WELCOME

TO

FDSPharmacy
Learn and Educate

This is an Education Platform

We Provide PDF Notes for Pharmacy Students

Web Site http://www.fdspharmacy.in/

You tube https://www.youtube.com/c/FDSpharmacy

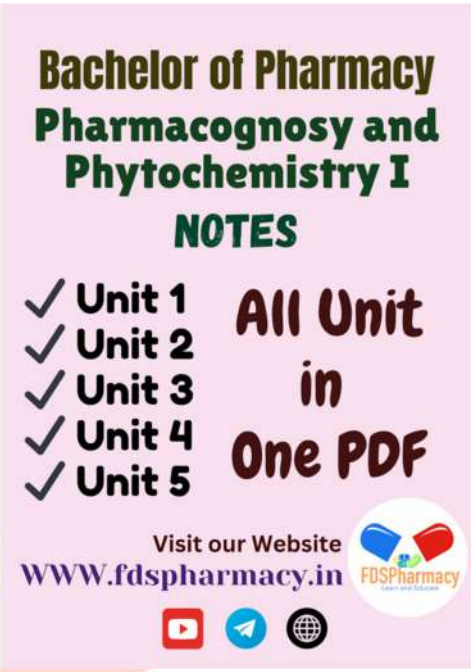
Telegram https://t.me/Fdspharmacy

App https://play.google.com/store/apps/details?id=com.FDSPharmacyMedia.FDSPharmacy

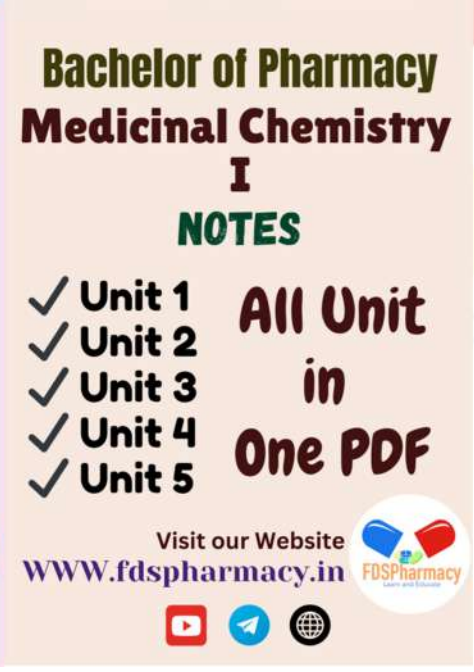
E-mail fdspharmacyinfo@gmail.com


Bachelor of Pharmacy
Physical Pharmaceutics II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdspharmacy.in
FDSPharmacy


Bachelor of Pharmacy
Pharmacology I
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdspharmacy.in
FDSPharmacy


Bachelor of Pharmacy
Pharmacognosy and Phytochemistry I
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdspharmacy.in
FDSPharmacy


Bachelor of Pharmacy
Pharmaceutical Organic Chemistry III
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdspharmacy.in
FDSPharmacy


Bachelor of Pharmacy
Medicinal Chemistry I
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdspharmacy.in
FDSPharmacy

Pharmacy
Learn and Educate

FDPharmacy

D.Pharma
B.Pharma

- PDF Notes
- Practical Manual
- Important Questions
- Assignment etc

Download Now

ANDROID APP ON Google play

www.fdpharmacy.in

PHARMACEUTICAL ORGANIC CHEMISTRY – III

UNIT 2

TOPIC :

- **Geometrical isomerism**

  Nomenclature of geometrical isomers (Cis Trans, EZ, Syn Anti systems)

  Methods of determination of configuration of geometrical isomers.

  Conformational isomerism in Ethane, n-Butane and Cyclohexane.

  Stereo isomerism in biphenyl compounds (Atropisomerism) and conditions for optical

  activity.

