Stereochemistry of Carbon Compounds
Basic Concepts

FOR 2nd Education Student
2023

Dr. Ahmed Gaber Mohammed Taha

الكيمياء الفراغية

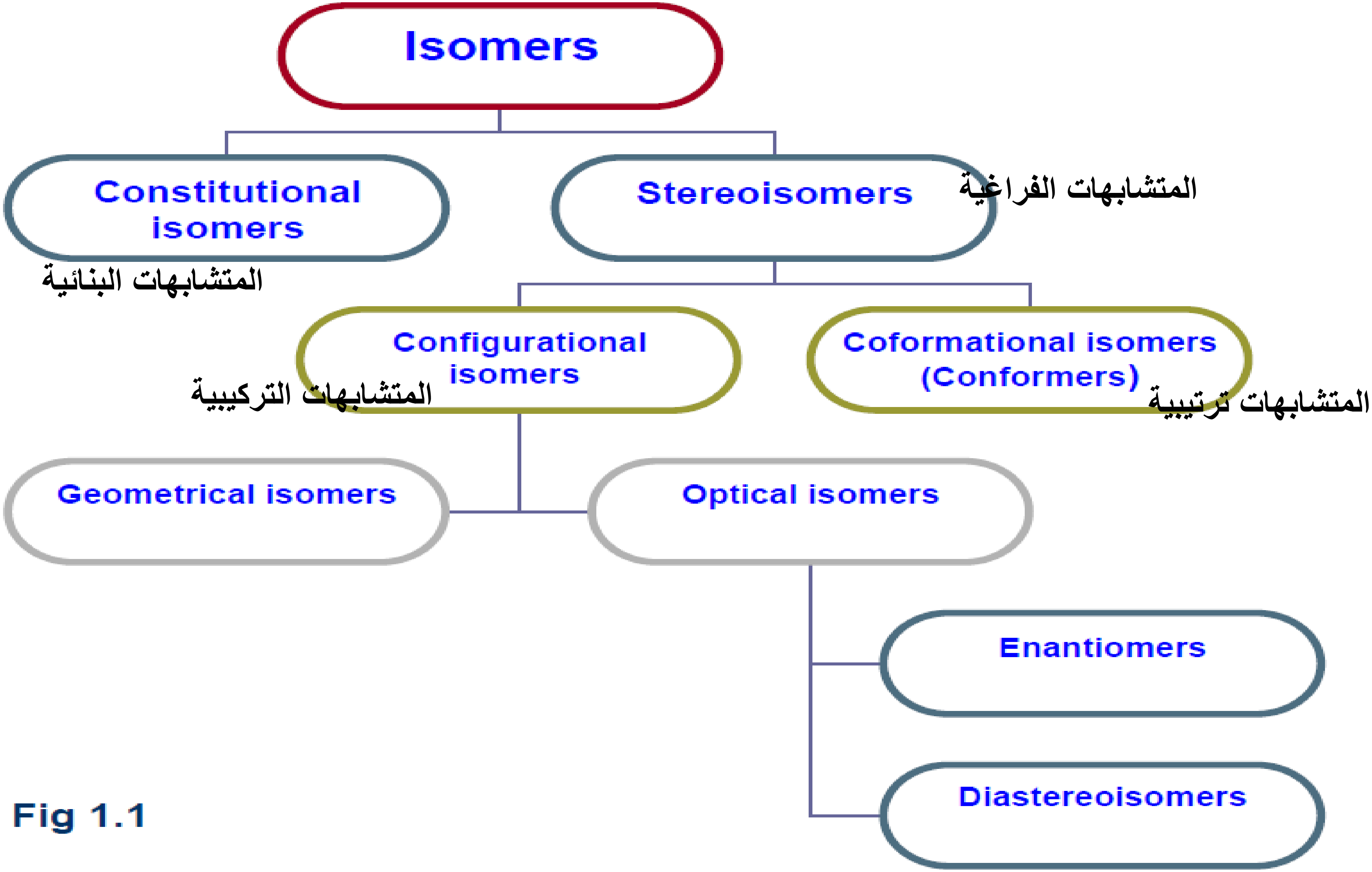
إعداد

د. احمد جابر محمد طه

للفرقة الثانية تربية احياء باللغة الانجليزية
للعام الدراسي ٢٠٢٣-٢٠٢٤

Isomers :

isomers are compounds that have the same molecular formula



Isomers

Constitutional isomers

المتشابهات البنائية

Stereoisomers

المتشابهات الفراغية

Configurational isomers

المتشابهات التركيبية

Coformational isomers (Conformers)

المتشابهات ترتيبية

Geometrical isomers

Optical isomers

Enantiomers

Diastereoisomers

Fig 1.1

- **Constitutional isomers:** are isomers that differ because their atoms are connected in a different order.

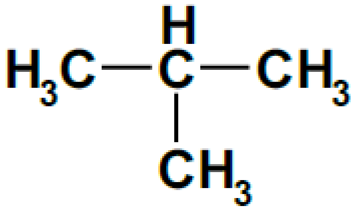
Example 1;

Molecular formula

Constitutional isomers

C_4H_{10}

$CH_3CH_2CH_2CH_3$ and



$H_3C-\underset{CH_3}{\overset{H}{C}}-CH_3$

Butane

Isobutane

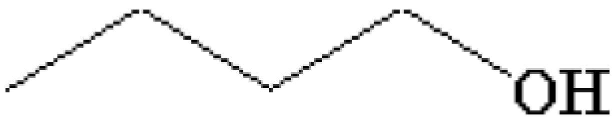
C_2H_6O

CH_3OCH_3

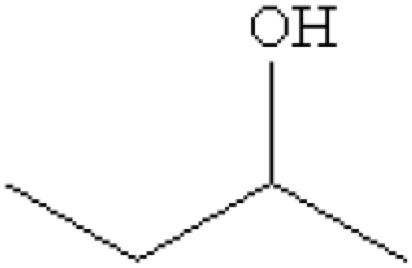
CH_3CH_2OH

Example 2;

The molecular formula $C_4H_{10}O$ may takes the following structures:

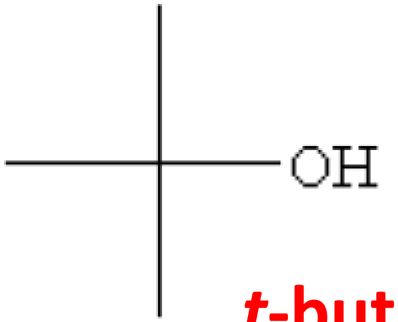


n-Butanol



2-butanol

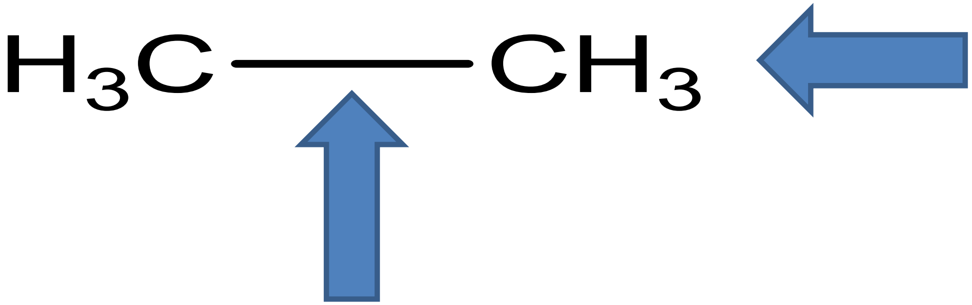
1-methyl-propanol



t-butanol

- **Stereoisomers:** are isomers that have same formula and connectivity but differ in the position of the atoms in space

- ✓ **Conformational isomers:** are isomers that interconvert easily at room temperature through rotations about single bonds.

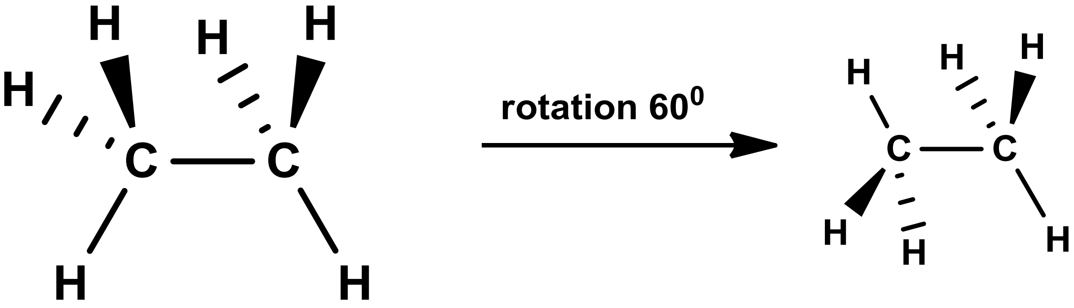


$H_3C—CH_3$

Newman Projection

Sawhorse projection

Sawhorse projection



Eclipsed

High energy

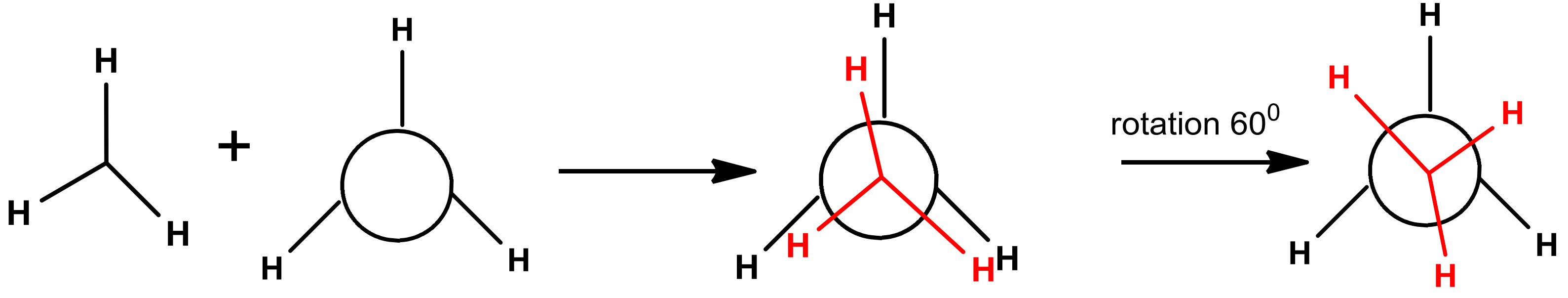
Low stability

staggered

Low energy

high stability

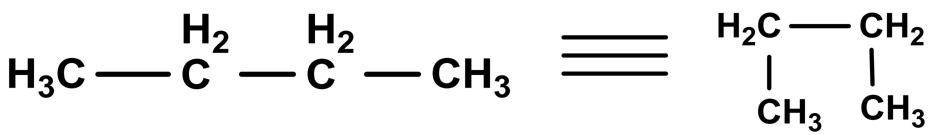
Newman Projection



Eclipsed **staggered**

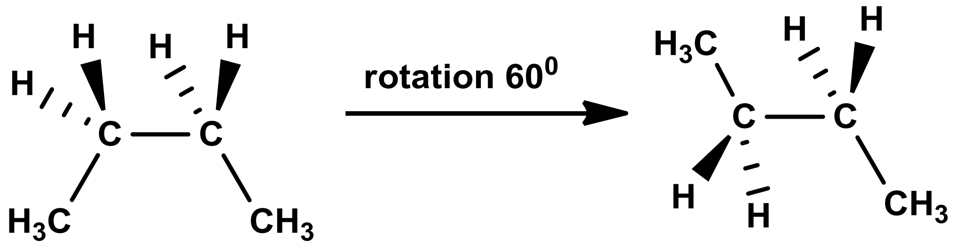
High energy

Low stability

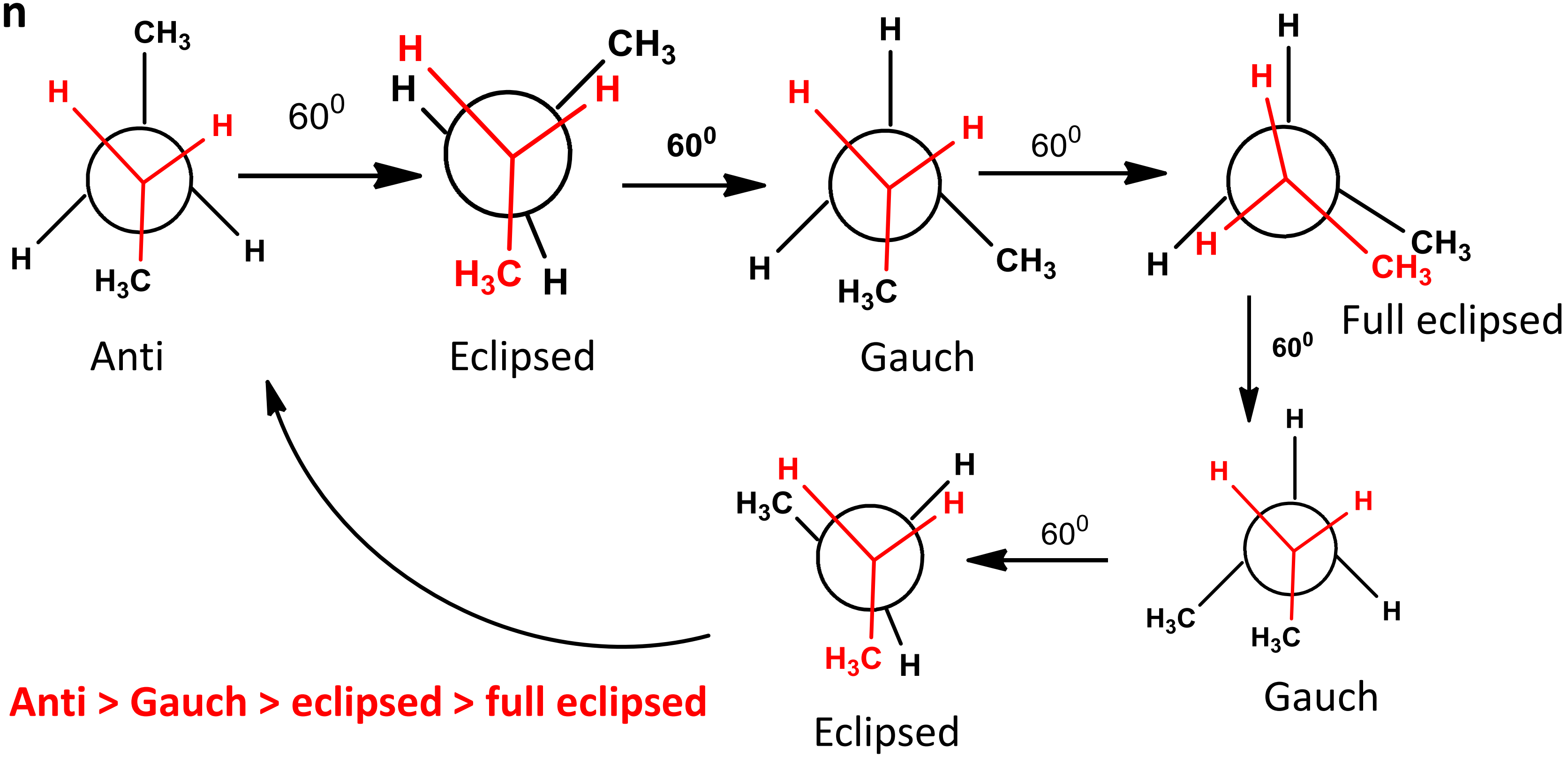


$H_3C-CH_2-CH_2-CH_3 \equiv H_2C(CH_3)-CH_2(CH_3)$

1) Sawhorse



2)Newman



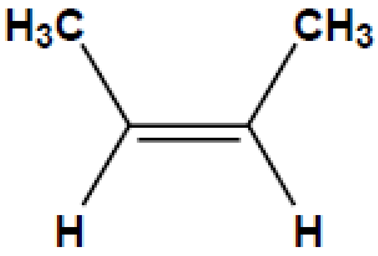
Stability : Anti > Gauch > eclipsed > full eclipsed

Q- Draw a Newman projection of the most stable conformation of 2-methylpropane?

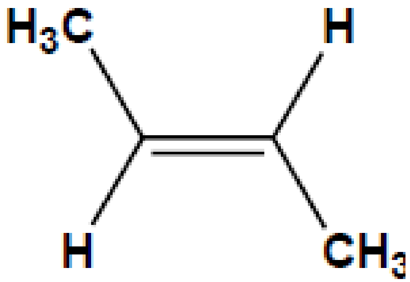
Q- Draw a Newman projections for pentane looking down the C2-C3 bond through a full 360 degree rotation?

- **Configurational isomers: are divided into two types optical and geometrical isomers.**

a) Geometrical or *cis-trans* isomers: are types of stereoisomers resulting from difference in the special arrangement of the atoms or groups attached to the bonds around which rotation is largely restricted.



cis-butene



trans-butene

b) Optical isomers: are isomers that resulting from presence of one or more chiral centers within a molecule.

