Stereochemistry - Chirality

Chapter 5

Organic Chemistry, *8th Edition*

John E. McMurry

Isomerism

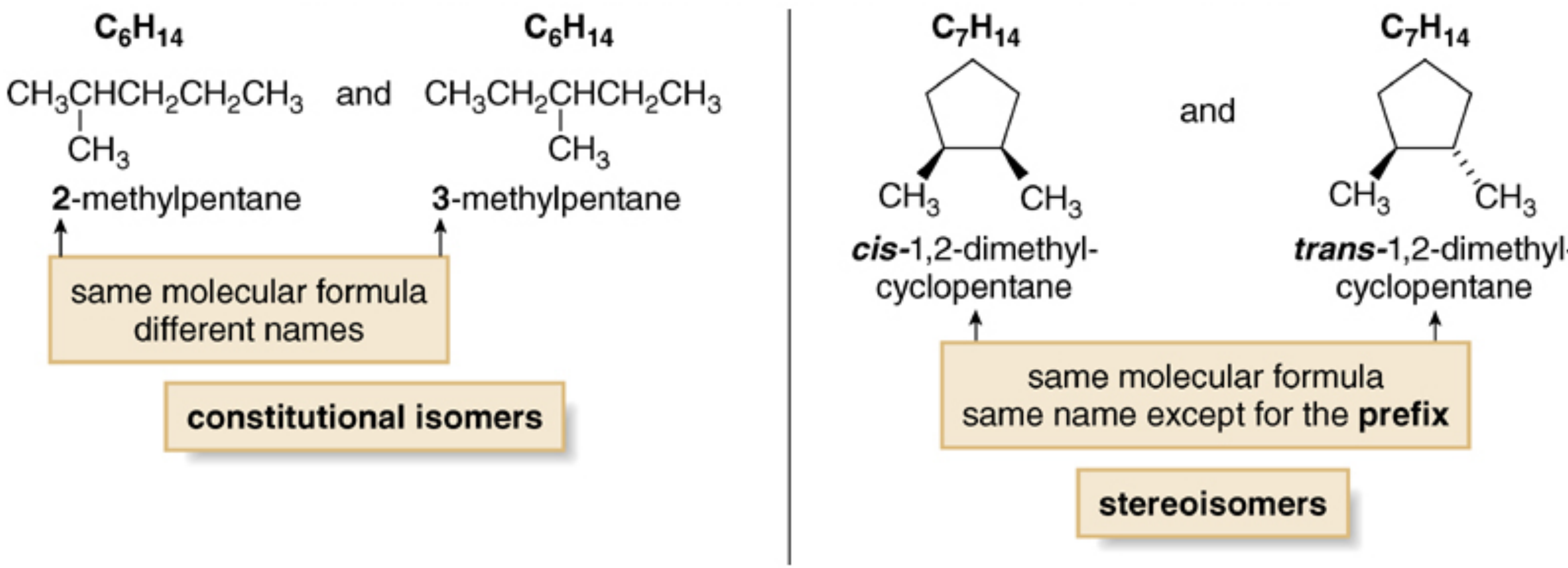
- The two major classes of isomers are constitutional isomers and stereoisomers.

  - Constitutional/structural isomers have different IUPAC names, different physical and chemical properties, and may have different functional groups.

  - 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).

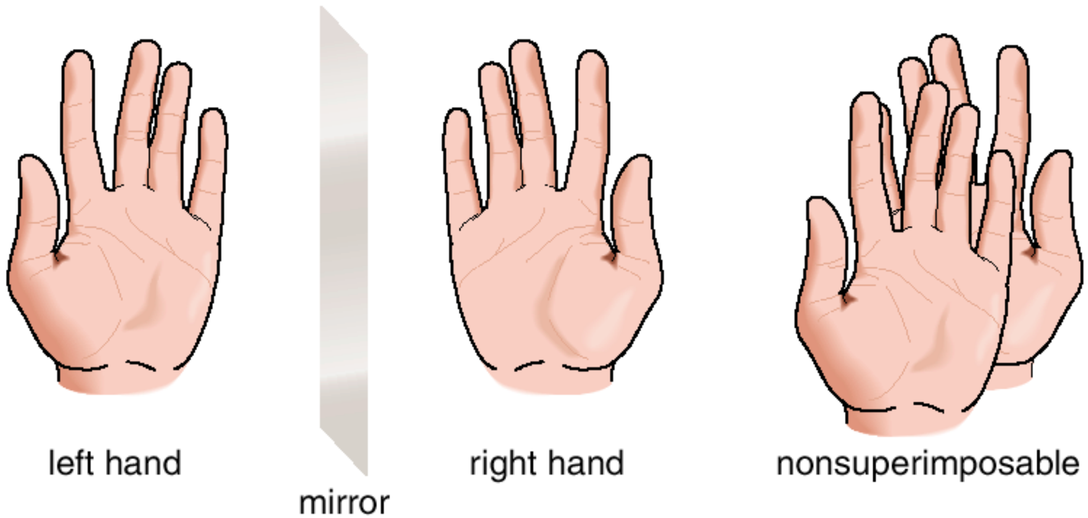
- A particular three-dimensional arrangement is called a configuration. Stereoisomers differ in configuration.

Stereoisomers



Chirality

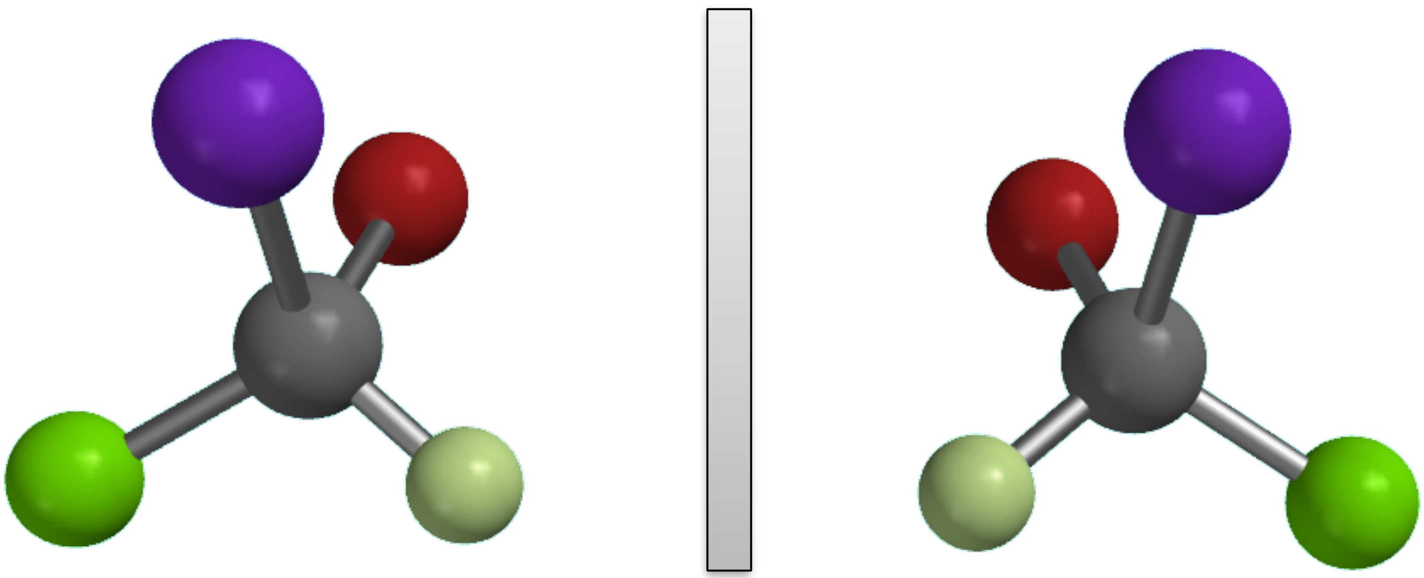
- Every object has a mirror image: mirror images may or may not be superimposable.
- Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or superimposable.



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

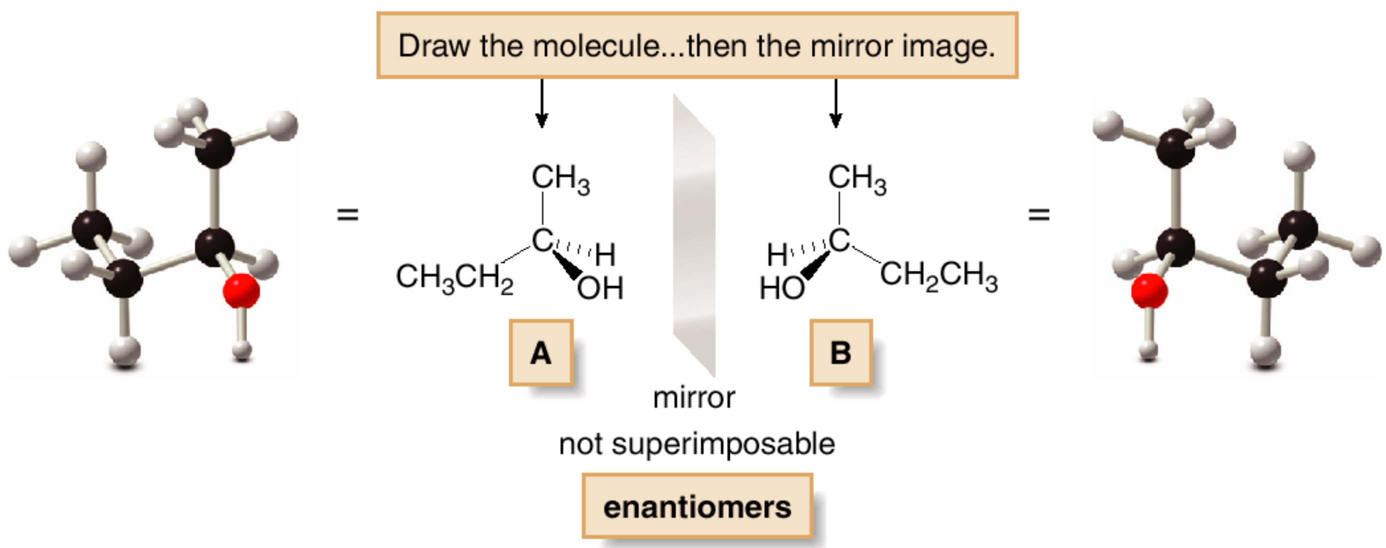
Chirality

Enantiomers of bromo-chloro-fluoro-iodometahane

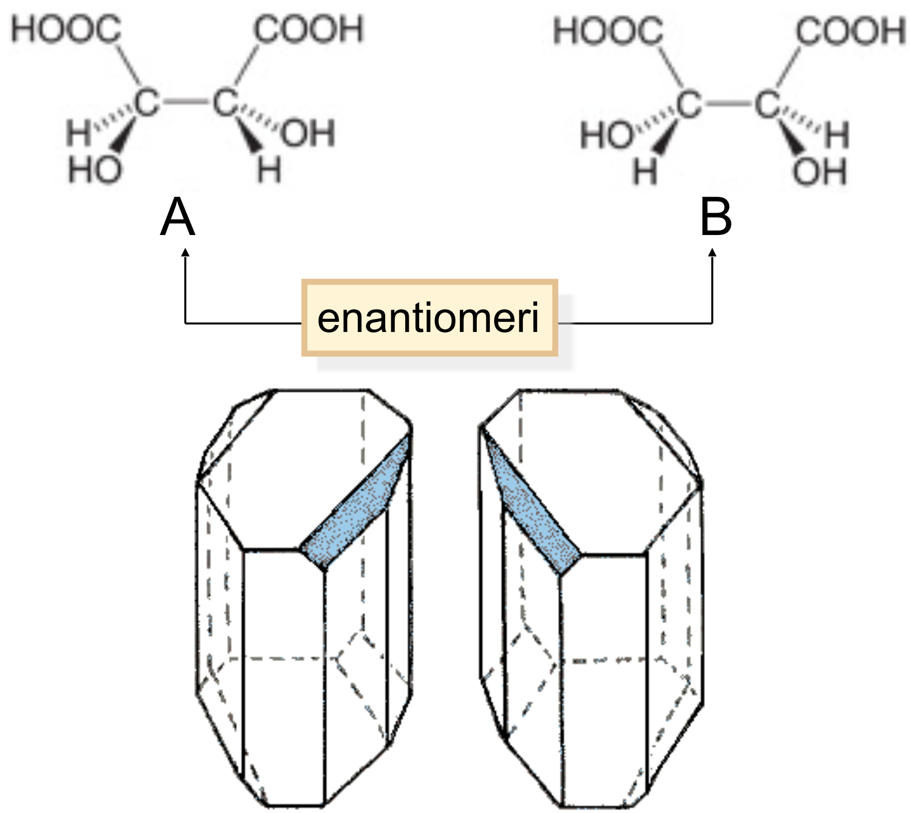


Chirality

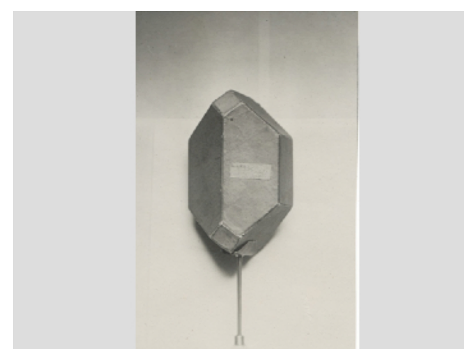
- A and B are stereoisomers—specifically, they are enantiomers.
- A carbon atom with four different groups is a tetrahedral stereogenic center.



