNB derivatives of several other amino acids (e.g., **CSP 4**) and diamines have also been explored.¹⁹⁷



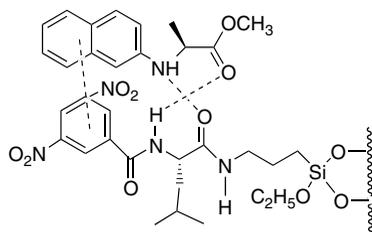
dinitrobenzoyl derivatives of amino acids
as chiral stationary phases

¹⁹⁵ E. Yashima, H. Fukaya, and Y. Okamoto, *J. Chromatogr. A*, **677**, 11 (1994).

¹⁹⁶ C. Yamamoto, E. Yashima, and Y. Okamoto, *Bull. Chem. Soc. Jpn.*, **72**, 1815 (1999).

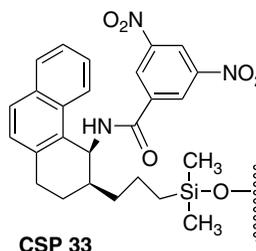
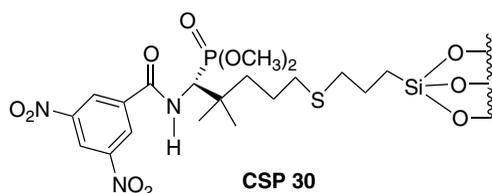
¹⁹⁷ C. J. Welch, *J. Chromatogr. A*, **666**, 3 (1994); C. J. Welch, *Adv. Chromatogr.*, **35**, 171 (1995).

These materials generally show good resolving power toward compounds that have aromatic rings and polar groups. A combination of π - π interactions and hydrogen bonding is believed to be the basis of chiral recognition.¹⁹⁸ The relative electronic character of the aromatic rings is important. Complementary donor-acceptor capacity enhances selectivity.¹⁹⁹



suggested recognition mechanism for
resolution of *N*-(2-naphthyl)amino acids
on dinitrobenzoylamino acid CSP

Several variations of these CSPs have been developed, such as the phosphonate ester **CSP 30** and the tetrahydrophenanthryl amide **CSP 33**. These compounds are used in pharmaceutical studies. The former CSP is a good resolving agent for the β -adrenergic blocker class of compounds, such as propranolol,²⁰⁰ whereas the latter is a good CSP for separation of NSAIDs, such as naproxen and ibuprofen.²⁰¹



T.2.1.2.2. Resolution by Capillary Electrophoresis. Another methodology that has been adapted to analysis of enantiomers is *capillary electrophoresis*.²⁰² The principle of electrophoretic separation is differential migration of a charged molecule in a

¹⁹⁸ W. H. Pirkle and T. C. Pochapsky, *J. Am. Chem. Soc.*, **108**, 5627 (1986); W. H. Pirkle and T. C. Pochapsky, *J. Am. Chem. Soc.*, **109**, 5975 (1987); W. H. Pirkle, J. A. Burke, III, and S. R. Wilson, *J. Am. Chem. Soc.*, **111**, 9222 (1989); M. H. Hyun, J.-J. Ryoo, and W. H. Pirkle, *J. Chromatogr. A*, **886**, 47 (2000).

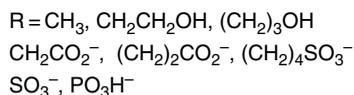
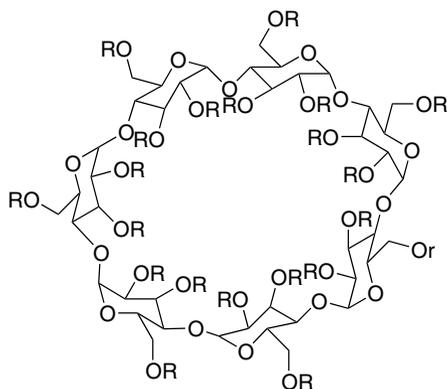
¹⁹⁹ W. H. Pirkle, T. C. Pochapsky, G. S. Mahler, D. E. Corey, D. S. Reno, and D. M. Alessi, *J. Org. Chem.*, **51**, 4991 (1986).

²⁰⁰ W. H. Pirkle and J. A. Burke, *Chirality*, **1**, 57 (1989).

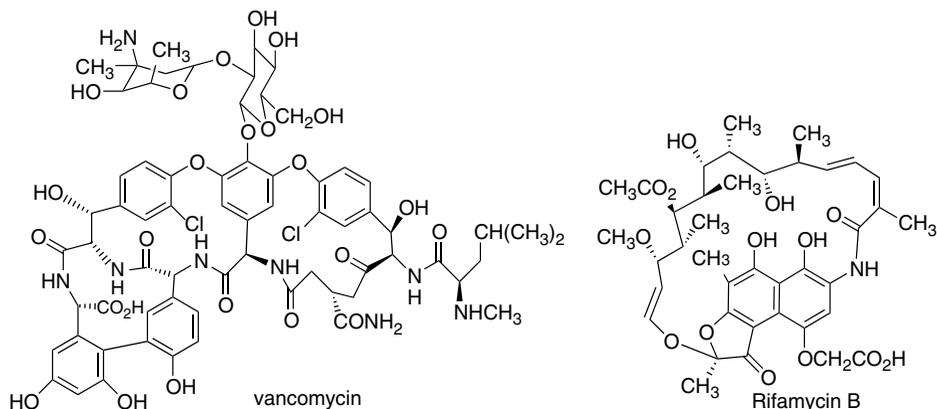
²⁰¹ W. H. Pirkle, C. J. Welch, and B. Lamm, *J. Org. Chem.*, **57**, 3854 (1992).

²⁰² A. Rizzi, *Electrophoresis*, **22**, 3079 (2001); G. Gubitza and M. G. Schmid, *J. Chromatogr. A*, **792**, 179 (1997).

polymer matrix under the influence of an electric field. Gel electrophoresis, a very important bioanalytical technique, is done in a polyacrylamide gel and depends on molecular size and charge differences to achieve differential migration. This method is primarily applied to macromolecules, such as polypeptides and oligonucleotides. Capillary electrophoresis (CE) has been developed as a technique for analysis of small chiral molecules, especially drugs. The most widely applied method of analysis is *capillary zone electrophoresis*, in which a *chiral selector* is added to the electrolyte buffer. The difference in binding between the chiral selector and the two enantiomers being analyzed then determines the rate of migration. Among the most commonly used chiral selectors are cyclodextrins, which are cyclic oligosaccharides. The cyclodextrins can be modified to incorporate polar, anionic, or cationic groups.



Macrocyclic antibiotics such as vancomycin and rifamycin B are also used as chiral selectors.



Another approach to chiral electrophoresis involves covalent attachment of the chiral selector to either the capillary wall or the packing material.²⁰³ For open columns, where the packing material is attached to the capillary wall, a completely methylated β -cyclodextrin is linked to the surface through a polysiloxane (Chirasil-Dex 1). The packed columns use silica bound to the methylated cyclodextrin (Chirasil-Dex 2).

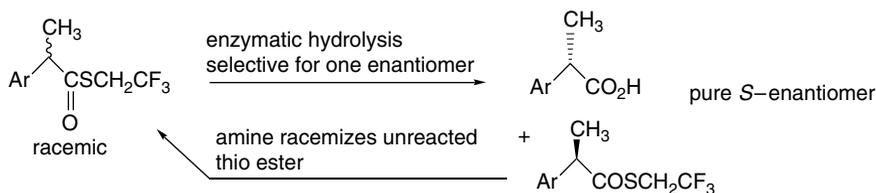
²⁰³ V. Schurig and D. Wistuba, *Electrophoresis*, **20**, 2313 (1999).

The strength of CE as an analytical tool is the very high degree of enantioselection that can be achieved, along with high speed and sensitivity. It is more difficult to use CE on a preparative scale, although successful separation has been reported on the milligram scale.²⁰⁴

We have seen that in each of these means of enantiomeric separation, chiral recognition depends upon a combination of intermolecular forces, including electrostatic attractions, hydrogen bonding, and π - π stacking. These differential interactions then lead to distinctions between the properties of the two enantiomers, such as chemical shifts in NMR methods or relative mobility in chiral chromatography and electrophoresis. There is much current interest in both the analysis of these interactions and manipulation of structure to increase selectivity.

Topic 2.2. Enzymatic Resolution and Desymmetrization

Enzymatic resolution is based on the ability of enzymes (catalytic proteins) to distinguish between *R*- and *S*-enantiomers or between enantiotopic pro-*R* and pro-*S* groups in prochiral compounds.²⁰⁵ The selective conversion of pro-*R* and pro-*S* groups is often called *desymmetrization* or *asymmetrization*.²⁰⁶ Note that in contrast to enzymatic resolution, which can at best provide half the racemic product as resolved material, prochiral compounds can be completely converted to a single enantiomer, provided that the selectivity is high enough. Complete conversion of a racemic mixture to a single enantiomeric product can sometimes be accomplished by coupling an enzymatic resolution with another reaction (chemical or enzymatic) that racemizes the reactant. This is called *dynamic resolution*,²⁰⁷ and it has been accomplished for several α -arylpropanoic acids via the thioesters, using an amine to catalyze racemization.²⁰⁸ Trifluoroethyl thioesters are advantageous because of their enhanced rate of exchange and racemization.



The criterion for a successful enzymatic resolution is that one enantiomer be a preferred substrate for the enzyme. Generally speaking, the enantioselectivity is quite high, since enzyme-catalyzed reactions typically involve a specific fit of the reactant (substrate) into the catalytically active site. The same necessity for a substrate fit, however, is the primary limitation on enzymatic resolution. The compound to be

²⁰⁴. F. Glukhovskiy and G. Vigh, *Electrophoresis*, **21**, 2010 (2000); A. M. Stalcup, R. M. C. Sutton, J. V. Rodrigo, S. R. Gratz, E. G. Yanes, and P. Painuly, *Analyst*, **125**, 1719 (2000).

²⁰⁵. C. J. Sih and S. H. Wu, *Top. Stereochem.*, **19**, 63 (1989).

²⁰⁶. E. Schoffers, A. Golebiowski, and C. R. Johnson, *Tetrahedron*, **52**, 3769 (1996).

²⁰⁷. S. Caddick and K. Jenkins, *Chem. Soc. Rev.*, **25**, 447 (1996); H. Stecher and K. Faber, *Synthesis*, **1** (1997).

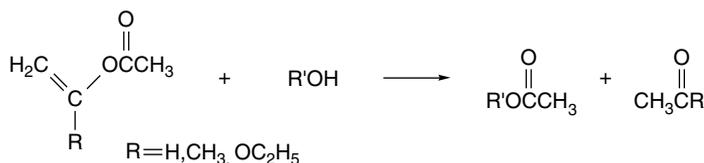
²⁰⁸. L. S. Chang, S. W. Tsai, and J. Kuo, *Biotechnol Bioeng.*, **64**, 120 (1999); C. Y. Chen, Y. S. Chang, S. A. Lin H.-I. Wen, Y.-C. Cheng, and S.-W. Tsai, *J. Org. Chem.*, **67**, 3323 (2002); P.-J. Um and D. G. Drueckhammer, *J. Am. Chem. Soc.*, **120**, 5605 (1998).

resolved must be an acceptable substrate for the enzyme. If not, there will be no reaction with either enantiomer. The types of reactions that are suitable for enzymatic resolutions are somewhat limited. The most versatile enzymes—*esterases* and *lipases*—catalyze formation or hydrolysis of esters. There are also enzymes that catalyze amide formation and hydrolysis, which can be broadly categorized as *acylases* or *amidases*. We also discuss *epoxide hydrolases*, which open epoxide rings. Another important family is the *oxido-reductases*, which interconvert alcohols and carbonyl compound by oxidation and reduction.

T.2.2.1. Lipases and Esterases

The most widely applied enzymes for resolution are lipases and esterases, which can catalyze either the hydrolysis or the formation of esters.²⁰⁹ The natural function of these enzymes is to catalyze hydrolysis of fatty acid esters of glycerol. There are a number of such enzymes that are commercially available. A very important property of these esterases and lipases is that they can accept a fairly wide variety of molecules as substrates. They are also adaptable for use in organic solvents, which further enhances their practical utility.²¹⁰

The esterases and lipases are members of a still larger group of enzymes that catalyze acyl transfer, either in the direction of solvolysis or by acylation of the substrate. Both types of enzymes are called *hydrolases*. In water, hydrolysis occurs, but in the presence of alcohols, transesterification can occur. Reactions in the acylation direction are done in the presence of acyl donors. Esters of enols such as vinyl acetate or isopropenyl acetate are often used as sources of the acyl group. These enol esters are more reactive than alkyl esters, and the enol that is displaced on acyl transfer is converted to acetaldehyde or acetone. To avoid side products arising from these carbonyl compounds, one can use 1-ethoxyvinyl esters, which give ethyl acetate as the by-product.²¹¹



The esterases, lipases, and other enzymes that catalyze acyl transfer reactions share a common mechanism. The active site in these enzymes involves a *catalytic triad* consisting of the imidazole ring from a histidine, the hydroxyl group of a serine, and a carboxy group from an aspartic acid.²¹² The three moieties, working together, effect transfer of an acyl group to the serine. In solvolysis, this acyl group is then transferred to the solvent, whereas in acylation it is transferred to the substrate. The mechanism is outlined in Figure 2.27. We discuss the catalytic mechanisms of these triads in more detail in Section 7.5.

²⁰⁹ P. Andersch, M. Berger, J. Hermann, K. Laumen, M. Lobell, R. Seemayer, C. Waldinger, and M. P. Schneider, *Meth. Enzymol.*, **286**, 406 (1997).

²¹⁰ A. M. Klibanov, *Acc. Chem. Res.*, **23**, 114 (1990); G. Carrea and S. Riva, *Angew. Chem. Int. Ed. Engl.*, **39**, 2227 (2000).

²¹¹ Y. Kita, Y. Takebe, K. Murata, T. Naka, and S. Akai, *J. Org. Chem.*, **65**, 83 (2000).

²¹² R. J. Kazlauskas and H. K. Weber, *Curr. Opinion Chem. Biol.*, **2**, 121 (1998).

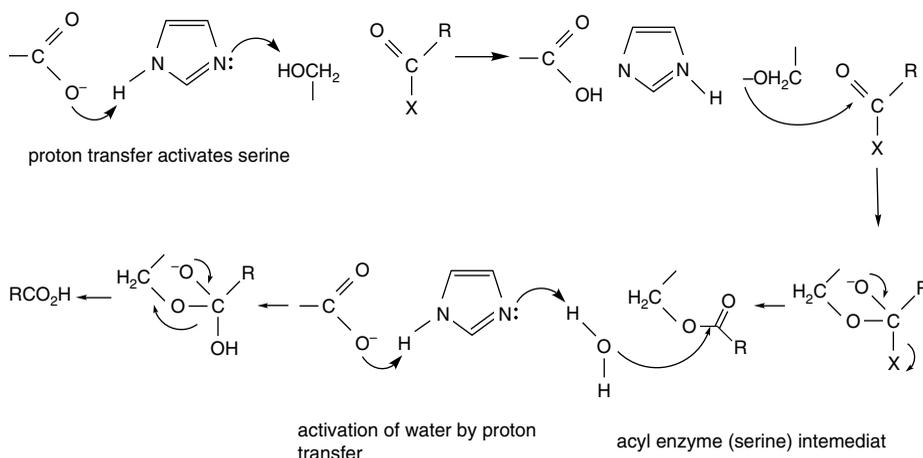


Fig. 2.27. Mechanism for carboxylate-histidine-serine triad catalysis of acyl transfer.