Optical isomers

Optical Activity: the ability of some compounds to rotate plane polarized light either to right or left

- ✓ **Dextrorotatory :** If the compound rotates the plane of polarization to the right(clockwise) it is said to be dextrorotatory) and is denoted by (+), or ‘d’.
- ✓ **Laevorotatory :** If the compound rotates the plane of polarization to the left(anticlockwise) it is said to be laevorotatory and is denoted by (-) or ‘l’

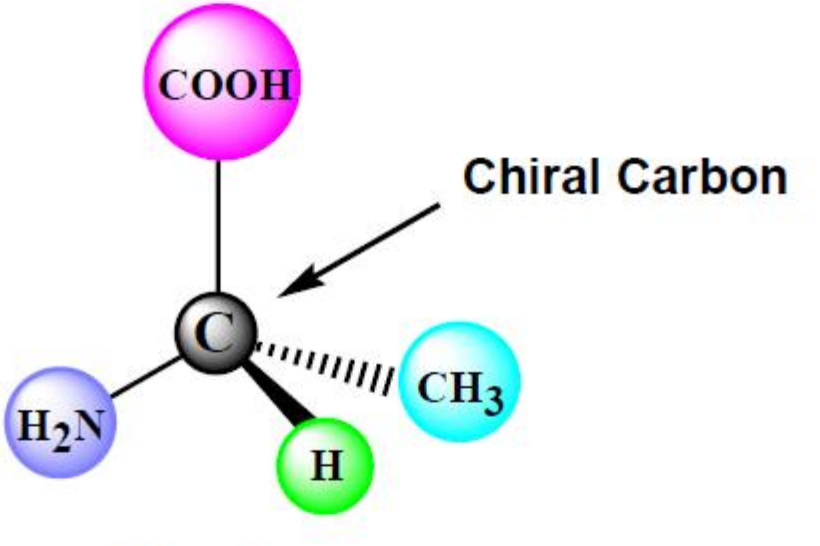
➢ **Organic compound became optically active if contain:**

- **Chiral center**
- **no element of symmetry**

Chirality: refers to the compound and its mirror are non–superimposable and the term derives from the fact that left and right hands are examples of chiral objects.

Chiral carbon atom: is a carbon atom attached to four different atoms or groups.

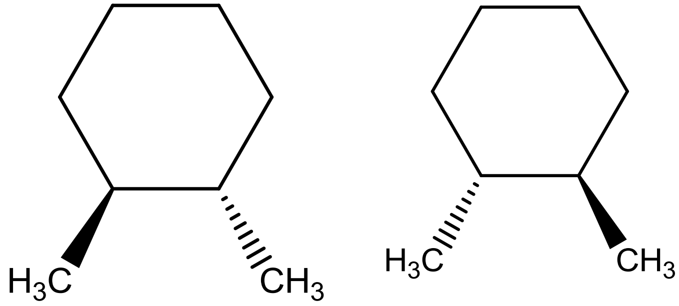
Ex: Alanine (**H2N*CH(CH3)COOH**), in which the starred carbon atom is a chiral, being substituted by (**NH2**, **H**, **CH3**, and **COOH**)



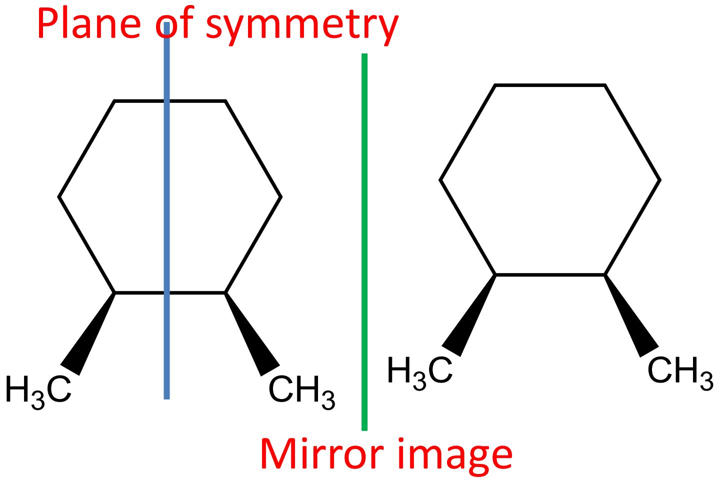
Alanine

Achiral: any molecule that is not chiral.

- **No chiral center**
- **May contain chiral center but the compound and its mirror image are superimposable**
- **Has element of symmetry**
- **Optically inactive**



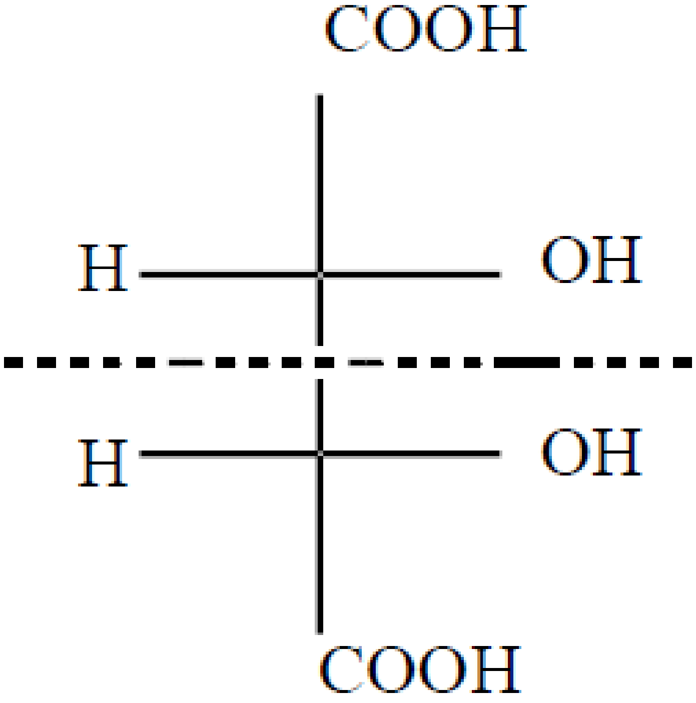
Chiral compound
Enantiomers
Optically active



AChiral compound
Meso compounds
Optically inactive

Element of symmetry

- Plane of symmetry
- Center of symmetry



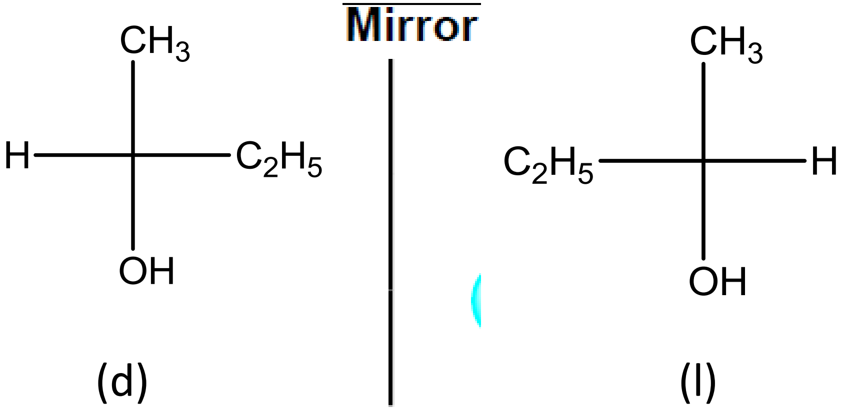
Achiral due to presence of plane of symmetry

Optical isomers : can be divided into two general categories:

a- Enantiomers

b- distereoisomers

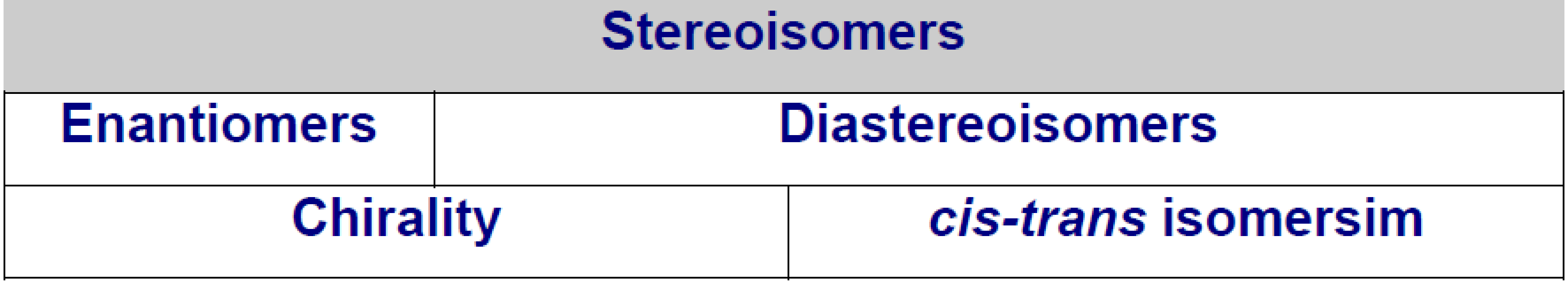
- **Enantiomers**: are two stereoisomers which differ only in their ability to rotate plane polarized light in an equal and opposite direction.
- and each one is a mirror image to the other
- and both enantiomers are non- superimposable.



Enantiomers

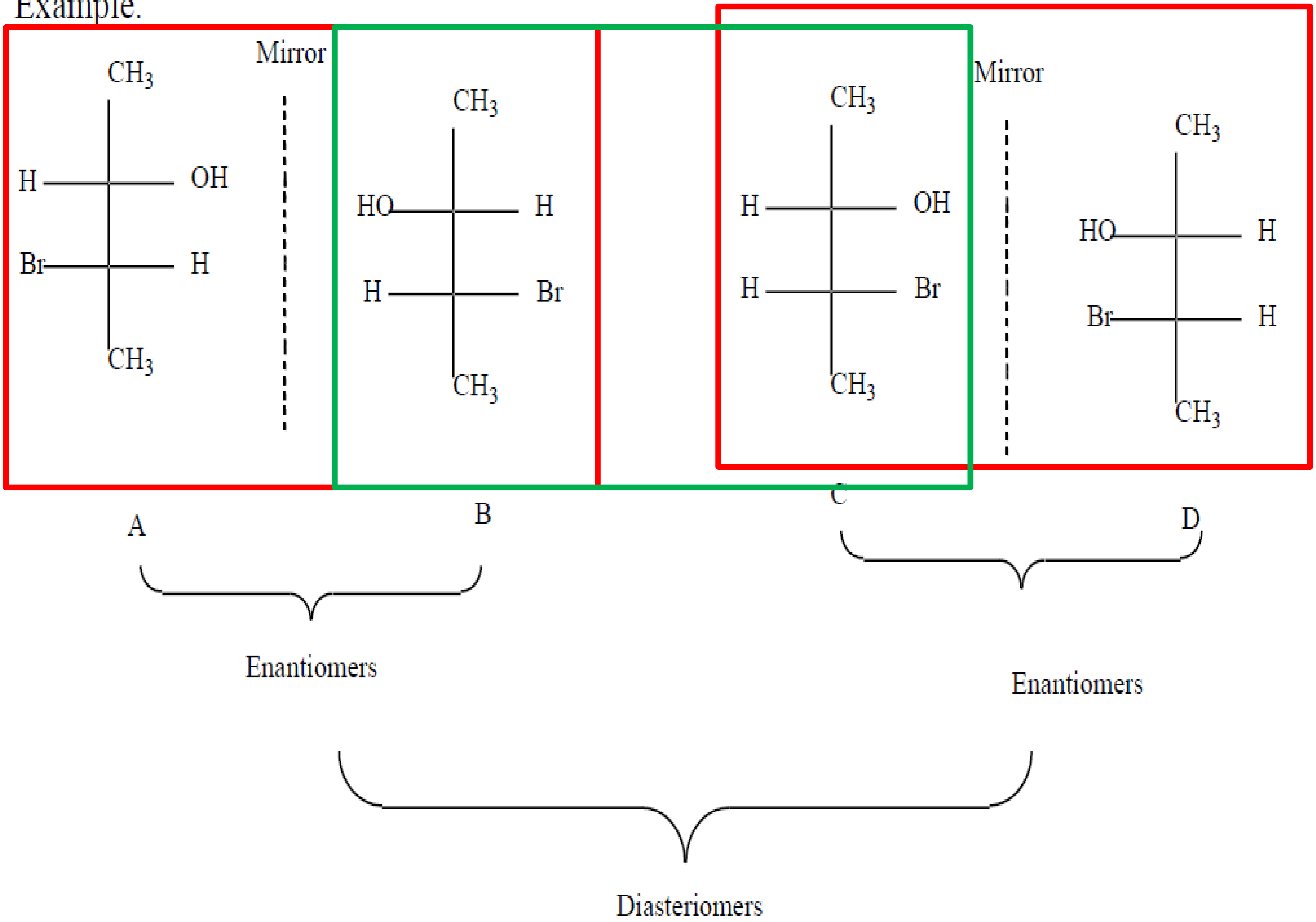
- **Diastereoisomers**: are all other stereoisomers that able to rotate plane polarized light or not, and whose molecules are not mirror images.

Note that: Enantiomers result from chirality only: diastereoisomers result from chirality or *cis-trans* isomerism. Also, chiral system may be enantiomeric or diastereoisomeric: *cis-trans* isomers are only diastereoisomeric.



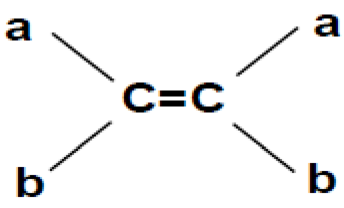
<table>
<tr><th colspan="3">Stereoisomers</th></tr>
<tr><td>Enantiomers</td><td colspan="2">Diastereoisomers</td></tr>
<tr><td colspan="2">Chirality</td><td>*cis-trans* isomersim</td></tr>
</table>

Example.

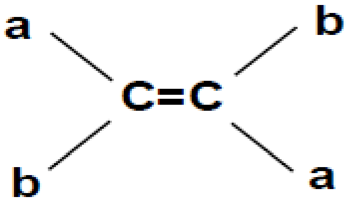

Mirror
CH3
H
OH
Br
H
CH3
CH3
HO
H
H
Br
CH3
A
B
Enantiomers
Mirror
CH3
H
OH
H
Br
CH3
CH3
HO
H
Br
H
CH3
C
D
Enantiomers
Diasteriomers

Geometrical isomerism (*cis- trans* isomerism)

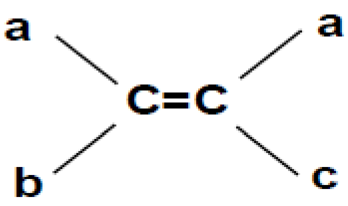
A) Geometrical isomerism due to carbon-carbon double bond



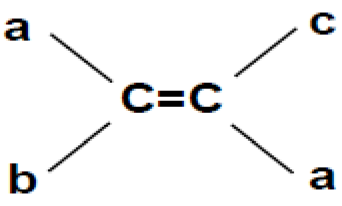
cis



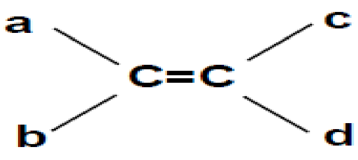
trans



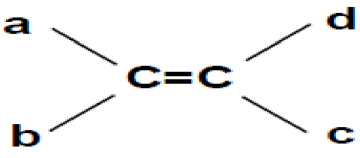
cis



trans



A

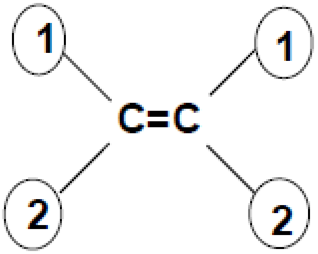


B

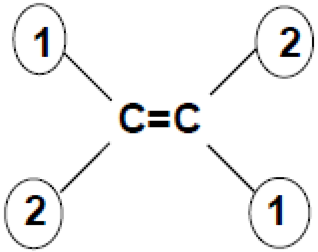
The prefixes "***cis***" and "***trans***" being used when the two equal groups are on the same or opposite sides.

The symbols (*E*) and (*Z*)

- The new terms (***E***) and (***Z***) replace the older terms (***cis***) and (***trans***).
- The method is based on a priority system developed by Cahn, Ingold and Prelog (1956, 1966) for use with optically active molecules.
- Groups on each carbon atom of the double bond are assigned a first (1) or second (2) then priority compared at one carbon relative to the other.
- When both first priority groups are on the same side of the double bond, the configuration is designated as ***Z (together).***
- If the first priority groups are on the opposite sides, the designation is ***E (opposite).***



Z (together)

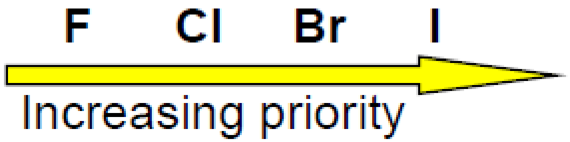


E (opposite)

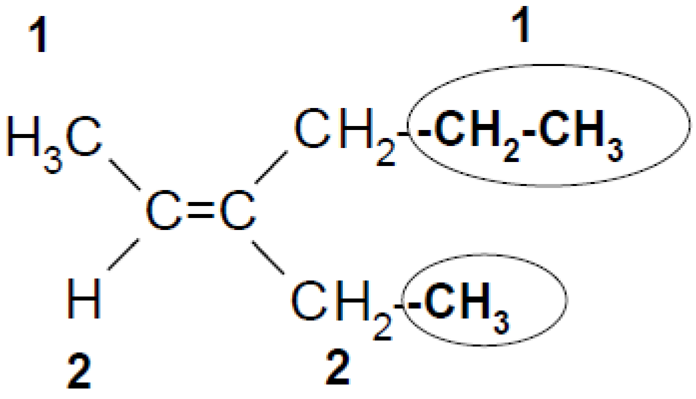
The sequence rules

In the Cahn- Ingold- Prelog system, a set of sequence rules to determine order of priority has been developed.

(i) Higher priority is assigned to atoms of higher atomic number.



