Stereochemistry

Dr. D. G. Karpe

Isomers – different compounds with the same molecular formula.

Structural Isomers – isomers that differ in which atoms are bonded to which atoms.

eg. C_4H_{10} $CH_3CH_2CH_2CH_3$ CH_3CHCH_3 (CH_3)

***n*-butane** **isobutane**

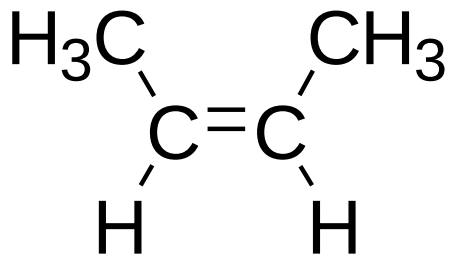
Stereochemistry

The Two Major Classes of Isomers:

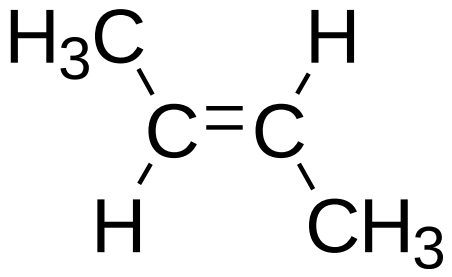
- **Recall that isomers are different compounds with the same molecular formula.**
- **The two major classes of isomers are constitutional isomers and stereoisomers.**
  - **Constitutional/structural isomers have different IUPAC names, the same or different functional groups, different physical properties 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.**

Stereoisomers – isomers that differ in the way the atoms are oriented in space, but <u>not</u> in which atoms are bonded to which atoms.

eg. *cis*-2-butene

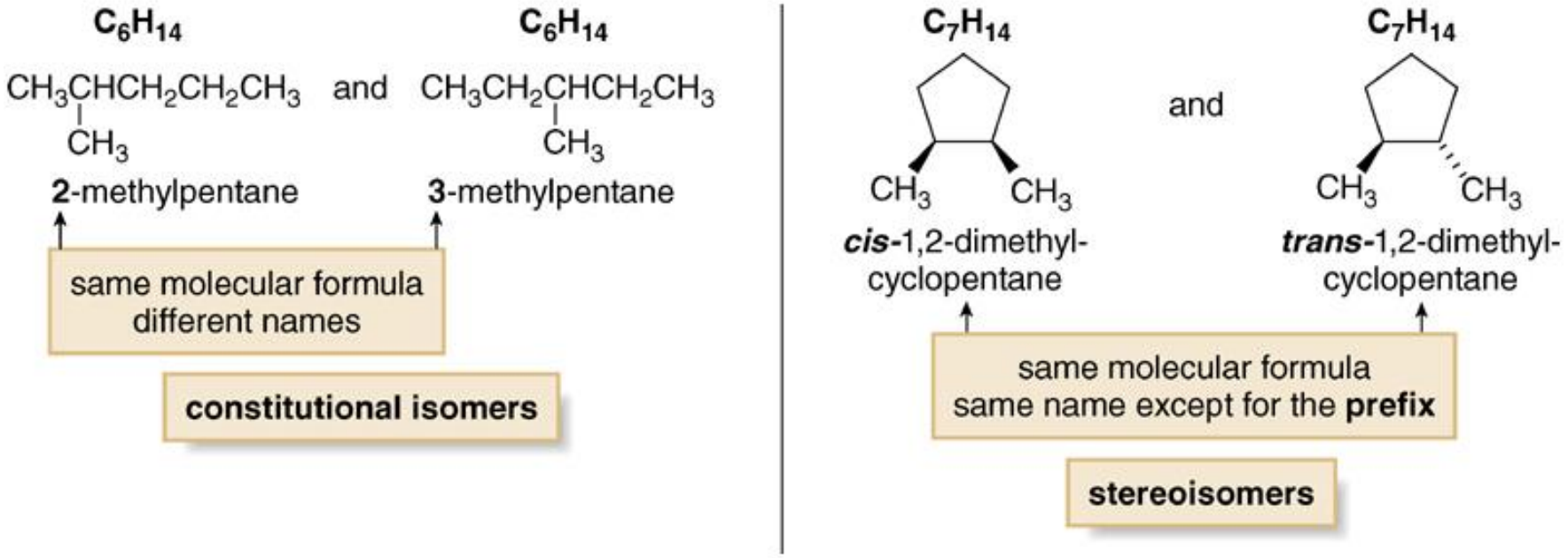


***trans*-2-butene**



Stereochemistry

A comparison of consitutional isomers and geometric stereoisomers



Stereoisomers may be geometric (cis/trans) or optical.
Optical isomers are chiral and exhibit optical activity.

Stereochemistry

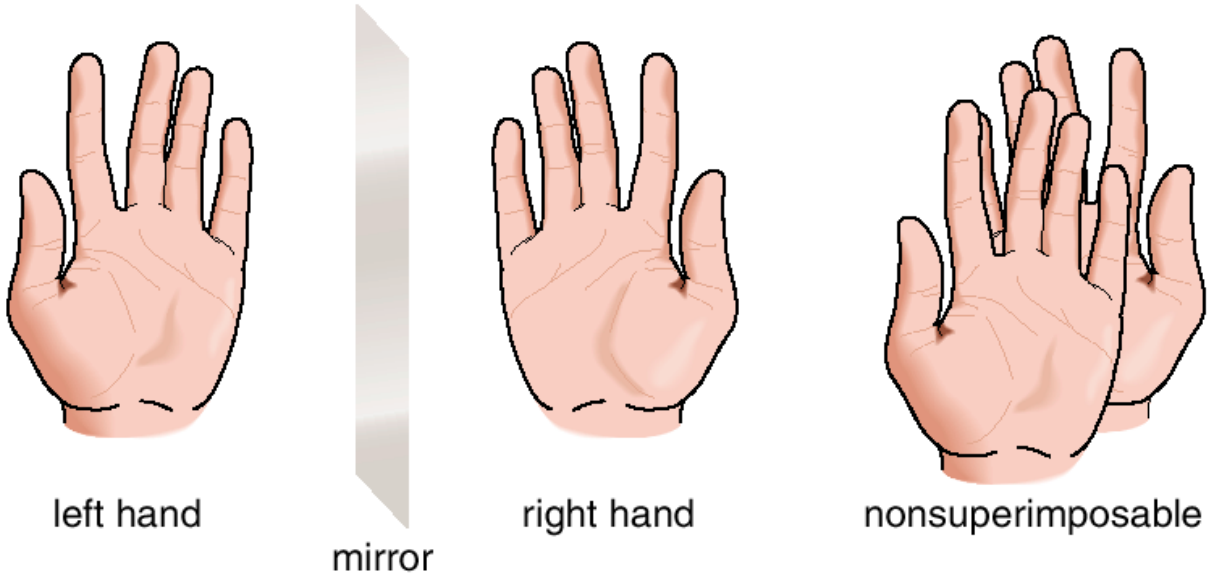
Chiral and Achiral Molecules:

- **Although everything has a mirror image, mirror images may or may not be superimposable.**
- **A molecule or object that is superimposable on its mirror image is said to be achiral (lacking-chirality).**
- **A molecule or object that is not superimposable on its mirror image is said to be chiral.**
- **Generally, a chiral carbon atom is sp^3 with four different attachments.**

Stereochemistry

Chiral and Achiral Molecules:

- **Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or superimposable.**

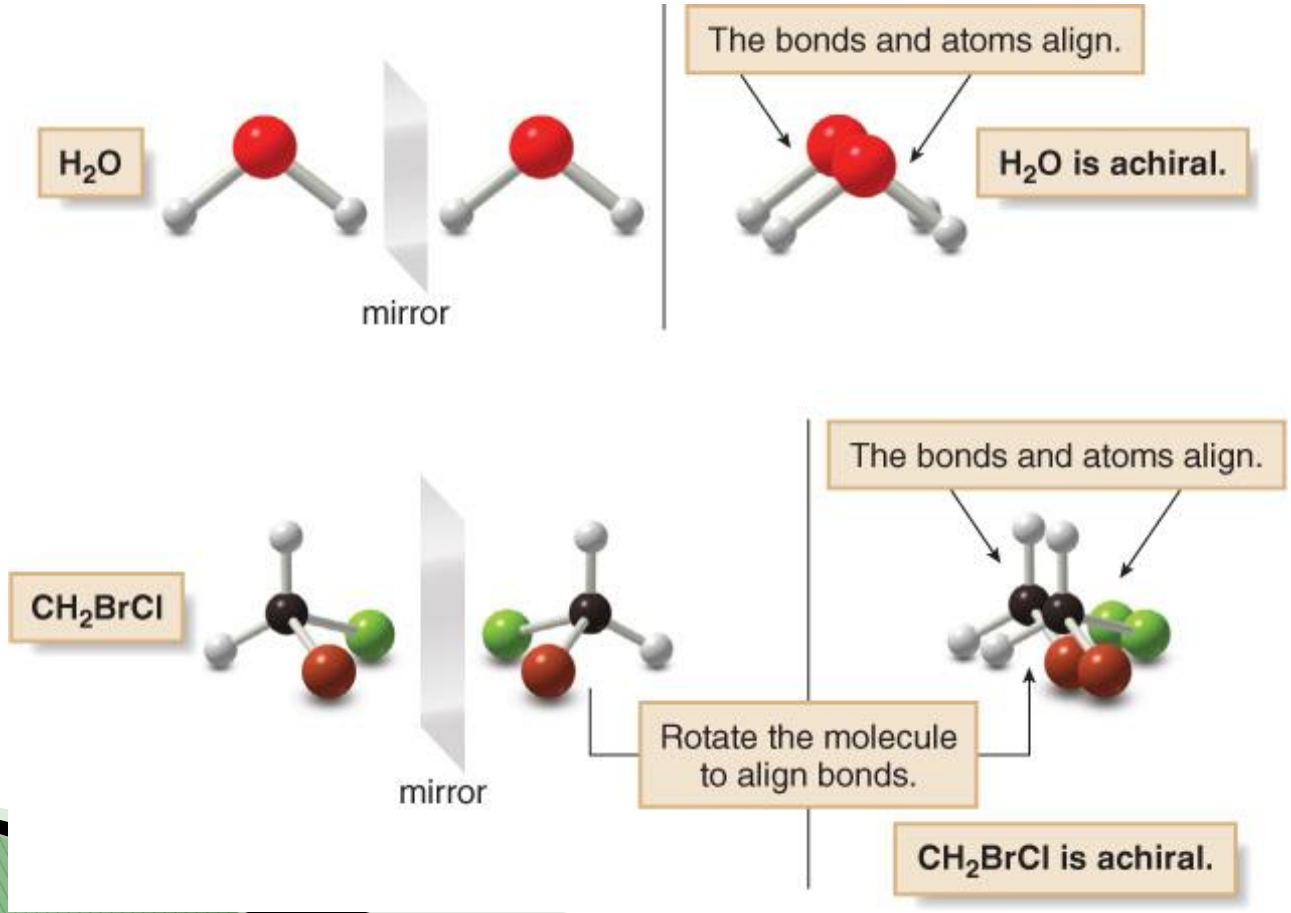


- A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral.*

Stereochemistry

Chiral and Achiral Molecules:

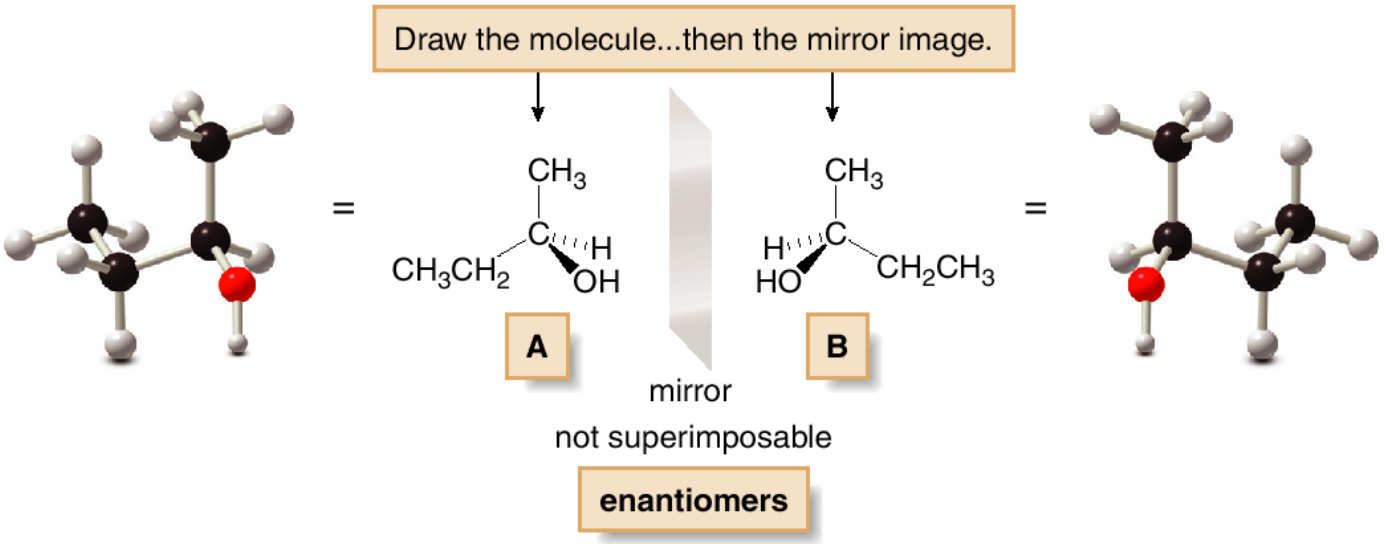
- **We can now consider several molecules to determine whether or not they are chiral.**