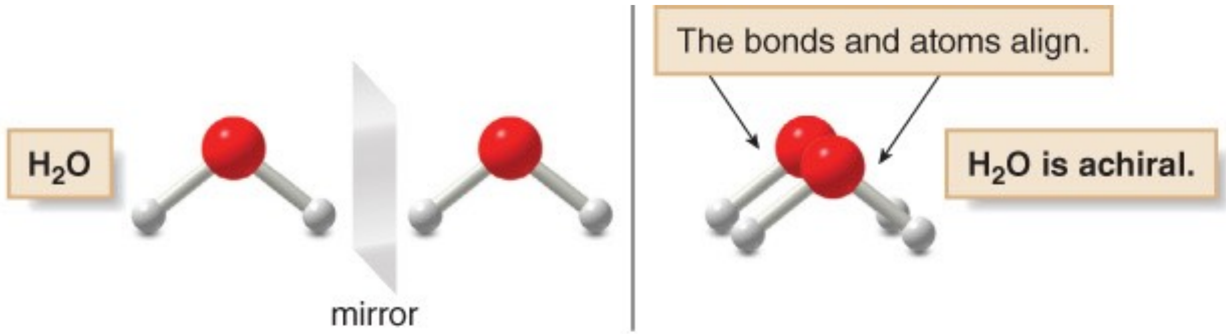
Tartaric acid



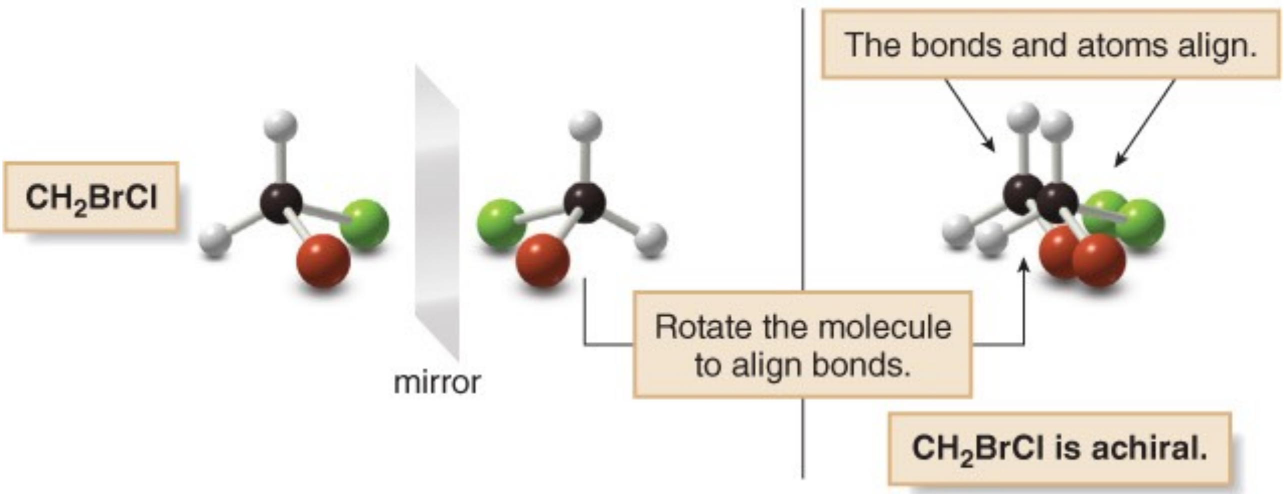
Louis Pasteur



Chirality

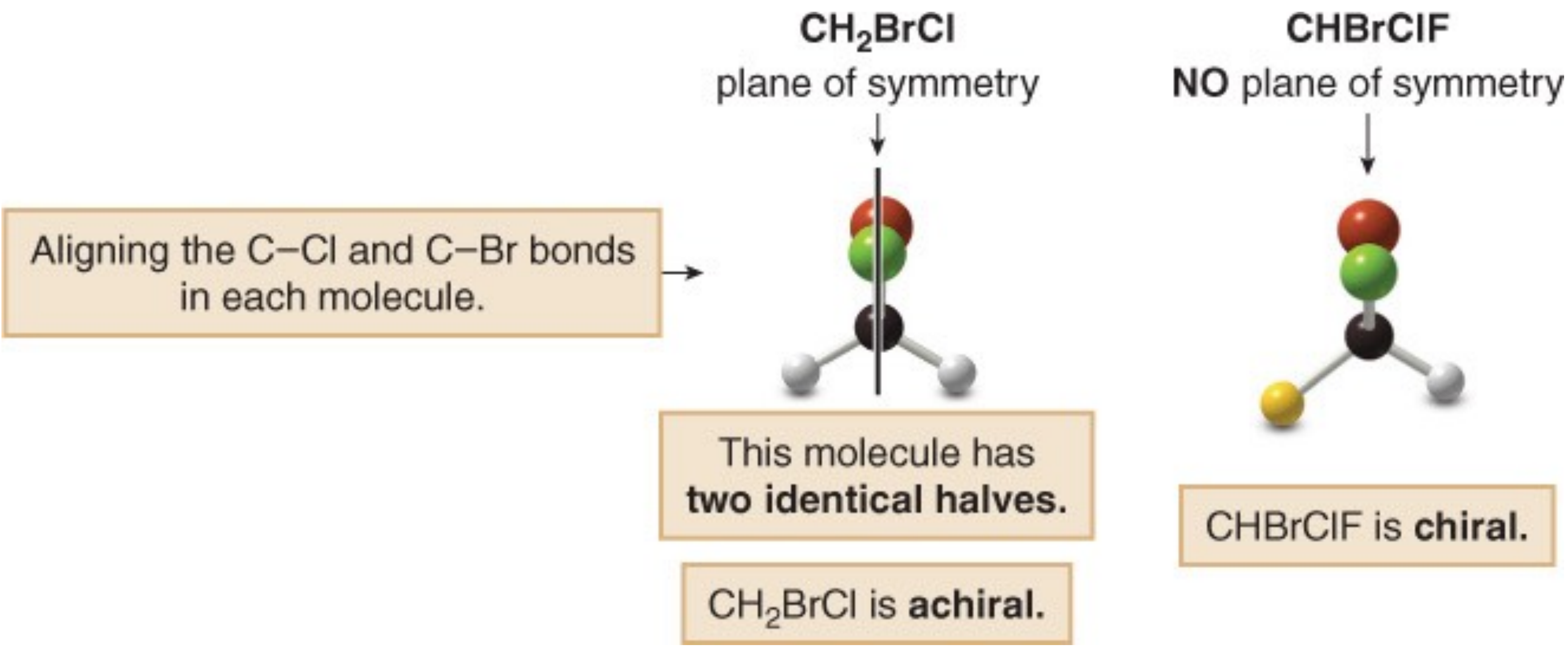


H_2O
mirror
The bonds and atoms align.
H_2O is achiral.

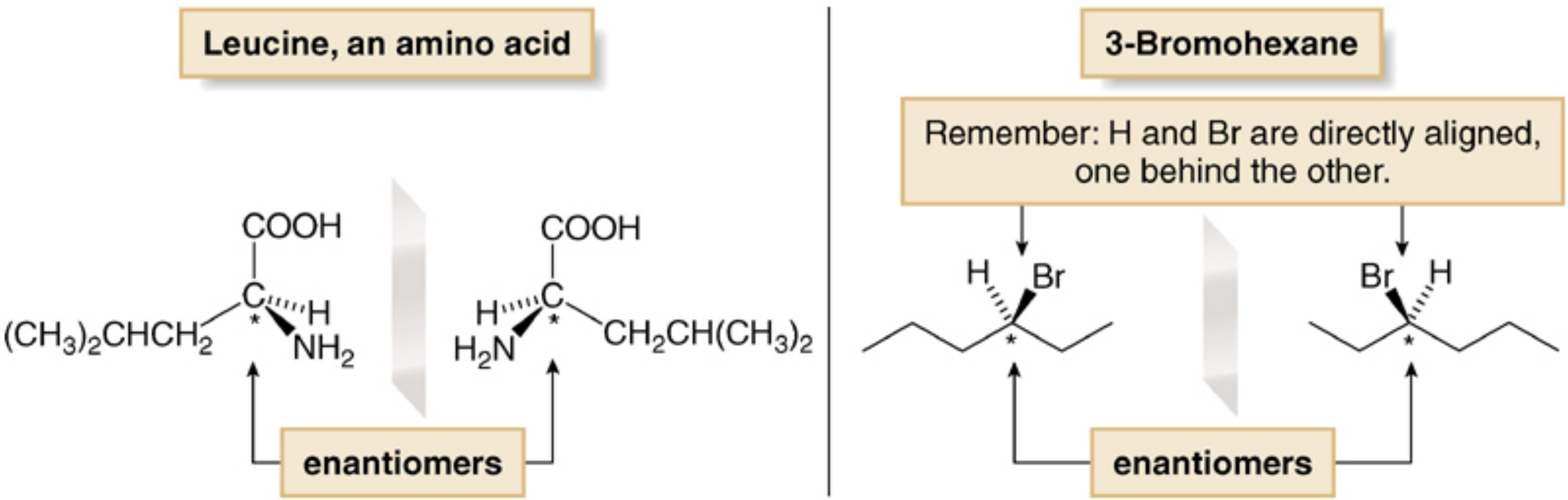


CH_2BrCl
mirror
The bonds and atoms align.
Rotate the molecule to align bonds.
CH_2BrCl is achiral.

Chirality and Symmetry



Stereogenic Centers

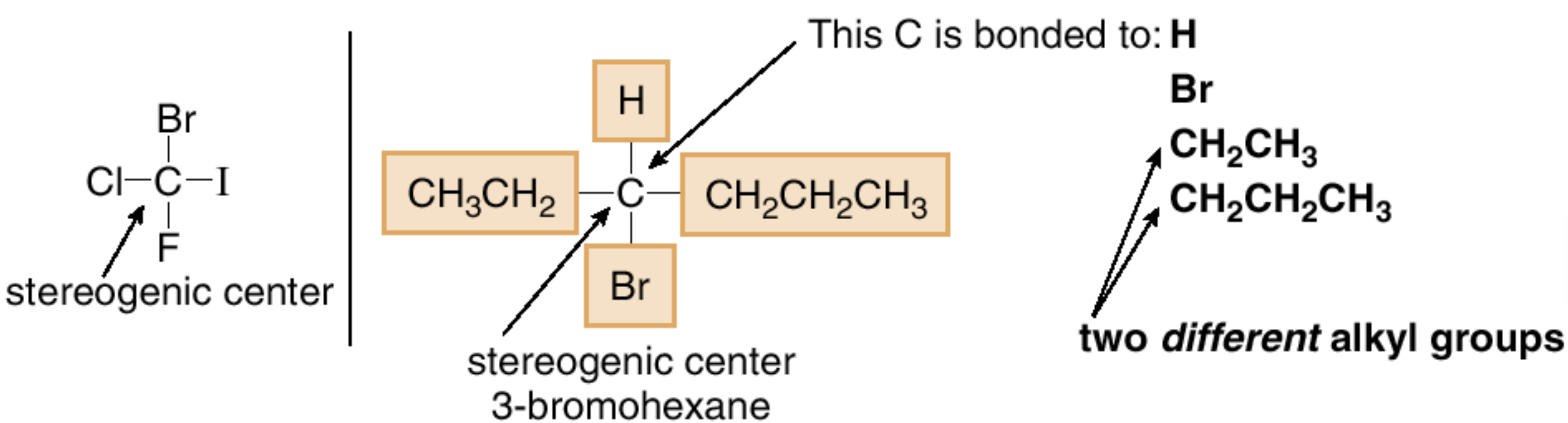


[* = stereogenic center]

Stereogenic Centers

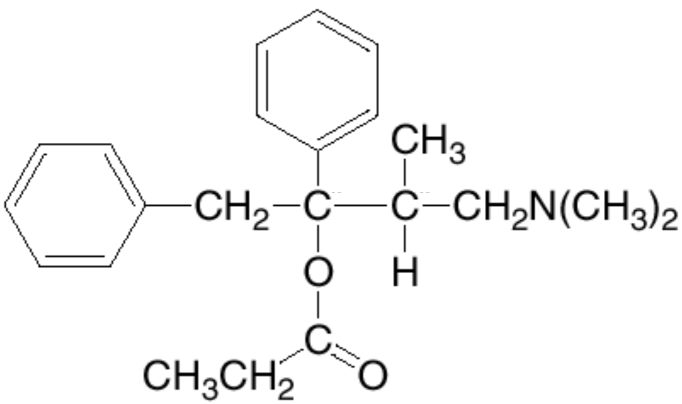
- To locate a stereogenic center, examine each tetrahedral carbon atom in a molecule, and look at the four groups—not the four atoms—bonded to it.

