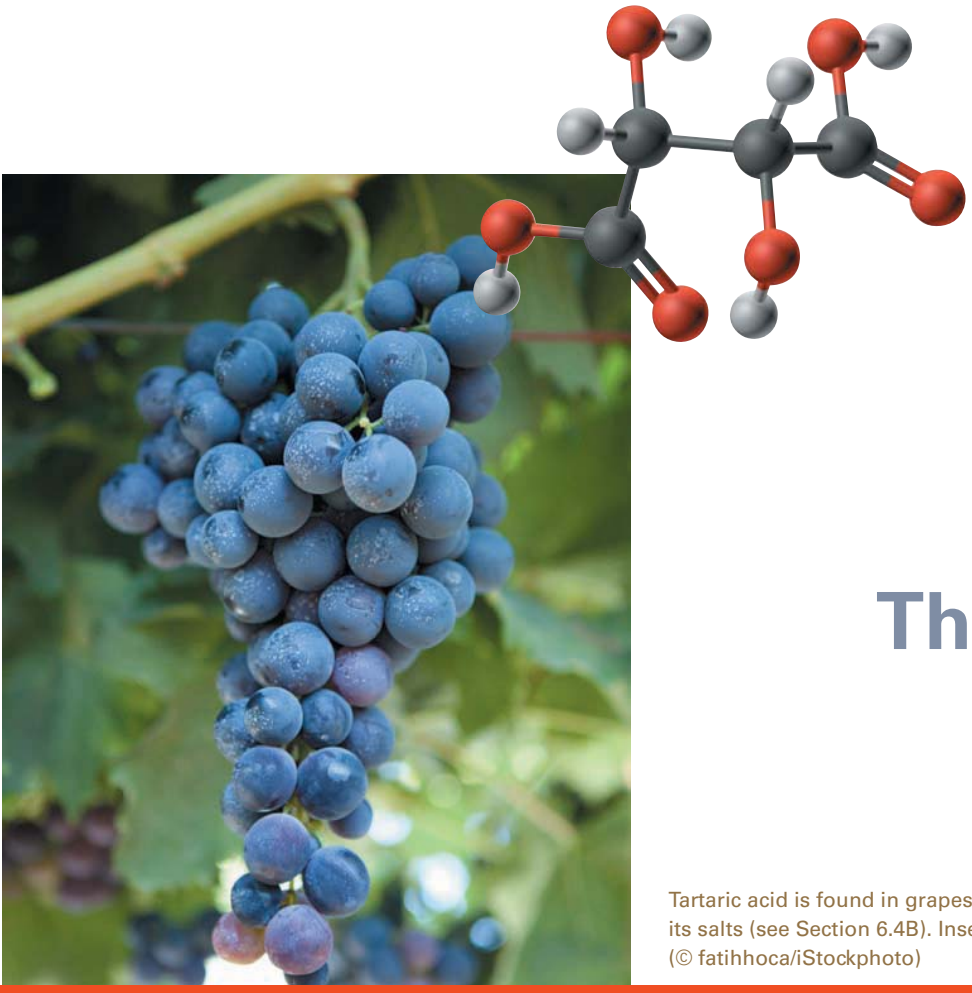
06



Chirality: The Handedness of Molecules

Tartaric acid is found in grapes and other fruits, both free and as its salts (see Section 6.4B). Inset: A model of tartaric acid. (© fatihhoca/iStockphoto)

KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

IN THIS CHAPTER, we will explore the relationships between three-dimensional objects and their mirror images. When you look in a mirror, you see a reflection, or **mirror image**, of yourself. Now, suppose your mirror image becomes a three-dimensional object.

Mirror image The reflection of an object in a mirror.

William H. Brown

The horns of this African gazelle show chirality and are mirror images of each other.

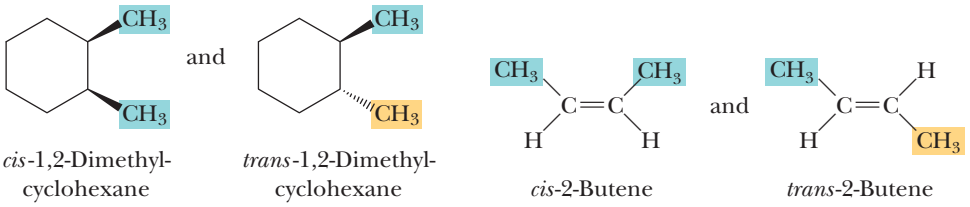
We could then ask, "What is the relationship between you and your mirror image?" By relationship, we mean "Can your reflection be superposed on the original 'you' in such a way that every detail of the reflection corresponds exactly to the original?" The answer is that you and your mirror image are not superposable. If you have a ring on the little finger of your right hand, for example, your mirror image has the ring on the little finger of its left hand. If you part your hair on your right side, the part will be on the left side in your mirror image. Simply stated, you and your reflection are different objects. You cannot superpose one on the other.

An understanding of relationships of this type is fundamental to an understanding of organic chemistry and biochemistry. In fact, the ability to visualize molecules as three-dimensional objects is a survival skill in organic chemistry and biochemistry. We suggest that you purchase a set of molecular models. Alternatively you may have access to a computer lab with a modeling program. We urge you to use molecular models frequently as an aid to visualizing the spatial concepts in this and later chapters.

6.1 What Are Stereoisomers?

Stereoisomers Isomers that have the same molecular formula and the same connectivity, but different orientations of their atoms in space.

Stereoisomers have the same molecular formula and the same connectivity of atoms in their molecules, but different three-dimensional orientations of their atoms in space. The one example of stereoisomers we have seen thus far is that of *cis–trans* isomers in cycloalkanes (Section 3.7) and alkenes (Section 4.1C):



cis-1,2-Dimethylcyclohexane | *trans*-1,2-Dimethylcyclohexane | *cis*-2-Butene | *trans*-2-Butene

In this chapter, we study enantiomers and diastereomers (Figure 6.1).

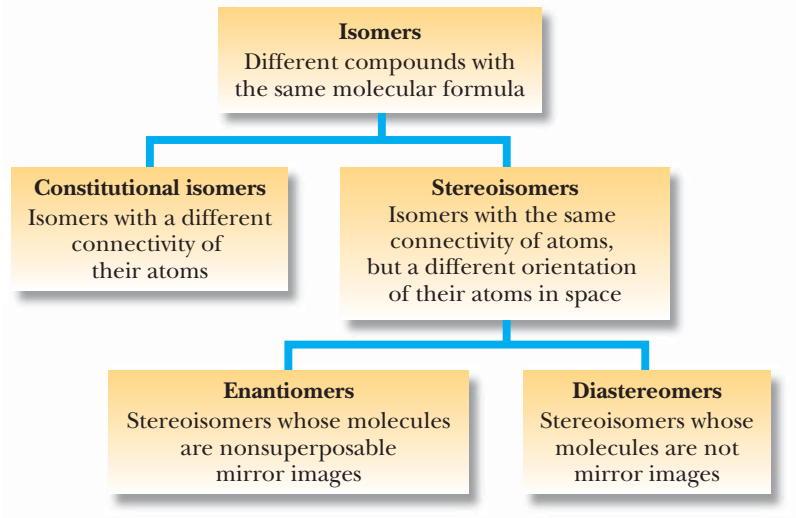


FIGURE 6.1
Relationships among isomers.

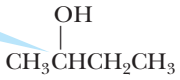
6.2 What Are Enantiomers?

Enantiomers
Stereoisomers that are nonsuperposable mirror images; the term refers to a relationship between pairs of objects.

Enantiomers are stereoisomers that are nonsuperposable mirror images. The significance of enantiomerism is that, except for inorganic and a few simple organic compounds, the vast majority of molecules in the biological world show this type of isomerism, including carbohydrates (Chapter 17), lipids (Chapter 19), amino acids and proteins (Chapter 18), and nucleic acids (DNA and RNA, Chapter 20). Further, approximately one-half of the medications used in human medicine also show this type of isomerism.

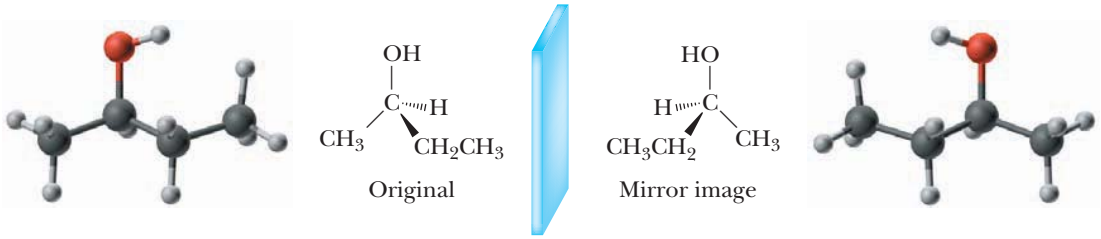
As an example of a molecule that exhibits enantiomerism, let us consider 2-butanol. As we go through the discussion of this molecule, we focus on carbon 2, the carbon bearing the —OH group. What makes this carbon of interest is that it has four different groups bonded to it. The most common cause of enantiomerism among organic molecules is a carbon bonded to four different groups.

the four different "groups" bonded to this carbon are —H, —OH, —CH_3, and —CH_2CH_3



2-Butanol

The structural formula we have just drawn does not show the shape of 2-butanol or the orientation of its atoms in space. To do this, we must consider the molecule as a three-dimensional object. On the left are a ball-and-stick model of 2-butanol and a perspective drawing of what we will call the "original" molecule. In this drawing, the —OH and —CH_3 groups on carbon-2 are in the plane of the paper; the —H is behind the plane and the —CH_2CH_3 group is in front of the plane.

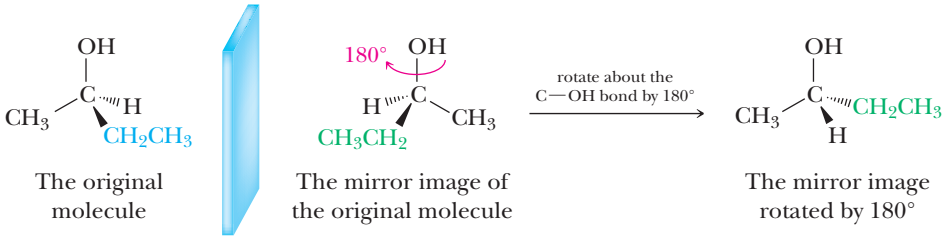


Original Mirror image

To the right in the preceding diagram is the mirror image of the original molecule. Every molecule and, in fact, every object in the world around us, has a mirror image. The question we now need to ask is "What is the relationship between the original of 2-butanol and its mirror image?" To answer this question, you need to imagine that you can pick up the mirror image and move it in space in any way you wish. If you can move the mirror image in space and find that it fits over the original so that every bond, atom, and detail of the mirror image exactly matches the bonds, atoms, and details of the original, then the two are **superposable**. In this case, the mirror image and the original represent the same molecule; they are only oriented differently in space. If, however, no matter how you turn the mirror image in space, it will not fit exactly on the original with every detail matching, then the two are **nonsuperposable**; they are different molecules.

The key point here is that either an object is superposable on its mirror image or it isn't. Now let us look at 2-butanol and its mirror image and ask, "Are they or are they not superposable?"

The following drawings illustrate one way to see that the mirror image of 2-butanol is not superposable on the original molecule:



The original molecule

The mirror image of the original molecule

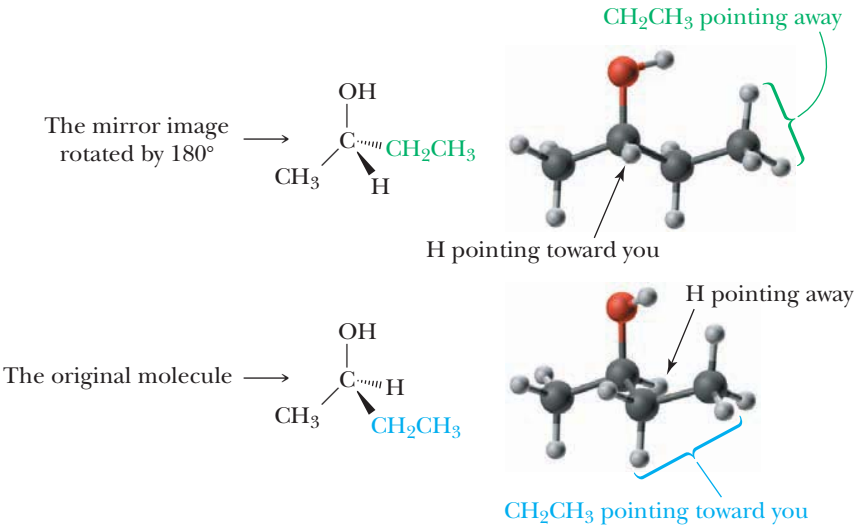
The mirror image rotated by 180°

Imagine that you hold the mirror image by the C—OH bond and rotate the bottom part of the molecule by 180° about this bond. The —OH group retains its position in space, but the —CH_3 group, which was to the right and in the plane of the paper, is still in the plane of the paper, but now to the left. Similarly, the —CH_2CH_3 group, which was in front of the plane of the paper and to the left, is now behind the plane and to the right.

Now move the rotated mirror image in space, and try to fit it on the original so that all bonds and atoms match:

Charles D. Winters

Left- and right-handed sea shells. If you cup a right-handed shell in your right hand with your thumb pointing from the narrow end to the wide end, the opening will be on your right.



By rotating the mirror image as we did, its —OH and —CH_3 groups now fit exactly on top of the —OH and —CH_3 groups of the original. But the —H and —CH_2CH_3 groups of the two do not match: The —H is away from you in the original, but toward you in the mirror image; the —CH_2CH_3 group is toward you in the original, but away from you in the mirror image. We conclude that the original of 2-butanol and its mirror image are nonsuperposable and, therefore, are different compounds.

