Stereochemistry

Ref. Books:
- Organic Chemistry - I.L. Finar Vol. 2
- Stereochemistry of Carbon Compounds - E.L. Eliel
- Stereochemistry Conformation & Mechanism - P.S. Kalsi

The branch of chemistry that deals with spatial arrangements of atoms in molecules and the effects of these arrangements on the chemical and physical properties of substances.

Stereochemistry refers to the 3-dimensional properties and reactions of molecules.

Do the compounds have the same molecular formula?

- Yes
- No

Isomers

Do the compounds have the same connectivity?

- Yes
- No

Constitutional

Stereoisomers

Can the compounds be interconverted by rotation about single bond?

- Yes
- No

Conformational

Configurational

Is the isomerism at a tetrahedral central?

- Yes
- No

Configurational

Geometric

Optical

Are the compounds non-superimposable mirror image?

- Yes
- No

Diastereomers

Enantiomers
**Stereochemistry**

Deals with:
- Determination of the relative positions in space of atoms, groups of atoms
- Effects of positions of atoms on the properties

**Sterical structure:**
- **Constitution**: differ in their bonding sequence; their atoms are connected differently.
- **Configuration**: same bonding connectivity, different arrangement in space
- **Conformation**: interconvertible by rotations about single bonds

**Definitions**
- **Steroisomers**: compounds with the same connectivity, different arrangement in space
- **Enantiomers**: stereoisomers that are non-superimimposable mirror images; only properties that differ are direction (+ or -) of optical rotation
- **Diastereomers**: stereoisomers that are not mirror images; different compounds with different physical properties
- **Optical activity**: the ability to rotate the plane of plane–polarized light
- **Polarimeter**: device that measures the optical rotation of the chiral compound

**Chiral Carbons**

- Carbons with four different groups attached are chiral.
- It's mirror image will be a different compound (enantiomer).

**Chiral**: ("handed") different from its mirror image; having an enantiomer

A chiral compound always has an enantiomer (a nonsuperimposable mirror image).

**Achiral Compounds**

A carbon atom bonded to just three different types of groups is not chiral.

When the mirror images can be superposed the compound is *achiral*. 
- Any compound that is chiral must have an enantiomer.
- Any compound that is achiral cannot have an enantiomer.

**Achiral:** ("not handed") identical with its mirror image; not chiral

- Planes of Symmetry

- A molecule that has a plane of symmetry is **achiral**.

- Mirror image is superimposable on the original molecule even it has no internal mirror plane of symmetry.
Centre of symmetry or inversion (i) or (C\textsubscript{i})

- A centre of symmetry (centre of inversion) is defined as a point within the molecule such that if an atom is joined to it by a straight line which if extrapolated to an equal distance beyond it in opposite direction meets an equivalent atom.

Stereochemistry of biphenyl derivatives

- \text{C}_6\text{H}_5 – \text{C}_6\text{H}_5

- Kaufler (1907) proposed butterfly formula

Michler and Zimmermann (1881) had condensed benzidine with carbonyl chloride and obtained a product

- According to Kaufler co-axil structure I is impossible, since the two amino-group are too far apart to react simultaneously with carbonyl chloride

- Re-investigation of these reactions by Turner et al. (1926) reported that the product obtained from benzidine and carbonyl chloride was not structure I or II, but free amino group, i.e., [NH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}C\textsubscript{6}H\textsubscript{5}NH\textsubscript{2}]CO

Barber and Smiles(1928) prepared three dimercapto biphenyls and on oxidation only 2,2'-derivatives gave diphenylene disulphide

- 4,4' derivatives shows a center of symmetry
- Dipole moment of 4,4'-dichlorobiphenyl is zero

This is only possible if the two benzene rings are co-axial
Structure of biphenyl compound

\[ \text{C}_6\text{H}_5 - \text{C}_6\text{H}_5 \]

Biphenyl or diphenyl

Optical activity of biphenyl compounds

- Conditions to exhibit optical activity for biphenyl compounds
- Neither ring must have a plane of symmetry
- Ortho-positions must be occupied by large groups or atoms