- 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

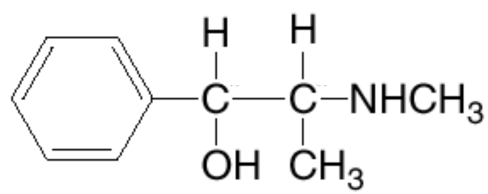


Stereogenic Centers

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

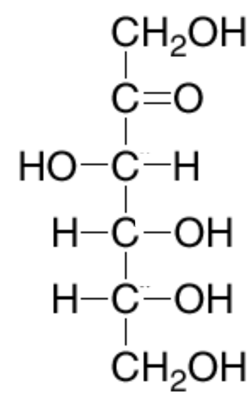


propoxyphene
Trade name: Darvon
(analgesic)



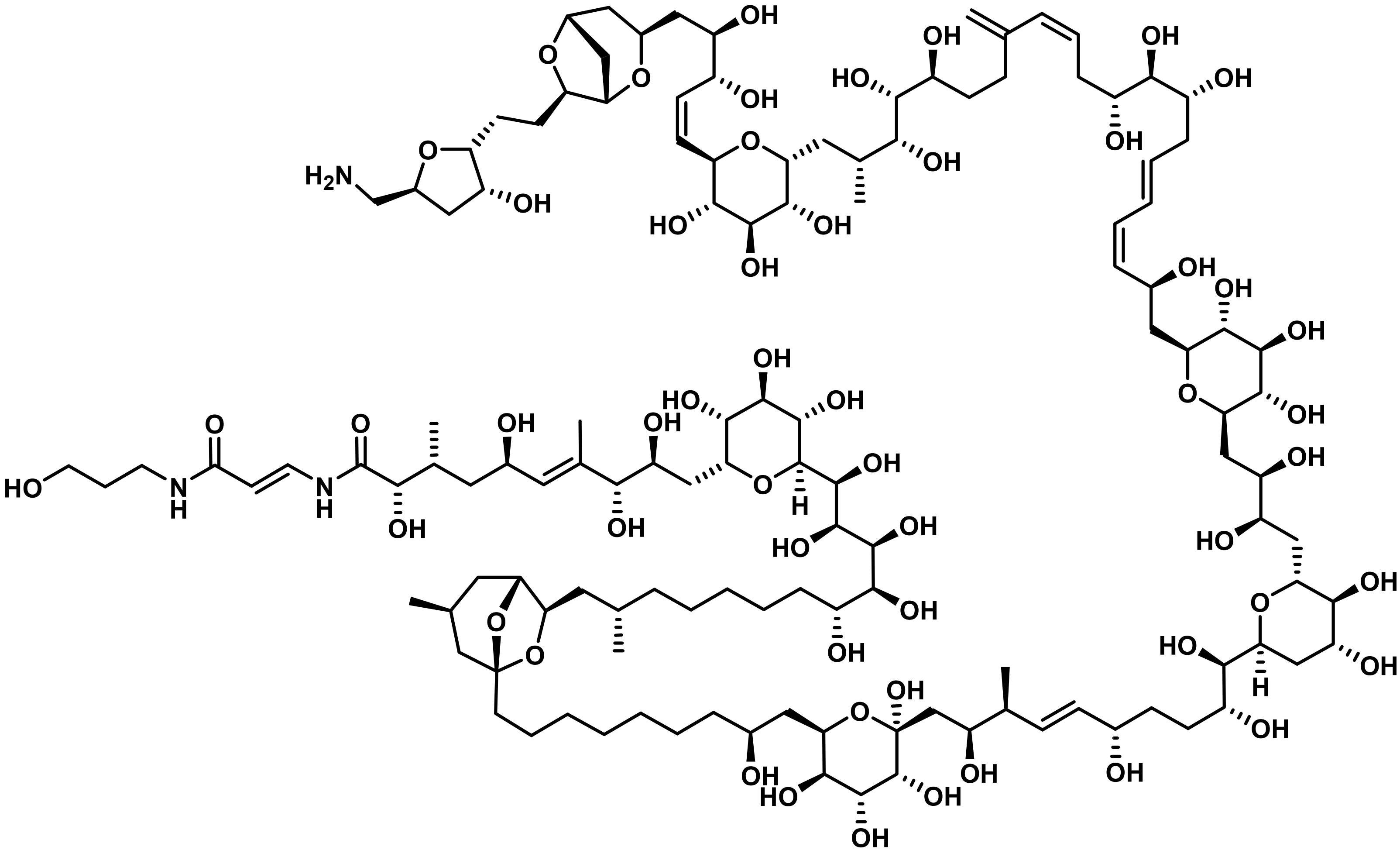
ephedrine
(bronchodilator, decongestant)

[* = stereogenic center]



fructose
(a simple sugar)

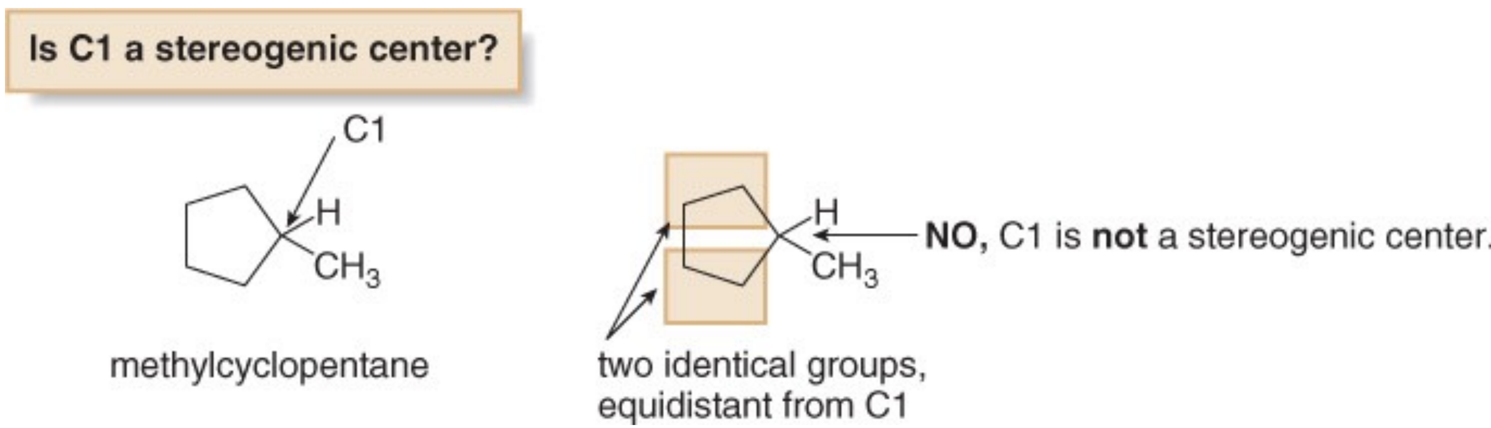
Stereogenic Centers

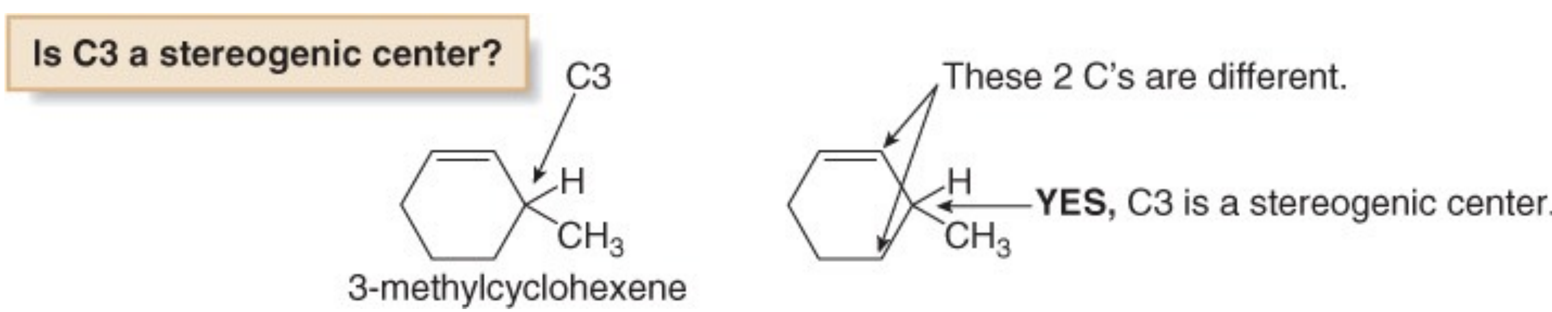


Palytoxin: 64 chiral centers

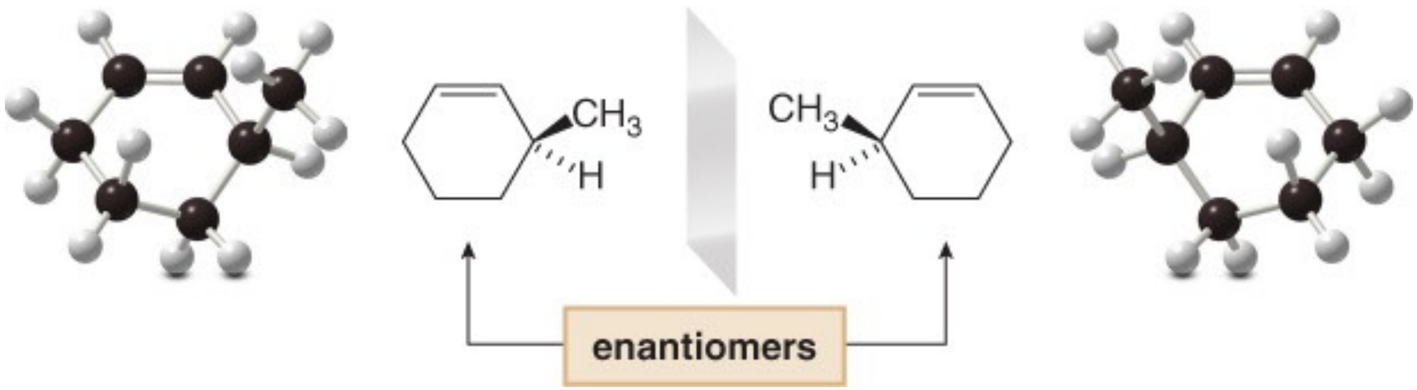
Cyclic Compounds

- 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.





Cyclic Compounds



Chirality and Symmetry

- In general, a molecule with no stereogenic centers will not be chiral.

- With one stereogenic center, a molecule will always be chiral.

- With two or more stereogenic centers, a molecule may or may not be chiral.

