

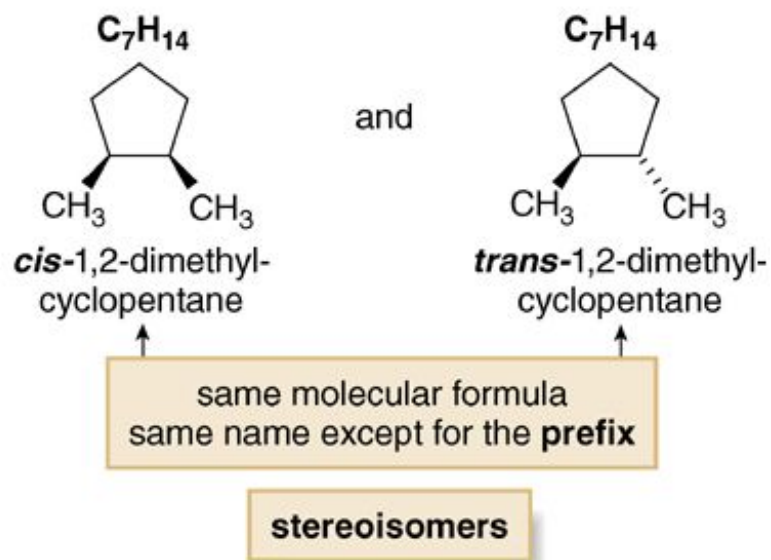
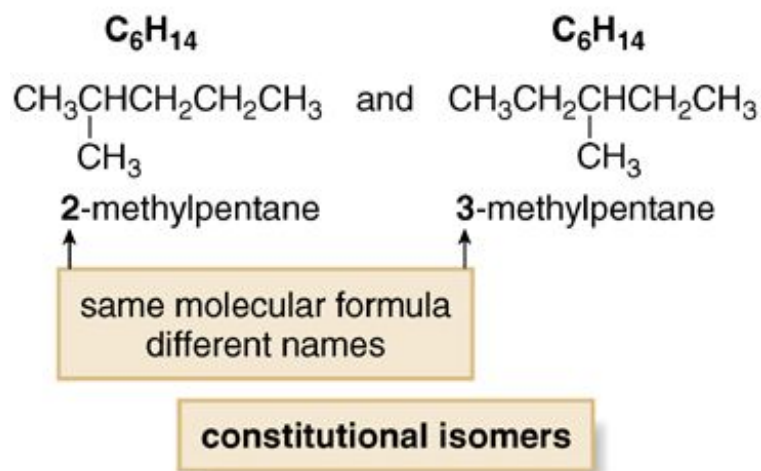
# Stereochemistry

## The Two Major Classes of Isomers

- Recall that 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, the same or different functional groups, different physical properties and different chemical properties.
  - **Stereoisomers** differ only in the way the atoms are oriented in space. They have identical IUPAC names (except for a prefix like *cis* or *trans*). They always have the same functional group(s).
- A particular three-dimensional arrangement is called a **configuration**. **Stereoisomers differ in configuration.**

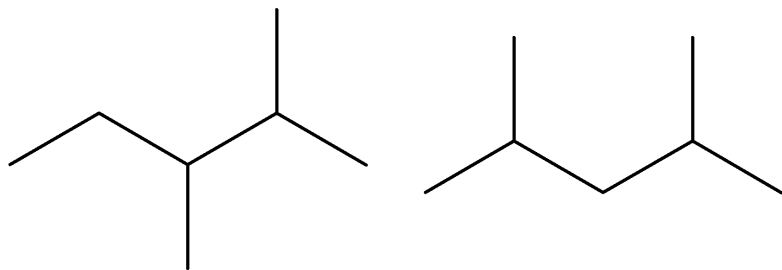
Figure 5.3

A comparison of constitutional isomers and stereoisomers



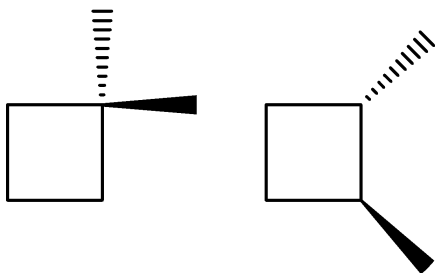
**Are the following pairs of compounds constitutional isomers or stereoisomers?**

**a)**



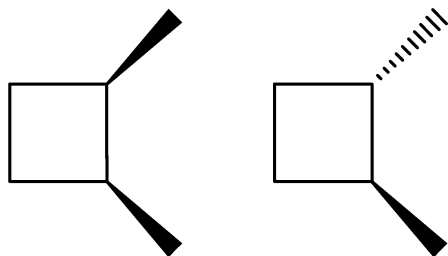
**constitutional**

**b)**



**constitutional**

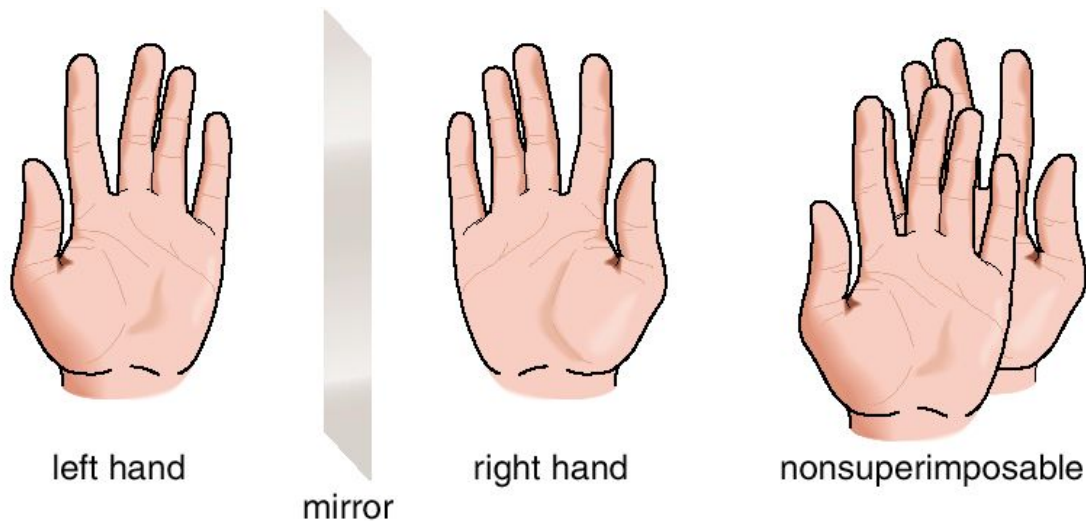
**c)**



**stereoisomer**

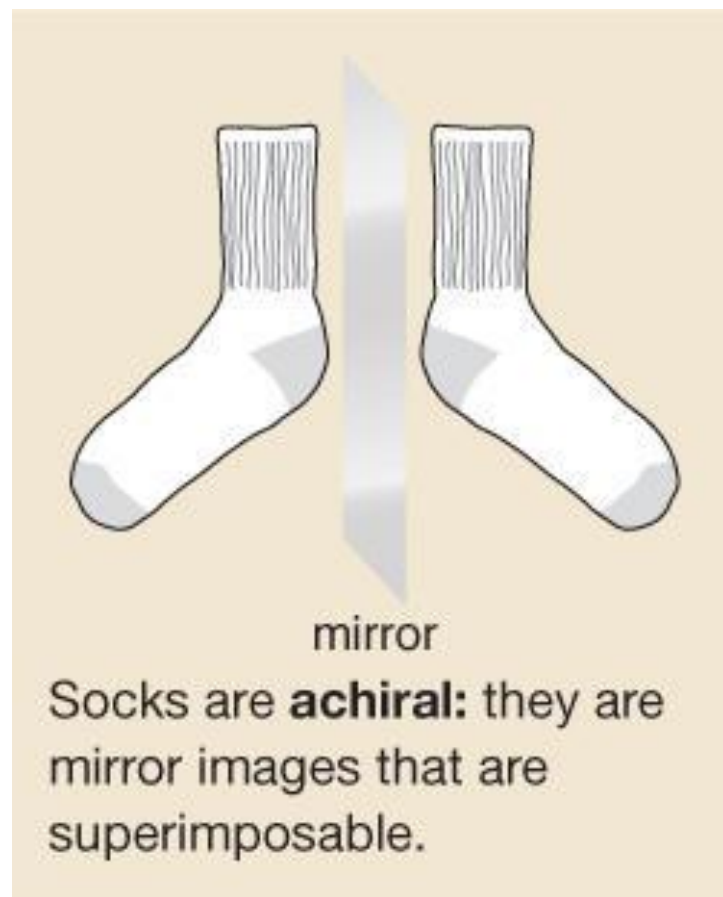
# Chiral and Achiral Molecules

- Although everything has a mirror image, mirror images may or may not be **superimposable**.
- Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or **superimposable**.

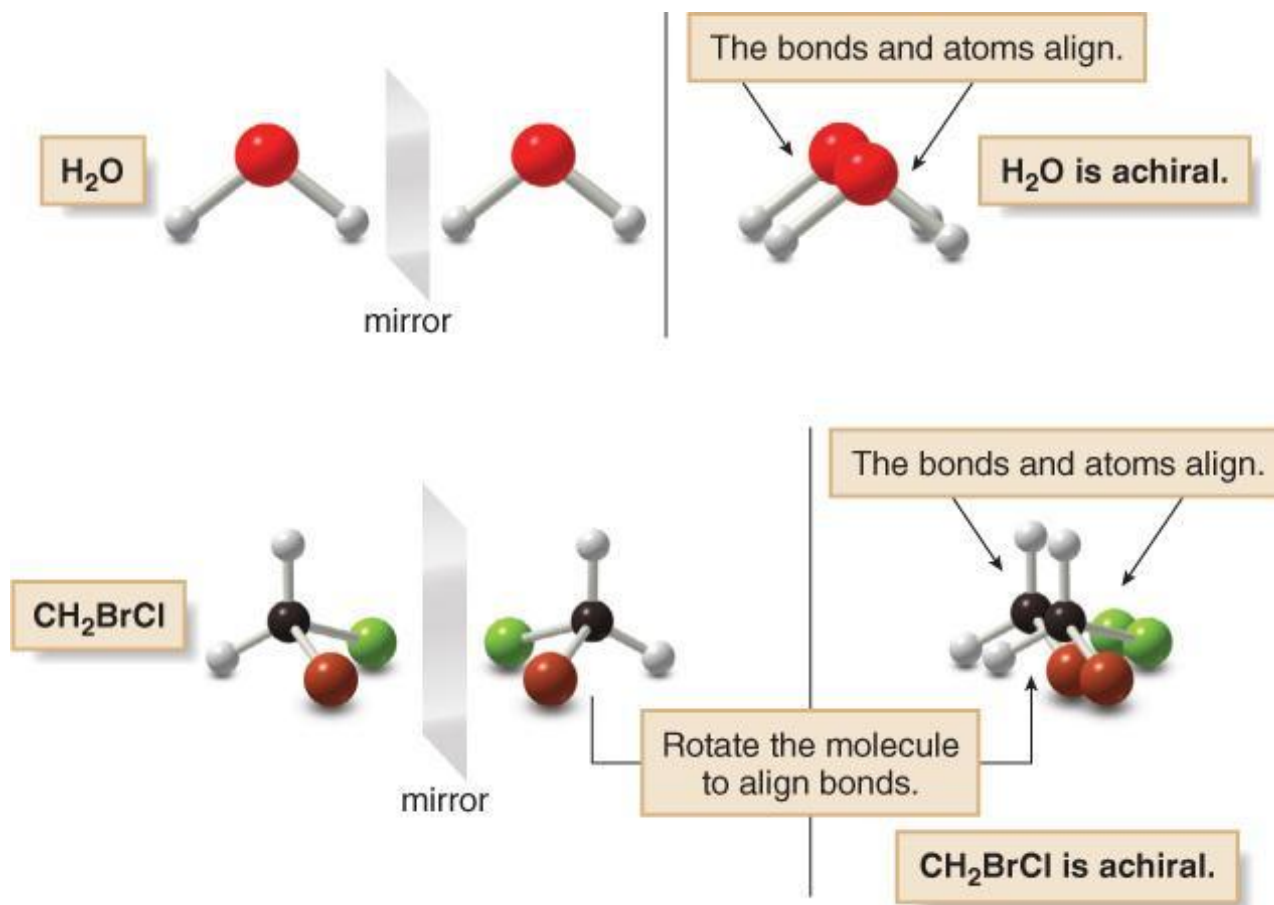


- A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral*.

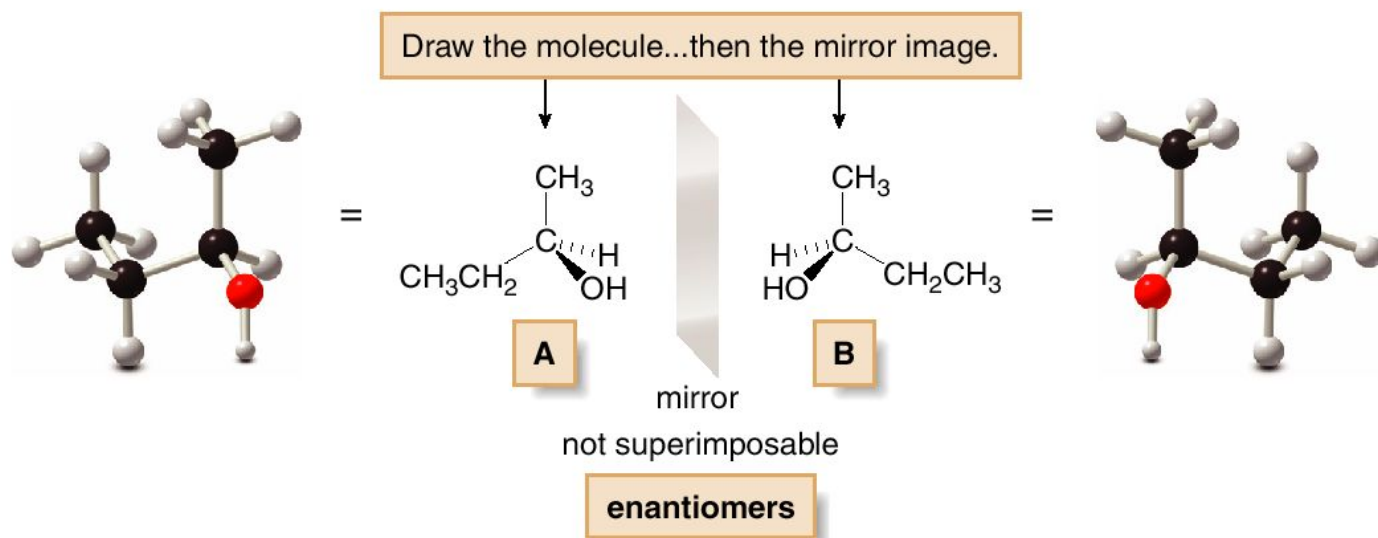
- Other molecules are like socks. Two socks from a pair are mirror images that are superimposable. A sock and its mirror image are identical.
- A molecule or object that is superimposable on its mirror image is said to be **achiral**.
- A molecule or object that is not superimposable on its mirror image is said to be **chiral**.



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



- 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, 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**.



- In general, a molecule with no stereogenic centers will not be chiral. There are exceptions to this that will be considered in Chapter 17.
- With one stereogenic center, a molecule will always be chiral.
- With two or more stereogenic centers, a molecule may or may not be chiral.
- Achiral molecules usually contain a **plane of symmetry** but chiral molecules do not.
- **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.



Aligning the C–Cl and C–Br bonds  
in each molecule.

