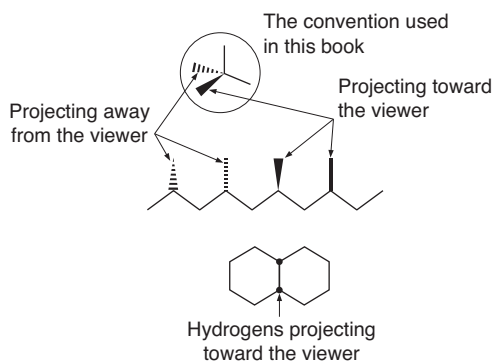# Stereochemistry

Intent and Purpose

Stereochemistry is the study of the static and dynamic aspects of the three-dimensional shapes of molecules. It has long provided a foundation for understanding structure and reactivity. At the same time, stereochemistry constitutes an intrinsically interesting research field in its own right. Many chemists find this area of study fascinating due simply to the aesthetic beauty associated with chemical structures, and the intriguing ability to combine the fields of geometry, topology, and chemistry in the study of three-dimensional shapes. In addition, there are extremely important practical ramifications of stereochemistry. Nature is inherently chiral because the building blocks of life (α-amino acids, nucleotides, and sugars) are chiral and appear in nature in enantiomerically pure forms. Hence, any substances created by humankind to interact with or modify nature are interacting with a chiral environment. This is an important issue for bioorganic chemists, and a practical issue for pharmaceutical chemists. The Food and Drug Administration (FDA) now requires that drugs be produced in enantiomerically pure forms, or that rigorous tests be performed to ensure that both enantiomers are safe.

In addition, stereochemistry is highly relevant to unnatural systems. As we will describe herein, the properties of synthetic polymers are extremely dependent upon the stereochemistry of the repeating units. Finally, the study of stereochemistry can be used to probe reaction mechanisms, and we will explore the stereochemical outcome of reactions throughout the chapters in parts II and III of this text. Hence, understanding stereochemistry is necessary for most fields of chemistry, making this chapter one of paramount importance.

All introductory organic chemistry courses teach the fundamentals of stereoisomerism, and we will only briefly review that information here. We also take a slightly more modern viewpoint, emphasizing newer terminology and concepts. The goal is for the student to gain a fundamental understanding of the basic principles of stereochemistry and the associated terminology, and then to present some of the modern problems and research topics in this area.

6.1 Stereogenicity and Stereoisomerism

Stereochemistry is a field that has often been especially challenging for students. No doubt one reason for this is the difficulty of visualizing three-dimensional objects, given two-dimensional representations on paper. Physical models and 3-D computer models can be of great help here, and the student is encouraged to use them as much as possible when working through this chapter. However, only simple wedges and dashes are given in most of our drawings. It is these kinds of simple representations that one must master, because attractive, computer generated pictures are not routinely available at the work bench. The most common convention is the familiar "wedge-and-dash" notation. Note that there is some variability in the symbolism used in the literature. Commonly, a dashed wedge that gets larger as it emanates from the point of attachment is used for a receding group. However, considering the art of perspective drawing, it makes no sense that the wedge gets bigger as

The convention used
in this book

Projecting away
from the viewer

Projecting toward
the viewer

Hydrogens projecting
toward the viewer

it moves further away. Yet, this is the most common convention used, and it is the convention we adopt in this book. Many workers have turned to a simple dashed line instead (see above), or a dash that does get smaller. Similarly, both a bold wedge and a bold line are used to represent forward-projecting substituents. Another common convention is the bold "dot" on a carbon at a ring junction, representing a hydrogen that projects toward the viewer.

The challenge of seeing, thinking, and drawing in three dimensions is not the only cause for confusion in the study of stereochemistry. Another major cause is the terminology used. Hence, we start this chapter off with a review of basic terminology, the problems associated with this terminology, and then an extension into more modern terminology.

6.1.1   Basic Concepts and Terminology

There was considerable ambiguity and imprecision in the terminology of stereochemistry as it developed during the 20th century. In recent years, stereochemical terminology has clarified. We present here a discussion of the basics, not focused solely on carbon. However, in Section 6.2.4 we will examine carbon specifically. While most of this should be review, perhaps the perspective and some of the terminology will be new.

Let's start by delineating the difference between a stereoisomer and other kinds of isomers. Recall that **stereoisomers** are molecules that have the same connectivity but differ in the arrangement of atoms in space, such as *cis-* and *trans*-2-butene. Even gauche and anti butane are therefore stereoisomers. This is in contrast to **constitutional isomers**, which are molecules with the same molecular formula but different connectivity between the atoms, such as 1-bromo- and 2-bromobutane. The **constitution** of a molecule is defined by the number and types of atoms and their connectivity, including bond multiplicity. These definitions are straightforward and clear (as long as we can agree on the definition of connectivity—see the Going Deeper highlight on page 300).

An historical distinction, but one that is not entirely clear cut, is that between **configurational isomers** and **conformational isomers**. Conformational isomers are interconvertible by rotations about single bonds, and the **conformation** of a molecule concerns features related to rotations about single bonds (see Chapter 2). There is some fuzziness to this distinction, attendant with the definition of a "single" bond. Is the C–N bond of an amide a single bond, even though resonance arguments imply a significant amount of double bond character and the rotation barrier is fairly large? Also, some olefinic "double" bonds can have quite low rotation barriers if the appropriate mix of substituents if present. Because of these examples, as well as other issues concerning stereochemistry, we simply have to live with a certain amount of terminological ambiguity. A related term is **atropisomers**, which are stereoisomers that can be interconverted by rotation about single bonds but for which the barrier to rotation is large enough that the stereoisomers can be separated and do not interconvert readily at room temperature (examples are given in Section 6.5).

The term configurational isomer is a historic one that has no real value in modern stereochemistry. It is generally used to encompass enantiomers and disastereomers as isomers (see definitions for these below), but stereochemical isomers is a better term. The term **con-**
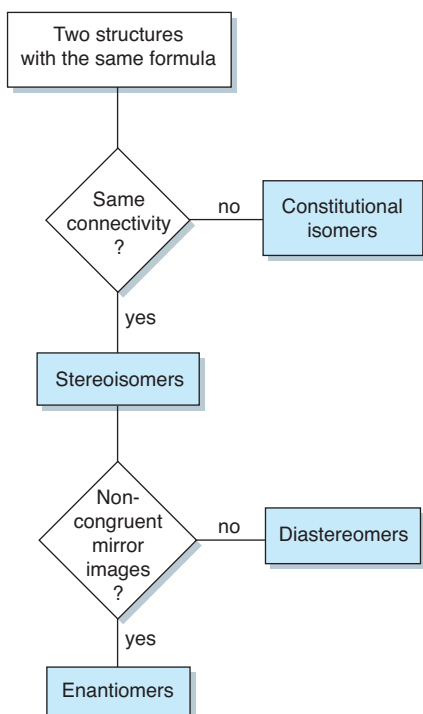
Figure 6.1
Simple flowchart for classifying various kinds of isomers.

figuration is still useful. Mislow defines configuration as "the relative position or order of the arrangement of atoms in space which characterizes a particular stereoisomer". A related term is **absolute configuration**, which relates the configuration of a structure to an agreed upon stereochemical standard. For example, later in this chapter we discuss the D and L nomenclature system, where the arrangement of atoms in space is related to that of (+)-glyceraldehyde. If the arrangement of atoms in space in a molecule can be related to (+)-glyceraldehyde, or some other standard, we state that we know that molecule's absolute configuration.
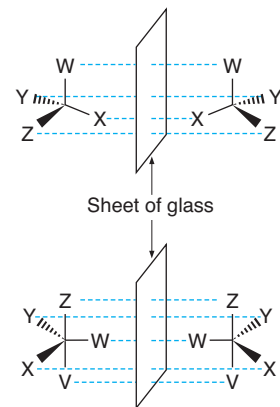
When two stereoisomers are nonsuperposable mirror images of each other, they are known as **enantiomers** (see the schematic examples in the margin). To achieve the mirror image of a molecule, simply imagine a sheet of glass placed alongside the molecule of interest, then pass each atom through the glass such that each atom ends up the same distance from the sheet of glass as in the original structure. Stereoisomers that are not enantiomers are known as **diastereomers**. Figure 6.1 shows a simple flow chart for classifying isomers.

Any object that is nonsuperposable (noncongruent) with its mirror image is **chiral**. If an object is not chiral—that is, if its mirror image is congruent with the original—it is **achiral**.

Enantiomers: non-superimposable mirror images

Classic Terminology

There are a series of terms used in the context of stereochemistry that are ingrained in the literature, and several you are likely familiar with from beginning organic chemistry. We define many of these terms here, and examine how they can be misleading. After a look at this classic terminology, more modern and concise terms are given.

Confusion with respect to terminology arises with terms such as "optically active" and "chiral center", which often mislead as much as they inform. **Optically active** refers to the ability of a collection of molecules to rotate plane polarized light (a phenomenon that we explore in detail in Section 6.1.3). In order for a sample to be optically active, it must have an excess of one enantiomer. Now comes the confusion. Optically active was generally used as a synonym for chiral in the earlier literature, and unfortunately this usage continues at times even today. We discourage this use. The problem is that there are many examples of chemical
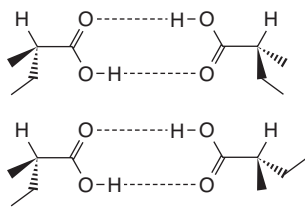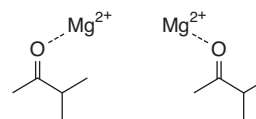
Connections

Stereoisomerism and Connectivity

A crucial concept in the definition of stereoisomers given above is "connectivity". In methane or 2,3-dichlorobutane, there is no doubt as to the connectivity of the system. However, there is an innate arbitrariness to the term, and this can lead to some ambiguity about stereo-isomerism. For example, do hydrogen bonds count in our list of connectivity? No, but consider the implications of this. If hydrogen bonds "don't count", then how do we think about isomerism in double-helical DNA? Do we just ignore the interaction of the two strands? As a simpler example, in a solution of a racemic carboxylic acid, does dimerization create true diastereomers?

Do diastereomers exist in
a solution of enantiomeric
carboxylic acids?

Further, what about metal coordination? We are comfortable with a clear connectivity pattern in inorganic complexes such as iron pentacarbonyl or a porphyrin complex. But what about Mg^{2+} ions complexing a carbonyl? When is a bond too weak to be considered relevant for stereoisomerism?
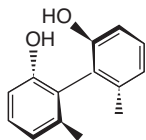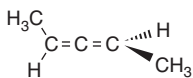

Stereoisomers?

Finally, there has been a modern emphasis on "topological isomerism", structures with loops or interlocking rings in which large parts of the molecule are not connected to each other in any conventional way. This can produce novel stereochemical situations, as we will see in Section 6.6.

In the end, there is no universally agreed upon convention for connectivity as it relates to stereoisomerism. Usually, the connectivity of a system is clear. When there is the potential for ambiguity, though, a clear statement of the ground rules should be made.
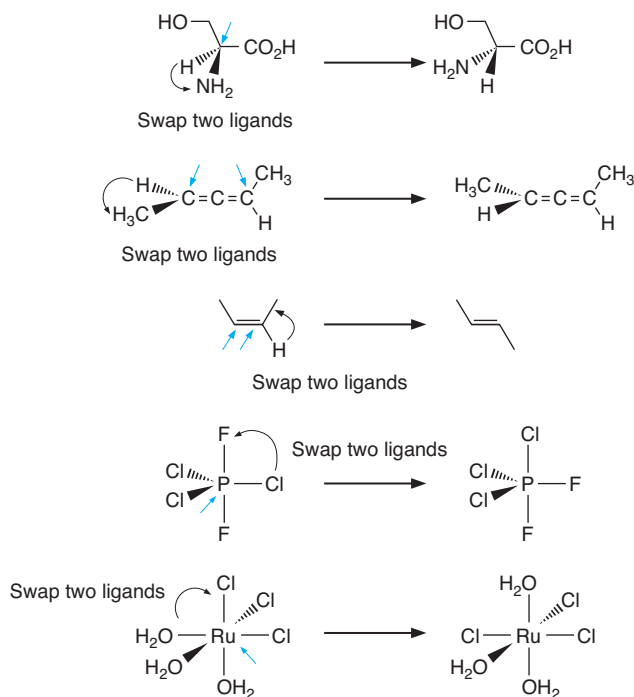
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samples that contain chiral molecules, but the samples themselves are not optically active. A **racemic** mixture, a 50:50 mixture of enantiomers, is not optically active, but every molecule in the sample is chiral. It is important to distinguish between a sample that is optically inactive because it contains a racemic mixture and a sample that is optically inactive because it contains achiral molecules, and the earlier terminology made this difficult.

Also, it is easy to imagine molecules, even when enantiomerically pure, that would not rotate plane polarized light to any *measurable* extent. The extent of rotation of plane polarized light depends upon differences in the refractive indices with respect to right and left circularly polarized light as it passes through the sample. Enantiomers that do not have dramatically different refractive indices would not result in measurable rotations. Examples would be a carbon with four different *n*-alkyl chains attached, with chain lengths of maybe 10, 11, 12, and 13 carbons; or one with four C_{10} chains, but terminating in $-CH_3$, $-CH_2D$, $-CHD_2$, and $-CD_3$. In each case the molecule is chiral, but any rotation of plane polarized light would be immeasurably small. Operationally, they are optically inactive. Finally, even an enantiomerically pure sample of a chiral molecule will show zero rotation at certain wavelengths of light, as we move from $(+)$ rotation to $(-)$ rotation in the optical rotatory dispersion (ORD) curve (see Section 6.1.3). "Optically active" is an ambiguous description.

Chiral molecules without
a "chiral center"

More confusion arises with terms that are meant to focus on the chirality at a particular point in a molecule. The prototype is the **chiral center** or **chiral carbon**, which is defined as an atom or specifically carbon, respectively, that has four different ligands attached. Here, the term "ligand" refers to any group attached to the carbon, such as H, R, Ar, OH, etc. The particular case of a carbon with four different ligands has also been termed an **asymmetric carbon**. One problem with such terms, as we will show below, is that "asymmetric carbons" and "chiral centers/carbons" exist in molecules that are neither asymmetric nor chiral. In addition, many molecules can exist in enantiomeric forms without having a "chiral center". Classic examples include dimethylallene and the twisted biphenyl shown in the margin—we'll see more below. Given all this, although the terms may already be part of your vocabulary, we discourage their use.

Figure 6.2
Molecules with stereogenic centers. The stereogenic centers are marked with colored arrows, and a curved black arrow is used to show how ligand interchange at a stereogenic center produces a new stereoisomer.

More Modern Terminology

Much of the confusion that can be generated with the terms given above was eliminated with the introduction of the **stereogenic center** (or, equivalently, **stereocenter**) as an organizing principle in stereochemistry. An atom, or a grouping of atoms, is considered to be a stereogenic center if the interchange of two ligands attached to it can produce a new stereoisomer. Not all interchanges have to give a new stereoisomer, but if one does, then the center is stereogenic. The center therefore "generates" stereochemistry. A **non-stereogenic center** is one in which exchange of any pair of ligands does not produce a stereoisomer. The term "stereogenic center" is, in a sense, broader than the term "chiral center". It implies nothing about the molecule being chiral, only that stereoisomerism is possible. The structures in Figure 6.2 show several stereogenic centers. Note that in more complex geometries, such as pentacoordinate or hexacoordinate atoms, we do not need all the ligands to be inequivalent in order to have a stereogenic center. Given these new terms, we strongly encourage students to abandon the term "chiral center" and to reserve "optically active" as a description of an experimental measurement.

A related and more encompassing concept is that of a **stereogenic unit**. A stereogenic unit is an atom or grouping of atoms such that interchange of a pair of ligands attached to an atom of the grouping produces a new stereoisomer. For example, the C=C group of *trans*-2-butene is a stereogenic unit because swapping a CH_3/H pair at one carbon produces *cis*-2-butene. A tetrahedral atom is a stereogenic unit, where swapping the positions of any two of four different ligands gives a stereoisomer (see below).

In the examples of chiral molecules without "chiral centers" noted above, the C=C=C unit of the allene and the biphenyl itself are stereogenic units. Many workers have adopted terms such as **planar chirality** and **axial chirality** to describe systems such as chiral biphenyl and allene based structures, respectively. The justification for these terms is that such molecules do not have stereogenic centers, but rather stereogenic units. Admittedly, terms that address chirality without stereogenic centers could be useful. However, since a molecule that is truly planar (i.e., has a plane of symmetry) must be achiral, planar chirality is an odd use of the word "planar". Developing precise, unambiguous definitions of these terms is a challenge that, in our view, has not yet been met. Currently, the best term is "stereogenic unit", where the biphenyl or allene groups have the ability to create chirality, just as a tetrahedral atom has the ability to generate chirality.
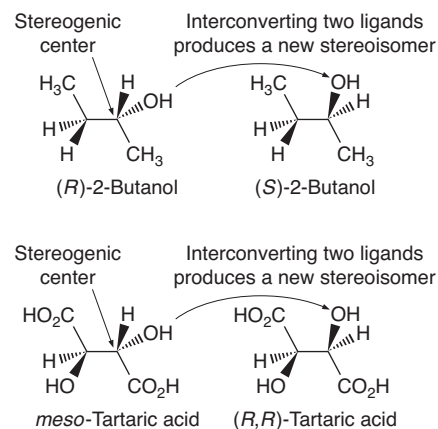
Figure 6.3
Illustration of the concept of the stereogenic center in the context of carbon. Whether in a chiral molecule like 2-butanol or an achiral molecule like *meso*-tartaric acid, interconversion of two ligands at a stereocenter produces a new stereoisomer.

To illustrate the value of the newer terminology, let's review two prototypes of organic stereochemistry. First, consider a molecule that has a carbon with four different ligands, a carbon we will describe as CWXYZ. A specific example is 2-butanol (Figure 6.3). If we interchange any two ligands at carbon 2, we obtain a stereoisomer—the enantiomer—of the original structure. Thus, C2 of 2-butanol is a stereogenic center. The analysis can get more complicated in systems with more than one CWXYZ center. Let's consider such a case.

Figure 6.3 also shows tartaric acid. Beginning with the structure labeled "meso", if we interchange two ligands at either C2 or C3, we obtain a new structure, such as (*R,R*)-tartaric acid. (If you do not recall the *R* and *S* notation, look ahead to Section 6.1.2.) This structure has the same connectivity as *meso*-tartaric acid, but the two are not congruent (verify for yourself), and so the new structure is a stereoisomer of the original. However, (*R,R*)- and *meso*-tartaric acid are *not* mirror images, so they are not enantiomers. They are diastereomers.

Note that the meso form of tartaric acid is achiral; verify for yourself that it is congruent with its mirror image. However, C2 and C3 of *meso*-tartaric acid are stereogenic centers; that is, swapping any two ligands at either center produces a new stereoisomer. This is one value of the stereogenic center concept. As we noted above, in earlier literature a CWXYZ center such as C2 or C3 was called a chiral center, but it seems odd to say we have *two* chiral centers in an achiral molecule! A CWXYZ center does not guarantee a chiral molecule. However, *a CWXYZ group is always a stereogenic center*.

Tartaric acid has two stereogenic centers and exists as three possible stereoisomers. This is an exception to the norm. Typically, a molecule with n stereogenic, tetracoordinate carbons will have 2^n stereoisomers–2^{n-1} diastereomers that each exist as a pair of enantiomers. For example, a structure with two stereogenic centers will exist as *RR*, *SS*, *RS*, and *SR* forms. In tartaric acid the *RS* and *SR* forms are identical—they are both the meso form—because C2 and C3 have the same ligands.

The 2^n rule quickly creates complexity in molecules with multiple stereogenic centers. In complex natural products that are often targets of total synthesis efforts, it is conventional to note the number of possible stereoisomers (for example, 10 stereogenic centers implies 1024 stereoisomers), with only one combination defining the proper target (see the Following Connections highlight). Polymers, both natural and synthetic, can produce extraordinary stereochemical diversity when each monomer carries a stereogenic center. We'll return to this issue below.

When many stereogenic centers are present in a molecule, it becomes difficult to refer to all the possible stereoisomers. It is often useful to consider only two different isomers, called epimers. **Epimers** are diastereomers that differ in configuration at only one of the several stereogenic centers. Imagine taking any one of the many stereogenic centers in everninomicin (shown in the next Connections highlight) and changing the stereochemistry at only that one stereogenic center. This creates an epimer of the original structure. Another example is the difference between the α- and β-anomers of glucose, which are epimeric forms of the sugar (look ahead to Figure 6.18 for definitions of α- and β-anomers).

Connections

Total Synthesis of an Antibiotic with a Staggering Number of Stereocenters

Synthetic chemists are continually in search of new methods to control the stereochemical outcome of synthetic transformations. Although the exact methods used are best described in textbooks with a focus upon asymmetric synthesis, it is worth mentioning here how sophisticated the field is becoming. By analyzing how the topicity relationships within reactants will influence enantiomeric and disastereomeric selectivities, a multitude of reactions with good stereochemical control have been developed. One particular example that highlights just how far advanced

these techniques have become is the total synthesis of everninomicin 13,384–1. This compound contains 13 rings and 35 stereocenters (3.4×10^{10} possible stereoisomers). Although many of the stereocenters were derived from the "chiral pool" (see Section 6.8.3), several stereocenters associated with the ring connections and ring-fusions were set with reactions that proceed with varying degrees of stereoselectivity and specificity.

Nicolaou, K. C., Mitchell, H. J., Suzuki, H., Rodriguez, R. M., Baudoin, O., and Fylaktakidou, C. "Total Synthesis or Everninomicin 13,384–1—Part 1: Synthesis of A1B(A)C Fragment." *Angew. Chem. Int. Ed. Eng.*, **38**, 3334–3339 (1999), and subsequent communications.


Everninomicin 13,384–1
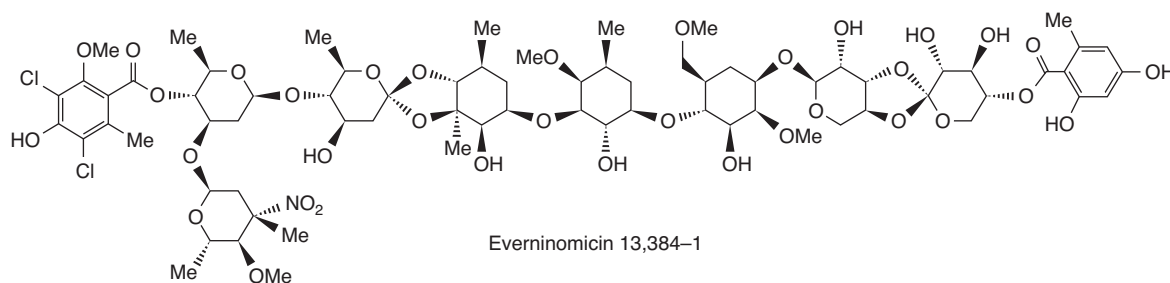
6.1.2 Stereochemical Descriptors

All introductory organic chemistry texts provide a detailed presentation of the various rules for assigning descriptors to stereocenters. Here we provide a brief review of the terminology to remind the student of the basics.

Many of the descriptors for stereogenic units begin with assigning priorities to the attached ligands. Higher atomic number gets higher priority. If two atoms under comparison are isotopes, the one with higher mass is assigned the higher priority. Ties are settled by moving out from the stereocenter until a distinction is made. In other words, when two attached atoms are the same, one examines the next atoms in the group, only looking for a winner by examining individual atomic numbers (do not add atomic numbers of several atoms).