Has plane of symmetry
Optically inactive

No plane of symmetry
Optically active,

- When o-position contains **two similar groups**, the molecule is optically inactive due to presence of plane of symmetry. For example

```
HO_2C     CO_2H
\[ \text{HO}_2C - \text{CO}_2H \]
\[ \text{O}_2\text{N} - \text{CO}_2\text{H} \]
```

Optically inactive due to presence of plane of symmetry

Ring B is symmetrically substituted. A plane drawn perpendicular to ring B contains all the atoms and groups in ring A; exists a plane of symmetry and the compound is achiral.

```
\[ \text{HOOC} - \text{COOH} \]
\[ \text{Cl} - \text{NO}_2 \]
```

No plane of symmetry, chiral molecule
Diphenic acid, has a plane of symmetry
Opically inactive

Diphenic acid, has a centre of symmetry
Opically inactive

Diphenic acid is not optically active, and (II) is its most probable configuration

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**Atropisomers of biphenyl**

- Optical isomers produced due to restricted rotation about single bond is called **atropisomers**.

- Restricted rotation produce when o-position contains **two different bulky groups** and hence molecule is optically active.

- Required large energy barriers (75-105 kJ/mol) to produce separable rotational isomers

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Optically active
free rotation is possible

Optically active
F is a small atom so permit by free rotation

9,10-dihydrophenanthrene

Has been resolvable, optically active
When n=3, the molecules are highly optically stable
Chiral compounds without chiral atoms

- There are some molecules that do not contain chiral carbons but are chiral.

**Biphenyls**: some ortho substituted biphenyls are locked into one of two chiral, enantiomeric staggered conformations.

It is not always necessary for four large ortho groups to be present in order for rotation to be prevented

- Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved.

Diphenyl 2,2'-disulphonic acid, **optically active**, non-coplanar due to steric hindrance, **readily recemised on heating**

Enantiomers with no chiral carbon atoms

- Conformers that cannot interconvert (due to steric hindrance) can be enantiomers

**Diphenyl 2,2’-disulphonic acid**, optically active, non-coplanar due to steric hindrance, readily recemised on heating

- Loses its optical activity with a half-life of 9.4 min in ethanol at 25°C
**Buttressing effect**

The steric effect observed by a variable substituent in the 3’ position is called **buttressing effect**

\[
\text{Less steric hindrance} \quad \text{More steric hindrance}
\]

**Order of buttressing effect of groups:**
\[
\text{NO}_2 > \text{Br} > \text{Cl} > \text{Me}
\]

**Fischer Projections**

180° Rotation

- A rotation of 180° is allowed because it will not change the configuration.

90° Rotation

- A 90° rotation will change the orientation of the horizontal and vertical groups.
- Do not rotate a Fischer projection 90°.

**Absolute configuration of biphenyls**

(R,S-nomenclature of biphenyls)

- Since biphenyls do not owe their asymmetry to the presence of asymmetric carbon atoms, the criterion now is the presence of a chiral axis.
- To apply the sequence rule to axial chirality, with respect to an external point on the chiral axis, **groups at the near end of the axis are given precedence over groups at the far end**.
Correct tetrahedron

In correct tetrahedron

(2 interchanges)

(R)
**R,S-nomenclature of biphenyls**

- In biphenyl the two rings are perpendicular along the axis of the bond joining the rings, projection of four ortho substituents on a plane at right angles to this bond is very similar to a Fisher projection formula.
- Near groups precede far groups

- Asymmetric synthesis, (also called chiral synthesis, enantioselective synthesis or stereoselective synthesis):
  - Asymmetric is the synthesis of chiral compounds enriched in one enantiomer. It can be defined as the conversion of an achiral unit of a substrate molecule into a chiral unit, in such a way that the possible stereoisomeric products are formed in unequal amounts. Such stereocontrol can be achieved using either chiral starting materials or chiral reagents (or both).