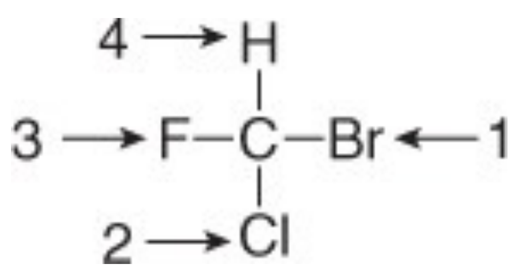
- Achiral molecules usually contain a plane of symmetry but chiral molecules do not.

- 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.

Cahn-Ingold-Prelog System

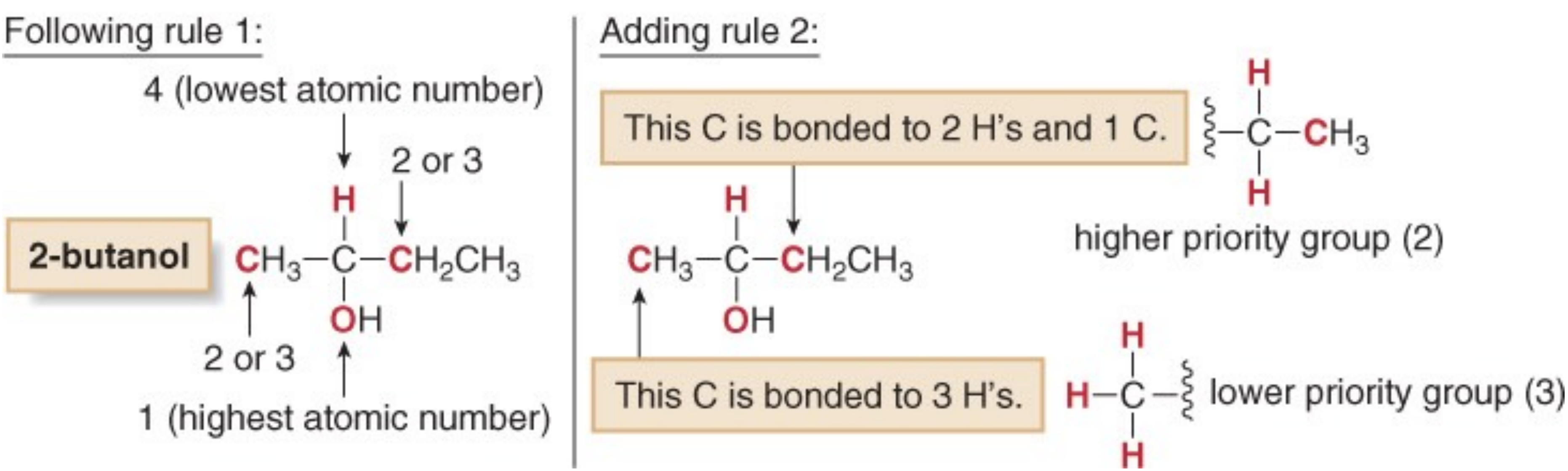
- Naming enantiomers with the prefixes *R* or *S* is called the Cahn-Ingold-Prelog system.

- Priority rule 1. The atom of highest atomic number gets the highest priority (1).



Cahn-Ingold-Prelog System

- Priority 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.



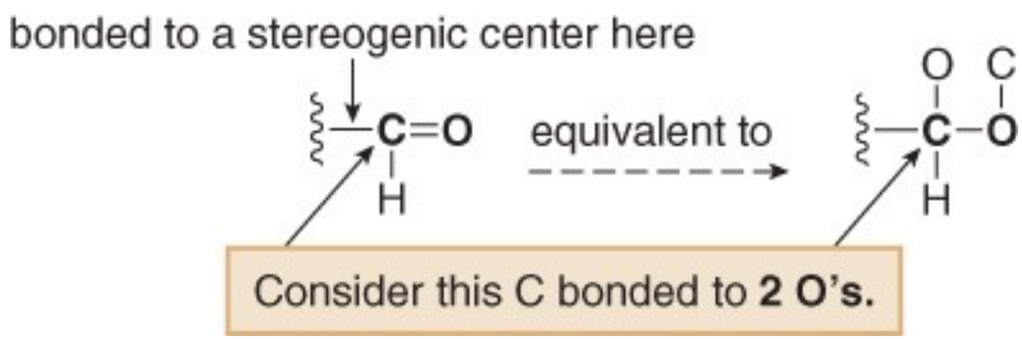
Cahn-Ingold-Prelog System

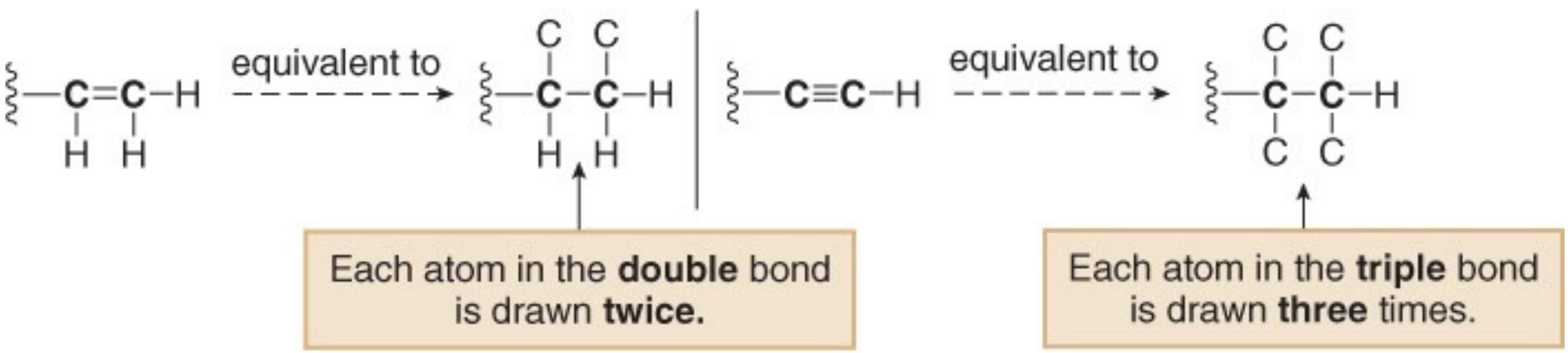
- Priority rule 3. If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing mass number. Thus, in comparing the three isotopes of hydrogen, the order of priorities is:

	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

Cahn-Ingold-Prelog System

- Priority 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.

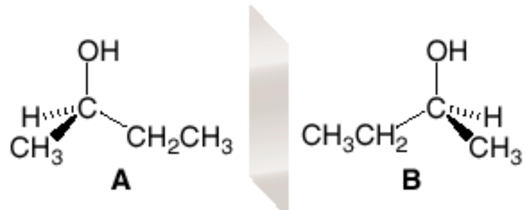




Cahn-Ingold-Prelog System

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

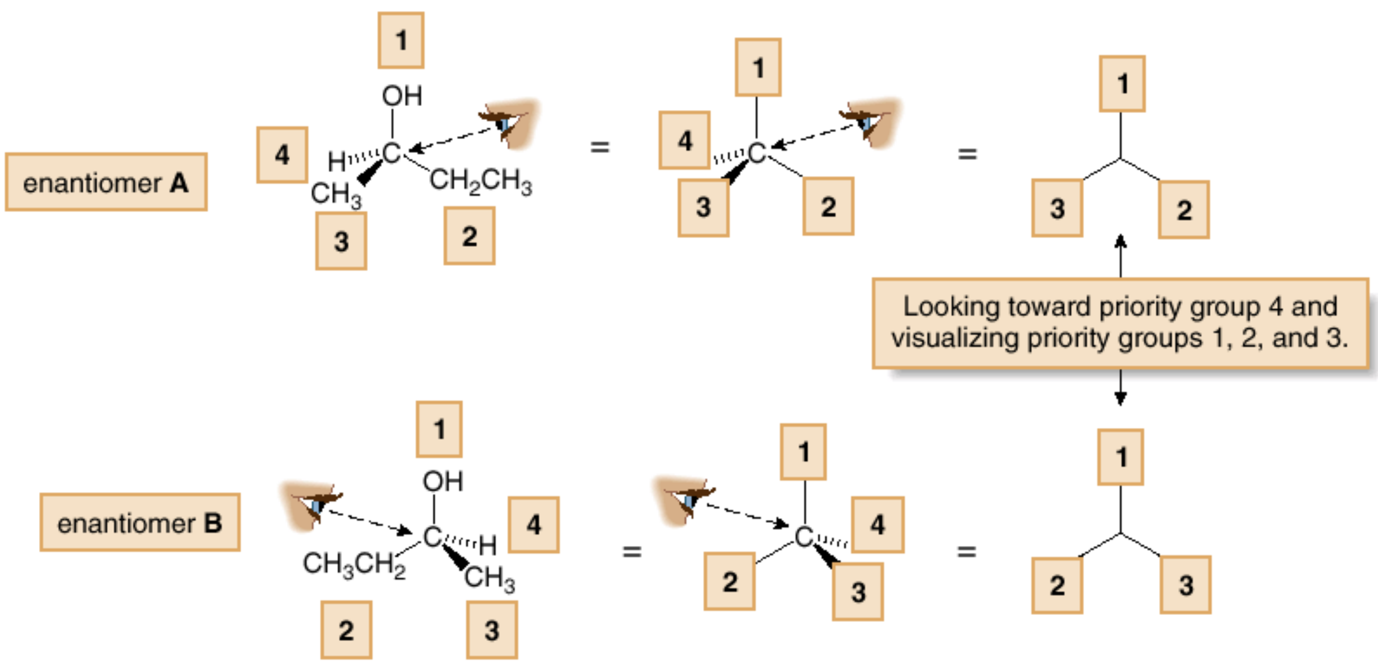
Decreasing priority →

Cahn-Ingold-Prelog System

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).

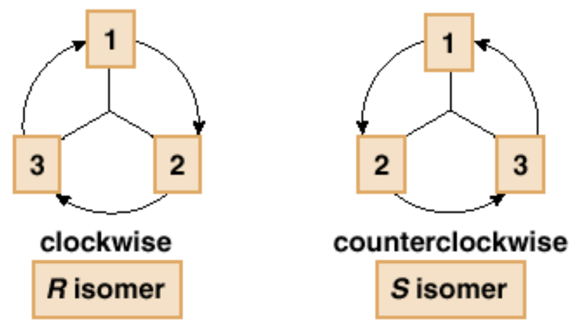
- For each enantiomer of 2-butanol, look toward the lowest priority group, drawn behind the plane, down the C–H bond.



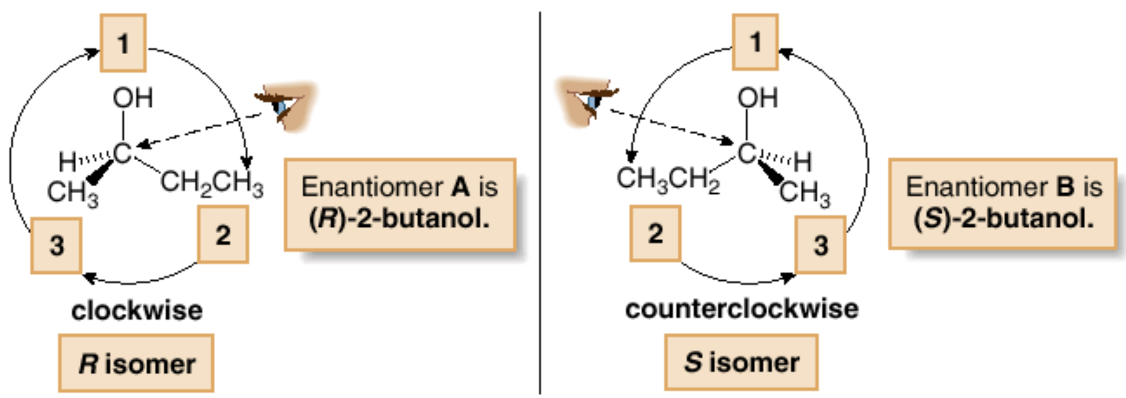
Cahn-Ingold-Prelog System

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

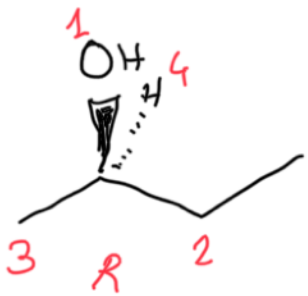
- If tracing the circle goes in the **clockwise** direction—to the right from the noon position—the isomer is named ***R*.**
- If tracing the circle goes in the **counterclockwise** direction—to the left from the noon position—the isomer is named ***S*.**

