# Stereochemistry: Life in Three Dimensions

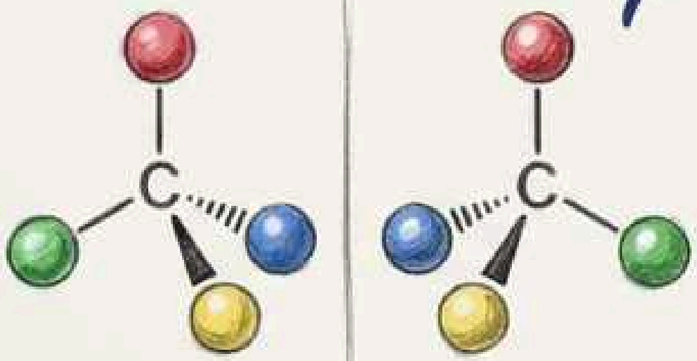
¶ 4.1

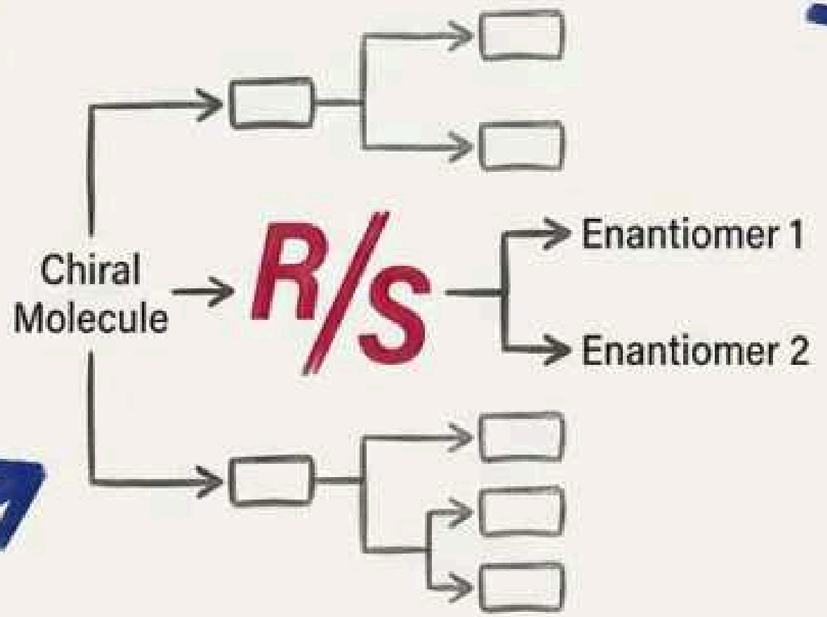
Stereochemistry explains the physical facts of biochemistry by studying molecules in 3D space.

Why do molecules have left and right hands?

How do we name and separate them?

Why does it matter for cells and medicines?