$\text{CH}_2\text{BrCl}$   
plane of symmetry



This molecule has  
**two identical halves.**

$\text{CH}_2\text{BrCl}$  is **achiral.**

$\text{CHBrCIF}$   
NO plane of symmetry



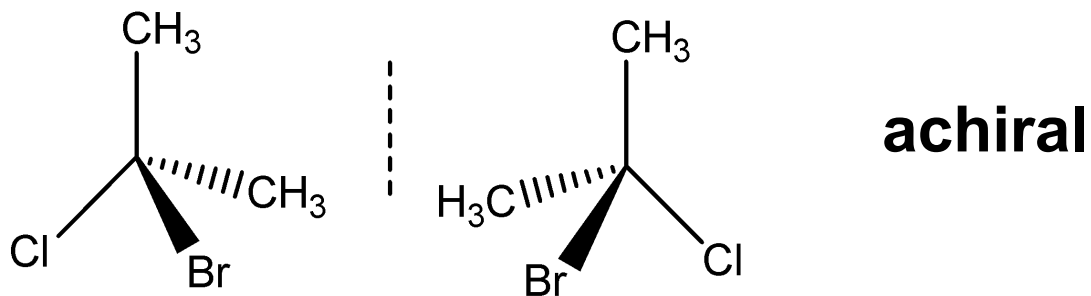
$\text{CHBrCIF}$  is **chiral.**

## **Summary of the Basic Principles of Chirality:**

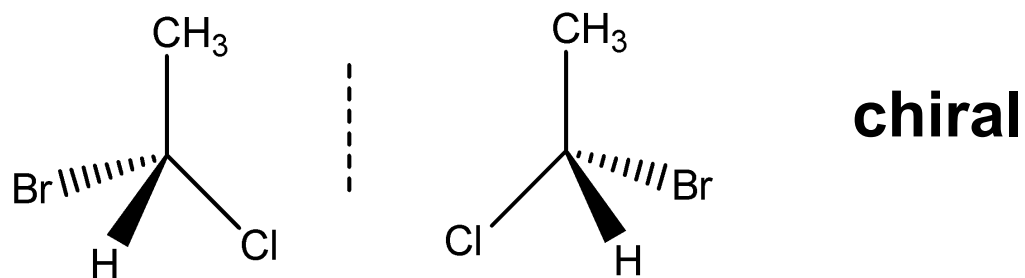
- Everything has a mirror image. The fundamental question is whether the molecule and its mirror image are superimposable.**
- If a molecule and its mirror image are not superimposable, the molecule and its mirror image are chiral.**
- The terms stereogenic center and chiral molecule are related but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

**Classify each of the following pairs as chiral or achiral.**

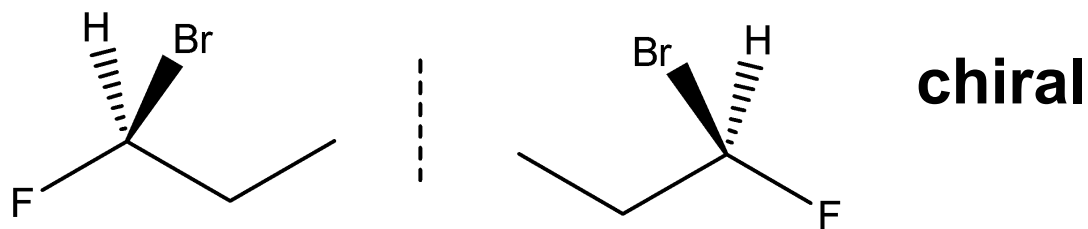
**a)**



**b)**

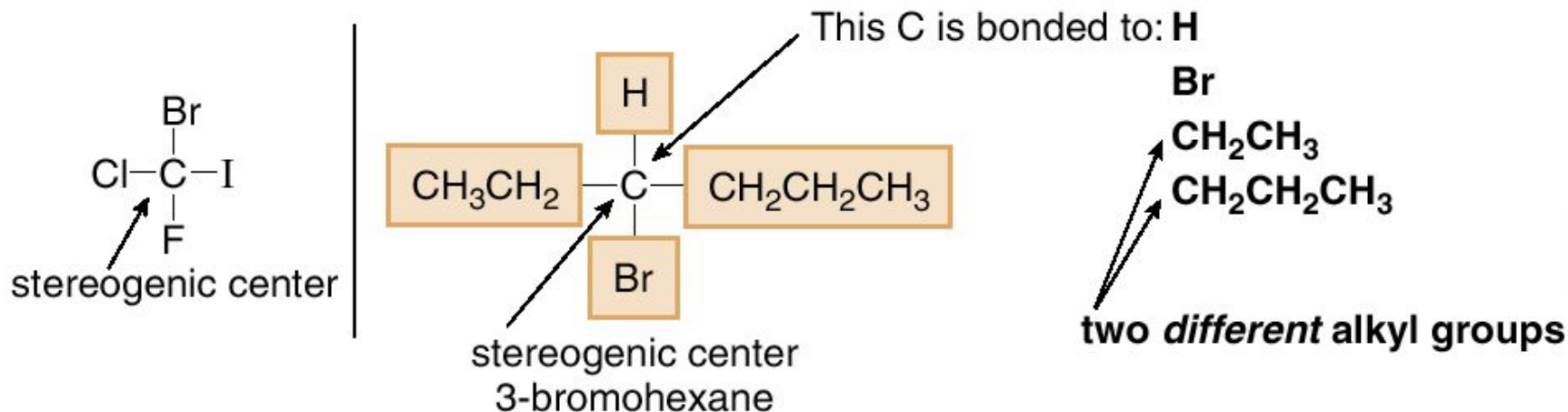


**c)**

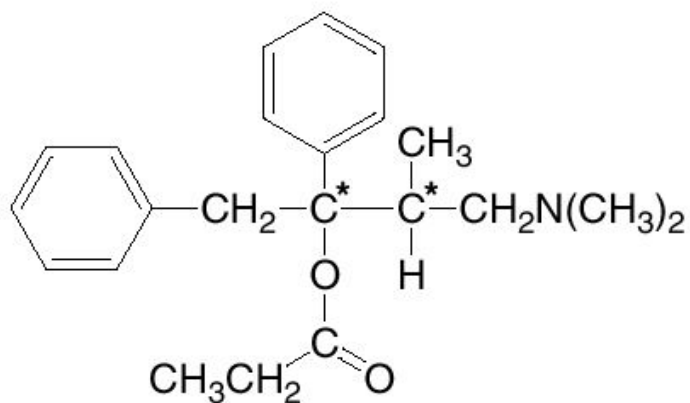


# Stereogenic Centers

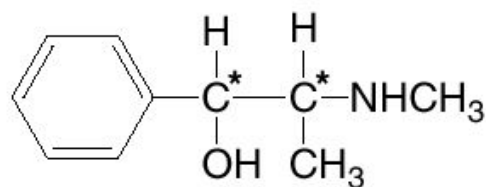
- To locate a stereogenic center, examine each tetrahedral carbon atom in a molecule, and look at the four groups—not the four atoms—bonded to it.
- Always omit from consideration all C atoms that cannot be tetrahedral stereogenic centers. These include
  - $\text{CH}_2$  and  $\text{CH}_3$  groups
  - Any  $sp$  or  $sp^2$  hybridized C



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

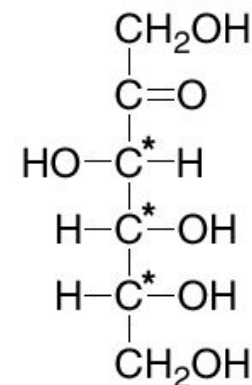


propoxyphene  
Trade name: Darvon  
(analgesic)



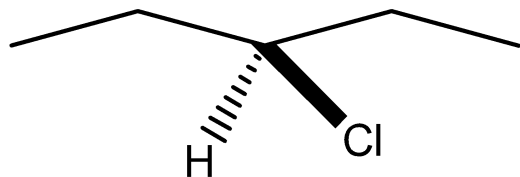
ephedrine  
(bronchodilator, decongestant)

[\* = stereogenic center]

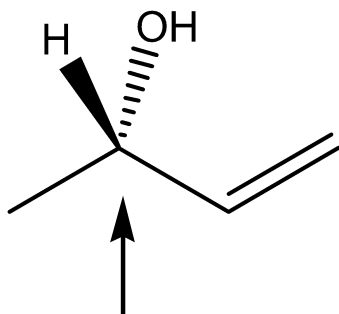
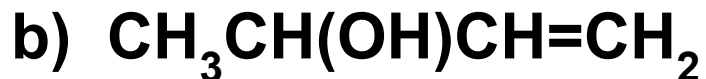


fructose  
(a simple sugar)

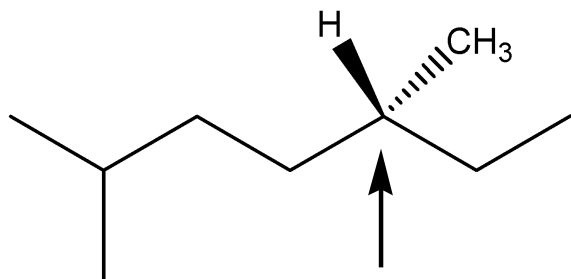
Label the stereogenic centers in each molecule and decide if it is chiral.



achiral



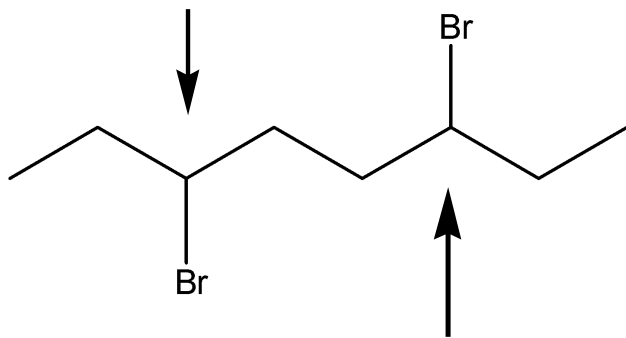
chiral



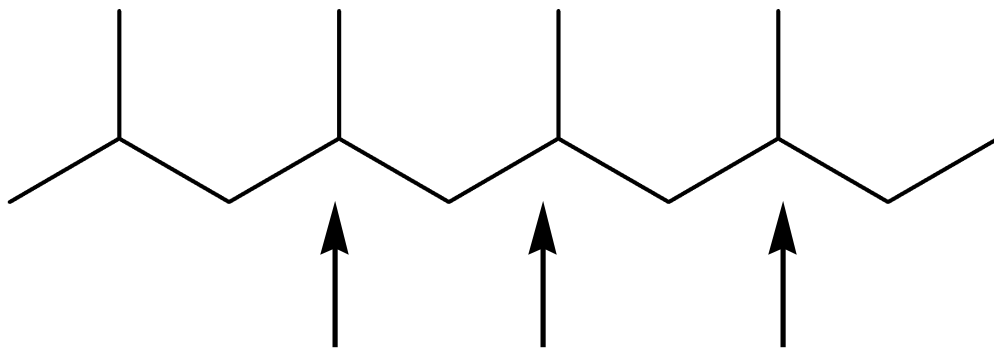
chiral

**How many stereogenic centers does each molecule have?**

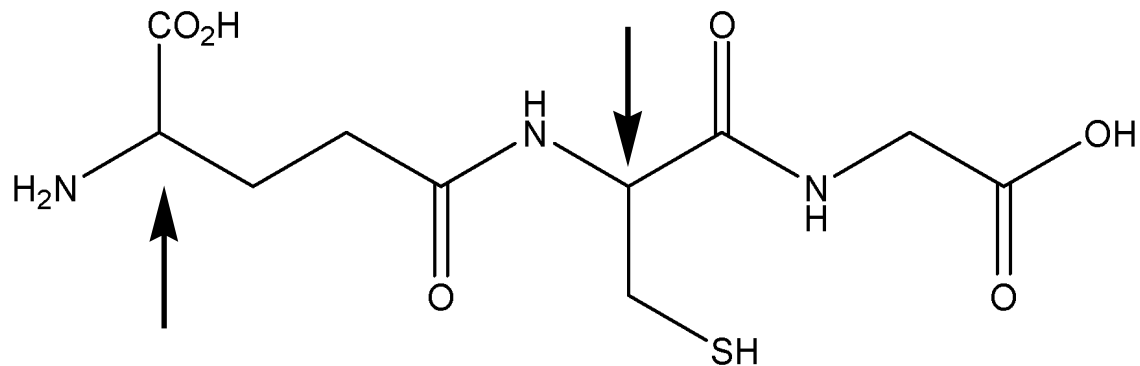
**a)**



**b)**



c)



**Only carbons attached to four different groups.**



- To draw both enantiomers of a chiral compound such as 2-butanol, use the typical convention for depicting a tetrahedron: place two bonds in the plane, one in front of the plane on a wedge, and one behind the plane on a dash. Then, to form the first enantiomer, arbitrarily place the four groups—H, OH, CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub>—on any bond to the stereogenic center. Then draw the mirror image.

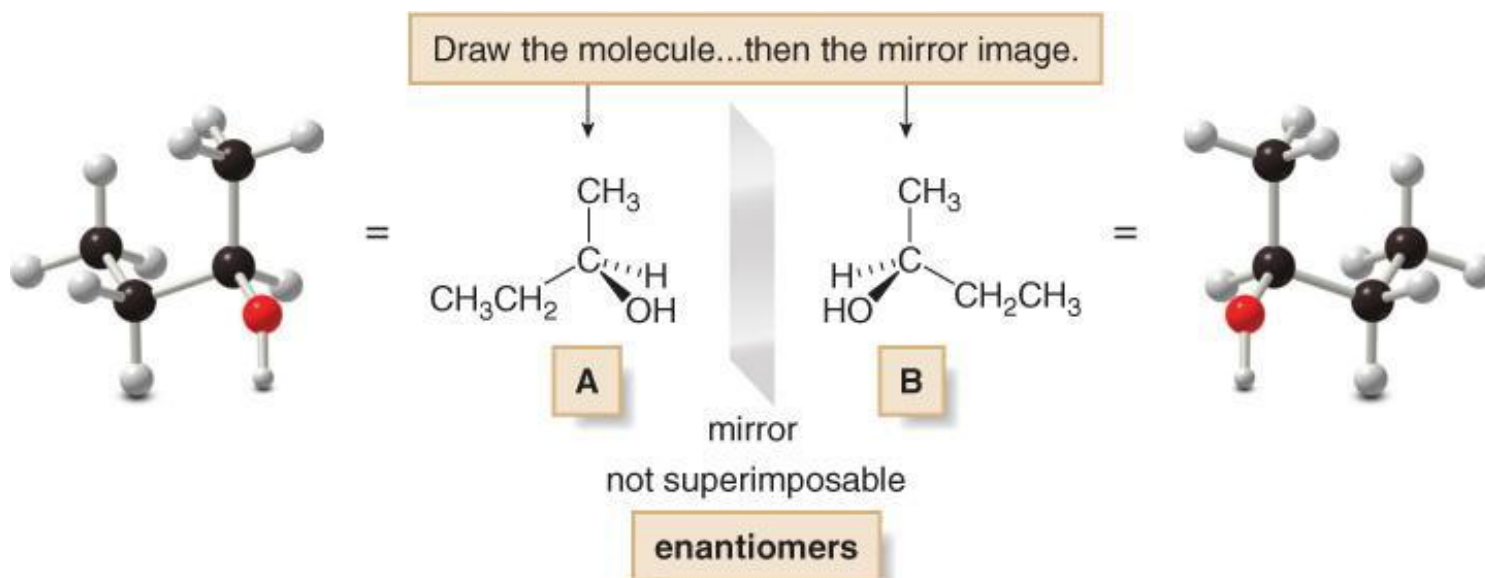
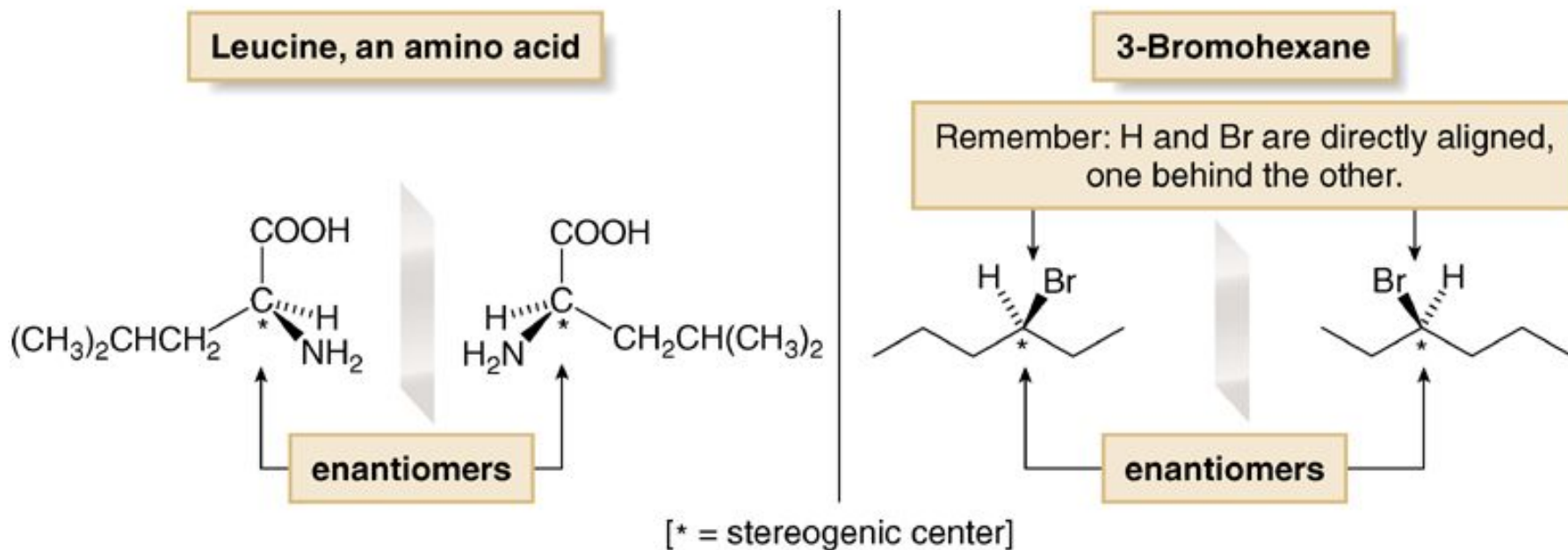
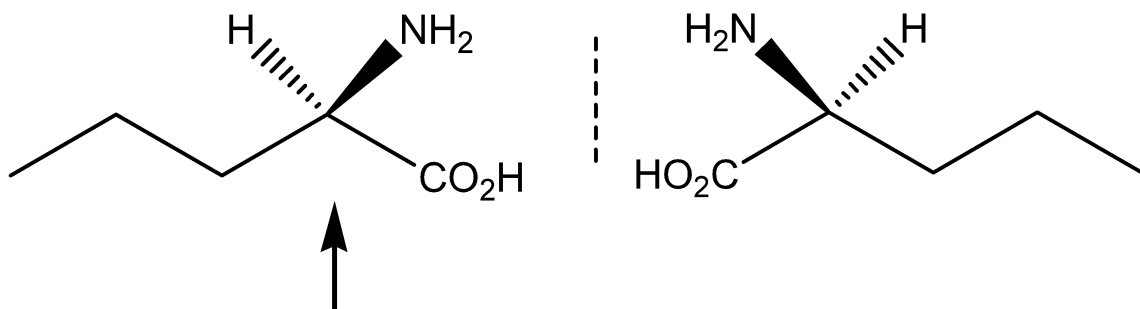
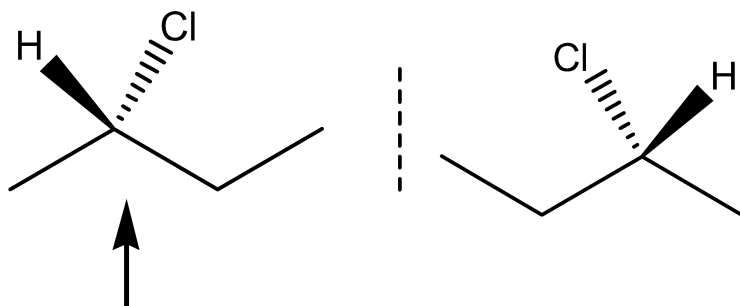
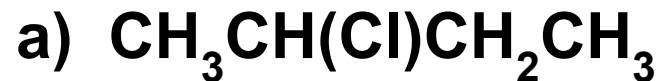


