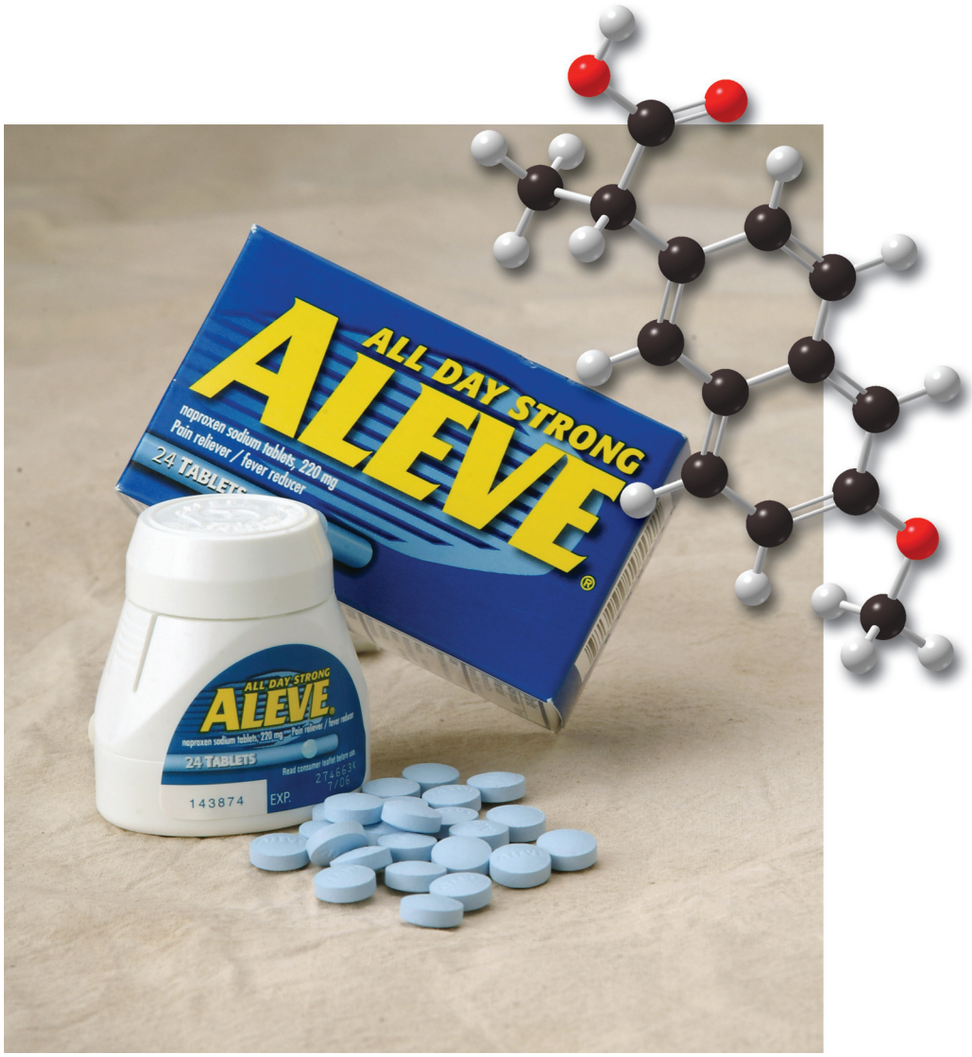
chapter

5 Stereochemistry



(*S*)-Naproxen is the active ingredient in the widely used pain relievers Naprosyn and Aleve. The three-dimensional orientation of two atoms at a single carbon in naproxen determines its therapeutic properties. Changing the position of these two atoms converts this anti-inflammatory agent into a liver toxin. In Chapter 5 we learn more about stereochemistry and how small structural differences can have a large effect on the properties of a molecule.

Are you left-handed or right-handed? If you're right-handed, you've probably spent little time thinking about your hand preference. If you're left-handed, though, you probably learned at an early age that many objects—like scissors and baseball gloves—"fit" for righties, but are "backwards" for lefties. **Hands, like many objects in the world around us, are mirror images that are *not* identical.**

In Chapter 5 we examine the "handedness" of molecules, and ask, "How important is the three-dimensional shape of a molecule?"

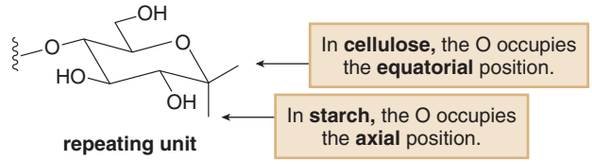
5.1 Starch and Cellulose

Recall from Chapter 4 that ***stereochemistry* is the three-dimensional structure of a molecule.** How important is stereochemistry? Two biomolecules—starch and cellulose—illustrate how apparently minute differences in structure can result in vastly different properties.

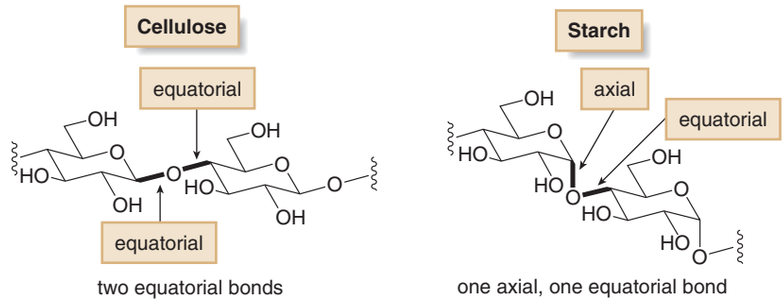
Starch and **cellulose** are two polymers that belong to the family of biomolecules called **carbohydrates** (Figure 5.1).

Starch is the main carbohydrate in the seeds and roots of plants. When we humans ingest wheat, rice, or potatoes, for example, we consume starch, which is then hydrolyzed to the simple sugar **glucose,** one of the compounds our bodies use for energy. **Cellulose,** nature's most abundant organic material, gives rigidity to tree trunks and plant stems. Wood, cotton, and flax are composed largely of cellulose. Complete hydrolysis of cellulose also forms glucose, but unlike starch, humans cannot metabolize cellulose to glucose. In other words, we can digest starch but not cellulose.

Cellulose and starch are both composed of the same repeating unit—a six-membered ring containing an oxygen atom and three OH groups—joined by an oxygen atom. They differ in the position of the O atom joining the rings together.



- **In cellulose, the O atom joins two rings using two equatorial bonds.**
- **In starch, the O atom joins two rings using one equatorial and one axial bond.**



Starch and cellulose are **isomers** because they are different compounds with the same molecular formula $(C_6H_{10}O_5)_n$. They are **stereoisomers** because only the three-dimensional arrangement of atoms is different.

How the six-membered rings are joined together has an enormous effect on the shape and properties of these carbohydrate molecules. Cellulose is composed of long chains held together by intermolecular hydrogen bonds, thus forming sheets that stack in an extensive

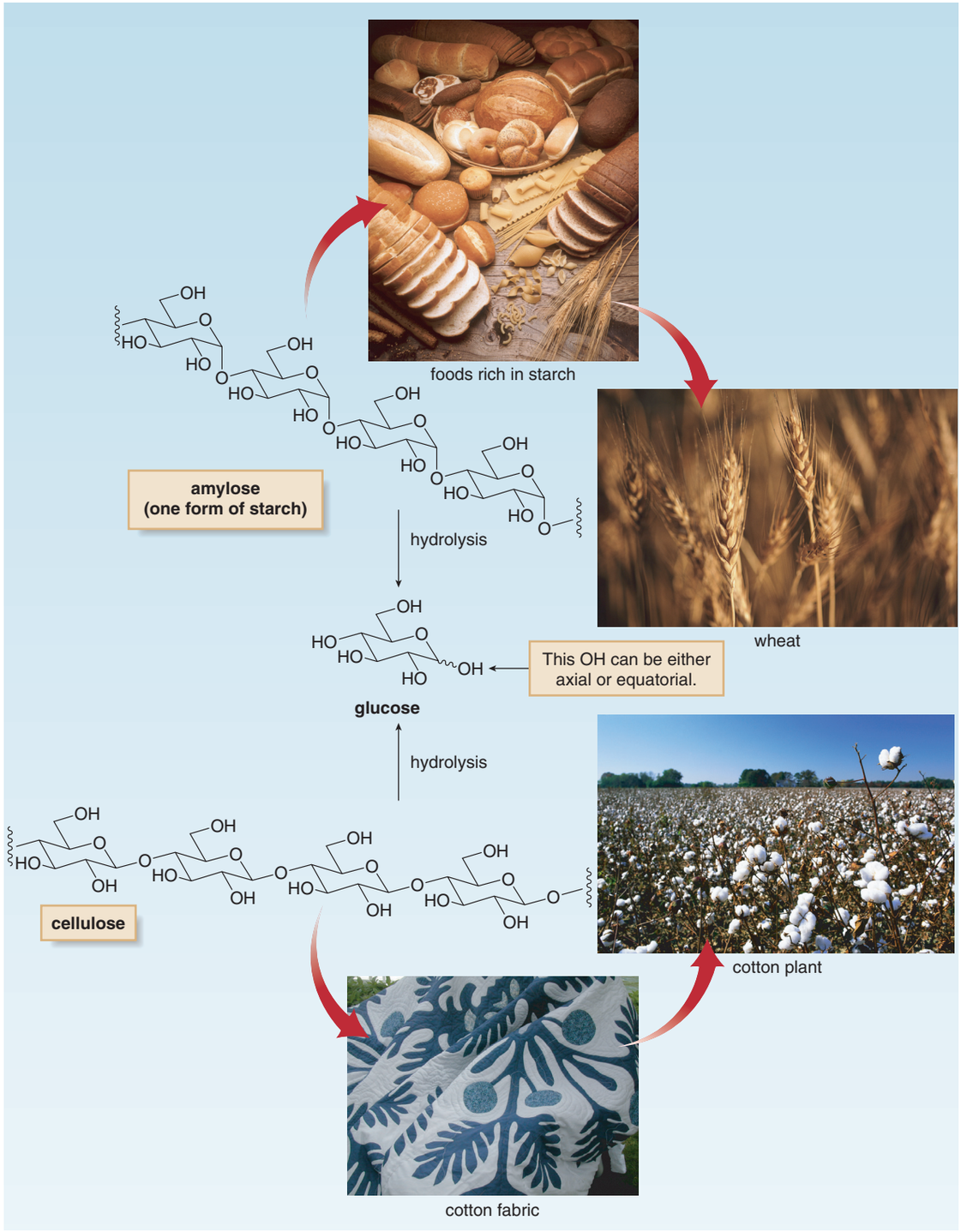
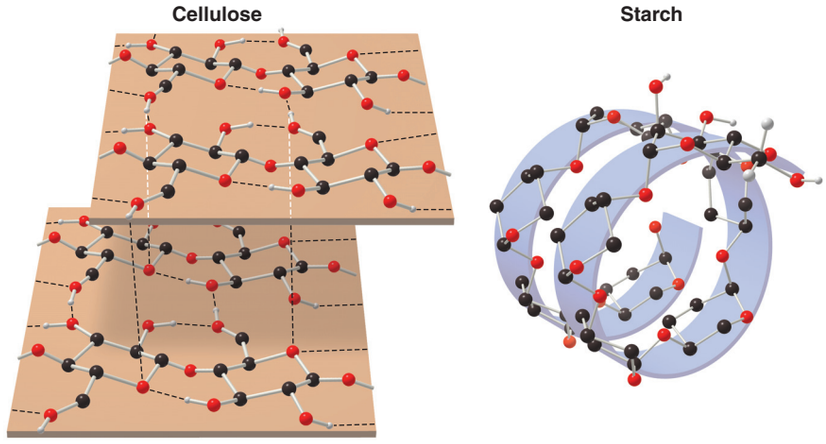


Figure 5.1
Starch and cellulose—Two common carbohydrates

three-dimensional network. The axial–equatorial ring junction in starch creates chains that fold into a helix (Figure 5.2). Moreover, the human digestive system contains the enzyme necessary to hydrolyze starch by cleaving its axial C−O bond, but not an enzyme to hydrolyze the equatorial C−O bond in cellulose.

Thus, an **apparently minor difference in the three-dimensional arrangement of atoms confers very different properties on starch and cellulose.**

Figure 5.2
Three-dimensional structure of cellulose and starch



Cellulose consists of an extensive three-dimensional network held together by hydrogen bonds.

The starch polymer is composed of chains that wind into a helix.

Problem 5.1 Cellulose is water insoluble, despite its many OH groups. Considering its three-dimensional structure, why do you think this is so?

5.2 The Two Major Classes of Isomers

Because an understanding of isomers is integral to the discussion of stereochemistry, let's begin with an overview of isomers.

- **Isomers are different compounds with the same molecular formula.**

There are two major classes of isomers: **constitutional isomers** and **stereoisomers.** ***Constitutional (or structural) isomers*** **differ in the way the atoms are connected to each other.** Constitutional isomers have:

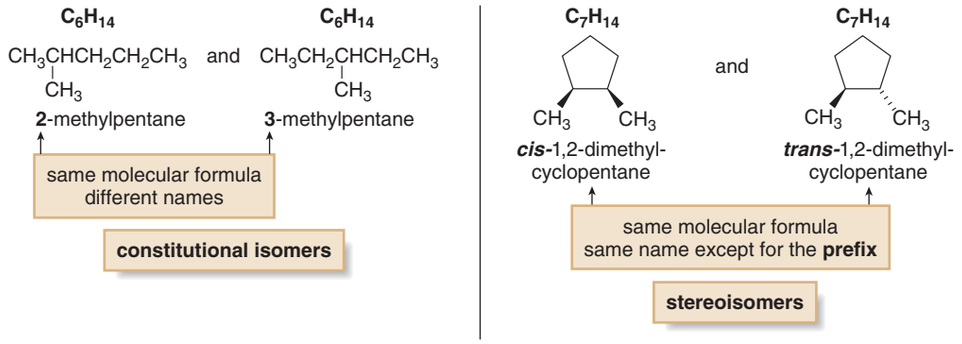
- different IUPAC names;
- the same or different functional groups;
- different physical properties, so they are separable by physical techniques such as distillation; and
- different chemical properties. They behave differently or give different products in chemical reactions.

Stereoisomers **differ *only* in the way atoms are oriented in space.** Stereoisomers have identical IUPAC names (except for a prefix like cis or trans). Because they differ only in the three-dimensional arrangement of atoms, stereoisomers always have the same functional group(s).

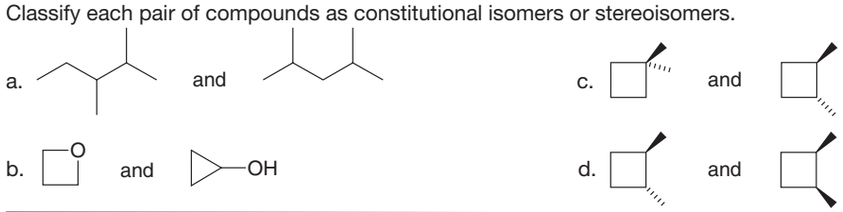
A particular three-dimensional arrangement is called a *configuration.* Thus, stereoisomers differ in configuration. The cis and trans isomers in Section 4.13B and the biomolecules starch and cellulose in Section 5.1 are two examples of stereoisomers.

Figure 5.3 illustrates examples of both types of isomers. Most of Chapter 5 relates to the types and properties of stereoisomers.

Figure 5.3
A comparison of constitutional isomers and stereoisomers



Problem 5.2 Classify each pair of compounds as constitutional isomers or stereoisomers.