The most commonly used of the hydrolytic enzymes is *pig liver esterase* (PLE). The natural function of this enzyme is to hydrolyze esters during digestion and it has a fairly broad range of substrate reactivity. It has been used to resolve chiral alcohols and esters by acylation or hydrolysis, respectively. *Meso*-derivatives of succinic and glutaric acid diesters are generally good substrates for PLE and are good examples of substrates for desymmetrization. A predictive model for the stereoselectivity of PLE was developed by analysis of many cases.²¹³ The model pictures two hydrophobic pockets, one larger (H_L) and one smaller (H_S) and two polar pockets, one front (P_F) and one back (P_B). These pockets are specifically located in relation to the catalytic serine, and the fit of the substrate then determines the enantioselectivity. Alkyl and aryl groups fit into either the H_L or H_S sites based on size. The P_F site can accommodate moderately polar groups, such as the ester substituent in diesters, whereas the P_B site accepts more polar groups, including hydroxy and carbonyl groups, and excludes nonpolar groups. This model successfully correlates and predicts the results for a variety of esters and diesters. For example, Figure 2.28 shows the fit of an α -sulfinyl ester into the catalytic site.²¹⁴

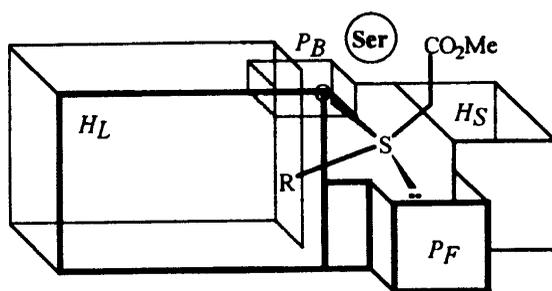


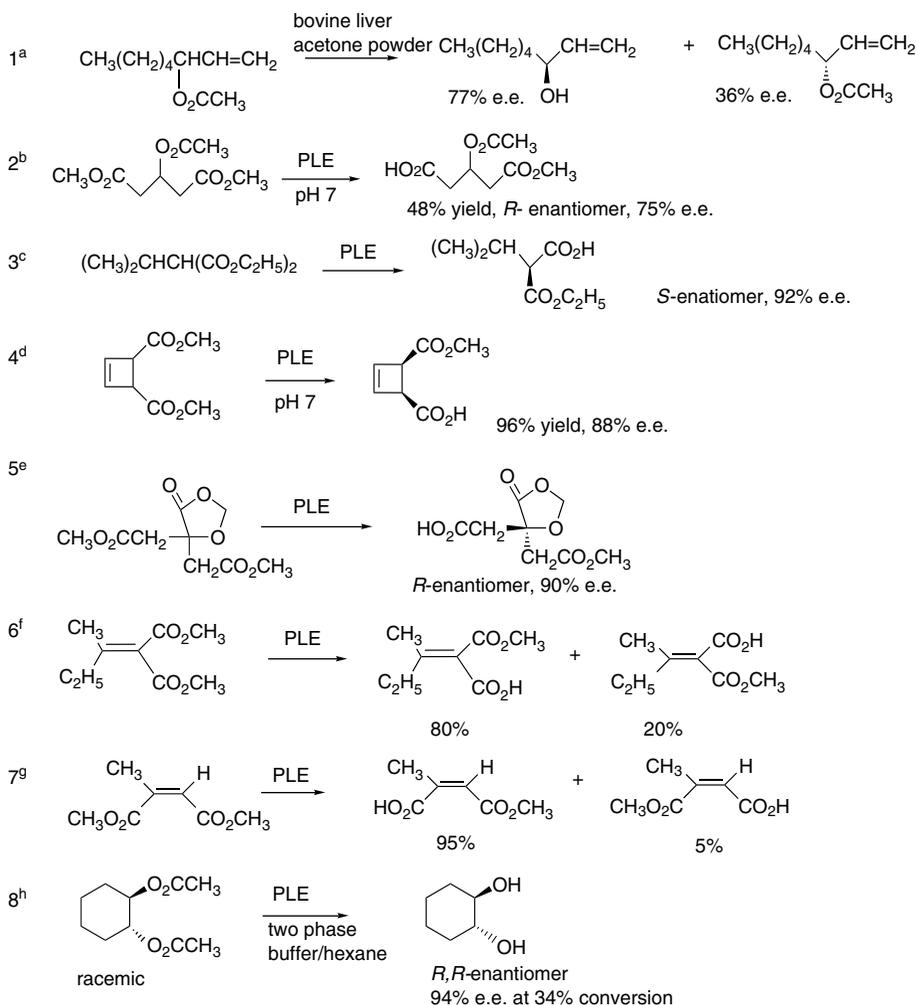
Fig. 2.28. Accommodation of preferred *S*-enantiomer of α -sulfinylacetate esters in the Jones model of a PLE active site. Reproduced from *Tetrahedron: Asymmetry*, **11**, 911 (2000), by permission of Elsevier.

²¹³ E. J. Toone, M. J. Werth, and J. B. Jones, *J. Am. Chem. Soc.*, **112**, 4946 (1990); L. Provencher, H. Wynn, J. B. Jones, and A. Krawczyk, *Tetrahedron: Asymmetry*, **4**, 2025 (1993); L. Provencher and J. B. Jones, *J. Org. Chem.*, **59**, 2729 (1994).

²¹⁴ P. Kielbasinski, *Tetrahedron Asymmetry* **11**, 911 (2000).

Scheme 2.13 shows a few examples of resolutions and desymmetrization using esterases. Entry 1 shows the partial resolution of a chiral ester using a crude enzyme source. The enantioselectivity is only moderate. Entries 2 to 5 are examples of desymmetrization, in which prochiral ester groups are selectively hydrolyzed. Entries 6 and 7 are examples of selective hydrolysis of unsaturated esters that lead to isomeric monoesters. These cases are examples of diastereoselectivity. In Entry 8, the *R,R*-enantiomer of a racemic diester is selectively hydrolyzed. In all these cases, the

Scheme 2.13. Representative Resolutions and Desymmetrizations Using Esterases



- a. D. Basavaiah and S. B. Raju, *Tetrahedron*, **50**, 4137 (1994).
 b. B. Loubinoux, J.-L. Sinnes, A. C. O'Sullivan, and T. Winkler, *Tetrahedron*, **51**, 3549 (1995).
 c. B. Klotz-Berendes, W. Kleemis, U. Jegelka, H. J. Schaefer, and S. Kotila, *Tetrahedron: Asymmetry*, **8**, 1821 (1997).
 d. I. Harvey and D. H. G. Crout, *Tetrahedron: Asymmetry*, **4**, 807 (1993).
 e. R. Chenevert, B. T. Ngatcha, Y. S. Rose, and D. Goupil, *Tetrahedron: Asymmetry*, **9**, 4325 (1998).
 f. T. Schirmeister and H. H. Otto, *J. Org. Chem.*, **58**, 4819 (1993).
 g. R. Schmid, V. Partali, T. Anthonsen, H. W. Anthonsen, and L. Kvittingen, *Tetrahedron Lett.*, **42**, 8543 (2001).
 h. G. Caron and R. J. Kazlauskas, *J. Org. Chem.*, **56**, 7251 (1991).

stereoselectivity of the reaction is determined by the relative fit in the binding site of the esterases.

Lipases are another important group of hydrolases. The most commonly used example is porcine pancreatic lipase (PPL). Lipases tend to function best at or above the solubility limit of the hydrophobic substrate. In the presence of water, the substrate forms an insoluble phase (micelles); the concentration at which this occurs is called the *critical micellar concentration*. The enzyme is activated by a conformational change that occurs in the presence of the micelles and results in the opening of the active site. Lipases work best in solvents that can accommodate this activation process.²¹⁵ PPL is often used as a relatively crude preparation called “pancreatin” or “steapsin.” The active site in PPL has not been as precisely described as the one for PLE. There are currently two different models, but they sometimes make contradictory predictions.²¹⁶ It has been suggested that the dominant factors in binding are the hydrophobic and polar pockets (sites B and C in Figure 2.29), but that the relative location of the catalytic site is somewhat flexible and can accommodate to the location of the hydrolyzable substituent.²¹⁷

A more refined model of stereoselectivity has been proposed on the basis of the X-ray structure of PPL²¹⁸ and the stereoselectivity toward several aryl-substituted diols. This model proposes an important π - π stacking interaction between the aryl

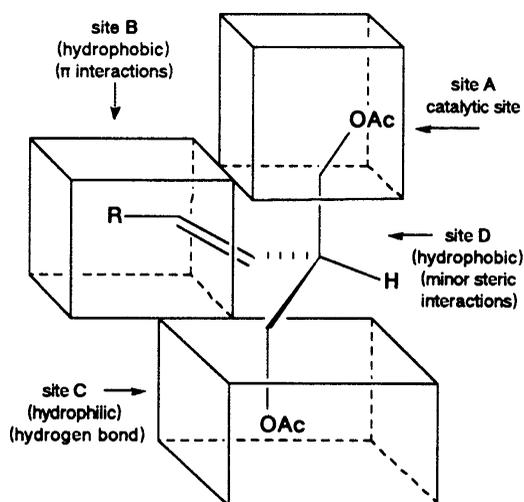


Fig. 2.29. Preferred accommodation of 2-*E*-alkenyl-1,3-propanediol diacetates in an active site model for PPL. Reproduced from *J. Org. Chem.*, **57**, 1540 (1992), by permission of the American Chemistry Society.

- ²¹⁵ B. Rubin, *Nature Struct. Biol.*, **1**, 568 (1994); R. D. Schmid and R. Verger, *Angew. Chem. Intl. Ed. Engl.*, **37**, 1609 (1998).
- ²¹⁶ J. Ehrler and D. Seebach, *Liebigs Ann. Chem.*, 379 (1990); P. G. Hultin and J. B. Jones, *Tetrahedron Lett.*, **33**, 1399 (1992); Z. Wimmer, *Tetrahedron*, **48**, 8431 (1992).
- ²¹⁷ A. Basak, G. Bhattacharya, and M. H. Bdour, *Tetrahedron*, **54**, 6529 (1998). A. Basak, K. R. Rudra, H. M. Bdour, and J. Dasgupta, *Biorg. Med. Chem. Lett.*, **11**, 305 (2001); A. Basak, K. R. Rudra, S. C. Ghosh, and G. Bhattacharya, *Ind. J. Chem. B.*, **40**, 974 (2001).
- ²¹⁸ J. Hermoso, D. Pignol, B. Kerfelec, I. Crenon, C. Chapus, and J. C. Fontecilla-Camps, *J. Biol. Chem.*, **271**, 18007 (1996); J. Hermoso, D. Pignol, S. Penel, M. Roith, C. Chapus, and J. C. Fontecilla-Camps, *EMBO J.*, **16**, 5531 (1997).

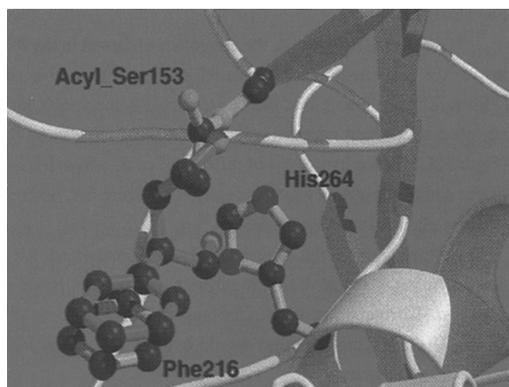
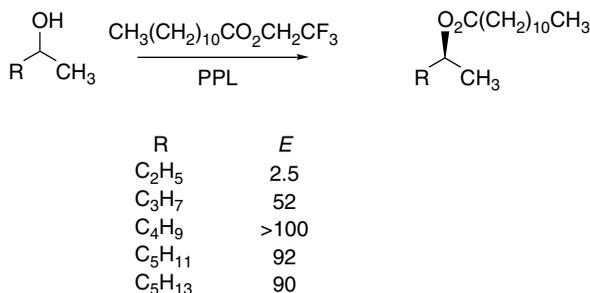


Fig. 2.30. Active site model of PPL showing the binding of 2-phenylpentane-1,4-diol in an active site. Note the $\pi - \pi$ stacking with Phe-216 and placement of the C(4) hydroxyl near the acyl serine-153 residue. Reproduced from *Tetrahedron*, **55**, 14961 (1999), by permission of Elsevier. (See also color insert.)

group and a phenylalanine residue near the active site.²¹⁹ Based on the detailed protein structure, this model is consistent with the model proposed by Guanti et al.²²⁰ The model (Figure 2.30) suggests a hydrophilic site and a rather selective hydrophobic site. The D site is considered to be quite flexible, whereas the B site is particularly favorable for unsaturated groups.

The enantioselectivity of PPL depends on discrimination in binding of the substrate. In the case of acylation of simple secondary alcohols, there is poor discrimination for 2-butanol, but 2-hexanol exhibits the maximal E value, and larger alcohols show good enantioselectivity.²²¹ (The definition of E is given on p. 140.)



Two other lipases of microbiological origin are also used frequently in organic chemistry. A lipase from *Pseudomonas cepacia* (formerly identified as *Pseudomonas fluorescens*) is often referred to as *lipase PS*. The binding site for this enzyme is narrower than those of the other commonly used lipases, and it often has excellent

²¹⁹ I. Borreguero, J. V. Sinisterra, A. Rumero, J. A. Hermoso, M. Martinez-Ripoll, and A. R. Alcantara, *Tetrahedron*, **55**, 14961 (1999).

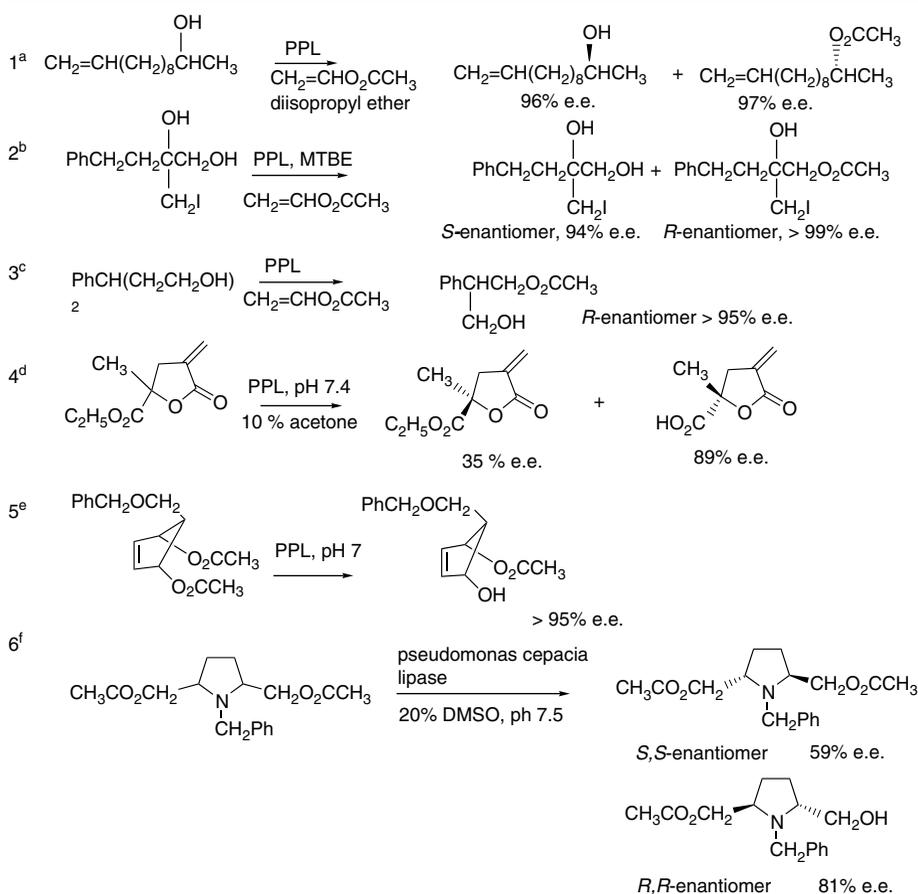
²²⁰ G. Guanti, L. Banfi, and E. Narisano, *J. Org. Chem.*, **57**, 1540 (1992).

