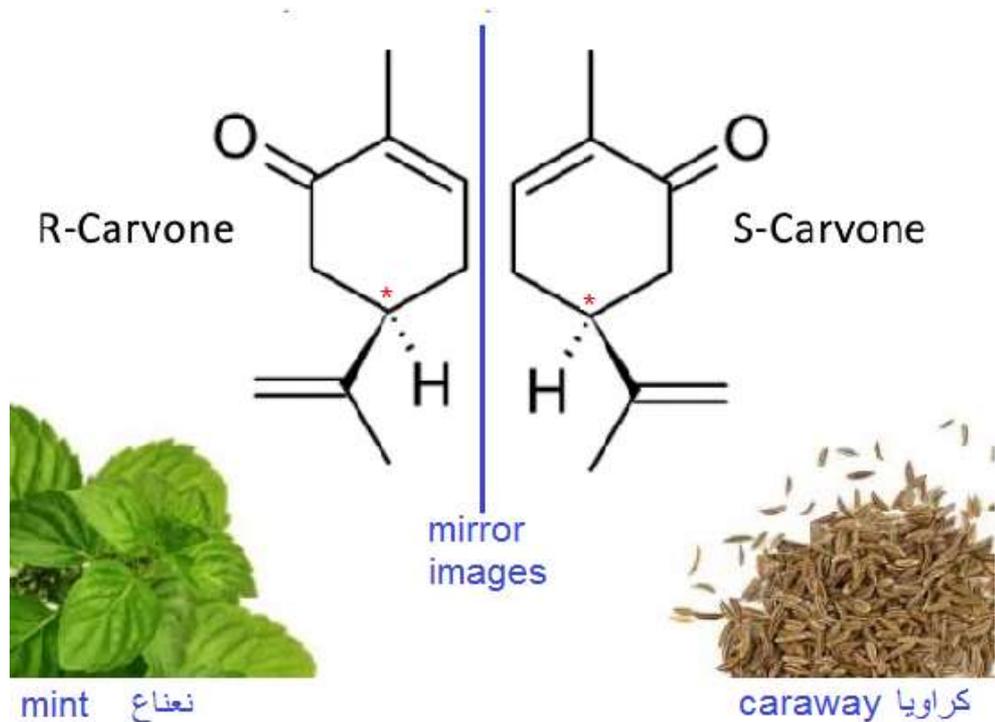


# Chapter 5

## Stereoisomerism



They differ only in the arrangement  
at this Chiral Carbon Atom (\* )

**Stereoisomers:** **molecules** having same order of attachment of atoms, but different arrangements of the atoms in space.

## Chirality and Enantiomers :

A Molecule (or object) can be : **1) chiral** or **2) achiral**

**Chiral (handed) molecules** : Can be : **1- left**-handed, or **2- right**-handed)

**Chirality** : Property of **handedness**

> How to know if a molecule (or object) is chiral or achiral?

Compare **molecule** and its **mirror image**:

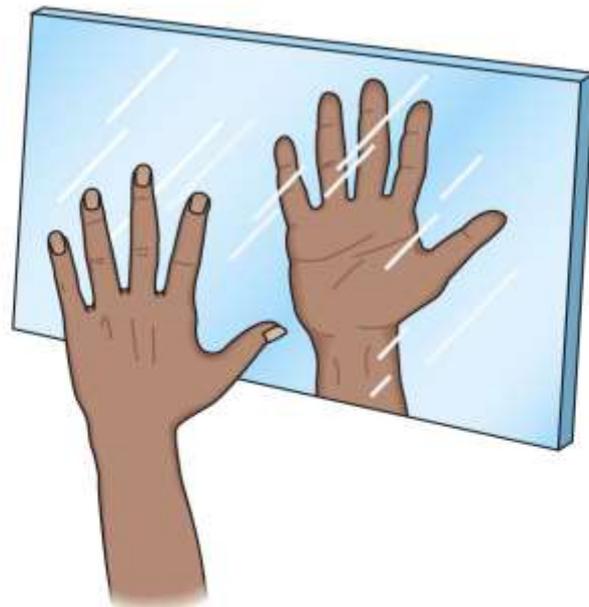
**1-** If **non-superimposable**, then molecule is **Chiral**

(Non-superimposable mirror images called **Enantiomers**)

**2-** If **superimposable** (identical) , it is **Achiral**,

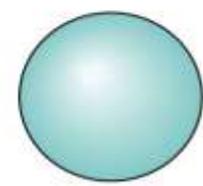
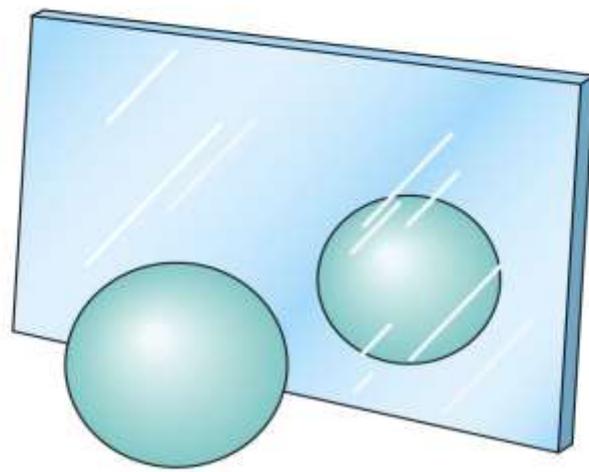
(Superimposable mirror images are **Identical**)

The mirror image of a left hand is not a left hand, but a right hand.

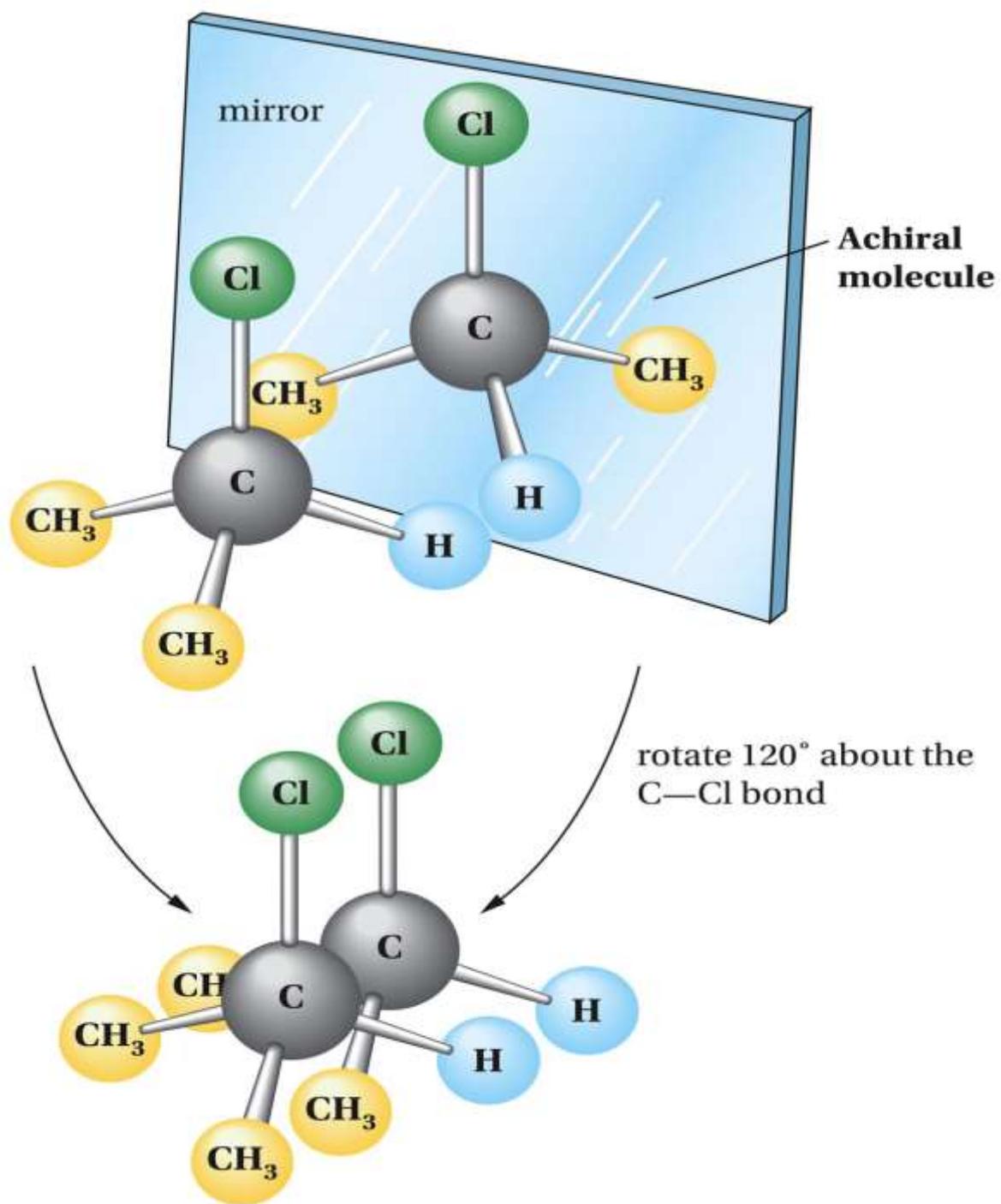


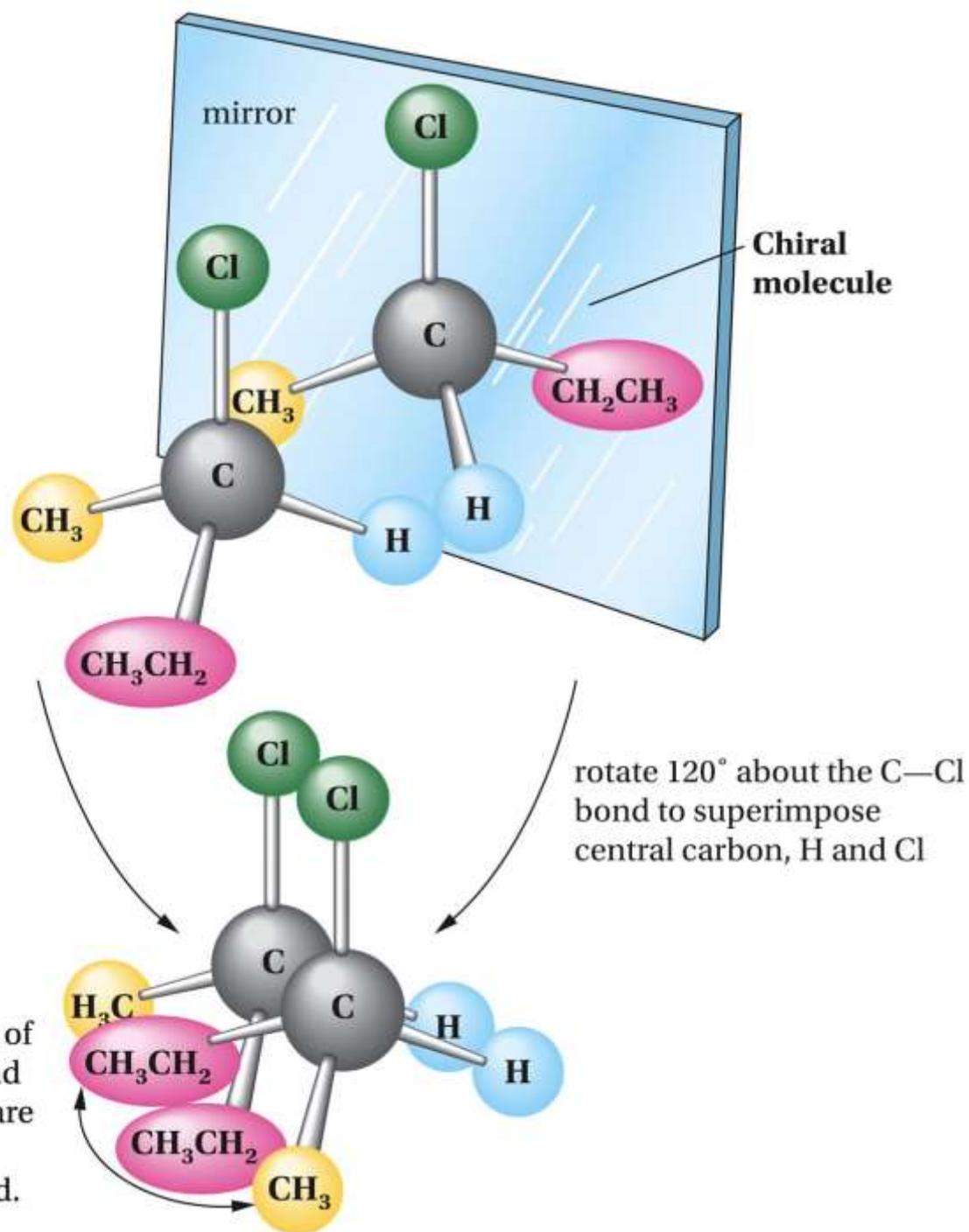
**Chiral object**

The mirror image of a ball is identical with the object itself.



