Organic Chemistry, *Fourth Edition*

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Chapter 5

Stereochemistry

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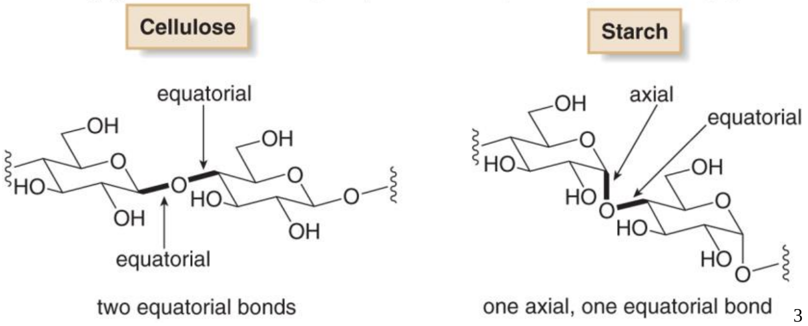
Stereochemistry

- **Stereochemistry** refers to the three-dimensional structure of a molecule.
- As a consequence of stereochemistry, apparently minor differences in 3-D structure can result in vastly different properties.
- We can observe this by considering starch and cellulose, which are both composed of the same repeating unit.

Stereochemistry of Starch and Cellulose

- **In cellulose, the O atom joins two rings using equatorial bonds.**
- **In starch, the O atom joins two rings using one equatorial and one axial bond.**
- **Due to these differences in stereochemistry, humans can metabolize starch for energy but we cannot digest cellulose.**

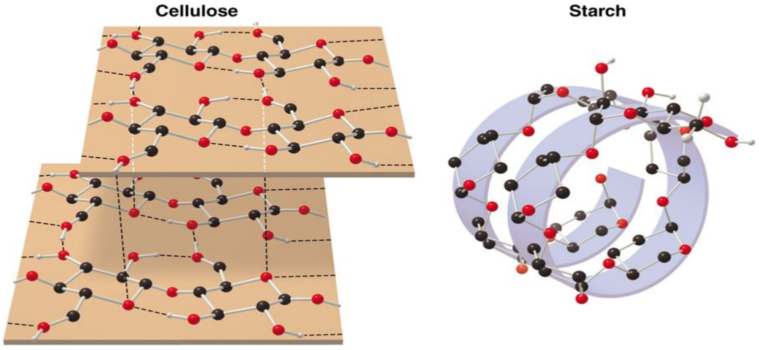


two equatorial bonds

one axial, one equatorial bond

3-D Structure of Starch and Cellulose

Figure 5.2



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.

Constitutional Isomers

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

- The two major classes of isomers are **constitutional** isomers and **stereoisomers**.

  - **Constitutional/structural isomers** have:
    - different IUPAC names
    - same or different functional groups
    - different physical properties
    - different chemical properties

Stereoisomers

- **Stereoisomers:**

  - Differ only in the way the atoms are oriented in space.

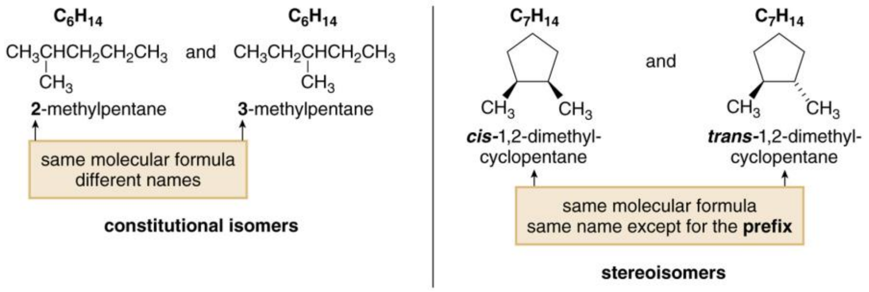
  - Have identical IUPAC names (except for a prefix like *cis* or *trans*).

  - Always have the same functional group(s).

  - Differ in **configuration** (three-dimensional arrangement).

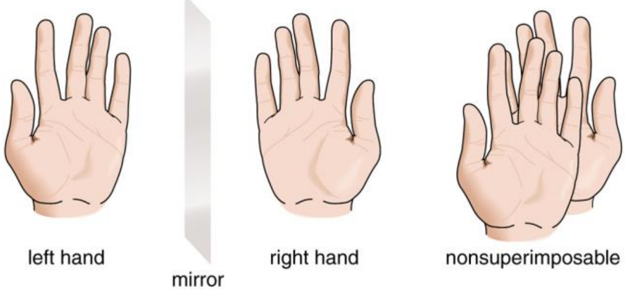
Constitutional and Stereoisomers

Figure 5.3



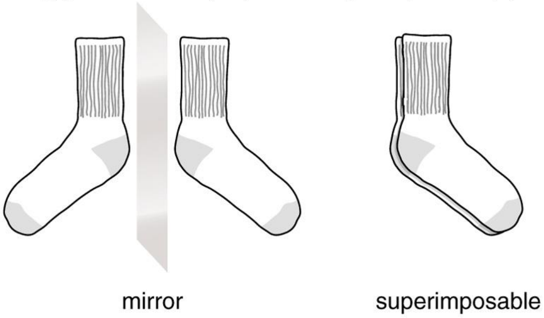
Nonsuperimposable Mirror Images

- **Although everything has a mirror image, mirror images may or may not be superimposable.**
  - **To superimpose means to align all parts of two objects**
- **Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or superimposable.**
- **A molecule (or object) that is not superimposable on its mirror image is said to be chiral.**



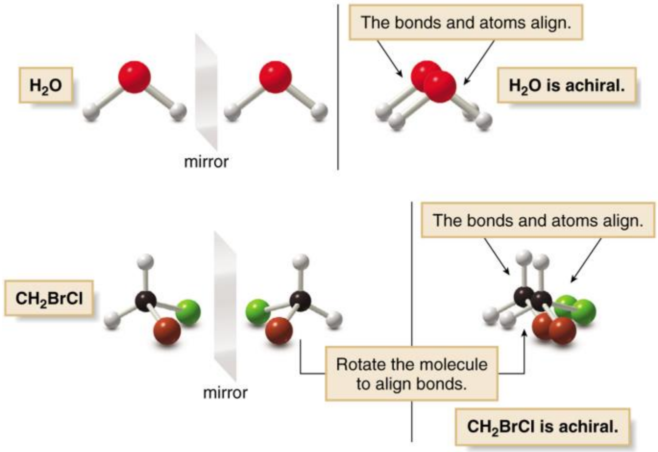
Superimposable (Achiral) Objects

- **Other molecules are like socks.**
  - **Two socks from a pair are mirror images that are superimposable.**
  - **A sock and its mirror image are identical.**
- **A molecule or object that is superimposable on its mirror image is said to be achiral.**



Achiral Molecules

- **We can now consider several molecules to determine whether or not they are chiral.**



The bonds and atoms align.