Multiple bonds are treated as multiple ligands; that is, C=O is treated as a C that is singly bonded to two oxygens with one oxygen bound to a C. For example, the priorities shown below for the substituted alkene are obtained, giving an *E*-stereochemistry.
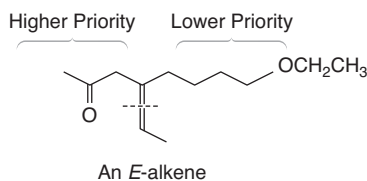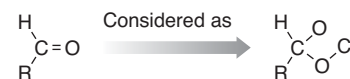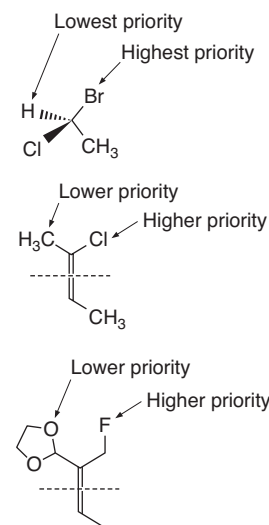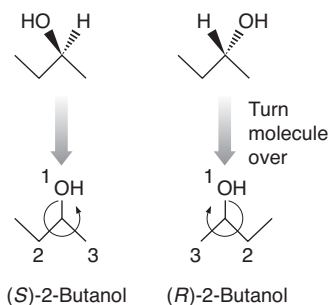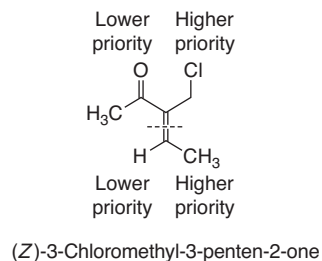
R,S System

For tetracoordinate carbon and related structures we use the Cahn–Ingold–Prelog system. The highest priority group is given number 1, whereas the lowest priority group is given number 4. Sight down the bond from the stereocenter to the ligand of lowest priority behind. If moving from the highest (#1), to the second (#2), to the third (#3) priority ligand involves a clockwise direction, the center is termed *R*. A counterclockwise direction implies *S*.
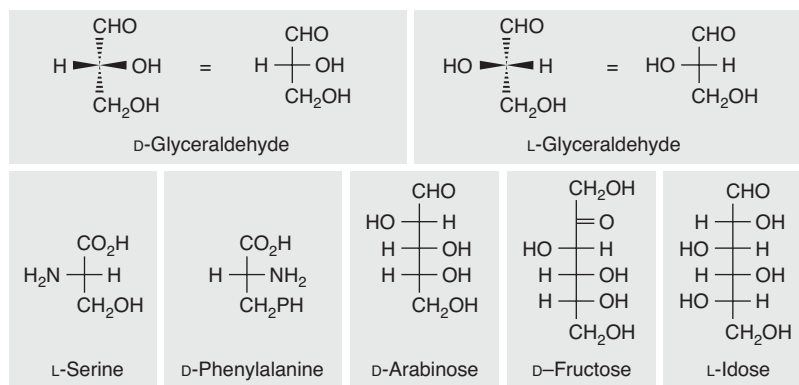
E,Z System

For olefins and related structures we use the same priority rules, but we divide the double bond in half and compare the two sides. For each carbon of an olefin, assign one ligand high priority and one low priority according to the rules above. If the two high priority ligands lie on the same side of the double bond, the system is *Z* (zusammen); if they are on opposite sides, the system is *E* (entgegen). If an H atom is on each carbon of the double bond, however, we can also use the traditional "cis" and "trans" descriptors.

D and L

The descriptors D and L represent an older system for distinguishing enantiomers, relating the sense of chirality of any molecule to that of D- and L-glyceraldehyde. D- and L-glyceraldehyde are shown below in **Fischer projection** form. In a Fischer projection, the horizontal lines represent bonds coming out of the plane of the paper, while the vertical lines represent bonds projecting behind the plane of the paper. You may want to review an introductory text if you are unfamiliar with Fischer projections. The isomer of glyceraldehyde that rotates plane polarized light to the right (*d*) was labelled D, while the isomer that rotates plane polarized light to the left (*l*) was labelled L.

To name more complex carbohydrates or amino acids, one draws a similar Fischer projection where the CH_2OH or R is on the bottom and the carbonyl group (aldehyde, ketone, or carboxylic acid) is on the top. The D descriptor is used when the OH or NH_2 on the penultimate (second from the bottom) carbon points to the right, as in D-glyceraldehyde, and L is used when the OH or NH_2 points to the left. See the following examples.

The D and L nomenclature system is fundamentally different than the R/S or E/Z systems. The D and L descriptors derive from only one stereogenic center in the molecule and are used to name the entire molecule. The name of the sugar defines the stereochemistry of all the other stereogenic centers. Each sugar has a different arrangement of the stereogenic centers along the carbon backbone. In contrast, normally a separate R/S or E/Z descriptor is used to name each individual stereogenic unit in a molecule. The D/L nomenclature is a carry over from very early carbohydrate chemistry. The terms are now reserved primarily for sugars and amino acids. Thus, it is commonly stated that all natural amino acids are L, while natural sugars are D.

Erythro and Threo

Another set of terms that derive from the stereochemistry of saccharides are erythro and threo. The sugars shown below are D-erythrose and D-threose, which are the basis of a nomenclature system for compounds with two stereogenic centers. If the two stereogenic centers have two groups in common, we can assign the terms erythro and threo. To determine the use of the erythro and threo descriptors, draw the compound in a Fischer projection with the distinguishing groups on the top and bottom. If the groups that are the same are both on the right or left side, the compound is called **erythro**; if they are on opposite sides, the compound is called **threo**. See the examples given below. Note that these structures have enantiomers, and hence require R and S descriptors to distinguish the specific enantiomer. The erythro/threo system distinguishes diastereomers.
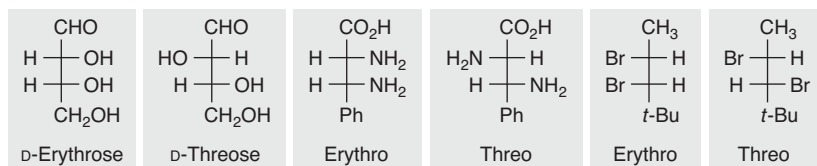

Helical Descriptors—M and P

Many chiral molecules lack a conventional center that can be described by the R/S or E/Z nomenclature system. Typically these molecules can be viewed as helical, and may have propeller, or screw-shaped structures. To assign a descriptor to the sense of twist of such structures, we sight down an axis that can be associated with the helix, and consider separately the "near" and "far" substituents, with the near groups taking priority. We then determine the highest priority near group and the highest priority far group. Sighting down the axis, if moving from the near group of highest priority to the corresponding far group requires a clockwise rotation, the helix is a right-handed helix and is described as P (or plus). A counterclockwise rotation implies a left-handed helix and is designated as M (or minus). As in all issues related to helicity, it does not matter what direction we sight down the axis, because we will arrive at the same descriptor. Three examples of molecules with M/P descriptors are shown below.
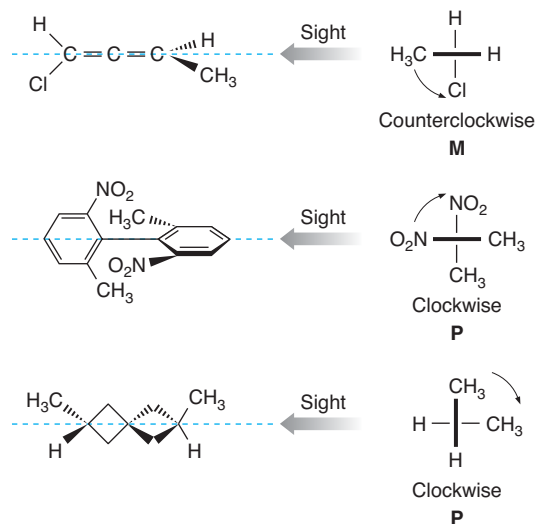
As another example, consider triphenylborane (Eq. 6.1, where a, b, and c are just labels of hydrogens so that you can keep track of the rotations shown). Triphenylborane cannot be fully planar because of steric crowding, and so it adopts a conformation with all three rings twisted in the same direction, making a right- or left-handed propeller. The M or P descrip-

tors are most easily assigned by making an analogy to a common screw or bolt. Common screws or bolts are right-handed ("reverse thread" screws and bolts are left-handed). If the sense of twist is the same as a screw or bolt, it is assigned the *P* descriptor (check the *P* and *M* descriptors for yourself in Eq. 6.1).
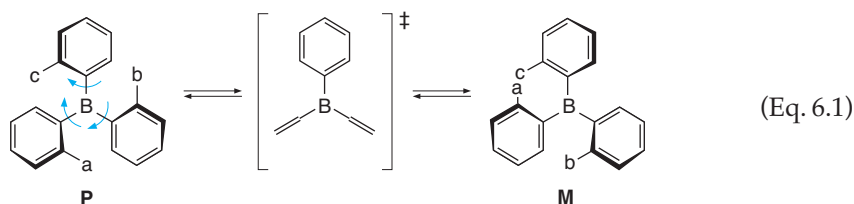
(Eq. 6.1)

Rotation about the C–B bonds of triphenylborane is relatively facile, and the motions of the rings are correlated in the sense shown (Eq. 6.1). In Eq. 6.1 the arrows denote the direction of bond rotation, not the helical direction. Two rings rotate through a perpendicular conformation while one moves in the opposite way. This "two-ring flip" reverses helicity and, in a substituted case (now a, b, and c in Eq. 6.1 are substituents), creates a new diastereomer.

Ent and Epi

Because of the stereochemical complexity of many natural products, short and simple descriptors have come into common use to relate various stereochemical relationships. For example, the enantiomer of a structure with many stereogenic centers has the prefix **ent**-. Ent-everninomicin is a trivial name that can be given to the enantiomer of everninomicin. Similarly, due to the stereochemical complexity of many natural products, the prefix **epi**- has become a convenient way to name structures where only one stereogenic center has undergone a change in configuration. For example, any epimer of everninomicin can be called epi-everninomicin. Usually, a number precedes "epi-" to distinguish which center has changed configuration.

Using Descriptors to Compare Structures

Compounds that have the same sense of chirality at their individual stereogenic centers are called **homochiral**. Homochiral molecules are not identical—they just have the same sense of chirality, much like all people's right hands are distinct but of the same chirality. As a chemical example, the amino acids L-alanine and L-leucine are homochiral. Those molecules with a differing sense of chirality at their stereogenic centers are called **heterochiral**. The same sense of chirality can often, but not always, be analyzed by examining whether the different kinds of stereochemical descriptors at the stereogenic centers are the same. For example, (*R*)-2-butanol and (*R*)-2-aminobutane are homochiral. Further, all the naturally occurring amino acids are L, so they are all homochiral (see the next Connections highlight).

Homochiral has been used by some as a synonym for "enantiomerically pure". This is another usage of a term that should be discouraged, as homochiral already had a clear and useful definition, and using the same term to signify two completely different concepts can only lead to confusion. A better term for designating an enantiomerically pure sample is simply **enantiopure**.

6.1.3 Distinguishing Enantiomers

Enantiomers are distinguishable if and only if they are placed in a chiral environment, and all methods to separate or characterize enantiomers are based on this principle. Suppose, for example, that we have a collection of right- and left-handed gloves, and we want to retrieve only the right-handed ones. Using a simple hook to reach into the pile cannot succeed because a hook is achiral—it cannot distinguish handedness. A chiral object, however, like a right hand, can distinguish between the gloves just by trying them on.

Connections

The Descriptors for the Amino Acids Can Lead to Confusion

As just noted, all amino acids have the same sense of chirality in that they are all L in the D/L terminology system. Yet, in the more modern Cahn–Ingold–Prelog system, they do not all have the same designators. All have the S stereochemisty, except cysteine, which has the same sense of chirality but is R because the sulfur makes the sidechain have a higher priority than the carbonyl carbon. In addition, the amino acids threonine and isoleucine have two stereocenters and can exist as diastereomers. In the natural amino acids, the sidechain is R for threonine and S for isoleucine. The diastereomers obtained by reversing the stereocenter at the sidechain only are termed allo-threonine and allo-isoleucine.

L-Alanine   L-Cysteine   L-Threonine   L-Allo-threonine   L-Isoleucine   L-Allo-isoleucine
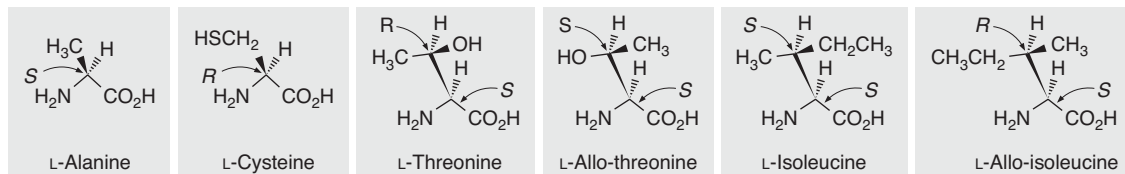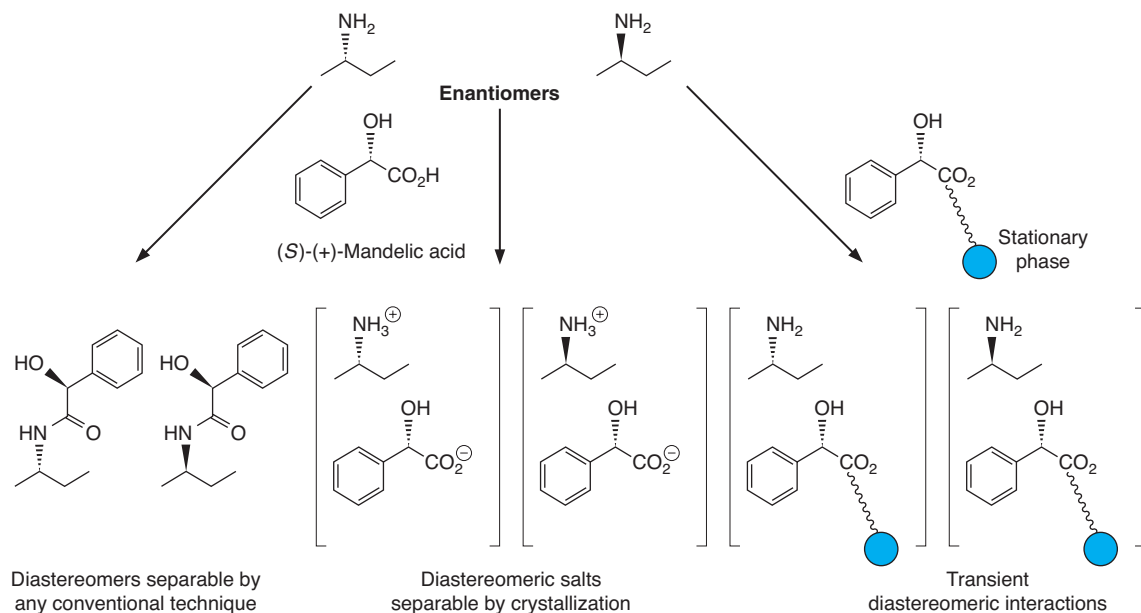
Figure 6.4 shows some chemical examples of this. If a racemic mixture of 2-aminobutane is allowed to react with an enantiomerically pure sample of mandelic acid, the two amides that are produced are diastereomers. The two diastereomers can be separated by any conventional method (such as crystallization or chromatography), and subsequent hydrolysis of a pure diastereomer gives enantiomerically pure 2-aminobutane.

The interaction that creates diastereomers out of enantiomers need not be covalent. Weaker, non-covalent complexes are often discriminating enough to allow separation of enantiomers. The most classical way to separate enantiomeric amines is to form salts with a

Diastereomers separable by any conventional technique   Diastereomeric salts separable by crystallization   Transient diastereomeric interactions

Figure 6.4
Strategies for separating enantiomers, using 2-aminobutane as an example. Left: Forming diastereomeric derivatives—in this case, amides of mandelic acid. Center: Forming diastereomeric salts that can be separated by crystallization. Right: Chiral chromatography, making use of transient, diastereomeric interactions between the enantiomers of 2-aminobutane and the chiral stationary phase.

chiral acid and use crystallization to separate the diastereomeric salts. There are many variations on this theme, and this traditional approach is still very commonly used, especially for large scale, industrial applications.

For the smaller scales associated with the research laboratory, chiral chromatography is increasingly becoming the method of choice for analyzing and separating mixtures of enantiomers. We show in Figure 6.4 a hypothetical system in which the mandelic acid we have used in the previous examples is attached to a stationary phase. Now, transient, diastereomeric interactions between the 2-aminobutane and the stationary phase lead to different retention times and thus to separation of the enantiomers. Both gas chromatography and liquid chromatography are commonly used to separate enantiomers.

With a tool to discriminate enantiomers in hand, we can determine the **enantiomeric excess (ee)** of a sample. This commonly used metric is defined as $X_a - X_b$, where X_a and X_b represent the mole fraction of enantiomers a and b, respectively. Usually ee is expressed as a percentage, which is $100\%(X_a - X_b)$. Analogous terms such as **diastereomeric excess (de)** are also used. The traditional tools for evaluating ee are the chiroptical methods discussed below. However, methods such as high field NMR spectroscopy with chiral shift reagents (see the Going Deeper highlight below), NMR spectroscopy of derivatives that are diastereomeric, and chromatography (HPLC and GC) with chiral stationary phases, are becoming ever more powerful and popular.


Going Deeper

Chiral Shift Reagents

A convenient technique to measure the ratio of enantiomers in a solution is to differentiate them in the NMR spectrum using what is known as a **chiral shift reagent**. These reagents are typically paramagnetic, enantiomerically pure metal compounds that associate with the enantiomers to form complexes. The complexes formed between the chiral shift reagent and the enantiomers are diastereomeric, and thus can be resolved in NMR spectroscopy. The paramagnetic nature of the reagents induces large chemical shifts, further assisting with the resolution of the spectral peaks associated with the diastereomeric complexes.

For example, the enantiomeric forms of 2-deuterio-2-phenylethanol can be readily distinguished in the NMR using a complex known as Eu(dcm). Coordination of the alcohol to the Eu center leads to diastereomers. The ^{1}H NMR spectrum shown to the side of the H on the stereogenic center of 2-deuterio-2-phenylethanol indicates that the two enantiomers (in a 50:50 ratio) are easily distinguished.
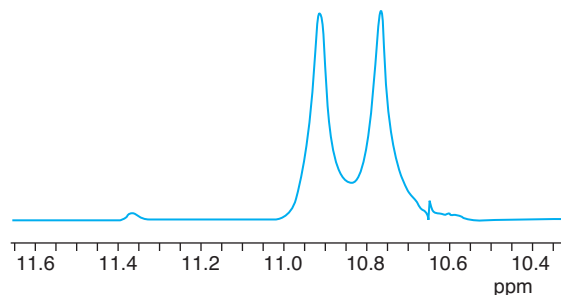
McCreary, M. D., Lewis, D. W., Wernick, D. L., and Whitesides, G. M. "Determination of Enantiomeric Purity Using Chiral Lanthanide Shift Reagents." *J. Am. Chem. Soc.*, **96**, 1038 (1974). Buchwald, S. L., Anslyn, E. V., and Grubbs, R. H. "Reaction of Dicyclopentadienylmethylenetitanium with Organic Halides: Evidence for a Radical Mechanism." *J. Am. Chem. Soc.*, **107**, 1766 (1985).


Eu(dcm)   +   50/50
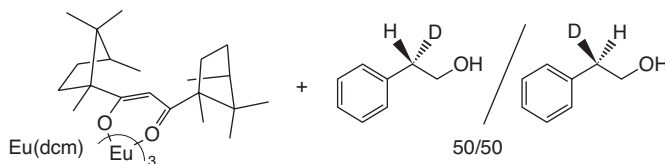
Optical Activity and Chirality

Historically, the most common technique used to detect chirality and to distinguish enantiomers has been to determine whether a sample rotates plane polarized light. **Optical activity** and other **chiroptical properties** that can be measured using ORD and CD (see below) have long been essential for characterizing enantiomers. Their importance has lessened somewhat with the development of powerful NMR methods and chiral chromatographic methods, but their historical importance justifies a brief discussion of the methodology.

All introductory organic chemistry textbooks cover the notion of optical activity—the ability of a sample to rotate a plane of polarized light. We check to see if the plane in which the polarized light is oscillating has changed by some angle relative to the original plane of oscillation on passing through the sample. A solution consisting of a mixture of enantiomers at a ratio other than 50:50 can rotate plane polarized light to either the right (clockwise) or the left (counterclockwise). A rotation to the right is designated (+); a rotation to the left is designated (–). Earlier nomenclature used **dextrorotatory** (designated as *d*) or **levorotatory** (designated as *l*) instead of (+) or (–), respectively. Typically, light of one particular wavelength, the Na "D-line" emission, is used in such studies. However, we can in principle use any wavelength, and a plot of optical rotation vs. wavelength is called an **optical rotatory dispersion** (ORD) curve. Note that as we scan over a range of wavelengths, any sample will have some wavelength regions with + rotation and others with – rotation. Since the rotation must pass through zero rotation as it changes from + to –, any chiral sample will be optically inactive at some wavelengths. If one of those unique wavelengths happens to be at (or near) the Na D line, we could be seriously misled by simple optical activity measurements. Furthermore, at the Na D line, rotation is often small for conventional organic molecules. In addition, we previously discussed instances in which a chiral sample might be expected to fail to rotate plane polarized light. Thus, optical activity establishes that a sample is chiral, but a lack of optical activity does not prove a lack of chirality.

Why is Plane Polarized Light Rotated by a Chiral Medium?

We have said that we need a chiral environment to distinguish enantiomers, and so it may seem odd that **plane polarized light** can do so. To understand this, we must recall that electromagnetic radiation consists of electric and magnetic fields that oscillate at right angles to each other and to the direction of propagation (see Figure 6.5 **A**). In normal light (such as that coming from a light bulb or the sun), the electric fields are oscillating at all possible angles when viewing the radiation propagating toward you (Figure 6.5 **B**). Plane polarized light has all the electric fields oscillating in the same plane (Figure 6.5 **B** and **C**), and can be viewed as the single oscillation shown in Figure 6.5 **A**. The representation in Figure 6.5 **A**
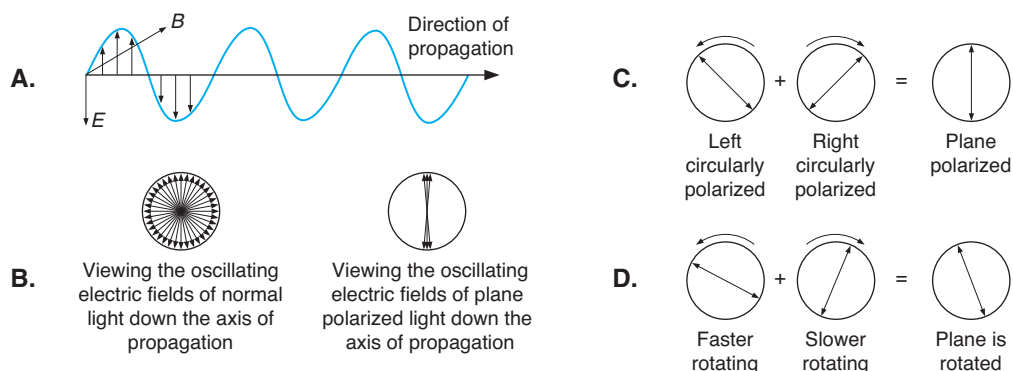
Figure 6.5
The phenomenon of optical activity. **A.** Oscillating electric and magnetic fields. **B.** The difference between normal (non-polarized) light and plane polarized light, viewing the oscillating electric fields down the axis of propagation. **C.** Plane polarized light is a combination of right and left circularly polarized light. **D.** If the differential index of refraction causes one form to "rotate" faster than the other, the effect is to rotate the plane of polarization.

does not look chiral, yet plane polarized light can be used to distinguish enantiomers. To reconcile this, we must appreciate that plane polarized light can be considered to be created by two circularly polarized beams of light, one rotating clockwise and one counterclockwise. **Circular polarization** means that the plane of the oscillating electric field does not remain steady, but instead twists to the right or the left, referred to as right or left **circularly polarized light**. In other words, the linear vector that traces out the plane polarized wave is formed from two circularly polarized waves, one rotating clockwise and one rotating counterclockwise (Figure 6.5 **D**). Taken separately, these circularly polarized beams are rotating in a helical fashion, and hence are chiral. The right and left polarized beams of light are therefore enantiomers of each other. So, indeed, we again find that it takes chiral entities to distinguish between chiral chemical structures.