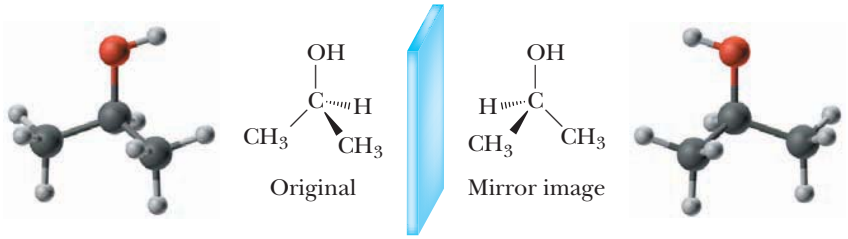
To summarize, we can rotate the mirror image of 2-butanol in space in any way we want, but as long as no bonds are broken or rearranged, only two of the four groups bonded to carbon-2 of the mirror image can be made to coincide with those on the original. Because 2-butanol and its mirror image are not superposable, they are enantiomers. Like gloves, enantiomers always occur in pairs.

Chiral From the Greek *cheir*, meaning hand; objects that are not superposable on their mirror images.

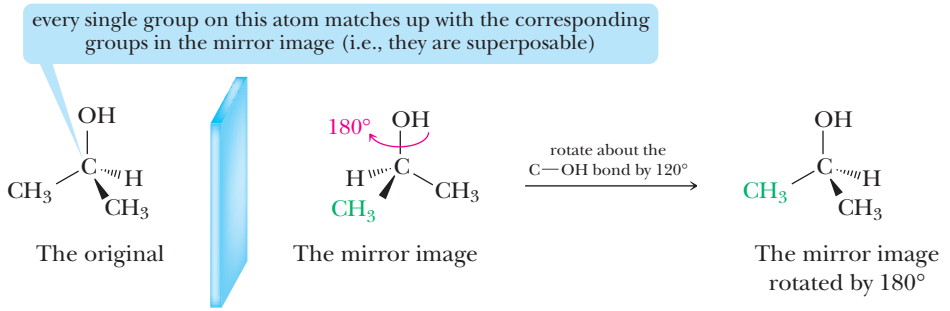
Objects that are not superposable on their mirror images are said to be **chiral** (pronounced ki′-ral, rhymes with spiral; from the Greek: *cheir*, hand); that is, they show handedness. Chirality is encountered in three-dimensional objects of all sorts. Your left hand is chiral, and so is your right hand. A spiral binding on a notebook is chiral. A machine screw with a right-handed twist is chiral. A ship's propeller is chiral. As you examine the objects in the world around you, you will undoubtedly conclude that the vast majority of them are chiral.

As we said before we examined the original and the mirror image of 2-butanol, the most common cause of enantiomerism in organic molecules is the presence of a carbon with four different groups bonded to it. Let us examine this statement further by considering a molecule such as 2-propanol, which has no such carbon. In this molecule, carbon-2 is bonded to three different groups, but no carbon is bonded to four different groups. The question we ask is, "Is the mirror image of 2-propanol superposable on the original, or isn't it?"

In the following diagram, on the left is a three-dimensional representation of 2-propanol, and on the right is its mirror image:



The question we now ask is "What is the relationship of the mirror image to the original?" This time, let us rotate the mirror image by 120° about the C—OH bond and then compare it with the original. When we do this rotation, we see that all atoms and bonds of the mirror image fit exactly on the original. This means that the structures we first drew for the original and its mirror image are, in fact, the same molecule viewed from different perspectives:



If an object and its mirror image are superposable, then the object and its mirror image are identical, and there is no possibility of enantiomerism. We say that such an object is **achiral** (without chirality).

An achiral object has at least one plane of symmetry. A **plane of symmetry** (also called a *mirror plane*) is an imaginary plane passing through an object and dividing it so that one-half of the object is the reflection of the other half. The beaker shown in Figure 6.2 has a single plane of symmetry, whereas a cube has several planes of symmetry. 2-Propanol also has a single plane of symmetry.

To repeat, the most common cause of chirality in organic molecules is a tetrahedral carbon atom with four different groups bonded to it. We call such a carbon atom a **chiral center**. Chiral centers are one type of **stereocenter**, which describes an atom at which the interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer. 2-Butanol has one stereocenter; 2-propanol has none.

As another example of a molecule with a stereocenter, consider 2-hydroxypropanoic acid, more commonly named lactic acid. Lactic acid is a product of anaerobic glycolysis

Achiral An object that lacks chirality; an object that has no handedness and is superposable on its mirror image.

Plane of symmetry An imaginary plane passing through an object and dividing it such that one half is the mirror image of the other half.

Chiral center An atom, such as carbon, with four different groups bonded to it.

Stereocenter An atom at which the interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer.

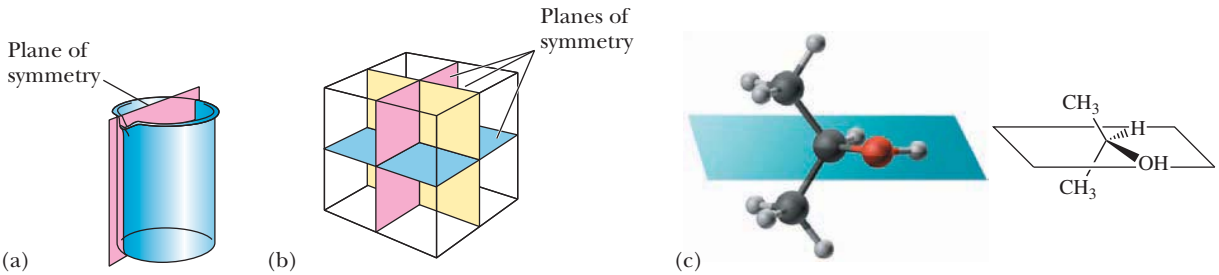


FIGURE 6.2
Planes of symmetry in (a) a beaker, (b) a cube, and (c) 2-propanol. The beaker and 2-propanol each have one plane of symmetry; the cube has several planes of symmetry, only three of which are shown in the figure.

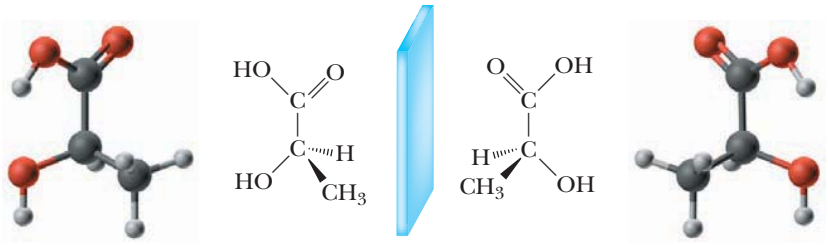


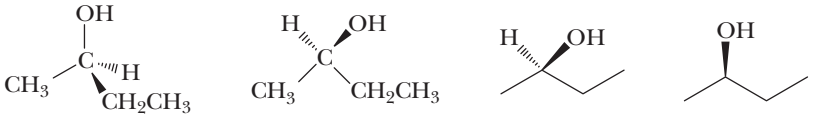
FIGURE 6.3
Three-dimensional representations of lactic acid and its mirror image.

and is what gives sour cream its sour taste. Figure 6.3 shows three-dimensional representations of lactic acid and its mirror image. In these representations, all bond angles about the central carbon atom are approximately 109.5°, and the four bonds projecting from it are directed toward the corners of a regular tetrahedron. Lactic acid shows enantiomerism; that is, it and its mirror image are not superposable, but rather are different molecules.

Draw Enantiomers

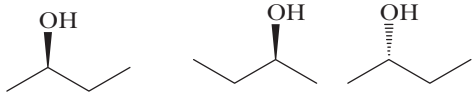
HOW TO 6.1

Now that we know what enantiomers are, we can think about how to represent their three-dimensional structures on a two-dimensional page. Let us take one of the enantiomers of 2-butanol as an example. Following are four different representations of this enantiomer:



(1) (2) (3) (4)

In our initial discussions of 2-butanol, we used (1) to show the tetrahedral geometry of the stereocenter; in it, two groups are in the plane of the paper, a third is coming out of the plane toward us, and the fourth is behind the plane, away from us. We can turn (1) slightly in space and tip it a bit to place the carbon framework in the plane of the paper. Doing so gives us representation (2), in which we still have two groups in the plane of the paper, one coming toward us and one going away from us. For an even more abbreviated representation of this enantiomer of 2-butanol, we can turn (2) into the line-angle formula (3). Although we don't normally show hydrogens in a line-angle formula, we do so in (3) just to remind ourselves that the fourth group on this stereocenter is really there and that it is H. Finally, we can carry the abbreviation a step further and write 2-butanol as (4). Here, we omit the H on the stereocenter, but we know that it must be there (carbon needs four bonds), and we know that it must be behind the plane of the paper. Clearly, the abbreviated formulas (3) and (4) are the easiest to draw, and we will rely on these representations throughout the remainder of the text. When you have to draw three-dimensional representations of stereocenters, try to keep the carbon framework in the plane of the paper and the other two atoms or groups of atoms on the stereocenter toward and away from you, respectively. Using representation (4) as a model, we get the following two different representations of its enantiomer:

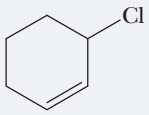


One enantiomer of 2-butanol — Alternative representations for its mirror image

Notice that in the first alternative, the carbon skeleton has been reversed.

EXAMPLE 6.1

Each of the following molecules has one stereocenter:

(a) $CH_3\overset{\overset{Cl}{|}}{C}HCH_2CH_3$ (b) 

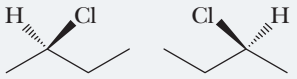
Identify the stereocenter in each and draw stereorepresentations of the enantiomers of each.

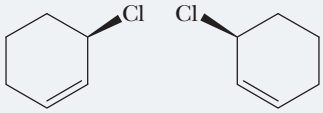
STRATEGY

When locating stereocenters, it is often helpful to draw in the hydrogens in line-angle drawings. Carbon atoms with only one or two lines extending from them, as well as sp^2 and *sp* hybridized carbons, can be excluded from consideration. Once the stereocenters are identified, use dashed and solid wedges to show the bonds to substituents.

SOLUTION

You will find it helpful to study models of each pair of enantiomers and to view them from different perspectives. As you work with these models, notice that each enantiomer has a carbon atom bonded to four different groups, which makes the molecule chiral. Translate what you see in each model by using perspective drawings. The hydrogen at the stereocenter is shown in (a) but not in (b).

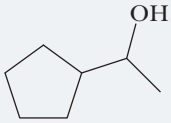
(a) 

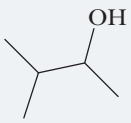
(b) 

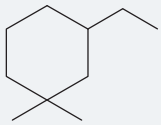
See problems 6.15, 6.19–6.22

PROBLEM 6.1

Each of the following molecules has one stereocenter:

(a) 

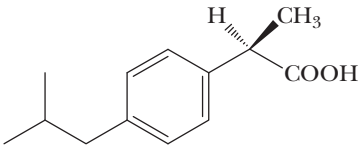
(b) 

(c) 

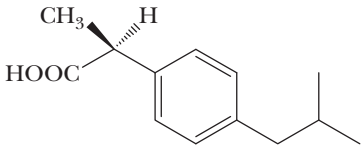
Identify the stereocenter in each and draw stereorepresentations of the enantiomers of each.

6.3 How Do We Designate the Configuration of a Stereocenter?

Because enantiomers are different compounds, each must have a different name. The over-the-counter drug ibuprofen, for example, shows enantiomerism and can exist as the pair of enantiomers shown here:



The inactive enantiomer of ibuprofen

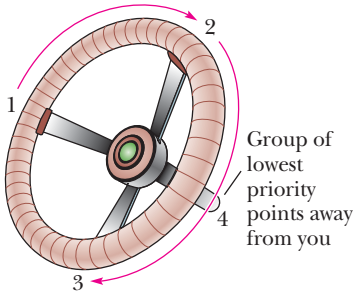


The active enantiomer

Only one enantiomer of ibuprofen is biologically active. This enantiomer reaches therapeutic concentrations in the human body in approximately 12 minutes. However, in this case, the inactive enantiomer is not wasted. The body converts it to the active enantiomer, but that takes time.

What we need is a way to name each enantiomer of ibuprofen (or any other pair of enantiomers for that matter) so that we can refer to them in conversation or in writing. To do so, chemists have developed the **R,S system**. The first step in assigning an R or S

R,S system A set of rules for specifying the configuration about a stereocenter.



R From the Latin *rectus*, meaning right; used in the R,S system to show that the order of priority of groups on a stereocenter is clockwise.

S From the Latin *sinister*, meaning left; used in the R,S system to show that the order of priority of groups on a stereocenter is counterclockwise.

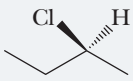
configuration to a stereocenter is to arrange the groups bonded to it in order of priority. For this, we use the same set of **priority rules** we used in Section 4.2C to assign an E,Z configuration to an alkene.

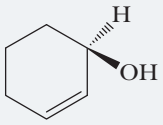
To assign an R or S configuration to a stereocenter,

1. Locate the stereocenter, identify its four substituents, and assign a priority from 1 (highest) to 4 (lowest) to each substituent.
2. Orient the molecule in space so that the group of lowest priority (4) is directed away from you, as would be, for instance, the steering column of a car. The three groups of higher priority (1–3) then project toward you, as would the spokes of a steering wheel.
3. Read the three groups projecting toward you in order, from highest priority (1) to lowest priority (3).
4. If reading the groups proceeds in a clockwise direction, the configuration is designated **R** (Latin: *rectus*, straight, correct); if reading proceeds in a counterclockwise direction, the configuration is **S** (Latin: *sinister*, left). You can also visualize this situation as follows: Turning the steering wheel to the right equals R, and turning it to the left equals S.

EXAMPLE 6.2

Assign an R or S configuration to each stereocenter:

(a) 

(b) 

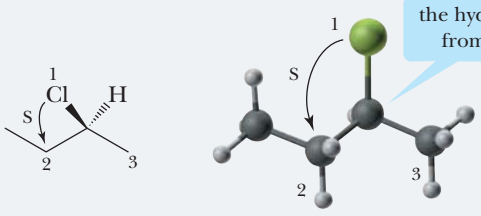
STRATEGY

First determine the priorities of the groups bonded to the stereocenter. If necessary reorient the molecule so that the group of lowest priority is away from you. Then read the R/S configuration by going from highest to lowest priority.