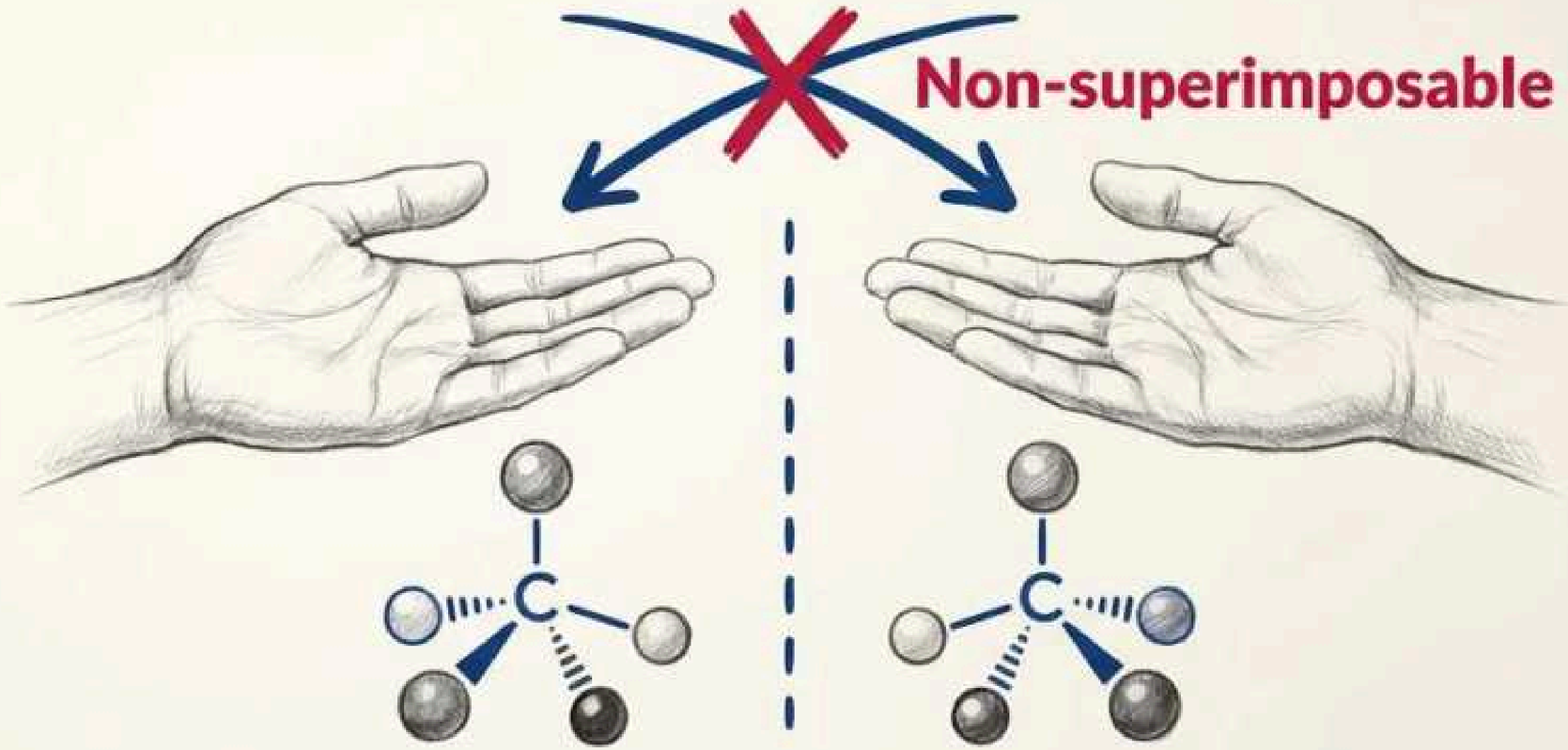





# The Benchmark for Chirality

¶ 4.2

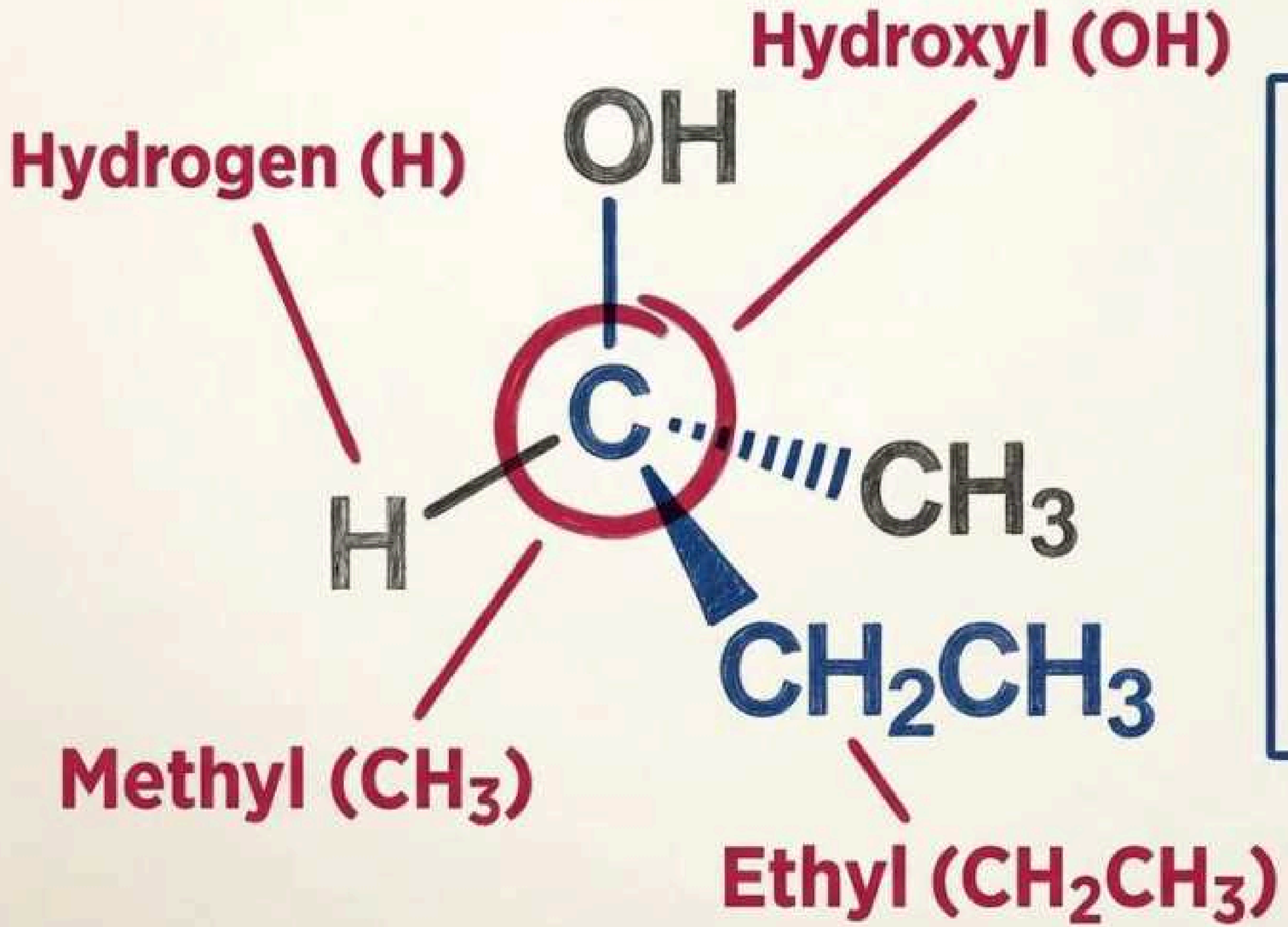



**Chiral:**
From the Greek word for hand.
An object that cannot be superimposed on its mirror image.

**Enantiomers:**
A pair of non-superimposable mirror-image molecules. They share nearly all physical properties.