Figure 5.5  
Three-dimensional  
representations for pairs  
of enantiomers

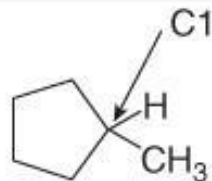


Locate each stereogenic center and draw both enantiomers.

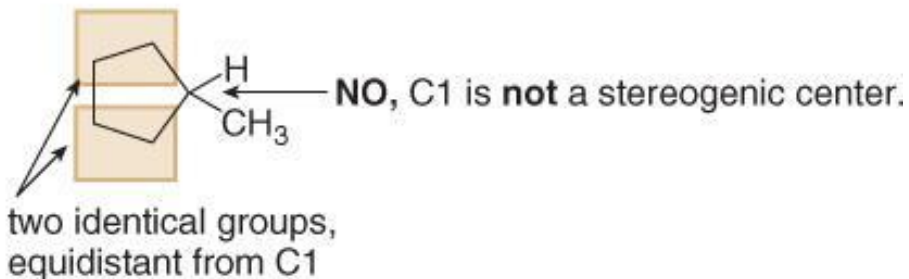


- **Stereogenic centers may also occur at carbon atoms that are part of a ring.**
- **To find stereogenic centers on ring carbons, always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups.**

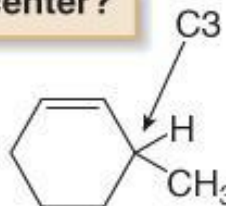
Is C1 a stereogenic center?



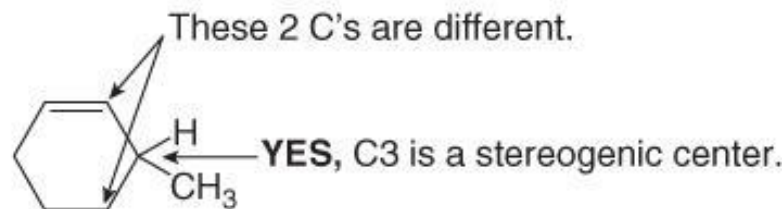
methylcyclopentane



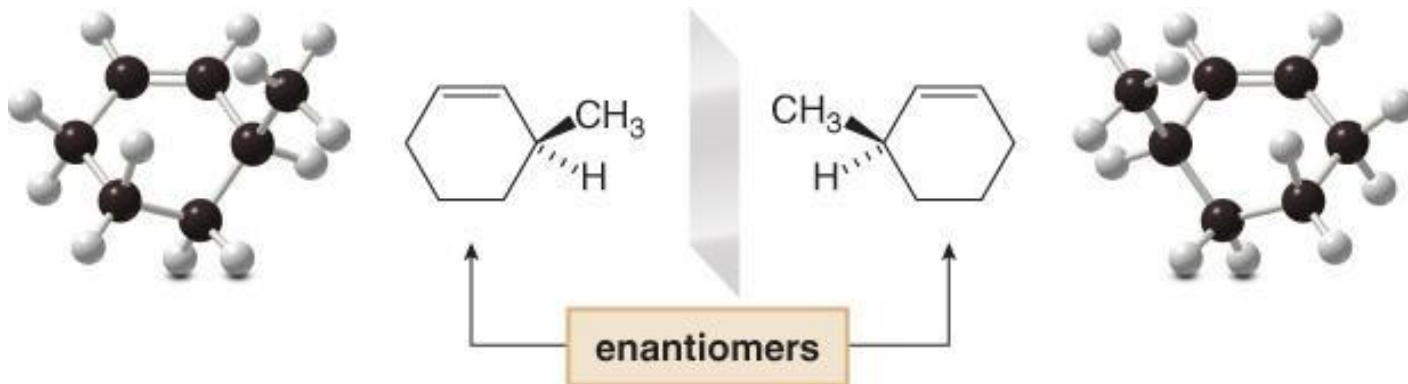
Is C3 a stereogenic center?



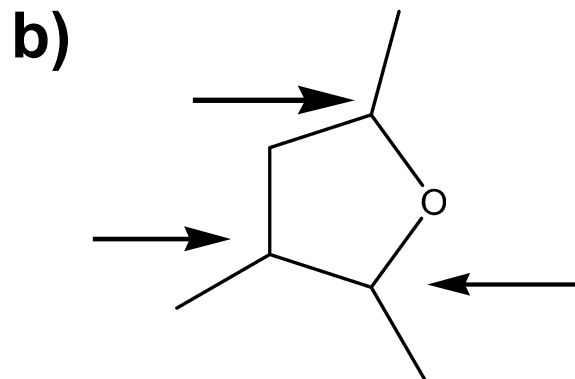
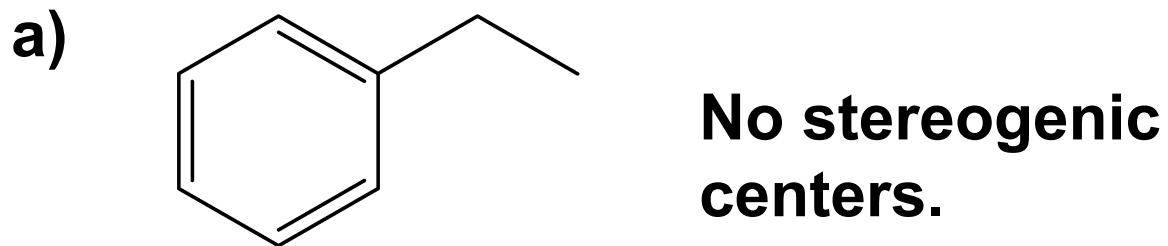
3-methylcyclohexene



- In 3-methylcyclohexene, the  $\text{CH}_3$  and H substituents that are above and below the plane of the ring are drawn with wedges and dashes as usual.

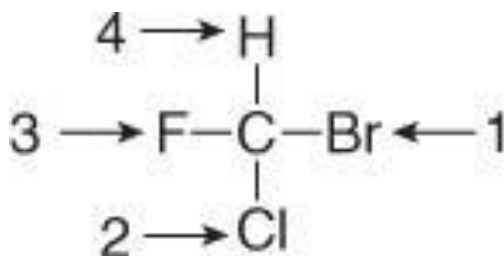


**Locate the stereogenic center in the following:**



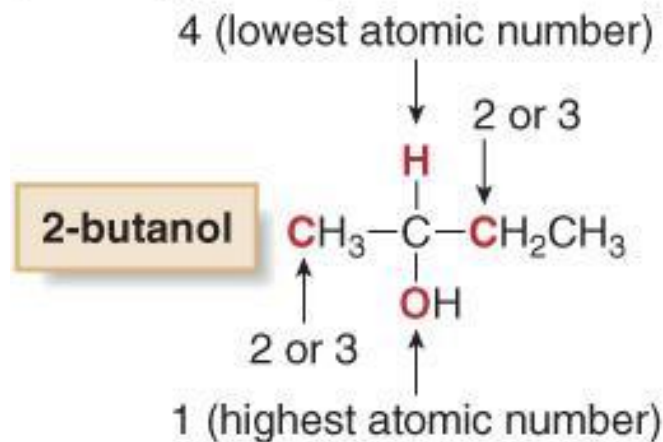
## Labeling Stereogenic Centers with *R* or *S*

- 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.
- Naming enantiomers with the prefixes *R* or *S* is called the **Cahn-Ingold-Prelog** system.
- 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).

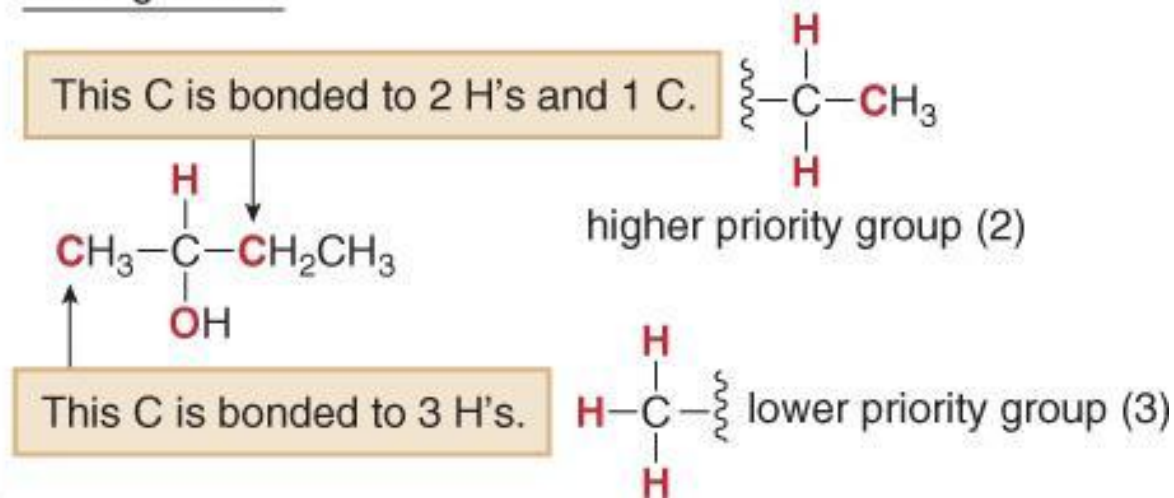


- If two atoms on a stereogenic center are the same, assign priority based on the atomic number of the atoms bonded to these atoms. *One* atom of higher atomic number determines the higher priority.

Following rule 1:



Adding rule 2:



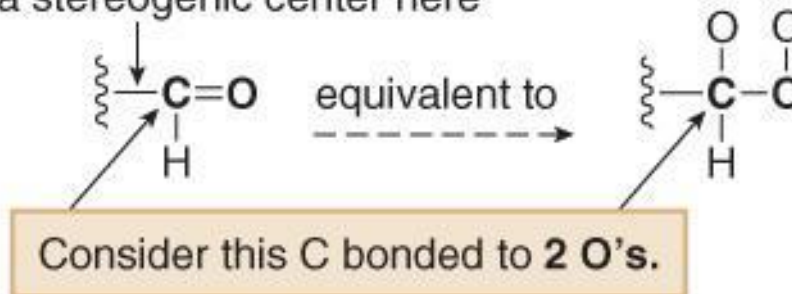


- **If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing mass number. Thus, in comparing the three isotopes of hydrogen, the order of priorities is:**

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

- 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.

bonded to a stereogenic center here



- Other common multiple bonds are drawn below:

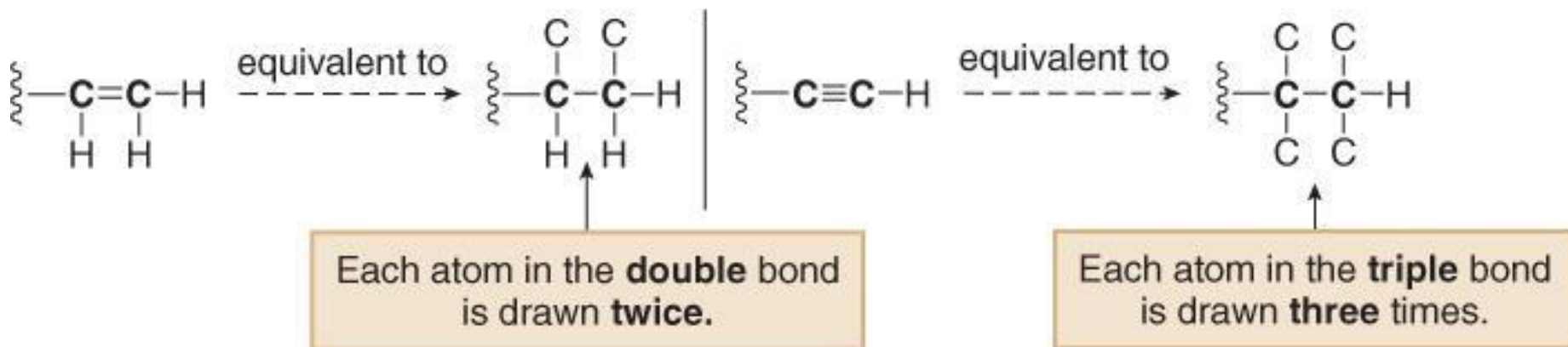
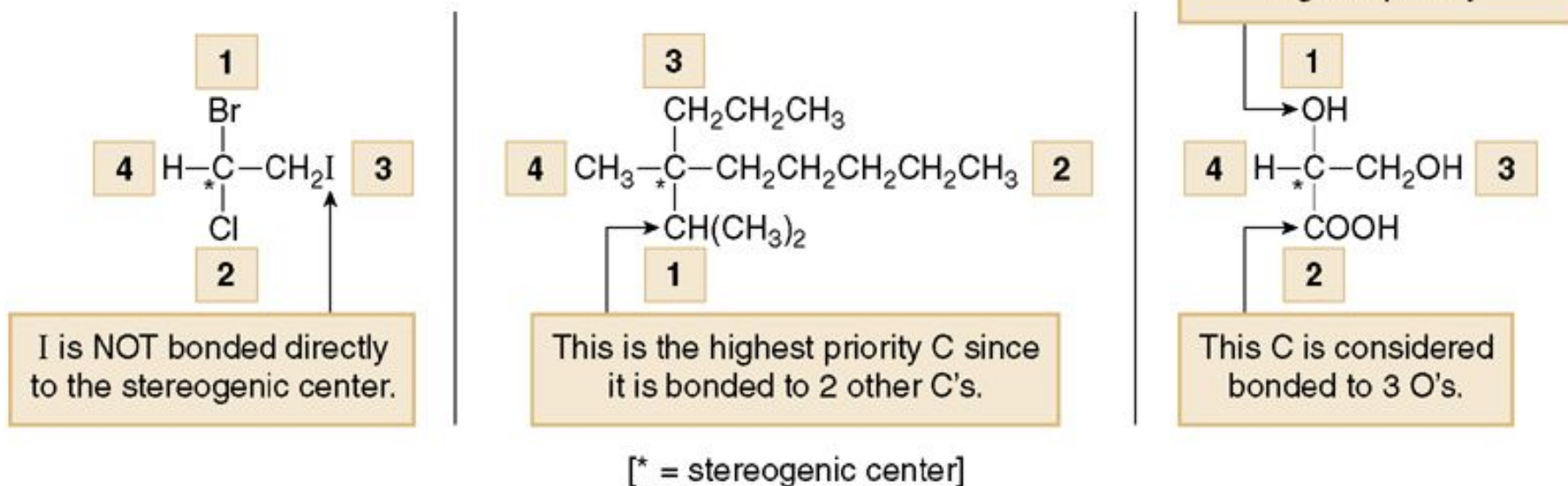