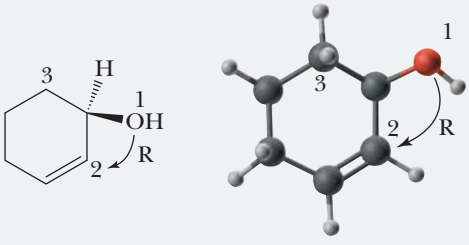
SOLUTION

View each molecule through the stereocenter and along the bond from the stereocenter toward the group of lowest priority.

(a) The order of priority is —Cl > —CH_2CH_3 > —CH_3 > —H. The group of lowest priority, H, points away from you. Reading the groups in the order 1, 2, 3 occurs in the counterclockwise direction, so the configuration is S.



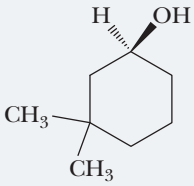
(b) The order of priority is —OH > —CH=CH > —CH_2 —CH_2 > —H. With hydrogen, the group of lowest priority, pointing away from you, reading the groups in the order 1, 2, 3 occurs in the clockwise direction, so the configuration is R.

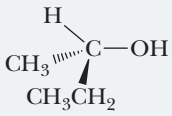


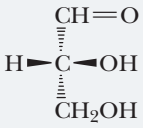
See problems 6.24–6.27, 6.29, 6.39

PROBLEM 6.2

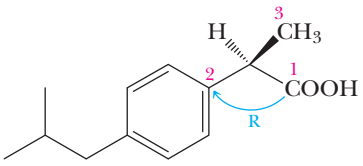
Assign an R or S configuration to each stereocenter:

(a) 

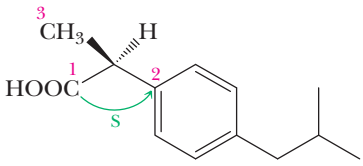
(b) 

(c) 

Now let us return to our three-dimensional drawing of the enantiomers of ibuprofen and assign each an R or S configuration. In order of decreasing priority, the groups bonded to the stereocenter are —COOH > —C_6H_4 > —CH_3 > H. In the enantiomer on the left, reading the groups on the stereocenter in order of priority occurs clockwise. Therefore, this enantiomer is (*R*)-ibuprofen, and its mirror image is (*S*)-ibuprofen:



(*R*)-Ibuprofen
(the inactive enantiomer)



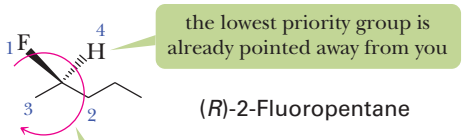
(*S*)-Ibuprofen
(the active enantiomer)

Determine the R & S Configuration without Rotating the Molecule

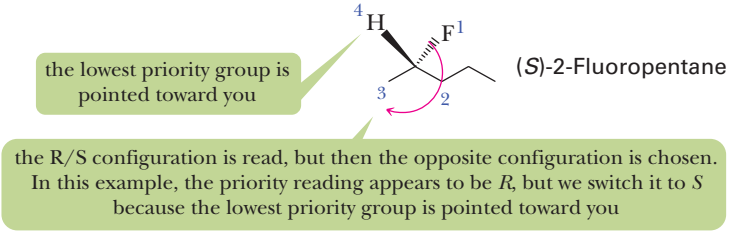
HOW TO 6.2

If you are having difficulty visualizing the spatial rotation of perspective drawings, the following techniques may be of use.

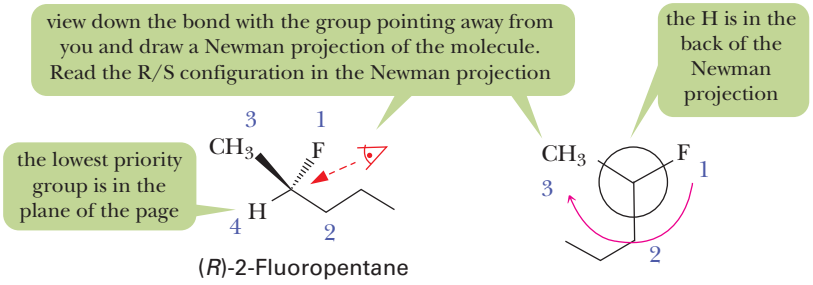
SCENARIO 1: **The lowest priority group is already directed away from you.** If the perspective drawing contains the lowest priority group on a dashed bond, it is a simple matter of reading the other three groups from highest to lowest priority.



SCENARIO 2: **The lowest priority group is directed toward you.** If the perspective drawing contains the lowest priority group on a wedged bond, read the priority of the other three groups, but assign a configuration that is opposite to what is actually read.



SCENARIO 3: **The lowest priority group is in the plane of the page.** If the perspective drawing contains the lowest priority group in the plane of the page, view down the bond connecting the group to the stereocenter and draw a Newman projection (Section 3.6A).



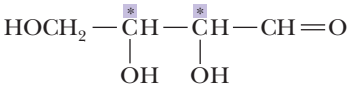
(*R*)-2-Fluoropentane

6.4 What Is the 2^n Rule?

Now let us consider molecules with two stereocenters. To generalize, for a molecule with ***n*** stereocenters, the maximum number of stereoisomers possible is $\mathbf{2^n}$. We have already verified that, for a molecule with one stereocenter, $2^1 = 2$ stereoisomers (one pair of enantiomers) are possible. For a molecule with two stereocenters, $2^2 = 4$ stereoisomers are possible; for a molecule with three stereocenters, $2^3 = 8$ stereoisomers are possible, and so forth.

A. Enantiomers and Diastereomers

We begin our study of molecules with two stereocenters by considering 2,3,4-trihydroxybutanal. Its two stereocenters are marked with asterisks:



2,3,4-Trihydroxybutanal

The maximum number of stereoisomers possible for this molecule is $2^2 = 4$, each of which is drawn in Figure 6.4.

Stereoisomers (a) and (b) are nonsuperposable mirror images and are, therefore, a pair of enantiomers. Stereoisomers (c) and (d) are also nonsuperposable mirror images and are a second pair of enantiomers. We describe the four stereoisomers of 2,3,4-trihydroxybutanal by saying that they consist of two pairs of enantiomers. Enantiomers (a) and (b) are named **erythrose**, which is synthesized in erythrocytes (red blood cells)—hence the name. Enantiomers (c) and (d) are named **threose**. Erythrose and threose belong to the class of compounds called carbohydrates, which we discuss in Chapter 17.

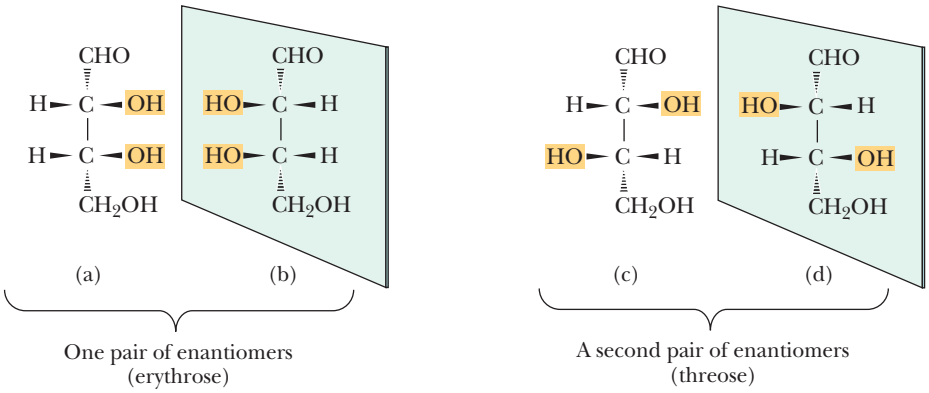


FIGURE 6.4
The four stereoisomers of 2,3,4-trihydroxybutanal, a compound with two stereocenters. Configurations (a) and (b) are (2*R*,3*R*) and (2*S*,3*S*), respectively. Configurations (c) and (d) are (2*R*,3*S*) and (2*S*,3*R*), respectively.

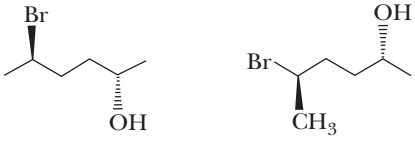
We have specified the relationship between (a) and (b) and between (c) and (d). What is the relationship between (a) and (c), between (a) and (d), between (b) and (c), and between (b) and (d)? The answer is that they are diastereomers. **Diastereomers** are stereoisomers that are not enantiomers; that is, they are stereoisomers that are not mirror images of each other.

Diastereomers
Stereoisomers that are not mirror images of each other; the term refers to relationships among objects.

HOW TO 6.3 Determine Whether Two Compounds Are the Same, Enantiomers, or Diastereomers without the Need to Spatially Manipulate the Molecule

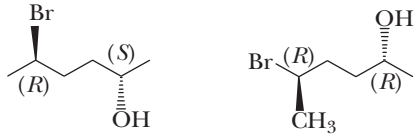
If you are having difficulty visualizing the spatial rotation of perspective drawings, the following technique may be of use.

STEP 1: Verify that the compounds are stereoisomers. Make sure that the two compounds in question have the same molecular formula and the same connectivity of atoms.

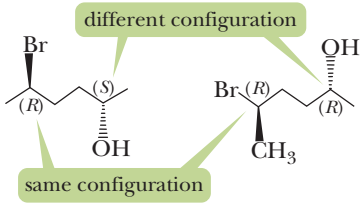


Chemical Formula for both: $C_6H_{13}BrO$
Both have a 6-carbon chain with Br at the 5 position and OH at the 2 position

STEP 2: Assign R/S configurations to each stereocenter in both compounds. See How To 6.2 for instructions.



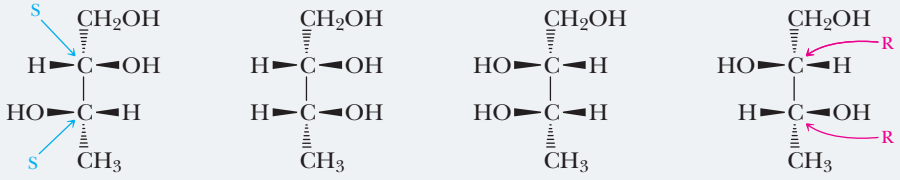
STEP 3: Compare the configuration at corresponding stereocenters. If the configurations match, the compounds are identical. If the configurations are opposite at each corresponding stereocenter, the compounds are enantiomers. Any other scenario indicates that the compounds are diastereomers.



Possible Scenario	Relationship
all configurations the same	identical compounds
all configurations opposite	enantiomers
any other scenario	diastereomers

EXAMPLE 6.3

Following are stereorepresentations of the four stereoisomers of 1,2,3-butanetriol:



Configurations are given for the stereocenters in (1) and (4).

(a) Which compounds are enantiomers? **(b)** Which compounds are diastereomers?

STRATEGY

Determine the R/S configuration of the stereocenters in each compound and compare corresponding stereocenters to determine their relationship (see HowTo 6.3).

SOLUTION

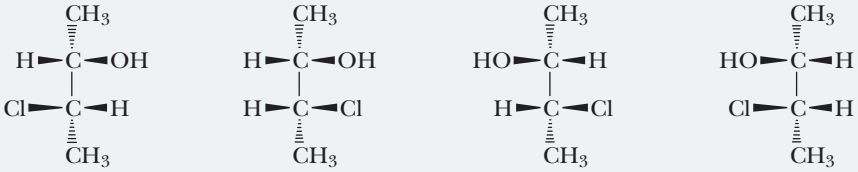
(a) Compounds (1) and (4) are one pair of enantiomers, and compounds (2) and (3) are a second pair of enantiomers. Note that the configurations of the stereocenters in (1) are the opposite of those in (4), its enantiomer.

(b) Compounds (1) and (2), (1) and (3), (2) and (4), and (3) and (4) are diastereomers.

See problem 6.23

PROBLEM 6.3

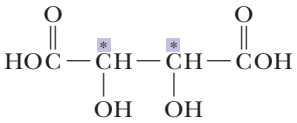
Following are stereorepresentations of the four stereoisomers of 3-chloro-2-butanol:



(a) Which compounds are enantiomers? **(b)** Which compounds are diastereomers?

B. Meso Compounds

Certain molecules containing two or more stereocenters have special symmetry properties that reduce the number of stereoisomers to fewer than the maximum number predicted by the 2^n rule. One such molecule is 2,3-dihydroxybutanedioic acid, more commonly named tartaric acid:



2,3-Dihydroxybutanedioic acid
(tartaric acid)

Tartaric acid is a colorless, crystalline compound occurring largely in the vegetable kingdom, especially in grapes. During the fermentation of grape juice, potassium bitartrate (one —COOH group is present as a potassium salt, $-COO^- K^+$) deposits as a crust on the sides of wine casks. Then, collected and purified, it is sold commercially as cream of tartar.

Carbons 2 and 3 of tartaric acid are stereocenters, and, from the 2^n rule, the maximum number of stereoisomers possible is $2^2 = 4$. Figure 6.5 shows the two pairs of mirror images of this compound. Structures (a) and (b) are nonsuperposable mirror images and, therefore, are a pair of enantiomers. Structures (c) and (d) are also mirror images, but they are superposable. To see this, imagine that you rotate (d) by 180° in the plane of the paper, lift it out of the plane of the paper, and place it on top of (c). If you do this mental manipulation correctly, you will find that (d) is

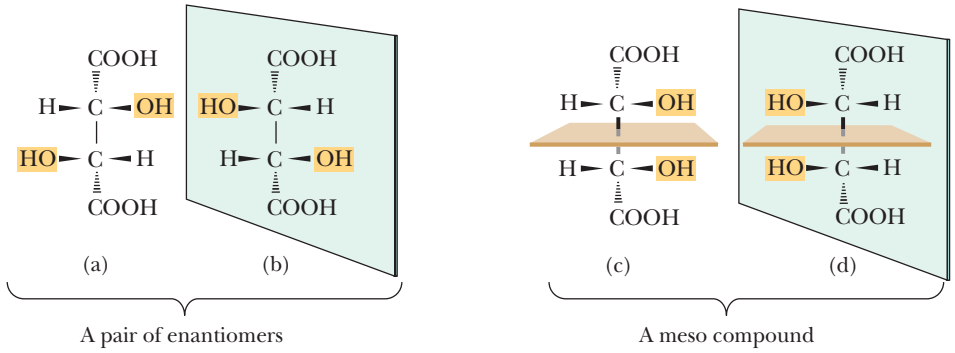


FIGURE 6.5
Stereoisomers of tartaric acid. One pair of enantiomers and one meso compound. The presence of an internal plane of symmetry indicates that the molecule is achiral.

superposable on (c). Therefore, (c) and (d) are *not* different molecules; they are the same molecule, just oriented differently. Because (c) and its mirror image are superposable, (c) is achiral.