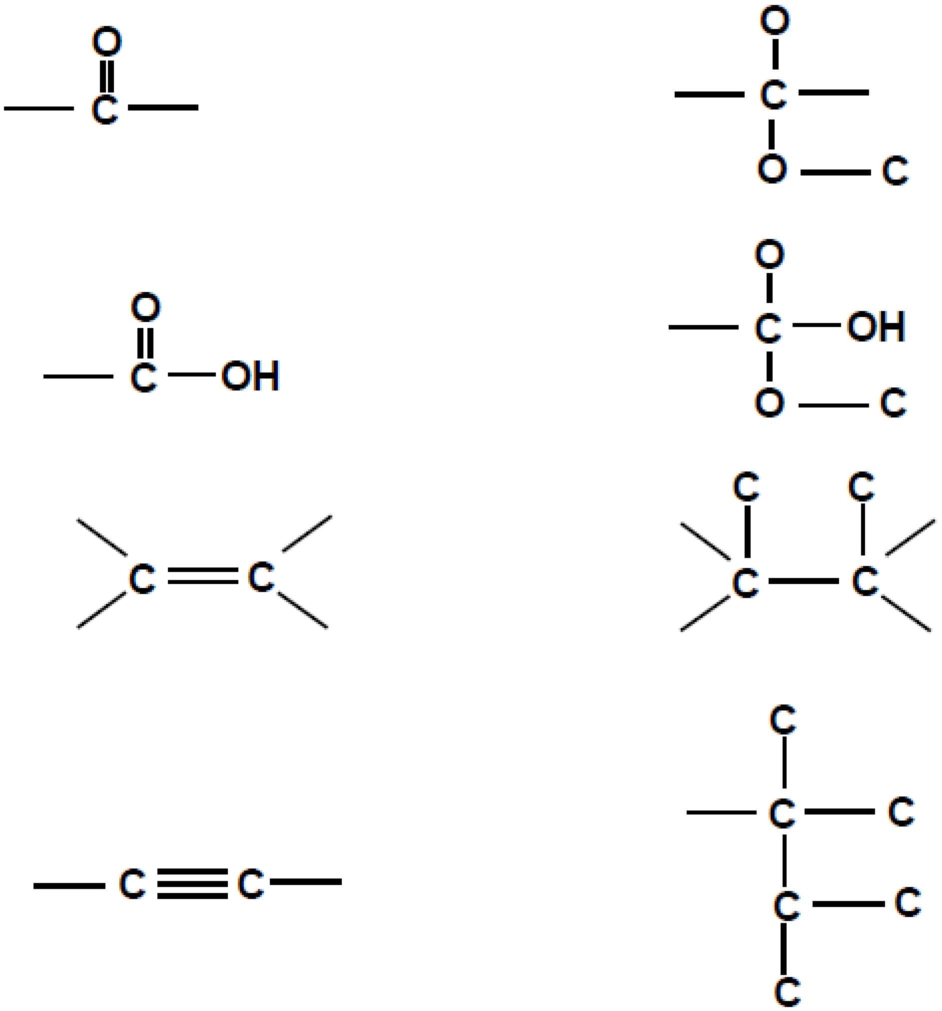
(ii) When two atoms have the same priority attached directly to a double bond, the second atoms are considered.

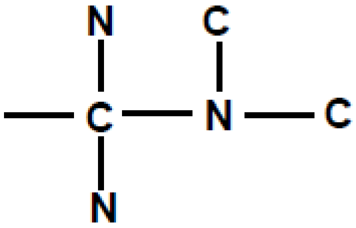


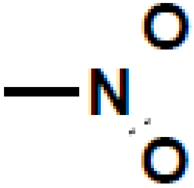
Z-3-ethyl-2-hexene

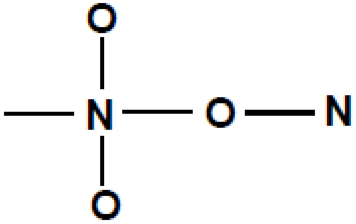
(iv) When groups under priority determination have double or triple bonds, the multiply-bonded atom is replaced conceptually by two or three single bonds to that same kind of atom.

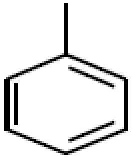
group **Equivalent for priority**

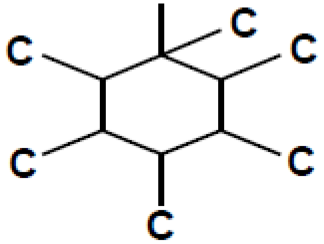












(v) Lone-pair electrons are regulated as an atom with atomic number 0.

- The order of decreasing priority of some atoms and groups is arranged as the following:

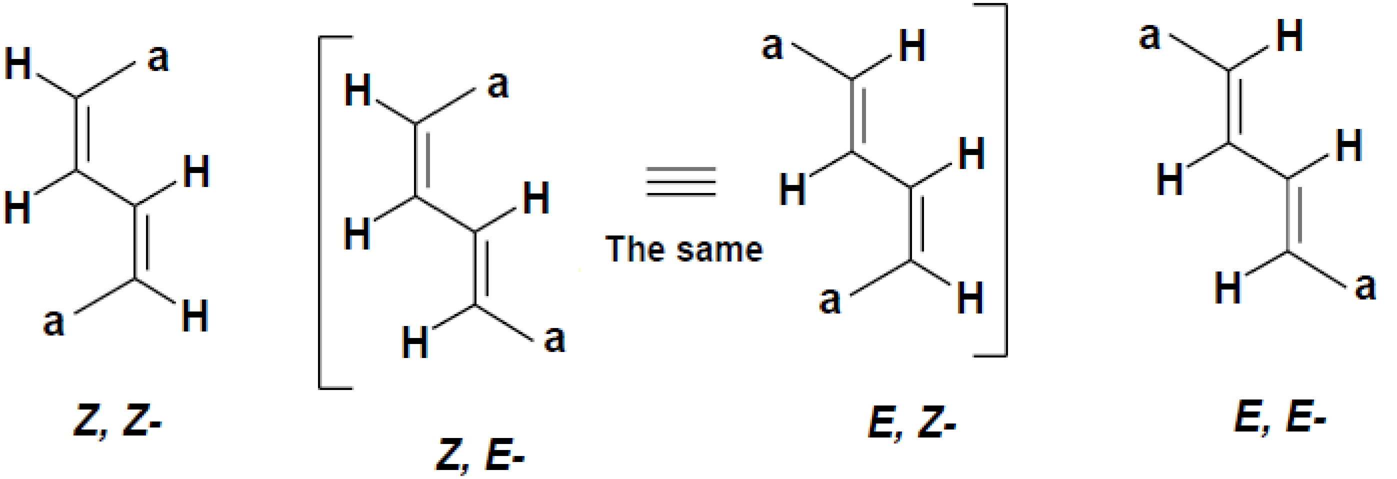
Decreasing priority →

Atoms: I, Br, Cl, S, P, F, O, N, C, H, lone-pair electrons.

Groups: -OCOR, -OR, OH.
$-NO_2$, $-NR_2$, -NHCOR, -NHR, $-NH_2$.
-COCl, -COOR, -COOH, $-CONH_2$, -COR, -CHO.
$-C(R)_2OH$, -CH(R)OH, $-CH_2OH$.
-CN, $-C_6H_5$, $-C\equiv CR$, $-C\equiv CH$, $-C=CH_2$, $-CH(CH_3)_2$.
$-C(R)_3$, $-CH(R)_2$, $-CH_2R$, $-CH_3$.

B) Stereoisomerism in compounds with more than C=C group

- The number of geometrical isomers increase when a molecule contains more than one C=C group.
- If the terminal double bonds are **not identical**, e.g., **aHC=CH-CH=CHb**, a≠b. The number of geometrical isomers = 2**n** , where (n) is the No. of double bonds.
- If the terminal double bonds are **identical**, e.g., **aHC=CH-CH=CHa**, the No. of isomers =3 .

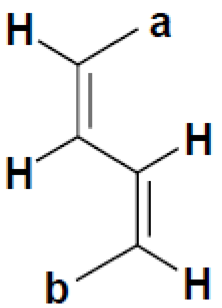


Z, Z-

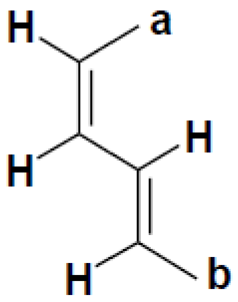
Z, E-

E, Z-

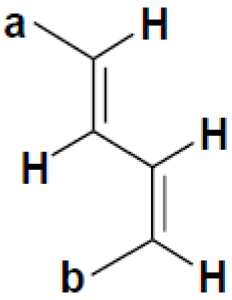
E, E-



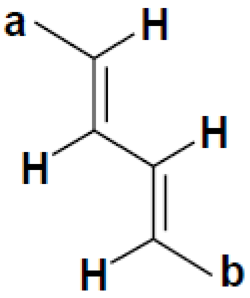
Z, Z-



Z, E-

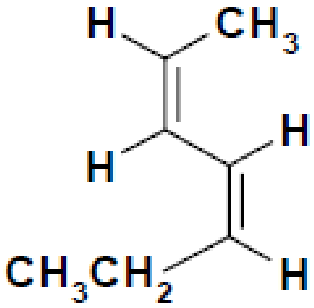


E, Z-

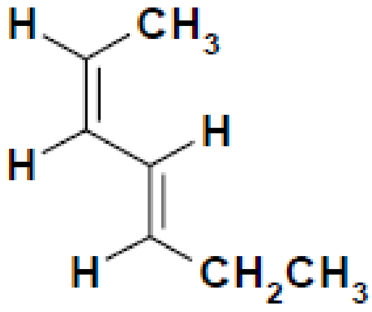


E, E-

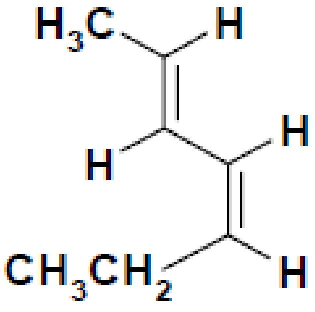
EX: ***hepta-2,4-diene*** is has a terminal double bonds exists as 4 geometrical isomers



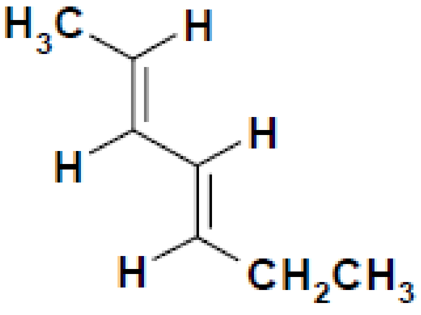
(Z)-2,(Z)-4



(Z)-2,(E)-4



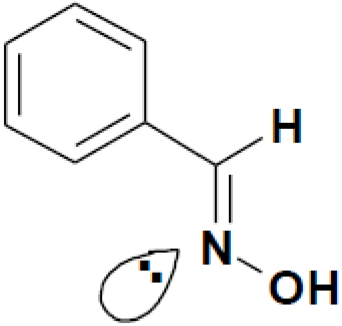
(E)-2,(Z)-4



(E)-2,(E)-4

c) Geometrical isomerism due to carbon-nitrogen (C=N) double bond

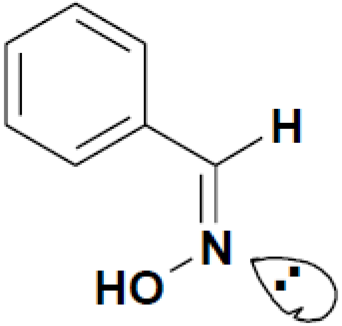
- The illustrative examples of compounds in which geometrical isomerism is due to the presence of carbon-nitrogen double bond are oximes.
- there are two geometrical forms which are designated by the prefixes ***syn***- (***E***) and ***anti***- (***Z***) .
- The ***syn***-isomer is the one in which the **H** and **OH** lie ***cis*** to each other .
- The ***anti***-isomer is the one in which these are ***trans*** to each other .



syn-benzaldoxime

_E_-benzaldoxime

(H/OH, _cis_)



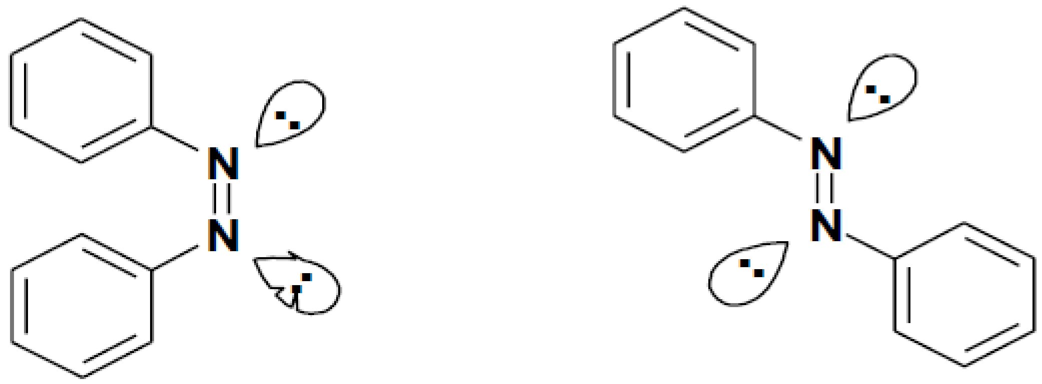
anti-benzaloxime

_Z_-benzaldoxime

(H/OH, _trans_)

d) Geometrical isomerism due to nitrogen- nitrogen (N=N) double bond

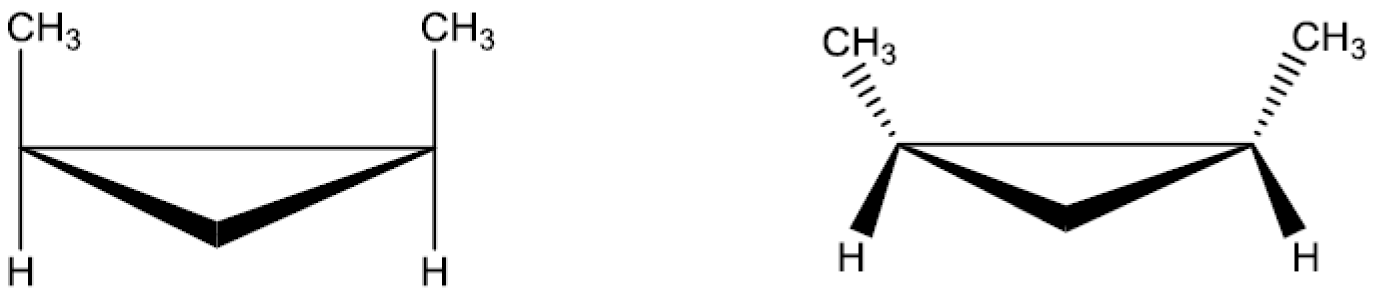
- a molecule contains **N=N** exhibits two geometrical isomers as in *azo* – compounds