H_2O is achiral.

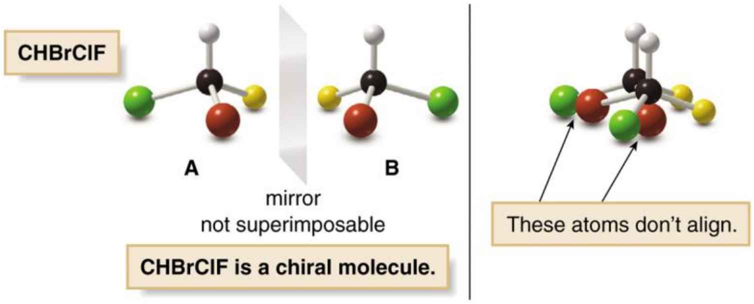
The bonds and atoms align.

Rotate the molecule to align bonds.

CH_2BrCl is achiral.

Chiral Molecules

- 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.
  - Thus, $\mathrm{CHBrClF}$ is a chiral molecule, and A and B are different compounds.
- A and B are stereoisomers—specifically, they are enantiomers.
- A carbon atom with four different groups is a tetrahedral stereogenic center.

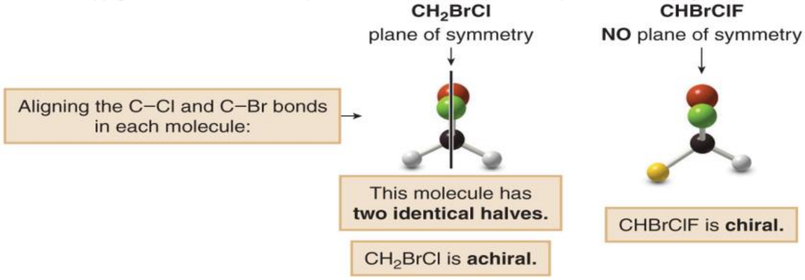


Stereogenic Centers

- In general, a molecule with no stereogenic centers will not be chiral (exceptions to this will be considered in section 17.5).
- With one stereogenic center, a molecule will always be chiral.
- With two or more stereogenic centers, a molecule may or may not be chiral.

Planes of Symmetry

- A plane of symmetry is a mirror plane that cuts the 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.



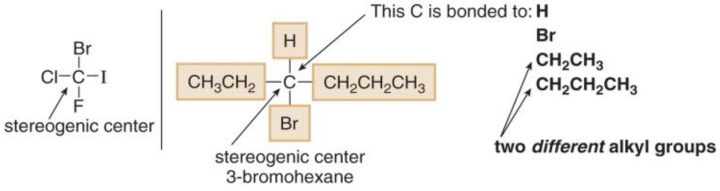
Summary of Chirality

- Everything has a mirror image.
- The fundamental question is whether a molecule and its mirror image are superimposable.
  - If not, they are chiral and do not contain a plane of symmetry.
  - If they are superimposable, they are achiral and will contain a plane of symmetry.
- The terms stereogenic center and chiral molecule are related but distinct.
- A chiral molecule must have one or more stereogenic centers.

Stereogenic Centers

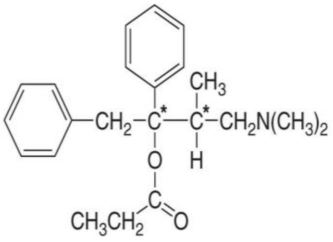
- **To locate** a stereogenic center, examine each **tetrahedral** carbon atom in a molecule, and look at the four groups—not the four atoms—bonded to it.

- **Always omit from consideration all C atoms that cannot be tetrahedral stereogenic centers. These include:**
  - **CH_2 and CH_3 groups**
  - **Any *sp* or *sp*^{2} hybridized C**

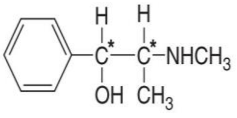


Multiple Stereogenic Centers

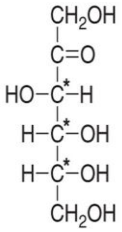
- **Larger organic** molecules can have two, three, or even hundreds of stereogenic centers.



propoxyphene
Trade name: Darvon
(analgesic)



ephedrine
(bronchodilator, decongestant)



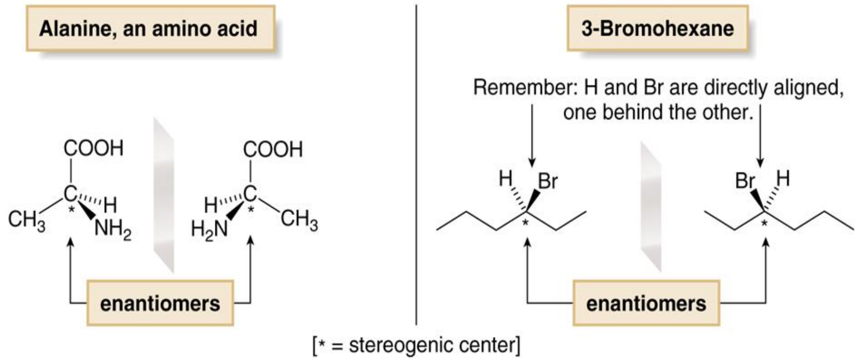
fructose
(a simple sugar)

[* = stereogenic center]

Enantiomers

- **Enantiomers** are **non-superimposable** mirror image molecules.
- **Any molecule with one stereogenic center exists as a pair of enantiomers.**

Figure 5.5



Alanine, an amino acid

3-Bromohexane

Remember: H and Br are directly aligned, one behind the other.

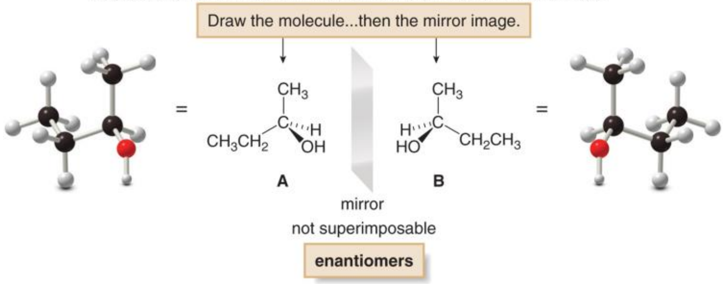
enantiomers

enantiomers

[* = stereogenic center]

Drawing Enantiomers

- **To draw both enantiomers of a chiral compound such as 2-butanol, use the typical convention for depicting a tetrahedron.**
  - **To form the first enantiomer, arbitrarily place the four groups—H, OH, CH_3 and CH_2CH_3—on any bond to the stereogenic center.**
  - **Then draw the mirror image.**



Draw the molecule...then the mirror image.