# Anatomy of a Stereocenter

¶ 4.3




**The Cause:**
A carbon atom bonded to four different groups.

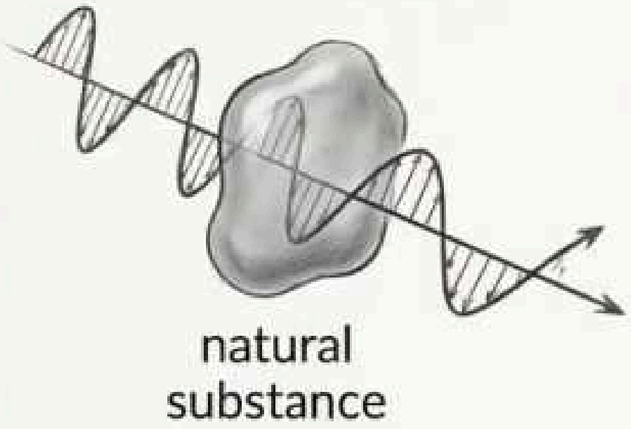
**The Rule:**
Swap any two groups, and you generate the exact mirror image (the other enantiomer).

# The Discovery in Light and Crystal

¶ 4.4

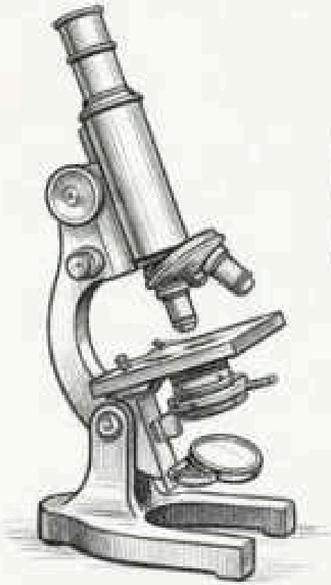
**1815** (Jean-Baptiste Biot)

