Stereochemistry of organic compounds

Stereochemistry is a branch of chemistry which deals with the study of three-dimensional arrangement of atoms or groups in molecules. The isomers which have the same molecular and structural formula but differ in the structural arrangement of groups or atoms in space are known as stereoisomers. The phenomenon due to which these stereoisomers exist is called stereoisomerism.

Types of stereoisomerism

There are three types of stereoisomerism,

i) Optical isomerism
ii) Geometrical isomerism
iii) Conformational isomerism

i) Optical isomerism

The stereoisomers which have the same physical and chemical properties but differ in optical rotation of plane polarized light, are called optical isomers and the phenomenon is called optical isomerism.

E.g. Lactic acid

\[ \theta = \frac{\theta}{(C \times l)} \]

Therefore, optical rotation is always expressed in terms of specific rotation which can be defined as, optical rotation produced by solution having concentration unit (1) and placed in polarimeter tube having length unit. It is expressed in terms of \([\alpha]\)

\[ [\alpha]_\lambda = \frac{\theta}{(C \times l)} \]
Where, $\theta =$ observed angle  
\[ C = \text{Concentration of solution,} \quad t = \text{temp.} \]
\[ l = \text{length of polarimeter tube,} \quad \lambda = \text{wavelength} \]

under given set of conditions specific rotation is constant and it is characteristic of that compound.

**Plane polarized light**: Ordinary light consist of waves vibrate in all directions. When such ordinary light is passed through nicol prism we get light in which waves are vibrates in only one direction, such light is called plane polarized light.

**Elements of symmetry**
There are three elements of symmetry,

1) Plane of symmetry
2) Centre of symmetry
3) Alternating axis of symmetry.

If molecule contains any one of these element of symmetry, then the molecule is called to be symmetric and it is optically inactive.

1) **Plane of symmetry**

   It is an imaginary plane, which divides the molecule into two equal parts which are mirror images of each other. The presence of plane of symmetry makes the molecule optically inactive.
ii) Centre of symmetry

It is an imaginary point inside the molecule from which similar groups are lie opposite at equal distance.

e.g. i) 2,4, dimethyl-1,3-cyclobutane dicarboxylic acid

iii) Improper (or alternating) axis of symmetry

The molecule is said to have ‘n’ fold alternating axis of symmetry, when it is rotated through \((360/n)^0\) and then reflected in plane perpendicular to axis of rotation, then identical structure results.

e.g. i) 1,2,3,4-tetra methyl cyclobutane

Structure similar to (I)
In above example if we rotate the molecule through \((360/4) \times 90^\circ\), then we get \(\text{str.}( \ II \ )\) and further reflection of \(\text{str.}( \ II \ )\) in plane perpendicular to axis of rotation, then we get \(\text{str.}( \ III \ )\), which is similar to \(\text{str.}( \ I \ )\). Thus 1,2,3,4-tetra methyl cyclobutane is said to have four \(4^\circ\) fold alternating axis of symmetry.

**Chiral Center**

A carbon to which four different atoms or groups are attached is called chiral (asymmetric) carbon. It is represented by an asterisk mark \((^*\)\). The presence of chiral carbon is necessary condition for optical activity.

*\(\text{e.g.}\) lactic acid contains chiral carbon and it optically active.*

![](image)

The presence of chiral enter makes the molecule asymmetric (dissymmetric). But every time this is not true, because there are some optically active molecules which do not contain chiral center.

*\(\text{e.g.}\) Cumulene*

![](image)

Thus presence or absence of chiral center is not sufficient condition for optical activity. The necessary and sufficient condition for optical activity is chirality i.e. molecule should not superimpose on its mirror image.

- Left and right hands are an example of non-superimposable mirror images.

**Optical isomerism in tartaric acid**

\(\text{HOOC-Ch(OH)-Ch(OH)-COOH}\)

Tartaric acid contains two chiral carbons hence there are four\((2^2)\) possible stereoisomers. They are represented as,
Formulae (I) and (II) are non superimposable mirror images, so they are enantiomers and optical isomer. If (I) is dextrorotatory, then (II) is laevorotatory.