As the plane polarized light passes through a chiral sample, several different kinds of interactions between the light and the material are possible. One is actual absorption of the light, which we explore below when circular dichroism is discussed. However, another is simple refraction. The indices of refraction of the chiral material for the right and left polarized light are expected to be different, which means that the speed of light through the medium is different for the two polarizations, a phenomena called **circular birefringence**. Therefore, one of the light components will lag behind the other. "Lagging behind" means a slower rate of propagation due to a different refractive index for that form of light (Figure 6.5 **D**). The result is that right- and left-handed twists no longer have the same phase matching to cancel along the original plane, but instead they cancel along a slightly different plane, rotated away from the original plane.

Circular Dichroism

In the discussion above, plane polarized light was described as a combination of right and left circularly polarized light. Just as a chiral medium must refract left and right circularly polarized light differently, chiral molecules must have different absorptions of the left and right circularly polarized light. **Circular dichroism** (CD) spectroscopy measures this differential absorption. This technique involves the same absorption phenomenon that occurs in UV/vis spectroscopy, which is discussed in Chapter 16.

One collects a CD spectrum by measuring the difference in absorption of right and left circularly polarized light as a function of the wavelength of the light. At certain wavelengths of circularly polarized light, the right-handed form is absorbed more (defined as a positive value) than the left-handed form, and vice versa at other wavelengths. There are specific rules related to **exciton coupling** (coupling of electronic states between two or more chromophores) that dictate which form of light is absorbed the most at various wavelengths. This is beyond the scope of this chapter, but extensive discussions of this phenomenon are available in the more specialized texts cited at the end of this chapter.

Because of the predictability of CD spectra, in earlier times, CD was frequently used as a means of establishing the absolute configuration of chiral molecules, and extensive correlations of CD spectra with molecular structure were developed based upon empirical rules. The shapes of the curves, called either plain curves or curves possessing positive and/or negative **Cotton effects**, can be correlated with structure. In more recent times, x-ray crystallography has become the most common way to establish absolute configuration (see below). One area in which CD has remained quite a powerful and commonly used tool is in studies of protein secondary structure. We will discuss this application of CD later in this chapter.

X-Ray Crystallography

If we have a crystal of an enantiomerically pure compound, and we determine its crystal structure, you might think that we would then know its absolute configuration. Actually, this is typically not the case. Nothing in the data collection or analysis of x-ray crystallography is inherently chiral, and so we cannot tell which enantiomer we are imaging in a typical crystallography study. There are two ways around this. One is an advanced crystallographic technique called **anomalous dispersion**. Anomalous dispersion occurs when the x-ray wavelength is very close to the absorption edge of one of the atoms in the structure. This

leads to an unusual scattering interaction that contains the necessary phase information to allow enantiomer discrimination. Originally a somewhat exotic technique, the method has become more common as more diverse and brighter x-ray sources have become available.

The alternative approach to determine absolute configuration by x-ray crystallography is to functionalize the molecule of interest with a chiral reagent of known absolute configuration. Returning to the example of Figure 6.4, if we determine the crystal structure of one of the separated amide diastereomers, crystallography will unambiguously establish the *relative* configurations of the original molecule and the appended carboxylic acid. Since we independently know the absolute configuration of the the (S)-($+$)-mandelic acid that we used, we know the absolute configuration of the 2-aminobutane.

6.2 Symmetry and Stereochemistry

Stereochemistry and symmetry are intimately connected, and in developing some more advanced aspects of modern stereochemistry, it is convenient to be able to invoke certain symmetry operations. A proper understanding of symmetry can greatly clarify a number of concepts in stereochemistry that can sometimes seem confusing. One operation that we have already used extensively is that of reflection through a mirror plane, and simple guidelines using imaginary sheets of glass were given. We will not need to develop the entire concept of point group symmetries in this textbook. For those who are familiar with point groups and irreducible representations, we will occasionally mention them where appropriate, but they are not required. However, for those students not well versed in symmetry operations, we now give a very short summary of some of the basics.

6.2.1 Basic Symmetry Operations

A **symmetry operation** is a transformation of a system that leaves an object in an indistinguishable position. For molecular systems, we need be concerned with only two types of symmetry operations: **proper rotations** (C_n) and **improper rotations** (S_n). A C_n is a rotation around an axis by $(360/n)°$ that has the net effect of leaving the position of the object unchanged. Thus, a C_2 is a 180° rotation, a C_3 a 120° rotation, and so on. These are termed "proper" rotations, because it is actually physically possible to rotate an object by 180° or 120°. Some examples are shown below, with the atoms labeled only to highlight the operation.
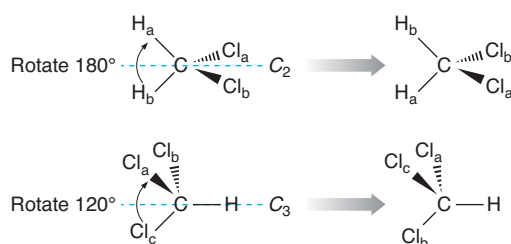
In contrast, improper rotations are not physically possible. An S_n involves a rotation of $(360/n)°$, combined with a reflection across a mirror plane that is perpendicular to the rotation axis (see examples on the next page). Note that S_1 is equivalent to just a mirror reflection (denoted with a σ), while S_2 is equivalent to a center of inversion (denoted with an i). The C_1 operation also exists. It leaves an object completely unmoved and is also termed the **identity operation**, sometimes symbolized as E. An internal σ plane that includes a C_2 axis is designated a σ_v, while a σ plane perpendicular to a C_2 axis is designated σ_h.

6.2.2 Chirality and Symmetry

Now we can further refine the connection between symmetry and chirality. Quite simply, for a rigid molecule (or object of any sort), *a necessary and sufficient criterion for chirality is*
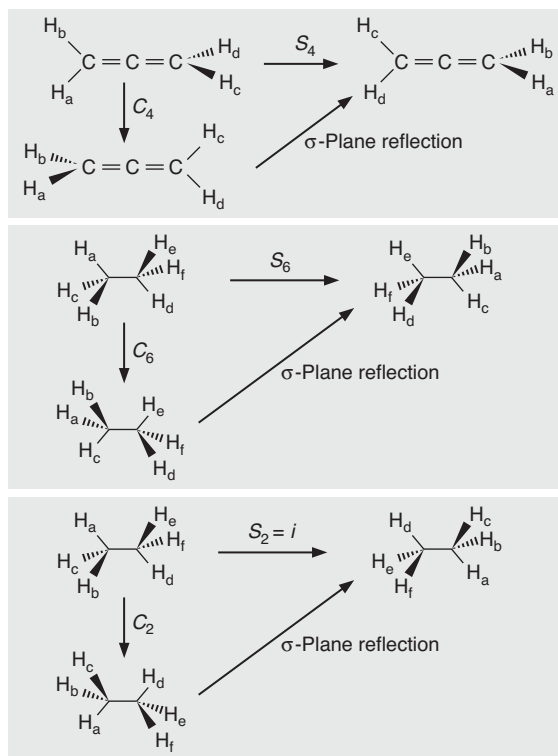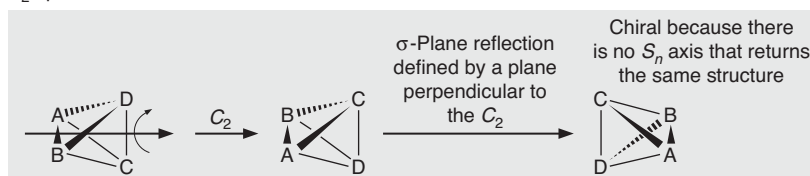
an absence of S_n axes; the existence of any S_n axis renders an object achiral. For example, consider the two structures shown below. The first object has an S_2 axis and is not chiral, while the second object does not have an S_2 axis, let alone any S_n axis, and so the structure is chiral.
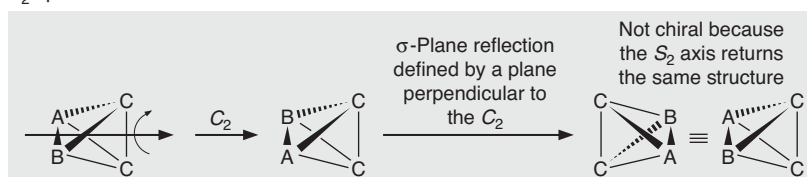
In addition, when a chiral molecule is subjected to any improper rotation, it is converted into its enantiomer. Since the simplest improper axis to use is an S_1, the σ plane (see many of our examples above), most chemists first look for an internal mirror plane in a molecule to decide if it is chiral or not. If the molecule possesses an internal mirror plane in any readily accessible conformation, then the molecule is achiral. For those familiar with point groups, it is a simple matter to show that all chiral molecules fall into one of five point groups: C_n, D_n, T, O, or I. All other point groups contain an S_n axis.

Chiral molecules need not be asymmetric. **Asymmetric** is defined as the complete absence of symmetry. However, many chiral molecules have one or more *proper* rotation axes —just no improper axes are present. These compounds can be referred to as **dissymmetric**, essentially a synonym for chiral. Thus, while all asymmetric (point group C_1) molecules are

chiral, not all chiral molecules are asymmetric. Importantly, high symmetry chiral molecules play a special role in many processes, especially in efforts to influence the stereochemistry of synthetic reactions (see the following Connections highlight).


Connections

C_2 Ligands in Asymmetric Synthesis

The use of C_2 symmetric ligands in catalytic asymmetric induction is a common design motif. Below are shown a series of chiral Lewis acid catalysts that have been used for Diels–Alder reactions. In every case a C_2 axis exists in the structures. Also, in every case the metal is non-stereogenic. Most catalytic processes involve weak interactions between substrate and catalyst, and this often leads to a situation in which several different binding interactions between substrate and catalyst are possible. Each different binding interaction might produce different stereoselectivity, making it difficult to achieve high enantio-

meric excess. Since the metal is non-stereogenic in a C_2 symmetric complex, coordination of the Diels–Alder reactants to either face of the metal produces identical complexes. We ask that you show this in an Exercise at the end of the chapter. The environment around the metal is still chiral, however, and so asymmetric induction is possible. This same motif will be seen in a Going Deeper highlight on polymerization reactions given in Section 6.7.

Evans, D. A., Miller, S. J., Lectka, T., and von Matt, P. "Chiral Bis(oxazoline)copper(II) Complexes as Lewis Acid Catalysts for the Enantioselective Diels–Alder Reaction." *J. Am. Chem. Soc.*, **121**, 7559–7573 (1999).


C_2 symmetric catalysts
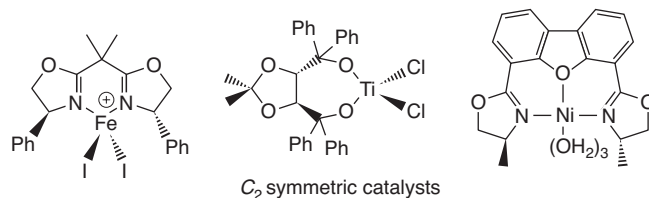
6.2.3   Symmetry Arguments

We argued above that any rigid molecule lacking an S_n axis is chiral. We don't need to know anything else about the molecule to reach this conclusion with confidence. This is an example of a **symmetry argument**—a statement from first principles that depends only on the symmetry, not on the precise nature, of the system under consideration.

Two important features of symmetry arguments must always be remembered. First, the most compelling symmetry arguments are based on an *absence* of symmetry. If we can be sure that a certain kind of symmetry is lacking, then firm conclusions can be reached. Stated differently, two objects (molecules or parts of molecules in our context) are equivalent if and only if they are interconvertible by a symmetry operation of the system. On the other hand, if two objects are not interconvertible by a symmetry operation, they are expected to be different, and they are different in essentially all ways. We cannot rule out the possibility of accidental equivalence. However, we expect that, in most instances, if the precision of our measurement is high, objects that are not symmetry equivalent will be measurably different. We will generally use a phrase such as "are expected to be different" to acknowledge the possibility that in some systems the differences between two symmetry inequivalent objects may be too small to be detected at the present level of precision.

For example, consider the C1–C2 vs. the C2–C3 bonds of *n*-butane. We can be certain that there can never be a symmetry operation of butane that will interconvert these two bonds. As such, they are different, and they are different in all ways. They will have different bond lengths, different IR stretching frequencies, and different reactivities.

The absence of symmetry can be unambiguous—we know for sure that the two C–C bonds discussed above cannot be interconverted by symmetry. On the other hand, we must be careful about using a symmetry argument to declare two objects to be equivalent, because that can be a cyclic argument. For example, consider a CH_2 group in cyclobutane. It is tempt-

really

Cyclobutane
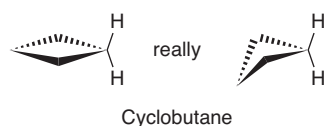
ing to conclude that the two hydrogens are equivalent. If we draw the molecule as square and planar, there are symmetry operations that interconvert them (a C_2 axis and a σ plane). We had to assume a structure for the system, and we chose a high symmetry structure. However, there is no law that molecules will adopt the highest possible symmetry, and in the particular case of cyclobutane, the molecule indeed adopts a lower symmetry form, as we saw in Section 2.3.2. Cyclobutane is nonplanar, and the hydrogens of a given CH_2 are inequivalent (the time scale is of importance in this argument, as we discuss later in the chapter). Thus, in the absence of independent information about the symmetry of a system, it is risky to simply look at a structure and say two parts are equivalent.

On the other hand, if we have independent evidence that a molecule has certain symmetry elements—for example, from an x-ray structure—then we can use those symmetry elements to make statements about equivalence. Restating, two objects are equivalent if and only if they are interconverted by a symmetry operation of the system, and if they are not interconverted by a symmetry operation of the system, they are expected to be different.

Another important aspect of symmetry arguments is that they tell us *nothing about magnitudes*. We can conclude that two angles are expected to be different, but they may differ by 10° or by 0.0000000001°. Symmetry arguments are oblivious to such distinctions. Objects are either different or not; that is all we can conclude.

6.2.4   Focusing on Carbon

While most chemists are justifiably enamored of symmetry, in a sense it is the absence of symmetry that makes things happen. Let's illustrate this by considering the desymmetrization of methane. The carbon in methane is not a stereogenic center—that is, interchanging the positions of two hydrogens does not produce a new stereoisomer in this high symmetry structure. We often say that a carbon atom with four covalent ligands has "tetrahedral" symmetry. What does that mean? It means that in CH_4 the four hydrogens lie at the vertices of a regular tetrahedron, with the C at the center (Figure 6.6). Every H–C–H angle is arc cos($-\frac{1}{3}$) $\sim$ 109.47°, and every bond length is the same. These two descriptors (one length, one angle) are enough to fully describe such a system, and the same geometry holds for most CX_4 systems.
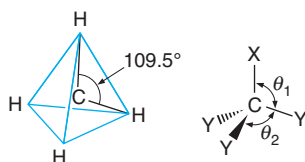
Figure 6.6
Left: The "tetrahedral" carbon atom.
Right: Differing angles in a CXY_3 molecule.

Things get more interesting when all four ligands are different. As first appreciated by Pierre Curie, it is the *lack of symmetry* that gives rise to observable phenomena. For example, in CXY_3, a desymmetrized CX_4, there are now two different valence angles (X–C–Y and Y–C–Y) (Figure 6.6) and two bond lengths, so there was an increase in the number of observables on lowering the symmetry. Desymmetrization to produce a CXY_3 structure also leads to a new molecular property that is not possible for CX_4—a dipole moment (Chapter 2). With further desymmetrization to CX_2Y_2, three angles are now possible, and so on. These systems no longer correspond to a perfect, regular tetrahedron, but we still tend to refer to them as "tetrahedral". They just happen to be irregular tetrahedrons.

Full desymmetrization to produce CWXYZ gives four different bond lengths and six different angles. As already discussed, this complete desymmetrization also leads to chirality. We noted in Chapters 1 and 2 that most organic molecules do not have perfect tetrahedral angles, and that all C–C bonds lengths are not the same. In that context, we focused on the quantitative deviations from the standard norms, and how specific bonding theories could rationalize them. Here, we are arriving at similar conclusions, but from a different perspective. Our argument that a CXY_3 molecule has two different angles can be made with confidence and without any knowledge of what X and Y are, as long as they are different. It is a symmetry argument, and so it is incontrovertible, but qualitative in nature.

6.3   Topicity Relationships

Thus far we have focused on terminology appropriate for describing the stereochemical relationships between molecules. As we will see, it is also convenient to describe relationships between regions of molecules such as two different methyl groups or two faces of a π system. In such cases we are considering the **topicity** of the system. The topicity nomenclature is derived from the same roots as topography and topology, relating to the spatial position of an object.

6.3.1   Homotopic, Enantiotopic, and Diastereotopic

If two objects cannot be interconverted by a symmetry operation, they are expected to be different. This reasoning applies not only to entire molecules, but also to differing regions within a molecule. When the groups can be interconverted by a symmetry operation, they are chemically identical. Yet, depending upon the symmetry operation, they can act differently. The terms we introduce here have the suffix *-topic*, which is Greek for "place". When identical groups or atoms are in inequivalent environments, they are termed **heterotopic**. They can be either constitutionally heterotopic or stereoheterotopic. **Constitutionally heterotopic** means that the connectivity of the groups or atoms is different in the molecule. **Stereoheterotopic** means the groups or atoms have different stereochemical relationships in the molecule under analysis.

Consider the CH_2 group of 2-butanol. There are no symmetry operations in 2-butanol, and as such the two hydrogens of the CH_2 cannot be interconverted by a symmetry operation. Therefore, these two hydrogens are expected to be different from one another in all meaningful ways, such as NMR shift, acidity, C–H bond length, bond dissociation energy, reactivity, etc. They have the same connectivity, but there is no symmetry operation that interconverts them in any conformation. They are stereoheterotopic, and defined specifically as **diastereotopic**.

Now consider the CH_2 group of propane. There is, or more properly can be, a C_2 operation that interconverts the two hydrogens, and so they are considered to be equivalent. The modern terminology is **homotopic**, and is defined as interconvertable by a C_n axis of the molecule. These hydrogens are equivalent in all ways.

We have one more case to consider, exemplified by the CH_2 group in ethyl chloride. There is a symmetry element that interconverts the two hydrogens—a mirror plane. Here is where the distinction between proper and improper symmetry elements becomes important. These hydrogens are equivalent because they are interconverted by a symmetry element. However, just as with two enantiomers, such an equivalence based upon a mirror plane will be destroyed by any chiral influence. As such, these hydrogens are termed **enantiotopic**—that is, interconverted by an S_n axis of the molecule. Enantiotopic groups, when exposed to a chiral influence, become distinguishable, as if they were diastereotopic. The example of the use of a chiral shift reagent given on page 308 illustrates this point.

Homotopic groups remain equivalent even in the presence of a chiral influence. Since chiral molecules need not be asymmetric (they can have C_n axes), groups can be homotopic even though they are part of a chiral molecule. Consider the chiral acetal shown in the margin. The methyl groups are homotopic because they are interconvertable by a C_2 operation. A chiral influence cannot distinguish these methyl groups.

Another common situation where topicity issues become important is at trigonal centers, such as carbonyls and alkenes. As some examples, let's focus on carbonyl groups. The two *faces* of the carbonyl are homotopic in a ketone substituted by the same groups [R(C=O)R], such as acetone, because the molecule contains a C_2 axis (see below). The faces are enantiotopic in an unsymmetrically substituted ketone, such as 2-butanone, because they are interconverted by a σ plane. The faces are diastereotopic in a structure such as either enantiomer of 3-chloro-2-butanone, because there are no symmetry elements that interconvert the faces.

Different in all ways
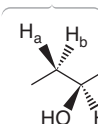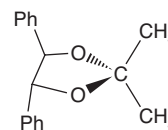
Diastereotopic hydrogens
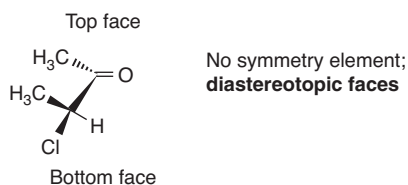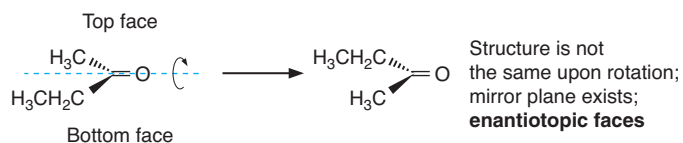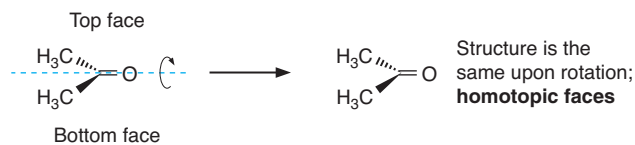
Equivalent in all ways

Homotopic hydrogens

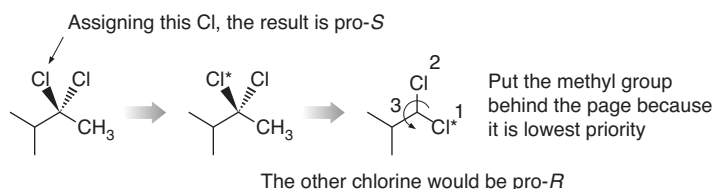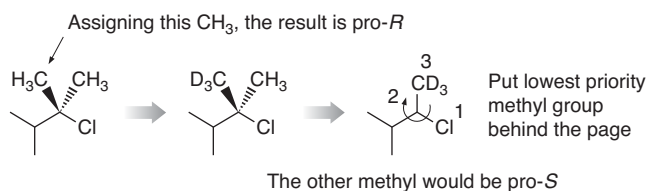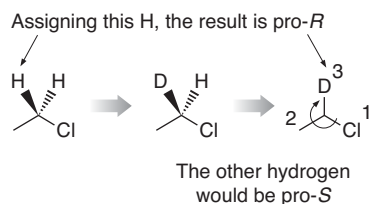Equivalent unless within a chiral environment

Enantiotopic hydrogens

Chiral molecule with homotopic methyl groups

Top face

H₃C⁪⁪⁪⁪=O ↻

H₃C

Bottom face

H₃C⁪⁪⁪⁪=O

H₃C

Structure is the
same upon rotation;
homotopic faces

Top face

H₃C⁪⁪⁪⁪=O ↻

H₃CH₂C

Bottom face

H₃CH₂C⁪⁪⁪⁪=O

H₃C

Structure is not
the same upon rotation;
mirror plane exists;
enantiotopic faces

Top face

H₃C⁪⁪⁪⁪=O

H₃C

Cl   H

Bottom face

No symmetry element;
diastereotopic faces

6.3.2 Topicity Descriptors—Pro-*R*/ Pro-*S* and *Re*/*Si*

Assigning this H, the result is pro-*R*

H H

Cl

D H

Cl

The other hydrogen
would be pro-*S*

D³

2   Cl¹

Just as it was convenient to have descriptors to distinguish enantiomeric molecules, it is also useful to be able to identify enantiotopic hydrogens. To do so, we use something similar to the *R* / *S* notation. For a CH₂ group, first take the hydrogen that is being assigned a descriptor and mentally promote it to a deuterium. Now assign priorities in the normal way. If the result is that the newly formed stereogenic center is *R*, the hydrogen that we mentally replaced by deuterium is denoted **pro-*R***, and if the new stereocenter is *S*, the hydrogen is denoted **pro-*S***. An example using chloroethane is given in the margin. The same nomenclature convention can be used with diastereotopic hydrogens.

The "pro" terminology is meant to imply that the center would become stereogenic (and hence worthy of an *R* / *S* descriptor) if the substitution were made. For this reason, the carbon containing the enantiotopic hydrogens is also referred to as a **prochiral** center. While some find this term useful, it can lead to confusion, and as such, describing the situation in terms of enantiotopic groups is preferable. It should be apparent that the enantiotopic groups need not be hydrogens. For example, two methyl groups or two chlorines can be enantiotopic. The pro-*R*/*S* distinction would be made by converting the methyl to be named to a CD₃ group, and the Cl to be named to a higher isotope (see below).