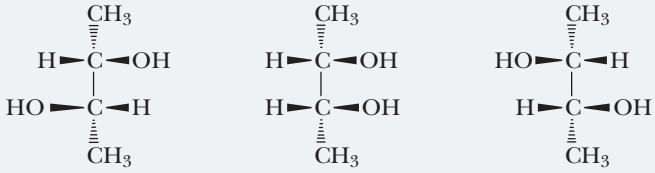
Another way to verify that (c) is achiral is to see that it has a plane of symmetry that bisects the molecule in such a way that the top half is the reflection of the bottom half. Thus, even though (c) has two stereocenters, it is achiral. The stereoisomer of tartaric acid represented by (c) or (d) is called a **meso compound**, defined as an achiral compound that contains two or more stereocenters.

Meso compound An achiral compound possessing two or more stereocenters.

We can now return to the original question: How many stereoisomers are there of tartaric acid? The answer is three: one meso compound and one pair of enantiomers. Note that the meso compound is a diastereomer of each of the other stereoisomers.

EXAMPLE 6.4

Following are stereorepresentations of the three stereoisomers of 2,3-butanediol:



(a) Which are enantiomers? **(b)** Which is the meso compound?

STRATEGY

Enantiomers are nonsuperposable mirror images. A meso compound is an achiral compound with two or more stereocenters, that is, a compound with two or more stereocenters that has a superposable mirror image.

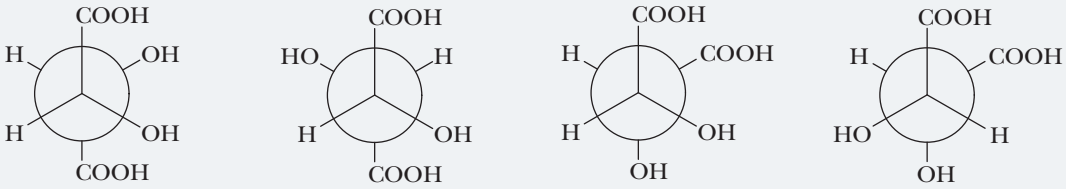
SOLUTION

(a) Compounds (1) and (3) are enantiomers.
(b) Compound (2) has an internal plane of symmetry and, therefore, is a meso compound.

See problems 6.23, 6.36, 6.38

PROBLEM 6.4

Following are four Newman projection formulas for tartaric acid:



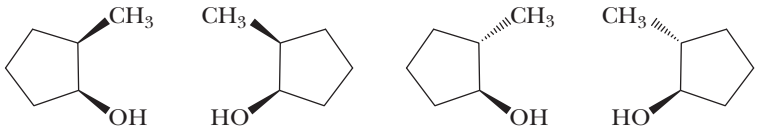
(a) Which represent the same compound? **(b)** Which represent enantiomers? **(c)** Which represent(s) meso tartaric acid?

6.5 How Do We Describe the Chirality of Cyclic Molecules with Two Stereocenters?

In this section, we concentrate on derivatives of cyclopentane and cyclohexane that contain two stereocenters. We can analyze chirality in these cyclic compounds in the same way we analyzed it in acyclic compounds.

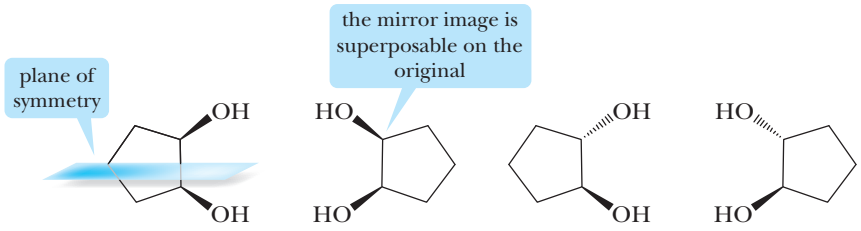
A. Disubstituted Derivatives of Cyclopentane

Let us start with 2-methylcyclopentanol, a compound with two stereocenters. Using the 2^n rule, we predict a maximum of $2^2 = 4$ stereoisomers. Both the *cis* isomer and the *trans* isomer are chiral. The *cis* isomer exists as one pair of enantiomers, and the *trans* isomer exists as a second pair:



cis-2-Methylcyclopentanol (a pair of enantiomers) | *trans*-2-Methylcyclopentanol (a pair of enantiomers)

1,2-Cyclopentanediol also has two stereocenters; therefore, the 2^n rule predicts a maximum of $2^2 = 4$ stereoisomers. As seen in the following stereodrawings, only three stereoisomers exist for this compound:



cis-1,2-Cyclopentanediol (a meso compound) | *trans*-1,2-Cyclopentanediol (a pair of enantiomers)

The *cis* isomer is achiral (meso) because it and its mirror image are superposable. Alternatively, the *cis* isomer is achiral because it possesses a plane of symmetry that bisects the molecule into two mirror-image halves. The *trans* isomer is chiral and exists as a pair of enantiomers.

EXAMPLE 6.5

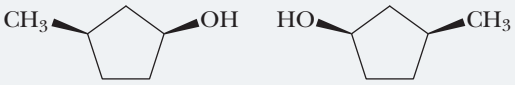
How many stereoisomers are possible for 3-methylcyclopentanol?

STRATEGY

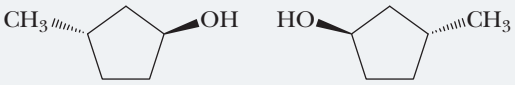
First identify all possible stereocenters, draw all possible pairs of stereoisomers, and determine which, if any, of the possible pairs of stereoisomers are meso compounds.

SOLUTION

There are two stereocenters in this compound and, therefore, four stereoisomers of 3-methylcyclopentanol. The *cis* isomer exists as one pair of enantiomers and the *trans* isomer as a second pair:



cis-3-Methylcyclopentanol
(a pair of enantiomers)



trans-3-Methylcyclopentanol
(a pair of enantiomers)

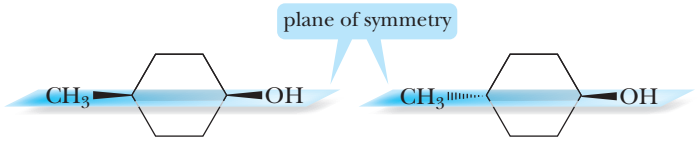
See problems 6.31, 6.33–6.35, 6.38, 6.39

PROBLEM 6.5

How many stereoisomers are possible for 1,3-cyclopentanediol?

B. Disubstituted Derivatives of Cyclohexane

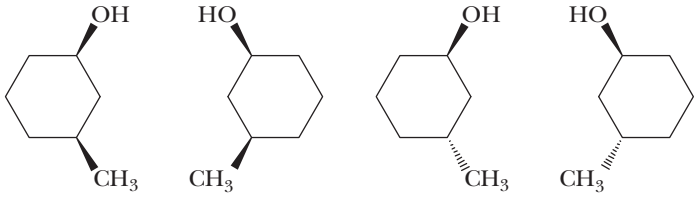
As an example of a disubstituted cyclohexane, let us consider the methylcyclohexanols. 4-Methylcyclohexanol can exist as two stereoisomers—a pair of *cis*–*trans* isomers:



cis-4-Methylcyclohexanol *trans*-4-Methylcyclohexanol

Both the *cis* and the *trans* isomers are achiral. In each, a plane of symmetry runs through the CH_3 and OH groups and the two attached carbons.

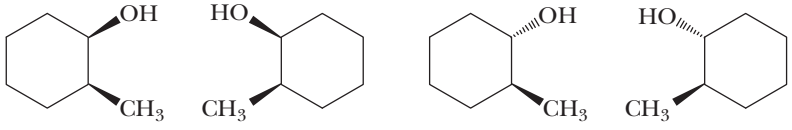
3-Methylcyclohexanol has two stereocenters and exists as $2^2 = 4$ stereoisomers, with the *cis* isomer existing as one pair of enantiomers and the *trans* isomer as a second pair:



cis-3-Methylcyclohexanol
(a pair of enantiomers)

trans-3-Methylcyclohexanol
(a pair of enantiomers)

Similarly, 2-methylcyclohexanol has two stereocenters and exists as $2^2 = 4$ stereoisomers, with the *cis* isomer existing as one pair of enantiomers and the *trans* isomer as a second pair:



cis-2-Methylcyclohexanol
(a pair of enantiomers)

trans-2-Methylcyclohexanol
(a pair of enantiomers)

EXAMPLE 6.6

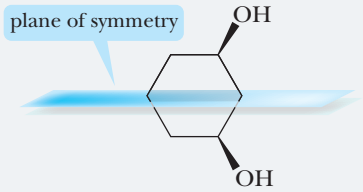
How many stereoisomers exist for 1,3-cyclohexanediol?

STRATEGY

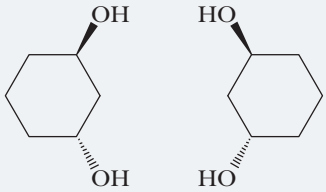
Locate all stereocenters and use the 2^n rule to determine the maximum number of stereoisomers possible. Determine which, if any, of the possible stereoisomers are meso compounds.

SOLUTION

1,3-Cyclohexanediol has two stereocenters, and, according to the 2^n rule, a maximum of $2^2 = 4$ stereoisomers is possible. The *trans* isomer of this compound exists as a pair of enantiomers. The *cis* isomer has a plane of symmetry and is a meso compound. Therefore, although the 2^n rule predicts a maximum of four stereoisomers for 1,3-cyclohexanediol, only three exist—one pair of enantiomers and one meso compound:



cis-1,3-Cyclohexanediol
(a meso compound)



trans-1,3-Cyclohexanediol
(a pair of enantiomers)

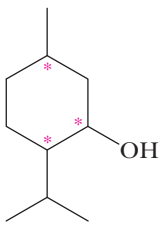
See problems 6.31, 6.33–6.35, 6.38, 6.39

PROBLEM 6.6

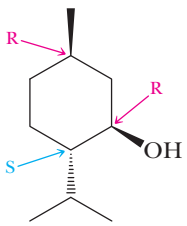
How many stereoisomers exist for 1,4-cyclohexanediol?

6.6 How Do We Describe the Chirality of Molecules with Three or More Stereocenters?

The 2^n rule applies equally well to molecules with three or more stereocenters. Here is a disubstituted cyclohexanol with three stereocenters, each marked with an asterisk:



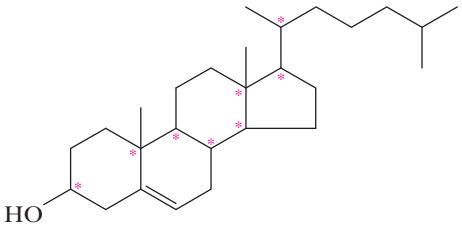
2-Isopropyl-5-methyl-
cyclohexanol



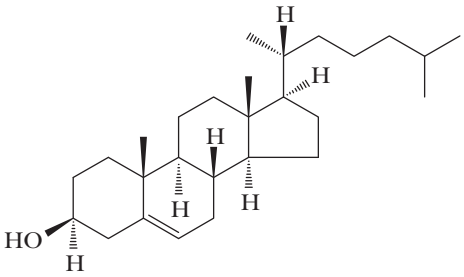
Menthol

There is a maximum of $2^3 = 8$ stereoisomers possible for this molecule. Menthol, one of the eight, has the configuration shown on the right. The configuration at each stereocenter is indicated. Menthol is present in peppermint and other mint oils.

Cholesterol, a more complicated molecule, has eight stereocenters:



Cholesterol has 8 stereocenters; 256 stereoisomers are possible



This is the stereoisomer found in human metabolism

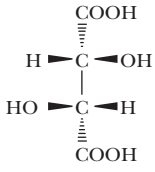
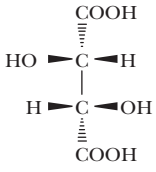
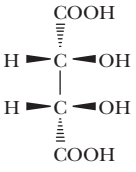
To identify the stereocenters, remember to add an appropriate number of hydrogens to complete the tetravalence of each carbon you think might be a stereocenter.

6.7 What Are the Properties of Stereoisomers?

Enantiomers have identical physical and chemical properties in achiral environments. The enantiomers of tartaric acid (Table 6.1), for example, have the same melting point, the same boiling point, the same solubilities in water and other common solvents, and the same values of pK_a (the acid ionization constant), and they all undergo the same acid–base reactions. The enantiomers of tartaric acid do, however, differ in optical activity (the ability to rotate the plane of polarized light), a property that is discussed in the next section.

Diastereomers have different physical and chemical properties, even in achiral environments. Meso-tartaric acid has different physical properties from those of the enantiomers.

TABLE 6.1 Some Physical Properties of the Stereoisomers of Tartaric Acid

	 (*R,R*)-Tartaric acid	 (*S,S*)-Tartaric acid	 Meso-tartaric acid
Specific rotation*	+12.7	−12.7	0
Melting point (°C)	171–174	171–174	146–148
Density at 20 °C (g/cm^3)	1.7598	1.7598	1.660
Solubility in water at 20 °C (g/100 mL)	139	139	125
pK_1 (25 °C)	2.98	2.98	3.23
pK_2 (25 °C)	4.34	4.34	4.82

*Specific rotation is discussed in the next section.