Formulae (III) and (IV) are also mirror images, but by turning (III) upside down through 180°, we get (IV), So (III) and (IV) represent one and the same, so they are not enantiomers.

Thus for tartaric acid there are only three stereoisomers and they are represented as,

On the basis of optical activity, there are following four types of tartaric acid,

1) (+) or d-tartaric acid  (I)   It rotates plane polarized light in right or clockwise direction. Here both chiral centers act in the same direction. It is called dextrorotatory.  \[ [\alpha] = +12^0 \]

2) (-) or l-tartaric acid  (II)   It rotates plane polarized light in left or anticlockwise direction. Here both chiral centers act in the same direction. It is called laevorotatory.  \[ [\alpha] = -12^0 \]

3) Meso tartaric acid  (III)  
   It posses plane of symmetry, hence it is optically inactive. Here two chiral centers acts in opposite directions, i.e. one chiral center is dextrorotatory, while other is laevorotatory. Thus overall molecule is optically inactive. Such compounds are called Meso compounds in which optical inactivity is due to internal compensation i.e optical Rotation produced by one half of molecule is exactly nullified by other half by rotation in opposite direction and overall molecule is optically inactive.  \[ [\alpha] = 0 \]

4) dl or (+) tartaric acid  
   It is equimoler mixture of d (I) and l (II) tartaric acid. It is obtained by mechanical mixing of equal amounts of (+) and (-) isomers. It is called dl or (+) mixture. It is optically inactive.

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Here optical inactivity is due to external compensation i.e. optical rotation produced by one isomer is nullified by other isomer.

Non superimposable mirror images of stereoisomers are called enantiomers. In tartaric acid (I) and (II) are pair of **enantiomers** and they are pair of optical isomers.

Str. (I) and (III), (II) and (III) are pairs which do not exhibit mirror image relation. They are called **diastereomers**. Enantiomers have same physical properties except optical rotation, while diastereomers have different properties.

**Optical isomerism in 2,3-dihydroxy butanoic acid**

\[
\text{H}_3\text{C}-\text{CH(OH)}-\text{CH(OH)}-\text{COOH}
\]

2,3-dihydroxy butanoic acid contains two chiral carbons hence there are four \(2^2\) possible stereoisomers. They are represented as,

(I) \hspace{1cm} (II) \hspace{1cm} (III) \hspace{1cm} (IV)

Formulae (I) and (II) are non superimposable mirror images, so they are enantiomers and optical isomer. If (I) is dextrorotatory, then (II) is levorotatory. Degree of rotation for (I) and (II) is same but in opposite direction. Equimoler mixture of (I) and (II) forms dl mixture and it is optically inactive.

Formulae (III) and (IV) are also non superimposable mirror images, so they are enantiomers and optical isomer. If (III) is dextrorotatory, then (IV) is levorotatory. Degree of rotation for (III) and (IV) is same but in opposite direction. Equimoler mixture of (III) and (IV) forms dl mixture and it is optically inactive.

Str. (I) and (III), (II) and (III), (I) and (IV), and (II) and (IV) do not mirror images and are pairs of diastereomers.

**Enantiomers OR optical antipodes OR enantimorphs**

A pair of nonsuperimposable mirror images of stereoisomers are called enantiomers. They are optical isomers and optically active.

e.g. lactic acid contains one chiral carbon and there is one pair of enantiomer.
Enantiomers have following properties,

i) They cannot interconverted without breaking of bonds.

ii) They are nonsuperimposable mirror images,

iii) They are optically active,

iv) They have similar physical properties e.g. M.P., B.P., density etc. but they differ in their action on plane polarized light. If one enantiomer is dextrorotatory, then other is levorotatory.

v) They form crystals of identical geometry but crystals of one enantiomer is mirror image of other.

vi) Compound containing one chiral carbon contains one pair of enantiomer. The number of enantiomers increases with number of chiral carbons.

vii) Equimolar mixture of enantiomer forms racemic mixture, which is optically inactive.