²²¹ B. Morgan, A. C. Oehschlager, and T. M. Stokes, *Tetrahedron*, **47**, 1611 (1991).

selectivity. Lipases from *Candida rugosa* (formerly *Candida cylindracea*), *C. antarctica*, and *C. lipolytica* are also used frequently.²²² Like the esterases, lipases can act as hydrolysis catalysts toward esters or as acylation catalysts toward alcohols. Unlike PLE, the lipases have a specific type of natural substrate, namely triacyl glycerides. They are somewhat more selective in terms of substrate than PLE. Generally, neither α,α -disubstituted carboxylates nor esters of tertiary alcohols are accepted as substrates. As with PLE, either kinetic resolution or desymmetrization of prochiral reactants can be achieved. The enantioselectivity of lipases depends upon discrimination between the enantiomeric substrates at the active site. A large hydrophobic site acts as the receptor for the largest nonpolar substituent.

Some examples of some lipase-catalyzed reactions are given in Scheme 2.14. The first three examples in Scheme 2.14 are acylations. Entries 1 and 2 are enantioselective

Scheme 2.14. Representative Resolutions Using Various Lipases



a. A. Sharma, S. Sankaranarayanan, and S. Chattopadhyay, *J. Org. Chem.*, **61**, 1814 (1996).

b. S.-T. Chen and J.-M. Fang, *J. Org. Chem.*, **62**, 4349 (1997).

c. A. Rumbero, I. Borroguero, J. V. Sinisterra, and A. R. Alcantara, *Tetrahedron*, **55**, 14947 (1999).

d. G. Pitacco, A. Sessanta, O. Santi, and E. Valentin, *Tetrahedron: Asymmetry*, **11**, 3263 (2000).

e. I. C. Cotterill, P. B. Cox, A. F. Drake, D. M. LeGrand, E. J. Hutchinson, R. Latouche, R. B. Pettman, R. J. Pryce,

S. M. Roberts, G. Ryback, V. Sik, and J. O. Williams, *J. Chem. Soc., Perkin Trans. 1*, 3071 (1991).

f. Y. Kawanami, H. Moriya, Y. Goto, K. Tsukao, and M. Hashimoto, *Tetrahedron*, **52**, 565 (1996).

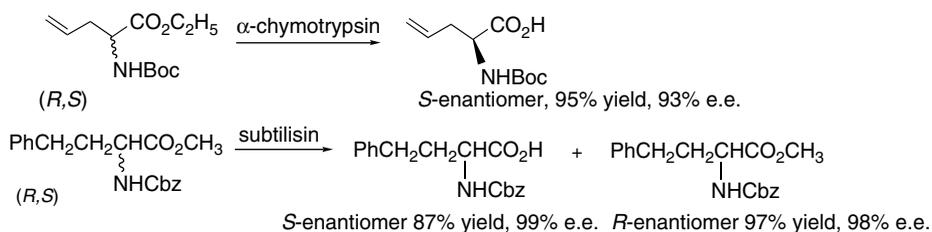
²²² F. Theil, *Chem. Rev.*, **95**, 2203 (1995).

acylations of a chiral secondary alcohol. Entry 3 is a desymmetrization of a 3-phenylpentane-1,5-diol. Entry 4 is a resolution of an ester group attached to a methylene- γ -lactone. Entries 5 and 6 are desymmetrizations of diesters.

T.2.2.2. Proteases and Acylases

Proteases and *acylases* have the capacity to catalyze hydrolysis and formation of amide bonds. Proteases find extensive application in analytical biochemistry.²²³ The proteases are used to break down large proteins into polypeptides. Various proteases exhibit selectivity for particular sequences in peptides and proteins. Many of the proteases are digestive enzymes and in general they have much more stringent structural requirements for substrates than esterases and lipases. For example, chymotrypsin is selective for hydrolysis at the carboxy group of aromatic amino acids, while trypsin cleaves at the carboxy group of the basic (protonated) amino acids lysine and arginine. The proteases, like the esterases and lipases, function on the basis of a catalytic triad involving a serine, histidine, and aspartic acid.²²⁴ They can catalyze formation and hydrolysis of esters as well as amides.²²⁵

Considerable attention has also been given to enantioselective enzymatic hydrolysis of esters of α -amino acids. This is of particular importance as a means of preparing enantiopure samples of unusual (non-proteinaceous) α -amino acids.²²⁶ The readily available proteases α -chymotrypsin (from bovine pancreas) and subtilisin (from *Bacillus licheniformis*) selectively hydrolyze the L-esters, leaving D-esters unreacted. These enzymatic hydrolysis reactions can be applied to *N*-protected amino acid esters, such as those containing *t*-Boc²²⁷ and Cbz²²⁸ protecting groups.



Much of the interest in acylases originated from work with the penicillins. Structurally modified penicillins can be obtained by acylation of 6-aminopenicillamic acid. For example, the semisynthetic penicillins such as amoxicillin and ampicillin are obtained using enzymatic acylation.²²⁹ Acylases are used both to remove the phenylacetyl group from the major natural penicillin, penicillin G, and to introduce the modified acyl substituent.

²²³ A. J. Barrett, N. D. Rawlings, and J. F. Woessner, eds., *Handbook of Proteolytic Enzymes*, 2nd Edition, Elsevier, 2004.

²²⁴ L. Polgar in *Mechanisms of Protease Action*, CRC Press, Boca Raton, FL, Chap. 3, 1989; J. J. Perona and C. S. Craik, *Protein Sci.*, **4**, 337 (1995).

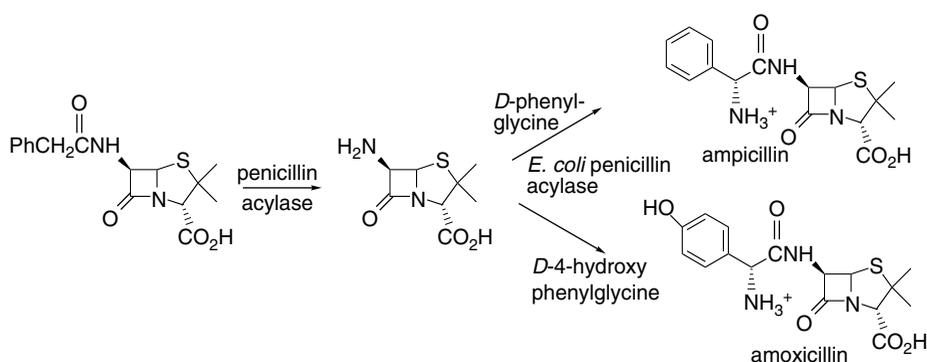
²²⁵ K. Watanabe and S. Ueji, *J. Chem. Soc., Perkin Trans. 1*, 1386 (2001); T. Ke, C. R. Westcott, and A. M. Klivanov, *J. Am. Chem. Soc.*, **118**, 3366 (1996).

²²⁶ T. Miyazawa, *Amino Acids*, **16**, 191 (1999).

²²⁷ B. Schrickler, K. Thirring, and H. Berner, *Biorg. Med. Chem. Lett.*, **2**, 387 (1992).

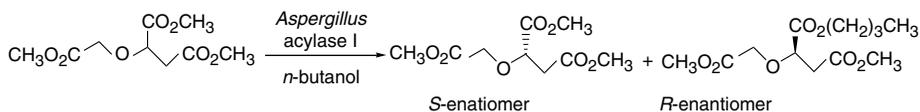
²²⁸ S.-T. Chen, S.-Y. Chen, S.-C. Hsiao, and K.-T. Wang, *Biotechnol. Lett.*, **13**, 773 (1991).

²²⁹ A. Bruggink, E. C. Roos, and E. de Vroom, *Org. Process Res. Dev.*, **2**, 128 (1998).

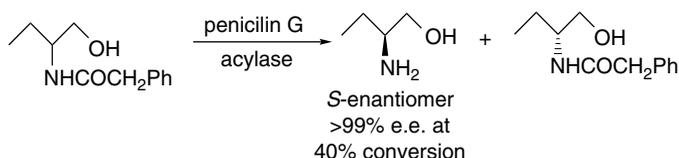


Similar reactions are used in preparation of the related cephalosporin antibiotics.

A related group of acylases catalyzes amide formation and hydrolysis. *Aspergillus* is one source of such enzymes. One class of substrates is made up of di- and triesters with α -heteroatom substituents. Such substrates show selectivity for the carboxy group that is α to the heteroatom, which is the position analogous to the amide bond in peptides.

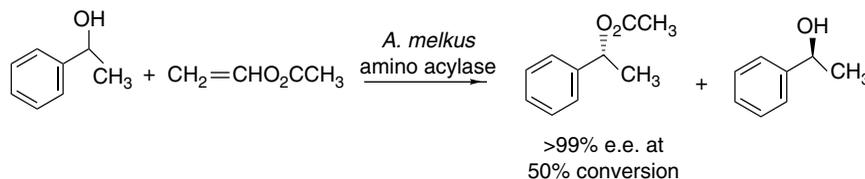


Ref. 230



Ref. 231

Acylases can be used to catalyze esterification of alcohols. These reactions are usually carried out by using vinyl esters. The selectivity (*E*) values for such reactions can be quite high.



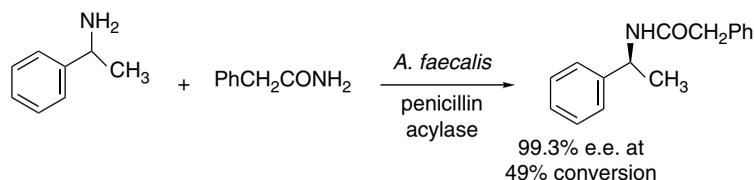
Ref. 232

²³⁰. A. Liljeblad, R. Aksela, and L. T. Kanerva, *Tetrahedron: Asymmetry*, **12**, 2059 (2001).

²³¹. N. W. Fadnavis, M. Sharfuddin, and S. K. Vadivel, *Tetrahedron: Asymmetry*, **10**, 4495 (1999).

²³². M. Bakker, A. S. Spruijt, F. van Rantwijk, and R. A. Sheldon, *Tetrahedron: Asymmetry*, **11**, 1801 (2000).

Enantioselective acylation of amines is generally more challenging and less explored, although good results have been reported in some cases. A number of 1-phenylethylamines and 4-phenylbutane-2-amine were resolved using an acylase from *Alcaligenes faecalis*.



Ref. 233

T.2.2.3. Epoxide Hydrolases

Epoxide hydrolases (EH) catalyze the hydrolytic ring opening of epoxides to diols. The natural function of the epoxide hydrolases seems to be to detoxify epoxides, and they have a fairly broad range of acceptable substrates. The epoxide hydrolases use a catalytic triad active site, reminiscent of the lipases and esterases. In the hydrolases, however, an aspartate carboxylate, rather than a serine hydroxy, functions as the nucleophile to open the epoxide ring. The glycol monoester intermediate is then hydrolyzed, as shown in Figure 2.31. According to this mechanism, and as has been experimentally confirmed, the oxygen that is introduced into the diol originates in the aspartate carboxylate group.²³⁴

There are several forms of EHs that have been used to effect enantioselective opening of epoxides. One commonly used form is isolated as a crude microsomal preparation from rodent livers. EH can also be isolated from bacteria, fungi, and yeasts.²³⁵ The structure of the EH from *Agrobacterium radiobacter* AD1 has been solved by X-ray crystallography.²³⁶ In this enzyme, the catalytic triad involves His-275, Asp-107, and Tyr-152 and/or Tyr-215. The tyrosine functions as a general acid

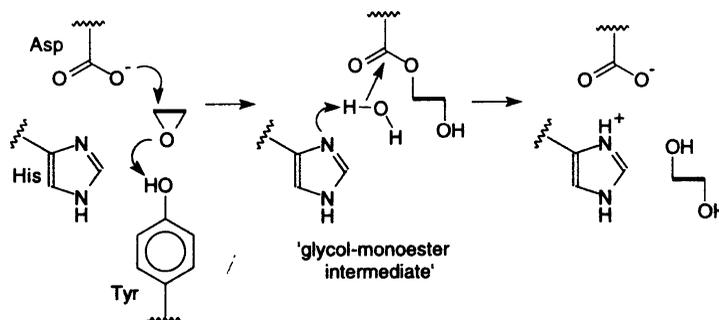


Fig. 2.31. Proposed mechanism of microsomal epoxide hydrolase.

- ²³³ D. T. Guranda, L. M. van Langen, F. van Rantwijk, R. A. Sheldon, and V. K. Svedas, *Tetrahedron: Asymmetry*, **12**, 1645 (2001).
- ²³⁴ G. M. Lacourciere and R. N. Armstrong, *J. Am. Chem. Soc.*, **115**, 10466 (1993); B. Borhan, A. D. Jones, F. Pinot, D. F. Grant, M. J. Kurth, and B. D. Hammock, *J. Biol. Chem.*, **270**, 26923 (1995).
- ²³⁵ C. A. G. M. Weijers and J. A. M. de Bont, *J. Mol. Catal. B, Enzymes*, **6**, 199 (1999).
- ²³⁶ M. Nardini, I. S. Ridder, H. J. Rozeboom, K. H. Kalk, R. Rink, D. B. Janssen, and B. W. Dijkstra, *J. Biol. Chem.*, **274**, 14579 (1999); M. Nardini, R. B. Rink, D. B. Janssen, and B. W. Dijkstra, *J. Mol. Catal. B, Enzymatic*, **11**, Spec. Issue, 1035 (2001).

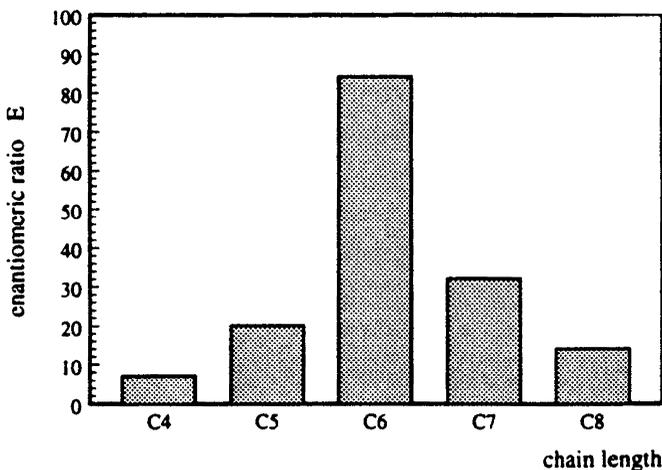


Fig. 2.32. Effect of chain length on enantioselectivity ratio E for unbranched monosubstituted epoxides. Reproduced from *Tetrahedron: Asymmetry*, **9**, 467 (1998), by permission of Elsevier.

catalyst. A crystal structure has also been determined for the *Aspergillus niger* EH.²³⁷ The essential amino acids in these and other EHs have been identified by site-specific mutagenesis experiments.²³⁸

One of the more extensively investigated EHs is from the fungus *Aspergillus niger*.²³⁹ The best studied of the yeast EH is from *Rhodotorula glutina*,²⁴⁰ which can open a variety of mono-, di-, and even trisubstituted epoxides. The E values for simple monosubstituted epoxides show a sharp maximum in selectivity for the hexyl substituent, as can be seen in Figure 2.32. This indicates that there is a preferential size for binding of the hydrophobic groups.