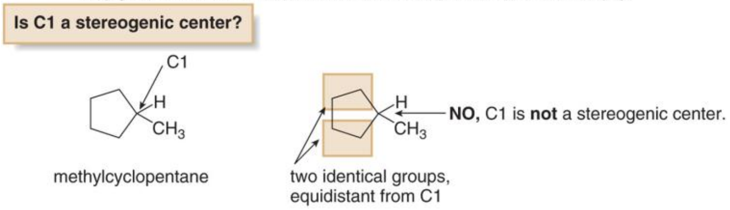
mirror

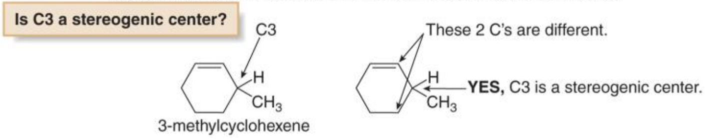
not superimposable

enantiomers

Stereogenic Centers in Cyclic Compounds

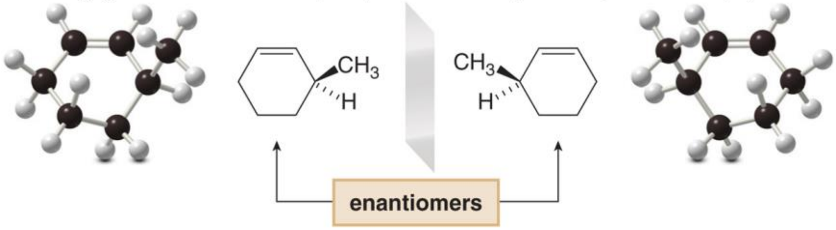
- Stereogenic centers may also occur at carbon atoms that are part of a ring.
- To find stereogenic centers on ring carbons, always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups.



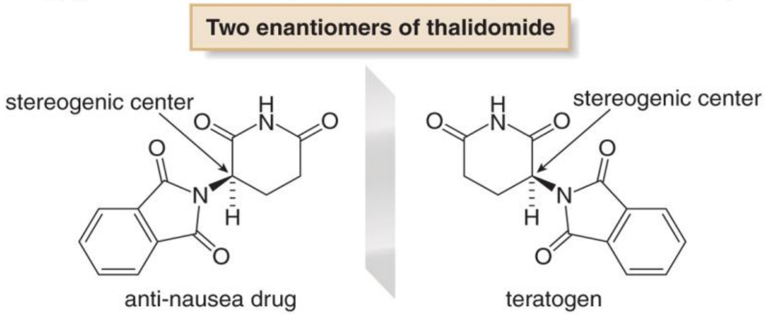


Stereogenic Centers

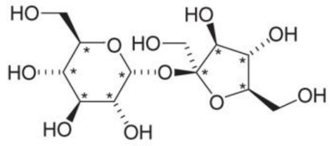
- In 3-methylcyclohexene, the CH_3 and H substituents that are above and below the plane of the ring are drawn with wedges and dashes as usual.



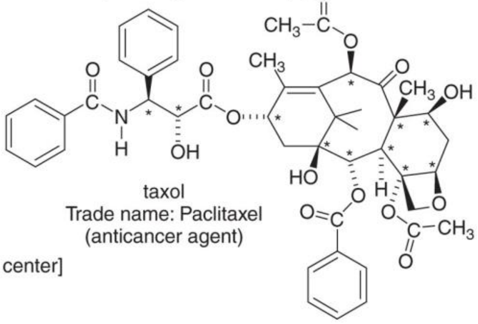
Some Biologically Active Molecules with Stereogenic Centers on Rings



Some Biologically Active Molecules with Stereogenic Centers on Rings



sucrose
(table sugar)

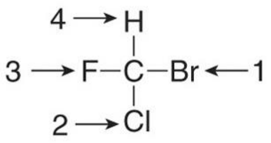


taxol
Trade name: Paclitaxel
(anticancer agent)

[* = stereogenic center]

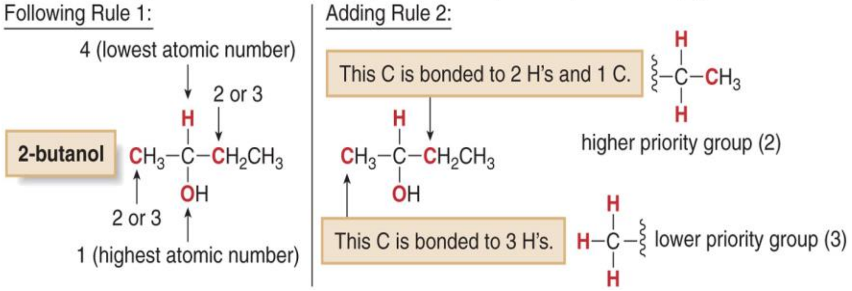
Labeling Stereogenic Centers with *R* or *S*

- Since enantiomers are two different compounds, they need to be distinguished by name.
  - This is done by adding the prefix ***R*** or ***S*** to the IUPAC name of the enantiomer.
  - A counterclockwise direction is an S (Latin for *sinister*, left) configuration. A clockwise direction is an R (Latin for *rectus*, right) configuration
- **RULE 1:** To designate enantiomers as ***R*** **or** ***S*****, priorities** must be assigned to each group bonded to the stereogenic center, in order of **decreasing atomic number**.
- The atom of highest atomic number gets the highest priority (1).



Assigning Priority for *R* and *S*

- **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 the higher priority.