Assigning this CH₃, the result is pro-*R*

H₃C   CH₃

Cl

D₃C   CH₃

Cl

3
CD₃
2   1
Cl

Put lowest priority
methyl group
behind the page

The other methyl would be pro-*S*

Assigning this Cl, the result is pro-*S*

Cl   Cl

CH₃

Cl*   Cl

CH₃

2
Cl
3   1
Cl*

Put the methyl group
behind the page because
it is lowest priority

The other chlorine would be pro-*R*

When assigning a descriptor to the enantiotopic faces of a trigonal structure, start by simply placing the molecule in the plane of the paper. Next assign priorities to the groups using the same methods for R/S and E/Z. If the result is a clockwise rotation, the face we are looking at is referred to as *Re*; if it is a counterclockwise rotation, the face is *Si*. An example using 2-butanone is given in the margin. Once again, it is common to refer to the carbon of the carbonyl as prochiral, because attachment of a different fourth ligand will create a stereogenic center and possibly a chiral molecule.

The *Re* face   The *Si* face
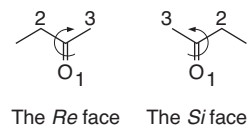
6.3.3 Chirotopicity

The terms enantiotopic and diastereotopic describe the relationship between a pair of atoms or groups in a molecule. Sometimes it is also useful to describe the local environment of a single atom, group, or location in a molecule (even if it does not coincide with an atomic center) as chiral or not. A **chirotopic** atom or point in a molecule is one that resides in a chiral environment, whereas an **achirotopic** atom or point does not. All atoms and all points associated with a chiral molecule are chirotopic. In achiral molecules, achirotopic points are those that remain unchanged (are invariant) upon execution of an S_n that is a symmetry operation of the molecule. For most situations, this means that the point either lies on a mirror plane or is coincident with the center of inversion of the molecule. Importantly, there will generally be chirotopic points even in achiral molecules.

These terms can be clarified by looking at some specific examples. In the following rotamers of *meso*-1,2-dichloro-1,2-dibromoethane, the only achirotopic site in rotamer A is the point of inversion in the middle of the structure. Every atom is in a locally chiral environment, and so is chirotopic. For rotamer B, all points in the mirror plane (a plane perpendicular to the page of the paper) are achirotopic. All other points in these conformers are chirotopic, existing at sites of no symmetry. In other words, all other points in these conformers feel a chiral environment, even though the molecule is achiral.

As another example, consider once again the chiral acetal shown in the margin. The C atom indicated resides on a C_2 axis but not on any type of S_n axis, and so it is chirotopic. Note, however, that the C is non-stereogenic. Hence, non-stereogenic atoms can reside in chiral environments. Refer back to the first Connections highlight in Section 6.2.2. In this highlight all the metals are chirotopic but nonstereogenic. The term "chirotopic" focuses us on the points in a molecule that are under a chiral influence, which is the most important factor for using stereochemical principles to understand spectroscopy and reactivity.

A. Achirotopic point

B. Achirotopic plane

Carbon is chirotopic
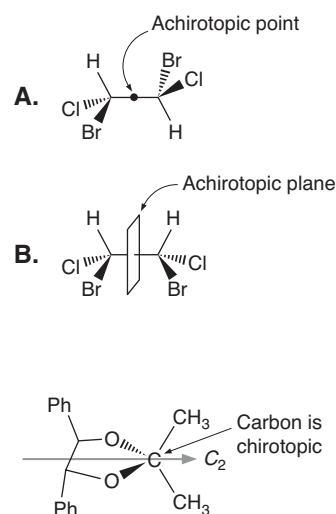
6.4 Reaction Stereochemistry: Stereoselectivity and Stereospecificity

Topicity relationships and symmetry arguments provide a powerful approach to anticipating reactivity patterns. Whether by habit, intuition, or full realization, it is the topicity relationships discussed above that synthetic chemists use to develop chemical transformations that yield asymmetric induction.

6.4.1 Simple Guidelines for Reaction Stereochemistry

Consider the three ketones in Figure 6.7 and the topicities of their carbonyl faces. In acetone, the two faces of the carbonyl are homotopic—interconverted by a C_2 rotation. In 2-butanone, the faces are enantiotopic (prochiral)—interconverted only by a mirror plane. In (R)-3-chloro-2-butanone, the two faces are diastereotopic. This molecule is asymmetric, and so there can be no symmetry operation that interconverts the two faces of the carbonyl. A consequence of this lack of symmetry in (R)-3-chloro-2-butanone is that the carbonyl group is expected to be nonplanar—that is, O, C2, C1, and C3 *will not* all lie in a plane. The point is that because the two faces of the carbonyl are inequivalent, the carbonyl cannot be planar. This is a symmetry argument of the sort mentioned previously, and as with all symmetry arguments, we cannot predict how large the deviation from planarity must be, only that it is expected to be there. As such, if we obtain a crystal structure of (R)-3-chloro-2-butanone, we should not be surprised to find a nonplanar carbonyl.
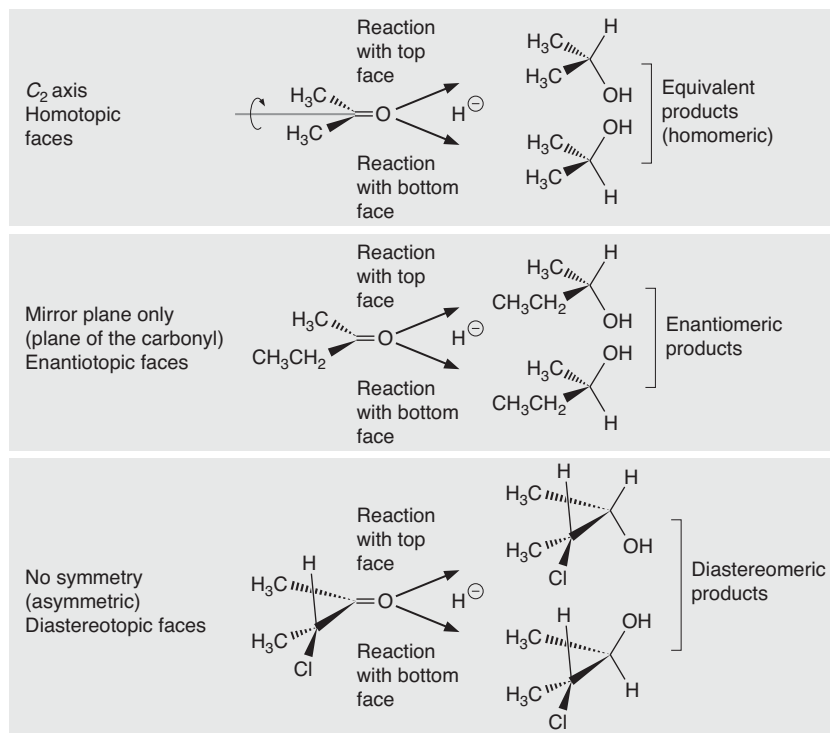
Figure 6.7
Stereochemical consequences of reacting three different types of
carbonyls with a hydride reducing agent.

Let's consider the reactivity of the three carbonyls shown in Figure 6.7. For acetone, reaction with an achiral reagent such as $LiAlH_4$ produces the same product regardless of which carbonyl face reacts. This will always be the case for homotopic faces. For 2-butanone, reaction with $LiAlH_4$ at enantiotopic faces gives enantiomeric products, (R)- and (S)-2-butanol. For (R)-3-chloro-2-butanone, the two carbonyl faces are different. They will give different products from the reaction with $LiAlH_4$—namely, (R,S)- and (R,R)-2-chloro-3-butanol, which are diastereomers.

As we can anticipate the stereochemical relationships among the products, we can also evaluate the symmetry properties of the transition states of the hydride addition reactions. For acetone, there is only one possible transition state and only one product. For 2-butanone, the transition states derived from "top" and "bottom" attack are enantiomeric. As such they will have equal energies, and so $\Delta G^{\ddagger}$ will be the same for the formation of the two enantiomeric products. As a result, a racemic mixture must form. Finally, in the reduction of (R)-3-chloro-2-butanone, the two transition states are diastereomeric, and so they are expected to have different energies (diastereomers differ in all ways). Since the starting point for the two reactions is the same, $\Delta G^{\ddagger}$ is expected to be different for the two, and therefore the rates for formation of the two diastereomeric products cannot be the same. Since the rates of formation of the two products are not the same, we can state with certainty that the reduction of (R)-3-chloro-2-butanone *is expected to not produce a 50:50 mixture of the two products* in the initial reaction. This can be anticipated from first principles. When we start from a single reactant and produce two diastereomeric products, we do not expect to get exactly a 50:50 mixture of products. However, as is always true of a symmetry argument, we cannot anticipate how large the deviation from 50:50 will be—it may be 50.1:49.9 or 90:10. We can only say that it is not 50:50.

Let's examine what happens if we use a single enantiomer of a chiral hydride reducing agent. Acetone still gives only one product—isopropanol. However, we would now expect the two enantiotopic faces of 2-butanone to be distinguished. The transition states corresponding to attack from opposite faces of the carbonyl are now diastereomeric, and something other than a 50:50 mixture of the enantiomeric products (a non-racemic sample) is expected to result from such a reaction. Achieving **asymmetric induction** is therefore anticipated by simple symmetry arguments. The only issue is whether the magnitude of the effect is small or large. To visualize how a chiral environment can distinguish enantiotopic groups, see the Connections highlight below that describes enzyme catalysis and molecular imprints.

Lastly, in the reduction of (*R*)-3-chloro-2-butanone, the different faces of the ketone were already diastereotopic due to the presence of the stereogenic center. Hence, even an achiral reducing agent such as LiAlH$_4$ will give something other than a 50:50 ratio of *R*- and *S*-centers at the newly formed alcohol. Interestingly, switching from LiAlH$_4$ to a chiral hydride agent has no impact (from a symmetry standpoint) on the reduction of (*R*)-3-chloro-2-butanone; we still expect something other than a 50:50 mixture of two diastereomers.

In summary:

1. *Homotopic groups cannot be differentiated by chiral reagents.*

2. *Enantiotopic groups can be differentiated by chiral reagents.*

3. *Diastereotopic groups are differentiated by achiral and chiral reagents.*

6.4.2   Stereospecific and Stereoselective Reactions

The terms stereospecific and stereoselective describe the stereochemical outcomes of the sort we have been discussing. Even these terms, though, are sometimes used in confusing ways. Figure 6.8 illustrates the definitions of these terms as originally presented. In a **stereospecific** reaction, one stereoisomer of the reactant gives one stereoisomer of the product, while a different stereoisomer of the reactant gives a different stereoisomer of product. Hence, to determine whether a reaction is stereospecific, one has to examine the product ratio from the different stereoisomers of the reactant. An example would be the epoxidation of 2-butene by mCPBA. The trans olefin gives the trans epoxide and the cis olefin gives the cis epoxide (Figure 6.8 **A**). S$_N$2 reactions are also stereospecific, in that inversion of the stereo-
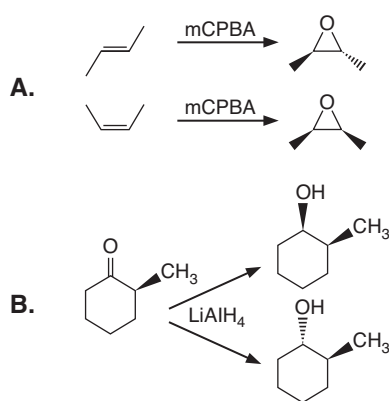
Figure 6.8
A. An example of a stereospecific reaction (mCPBA is *meta*-chloroperbenzoic acid). **B.** An example of a stereoselective reaction. If the enantiomer were analyzed, the reaction would also be stereospecific.

Connections

Enzymatic Reactions, Molecular Imprints, and Enantiotopic Discrimination

The general concept that enantiotopic groups can be distinguished chemically by a chiral environment is of paramount importance to enzymatic catalysis. Since enzymes are constructed from chiral entities—α-amino acids—they are themselves chiral. Enzymes are well known for their stereoselectivity. The fact that enzymatic reactions are diastereoselective or enantioselective is not surprising; this is expected to happen when the reagent (the enzyme) is chiral and enantiomerically pure. The remarkable feature of enzymatic reactions is the high *degree* of stereoselectivity they generally display.

Enzymes possess binding sites that are complementary to their substrates using the same principles of complementarity and preorganization introduced for synthetic receptors in Chapter 4. As a simplification of the notion of complementarity, we can consider an enzyme binding site as an imprint of the substrate, similar to the imprint of an object in wet sand. The analogy leads to a very simple visual image of how an enzyme can distinguish enantiotopic groups. Consider the picture of the molecular model of ethyl chloride sitting in wet sand shown below with one enantiotopic hydrogen of the CH_2 group embedded in the sand (**A**). After removing the plastic model, an impression is left in the sand (**B**). We cannot pick up and place the ethyl chloride back into the impression in any way besides the original placement (**A**). Hence, this impression in the sand leads to only one of the two enantiotopic hydrogens buried in the sand, thus clearly differentiating among these two hydrogens.

A.   **B.**   **C.**
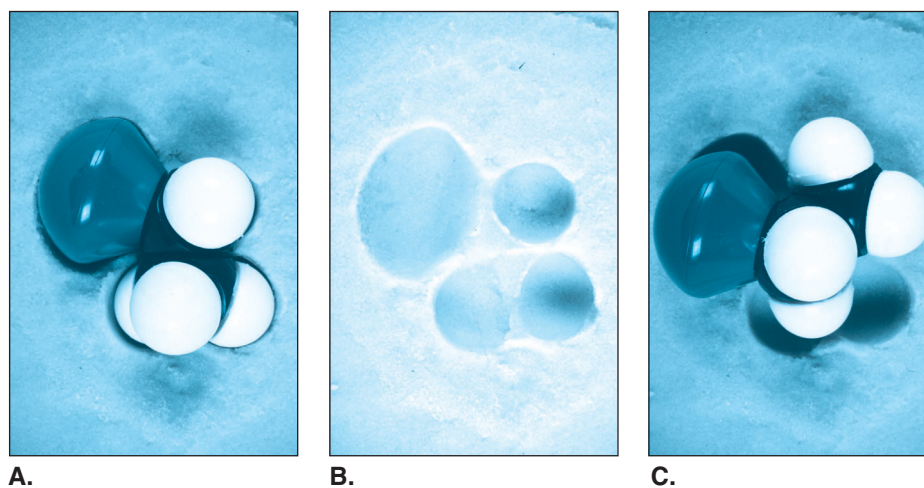
chemistry on stereogenic centers is consistently observed, so that enantiomers of reactants must give different enantiomers of the products. For a few other examples, see Table 6.1 **A**. A reaction need not be perfectly stereospecific. If an 80:20 mixture of stereoisomers is produced, we could call the reaction 80% stereospecific.
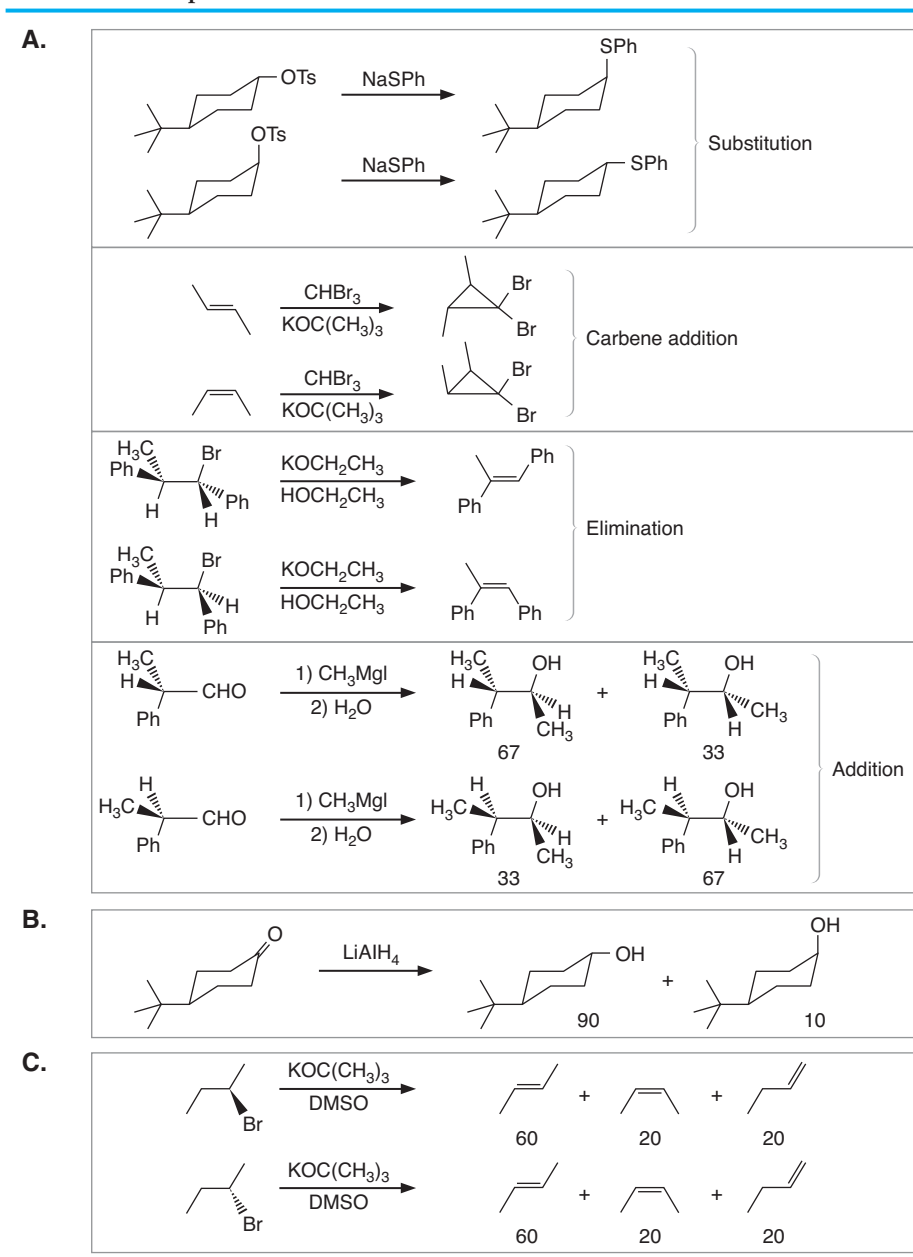
Whether a reaction is or is not stereospecific has significant mechanistic implications, and we will look at stereochemical analyses of this sort in future chapters. In essence, when a reaction is stereospecific, a common intermediate *cannot* be involved in the mechanisms of reaction of the two stereoisomeric reactants.

A **stereoselective** reaction is one in which a single reactant can give two or more stereoisomeric products, and one or more of these products is preferred over the others—even if the preference is very small. Now we only need to examine one stereoisomer of the reactant to make this determination for a reaction. In fact, the reactant may not even exist as stereoisomers, yet the reaction can be stereoselective. See the example in Table 6.1 **B**.

A reaction is also stereoselective when two stereoisomers of the starting material give the same ratio of stereoisomeric products, as long as the ratio is not 50:50. This just means the reaction is not stereospecific. For example, this may occur if the mechanisms of reaction for

Table 6.1
Stereospecific Reactions (A), a Stereoselective Reaction (B), and Stereoselective but Not Stereospecific Reactions (C)

A.

Substitution

CHBr$_3$ / KOC(CH$_3$)$_3$ — Carbene addition

KOCH$_2$CH$_3$ / HOCH$_2$CH$_3$ — Elimination

1) CH$_3$MgI 2) H$_2$O — Addition

67   33

33   67

B.

LiAlH$_4$

90   10

C.

KOC(CH$_3$)$_3$ / DMSO

60   20   20

KOC(CH$_3$)$_3$ / DMSO

60   20   20

the two stereoisomeric reactants proceed through a common intermediate, and that intermediate gives two stereoisomeric products with one in excess. However, there are also reactions where the different stereoisomeric reactants give the same ratio of stereoisomeric products, even when a common intermediate is not formed (Table 6.1 **C**). All stereospecific reactions are stereoselective, but the converse is not true.

Another example of a stereoselective reaction is the previously discussed reduction of (*R*)-3-chloro-2-butanone (see Figure 6.7). In this case the two products are diastereomers, and the reaction is referred to as **diastereoselective**. This reaction is also stereospecific, in that (*S*)-3-chloro-2-butanone will give a different ratio of products with the same reducing agent. If the two products are enantiomers [as in the reduction of 2-butanone (Figure 6.7)], the reaction is **enantioselective** if one enantiomer is formed preferentially.

Unfortunately, an alternative usage of these terms exists. Often in the organic synthesis literature, stereospecific is taken to mean 100% stereoselective. This is a necessarily vague distinction, because it depends on the tools used to measure the product ratios. A reaction that appears "stereospecific" by a relatively crude measure such as optical activity, may turn into a "stereoselective" reaction when chiral HPLC reveals a 99:1 product ratio. Also, the mechanistic implications of stereospecificity are lost in this alternative usage. However, it seems likely that both usages will exist side-by-side for some time, and the student needs to be aware of the distinction.

Terminology aside, the reaction of a chemical sample composed of only achiral molecules (such as 2-butanone) cannot give rise to products with any chiral bias (i.e., any enantiomeric excess) without the intervention of an external chiral influence. This observation has significant implications for discussions of such topics as the origin of chirality in natural systems (see Section 6.8.3).

A term similar to stereoselective is regioselective. "Regio" in this context is defined as a site in a molecule where a reaction can occur, and the difference in the reactivity of various sites is called **regiochemistry**. When more than one site reacts, a **regioselective reaction** is one where an excess of one of the possible products results. A common example is the Markovnikov addition of HCl to a double bond (see Chapter 10), where the chloride preferentially adds to the more substituted carbon (Eq. 6.2). Hence, this is a regioselective reaction. Here, the two carbons of the alkene are considered to be the two "regions" or sites in the molecule that can react. Once again, there are varying degrees of regioselectivity, ranging from 100% (completely selective) to 0% (completely unselective).


$$\text{(Eq. 6.2)}$$

Major   +   Minor
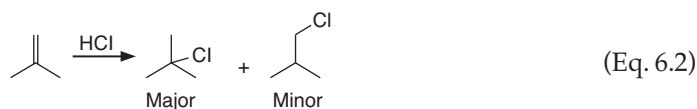
6.5   Symmetry and Time Scale

2-Butanol is asymmetric, so the two hydrogens of the CH_2 group are diastereotopic. Shouldn't the three hydrogens of the CH_3 group at C1 (or C4) be diastereotopic also? It depends. In particular, it depends on the time scale of our observation of the molecule.

When considering the symmetry of any system, we must *always* include a time scale. In Section 6.2.2 when we gave a symmetry argument for predicting chirality, we explicitly limited ourselves to rigid molecules. Symmetry arguments and stereochemistry are much simpler if we treat all molecules as rigid, geometric objects. However, real molecules are in motion, and if the motion is fast compared to the time scale of observation, we have to include the motion in our analysis of symmetry. If we are considering 2-butanol at room temperature, the rotation of the CH_3 groups will be fast under most time scales of observation. Since that rotation interconverts the three hydrogens, they become equivalent; they are not diastereotopic under these conditions. However, there is no rotation that ever interconverts the hydrogens on the methylene group, and therefore the methylene hydrogens are *always* diastereotopic, regardless of the time scale.

If we lower the temperature or greatly increase our speed of observation, rotation will appear to be slow, and the hydrogens of the CH_3 groups will be different. In practice this is difficult. However, computational methods typically produce static structures. Look carefully at the output of a computed structure of even a simple asymmetric molecule using molecular mechanics or quantum mechanics. In the particular case of 2-butanol, there are three different C–H bond lengths calculated for both of the methyl groups.