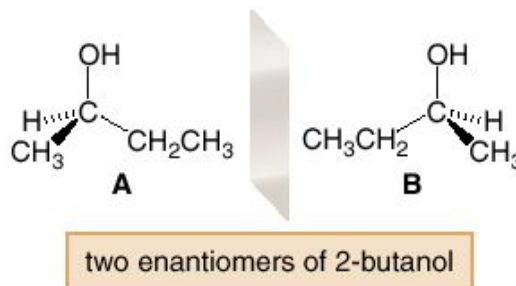
Figure 5.6

Examples of assigning priorities to stereogenic centers



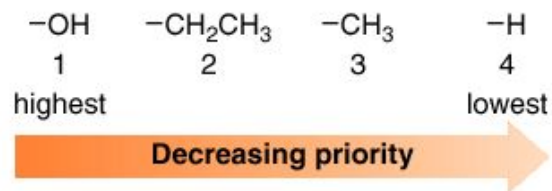
## How To Assign *R* or *S* to a Stereogenic Center

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.

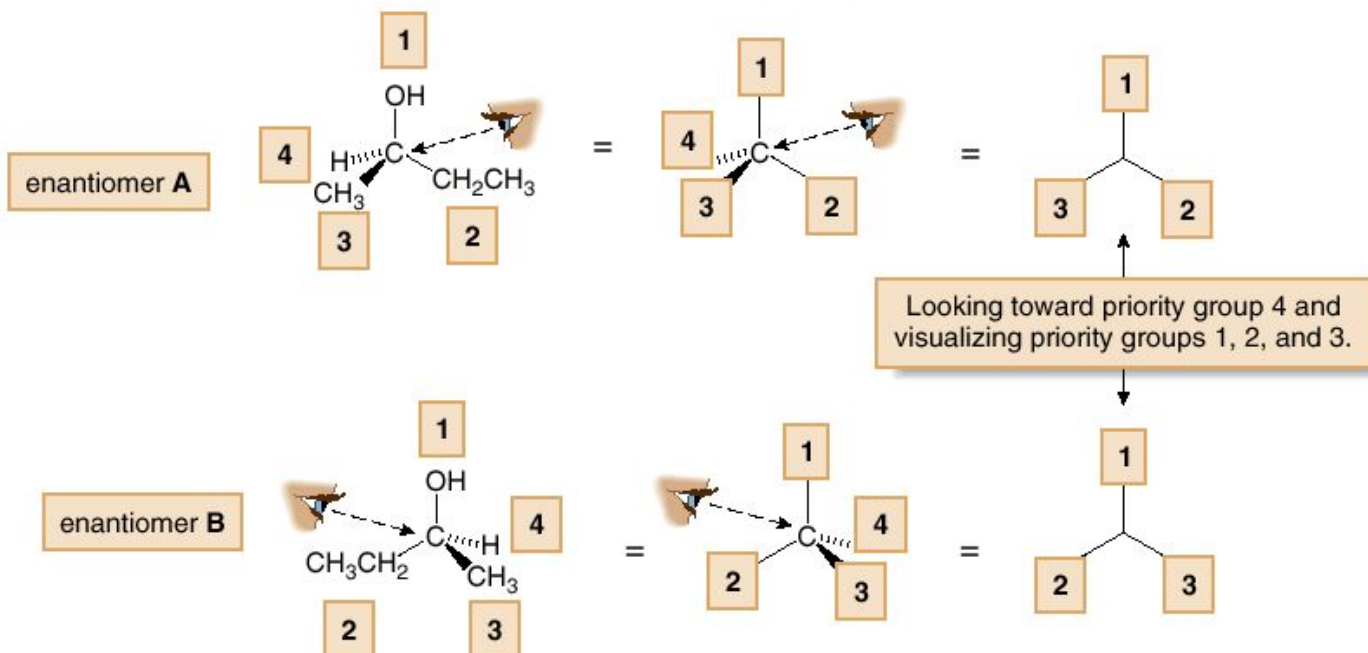


# Labeling Stereogenic Centers with *R* or *S*

## How To, continued . . .

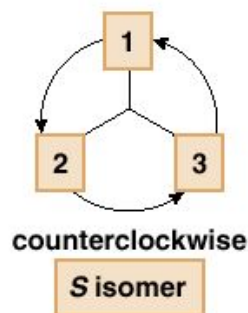
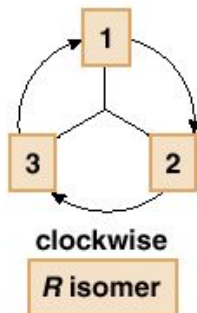
Step [2] Orient the molecule with the lowest priority group (4) *back* (on a *dash*), and visualize the relative positions of the remaining three groups (priorities 1, 2, and 3).

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



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:

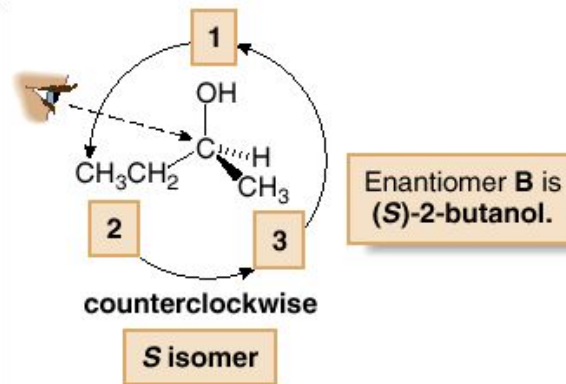
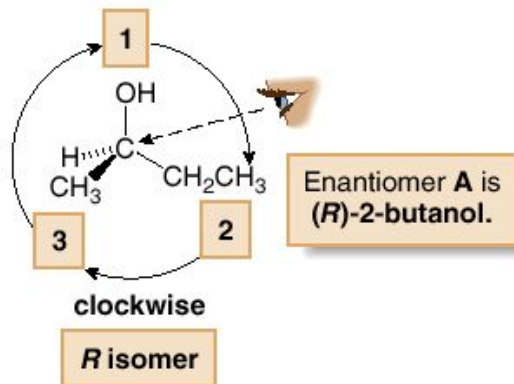
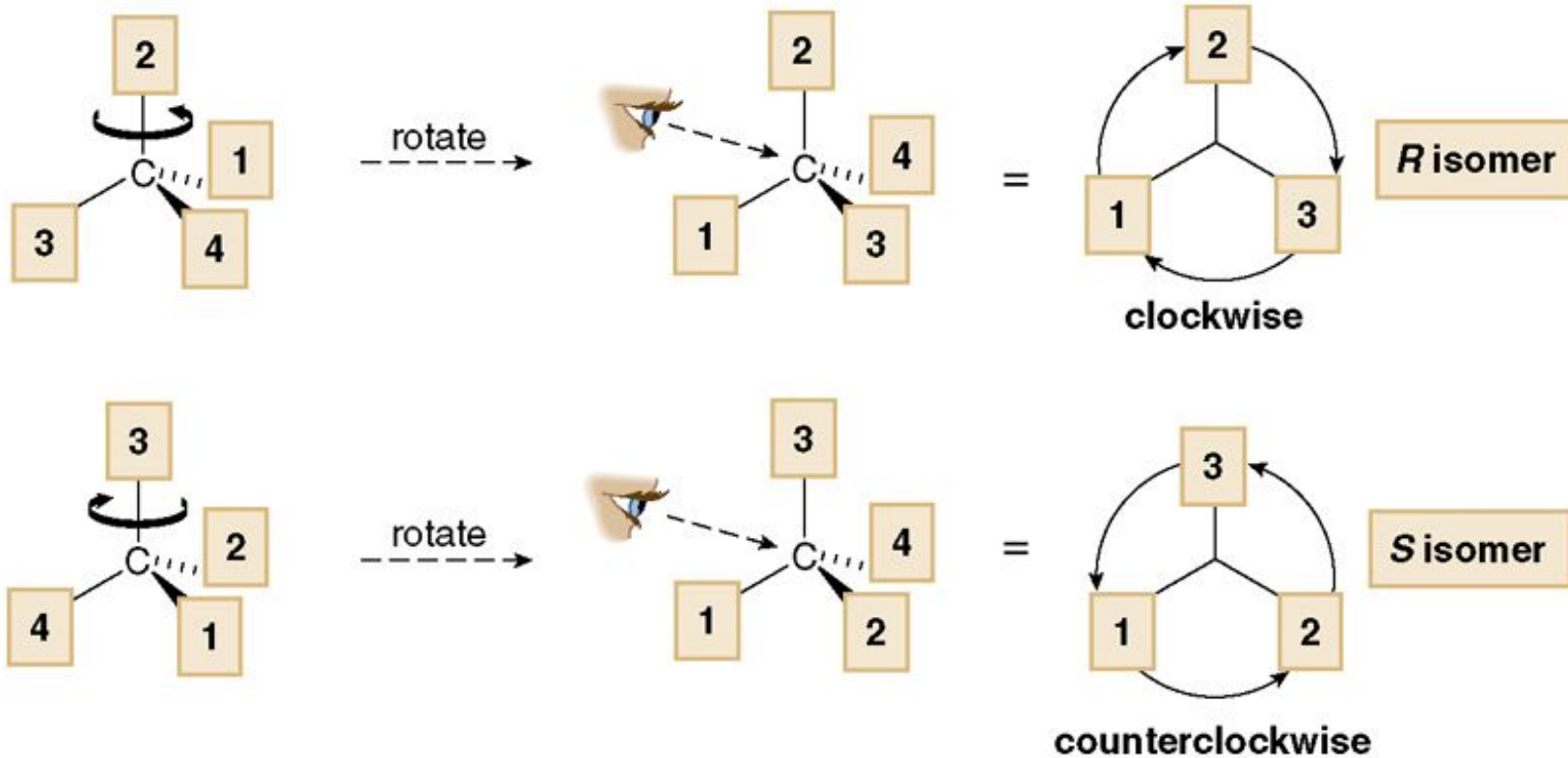


Figure 5.7

Examples: Orienting the lowest priority group in back



Which group in each pair has the highest priority?

a)  $-\text{CH}_3$  or  $-\text{CH}_2\text{CH}_3$

$-\text{CH}_2\text{CH}_3$

b)  $-\text{I}$  or  $-\text{Br}$

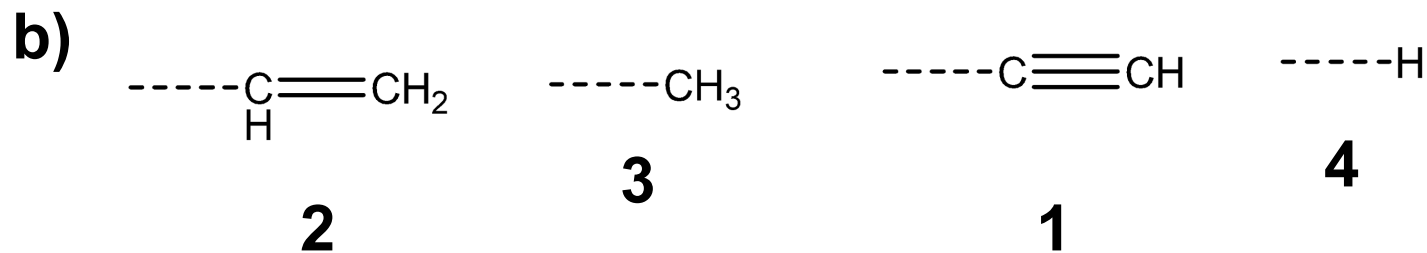
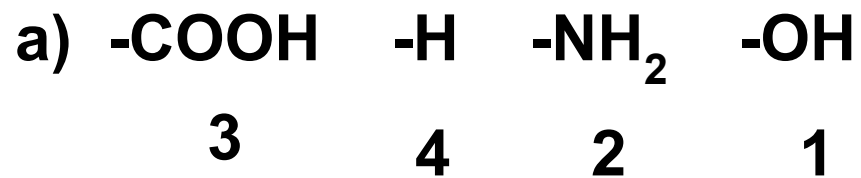
$-\text{I}$

c)  $-\text{CH}_3\text{Br}$  or  $-\text{CH}_2\text{CH}_2\text{Br}$

$-\text{CH}_3\text{Br}$

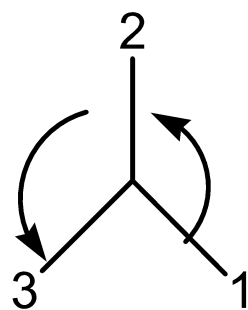
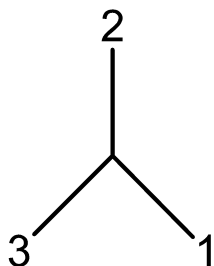
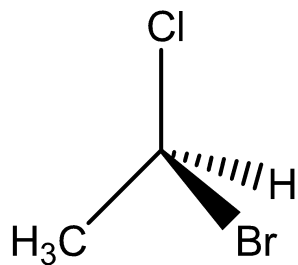


Rank in order of decreasing priority:



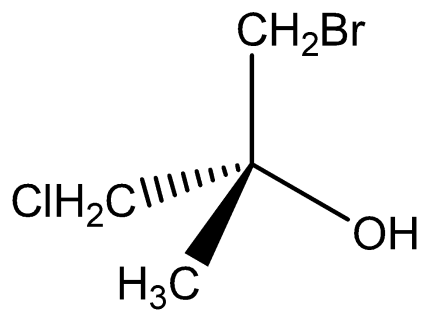
Label each compound as R or S.

a)

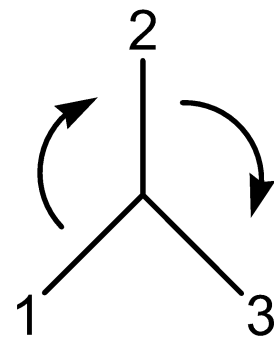
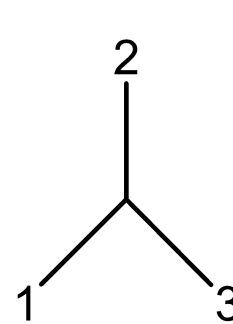
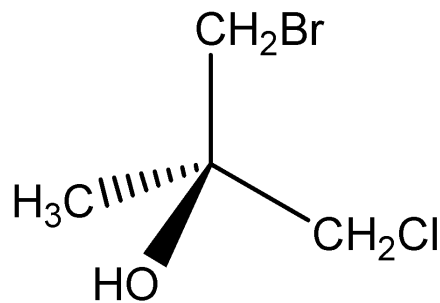


**S**

b)



rotate  
→



**R**

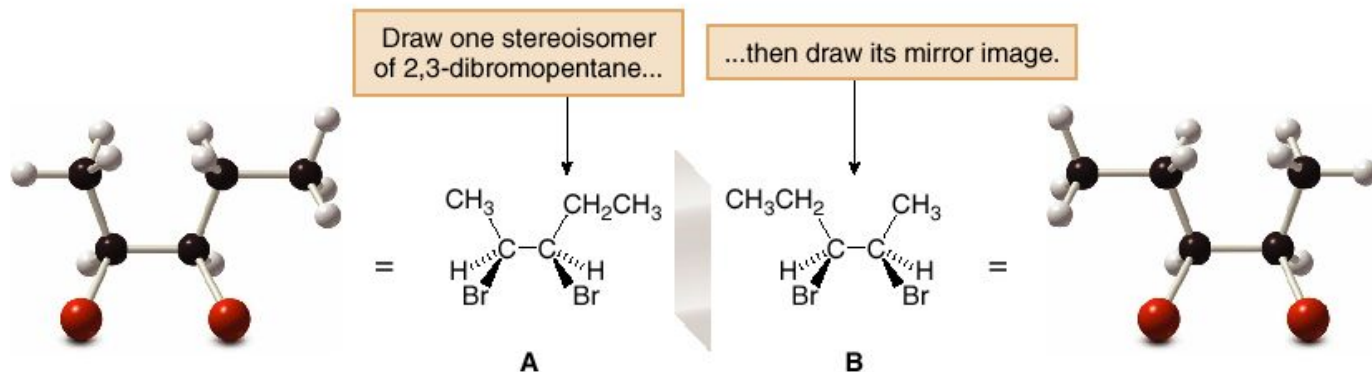
# Diastereomers

- For a molecule with  $n$  stereogenic centers, the maximum number of stereoisomers is  $2^n$ . Let us consider the stepwise procedure for finding all the possible stereoisomers of 2,3-dibromopentane.