**Achiral object**





The positions of the methyl and ethyl groups are *not* superimposed.

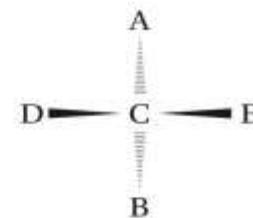
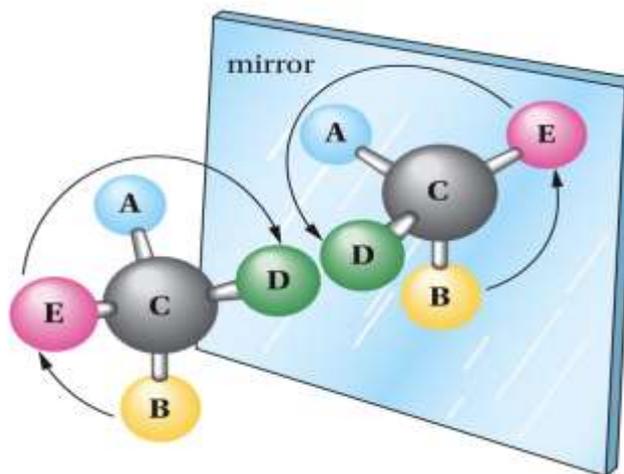
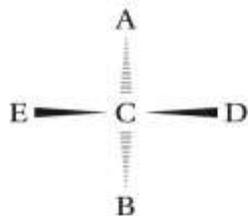
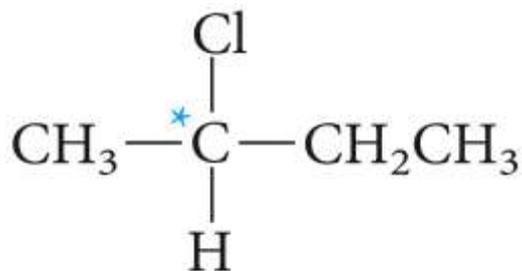
**Chiral molecules** : Handed (**right-handed, or left-handed**) : 2 forms

**Achiral molecules** : Not handed.

**Enantiomers** : configurational stereoisomers which are **non-superimposable mirror images on one another.**

**Stereogenic Center** : creates two stereoisomeric forms : a **Chiral Carbon** (having **4 different groups**) is a stereogenic center. It creates **two enantiomeric (stereoisomeric) forms** (left-handed + right-handed form)

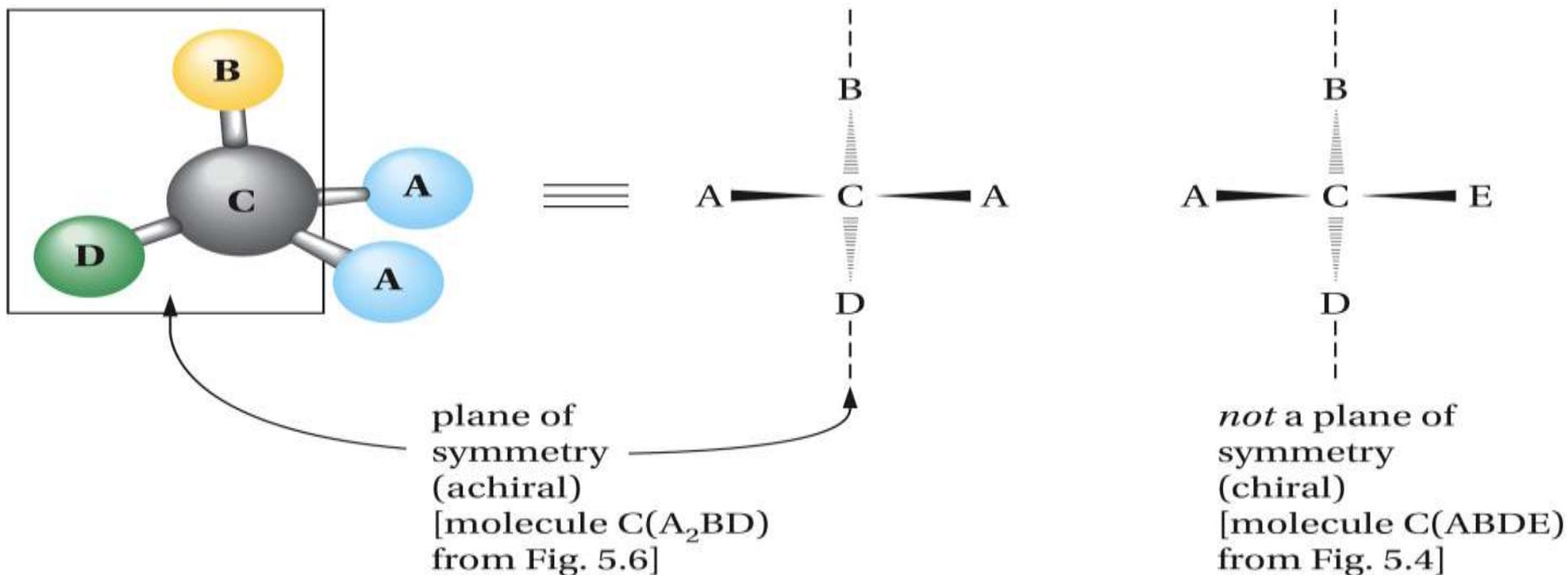
Molecule with a chiral center is **Chiral. Non-superimposable** on its **mirror image**). Can exist in **two enantiomeric** forms.



**Plane of symmetry :** plane which divides the molecule into two halves, each half is mirror image of the other half.

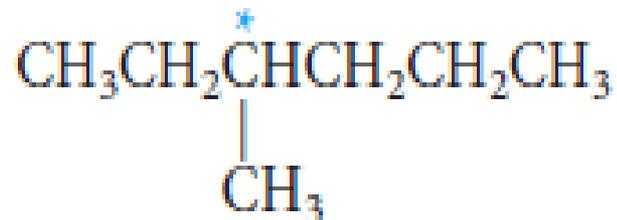
\* Molecules which have plane of symmetry are **Achiral** (not chiral)

\* Chiral molecules do not have **any** Planes of Symmetry.

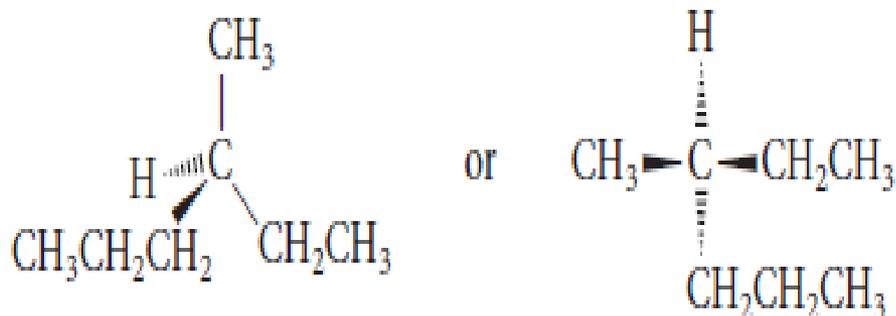
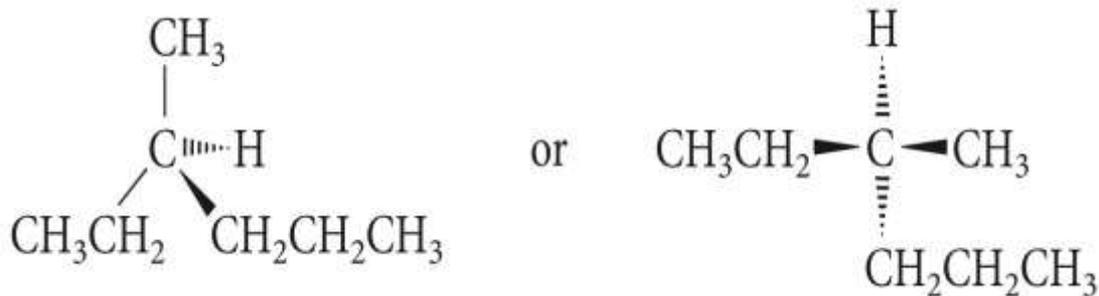


**Q :** How many **stereogenic** carbons does 3-methylhexane have?

(Stereogenic center : center which creates stereoisomers)



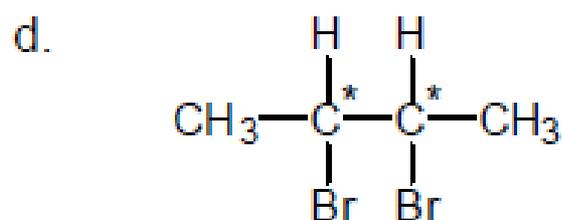
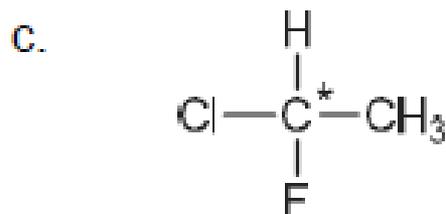
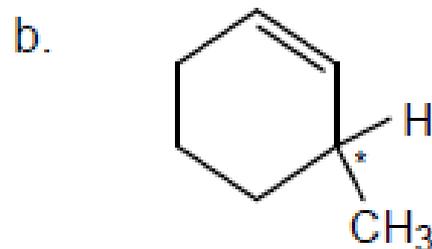
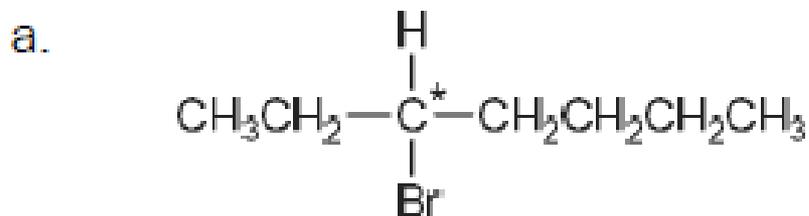
**Q :** Draw the two **enantiomers** of 3-methylhexane.