6.8 How Is Chirality Detected in the Laboratory?

As we have already established, enantiomers are different compounds, and we must expect, therefore, that they differ in some property or properties. One property that differs between enantiomers is their effect on the plane of polarized light. Each member of a pair of enantiomers rotates the plane of polarized light, and for this reason, enantiomers are said to be **optically active**. To understand how optical activity is detected in the laboratory, we must first understand plane-polarized light and a polarimeter, the instrument used to detect optical activity.

Optically active Showing that a compound rotates the plane of polarized light.

A. Plane-Polarized Light

Ordinary light consists of waves vibrating in all planes perpendicular to its direction of propagation (Figure 6.6). Certain materials, such as calcite and Polaroid™ sheet (a plastic film containing properly oriented crystals of an organic substance embedded in it), selectively transmit light waves vibrating in parallel planes. Electromagnetic radiation vibrating in only parallel planes is said to be **plane polarized**.

Plane-polarized light Light vibrating only in parallel planes.

Richard Megna, 1992/ Fundamental Photographs

A polarimeter is used to measure the rotation of plane-polarized light as it passes through a sample.

B. A Polarimeter

A **polarimeter** consists of a light source, a polarizing filter and an analyzing filter (each made of calcite or Polaroid™ film), and a sample tube (Figure 6.6). If the sample tube is empty, the intensity of light reaching the detector (in this case, your eye) is at its maximum when the polarizing axes of the two filters are parallel. If the analyzing filter is turned either clockwise or counterclockwise, less light is transmitted. When the axis of the analyzing filter is at right angles to the axis of the polarizing filter, the field of view is dark. This position of the analyzing filter is taken to be 0° on the optical scale.

The ability of molecules to **rotate the plane of polarized light** can be observed with the use of a polarimeter in the following way: First, a sample tube filled with solvent is placed in the polarimeter, and the analyzing filter is adjusted so that no light passes through to the observer; that is, the filter is set to 0°. Then we place a solution of an optically active compound in the sample tube. When we do so, we find that a certain amount of light now passes through the analyzing filter. We also find that the plane of polarized light from the polarizing filter has been rotated so that it is no longer at an angle of 90° to the analyzing filter. Consequently, we rotate the analyzing filter to restore darkness in the field of view. The number of degrees, α, through which we must rotate the analyzing filter to restore darkness to the field of view is called the **observed rotation**. If we must turn the analyzing

Polarimeter An instrument for measuring the ability of a compound to rotate the plane of polarized light.

Observed rotation The number of degrees through which a compound rotates the plane of polarized light.

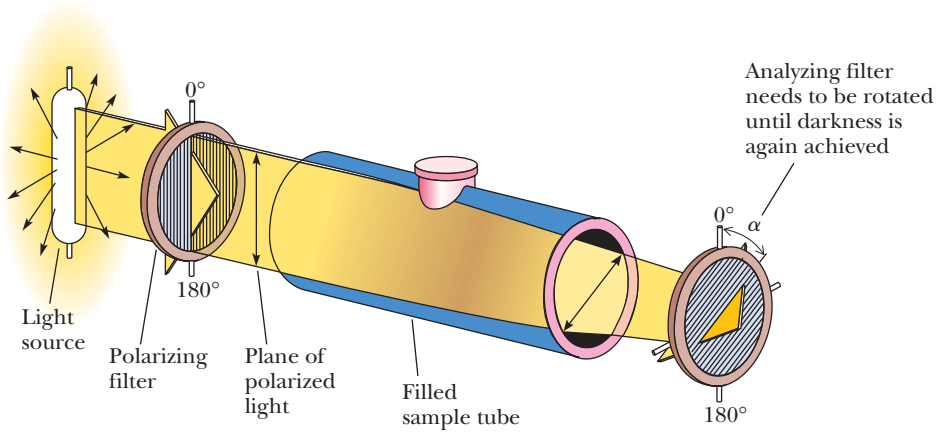


FIGURE 6.6
Schematic diagram of a polarimeter with its sample tube containing a solution of an optically active compound. The analyzing filter has been turned clockwise by α degrees to restore the dark field.

filter to the right (clockwise) to restore the dark field, we say that the compound is **dextrorotatory** (Latin: *dexter*, on the right side); if we must turn it to the left (counterclockwise), we say that the compound is **levorotatory** (Latin: *laevus*, on the left side).

Dextrorotatory Rotating the plane of polarized light in a polarimeter to the right.

Levorotatory Rotating the plane of polarized light in a polarimeter to the left.

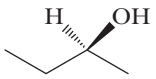
The magnitude of the observed rotation for a particular compound depends on its concentration, the length of the sample tube, the temperature, the solvent, and the wavelength of the light used. The **specific rotation**, $[\alpha]$, is defined as the observed rotation at a specific cell length and sample concentration expressed in grams per milliliter.

Specific rotation Observed rotation of the plane of polarized light when a sample is placed in a tube 1.0 dm long at a concentration of 1.0 g/mL.

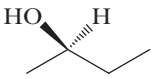
$$\text{Specific rotation} = [\alpha]_{\lambda}^{T} = \frac{\text{Observed rotation (degrees)}}{\text{Length (dm)} \times \text{Concentration}}$$

The standard cell length is 1 decimeter (1 dm = 0.1 m). For a pure liquid sample, the concentration is expressed in grams per milliliter (g/mL; density). The temperature (T, in degrees centigrade) and wavelength (λ, in nanometers) of light are designated, respectively, as superscripts and subscripts. The light source most commonly used in polarimetry is the sodium D line ($\lambda = 589$ nm), the same line responsible for the yellow color of sodium-vapor lamps.

In reporting either observed or specific rotation, it is common to indicate a dextrorotatory compound with a plus sign in parentheses, (+), and a levorotatory compound with a minus sign in parentheses, (−). For any pair of enantiomers, one enantiomer is dextrorotatory and the other is levorotatory. For each member, the value of the specific rotation is exactly the same, but the sign is opposite. Following are the specific rotations of the enantiomers of 2-butanol at 25 °C, observed with the D line of sodium:



(*S*)-(+)-2-Butanol
$[\alpha]_{D}^{25}$ + 13.52°



(*R*)-(−)-2-Butanol
$[\alpha]_{D}^{25}$ −13.52°

C. Racemic Mixtures

An equimolar mixture of two enantiomers is called a **racemic mixture**, a term derived from the name "racemic acid" (Latin: *racemus*, a cluster of grapes), originally given to an equimolar mixture of the enantiomers of tartaric acid (Table 6.1). Because a racemic mixture contains equal numbers of the dextrorotatory and the levorotatory molecules, its specific rotation is zero. Alternatively, we say that a racemic mixture is **optically inactive**. A racemic mixture is indicated by adding the prefix (±) to the name of the compound.

Racemic mixture A mixture of equal amounts of two enantiomers.

Optically inactive Showing that a compound or mixture of compounds does not rotate the plane of polarized light.

6.9 What Is the Significance of Chirality in the Biological World?

Except for inorganic salts and a relatively few low-molecular-weight organic substances, the molecules in living systems, both plant and animal, are chiral. Although these molecules can exist as a number of stereoisomers, almost invariably only one stereoisomer is found in nature. Of course, instances do occur in which more than one stereoisomer is found, but these rarely exist together in the same biological system.

A. Chirality in Biomolecules

Perhaps the most conspicuous examples of chirality among biological molecules are the enzymes, all of which have many stereocenters. An example is chymotrypsin, an enzyme found in the intestines of animals. This enzyme catalyzes the digestion of proteins (Section 19.5). Chymotrypsin has 251 stereocenters. The maximum number of stereoisomers possible is

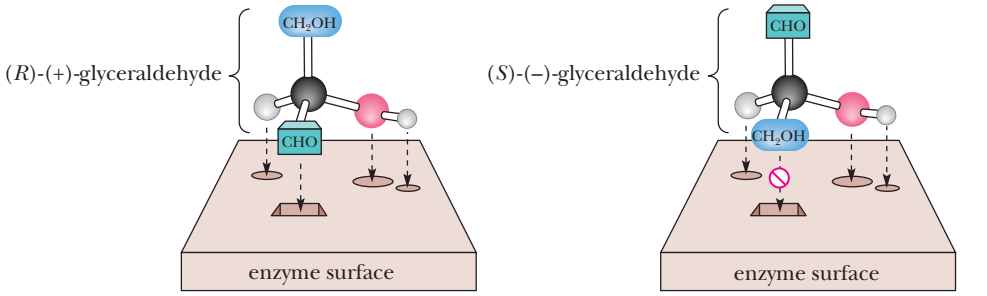


FIGURE 6.7
A schematic diagram of an enzyme surface capable of interacting with (*R*)-(+)-glyceraldehyde at three binding sites, but with (*S*)-(−)-glyceraldehyde at only two of these sites.

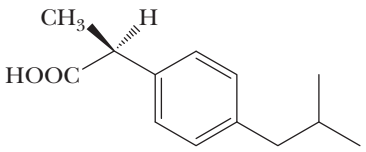
thus 2^{251}, a staggeringly large number, almost beyond comprehension. Fortunately, nature does not squander its precious energy and resources unnecessarily: Only one of these stereoisomers is produced and used by any given organism.

Because enzymes are chiral substances, most either produce or react with only substances that match their stereochemical requirements.

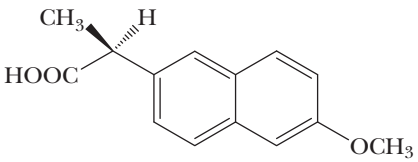
B. How an Enzyme Distinguishes between a Molecule and Its Enantiomer

An enzyme catalyzes a biological reaction of a molecule by first positioning it at a **binding site** on the enzyme's surface. An enzyme with binding sites specific for three of the four groups on a stereocenter can distinguish between a molecule and its enantiomer or one of its diastereomers. Assume, for example, that an enzyme involved in catalyzing a reaction of glyceraldehyde has on its surface a binding site specific for —H, a second specific for —OH, and a third specific for —CHO. Assume further that the three sites are arranged on the enzyme surface as shown in Figure 6.7. The enzyme can distinguish (*R*)-(+)-glyceraldehyde (the natural, or biologically active, form) from its enantiomer because the natural enantiomer can be absorbed, with three groups interacting with their appropriate binding sites; for the S enantiomer, at best only two groups can interact with these binding sites.

Because interactions between molecules in living systems take place in a chiral environment, it should come as no surprise that a molecule and its enantiomer or one of its diastereomers elicit different physiological responses. As we have already seen, (*S*)-ibuprofen is active as a pain and fever reliever, whereas its R enantiomer is inactive. The S enantiomer of the closely related analgesic naproxen is also the active pain reliever of this compound, but its R enantiomer is a liver toxin!



(*S*)-Ibuprofen



(*S*)-Naproxen

6.10 How Can Enantiomers Be Resolved?

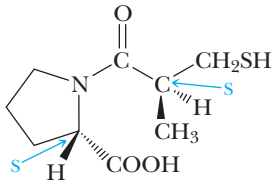
Resolution Separation of a racemic mixture into its enantiomers.

Resolution is the separation of a racemic mixture into its enantiomers. Because two enantiomers have the same physical properties, separating them, in general, is difficult, but scientists have developed a number of ways to do it. In this section, we illustrate just two of the several laboratory methods for resolution: the use of enzymes as chiral catalysts and the use of solid chiral materials to differentiate between enantiomers made to come in contact with these materials.

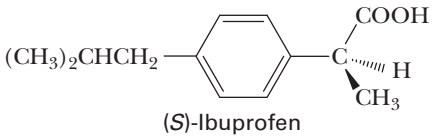
Chemical Connections 6A

CHIRAL DRUGS

Some of the common drugs used in human medicine (for example, aspirin, Section 14.4B) are achiral. Others are chiral and are sold as single enantiomers. The penicillin and erythromycin classes of antibiotics and the drug Captopril are all chiral drugs. Captopril, which is highly effective for the treatment of high blood pressure and congestive heart failure, was developed in a research program designed to discover effective inhibitors of angiotensin-converting enzyme (ACE). Captopril is manufactured and sold as the (*S,S*)-stereoisomer. A large number of chiral drugs, however, are sold as racemic mixtures. The popular analgesic ibuprofen (the active ingredient in Motrin®, Advil®, and many other nonaspirin analgesics) is an example. Only the S enantiomer of the pain reliever ibuprofen is biologically active.

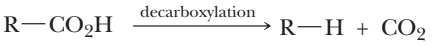


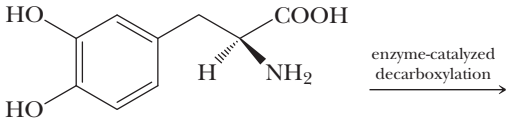
Captopril



(*S*)-Ibuprofen

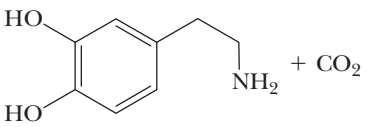
For racemic drugs, most often only one enantiomer exerts the beneficial effect, whereas the other enantiomer either has no effect or may exert a detrimental effect. Thus, enantiomerically pure drugs should, more often than not, be more effective than their racemic counterparts. A case in point is 3,4-dihydroxyphenylalanine, which is used in the treatment of Parkinson's disease. The active drug is dopamine. Unfortunately, this compound does not cross the blood–brain barrier to the required site of action in the brain. Consequently, what is administered instead is the prodrug, a compound that is not active by itself, but is converted in the body to an active drug. 3,4-Dihydroxyphenylalanine is such a prodrug; it crosses the blood–brain barrier and then undergoes decarboxylation, catalyzed by the enzyme dopamine decarboxylase, to give dopamine. Decarboxylation is the loss of carbon dioxide from a carboxyl group (R—CO_2H).





