BP305T · UNIT II

BP305T Heterocyclic Compounds and Stereochemistry

Unit II — Optical Isomerism

B.Pharm Semester III · Theory Notes

Chapters 5–6

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CHAPTER 5 — Optical Isomerism I: Chirality, Enantiomers, Diastereomers, Meso Compounds

5.1 Learning Objectives

- Define stereoisomerism and list its types with examples.
- Define optical activity, chirality, elements of symmetry, chiral and achiral molecules.
- Distinguish enantiomers, diastereomers and meso compounds with examples.
- Explain the origin of chirality in simple language.

5.2 Definitions

Stereoisomerism: Isomerism in which compounds have the SAME molecular formula and SAME order of atoms, but DIFFERENT arrangement of atoms in space (3D). Example: the two mirror-image forms of lactic acid.

Optical activity: The ability of a compound to rotate the plane of plane-polarised light. Measured with a polarimeter; reported as (+) dextrorotatory (clockwise) or (−) laevorotatory (anticlockwise).

Chirality: The property of an object that cannot be superimposed on its mirror image — like your left and right hands. From the Greek *cheir* = hand.

Enantiomers: A pair of non-superimposable mirror images. Example: (+)-lactic acid and (−)-lactic acid.

Diastereomers: Stereoisomers that are NOT mirror images of each other. Example: the meso and optically active forms of tartaric acid.

Meso compound: A molecule with chiral centres that is ACHIRAL overall because it has an internal plane of symmetry — it is optically inactive. Example: meso-tartaric acid.

5.3 Terminology

- **Plane-polarised light:** light waves vibrating in only one plane.
- **Chiral centre (stereocentre):** usually a carbon attached to FOUR DIFFERENT groups (asymmetric carbon).
- **Achiral:** superimposable on its mirror image (e.g., CH_3CH_2OH, meso-tartaric acid).
- **Elements of symmetry:** plane of symmetry (σ), centre of symmetry (i), alternating axis — if a molecule has any of these, it is achiral.
- **Plane of symmetry:** an imaginary plane that cuts the molecule into two mirror-image halves.

5.4 Explanation — The Origin of Chirality (from absolute zero)

Hold up your hands, palms facing you. The left hand is the mirror image of the right — but try to lay one exactly on top of the other: the thumbs point opposite ways. They never match. That is chirality: **non-superimposable mirror image**. Now imagine a carbon with four different groups (say –H, –OH, $–CH_3$, –COOH, as in lactic acid). Its mirror image has the groups arranged the other way round, and no rotation can make them coincide — the molecule is chiral, like your hands. If any TWO groups are the same, the mirror image can be rotated to match — the molecule is achiral, like a plain ball.

5.5 Types of Stereoisomerism — Classification Chart

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Stereoisomerism
  ├─ Optical isomerism (this chapter)
  │     ├─ Enantiomerism (mirror images; e.g., lactic acid pair)
  │     ├─ Diastereoisomerism (non-mirror stereoisomers; e.g., geometrical isomers also count)
  │     └─ Meso compounds (optically inactive despite chiral centres)
  └─ Geometrical isomerism (Chapter 7: cis/trans, E/Z)
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5.6 Elements of Symmetry — How to Test for Chirality

1. **Plane of symmetry (σ):** If you can draw a plane through the molecule so that one half is the mirror of the other → achiral (optically inactive).
2. **Centre of symmetry (i):** If every atom has an identical partner at an equal distance on the opposite side of a central point → achiral.
3. **Rule of thumb:** A carbon with four different groups = chiral centre. But the WHOLE molecule is chiral only if it has NO element of symmetry (meso compounds are the famous exception).

5.7 Enantiomers vs Diastereomers vs Meso — Master Table

Feature	Enantiomers	Diastereomers	Meso compound
Mirror images?	Yes (non-superimposable)	No	Has mirror plane internally
Optical activity	One (+), one (−), equal magnitude	May differ	Inactive (rotation cancels)
Physical properties	Identical (except rotation sign)	Different (mp, bp, solubility)	Different from chiral pair
Example	(+)/(−) lactic acid	meso vs (±) tartaric acid	meso-tartaric acid

5.8 Worked Examples

1. **Lactic acid** CH_3–CH(OH)–COOH: the middle carbon has –H, –OH, –CH_3, –COOH (four different groups) → chiral → one pair of enantiomers.
2. **Tartaric acid** HOOC–CH(OH)–CH(OH)–COOH: two chiral centres → three stereoisomers: (+), (−) (enantiomeric pair) and meso (plane of symmetry, inactive).
3. **2-Butanol** $CH_3CH(OH)CH_2CH_3$: C-2 has four different groups → chiral → enantiomeric pair.