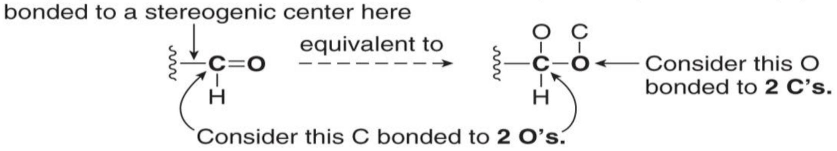
Assigning Priority for *R* and *S*–Isotopes

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

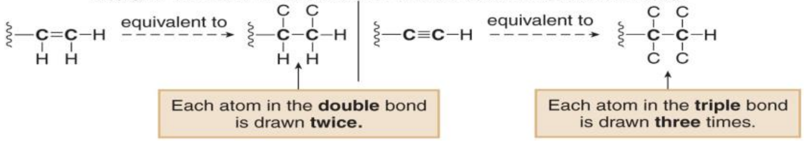
Assigning Priority for *R* and *S*–Multiple Bonds

- **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.**



Assigning Priority for *R* and *S*–Multiple Bonds

- **Other common multiple bonds are drawn below:**

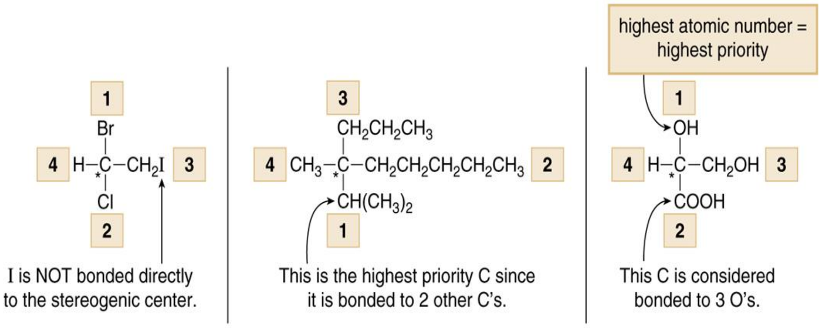


Each atom in the **double** bond is drawn **twice.**

Each atom in the **triple** bond is drawn **three** times.

Assigning Priorities to Stereogenic Centers

Figure 5.6



highest atomic number = highest priority

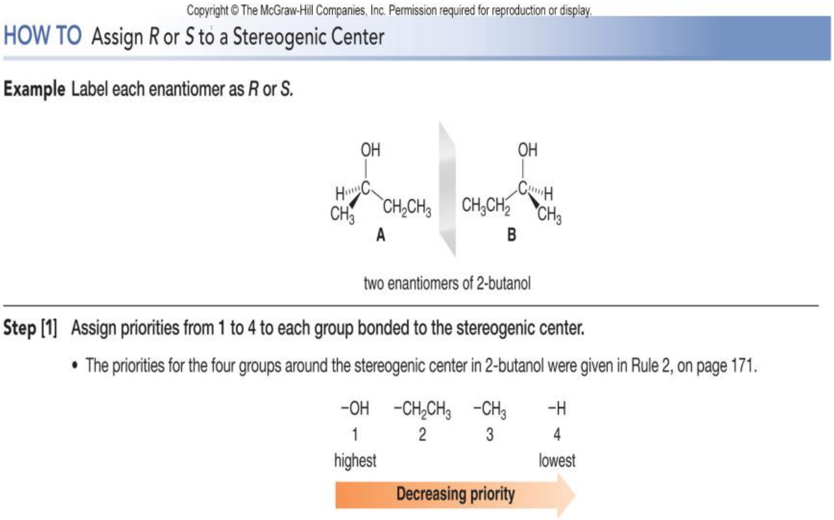
I is NOT bonded directly to the stereogenic center.

This is the highest priority C since it is bonded to 2 other C's.

This C is considered bonded to 3 O's.

[* = stereogenic center]

How To Assign *R* or *S*



HOW TO Assign *R* or *S* to a Stereogenic Center

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

two enantiomers of 2-butanol

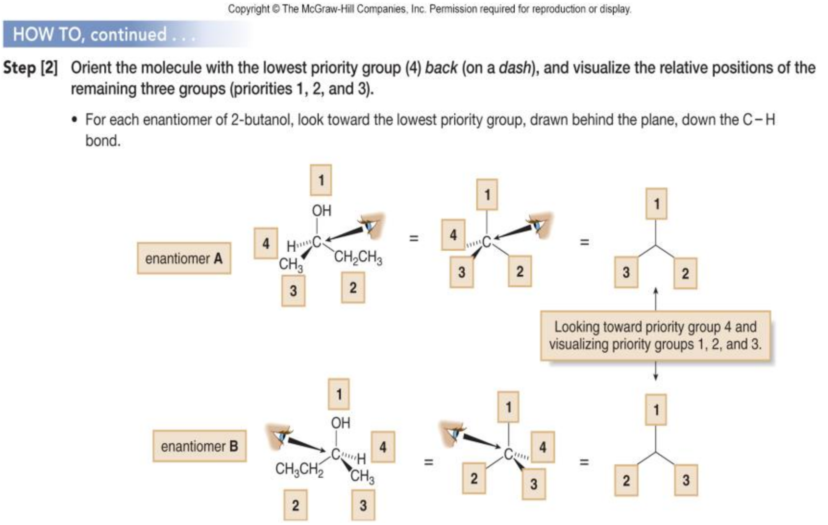
Step [1] Assign priorities from 1 to 4 to each group bonded to the stereogenic center.

- The priorities for the four groups around the stereogenic center in 2-butanol were given in Rule 2, on page 171.

$-OH$	$-CH_2CH_3$	$-CH_3$	$-H$
1	2	3	4
highest			lowest

Decreasing priority

How To Assign *R* or *S*



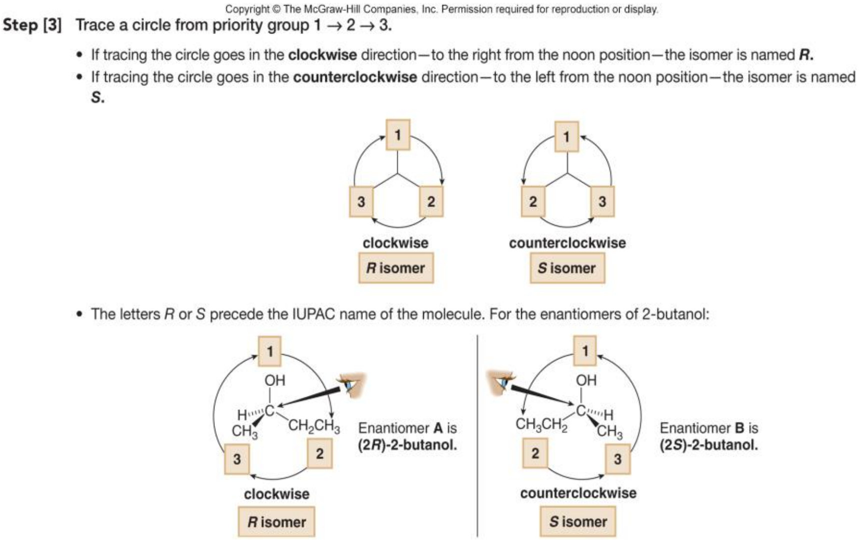
HOW TO, continued . . .