**Diastereoisomers**

Stereoisomers which do not exhibit mirror image relation with each other are called Diastereoisomers.

E.g. 2,3-dihydroxy butanoic acid contains two chiral carbons hence there are four ($2^2$) possible stereoisomers. They are represented as,

\[
\begin{align*}
\text{(I)} & \quad \text{(II)} & \quad \text{(III)} & \quad \text{(IV)} \\
\text{(-) lactic acid in sour milk} \quad & \quad \text{(+)} \text{ lactic acid in muscles} \\
\end{align*}
\]

Str. (I) and (III), (II) and (III), (I) and (IV), and (II) and (IV) do not have mirror image relation, hence they are pairs of diastereomers.
i) The compound containing only one chiral carbon do not have diastereoisomers.

ii) Diastereoisomers contain more than one chiral carbons and number of diastereoisomers increases with increase in chiral carbons.

iii) Distereoisomers may or maynot be optically active.

iv) Distereoisomers posses different physical properties like M.P, B.P., density, specific rotation etc.

v) They show similar but not identical chemical properties.

vi) A molecule containing two or more similar chiral carbons have less than $2^n$ diastereoisomeric pairs ($n=$ no. of chiral carbons)

*Racemic modification*

Homogeneous mixture containing equimolar quantities of pair of enantiomers of an optically active compound is called racemic mixture OR modification. It is represented as $(\pm)$ or dl.

A racemic mixture does not show optical activity. The optical inactivity is due to external compensation i.e. optical rotation produced by one isomer is nullified by other isomer by opposite rotation.

Racemic mixture can be obtained by,

i) Mechanical mixing

   d and l isomer of an optically active compound are homogeneously mixed in equimolar proportion to form racemic mixture.

ii) Laboratory synthesis

   Synthesis of an optically active compounds in Lab always yields racemic mixture.

iii) Racemisation: Spontaneous interconversion of dd-isomer into l-isomer or vice versa occurs in suitable solvent on standing. This is called racemization.

Separation of racemic modification into enantiomers is called resolution. It can be achieved by any of following methods,

a) Mechanical separation

   It is used for enantiomers which can be crystalise into mirror image crystals. They are then mechanically separated.

b) Chemical methods

   Treatment of racemic mixture of acid (or base) with one enantiomer of chiral amine (or acid) produce a mixture of diastereoisomeric salts, which differ in physical properties and can be separated.

c) Biochemical methods

   Enzymes are bio-catalysts and are specific i.e. they selectively consumes only one of the enantiomer leaving behind the other.
Geometric isomers

Stereoisomers which arises due to restricted rotation are called geometrical or ci-trans isomers and the phenomenon is called geometrical isomerism. Restricted rotation is around double bond or single bond in ring.

e.g. The most likely example of geometric isomerism is but-2-ene. In one case, the CH₃ groups are on opposite sides of the double bond, and in the other case they are on the same side.

![Geometric Isomers Example](https://via.placeholder.com/150)

The isomer in which two similar groups are on same side of double bond or ring plane is called ‘cis’, while the isomer in which two similar groups are on opposite side of double bond or ring plane is called ‘trans’.

Cause of Geometrical isomerism

Restricted rotation around a C-C bond is principal cause of geometrical isomerism. Restricted rotation does not allow the movement of substituent groups over atoms in space, so their orientation in space is fixed and they exist as independent compounds.

Restricted rotation is in following case,

a) Around double bond

Pi-bond is formed by lateral overlapping of unhybridised P orbitals parallel to each other. Thus rotation around pi-bond is restricted and two different arrangements are possible around double bond like

![Double Bond Geometric Isomers](https://via.placeholder.com/150)

b) Around Single bond of ring system

Rotation around single bond of ring leading to ring rupture and hence there is also restricted rotation to cause geometrical isomerism.