5.9 Infographic Concept Box — "Chirality in One Picture"

Left hand vs right hand (mirror, never superimpose). Centre: carbon with 4 different coloured balls = chiral centre. Arrows: no symmetry element → chiral → enantiomer pair (+)/(−). Symmetry plane present → achiral → inactive (meso example: tartaric acid with dashed mirror plane). Bottom line: same formula + same connections + different 3D = stereoisomers.

5.10 Pharmacy Relevance & India Context

- The body is chiral (enzymes, receptors are chiral) — enantiomers of a drug can behave like completely different drugs (see Chapter 6 for examples).
- Indian pharmacopoeia specifies optical rotation for many drugs (e.g., dextrose) as a purity test.

5.11 Common Confusions / Mistakes / Mnemonics

- **Confusion:** "Chiral centre" vs "chiral molecule" — a molecule can have chiral centres yet be achiral (meso). Always check for a plane of symmetry.
- **Mistake:** Saying enantiomers have different melting points — they don't (identical physical properties in achiral environments).
- **Mnemonic:** "MEs o = Mirror cancEls Out" — meso is inactive.

5.12 Exam Summary & One-Minute Revision

- Stereoisomers: same formula, same connections, different 3D arrangement.
- Chirality = non-superimposable mirror image (hands); chiral centre = C with 4 different groups.
- No symmetry element → chiral; plane/centre of symmetry → achiral.
- Enantiomers: mirror pair, (+)/(−), identical properties. Diastereomers: non-mirror, different properties. Meso: internal plane, inactive.

5.13 Exam Questions

Short: 1. Define chirality with one example. 2. Why is meso-tartaric acid optically inactive? 3. What are elements of symmetry? **Long:** 1. Explain enantiomerism, diastereoisomerism and meso compounds with examples. 2. Describe the origin of chirality and the elements of symmetry. **MCQs:** 1. Meso-tartaric acid is optically inactive because of: (a) no chiral centre (b) plane of symmetry (c) racemic mixture → (b). 2. Enantiomers differ in: (a) melting point (b) direction of rotation of polarised light (c) molecular formula → (b). 3. Number of stereoisomers of tartaric acid: (a) 2 (b) 3 (c) 4 → (b). **Viva:** Give an example of a chiral molecule without a chiral carbon? (Answer: allenes, biphenyls — see Chapter 7.) **Application-based:** A compound has two chiral centres. How many stereoisomers are possible, and when would one be meso?

5.14 References

1. Finar, I. L. *Organic Chemistry: Stereochemistry and Natural Products, Vol. 2.* Pearson Education.
2. Eliel, E. L. and Wilen, S. H. *Stereochemistry of Organic Compounds.* Wiley.
3. Bahl, B. S. and Bahl, A. *Textbook of Organic Chemistry.* S. Chand.

CHAPTER 6 — Optical Isomerism II: Configuration (D/L, R/S), Medicinal Importance, Resolution

6.1 Learning Objectives

- Assign D and L configurations using the Fischer projection rules.
- Apply the Cahn–Ingold–Prelog sequence rules to assign R and S.
- Explain the medicinal importance of optical isomers with examples.
- Define racemic mixture and describe methods of resolution.

6.2 Definitions

Configuration: The fixed 3D arrangement of groups around a chiral centre (as opposed to conformation, which changes by rotation).

D & L system: A relative configuration system based on glyceraldehyde as the reference. In Fischer projection, –OH on the RIGHT = D, on the LEFT = L (for the highest-numbered chiral carbon in sugars; for amino acids the $–NH_2$ position is used).

R & S system (Cahn–Ingold–Prelog): An absolute configuration system: prioritise the four groups (1 → 4), put the lowest priority to the back, then 1 → 2 → 3 clockwise = R (*rectus*), anticlockwise = S (*sinister*).

Racemic mixture (±): A 50:50 mixture of enantiomers — optically inactive (rotations cancel).

Resolution: Separation of a racemic mixture into its individual enantiomers.

6.3 Sequence Rules (Cahn–Ingold–Prelog) — Step by Step

1. Rank the four atoms directly attached to the chiral centre by ATOMIC NUMBER (higher = higher priority).
2. If there is a tie, move out to the next atoms along each chain until the tie breaks (list atoms at each sphere in decreasing order).
3. Multiple bonds count as duplicated atoms (C=O counts as C bonded to O, O).
4. Put priority-4 (lowest) pointing AWAY from you (dashed bond).
5. Read 1 → 2 → 3: clockwise = **R**, anticlockwise = **S**.

- **Worked example — lactic acid** $CH_3–CH(OH)–COOH$: groups on chiral C: –OH (O, 8) = 1; –COOH (C attached to O,O,OH) = 2; $–CH_3$ (C attached to H,H,H) = 3; –H = 4. With H at back, 1 → 2 → 3 clockwise → **R**.