  It is of two types:
  (a) Partial asymmetric synthesis
  (b) Absolute asymmetric synthesis
Partial asymmetric synthesis: Method for preparing optically active compounds from symmetric compounds by the intermediate use of optically active compounds, but without the necessity of resolution. In ordinary laboratory synthesis, a symmetric compound always produces the racemic modification. Marckwald (1904)

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Enantiomeric excess (ee): The excess of one enantiomer over the other in a mixture of enantiomers.

Expressed mathematically:

\[
enantiomeric\ excess = \%\ of\ major\ enantiomer - \%\ of\ minor\ enantiomer\]

Example: A mixture composed of

86% R enantiomer
14% S enantiomer

ee of the mixture = 86% - 14% = 72%

\[
e.e = \frac{d-l}{d+l} \times 100
= \frac{(excess\ of\ one\ over\ the\ other)}{(entire\ mixture)} \times 100
\]

Absolute asymmetric synthesis: The formation of an optically active compound from an inactive one, without the intermediate use of an optically active reagent is known as absolute asymmetric synthesis or absolute asymmetric decomposition (or destruction).

Kuhn and Braun (1929)

\[
\text{CH}_{3}C-COO\text{menthyl(1)} \xrightarrow{\text{Al/Hg}} \text{CH}_{3}C-C\text{COOCH}_{3}
\]

\[
\text{H}_{2}\text{C}C-C\text{COOH} \xrightarrow{\text{H}_2\text{O}} \text{H}_{2}\text{C}C-C\text{COOH}
\]

Davis and Heggie (1935)

\[
\text{C}_2\text{H}_4\text{OOC} \xrightarrow{\text{H}_2\text{O/other}} \text{C}_2\text{H}_4\text{OOC}C-C\text{COOC}_2\text{H}_5
\]

Optical Purity

Optical Purity: The optical purity is a measure of enantiomeric purity of a compound and is given in terms of its enantiomeric excess (ee). Optical purity is expressed as a percentage.

- A pure enantiomer would have an optical purity and enantiomeric excess of 100%.
- A fully racemised compound has 0% optical purity.
- If the enantiomeric excess is 90%, means 90% pure enantiomer, remaining 10% contains equal amounts of each enantiomer (i.e. 5% + 5%).
- Enantiomeric excess of a mixture of enantiomers is numerically equal to its optical purity.
Optical Purity

- Optical purity (o.p.) is sometimes called enantiomeric excess (e.e.).
- One enantiomer is present in greater amounts.

\[
\text{o.p.} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100
\]

Problem: The specific rotation of (S)-2-iodobutane is +15.90°. Determine the % composition of a mixture of (R)- and (S)-2-iodobutane if the specific rotation of the mixture is -3.18°.

\[
o.p. = \frac{3.18}{15.90} \times 100 = 20%
\]

\[
l = \text{ee} + \frac{(100-20)}{2} = 60%
\]

\[
d = \frac{(100-20)}{2} = 40%
\]

Enantiomeric Excess (e.e.)

Problem: When optically pure (R)-2-bromobutane is heated with water, 2-butanol is the product. Twice as much (S)-2-butanol forms as (R)-2-butanol. Find the e.e. and the observed rotation of the product. \([\alpha] = 13.50°\) for pure (S)-2-butanol.

Let consider \(x = \) amount of (R) enantiomer formed

\[
e.e = \frac{|d-l|}{d+l} \times 100 = \frac{2x-x}{2x+x} \times 100 = \frac{x}{3x} \times 100 = 33%
\]

We know, e.e. = o.p.

\[
o.p. = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100
\]

\[
\text{observed rotation} = \frac{33 \times 13.50}{100} = +4.5°
\]

Enantiotopic atoms or groups:

- Two atoms or groups that upon replacement with a third group give enantiomers

- Two compounds upon replacement of H by Z are not identical but enantiomeric, the hydrogens are not equivalent and are called enantiotopic hydrogens

Prochiral: There is a special term for molecules that are achiral but which can be converted to molecules with chiral centers by a single chemical substitution or addition reaction is called prochiral.