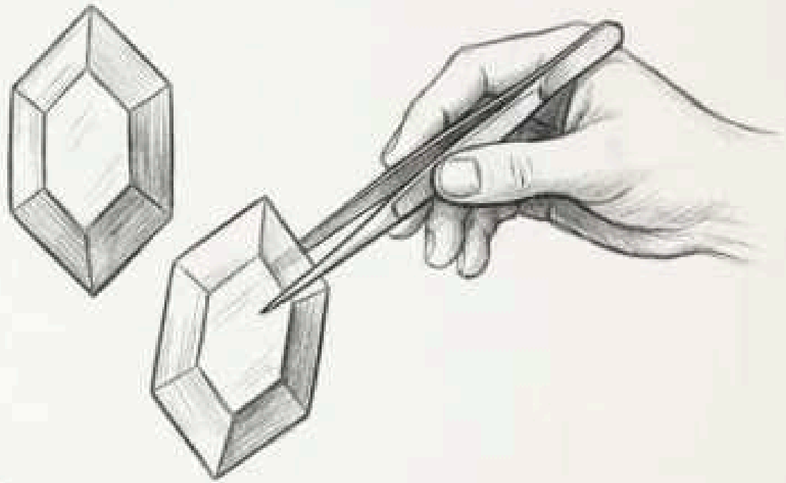





Discovers some natural substances rotate the plane of polarized light.

**1848** (Louis Pasteur, age 25)

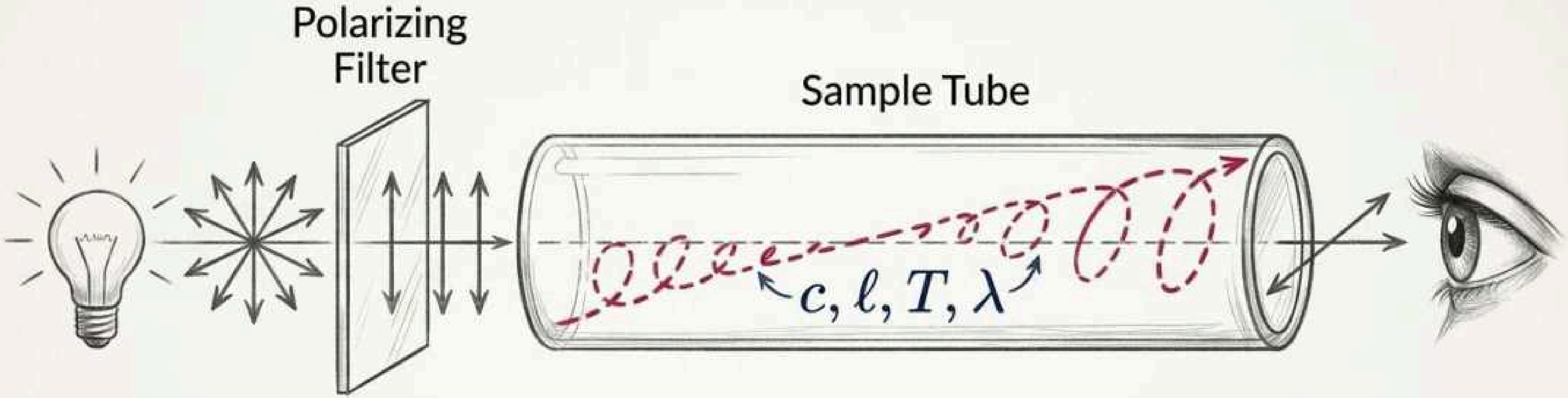




Manually sorts mirror-image crystals of tartaric acid salt. Finds their solutions rotate light in opposite directions. Enantiomers are separated for the first time.

# Measuring Optical Activity

¶ 4.5




| (+) Dextrorotatory = | (–) Levorotatory = |
| --- | --- |
| Clockwise rotation | Counter-clockwise rotation |

**Specific rotation** is a **physical constant** (like a melting point).
**Note:** The (+) or (–) sign cannot be predicted from the molecular structure alone.