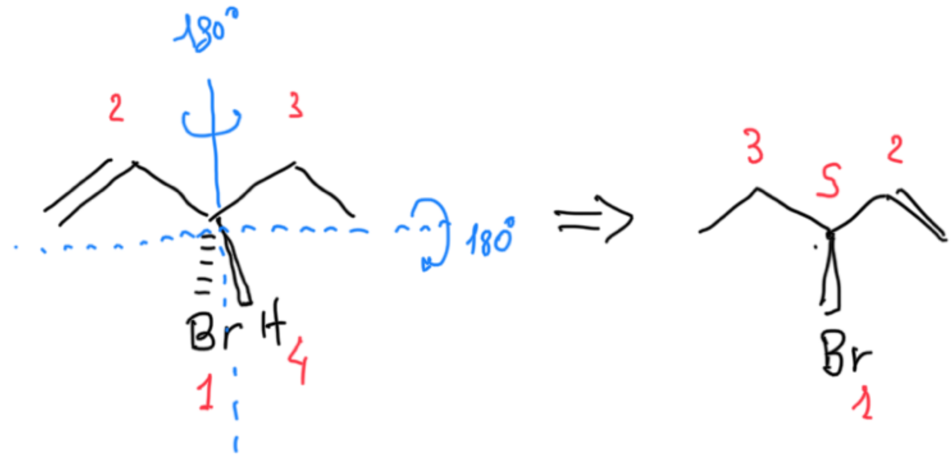


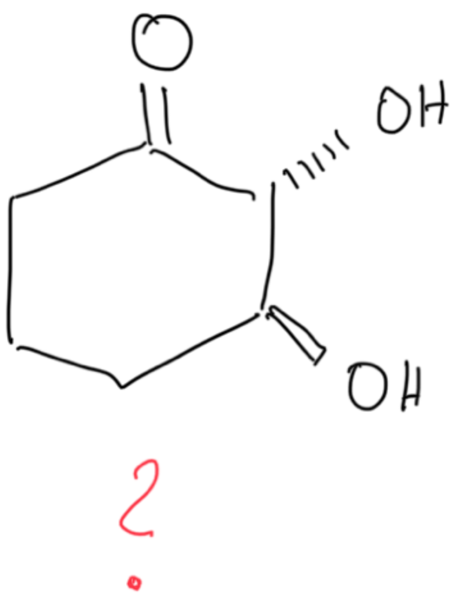
- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:



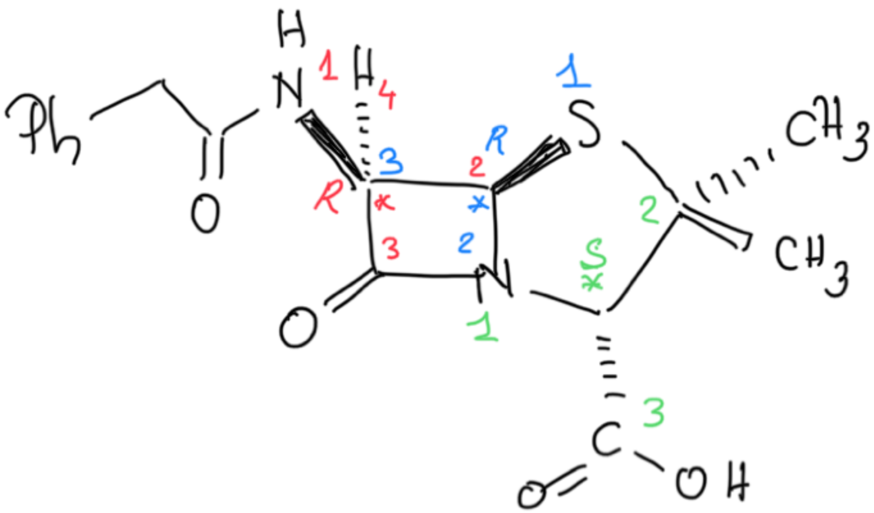
Cahn-Ingold-Prelog Rules



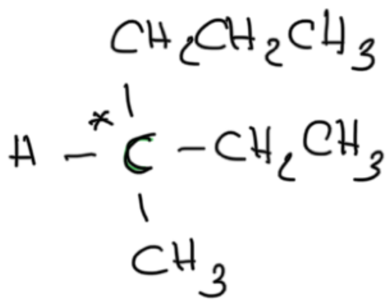




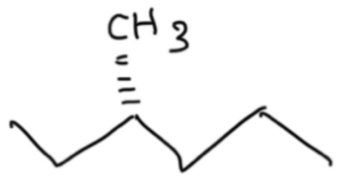
Configuration of Benzylpenicillin



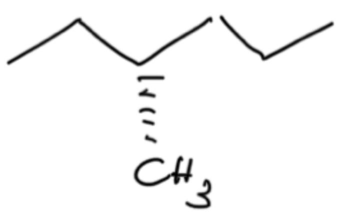
The Smallest Chiral Alkane



(S)-3-metilesano

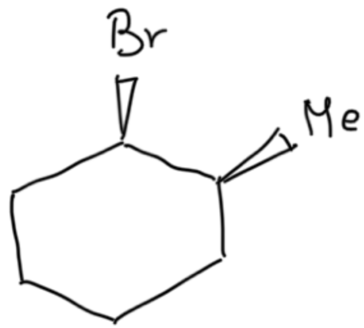


(R)-3-metilesano

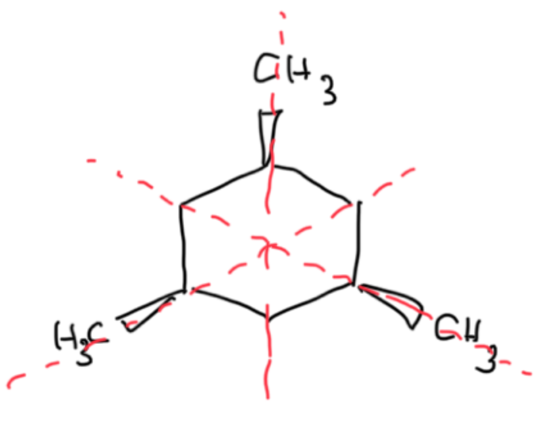


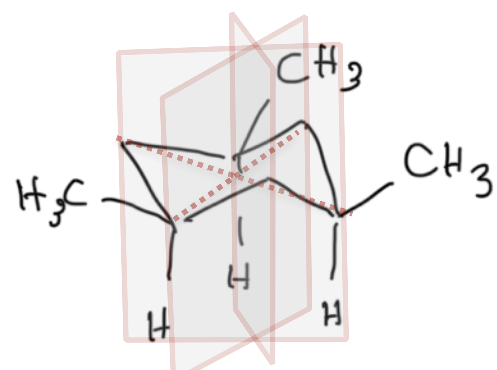
Chirality and Simmetry

CHIRALE



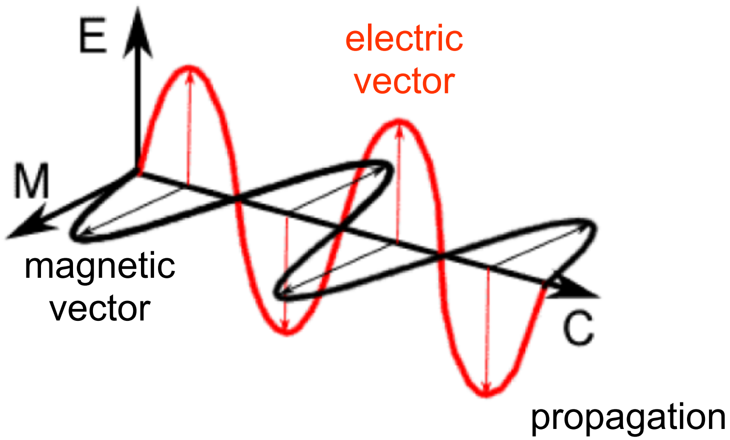
ACHIRALE

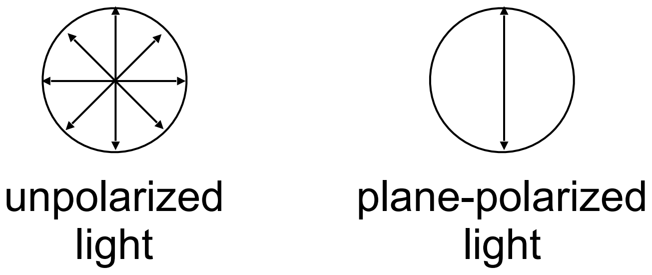




Optical Activity

- The physical properties of two enantiomers are identical except for how they interact with plane-polarized light.
- In ordinary light the electric vector oscillates in all planes perpendicular to the propagation direction.
- In plane polarized light the vector oscillates in a single plane. Polarized light is obtained with a polarizer.

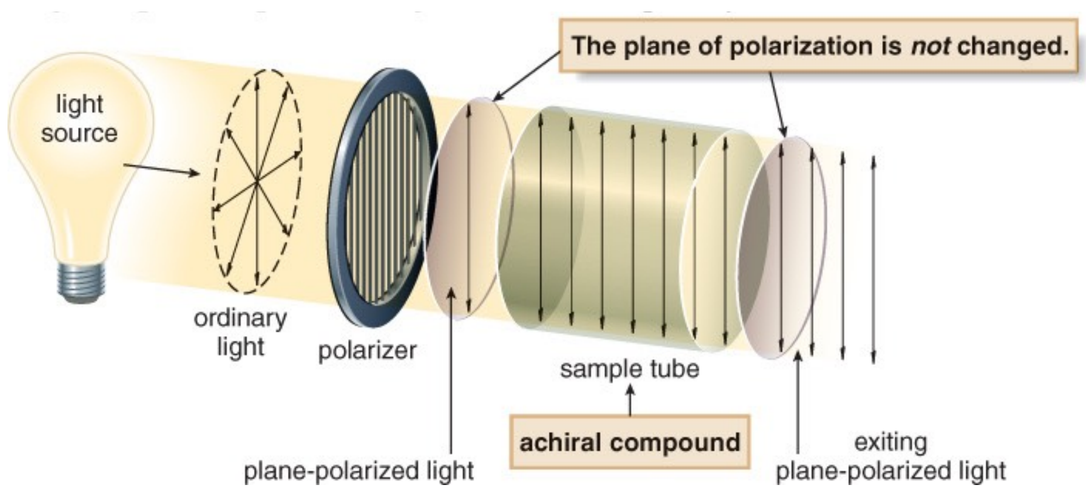




Optical Activity

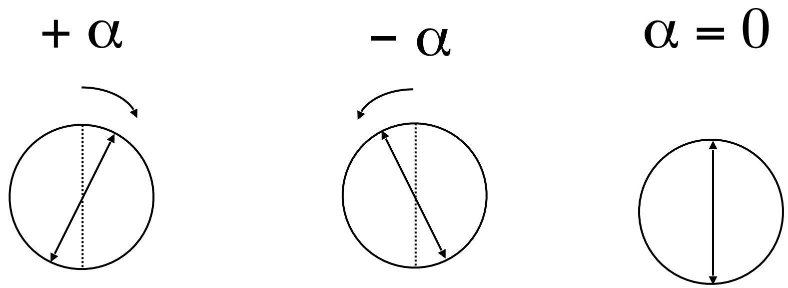
- In a polarimeter polarized light travels through a sample tube containing an organic compound.

- 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.



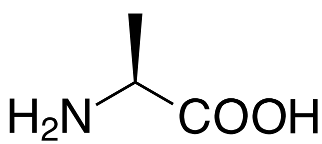
Optical Activity

- Two enantiomers rotate plane-polarized light to an equal extent but in opposite directions.

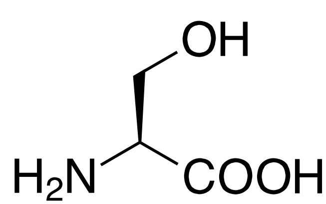


dextrorotatory (+)	levorotatory (−)	
Optically active	Optically active	Optically inactive

- No relationship exists between *R* and *S* prefixes and the (+) and (-) designations that indicate optical rotation.



(*S*)-(+)



(*S*)-(-)

Optical Activity

- Specific rotation is a standardized physical constant for the amount that a chiral compound rotates plane-polarized light.