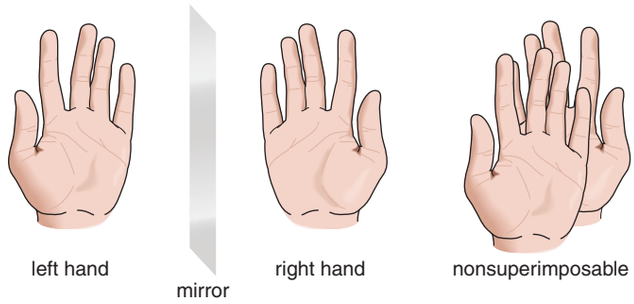


5.3 Looking Glass Chemistry—Chiral and Achiral Molecules

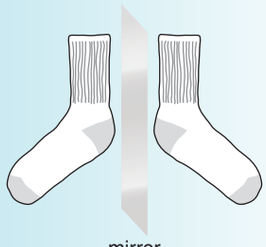
The dominance of right-handedness over left-handedness occurs in all races and cultures. Despite this fact, even identical twins can exhibit differences in hand preference. Pictured are Matthew (right-handed) and Zachary (left-handed), identical twin sons of the author.

Everything has a mirror image. What's important in chemistry is **whether a molecule is *identical* to or *different* from its mirror image.**

Some molecules are like hands. **Left and right hands are mirror images of each other, but they are *not* identical.** If you try to mentally place one hand inside the other hand, you can never superimpose either all the fingers, or the tops and palms. To *superimpose* an object on its mirror image means to align *all* parts of the object with its mirror image. With molecules, this means aligning all atoms and all bonds.



- A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral.*



Socks are **achiral:** they are mirror images that are superimposable.

Other molecules are like socks. **Two socks from a pair are mirror images that *are* superimposable.** One sock can fit inside another, aligning toes and heels, and tops and bottoms. A sock and its mirror image are *identical*.

- A molecule (or object) that *is* superimposable on its mirror image is said to be *achiral.*

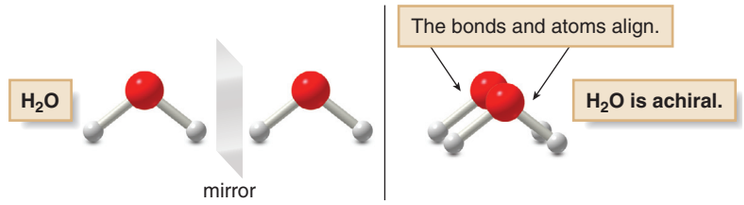
Let's determine whether three molecules—H_2O, CH_2BrCl, and CHBrClF—are superimposable on their mirror images; that is, **are H_2O, CH_2BrCl, and CHBrClF chiral or achiral?**

To test chirality:

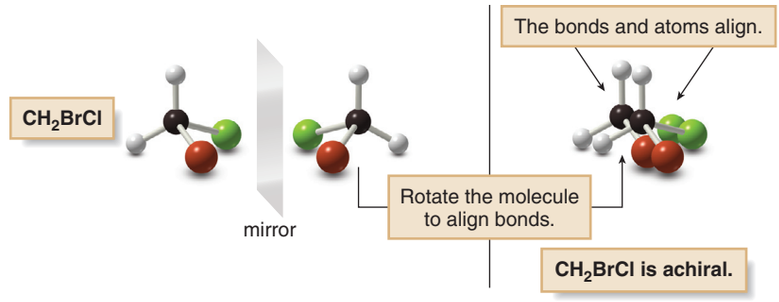
- Draw the molecule in three dimensions.
- Draw its mirror image.
- Try to align all bonds and atoms. To superimpose a molecule and its mirror image you can perform any rotation but **you cannot break bonds.**

The adjective ***chiral*** comes from the Greek *cheir*, meaning hand. Left and right hands are **chiral:** they are mirror images that do not superimpose on each other.

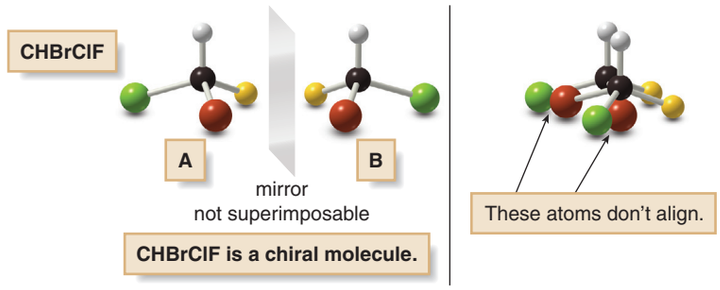
Following this procedure, H_2O and CH_2BrCl are both **achiral** molecules because each molecule is superimposable on its mirror image.



Few beginning students of organic chemistry can readily visualize whether a compound and its mirror image are superimposable by looking at drawings on a two-dimensional page. Molecular models can help a great deal in this process.



With CHBrClF, the result is different. The molecule (labeled **A**) and its mirror image (labeled **B**) are not superimposable. No matter how you rotate **A** and **B,** all the atoms never align. **CHBrClF is thus a chiral molecule,** and **A** and **B** are different compounds.



A and **B** are **stereoisomers** because they are isomers differing only in the three-dimensional arrangement of substituents. These stereoisomers are called **enantiomers.**

- *Enantiomers* are mirror images that are not superimposable.

Naming a carbon atom with four different groups is a topic that currently has no firm agreement among organic chemists. The IUPAC recommends the term *chirality center*, but the term has not gained wide acceptance among organic chemists since it was first suggested in 1996. Other terms in common use are chiral center, chiral carbon, asymmetric carbon, and stereogenic center, the term used in this text.

CHBrClF contains a carbon atom bonded to four different groups. **A carbon atom bonded to four different groups is called a tetrahedral *stereogenic center.*** Most chiral molecules contain one or more stereogenic centers.

The general term *stereogenic center* refers to any site in a molecule at which the interchange of two groups forms a stereoisomer. A **carbon atom with four different groups is a *tetrahedral* stereogenic center,** because the interchange of two groups converts one enantiomer into another. We will learn about another type of stereogenic center in Section 8.2B.

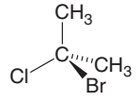
We have now learned two related but different concepts, and it is necessary to distinguish between them.

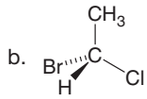
- A molecule that is not superimposable on its mirror image is a *chiral molecule.*
- A carbon atom bonded to four different groups is a *stereogenic center.*

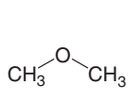
Molecules can contain zero, one, or more stereogenic centers.

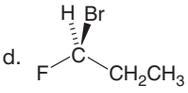
- **With no stereogenic centers, a molecule generally is not chiral.** H_2O and CH_2BrCl have *no* stereogenic centers and are *achiral* molecules. (There are a few exceptions to this generalization, as we will learn in Section 17.5.)
- **With one tetrahedral stereogenic center, a molecule is *always* chiral.** CHBrClF is a *chiral* molecule containing *one* stereogenic center.
- **With two or more stereogenic centers, a molecule *may* or *may not* be chiral,** as we will learn in Section 5.8.

Problem 5.3 Draw the mirror image of each compound. Label each molecule as chiral or achiral.

a. 

b. 

c. 

d. 

When trying to distinguish between chiral and achiral compounds, keep in mind the following:

- **A *plane of symmetry* is a mirror plane that cuts a molecule in half, so that one half of the molecule is a reflection of the other half.**

- **Achiral molecules usually contain a plane of symmetry but chiral molecules do not.**

The achiral molecule CH_2BrCl has a plane of symmetry, but the chiral molecule CHBrClF does not.

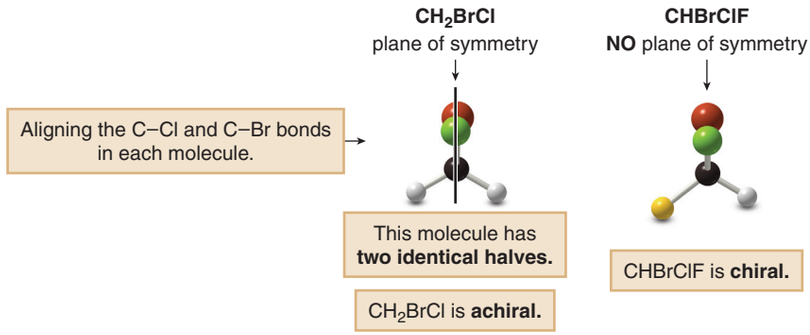
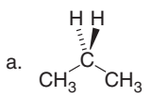
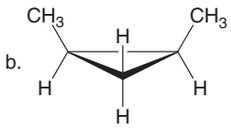
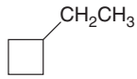


Figure 5.4 summarizes the main facts about chirality we have learned thus far.

Problem 5.4 Draw in a plane of symmetry for each molecule.

a. 

b. 

c. 

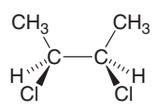
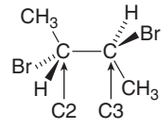
d. 

Figure 5.4
Summary: The basic principles of chirality

- Everything has a mirror image. The fundamental question is whether a molecule and its mirror image are superimposable.
- If a molecule and its mirror image are *not* superimposable, the molecule and its mirror image are *chiral.*
- The terms *stereogenic center* and *chiral molecule* are related but distinct. In general, a chiral molecule must have one or more stereogenic centers.
- The presence of a *plane of symmetry* makes a molecule achiral.

Problem 5.5 A molecule is achiral if it has a plane of symmetry in *any* conformation. The given conformation of 2,3-dibromobutane does not have a plane of symmetry, but rotation around the C2 – C3 bond forms a conformation that does have a plane of symmetry. Draw this conformation.



The snail *Liguus virgineus* possesses a chiral, right-handed helical shell.

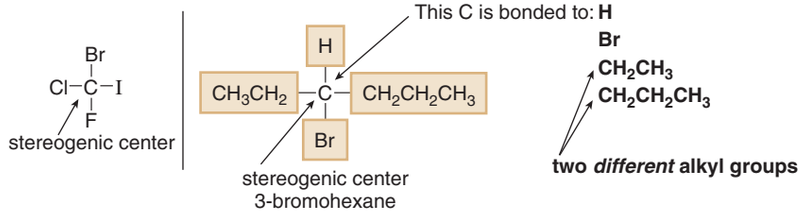
Stereochemistry may seem esoteric, but chirality pervades our very existence. On a molecular level, many biomolecules fundamental to life are chiral. On a macroscopic level, many naturally occurring objects possess handedness. Examples include chiral helical seashells shaped like right-handed screws, and plants such as honeysuckle that wind in a chiral left-handed helix. The human body is chiral, and hands, feet, and ears are not superimposable.

5.4 Stereogenic Centers

A necessary skill in the study of stereochemistry is the ability to locate and draw tetrahedral stereogenic centers.

5.4A Stereogenic Centers on Carbon Atoms That Are Not Part of a Ring

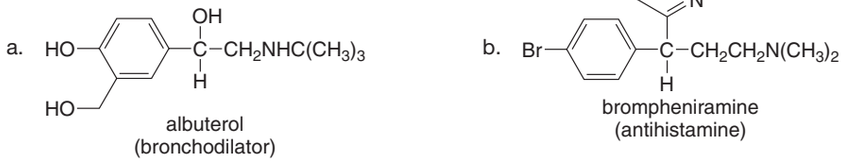
Recall from Section 5.3 that any carbon atom bonded to four different groups is a tetrahedral stereogenic center. To locate a stereogenic center, examine each *tetrahedral* carbon atom in a molecule, and look at the four ***groups***—not the four *atoms*—bonded to it. CBrClFI has one stereogenic center because its central carbon atom is bonded to four different elements. 3-Bromohexane also has one stereogenic center because one carbon is bonded to H, Br, CH_2CH_3, and $CH_2CH_2CH_3$. We consider all atoms in a group as a *whole unit*, not just the atom directly bonded to the carbon in question.



Always omit from consideration all C atoms that can't be tetrahedral stereogenic centers. These include:

- CH_2 and CH_3 groups (more than one H bonded to C)
- any *sp* or sp^2 hybridized C (less than four groups around C)

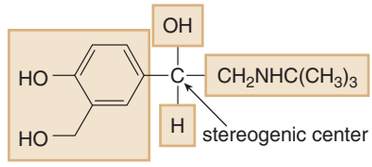
Sample Problem 5.1 Locate the stereogenic center in each drug.

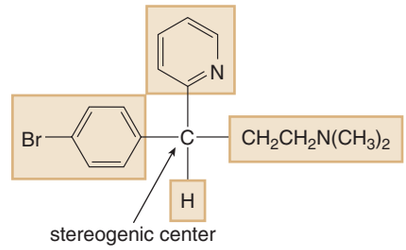


Heteroatoms surrounded by four different groups are also stereogenic centers. Stereogenic N atoms are discussed in Chapter 25.

Solution

Omit all CH_2 and CH_3 groups and all doubly bonded (sp^2 hybridized) C's. In albuterol, one C has three CH_3 groups bonded to it, so it can be eliminated as well. This leaves one C in each molecule with four different groups bonded to it.

a. 

b. 

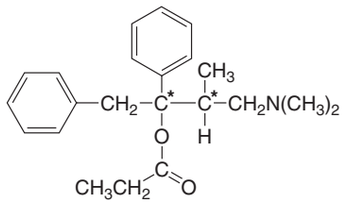
Problem 5.6

Locate any stereogenic center in the given molecules. (Some compounds contain no stereogenic centers.)

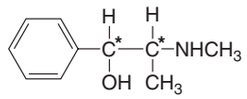
a. $CH_3CH_2CH(Cl)CH_2CH_3$
b. $(CH_3)_3CH$
c. $CH_3CH(OH)CH{=}CH_2$
d. $CH_3CH_2CH_2OH$
e. $(CH_3)_2CHCH_2CH_2CH(CH_3)CH_2CH_3$
f. $CH_3CH_2CH(CH_3)CH_2CH_2CH_3$

Ephedrine is isolated from ma huang, an herb used to treat respiratory ailments in traditional Chinese medicine. Once a popular drug to promote weight loss and enhance athletic performance, ephedrine has now been linked to episodes of sudden death, heart attack, and stroke.

Larger organic molecules can have two, three, or even hundreds of stereogenic centers. **Propoxyphene** and **ephedrine** each contain two stereogenic centers, and **fructose,** a simple carbohydrate, has three.

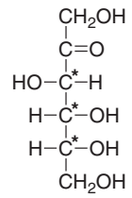


propoxyphene
Trade name: Darvon
(analgesic)



ephedrine
(bronchodilator, decongestant)

[* = stereogenic center]



fructose
(a simple sugar)

Problem 5.7

Locate the stereogenic centers in each molecule. Compounds may have one or more stereogenic centers.

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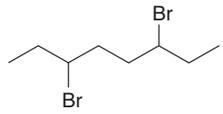
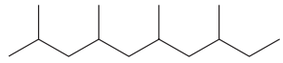
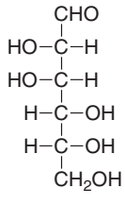
b. $(CH_3)_2CHCH_2CH(NH_2)COOH$
c. 

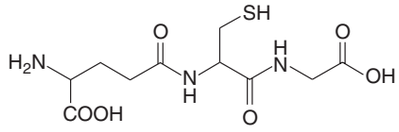
d. 

Problem 5.8

Locate the stereogenic centers in each biomolecule.