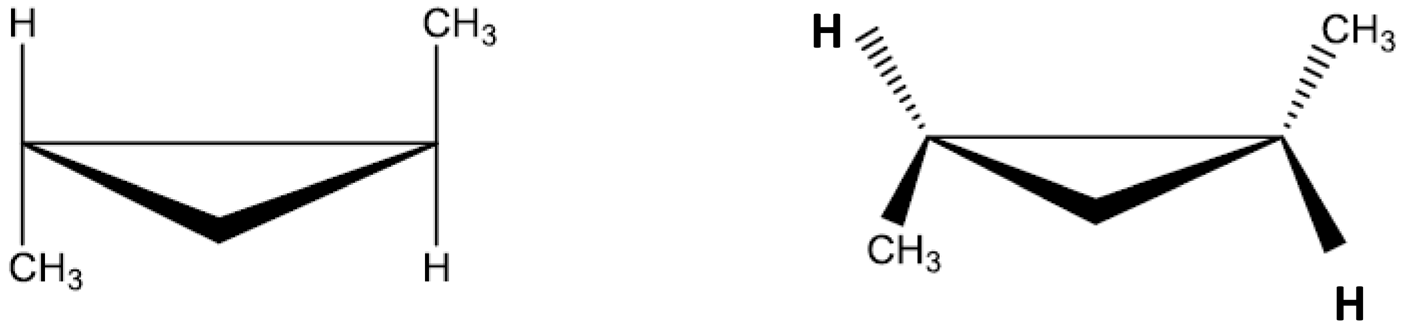
syn-benzaldoxime
Z-benzaldoxime

anti-benzaloxime
E-benzaldoxime

❖*cis- trans-* isomerism in cyclic compounds

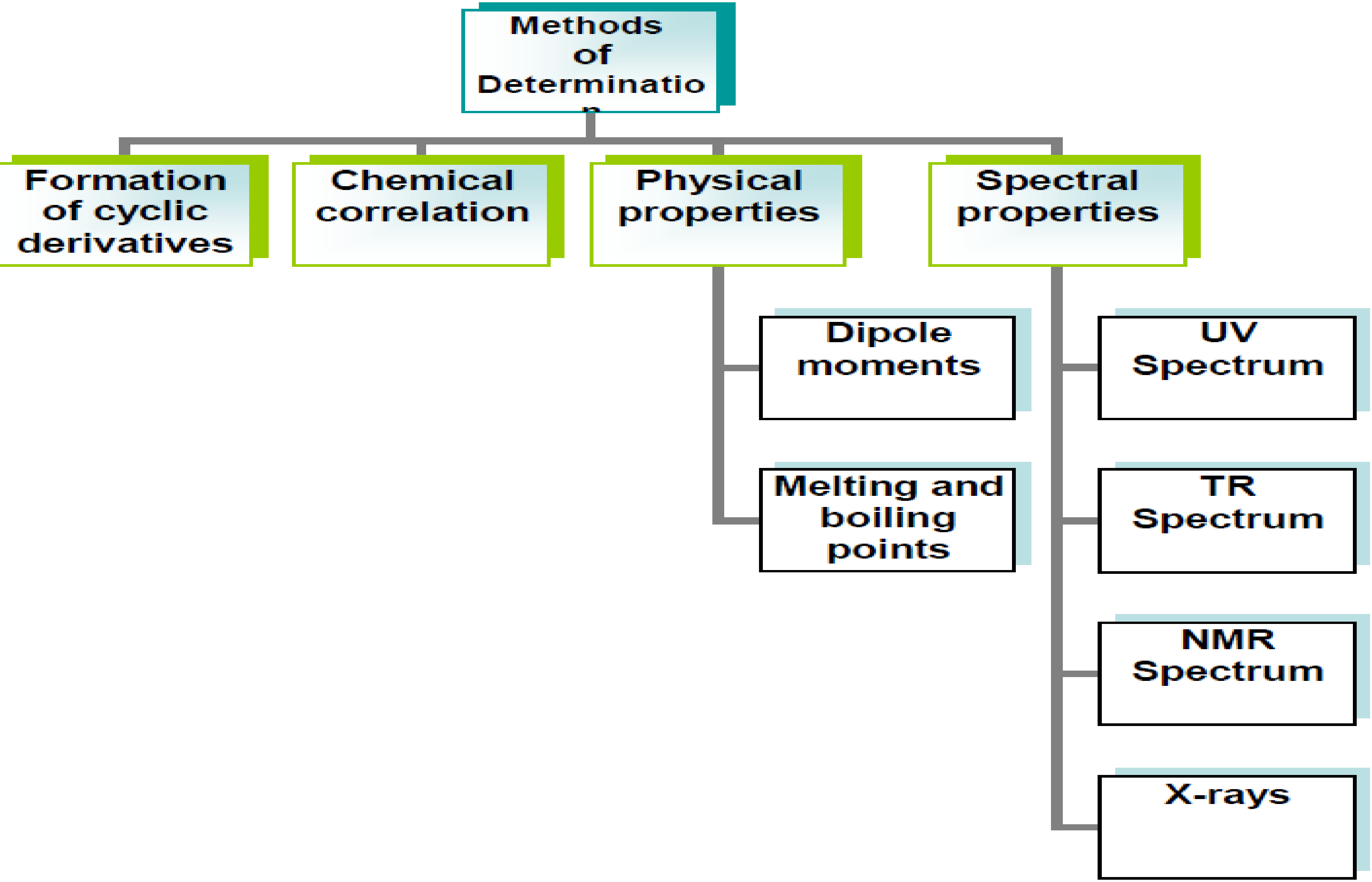


***cis*-1,2-dimethylcyclopropane**



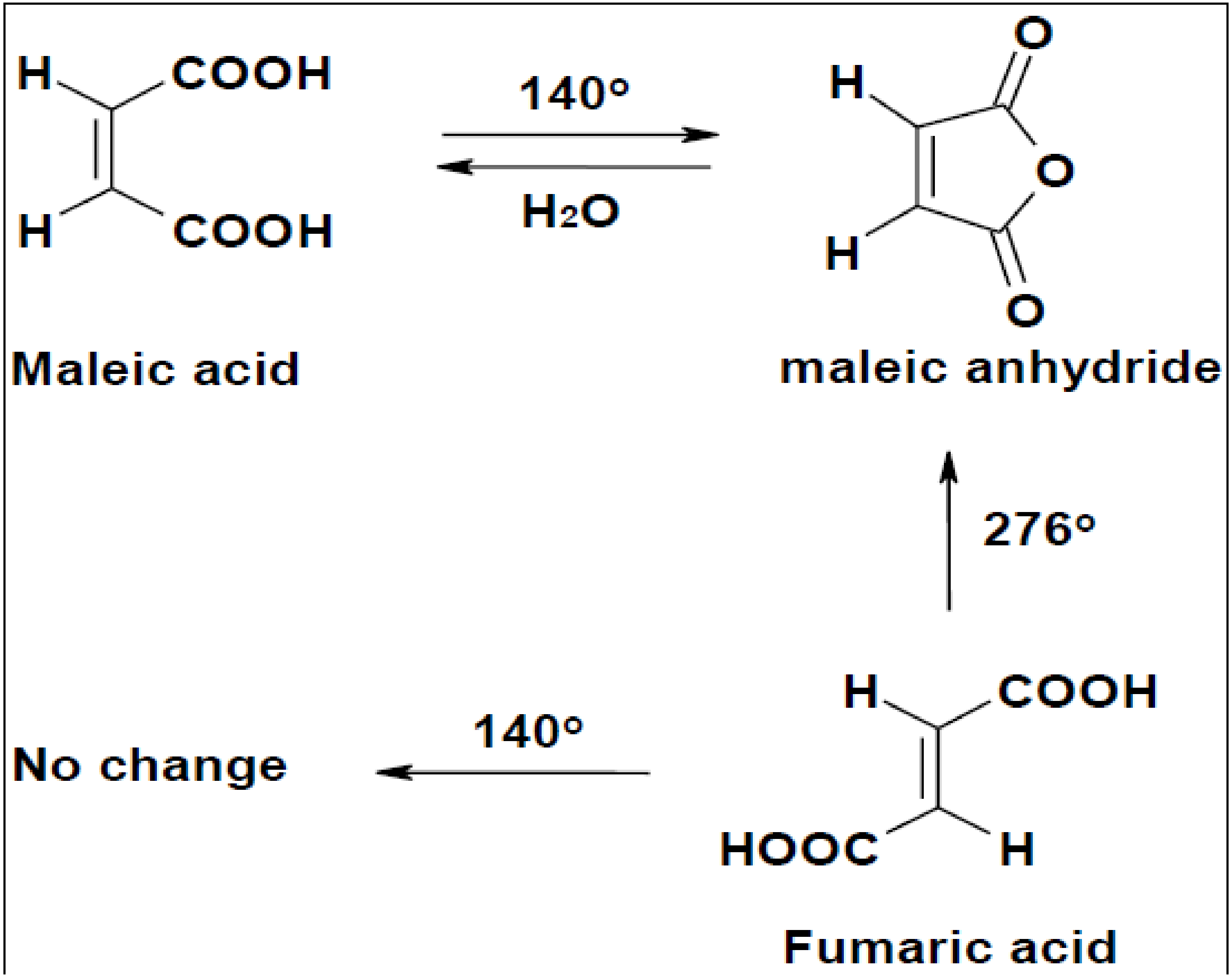
***trans*-1,2-dimethylcyclopropane**

Determination of the configuration of geometrical isomers



- Methods of Determination
  - Formation of cyclic derivatives
  - Chemical correlation
  - Physical properties
    - Dipole moments
    - Melting and boiling points
  - Spectral properties
    - UV Spectrum
    - TR Spectrum
    - NMR Spectrum
    - X-rays

➢Formation of cyclic derivatives



- Maleic acid (mp 130) readily forms a monomeric anhydride upon heating to ~ 140.
- Water regenerates the acid from its anhydride.
- Fumaric acid (mp 270) does not readily form an anhydride upon heating to ~ 140O, but vigorous heating to ~ 276 is converted it to the anhydride of maleic acid.
- It may be concluded that the two carboxylic groups must be on the same side of the alkene double bond system in maleic acid and on the opposite side in fumaric acid. Hence, maleic acid is the ***cis***-isomer and fumaric acid is the ***trans***

Activities: 2-methyl-2-butenedicarboxylic acid can not lose a molecule of water. Is 2-methyl-2-butenedicarboxylic acid exists in the *cis*- or in the *trans*- form?

Chemical correlation

- This method depends on conversion of unknown configurational isomer into a different known isomer.

- An example of the correlation method is the transformation of trichlorocrotonic acid (mp 114), into fumaric acid by hydrolysis, and by reduction into crotonic acid (mp 72).
- Since fumaric acid has the ***trans*** configuration, the trichlorocrotonic acid and the crotonic acid must also be ***trans***-isomers .

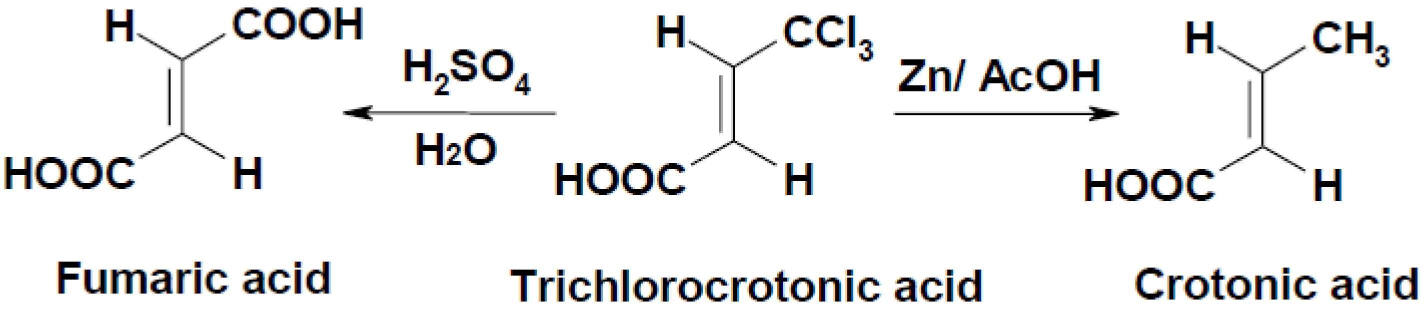


Fig. 4.3

Can *cis*- and *trans*- isomers be interconvert ?

- The conversion of ***cis***- to ***trans***-isomers or the reverse process is known as ***stereomutation*** which can be affected in two ways:
- A) either by a series of chemical reactions by which the alkene is converted to the other alternative isomer.
- B) or by the reversible procedure converting the double bond to single bond in which free rotation is possible before regeneration of the alkene.
- This reversible process may by affected by free radical, by pyrrolysis, and by vigorous heating.

Stereomutation: is a conversion of cis to trans-isomers or the reverse process.

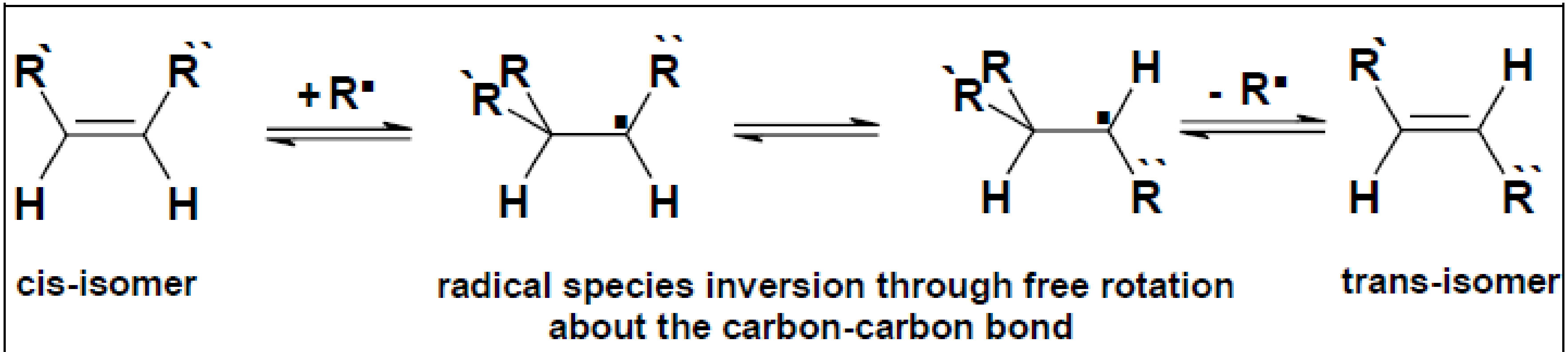


Fig. 4.4

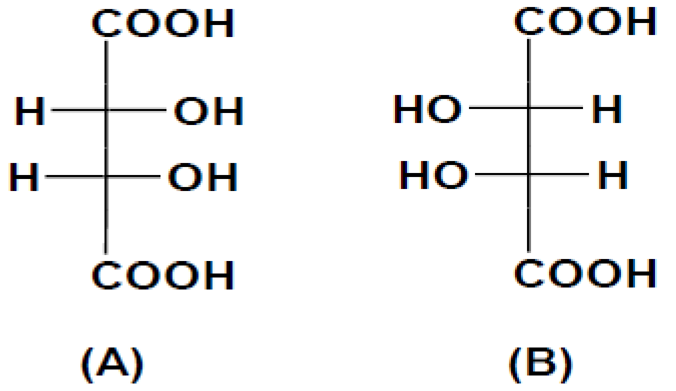
❑ Representing three-dimensional molecules in two-dimensions

The most common representations for the spatial relationship between ligands attached to two adjacent carbon atoms are:

- Fisher projections,
- Wedge projections,
- Sawhorse projections
- and Newman projections.

Fischer Projections

- In which The main carbon chain is drawn as a vertical line and bonds to all substituents are drawn as horizontal lines. All vertical lines represent bonds behind the plane of the page and all horizontal lines represent bonds in front of the plane of the page.

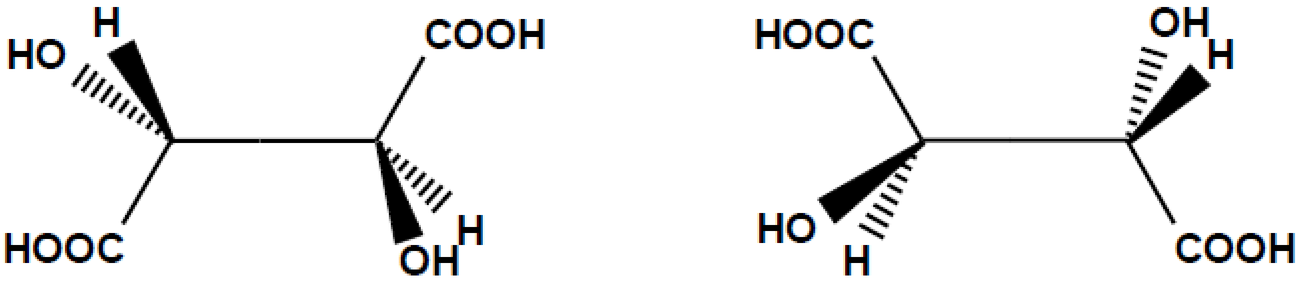


Fischer projections of tartaric acid

Fig. 5.1

➢Wedge projections

A wedge representation shows the side of the carbon— carbon bond being drawn. The bold wedges represent bonds that project out of the plane of the paper toward you, the lines are bonds in the plane of the paper, and the dashed wedges represent bonds receding away from you behind the plane of the paper.



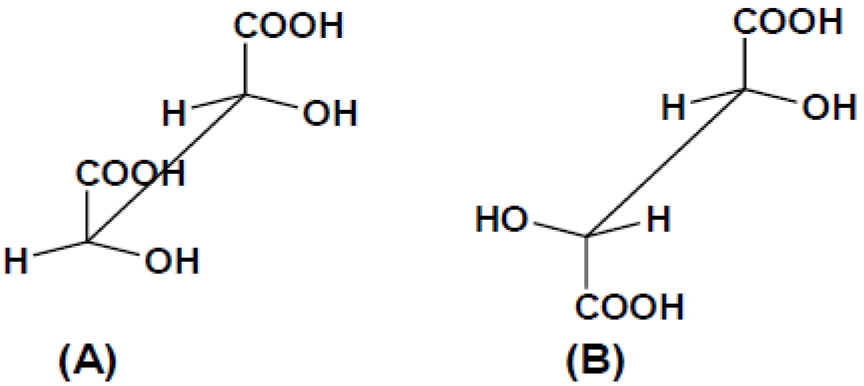
(A) (B)

Wedge projection of tartaric acid

Fig. 5.2

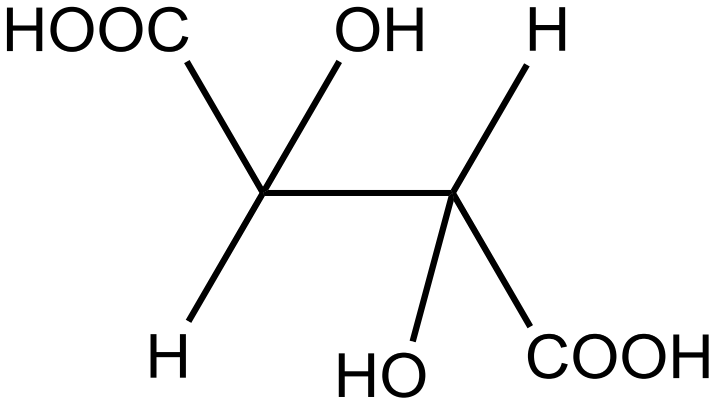
➢ Sawhorse projection

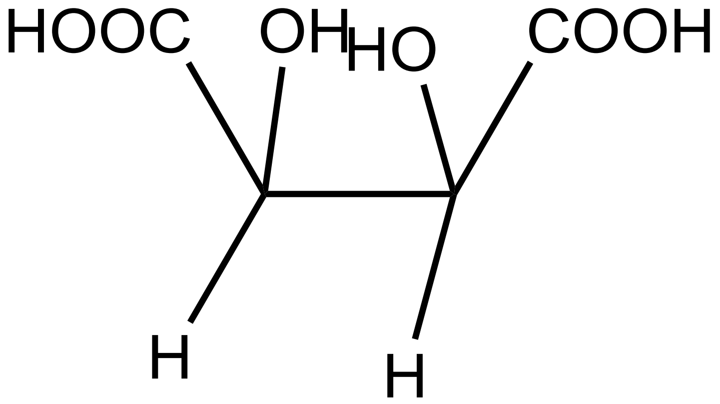
Sawhorse projection views the molecule from slightly above and to the right of one carbon-carbon bond and all bonds are drown as straight lines.