- Specific rotation $[\alpha]$ is defined using a specific sample tube length (l, in dm), concentration (c in g/mL; for pure liquids c = d), temperature (generally 20 or 25 ^{0}C) and wavelength (generally 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]

Optical Activity

temperature (25 °C)

$$[\alpha]_D^{25}$$

wavelength
(sodium D-line = 589 nm)

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.

Property	(+) Enantiomer	(-) Enantiomer	Racemic mixture
melting point	identical		may be different
boiling point	identical		may be (slightly) different
optical rotation	$+ \alpha$	$- \alpha$	0

Optical Purity

- Enantiomeric excess (optical purity) is a measurement of how much one enantiomer is present in excess of the racemic mixture.

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

- 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.

  $$ee = ([\alpha] \text{ mixture}/[\alpha] \text{ pure enantiomer}) \times 100.$$

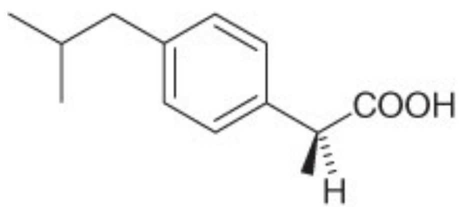
Enantiomeric Eccess

100% (+)	0% (−)	singolo enantiomero	e.e. = 100%
50% (+)	50% (−)	miscela racemica	e.e. = 0%
95% (+) (= 90% (+)	5% (−) 10% (±))	miscela	e.e. = 90% $[\alpha]_{mix} = 0.9\,[\alpha]_{(+)}$

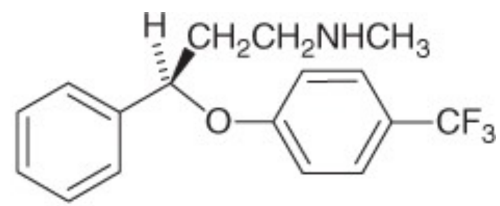
Chemical Properties of Enantiomers

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

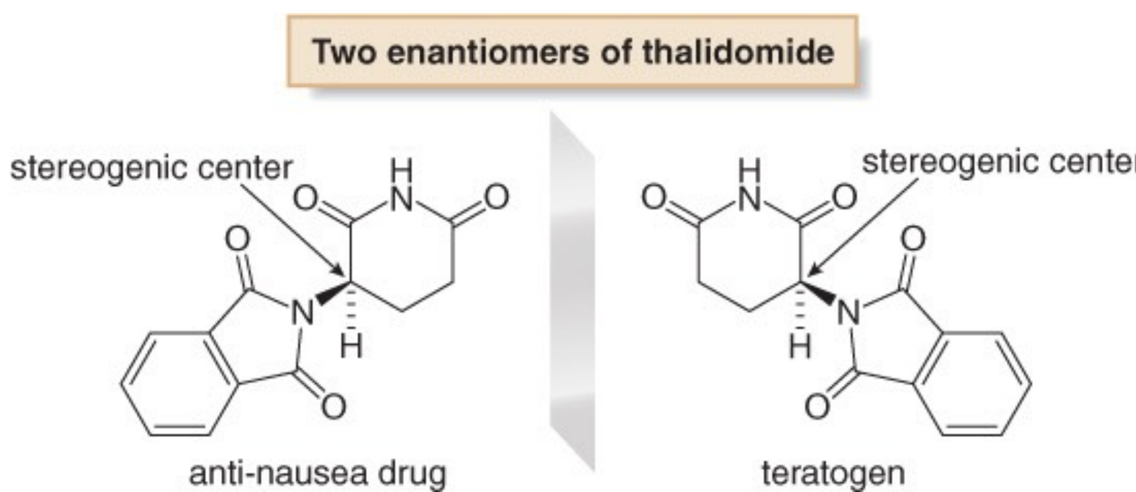
- Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective. One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective or toxic.



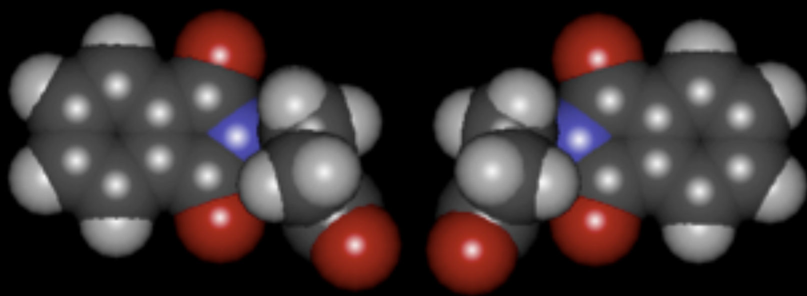
(*S*)-ibuprofen
anti-inflammatory agent

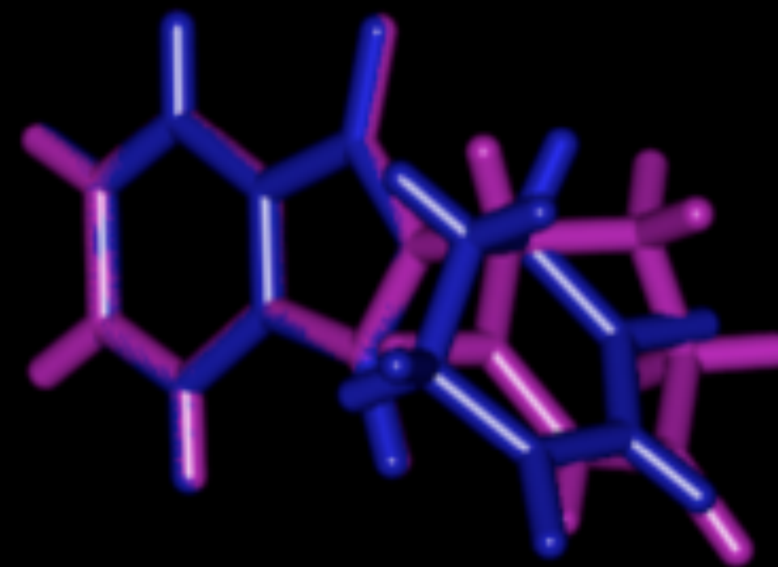


(*R*)-fluoxetine
antidepressant



Thalidomide

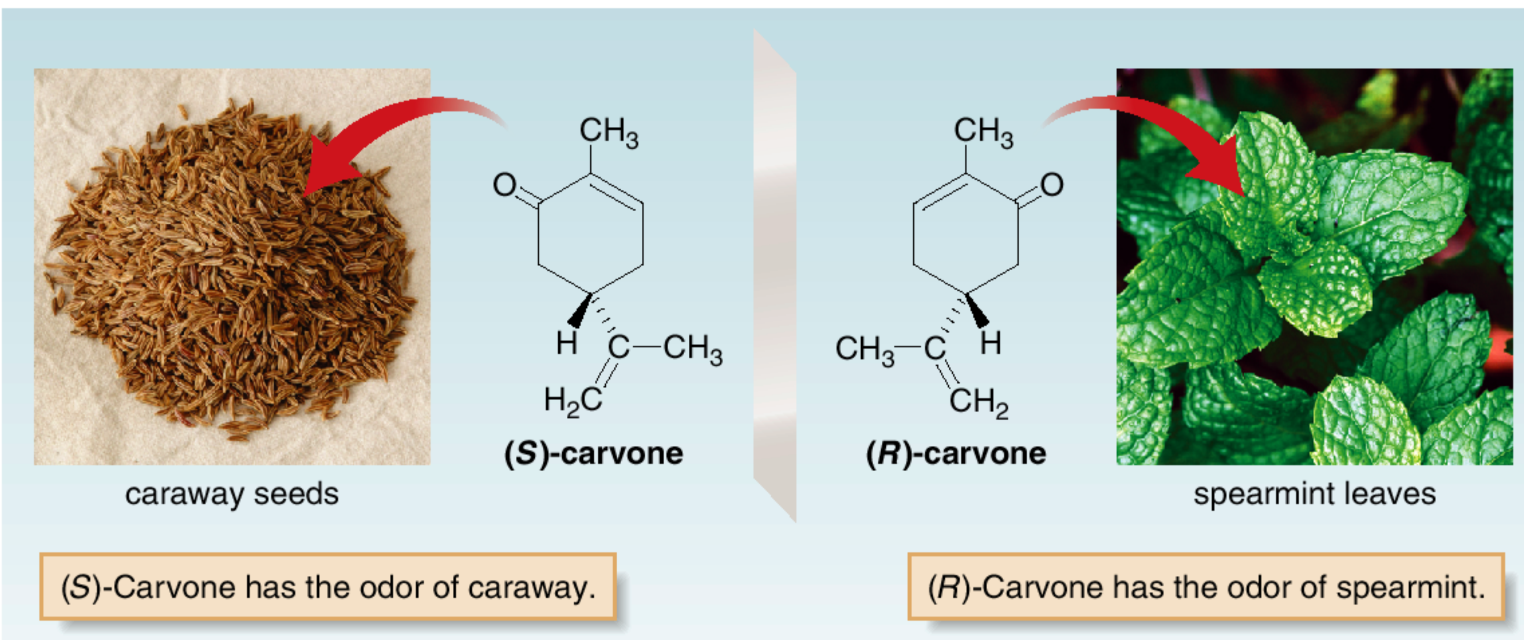




Chemical Properties of Enantiomers

- 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 odours.



1. Una soluzione di 400 mg di testosterone in 10,0 mL di etanolo è posta in una cella lunga 10,0 cm. La rotazione osservata per questo campione a 25°C usando la riga D del sodio è +4.36°. Calcolare la rotazione specifica del testosterone.

$$[\alpha] = \alpha / l \ \ c$$

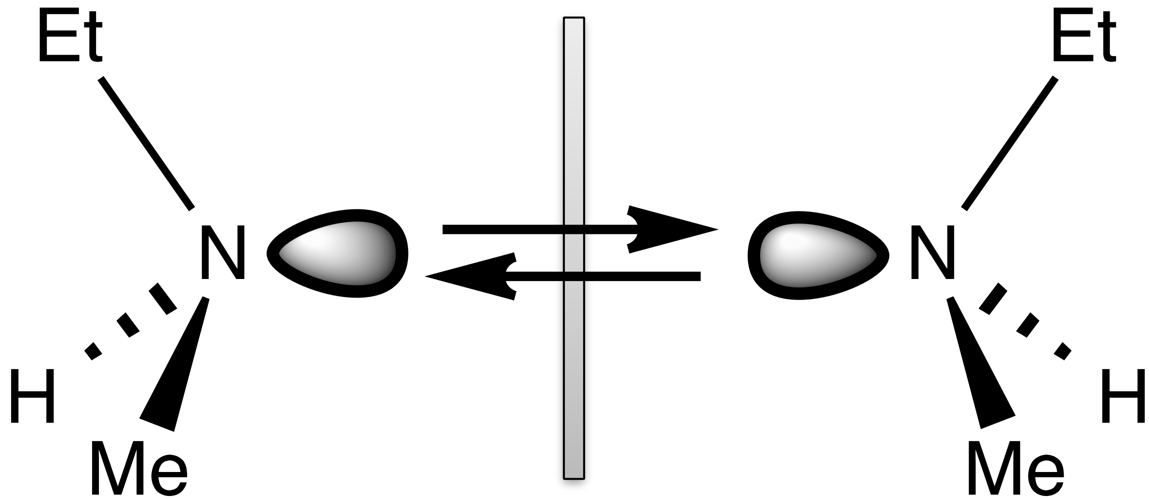
$$\alpha = +\ 4.36°; \ \ l = 1 \text{ dm}; \ c = 0.4 \text{ g}/10 \text{ mL} = 0.04 \text{ g/mL}$$

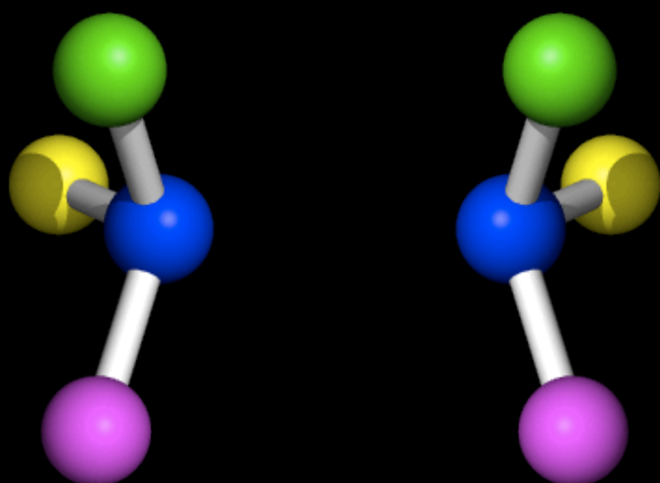
$$[\alpha] = +\ 4.36°/1 \times 0.04 = +109°$$

2. Una soluzione di un campione di canfora ottenuta sciogliendo 2.5 g del campione in 5 mL di metanolo ha una rotazione α = +10.5°, misurata in una cella di 5 cm. Sapendo che la rotazione specifica della (+) canfora è $[\alpha]$ = +44°, calcolare l'eccesso enantiomerico del campione.