**Condition to exhibit geometrical isomers**

To get geometric isomers the molecule should suffer following conditions,

1) Restricted rotation (often involving a carbon-carbon double bond or C-C bond in ring) around at least one bond in the molecule.
2) Two atoms between which there is restricted rotation should carry at least one similar group.

**Geometrical isomerism in olefinic compound** (\(>\text{C=C}<\))

The pi-bond in an alkene does not permit rotation, thus all of the atoms attached directly to the doubly bonded C in alkene lie in a plane and could be positioned on the same side or on opposite sides of pi-bond in the alkene. Such compounds are different in chemical and physical properties as well as in their geometry, and are called geometrical isomers.

e.g. In 2-butene the methyl groups can be located on the same side or on the opposite side of the double bond, giving rise to two geometrical isomers.

The isomer with the similar (methyl) groups on the same side of double bond is called the cis isomer, while the isomer with the similar (methyl) groups located on opposite sides is called the trans isomer. Trans isomers of compounds are usually more stable than cis isomers.

**GEOMETRICAL ISOMERISM IN OXIMES**

Aldehyde and ketones react with hydroxyl amine to form oxime

\[
\text{R}^1\text{R}
\text{O} + \text{H}_2\text{N}--\text{OH} \rightarrow \text{R}^1\text{R}
\text{N}--\text{OH}
\]

oxime

The oximes are of two types:
1) Aldoximes: These are derived from aldehydes. In this case, at least either R or R\(^1\) is hydrogen.
2) Ketoximes: These are derived from ketones. In this case, both R or R\(^1\) are alkyl or aryl groups only.

In oxime C & N are SP\(^2\) hybridised and in this state both C & N are joined together by double bond (one \(\sigma\) & one \(\Pi\)), out of remaining two SP\(^2\) hybrid orbitals of N, one is half filled & forms \(\sigma\) bond with \(-\text{OH}\) gr. and other is completely filled and remains nonbonding. Angle between any two SP\(^2\) hybrid orbital is 120° thus \(-\text{OH}\) joined to N does not lie on the line.

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joining C-N axis, but it lie either right or left to line joining C-N axis. Thus two different arrangements Of –OH gr. are possible in oxime and due to presence of double bond between C & N, rotation around C=N bond is restricted. Hence geometrical isomerism is possible in oximes.

\[
\text{R} = \begin{array}{c}
\text{OH} \\
\text{a} \\
\text{OH}
\end{array}
\]

**Aldoxime**

In aldoxime depending on position of –H & -OH gr. two different arrangements are possible. In aldoxime the stereoisomer in which –H & -OH gr. are on same side of double bond is Called ‘syn’, while the stereoisomer in which –H & -OH gr. are on opposite side of double bond is called as ‘anti’

\[\text{H}_3\text{C} = \begin{array}{c}
\text{N} \\
\text{OH}
\end{array} \quad \text{H}_3\text{C} = \begin{array}{c}
\text{N} \\
\text{OH}
\end{array}\]

syn acetaldoxime  

anti acetaldoxime

**Ketoxime**  In Ketoxime word ‘Syn’ and ‘anti’ are used to indicate position of group with respect to –OH gr.

\[\text{H}_3\text{C} = \begin{array}{c}
\text{N} \\
\text{OH}
\end{array} \quad \text{H}_3\text{C} = \begin{array}{c}
\text{N} \\
\text{OH}
\end{array}\]

Syn ethyl methyl ketoxime  syn methyl ethyl ketoxime

Anti methyl ethyl ketoxime  anti ethyl methyl ketoxime

**Determination of configuration of aldoxime:**

Configuration of aldoxime can be determined by acetylation method. Here aldoxime is acetylated to give acetyl derivative, which further subjected to hydrolysis With aq. Sodium carbonate. The nature of products of this reaction depends on stereochemistry of starting aldoxime i.e. syn isomer and anti isomer gives different products.