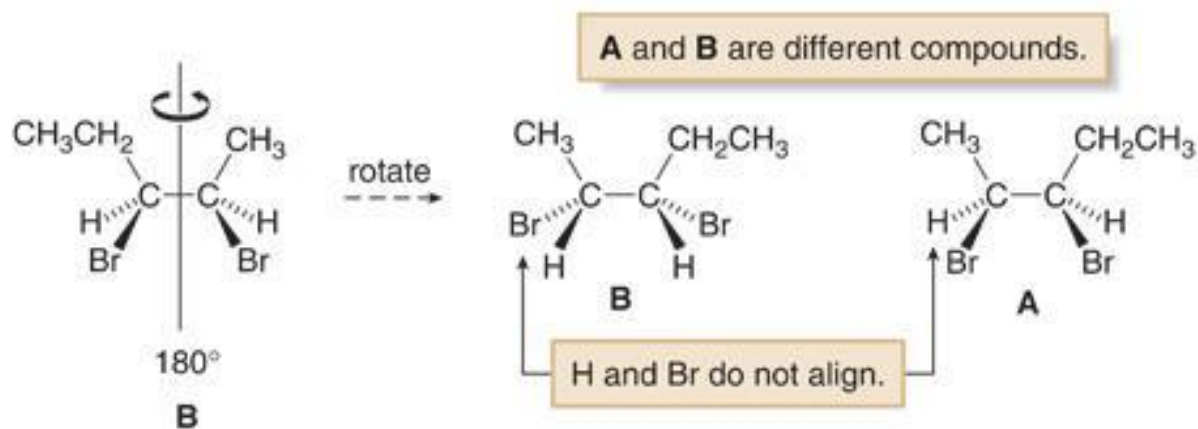
## How To

### 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.



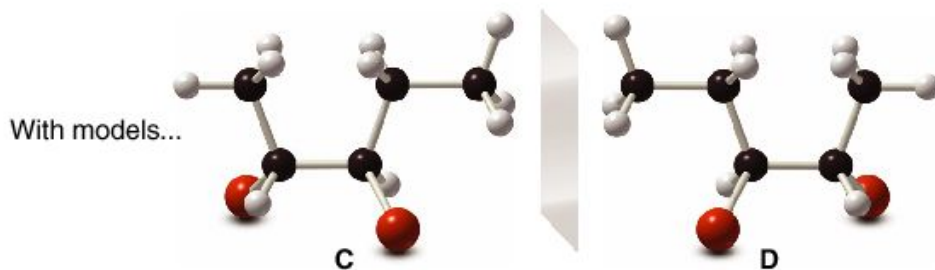
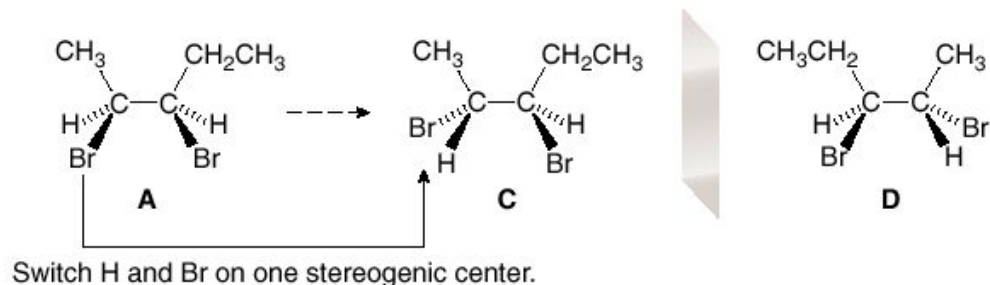
- If you have drawn the compound and the mirror image in the described manner, you have only to do two operations to see if the atoms align. Place B directly on top of A; and rotate B 180° and place it on top of A to see if the atoms align.



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

- 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 A and B. The mirror image of C is labeled D. C and D are enantiomers.

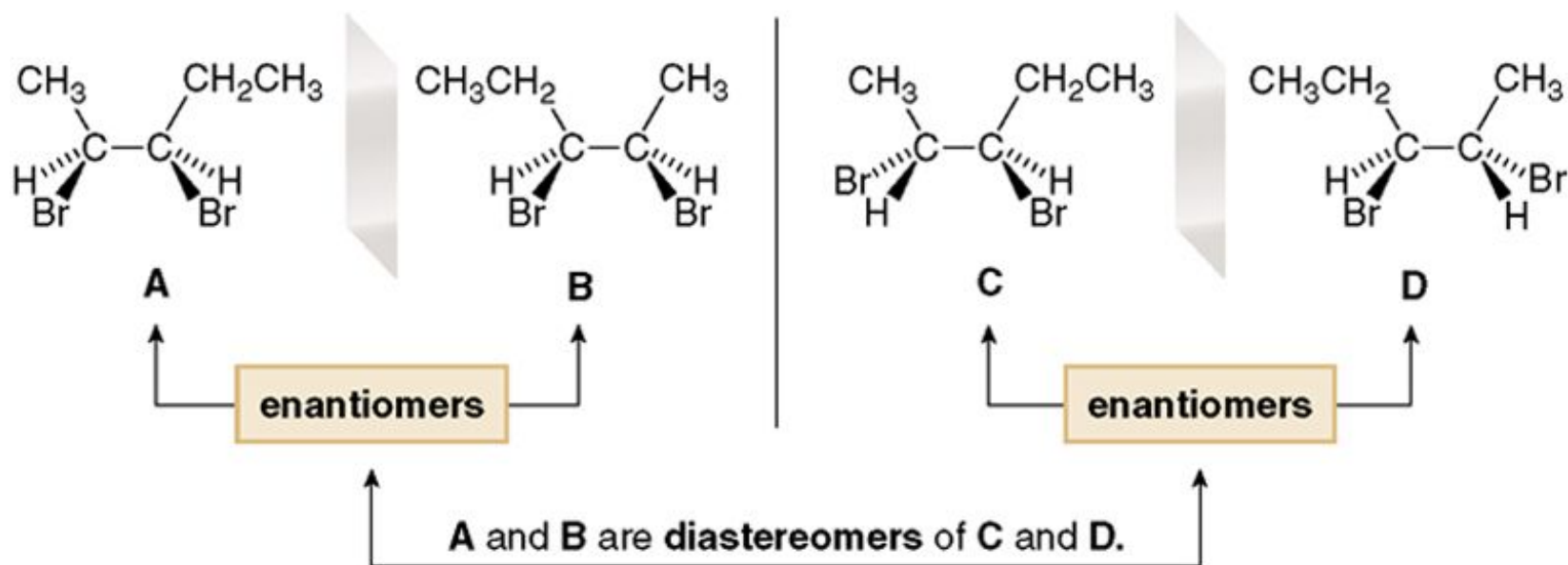
*How To, continued . . .*



- Stereoisomers that are not mirror images of one another are called **diastereomers**. For example, A and C are diastereomers.

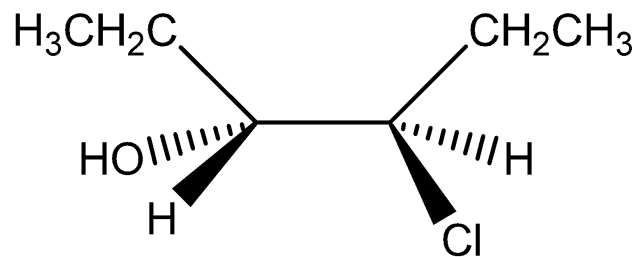
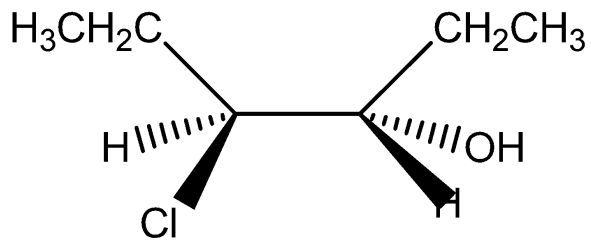
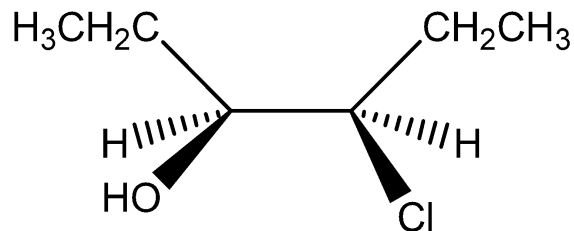
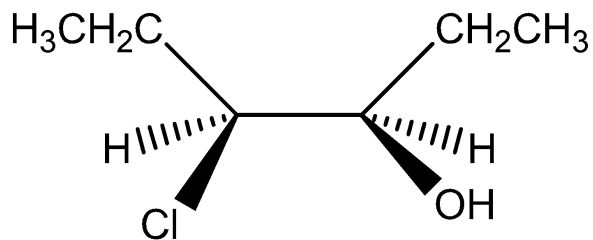
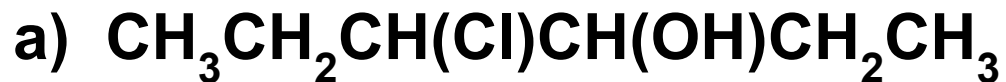
Figure 5.8

Summary: The four stereoisomers of 2,3-dibromopentane



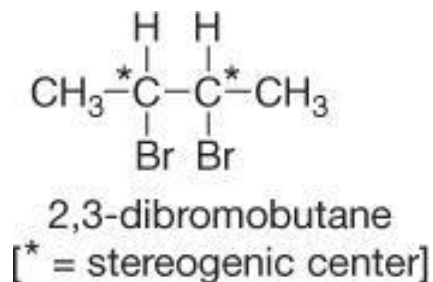
- Pairs of enantiomers: **A and B**; **C and D**.
- Pairs of diastereomers: **A and C**; **A and D**; **B and C**; **B and D**.

Label the stereogenic centers and draw all stereoisomers.

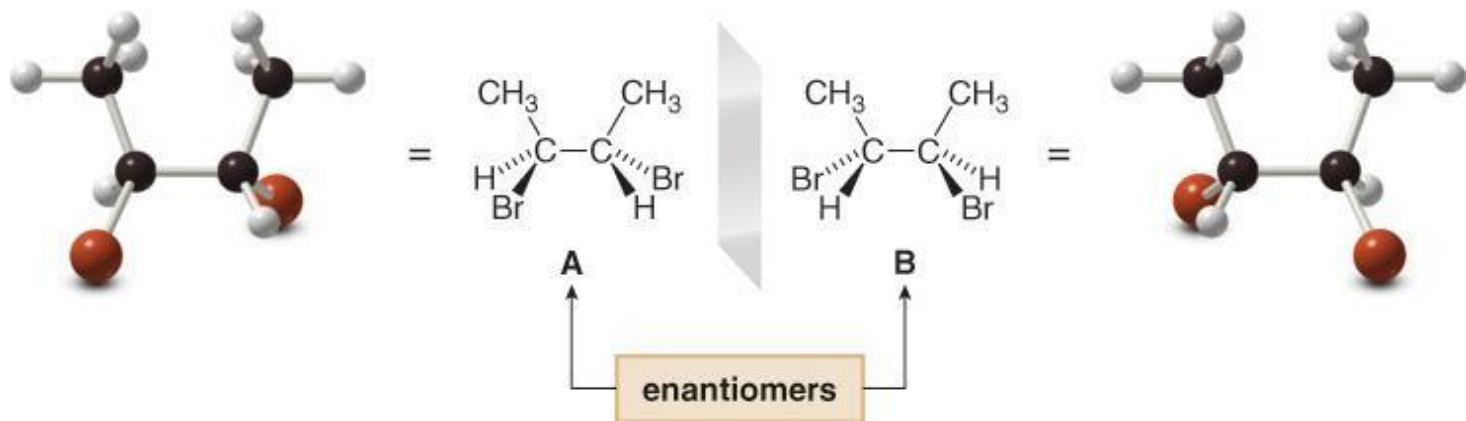


## Meso Compounds

- Let us now consider the stereoisomers of 2,3-dibromobutane. Since this molecule has two stereogenic centers, the maximum number of stereoisomers is 4.

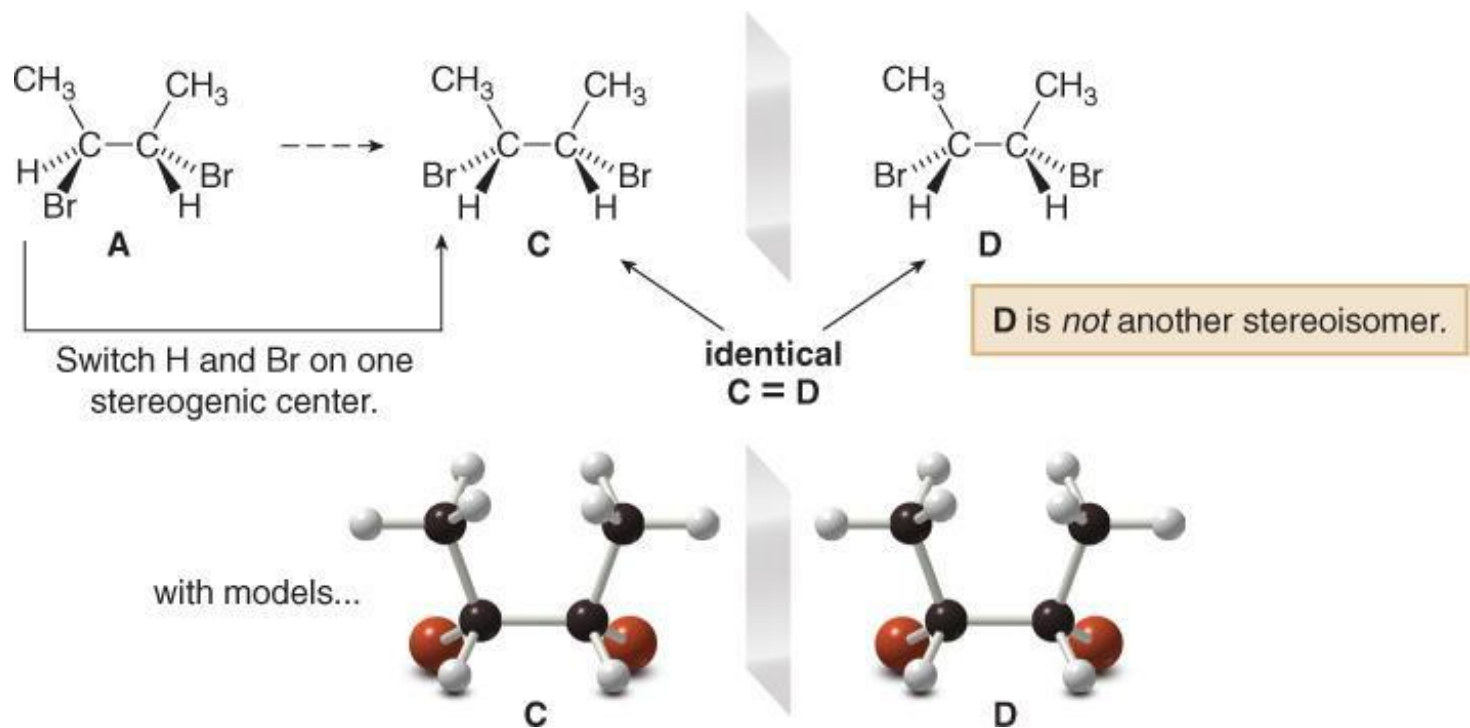


- To find all the stereoisomers of 2,3-dibromobutane, arbitrarily add the H, Br, and CH<sub>3</sub> groups to the stereogenic centers, forming one stereoisomer A, and then draw its mirror image, B.