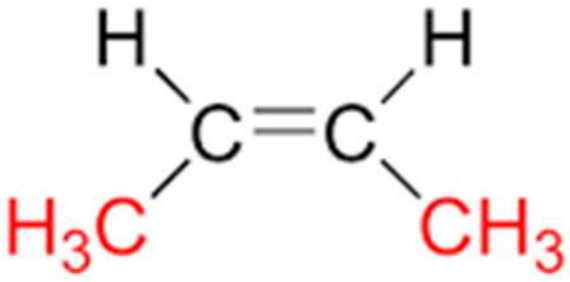
  Stereospecific and stereoselective reactions

Geometrical Isomerism

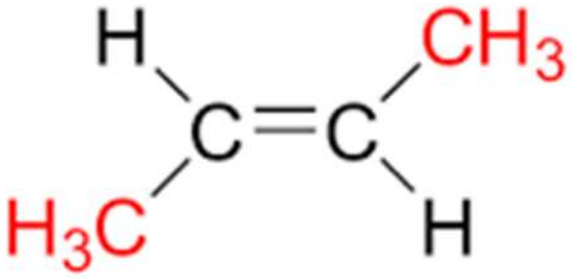
- Geometrical isomerism is a type of stereoisomerism in which compounds have the same molecular formula and the same connectivity of atoms, but differ in the spatial arrangement of substituent groups around a rigid structure such as a double bond or a cyclic system.
  This phenomenon arises because rotation around the double bond or ring is restricted, leading to fixed positions of groups in space.

Example:

- **Cis-2-butene** → Both CH_3 groups are on the same side of the double bond.
- **Trans-2-butene** → CH_3 groups are on opposite sides of the double bond.



cis-2-butene



trans-2-butene

Conditions for Geometrical Isomerism

For a compound to exhibit geometrical isomerism, the following conditions must be fulfilled:

1. **Restricted Rotation**
   - There must be a structural feature that prevents free rotation.
   - Commonly occurs in C=C double bonds (due to π bond) and in cyclic structures (due to ring strain).
2. **Different Groups Attached**
   - Each carbon atom of the double bond must have two different substituents.
   - If any carbon has identical groups, geometrical isomerism is not possible.

   Example:

   - **CH_2=CH_2 (Ethene)** → No geometrical isomerism (each carbon has identical groups H,H).
   - **CH_3–CH=CH–CH_3 (But-2-ene)** → Shows geometrical isomerism (cis and trans forms).
3. **Planar Structure**
   - The molecule should be planar so that substituents can be positioned either on the same side (cis) or on opposite sides (trans).

Nomenclature of Geometrical Isomerism

To distinguish between different geometrical isomers, certain nomenclature systems are used. The main ones include:

1. **Cis-Trans Nomenclature**
2. **E–Z Nomenclature (Cahn–Ingold–Prelog system)**
3. **Syn-Anti Nomenclature**

1. Cis-Trans Nomenclature

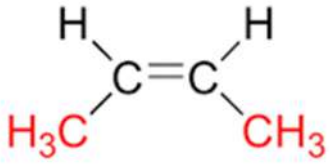
The cis-trans system is the simplest way of naming geometrical isomers. It is commonly applied to alkenes and cyclic compounds**.**

(a) Cis-Trans in Alkenes

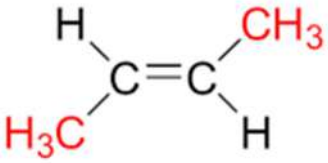
- **Cis-isomer** → Similar or identical groups are on the same side of the double bond.
- **Trans-isomer** → Similar or identical groups are on the opposite sides of the double bond.

Example: 2-Butene

- **Cis-2-butene**: Both $-CH_3$ groups are on the same side of C=C.
- **Trans-2-butene**: $-CH_3$ groups are on opposite sides of C=C.



cis-2-butene



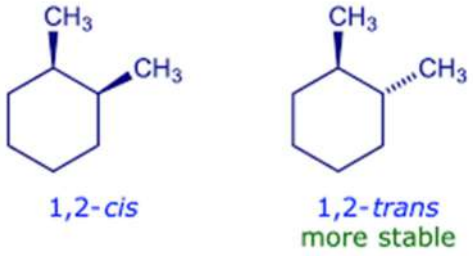
trans-2-butene

(b) Cis-Trans in Cyclic Compounds

- In cyclic structures, free rotation is restricted due to the rigidity of the ring**.**
- Substituents attached to the ring can therefore give rise to cis-trans isomerism.
- **Cis-isomer** → Substituents are on the same side of the ring plane.
- **Trans-isomer** → Substituents are on opposite sides of the ring plane.

Example: 1,2-Dimethylcyclohexane

- **Cis-1,2-dimethylcyclohexane**: Both –CH_3 groups are on the same face of the ring.
- **Trans-1,2-dimethylcyclohexane**: –CH_3 groups are on opposite faces of the ring.