Stereochemistry

Chiral and Achiral Molecules:

- **A carbon atom with four different groups is a chiral center.**
- **The case of 2-butanol. A and its mirror image labeled B are not superimposable. Thus, 2-butanol is a chiral molecule and A and B are isomers.**
- **Non-superimposable mirror image stereoisomers like A and B are called enantiomers .**



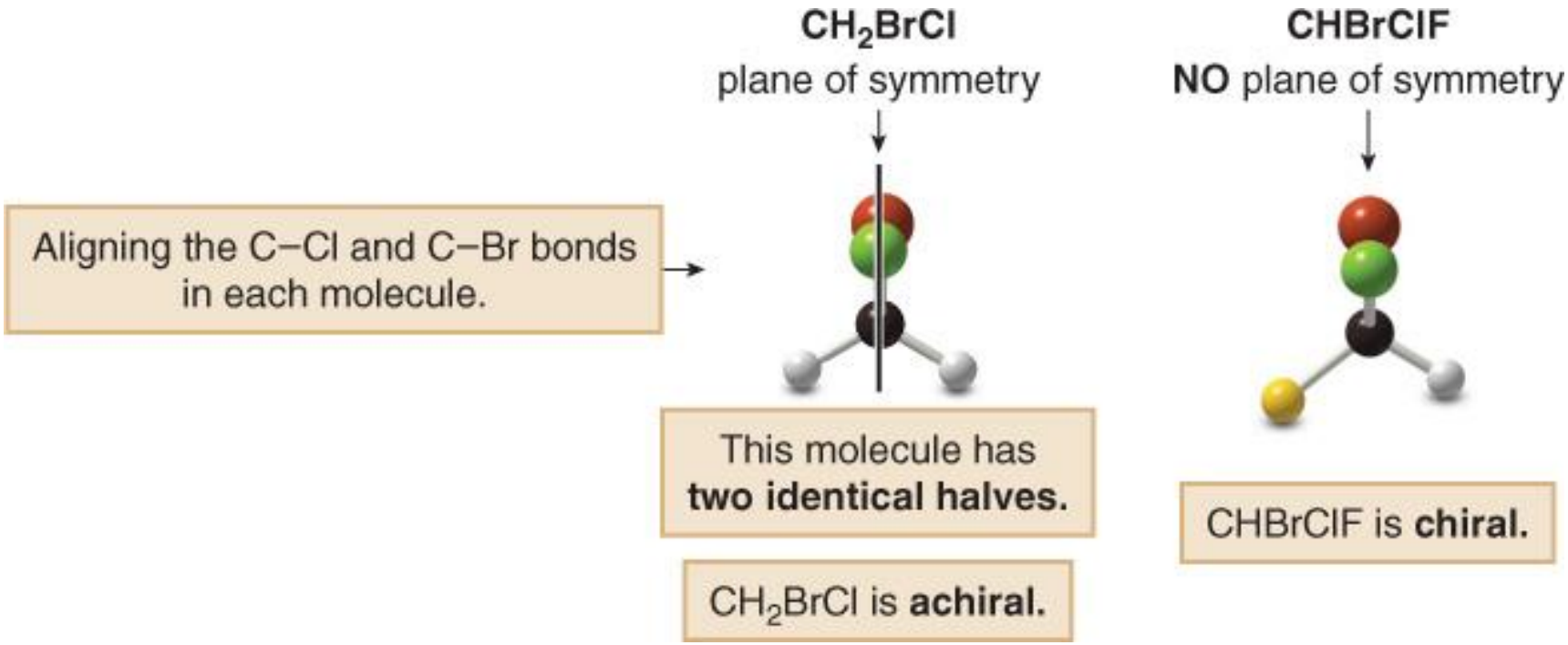
Stereochemistry

Chiral and Achiral Molecules:

- **In general, a molecule with no stereogenic centers will not be chiral. There are exceptions to this.**
- **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.**

Stereochemistry

Chiral and Achiral Molecules:



Two identical attachments on an sp^3 carbon atom eliminates the possibility of a chiral center.

Stereochemistry

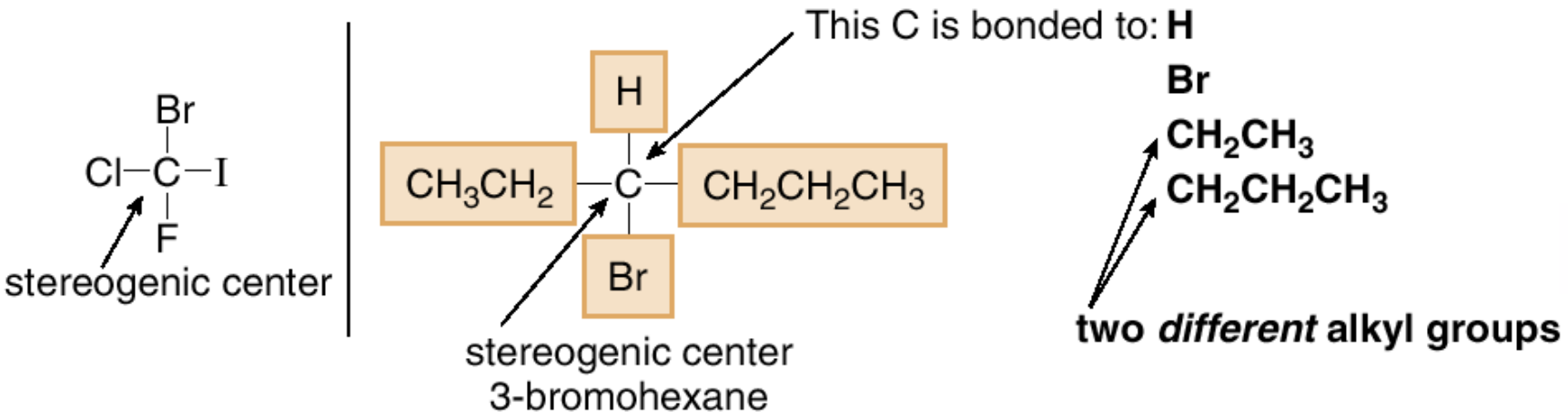
Summary of the Basic Principles of Chirality

- **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 presence of a plane of symmetry makes a molecule achiral.**

Stereochemistry

Stereogenic Centers:

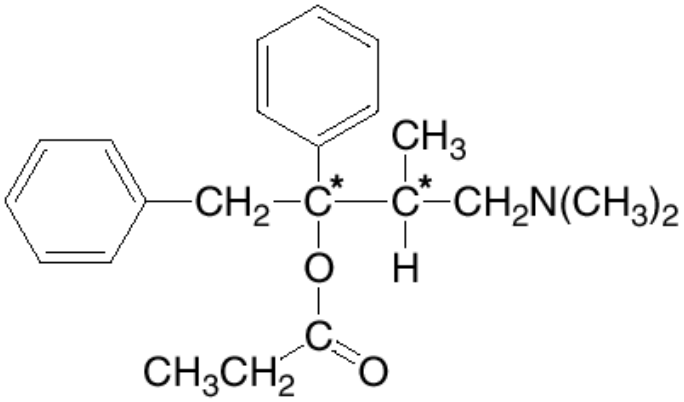
- **To locate a stereogenic center, examine each tetrahedral carbon atom in a molecule, and look at the four groups—not the four atoms—bonded to it.**
- **Always omit from consideration all C atoms that cannot be tetrahedral stereogenic centers. These include**
  - **CH_2 and CH_3 groups**
  - **Any *sp* or sp^2 hybridized C**



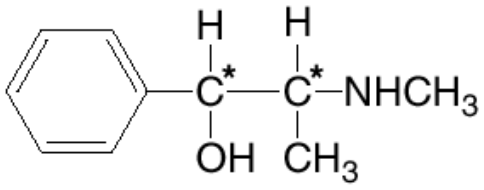
Stereochemistry

Identifying of Stereogenic Centers:

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

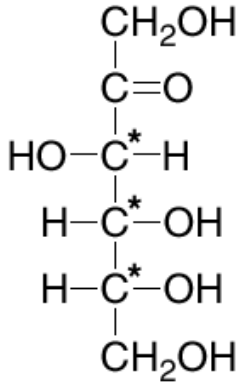


propoxyphene
Trade name: Darvon
(analgesic)



ephedrine
(bronchodilator, decongestant)

[* = stereogenic center]

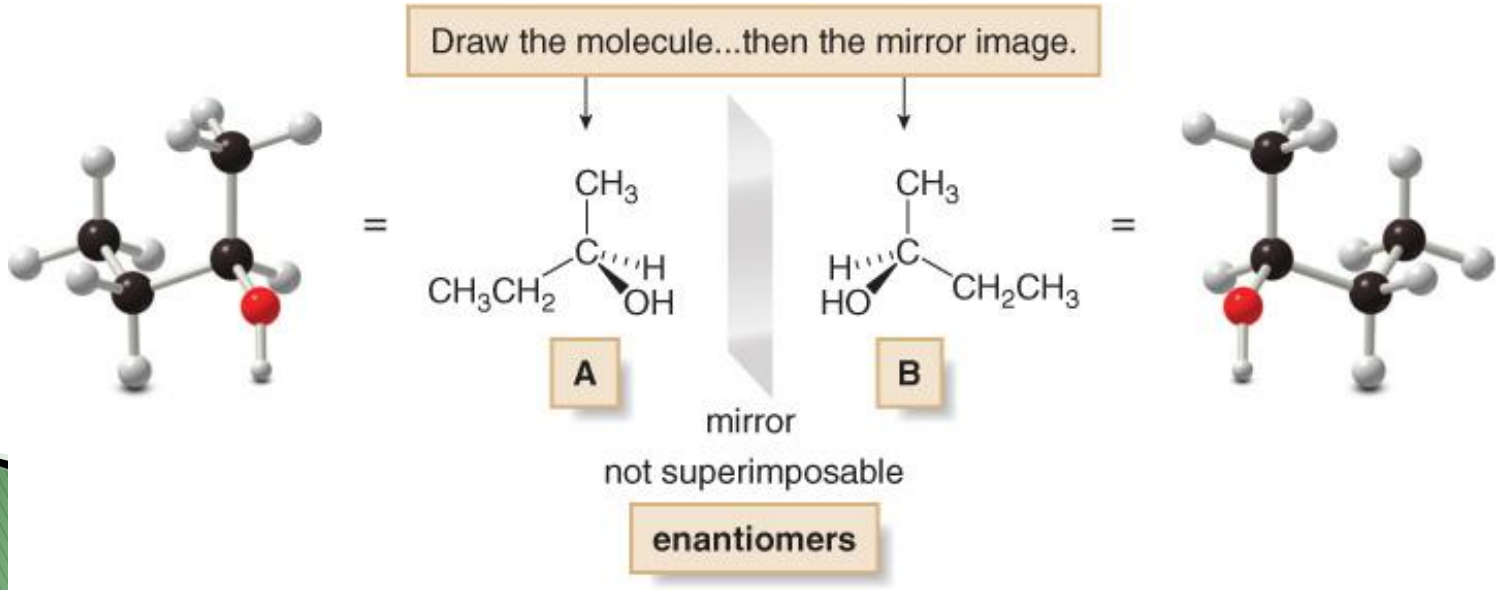


fructose
(a simple sugar)

Stereochemistry

Drawing Stereogenic Centers - the wedge diagram:

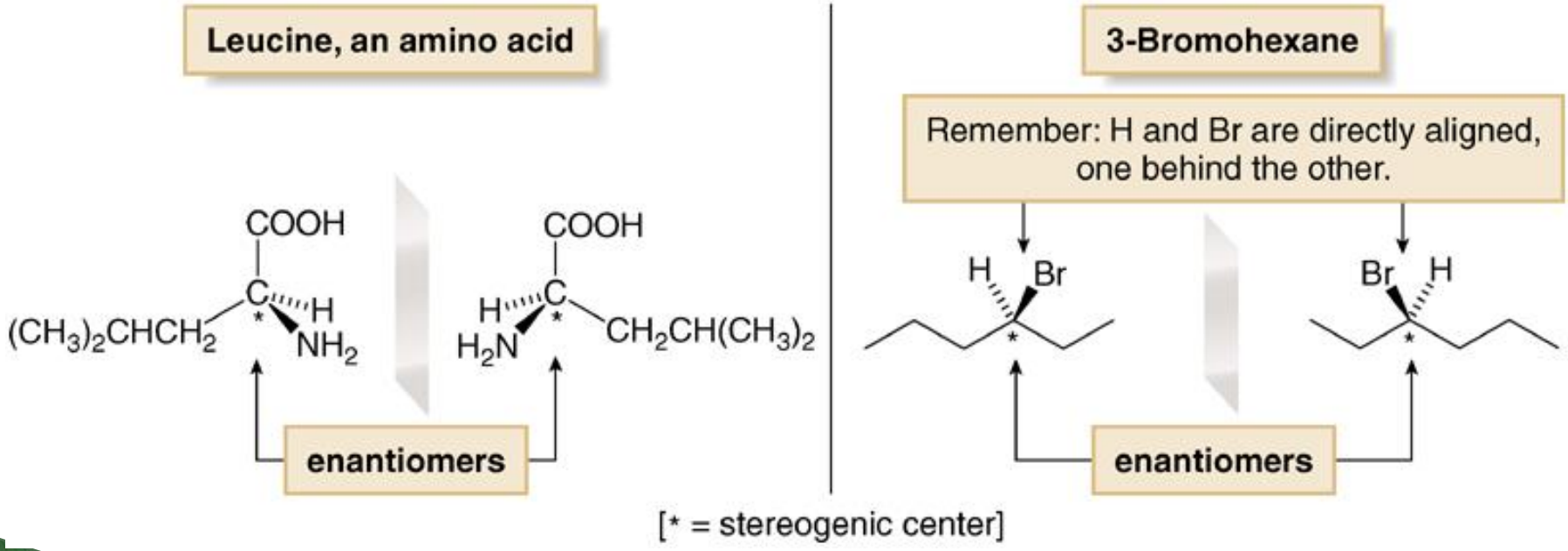
- **To draw both enantiomers of a chiral compound such as 2-butanol, use the typical convention for depicting a tetrahedron: place two bonds in the plane, one in front of the plane on a wedge, and one behind the plane on a dash. Then, to form the first enantiomer, arbitrarily place the four groups—H,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



Stereochemistry

Drawing Stereogenic Centers - the wedge diagram:

Three-dimensional representations for pairs of enantiomers

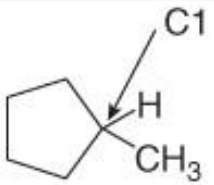


Stereochemistry

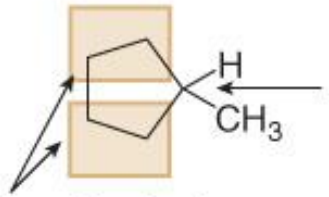
Identifying of Stereogenic Centers:

- **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

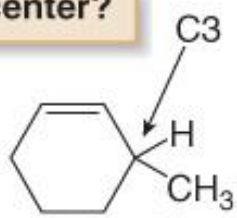


two identical groups, equidistant from C1

NO, C1 is **not** a stereogenic center.

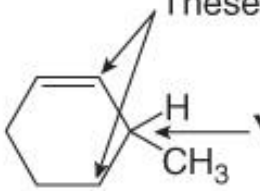
Contains a plane of symmetry

Is C3 a stereogenic center?



3-methylcyclohexene

These 2 C's are different.

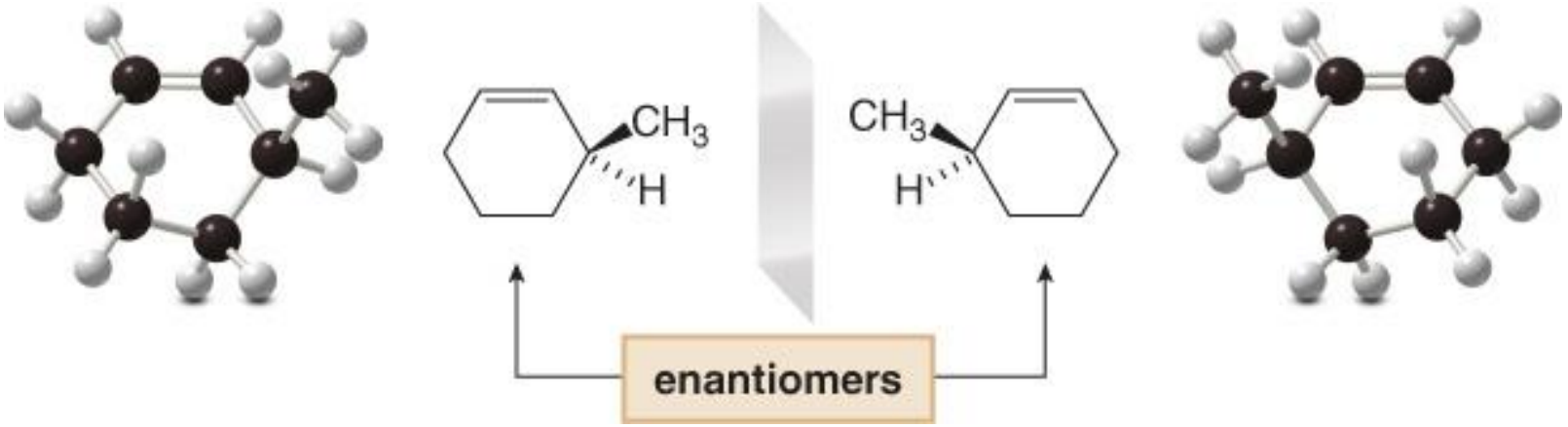


YES, C3 is a stereogenic center.

Stereochemistry

Drawing Stereogenic Centers - the wedge diagram:

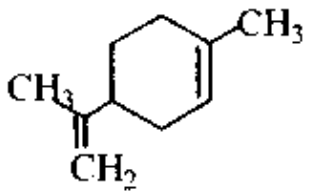
- **In 3-methylcyclohexene, the CH_3 and H substituents that are above and below the plane of the ring are drawn with wedges and dashes as usual.**



Stereochemistry

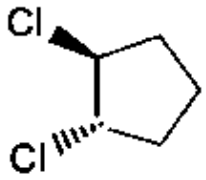
Identifying of Stereogenic Centers:

- **Identify the chiral carbons in the compounds below.**



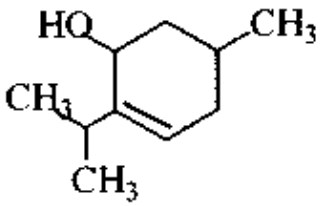
Limonene

1



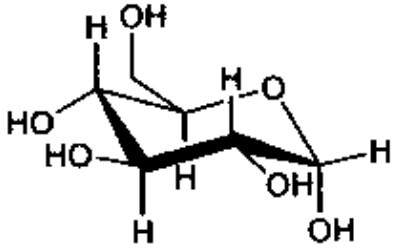
Dichlorocyclopentane
cis = meso
trans = enantiomeric

2



Menthol

2



Glucose

5

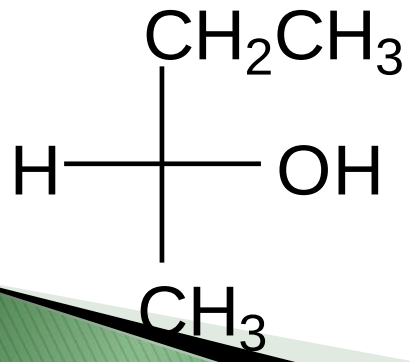
Stereochemistry

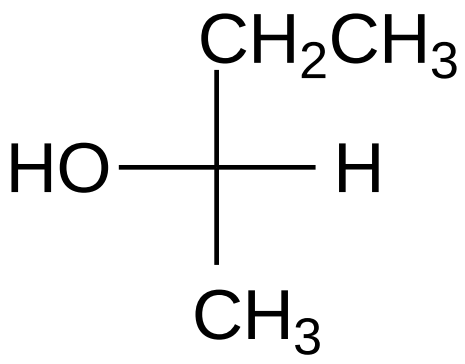
Drawing Stereogenic Centers – the Fischer Projection:

- **In a Fischer projection of a chiral carbon and its mirror image:**

  horizontal bonds project toward the viewer and vertical bonds project away from the viewer.

- **The test for non-superimposability is to slide one on top of the other or rotate 180º and attempt the same.**
- **Fischer projections of the two enantiomers of 2-butanol:**





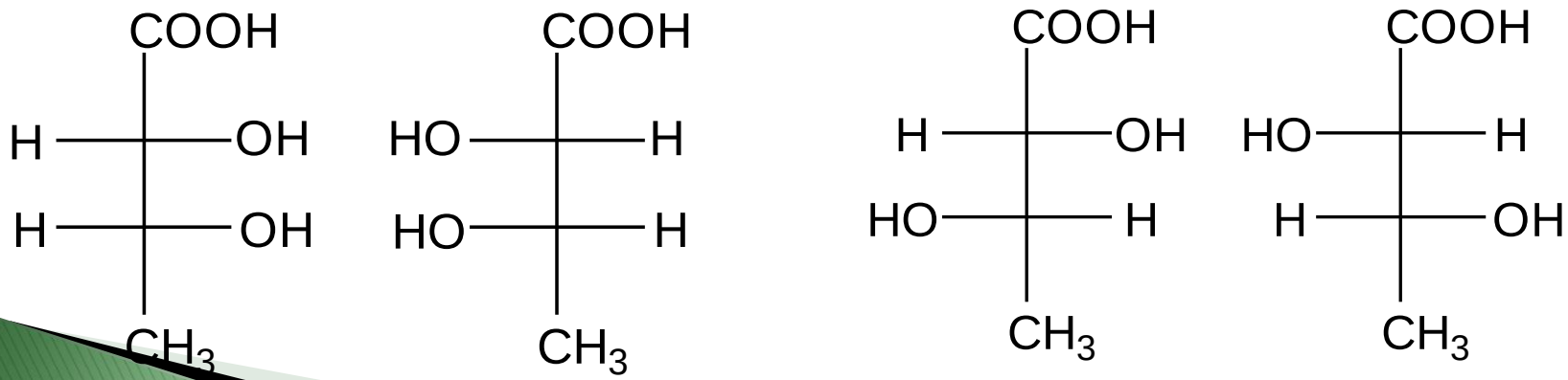
The chiral carbon atom is at the center of the crossed lines.

Stereochemistry

Drawing Stereogenic Centers – the Fischer Projection:

- **Fischer projections of a compound with 2 chiral carbons, (two pairs of enantiomers).**
- **The maximum number of optical isomers is 2^n.**
  (where n = the number of chiral carbon atoms.)

The pairs are diastereomerically related.



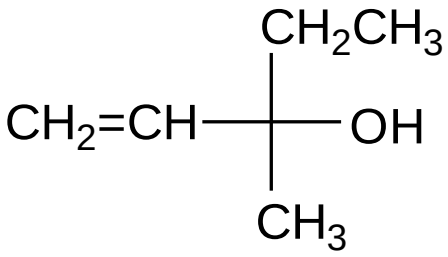
Stereochemistry

Drawing Stereogenic Centers – the Fischer Projection:

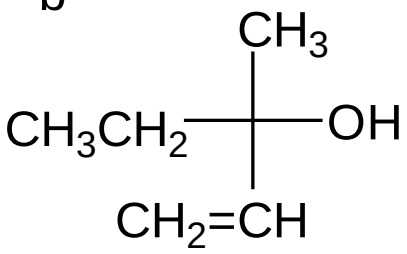
- **However, there may be several different Fischer projections for the same compound depending upon the direction from which is is viewed.**

Are these structures the same or different ?

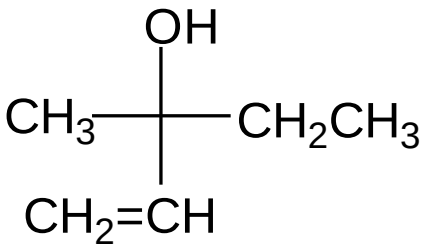
a



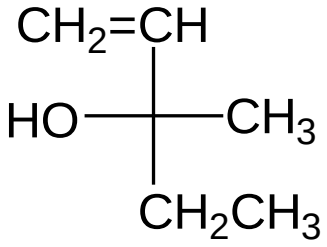
b



c



d



Stereochemistry

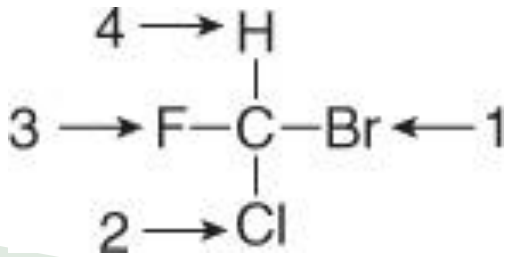
Labeling Stereogenic Centers:

- **The three dimensional arrangement about a tetrahedral carbon atom is referred to as its configuration.**
- **Early workers in the late 1800s including Fischer used the terms D and L to label the two molecules in a non-superimposable mirror image pair.**
- **D and L assignments were chemically related to the structures of glyceraldehyde.**
- **More recently Cahn, Ingold and Prelog developed the *R* and *S* system of assignment which is more convenient.**