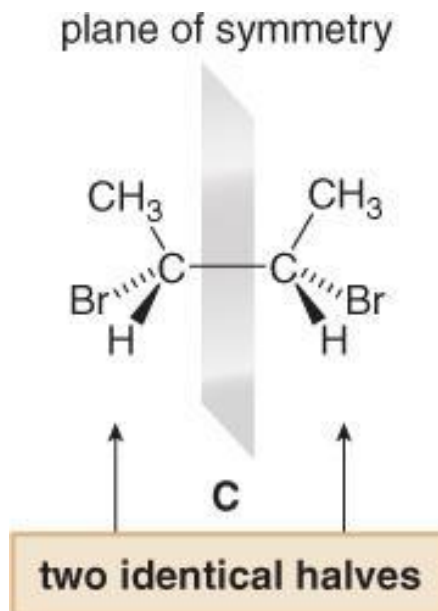


- To find the other two stereoisomers if they exist, switch the position of two groups on one stereogenic center of one enantiomer only. In this case, switching the positions of H and Br on one stereogenic center of A forms C, which is different from both A and B.



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

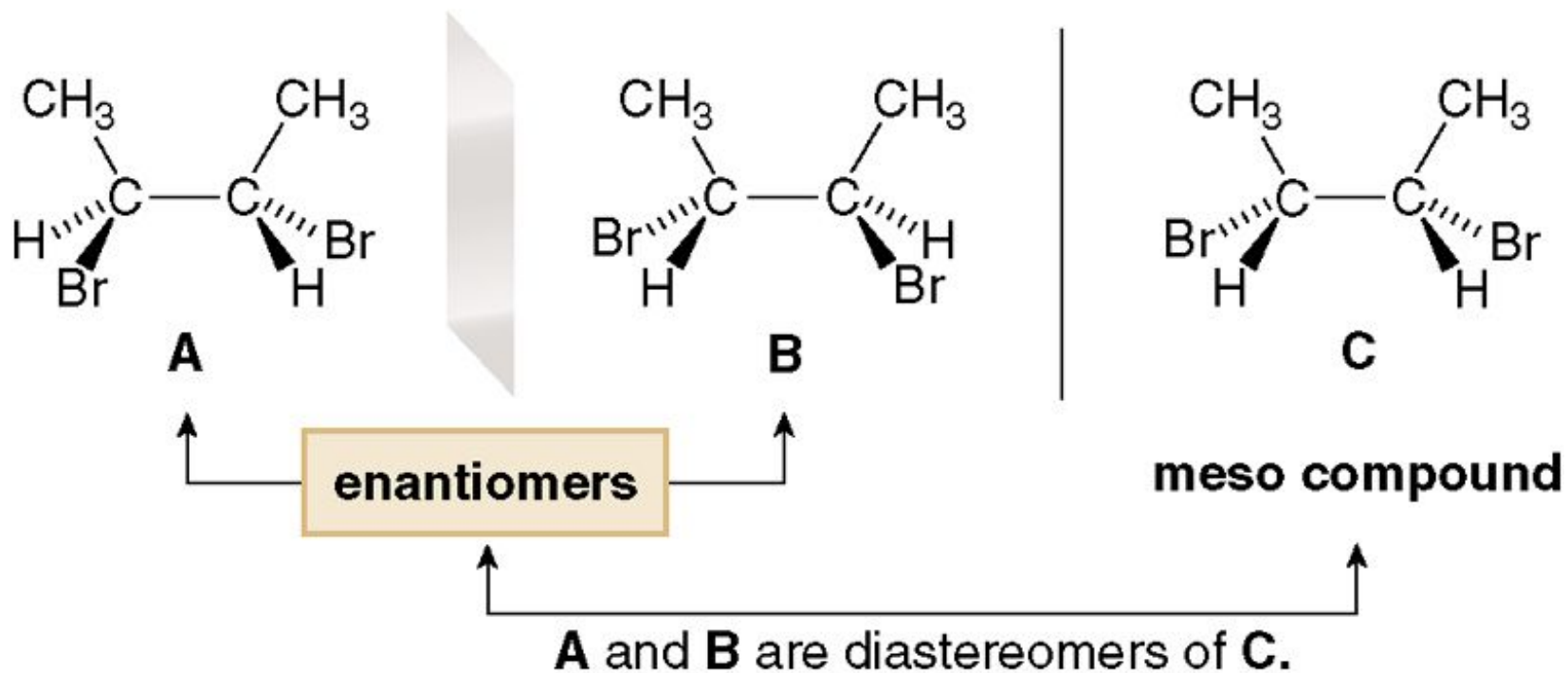
- **Compound C** contains a plane of symmetry, and is achiral.
- **Meso compounds generally contain a plane of symmetry** so that they possess two identical halves.



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

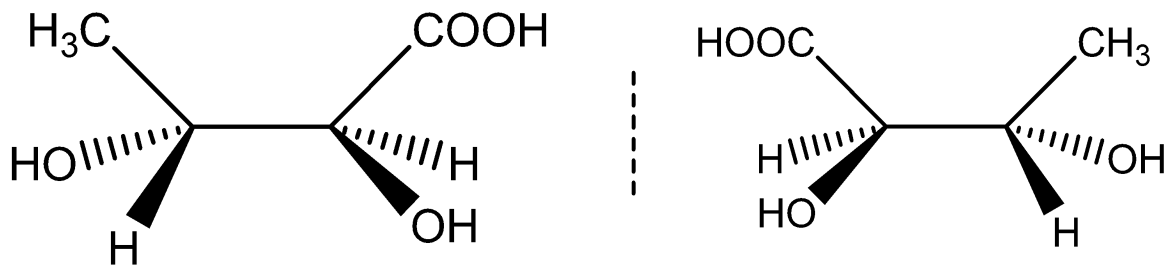
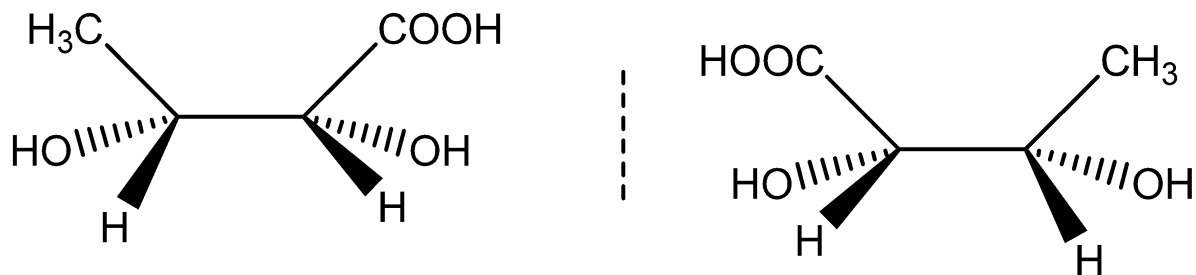
Figure 5.9

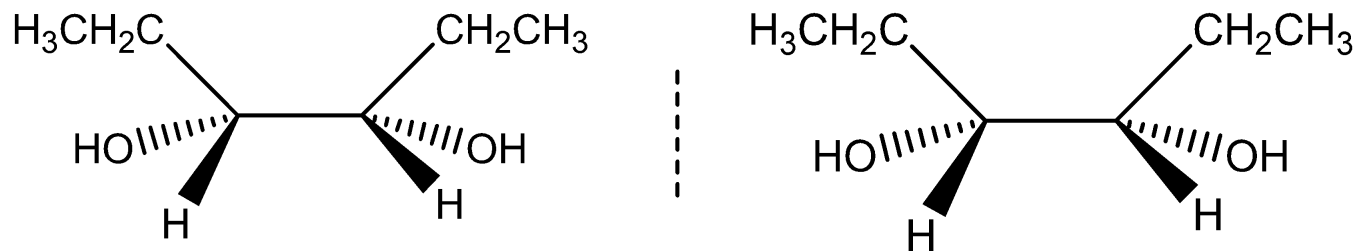
Summary: The three stereoisomers 2,3-dibromobutane



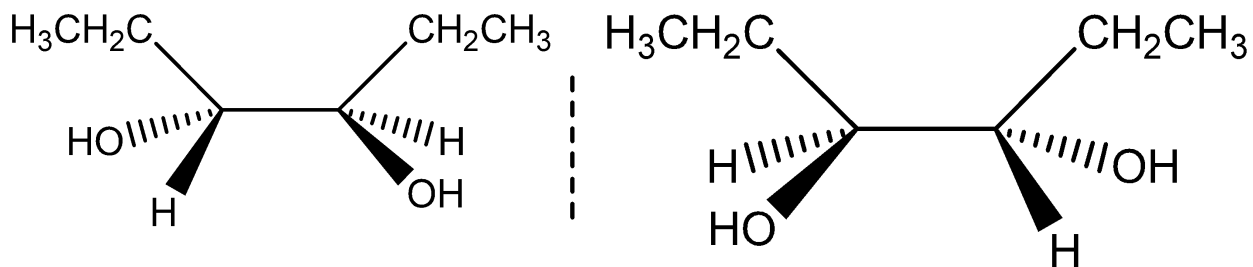
- Pair of enantiomers: **A** and **B**.
- Pairs of diastereomers: **A** and **C**; **B** and **C**.

Draw the enantiomer and one diastereomer for the following compound.





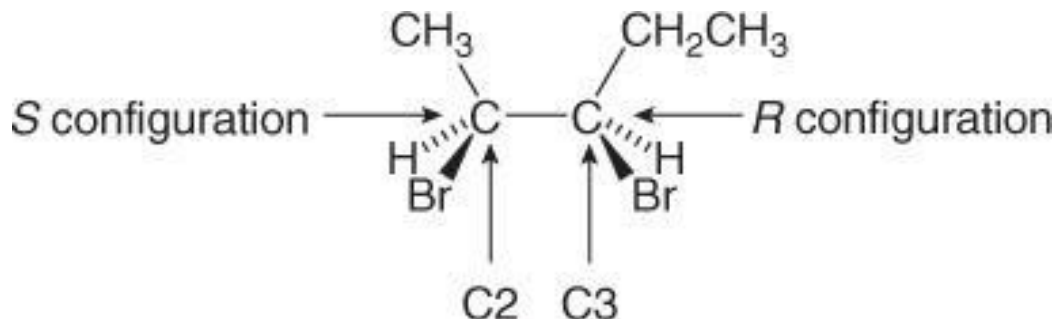
**Superimposable mirror images, same compound**



**Meso compound due to presence of plane of symmetry.**

# 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.

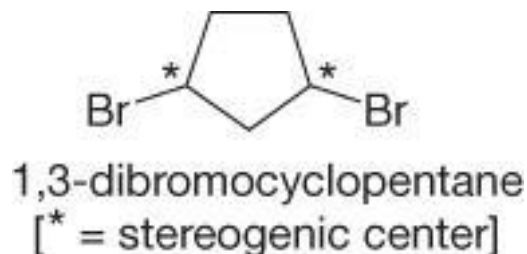


One stereoisomer of 2,3-dibromopentane  
The complete name is **(2*S*,3*R*)-2,3-dibromopentane**

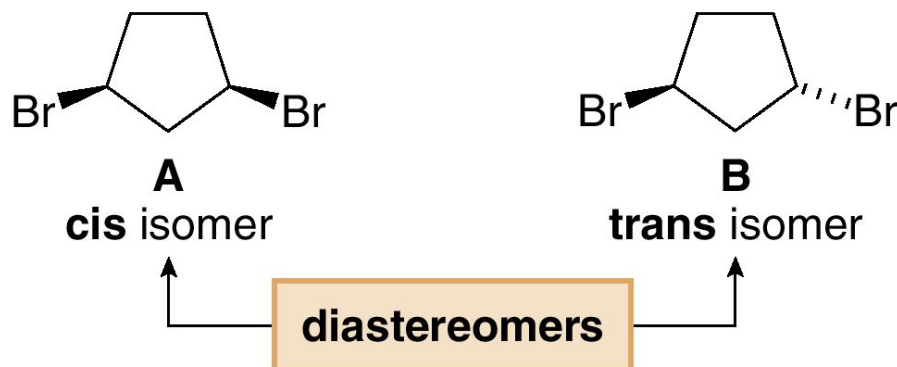
- Identical compounds have the *same* *R,S* designations at every tetrahedral stereogenic center.
- Enantiomers have exactly *opposite* *R,S* designations.
- Diastereomers have the *same* *R,S* designation for at least one stereogenic center and the *opposite* for at least one of the other stereogenic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

# Disubstituted Cycloalkanes

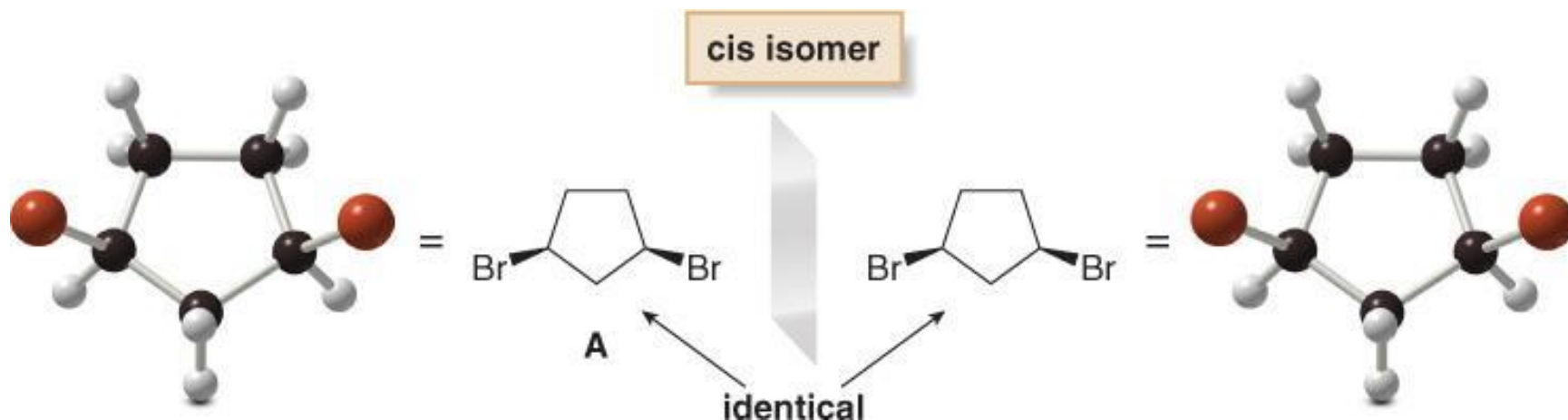
- Consider 1,3-dibromocyclopentane. Since it has two stereogenic centers, it has a maximum of four stereoisomers.



- Recall that a disubstituted cycloalkane 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.