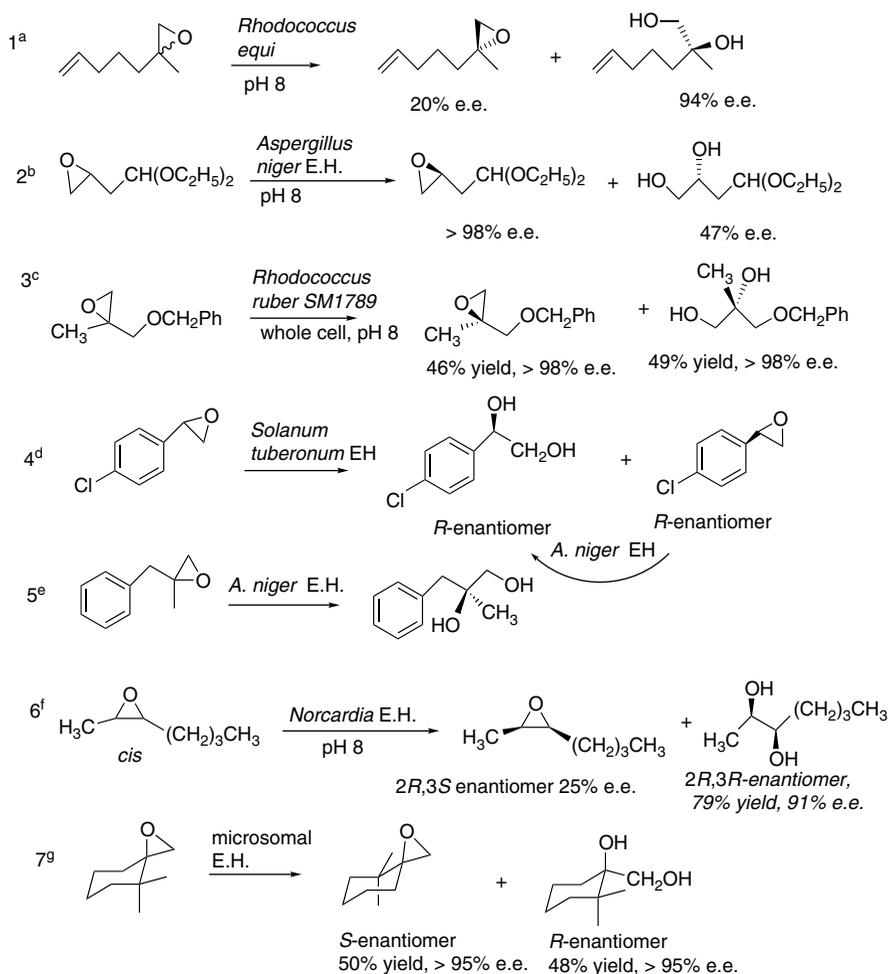
Scheme 2.15 gives some examples of the use of epoxide hydrolases in organic synthesis. Entries 1 to 3 are kinetic resolutions. Note that in Entry 1 the hydrolytic product is obtained in high e.e., whereas in Entry 2 it is the epoxide that has the highest e.e. In the first case, the reaction was stopped at 18% conversion, whereas in the second case hydrolysis was carried to 70% completion. The example in Entry 3 has a very high E (> 100) and both the unreacted epoxide and diol are obtained with high e.e. at 50% conversion. Entry 4 shows successive use of two separate EH reactions having complementary enantioselectivity to achieve nearly complete

²³⁷ J. Y. Zou, B. M. Halberg, T. Bergfors, F. Oesch, M. Arnold, S. L. Mowbry, and T. A. Jones, *Structure with Folding and Design*, **8**, 111 (2000).

²³⁸ H. F. Tzeng, L. T. Laughlin, and R. N. Armstrong, *Biochemistry*, **37**, 2905 (1998); R. Rink, J. H. L. Spelberg, R. J. Pieters, J. Kingma, M. Nardini, R. M. Kellogg, B. K. Dijkstra, and D. B. Janssen, *J. Am. Chem. Soc.*, **121**, 7417 (1999); R. Rink, J. Kingma, J. H. L. Spelberg, and D. B. Janssen, *Biochemistry*, **39**, 5600 (2000).

²³⁹ S. Pedragosa-Moreau, A. Archelas, and R. Furstoss, *J. Org. Chem.*, **58**, 5533 (1993); S. Pedragosa-Moreau, C. Morisseau, J. Zylber, A. Archelas, J. Baratti, and R. Furstoss, *J. Org. Chem.*, **61**, 7402 (1996); S. Pedragosa-Moreau, A. Archelas, and R. Furstoss, *Tetrahedron*, **52**, 4593 (1996).

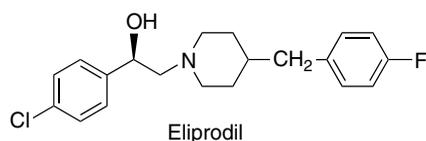
²⁴⁰ C. A. G. M. Weijers, *Tetrahedron: Asymmetry*, **8**, 639 (1997); C. A. G. M. Weijers, A. L. Botes, M. S. van Dyk, and J. A. M. de Bont, *Tetrahedron: Asymmetry*, **9**, 467 (1998).



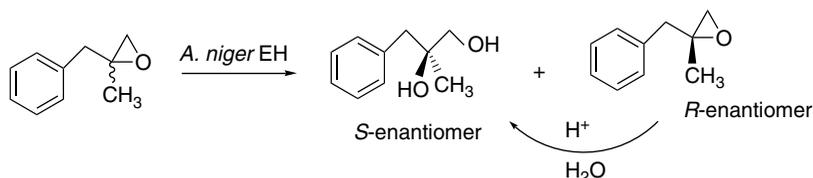
- a. W. Kroutil, I. Osprian, M. Mischitz, and K. Faber, *Synthesis*, 156 (1997).
 b. C. Guerard, F. Alphand, A. Archelas, C. Demuyneck, L. Hecquet, R. Furstoss, and J. Bolte, *Eur. J. Org. Chem.*, 3399 (1999).
 c. A. Steinreiber, H. Hellstrom, S. F. Mayer, R. V. A. Orru, and K. Faber, *Synlett*, 111 (2001).
 d. K. B. Manoj, A. Archelas, J. Baratti, and R. Furstoss, *Tetrahedron*, **57**, 695 (2001).
 e. R. V. A. Orru, I. Osprian, W. Kroutil, and K. Faber, *Synthesis*, 1259 (1998).
 f. W. Kroutil, M. Mischitz, and K. Faber, *J. Chem. Soc., Perkin Trans. 1*, 3629 (1997).
 g. G. Bellucci, C. Chiappe, G. Ingrosso, and C. Rosini, *Tetrahedron: Asymmetry*, **6**, 1911 (1995).

conversion of 4-chlorophenylloxirane to the *R*-enantiomer, which is used to prepare the drug Eliprodil.²⁴¹ This compound is a glutamate antagonist that has promising neuro-protective activity in the treatment of stroke. First, an EH from *Solanum tuberosum* that hydrolyzes the *S*-enantiomer was used, leaving the *R*-enantiomer unchanged. When the reaction is complete, *Aspergillus niger* EH converts the *R*-enantiomer to the *R*-3-diol, which can be converted to the *R*-epoxide by chemical means.

²⁴¹ K. M. Manoj, A. Archelas, J. Baratti, and P. Furstoss, *Tetrahedron*, **57**, 695 (2001).



Entry 5 is an interesting example that entails both enzymatic and hydrolytic epoxide conversion. In the first step, an enzymatic hydrolysis proceeds with *retention* of the configuration at the tertiary center. This reaction is selective for the *S*-epoxide. The remaining *R*-epoxide is then subjected to acid-catalyzed hydrolysis, which proceeds with *inversion* at the center of chirality (see p. 186). The combined reactions give an overall product yield of 94%, having 94% e.e.²⁴²



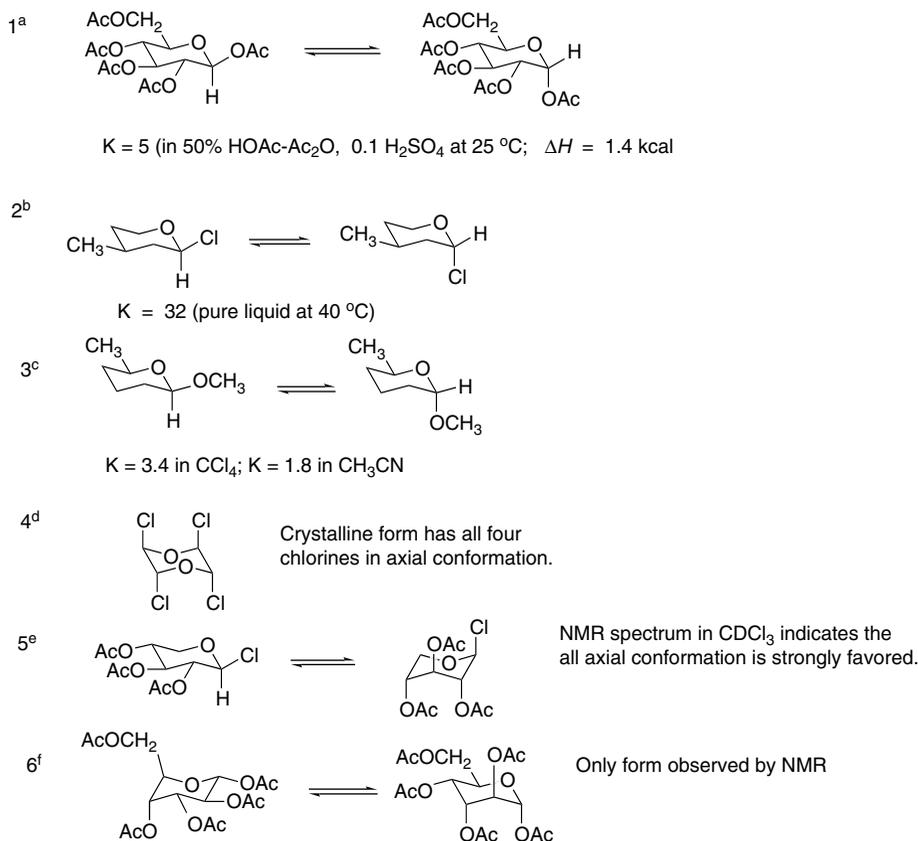
Entry 6 is one of several examples demonstrating enantioselectivity for both the *cis* and *trans* isomers of heptane-2,3-epoxide. Entry 7 shows the kinetic resolution of an exocyclic cyclohexane epoxide. The two stereoisomeric monomethyl analogs were only partially resolved and the 3-methyl isomer showed no enantioselectivity. This shows that the steric or hydrophobic effect of the dimethyl substituents is critical for selective binding.

Topic 2.3. The Anomeric Effect in Cyclic Compounds

The incorporation of heteroatoms into rings can result in stereoelectronic effects that significantly affect conformation and, ultimately, reactivity. It is known from many examples in carbohydrate chemistry that pyranose (six-membered oxygen-containing rings) sugars substituted with an electron-withdrawing group such as halogen or alkoxy at C(2) are often more stable when the substituent has an axial rather than an equatorial orientation. This tendency is not limited to carbohydrates but carries over to simpler ring systems such as 2-substituted tetrahydropyrans. The phenomenon is known as the *anomeric effect*, since it involves a substituent at the anomeric position in carbohydrate pyranose rings.²⁴³ Scheme 2.16 lists several compounds that exhibit the anomeric effect, along with some measured equilibrium compositions. In Entries 1 to 3, the

²⁴². R. V. Orru, I. Osprian, W. Kroutil, and K. Faber, *Synthesis*, 1259 (1998).

²⁴³. For reviews, see R. U. Lemieux, *Pure Appl. Chem.* **25**, 527 (1971); W. A. Szarek and D. Horton, eds., *Anomeric Effects*, ACS Symposium Series, No. 87, American Chemical Society, Washington, DC, 1979; A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983; P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983; M. L. Sinot, *Adv. Phys. Org. Chem.*, **24**, 113 (1988); P. R. Graczyk and M. Mikolajczyk, *Top. Stereochem.*, **21**, 159 (1994); E. Juraisti and G. Cuevas, *The Anomeric Effect*, CRC Press, Boca Raton, FL, 1995; C. J. Cramer, *Theochem*, **370**, 135 (1996).



a. W. A. Bonner, *J. Am. Chem. Soc.*, **73**, 2659 (1951).

b. C. B. Anderson and D. T. Tepp, *J. Org. Chem.*, **32**, 607 (1967).

c. E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).

d. E. W. M. Rutten, N. Nibbering, C. H. MacGillavry, and C. Romers, *Rec. Trav. Chim. Pays-Bas*, **87**, 888 (1968).

e. C. V. Holland, D. Horton, and J. S. Jewell, *J. Org. Chem.*, **32**, 1818 (1967).

f. B. Coxon, *Carbohydrate Res.*, **1**, 357 (1966).

equilibria are between diastereoisomers and involve reversible dissociation of the 2-substituent. In all cases, the more stable isomer is written on the right. The magnitude of the anomeric effect depends on the nature of the substituent and decreases with increasing dielectric constant of the medium.²⁴⁴ The effect of the substituent can be seen by comparing the related 2-chloro- and 2-methoxy substituted tetrahydropyrans in Entries 2 and 3. The 2-chloro compound exhibits a significantly greater preference for the axial orientation than the 2-methoxy. Entry 3 also provides data relative to the effect of solvent polarity, where it is observed that the equilibrium constant is larger in carbon tetrachloride ($\epsilon = 2.2$) than in acetonitrile ($\epsilon = 37.5$).

Compounds in which conformational, rather than configurational, equilibria are influenced by the anomeric effect are depicted in Entries 4 to 6. X-ray diffraction studies have unambiguously established that all the chlorine atoms of *trans*, *cis*, *trans*-2,3,5,6-tetrachloro-1,4-dioxane occupy axial sites in the crystal (Entry 4). Each chlorine

²⁴⁴ K. B. Wiberg and M. Marquez, *J. Am. Chem. Soc.*, **116**, 2197 (1994).

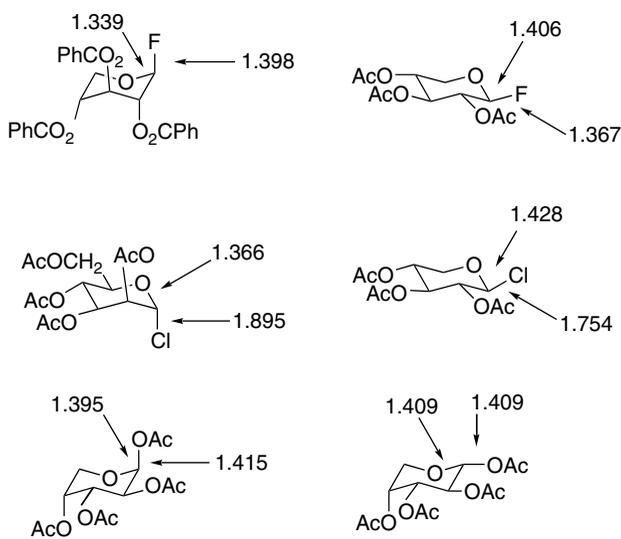
in the molecule is bonded to an anomeric carbon and is subject to the anomeric effect. Equally striking is the observation that all the substituents of the tri-*O*-acetyl- β -D-xylopyranosyl chloride shown in Entry 5 are in the axial orientation *in solution*. Here, no special crystal packing forces can favor the preferred conformation. The anomeric effect of a single chlorine is sufficient to drive the equilibrium in favor of the conformation that puts the three acetoxy groups in axial positions.