Stereochemistry

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

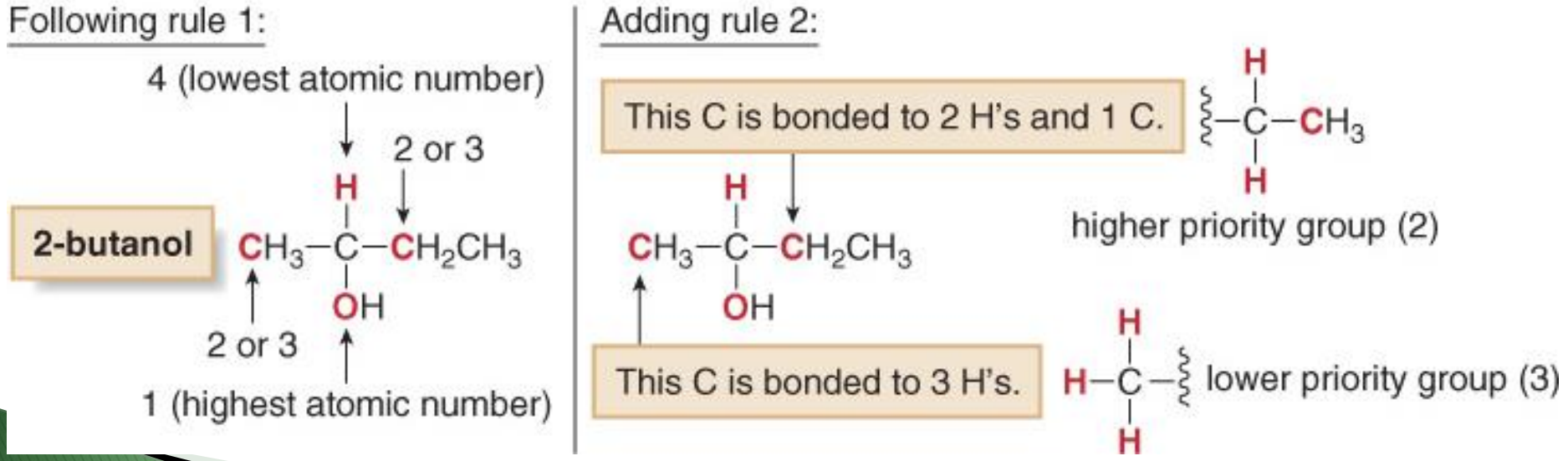
- **Since enantiomers are two different compounds, they need to be distinguished by name. This is done by adding the prefix *R* or *S* to the IUPAC name of the enantiomer.**
- **Naming enantiomers with the prefixes *R* or *S* is called the Cahn-Ingold-Prelog system.**
- **To designate enantiomers as *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).**



Stereochemistry

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

- **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.**



Stereochemistry

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

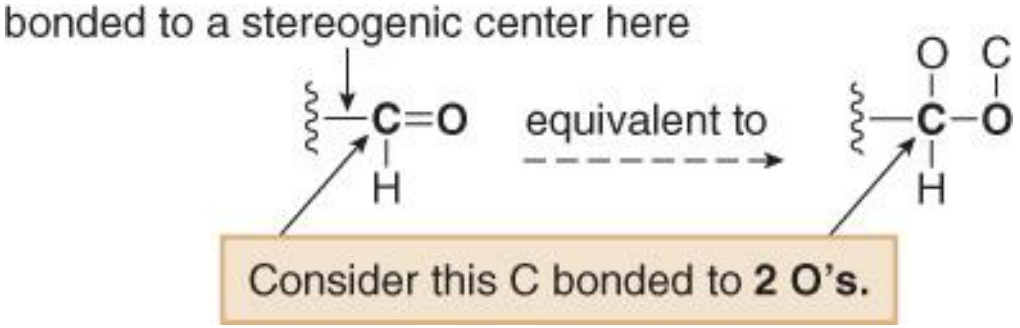
- **If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing mass number. Thus, in comparing the three isotopes of hydrogen, the order of priorities is:**

	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

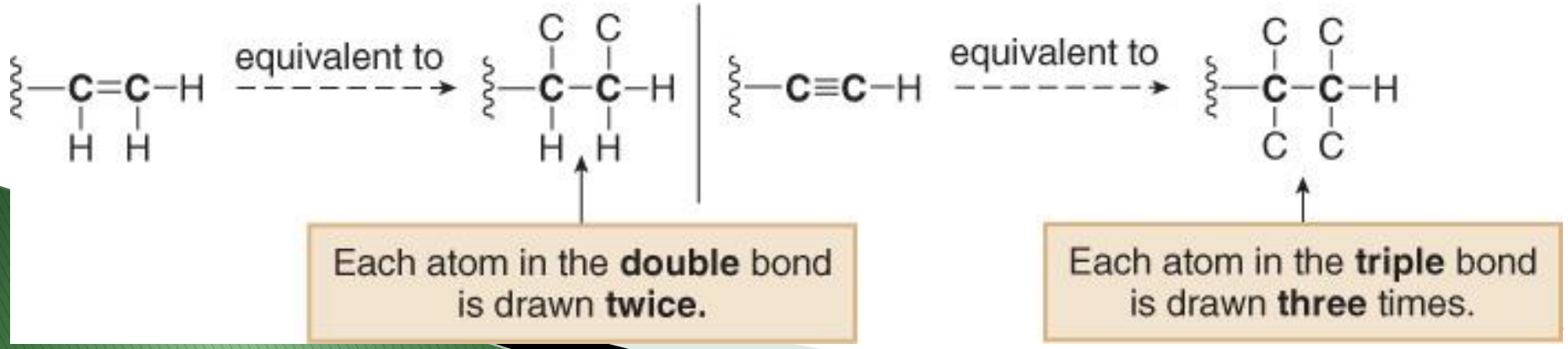
Stereochemistry

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

- **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.**



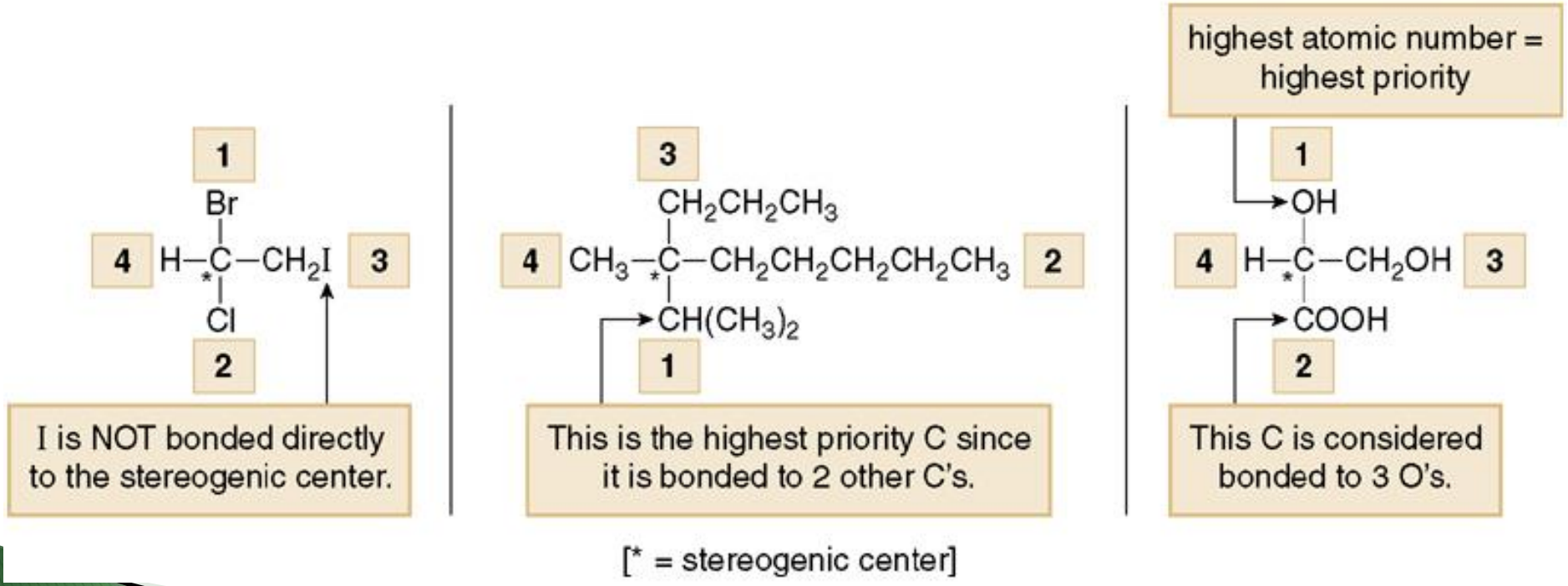
- **Other common multiple bonds are drawn below:**



Stereochemistry

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

Figure 5.6 **Examples of assigning priorities to stereogenic centers**

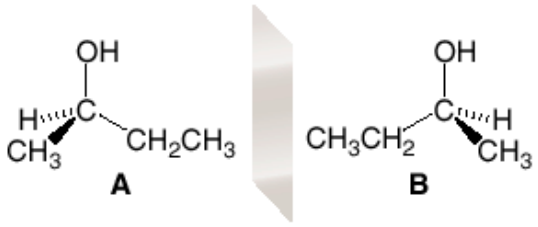


Stereochemistry

Labeling Stereogenic Centers with *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 172.

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

Decreasing priority

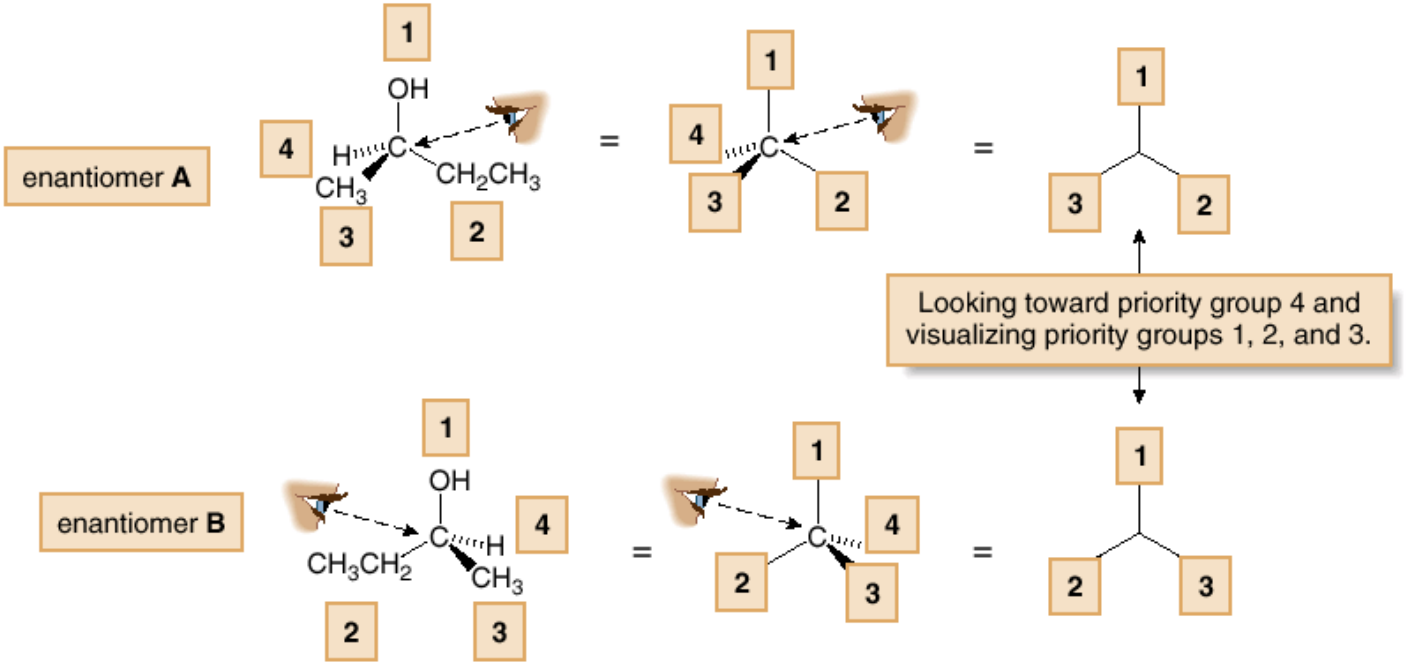
Stereochemistry

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.

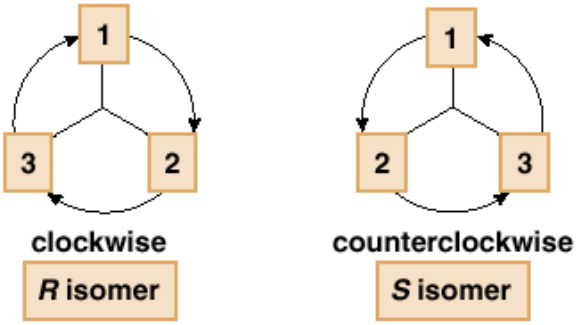


Stereochemistry

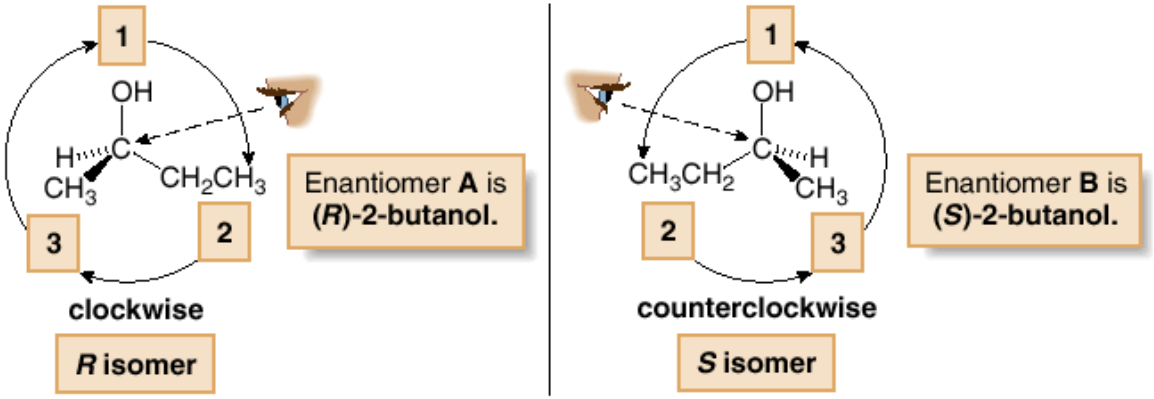
Labeling Stereogenic Centers with *R* or *S*:

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***.