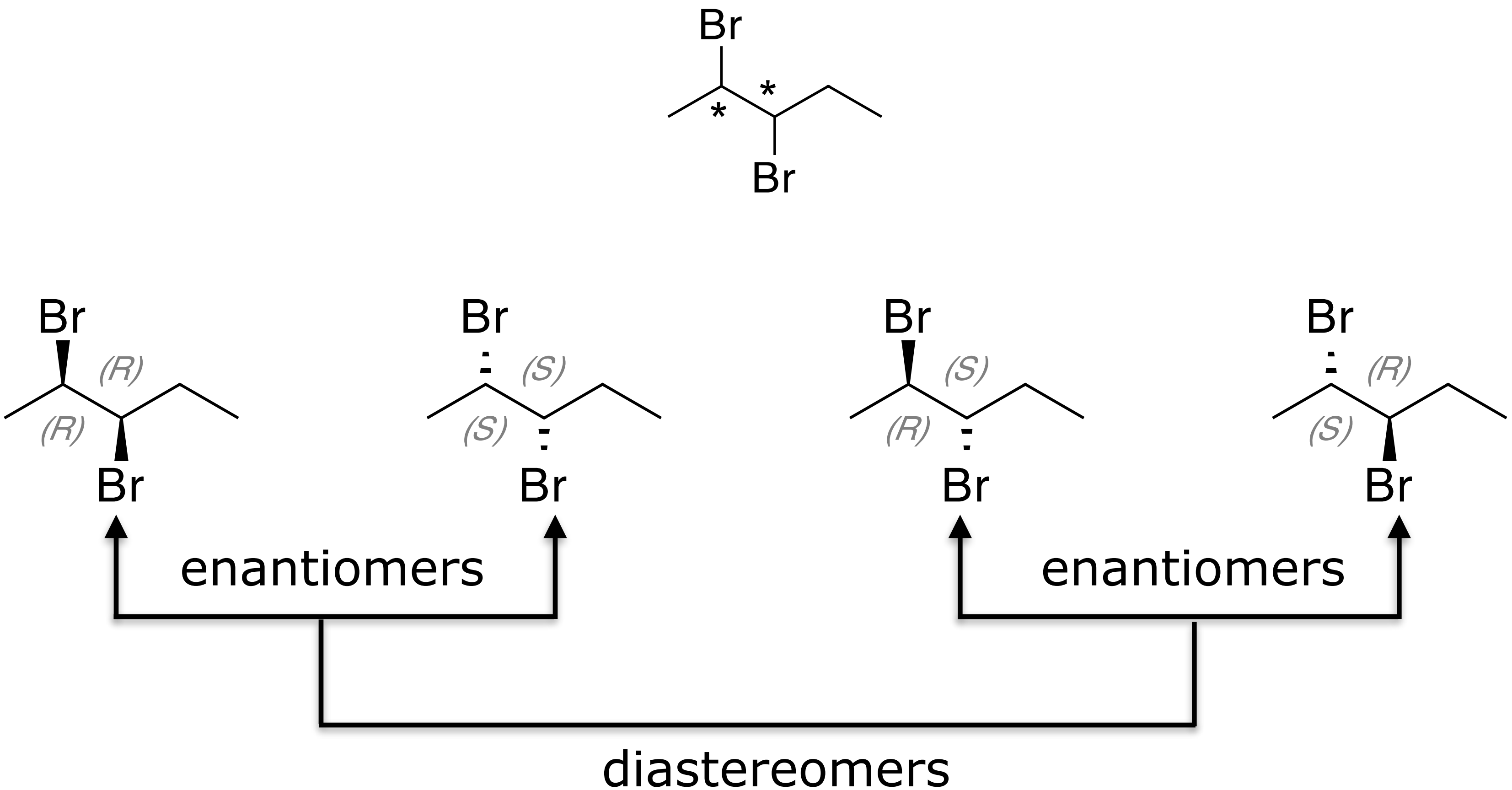
$[\alpha]=\alpha/l*c$ = 10.5°/(0.5x2.5/5) = +42°; e.e = +42/+44=95%

Amines are Achiral



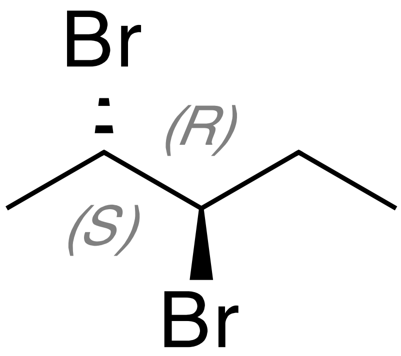


Diastereomers



Diastereomers

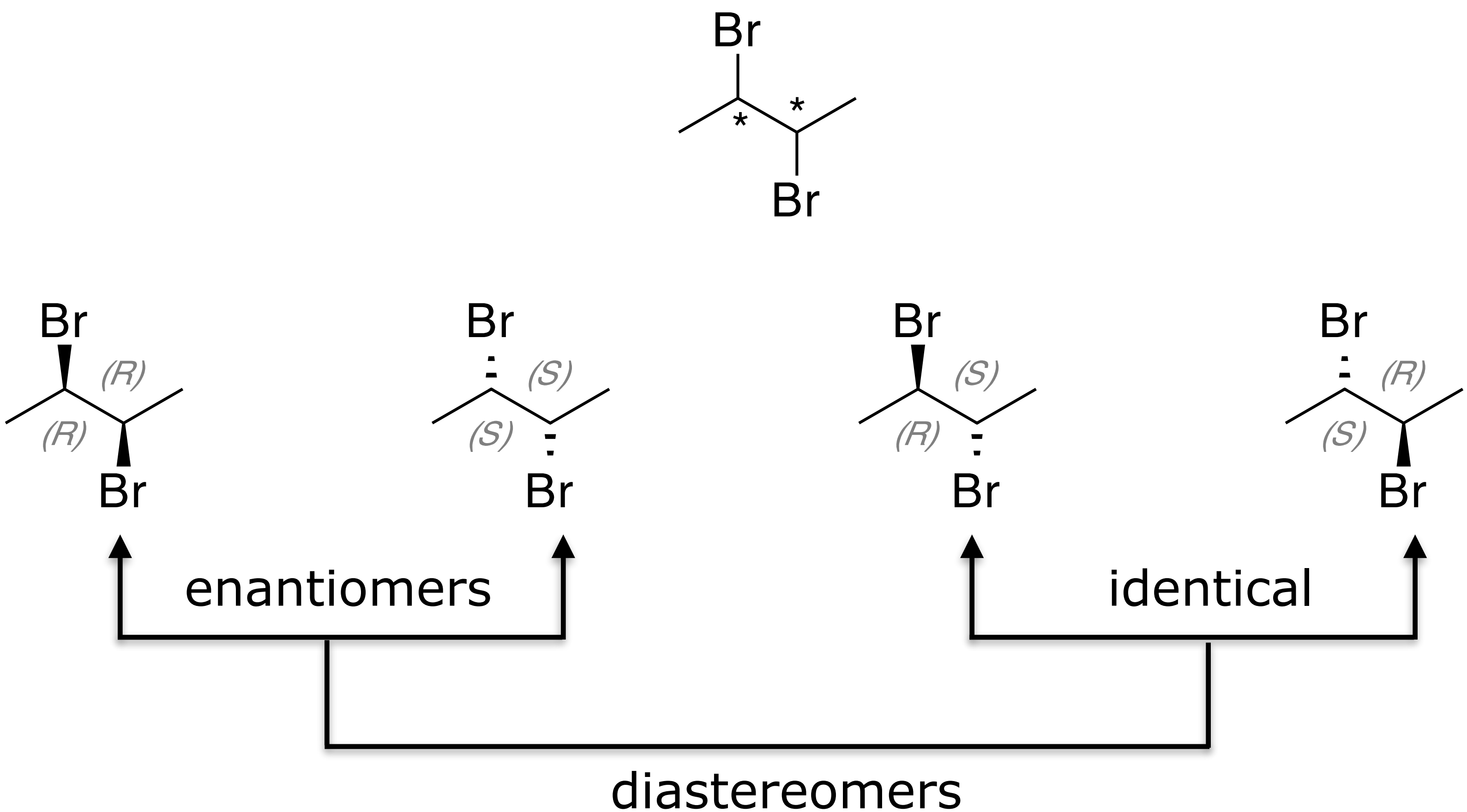
- When a compound has more than one stereogenic center, R and S configurations must be assigned to each of them.



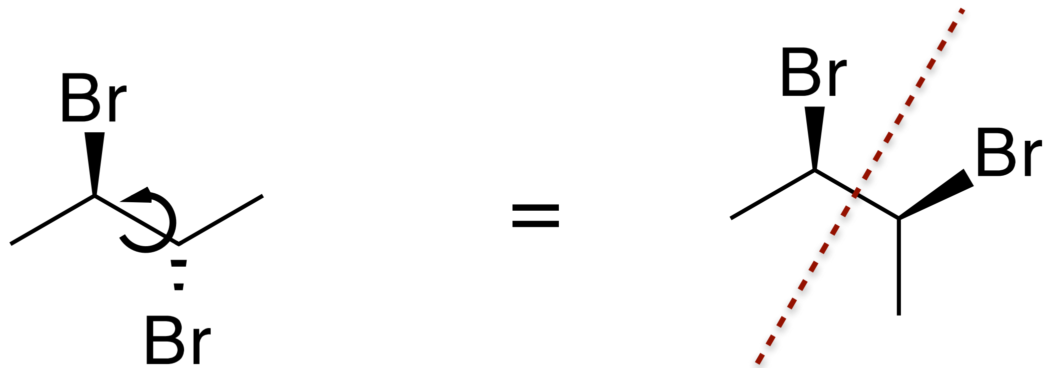
(*2S*,*3R*)-2,3-dibromopentane

In general: n stereogenic centers ⇒ 2^n stereoisomers

Meso Compounds



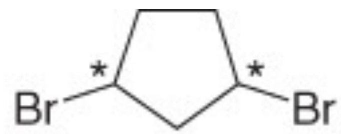
Meso Compounds



- Meso compounds contain a plane of symmetry, and are achiral.