Changes in bond lengths are also frequently observed in connection with the anomeric effect. The exocyclic bond is shortened and the ring C–O bond to the anomeric center is lengthened. Scheme 2.17 shows some comparisons.

In 2-alkoxytetrahydropyran derivatives there is a correlation between the length of the exocyclic C–O bond and the nature of the oxygen substituent. Figure 2.33 shows bond length data for a series of monocyclic and bicyclic 2-aryloxytetrahydropyran derivatives. The more electron withdrawing the group, the longer the bond to the exocyclic oxygen and the shorter the ring C–O bond. This indicates that the extent of the anomeric effect *increases with the electron-accepting capacity of the exocyclic oxygen*.²⁴⁵

Several structural factors have been considered as possible causes of the anomeric effect. In localized valence bond terminology, there is a larger dipole-dipole repulsion between the polar bonds at the anomeric carbon in the equatorial conformation.²⁴⁶ This dipole-dipole interaction is reduced in the axial conformation and this factor contributes to the solvent dependence of the anomeric effect. The preference for the axial orientation is highest in nonpolar solvent effects, where the effect of dipolar

Scheme 2.17. Bond Distances in Å at Anomeric Carbons^a



a. From H. Paulsen, P. Luger, and F. P. Heiker, *Anomeric Effect: Origin and Consequences*, W. A. Szarek and D. Horton, eds., ACS Symposium Series No. 87, American Chemical Society, 1979, Chap.5.

²⁴⁵. A. J. Briggs, R. Glenn, P. G. Jones, A. J. Kirby, and P. Ramaswamy, *J. Am. Chem. Soc.* **106**, 6200 (1984).

²⁴⁶. J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

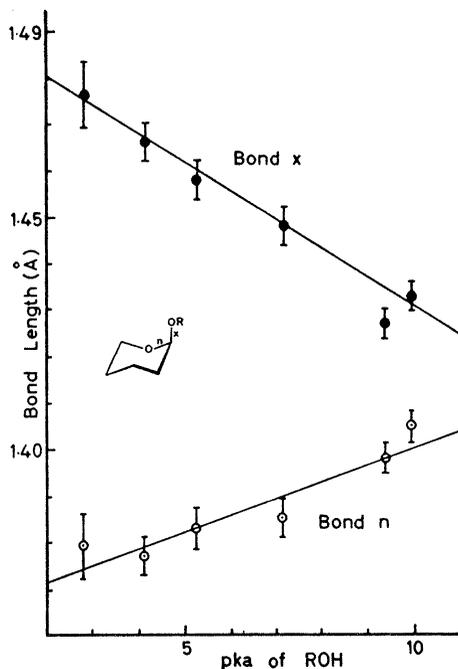
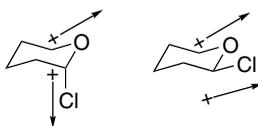


Fig. 2.33. Relationship between pK_a of alkoxy substituents and bond lengths in anomeric systems. The points represented are (left to right) 2,4-dinitrophenyl, 3,5-dinitrophenyl, 2,5-dinitrophenyl, 4-nitrophenyl*, 4-chlorophenyl*, and phenyl*. For the groups marked with an asterisk, the data are from a bicyclic structure. Reproduced from *J. Am. Chem. Soc.*, **106**, 6200 (1984), by permission of the American Chemical Society.

interactions would be strongest. For example, Table 2.7 shows the solvent dependence of 2-methoxytetrahydropyran.²⁴⁷



In general, electrostatic interactions alone do not seem to be sufficient to account for the magnitude of the anomeric effect and do not directly explain the bond length changes that are observed.²⁴⁸ These factors led to the proposal that the anomeric effect is, at least in part, due to $\sigma \rightarrow \sigma^*$ hyperconjugation effects.²⁴⁹ From the molecular orbital viewpoint, the anomeric effect is expressed as resulting from an interaction

²⁴⁷ R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Can. J. Chem.*, **47**, 4427 (1969).

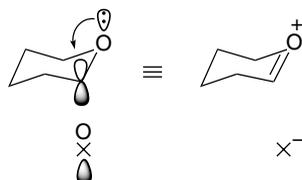
²⁴⁸ C. Altona, C. Knobler, and C. Romers, *Acta Cryst.*, **16**, 1217 (1963); C. Altona and C. Romers, *Acta Cryst.*, **16**, 1225 (1963).

²⁴⁹ C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969).

Table 2.7. Solvent Dependence of Conformational Equilibrium for 2-Methoxytetrahydropyran

Solvent	Dielectric constant	% Axial conformer
CCl ₄	2.2	83
Benzene	2.3	82
Chloroform	4.7	71
Acetone	20.7	72
Methanol	32.6	69
Acetonitrile	37.5	68
Water	78.5	52

between the lone-pair electrons on the pyran oxygen and the σ^* orbital associated with the bond to the electronegative substituent.²⁵⁰ When the C–X bond is axial, an interaction between an occupied p -type orbital on oxygen (unshared electrons) and the antibonding σ^* orbital of the C–X combination is possible. This interaction permits delocalization of the unshared electrons and would be expected to shorten and strengthen the C–O bond while lengthening and weakening the C–X bond, as is observed. These are the same structural factors identified in Topic 1.2, where the effect of hyperconjugation on conformation of acyclic compounds is discussed.



There have been various studies aimed at determining the energy differences associated with the anomeric effect. Temperature-dependent ¹³C-NMR chemical shift studies of 2-methoxytetrahydropyran determined ΔG values ranging from 0.5 to 0.8 kcal/mol, depending on the solvent.²⁵¹ Wiberg and Marquez measured a difference of 1.2 kcal/mol between the axial and equatorial methoxy group in the conformationally biased 3,5-dimethyltetrahydropyran ring.²⁴⁴ The energy difference decreased in more-polar solvents; the equatorial isomer is preferred in water.

There have also been a number of computational investigations into the nature of the anomeric effect. The axial-equatorial conformational equilibria for 2-fluoro and 2-chlorotetrahydropyran have been investigated with several MO calculations, including the MP2/6-31G* level. The MP2/6-31G* calculations give values of 3.47 and 2.84 kcal/mol, respectively, for the energy favoring the axial conformer.²⁵² Solvent effects were also explored computationally and show the usual trend of reduced stability for the axial conformation as solvent polarity increases. Salzner and Schleyer applied

²⁵⁰. S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmaida, *J. Chem. Soc. B*, 136 (1971); S. O. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Am. Chem. Soc.* **95**, 306 (1973); F. A. Van-Catledge, *J. Am. Chem. Soc.*, **96**, 5693 (1974).

²⁵¹. H. Booth, J. M. Dixon, and S. A. Readshaw, *Tetrahedron*, **48**, 6151 (1992).

²⁵². I. Tvaroska and J. P. Carver, *J. Phys. Chem.*, **98**, 6452 (1994).

Table 2.8. Calculated Energy Differences for Tetrahydropyrans (kcal/mol)

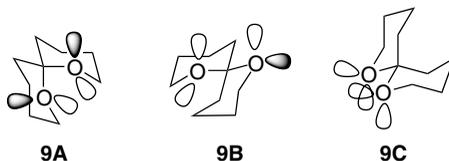
Substituent	ΔE_{total}	ΔE_{local}	ΔE_{deloc}
F	2.8	-1.2	4.0
CH ₃ O	1.5	-0.3	1.8
HO	1.3	-0.5	1.8
H ₂ N	-2.8	-6.4	3.6
H ₃ N ⁺	-3.0	-15	12
Cl	2.5	-5.4	7.9

an NBO analysis (see Section 1.4.2) to separate steric, polar, and other localized effects from the delocalization components of the anomeric effect.²⁵³ Using MP2/6-31G* level calculations, they arrived at the results in Table 2.8.

According to this analysis, the $\sigma \rightarrow \sigma^*$ (ΔE_{deloc}) interaction is stabilizing for all substituents. However, opposing electrostatic and steric effects (ΔE_{local}) are larger for the NH₂ and NH₃⁺ groups. Cortes and co-workers carried out a similar analysis for 1,3-dioxanes using B3LYP/6-31G(*d,p*) computations. The results are shown in Table 2.9

The B3LYP computations arrive at much larger values than found for the tetrahydropyrans, especially for the Cl and H₃N⁺ substituents, although there are also large compensating localization effects. These theoretical efforts provide support for $\sigma \rightarrow \sigma^*$ delocalization as a component of the anomeric effect, although leaving uncertainty as to the relative energies that are involved.

In bicyclic systems such as **9**, the dominant conformation is the one with the maximum anomeric effect. In the case of **9**, only conformation **9A** provides the preferred *anti*-periplanar geometry for both oxygens.²⁵⁴ *Anti* periplanar relationships are indicated by the shaded oxygen orbitals. Other effects, such as torsional strain and nonbonded repulsion contribute to the conformational equilibrium, of course.

**Table 2.9. Calculated Energy Differences in 1,3-Dioxanes (kcal/mol)**

Substituent	ΔE_{total}	ΔE_{local}	ΔE_{deloc}
F	4.0	1.66	2.34
CH ₃ O	2.30	5.17	2.87
HO	-0.98	2.06	3.04
H ₂ N	1.75	6.01	-4.26
H ₃ N ⁺	-1.32	-52.67	51.36
Cl	6.79	-12.69	19.45

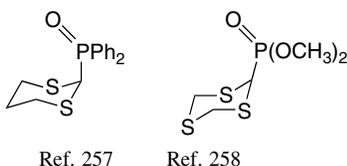
²⁵³ U. Salzner and P. v. R. Schleyer, *J. Org. Chem.*, **59**, 2138 (1994).

²⁵⁴ P. Deslongchamps, D. D. Rowan, N. Pothier, G. Sauve, J. K. Saunders *Can. J. Chem.*, **59**, 1132 (1981).

Anomeric effects are also observed for elements in the heavier rows of the periodic table. For example, *trans*-2,3-dichloro-1,4-dithiane exists in the diaxial conformation.²⁵⁵



Tetravalent phosphorus groups prefer axial orientations in 1,3-dithianes and 1,3,5-trithianes. NMR studies have indicated a preference of about 1 kcal for the diphenylphosphoryl group. When combined with the conformational energy in a cyclohexane ring, this suggests an anomeric effect of around 3 kcal.²⁵⁶



The anomeric effect is not limited to six-membered ring compounds. In five-membered rings the anomeric effect can affect both ring and substituent conformation. The 1,3-dioxole ring adopts a puckered conformation as a result of an anomeric effect.²⁵⁹ Similar effects are observed, although attenuated, in 1,3-benzodioxoles.²⁶⁰



The anomeric effect is also believed to be an important factor in the conformation of ribonucleosides. The anomeric effect with the exocyclic nitrogen is stronger when the heterocyclic base is in the pseudoaxial position. Steric factors, on the other hand, favor the pseudoequatorial conformation. By analysis of the pH-dependent conformational equilibria, a contribution from the anomeric effect of as much as 5.6 kcal for adenosine and 9.0 kcal for guanosine has been suggested.²⁶¹

²⁵⁵ H. T. Kalf and C. Romers, *Acta Cryst.*, **18**, 164 (1965).

²⁵⁶ E. Juaristi, N. A. Lopez-Nunez, R. S. Glass, A. Petsom, R. O. Hutchins, and J. P. Stercho, *J. Org. Chem.*, **51**, 1357 (1986).

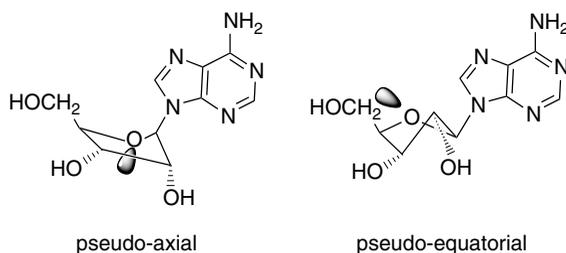
²⁵⁷ E. Juaristi, L. Valle, C. Mora-Uzeta, B. A. Valenzuela, P. Joseph-Nathan, and M. Fredrich, *J. Org. Chem.*, **47**, 5038 (1982).

²⁵⁸ M. Mikolajczyk, M. Balczewski, K. Wroblewski, J. Karolak-Wojciechowska, A.J. Miller, M. W. Wiczorek, M. Y. Antipin, and Y. T. Struchkov, *Tetrahedron*, **40**, 4885 (1984).

²⁵⁹ D. Suarez, T. L. Sordo, and J. A. Sordo, *J. Am. Chem. Soc.*, **118**, 9850 (1996).

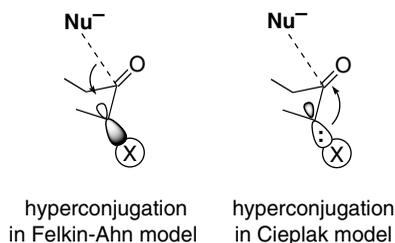
²⁶⁰ S. Sakurai, N. Meinander, K. Morris, and J. Laane, *J. Am. Chem. Soc.*, **121**, 5056 (1999).

²⁶¹ J. Plavec, C. Thibaudeau, and J. Chattopadhyaya, *Pure Appl. Chem.*, **68**, 2137 (1996); I. Luyten, C. Thibaudeau, and J. Chattopadhyaya, *J. Org. Chem.*, **62**, 8800 (1997).



Topic 2.4. Polar Substituent Effects in Reduction of Carbonyl Compounds

The stereoselectivity of hydride reduction was discussed in terms of steric approach and torsional effects in Section 2.4.1.2. Two additional factors have to be considered when polar substituents are present. The polar substituents enhance the importance of hyperconjugation involving σ and σ^* orbitals. Polar substituents also introduce bond dipoles and the potential for electrostatic interactions. Both the hyperconjugative and dipolar interactions depend on the equatorial or axial orientation of the substituent. There are two contrasting views of the nature of the hyperconjugative effects. One is the *Felkin-Ahn model*, which emphasizes stabilization of the developing negative charge in the forming bond by interaction with the σ^* orbital of the substituent. The preferred alignment for this interaction is with an axial position and the strength of the interaction should increase with the electron-accepting capacity of the substituent.²⁶² The Cieplak model²⁶³ emphasizes an alternative interaction in which the σ orbital of the C–X bond acts as a donor to the developing antibonding orbital.²⁶⁴ It has been pointed out that both of these interactions can be present, since they are not mutually exclusive, although one should dominate.²⁶⁵ Moreover, hydride reductions involve *early transition states*. The electronic effects of substituents on the reactant should be more prominent than effects on the TS.



There have been computational efforts to understand the factors controlling axial and equatorial approaches. A B3LYP/6-31G* calculation of the TS for addition of lithium hydride to cyclohexanone is depicted in Figure 2.34.²⁶⁶ The axial approach is

²⁶² N. T. Ahn, *Top. Current Chem.*, **88**, 145 (1980).

²⁶³ A. S. Cieplak, *J. Am. Chem. Soc.*, **103**, 4540 (1981).

²⁶⁴ Both the Felkin-Ahn and Cieplak models are also applied to alkyl substituents.

²⁶⁵ H. Li and W. J. le Noble, *Recl. Trav. Chim. Pays-Bas*, **111**, 199 (1992).