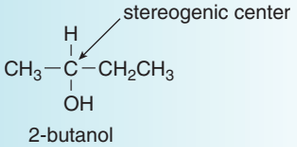
a. 

mannose
(a simple carbohydrate)

b. 

glutathione
(naturally occurring antioxidant)

5.4B Drawing a Pair of Enantiomers

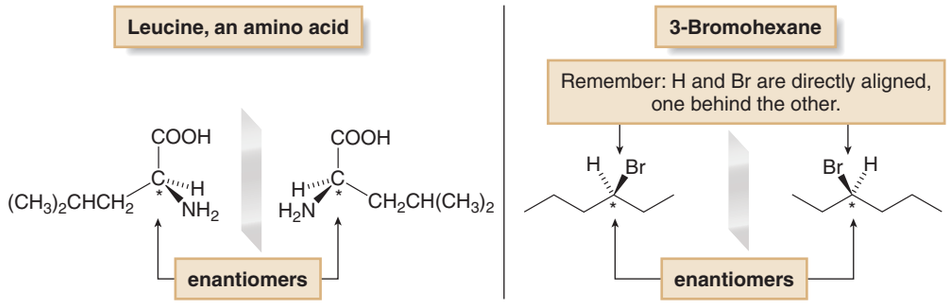


2-butanol

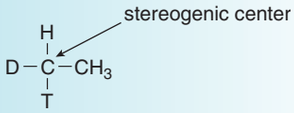
- **Any molecule with one tetrahedral stereogenic center is a chiral compound and exists as a pair of enantiomers.**

2-Butanol, for example, has one stereogenic center. To draw both enantiomers, use the typical convention for depicting a tetrahedron: **place two bonds in the plane, one in front of the plane**

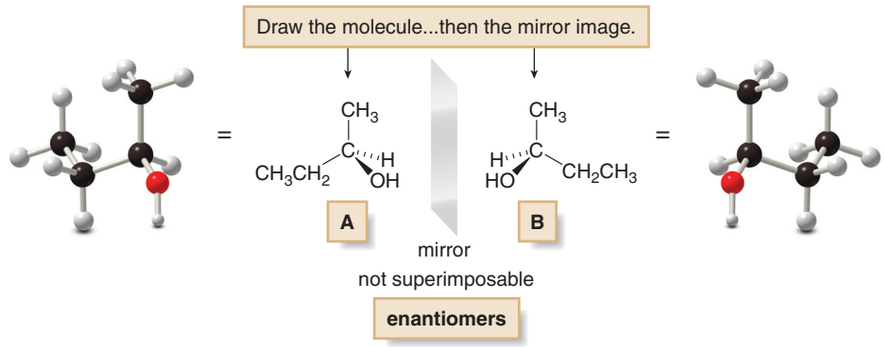
Figure 5.5
Three-dimensional representations for pairs of enantiomers



The smallest chiral hydrocarbon ever prepared in the laboratory has one stereogenic center substituted by the three isotopes of hydrogen [hydrogen (H), deuterium (D), and tritium (T)] and a methyl group (*Journal of the American Chemical Society*, **1997,** *119*, 1818–1827).



on a wedge, and one behind the plane on a dash. Then, to form the first enantiomer **A,** arbitrarily place the four groups—H, OH, CH_3, and CH_2CH_3—on any bond to the stereogenic center.



Then, draw a mirror plane and arrange the substituents in the mirror image so that they are a reflection of the groups in the first molecule, forming **B.** No matter how **A** and **B** are rotated, it is impossible to align all of their atoms. Because **A** and **B** are mirror images and not superimposable, **A** and **B** are a pair of **enantiomers.** Two other pairs of enantiomers are drawn in Figure 5.5.

Problem 5.9 Locate the stereogenic center in each compound and draw both enantiomers.

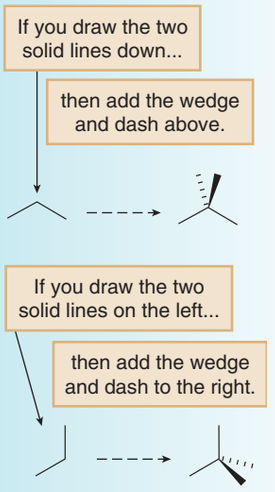
a. $CH_3CH(Cl)CH_2CH_3$ b. $CH_3CH_2CH(OH)CH_2OH$ c. $CH_3SCH_2CH_2CH(NH_2)COOH$

5.5 Stereogenic Centers in Cyclic Compounds

Stereogenic centers may also occur at carbon atoms that are part of a ring. To find stereogenic centers on ring carbons always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups, as usual. Each ring carbon is bonded to two other atoms in the ring, as well as two substituents attached to the ring. When the two substituents on the ring are *different,* we must compare the ring atoms equidistant from the atom in question.

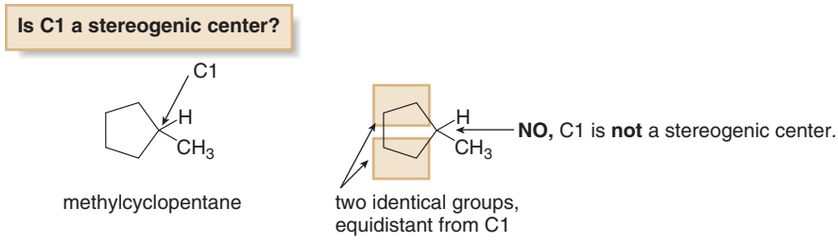
Does methylcyclopentane have a stereogenic center? All of the carbon atoms are bonded to two or three hydrogen atoms except for C1, the ring carbon bonded to the methyl group. Next, compare the ring atoms and bonds on both sides equidistant from C1, and continue until a point of difference is reached, or until both sides meet, either at an atom or in the middle of a bond. In this case, there is no point of difference on either side, so C1 is bonded to identical alkyl groups that happen to be part of a ring. **C1 is therefore *not* a stereogenic center.**

In drawing a tetrahedron using solid lines, wedges, and dashes, always draw the two solid lines first; then draw the wedge and the dash on the *opposite side* of the solid lines.

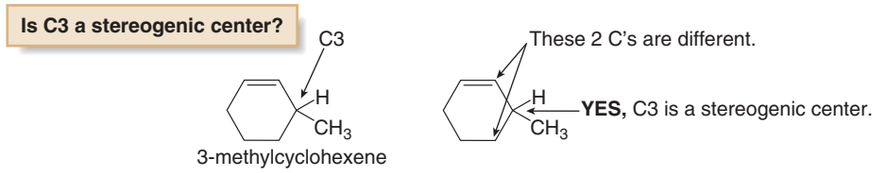


Two enantiomers are *different* compounds. To convert one enantiomer to another you must **switch the position of two atoms.** This amounts to breaking bonds.

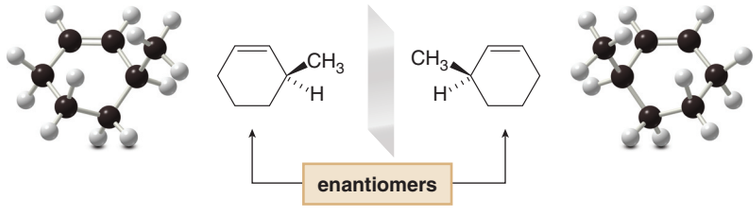
Although it is a potent teratogen (a substance that causes fetal abnormalities), thalidomide exhibits several beneficial effects. It is now prescribed under strict control for the treatment of Hansen's disease (leprosy) and certain forms of cancer.



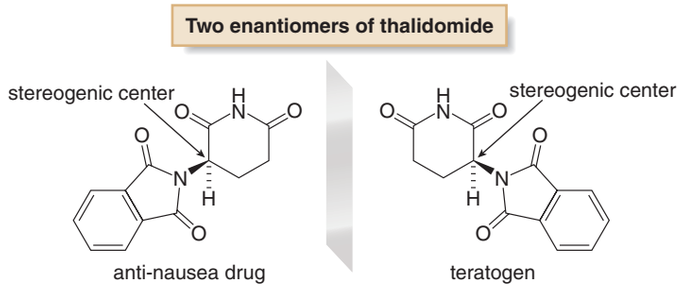
With 3-methylcyclohexene, the result is different. All carbon atoms are bonded to two or three hydrogen atoms or are sp^2 hybridized except for C3, the ring carbon bonded to the methyl group. In this case, the atoms equidistant from C3 are different, so C3 is bonded to *different* alkyl groups in the ring. **C3 is therefore bonded to four different groups, making it a stereogenic center.**



Because 3-methylcyclohexene has one tetrahedral stereogenic center it is a chiral compound and exists as a pair of enantiomers.



Many biologically active compounds contain one or more stereogenic centers on ring carbons. For example, **thalidomide,** which contains one such stereogenic center, was used as a popular sedative and anti-nausea drug for pregnant women in Europe and Great Britain from 1959–1962.

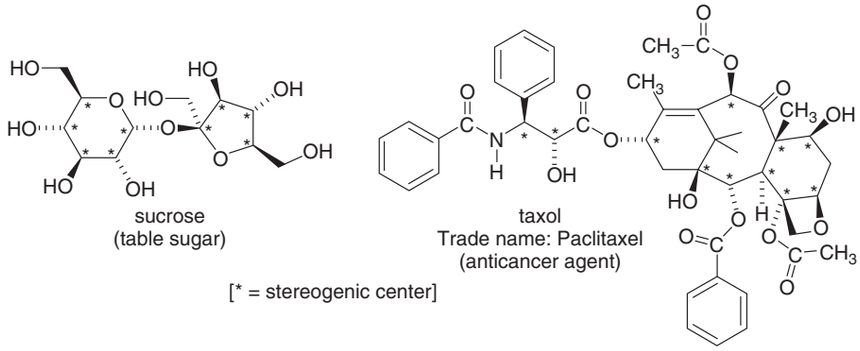


Unfortunately thalidomide was sold as a mixture of its two enantiomers, and each of these stereoisomers has a different biological activity. This is a property not uncommon in chiral drugs, as we will see in Section 5.13. Although one enantiomer had the desired therapeutic effect, the other enantiomer was responsible for thousands of catastrophic birth defects in children born to women who took the drug during pregnancy. Thalidomide was never approved for use in the United States due to the diligence of Frances Oldham Kelsey, a medical reviewing officer for the Food and Drug Administration, who insisted that the safety data on thalidomide were inadequate.

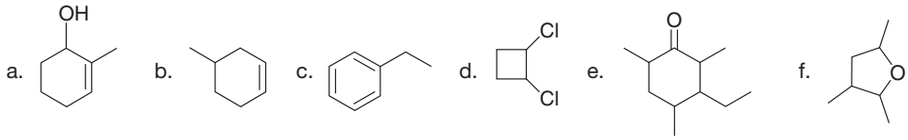
Sucrose and **taxol** are two useful molecules with several stereogenic centers at ring carbons. Identify the stereogenic centers in these more complicated compounds in exactly the same way,

looking at one carbon at a time. **Sucrose,** with nine stereogenic centers on two rings, is the carbohydrate used as table sugar. **Taxol,** with 11 stereogenic centers, is an anticancer agent active against ovarian, breast, and some lung tumors.

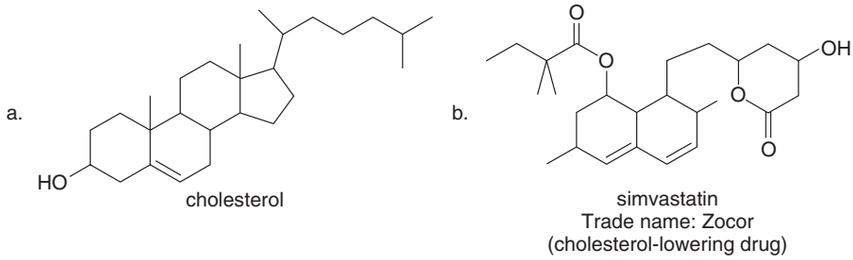
Initial studies with taxol were carried out with material isolated from the bark of the Pacific yew tree, but stripping the bark killed these magnificent trees. Taxol can now be synthesized in four steps from a compound isolated from the needles of the common English yew tree.



Problem 5.10 Locate the stereogenic centers in each compound. A molecule may have zero, one, or more stereogenic centers.



Problem 5.11 Locate the stereogenic centers in each compound.



5.6 Labeling Stereogenic Centers with *R* or *S*

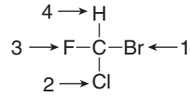
Naming enantiomers with the prefixes *R* or *S* is called the Cahn–Ingold–Prelog system after the three chemists who devised it.

Because enantiomers are two different compounds, we need to distinguish them by name. This is done by adding the prefix *R* or *S* to the IUPAC name of the enantiomer. To designate an enantiomer as *R* or *S*, first **assign a priority** (1, 2, 3, or 4) to each group bonded to the stereogenic center, and then use these priorities to label one enantiomer *R* and one *S*.

Rules Needed to Assign Priority

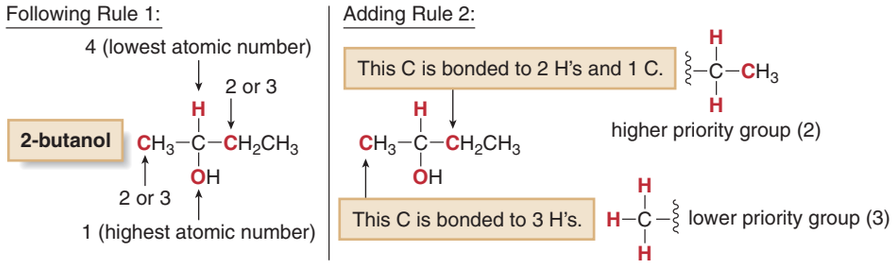
Rule 1 **Assign priorities (1, 2, 3, or 4) to the atoms directly bonded to the stereogenic center in order of decreasing atomic number. The atom of *highest* atomic number gets the *highest* priority (1).**

- In CHBrClF, priorities are assigned as follows: Br (1, highest) → Cl (2) → F (3)→ H (4, lowest). In many molecules the lowest priority group will be H.



Rule 2 If two atoms on a stereogenic center are the ***same,*** assign priority based on the atomic number of the atoms bonded to these atoms. ***One*** atom of higher atomic number determines a higher priority.

- With 2-butanol, the O atom gets highest priority (1) and H gets lowest priority (4) using Rule 1. To assign priority (either 2 or 3) to the two C atoms, look at what atoms (other than the stereogenic center) are bonded to each C.



- The order of priority of groups in 2-butanol is: $-OH$ **(1),** $-CH_2CH_3$ **(2)** $-CH_3$ **(3),** and $-H$ **(4).**
- If priority still cannot be assigned, continue along a chain until a point of difference is reached.

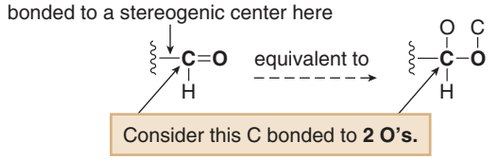
Rule 3 If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing *mass* number.

- In comparing the three isotopes of hydrogen, the order of priorities is:

	Mass number	Priority
T (tritium)	3 (1 proton + 2 neutrons)	1
D (deuterium)	2 (1 proton + 1 neutron)	2
H (hydrogen)	1 (1 proton)	3

Rule 4 To assign a priority to an atom that is part of a multiple bond, treat a multiply bonded atom as an equivalent number of singly bonded atoms.

- For example, the C of a C=O is considered to be bonded to two O atoms.



- Other common multiple bonds are drawn below.