(*S*)-(–)-3,4-Dihydroxyphenylalanine
(L-DOPA)

$[\alpha]_D^{13}$ –13.1°

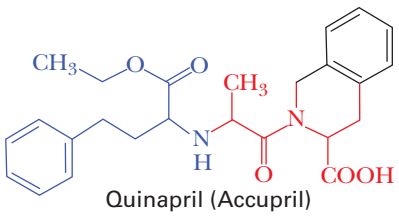


Dopamine

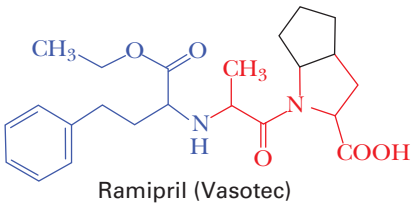
Dopamine decarboxylase is specific for the S enantiomer, which is commonly known as L-DOPA. It is essential, therefore, to administer the enantiomerically pure prodrug. Were the prodrug to be administered in a racemic form, there could be a dangerous buildup of the R enantiomer, which cannot be metabolized by the enzymes present in the brain.

Question

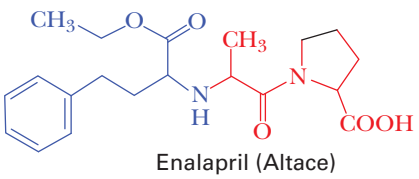
Following are structural formulas for three other angiotensin-converting enzyme (ACE) inhibitors, all members of the *"pril"* family. Which are chiral? For each that is chiral, determine the number of stereoisomers possible for it. List the similarities in structure among each of these four drugs.



Quinapril (Accupril)



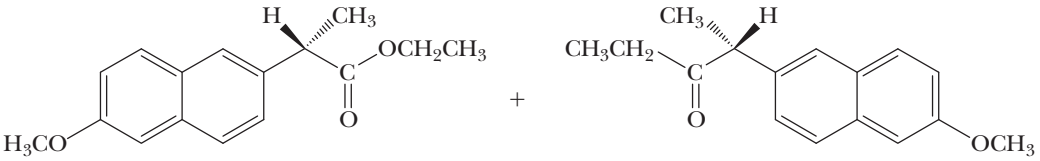
Ramipril (Vasotec)



Enalapril (Altace)

A. Enzymes as Resolving Agents

One class of enzymes that has received particular attention in this regard is the esterases, which catalyze the hydrolysis of esters (Section 14.1C) to give an alcohol and a carboxylic acid. We illustrate this method by describing the resolution of (*R,S*)-naproxen. The ethyl esters of both (*R*)- and (*S*)-naproxen are solids with very low solubilities in water. Chemists then use an esterase in alkaline solution to selectively hydrolyze the (*S*)-ester, which goes into the aqueous solution as the sodium salt of the (*S*)-carboxylic acid. The (*R*)-ester is unaffected by these conditions. Filtering the alkaline solution recovers the crystals of the (*R*)-ester. After the crystals are removed, the alkaline solution is acidified to precipitate pure (*S*)-naproxen. The recovered (*R*)-ester can be racemized (converted to an *R,S*-mixture) and again treated with the esterase. Thus, by recycling the (*R*)-ester, all the racemic ester is converted to (*S*)-naproxen.

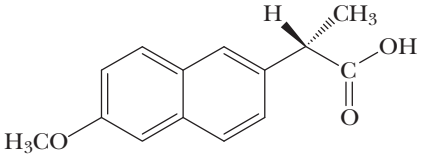


Ethyl ester of (*S*)-naproxen

Ethyl ester of (*R*)-naproxen
(not affected by the esterase)

1) esterase
2) HCl, H_2O

$NaOH, H_2O$



(*S*)-Naproxen

The sodium salt of (*S*)-naproxen is the active ingredient in Aleve® and a score of other over-the-counter nonsteroidal anti-inflammatory preparations.

B. Resolution by Means of Chromatography on a Chiral Substrate

Chromatography is a term used to describe the purification of substances in which a sample to be purified interacts with a solid material, and different components of the sample separate based on differences in their interactions with the solid material. The solid material is packed into a column, and a solution of the substance dissolved in a suitable solvent is passed down the column. The more weakly bound components of the mixture pass through the column more quickly than the more tightly bound components.

A common method for resolving enantiomers today is chromatography using a chiral packing material in the column. Each enantiomer in principle interacts differently with the chiral packing material, and the elution time will be different for each enantiomer. A wide variety of chiral column packing materials have been developed for this purpose.

Recently, the U.S. Food and Drug Administration established new guidelines for the testing and marketing of chiral drugs. After reviewing these guidelines, many drug companies have decided to develop only single enantiomers of new chiral drugs. In addition to regulatory pressure, there are patent considerations: If a company has patents on a racemic drug, a new patent can often be taken out on one of its enantiomers.

SUMMARY OF KEY QUESTIONS

6.1 What Are Stereoisomers?

- **Stereoisomers** have the same connectivity of their atoms, but a different three-dimensional orientation of their atoms in space.
- A **mirror image** is the reflection of an object in a mirror.

6.2 What Are Enantiomers?

- **Enantiomers** are a pair of stereoisomers that are nonsuperposable mirror images. A molecule that is not superposable on its mirror image is said to be **chiral**.
- Chirality is a property of an object as a whole, not of a particular atom.
- An **achiral** object possesses a **plane of symmetry**—an imaginary plane passing through the object and dividing it such that one half is the reflection of the other half.
- A **stereocenter** is an atom at which the interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer.
- The most common type of stereocenter among organic compounds is a **chiral center**, a tetrahedral carbon atom with four different groups bonded to it.

6.3 How Do We Designate the Configuration of a Stereocenter?

- The **configuration** at a stereocenter can be specified by the **R,S convention**.
- To apply this convention, (1) each atom or group of atoms bonded to the stereocenter is assigned a priority and numbered from highest priority to lowest priority, (2) the molecule is oriented in space so that the group of lowest priority is directed away from the observer, and (3) the remaining three groups are read in order, from highest priority to lowest priority.
- If the reading of groups is clockwise, the configuration is **R** (Latin: *rectus*, right). If the reading is counterclockwise, the configuration is **S** (Latin: *sinister*, left).

6.4 What Is the 2^n Rule?

- For a molecule with ***n*** stereocenters, the maximum number of stereoisomers possible is $\mathbf{2^n}$.
- **Diastereomers** are stereoisomers that are not mirror images.
- Certain molecules have special symmetry properties that reduce the number of stereoisomers to fewer than that predicted by the $\mathbf{2^n}$ **rule**.
- A **meso** compound contains two or more stereocenters assembled in such a way that its molecules are achiral.
- Enantiomers have identical physical and chemical properties in achiral environments.
- Diastereomers have different physical and chemical properties.

6.5 How Do We Describe the Chirality of Cyclic Molecules with Two Stereocenters?

- When evaluating the symmetry of cyclic structures, such as derivatives of cyclohexane and cyclopentane, it is helpful to evaluate planar representations.

6.6 How Do We Describe the Chirality of Molecules with Three or More Stereocenters?

- For a molecule with *n* stereocenters, the maximum number of stereoisomers possible is 2^n.

6.7 What Are the Properties of Stereoisomers?

- Enantiomers have identical physical and chemical properties in achiral environments.
- Diastereomers have different physical and chemical properties.

6.8 How Is Chirality Detected in the Laboratory?

- Light that vibrates in only parallel planes is said to be **plane polarized**.
- A **polarimeter** is an instrument used to detect and measure the magnitude of optical activity. **Observed rotation** is the number of degrees the plane of polarized light is rotated.

- **Specific rotation** is the observed rotation measured with a cell 1 dm long and a solution with a concentration of 1.00 g/mL.
- If the analyzing filter must be turned clockwise to restore the zero point, the compound is **dextrorotatory**. If the analyzing filter must be turned counterclockwise to restore the zero point, the compound is **levorotatory**.
- A compound is said to be **optically active** if it rotates the plane of polarized light. Each member of a pair of enantiomers rotates the plane of polarized light an equal number of degrees, but opposite in direction.
- A **racemic mixture** is a mixture of equal amounts of two enantiomers and has a specific rotation of zero.
- A **meso** compound is optically inactive.

6.9 What Is the Significance of Chirality in the Biological World?

- An enzyme catalyzes the biological reactions of molecules by first positioning them at a binding site on its surface. An enzyme with a binding site specific for three of the four groups on a stereocenter can distinguish between a molecule and its enantiomer or its diastereomers.

6.10 How Can Enantiomers Be Resolved?

- **Resolution** is the experimental process of separating a mixture of enantiomers into two pure enantiomers.
- One means of resolution is to treat the racemic mixture with an enzyme that catalyzes a specific reaction of one enantiomer, but not the other.
- A common method for resolving enantiomers is chromatography using a chiral packing material in the column. Each enantiomer in principle interacts differently with the chiral packing material and the elution time will be different for each enantiomer.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. Enantiomers are always chiral. (6.2)
2. An unmarked cube is chiral. (6.1)
3. Stereocenters can be designated using E and Z. (6.3)
4. A chiral molecule will always have a diastereomer. (6.2)
5. Every object in nature has a mirror image. (6.1)
6. A molecule that possesses an internal plane of symmetry can never be chiral. (6.2)
7. Pairs of enantiomers have the same connectivity. (6.1)
8. Enantiomers, like gloves, occur in pairs. (6.2)
9. A cyclic molecule with two stereocenters will always have only three stereoisomers. (6.5)
10. An achiral molecule will always have a diastereomer. (6.2)
11. The *cis* and *trans* isomers of 2-butene are chiral. (6.1)
12. A human foot is chiral. (6.1)
13. A compound with n stereocenters will always have 2^n stereoisomers. (6.4)
14. A molecule with three or more stereocenters cannot be meso. (6.6)
15. A molecule with three or more stereocenters must be chiral. (6.6)
16. Each member of a pair of enantiomers will have the same boiling point. (6.7)
17. If a molecule is not superposable on its mirror image, it is chiral. (6.1)
18. For a molecule with two tetrahedral stereocenters, four stereoisomers are possible. (6.2)
19. Constitutional isomers have the same connectivity. (6.1)
20. Enantiomers can be separated by interacting them with the same chiral environment or chemical agent. (6.10)
21. Enzymes are achiral molecules that can differentiate chiral molecules. (6.9)
22. *Cis* and *trans* stereoisomers of a cyclic compound can be classified as diastereomers. (6.5)
23. 3-Pentanol is the mirror image of 2-pentanol. (6.2)
24. Diastereomers do not have a mirror image. (6.2)
25. The most common cause of chirality in organic molecules is the presence of a tetrahedral carbon atom with four different groups bonded to it. (6.1)
26. Each member of a pair of enantiomers will have the same density. (6.7)
27. The carbonyl carbon of an aldehyde or a ketone cannot be a stereocenter. (6.1)
28. For a molecule with three stereocenters, $3^2 = 9$ stereoisomers are possible. (6.2)
29. Diastereomers can be resolved using traditional methods such as distillation. (6.10)
30. A racemic mixture is optically inactive. (6.8)
31. 2-Pentanol and 3-pentanol are chiral and show enantiomerism. (6.2)
32. A diastereomer of a chiral molecule must also be chiral. (6.2)
33. In order to designate the configuration of a stereocenter, the priority of groups must be read in a clockwise or

counterclockwise fashion after the lowest priority group is placed facing toward the viewer. (6.3)

34. A compound with *n* stereocenters will always be one of the 2^n stereoisomers of that compound. (6.4)
35. Each member of a pair of enantiomers could react differently in a chiral environment. (6.7)
36. A chiral molecule will always have an enantiomer. (6.2)
37. Each member of a pair of diastereomers will have the same melting point. (6.7)
38. If a chiral compound is dextrorotatory, its enantiomer is levorotatory by the same number of degrees. (6.8)
39. All stereoisomers are optically active. (6.8)
40. There are usually equal amounts of each enantiomer of a chiral biological molecule in a living organism. (6.9)

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) T (2) F (3) F (4) F (5) T (6) T (7) T (8) T (9) F (10) F (11) F (12) T (13) F (14) F (15) F (16) T (17) T (18) T (19) F (20) T (21) F (22) T (23) F (24) F (25) T (26) T (27) T (28) F (29) T (30) T (31) F (32) F (33) F (34) T (35) T (36) T (37) F (38) T (39) F (40) F

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

Section 6.1 Chirality

6.7 Define the term *stereoisomer*. Name four types of stereoisomers.

6.8 In what way are constitutional isomers different from stereoisomers? In what way are they the same?

6.9 Compare and contrast the meaning of the terms *conformation* and *configuration*.

***6.10** Which of these objects are chiral (assume that there is no label or other identifying mark)?

(a) A pair of scissors (b) A tennis ball
(c) A paper clip (d) A beaker
(e) The swirl created in water as it drains out of a sink or bathtub

***6.11** Think about the helical coil of a telephone cord or the spiral binding on a notebook, and suppose that you view the spiral from one end and find that it has a left-handed twist. If you view the same spiral from the other end, does it have a right-handed twist or a left-handed twist from that end as well?

***6.12** Next time you have the opportunity to view a collection of augers or other seashells that have a helical twist, study the chirality of their twists. Do you find an equal number of left-handed and right-handed augers, or, for example, do they all have the same handedness? What about the handedness of augers compared with that of other spiral shells?

Kaz Chiba/Getty Images, Inc.

Median cross section through the shell of a chambered nautilus found in the deep waters of the Pacific Ocean. The shell shows handedness; this cross section is a right-handed spiral.

***6.13** Next time you have an opportunity to examine any of the seemingly endless varieties of spiral pasta (rotini, fusilli, radiatori, tortiglioni), examine their twist. Do the twists of any one kind all have a right-handed twist, do they all have a left-handed twist, or are they a racemic mixture?

6.14 One reason we can be sure that sp^3-hybridized carbon atoms are tetrahedral is the number of stereoisomers that can exist for different organic compounds.

(a) How many stereoisomers are possible for $CHCl_3$, CH_2Cl_2, and CHBrClF if the four bonds to carbon have a tetrahedral geometry?
(b) How many stereoisomers are possible for each of the compounds if the four bonds to the carbon have a square planar geometry?