Sawhorse projection of tartaric acid

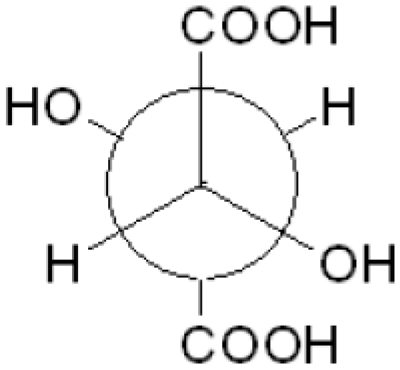
Fig. 5.3

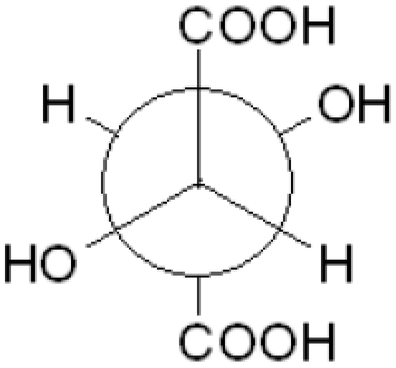




➢Newman projections

A Newman projection shows the two bonded carbons under consideration with one directly in front of the other. The point represents the front carbon and the open circle represents the rear carbon.





Optical isomerism

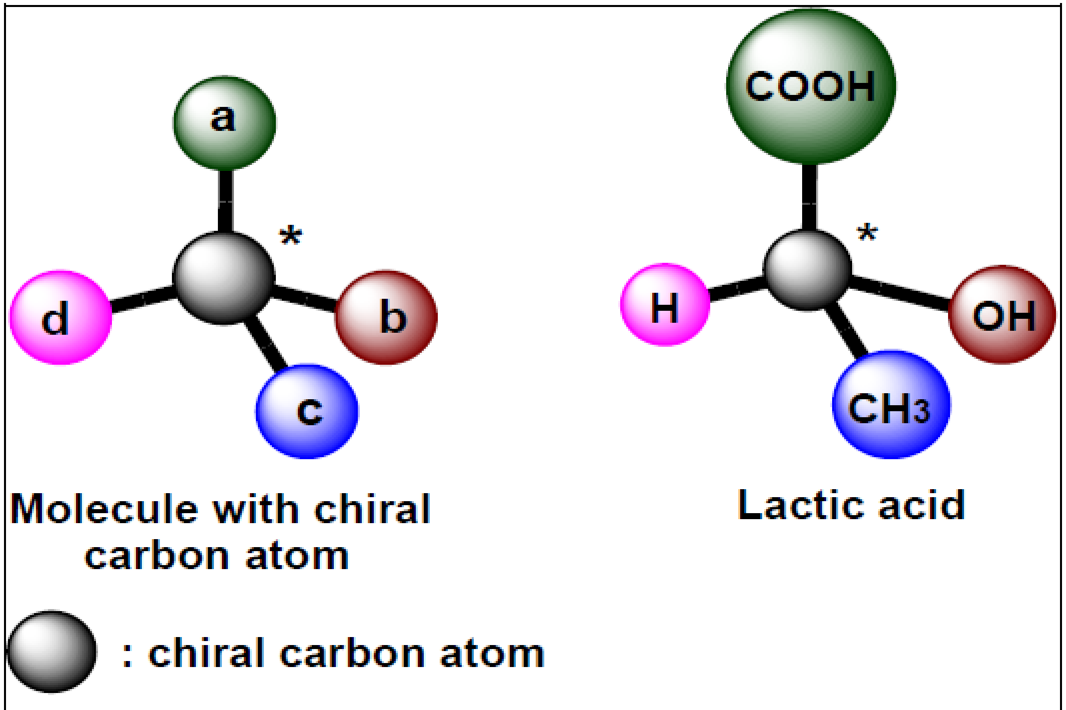
- ✓ **Optical Activity:** the ability of some compounds to rotate plane polarized light.
- ✓ Le bel and Van't Hoff in 1874 proposed that the optical activity of organic compounds is due to the presence of asymmetric carbon atoms.

☐ Optical Isomerism due to asymmetric carbon atoms

- These isomers do not differ in their chemical properties and most physical properties. However, they differ in their action towards plane polarized light.
- Plane polarized light has all the light rays vibrating in one plane and the property, because of which certain substance rotate its plane of polarization, is known as **optical activity**.

❑ Compounds with one asymmetric (chiral) carbon atom:

- Chiral carbon atom: is a carbon atom attached to four different atoms or groups

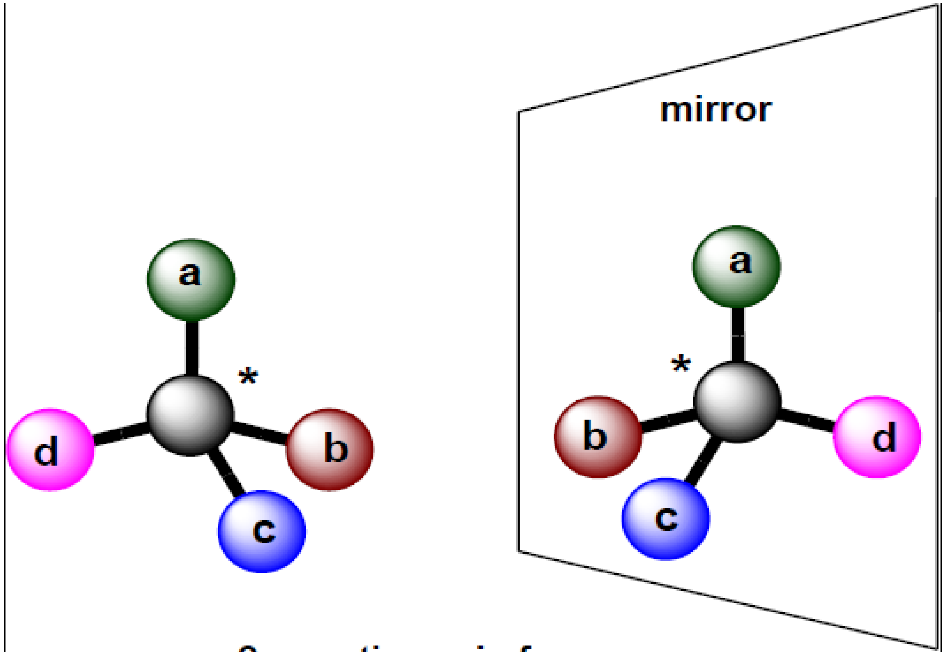


Molecule with chiral carbon atom

Lactic acid

Fig. 6.1

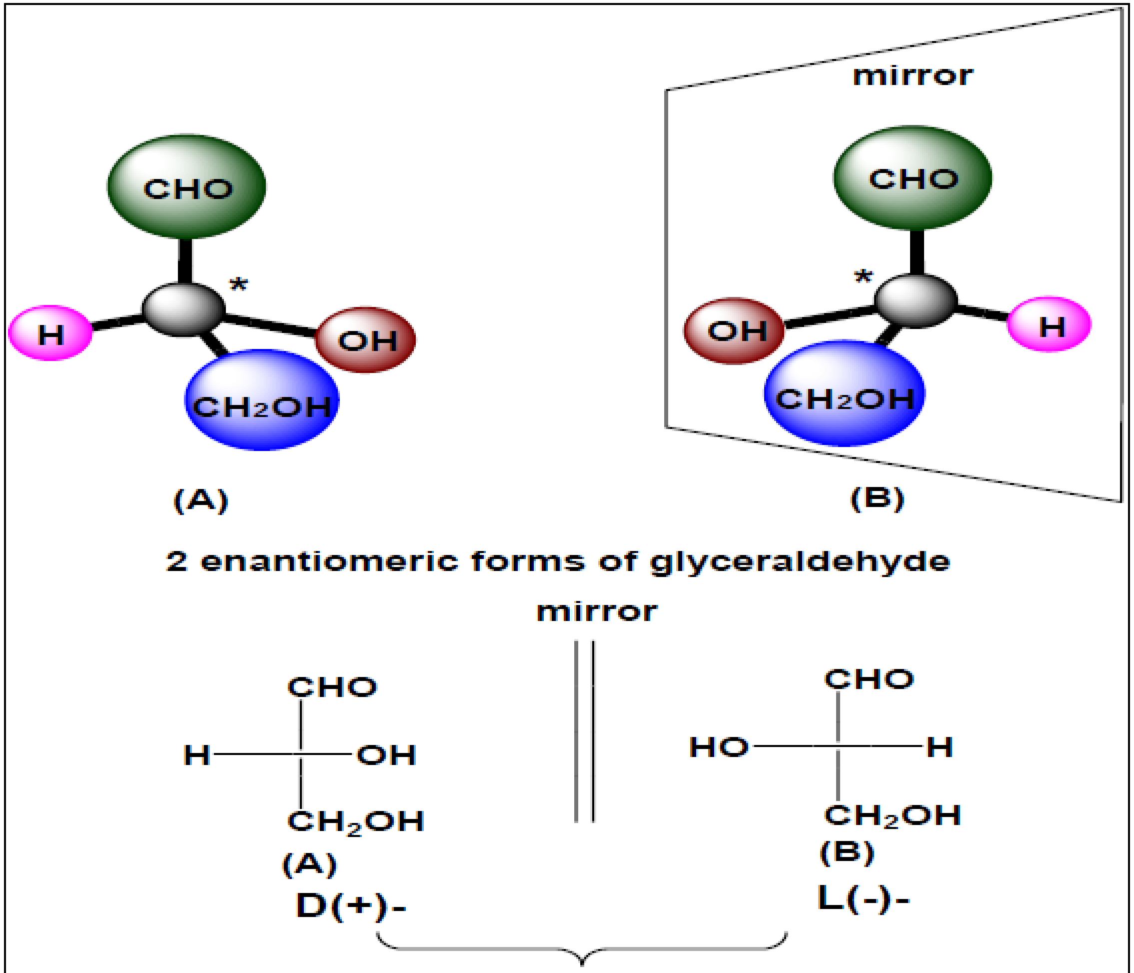
- **Enantiomers:** are stereoisomeric pair have the same chemical and physical properties but differ in the rotation of plane polarized light, one of them is mirror image of the other .
- **Dextrorotatory (+):** an optically active compound that rotates plane polarized light in a clockwise direction.
- **Levorotatory (-):** an optically active compound that rotates plane polarized light in a counterclockwise direction.
- **An enantiomer:** is one of a pair of stereoisomers that are related as non–superimposable mirror images.
- **Diastereoisomers:** are stereoisomers that have different chemical and physical properties in any type of environment and not to be enantiomers.



2 enantiomeric forms

Fig. 6.2

- **A racemic mixture**: is a 50:50 mixture of the 2 enantiomers of a chiral compound. It is optically inactive and its components can be separated by a process described as resolution. A racemic mixture may be prefixed by the symbols (±).



(±)Racemic mixture (A+B, 1:1)

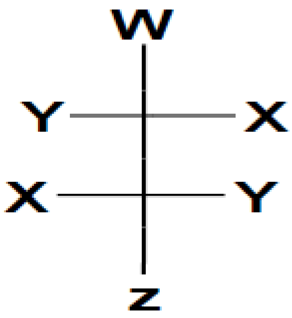
2 enantiomeric forms of glyceraldehyde

Fig. 6.3

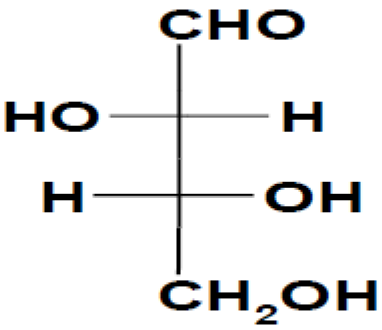
1. Glyceraldehyde exists in two enantiomeric forms (**A**) and (**B**) represented by Fischer projection.
2. An equal amounts of (**A**) and (**B**) forms give racemic mixture symbolic as (**±**).
3. A racemic mixture: is a 50:50 mixture of the 2 enantiomers of a chiral
compound.
4. In case of the two glyceraldehyde structures, the structure (**A**) with the (**OH**) group to the right is prefixed by the symbol **D** (Dextro), and the structure (**B**) with the (**OH**) group to the left is prefixed by the symbol **L** (Levo).
5. Clockwise rotation of polarized light is abbreviated to (+), anticlockwise rotation is indicated by the term (-).

❑Compounds with two or more chiral centers:

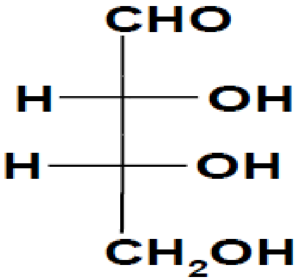
- In general, molecules with **n** different chiral centers exist in **2n** enantiomeric forms, which can be combined in pairs to form that number (**2n-1**) of racemic mixtures.
- **Ex:** the **4C** sugars with two different chiral centers are exist in 4 enantiomeric forms and as two racemic mixtures. These are known as therose and erythros e



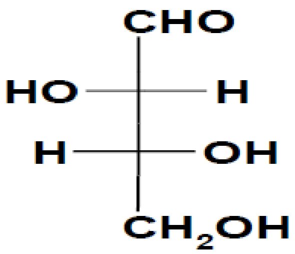
Thero-form



D-Therose

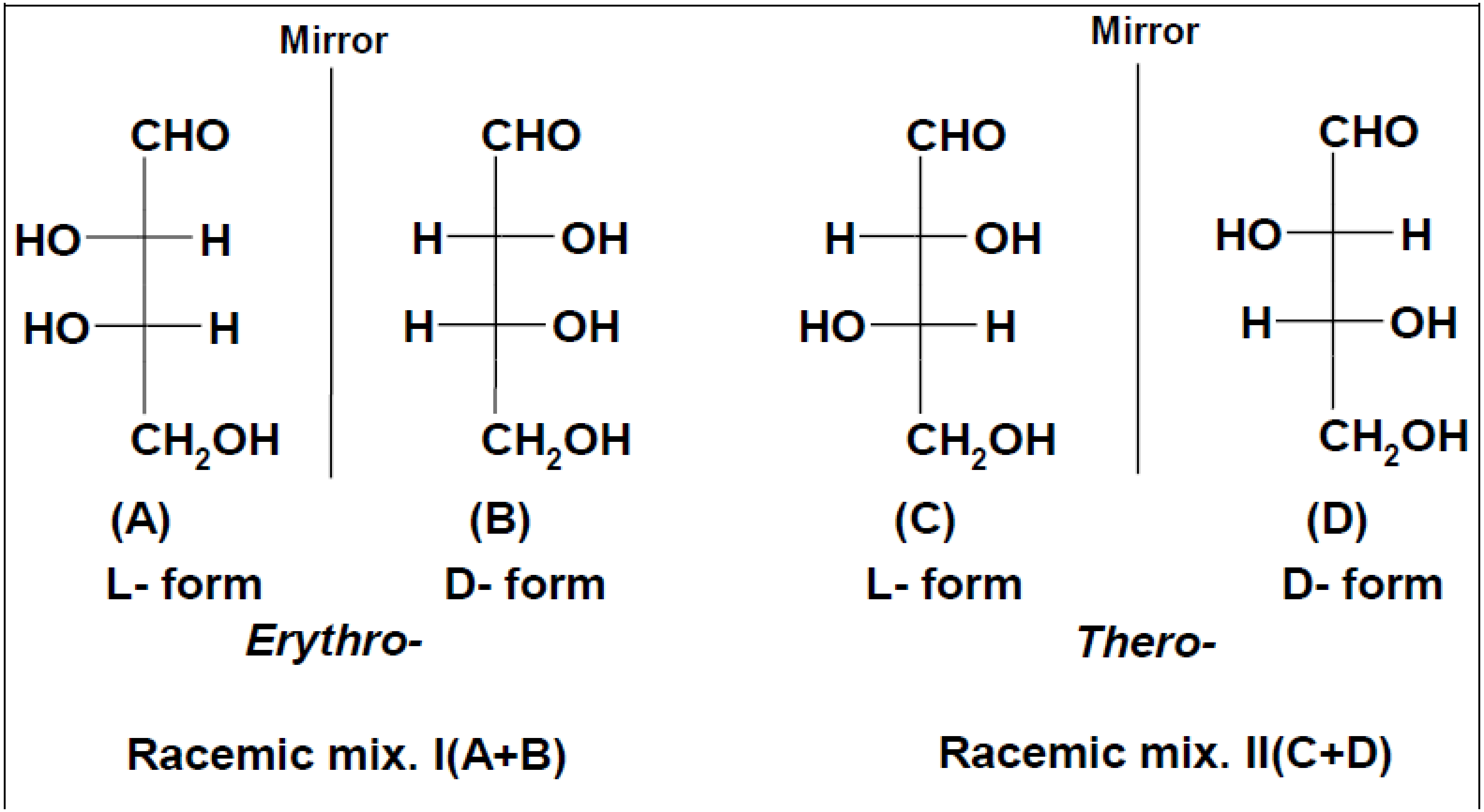


D- Erythrose



D-Therose

Erythrose exists in two enantiomeric forms (**A** and **B**) as does therose (**C** and **D**) (Fig. 6.5).



1- Structures (**A** and **B**) or (**C** and **D**) are enantiomers, while (**A** and **C**; **A** and **D**) or (**B** and **C**; **B** and **D**) are diastereoisomers.

2- When the two identical or similar groups attached to the two chiral carbons are on the same side, the compound is prefixed by (***erythro***) as in structures (**A**) and (**B**), and when the two identical or similar groups are on opposite sides, the compound is prefixed by (***thero***) as in structures (**C**) and (**D**).

❑ Compounds with two identical chiral centers, Meso-form

- A molecule that contains two chiral centers but the two ligands attached to one chiral carbon atom are the same as those attached to the second chiral atom exists in only three stereoisomers as in tartaric acid .