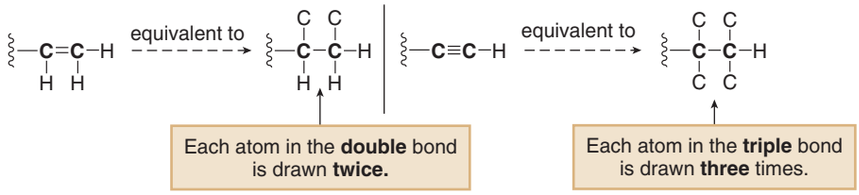
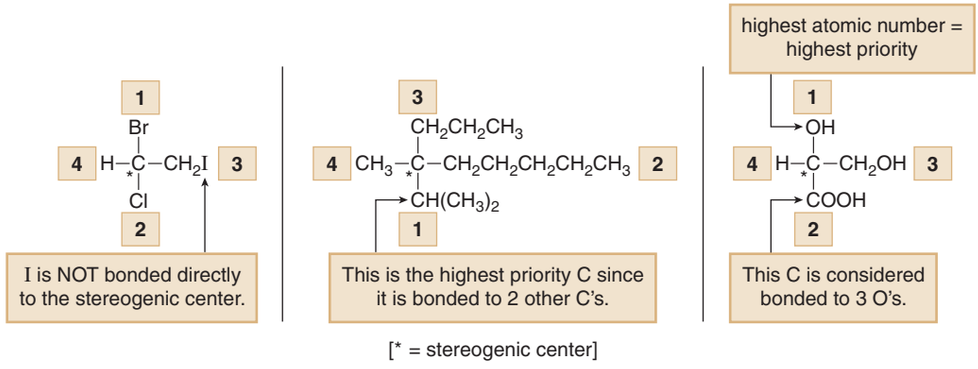


Figure 5.6 gives examples of priorities assigned to stereogenic centers.

Figure 5.6
Examples of assigning priorities to stereogenic centers



Problem 5.12 Which group in each pair is assigned the *higher* priority?

a. $-CH_3$, $-CH_2CH_3$
b. $-I$, $-Br$
c. $-H$, $-D$
d. $-CH_2Br$, $-CH_2CH_2Br$
e. $-CH_2CH_2Cl$, $-CH_2CH(CH_3)_2$
f. $-CH_2OH$, $-CHO$

Problem 5.13 Rank the following groups in order of *decreasing* priority.

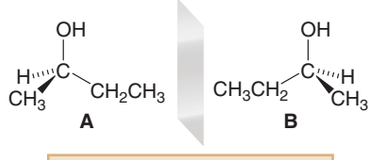
a. $-COOH$, $-H$, $-NH_2$, $-OH$
b. $-H$, $-CH_3$, $-Cl$, $-CH_2Cl$
c. $-CH_2CH_3$, $-CH_3$, $-H$, $-CH(CH_3)_2$
d. $-CH{=}CH_2$, $-CH_3$, $-C{\equiv}CH$, $-H$

R is derived from the Latin word *rectus* meaning "right" and *S* is from the Latin word *sinister* meaning "left."

Once priorities are assigned to the four groups around a stereogenic center, we can use three steps to designate the center as either *R* or *S*.

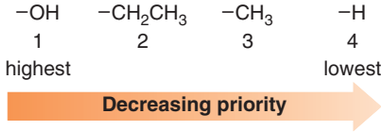
How To Assign *R* or *S* to a Stereogenic Center

Example **Label each enantiomer as *R* or *S*.**



Step [1] **Assign priorities from 1 to 4 to each group bonded to the stereogenic center.**

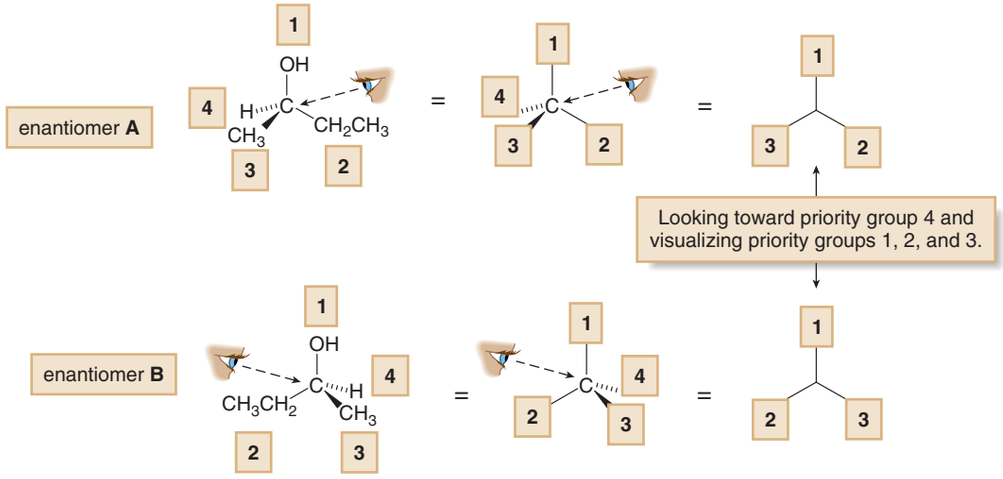
- The priorities for the four groups around the stereogenic center in 2-butanol were given in Rule 2, on page 172.



How To, continued . . .

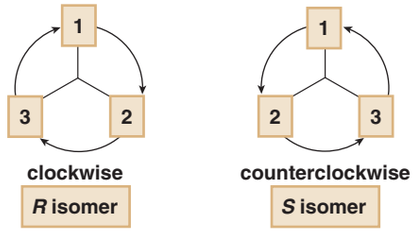
Step [2] **Orient the molecule with the lowest priority group (4) *back* (on a *dash*), and visualize the relative positions of the remaining three groups (priorities 1, 2, and 3).**

- For each enantiomer of 2-butanol, look toward the lowest priority group, drawn behind the plane, down the C – H bond.



Step [3] **Trace a circle from priority group 1 → 2 → 3.**

- If tracing the circle goes in the **clockwise** direction—to the right from the noon position—the isomer is named ***R*.**
- If tracing the circle goes in the **counterclockwise** direction—to the left from the noon position—the isomer is named ***S*.**



- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:

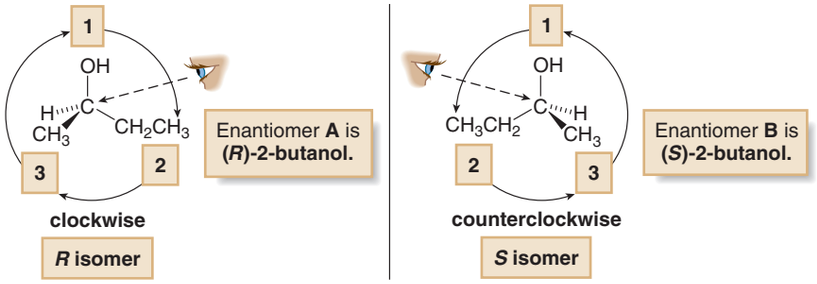
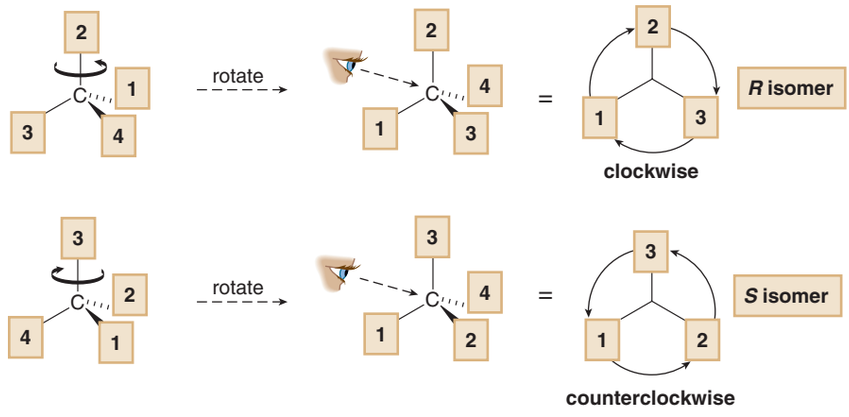
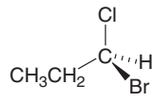


Figure 5.7
Examples: Orienting the lowest priority group in back



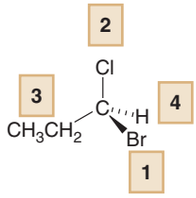
Sample Problem 5.2

Label the following compound as *R* or *S*.

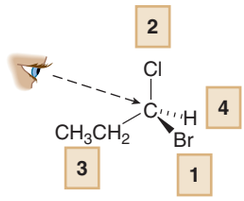


Solution

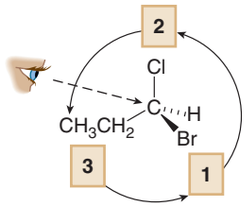
[1] Assign priorities.



[2] Look down the C–H bond, toward the lowest priority group (H).



[3] Trace a circle, 1→2→3



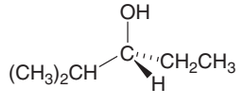
counterclockwise

Answer: ***S*** isomer

How do you assign *R* or *S* to a molecule when the lowest priority group is not oriented toward the back, on a dashed line? You could rotate and flip the molecule until the lowest priority group is in the back, as shown in Figure 5.7; then follow the stepwise procedure for assigning the configuration. Or, if manipulating and visualizing molecules in three dimensions is difficult for you, try the procedure suggested in Sample Problem 5.3.

Sample Problem 5.3

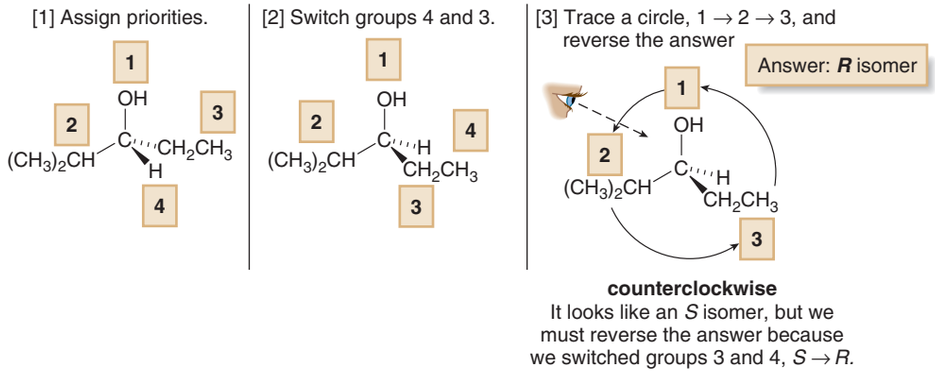
Label the following compound as *R* or *S*.



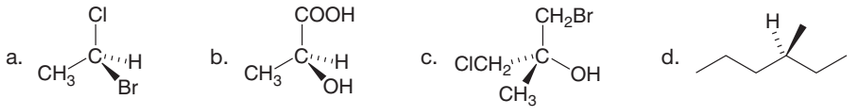
Solution

In this problem, the lowest priority group (H) is oriented in **front** of, not behind, the page. To assign *R* or *S* in this case:

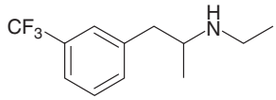
- **Switch** the position of the lowest priority group (H) with the group located behind the page ($-CH_2CH_3$).
- Determine *R* or *S* in the usual manner.
- **Reverse the answer.** Because we switched the position of two groups on the stereogenic center to begin with, and there are only two possibilities, the answer is **opposite** to the correct answer.



Problem 5.14 Label each compound as *R* or *S*.



Problem 5.15 Draw both enantiomers of fenfluramine, one component of the appetite suppressant Fen–Phen. The *S* enantiomer was sold independently under the name dexfenfluramine. Which enantiomer is dexfenfluramine? (Fen–Phen was withdrawn from the market in 1997, after it was shown to damage heart valves in some patients.)



fenfluramine

5.7 Diastereomers

We have now seen many examples of compounds containing one tetrahedral stereogenic center. The situation is more complex for compounds with two stereogenic centers, because more stereoisomers are possible. Moreover, a molecule with two stereogenic centers ***may* or *may not* be chiral.**

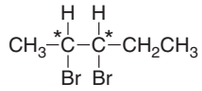
- For *n* stereogenic centers, the maximum number of stereoisomers is 2^n.

- When $n = 1$, $2^1 = 2$. With one stereogenic center there are always two stereoisomers and they are **enantiomers.**
- When $n = 2$, $2^2 = 4$. With two stereogenic centers, the maximum number of stereoisomers is four, although sometimes there are *fewer* than four.

Problem 5.16 What is the maximum number of stereoisomers possible for a compound with: (a) three stereogenic centers; (b) eight stereogenic centers?

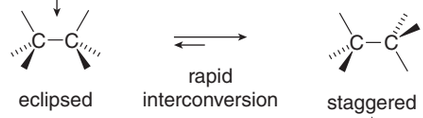
Let's illustrate a stepwise procedure for finding all possible stereoisomers using 2,3-dibromopentane.

In testing to see if one compound is superimposable on another, rotate atoms and flip the entire molecule, but **do not break any bonds.**



2,3-dibromopentane
[* = stereogenic center]
maximum number of stereoisomers = **4**

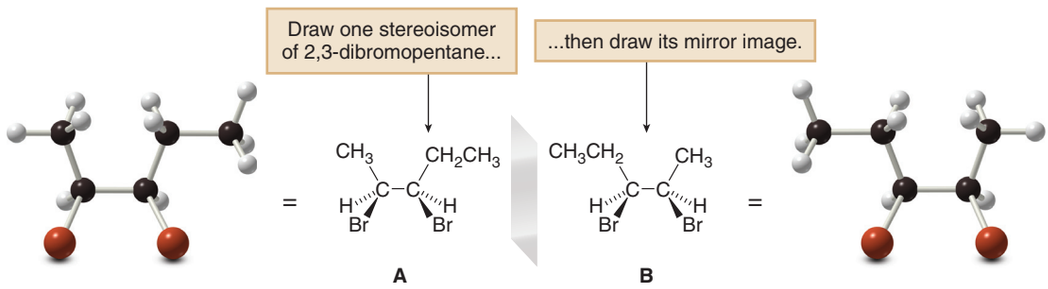
Add substituents around stereogenic centers with the bonds **eclipsed,** for easier visualization.



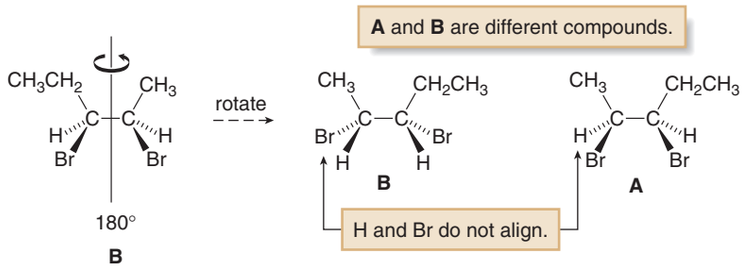
Don't forget, however, that the staggered arrangement is more stable.

How To Find and Draw All Possible Stereoisomers for a Compound with Two Stereogenic Centers

Step [1] **Draw one stereoisomer by arbitrarily arranging substituents around the stereogenic centers. Then draw its mirror image.**



- Arbitrarily add the H, Br, CH_3, and CH_2CH_3 groups to the stereogenic centers, forming **A.** Then draw the mirror image **(B)** so that substituents in **B** are a reflection of the substituents in **A.**
- Determine whether **A** and **B** are superimposable by flipping or rotating one molecule to see if all the atoms align.
- If you have drawn the compound and the mirror image in the described manner, you only have to do two operations to see if the atoms align. Place **B** directly on top of **A** (either in your mind or use models); and, rotate **B** 180° and place it on top of **A** to see if the atoms align.