Alternatively, in very crowded systems we can slow methyl rotation enough to see individual hydrogens of a CH_3. The structure shown in the margin, a triptycene derivative of the kind we have seen before (Section 2.5.3, Figure 2.22), gives three unique NMR signals for the colored hydrogens at −90 °C. Nevertheless, under most experimental circumstances it is safe to treat the three hydrogens of a methyl group as equivalent.

The H's of the methyl group are actually inequivalent
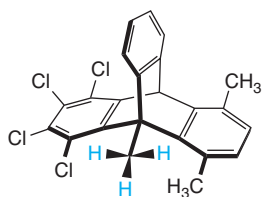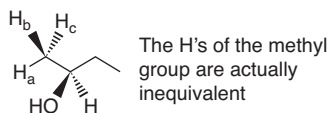
Slowed rotation in a methyl group

Symmetry and time scale are always tightly coupled. For example, we discussed in Chapter 2 that cyclobutane is not planar, but rather adopts a lower symmetry, puckered geometry. The methylene hydrogens are diastereotopic in this geometry. However, the interconversion of the puckered forms is rapid on most time scales, and so for most analyses of cyclobutane, all hydrogens appear equivalent. In fact, a planar representation (the time average of two interconverting puckered forms) is acceptable for many analyses. The molecule is only planar when the fleeting transition state between the puckered forms is achieved, but on most time scales it behaves *as if* it were planar. The same analysis can be made for the CH_2 groups in cyclohexane. However, the time scale must be considerably more leisurely for the averaging of the axial and equatorial hydrogens of cyclohexane to occur, because of the much higher barrier (and therefore slower rate) for ring inversion in cyclohexane compared to other cyclic hydrocarbons.

Typically, if a flexible molecule can achieve a reasonable conformation that contains a symmetry element, the molecule will behave as if it has that symmetry element. The classic example is an amine with three different substituents. The pyramidal form is chiral, but the two enantiomers interconvert rapidly by pyramidal inversion (Eq. 6.3). That rapid inversion leads to an effectively achiral system is appreciated when we consider that the transition state for inversion is a planar, achiral structure.
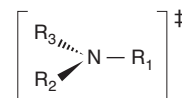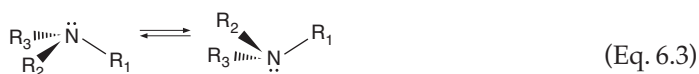
Planar, achiral transition state

$$R_3\text{''''}\ddot{N}\diagdown R_1 \over R_2 \rightleftharpoons {R_2 \over R_3\text{''''}}\diagup N \diagdown R_1 \qquad\qquad (Eq.\ 6.3)$$

Time scale is important for *all* stereochemical concepts. Even our most cherished stereochemical concept, the stereogenic tetracoordinate carbon, is undone if we are at high enough temperatures and long enough time scales that inversion of the center is possible through bond cleavage reactions.

There are many chiral molecules for which enantiomeric forms can be interconverted by a rotation about a single bond. The enantiomeric conformations of gauche butane provide an example, where rapid rotation interconverts the two under most conditions. If the rotation that interconverts a pair of such enantiomers is slow at ambient temperature, however, the two enantiomers can be separated and used. Recall from our first introduction of isomer terminology (Section 6.1) that stereoisomers that can be interconverted by rotation about single bonds, and for which the barrier to rotation about the bond is so large that the stereoisomers do not interconvert readily at room temperature and can be separated, are called atropisomers. One example is the binaphthol derivative shown in the margin. It is a more sterically crowded derivative of the biphenyl compound discussed previously as an example of a chiral molecule with no ''chiral center''. A second example is *trans*-cyclooctene, where the hydrocarbon chain must loop over either face of the double bond (Eq. 6.4). This creates a chiral structure, and the enantiomers interconvert by moving the loop to the other side of the double bond.

Binaphthol

$$\text{(Eq. 6.4)}$$
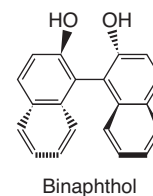
Facile rotation does not guarantee interconversion of conformational isomers. One of the most fascinating dynamic stereochemistry systems is exemplified by the triarylborane shown in Eq. 6.1. Correlated rotation of the rings, the ''two-ring flip'', is facile at room temperature. There are three different two-ring flips possible, depending on which ring does the ''non-flip''. All two-ring flips are fast, but in a highly substituted system, not all possible conformations can interconvert. As long as only two-ring flips can occur, we have two sets of rapidly interconverting isomers, but no way to go from one set to the other. This has been termed **residual stereoisomerism**. We have two separate stereoisomers, each of which is a collection of rapidly interconverting isomers. Clearly, stereoisomerism and time scale are intimately coupled in such systems.

6.6 Topological and Supramolecular Stereochemistry

One of the more interesting aspects of modern stereochemistry is the preparation and characterization of molecules with novel topological features. As we indicated in Chapter 4, supramolecular chemistry has produced a number of structures with novel topologies such as catenanes and rotaxanes. "Simple" molecules (i.e., not supramolecules) can also have novel topological features such as knots or Möbius strips. Here we will introduce some current topics in this fascinating area, emphasizing the aspects that relate to stereoisomerism. But first, we must agree upon a definition of "topology".

The mathematical definition of **topology**, and the one that is best suited to stereochemistry, concerns studies of the features of geometrical objects that derive solely from their connectivity patterns. Metric issues—that is, those associated with numerical values (such as bond lengths and bond angles)—are unimportant in topology. The easiest way to see this is to consider two-dimensional topology as the study of geometric figures that have been drawn on a rubber sheet. You can stretch and bend and flex the sheet as much as you like without changing the topology of a figure on the sheet (Figure 6.9 **A**). Thus, a circle, a triangle, and a square are topologically equivalent because we can deform one to the other. Topologically, all three are just a closed loop. In three dimensions the same concept applies, with the additional requirements that you cannot break a line or allow any lines to cross, and you cannot destroy a vertex. In a dictionary, one will often see a second definition of topology that does include metric issues, so it is a synonym for topography. In topography (i.e., map making), it matters how high the mountain is, but in the mathematical definition of topology we will use here, it does not (in fact, the mountain can be "stretched flat").

With the very few special exceptions discussed below, all stereoisomers are, perhaps surprisingly, topologically equivalent. If you are allowed to stretch and bend bonds at will, it is a simple matter (Figure 6.9 **B**) to interconvert the enantiomers of 2-butanol without crossing any bonds (simple mathematically, but not chemically!). Similar distortions are possible with almost any molecule, allowing stereoisomers to interconvert. This is consistent with our definition of stereoisomers as molecules with the same connectivities (topologies) but different arrangements of atoms in space. Since topology concerns only issues that derive from the connectivity of the system, structures with the same connectivity have the same topology. There are stereoisomers that have different topologies, however, and that is the topic of this section.

We should first make explicit the natural connection between chemistry and mathematics that allows us to discuss topology. Topology deals with graphs—objects that consist of edges and vertices (points where two or more edges meet). In considering chemical topology, we are considering a **chemical graph**, in which the edges are bonds and the vertices are atoms. The ambiguity concerning connectivity still applies (see the Going Deeper highlight in Section 6.1.1), but once we agree on a definition we can consider topological issues.
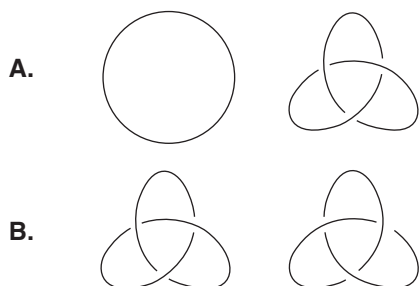
Figure 6.9
The interconversion of topologically equivalent structures.
A. Topologically, the triangle, circle, and square are all just closed loops (as long as we do not consider the "corners" of the triangle and square to be vertices).
B. Interconversion of the enantiomers of 2-butanol can be accomplished by flexing and bending without crossing any bonds, and so the two enantiomers are topologically equivalent.
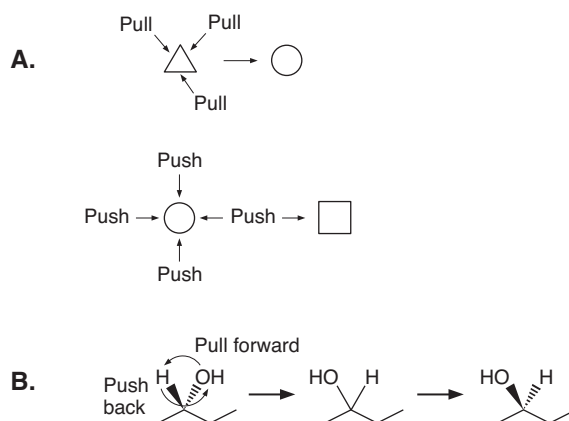
6.6.1   Loops and Knots

What are the simplest systems that can produce topological stereoisomers? All we need is a cyclic structure. Figure 6.10 **A** shows a circle and a classic trefoil knot. Both structures are simply a single, closed loop (which is the definition of a knot, with a circle being the simplest knot or the "unknot"). It is not possible to interconvert the two structures without crossing edges—they are topologically different. Molecular realizations of the circle and the trefoil knot would be examples of **topological stereoisomers**. Since they are not non-congruent mirror images, it is sensible to call them **topological diastereomers**. To create a chemical version of this situation, a structure as simple as $(CH_2)_n$ could serve the purpose. Interestingly, knots are actually relatively common in biochemistry, as the next Connections highlight describes.

A.

Figure 6.10
A. Topological stereoisomers—a circle and a trefoil knot.
B. Enantiomorphous trefoil knots.

B.

How are these stereoisomers different from conventional diastereomers? The circle and the knot can be infinitely deformed—bent, twisted, stretched, and compressed—but they will never be interconverted (as long as we don't cross any bonds). Conventional isomers can be interconverted by deformation, as in the case of 2-butanol in Figure 6.9. Conventional stereoisomerism depends on the precise location of the atoms in space, leading to the terms **geometric** or **Euclidian isomerism**. With topological stereoisomers, we can move the atoms all around, and retain our isomerism.

Going Deeper

Biological Knots—DNA and Proteins

All we need to make a knot is a cyclic structure. If the ring is large enough to allow the necessary twisting, a knotted structure could form. While it may seem fanciful to consider such structures, and we might expect their preparation to depend on exotic synthetic methods, knotted structures turn out to be common in nature. Circular, double-stranded DNA molecules have been known for some time, with very large "ring sizes" (thousands of nucleotides). Indeed, these large cycles do form knots, which are in fact fairly common structures that can be directly observed by electron microscopy. Catenated circular DNAs have also been observed.

What about proteins? Typically, naturally occurring proteins are not closed circles as in cyclic DNA; the C and N termini are not connected. However, cycles are introduced when crosslinks occur between separate regions of the backbone, most typically via disulfide bonds. Rare examples of unique topologies in such systems are known. However, it was recently realized that when the analysis includes cofactors and prosthetic groups such as seen in quinoproteins or iron–sulfur cluster proteins, interesting topologies including knots and catenanes are in fact more common than previously realized. As always, in considering stereochemical phenomena, our definition of connectivity is crucial. Earlier studies had counted only the amino acids as contributing to the connectivity of the system. When cofactors are included, more complex connectivities result.

Liang, C., and Mislow, K. "Knots in Proteins." *J. Am. Chem. Soc.,* **116**, 11189 (1994).

6.6.2 Topological Chirality

If we can have topological diastereomers, can we have topological enantiomers—that is, is there **topological chirality**? There is, and the trefoil knot is a simple example. Figure 6.10 **B** shows two trefoil knots, and these two knots are enantiomorphs. The term enantiomers is reserved for molecules; **enantiomorphs** applies to geometrical objects. How do we know, however, that we could not just deform one structure into the other by stretching and pulling? If we could, the two forms would be topologically equivalent and thus not enantiomers, and the trefoil knot would be topologically achiral. Perhaps surprisingly, there is no general way to prove a knot is chiral. One can prove it is achiral by just finding one way to draw the knot (called a presentation) that is itself achiral. However, if you fail to find an achiral presentation, that doesn't prove the knot is chiral; maybe you just weren't able to find the achiral presentation. In the case of the trefoil knot, however, the structure is indeed chiral.

6.6.3 Nonplanar Graphs

We mention briefly here another topological issue that has fascinated chemists. For the overwhelming majority of organic molecules, we can draw a two-dimensional representation with no bonds crossing each other. This is called a **planar graph**. If you cannot represent the connectivity of a system without some crossing lines, you have a **nonplanar graph**. It may seem surprising, but most molecules have planar graphs. Figure 6.11 **A** shows some examples that illustrate that this is so. Remember, we are doing topology, so we can stretch and bend bonds at will.

Graph theory is a mature branch of mathematics, and graph theorists have established that all nonplanar graphs will conform to one of two prototypes, called K_5 and $K_{3,3}$ in graph theory terminology (Figure 6.11 **B**). K_5 is simply five vertices, maximally connected. Every vertex is connected to every other. $K_{3,3}$ contains two sets of three vertices, with every vertex of one set connected to every vertex of the other set. The fact that $K_{3,3}$ is nonplanar is proof of
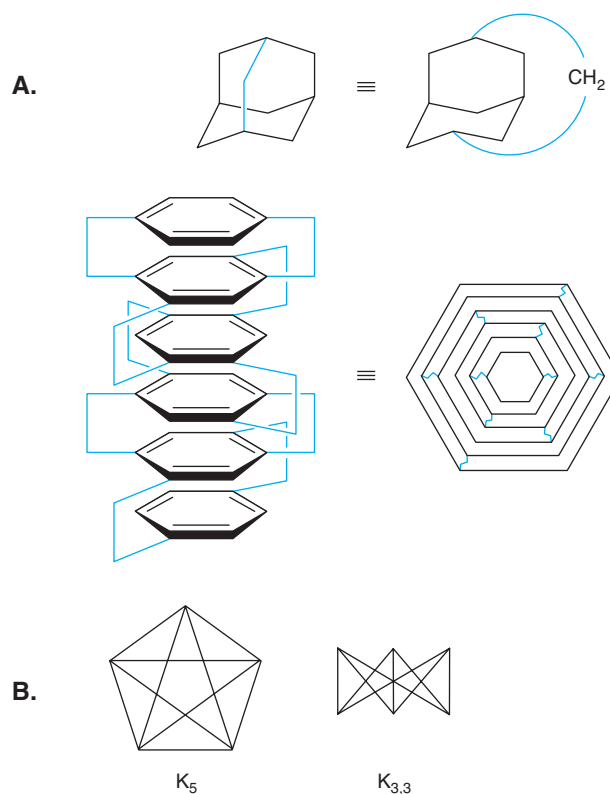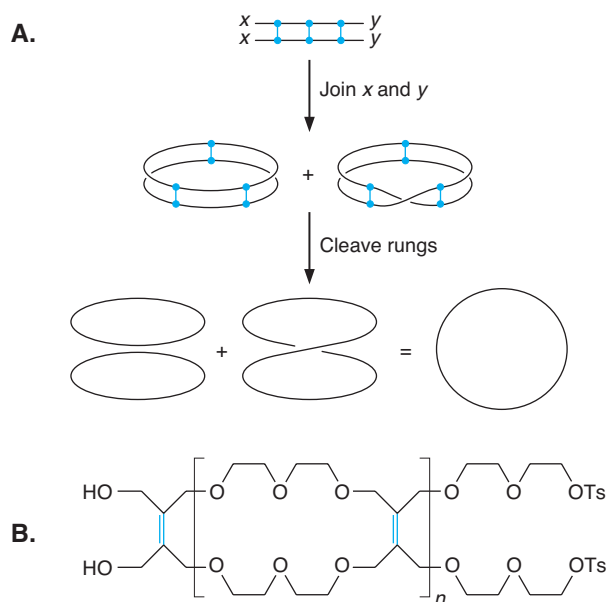

Figure 6.11
A. Examples of how most chemical structures can be represented as planar graphs.
B. K_5 and $K_{3,3}$ nonplanar graphs.

the architectural conundrum, "three houses, three utilities". It is impossible to have three houses, each connected to three utilities (such as water, electric, and phone) without at least one instance of "lines" crossing. We will see molecular versions of these nonplanar graphs below.

6.6.4 Achievements in Topological and Supramolecular Stereochemistry

Recent efforts have produced chemical structures that successfully realize many interesting and novel topologies. A landmark was certainly the synthesis of a trefoil knot using Sauvage's Cu^+/phenanthroline templating strategy described in Section 4.3.2. This nonplanar, topologically chiral structure is a benchmark for the field. Other more complicated knots have also been prepared by this strategy. Vögtle and co-workers have described an "all organic" approach to amide-containing trefoil knots, and have been able to separate the two enantiomeric knots using chiral chromatography.

Another seminal advance in the field was the synthesis and characterization of a "Möbius strip" molecule (Figure 6.12). A **Möbius strip** can be thought of as a closed ribbon with a twist, and it has long fascinated mathematicians and the general public. Although the concept behind the Möbius strategy for preparing novel topologies was enunciated in the late 1950s, it was not chemically realized until the 1980s. A clever strategy based on tetrahydroxymethylethylene (THYME) ethers was developed by Walba. Ring closure could proceed with or without a twist, and when the reaction is performed, the two are formed in roughly equal amounts. An important design feature was that the "rungs" of the ladder system were olefins, which could be selectively cleaved by ozonolysis. Cleavage of the untwisted product produced two small rings, but cleavage of the Möbius product gives a single, larger macrocycle, thereby differentiating the two topological stereoisomers.
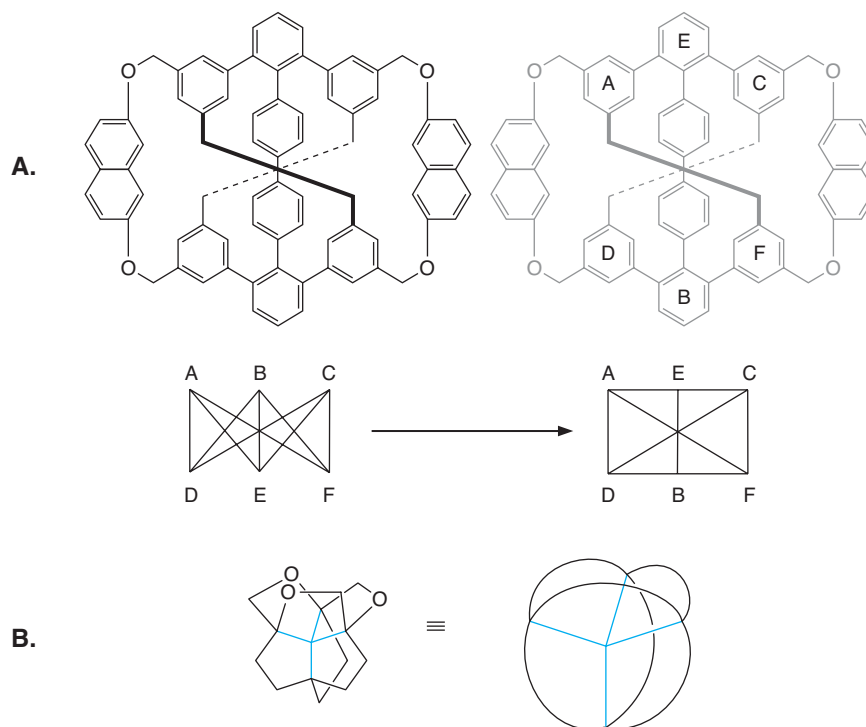

Figure 6.12
A. The synthetic strategy for the preparation of a molecular Möbius strip, and the results of rung cleavage.
B. A THYME polyether that can ring close to make a Möbius strip.

Even without the twist, the three-rung Möbius ladder compound is a molecular realization of an interesting topology. It is a simple example of a nonplanar graph with the $K_{3,3}$ topology. Another example of a recently prepared molecule with a $K_{3,3}$ topology is given in Figure 6.13 **A**. A structure with the K_5 nonplanar graph has also been prepared, and it is shown in Figure 6.13 **B**.

As suggested in our discussion of supramolecular chemistry in Section 4.3, the facile preparation of complex catenanes and rotaxanes using the various preorganization strategies has led to the consideration of a number of novel stereochemical situations. Topolog-

Figure 6.13
Examples of structures with nonplanar graphs. **A.** A $K_{3,3}$ molecule. To see this as a $K_{3,3}$, begin with the schematic graph as presented in Figure 6.11 **B**, and move the vertices B and E. This is topology, so that is legal because all the connectivities stay the same. The structure on the right, then, is labeled in the same way. See also the three-rung ladder molecule of Figure 6.12 **A** for another example of a $K_{3,3}$ molecule.
**B.** A K_5 molecule, and a schematic showing the sense that it has the K_5 connectivity.

ical stereoisomers have become commonplace. In addition, other types of isomerism that really do not fit any pre-existing categories are perhaps best regarded as **supramolecular stereoisomerism**.

For example, rotaxanes and catenanes can often exist in different forms that are stereoisomers, but with some unique properties. Figure 6.14 shows several examples. The rotaxane of Figure 6.14 **A** has been studied using electrochemistry, which drives the macrocycle from one "station" to the other. However, without oxidation or reduction of the paraquat, we expect an equilibrium between two forms that are differentiated solely by the position of the macrocycle along the rotaxane axle. Likewise, a catenane with two different building blocks in one of the rings will exist in two different forms (Figure 6.14 **B**). A similar form of supramolecular stereoisomerism arises in the "container compounds" discussed in Section 4.3.3. As shown in the schematic of Figure 6.14 **C**, when the container has two distinguishable "poles", an unsymmetrical guest can lie in isomeric positions. Such isomerism has been observed for both covalent and non-covalent container compounds.

For each case in Figure 6.14, we have stereoisomers—structures with the same connectivities but differing arrangements of the atoms in space. They are not enantiomers, so they must be diastereomers. The novelty lies in the fact that these stereoisomers interconvert by a *translation or reorientation* of one component relative to the other. In some ways these structures resemble conformers or atropisomers, which involve stereoisomers that interconvert by rotation about a bond. For the supramolecular stereoisomers, however, interconversion involves rotation or translation of an entire molecular unit, rather than rotation around a bond. Note that for none of the situations of Figure 6.14 do we have topological stereoisomers. In each case we can interconvert stereoisomers without breaking and reforming bonds.
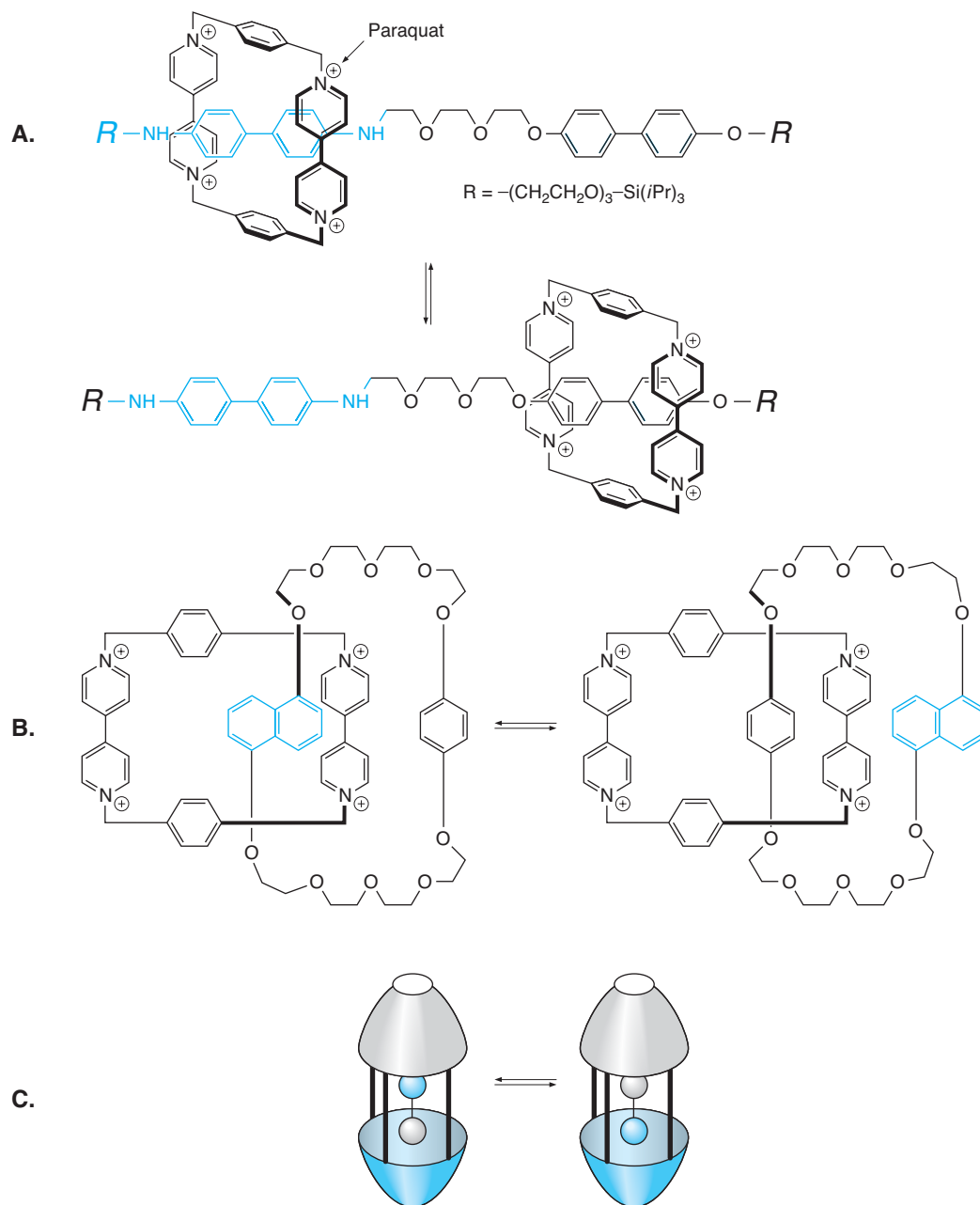
Figure 6.14
Supramolecular isomerism in rotaxanes, catenanes, and "container" compounds. **A.** Moving along a rotaxane axle can lead to isomerism if there are two different "docking stations". **B.** Similarly, catenanes can exist in isomeric forms if there is structural diversity in one of the rings. **C.** A conceptualization of isomerism in a container compound.