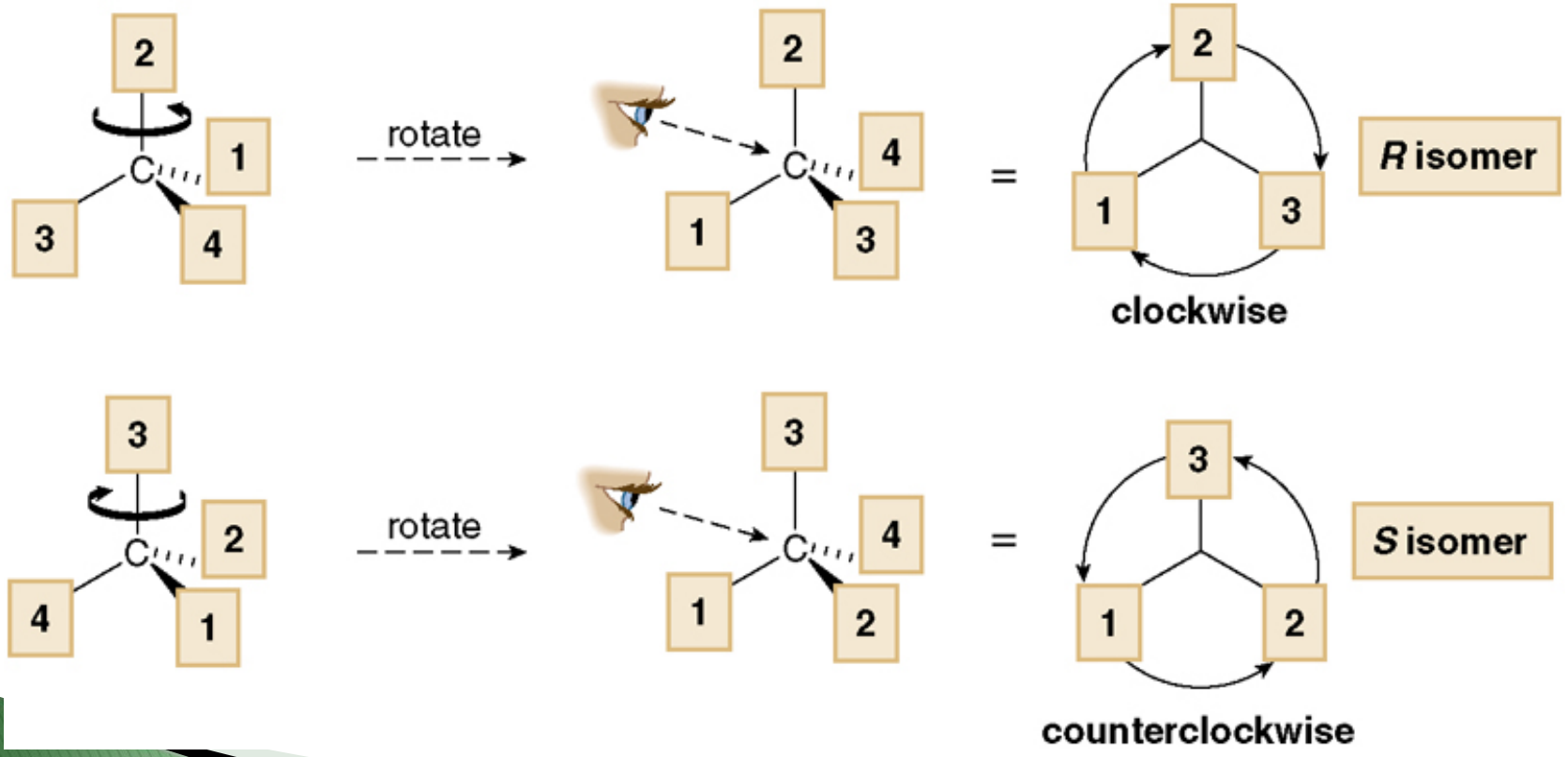
- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:



Stereochemistry

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

Figure 5.7 Examples: Orienting the lowest priority group in back



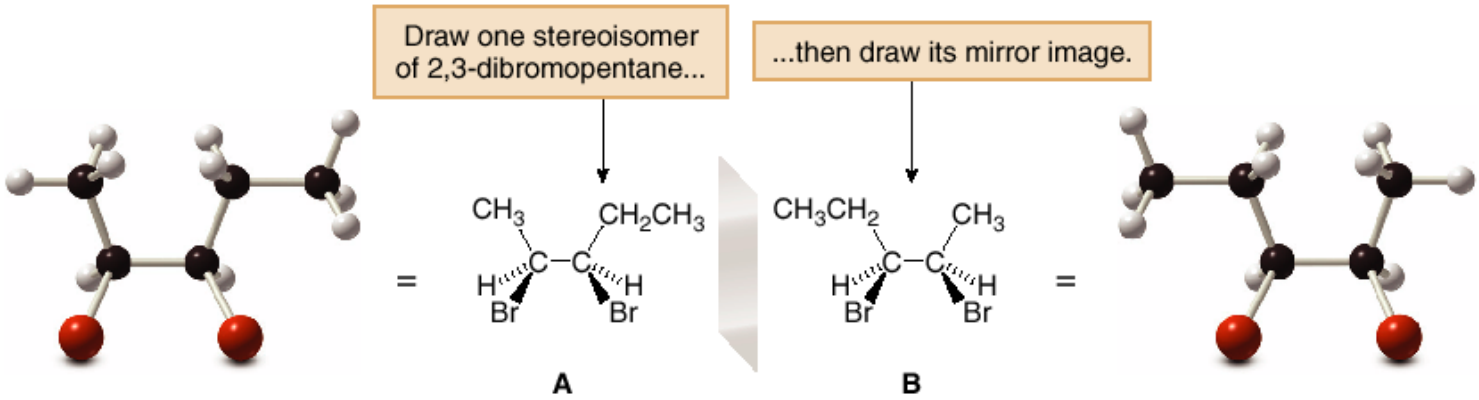
Stereochemistry

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**

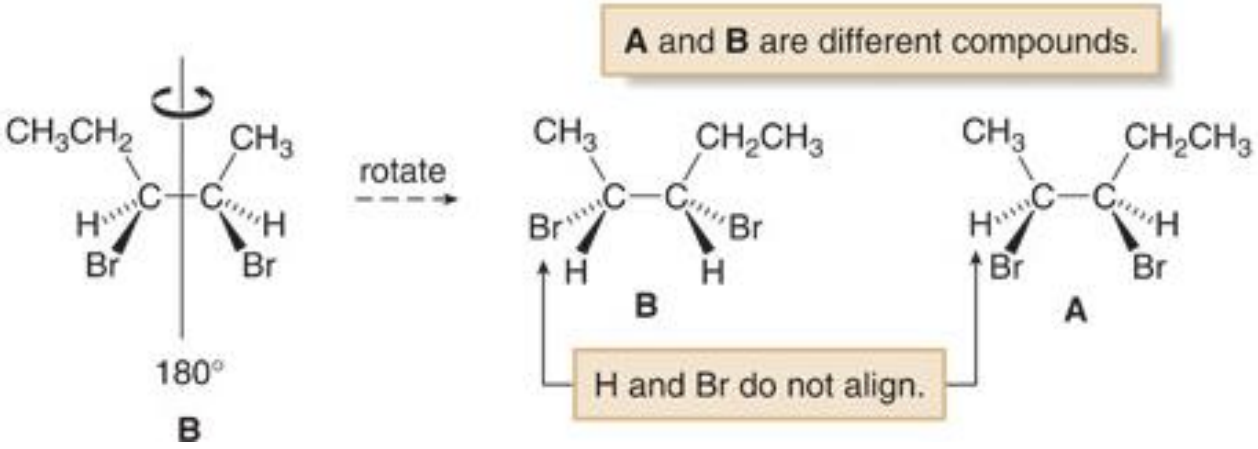
Step [1] Draw one stereoisomer by arbitrarily arranging substituents around the stereogenic centers. Then draw its mirror image.



Stereochemistry

Diastereomers:

- **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.**



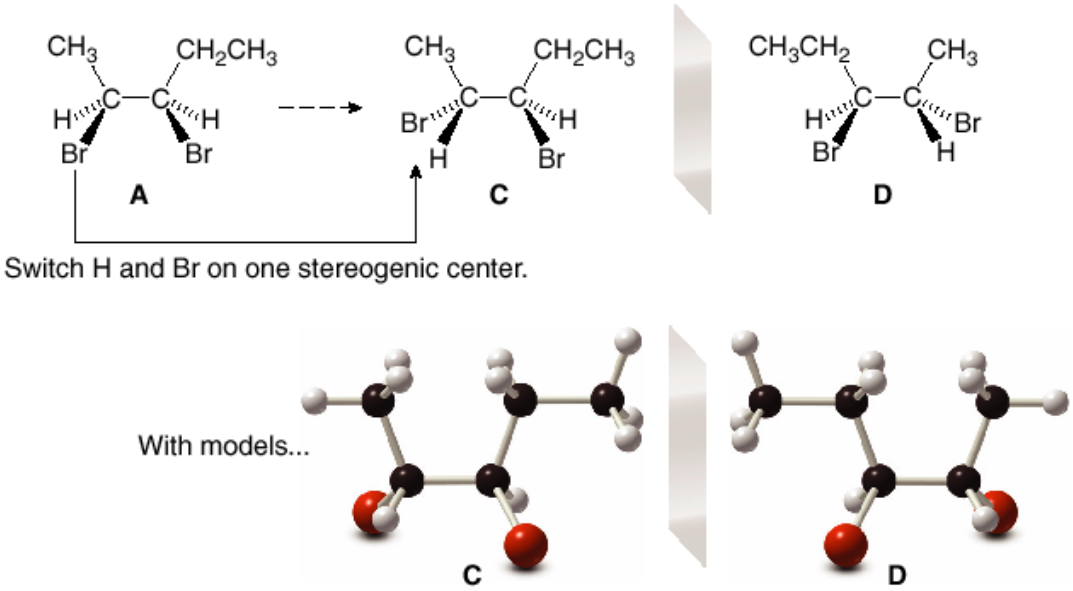
- **In this case, the atoms of A and B do not align, making A and B nonsuperimposable mirror images—i.e., enantiomers. Thus, A and B are two of the four possible stereoisomers of 2,3-dibromopentane.**

Stereochemistry

Diastereomers:

- **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 . . .

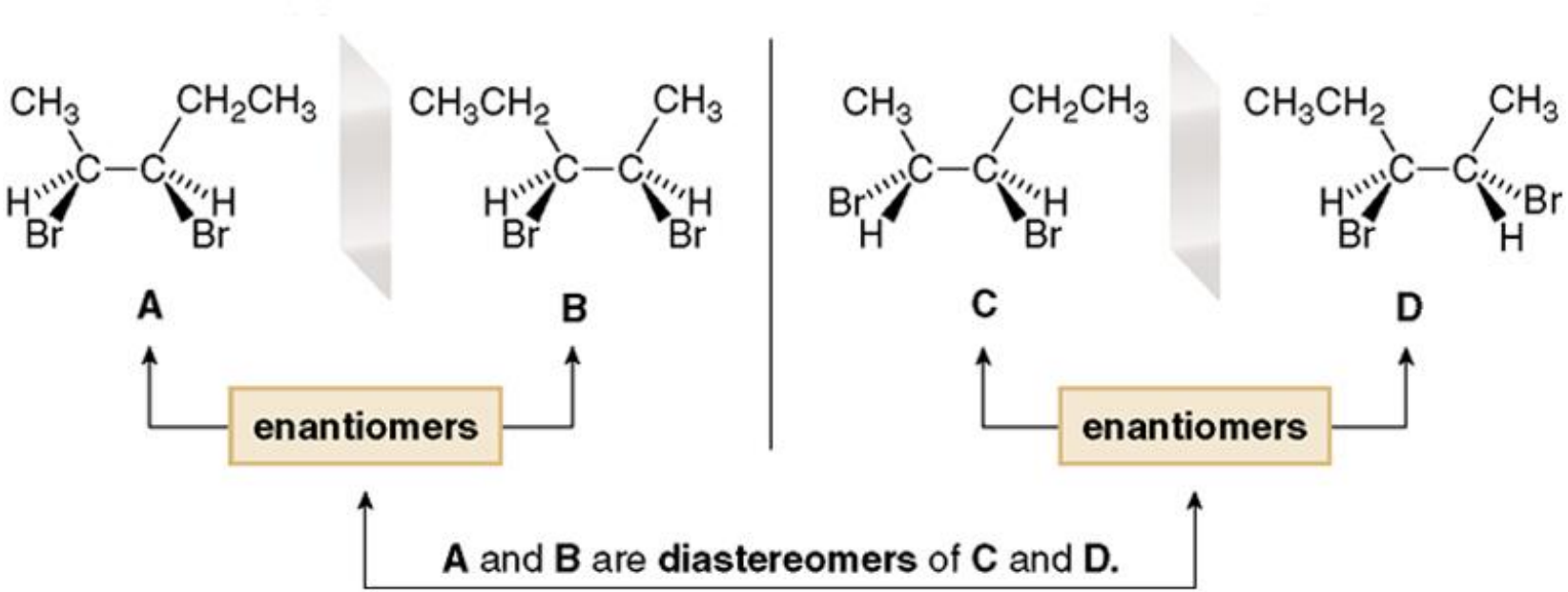


- **Stereoisomers that are not mirror images of one another are called diastereomers. For example, A and C are diastereomers.**