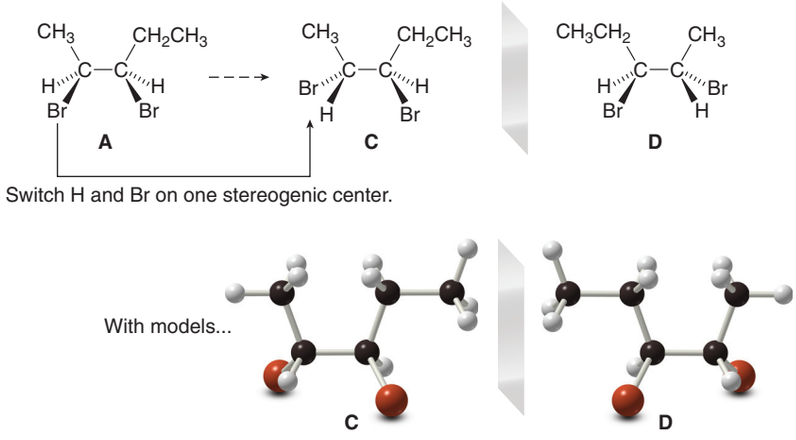


- In this case, the atoms of **A** and **B** do not align, making **A** and **B** nonsuperimposable mirror images—**enantiomers. A** and **B** are two of the four possible stereoisomers for 2,3-dibromopentane.

Step [2] **Draw a third possible stereoisomer by switching the positions of any two groups on *one* stereogenic center only. Then draw its mirror image.**

- Switching the positions of H and Br (or any two groups) on one stereogenic center of either **A** or **B** forms a new stereoisomer (labeled **C** in this example), which is different from both **A** and **B.** Then draw the mirror image of **C,** labeled **D. C** and **D** are nonsuperimposable mirror images—**enantiomers.** We have now drawn four stereoisomers for 2,3-dibromopentane, the maximum number possible.

How To, continued . . .



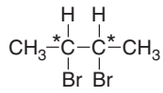
There are only two types of stereoisomers: ***Enantiomers*** **are stereoisomers that *are* mirror images.** ***Diastereomers*** **are stereoisomers that are *not* mirror images.**

There are four stereoisomers for 2,3-dibromopentane: enantiomers **A** and **B,** and enantiomers **C** and **D.** What is the relationship between two stereoisomers like **A** and **C? A** and **C** represent the second broad class of stereoisomers, called **diastereomers.** ***Diastereomers*** **are stereoisomers that are not mirror images of each other. A** and **B** are diastereomers of **C** and **D,** and vice versa. Figure 5.8 summarizes the relationships between the stereoisomers of 2,3-dibromopentane.

Problem 5.17 Label the two stereogenic centers in each compound and draw all possible stereoisomers: (a) $CH_3CH_2CH(Cl)CH(OH)CH_2CH_3$; (b) $CH_3CH(Br)CH_2CH(Cl)CH_3$.

5.8 Meso Compounds

Whereas 2,3-dibromopentane has two stereogenic centers and the maximum of four stereoisomers, **2,3-dibromobutane** has two stereogenic centers but fewer than the maximum number of stereoisomers.

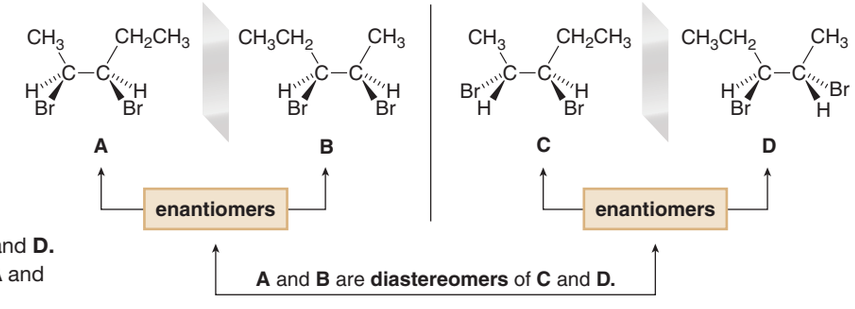


2,3-dibromobutane
[* = stereogenic center]

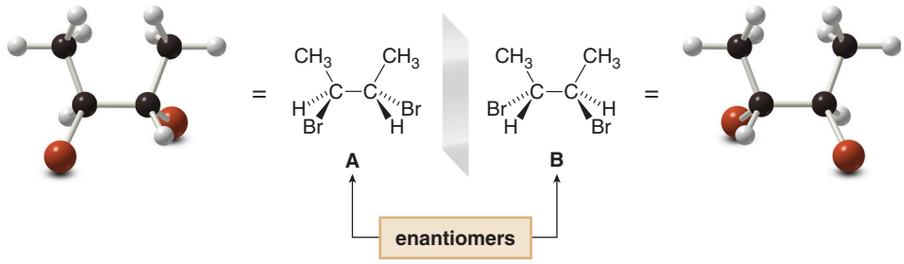
With two stereogenic centers, the **maximum** number of stereoisomers = **4.**

To find and draw all the stereoisomers of 2,3-dibromobutane, follow the same stepwise procedure outlined in Section 5.7. Arbitrarily add the H, Br, and CH_3 groups to the stereogenic centers, forming one stereoisomer **A,** and then draw its mirror image **B. A** and **B** are nonsuperimposable mirror images—**enantiomers.**

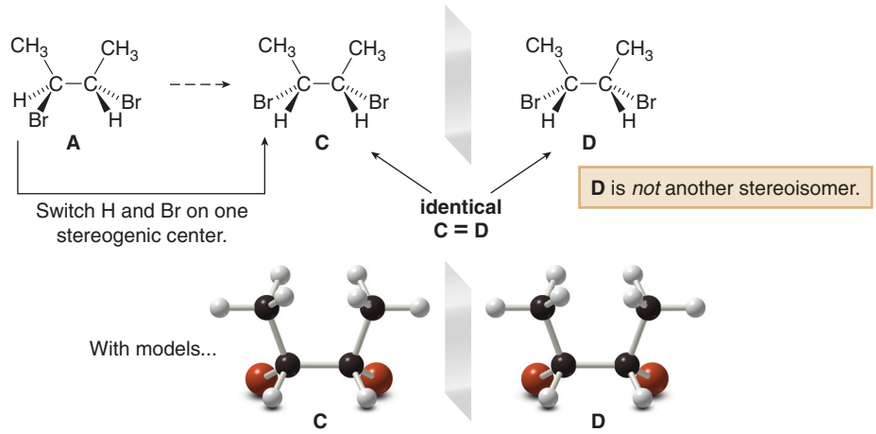
Figure 5.8
Summary: The four stereoisomers of 2,3-dibromopentane



- Pairs of enantiomers: **A** and **B; C** and **D.**
- Pairs of diastereomers: **A** and **C; A** and **D; B** and **C; B** and **D.**



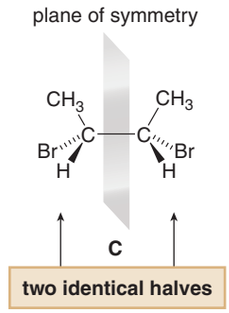
To find the other two stereoisomers (if they exist), switch the position of two groups on *one* stereogenic center of *one* enantiomer only. In this case, switching the positions of H and Br on one stereogenic center of **A** forms **C,** which is different from both **A** and **B** and is thus a new stereoisomer.



However, the mirror image of **C,** labeled **D,** is superimposable on **C,** so **C** and **D** are identical. Thus, **C** is achiral, even though it has two stereogenic centers. **C** is a **meso compound.**

- A *meso compound* is an achiral compound that contains tetrahedral stereogenic centers.

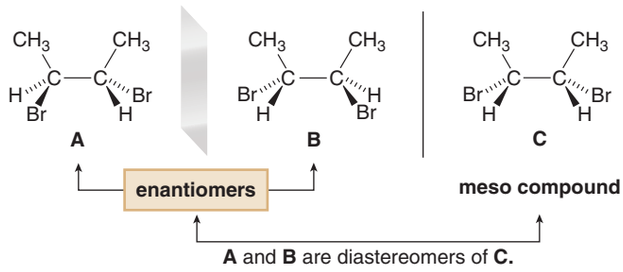
C contains a **plane of symmetry. Meso compounds generally have a plane of symmetry,** so they possess two identical halves.



Because one stereoisomer of 2,3-dibromobutane is superimposable on its mirror image, there are only three stereoisomers and not four, as summarized in Figure 5.9.

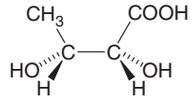
Figure 5.9
Summary: The three stereoisomers of 2,3-dibromobutane

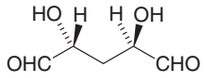
- Pair of enantiomers: **A** and **B.**
- Pairs of diastereomers: **A** and **C; B** and **C.**



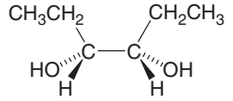
Problem 5.18 Draw all the possible stereoisomers for each compound and label pairs of enantiomers and diastereomers: (a) $CH_3CH(OH)CH(OH)CH_3$; (b) $CH_3CH(OH)CH(Cl)CH_3$.

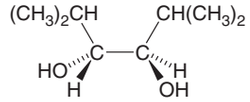
Problem 5.19 Draw the enantiomer and one diastereomer for each compound.

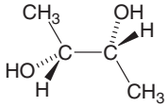
a. 

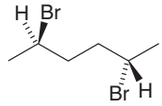
b. 

Problem 5.20 Which compounds are meso compounds?

a. 

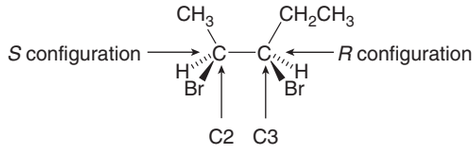
b. 

c. 

d. 

5.9 *R* and *S* Assignments in Compounds with Two or More Stereogenic Centers

When a compound has more than one stereogenic center, the *R* and *S* configuration must be assigned to each of them. In the stereoisomer of 2,3-dibromopentane drawn here, C2 has the *S* configuration and C3 has the *R*, so the complete name of the compound is (2*S*,3*R*)-2,3-dibromopentane.



one stereoisomer of 2,3-dibromopentane

Complete name:
(2*S*,3*R*)-2,3-dibromopentane

R,S configurations can be used to determine whether two compounds are identical, enantiomers, or diastereomers.

- **Identical compounds have the *same R,S* designations at every tetrahedral stereogenic center.**
- **Enantiomers have exactly *opposite R,S* designations.**
- **Diastereomers have the *same R,S* designation for at least one stereogenic center and the *opposite* for at least one of the other stereogenic centers.**

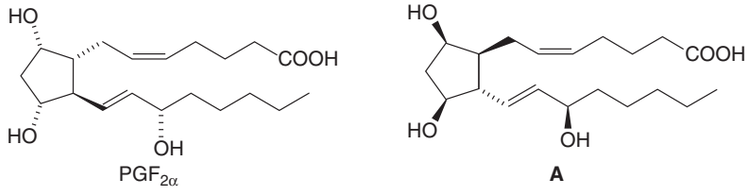
For example, if a compound has two stereogenic centers, both with the *R* configuration, then its enantiomer is *S*,*S* and the diastereomers are either *R*,*S* or *S*,*R*.

Problem 5.21 If the two stereogenic centers of a compound are *R,S* in configuration, what are the *R,S* assignments for its enantiomer and two diastereomers?

Problem 5.22 Without drawing out the structures, label each pair of compounds as enantiomers or diastereomers.

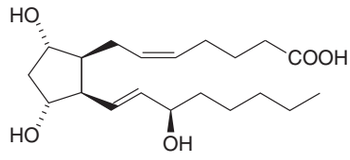
a. (2*R*,3*S*)-2,3-hexanediol and (2*R*,3*R*)-2,3-hexanediol
b. (2*R*,3*R*)-2,3-hexanediol and (2*S*,3*S*)-2,3-hexanediol
c. (2*R*,3*S*,4*R*)-2,3,4-hexanetriol and (2*S*,3*R*,4*R*)-2,3,4-hexanetriol

Problem 5.23 (a) Label the five tetrahedral stereogenic centers in $PGF_{2\alpha}$ (Section 4.15), **A,** and **B** as *R* or *S.* (b) How are $PGF_{2\alpha}$ and **A** related? (c) How are $PGF_{2\alpha}$ and **B** related?



$PGF_{2\alpha}$

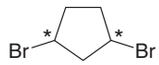
A



B

5.10 Disubstituted Cycloalkanes

Let us now turn our attention to disubstituted cycloalkanes, and draw all possible stereoisomers for **1,3-dibromocyclopentane.** Because 1,3-dibromocyclopentane has two stereogenic centers, it has a maximum of four stereoisomers.

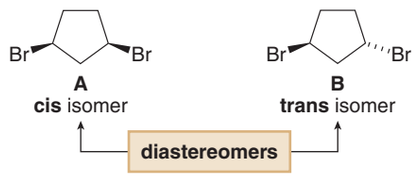


1,3-dibromocyclopentane
[* = stereogenic center]

With two stereogenic centers, the **maximum** number of stereoisomers = **4.**

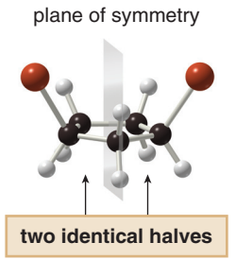
To draw all possible stereoisomers, remember that a disubstituted cycloalkane can have two substituents on the same side of the ring (**cis isomer,** labeled **A**) or on opposite sides of the ring (**trans isomer,** labeled **B**). These compounds are **stereoisomers but not mirror images of each other,** making them **diastereomers. A** and **B** are two of the four possible stereoisomers.

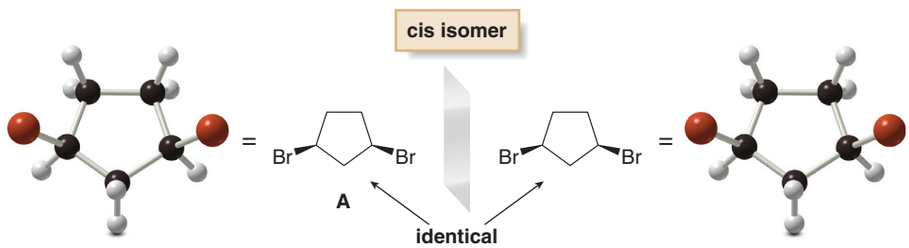
Remember: In determining chirality in substituted cycloalkanes, always draw the rings as **flat polygons.** This is especially true for cyclohexane derivatives, where having two chair forms that interconvert can make analysis especially difficult.



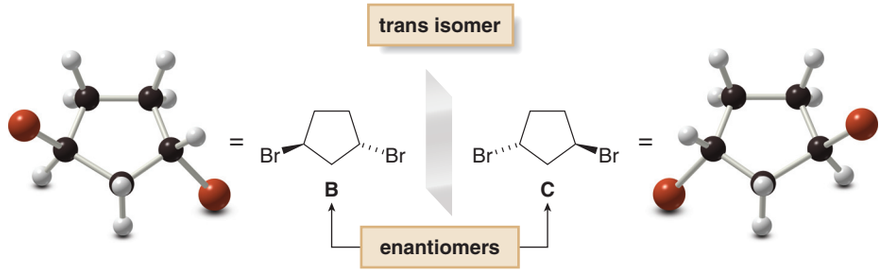
To find the other two stereoisomers (if they exist), draw the mirror image of each compound and determine whether the compound and its mirror image are superimposable.

cis-1,3-Dibromocyclopentane contains a plane of symmetry.