**Q :** Find the stereogenic centers in the following:



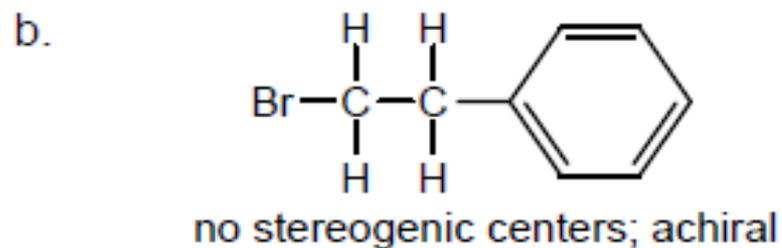
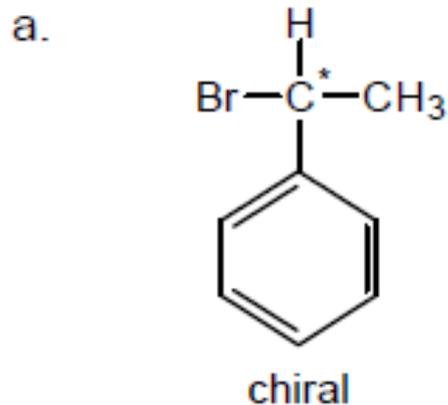
**Answer:**



**Q :** Which of the following compounds is chiral?

- a. 1-bromo-1-phenylethane
- b. 1-bromo-2-phenylethane

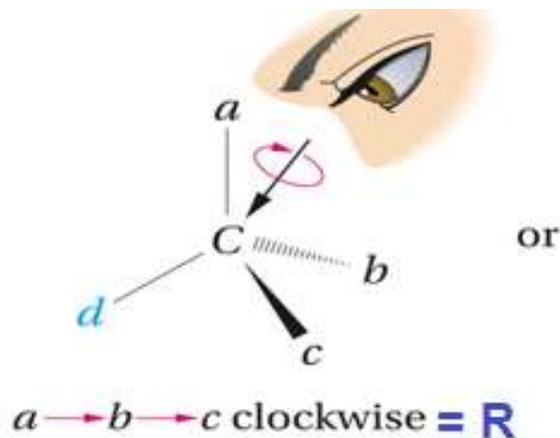
**Answer :**



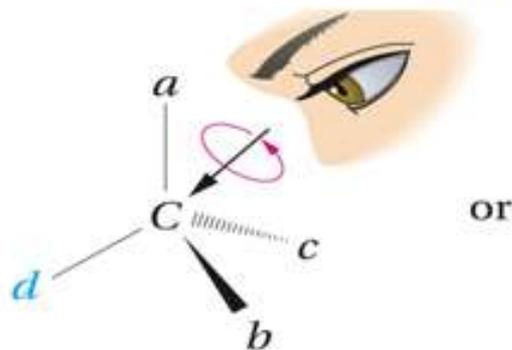
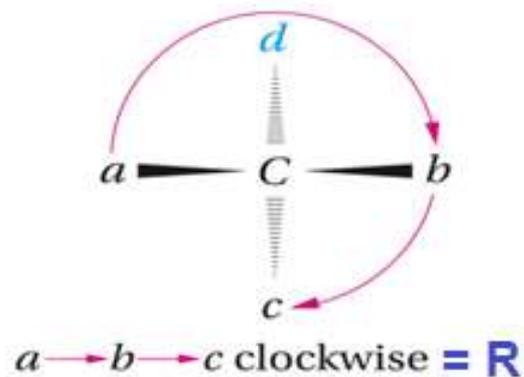
# Configuration and the *R-S* Convention :

Enantiomers differ only in arrangements of groups at stereogenic (chiral) center. They have **different configuration** at the chiral center.

So, Enantiomers are **configurational stereoisomers** (like *cis*, *trans*). They have **opposite configurations** of chiral center (**R** or **S**-configuration)



or



or

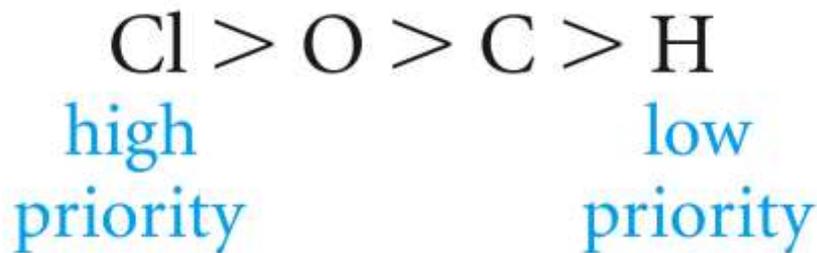


# How to determine configuration of a chiral center (**R** or **S**) :

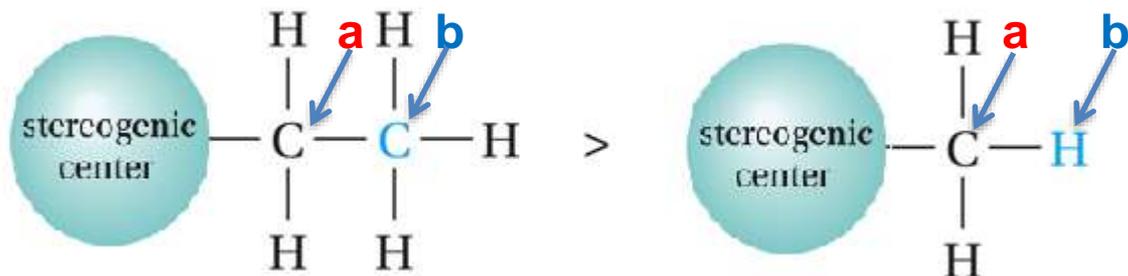
## Priority Rules :

**1-** Atoms directly attached to the chiral center are ranked according to atomic number.

The higher the atomic number, the higher the priority



**2-** If a decision cannot be made (position **a**), proceed to next atoms (position **b**).



**Q :** Assign a priority order to the following sets of groups:

- a. -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>3</sub>, -H, -NH<sub>2</sub>  
b. -OH, -Br, -CH<sub>3</sub>, -CH<sub>2</sub>OH  
c. -OCH<sub>3</sub>, -NH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>NH<sub>2</sub>, -OH  
d. -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>

a. -NH<sub>2</sub> > -CH(CH<sub>3</sub>)<sub>2</sub> > -CH<sub>3</sub> > -H

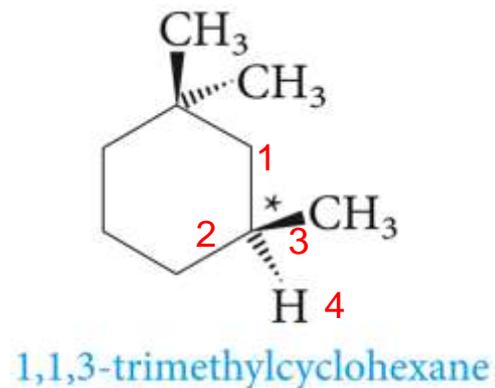
b. -Br > -OH > CH<sub>2</sub>OH > -CH<sub>3</sub>

c. -OCH<sub>3</sub> > -OH > -N(CH<sub>3</sub>)<sub>2</sub> > -CH<sub>2</sub>NH<sub>2</sub>

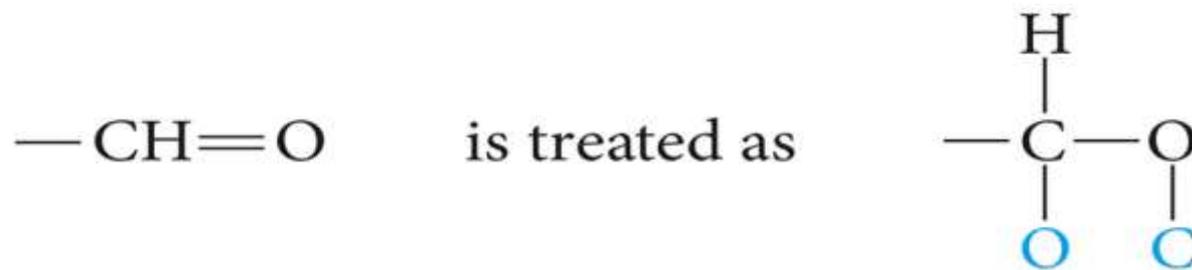
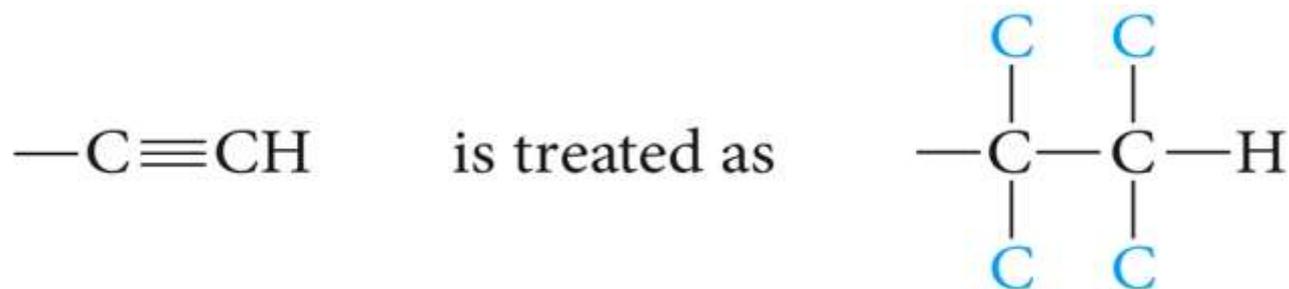
The oxygen in the methoxy group (-OCH<sub>3</sub>) is bonded to carbon, whereas the hydroxyl oxygen (-OH) is bonded only to hydrogen.

d. -C(CH<sub>3</sub>)<sub>3</sub> > -CH(CH<sub>3</sub>)<sub>2</sub> > -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> > -CH<sub>2</sub>CH<sub>3</sub>

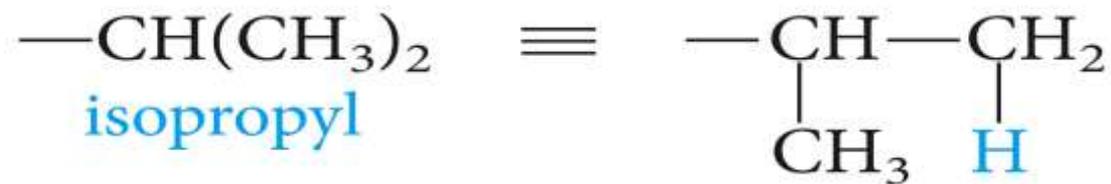
Cyclic compounds : same rule followed :



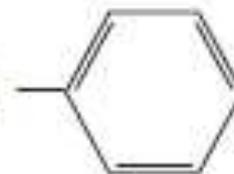
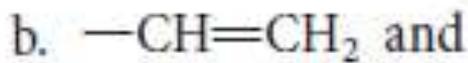
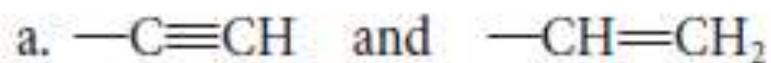
**3-** Multiple bonds are treated as if they were all single bonds.



Q : Which group has the higher priority, isopropyl or vinyl?



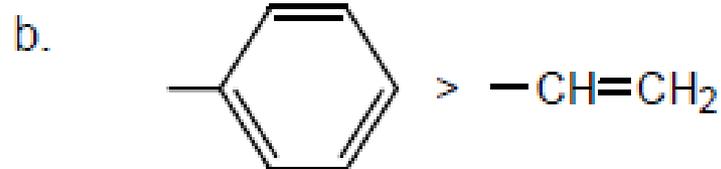
**PROBLEM 5.9** Assign a priority order to



Answer :



The acetylenic carbon ( $-\text{C}\equiv$ ) is treated as though it is bonded to three carbons, while the olefinic carbon ( $-\text{CH}=\text{}$ ) is treated as though it is bonded to two carbons and a hydrogen (see Sec. 5.3).



The phenyl carbon is treated as though it is bonded to three carbons.

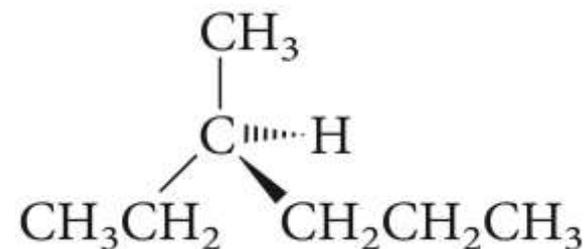


The aldehyde carbon is treated as though it is bonded to two oxygens.