In general, both enantiomers are formed in equal amount
An \( sp^3 \) carbon with two groups same is also a **prochiral center**

- The two identical groups are distinguished by considering either and seeing if it was increased in priority in comparison with the other
- If the center becomes \( R \) the group is **pro-R** and **pro-S** if the center becomes \( S \)

**Prochiral**

**Chiral**

**Enantiotopic faces**: Flat molecules (trigonal) have two faces and are not stereochemically equivalent. Attachment of a ligand to one or the other of them gives rise to one or other of a pair of enantiomers.

**Diastereotopic atoms or groups**: Two atoms or groups in a molecule are in such positions that replacing each of them with a group \( Z \) gives rise to diastereomers, the atoms or groups are called diastereotopic.
**Diastereotopic face:** If a transformation at opposite faces of a trigonal center generates two different diastereomers, the faces are diastereotopic.

![Diastereomers](image)

**Diastereomers**

**Homotopic atoms or groups:** Aliphatic protons which are interconvertible by a rotational axis are termed homotopic and are chemically and magnetically equivalent.

![Homotopic groups](image)

**Homotopic groups** are always equivalent, they give a single NMR absorption. Homotopic groups are interchangeable by rotational symmetry. The simplest way to recognize homotopic groups is by means of a substitution test.

**Homotopic face:** If a transformation at opposite faces of a trigonal center generates two identical compounds, the faces are homotopic.

![Identical compound](image)

**Identical compound**

**Stereoselective:** Any reaction in which only one of a set of stereoisomers is formed exclusively or predominantly is called a stereoselective synthesis.

Stereoselective reactions give one predominant product because the reaction pathway has a choice. Either the pathway of lower activation energy is preferred (kinetic control) or the more stable product (thermodynamic control).

![Stereoselective reaction](image)

70-85%  30-15%
**Stereoconvergence**: It can be considered an opposite of stereoselectivity, when the reaction of two different stereoisomers yield a single product stereoisomer.

*Endo-* and *exo-* trimethylsilyl-3-phenyl-2-thiabicyclo[2.2.1] hept-5-enes and derivatives were protodesilylated with fluoride ion.

**Stereospecific**: In a stereospecific reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product.

The reaction gives a different diastereoisomer of the product from each stereoisomer of the starting material.

**Chemoselective**: When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be chemoselective.

**Regioselective**: A reaction is described as *regioselective* if an unsymmetrical alkene gives a predominance of one of the two isomeric addition products.

\[
R_2C\text{CHR}^\prime + \text{HX} \rightarrow R_2C\text{CH}_2\text{CHR}^\prime + R_2\text{CH}\text{CHR}^\prime
\]

**Major**

**Minor**

● There are three main types of selectivity
- Chemoselectivity: *which* functional group will react
- Regioselectivity: *where* it will react
- Stereoselectivity: *how* it will react (stereochemistry of the products)
Substrate and reagent control stereoselectivity

Active Substrate:
- If a new chiral center is created in a molecule that is already optically active, the two diastereomers are not formed in equal amounts.
- The reason is that the direction of attack by the reagent is determined by the groups already there.
- For certain additions to the carbon–oxygen double bond of ketones containing an asymmetric $\alpha$-carbon, it can be predicted which of two diastereomers will predominate by two rules:

Cram’s rule: The oxygen of the carbonyl orients itself between the small- and the medium-sized groups, the largest group was eclipsed with the other carbonyl substituent. The rule is that the incoming group preferentially attacks on the side of the plane containing the small group.

Felkin-Ahn model: The largest substituent places perpendicular to the carbonyl group. The major product results from the nucleophile approaching opposite to the largest substituent.
Rotate around central bond so that substituents are staggered.

- Two favoured as largest substituent (Ph) furthest from O & H
- Continue to rotate around central bond and find 6 possible conformations

- Three are disfavored due to steric hindrance of Ph or Me

Chelation-controlled carbonyl conformations

http://dept.ru.ac.bd/chemistry/roushown.htm