More complex catenanes can produce topological stereoisomers. Consider a [3]catenane with two types of rings, symbolized in Figure 6.15 **A**. Having the unique ring in the outer position vs. the inner position defines two stereochemical possibilities. These structures are now topological diastereomers. They cannot be interconverted without breaking bonds. A large number of stereoisomers becomes possible with [n]catenanes as n gets larger and each ring is different.
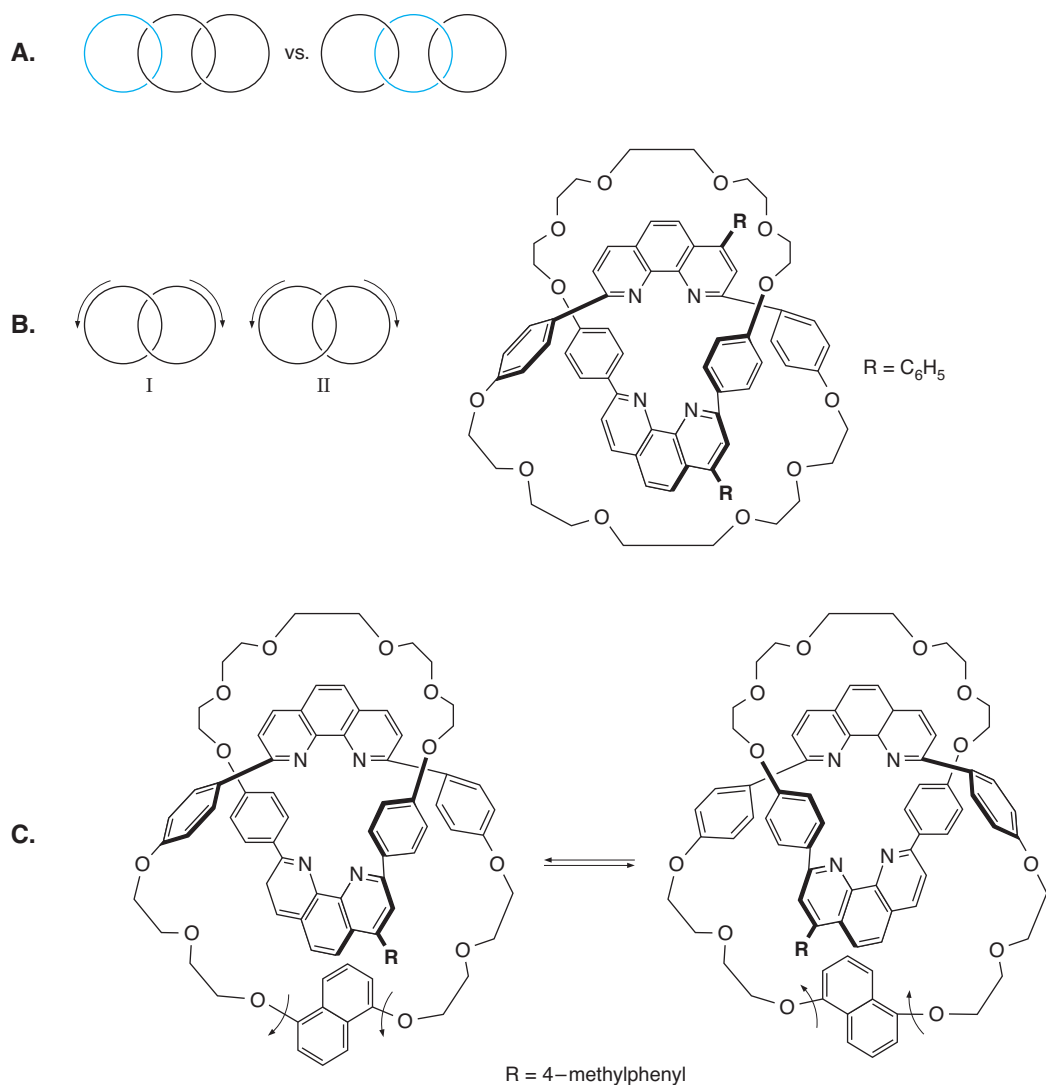
Figure 6.15
Topological isomerism in simple catenanes. **A.** A kind of "positional" isomerism that can occur in a [3]catenane with two different kinds of ring. **B.** A more subtle isomerism that involves "oriented" rings, and a chemical example. **C.** The "toplogical rubber glove", a pair of enantiomers that can interconvert readily without ever going through an achiral conformation.

A more subtle case of topological isomerism arises in a [2]catenane in which the two rings are not simple, symmetrical circles, but rather have a sense of direction (Figure 6.15 **B**). Now, topological enantiomers (I vs. II) are possible. This may be easier to see with a real chemical example (Figure 6.15 **B**). Again, the Sauvage Cu⁺/phenanthroline templating strategy was used to assemble two directional rings, producing a topologically chiral [2]catenane. You should convince yourself that the catenane shown can exist as a pair of enantiomers, and that no amount of spinning the rings can interconvert them.

If one ring has a sense of direction, but the other does not, an even more subtle phenomenon occurs. Figure 6.15 **C** shows such a case. The molecule is chiral. The two enantiomers, however, can interconvert readily by simply rotating the 1,5-dioxynaphthyl ring and translating the other macrocycle. Sauvage and Mislow realized, however, that at no point during this process does an achiral conformation appear. In fact, it is impossible to create an achiral representation of this structure. The molecule has been referred to as a "topological rubber glove", referring to the fact that a rubber glove can be converted from right-handed to left-handed by pulling it inside out, but at no point in the process does an achiral form appear.

6.7 Stereochemical Issues in Polymer Chemistry

Many unnatural polymers of considerable commercial importance have one stereocenter per monomer, such as in polypropylene and polystyrene (Figure 6.16). Unlike the "polymerization" involved in forming a protein or nucleic acid (see the next section), these unnatural systems typically start with a simple, achiral monomer (propene or styrene), and the polymerization generates the stereogenic centers. Control over the sense of chirality for each polymerization step is often absent. As a result, considerable stereochemical complexity can be expected for synthetic polymers. For example, molecular weight 100,000 polypropylene has approximately 2400 monomers, and so 2400 stereogenic centers (look at the next Going Deeper highlight for an interesting ramification of this). There are thus 2^{2400} or approximately 10^{720} stereoisomers! The R,S system is not very useful here. Hence, polymer stereochemistry is denoted by a different criterion called tacticity.

Tacticity describes only local, relative configurations of stereocenters. The terms are best defined pictorially, as in Figure 6.16. Thus, **isotactic** polypropylene has the same configuration at all stereocenters. Recall the two faces of propylene are enantiotopic, and the isotactic polymer forms when all new bonds are formed on the same face of the olefin. If, instead, there is an alternation of reactive faces, the polymer stereocenters alternate, and a **syndiotactic** polymer is produced. Finally, a random mixture of stereocenters produces **atactic** polymer.

Control of polymer stereochemistry is a major research area in academic and industrial laboratories. This is because polymers with different stereochemistries often have very different properties. For example, atactic polypropylene is a gummy, sticky paste sometimes used as a binder, while isotactic polypropylene is a rugged plastic used for bottle caps. Recent advances (see the Going Deeper highlight on the next page and Chapter 13) have greatly improved the ability to control polymer stereochemistry, leading to commercial production of new families of polymers with unprecedented properties.

Another stereochemical issue is helicity, as some simple polymers can adopt a helical shape. We defer discussion of this to Section 6.8.2, in which we discuss helicity in general.
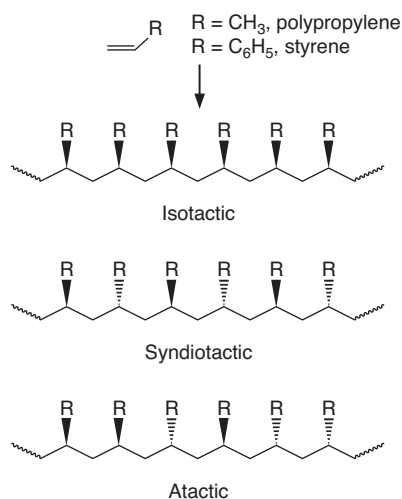
Figure 6.16
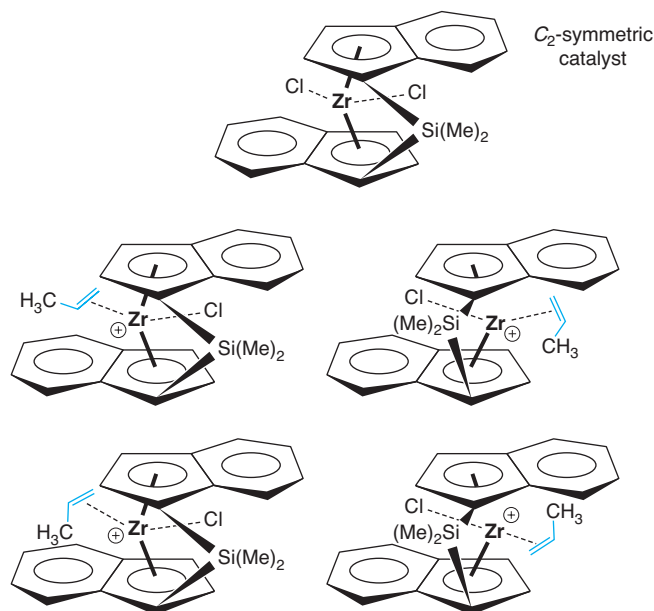Different forms of polypropylene and polystyrene.

Going Deeper

Controlling Polymer Tacticity—The Metallocenes

The C_2-symmetric Zr metallocene catalyst (top) and a highly schematic view of propylene complexing to it. The middle two structures use the same face of the propylene, and lead to the same tacticity because of the C_2 symmetry of the catalyst. The bottom two structures use the opposite face of the olefin. The adverse steric interaction of the CH_3 with the aromatic ring disfavors these structures.

One of the most exciting recent advances in organic and organometallic chemistry has been the development of new catalysts that produce polypropylene with high stereochemical purity. Both isotactic and syndiotactic polypropylene are now made commercially with a new class of metallocene catalysts, prototypes of which are shown below. The mechanism of the polymerization reaction is discussed in Chapter 17. Here we will focus on the stereochemistry, because symmetry principles of the sort we discussed above were crucial in the design of this chemistry.

A key step in metal-induced olefin polymerization has the olefin π face complexing to the metal center. The two faces of the propylene double bond are enantiotopic. Isotactic polypropylene forms when only one face of the propylene monomer consistently reacts to make polymer. Thus, a chiral catalyst is needed to distinguish enantiotopic faces of an olefin. But, how do we ensure that only one face reacts? It is a complicated problem, because when an olefin like propylene complexes to a metal center in a typical chiral environment, not only will both faces complex to some extent, but many orientations are possible for each complex. This leads to many different reaction rates, and a mixture of stereochemistries. A key to the solution, then, was to develop a catalyst that is chiral but not asymmetric. In particular, the C_2-symmetric metallocene shown below was prepared. The metal is chirotopic but non-

stereogenic. Hence, the chlorines are homotopic and either can be replaced with propylene, giving identical structures. By making one side of the coordination site much more bulky than the other, the propylene will complex to the metal (the first step in the reaction) with the methyl group away from the crowded side. There are two different ways to do this, but they are symmetry equivalent, and both involve the same face of the propylene. If the catalyst is enantiomerically pure, stereochemical control becomes possible.

The production of pure, syndiotactic polypropylene was even more challenging, but again symmetry notions played a key role. Syndiotactic polypropylene requires an alternation of stereochemistry at the catalyst center. Formally, a syndiotactic polymer is like a meso compound, and so a chiral catalyst is not required. To achieve the desired stereochemistry, a catalyst with a mirror plane of symmetry (C_s) was developed (see next page). The idea was that the growing polymer would move back and forth between mirror-image (enantiotopic) sites of the catalyst (caused by steric influences of the growing chain), and this alternating behavior would lead to an alternation in the stereochemistry of monomer incorporation. This was a bold suggestion, but this strategy has been successfully implemented into commercially viable processes.
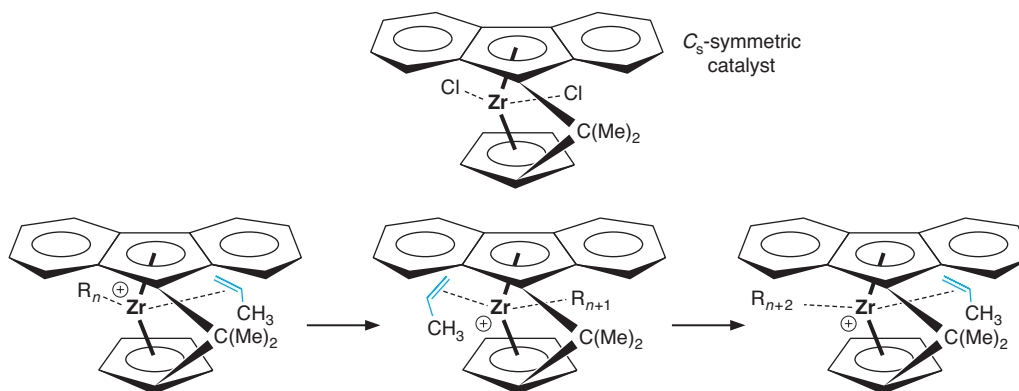
Coates, G. W., "Precise Control of Polyolefin Stereochemistry Using Single-Site Metal Catalysts." *Chem. Rev.*, **100**, 1223–1252 (2000); Resconi, L., Cavallo, L., Fait, A., and Piemontesi, F. "Selectivity in Propene Polymerization with Metallocene Catalysts." *Chem. Rev.*, **100**, 1253–1345 (2000).

6.8   Stereochemical Issues in Chemical Biology

Molecular shape is a crucial concept in chemical biology. The "lock-and-key" metaphor of enzyme–substrate or antigen–antibody interactions is useful for understanding biological phenomena, and it depends crucially on molecular shape. Despite the marvelous diversity and apparent complexity of biomolecules, at a fundamental level, biopolymers are built up from really fairly simple monomers and connecting units. The structural complexity arises from an accumulation of a large number of individually straightforward interactions. As such, only a few basic stereochemical notions are necessary for dealing with biopolymers. Since many of the complex chemical structures that make up life (proteins, nucleic acids, and polysaccharides) are biopolymers, our current understanding of small molecule stereochemistry and polymer topology allows us to explore the stereochemistry of these biological structures.

6.8.1   The Linkages of Proteins, Nucleic Acids, and Polysaccharides

As stated previously, polymer stereochemistry depends critically upon the structures of the monomers and how they are assembled. No new stereocenters are produced when amino acids are combined to make proteins, or nucleotides are combined to make nucleic acids. This is because the linkages created in forming the polymers are not stereogenic. The same is not true for polysaccharides, where the newly formed anomeric center is stereogenic. We will consider these three types of biopolymers separately.

Proteins

Proteins are polymers built from a concatenation of α-amino acid monomers. There are twenty common amino acids, and all but one (glycine) are chiral. Thus, a protein—a poly(α-amino acid)—could have a huge number of stereoisomers. This is no way to build a living organism. As such, living systems contain only one enantiomer of each amino acid. Polymerization then produces only one stereoisomer, an isotactic polymer (Figure 6.17 **A**). The polymerization itself—the peptide bond formation—does not create a new stereogenic center. As a result, unlike polypropylene, the polymerization of amino acids does not require any special stereochemical control of the bond forming reaction.

The newly formed peptide bond is not a stereogenic unit, so amino acid polymerization is in some ways different than propylene polymerization. However, as we noted earlier in
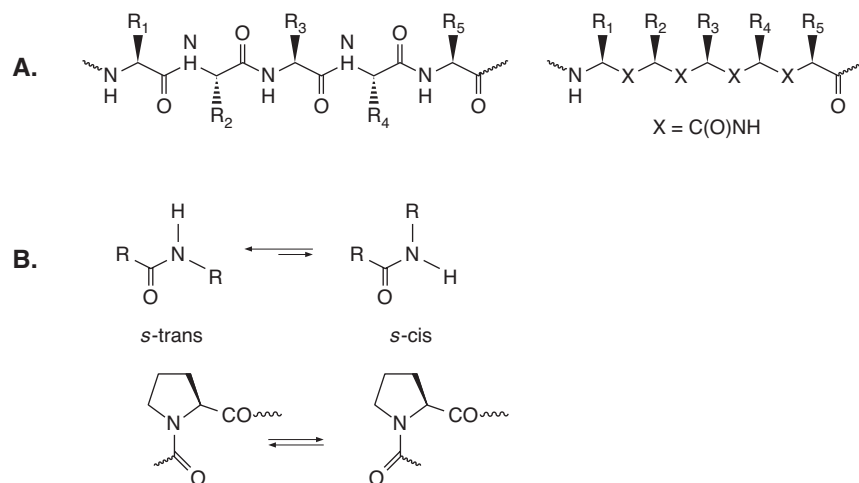
Figure 6.17
Basic stereochemical issues in protein structures. **A.** The conventional representation of a protein chain, and an alternative representation that emphasizes the isotactic nature of the polymer. **B.** *S*-cis and *s*-trans geometries in a conventional peptide bond and in a peptide bond involving proline.

Chapter 1, the peptide bond does have significant conformational preferences. The group is planar, and in secondary amides of the sort found in most peptide bonds, there is a significant preference for what is termed the *s*-trans or the Z stereochemistry (Figure 6.17 **B**). This preference is typically on the order of 4 kcal/mol, and it has a profound effect on the potential shapes that proteins can adopt. The difference in this system from the polypropylene system is that the barrier separating the two forms of the peptide bond (~19 kcal/mol) is such that they equilibrate readily at conventional temperatures. Thus, exerting stereochemical control over the formation of the peptide bond would be futile, because the system would quickly adjust to the thermodynamic equilibrium. Still, this highlights the inherent ambiguity of many stereochemical concepts. If the rotation barrier in amides was 29 kcal/mol (or we lived at –78 °C!), the peptide bond would be a stereogenic center, and tacticity would be a key issue in protein chemistry. The conformational preference of the peptide bond results from several factors, including adverse steric interactions in the *s*-cis and a favorable alignment of bond dipoles in the *s*-trans form (Chapter 1). An exception arises when proline contributes the N to an amide bond (Figure 6.17 **B**). Now the N has two alkyl substituents, and the cis–trans energy difference is much smaller. As such, proteins often adopt unique conformations in the vicinity of a proline.

Nucleic Acids

The only stereogenic centers of DNA and RNA are found at the sugar carbons, and because the ribose or deoxyribose are enantiomerically pure, natural nucleic acids are isotactic. The P of the phosphodiester backbone of a nucleic acid is not a stereogenic center, but the two O⁻ groups of a connecting phosphate are diastereotopic. The phosphorus is thus prochiral. This has led to the use of labeled phosphates in mechanistic studies, as described with one example in a Connections highlight on the next page.
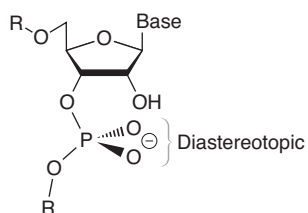
Polysaccharides

In contrast to proteins and nucleic acids, the linkages formed between saccharide monomers are made at stereogenic centers, and so stereochemical control of the polymerization step is critical. The crucial carbon, the **anomeric center**, is highlighted in Figure 6.18, which defines the nomenclature convention for this stereogenic center. This stereochemical distinc-

CD Used to Distinguish α-Helices from β-Sheets

The two most prominent secondary structural features of protein chemistry are the α-helix and the β-sheet (the basic structures are described in Appendix 4). As mentioned earlier, all helices have an inherent chirality. In contrast, sheets are in a sense flat, and therefore, they are not *inherently* chiral even though the peptide building blocks themselves are chiral. In addition to the α-helix and the β-sheet, peptides and proteins can lack any defined shape, called a random coil. Once again, no inherent chirality would be associated with this structure, although the building blocks are chiral. This suggests that spectroscopic methods that probe chirality could be used to probe protein secondary structure. Circular dichroism is by far the one most commonly employed.

The most useful region of the spectrum is from 190–240 nm. Absorbances in this region are dominated by the amide backbone rather than the sidechains, making them more sensitive to secondary structure. In a CD spectrum, two negative peaks of similar magnitude at 222 and 208 nm are indicative of an α-helix. A β-sheet is revealed by a negative band at 216 nm and a positive one of similar magnitude near 195 nm. Lastly, a strong negative band near 200 nm and often a positive one at 218 nm is indicative of a lack of well-defined structure (the random coil). These are empirical observations that have been confirmed in many systems. The figure shows prototype spectra of each struc-

tural type in black, and the experimental CD spectrum of myoglobin in color. Fitting the experimental spectrum as a linear combination of the three prototype curves leads to an estimate of 80% α-helix, with the rest mostly random coil. This is in good agreement with the value of 77% α-helix derived from the x-ray structure of myoglobin.
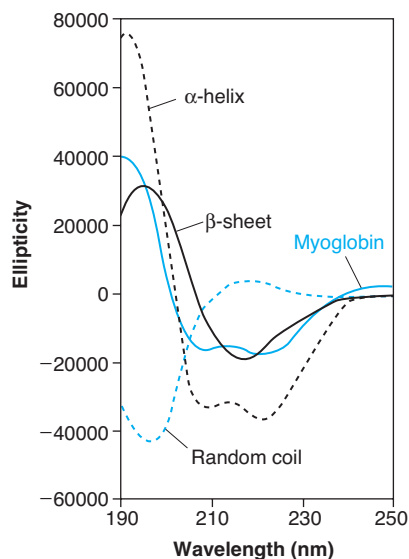

tion is crucial. For example, when glucose is polymerized exclusively with α-1,4-glycoside bonds, a helical structure called amylose (a starch) is obtained. Conversely, all β-1,4 linkages leads to a "rigid-rod" linear structure called cellulose. As with the stereoisomers of polypropylene, these two stereoisomeric polymers have distinctly different properties. Starch is formed by animals and is primarily used for energy storage, while cellulose is a structural material found in plants. Thus, the enzymes that make glycosidic bonds are well developed to control the stereochemistry of the coupling.