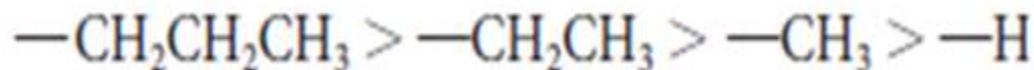
- 4- View the molecule from the side **opposite the lowest-priority** group , and determine arrangement of the remaining three groups, from **high to low** priority:

**Clockwise = ( R ) ,      Counterclockwise = ( S )**

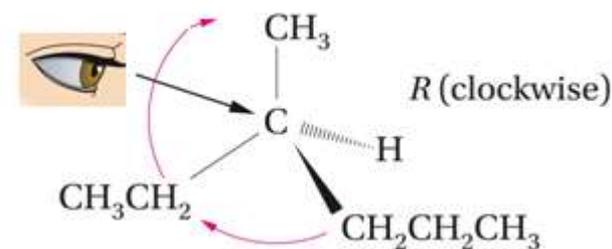
**Q :** Assign configuration to this 3-methylhexane:



- 1- **Assign priorities to groups attached to the stereogenic center :**



- 2- **View the molecule from the side opposite to lowest-priority group (-H) :**

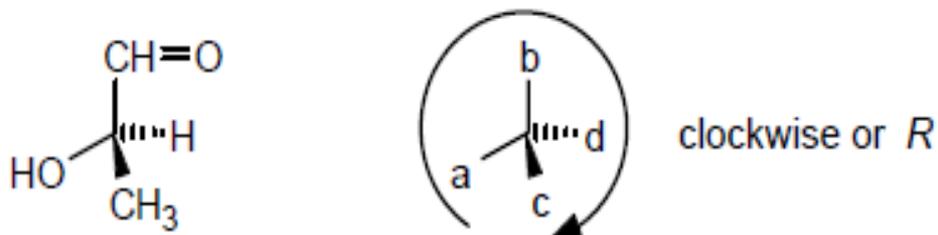


**Q :** Determine absolute configuration for stereogenic centers in the following compound:

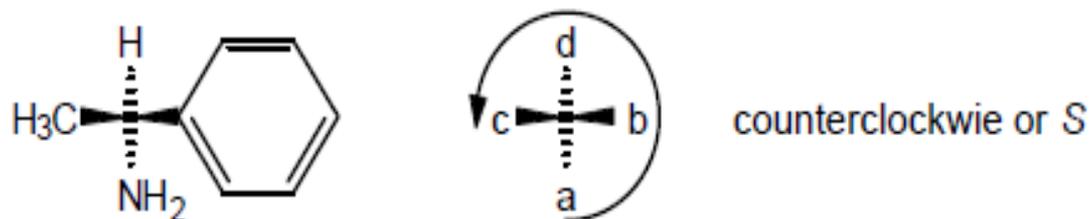


**Answer :**

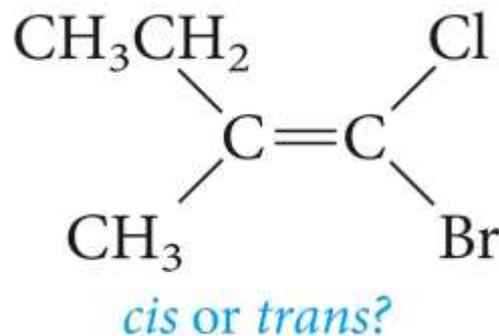
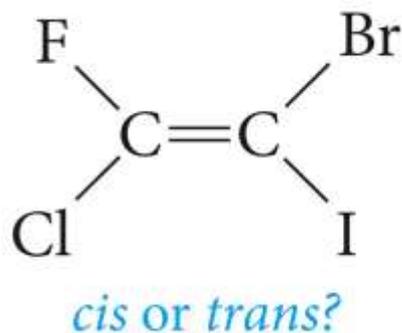
a. Priority order: OH > CH=O > CH<sub>3</sub> > H. Configuration is *R*.



b. Priority order: NH<sub>2</sub> > -C<sub>6</sub>H<sub>5</sub> > CH<sub>3</sub> > H. The configuration is *S*.

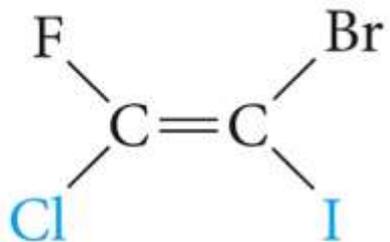


## 5.4 The *E-Z* convention for *Cis-Trans* Isomers :

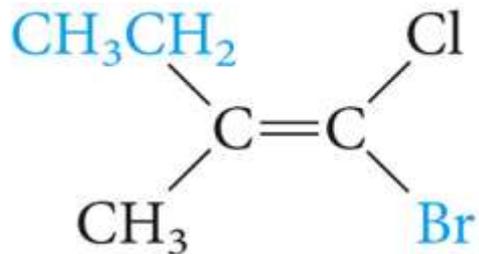


Assign priorities of the two groups at each carbon of  $\text{C}=\text{C}$  bond :

- two higher-priority groups on **opposite** sides : **E**
- two higher-priority groups on the **same** side : **Z**



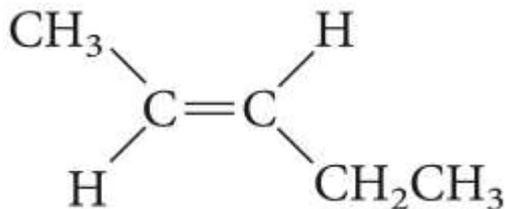
(*Z*)-1-bromo-2-chloro-2-fluoro-1-iodoethene



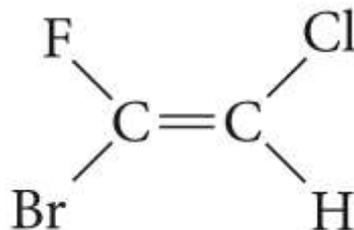
(*E*)-1-bromo-1-chloro-2-methyl-1-butene

**Q:** Name each compound by the ***E-Z*** system:

Answer :



(*E*)-2-pentene



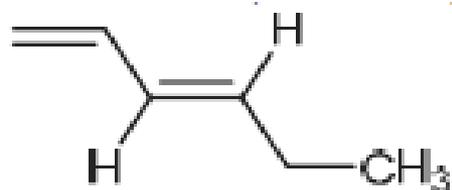
(*E*)-1-bromo-2-chloro-1-fluoroethene

**Q :** Write structure for

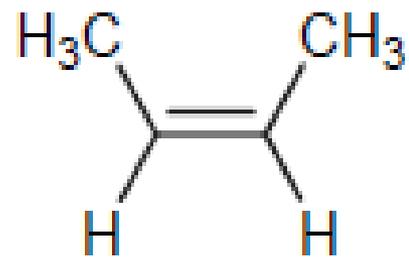
a. (*E*)-1,3-hexadiene

b. (*Z*)-2-butene

**Answer :**



(*E*)-1,3-hexadiene

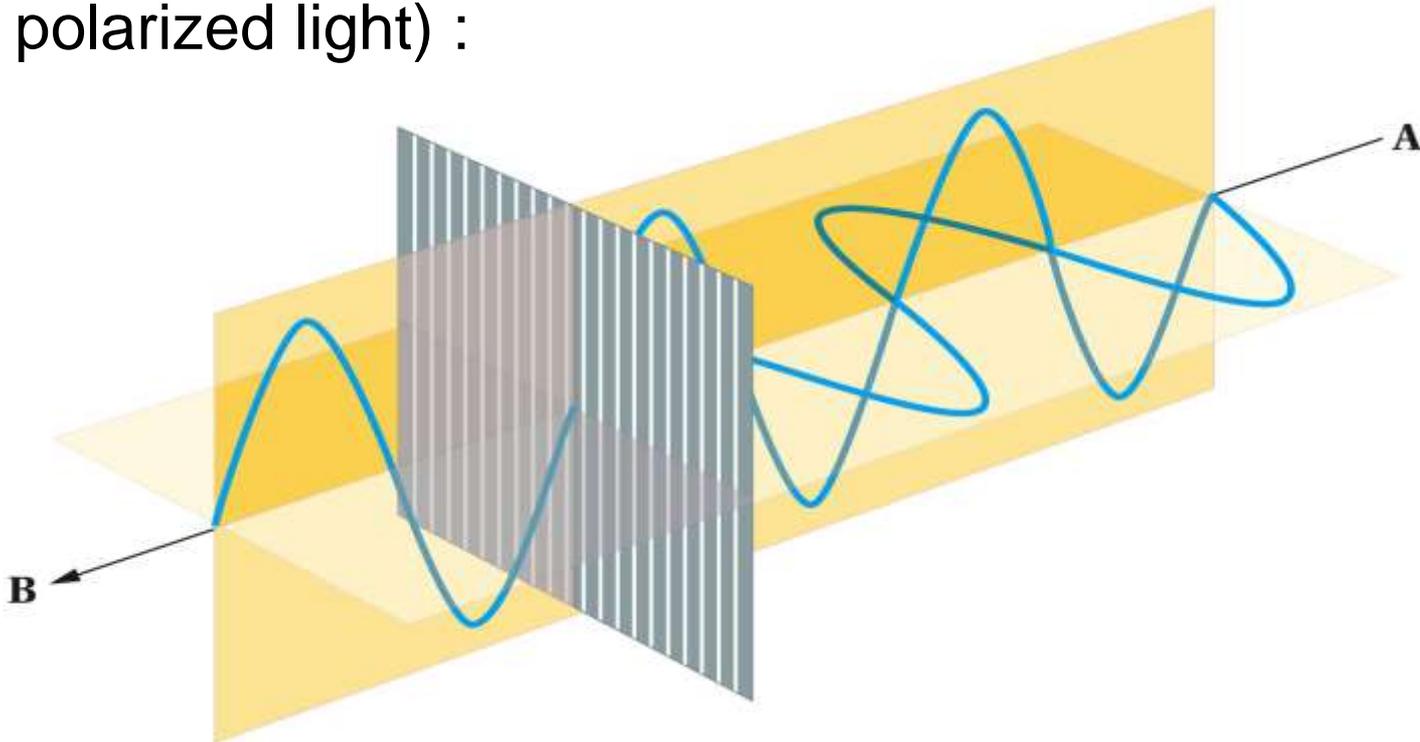


(*Z*)-2-butene

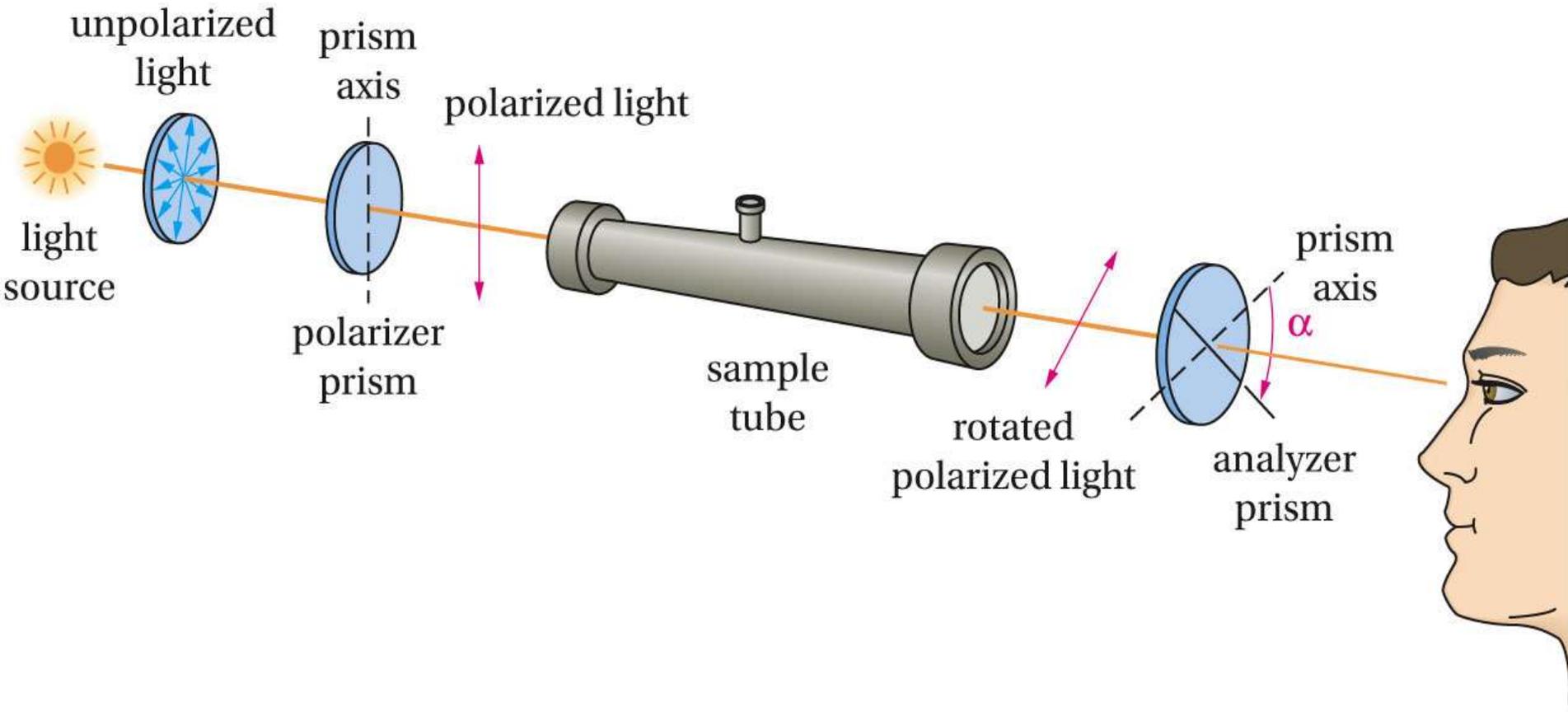
## 5.5 Polarized Light and Optical Activity :

Ordinary light waves vibrate in all possible planes perpendicular to its path. (**infinite** number of planes).