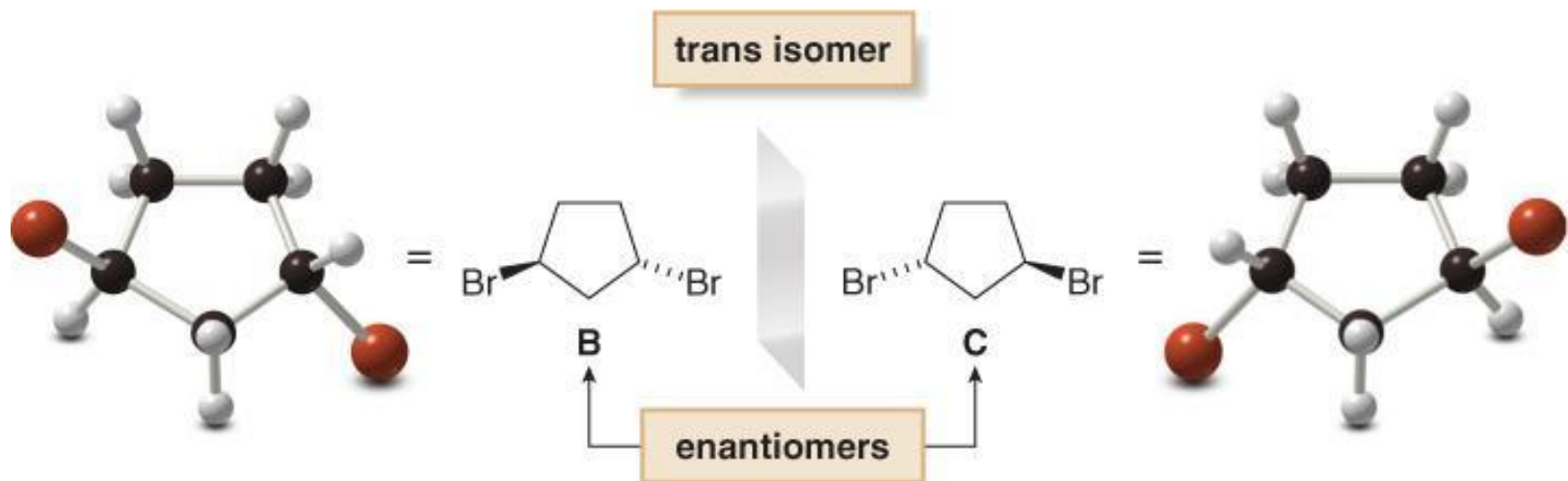
- To find the other two stereoisomers if they exist, draw the mirror images of each compound and determine whether the compound and its mirror image are superimposable.



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



- 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.

Figure 5.10

Summary—Types of isomers

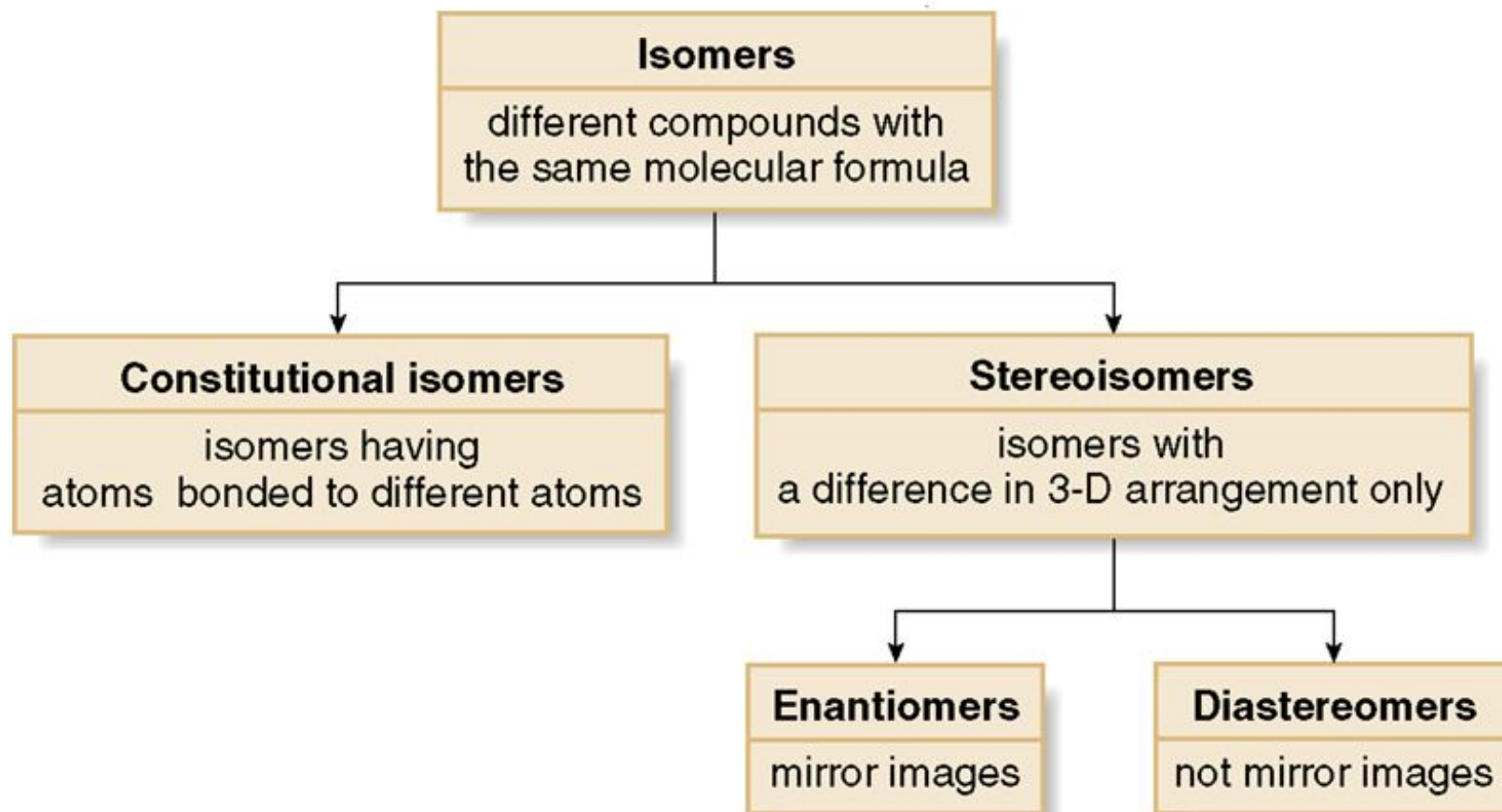
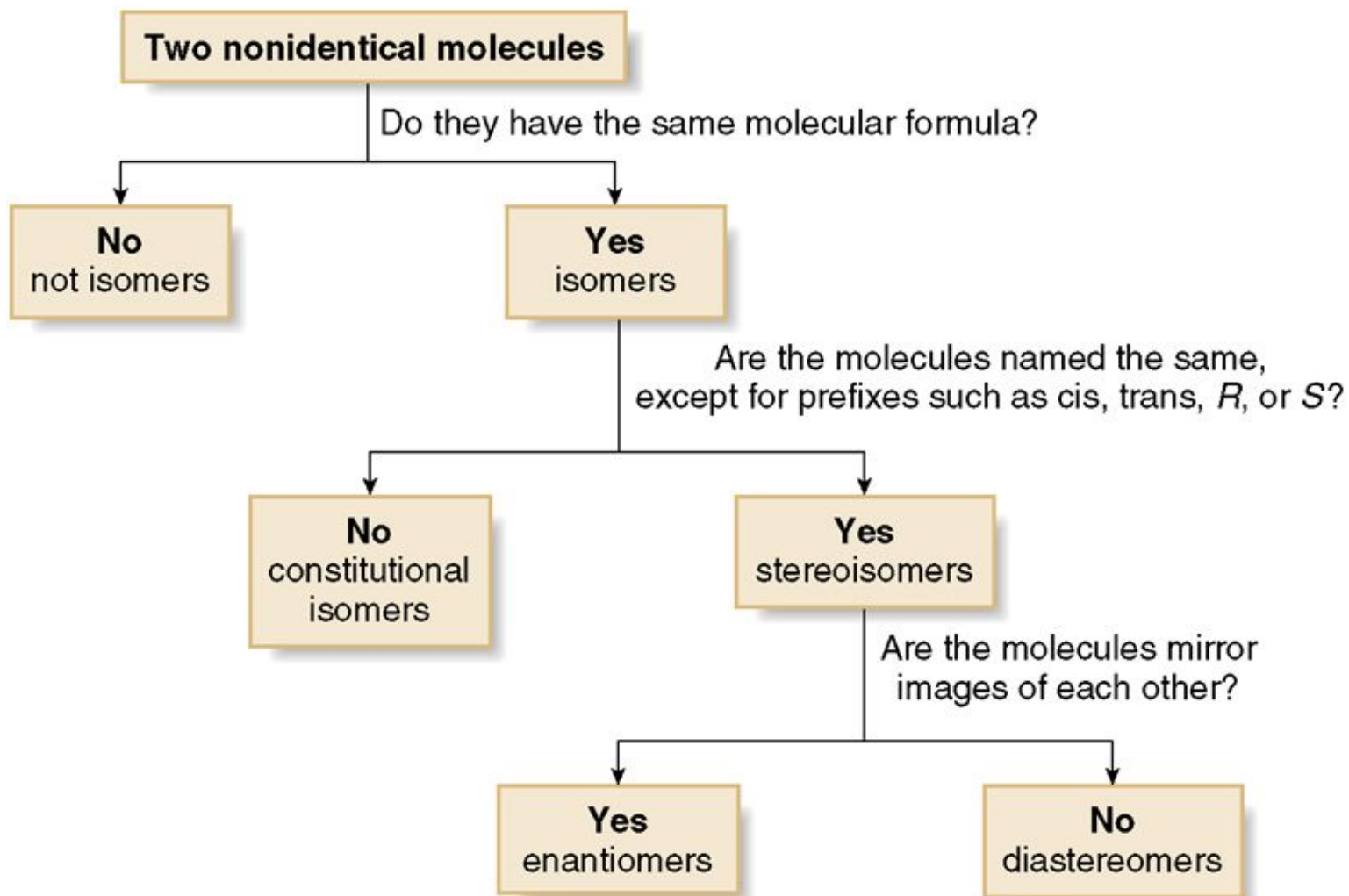


Figure 5.11

Determining the relationship between two nonidentical



**Without looking at the structures, label each pair as either enantiomers or diastereomers.**

**a) (2R,3S)-2,3-hexanediol or (2R,3S)-2,3-hexanediol**

**One changes, one stays the same, diastereomers**

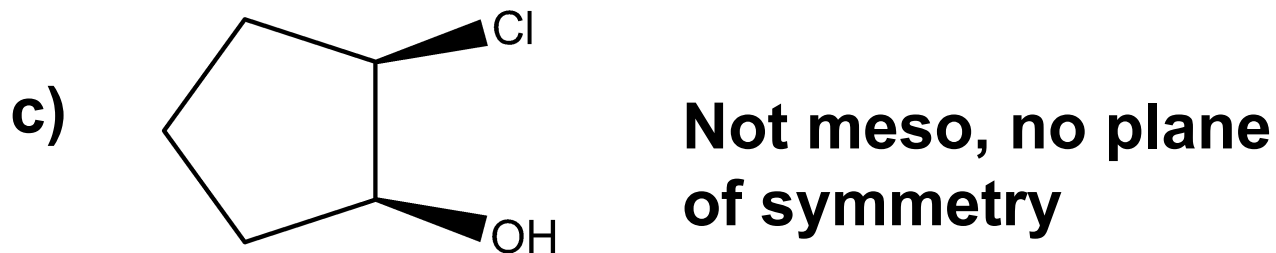
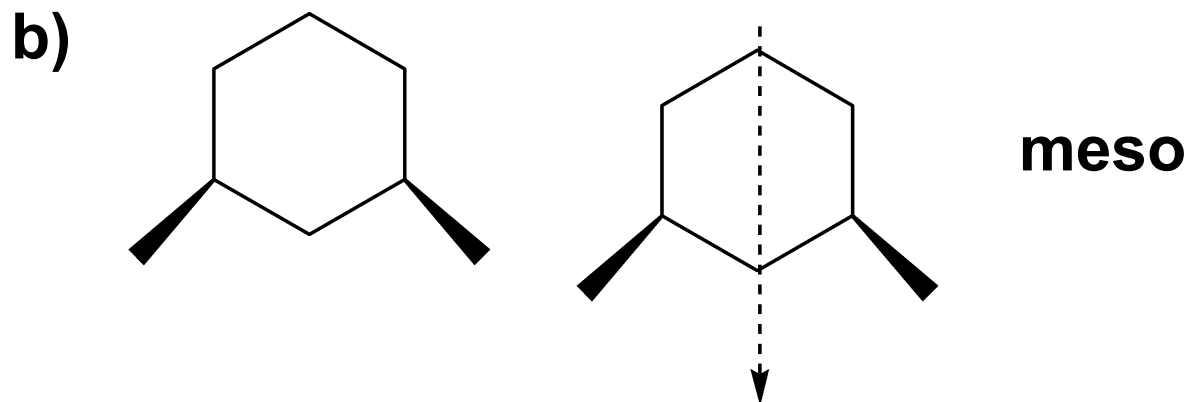
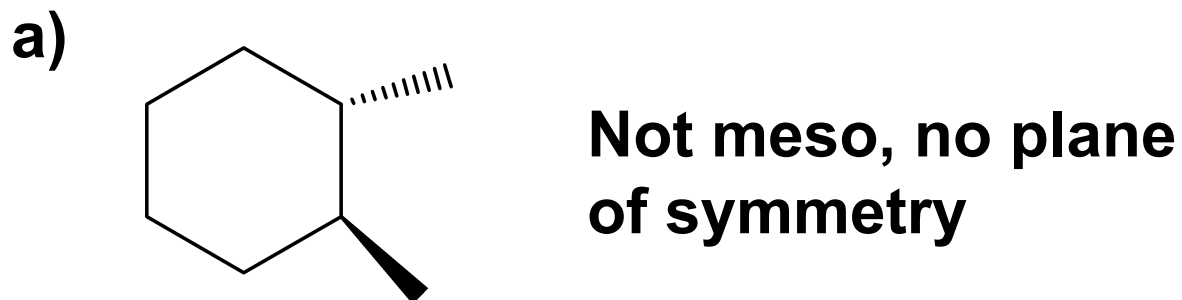
**b) (2R,3R)-2,3-hexanediol or (2S,3S)-2,3-hexanediol**

**Both change, enantiomers**

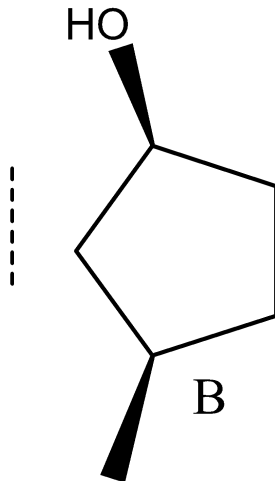
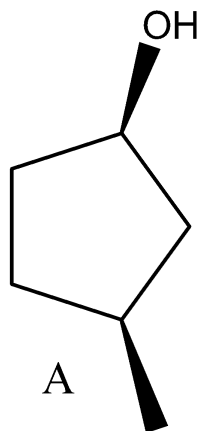
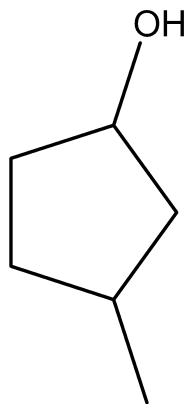
**c) (2R,3S,4R)-2,3,4-hexanetriol or  
(2S,3R,4R)-2,3,4-hexanetriol**

**2 change, one stays the same, diastereomers**

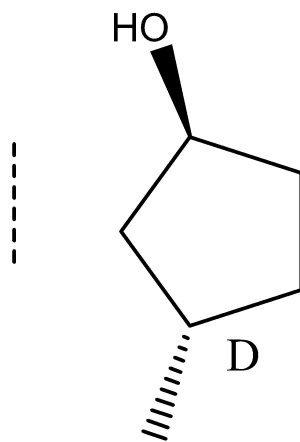
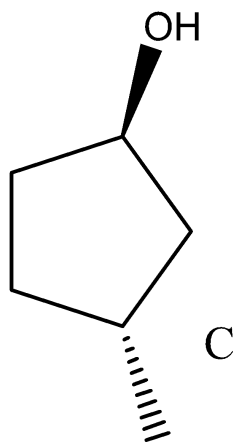
Which of the following are meso compounds?