### Creating Chiral Phosphates for Use as Mechanistic Probes

When one O^- in a phosphodiester of DNA or RNA is replaced by, for example, a specific isotope or by S^-, two stereoisomers are possible. This allows one to follow the stereochemistry of the reactions that take place at the phosphorus center, potentially revealing the mechanisms of these reactions. For example, RNase A (an enzyme) catalyzes ring opening of the specific diastereomer of the cyclic phosphodiester shown to the right, giving only a single product in methanol. This corresponds to what is known as an **in-line attack**, because the leaving group is in line with the nucleophilic attack (similar to an S_N2 reaction). We will examine the use of stereochemical analyses

to probe mechanisms many times in the context of organic reactions in part II of this book.
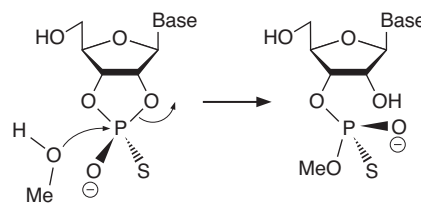
Stereogenic phosphodiester group

Usher, D. A., Erenrich, E. S., and Eckstein, F. "Geometry of the First Step of Reaction of Ribonuclease A." *Proc. Natl. Acad. Sci. USA*, **69**, 116 (1972).
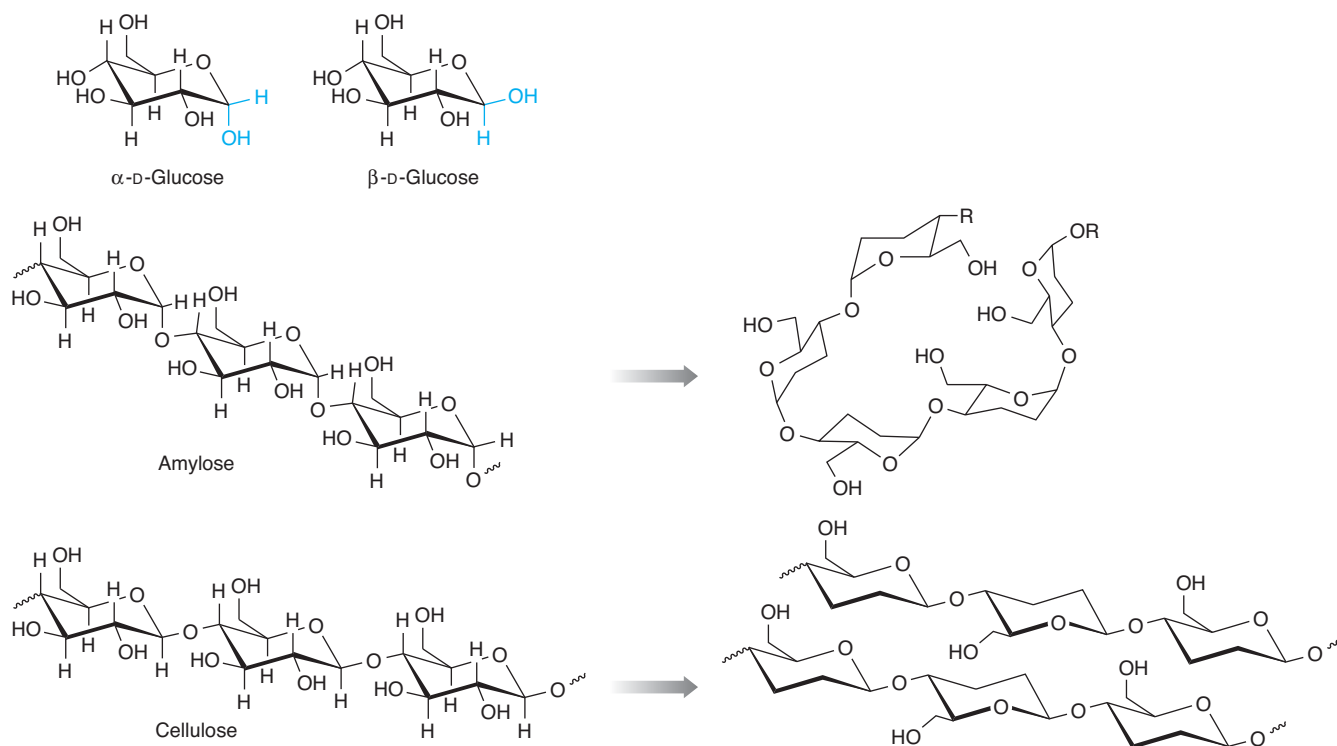
Figure 6.18
α- vs. β-D-Glucose with the key anomeric carbon highlighted, along with the structures of amylose and cellulose. For amylose and cellulose, the structures shown to the right of the arrows represent their structures in solution (with many hydroxyls eliminated for clarity).

6.8.2   Helicity

While helicity can be associated with many kinds of molecules, it is most frequently associated with polymers (especially biopolymers). Here we briefly cover the helix as a general stereochemical element. All helices are chiral, as evidenced by the fact that we refer to helices as right- or left-handed. Typically, with molecular helices the right- and left-handed forms are topologically equivalent—that is, we can interconvert the two without breaking or crossing bonds. A helix is a stereogenic unit, but it is not the interchange of ligands that interconverts opposite helices, but rather just the unwinding and rewinding of the helix.

In structural biology helices are associated with both DNA and proteins. Some polysaccharides adopt helical structures (see amylose in Figure 6.18), but this is not common. The double helix of DNA is right-handed. There is also a left-handed helical form of DNA termed Z-DNA. It is *not* the enantiomer of the much more common right-handed DNA. To make the enantiomer we would have to invert all the stereocenters of the deoxyribose sugars, which does not happen in nature. Z-DNA is a diastereomeric conformer, and it is favored by certain sequences and salt conformations, although its relevance to biology is debated. Thus, while in simple, prototype helices the right- and left-handed forms are enantiomers, in a system with enantiomerically pure, homochiral building blocks, reversing the sense of helicity produces a diastereomer.

In proteins, the most common structural motif is the α-helix discussed in Chapter 3 and depicted in Appendix 4. Again, because the building blocks (amino acids) are chiral and enantiomerically pure, right- and left-handed α-helices are diastereomers. In nature only the right-handed form is seen. A second, much less common helix, termed 3_{10} is also right-handed, and is just a conformer of the α-helix with different hydrogen bonding arrangements.

Synthetic Helical Polymers

Synthetic polymers that are isotactic are similar to biological building blocks in that all the stereocenters are homochiral. As such, it should not be surprising to learn that helical structures can show up in synthetic polymers, but usually not with the well-defined structural integrity of DNA or protein α-helices. In nucleic acids and proteins, there are strong stereochemical biases built into the monomers, and these lead to strong preferences for one helical form over the other. In synthetic polymers, such strong biases are often absent. However, in certain cases substantial helical biases can be seen in synthetic polymers (see the next Connections highlight for an example).

A truly remarkable example of a helical synthetic polymer is the series of polyisocyanates studied by Green and co-workers and summarized in Figure 6.19. The polyisocyanate backbone contains contiguous amide groupings reminiscent of a peptide or a nylon derivative [nylon-6 is $-C(O)(CH_2)_5NH-$; polyisocyanates have been termed nylon-1; see Chapter 13 for further discussion of nylons]. The structure shown describes the basic layout of the backbone, but steric clashing between the carbonyl oxygen and the R group precludes a planar geometry. A trade-off between conjugation and sterics produces a helical structure, but in a simple polyisocyanate we expect no particular bias for the right- or left-handed helix, as the two are enantiomers.

One way to produce a helical bias is to convert the enantiomeric helices into diastereomers by incorporating stereogenic centers into the sidechains (R), much as with natural biopolymers. This strategy works spectacularly well with polyisocyanates. As shown in Figure 6.19, making the sidechain stereogenic simply by virtue of isotopic substitution leads to a huge helical bias. That this is so is seen by the tremendous increase in optical activity and the reversal in sign on polymerizing the monomer. Both the magnitude and the change in sign establish that the inherent optical activity of the monomer is not responsible for the optical activity of the polymer. With a helical backbone, now the chromophoric amide units contribute to the optical rotation. Full CD studies support this analysis.

What is the cause of this effect? It has been estimated that the bias for one helical handedness over the other induced by the isotopic substitution is on the order of 1 cal/mol per subunit—a miniscule amount. Thus, we are seeing an extreme example of **cooperativity**. Once a tiny bias is established, it propagates down the chain, each successive monomer being more
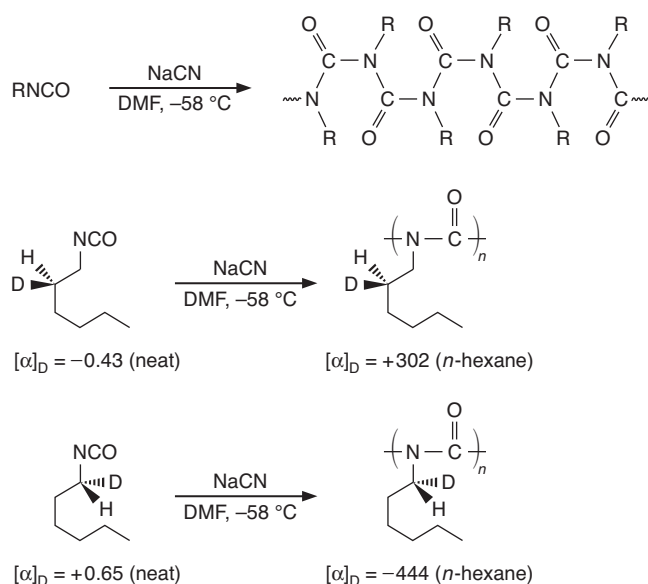
Figure 6.19
Examples of helicity in simple, non-natural polymers. Note that the optical rotation values given are on a per monomer basis, so the large increase in absolute value on polymerization is meaningful.

inclined to adopt the currently accepted chirality. It is truly amazing, though, that such a trivial inherent bias can ultimately lead to such an obvious effect. The detailed analysis of this sort of cooperativity involves some fairly complex math and physics, so we direct the interested student to the references at the end of the chapter.

The amplication of chirality inherent in the polyisocyanates described is an example of a phenomenon wherein a small initial chirality leads to a bias resulting in high enantiomeric excesses. This phenomenon has been termed the **sergeants and soldiers principle**, implying that the initial chiral influence is the "sergeant" that aligns all the "soldiers". This is a phenomenon that has been observed not only in polymer chemistry, but also with self-assembled supramolecular complexes driven by π interactions and hydrogen-bonded systems.

The optical rotations given in Figure 6.19 are extraordinarily large. The reason is not that these helical structures are somehow "more chiral" than typical molecules. Rather, the large rotations are due to the fact that with the polyisocyanates we are probing an **intrinsically chiral chromophore**. The feature of the molecule that is interacting most strongly with the light, the amide group, is itself distorted into a chiral shape. A more typical situation is a **chirally perturbed, intrinsically achiral chromophore**, such as a carbonyl group (intrinsically achiral, as in acetone) with a nearby stereogenic carbon. In such cases, much smaller rotations and differential absorptions are typically seen.

Connections

#### A Molecular Helix Created from Highly Twisted Building Blocks

The creation of helices using synthetic structures has attracted considerable attention due to the common helical motif in peptides and nucleic acids. Achieving a synthetic polymer with a complete right- or left-handed twist is difficult. One approach to helical molecules has been to make compounds known as **helicenes**, highly conjugated aromatic structures that naturally possess a twist due to the physical overlap of benzene rings. Convince yourself that if the [6]helicene shown were planar, unacceptable steric clashes would occur. The shapes of these structures are akin to that which one would get if one segment of a spring were cut off. Many helicenes have been made, including the [6]helicene shown and higher homologues. Not surprisingly, these structures show high optical rotations, because they are very much intrinsically chiral chromophores.

More recently, a polymer based on the helicene motif has been prepared. The key step in the synthesis of a helical polymer based upon a helicene is the condensation of a chiral [6]helicene that has salicylaldehyde functionality at each end with 1,2-phenylenediamine in the presence of a Ni salt. This gives the chemical structure shown to the right (bonds enormously stretched for clarity of presentation). The ORD spectra of structures of this kind display extraordinarily large rotations, and the circular dichroism spectra reveal comparably large differential extinction coefficients for right- and left-handed circular polarized light, confirming the helical nature of the polymers.

[6]Helicene
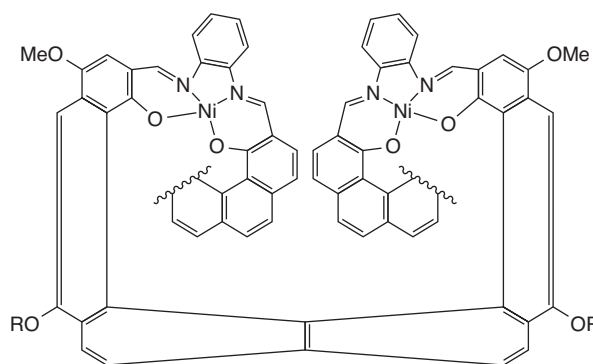
Dai, Y., Katz, T. J., and Nichols, D. A. "Synthesis of a Helical Conjugated Ladder Polymer." *Angew. Chem. Int. Ed. Eng.*, **35**, 2109 (1996).

6.8.3 The Origin of Chirality in Nature

The molecules of life are for the most part chiral, and in living systems they are almost always enantiomerically pure. In addition, groups of biomolecules are generally homochiral —all amino acids have the same sense of chirality and all sugars have the same sense of chirality. As already discussed, the chirality of the amino acids leads to chiral enzymes, which in turn produce chiral natural products. All the chiral compounds found in nature that are readily accessible to synthetic chemists for the construction of more complex molecules are referred to as the **chiral pool**.

What is the origin of the chirality of the molecules of life, and the reason for the homochirality? We cannot distinguish enantiomers unless we have a chiral environment. Further, in a reaction that forms a stereocenter, we cannot create an excess of one enantiomer over another without some chirality to start with. In the laboratory today, all enantiomeric excesses that we exploit ultimately derive from natural materials. Whether it is the interaction with an enantiomerically pure amino acid from a natural source, or an individual manually separating enantiomorphous crystals (first achieved by Pasteur), the source of enantiomeric excess in modern chemistry is always a living system. But how was this achieved in the absence of life? This is a fascinating, complex, and controversial topic that we can touch on only briefly here. This question is often phrased as the quest for the origin of chirality in nature, but more correctly it is the origin of enantiomeric excess and homochirality we seek.

Models for the origin of life generally begin with simple chemical systems that, in time, evolve to more complex, self-organizing, and self-replicating systems. It is easy to imagine prebiotic conditions in which simple condensation reactions produce amino acids or molecules that closely resemble them, and indeed experiments intended to model conditions on the primitive earth verify such a possibility. However, it is difficult to imagine such conditions producing anything other than a racemic mixture.

Essentially, there are two limiting models for the emergence of enantiomeric excess in biological systems. They differ by whether enantiomeric excess arose naturally out of the evolutionary process or whether an abiotic, external influence created a (presumably slight) initial enantiomeric excess that was then amplified by evolutionary pressure (maybe a type of sergeant–soldier effect). The first scheme is a kind of selection model. The building blocks (let's consider only amino acids here) are initially racemic. However, there is considerable advantage for an early self-replicating chemical system to use only one enantiomer. For example, consider a simple polymer of a single amino acid. If both enantiomers are used, the likely result is an atactic polymer, which may well have variable and ill-defined properties. However, if only a single enantiomer is used, only the isotactic polymer results. This kind of specificity could be self-reinforcing, such that eventually, only the single amino acid is used. The homochirality of nature could result because addition of a second amino acid to the mix might be less disruptive if the new one has the same handedness as the original. The details of how all this could happen are unknown, but the basic concept seems plausible. Certainly, the remarkable cooperativity seen in polyisocyanates provides an interesting precedent.

While we begin with racemic materials, there will never be *exactly* identical numbers of right- and left-handed molecules in a sample of significant size. This is a simple statistical argument. For example, earlier we considered the reduction of 2-butanone with lithium aluminum hydride under strictly achiral conditions (Figure 6.7), and stated that we expect a racemic mixture without a *significant* enantiomeric excess. However, if we start with 10^{23} molecules of ketone, the probability that we will produce *exactly* 0.5×10^{23} molecules of (R)- and 0.5×10^{23} molecules of (S)-alcohol is essentially nil. There will always be statistical fluctuations. For example, for a relatively small sample of 10^7 molecules there is an even chance that one will obtain a $\geq 0.021\%$ excess of one enantiomer over the other (we cannot anticipate which enantiomer will dominate in any given reaction). Perhaps such a small excess from a prebiotic reaction, or a significantly larger excess from a statistical fluke, got amplified through selective pressure, and ultimately led to the chirality of the natural world.

The alternative type of model emphasizes the possible role of an inherently chiral bias of external origin. One possibility for this bias is the inherent asymmetry of our universe re-

flected in the charge–parity (CP) violation of the weak nuclear force. In particular, β decay of ^{60}Co nuclei produces polarized electrons with a slight excess of the left- over the right-handed form. From this point, several mechanisms that translate the chirality of the emission to a molecular enantiomeric excess can be envisioned. Unfortunately, all attempts to measure such enantiomeric enrichment in the laboratory have produced at best extremely small enrichments that have proven difficult to reproduce. An alternative proposal for an external chiral influence is an enantioselective photochemical process involving circularly polarized light, which is well established in the laboratory to give significant enantiomeric excesses. At present, however, no clear mechanism for creating circularly polarized light with an excess of one handedness in the prebiotic world has been convincingly demonstrated, although models have been proposed. Only further experimentation in the lab, or perhaps examination of the chirality of extraterrestrial life forms, will resolve this issue.

6.9   Stereochemical Terminology

Stereochemistry has engendered a sometimes confusing terminology, with several terms that are frequently misused. Here we provide definitions of the most common terms. This collection is based in large measure on a much more extensive listing in the following book: Eliel, E. L., Wilen, S. H., and Mander, L. N. (1994). *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York.

Absolute configuration.   A designation of the position or order of arrangement of the ligands of a stereogenic unit in reference to an agreed upon stereochemical standard.

Achiral.   Not chiral. A necessary and sufficient criterion for achirality in a rigid molecule is the presence of any improper symmetry element (S_n, including σ and i).

Achirotopic.   The opposite of chirotopic. See "chirotopic" below.

Anomers.   Diastereomers of glycosides or related cyclic forms of sugars that are specifically epimers at the anomeric carbon (C_1 of an aldose, or C_2, C_3, etc., of a ketose).
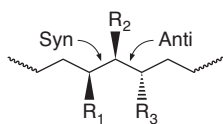

Anti.   Modern usage is to describe relative configuration of two stereogenic centers along a chain. The chain is draw in zigzag form, and if two substituents are on opposite sides of the plane of the paper, they are designated anti. See also "syn", "antiperiplanar", and "anticlinal".

Anticlinal.   A term describing a conformation about a single bond. In A–B–C–D, A and D are anticlinal if the torsion angle between them is between 90 and 150 or –90 and –150. See Figure 2.7.

Antiperiplanar.   A term describing a conformation about a single bond. In A–B–C–D, A and D are antiperiplanar if the torsion angle between them is between +150° to –150°. See Figure 2.7.

Apical, axial, basal, and equatorial.   Terms associated with the bonds and positions of ligands in trigonal bipyramidal structures.
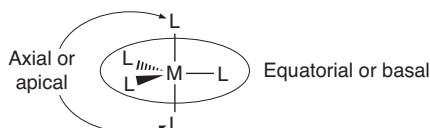
Asymmetric.   Lacking *all* symmetry elements (point group C_1). All asymmetric molecules are chiral.

Asymmetric carbon atom. Traditional term used to describe a carbon with four different ligands attached. Not recommended in modern usage.

Atactic.   A term describing the relative configuration along a polymer backbone. In an atactic polymer, the stereochemistry is random—no particular pattern or bias is seen.

Atropisomers.   Stereoisomers (can be either enantiomers or diastereomers) that can be interconverted by rotation about single bonds and for which the barrier to rotation is large enough that the stereoisomers can be separated and do not interconvert readily at room temperature.

Chiral.   Existing in two forms that are related as non-congruent mirror images. A necessary and sufficient criterion for chirality in a rigid molecule is the absence of any improper symmetry elements (S_n, including σ and i).

Chiral center.   Older term for a tetracoordinate carbon or similar atom with four different substituents. More modern, and preferable, terminology is "stereogenic center" (or "stereocenter").

Chirotopic.   The term used to denote that an atom, point, group, face, or line resides in a chiral environment.

Cis.   Describing the stereochemical relationship between two ligands that are on the same side of a double bond or a ring system. For alkenes only, Z is preferred.

Configuration.   The relative position or order of the arrangement of atoms in space that characterizes a particular stereoisomer.

Conformers or conformational isomers.   Stereoisomers that are interconverted by rapid rotation about a single bond.

Constitutionally heterotopic.   The same groups or atoms with different connectivities.

D and L.   An older system for identifying enantiomers, relating all stereocenters to the sense of chirality of D- or L-glyceraldehyde. See discussion in the text. Generally not used anymore, except for biological structures such as amino acids and sugars.

Diastereomers.   Stereoisomers that are not enantiomers.

Diastereomeric excess (de).   In a reaction that produces two diastereomeric products in amounts A and B, de $= 100\%(|A - B|)/(A + B)$.

Diastereotopic.   The relationship between two regions of a molecule that have the same connectivity but are not related by any kind of symmetry operation.

Dissymmetric.   Lacking improper symmetry operations. A synonym for "chiral", but not the same as "asymmetric".

Eclipsed.   A term describing a conformation about a single bond. In A–B–C–D, A and D are eclipsed if the torsion angle between them is approximately 0°.

Enantiomers.   Molecules that are related as non-congruent mirror images.

Enantiomeric excess (ee).   In a reaction that produces two enantiomeric products in amounts A and A′, ee = $100\%(|A - A'|)/(A + A')$.

Enantiotopic.   The relationship between two regions of a molecule that are related *only* by an improper symmetry operation, typically a mirror plane.

Endo.   In a bicyclic system, a substituent that is on a bridge is endo if it points toward the larger of the two remaining bridges. See also "exo".

Epimerization.   The interconversion of epimers.

Epimers.   Diastereomers that have the opposite configuration at only one of two or more stereogenic centers.

Erythro and threo.   Descriptors used to distinguish between diastereomers of an acyclic structure having two stereogenic centers. When placed in a Fischer projection using the convention proper for carbohydrates, erythro has the higher priority groups on the same side of the Fischer projection, and threo has them on opposite sides.

Exo.   In a bicyclic system, a substituent that is on a bridge is exo if it points toward the smaller of the two remaining bridges. See also "endo".

E, Z.   Stereodescriptors for alkenes (see discussion in the text).

Gauche. A term describing a conformation about a single bond. In A–B–C–D, A and D are gauche if the torsion angle between them is approximately 60° (or –60°). See section 2.3.1.

Geminal.   Attached to the same atoms. The two chlorines of 1,1-dichloro-2,2-difluoroethane are geminal. See also "vicinal".

Helicity.   The sense of chirality of a helical or screw shaped entity; right (P) or left (M).

Heterochiral.   Having an opposite sense of chirality. For example, ᴅ-alanine and ʟ-leucine are heterochiral. See also "homochiral".

Heterotopic.   The same groups or atoms in inequivalent constitutional or stereochemical environments.

Homochiral.   Having the same sense of chirality. For example, the 20 natural amino acids are homochiral—they have the same arrangement of amino, carboxylate, and side-chain groups. Has also been used as a synonym for "enantiomerically pure", but this is not recommended, because homochiral already was a well-defined term before this alternative usage became fashionable.