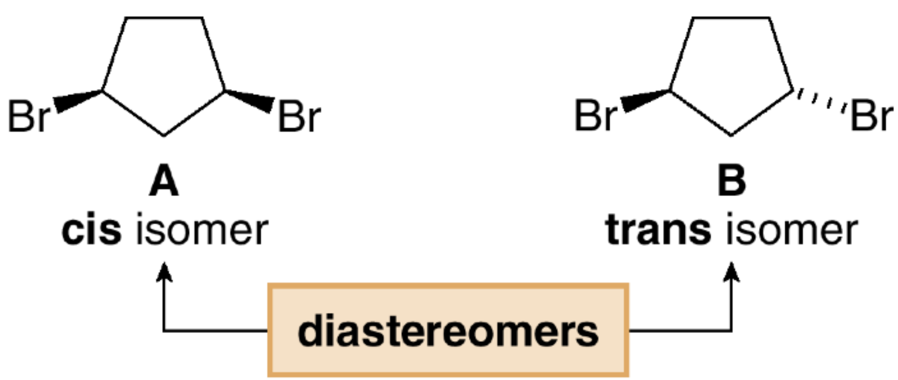
Diastereomers

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

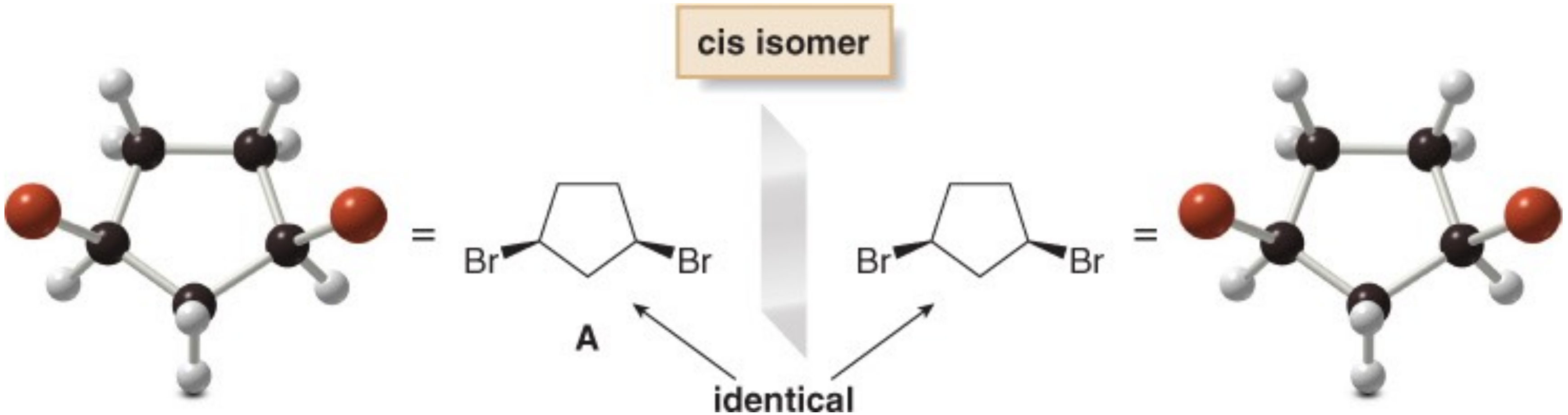


1,3-dibromocyclopentane
[* = stereogenic center]

- *cis* isomer (A) and *trans* isomer (B) are stereoisomers but not mirror images.

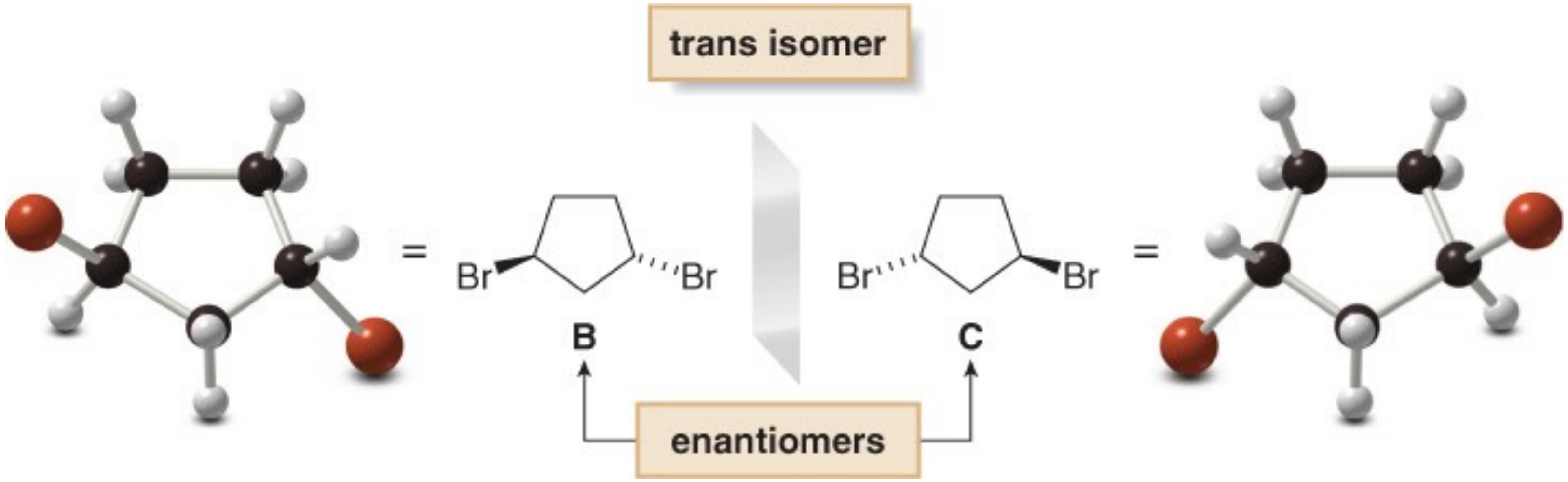


Diastereomers



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

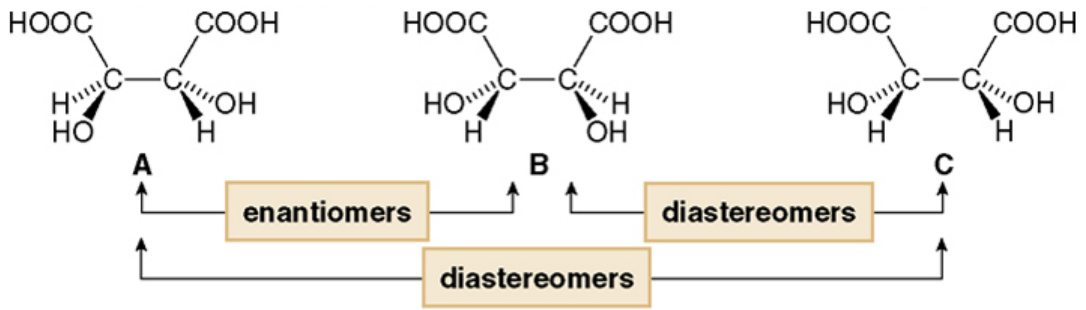
Diastereomers



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

Diastereomers

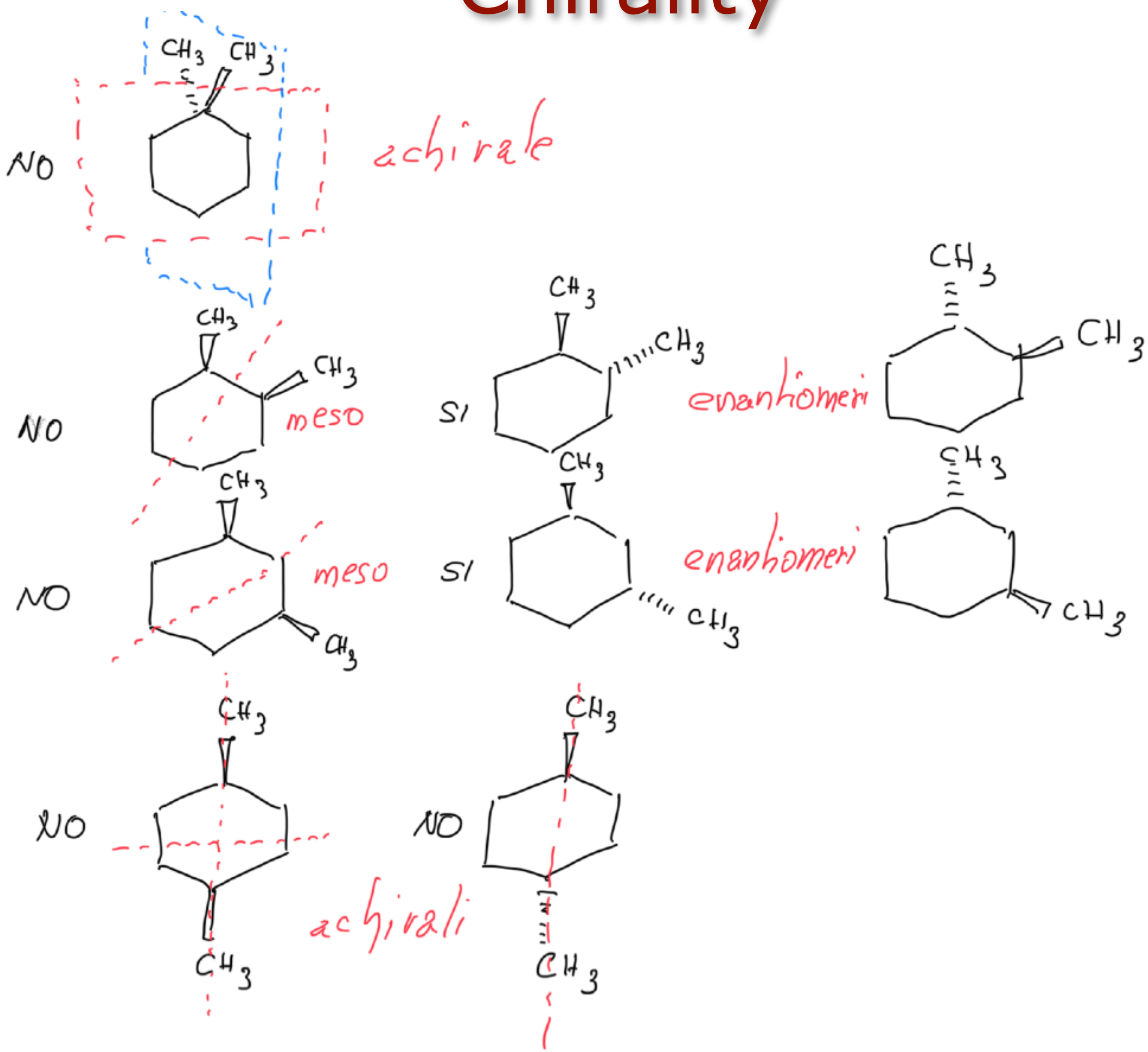
- Diastereomers have different physical properties, and therefore can be separated by common physical techniques.



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*

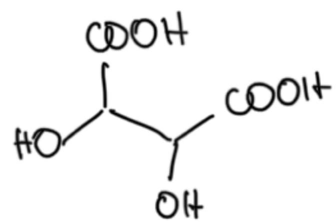
- The physical properties of **A** and **B** differ from their diastereomer **C.**
- The physical properties of a racemic mixture of **A** and **B** (last column) can also differ from either enantiomer and diastereomer **C.**
- **C** is an achiral meso compound, so it is optically inactive; [α] = 0.

Dimethylcyclohexanes: Symmetry and Chirality



Enantiomers and Meso-Compounds

Un campione di acido (+)-tartarico contiene il 10% di un'impurezza. Sapendo che la rotazione specifica dell'acido (+)-tartarico è $[\alpha]_D^{20}$ = + 12.4° e che quella del campione è $[\alpha]_D^{20}$ = + 11.2°, determinare se l'impurezza è acido (-)-tartarico o acido meso-tartarico



(R,S) = (S,R) : meso

(R,R)
(S,S) } enantiomeri

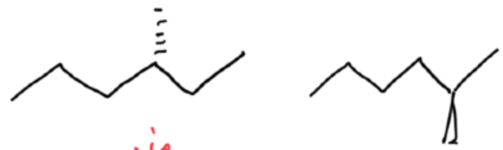
1) 90% (+) 10% (-)

$12.4 \times 0.9 - 12.4 \times 0.1 = 9.92$

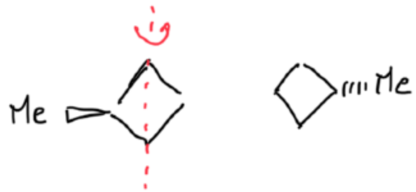
2) 90% (+) 10% (meso)

$12.4 \times 0.9 = 11.2$

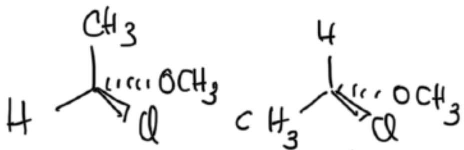
Isomeri



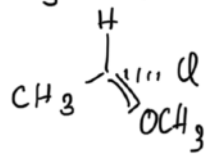
isomeri strutturali



identiche



enantiomeri



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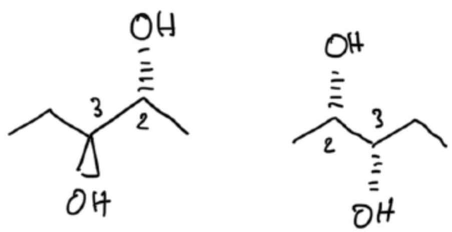
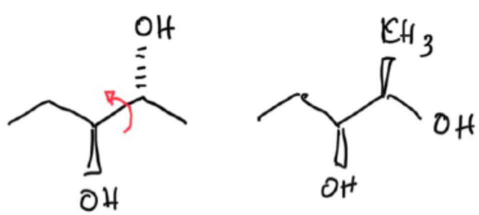


2R, 3S   2S, 3S

diastereoisomeri



isomeri conformazionali