Stereochemistry

Diastereomers:

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

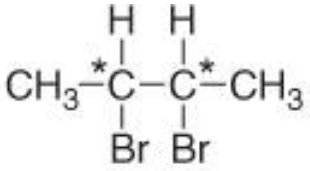


- Pairs of enantiomers: **A** and **B; C** and **D.**
- Pairs of diastereomers: **A** and **C; A** and **D; B** and **C; B** and **D.**

Stereochemistry

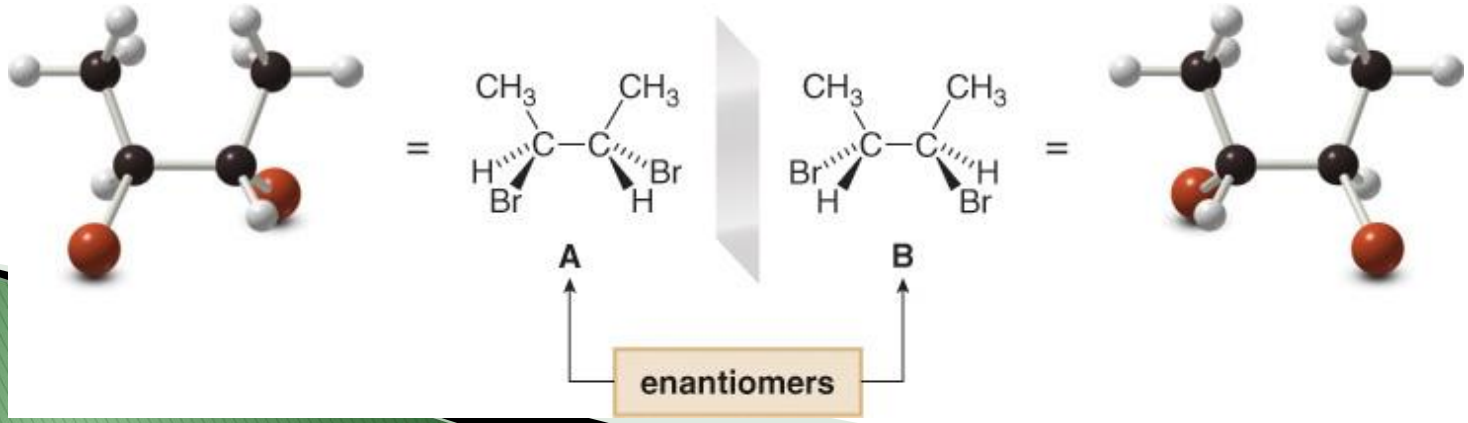
Meso Compounds:

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



2,3-dibromobutane
[* = stereogenic center]

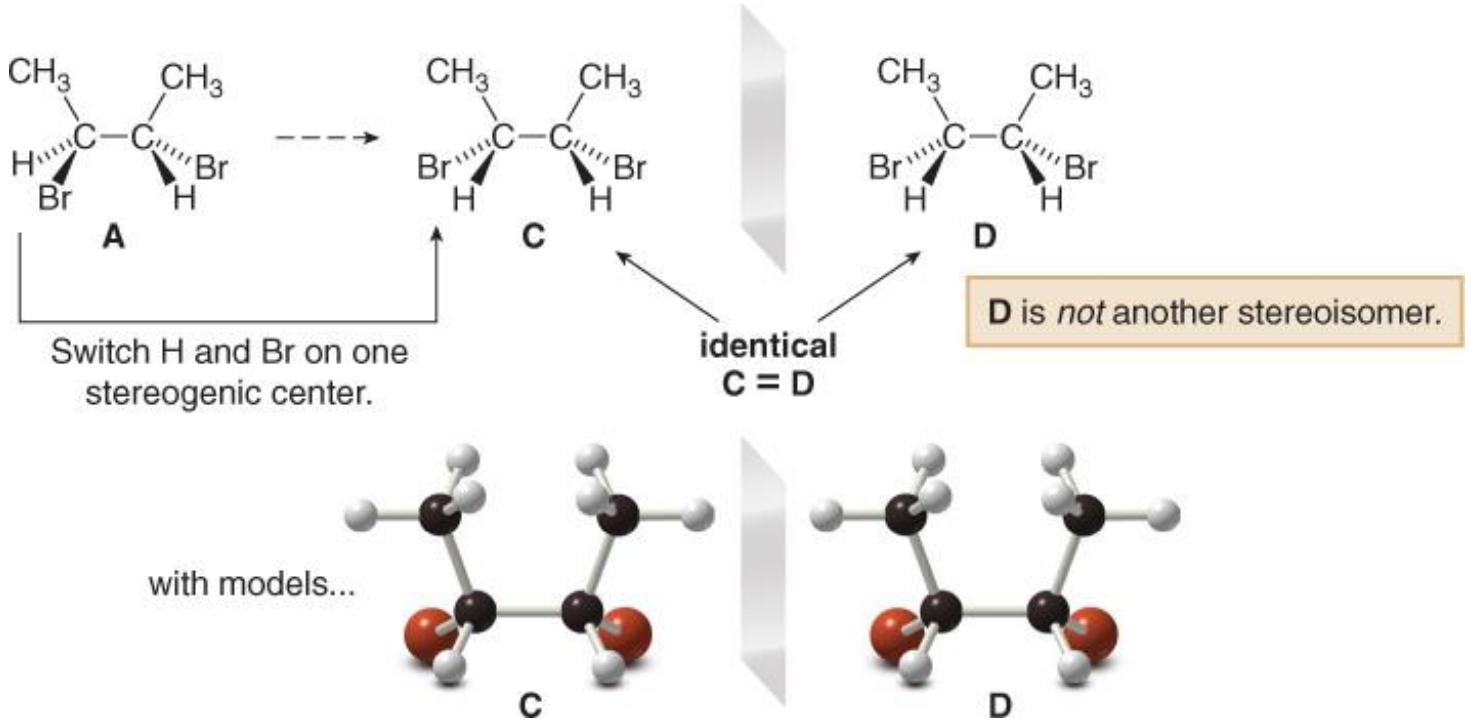
- **To find all the stereoisomers of 2,3-dibromobutane, arbitrarily add the H, Br, and CH_3 groups to the stereogenic centers, forming one stereoisomer A, and then draw its mirror image, B.**



Stereochemistry

Meso Compounds:

- **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.**

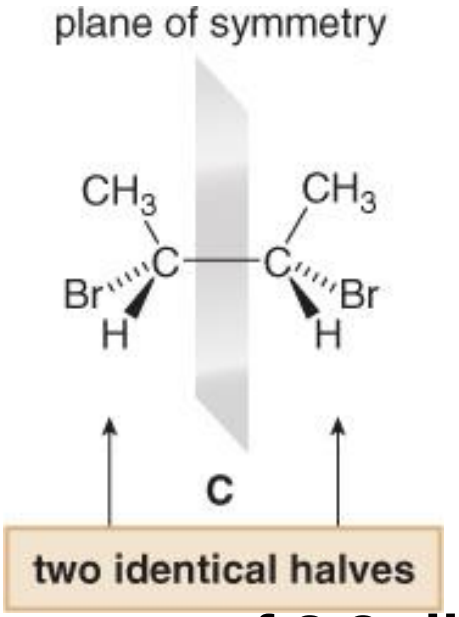


- **A meso compound is an achiral compound that contains tetrahedral stereogenic centers. C is a meso compound.**

Stereochemistry

Meso Compounds:

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

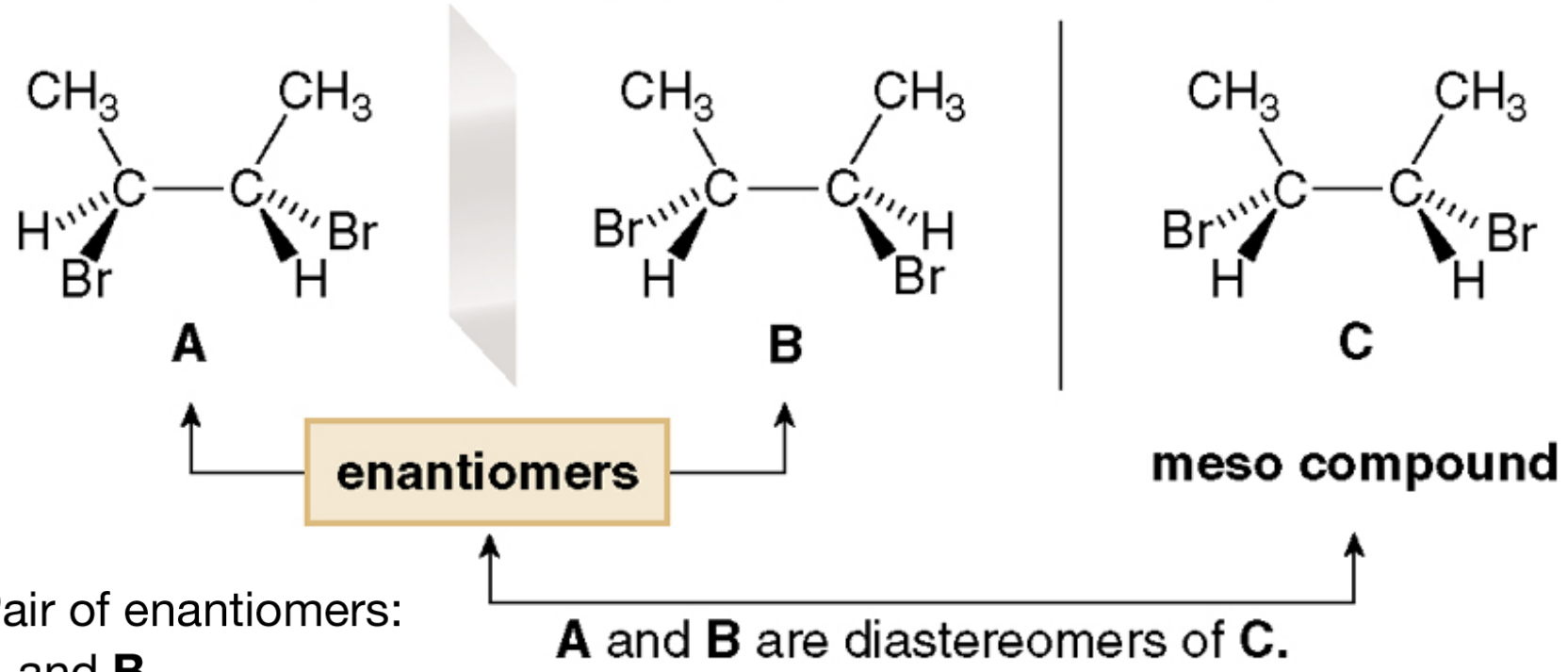


- **Because one stereoisomer of 2,3-dibromobutane is superimposable on its mirror image, there are only three stereoisomers, not four.**

Stereochemistry

Meso Compounds:

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

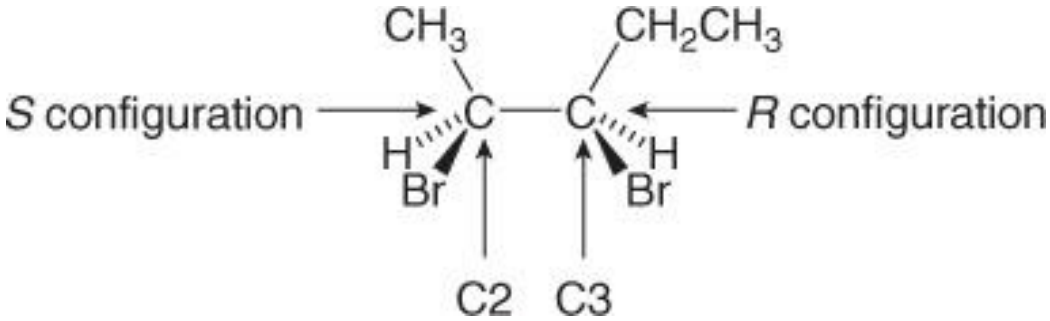


- Pair of enantiomers: **A** and **B.**
- Pairs of diastereomers: **A** and **C; B** and **C.**

Stereochemistry

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

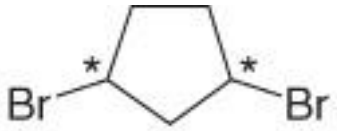
The complete name is (2*S*,3*R*)-2,3-dibromopentane

- 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.