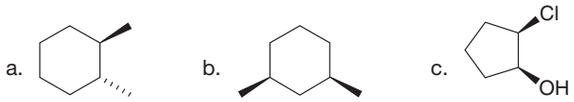
- The cis isomer is superimposable on its mirror image, making them *identical.* Thus, **A** is an **achiral meso compound.**



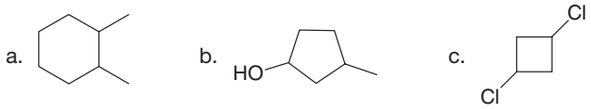
- The trans isomer **B** is *not* superimposable on its mirror image, labeled **C,** making **B** and **C** different compounds. Thus, **B** and **C** are **enantiomers.**

Because one stereoisomer of 1,3-dibromocyclopentane is superimposable on its mirror image, there are only three stereoisomers, not four. **A** is an achiral meso compound and **B** and **C** are a pair of chiral enantiomers. **A** and **B** are diastereomers, as are **A** and **C.**

Problem 5.24 Which of the following cyclic molecules are *meso* compounds?



Problem 5.25 Draw all possible stereoisomers for each compound. Label pairs of enantiomers and diastereomers.



5.11 Isomers—A Summary

Before moving on to other aspects of stereochemistry, take the time to review Figures 5.10 and 5.11. Keep in mind the following facts, and use Figure 5.10 to summarize the types of isomers.

- **There are two major classes of isomers: constitutional isomers and stereoisomers.**
- **There are only two kinds of stereoisomers: enantiomers and diastereomers.**

Then, to determine the relationship between two nonidentical molecules, refer to the flowchart in Figure 5.11.

Figure 5.10
Summary—Types of isomers

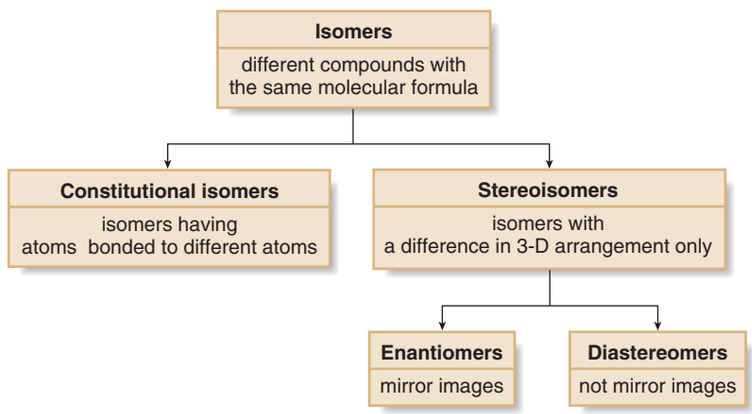
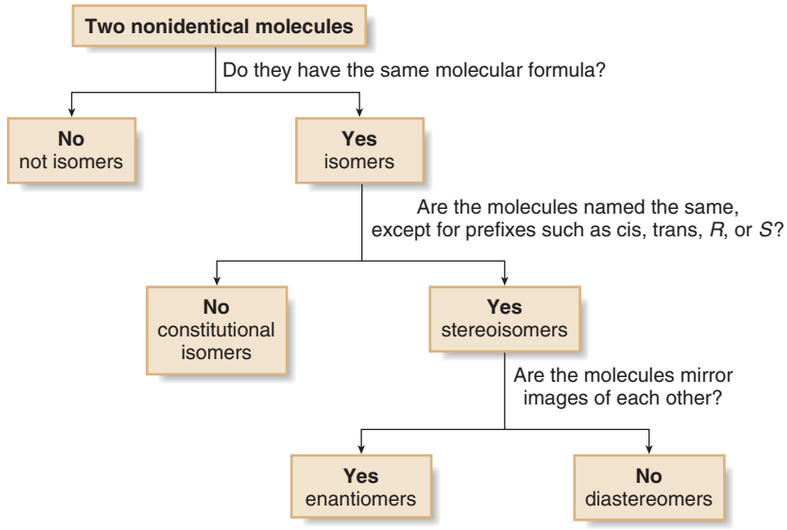
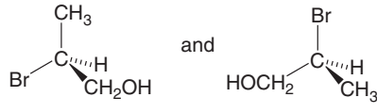
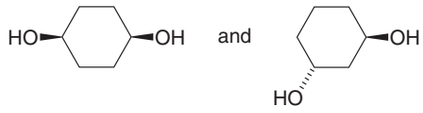


Figure 5.11
Determining the relationship between two nonidentical molecules

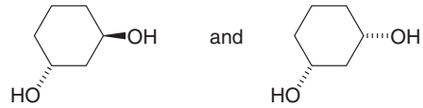


Problem 5.26 State how each pair of compounds is related. Are they enantiomers, diastereomers, constitutional isomers, or identical?

a. 

c. 

b. 

d. 

5.12 Physical Properties of Stereoisomers

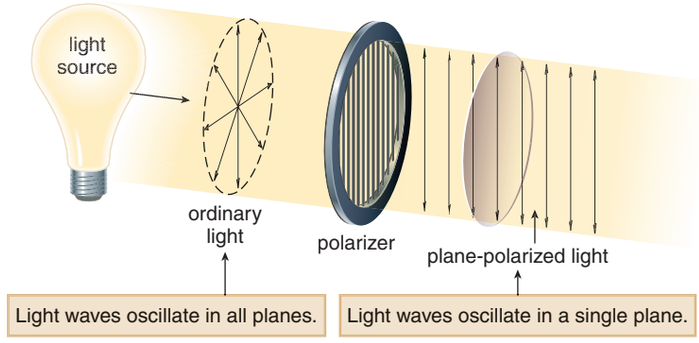
Recall from Section 5.2 that constitutional isomers have different physical and chemical properties. How, then, do the physical and chemical properties of enantiomers compare?

- **The chemical and physical properties of two enantiomers are *identical* except in their interaction with *chiral* substances.**

5.12A Optical Activity

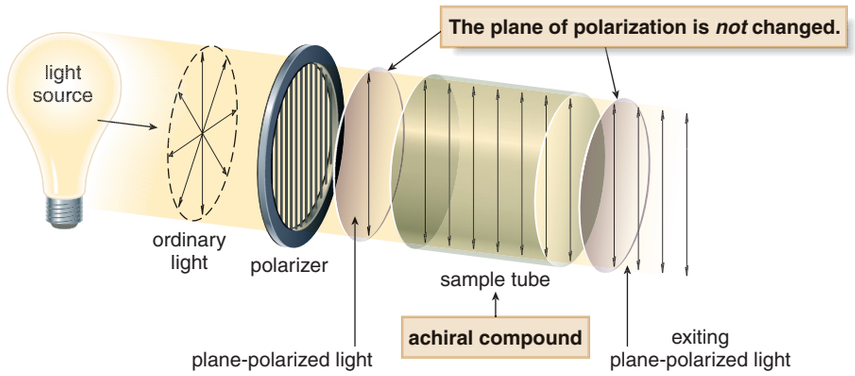
Two enantiomers have identical physical properties—melting point, boiling point, solubility—except for how they interact with plane-polarized light.

What is plane-polarized light? Ordinary light consists of electromagnetic waves that oscillate in all planes perpendicular to the direction in which the light travels. Passing light through a polarizer allows light in only one plane to come through. This is **plane-polarized light** (or simply **polarized light**), and it has an electric vector that oscillates in a single plane.

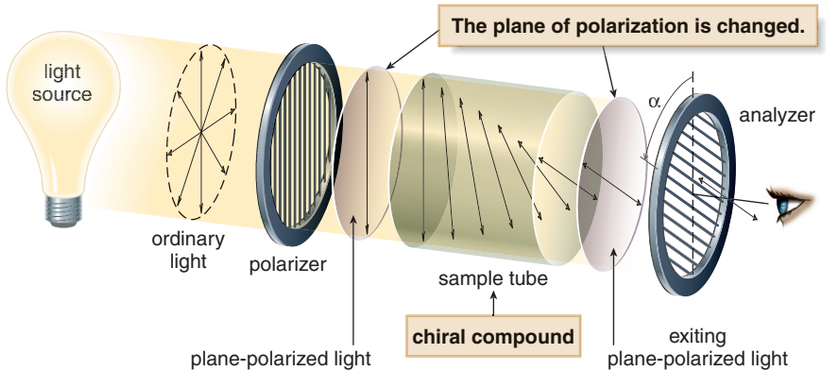


A **polarimeter** is an instrument that allows plane-polarized light to travel through a sample tube containing an organic compound. After the light exits the sample tube, an analyzer slit is rotated to determine the direction of the plane of the polarized light exiting the sample tube. There are two possible results.

With **achiral compounds,** the light exits the sample tube *unchanged,* and the plane of the polarized light is in the same position it was before entering the sample tube. **A compound that does not change the plane of polarized light is said to be *optically inactive*.**



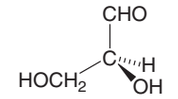
With **chiral compounds,** the plane of the polarized light is rotated through an angle α. The angle α, measured in degrees (°), is called the **observed rotation. A compound that rotates the plane of polarized light is said to be *optically active*.**



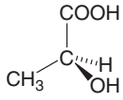
For example, the achiral compound CH_2BrCl is optically inactive, whereas a single enantiomer of CHBrClF, a chiral compound, is optically active.

The rotation of polarized light can be in the **clockwise** or **counterclockwise** direction.

- If the rotation is *clockwise* (to the right from the noon position), the compound is called *dextrorotatory.* The rotation is labeled *d* or (+).
- If the rotation is *counterclockwise* (to the left from noon), the compound is called *levorotatory.* The rotation is labeled *l* or (–).



(*S*)-glyceraldehyde
[α] = –8.7



(*S*)-lactic acid
[α] = +3.8

No relationship exists between the *R* and *S* prefixes that designate configuration and the (+) and (–) designations indicating optical rotation. For example, the *S* enantiomer of lactic acid is dextrorotatory (+), whereas the *S* enantiomer of glyceraldehyde is levorotatory (–).

How does the rotation of two enantiomers compare?

- **Two enantiomers rotate plane-polarized light *to an equal extent* but in the *opposite* direction.**

Thus, if enantiomer **A** rotates polarized light +5°, then the same concentration of enantiomer **B** rotates it –5°.

5.12B Racemic Mixtures

What is the observed rotation of an equal amount of two enantiomers? Because **two enantiomers rotate plane-polarized light to an equal extent but in opposite directions, the rotations cancel,** and no rotation is observed.

- **An equal amount of two enantiomers is called a *racemic mixture* or a *racemate.* A racemic mixture is optically inactive.**

Besides optical rotation, other physical properties of a racemate are not readily predicted. The melting point and boiling point of a racemic mixture are not necessarily the same as either pure enantiomer, and this fact is not easily explained. The physical properties of two enantiomers and their racemic mixture are summarized in Table 5.1.

5.12C Specific Rotation

The observed rotation depends on the number of chiral molecules that interact with polarized light. This in turn depends on the concentration of the sample and the length of the sample tube. To standardize optical rotation data, the quantity **specific rotation** ([α]) is defined using a specific sample tube length (usually 1 dm), concentration, temperature (25 °C), and wavelength (589 nm, the D line emitted by a sodium lamp).

$$\textbf{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation (°)
l = length of sample tube (dm)
c = concentration (g/mL)

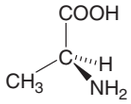
[dm = decimeter
1 dm = 10 cm]

Specific rotations are physical constants just like melting points or boiling points, and are reported in chemical reference books for a wide variety of compounds.

Table 5.1 **The Physical Properties of Enantiomers A and B Compared**

Property	A alone	B alone	Racemic A + B
Melting point	identical to **B**	identical to **A**	may be different from **A** and **B**
Boiling point	identical to **B**	identical to **A**	may be different from **A** and **B**
Optical rotation	equal in magnitude but opposite in sign to **B**	equal in magnitude but opposite in sign to **A**	0°

Problem 5.27 The amino acid (*S*)-alanine has the physical characteristics listed under the structure.



(*S*)-alanine
[α] = +8.5
mp = 297 °C

a. What is the melting point of (*R*)-alanine?
b. How does the melting point of a racemic mixture of (*R*)- and (*S*)-alanine compare to the melting point of (*S*)-alanine?
c. What is the specific rotation of (*R*)-alanine, recorded under the same conditions as the reported rotation of (*S*)-alanine?
d. What is the optical rotation of a racemic mixture of (*R*)- and (*S*)-alanine?
e. Label each of the following as optically active or inactive: a solution of pure (*S*)-alanine; an equal mixture of (*R*)- and (*S*)-alanine; a solution that contains 75% (*S*)- and 25% (*R*)-alanine.

Problem 5.28 A natural product was isolated in the laboratory, and its observed rotation was +10° when measured in a 1 dm sample tube containing 1.0 g of compound in 10 mL of water. What is the specific rotation of this compound?

5.12D Enantiomeric Excess

Sometimes in the laboratory we have neither a pure enantiomer nor a racemic mixture, but rather a mixture of two enantiomers in which one enantiomer is present in excess of the other. The **enantiomeric excess (*ee*),** also called the **optical purity,** tells how much more there is of one enantiomer.

- **Enantiomeric excess = *ee* = % of one enantiomer – % of the other enantiomer.**

Enantiomeric excess tells how much one enantiomer is present in excess of the racemic mixture. For example, if a mixture contains 75% of one enantiomer and 25% of the other, the enantiomeric excess is 75% – 25% = 50%. There is a 50% excess of one enantiomer over the racemic mixture.

Problem 5.29 What is the *ee* for each of the following mixtures of enantiomers **A** and **B**?
a. 95% **A** and 5% **B** b. 85% **A** and 15% **B**

Knowing the *ee* of a mixture makes it possible to calculate the amount of each enantiomer present, as shown in Sample Problem 5.4.

Sample Problem 5.4 If the enantiomeric excess is 95%, how much of each enantiomer is present?

Solution
Label the two enantiomers **A** and **B** and assume that **A** is in excess. A 95% *ee* means that the solution contains an excess of 95% of **A,** and 5% of the racemic mixture of **A** and **B.** Because a racemic mixture is an equal amount of both enantiomers, it has 2.5% of **A** and 2.5% of **B.**

- Total amount of **A** = 95% + 2.5% = 97.5%
- Total amount of **B** = 2.5% (or 100% – 97.5%)

Problem 5.30 For the given *ee* values, calculate the percentage of each enantiomer present.
a. 90% *ee* b. 99% *ee* c. 60% *ee*

The enantiomeric excess can also be calculated if two quantities are known—the specific rotation [α] of a mixture and the specific rotation [α] of a pure enantiomer.

$$ee = \frac{[\alpha]\ \text{mixture}}{[\alpha]\ \text{pure enantiomer}} \times 100\%$$

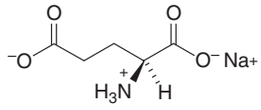
Sample Problem 5.5 Pure cholesterol has a specific rotation of –32. A sample of cholesterol prepared in the lab had a specific rotation of –16. What is the enantiomeric excess of this sample of cholesterol?

Solution

Calculate the *ee* of the mixture using the given formula.

$$ee = \frac{[\alpha] \text{ mixture}}{[\alpha] \text{ pure enantiomer}} \times 100\% = \frac{-16}{-32} \times 100\% = 50\%\ ee$$

Problem 5.31 Pure MSG, a common flavor enhancer, exhibits a specific rotation of +24. (a) Calculate the *ee* of a solution whose [α] is +10. (b) If the *ee* of a solution of MSG is 80%, what is [α] for this solution?