Section 6.2 Enantiomers

6.15 Which compounds contain stereocenters? **(See Example 6.1)**

(a) 2-Chloropentane
(b) 3-Chloropentane
(c) 3-Chloro-1-pentene
(d) 1,2-Dichloropropane

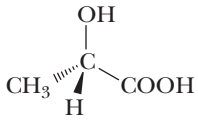
6.16 Using only C, H, and O, write a structural formula for the lowest-molecular-weight chiral molecule of each of the following compounds:

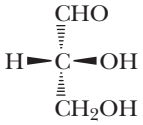
(a) Alkane (b) Alcohol
(c) Aldehyde (d) Ketone
(e) Carboxylic acid

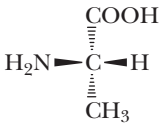
6.17 Which alcohols with the molecular formula $C_5H_{12}O$ are chiral?

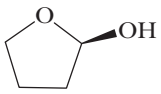
6.18 Which carboxylic acids with the molecular formula $C_6H_{12}O_2$ are chiral?

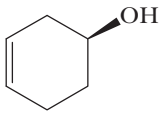
6.19 Draw the enantiomer for each molecule: **(See Example 6.1)**

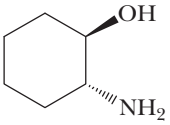
(a) 

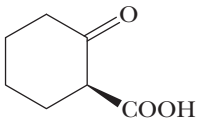
(b) 

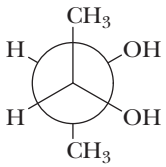
(c) 

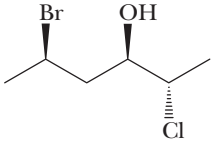
(d) 

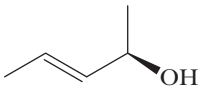
(e) 

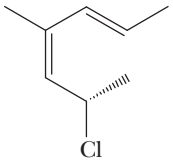
(f) 

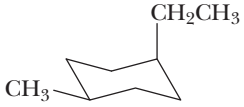
(g) 

(h) 

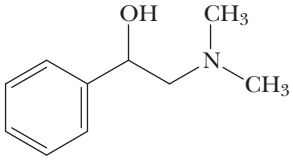
(i) 

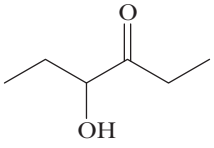
(j) 

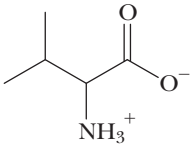
(k) 

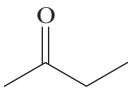
(l) 

6.20 Mark each stereocenter in these molecules with an asterisk (note that not all contain stereocenters): **(See Example 6.1)**

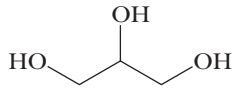
(a) 

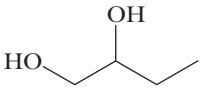
(b) 

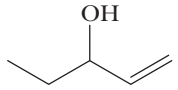
(c) 

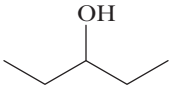
(d) 

6.21 Mark each stereocenter in these molecules with an asterisk (note that not all contain stereocenters): **(See Example 6.1)**

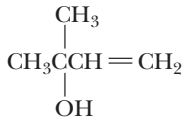
(a) 

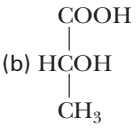
(b) 

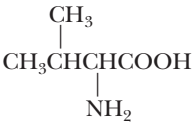
(c) 

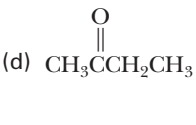
(d) 

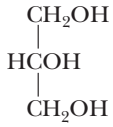
6.22 Mark each stereocenter in these molecules with an asterisk (note that not all contain stereocenters): **(See Example 6.1)**

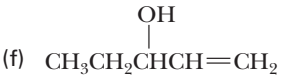
(a) 

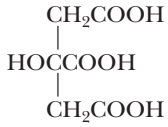
(b) 

(c) 

(d) 

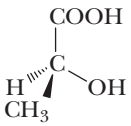
(e) 

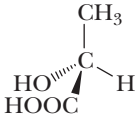
(f) 

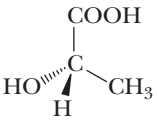
(g) 

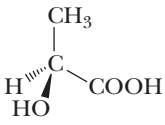
(h) $(CH_3)_3CCH_2CH(OH)CH_3$

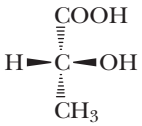
6.23 Following are eight stereorepresentations of lactic acid: **(See Examples 6.3, 6.4)**

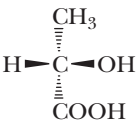
(a) 

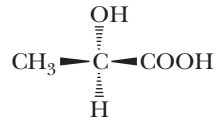
(b) 

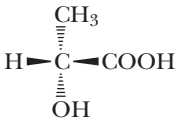
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

Take (a) as a reference structure. Which stereorepresentations are identical with (a) and which are mirror images of (a)?

Section 6.3 Designation of Configuration: The R,S Convention

6.24 Assign priorities to the groups in each set: **(See Example 6.2)**

(a) —H —CH_3 —OH —CH_2OH

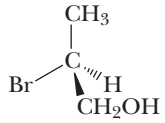
(b) —$CH_2CH{=}CH_2$ —$CH{=}CH_2$ —CH_3 —CH_2COOH

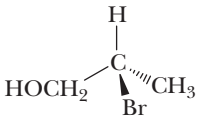
(c) —CH_3 —H —COO^- —NH_3^+

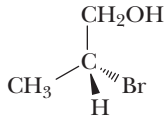
(d) —CH_3 —CH_2SH —NH_3^+ —COO^-

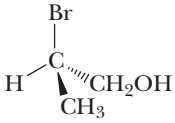
(e) —$CH(CH_3)_2$ —$CH{=}CH_2$ —$C(CH_3)_3$ —$C{\equiv}CH$

6.25 Which molecules have R configurations? **(See Example 6.2)**

(a) 

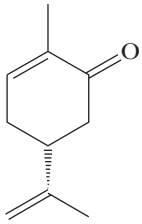
(b) 

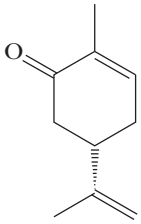
(c) 

(d) 

***6.26** Following are structural formulas for the enantiomers of carvone: **(See Example 6.2)**

(−)-Carvone (Spearmint oil)

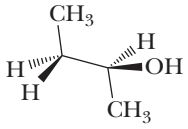




(+)-Carvone (Caraway and dillseed oil)

Each enantiomer has a distinctive odor characteristic of the source from which it can be isolated. Assign an R or S configuration to the stereocenter in each. How can they have such different properties when they are so similar in structure?

6.27 Following is a staggered conformation of one of the stereoisomers of 2-butanol: **(See Example 6.2)**



(a) Is this (*R*)-2-butanol or (*S*)-2-butanol?

(b) Draw a Newman projection for this staggered conformation, viewed along the bond between carbons 2 and 3.

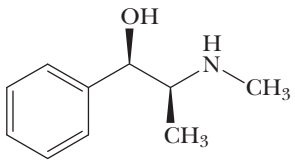
(c) Draw a Newman projection for one more staggered conformations of this molecule. Which of your conformations is the more stable? Assume that —OH and —CH_3 are comparable in size.

Sections 6.5 and 6.6 Molecules with Two or More Stereocenters

6.28 Write the structural formula of an alcohol with molecular formula $C_6H_{14}O$ that contains two stereocenters.

***6.29** For centuries, Chinese herbal medicine has used extracts of *Ephedra sinica* to treat asthma. Investigation of this plant resulted in the isolation of ephedrine, a potent dilator of the air passages of the lungs. The naturally occurring stereoisomer is levorotatory and has the following structure: **(See Example 6.2)**

Ephedrine



Assign an R or S configuration to each stereocenter.

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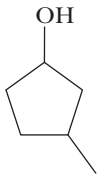
Ephedra sinica, a source of ephedrine, a potent bronchodilator.

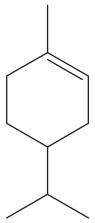
***6.30** The specific rotation of naturally occurring ephedrine, shown in Problem 6.29, is −41°. What is the specific rotation of its enantiomer?

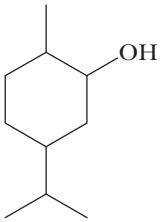
6.31 Label each stereocenter in these molecules with an asterisk and tell how many stereoisomers exist for each. **(See Examples 6.5, 6.6)**

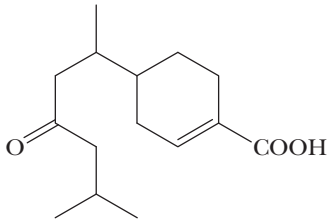
(a) $CH_3CHCHCOOH$ (HO, OH)

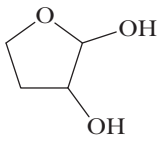
(b) $HO{-}CH(CH_2{-}COOH){-}COOH$

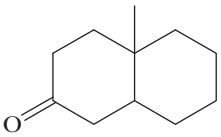
(c) 

(d) 

(e) 

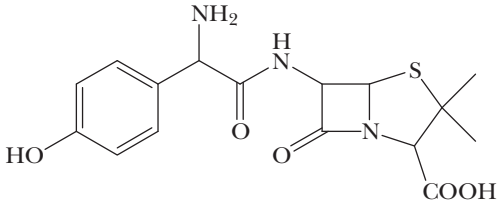
(f) 

(g) 

(h) 

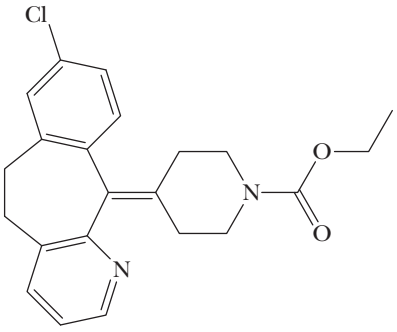
How many stereoisomers are possible for each molecule?

***6.32** Label the four stereocenters in amoxicillin, which belongs to the family of semisynthetic penicillins:

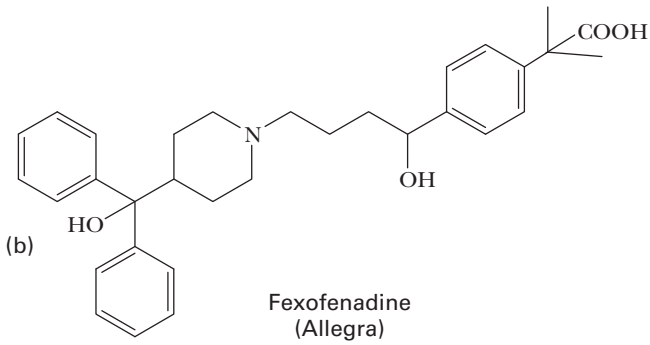


Amoxicillin

***6.33** Label all stereocenters in loratadine (Claritin®) and fexofenadine (Allegra®), now the top-selling antihistamines in the United States. Tell how many stereoisomers are possible for each. **(See Examples 6.5, 6.6)**

(a) 

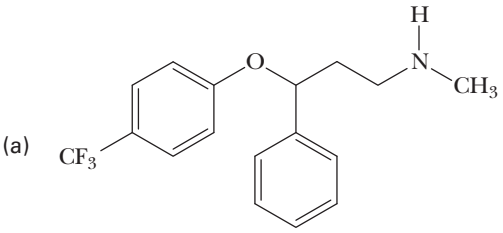
Loratadine
(Claritin)

(b) 

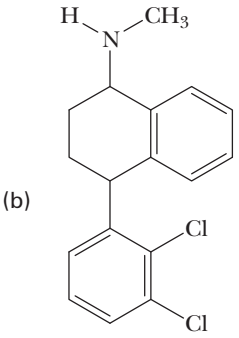
Fexofenadine
(Allegra)

How many stereoisomers are possible for each compound?

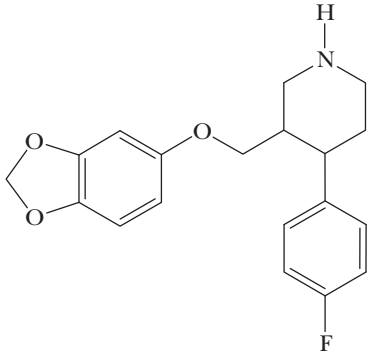
***6.34** Following are structural formulas for three of the most widely prescribed drugs used to treat depression. Label all stereocenters in each compound and tell how many stereoisomers are possible for each compound. **(See Examples 6.5, 6.6)**

(a) 

Fluoxetine
(Prozac®)

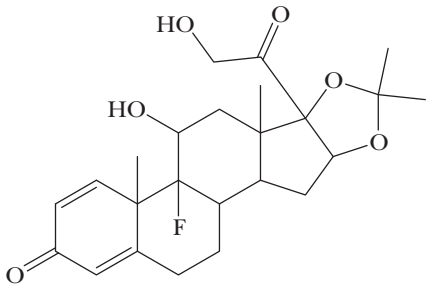
(b) 

Sertraline
(Zoloft®)

(c) 

Paroxetine
(Paxil®)

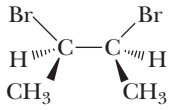
***6.35** Triamcinolone acetonide, the active ingredient in Azmacort® Inhalation Aerosol, is a steroid used to treat bronchial asthma: **(See Examples 6.5, 6.6)**

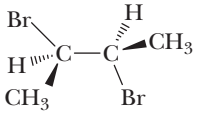


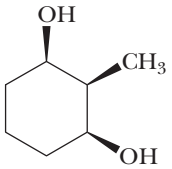
Triamcinolone acetonide

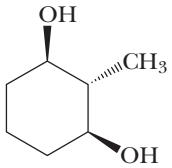
(a) Label the eight stereocenters in this molecule.
(b) How many stereoisomers are possible for the molecule? (Of this number, only one is the active ingredient in Azmacort.)