Homotopic. The relationship between two regions of a molecule that are related by a *proper* symmetry operation.

Isotactic.   A term describing the relative configuration along a polymer backbone. In an isotactic polymer, all stereogenic centers of the polymer backbone have the same sense of chirality.

Meso.   A term describing an achiral member of a collection of diastereomers that also includes at least one chiral member.

Optically active.   Rotating plane polarized light. Formerly used as a synonym for "chiral", but this is not recommended.

Prochiral.   A group is prochiral if it contains enantiotopic or diastereotopic ligands or faces, such that replacement of one ligand or addition to one face produces a stereocenter. See Section 6.3.2.

R, S. The designations for absolute stereochemistry (see earlier discussion in the text).

Racemic mixture or **racemate.**   Comprised of a 50:50 mixture of enantiomers.

Relative configuration.   This refers to the configuration of any stereogenic center with respect to another stereogenic center. If one center in a molecule is known as *R*, then other centers can be compared to it using the descriptors *R** or *S**, indicating the same or opposite stereochemistry, respectively.

Resolution.   The separation of a racemic mixture into its individual component enantiomers.

Scalemic.   A synonym for "non-racemic" or "enantiomerically enriched". It has not found general acceptance, but is used occasionally.

S-cis and *s*-trans.   Descriptors for the conformation about a single bond, such as the C2–C3 bond in 1,3–butadiene, or the C–N bond of an amide. If the substituents are synperiplanar, they are termed *s*-cis ("s" for "single"); if they are antiperiplanar, they are termed *s*-trans.

Stereocenter.   See "stereogenic center".

Stereogenic center.   An atom at which interchange of any two ligands produces a new stereoisomer. A synonym for "stereocenter".

Stereogenic unit.   An atom or grouping of atoms at which interchange of any two ligands produces a new stereoisomer.

Stereoisomers.   Molecules that have the same connectivity, but a different arrangement of atoms in space.

Stereoselective.   A term describing the stereochemical consequences of certain types of reactions. A stereoselective reaction is one for which reactant A can give two stereoisomeric products, B and B', and one product is preferred. There can be degrees of stereoselectivity. All stereospecific reactions are stereoselective, but the converse is not true.

Stereospecific.   A term describing the stereochemical consequences of certain types of reactions. A stereospecific reaction is one for which reactant A gives product B, and stereoisomeric reactant A' gives stereoisomeric product B'. There can be degrees of stereospecificity. Stereospecific does *not* mean 100% stereoselective.

Syn.   Modern usage is to describe the relative configuration of two stereogenic centers along a chain. The chain is drawn in zigzag form, and if two substituents are on the same side of the plane of the paper, they are syn. See also "anti", "synperiplanar", and "synclinal".
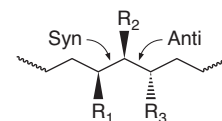
Synclinal.   A term describing a conformation about a single bond. In A–B–C–D, A and D are synclinal if the torsion angle between them is between 30° and 90° (or –30° and –90°). See Figure 2.7.

Syndiotactic.   A term describing the relative configuration along a polymer backbone. In a syndiotactic polymer, the relative configurations of backbone stereogenic centers alternate along the chain.

Synperiplanar.   A term describing a conformation about a single bond. In A–B–C–D, A and D are synperiplanar if the torsion angle between them is between +30° and −30°. See Figure 2.7.

Tacticity.   A generic term describing the stereochemistry along a polymer backbone. See "atactic", "isotactic", and "syndiotactic".

Trans.   A term describing the stereochemical relationship between two ligands that are on opposite sides of a double bond or a ring system. For alkenes only, *E* is preferred.

Vicinal.   Attached to adjacent atoms. In 1,1-dichloro-2,2-difluoroethane, the relationship of either chlorine to either fluorine is vicinal. See also "geminal".

Summary and Outlook

The excitement that chemists feel for the area of stereochemistry has hopefully rubbed off during your reading of this chapter. From simple enantiomers and diastereomers, to rotaxanes, catenanes, and knots, stereochemistry continues to challenge organic chemists to create molecules of increasing complexity, which inevitably leads to molecules with intriguing properties and simple aesthetic beauty.

Furthermore, stereochemical concepts shed important light on the study of reaction mechanisms. It is this topic that we still need to develop further. In our analyses of reaction mechanisms we will rely heavily upon the concepts and terminology introduced in this chapter. Further, in textbooks and journal articles related to chemical synthesis, the control of stereochemistry during chemical transformations is a topic of paramount importance. Now that we have a firm background on the fundamentals of stereochemistry, it is time to launch into the practical applications.

Exercises

1. We have stated that the stereogenic center in L-cysteine is *R*, while all other L-amino acids are *S*. Show this.

**2.** State whether the following sugars are L or D.
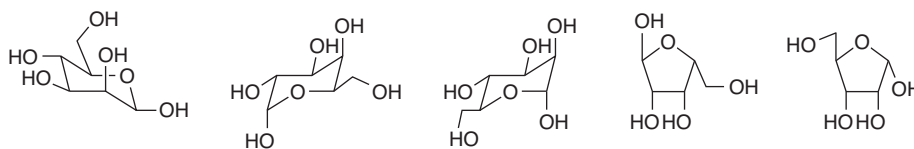
**3.** Label the following alkenes as either *Z* or *E*.
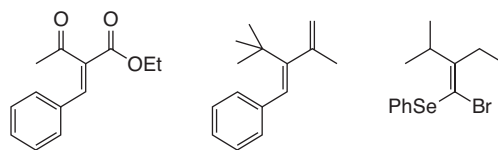
4. We have stated that the preferred conformation of a peptide bond is Z, also known as *s*-trans (referring to a trans arrangement of the single bond between C–N). Show that Z is the appropriate descriptor.

5. Show that propylene and styrene are prochiral, and label the faces of propylene as *Re* or *Si*.

6. How many diastereomers are there for the following compound? Draw them all with chair cyclohexane representations. Also, draw them flat in the page as shown below, except with solid dots on the bridgehead hydrogens to represent the cases where the hydrogens project up.
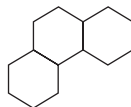
7. Draw enantiomers of the following compounds.
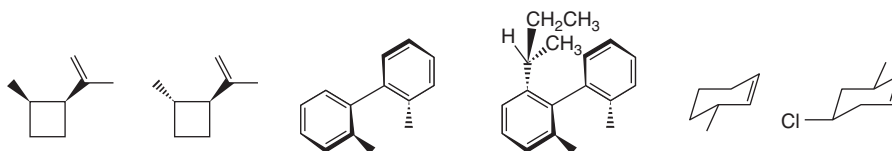
8. Identify the stereogenic centers or units in the following compounds.
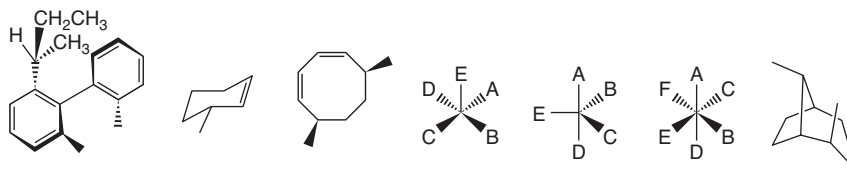
9. For each structure shown, label the pair of methyls as homotopic, enantiotopic, diastereotopic, or constitutionally heterotopic.
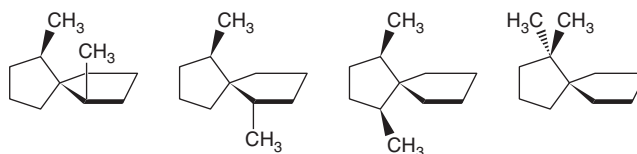
10. Is the structure shown chiral? Is it asymmetric?

11. Find the achirotopic points in the following compounds. If there are no achirotopic points, state this. If all points are achirotopic, state this also.
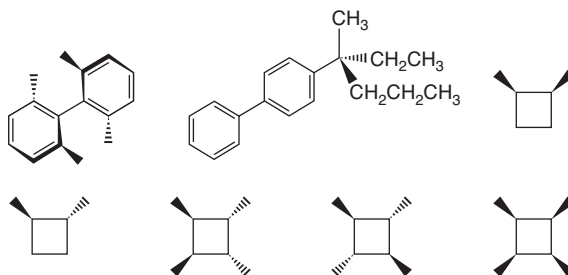

12. Label any C_n or S_n axes (including mirror planes) in the molecules in Exercise 11.

13. Draw a molecule that contains a C_3 axis and a single mirror plane.

14. Solutions of the molecule shown are optically active. However, upon reaction with itself, all optical activity vanishes. Explain this phenomenon. In addition, generalize the result. That is, describe the stereochemical features necessary for such a situation to occur.
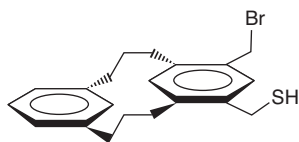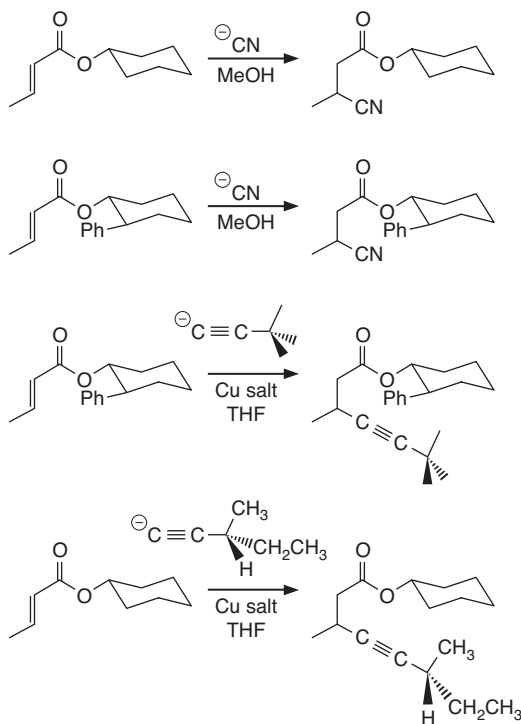

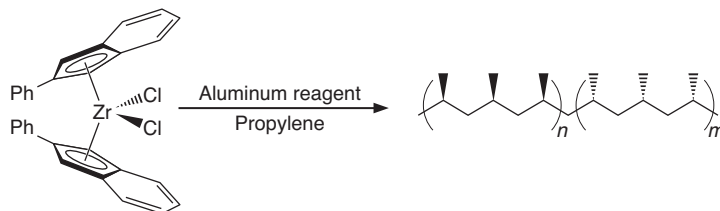**15.** Draw a diastereomer of the following molecule that is not an epimer.
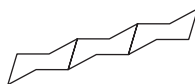
**16.** Find the prochiral hydrogens in the following molecules, and circle any pro-*S* hydrogens. If there are no prochiral hydrogens, state this.

17. Predict whether the product ratio of the following reactions will be 50:50 or a number other than 50:50.


18. The following polymerization catalyst produces blocks of isotactic polypropylene with alternating stereochemistry for each block. Explain how this happens.


TEAM SHERIF

19. Show that the hydrogens of the CH$_2$ groups of the following molecules are never equivalent in any conformation.
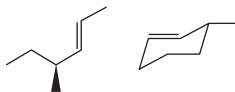

20. For each molecule shown, determine whether the two faces of the olefin or carbonyl are homotopic, enantiotopic, or diastereotopic. For ethyl phenyl ketone, designate the *Re* and *Si* faces.
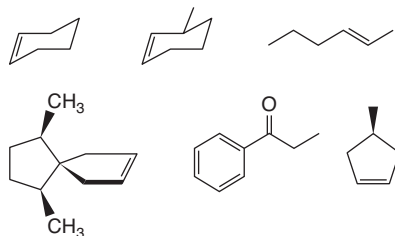

21. Show that the hydrogens of the CH$_3$ group of the following molecules are not equivalent in the conformation shown, but average due to bond rotation.
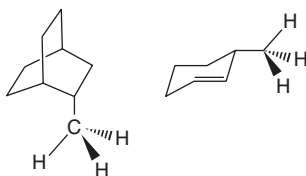

22. Define the following reactions as stereoselective and/or stereospecific, and if so, determine the percent stereoselectivity and/or stereospecificity. The products in **A**, **D**, **E**, and **F** are as shown. The product ratios in **B** and **C** are hypothetical for purposes of this question.

A.

B.

C.

D.

E.

F.
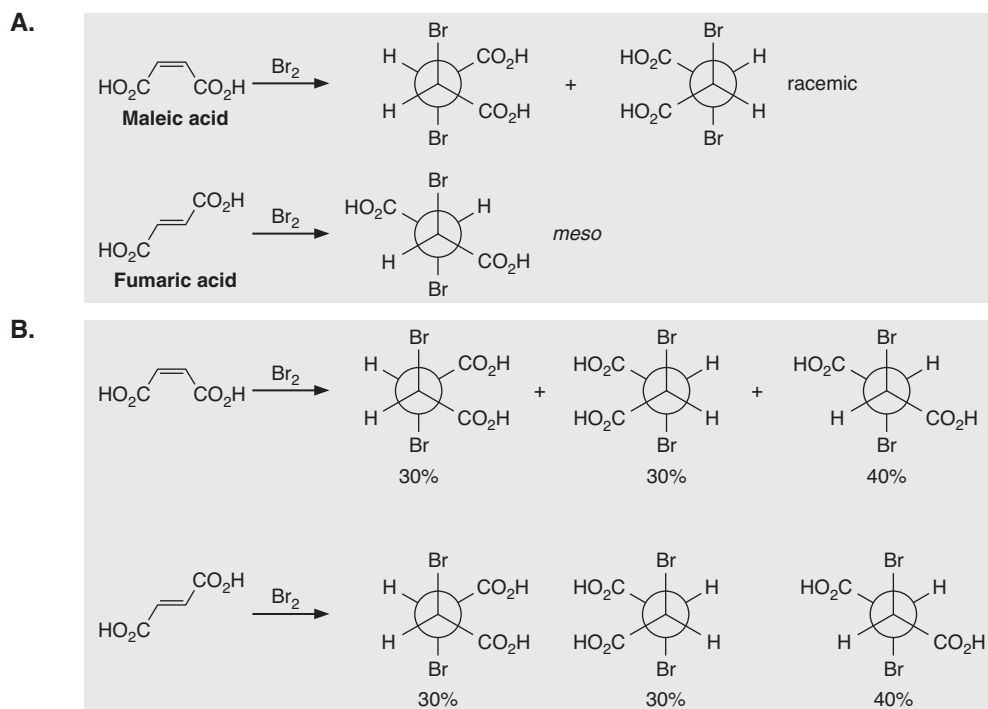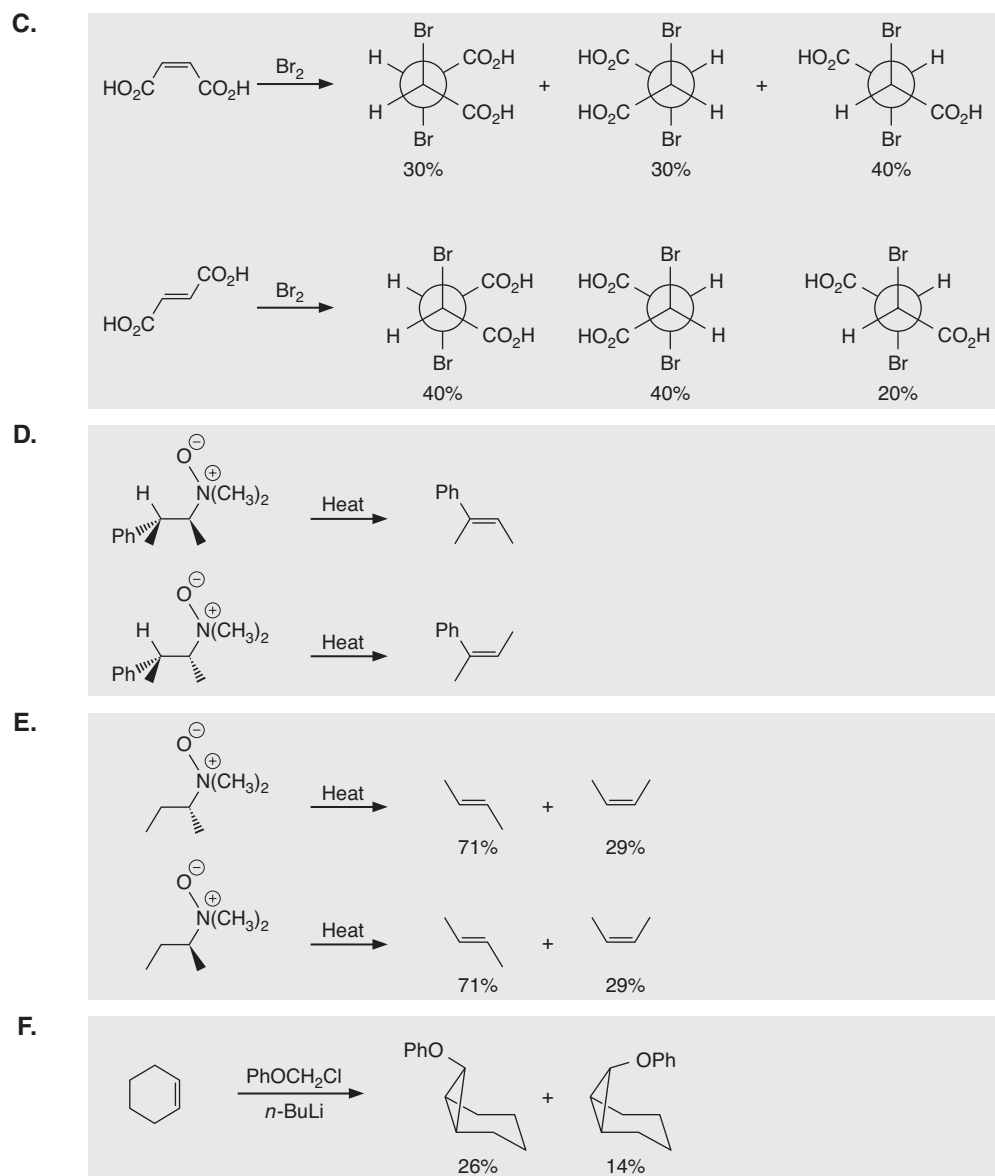
23. Draw any molecule that contains an enantiotopic pair of hydrogens that are not attached to the same atom.

24. We showed that rapid rotation about the C1–C2 bond of 2-butanol makes the three hydrogens at C1 symmetry eq
Why is it that rapid rotation about the C2–C3 bond (or any other bond) does not make the two hydrogens at C3 e

25. How many stereoisomers are possible for a linear [3]catenane? Which of these are chiral (presume that the indivi
have a mirror plane in the plane of the ring)? Consider separately three cases: a. all three rings are equivalent and
tional, b. all three rings are different but not directional, and c. all three rings are inequivalent and directional.

**26.** Convince yourself that C_{60} has a planar graph.
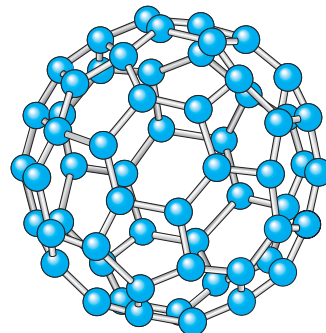
27. The THYME polyether of Figure 6.12 could also close with two twists. If it does, what would be the product of ozonolysis?

28. In the section on "Helical Descriptors" (part of Section 6.1.2), we showed an allene and two related structures and gave M/P assignments. Show that the same assignments are obtained if you sight down the opposite end of the axis shown.

29. Recall the [5]catenene olympiadane of Chapter 4. How many stereoisomers would be possible if each ring of the system were different, while maintaining the Olympic ring motif? Assume that all the rings are non-directional.

30. Ferrocene has two limiting conformations, an eclipsed form and a staggered form. Each has an S_n axis. What is n for each?


Eclipsed   Staggered
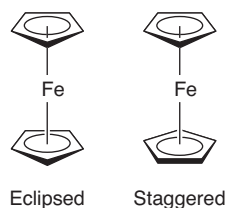
31. We discussed the "toplogical rubber glove", a system in which two enantiomers can interconvert without ever going through an achiral form. A related phenomenon was observed much earlier with the biphenyl derivative shown, first prepared by Mislow. The nitro groups are large enough that the biphenyls cannot rotate past one another on any meaningful time scale. Convince yourself that a. this molecule is chiral, b. the enantiomers can readily interconvert by rotations about single bonds, and c. at no time during the enantiomerization is a structure that is achiral involved.
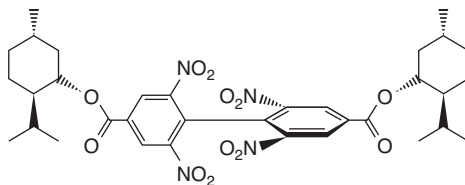
32. For each structure shown, determine whether the two methyl groups are homotopic, enantiotopic, diastereotopic, or constitutionally heterotopic, both on a time scale where ring inversion is slow and on a time scale where ring inversion is fast.
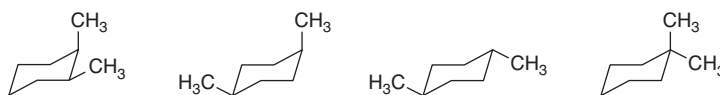

33. We saw in a Going Deeper highlight in Section 2.5.3 that hexaisopropylbenzene adopts a geared conformation. Consider a structure in which two adjacent isopropyl groups are replaced by 1-bromoethyl groups (that is, one CH_3 of an isopropyl is replaced by Br in two adjacent groups). Maintaining the rigorously geared structure, sketch all possible stereoisomers for this compound, and describe them as chiral or not and establish pair-wise relationships as enantiomeric or diastereomeric. Consider especially the consequences of reversing the direction around the ring of the geared array.

34. Convince yourself that the metals in the complexes shown in the Connections highlight entitled "C_2 Ligands in Asymmetric Synthesis" are indeed chirotopic but non-stereogenic. Also show that the coordination to either face of the metal in these complexes produces identical structures.

35. For the mathematically inclined, calculate the probability of obtaining an *exactly* 50:50 ratio of enantiomers from the LAH reduction of 2-butanone when the amount of starting material is a. 10 molecules, b. 10^3 molecules, and c. 10^{21} molecules.

36. In Section 6.8.1, a [6]helicene is shown in a Connections highlight. Assign an M or P descriptor to this helicene. Furthermore, what is the appropriate M or P descriptor for the binaphthol compound show in the margin of Section 6.5?

37. Draw the stereoisomers of tris(*o*-tolyl)borane. What bond rotations are required to interconvert diastereomers, and which are required to inconvert enantiomers?
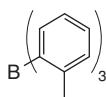
38. The reaction of phenylacetylene with Br_2 only gives (*Z*)-1,2-dibromo-1-phenylethene, and therefore the reaction is 100% stereoselective. Is the reaction also stereospecific? Explain your answer.

39. A famous topological construct is the **Borromean rings**, shown below. At first they appear to be just three interlocking rings, but look more closely. No two rings are interlocked. If we break any one ring, the entire construct falls apart. These rings hold together only if all three are intact. The symbolic significance of such a structure has been appreciated for centuries in many diverse cultures. Chemically, the challenge is clear. We cannot build up the Borromean rings by first linking a pair of rings and then adding another, because there are no pairwise linkages. Alternative strategies are required, and several have been suggested. For the synthetically intrepid, design a synthesis of the Borromean rings using the general metal templating strategies that Sauvage applied to the creation of catenanes. Focus on strategic and topological issues rather than detailed chemical issues. Very recently, a molecular realization of the Borromean rings has been brilliantly synthesized by Stoddart and coworkers. See Chickak, K. S., Cantrill, S., Pease, A. R., Sheng-Hsien, C., Cave, G. W. C., Atwood, J. L., and Stoddart, J. F. "Molecular Borromean Ring." *Science*, **304**, 1308 (2004).
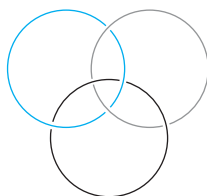
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