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.

Looking toward priority group 4 and visualizing priority groups 1, 2, and 3.

How To Assign *R* or *S*



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:

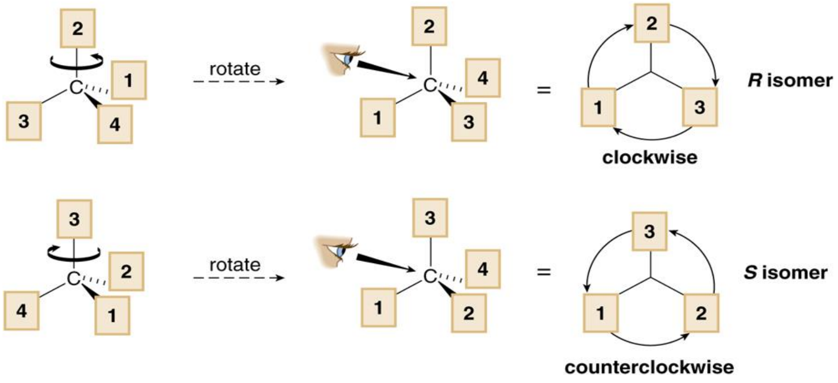
Enantiomer **A** is **(2*R*)-2-butanol.**

Enantiomer **B** is **(2*S*)-2-butanol.**

Orienting the Lowest Priority Group in Back

- **If the lowest priority group is not facing towards back, rotate the molecule 120º around a stationary bond axis.**

Figure 5.7



Diastereomers

- For a molecule with *n* stereogenic centers, the maximum number of stereoisomers is 2^n.
- When $n=2$, $2^2 = 4$.
  - With two stereogenic centers there are 4 stereoisomers that can be drawn, although some of them may be the same molecule.
  - Some of the stereoisomers will not be mirror images of each other.
  - **Diastereomers** are non-mirror image stereoisomers.

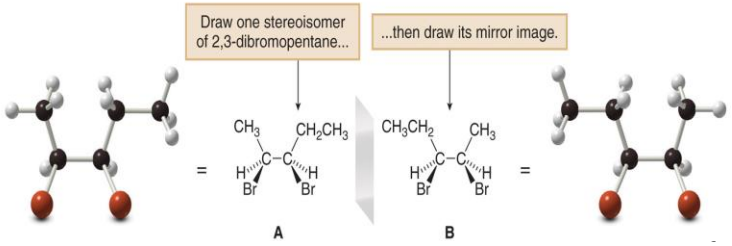
Finding All Possible Stereocenters

Example 1: stereoisomers of 2,3-dibromopentane

- Let us consider the stepwise procedure for finding all the possible .

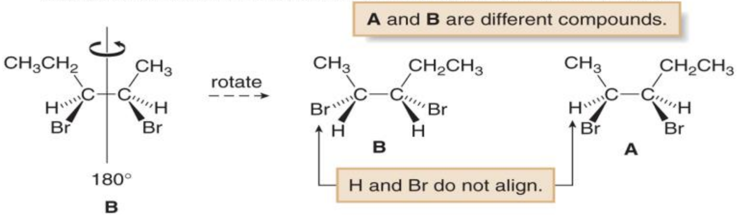
HOW TO Find and Draw All Possible Stereoisomers for a Compound with Two Stereogenic Centers

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



Finding All Possible Stereocenters

- **After drawing the compound and the mirror image, place B directly on top of A; and rotate B 180° and place it on top of A to see if the atoms align.**



A and B are different compounds.

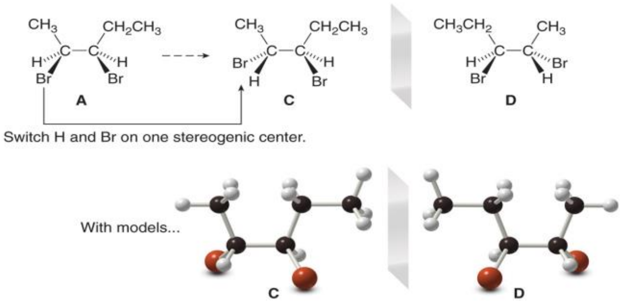
H and Br do not align.

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

Finding All Possible Stereocenters

- **Switching the positions of H and Br (<u>or any two groups</u>) on one stereogenic center of either A or B forms a new stereoisomer (labeled C in this example), which is different from A and B.**
- **The mirror image of C is labeled D.**

HOW TO, continued . . .



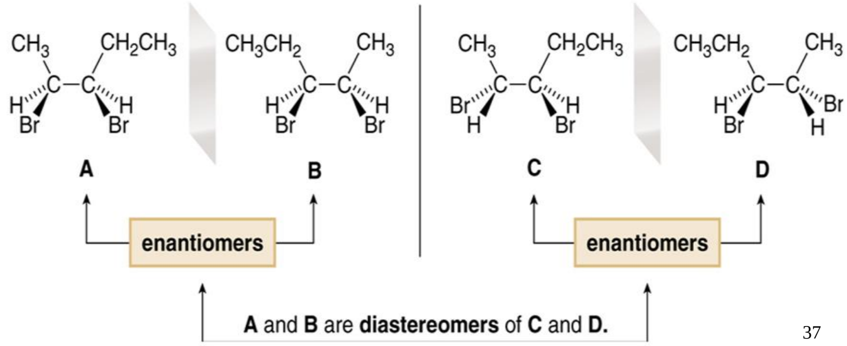
Switch H and Br on one stereogenic center.

With models...

Summary of Stereoisomers of 2,3-dibromopentane

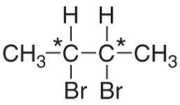
- A and B are enantiomers. C and D are enantiomers.
- A and C are diastereomers. A and D are diastereomers. B and C are diastereomers. B and D are diastereomers.

Figure 5.8



Example 2: stereoisomers of 2,3-dibromobutane

- Since this molecule has two stereogenic centers, the maximum number of stereoisomers is 4.