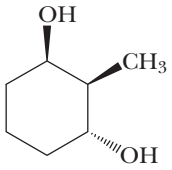
6.36 Which of these structural formulas represent meso compounds? **(See Example 6.4)**

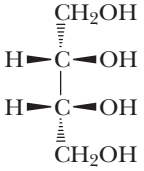
(a) 

(b) 

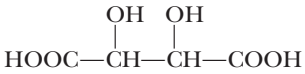
(c) 

(d) 

(e) 

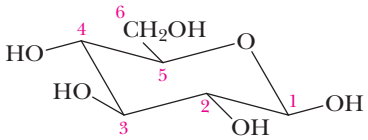
(f) 

6.37 Draw a Newman projection, viewed along the bond between carbons 2 and 3, for both the most stable and the least stable conformations of meso-tartaric acid:



6.38 How many stereoisomers are possible for 1,3-dimethylcyclopentane? Which are pairs of enantiomers? Which are meso compounds? **(See Examples 6.4–6.6)**

6.39 In Problem 3.59, you were asked to draw the more stable chair conformation of glucose, a molecule in which all groups on the six-membered ring are equatorial: **(See Examples 6.2, 6.5, 6.6)**

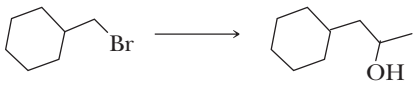


(a) Identify all stereocenters in this molecule.
(b) How many stereoisomers are possible?
(c) How many pairs of enantiomers are possible?
(d) What is the configuration (*R* or *S*) at carbons 1 and 5 in the stereoisomer shown?

6.40 What is a racemic mixture? Is a racemic mixture optically active? That is, will it rotate the plane of polarized light?

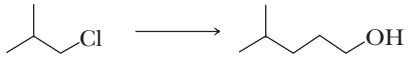
CHEMICAL TRANSFORMATIONS

6.41 Test your cumulative knowledge of the reactions learned so far by completing the following chemical transformations. Pay particular attention to the stereochemistry in the product. Where more than one stereoisomer is possible, show each stereoisomer. *Note that some transformations will require more than one step.*

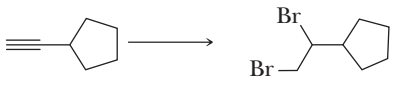
(a) 

(b) 

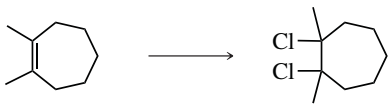
(c) 

(d) 

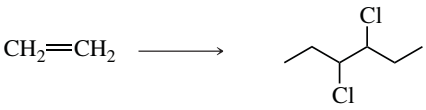
(e) 

(f) 

(g) 

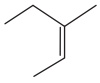
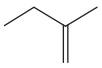
(h) 

(i) 

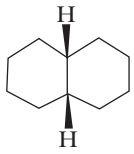
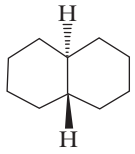
(j) 

LOOKING AHEAD

6.42 Predict the product(s) of the following reactions (in cases where more than one stereoisomer is possible, show each stereoisomer):

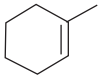
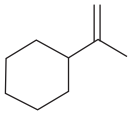
(a)  H_2, Pt (b)  H_2O, H_2SO_4

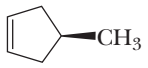
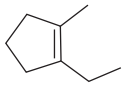
6.43 What alkene, when treated with H_2/Pd, will ensure a 100% yield of the stereoisomer shown?

(a)  (b) 

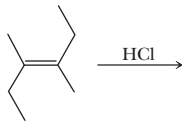
6.44 Which of the following reactions will yield a racemic mixture of products?

(a)  HCl (b)  H_2, Pt

(c)  HBr (d)  H_2, Pt

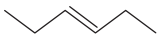
(e)  HBr (f)  H_2, Pt

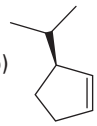
6.45 Draw all the stereoisomers that can be formed in the following reaction:



Comment on the utility of this particular reaction as a synthetic method.

6.46 Explain why the product of the following reaction does not rotate the plane of polarized light:

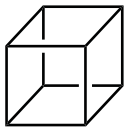
(a)  Br_2, CH_2Cl_2

(b)  H_2, Pt

GROUP LEARNING ACTIVITIES

***6.47** Identify objects in your surroundings and take turns deciding if each object is chiral or achiral.

6.48 Take turns identifying the planes of symmetry in cubane (note: the hydrogen atoms are not shown).



Cubane

6.49 Discuss whether the following pairs of objects are true enantiomers of each other. For those that are not true enantiomers, decide what it would take for them to be true enantiomers.

(a) your right hand and left hand
(b) your right eye and left eye
(c) a car with a left, front flat tire and the same car with a right, front flat tire

6.50 Compound **A** (C_5H_8) is not optically active and cannot be resolved. It reacts with Br_2 in CCl_4 to give compound **B** ($C_5H_8Br_2$). When compound **A** is treated with H_2/Pt, it is converted to compound **C** (C_5H_{10}). When treated with HBr, compound **A** is converted to compound **D** (C_5H_9Br). Given this information, propose structural formulas for **A**, **B**, **C**, and **D**. There are at least three possibilities for compound **A** and, in turn, three possibilities for compounds **B**, **C**, and **D**. As a group, try to come up with all the possibilities.

PUTTING IT TOGETHER

The following problems bring together concepts and material from Chapters 4–6. Although the focus may be on these chapters, the problems will also build on concepts discussed thus far.

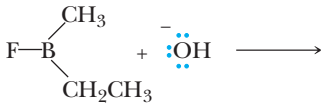
Choose the best answer for each of the following questions.

1. Which of the following will *not* rotate the plane of polarized light?
   (a) A 50:50 ratio of (*R*)-2-butanol and *cis*-2-butene.
   (b) A 70:20 ratio of (*R*)-2-butanol and *S*-2-butanol.
   (c) A 50:25:25 ratio of (*S*)-2-butanol, *cis*-2-butene, and *trans*-2-butene.
   (d) A 20:70 ratio of *trans*-2-butene and *cis*-2-butene.
   (e) None of the above (i.e., all of them will rotate plane-polarized light)

2. Which of the following *cis* isomers of dimethylcyclohexane is *not* meso?

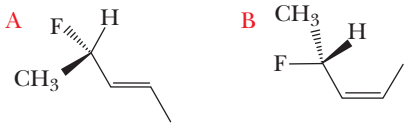
(a) *cis*-1,4-dimethylcyclohexane
(b) *cis*-1,3-dimethylcyclohexane
(c) *cis*-1,2-dimethylcyclohexane
(d) All of the above (i.e., none of them is meso)
(e) None of the above (i.e., all of them are meso)

3. How many products are possible in the following Lewis acid–base reaction?



(a) One (b) Two (c) Three (d) Four
(e) None (no reaction will take place)

4. What is the relationship between the following two molecules?

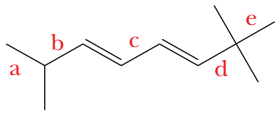


(a) They are identical.
(b) They are enantiomers.
(c) They are diastereomers.
(d) They are constitutional isomers.
(e) They are nonisomers.

5. Which stereoisomer of 2,4-hexadiene is the *least* stable?

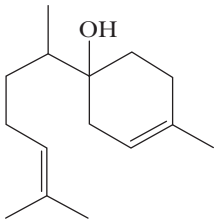
(a) *Z*,*Z*-2,4-hexadiene
(b) *Z*,*E*-2,4-hexadiene
(c) *E*,*Z*-2,4-hexadiene
(d) *E*,*E*-2,4-hexadiene
(e) All are equal in stability.

6. Select the shortest C—C single bond in the following molecule.



(a) a (b) b (c) c (d) d (e) e

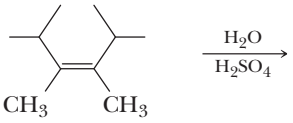
7. Which of the following statements is true of β-bisabolol?



β-Bisabolol

(a) There are 6 stereoisomers of β-bisabolol.
(b) β-Bisabolol is soluble in water.
(c) β-Bisabolol is achiral.
(d) β-Bisabolol has a meso stereoisomer.
(e) None of the above.

8. How many products are formed in the following reaction?

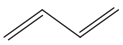


(a) 1 (b) 2 (c) 3 (d) 4 (e) 5

9. Which of the following is *true* when two isomeric alkenes are treated with H_2/Pt?

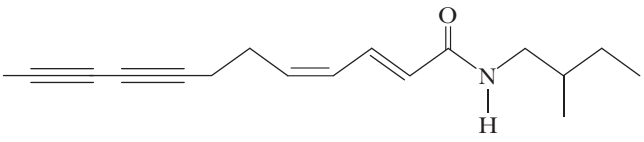
(a) The alkene that releases more energy in the reaction is the more stable alkene.
(b) The alkene with the lower melting point will release less energy in the reaction.
(c) The alkene with the lower boiling point will release less energy in the reaction.
(d) Both alkenes will release equal amounts of energy in the reaction.
(e) None of these statements is true.

10. An unknown compound reacts with two equivalents of H_2 catalyzed by Ni. The unknown also yields 5 CO_2 and 4 H_2O upon combustion. Which of the following could be the unknown compound?

(a) 
(b) 
(c) 
(d) 
(e) 

11. Provide structures for all possible compounds of formula C_5H_6 that would react quantitatively with $NaNH_2$.

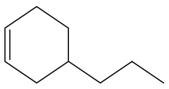
12. Answer the questions that follow regarding the following compound, which has been found in herbal preparations of *Echinacea*, the genus name for a variety of plants marketed for their immunostimulant properties.

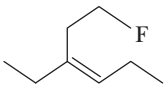


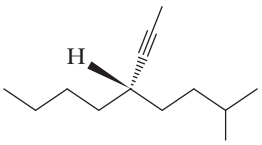
(a) How many stereoisomers exist for the compound shown?

(b) Would you expect the compound to be soluble in water?
(c) Is the molecule chiral?
(d) What would be the product formed in the reaction of this compound with an excess amount of H_2/Pt?

13. Provide IUPAC names for the following compounds.

(a) 

(b) 

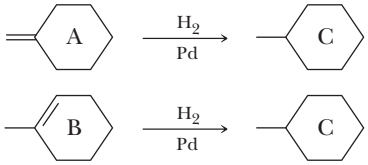
(c) 

14. Compound **A** is an optically inactive compound with a molecular formula of C_5H_8. Catalytic hydrogenation of **A** gives an optically inactive compound, **B** (C_5H_{10}), as the sole product. Furthermore, reaction of **A** with HBr results in a single compound, **C**, with a molecular formula of C_5H_9Br. Provide structures for **A**, **B**, and **C**.

15. An optically active compound, **A**, has a molecular formula of C_6H_{12}. Hydroboration–oxidation of **A** yields an optically active product, **B**, with a molecular formula of $C_6H_{14}O$. Catalytic hydrogenation of **A** yields an optically inactive product, **C**, with a molecular formula of C_6H_{14}. Propose structures for **A**, **B**, and **C**.

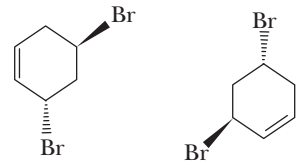
16. Based on the following hydrogenation data, which is more stable, the alkene **(A)** with the double bond outside of the ring or the alkene **(B)** with the double bond inside the ring? Use a reaction energy diagram to illustrate your point.

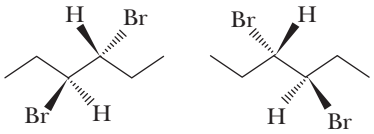
$$\Delta H = -23.84 \text{ kcal/mol}$$

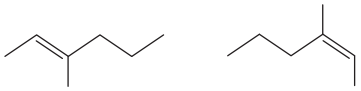


$$\Delta H = -20.69 \text{ kcal/mol}$$

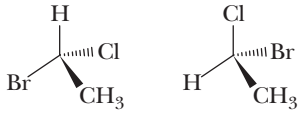
17. Explain whether the following pairs of compounds could be separated by resolution of enantiomers. If such separation is not possible, indicate so and explain your answer.

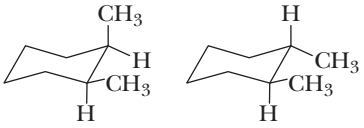
(a) 

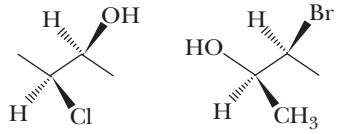
(b) 

(c) 

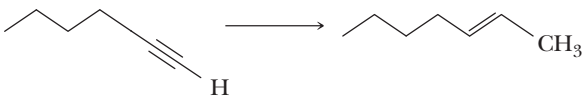
18. Predict whether solutions containing equal amounts of each pair of the structures shown would rotate the plane of polarized light.

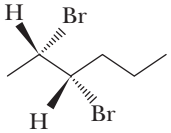
(a) 

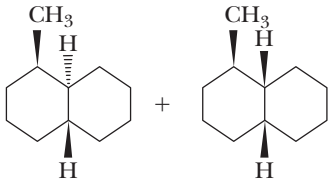
(b) 

(c) 

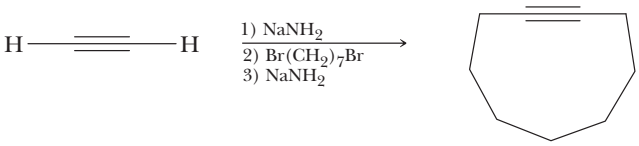
19. Complete the following chemical transformations.

(a) 

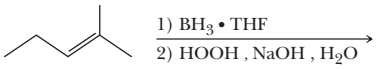
(b) Any alkyne ⟶  + enantiomer

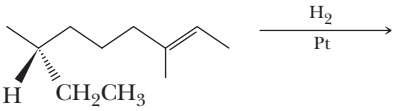
(c) Any alkene ⟶  +

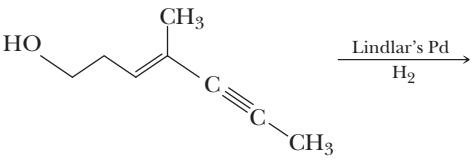
20. Provide a mechanism for the following series of reactions. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.

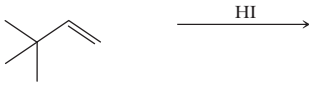


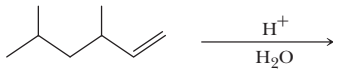
21. Predict the major product or products of each of the following reactions. Be sure to consider stereochemistry in your answers.

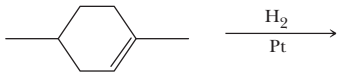
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

22. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.