Stereochemistry

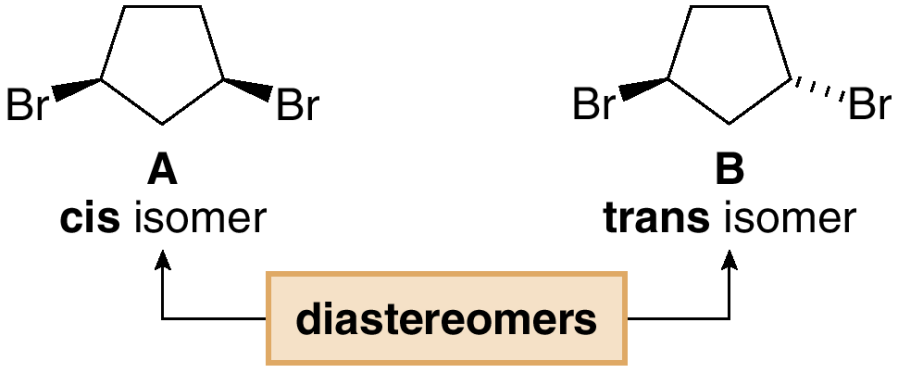
Disubstituted Cycloalkanes:

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



1,3-dibromocyclopentane
[* = stereogenic center]

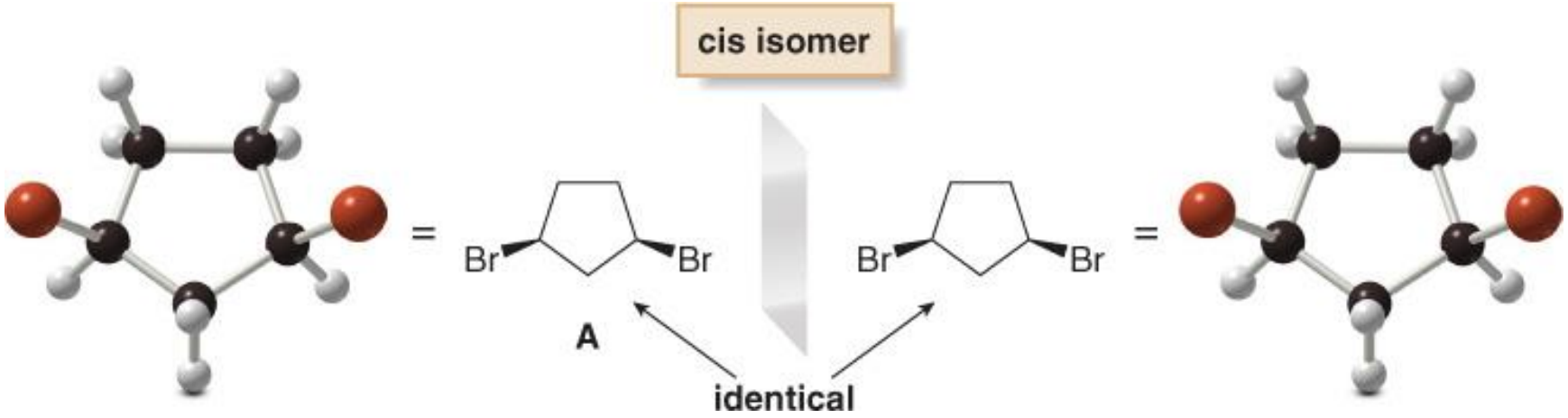
- **Recall that a disubstituted cycloalkane can have two substituents on the same side of the ring (*cis* isomer, A) or on opposite sides of the ring (*trans* isomer, B). These compounds are stereoisomers but not mirror images.**



Stereochemistry

Disubstituted Cycloalkanes:

- **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.**

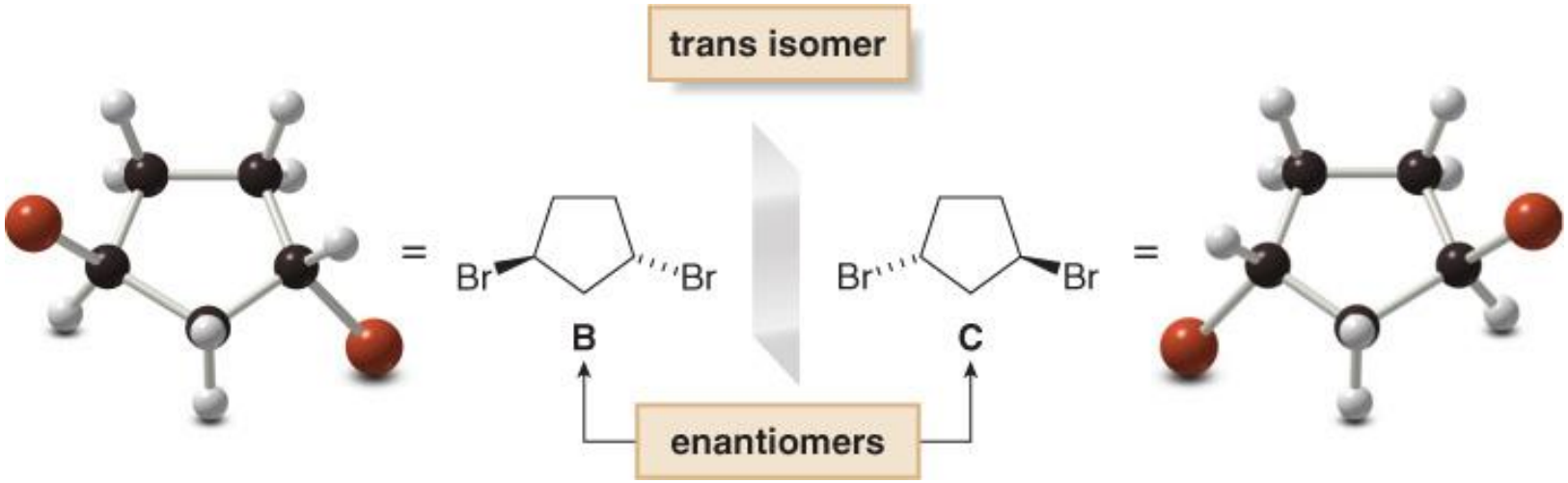


- **The *cis* isomer is superimposable on its mirror image, making the images identical. Thus, A is an achiral meso compound.**

Stereochemistry

Disubstituted Cycloalkanes:

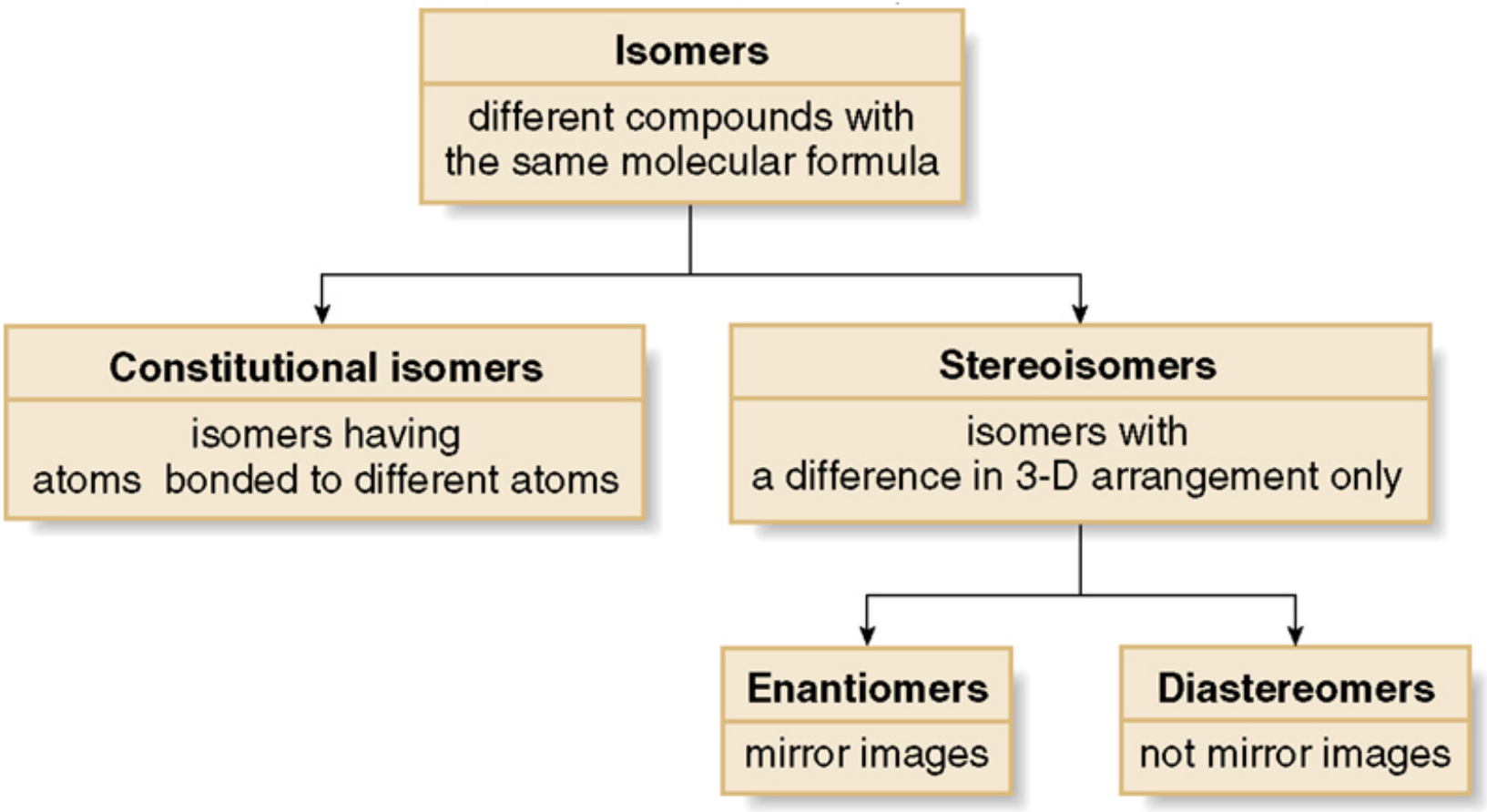
- **The trans isomer is not superimposable on its mirror image, labeled C, making B and C different compounds. B and C are enantiomers.**



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

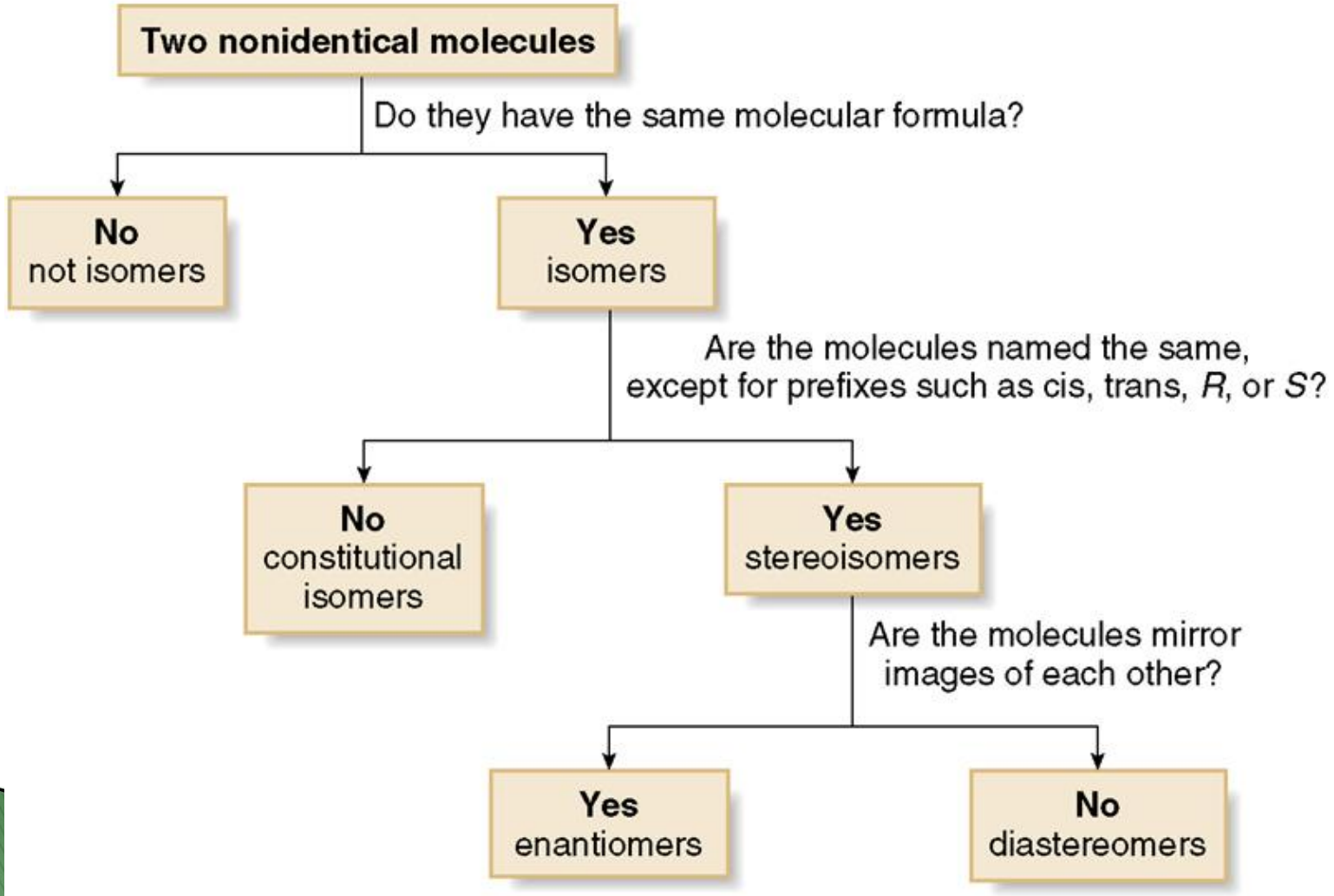
Stereochemistry

Figure 5.10 **Summary—Types of isomers**



Stereochemistry

Figure 5.11 **Determining the relationship between two nonidentical molecules**



Stereochemistry

Optical Activity

- **The chemical and physical properties of two enantiomers are identical except in their interaction with chiral substances.**
- **The physical property that differs is the behavior when subjected to plane-polarized light (this physical property is often called an optical property).**
- **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.**