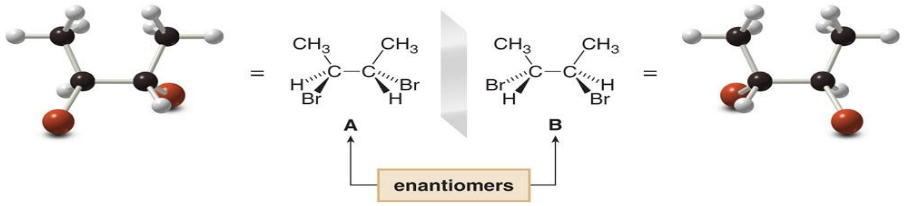
$$CH_3-\overset{H}{\underset{Br}{\overset{*}{C}}}-\overset{H}{\underset{Br}{\overset{*}{C}}}-CH_3$$

2,3-dibromobutane

[* = stereogenic center]

Stereoisomers of 2,3-dibromobutane

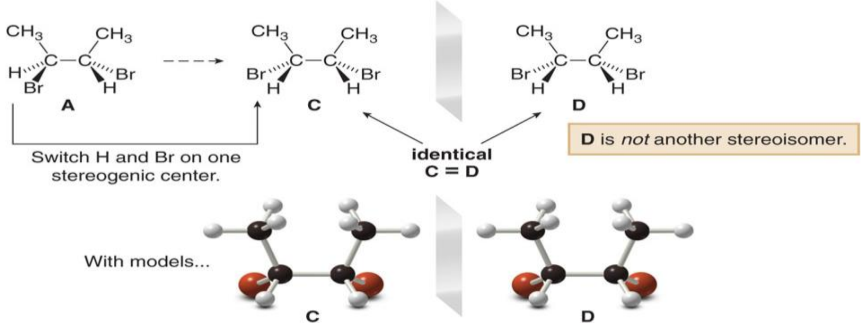
- To find all the stereoisomers of 2,3-dibromobutane, arbitrarily form one stereoisomer A, and then draw its mirror image, B.



enantiomers

Stereoisomers of 2,3-dibromobutane

- To find the other two stereoisomers if they exist, switch the position of two groups on one stereogenic center of one enantiomer only.
- Switching the positions of H and Br on one stereogenic center of A forms C, which is different from both A and B.



Switch H and Br on one stereogenic center.

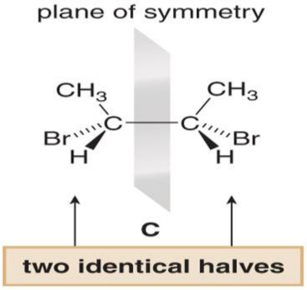
identical
C = D

D is *not* another stereoisomer.

With models...

Meso Compounds

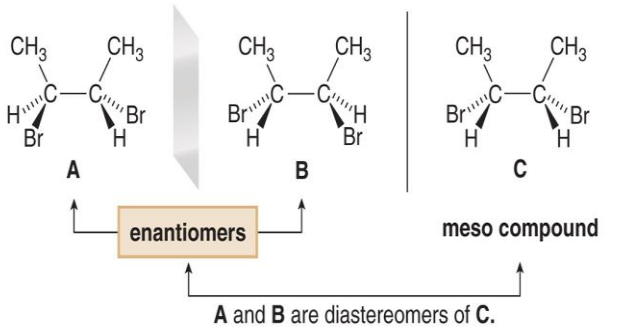
- **Compound C contains a plane of symmetry, and is achiral.**
- **A meso compound is an achiral compound that contains tetrahedral stereogenic centers. C is a meso compound.**
- **Meso compounds generally contain a plane of symmetry so that they possess two identical halves.**



- **Because one stereoisomer of 2,3-dibromobutane is superimposable on its mirror image, there are only three stereoisomers, not four.**

Stereoisomers of 2,3-dibromobutane

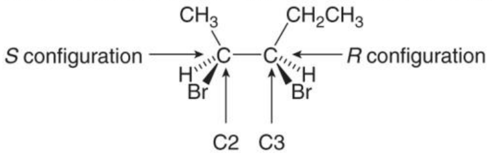
Figure 5.9



Pair of enantiomers: A and B
Pairs of diastereomers: A and C; B and C

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

- When a compound has more than one stereogenic center, *R* and *S* configurations must be assigned to each of them.



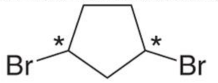
One stereoisomer of 2,3-dibromopentane

(2*S*,3*R*)-2,3-dibromopentane

- **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.

Example 3: 1,3-Dibromocyclopentane Stereoisomers

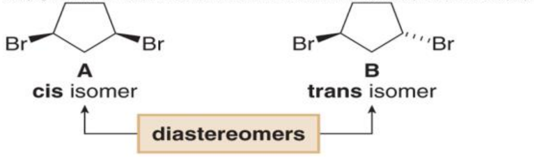
- Since it has two stereogenic centers, it has a maximum of four stereoisomers.



1,3-dibromocyclopentane

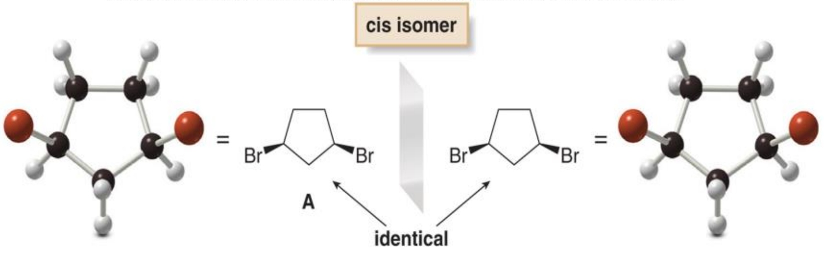
[* = stereogenic center]

- Disubstituted cycloalkanes can have two substituents on the same side of the ring (*cis* isomer, A) or on opposite sides of the ring (*trans* isomer, B).
- These compounds are stereoisomers but not mirror images.



Cis-1,3-Dibromocyclopentane Structures

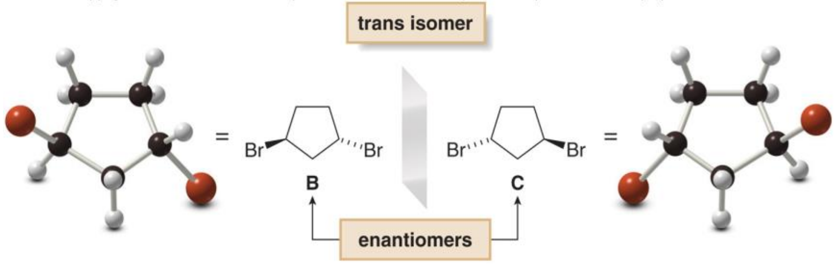
- To find the other two stereoisomers if they exist, draw the mirror images of each compound and determine whether the compound and its mirror image are superimposable.