1,2-*cis* 1,2-*trans*
more stable

2. E–Z Nomenclature

- The E–Z system is a precise method for naming geometrical isomers, especially when four different substituents are attached to the two carbons of a double bond.
  This method uses the Cahn–Ingold–Prelog (CIP) priority rules to determine the relative positions of substituents. It is more general than the cis-trans system and can be applied to all alkenes.

Steps to Assign E–Z Configuration

1. **Identify the C=C double bond.**
   - Look at each carbon atom involved in the double bond.
2. **Assign priorities** to the two groups on each double-bonded carbon using **CIP rules**:
   - The group with the higher atomic number gets higher priority.
   - If the first atoms are the same, move outward along the chain until a difference is found.
3. **Compare the relative positions of the highest priority groups:**
   - **Z-Isomer** (from German *Zusammen* = *together*) → Higher priority groups are on the same side of the double bond.
   - **E-Isomer** (from German *Entgegen* = *opposite*) → Higher priority groups are on **opposite sides** of the double bond.

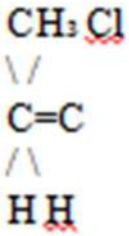
Example:

$CH_3–CH=CH–Cl$

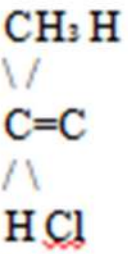
- On left carbon: CH_3 vs H → CH_3 has higher priority.
- On right carbon: Cl vs H → Cl has higher priority.
- If CH_3 and Cl are on the same side → Z-isomer.
- If CH_3 and Cl are on opposite sides → E-isomer.

Diagram:

- **Z-form**



- **E-form**



3. Syn–Anti System of Nomenclature

The Syn–Anti system is used to describe geometrical isomerism in compounds containing C=N double bonds, such as:

- **Oximes ($R_2C=NOH$)**
- **Aldoximes (R–CH=NOH)**

Since nitrogen double bonds also restrict rotation, these compounds can exist as two distinct isomers.

Rules for Syn–Anti Nomenclature

1. Look at the C=N bond and the –OH group attached to nitrogen.
2. Compare the relative position of the hydrogen atom (attached to carbon in case of aldoximes) or substituent with respect to the –OH group.

- **Syn-isomer** → The –OH group and the H (or substituent) are on the **same side** of the C=N bond.
- **Anti-isomer** → The –OH group and the H (or substituent) are on **opposite sides** of the C=N bond.

Example: Benzaldoxime (C_6H_5–CH=NOH)

- **Syn-benzaldoxime** → The –OH group and the H atom are on the **same side**.
- **Anti-benzaldoxime** → The –OH group and the H atom are on **opposite sides**.

Representation:

- **Syn-isomer:**

C_6H_5–CH=NOH
||
H OH (same side)

- **Anti-isomer:**

C_6H_5–CH=NOH
||
H OH (opposite side)

FDSPharmacy
Learn and Educate

Methods of Determination of Configuration of Geometrical Isomers

- The configuration of geometrical isomers (cis/trans or E/Z) can be determined by physical and chemical methods.

1. Physical Methods

(a) Melting and Boiling Points

- **Cis-isomers**:
  - Usually have lower melting points (less symmetry, poor crystal packing).
  - Have higher boiling points due to polarity.
  - Example: *Cis-2-butene* → BP = 4 °C.
- **Trans-isomers**:
  - Usually have higher melting points (better packing in crystal lattice).
  - Have lower boiling points due to being less polar.
  - Example: *Trans-2-butene* → BP = 1 °C.

(b) Dipole Moment Measurement

- **Cis-isomers**:
  - Polar groups are on the same side → dipoles add up → molecule has net dipole moment.
  - Example: *Cis-1,2-dichloroethene* → Dipole moment = 1.90 D.
- **Trans-isomers**:
  - Polar groups are on opposite sides → dipoles cancel → molecule is non-polar or less polar**.**
  - Example: *Trans-1,2-dichloroethene* → Dipole moment = 0 D.

(c) Solubility

- **Cis-isomers**:
  - Usually more soluble in polar solvents due to higher polarity.
  - Example: *Maleic acid (cis form)* → Solubility = 7.9 g/100 mL.
- **Trans-isomers**:
  - Less polar → lower solubility in polar solvents.
  - Example: *Fumaric acid (trans form)* → Solubility = 0.7 g/100 mL.

2. Chemical Methods

(a) Selective Reactions with Reagents

- Cis and trans isomers often show different reactivities.
- Example:
  - Cis-alkenes undergo halogenation reactions faster due to steric crowding and higher polarity.