Stereochemistry

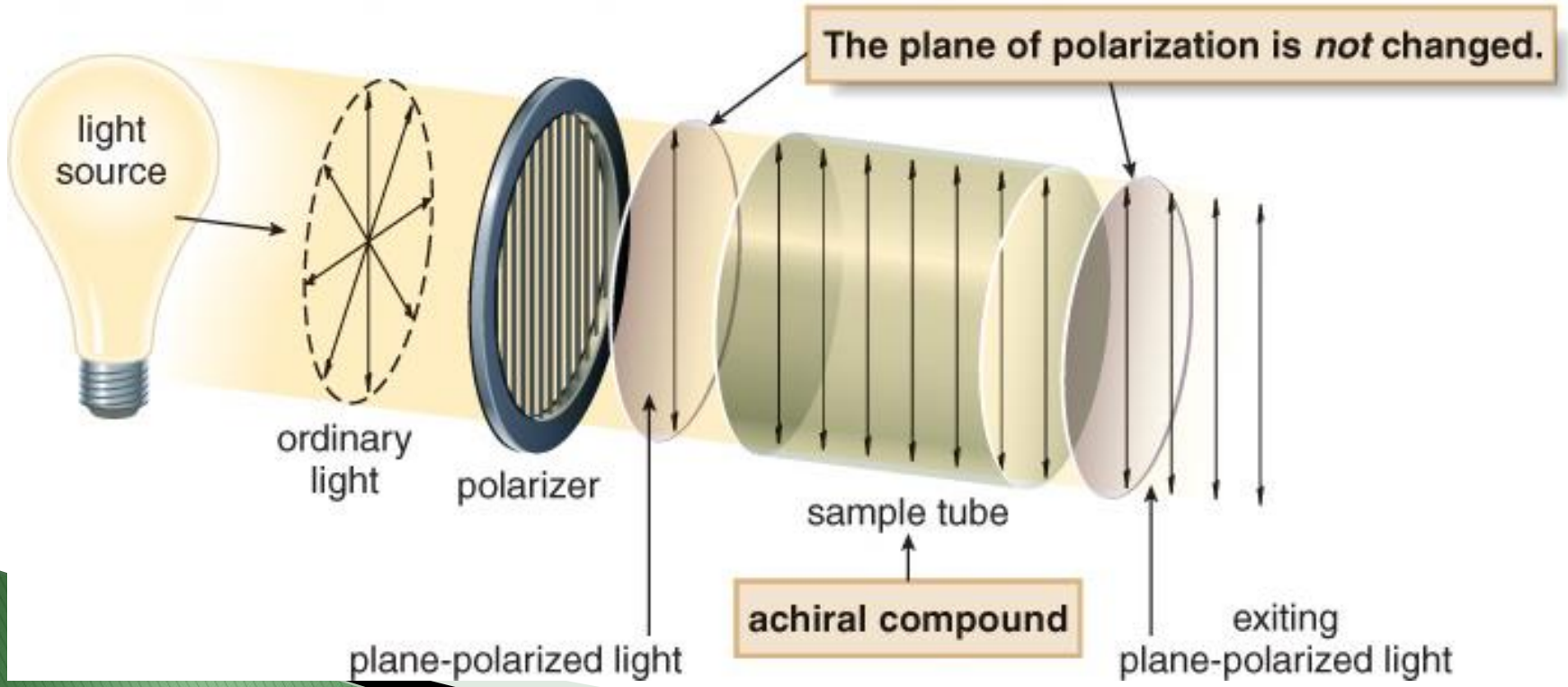
Optical Activity

- **Originally a natural polarizer, calcite or iceland spar, was used. Today, polarimeters use a polarized lens similar to that used in some sunglasses.**
- **A polarizer has a very uniform arrangement of molecules such that only those light rays of white light (which is diffuse) that are in the same plane as the polarizer molecules are able to pass through.**
- **A polarimeter is an instrument that allows polarized light to travel through a sample tube containing an organic compound and permits measurement of the degree to which the light is rotated.**

Stereochemistry

Optical Activity

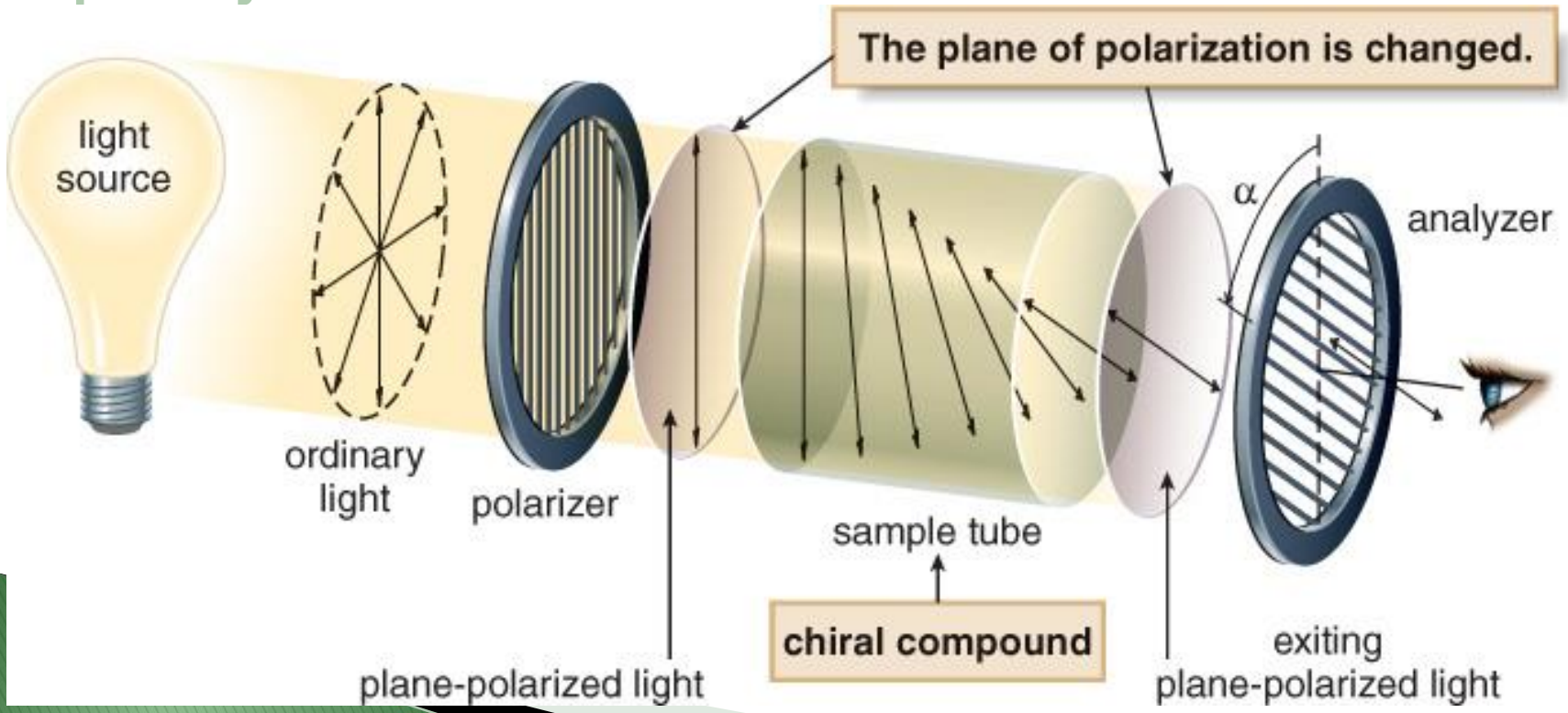
- **With achiral compounds, the light that exits the sample tube remains unchanged. A compound that does not change the plane of polarized light is said to be optically inactive.**



Stereochemistry

Optical Activity

- **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.**



Stereochemistry

Optical Activity

- The rotation of polarized light can be clockwise or counterclockwise.
- 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°, 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.

Stereochemistry

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.**

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°

Stereochemistry

Racemic Mixtures

- 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 [α] and defined using a specific sample tube length (*l*, in dm), concentration (*c* in g/mL), temperature (25^{0}C) and wavelength (589 nm).**

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

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

[dm = decimeter
1 dm = 10 cm]

Stereochemistry

Enantiomeric excess and Optical purity: ee and op

- **Enantiomeric excess (ee) is a measurement of the excess of one enantiomer over the racemic mixture.**

  ***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.**
- **ee is numerically equal to Optical Purity.**
- **The optical purity can be calculated if the specific rotation [α] of a mixture and the specific rotation [α] of a pure enantiomer are known.**

  ***op* = ([α] mixture/[α] pure enantiomer) x 100.**

Stereochemistry

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 physical techniques.**

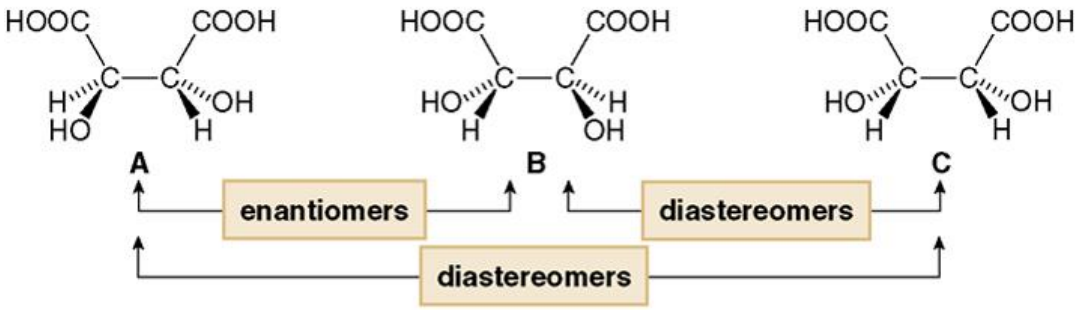


Figure 5.12 The physical properties of the three stereoisomers of tartaric acid.

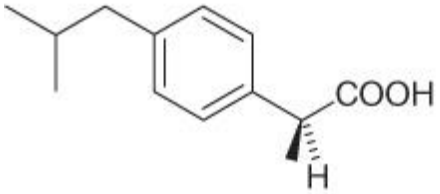
Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H_2O)	139	139	125	139
[α]	+13	–13	0	0
R,S designation	*R,R*	*S,S*	*R,S*	—
d,l designation	*d*	*l*	none	*d,l*

- 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.

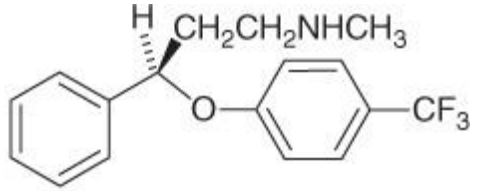
Stereochemistry

Chemical Properties of Enantiomers:

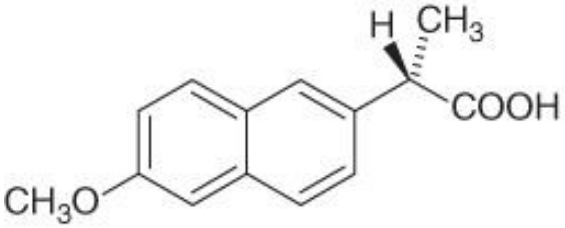
- **Two enantiomers have exactly the same chemical properties except for their reaction with chiral non-racemic reagents.**
- **Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective. One enantiomer of a drug may effectively treat a disease whereas its mirror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



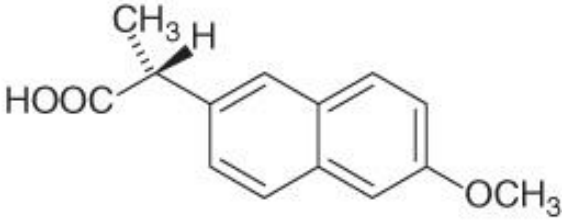
(*S*)-ibuprofen
anti-inflammatory agent



(*R*)-fluoxetine
antidepressant



(*S*)-naproxen
anti-inflammatory agent



(*R*)-naproxen
liver toxin