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

Trans-1,3-Dibromocyclopentane Structures

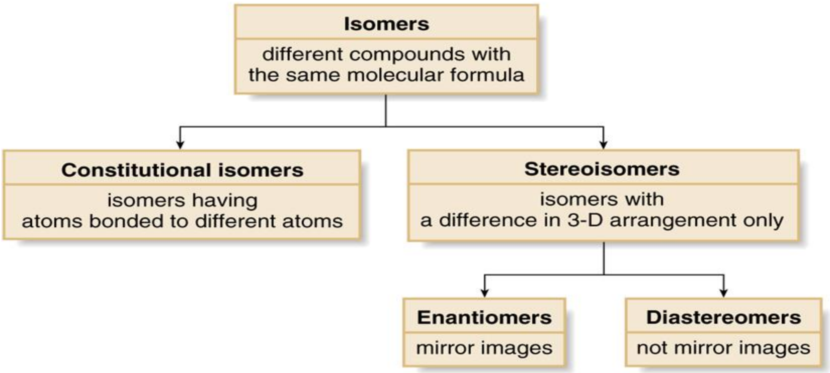
- The trans isomer is not superimposable on its mirror image, labeled C, making B and C different compounds.
- B and C are enantiomers.



- Because one stereoisomer of 1,3-dibromocyclopentane is superimposable on its mirror image, there are only three stereoisomers, not four.

Summary–Types of Isomers

Figure 5.10



Isomers
different compounds with the same molecular formula

Constitutional isomers
isomers having atoms bonded to different atoms

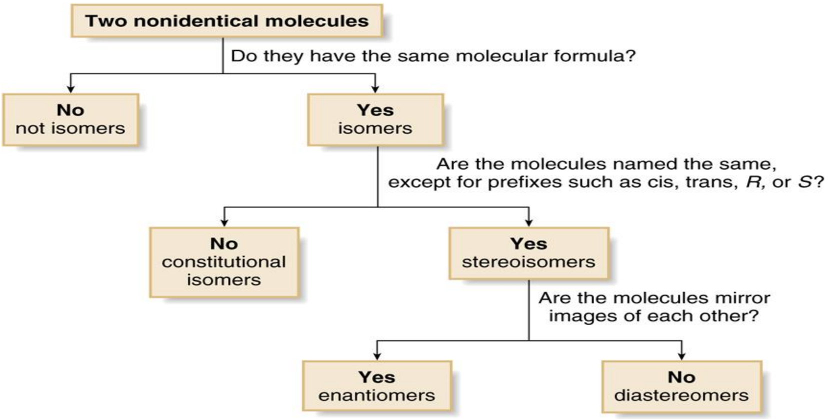
Stereoisomers
isomers with a difference in 3-D arrangement only

Enantiomers
mirror images

Diastereomers
not mirror images

Determining the Relationship Between Molecules

Figure 5.11



Two nonidentical molecules

Do they have the same molecular formula?

No
not isomers

Yes
isomers

Are the molecules named the same, except for prefixes such as cis, trans, *R*, or *S*?

No
constitutional isomers

Yes
stereoisomers

Are the molecules mirror images of each other?

Yes
enantiomers

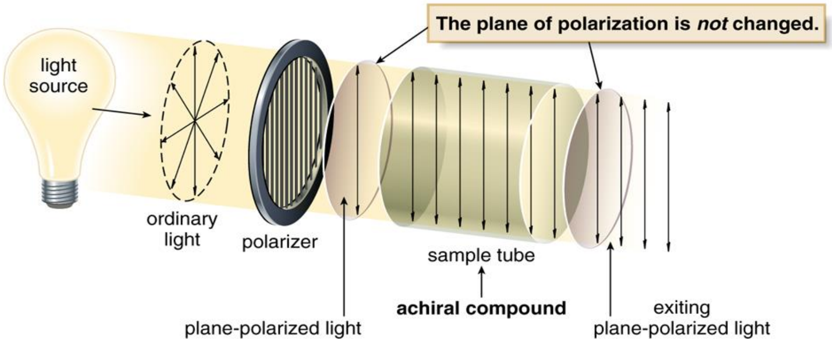
No
diastereomers

Optical Activity

- The chemical and physical properties of two enantiomers are identical except in their interaction with chiral substances.
- They have identical physical properties, except for how they interact with plane-polarized light.
- Plane-polarized (polarized) light is light that has an electric vector that oscillates in a single plane.
- Plane-polarized light arises from passing ordinary light through a polarizer.
- A polarimeter is an instrument that allows polarized light to travel through a sample tube containing an organic compound and permits the measurement of the degree to which an organic compound rotates plane-polarized light.

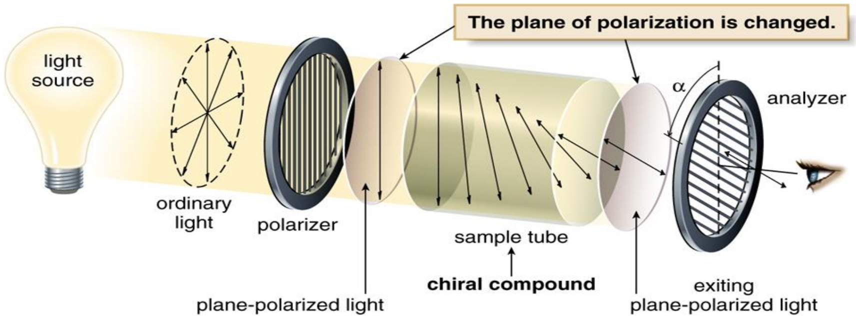
Plane-Polarized Light

- With achiral compounds, the light that exits the sample tube remains unchanged.
- A compound that does not change the plane of polarized light is said to be optically inactive.



Rotation of Plane-Polarized Light

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



Optical Activity Summary

- **The rotation of polarized light can be clockwise or counterclockwise.**
- **If the rotation is clockwise, the compound is called dextrorotatory. The rotation is labeled *d* or (+).**
- **If the rotation is counterclockwise, the compound is called levorotatory. The rotation is labeled *l* or (-).**
- **Two enantiomers rotate plane-polarized light to an equal extent but in opposite directions.**
  - **(e.g., if enantiomer A rotates polarized light +5°, the same concentration of enantiomer B rotates it –5°)**
- **No relationship exists between *R* and *S* prefixes and the (+) and (-) designations that indicate optical rotation.**

Racemic Mixtures

- An equal amount of two enantiomers is called a **racemic mixture** or a **racemate**.
- A racemic mixture is optically inactive.
- Because two enantiomers rotate plane-polarized light to an equal extent but in opposite directions, the rotations cancel, and no rotation is observed.