6.4 D & L System — Worked Examples

- Draw the Fischer projection (vertical chain = carbon backbone, horizontal bonds = coming out).
- **Glyceraldehyde:** CHO at top; –OH on right → D-glyceraldehyde; –OH on left → L-glyceraldehyde.
- **Glucose:** the –OH on C-5 (highest-numbered chiral carbon) on the right → D-glucose (natural glucose is D).
- **Key takeaway:** D/L tells you the FAMILY relative to glyceraldehyde — it does NOT tell you (+) or (−). D can be (+) or (−).

6.5 Medicinal Importance of Optical Isomers

- The body's receptors and enzymes are chiral, so enantiomers often have very different biological effects.
- **Examples:**
- **Thalidomide:** one enantiomer is sedative, the other caused birth defects (tragic lesson — now strictly controlled).
- **Ibuprofen:** the S-enantiomer is the active anti-inflammatory; the R form is much less active (sold as racemate; body partly converts R→S).
- **Ethambutol:** the (S,S) form is the anti-TB drug; the (R,R) form causes blindness.
- **L-DOPA:** the L form treats Parkinson's disease; the D form is inactive/toxic.
- **India context:** The Indian pharmaceutical industry now markets many single-enantiomer drugs ("chiral switches," e.g., esomeprazole vs omeprazole) for better safety and efficacy.

6.6 Racemic Mixture and Resolution

- **Racemic mixture:** 50:50 (+)/(−) — zero net rotation. Formed whenever a chiral centre is created from achiral starting materials without a chiral influence.
- **Methods of resolution:**

1. **Mechanical separation:** pick apart crystals by hand (Pasteur's famous tartaric acid experiment) — works only rarely.
2. **Chemical method (diastereomeric salt formation):** react the racemic acid with an optically pure base (e.g., brucine) → two DIASTEREOMERIC salts with different solubilities → separate by crystallisation → regenerate the pure enantiomers. Most widely used.
3. **Biochemical method:** use enzymes or microorganisms that react with only one enantiomer.
4. **Chromatographic method:** chiral HPLC columns separate enantiomers directly.

- > **Analogy:** Resolving enantiomers is like separating left and right gloves — you need something else chiral (a "hand") to tell them apart; an achiral tool cannot do it.

6.7 Infographic Concept Box — "Configuration & Resolution in One Picture"

Fischer cross: horizontal = wedges (out), vertical = dashed (back). D = –OH right, L = –OH left (like left/right hand). R/S dial: priorities 1→2→3, clockwise = R, anticlockwise = S (lowest priority to back). Drug strip: S-ibuprofen active / R weak; L-DOPA treats Parkinson's; (S,S)-ethambutol anti-TB. Resolution funnel: racemate + chiral base → diastereomeric salts → crystallise → pure enantiomers.

6.8 Common Confusions / Mistakes / Mnemonics

- **Confusion:** D/L vs (+)/(−) — D/L is configuration (structure), (+)/(−) is measured rotation. No fixed link between them.
- **Confusion:** R/S vs D/L — R/S is absolute (works for any molecule); D/L is relative (mainly sugars and amino acids).
- **Mistake:** Forgetting to put priority-4 to the back before reading R/S — if 4 is on a wedge, the answer flips.
- **Mnemonic:** "R = Right (clockwise), S = Sinister/left (anticlockwise)."

6.9 Exam Summary & One-Minute Revision

- D/L: Fischer, –OH right = D, left = L (reference: glyceraldehyde); not linked to (+)/(−).
- R/S: CIP priorities by atomic number; 4 to back; 1→2→3 clockwise = R, anticlockwise = S.
- Medicinal: enantiomers differ in body — S-ibuprofen, L-DOPA, (S,S)-ethambutol, thalidomide tragedy.
- Racemic = 50:50, inactive; resolution via diastereomeric salts (chiral base, crystallise), enzymes, chiral chromatography.

6.10 Exam Questions

Short: 1. What is a racemic mixture? 2. State the CIP sequence rules. 3. Why can't D/L predict (+)/(−)? **Long:** 1. Explain the R & S system with the lactic acid example. 2. Describe the medicinal importance of optical isomers with three examples. 3. What is resolution? Describe the chemical method of resolution. **MCQs:** 1. In Fischer projection, –OH on the right means: (a) D (b) L (c) R → (a). 2. 1→2→3 anticlockwise with 4 at back: (a) R (b) S → (b). 3. Active anti-TB enantiomer of ethambutol: (a) (R,R) (b) (S,S) → (b). **Viva:** What is the reference compound for D/L? Which enantiomer of ibuprofen is active? **Application-based:** A new drug is chiral and made as a racemate. Animal tests show one enantiomer is toxic. What manufacturing and testing strategy will you recommend?

6.11 References

1. Finar, I. L. *Organic Chemistry: Stereochemistry and Natural Products, Vol. 2.* Pearson Education.
2. Eliel, E. L. and Wilen, S. H. *Stereochemistry of Organic Compounds.* Wiley.
3. Nadendla, R. R. *Pharmaceutical Organic Chemistry: Heterocyclic and Natural Products.* Vallabh Prakashan.