Anti aldoxime on acetylation gives α-acetyl derivative, which on hydrolysis with aq. Na₂CO₃ undergo trans elimination to give nitrile.

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while, syn aldoxime on acetylation followed by hydrolysis gives back original oxime, since in syn isomer trans elimination is not favored.

Thus by observing products of acetylation we can decide configuration of aldoxime.

- **Determination of configuration of ketoxime**
  
  Configuration of ketoxime can be determined by Beckmann transformation method.

  **Beckmann rearrangement (transformation) (B.T.)**
  
  It is acid catalysed intramolecular rearrangement of ketoxime into N-substituted amide.
  
  During this rearrangement the group anti to –OH gr. in ketoxime, migrates from C to N to form N-substituted amide.

  B.T. can be used to decide configuration of ketoxime. Here product of B.T. (N-substituted Amide) is subjected to hydrolysis, when acid and amine are formed. The group which enter in amine in final product is the group anti to –OH gr. in original ketoxime, while the gr. Which enter in acid is the gr. Syn to –OH in ketoxime. Thus by observing hydrolysis products of Beckmann transformation it is possible to determine configuration of ketoxime.
**Geometric isomerism in Alicyclic compounds**

In Ring system carbon-carbon single bond cannot be rotated freely, as rotation would cause to break the ring, hence due to this restricted rotation position of groups or atoms attached to the ring carbons is fixed and different arrangements are possible to give geometric isomerism. The isomer containing similar groups on same side of ring plane is called cis, while the isomer containing similar groups on different side of ring plane is called trans.

e.g. i) 1,2-dichloro cyclopropane

![cis and trans isomers of 1,2-dichloro cyclopropane](image)

ii) 1,3-dimethyl cyclobutane

![cis and trans isomers of 1,3-dimethyl cyclobutane](image)

**Geometric isomerism in maleic and fumeric acid**

HOOC-CH=CH-COOH Butene dioicacid consist of C=C, hence there is restriction for rotation around C=C, further doublely bonded Carbons contain at least one similar group. Thus butane dioic acid satisfies both conditions of geometric isomerism and hence they exist in following two isomers,

![cis and trans isomers of maleic and fumeric acid](image)

Cis and trans isomers of butane dioic acid differ in following physical and chemical properties,

i) The M.P., B.P and stability of cis isomer is lower than trans isomer
ii) The density, solubility, dipole moment and refractive index of cis is higher than trans form.

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While trans isomer of butane dioic acid does not form anhydride under similar conditions, because two \( -\text{COOH} \) grs. Lie on opposite side in trans isomer and cannot undergo dehydration.

Fumeric acid

Thus due to different physical and chemical behavior of cis and trans isomers of butene dioic acid these two forms can be consider as two independent acids and cis isomer is called Maleic acid, while trans isomer is called fumeric acid.

**Nomenclature of stereoisomers**

1. D and L Nomenclature system

This nomenclature is used to assign configuration of optical isomers. In this system configuration at asymmetric center is decided on the basis of position of \( –\text{OH} \) OR \( –\text{NH}_2 \) Group, i.e. if \( –\text{OH} \) OR \( –\text{NH}_2 \) of asymmetric carbon lie on our right hand side then configuration is called as D, while if \( –\text{OH} \) OR \( –\text{NH}_2 \) lie on the left hand side then configuration is L

e.g. i)

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\text{CH}_2\text{OH} & \quad \text{HO} \\
\text{D-glyceraldehyde} & \quad \text{L-glyceraldehyde}
\end{align*}
\]

ii)

\[
\begin{align*}
\text{COOH} & \quad \text{COOH} \\
\text{CH}_2\text{OH} & \quad \text{HO} \\
\text{D-glyceric acid} & \quad \text{L-glyceric acid}
\end{align*}
\]
iii) L-alanine

D and L notation represent configuration and not optical rotation.