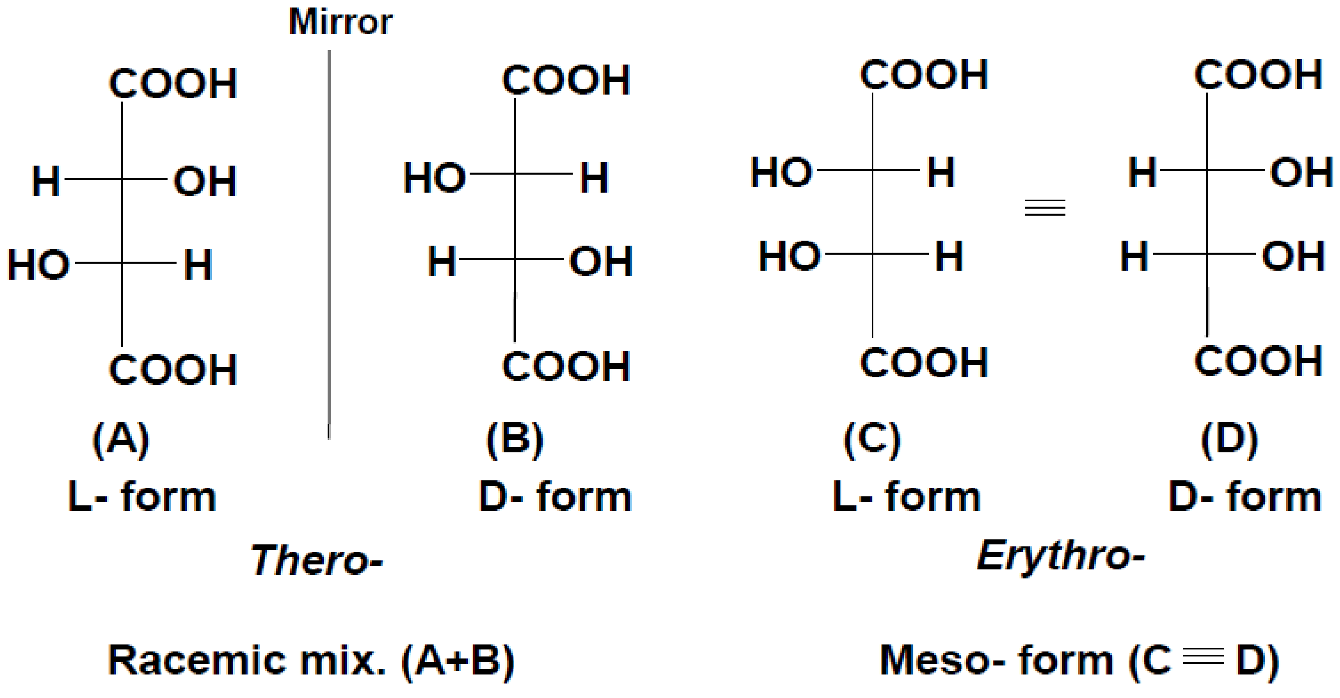
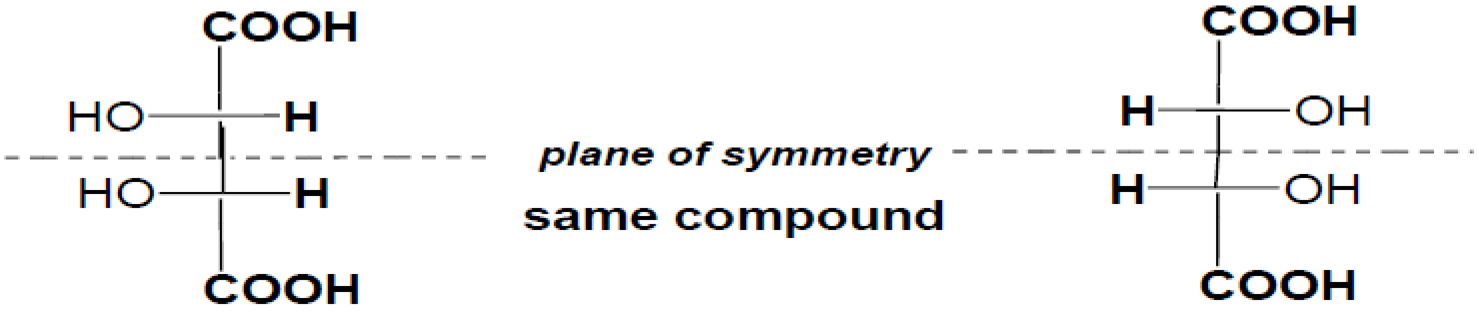


Fig. 6.6

1- The thero-isomers (**A** and **B**) are enantiomers and the one is the reflection of the other.
2- The structures (**C** and **D**) in erythro-form are in fact the same. This stereoisomer is represented correctly by the structure (**C**) or (**D**) and it is not optically active.
3- The optically inactive erythro-form is described as (Meso- Form).
4- Meso-compound contains a ***plane or center of symmetry*** dividing the molecule into two identical parts such that one is the reflection of the other.

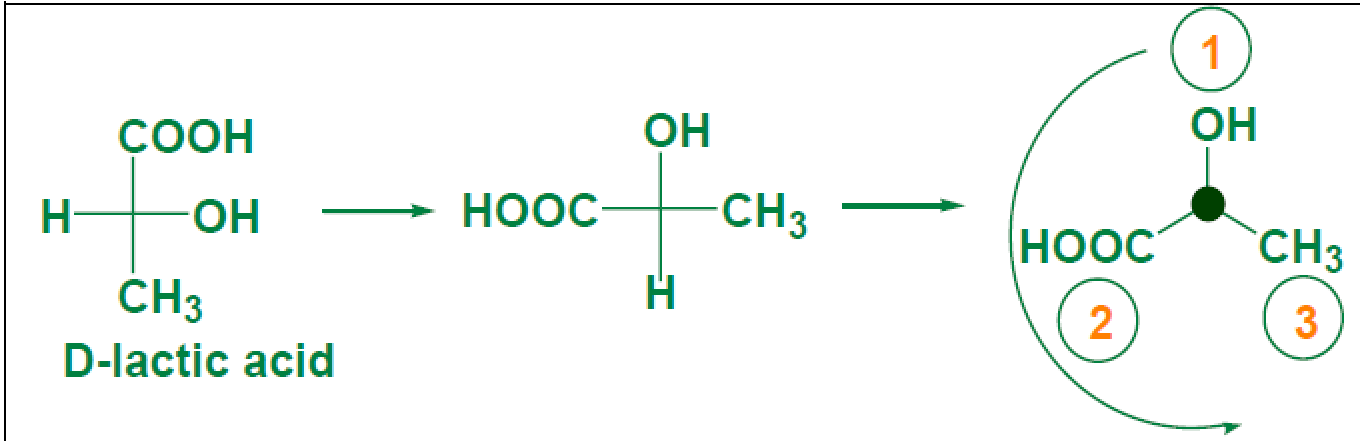


Meso- **tartaric acid**

❖(*R*) and (*S*) system

- In this system the atoms or groups linked to a chiral carbon are assigned priority on the basis of the sequence rules .

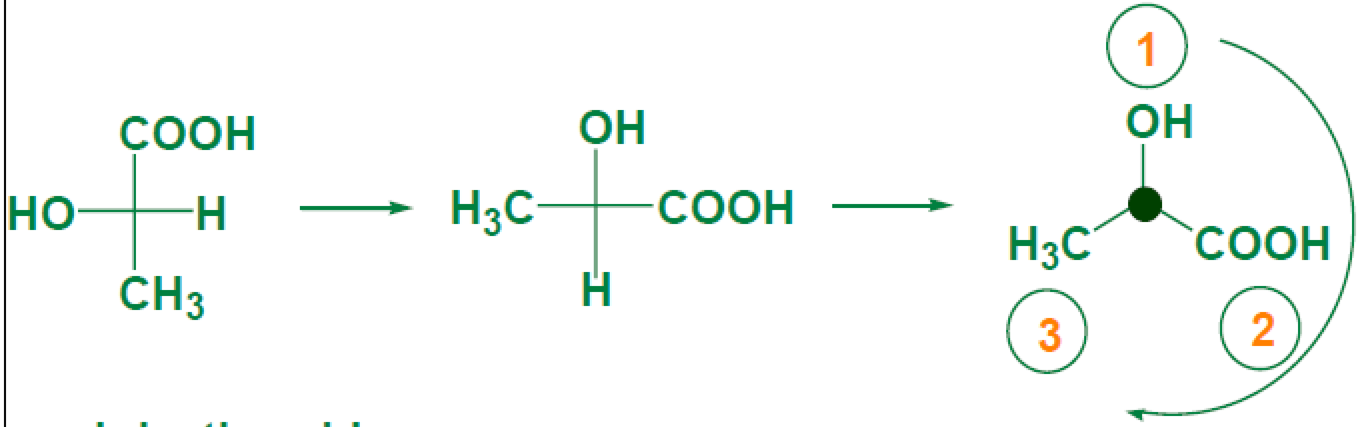
- If the arrangement of the groups (in moving from the top priority group to the second and then the third priority group) is clockwise, then the isomer has ***R***-configuration.
- If this arrangement is anticlockwise, it is assigned ***S***-configuration e.g. D-lactic acid has ***S***-configuration and L-lactic acid has ***R*** configuration. It is not necessary that the L isomer is ***S***; it can be ***S*** or ***R*** **.**



D-lactic acid

anticlockwise rotation

S-lactic acid



L-lactic acid

clockwise rotation

R-lactic acid

7. Method of stereoselective addition and elimination reactions

A- Use of stereoselective addition reactions.

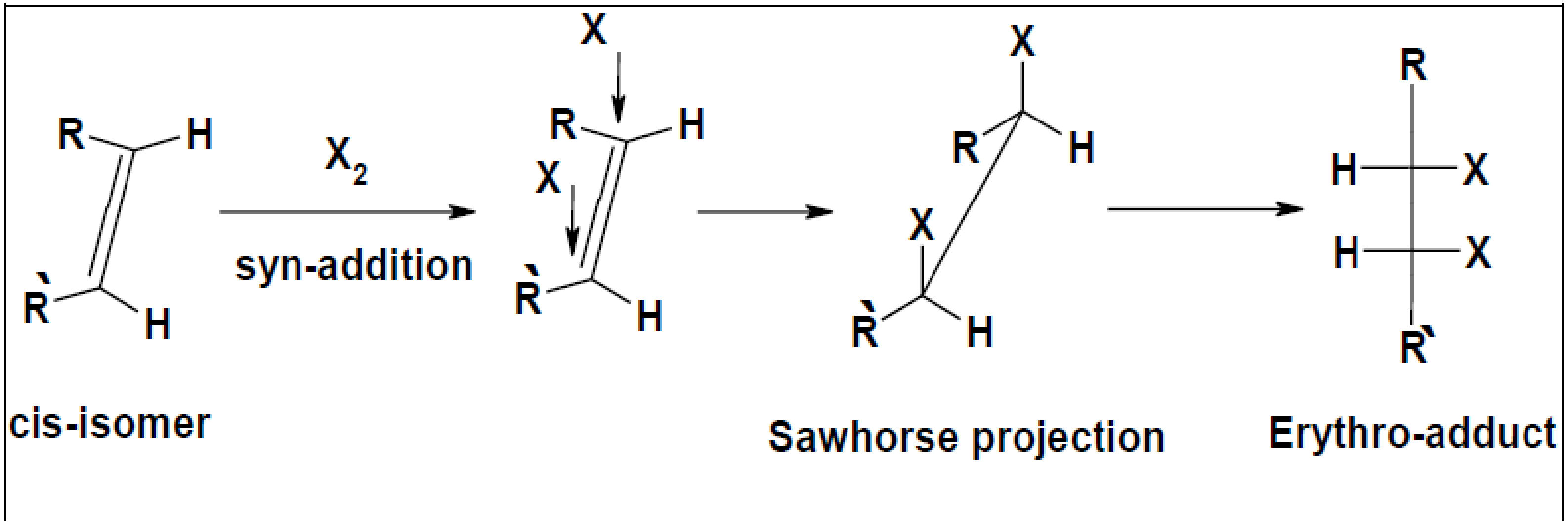
7.1 Experimental determination of the mode addition.

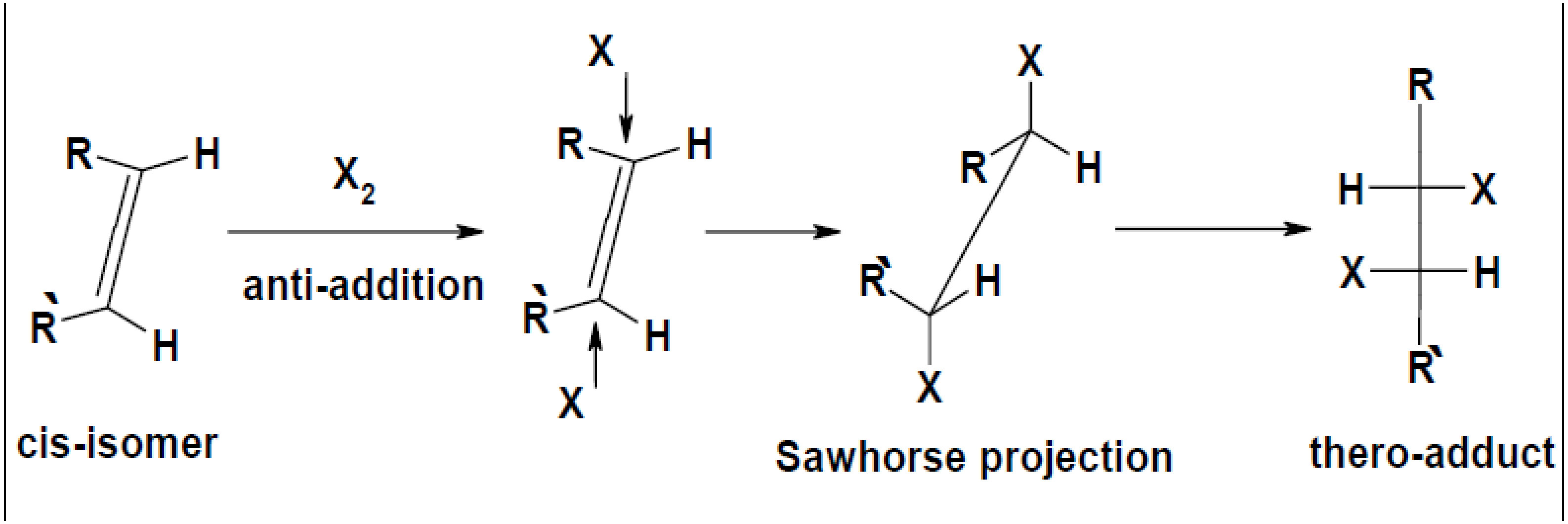
A reaction, which yields one stereoisomer of several possible stereoisomers, is called a **stereoselective** reaction. Some stereoselective addition reactions will be described such as addition of hydrogen, halogen and hydroxylation.

Simply terms will be used to indicate the stereochemical facts in addition reactions:

1- If the two groups may be added to the same side of the alkene double bond, the addition is described as ***syn***- or ***cis***-addition.

2- If the two groups may be added to the opposite sides, the addition is described as ***anti***- or ***trans***-addition (Scheme 7.1).


X2
syn-addition
cis-isomer
Sawhorse projection
Erythro-adduct


X2
anti-addition
cis-isomer
Sawhorse projection
thero-adduct

1- The above reaction is also stereospecific reaction in which different stereoisomers give stereochemically different products. i. e., the geometrical isomers give optical isomers through the addition reactions.