(b) Cyclization or Ring Formation Reactions

- **Cis-isomers**:
  - Reactive groups on the same side of the molecule → can easily interact → favor cyclization or dehydration reactions.
  - Example: *Maleic acid (cis form)* undergoes cyclization to give Maleic anhydride on heating.

$$Maleic acid \rightarrow Maleic anhydride + H_2O$$

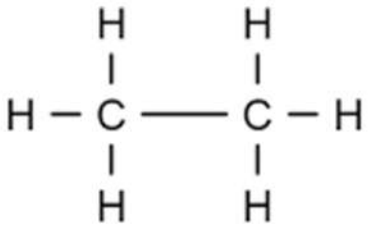
- **Trans-isomers**:
  - Reactive groups are far apart → do not undergo cyclization easily.
  - Example: *Fumaric acid (trans form)* does not form anhydride easily.

Conformational Isomerism

Conformational isomerism (also called rotational isomerism) is a type of stereoisomerism in which compounds with the same molecular formula and connectivity differ only by the rotation around a single sigma (σ) bond.

- Conformations are the different spatial arrangements of atoms resulting from rotation around C–C single bonds.
- These isomers are interconvertible without breaking any bonds.
- Example: Ethane shows conformations due to free rotation around the C–C bond.

Conformational Isomerism in Ethane



Key Points

- Ethane (CH_3–CH_3) has two carbon atoms connected by a C–C single bond.
- This σ-bond allows free rotation of one methyl group relative to the other.
- As a result, many conformations are possible.
- The most important are:
    1. **Staggered Conformation**
    2. **Eclipsed Conformation**

1. Staggered Conformation

- In this arrangement, the hydrogen atoms on one carbon are positioned as far apart as possible from those on the adjacent carbon.
- The angle between adjacent H–C–C–H bonds is 60° (torsional angle).
- It is the most stable form due to minimum electron repulsion between bonding pairs.
- Energy is lowest in this conformation.

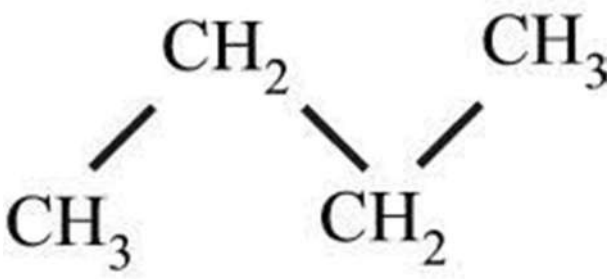
2. Eclipsed Conformation

- In this arrangement, the hydrogen atoms on one carbon are positioned directly behind those on the adjacent carbon.
- The torsional angle is 0°.
- It is the least stable form due to maximum electron repulsion between bonding pairs.
- Energy is highest in this conformation.

Energy Profile of Rotation in Ethane

- When the ethane molecule rotates around the C–C bond, the energy alternates between high (eclipsed) and low (staggered).
- Energy difference between staggered and eclipsed conformations is about 12 kJ/mol.
- Staggered conformation → Energy minima (stable).
- Eclipsed conformation → Energy maxima (unstable).

Conformational Isomerism in n-Butane



n-butane

- n-Butane ($CH_3–CH_2–CH_2–CH_3$) shows conformational isomerism due to rotation around the central C–C single bond ($C_2–C_3$ bond).
- Different spatial arrangements of atoms (conformations) arise as the bond rotates.
- The most important conformations are:
    1. Anti conformation
    2. Gauche conformation
    3. Eclipsed conformations (partially and fully eclipsed)

Main Conformations

1. Anti Conformation

- The two terminal methyl groups (CH_3) are positioned opposite to each other (180° apart).
- This is the most stable conformation because:
    - Steric hindrance is minimum.
    - Torsional strain is absent.
- Energy: Lowest.

2. Gauche Conformation

- The two methyl groups are separated by a dihedral angle of 60°.
- This arrangement introduces some steric hindrance between bulky – CH_3 groups.
- Less stable than anti conformation but more stable than eclipsed forms.

3. Eclipsed Conformations

When groups on adjacent carbons are aligned (overlapping), we get eclipsed conformations.

- **Partially Eclipsed (120°)**
  - One CH_3 group overlaps with a H atom.
  - Intermediate in stability.
- **Fully Eclipsed (0°)**
  - The two CH_3 groups overlap directly.
  - This is the least stable conformation due to maximum steric hindrance and torsional strain.
  - Energy: Highest.