MSG
monosodium glutamate

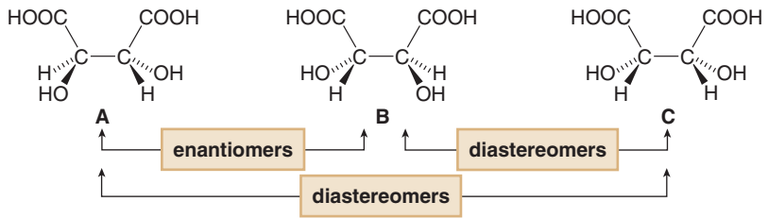
5.12E The Physical Properties of Diastereomers

Diastereomers are not mirror images of each other, and as such, **their physical properties are different, including optical rotation.** Figure 5.12 compares the physical properties of the three stereoisomers of tartaric acid, consisting of a meso compound that is a diastereomer of a pair of enantiomers.

Whether the physical properties of a set of compounds are the same or different has practical applications in the lab. Physical properties characterize a compound's physical state, and two compounds can usually be separated only if their physical properties are different.

- **Because two enantiomers have identical physical properties, they cannot be separated by common physical techniques like distillation.**
- **Diastereomers and constitutional isomers have different physical properties, and therefore they can be separated by common physical techniques.**

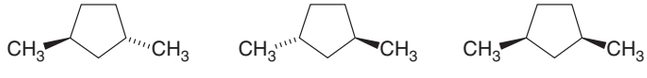
Figure 5.12 The physical properties of the three stereoisomers of tartaric acid



Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H_2O)	139	139	125	139
[α]	+13	–13	0	0
R,*S* designation	*R*,*R*	*S*,*S*	*R*,*S*	—
d,*l* designation	*d*	*l*	none	*d*,*l*

- The physical properties of **A** and **B** differ from their diastereomer **C.**
- The physical properties of a racemic mixture of **A** and **B** (last column) can also differ from either enantiomer and diastereomer **C.**
- **C** is an achiral meso compound, so it is optically inactive; [α] = 0.

Problem 5.32 Compare the physical properties of the three stereoisomers of 1,3-dimethylcyclopentane.



A **B** **C**

three stereoisomers of 1,3-dimethylcyclopentane

a. How do the boiling points of **A** and **B** compare? What about **A** and **C**?
b. Characterize a solution of each of the following as optically active or optically inactive: pure **A;** pure **B;** pure **C;** an equal mixture of **A** and **B;** an equal mixture of **A** and **C.**
c. A reaction forms a 1:1:1 mixture of **A, B,** and **C.** If this mixture is distilled, how many fractions would be obtained? Which fractions would be optically active and which would be optically inactive?

5.13 Chemical Properties of Enantiomers

When two enantiomers react with an achiral reagent, they react at the same rate, but when they react with a chiral, non-racemic reagent, they react at different rates.

- **Two enantiomers have exactly the same chemical properties except for their reaction with chiral, non-racemic reagents.**

For an everyday analogy, consider what happens when you are handed an achiral object like a pen and a chiral object like a right-handed glove. Your left and right hands are enantiomers, but they can both hold the achiral pen in the same way. With the glove, however, only your right hand can fit inside it, not your left.

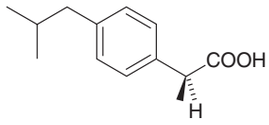
We will examine specific reactions of chiral molecules with both chiral and achiral reagents later in this text. Here, we examine two more general applications.

5.13A Chiral Drugs

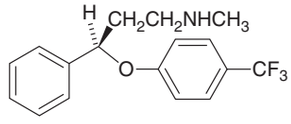
A living organism is a sea of chiral molecules. Many drugs are chiral, and often they must interact with a chiral receptor or a chiral enzyme to be effective. One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective. Alternatively, one enantiomer may trigger one biochemical response and its mirror image may elicit a totally different response.

Although (*R*)-ibuprofen shows no anti-inflammatory activity itself, it is slowly converted to the *S* enantiomer in vivo.

For example, the drugs ibuprofen and fluoxetine each contain one stereogenic center, and thus exist as a pair of enantiomers, only one of which exhibits biological activity. **(*S*)-Ibuprofen** is the active component of the anti-inflammatory agents Motrin and Advil, and **(*R*)-fluoxetine** is the active component in the antidepressant Prozac.

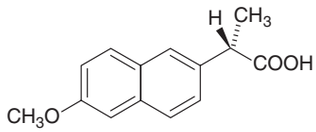


(*S*)-ibuprofen
anti-inflammatory agent

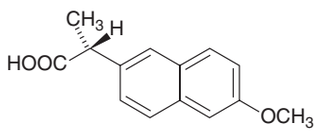


(*R*)-fluoxetine
antidepressant

The *S* enantiomer of **naproxen,** the molecule that introduced Chapter 5, is an active anti-inflammatory agent, but the *R* enantiomer is a harmful liver toxin. Changing the orientation of two substituents to form a mirror image can thus alter biological activity to produce an undesirable side effect in the other enantiomer.



(*S*)-naproxen
anti-inflammatory agent



(*R*)-naproxen
liver toxin

For more examples of two enantiomers that exhibit very different biochemical properties, see *Journal of Chemical Education*, **1996,** *73,* 481.

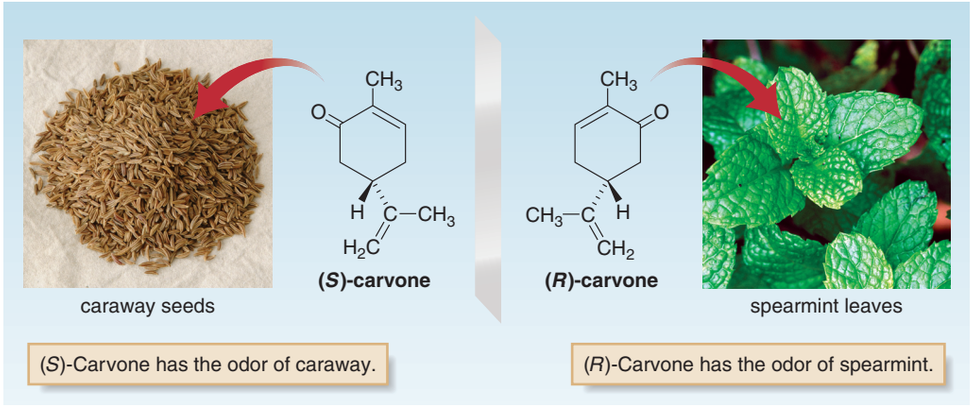
If a chiral drug could be sold as a single active enantiomer, it should be possible to use smaller doses with fewer side effects. Many chiral drugs continue to be sold as racemic mixtures, however, because it is more difficult and therefore more costly to obtain a single enantiomer. An enantiomer is not easily separated from a racemic mixture because the two enantiomers have the same physical properties. In Chapter 12 we will study a reaction that can form a single active enantiomer, an important development in making chiral drugs more readily available.

Recent rulings by the Food and Drug Administration have encouraged the development of so-called ***racemic switches,*** the patenting and marketing of a single enantiomer that was originally sold as a racemic mixture. To obtain a new patent on a single enantiomer, however, a company must show evidence that it provides significant benefit over the racemate.

5.13B Enantiomers and the Sense of Smell

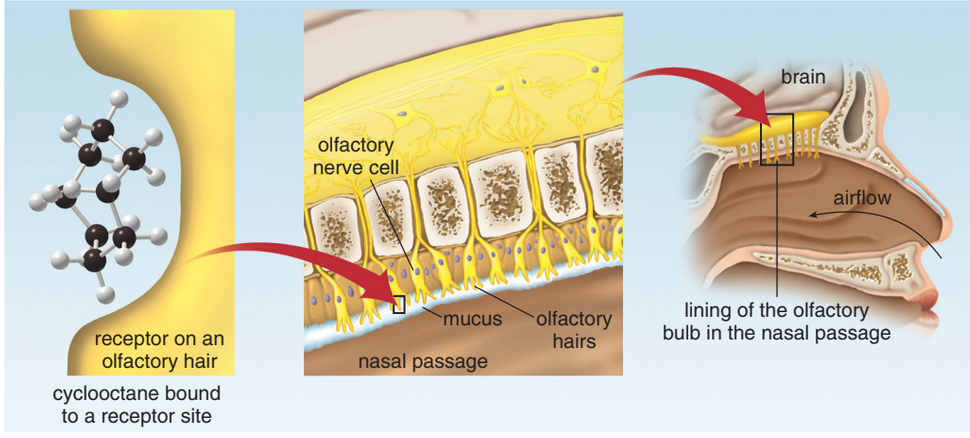
Research suggests that the odor of a particular molecule is determined more by its shape than by the presence of a particular functional group. For example, hexachloroethane (Cl_3CCCl_3) and cyclooctane have no obvious structural similarities, but they both have a camphor-like odor, a fact attributed to their similar spherical shape. Each molecule binds to spherically shaped olfactory receptors present on the nerve endings in the nasal passage, resulting in similar odors (Figure 5.13).

Because enantiomers interact with chiral smell receptors, some enantiomers have different odors. There are a few well-characterized examples of this phenomenon in nature. For example, (*S*)-carvone is responsible for the odor of caraway, whereas (*R*)-carvone is responsible for the odor of spearmint.



These examples demonstrate that understanding the three-dimensional structure of a molecule is very important in organic chemistry.

Figure 5.13
The shape of molecules and the sense of smell



Cyclooctane and other molecules similar in shape bind to a particular olfactory receptor on the nerve cells that lie at the top of the nasal passage. Binding results in a nerve impulse that travels to the brain, which interprets impulses from particular receptors as specific odors.

Key Concepts—Stereochemistry

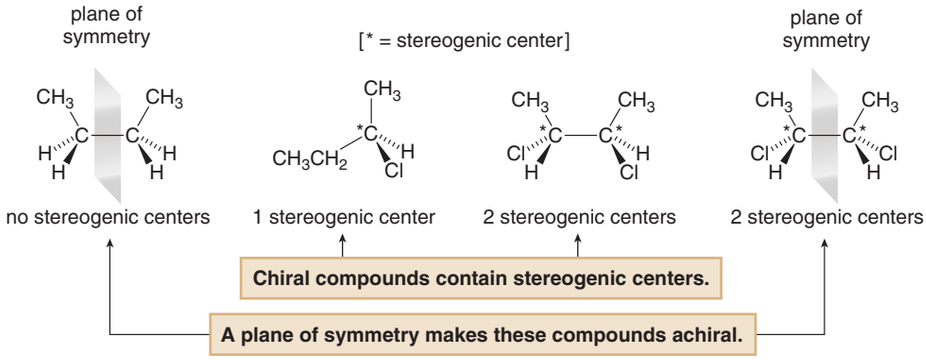
Isomers Are Different Compounds with the Same Molecular Formula (5.2, 5.11)

[1] **Constitutional isomers**—isomers that differ in the way the atoms are connected to each other. They have:
- different IUPAC names;
- the same or different functional groups; and
- different physical and chemical properties.

[2] **Stereoisomers**—isomers that differ only in the way atoms are oriented in space**.** They have the same functional group and the same IUPAC name except for prefixes such as cis, trans, *R,* and *S*.
- **Enantiomers**—stereoisomers that are nonsuperimposable mirror images of each other (5.4).
- **Diastereomers**—stereoisomers that are not mirror images of each other (5.7).

Some Basic Principles

- When a compound and its mirror image are **superimposable,** they are **identical achiral compounds.** When a compound has a plane of symmetry in one conformation, the compound is achiral (5.3).
- When a compound and its mirror image are **not superimposable,** they are **different chiral compounds** called **enantiomers.** A chiral compound has no plane of symmetry in any conformation (5.3).
- A **tetrahedral stereogenic center** is a carbon atom bonded to four different groups (5.4, 5.5).
- For ***n* stereogenic centers,** the maximum number of stereoisomers is $\mathbf{2^n}$ (5.7).



Optical Activity Is the Ability of a Compound to Rotate Plane-Polarized Light (5.12)

- An optically active solution contains a chiral compound.
- An optically inactive solution contains one of the following:
  - an achiral compound with no stereogenic centers
  - a meso compound—an achiral compound with two or more stereogenic centers
  - a racemic mixture—an equal amount of two enantiomers

The Prefixes *R* and *S* Compared with *d* and *l*

The prefixes *R* and *S* are labels used in nomenclature. Rules on assigning *R,S* are found in Section 5.6.

- An enantiomer has every stereogenic center opposite in configuration. If a compound with two stereogenic centers has the *R,R* configuration, its enantiomer has the *S,S* configuration.
- A diastereomer of this same compound has either the *R,S* or *S,R* configuration; one stereogenic center has the same configuration and one is opposite.

The prefixes *d* (or +) and *l* (or –) tell the direction a compound rotates plane-polarized light (5.12).

- Dextrorotatory (*d* or +) compounds rotate polarized light clockwise.
- Levorotatory (*l* or –) compounds rotate polarized light counterclockwise.
- There is no relation between whether a compound is *R* or *S* and whether it is *d* or *l*.

The Physical Properties of Isomers Compared (5.12)

Type of isomer	Physical properties
Constitutional isomers	Different
Enantiomers	Identical except for the direction polarized light is rotated
Diastereomers	Different
Racemic mixture	Possibly different from either enantiomer

Equations

- Specific rotation (5.12C):

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation (°)
l = length of sample tube (dm)
c = concentration (g/mL)

[dm = decimeter
1 dm = 10 cm]

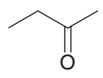
- Enantiomeric excess (5.12D):

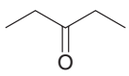
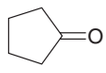
$$ee = \%\text{ of one enantiomer} - \%\text{ of the other enantiomer}$$
$$= \frac{[\alpha]\text{ mixture}}{[\alpha]\text{ pure enantiomer}} \times 100\%$$

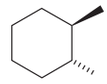
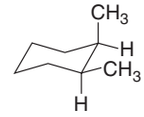
Problems

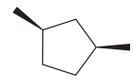
Constitutional Isomers versus Stereoisomers

5.33 Label each pair of compounds as constitutional isomers, stereoisomers, or not isomers of each other.

a.  and 

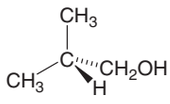
b.  and 

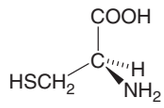
c.  and 

d.  and 

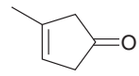
Mirror Images and Chirality

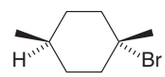
5.34 Draw the mirror image of each compound, and label the compound as chiral or achiral.

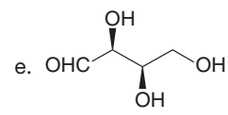
a. 

b. 

cysteine
(an amino acid)

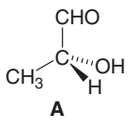
c. 

d. 

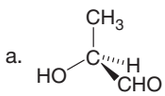
e. 

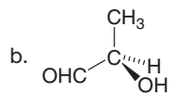
threose
(a simple sugar)

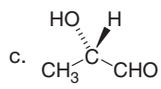
5.35 Determine if each compound is identical to or an enantiomer of **A.**



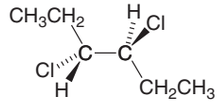
A

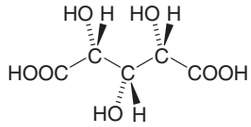
a. 

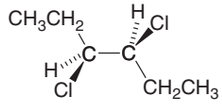
b. 

c. 

5.36 Indicate a plane of symmetry for each molecule that contains one. Some molecules require rotation around a carbon–carbon bond to see the plane of symmetry.

a. 

b. 

c. 

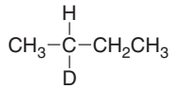
d. 

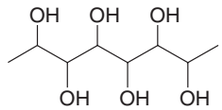
e. 