Racemic Mixtures

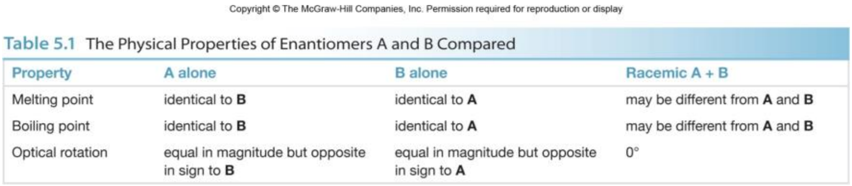


Table 5.1 The Physical Properties of Enantiomers A and B Compared

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°

Specific Rotation

- **Specific rotation** is a standardized physical constant for the amount that a chiral compound rotates plane-polarized light.
- Specific rotation is denoted by the symbol $[\alpha]$ and defined using a specific sample tube length (l, in dm), concentration (c in g/mL), temperature (25˚C) and wavelength (589 nm).

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

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

[dm = decimeter
1 dm = 10 cm]

Optical Purity

- **Enantiomeric excess (optical purity)** is a measurement of how much one enantiomer is present in excess of the racemic mixture.
- It is denoted by the symbol *ee*.

***ee* = % of one enantiomer - % of the other enantiomer**

- Consider the following example—If a mixture contains 75% of one enantiomer and 25% of the other, the enantiomeric excess is 75% - 25% = 50%.
- Thus, there is a 50% excess of one enantiomer over the racemic mixture or 50% *ee.*

Enantiomeric Excess

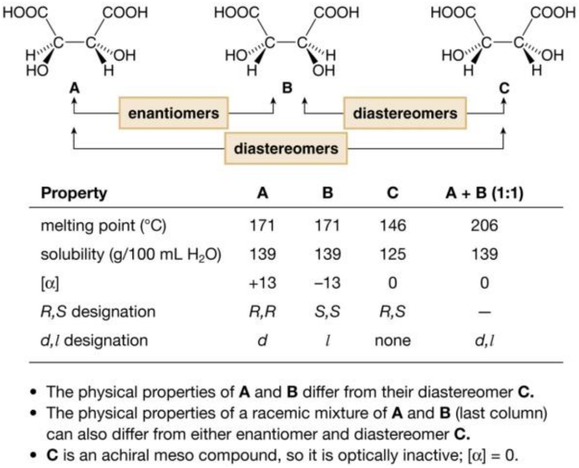
- **The enantiomeric excess can also be calculated if the specific rotation [α] of a mixture and the specific rotation [α] of a pure enantiomer are known.**

***ee* = ([α] mixture/[α] pure enantiomer) x 100%**

Physical Properties of Stereoisomers

- **Since 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 can be separated by common techniques.**

Figure 5.12

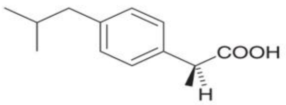


Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H_2O)	139	139	125	139
[α]	+13	−13	0	0
R,*S* designation	*R*,*R*	*S*,*S*	*R*,*S*	—
d,*l* designation	*d*	*l*	none	*d*,*l*

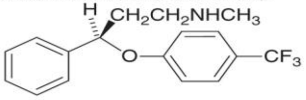
- The physical properties of **A** and **B** differ from their diastereomer **C.**
- The physical properties of a racemic mixture of **A** and **B** (last column) can also differ from either enantiomer and diastereomer **C.**
- **C** is an achiral meso compound, so it is optically inactive; [α] = 0.

Chemical Properties of Enantiomers

- Two enantiomers have exactly the same chemical properties except for their reaction with chiral, non-racemic reagents.
- Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective.
- (*S*)-ibuprofen is the active component agents in Motrin and Advil.
- (R)-fluoxetine is the active component in Prozac.



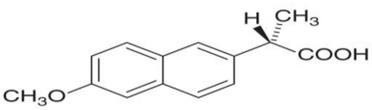
(*S*)-ibuprofen
anti-inflammatory agent



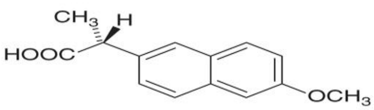
(*R*)-fluoxetine
antidepressant

Chemical Properties of Enantiomers

- One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective or toxic.
- Changing the orientation of the substituents on naproxen converts it from a common anti-inflammatory agent into a harmful liver toxin.



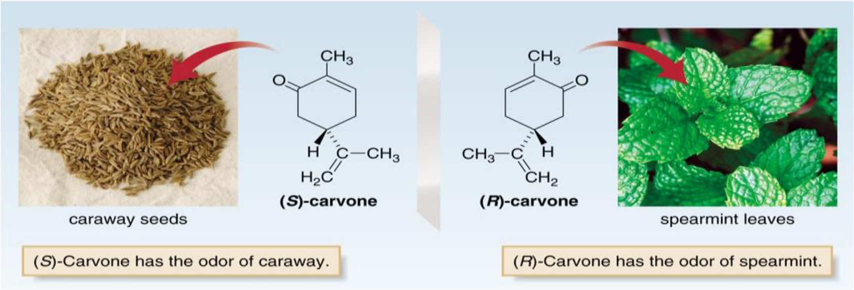
(*S*)-naproxen
anti-inflammatory agent



(*R*)-naproxen
liver toxin

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.**
- **Because enantiomers interact with chiral smell receptors, some enantiomers have different odors.**



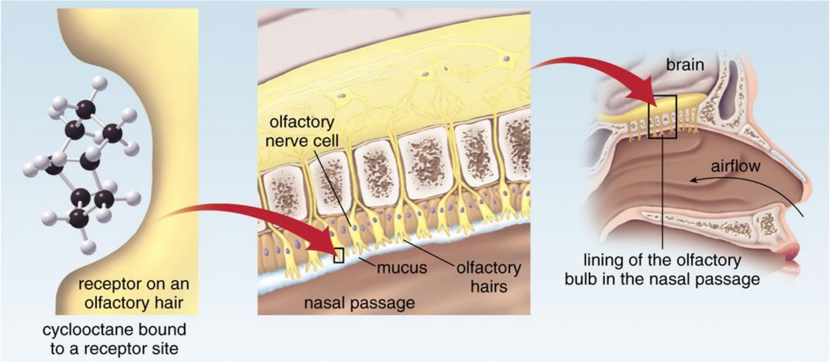
(*S*)-Carvone has the odor of caraway.

(*R*)-Carvone has the odor of spearmint.

(caraway): © The McGraw-Hill Companies, Inc./Elite Images; (spearmint): © David Sieren/Visuals Unlimited

Molecular Shape and the Sense of Smell

Figure 5.13



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.

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