If it passes through polarizing substance (prism), then waves of transmitted beam will be polarized (vibrate in only one plane (Plane polarized light) :



**Polarimeter** : instrument used to measure optical activity.



**Optically active** substance : rotates plane-polarized light.

**Optically inactive** substance does not rotate plane-polarized light.

**Observed rotation ( $\alpha$ ):** angle through which the analyzer prism is rotated = degrees that the optically active substance rotated plane-polarized light.

Analyzer rotated to the *right* (clockwise) : **dextrorotatory (+)**

Analyzer rotated to the *left* (counterclockwise) : **levorotatory (-)**

**Specific Rotation**  $[\alpha]_D^{25}$

$$[\alpha]_D^{25} = \frac{\alpha}{C \times \ell}$$

$\alpha$  observed rotation angle

$C$  concentration (g /mL)

$\ell$  tube length (dm)  
1 dm = 10 cm

25 : temperature

D : D-line of sodium  
emission spectrum

**Example :** The observed rotation of camphor (1.5g) in 50 mL ethanol using 5-cm tube is  $+0.66^\circ$  . Calculate specific rotation.

## 5.6 Properties of Enantiomers :

Enantiomers have same Achiral properties :

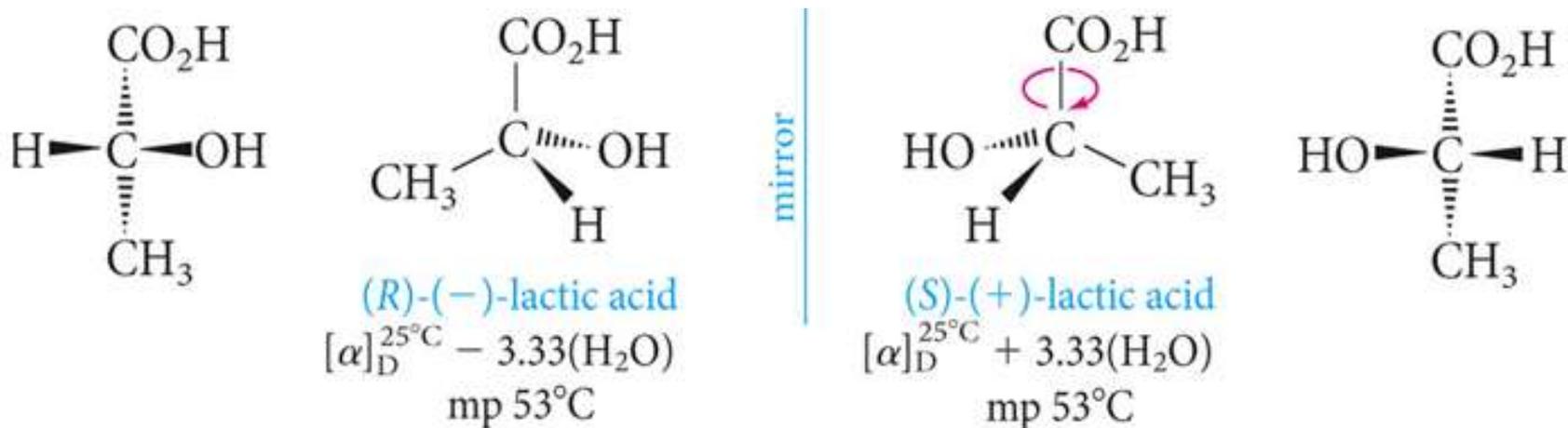
**Physical** : melting point, boiling point, density, solubility.

**Chemical** : reaction with achiral reagents.

**But** they have different Chiral properties :

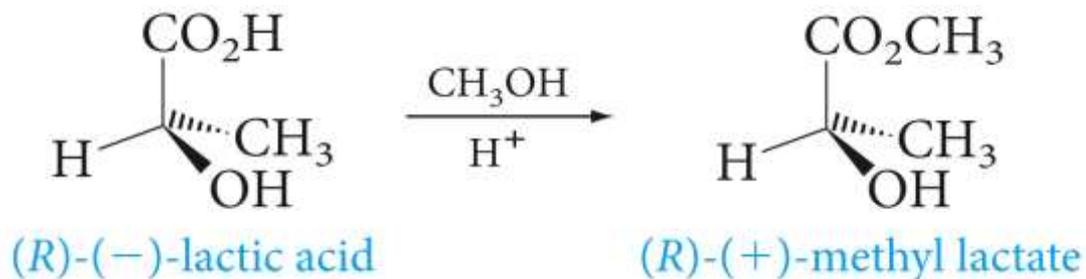
**Physical** : **direction** (+ or -) of rotation of polarized light, but **same value**

**Chemical** : reaction with **chiral reagents**, (e.g. biological systems, enzymes)

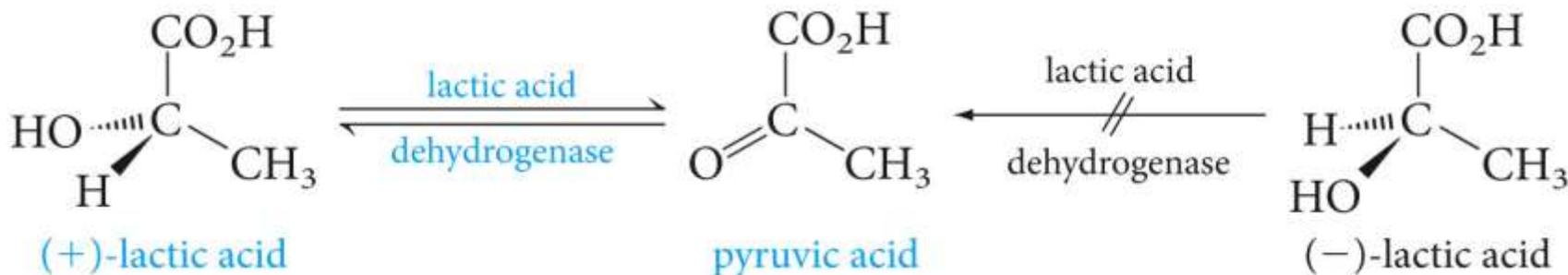


No relationship between configuration (**R**, **S**) and sign of rotation (**+** or **-**).

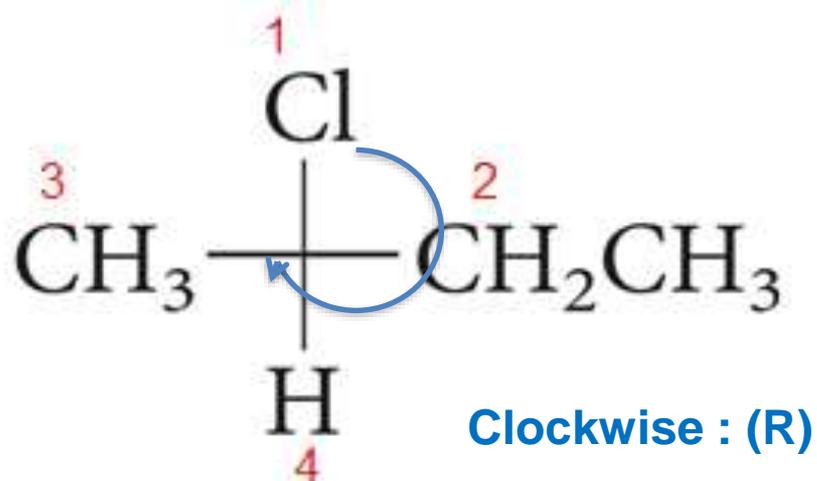
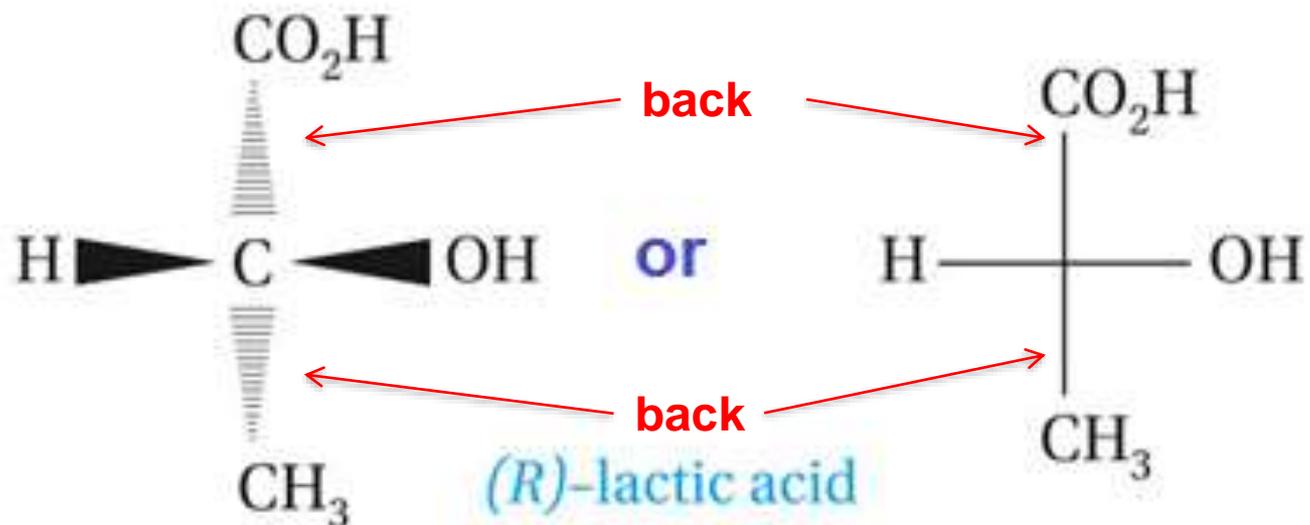
R- and S-enantiomers of different compounds may have same or opposite signs of specific rotation.