²⁶⁶ T. Senju, and S. Tomoda, *Chem. Lett.*, 431 (1997).

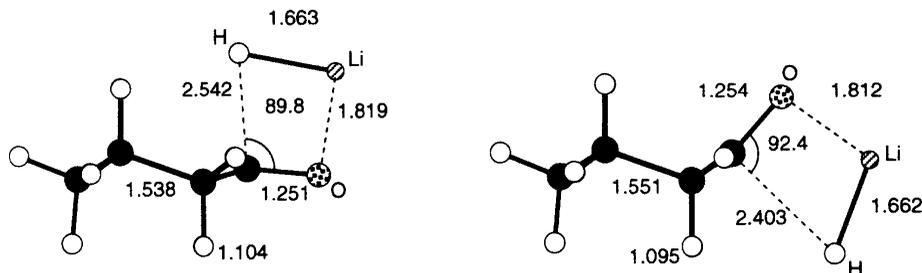
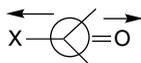


Fig. 2.34. B3LYP/6-31G* transition structures for axial and equatorial addition of LiH to cyclohexanone. Reproduced from *Chem. Lett.*, 431 (1997).

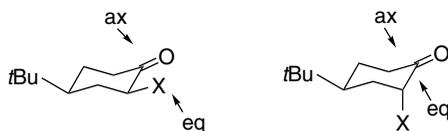
found to be 1.7 kcal more stable, in good agreement with the experimental ratio of 9:1. About half of the energy difference between the two TSs can be attributed to the torsional effect (see p. 177). An NBO analysis was applied to search for hyperconjugative interactions. The Felkin-Ahn interactions were minimal. The Cieplak effect was evident, but was similar in both the axial and equatorial approach TSs, raising doubts that it could determine the stereoselectivity.

Polar substituents may also affect stereoselectivity through an electrostatic effect that depends on the size and orientation of the bond dipole. These are relatively easy to determine for the ground state molecule but may be altered somewhat in the TS. The dipole from an electronegative substituent prefers to be oriented *anti* to the carbonyl substituent.



Rosenberg and co-workers approached the problem of separating the hyperconjugative and electrostatic interactions by examining the product ratios for NaBH₄ reduction of both axially and equatorially oriented substituents in 4-*t*-butylcyclohexanones.²⁶⁷ The product ratios were used to calculate the energy difference, $\Delta\Delta G$ (kcal/mol), for axial and equatorial approach. The results are given in Table 2.10.

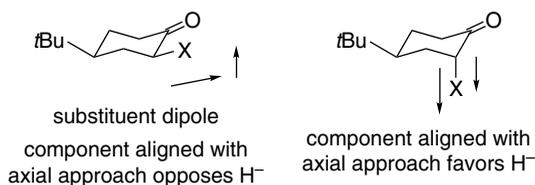
Table 2.10. Percent Axial and Equatorial Approach in Reduction of 2-Substituted 4-*t*-Butylcyclohexanones



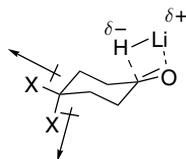
Substituent	% Equatorial	% Axial	$\Delta\Delta G$ (kcal/mol)	% Equatorial	% Axial	$\Delta\Delta G$ (kcal/mol)
H	9	91	0	9	91	0
CH ₃	11	89	0.12	5	95	-0.35
OCH ₃	67	33	1.64	8	92	-0.08
F	40	60	1.04	9	91	0
Cl	34	66	0.90	0.9	99.1	-1.30
Br	29	71	0.77	1.4	98.6	1.05

²⁶⁷ R. E. Rosenberg, R. L. Abel, M. D. Drake, D. J. Fox, A. K. Ignatz, D. M. Kwiat, K. M. Schaal, and P. R. Virkle, *J. Org. Chem.*, **66**, 1694 (2001).

The equatorial substituents all shift the ratio toward an increased equatorial approach in the order $\text{CH}_3\text{O} \gg \text{F} > \text{Cl} > \text{Br} \gg \text{CH}_3$. All axial substituents except F, which has no effect, favor increasing axial attack in the order $\text{F} < \text{CH}_3\text{O} < \text{CH}_3 < \text{Br} < \text{Cl}$. These results can be at least partially explained in terms of an electrostatic interaction between the dipole of the substituent and the approaching nucleophile. In the case of the equatorial substituents, the fraction of the dipole that is *opposed* to an approaching negative charge in the TS increases in the order Cl (0.28) < F (0.43) < OCH_3 (0.98), which agrees with the substituent effect. The dipole for axial substituents *favors axial attack*. Here, the fractional alignment of the dipoles is OCH_3 (0.49) < Cl (0.97) < F (0.98). There is an inherent preference for an axial approach in the case of the *trans* (axial) substituents, which is reinforced by Cl and Br but not by F or OCH_3 . In these cases some other factor(s) must be operating.



The role of orientation of substituent dipoles is also considered to be a major factor in 3- and 4-substituted cyclohexanones. Shi and Boyd used an AIM analysis to examine stereoselectivity in 3- and 4-substituted cyclohexanones.²⁶⁸ Little difference in charge depletion was found for the two faces of the cyclohexanone ring. Addition TSs for LiH, similar to those in Figure 2.34, were studied. Energies and charge distributions were obtained from HF/6-31G(*d*) and MP2/6-31G(*d*) calculations. Polar F and Cl substituents at C(4) reduce the TS barrier, which is in accord with experimental results. The effect for axial substituents was larger than for equatorial, so that the axial substituents are predicted to have a greater preference for axial approach. The authors suggest that the effect has its origins in the C–X bond dipoles. The axial dipole has a larger component perpendicular to the carbonyl group and favors axial approach by the hydride.

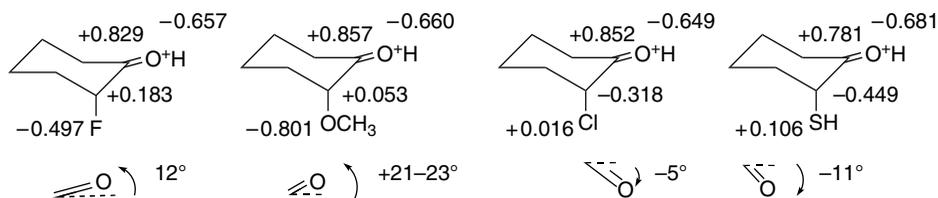


Another computational study²⁶⁹ examined how cyclohexanone substituent electronic effects respond to Lewis acid complexation. The metal cation was modeled by a H^+ (which represents the hard extreme of a Lewis acid). It was found that the complexation amplifies the effect of the α -donor substituents. The computations indicate that the electron-donor substituents cause pyramidalization at the carbonyl carbon and that this then controls the direction of nucleophile approach. The results

²⁶⁸ Z. Shi and R. J. Boyd, *J. Am. Chem. Soc.*, **115**, 9614 (1993).

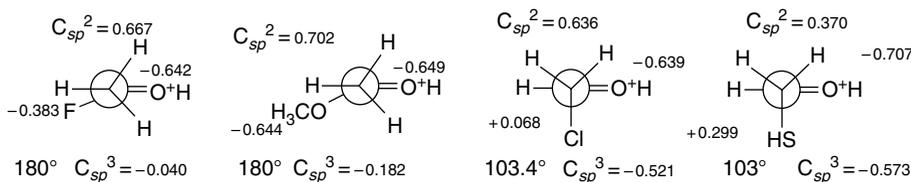
²⁶⁹ V. K. Yadav, D. A. Jeyaraj, and R. Balamurugan, *Tetrahedron*, **56**, 7581 (2000).

are summarized below. According to NPA charge analysis, the Cl and SH substituents are significant σ donors and lead to movement of oxygen to the equatorial direction, favoring axial approach by the nucleophile. The oxygen and fluoro substituents have the opposite effects and favor equatorial approach. Experimental data are available for the SH, Cl, and OCH_3 substituents and are in accord with these predictions. Looking at the data in Table 2.10, we see that axial OCH_3 and F have little effect, whereas Cl and Br favor axial approach. These results are in agreement with the better donor capacity attributed to third-row elements in the discussion of heteroatom hyperconjugation (Topic 1.2). This study concludes that the substituents effects operate in the ground state molecule and are accentuated by coordination of a cation at oxygen.



Angle quoted is change in pyramidalization upon protonation.

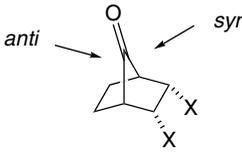
Yadav and co-workers also reported calculations aimed at comparing the relative donor ability of some heteroatom substituents.²⁶⁸ The preferred orientation of the substituent with respect to a carbonyl group was examined using substituted acetaldehydes as the model. The calculations were done at the MP2/6-31G(*d*) level and charges were assigned by the NPA method. According to these results, methoxy and fluoro substituents are poor σ donors and maintain a dihedral angle of 180° with respect to the carbonyl, presumably reflecting the strong opposing polarity of the $\text{C}=\text{O}$ and $\text{C}-\text{F}$ (or $\text{C}-\text{O}$) bonds. This orientation was also found for the protonated carbonyl group. On the other hand, when the carbonyl group is protonated, Cl and SH substituents assume nearly perpendicular angles that maximize hyperconjugation. They become positively charged, reflecting $\sigma \rightarrow \pi^*$ electron donation (Cieplak model).



In contrast to the case of cyclic ketones, there is not much experimental data for polar α -substituents for acyclic ketones. Moreover, in some cases, such as α -methoxy, chelation effects are the dominant factor.

Electronic effects have been examined using *endo,endo*-disubstituted norbornan-7-ones. The *endo* substituents are located so that there are no direct steric interactions with the reaction site. The amount of *anti* versus *syn* approach by NaBH_4 has been determined,²⁷⁰ and the results are given in Table 2.11

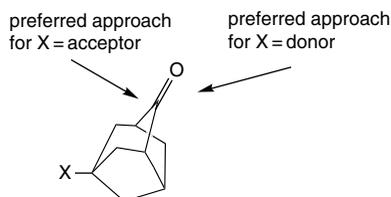
²⁷⁰ G. Mehta, F. A. Khan, *J. Am. Chem. Soc.*, **112**, 6140 (1990); H. Li, G. Mehta, S. Padma, and W. J. le Noble, *J. Org. Chem.*, **56**, 2006 (1991); G. Mehta, F. A. Khan, B. Ganguly, and J. Chandrasekhan, *J. Chem. Soc., Perkin Trans. 2*, 2275 (1994).

Table 2.11. Stereoselectivity in NaBH₄ Addition to Norbornan-7-ones


Substituent	% <i>syn</i>	% <i>anti</i>
CH ₃	45	55
C ₂ H ₅	20	80
CH ₂ =CH	36	64
CH ₃ OCH ₂	40	60
CH ₃ O ₂ C	84	16

The trend in the data is that electron-donor substituents favor *anti* addition, whereas acceptor substituents favor *syn* addition. A particularly intriguing point is that the 2,3-diethyl compound is more *anti* selective than the 2,3-dimethyl derivative. This is puzzling for any interpretation that equates the electronic effects of the methyl and ethyl groups. Two explanations have been put forward for the overall trend in the data. According to an orbital interaction (hyperconjugation) model, electron-withdrawing substituents decrease the stabilization of the LUMO (Cieplak model) and favor *syn* addition. An electrostatic argument focuses on the opposite direction of the dipole resulting from electron-releasing and electron-withdrawing substituents.²⁷¹ The dipoles of the electron-withdrawing groups will facilitate *syn* approach. Several levels of theory have been applied to these results.²⁷² Most recently, Yadav examined the effect using B3LYP/6-31G*-level calculations on both the neutral and the protonated ketones.²⁷³ The *anti*-periplanar orbital stabilization found for the diethyl compound was about 0.5 kcal/mol higher than for the dimethyl derivative. In this model, the resulting greater pyramidalization of the reactant accounts for the enhanced selectivity.

Adamantanone is another ketone where interesting stereoselectivity is noted. Reduction by hydride donors is preferentially *syn* to acceptor substituents at C(5) and *anti* to donor substituents.²⁷⁴ These effects are observed even for differentially substituted phenyl groups.²⁷⁵ As the substituents are quite remote from the reaction center, steric effects are unlikely to be a factor.



²⁷¹ G. Mehta, F. A. Khan, and W. Adcock, *J. Chem. Soc. Perkin Trans.*, **2**, 2189 (1995).

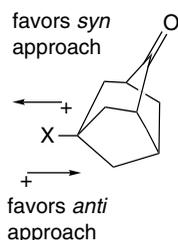
²⁷² M. N. Paddon-Row, Y.-D. Wu, and K. N. Houk, *J. Am. Chem. Soc.*, **114**, 10638 (1992); R. Ganguly, J. Chandrasekhan, F. A. Khan, and G. Mehta, *J. Org. Chem.*, **58**, 1734 (1993); G. M. Keseru, Z. Kovari, and G. Naray-Szabo, *J. Chem. Soc. Perkin Trans.*, **2**, 2231 (1996).

²⁷³ V. K. Yadav, *J. Org. Chem.*, **66**, 2501 (2001); V. K. Yadav and R. Balmurugan, *J. Chem. Soc. Perkin Trans.*, **2**, 1 (2001).

²⁷⁴ C. K. Cheung, L. T. Tseng, M.-H. Lin, S. Srivastava and W. J. Le Noble, *J. Am. Chem. Soc.*, **108**, 1598 (1986); J. M. Hahn and W. J. Le Noble, *J. Am. Chem. Soc.*, **114**, 1916 (1992).

²⁷⁵ I. H. Song and W. J. Le Noble, *J. Org. Chem.*, **59**, 58 (1994).

These effects are attributed to differences in the σ -donor character of the C–C bonds resulting from the substituent (Cieplak model). Electron-attracting groups diminish the donor capacity and promote *syn* addition. An alternative explanation invokes a direct electrostatic effect arising from the C–X bond dipole.²⁷⁶



The arguments supporting the various substituent effects on stereoselectivity in cyclic ketones have been discussed by some of the major participants in the field in a series of review articles in the 1999 issue of *Chemical Reviews*.²⁷⁷ While many of the details are still subject to discussion, several general points are clear. (1) For cyclohexanones, in the absence of steric effects, the preferred mode of attack by small hydride reducing agents is from the axial direction. Torsional effects are a major contributing factor to this preference. (2) When steric factors are introduced, either by adding substituents to the ketone or using bulkier reducing agents, equatorial approach is favored. Steric approach control is generally the dominant factor for bicyclic ketones. (3) In bicyclic ketones, electron donor substituents favor an *anti* mode of addition and acceptor substituents favor a *syn* approach.

The issues that remain under discussion are: (1) the relative importance of the acceptor (Felkin-Ahn) or donor (Cieplak) hyperconjugation capacity of α substituents; (2) the relative importance of electrostatic effects; and (3) the role of reactant pyramidalization in transmitting the substituent effects. Arguments have been offered regarding the importance of electrostatic effects in all the systems we have discussed. Consideration of electrostatic effects appears to be important in the analysis of stereoselective reduction of cyclic ketones. Orbital interactions (hyperconjugation) are also involved, but whether they are primarily ground state (e.g., reactant pyramidalization) or transition state (e.g., orbital stabilization) effects is uncertain.