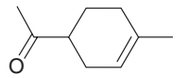
Finding and Drawing Stereogenic Centers

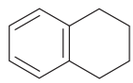
5.37 Locate the stereogenic center(s) in each compound. A molecule may have zero, one, or more stereogenic centers.

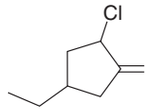
a. $CH_3CH_2CH_2CH_2CH_2CH_3$
b. $CH_3CH_2OCH(CH_3)CH_2CH_3$
c. $(CH_3)_2CHCH(OH)CH(CH_3)_2$
d. $(CH_3)_2CHCH_2CH(CH_3)CH_2CH(CH_3)CH(CH_3)CH_2CH_3$

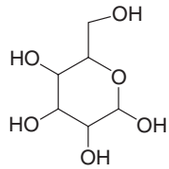
e. 

f. 

g. 

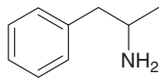
h. 

i. 

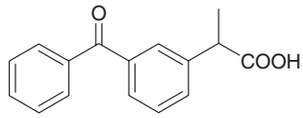
j. 

5.38 Draw the eight constitutional isomers having molecular formula $C_5H_{11}Cl$. Label any stereogenic centers.

5.39 Draw both enantiomers for each biologically active compound.

a. 

amphetamine
(a powerful central nervous stimulant)

b. 

ketoprofen
(analgesic and anti-inflammatory agent)

5.40 Draw the structure for the lowest molecular weight alkane (general molecular formula C_nH_{2n+2}, having only C and H and no isotopes) that contains a stereogenic center.

Nomenclature

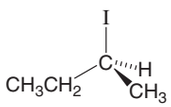
5.41 Which group in each pair is assigned the higher priority in *R,S* nomenclature?

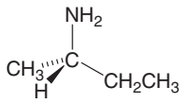
a. $-OH$, $-NH_2$
b. $-CD_3$, $-CH_3$
c. $-CH(CH_3)_2$, $-CH_2OH$
d. $-CH_2Cl$, $-CH_2CH_2CH_2Br$
e. $-CHO$, $-COOH$
f. $-CH_2NH_2$, $-NHCH_3$

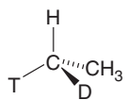
5.42 Rank the following groups in order of decreasing priority.

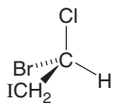
a. $-F$, $-NH_2$, $-CH_3$, $-OH$
b. $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-(CH_2)_3CH_3$
c. $-NH_2$, $-CH_2NH_2$, $-CH_3$, $-CH_2NHCH_3$
d. $-COOH$, $-CH_2OH$, $-H$, $-CHO$
e. $-Cl$, $-CH_3$, $-SH$, $-OH$
f. $-C\equiv CH$, $-CH(CH_3)_2$, $-CH_2CH_3$, $-CH=CH_2$

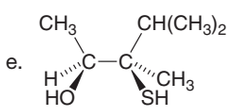
5.43 Label each stereogenic center as *R* or *S*.

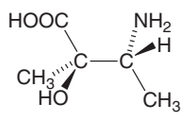
a. 

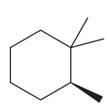
b. 

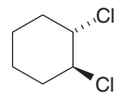
c. 

d. 

e. 

f. 

g. 

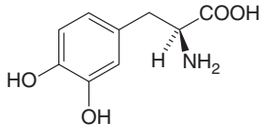
h. 

5.44 Draw the structure for each compound.

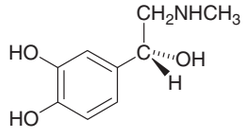
a. (3*R*)-3-methylhexane
b. (4*R*,5*S*)-4,5-diethyloctane
c. (3*R*,5*S*,6*R*)-5-ethyl-3,6-dimethylnonane
d. (3*S*,6*S*)-6-isopropyl-3-methyldecane

5.45 Draw the two enantiomers for the amino acid leucine, $HOOCCH(NH_2)CH_2CH(CH_3)_2$, and label each enantiomer as *R* or *S*. Only the *S* isomer exists in nature, and it has a bitter taste. Its enantiomer, however, is sweet.

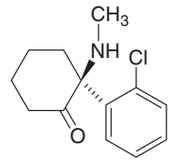
5.46 Label the stereogenic center in each biologically active compound as *R* or *S*.

a. 

L-dopa
(used to treat
Parkinson's disease)

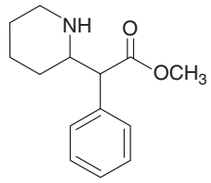
b. 

adrenaline
(hormone that increases heart rate,
dilates airways)

c. 

ketamine
(anesthetic)

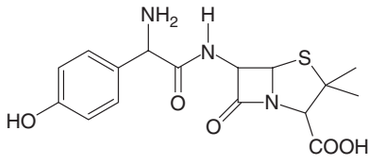
5.47 Methylphenidate (trade name: Ritalin) is prescribed for attention deficit hyperactivity disorder (ADHD). Ritalin is a mixture of *R,R* and *S,S* isomers, even though only the *R,R* isomer is active in treating ADHD. (The single *R,R* enantiomer, called dexmethylphenidate, is now sold under the trade name Focalin.) Draw the structure of the *R,R* and *S,S* isomers of methylphenidate.



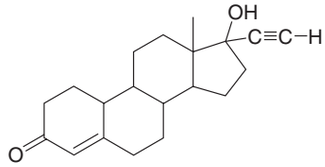
methylphenidate

Compounds with More Than One Stereogenic Center

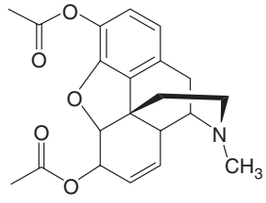
5.48 Locate the stereogenic centers in each drug.

a. 

amoxicillin
(an antibiotic)

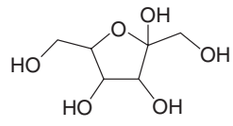
b. 

norethindrone
(oral contraceptive component)

c. 

heroin
(an opiate)

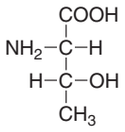
5.49 What is the maximum number of stereoisomers possible for each compound?

a. $CH_3CH(OH)CH(OH)CH_2CH_3$
b. $CH_3CH_2CH_2CH(CH_3)_2$
c. 

5.50 Draw all possible stereoisomers for each compound. Label pairs of enantiomers and diastereomers. Label any meso compound.

a. $CH_3CH(OH)CH(OH)CH_2CH_3$
b. $CH_3CH(OH)CH_2CH_2CH(OH)CH_3$
c. $CH_3CH(Cl)CH_2CH(Br)CH_3$
d. $CH_3CH(Br)CH(Br)CH(Br)CH_3$

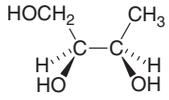
5.51 Threonine is a naturally occurring amino acid that contains two stereogenic centers.

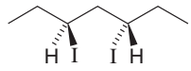


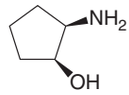
threonine

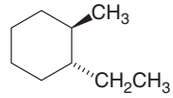
a. Label the two stereogenic centers in threonine.
b. Draw all possible stereoisomers and assign the *R,S* configuration to each isomer.
c. Only the 2*S*,3*R* isomer of threonine occurs in nature. (Numbering begins at the COOH group.) Which isomer in part (b) is naturally occurring?

5.52 Draw the enantiomer and a diastereomer for each compound.

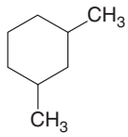
a. 

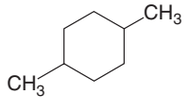
b. 

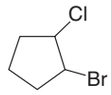
c. 

d. 

5.53 Draw all possible stereoisomers for each cycloalkane. Label pairs of enantiomers and diastereomers. Label any meso compound.

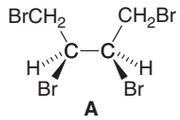
a. 

b. 

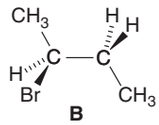
c. 

5.54 Draw all possible constitutional and stereoisomers for a compound of molecular formula C_6H_{12} having a cyclobutane ring and two methyl groups as substituents. Label each compound as chiral or achiral.

5.55 Explain why compound **A** has no enantiomer and why compound **B** has no diastereomer.



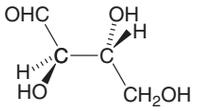
A



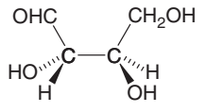
B

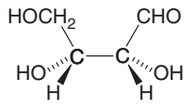
Comparing Compounds: Enantiomers, Diastereomers, and Constitutional Isomers

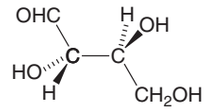
5.56 How is each compound related to the simple sugar D-erythrose? Is it an enantiomer, diastereomer, or identical?

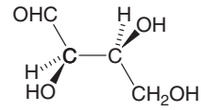


D-erythrose

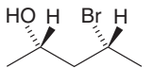
a. 

b. 

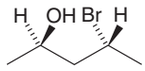
c. 

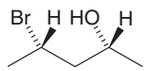
d. 

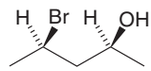
5.57 How is each compound related to **A?** Is it an enantiomer, diastereomer, or identical?

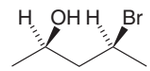


A

a. 

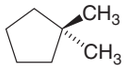
b. 

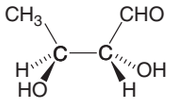
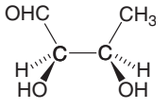
c. 

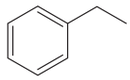
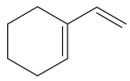
d. 

5.58 How are the compounds in each pair related to each other? Are they identical, enantiomers, diastereomers, constitutional isomers, or not isomers of each other?

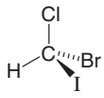
a.  and

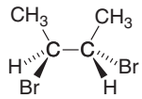
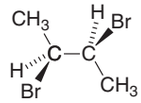
b.  and 

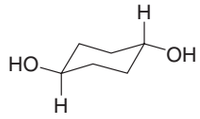
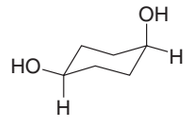
c.  and 

d.  and 

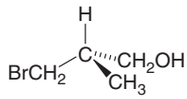
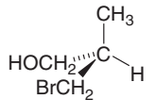
e.  and 

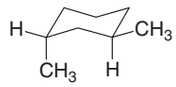
f.  and 

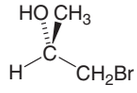
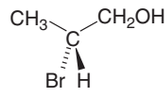
g.  and 

h.  and 

i.  and 

j.  and 

k.  and 

l.  and 

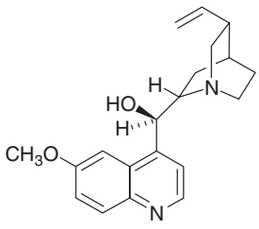
Physical Properties of Isomers

5.59 Drawn are four isomeric dimethylcyclopropanes.

A **B** **C** **D**

a. How are the compounds in each pair related (enantiomers, diastereomers, constitutional isomers): **A** and **B; A** and **C; B** and **C; C** and **D?**
b. Label each compound as chiral or achiral.
c. Which compounds, alone, would be optically active?
d. Which compounds have a plane of symmetry?
e. How do the boiling points of the compounds in each pair compare: **A** and **B; B** and **C; C** and **D?**
f. Which of the compounds are meso compounds?
g. Would an equal mixture of compounds **C** and **D** be optically active? What about an equal mixture of **B** and **C?**

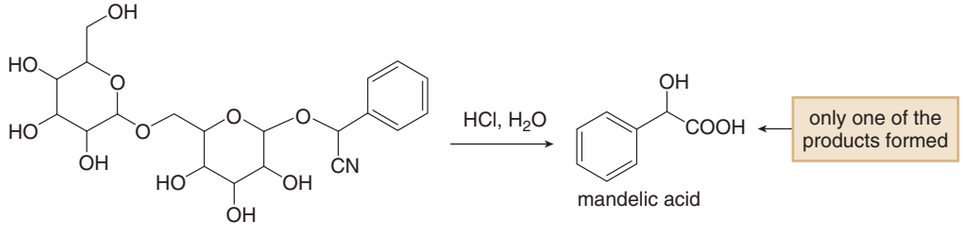
5.60 The [α] of pure quinine, an antimalarial drug, is –165.



quinine
(antimalarial drug)

a. Calculate the *ee* of a solution with the following [α] values: –50, –83, and –120.
b. For each *ee,* calculate the percent of each enantiomer present.
c. What is [α] for the enantiomer of quinine?
d. If a solution contains 80% quinine and 20% of its enantiomer, what is the *ee* of the solution?
e. What is [α] for the solution described in part (d)?

5.61 Amygdalin, a compound isolated from the pits of apricots, peaches, and wild cherries, is commonly known as *laetrile.* Although it has no known therapeutic value, amygdalin has been used as an unsanctioned anticancer drug both within and outside of the United States. One hydrolysis product formed from amygdalin is mandelic acid, used in treating common skin problems caused by photo-aging and acne.



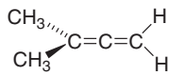
amygdalin
(laetrile)

mandelic acid

a. How many stereogenic centers are present in amygdalin? What is the maximum number of stereoisomers possible?
b. Draw both enantiomers of mandelic acid and label each stereogenic center as *R* or *S*.
c. Pure (*R*)-mandelic acid has a specific rotation of –154. If a sample contains 60% of the *R* isomer and 40% of its enantiomer, what is [α] of this solution?
d. Calculate the *ee* of a solution of mandelic acid having [α] = +50. What is the percentage of each enantiomer present?

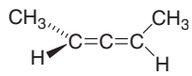
Challenge Problems

5.62



achiral

A



chiral

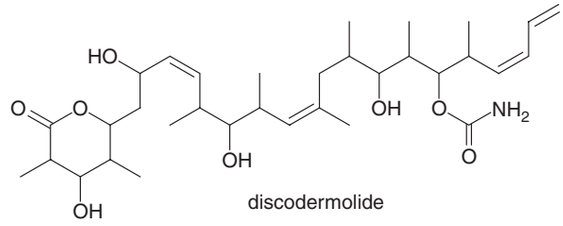
B

A limited number of chiral compounds having no stereogenic centers exist. For example, although **A** is achiral, constitutional isomer **B** is chiral. Make models and explain this observation. Compounds containing two double bonds that share a single carbon atom are called *allenes.*

5.63 a. Locate all the tetrahedral stereogenic centers in discodermolide, a natural product isolated from the Caribbean marine sponge *Discodermia dissoluta.* Discodermolide is a potent tumor inhibitor, and shows promise as a drug for treating colon, ovarian, and breast cancers.

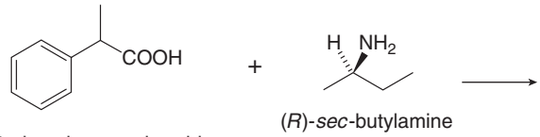
b. Certain carbon–carbon double bonds can also be stereogenic centers. With reference to the definition in Section 5.3, explain how this can occur, and then locate the three additional stereogenic centers in discodermolide.

c. Considering all stereogenic centers, what is the maximum number of stereoisomers possible for discodermolide?



discodermolide

5.64 An acid–base reaction of (*R*)-*sec*-butylamine with a racemic mixture of 2-phenylpropanoic acid forms two products having different melting points and somewhat different solubilities. Draw the structure of these two products. Assign *R* and *S* to any stereogenic centers in the products. How are the two products related? Choose from enantiomers, diastereomers, constitutional isomers, or not isomers.



2-phenylpropanoic acid
(racemic mixture)

(*R*)-*sec*-butylamine