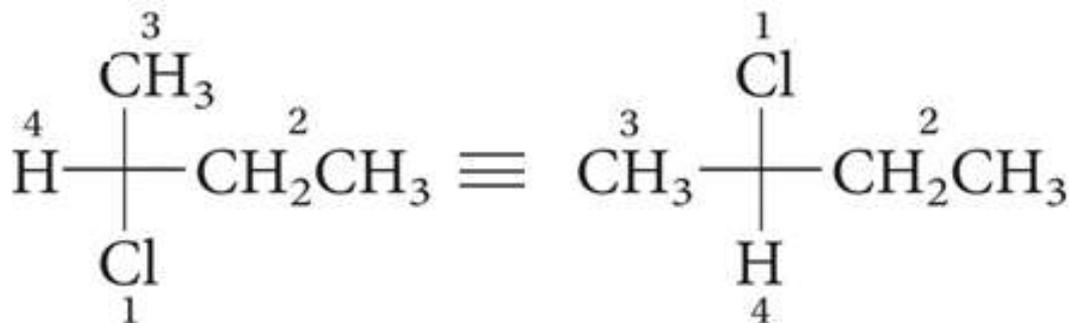
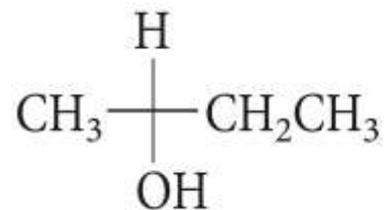
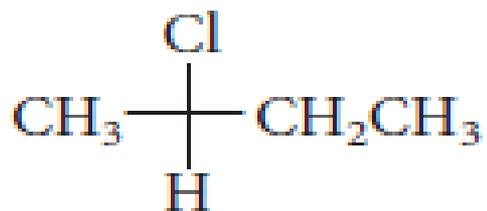
Lactic acid dehydrogenase enzyme oxidizes (+)-lactic acid to pyruvic acid (formed in glycolysis-Krebs Cycle), but not (-)-lactic acid



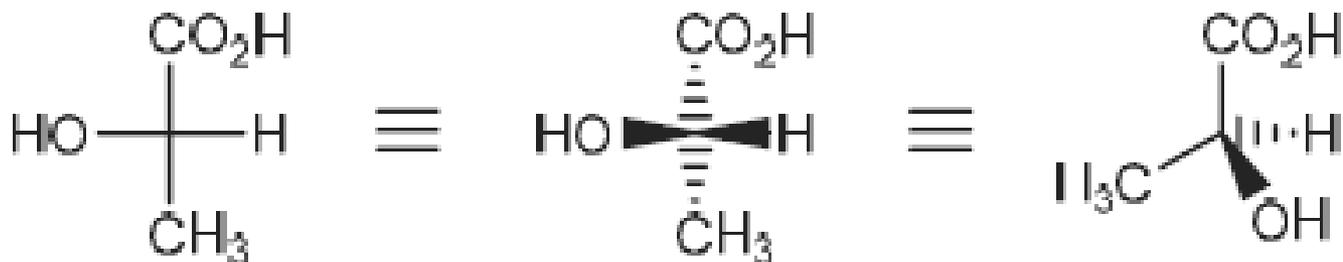
## 5.7 Fischer Projection Formulas :



Example : Determine the absolute (*R* or *S*) configuration :

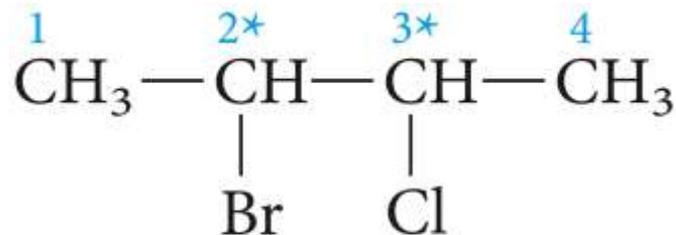


two exchanges =  
same configuration

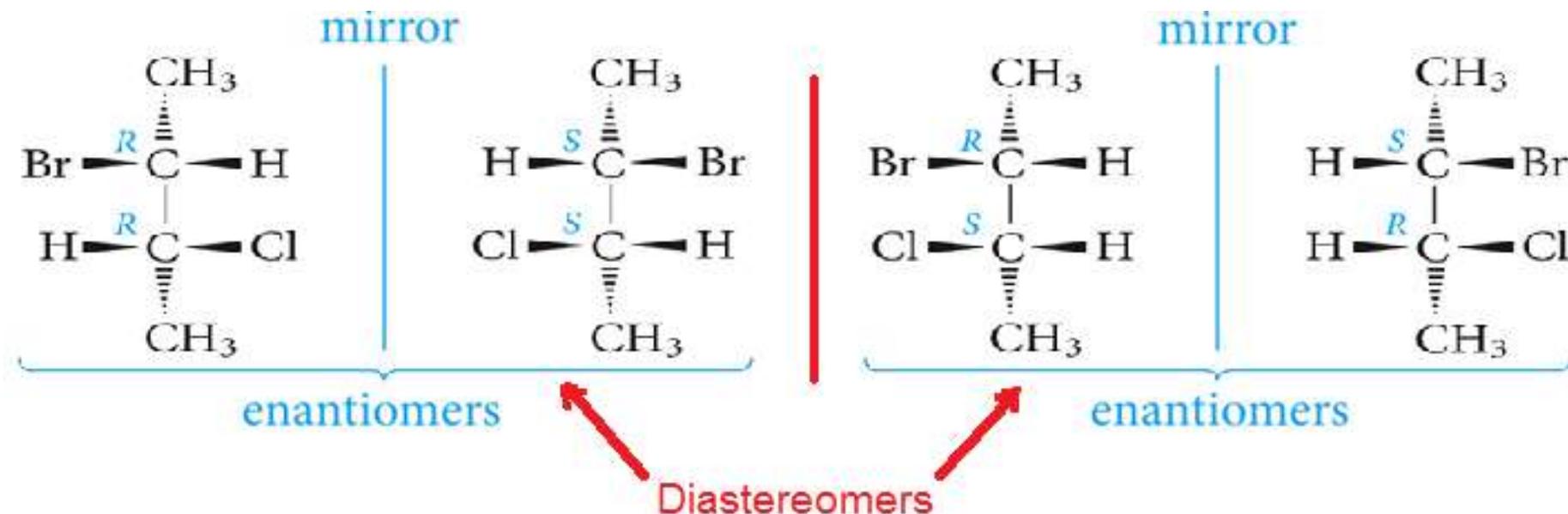


## 5.8 Compounds with more than one Stereogenic Center:

molecules with  $n$  chiral centers  
have  $2^n$  possible stereoisomers

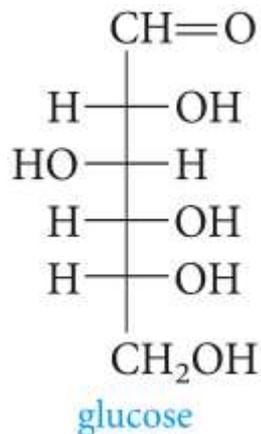


2-bromo-3-chlorobutane



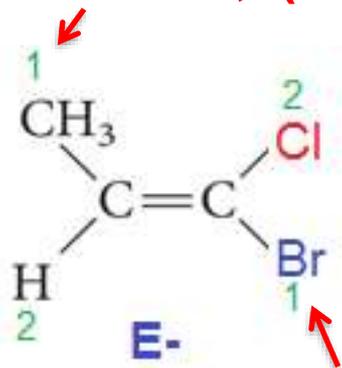
**Diastereomers** : stereoisomers that are not mirror images of each other.

Given is the Fischer projection of glucose (blood sugar), how many stereoisomers of this sugar are possible?

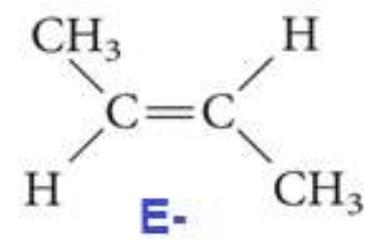
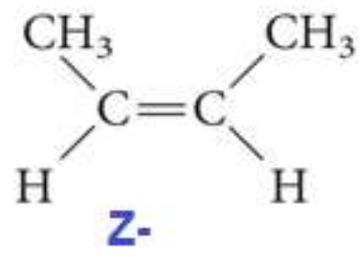
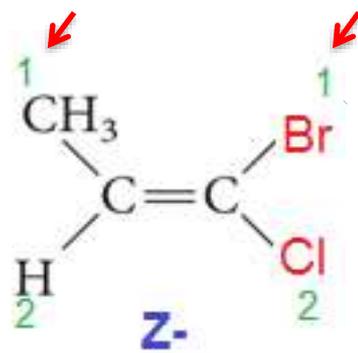


4 stereogenic centers  
 16 stereoisomers  
 (8 pairs of enantiomers)

**Cis-trans, (Z and E notation) :**



and

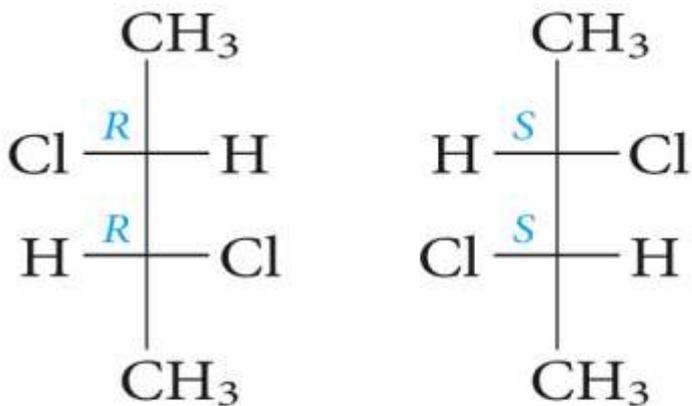
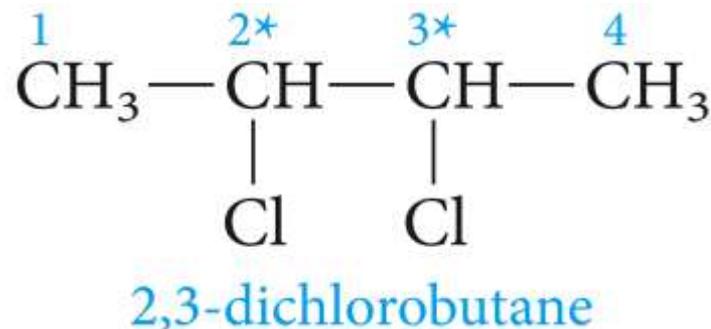


cis- , or trans- ??

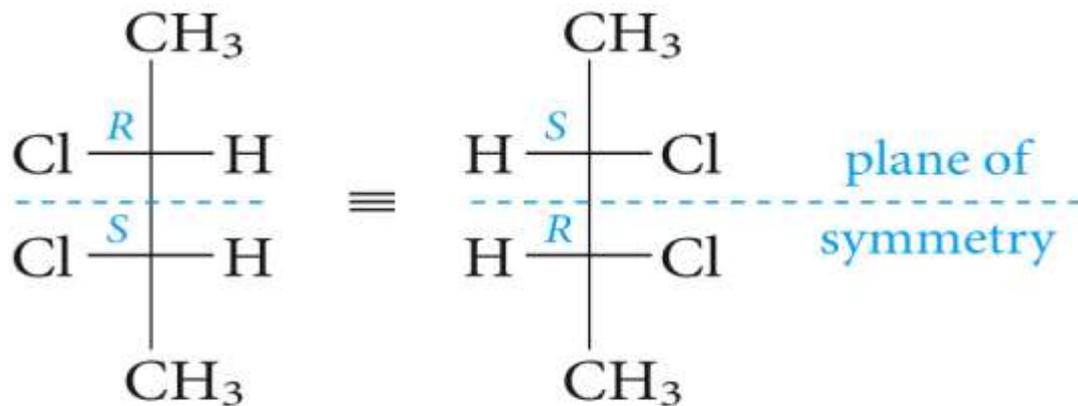
Can use (Z-, E-), or (cis-, trans-)<sub>30</sub>

## 5.9 Meso Compounds :

if both chiral centers have same groups, then **(R,S)** and **(S,R)** are **achiral**, they have plane of symmetry. They are **Identical (Meso Form)**