General References

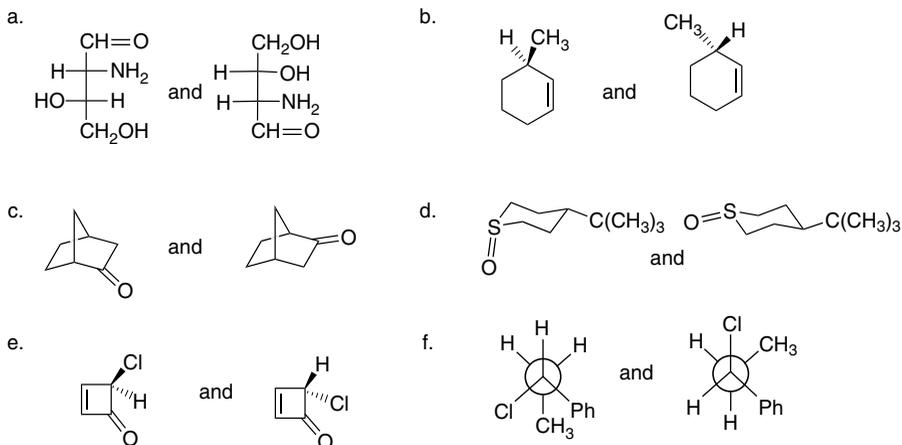
- D. Ager and M. B. East, *Asymmetric Synthetic Methodology*, CRC Press, Boca Raton, FL, 1996.
 R. S. Atkinson, *Stereoselective Synthesis*, John Wiley & Sons, New York, 1995.
 J. Dale, *Stereochemistry and Conformational Analysis*, Verlag Chemie, New York, 1978.
 E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Wiley-Interscience, New York, 1965.
 E. L. Eliel, S. H. Wilen, and L. N. Mander, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1993.
 E. Juaristi and G. Cuevas, *The Anomeric Effect*, CRC Press, Boca Raton, FL, 1995.
 A. J. Kirby, *Stereoelectronic Effects*, Oxford University Press, Oxford, 1996.

²⁷⁶ W. Adcock, J. Cotton, and N. A. Trout, *J. Org. Chem.*, **59**, 1867 (1994).

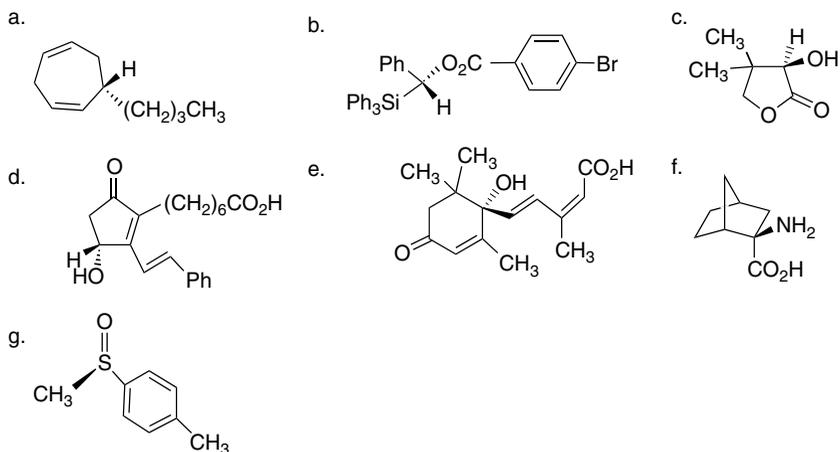
²⁷⁷ B. W. Gung and W. G. le Noble, eds., Thematic Issue on Diastereoselection, *Chemical Reviews*, **99**, No. 5, 1999.

(References for these problems will be found on page 1156.)

2.1. Indicate whether the following pairs of compounds are identical, enantiomers, diastereomers, or structural isomers.



2.2. Use the sequence rule to specify the configuration of the stereogenic center in each of the following molecules.



2.3. Draw structural formulas for each of the following compounds, clearly showing all aspects of the stereochemistry.

- E*-3,7-dimethyl-2,6-octadien-1-ol (geraniol)
- R*-4-methyl-4-phenylcyclohex-2-enone
- L*-*erythro*-2-(methylamino)-1-phenylpropan-1-ol [(-)-ephedrine]
- 7*R*,8*S*-7,8-epoxy-2-methyloctadecane (dispalure, a pheromone of the female gypsy moth)

- e. methyl 1*S*-cyano-2*R*-phenylcyclopropanecarboxylate
- f. *Z*-2-methyl-2-buten-1-ol
- g. *E*-(3-methyl-2-pentenylidene)triphenylphosphorane

2.4. Draw the structures of the product(s) described for each reaction. Specify all aspects of the stereochemistry.

- a. stereospecific *anti* addition of bromine to *cis*- and *trans*-cinnamic acid.
- b. methanolysis of *S*-3-bromooctane with 6% racemization.
- c. stereospecific *syn* thermal elimination of acetic acid from 1*R*,2*S*-diphenylpropyl acetate
- d. stereoselective epoxidation of bicyclo[2.2.1]hept-2-ene proceeding 94% from the *exo* face.

2.5. The preferred conformation of 1-methyl-1-phenylcyclohexane has the phenyl group in the axial orientation ($\Delta G = -0.32$ kcal/mol) even though its conformational free energy (2.9 kcal/mol) is greater than that of methyl (1.8 kcal/mol). Explain.

2.6. The computed (HF/6-31G*) rotational profiles for acetone (2-propanone), 2-butanone, and 3-methyl-2-butanone are given in Figure 2.6P. Draw Newman projections corresponding to each clear maximum and minimum in the curves for each compound. Analyze the factors that stabilize/destabilize each conformation and discuss the differences among them.

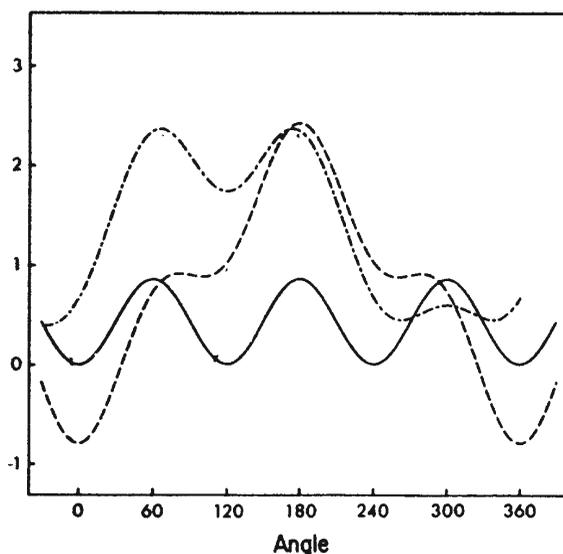
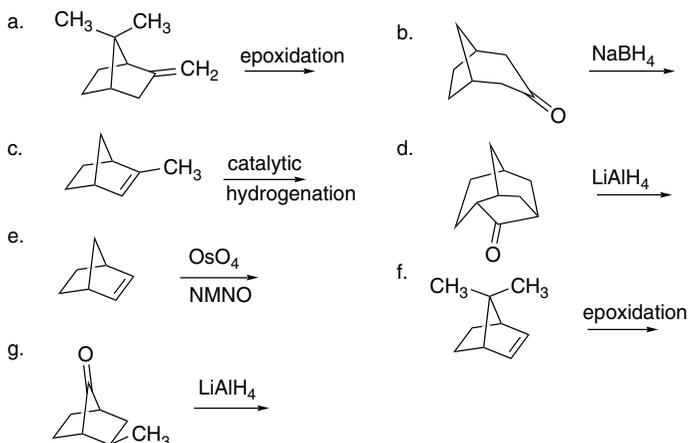
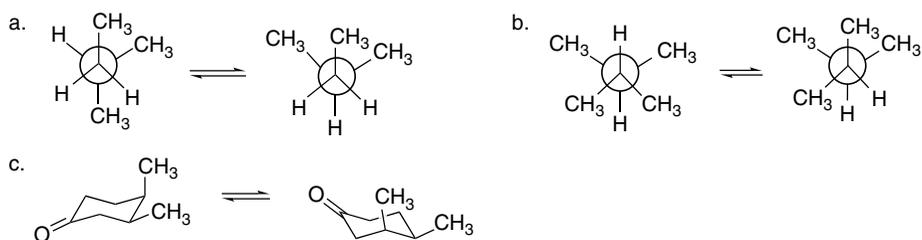


Fig. 2.6P. Rotational profile for acetone (A, solid line), 2-butanone (B, dashed line), and 3-methyl-2-butanone (C, dot-dashed line). Reproduced by permission of the American Chemical Society.

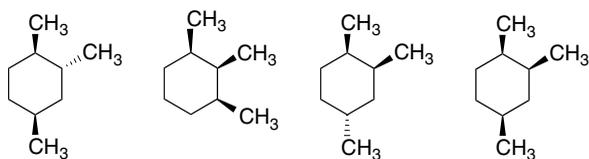
2.7. Predict the stereochemical outcome of the following reactions:



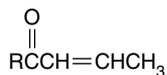
2.8. Estimate ΔH for each of the following conformational equilibria.



2.9. Estimate the free-energy difference between the stable and unstable chair conformations of the following trimethylcyclohexanes.

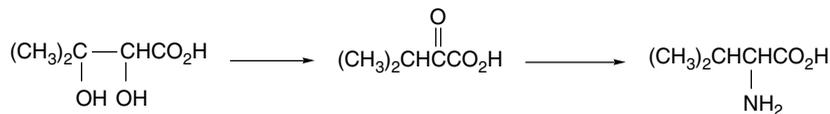


2.10. Predict the preferred conformation of the stereoisomeric *E*-enones **10-A**. How would you expect the conformational equilibrium to change as R becomes progressively larger?



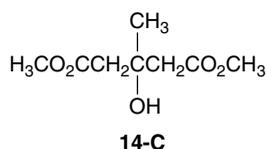
10-A

- c. The biosynthesis of valine by bacteria involves the following sequence:

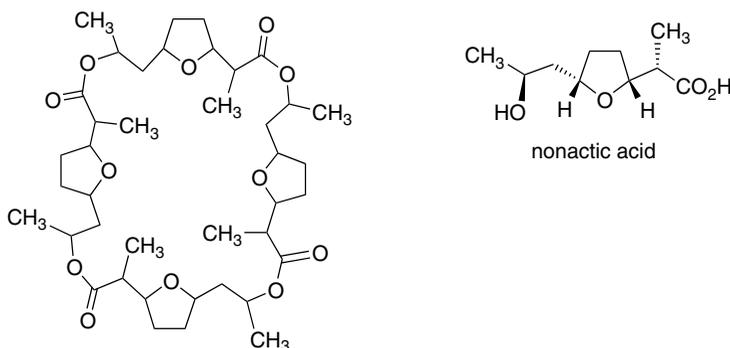


The stereochemistry of the reaction has been examined using the starting diol in which each methyl group was separately replaced by CD_3 . The diol- d_3 of the $2R,3R$ configuration produces $2S,3S$ -valine- d_3 , whereas the $2R,3S$ diol- d_3 produces $2S,3R$ -valine- d_3 . From this information deduce whether the C(2) and C(3) hydroxy are replaced with inversion or retention of configuration. Show the basis for your conclusion.

- d. A synthesis of the important biosynthetic intermediate mevalonic acid starts with the enzymatic hydrolysis of the diester **14-C** by pig liver esterase. The *pro-R* ester group is selectively hydrolyzed. Draw a three-dimensional structure of the product.



- 2.15. The structure of nonactin is shown below without any specification of stereochemistry. It is isolated as a pure substance from natural sources and gives no indication of being a mixture of stereoisomers. Although it is not optically active, it does not appear to be a racemic mixture, because it does not yield separate peaks on chiral HPLC columns. When completely hydrolyzed, it yields racemic nonactic acid. Deduce the stereochemical structure of nonactin from this information.



- 2.16. (a) The signals for the benzylic hydrogens in the ^1H NMR spectra of the *cis* and *trans* isomers of 1-benzyl-2,6-dimethylpiperidine have distinctly different appearances, as shown in Figure 2.16Pa. Answer the following questions about these spectra: (a) Which isomer corresponds to which spectrum and why do they have the appearances they do? (b) Only one isomer shows a multiplet corresponding to ring C–H hydrogens adjacent to nitrogen near 3 ppm. Why are these signals not visible in the other partial spectrum? (b) The partial ^1H NMR spectra corresponding to each benzyl ether of the diastereomeric 2,6-dimethylcyclohexanols are shown in Figure 2.16Pb. Assign the stereochemistry of each isomer.

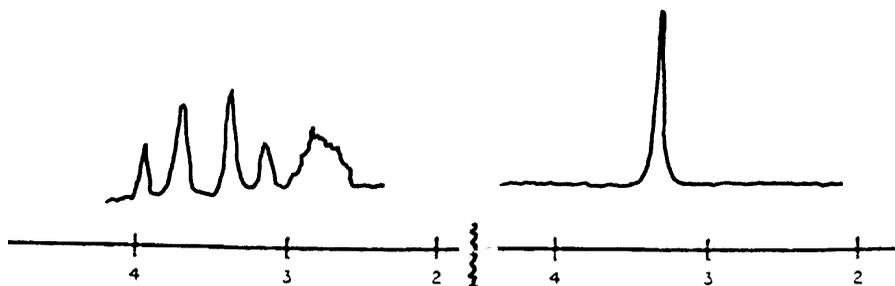


Fig. 2.16Pa. Partial ^1H NMR spectra of *cis* and *trans* isomers of 1-benzyl-2,6-dimethylpiperidine. Reproduced by permission of Elsevier.

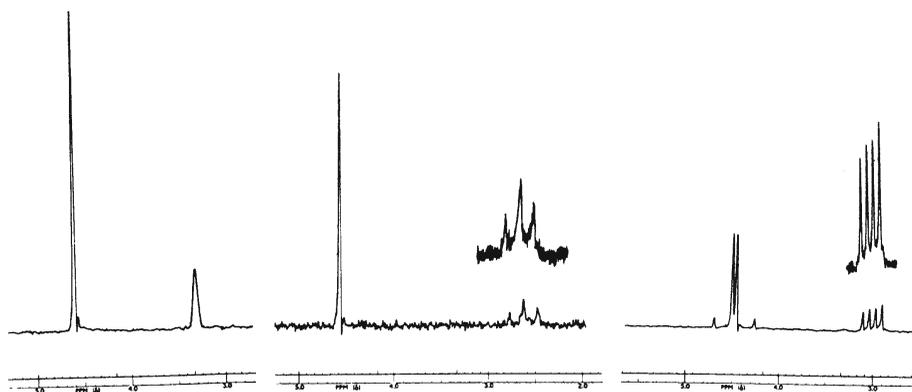


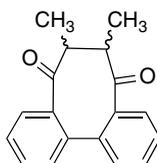
Fig. 2.16Pb. Partial ^1H NMR spectra of three stereoisomeric benzyl ethers of 2,6-dimethylcyclohexanol. Reproduced by permission of the American Chemical Society.

- 2.17. The *trans*:*cis* ratio of equilibrium for 4-*t*-butylcyclohexanol has been determined in several solvents near 80°C . From the data, calculate the conformational free energy, $-\Delta G_c$, for the hydroxy group in each solvent. What correlation do you find between the observed conformational equilibria and properties of the solvent?