Energy Profile of n-Butane

- Rotation around the C_2–C_3 bond produces repeating conformations with different energies.
- Order of stability (from most to least stable):
  Anti (lowest energy) > Gauche > Partially Eclipsed > Fully Eclipsed (highest energy).

Conformational Isomerism in Cyclohexane

- Cyclohexane (C_6H_{12}) is a six-membered cyclic compound.
- Due to the possibility of rotation around its single bonds, cyclohexane can adopt different three-dimensional shapes (conformations).
- These conformations help the molecule reduce strain and achieve greater stability.
- The main conformations are:
    1. **Chair**
    2. **Boat**
    3. **Twist-Boat**
    4. **Half-Chair**

1. Chair Conformation

- Shape resembles a reclining chair.
- Most stable and most commonly occurring form of cyclohexane.
- Features:
    - Bond angles = 109.5° (ideal tetrahedral angle).
    - No angle strain.
    - No torsional strain (bonds are staggered).
- Lowest energy conformation.

2. Boat Conformation

- Shape resembles a boat.
- Less stable than chair form because:
    - Hydrogen atoms at the "bow" and "stern" experience steric repulsion (flagpole interactions).
    - Several eclipsed interactions exist.
- Higher energy than chair.

3. Twist-Boat Conformation

- Obtained by twisting the boat form.

- Twist reduces steric interactions (flagpole H–H repulsion).
- More stable than boat, but still less stable than chair.

4. Half-Chair Conformation

- Resembles a partially lifted chair.
- Least stable conformation because:
  - Maximum angle strain.
  - Maximum torsional strain.
- Quickly converts into either chair or boat form.

Relative Stability Order

Chair (most stable, lowest energy) > Twist-Boat > Boat > Half-Chair (least stable, highest energy).

FDSPharmacy
Learn and Educate

Stereoisomerism in Biphenyl Compounds (Atropisomerism)

- Biphenyl compounds consist of two benzene rings joined by a single C–C bond.
- Normally, this bond allows free rotation, and stereoisomerism is not observed.
- However, under certain conditions, this free rotation is restricted, leading to stereoisomerism.

Restricted Rotation

- In simple biphenyl, the rings can rotate freely.
- When bulky substituents (e.g., $-NO_2$, –COOH, –Br, $-SO_3H$) are present at the ortho positions of both rings:
  - Steric hindrance occurs.
  - The rotation of the central C–C bond becomes restricted.
  - The molecule adopts a non-planar structure to reduce repulsion.

Atropisomerism

- Restricted rotation produces two possible mirror-image arrangements of the biphenyl molecule.
- These are non-superimposable enantiomers, even though the molecule has no chiral carbon atom.
- This special type of stereoisomerism is known as Atropisomerism.
- Atropisomers show optical activity because of their dissymmetric arrangement.

Example:

- 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid exists as enantiomers.

Conditions for Stereoisomerism in Biphenyls

1. Presence of bulky substituents at the ortho positions of both rings.
2. Restricted rotation around the central C–C bond.
3. Non-planar arrangement of the two benzene rings to minimize steric hindrance.
4. Molecule shows chirality without a chiral center (optical isomerism).

Stereospecific Reactions

- A stereospecific reaction is a chemical reaction in which the stereochemistry of the starting material directly determines the stereochemistry of the product.
- Different stereoisomers of the reactant always lead to different stereoisomers of the product.
- The reaction is 100% selective—no mixture of stereoisomers is formed, only the specific product.

Key Features

1. Dependence on reactant's stereochemistry – the stereochemical outcome is controlled by the stereoisomer used.
2. No by-products of different stereoisomers – only one stereoisomer of the product is formed.
3. The reaction has a fixed stereochemical pathway (either inversion or retention).
4. It is a special case of stereoselectivity where selectivity is absolute.

Example: SN2 Reaction

- Mechanism:
  - Occurs in a single step with backside attack of nucleophile.
  - This always results in inversion of configuration at the chiral carbon.
- Case Study:
  - Starting with (R)-2-bromobutane → gives (S)-2-butanol.
  - Starting with (S)-2-bromobutane → gives (R)-2-butanol.

$$CH_3\ CHBr\ CH_2\ CH_3 \xrightarrow{KOH} CH_3\ CH(OH)\ CH_2\ CH_3$$

Thus, the reactant stereochemistry uniquely defines the product stereochemistry.