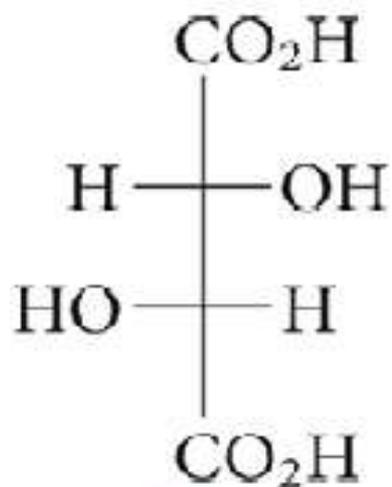
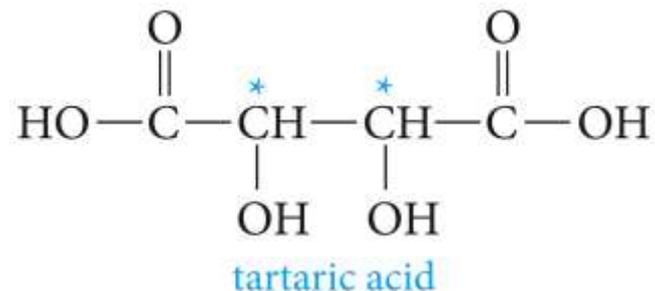
enantiomers, chiral



identical, achiral  
a meso form

(R,S) and (S,R) now represent a single compound

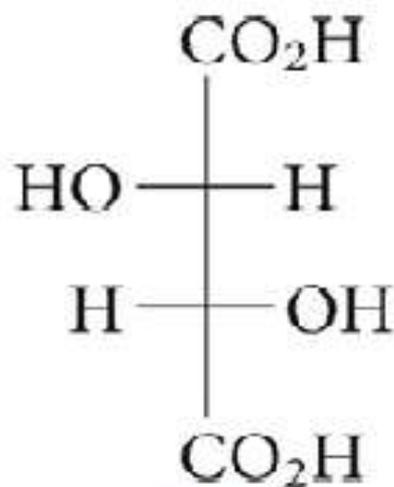
**Meso-compound** is an **achiral** diastereomer which **has chiral centers**



*(R,R)*

+12

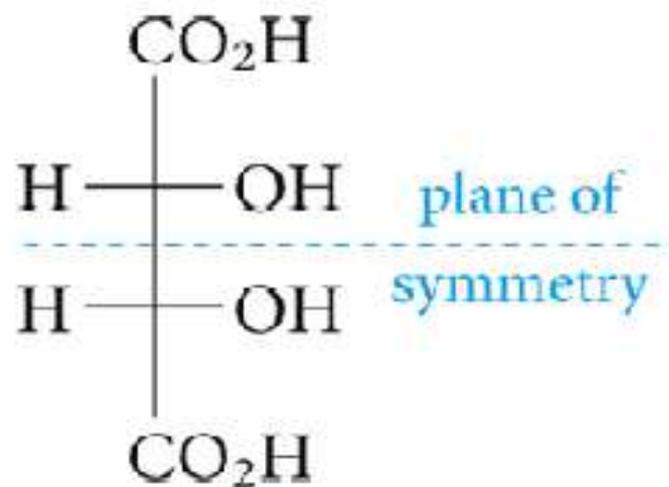
170



*(S,S)*

-12

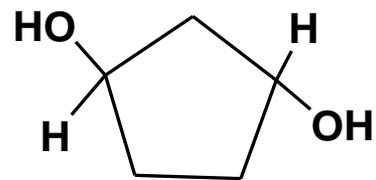
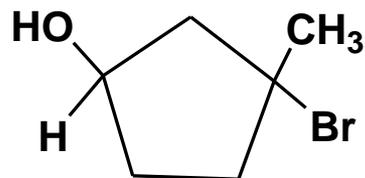
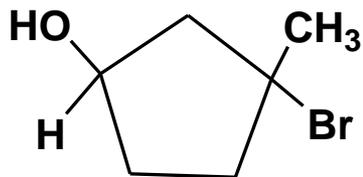
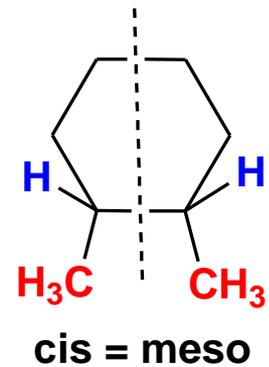
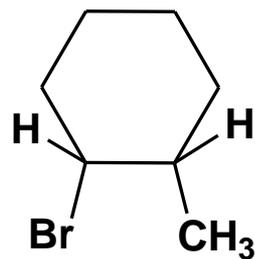
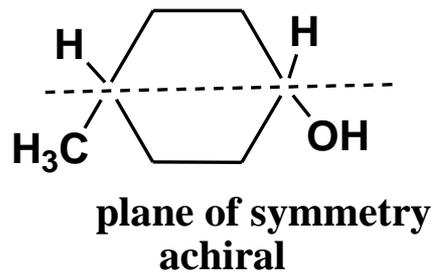
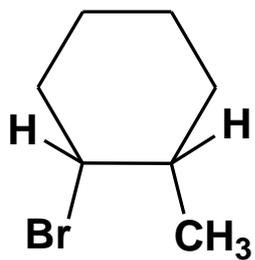
170



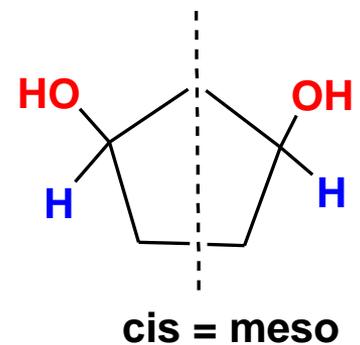
*meso (R,S)*

0  $[\alpha]_D^{20}$

140 Melting point



trans = chiral

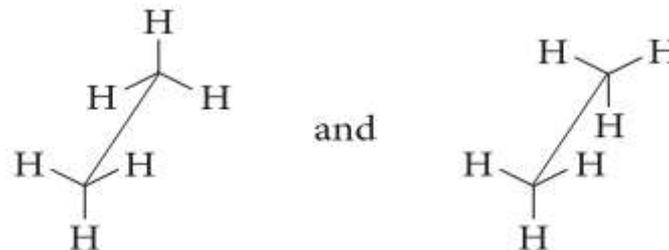


## 5.10 Stereochemistry A Recap of Definitions :

A	<i>Conformers:</i>	interconvertible by rotation about single bonds
	<i>Configurational Isomers:</i>	not interconvertible by rotation, only by breaking and making bonds
B	<i>Chiral:</i>	mirror image not superimposable on itself
	<i>Achiral:</i>	molecule and mirror image are identical
C	<i>Enantiomers:</i>	mirror images; have opposite configurations at all stereogenic centers
	<i>Diastereomers:</i>	stereoisomers but not mirror images; have same configuration at one or more centers, but differ at the remaining stereogenic centers

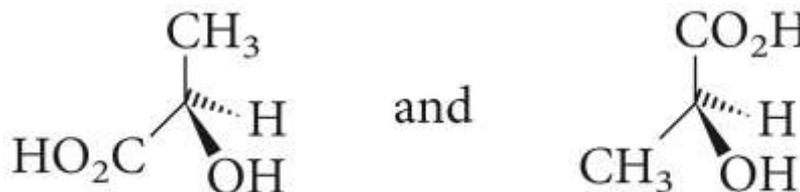
### 1- Staggered and eclipsed :

These are achiral conformational.  
They are diastereomeric conformers.



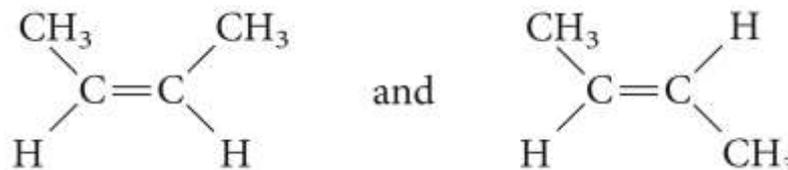
### 2- (R)- and (S)-enantiomers :

These are configurational, chiral.  
They are pair of enantiomers

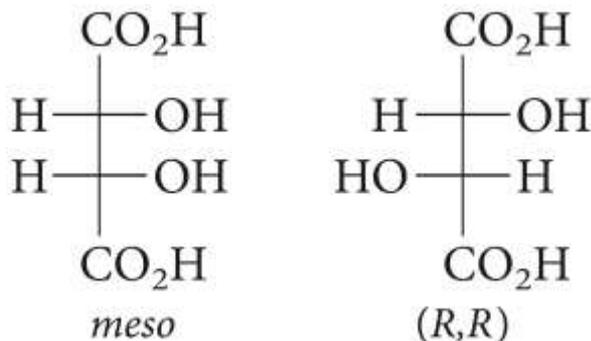


### 3- Cis-trans, (Z and E notation) :

These are configurational, achiral.  
They **are diastereomers**.



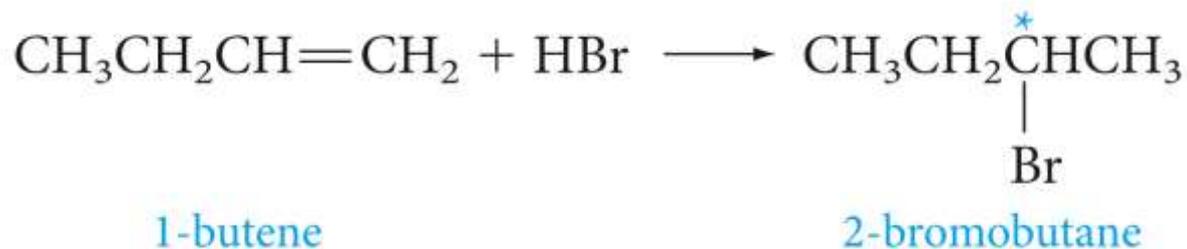
Q. What is the relationship between isomers of tartaric acid?



**diastereomers**

## 5.11 Stereochemistry and Chemical Reactions :

How important is stereochemistry in chemical reactions?