2- In the reaction of the type;

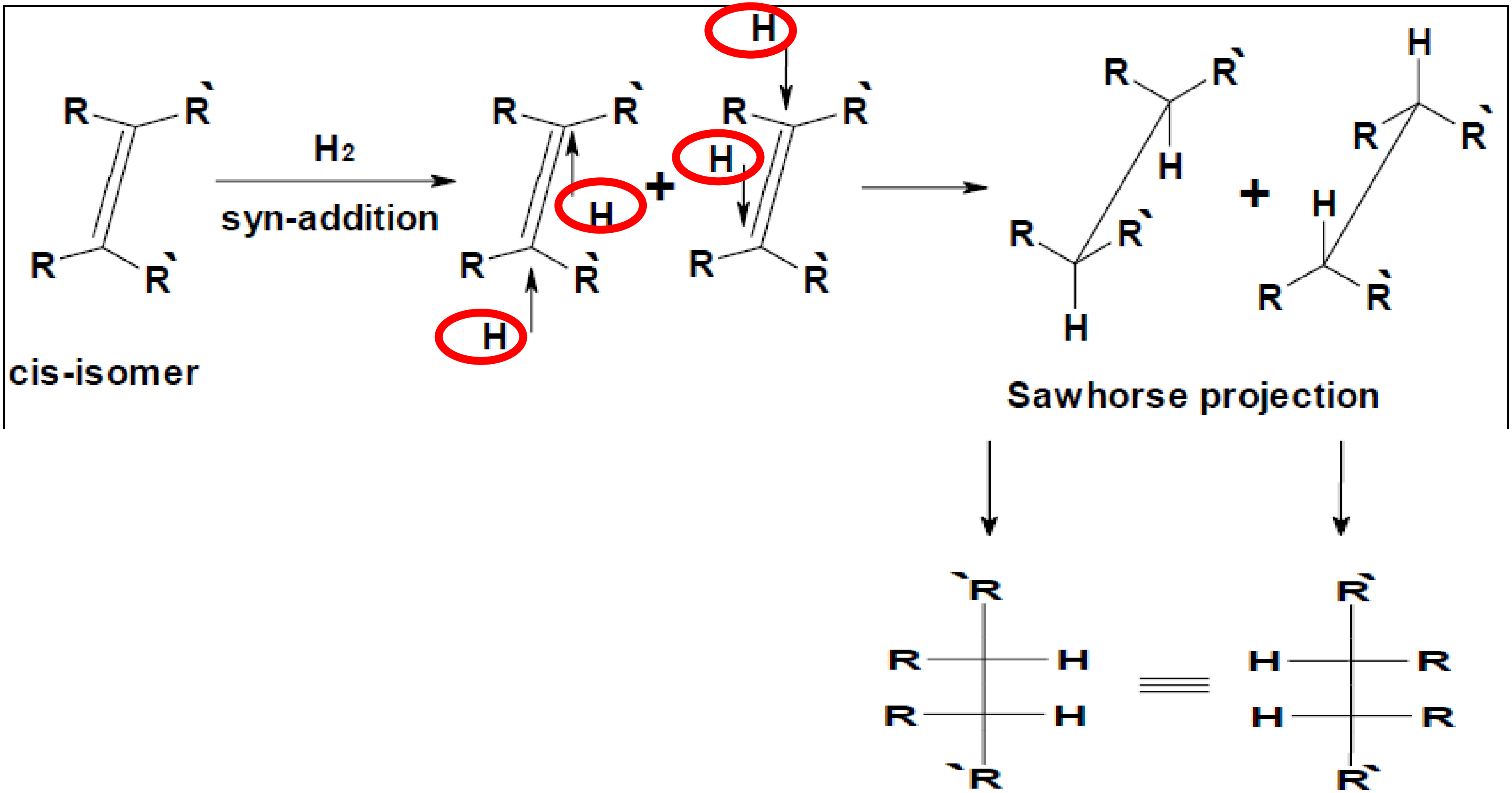
abC=Cab $\xrightarrow{\textbf{X2}}$ **abxC-Cabx .**

Racemic mix. (±) $\xleftarrow{\text{anti- addition}}$ $\boxed{\textbf{\textit{cis}}\text{-isomer}}$ $\xrightarrow{\text{syn-addition}}$ ***meso***-form

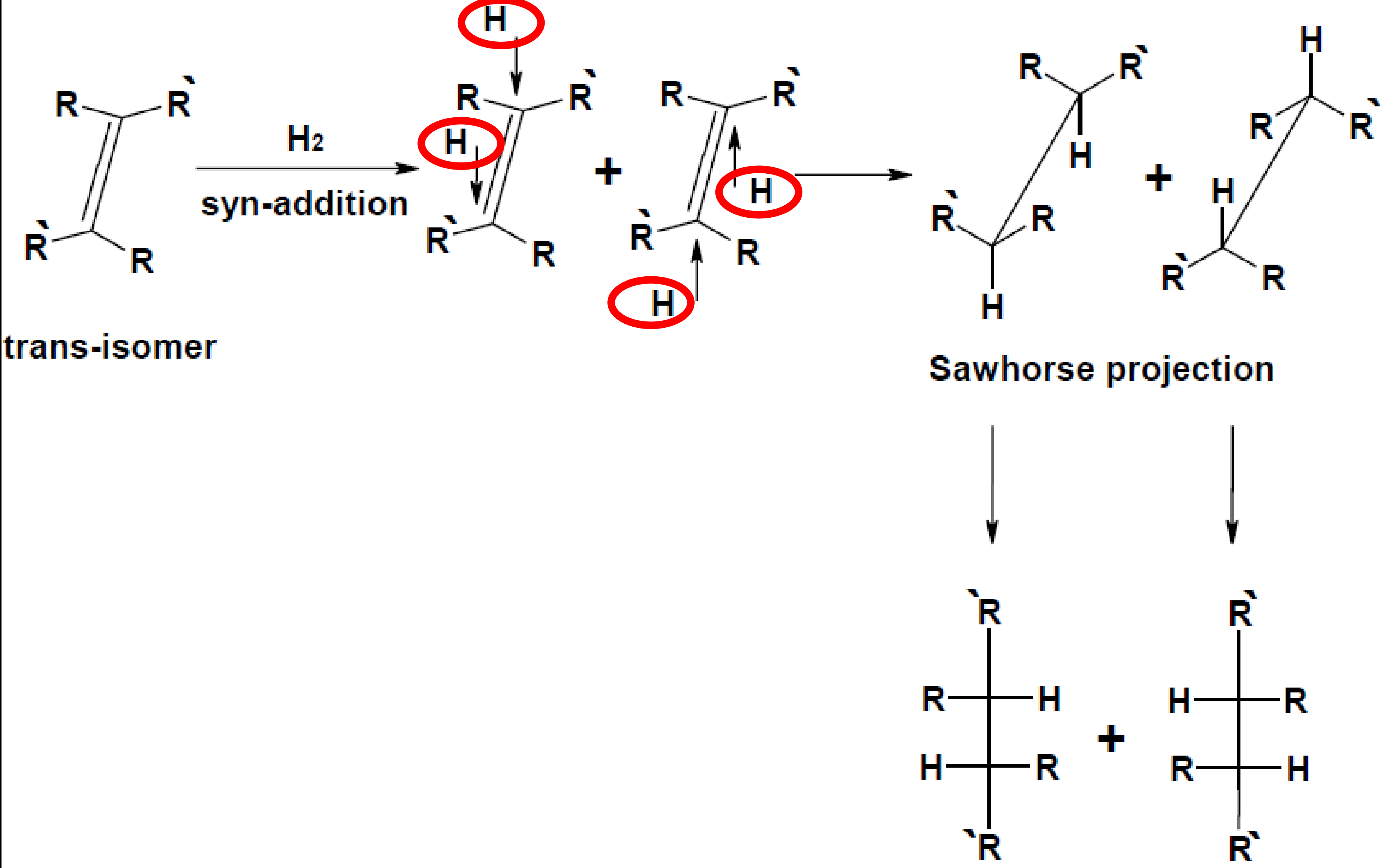
meso-form $\xleftarrow{\text{anti- addition}}$ $\boxed{\textbf{\textit{trans}}\text{-isomer}}$ $\xrightarrow{\text{syn-addition}}$ Racemic mix. (±)

(i) Hydrogenation:

Catalytic hydrogenation is usually a ***syn***-addition



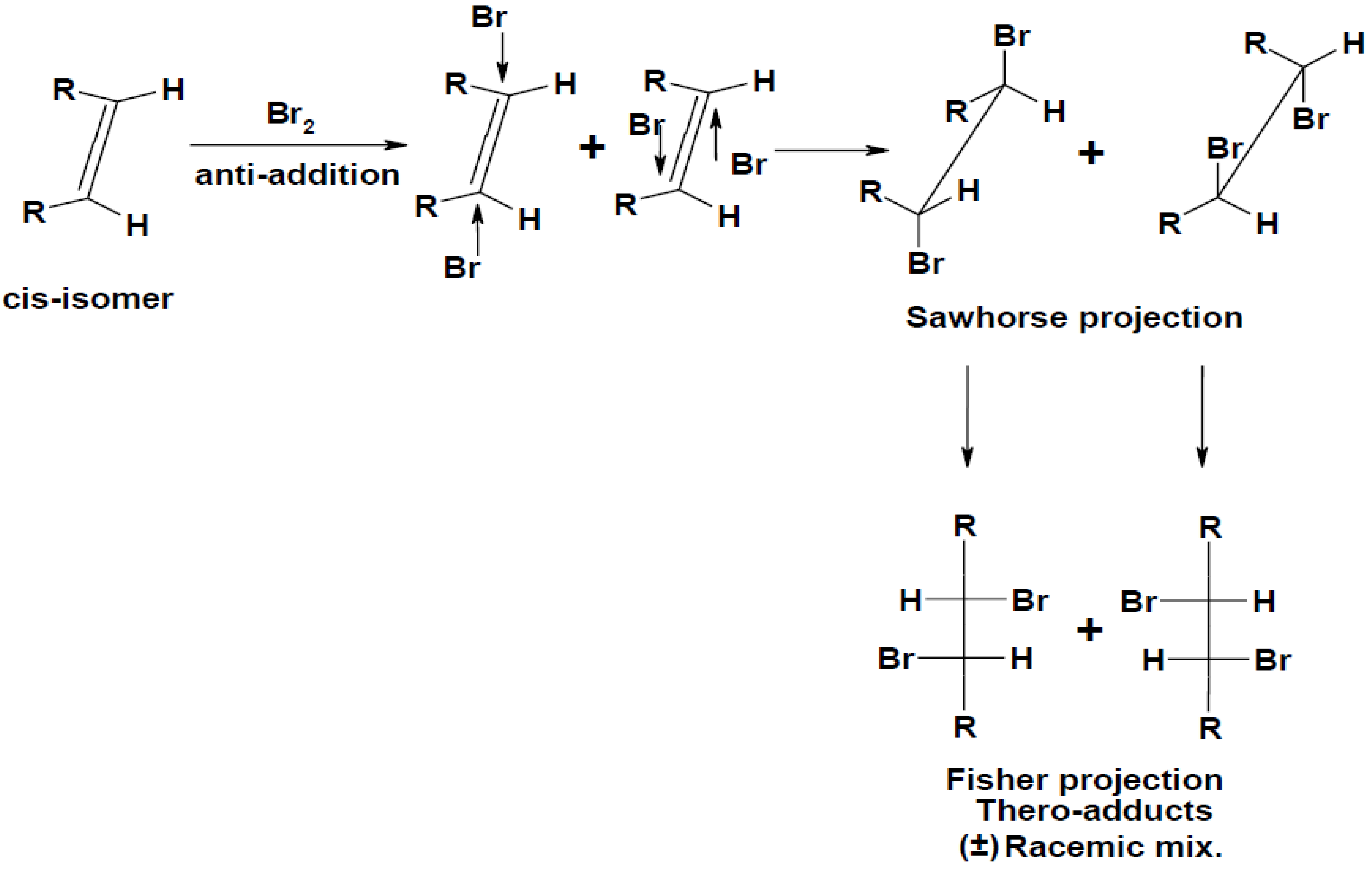
Fisher projection
Erythro-adduct
Meso-form

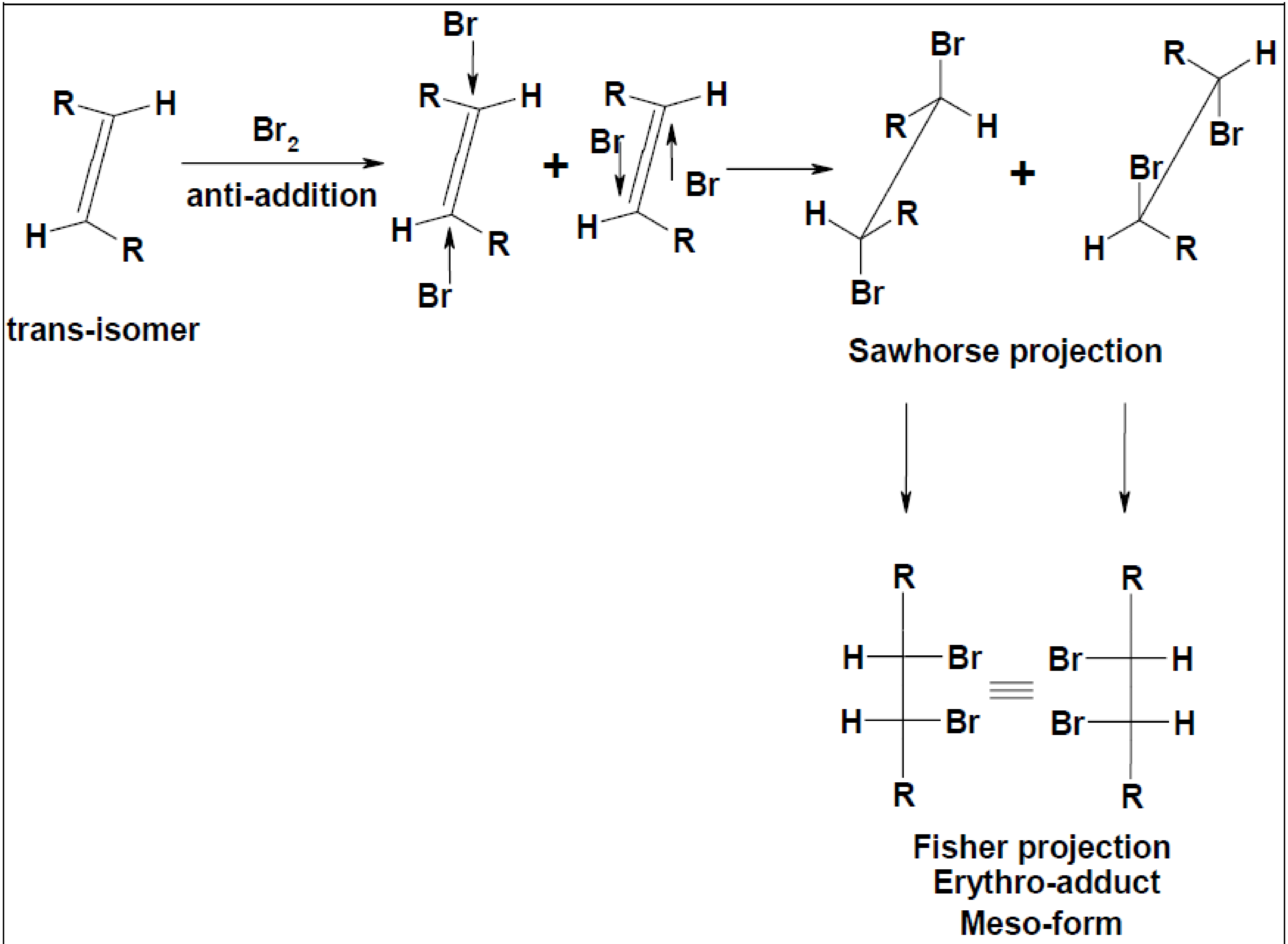


Fisher projection
Thero-adducts
(±) Racemic mixture

(ii) Halogenation (Bromination):

Bromination is usually an ***anti***-addition

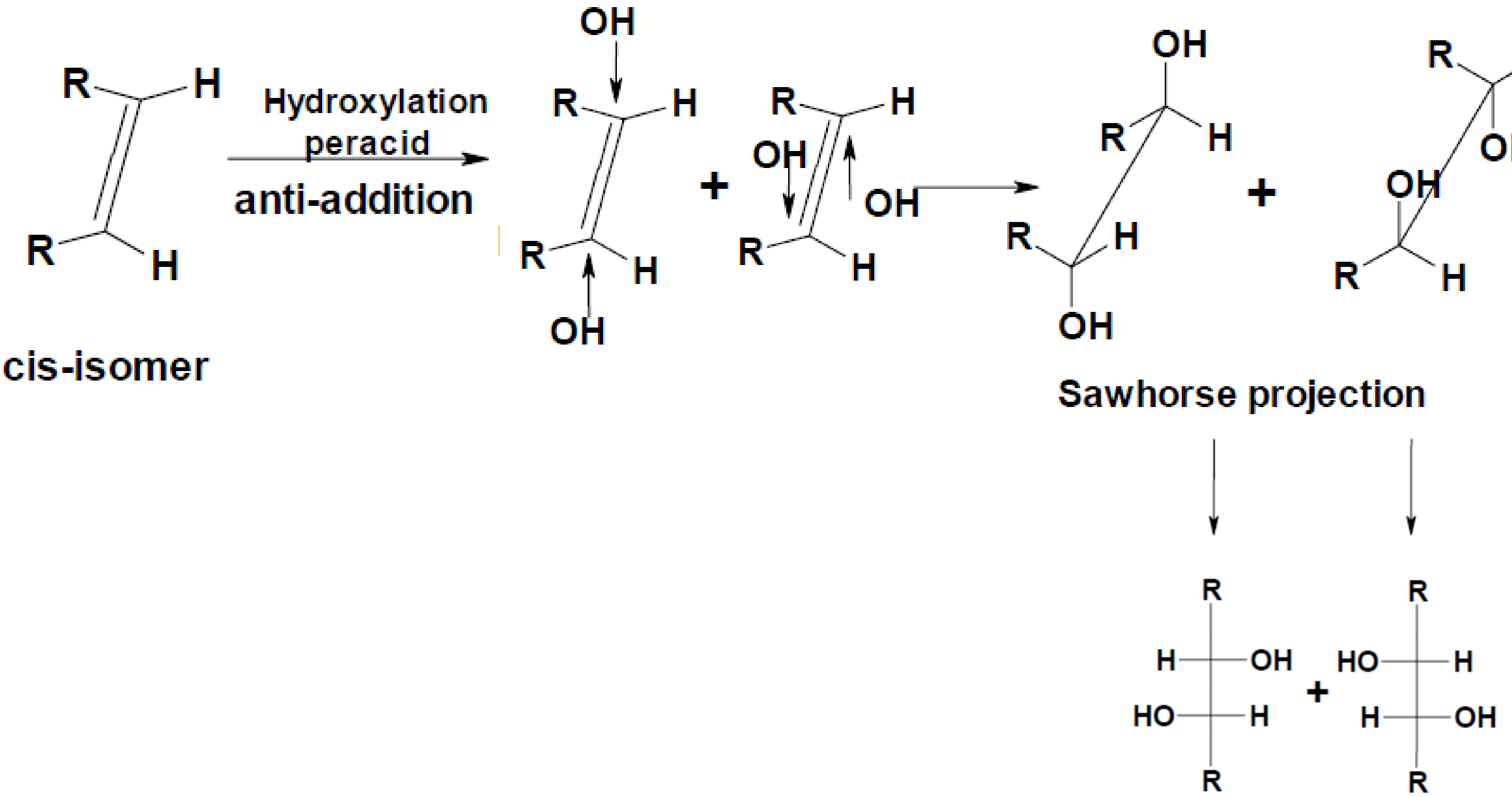



R
H
H
R
trans-isomer
Br_2
anti-addition
Br
R
H
H
R
Br
+
R
H
Br
Br
H
R
Br
R
H
H
R
Br
+
R
H
Br
Br
H
R
Sawhorse projection
R
H Br
H Br
R
R
Br H
Br H
R
Fisher projection
Erythro-adduct
Meso-form