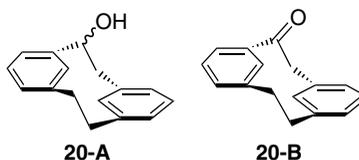
Solvent	<i>trans</i> (%)	<i>cis</i> (%)
Cyclohexane	70.0	30.0
Benzene	72.5	27.5
1,2-Dimethoxyethane	71.0	29.0
Tetrahydrofuran	72.5	27.5
<i>t</i> -Butyl alcohol	77.5	22.5
<i>i</i> -Propyl alcohol	79.0	21.0

- 2.18. *Trans*-3-alkyl-2-chlorocyclohexanones (alkyl=methyl, ethyl, isopropyl) exist with the substituents in the diequatorial conformation. In contrast, the corresponding *E*-*O*-methyloximes exist in the diaxial conformation. Explain the preference for the diaxial conformation of the oxime ethers.
- 2.19. The two stereoisomers (**19-A** and **19-B**) of the structure shown below have distinctly different NMR spectra. Isomer **19-A** shows single signals for the methyl

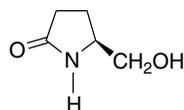
(doublet at 1.25) and methine (broad quartet at 2.94 ppm). Isomer **19-B** shows two methyl peaks (doublets at 1.03 and 1.22 ppm) and two quartets (2.68 and 3.47 ppm) for the methine hydrogens. Both spectra are temperature dependent. For isomer **19-A**, at -40°C the methyl doublet splits into two doublets of unequal intensity (1.38 and 1.22 ppm in the ratio of 9:5). The methine signal also splits into two broad signals at 3.07 and 2.89 ppm, also in the ratio of 9:5. For isomer **19-B**, pairs of doublets and quartets become single signals (still doublet and quartet, respectively) at 95°C . The spectrum shows no change on going to -40°C . Assign the stereochemistry of **19-A** and **19-B** and explain how the characteristics of the spectra are related to the stereochemistry.

**19-A**

- 2.20. Compound **20-A** can be resolved to give an enantiomerically pure substance with $[\alpha]_{\text{D}} = -124$. Oxidation gives an enantiomerically pure ketone **20-B**, $[\alpha]_{\text{D}} = -439$. Heating **20-A** establishes an equilibrium with a stereoisomer with $[\alpha]_{\text{D}} = +22$. Oxidation of this compound gives the enantiomer of **20-B**. Heating either enantiomer of **20-B** leads to racemization with $\Delta G^{\ddagger} = 25 \text{ kcal/mol}$. Deduce the stereochemical relationship between these compounds.

**20-A****20-B**

- 2.21. When partially resolved samples of *S*-5-(hydroxymethyl)pyrrolidin-2-one are allowed to react with benzaldehyde in the presence of an acid catalyst, two products **21-A** ($\text{C}_{12}\text{H}_{13}\text{NO}_2$) and **21-B** ($\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4$) are formed. The ratio of **21-A**:**21-B** depends on the enantiomeric purity of the starting material. When it is enantiomerically pure, only **21-A** is formed, but if it is racemic only **21-B** is formed. Partially resolved samples give **21-A** and **21-B** in a ratio corresponding to the e.e. The rotation of **21-A** is $[\alpha]_{\text{D}} = +269.6$, but **21-B** is not optically active. Develop an explanation for these observations including likely structures for **21-A** and **21-B**. Assign the configuration of all the stereogenic centers in the products you propose.

*S*-5-(hydroxymethyl)-
pyrrolidinone

2.22. Figure 2.22Pa,b shows energy as a function of rotation for a series of 2-substituted acetaldehydes, with $\theta = 0^\circ$ in the *syn* conformation and $\theta = 180^\circ$ in the *anti* conformation. The calculations were done by the PM3 method. Figure 2.P22a represents the isolated molecule, while Figure 2.P22b represents an elliptical solvent cavity with a dielectric constant of 4.7, approximating CHCl_3 . The Table 2.22P gives the calculated rotational barriers. Discuss the following aspects of the data. (a) Rationalize the $\text{Br} > \text{Cl} > \text{F}$ order of preference for *anti* conformation in the gas phase; (b) Why does the polar medium shift the equilibrium to favor more of the *syn* conformation?

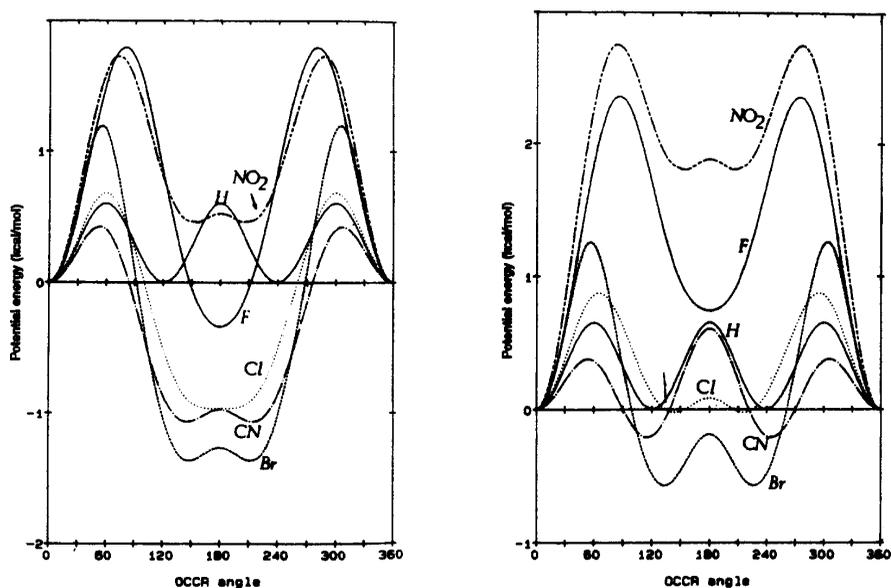
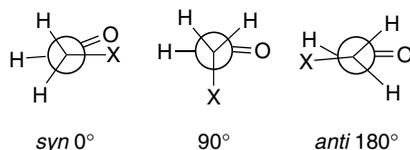


Fig. 2.22P. (a) Rotational profile of the isolated molecules. (b) Rotational profile in solvent cavity with dielectric constant 4.7. Reproduced by permission of Elsevier.

2.23. Provide a mechanistic explanation, including proposed transition structure(s), to account for the stereoselectivity observed in the following reactions:

a.

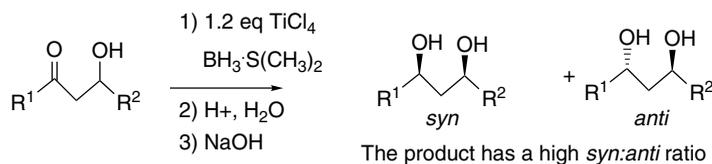
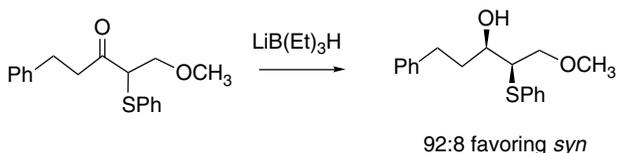


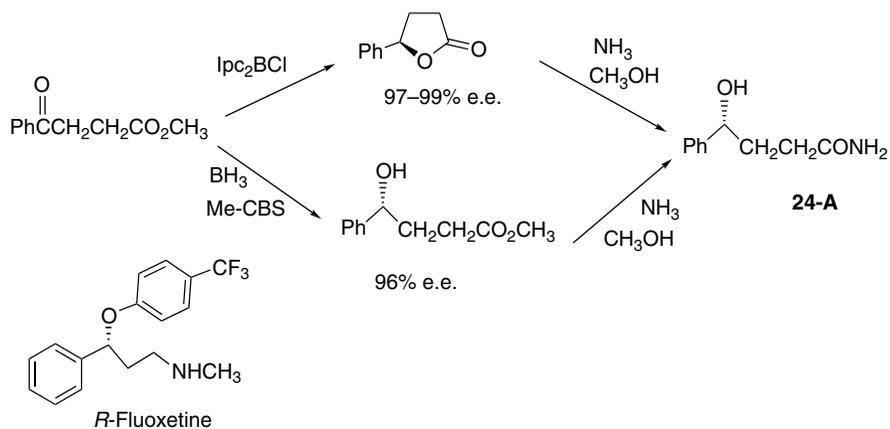
Table 2.22P. Energy Difference between *syn* and *anti* Conformations

Substituent	$E_{syn} - E_{anti}$ (kcal/mol)	
	Vacuum	$\epsilon = 4.7$
H	+0.60	+0.65
F	-0.34	+0.74
Cl	-0.97	-0.02
Br	-1.36	-0.57
CN	-1.07	-0.21
NO ₂	+0.46	+1.85

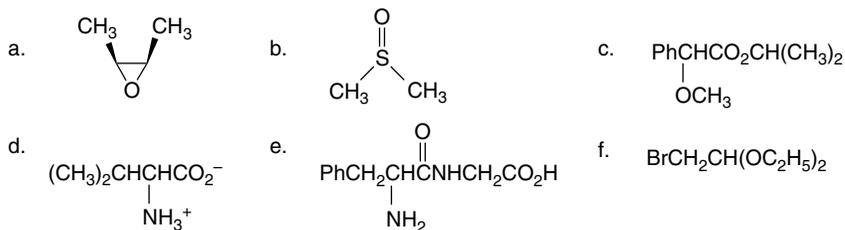
b.



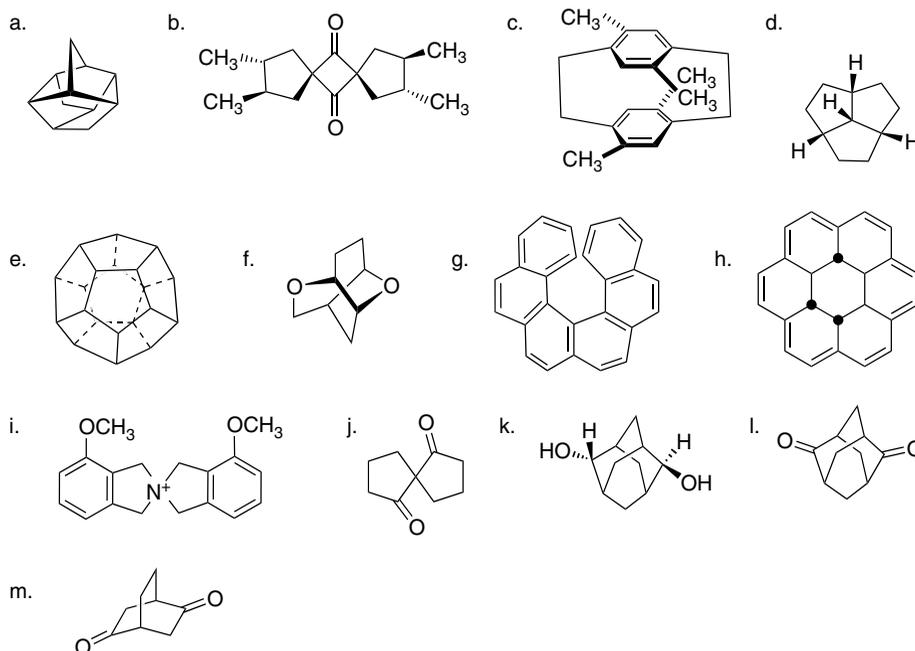
2.24. Either oxaborazolidine-catalysis (Me-CBS) or (Ipc)₂BCl reductions can be used to prepare **24-A** a precursor of Fluoxetine (Prozac)[®] in good yield and high e.e. Suggest transition structures that account for the observed enantioselectivity.



2.25 Some of the compounds shown below contain enantiotopic or diastereotopic atoms or groups. Which possess this characteristic? For those that do, indicate the atoms or groups that are diastereotopic and assign the groups as *pro-R* and *pro-S*.



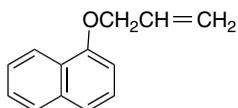
2.26. Indicate which of the following structures are chiral. For each molecule that is achiral, indicate an element of symmetry that is present in the molecule.



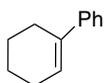
2.27. Predict the absolute configuration of the diols obtained from each of the following alkenes using either a dihydroquinidine or a dihydroquinine type dihydroxylation catalysts.



(b)



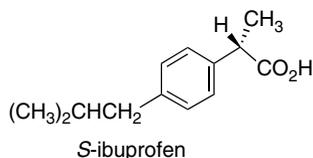
(d)



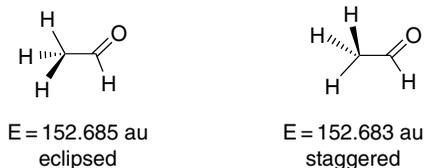
2.28. Based on the standard transition state models, predict the absolute configuration of the products of the following reactions:

- Reduction of 1-phenyl-1-propanone by $\text{BH}_3\text{-THF}$ using the oxaborazolidine catalyst derived from (*S*)- α , α -diphenylpyrrolidine-2-methanol.
- Reduction of 1,1,1-trifluorodec-3-yn-one by (*S*)-Alpine borane.
- Sharpless asymmetric epoxidation of *E*-hex-2-en-1-ol using (+)-diethyl tartrate.

- 2.29. Ibuprofen, an example of an NSAID, is the active ingredient in several popular over-the-counter analgesics. In the United States, it is sold in racemic form, even though only the *S*-enantiomer is pharmacologically active. Suggest methods that might be used to obtain or prepare ibuprofen in enantiomerically pure form, based on processes and reactions discussed in chapter 2.



- 2.30. Ab initio MO calculations (HF/4-31G) indicate that the eclipsed conformation of acetaldehyde is about 1.1 kcal more stable than the staggered conformation. Provide an explanation of this effect in terms of MO theory. Construct a qualitative MO diagram and point out the significant differences that favor the eclipsed conformation. Identify the interactions that are stabilizing and those that are destabilizing. Identify other factors that need to be considered to analyze the origin of the rotational barrier.

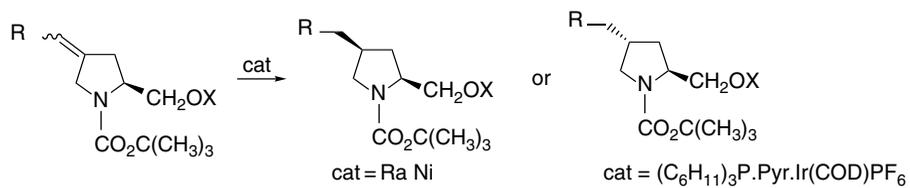


- 2.31. Treatment of alkylphosphoryl dichlorides with 1 equiv. of *L*-proline ethyl ester in the presence of 1-methylimidazole (acting as an acid-scavenger) leads to formation of a monophosphoramidate with low (< 20% diastereoselectivity). Addition of 0.25 equiv. of 4-nitrophenol then gives a 4-nitrophenylphosphoramidate with high (98%) diastereoselectivity, which in turn can be treated with methanol to isolate the methyl 4-nitrophenylphosphonate ester in high enantiomeric purity. This constitutes a kinetic resolution process. Write a mechanistic scheme that accounts for this series of transformations.
- 2.32. Use an appropriate computation program to compare the TS energies for hydroboration of the following alkenes by $(\text{CH}_3)_2\text{BH}$. Predict the *exo:endo* ratio for each compound. What factor might complicate the interpretation of the *exo:endo* ratio?



- 2.33. 9-BBN exhibits a high degree of stereoselectivity toward 1,3-dimethyl cycloalkenes such as 1,3-dimethylcyclopentene and 1,3-dimethylcyclohexene, giving exclusively the *trans*, *trans*-2,6-dimethyl cycloalkanols. Offer an explanation.
- 2.34. Diastereoselective reduction of a number of 4-alkylideneprolinols has been accomplished. With a silyl protecting group in place, using Raney nickel, the

cis isomers are formed in ratio of about 15:1. When the unprotected alcohols are used with the Crabtree catalyst, quite high selectivity for the *trans* isomer is found. Explain these results.



R	X = <i>t</i> -Butyldimethylsilyl	X = H
C ₂ H ₅	13:1	>40:1
Ph	15:1	>40:1
CH ₃ O ₂ C	15:1	16:1