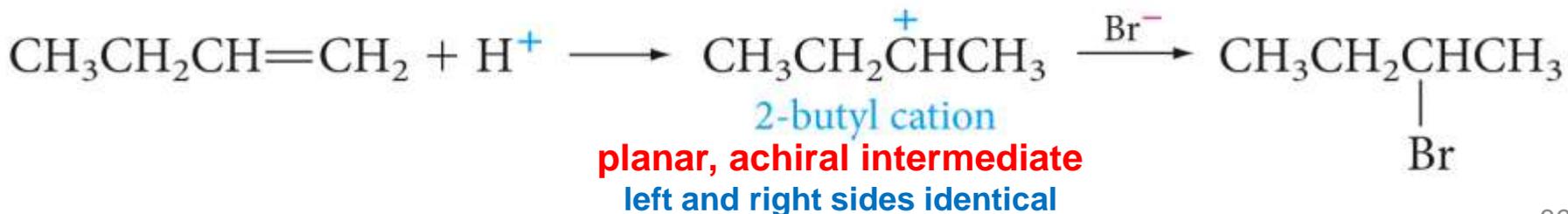


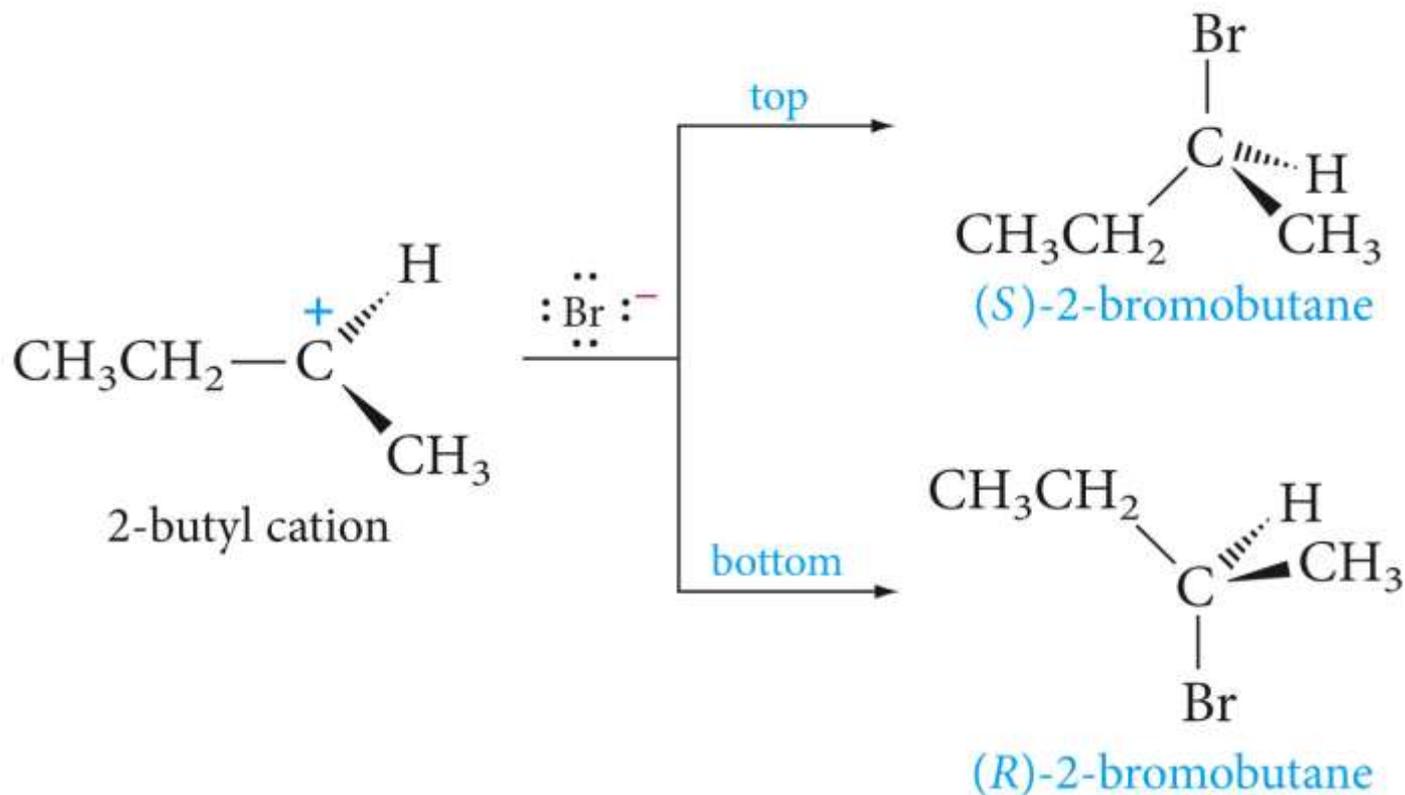
Both enantiomers are formed in **exactly equal** amounts.

Product is a 1:1 mixture of both enantiomers (**racemic mixture**)

Why? (enantiomers are equally stable, formed at equal rates)

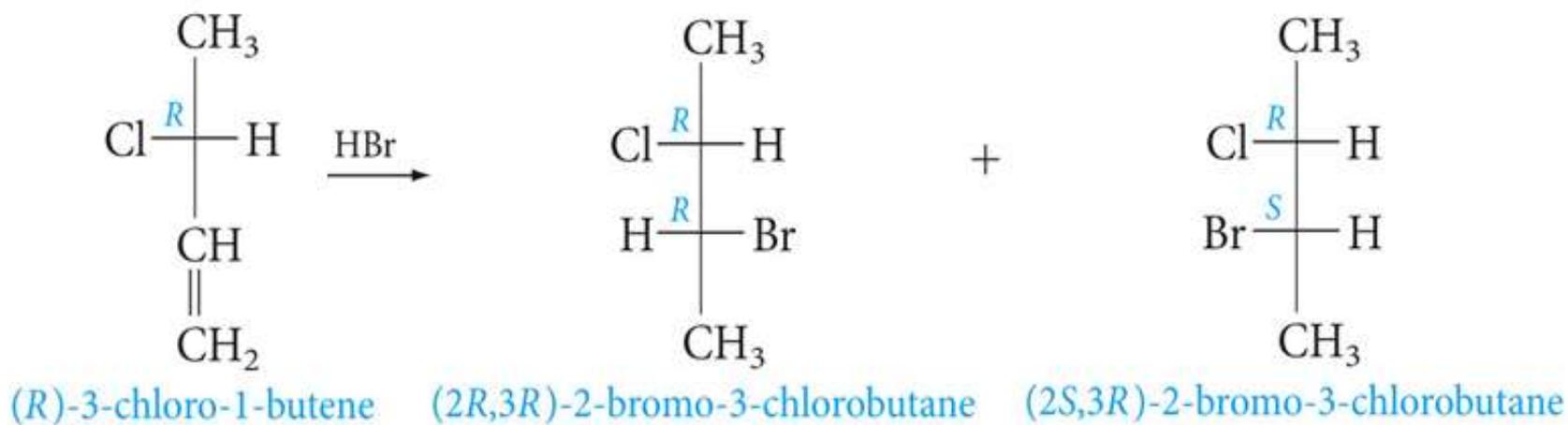
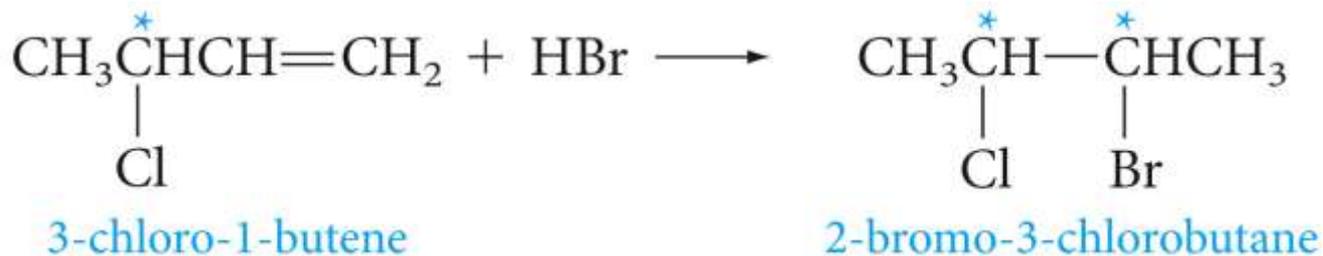
Mechanism : an achiral planar (symmetric) intermediate carbocation formed:





When chiral products are obtained from achiral reactants, both enantiomers are formed at the **same rates and in equal amounts**.

**Racemic mixture** : it is a **50:50** mixture of pair of enantiomers .  
It is **optically inactive**.



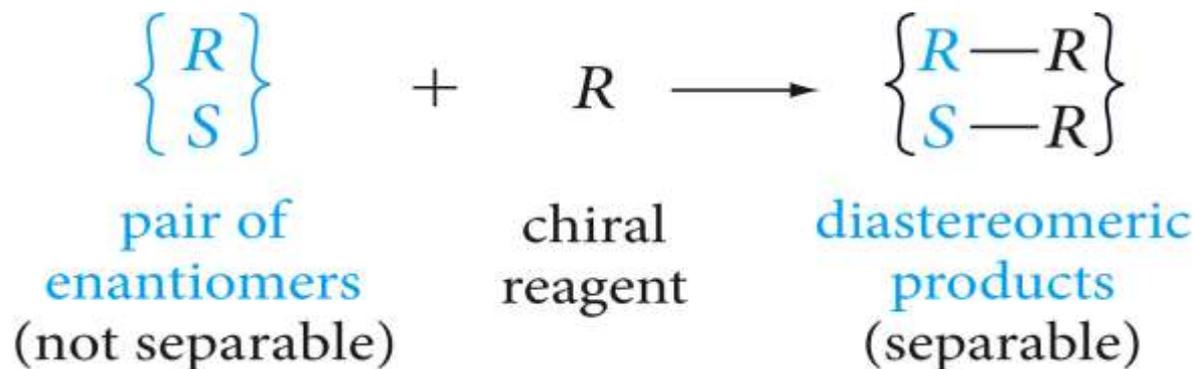
Reaction of **Chiral** compound in which a **new stereogenic center** is generated gives **diastereomers** (in unequal amounts)

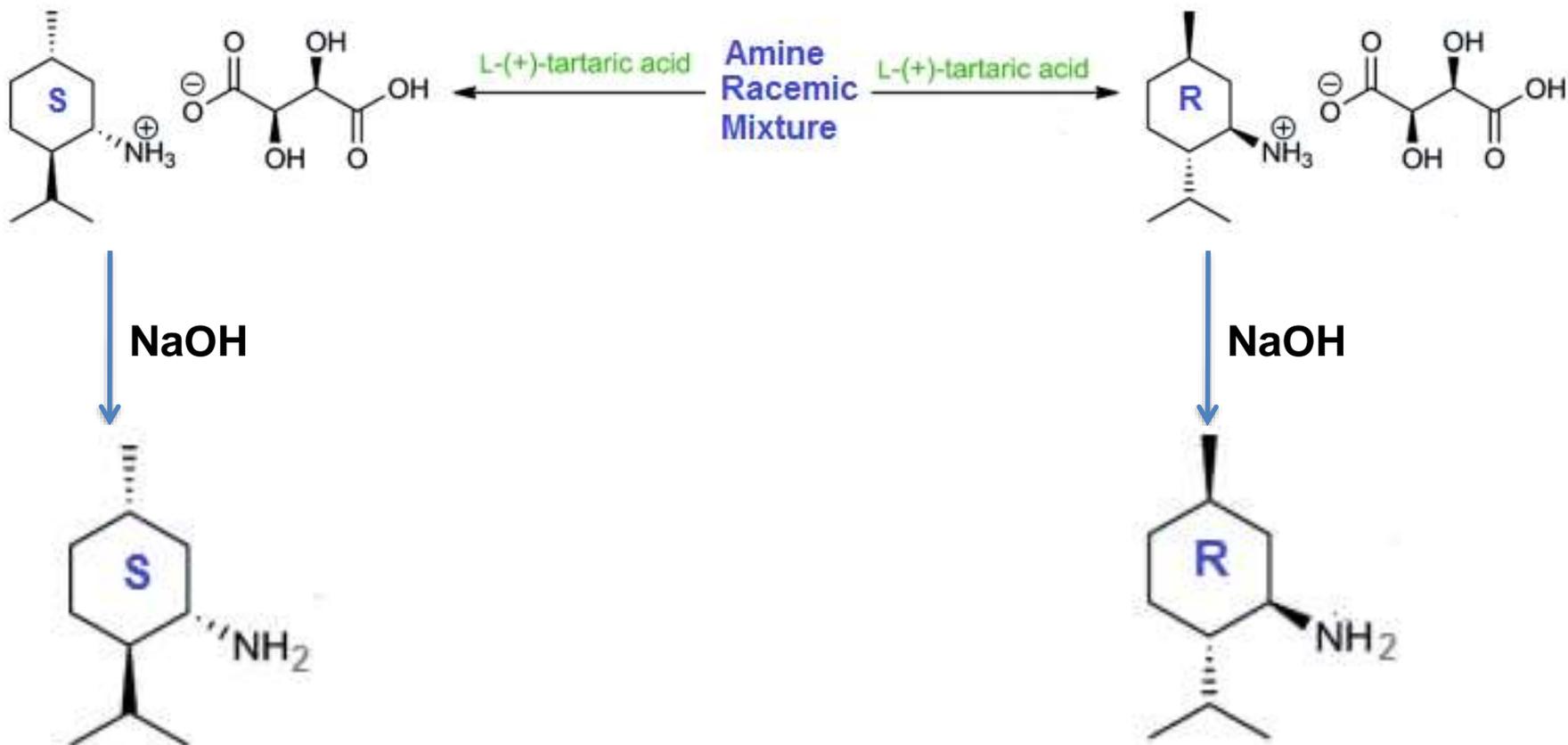
## 5.12 Resolution of a Racemic Mixture :

Enantiomers are not separable by ordinary methods because they have same physical properties.

To separate enantiomers from a racemic mixture:

- 1- React them with suitable **chiral reagent**. Two **diastereomers** are obtained with different physical properties (separable by ordinary methods)
- 2- Separate the diastereomers (depending on solubility, boiling points,...etc.)
- 3- Then from each diastereomer the corresponding enantiomer is regenerated (by a simple chemical reaction).





**Resolution** : separation of enantiomeric forms using chiral optically active reagent