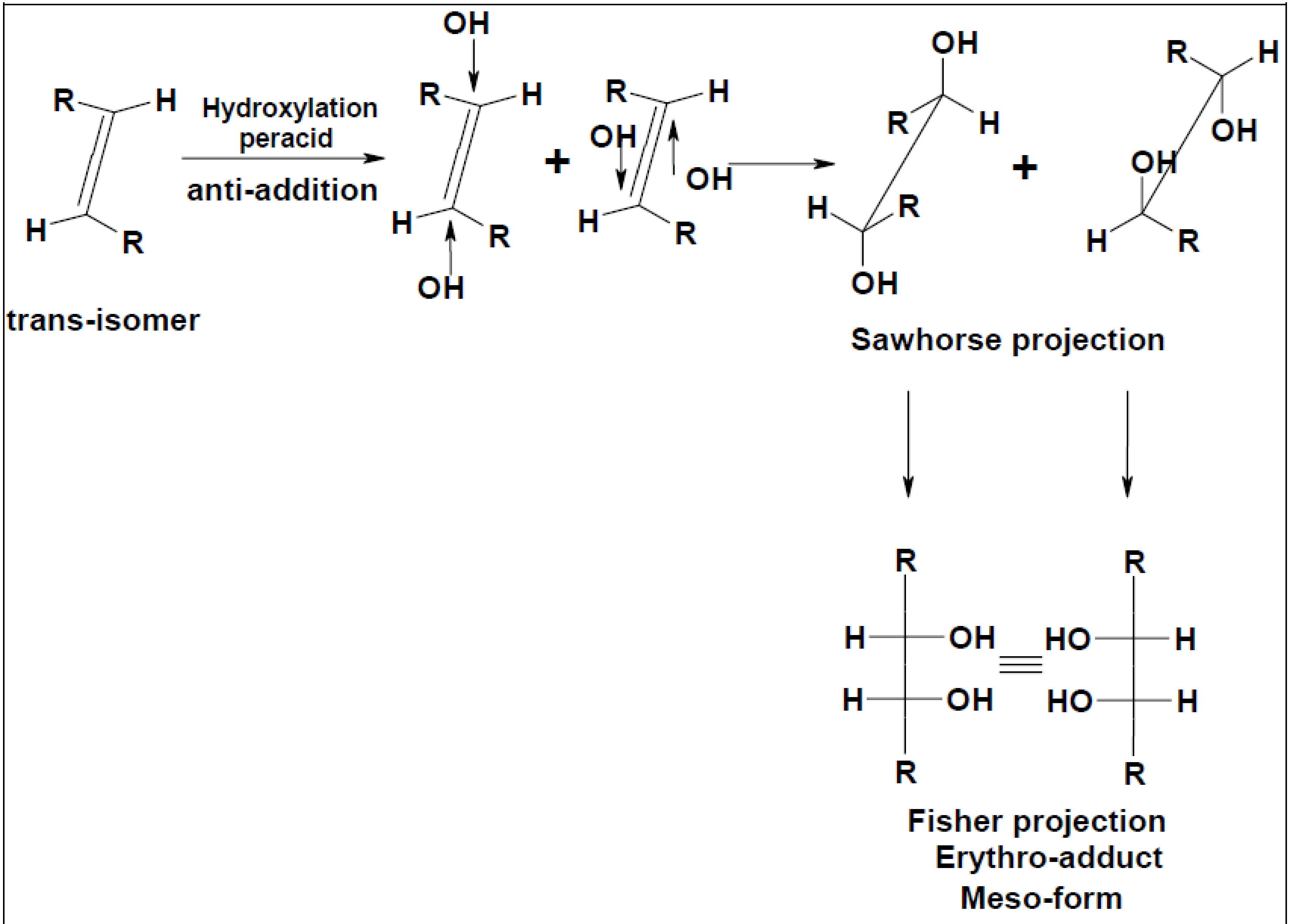
(iii) Hydroxylation:

Hydroxylation may be ***syn-*** or ***anti-*** depending on the choice of reagent.

- Hydroxylation with *peracids* is ***anti***-addition

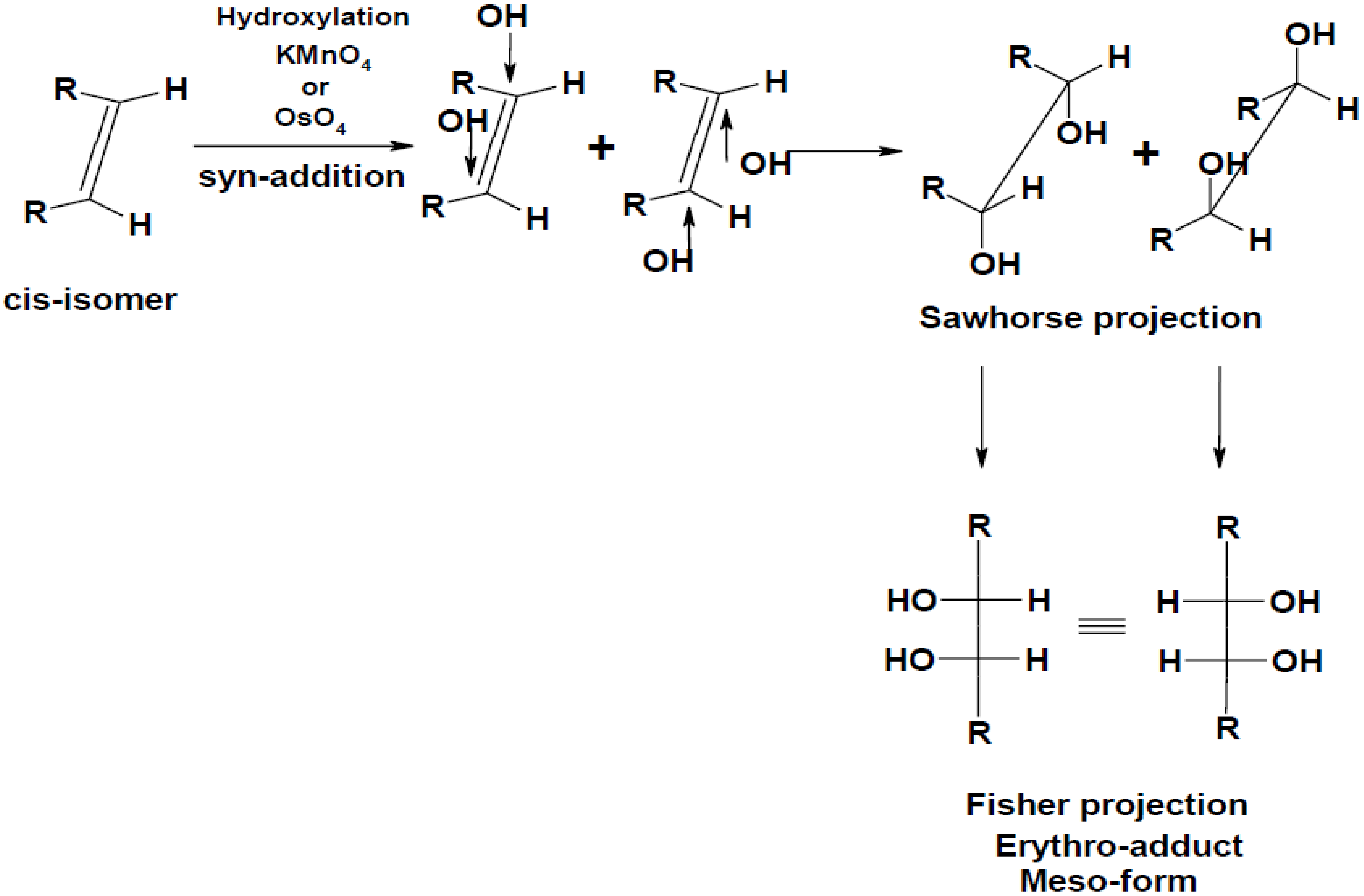


Fisher projection
Thero-adducts
(+)Racemic mix

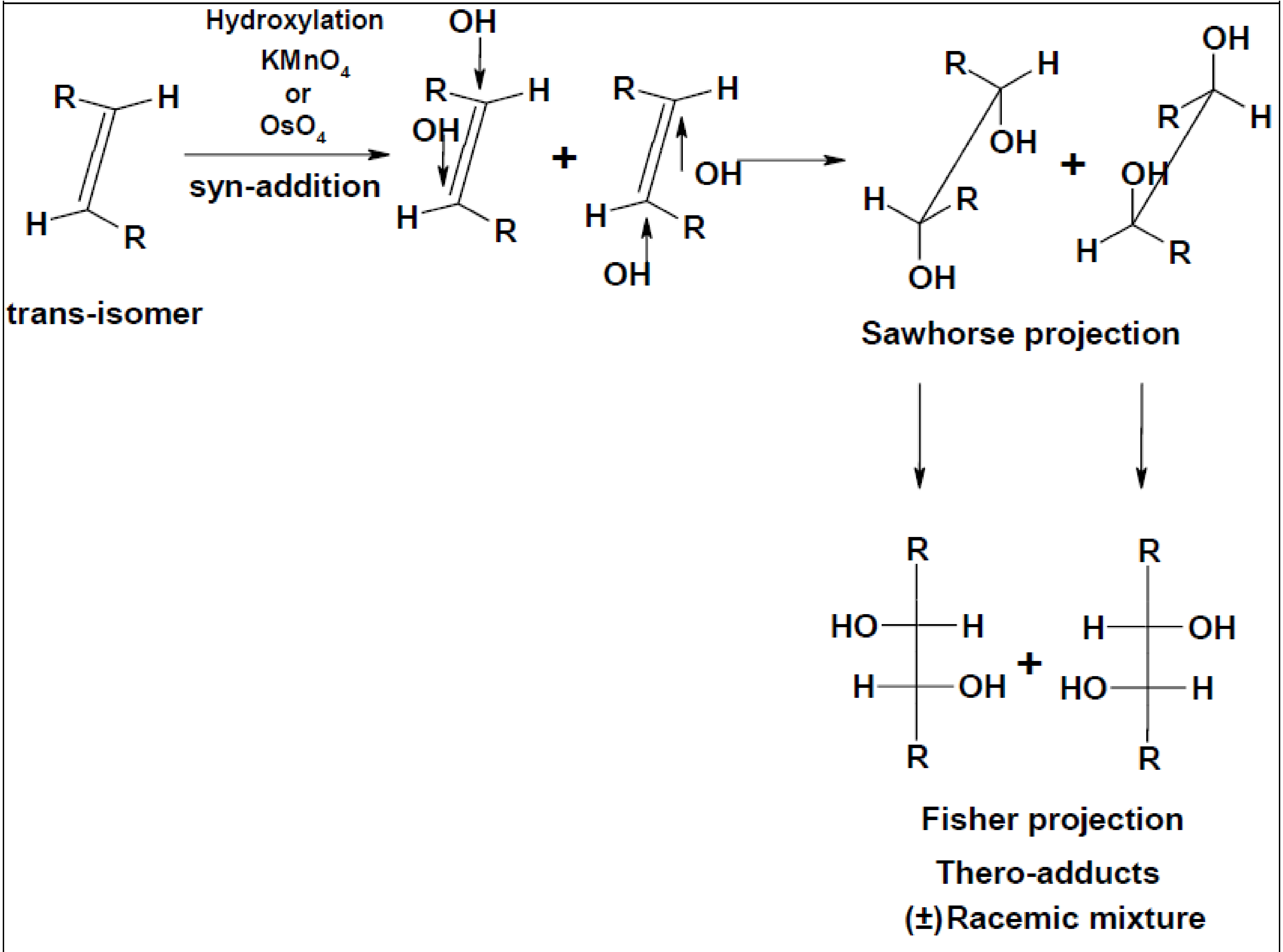

R
H
H
R
trans-isomer
Hydroxylation
peracid
anti-addition
OH
R
H
H
R
OH
+
R
H
OH
OH
H
R
OH
R
H
H
R
OH
+
R
H
OH
OH
H
R
Sawhorse projection
R
H
OH
H
OH
R
R
HO
H
HO
H
R
Fisher projection
Erythro-adduct
Meso-form

Scheme 7.7

- Hydroxylation with **$KMnO_4$** and **OsO_4** is ***syn*-addition**

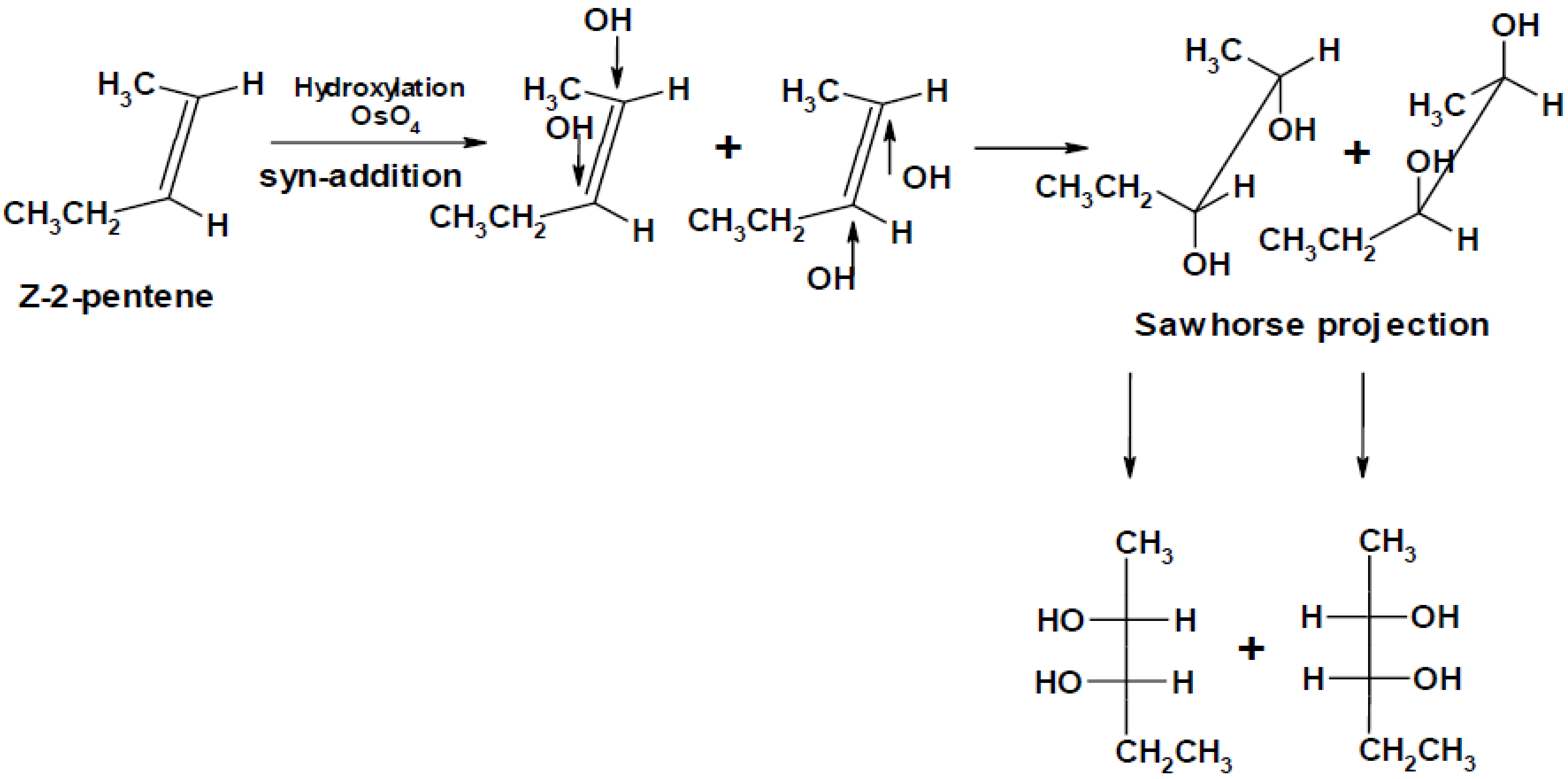


Fisher projection
Erythro-adduct
Meso-form


Hydroxylation
KMnO4
or
OsO4
syn-addition
trans-isomer
R
H
OH
+
Sawhorse projection
HO
Fisher projection
Thero-adducts
(±)Racemic mixture

Note that**:** If alkene used in the addition reactions is unsymmetrical, a racemic mixture of two erythro-adducts will be produce instead of a meso-form in any type of addition.

Ex: Hydroxylation of Z-2-pentene in presence of OsO_4



Fisher projection
Erythro-adducts
(±) Racemic mixture

7.2 Application of stereospecific addition for determination of configuration

The geometrical isomers are subjected to the same stereospecific reaction and the nature of the products investigated.

If the addition was ***anti***-addition, the alkene-isomer which gives a **racemic** mixture (±), it would be ***cis***-isomer, and the alkene-isomer which gives a **meso**-product , it would be the ***trans***-isomer, and *vice-versa* when the addition was ***syn***-addition.

Summary

- **Stereoselective reaction:** a reaction, which yields one stereoisomer of several possible stereoisomers.
- **Stereospecific reaction:** a reaction in which different stereoisomers give stereochemically different products.
- **Catalytic hydrogenation:** is usually a ***syn***-addition.
- **Bromination:** is usually an ***anti***-addition.
- **Hydroxylation:** may be ***syn***- or ***anti***- depending on the choice of reagent.
- **Hydroxylation:** with *peracids* is ***anti***-addition.
- **Hydroxylation:** with **$KMnO_4$** and **OsO_4** is ***syn***-addition.