**Draw all possible stereoisomers, then pair up enantiomers and diastereomers**



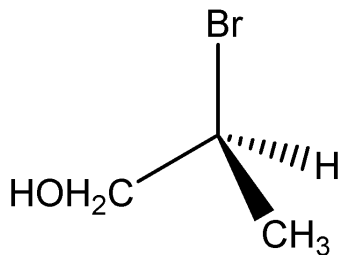
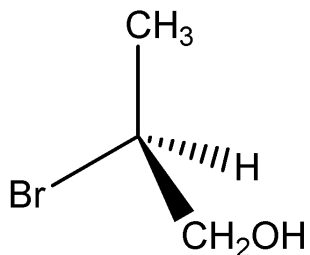
**A and B are enantiomers, and C and D are enantiomers.**



**A is a diastereomer of C and D. B is also a diastereomer of C and D.**

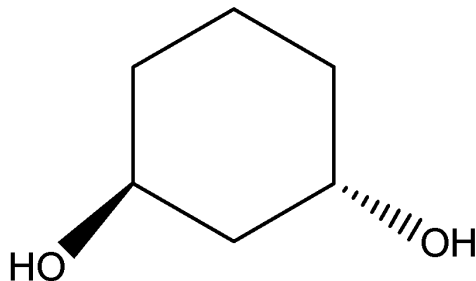
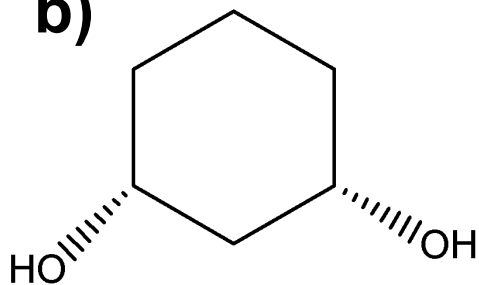
State how each pair are related: enantiomers, diastereomers, constitutional isomers or identical.

a)



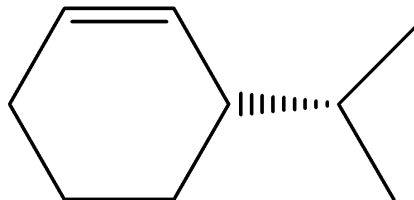
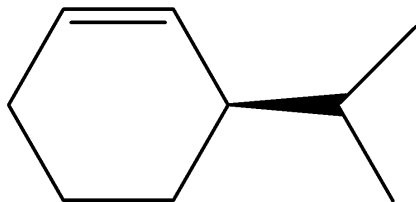
Same formula  
Same S configuration  
identical

b)



Same formula  
cis and trans  
diastereomers

c)



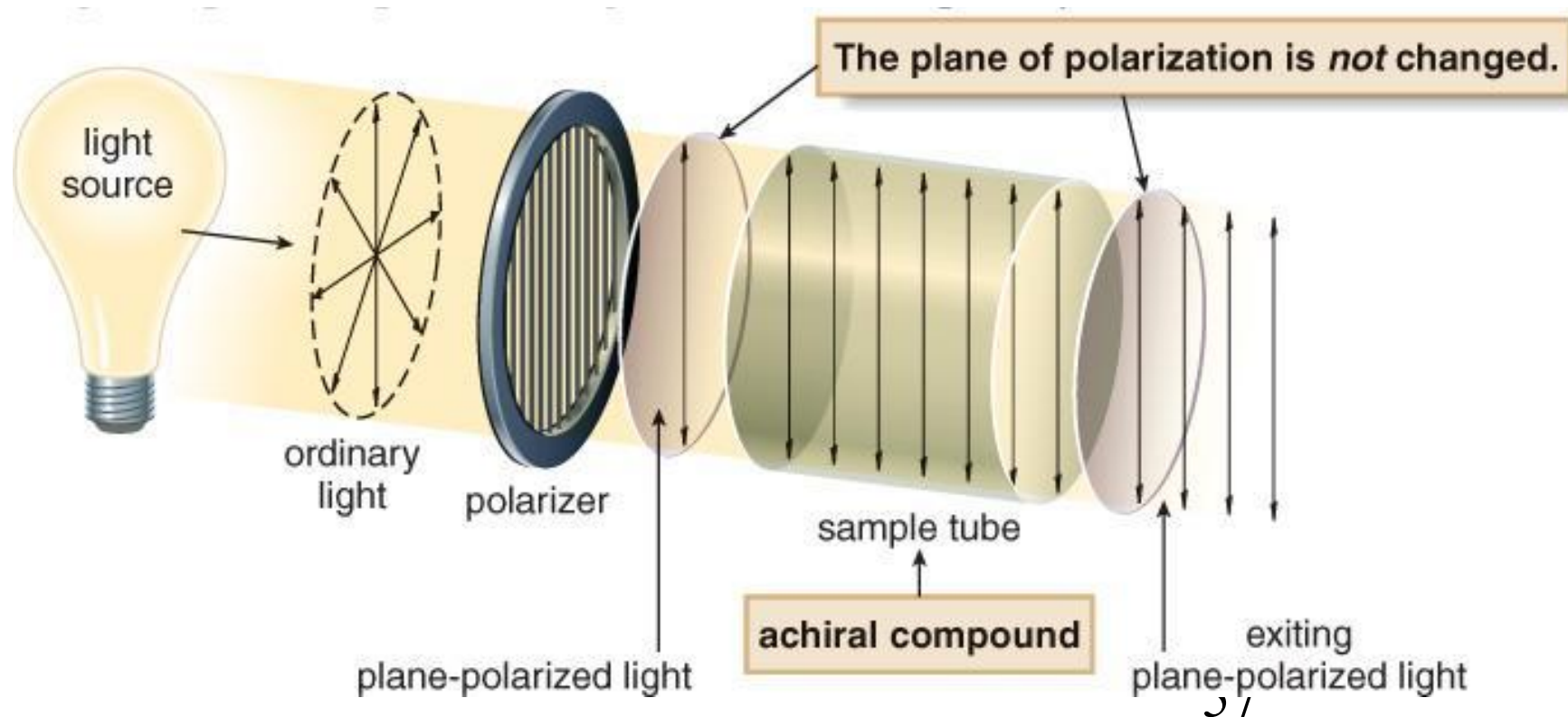
Same formula  
Opposite R and S  
configuration  
enantiomers

## Physical Properties of Stereoisomers—Optical Activity

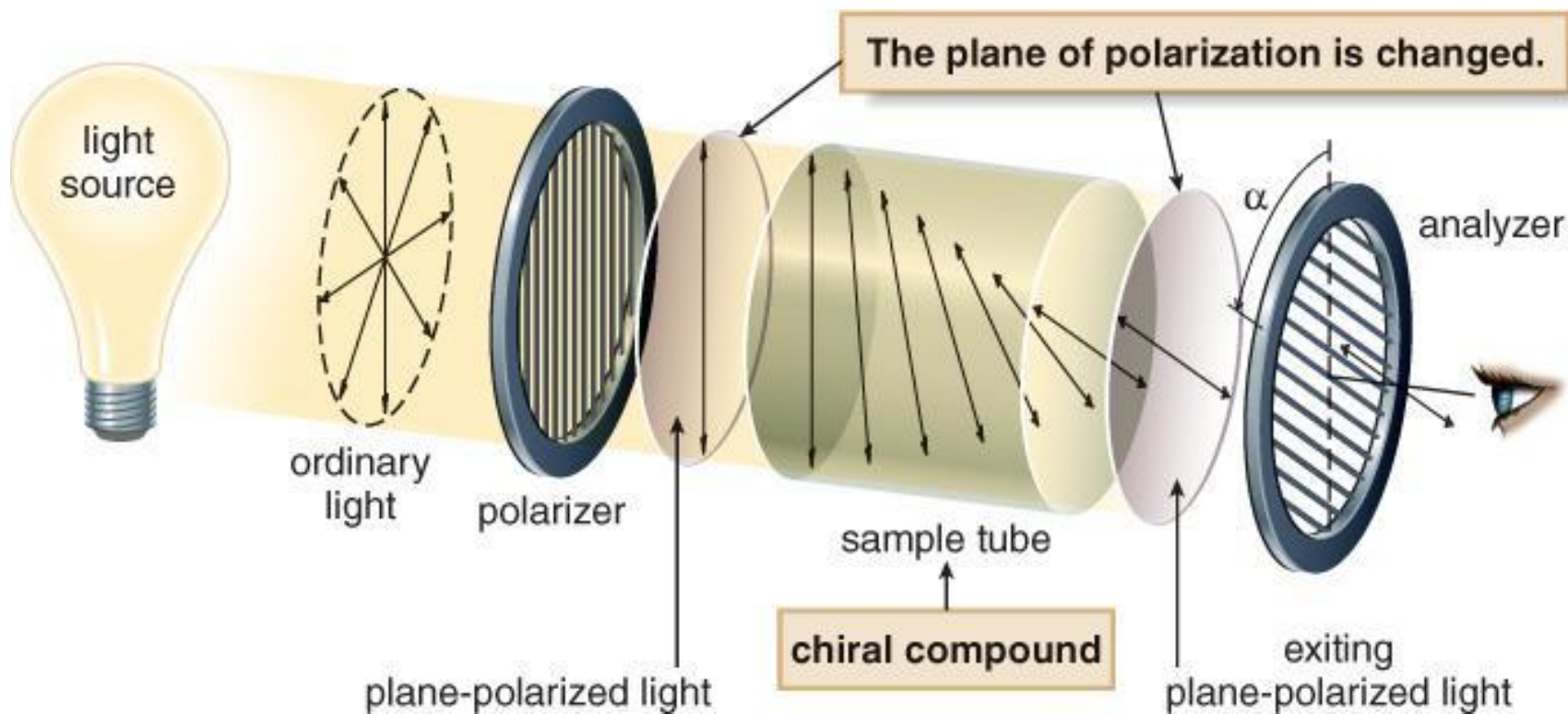
- The chemical and physical properties of two enantiomers are identical except in their interaction with chiral substances. They have identical physical properties, except for how they interact with **plane-polarized light**.
- **Plane-polarized (polarized) light** is light that has an electric vector 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. It permits the measurement of the degree to which an organic compound rotates 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**.



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



- The rotation of polarized light can be clockwise or anticlockwise.
- If the rotation is clockwise (to the right of the noon position), the compound is called **dextrorotatory**. The rotation is labeled ***d*** or **(+)**.
- If the rotation is counterclockwise, (to the left of noon), 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. Thus, if enantiomer A rotates polarized light  $+5^\circ$ , the same concentration of enantiomer B rotates it  $-5^\circ$ .
- No relationship exists between ***R*** and ***S*** prefixes and the **(+)** and **(-)** designations that indicate optical rotation.

# Physical Properties of Stereoisomers—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.

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*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>B</b>	identical to <b>A</b>	may be different from <b>A</b> and <b>B</b>
Boiling point	identical to <b>B</b>	identical to <b>A</b>	may be different from <b>A</b> and <b>B</b>
Optical rotation	equal in magnitude but opposite in sign to <b>B</b>	equal in magnitude but opposite in sign to <b>A</b>	0°

- **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 ( $25^{\circ}\text{C}$ ) and wavelength (589 nm).

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

$\alpha$  = observed rotation ( $^{\circ}$ )  
 $l$  = length of sample tube (dm)  
 $c$  = concentration (g/mL)

[ dm = decimeter  
1 dm = 10 cm ]

## Physical Properties of Stereoisomers—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.**

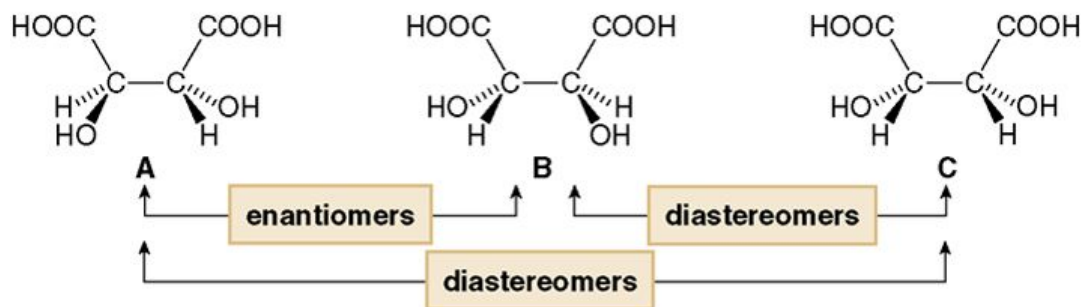
- Consider the following example—If a mixture contains 75% of one enantiomer and 25% of the other, the enantiomeric excess is  $75\% - 25\% = 50\%$ . Thus, there is a 50% excess of one enantiomer over the racemic mixture.
- The enantiomeric excess can also be calculated if the specific rotation  $[\alpha]$  of a mixture and the specific rotation  $[\alpha]$  of a pure enantiomer are known.

**ee = ( $[\alpha]$  mixture/ $[\alpha]$  pure enantiomer) x 100.**

- 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 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 <sub>2</sub> O)	139	139	125	139
[ $\alpha$ ]	+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; [ $\alpha$ ] = 0.

**A compound was isolated in the lab and the observed rotation was +10 when measured in a 1 dm. tube containing 1.0g of sample in 10ml of water. What is the specific rotation of this compound?**

$$\begin{aligned}[\alpha] &= \alpha / (\text{length} \times (\text{g/ml})) \\ &= 10 / (1\text{dm.} \times (1.0\text{g}/10\text{ml})) \\ &= +100\end{aligned}$$



**What is the ee of the following racemic mixture?**

**95% A and 5% B**

$$\begin{aligned} \text{ee} &= \% \text{ of A} - \% \text{ of B} \\ &= 95 - 5 = 90 \text{ ee} \end{aligned}$$

**Given the ee value, what percent is there of each isomer, 60% ee**

**60% excess A, then 40% racemic mixture( so 20% A and 20% B)**

**So, 60% + 20% = 80% A and leaves 20% B**

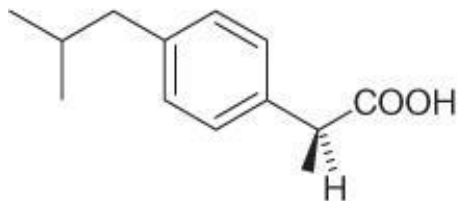
**A pure compound has a specific rotation of +24, a solution of this compound has a rotation of +10, what is the ee?**

$$\text{Ee} = [\alpha] \text{ of mixture} / [\alpha] \text{ of pure} \times 100$$

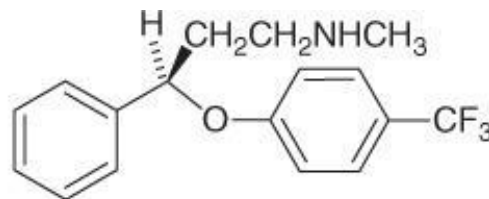
$$= +10 / +24 \times 100 = 42\%$$

## Chemical Properties of Enantiomers

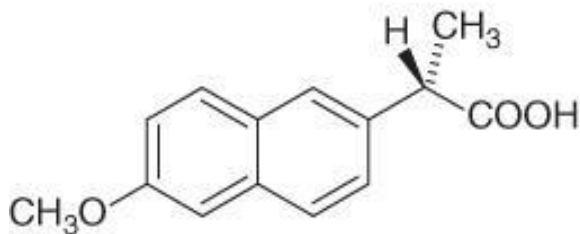
- Two enantiomers have exactly the same chemical properties except for their reaction with chiral non-racemic reagents.
- Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective. One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective or toxic.



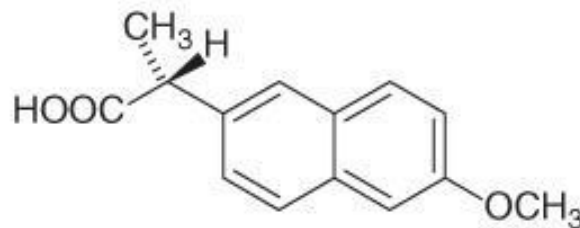
**(S)-ibuprofen**  
anti-inflammatory agent



**(R)-fluoxetine**  
antidepressant



**(S)-naproxen**  
anti-inflammatory agent



**(R)-naproxen**  
liver toxin

**4.33-39, 40-46,  
48-55, 57-61**