2) R and S Nomenclature system

More advanced method for representing configuration of asymmetric center is developed by Cohn, Ingold and Prelog, called R and S system. It involves following steps,

**Step-I** Giving priority to four groups attached to asymmetric carbon by following priority sequence rule,

i) If four atoms or group attached directly to chiral carbon are different, then the atom with highest atomic number is given top priority, while the atom with lower atomic number is given lower priority.

\[ \text{e.g.} \]

\[
\begin{array}{c}
\text{Br}^2 \\
\text{I}^1 \\
\text{Cl}^3 \\
\text{H}^4
\end{array}
\]

ii) When directly attached atoms are identical, then priority is determined by considering the next atom attached to that group.

\[ \text{e.g.} \]

\[
\begin{array}{c}
\text{OH}^1 \\
\text{H}_3^2\text{CH}_2\text{C} \\
\text{H}^4
\end{array}
\]

iii) While giving priority double bond is duplicated and triple bond is triplicated

\[ \text{i.e.} \]

\[
\begin{array}{c}
\text{R}^1 \\
\text{X}
\end{array}
\]

is considered as

\[
\begin{array}{c}
\text{R}^1 \\
\text{X}
\end{array}
\]

\[
\begin{array}{c}
\text{R}^1 \\
\text{X}
\end{array}
\]

**Step-II:** Construct the model of compound and orient it such that, the lowest priority gr. is remains at the bottom (away from us) and view molecule away from lowest priority gr. Now draw the arrow in descending priority i.e. from 1 \rightarrow 2 \rightarrow 3. If arrow is in clockwise direction, then configuration is R; while if arrow is in anticlockwise direction, the configuration is S.
S configuration

If molecule contain more than one chiral center then configuration at each chiral center decided.

**Step III:** If lowest priority gr does not lie at bottom, then make equal number of rearrangement To bring lowest priority gr at bottom.

R Configuration

### 3. E and Z system

The simple convention of denoting the geometrical isomers by cis/trans descriptors is not sufficient when there are more than two different substituents on a double bond. To differentiate the stereochemistry in them, a new system of nomenclature known as the E-Z notation method is to be adopted.

According to this method, if the groups with higher priorities are present on the opposite sides of the double bond, that isomer is denoted by E.

Where E = Entgegen (the German word for 'opposite')

However, if the groups with higher priorities are on the same side of the double bond, that isomer is denoted by Z.

Where Z = Zusammen (the German word for 'together')

The letters E and Z are represented within parentheses and are separated from the rest of the name with a hyphen.

**Step by step procedure to determine the E-Z configuration:**

The following procedure is to be adopted to denote the geometrical isomers by E & Z descriptors.

* First determine the higher priority group on each end of the double bond.

* If the higher priority groups are on the opposite sides of double bond, the isomer is denoted by the descriptor, E.

* Otherwise if they are on the same side of double bond, the Z descriptor must be used.

The priorities are assigned by following **Cahn-Ingold-Prelog sequence rules (CAN rules)** described below.
* Rank the atoms directly attached to the olefinic carbon according to their atomic number. High priority is given to the atom with higher atomic number.

* If isotopes of same element are present, the higher priority is given to the isotope with higher atomic mass.

  e.g. The Deuterium isotope (H₂ or D) has more priority than protium (H¹ or H).
  The C¹³ isotope has more priority than C¹².

* If the atoms are still identical, examine the next atoms along the chain until a “first point of difference” is found. This is done by making a list of atoms linked directly to the first atom. Each list is arranged in order of decreasing atomic number. Then the higher priority is given to the list which contain atom with higher atomic number at first point of difference.

  *The multiple bonds are counted as multiples of that same atom i.e., each π bond is treated as if it were another σ bond to that type of atom.

  e.g.

  ![Illustrations diagram]

  **Illustrations:**

  1) The cis and trans 2-butenes can also be represented as Z and E isomers respectively.

  ![Illustrations diagram]

  Since the double bond is at 2nd carbon of the butene, the number 2 is used before the descriptors i.e., '2Z' or '2E'.