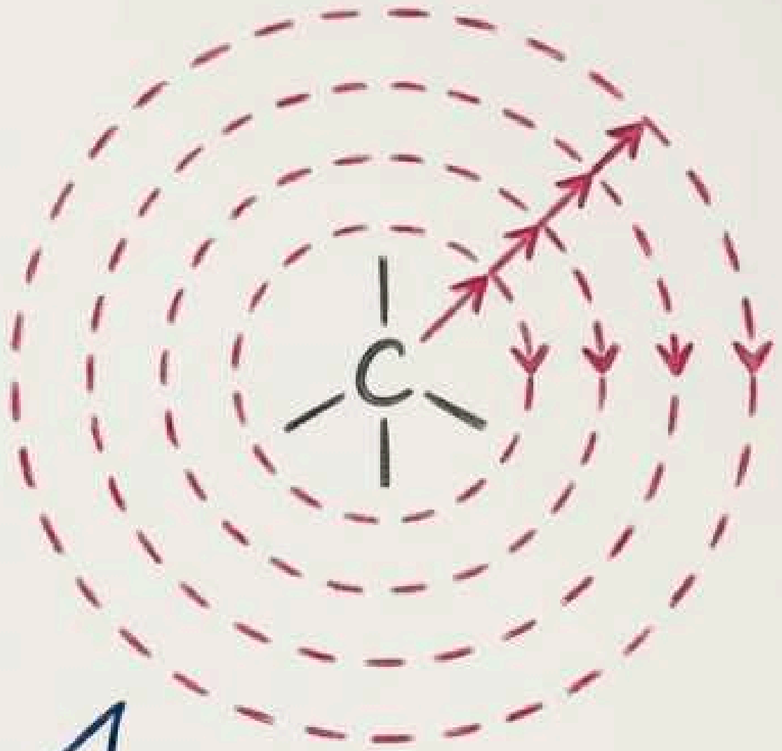
# Priority Rules (Cahn-Ingold-Prelog, 1956)

¶ 4.6

Step 1: Look at atoms directly attached to the stereocenter.

Step 2: Rank by atomic number (Higher number = Higher priority).

**Step 3 (Tie-breaker):** If tied, move outward to the next concentric ring of atoms until the tie breaks.





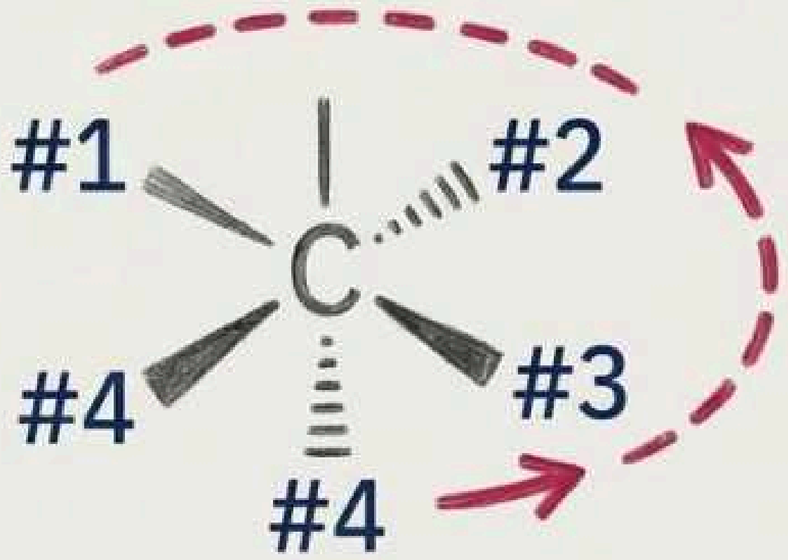


Double bonds count as if the atom were duplicated.

# Steering the Molecule: R and S

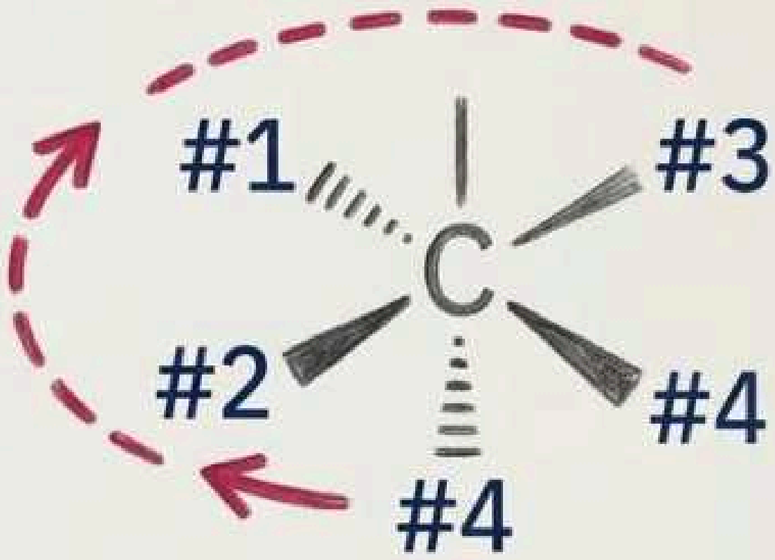
¶ 4.7

Left Wheel (Clockwise)




**R** (Rectus / Right)

Right Wheel (Counter-clockwise)

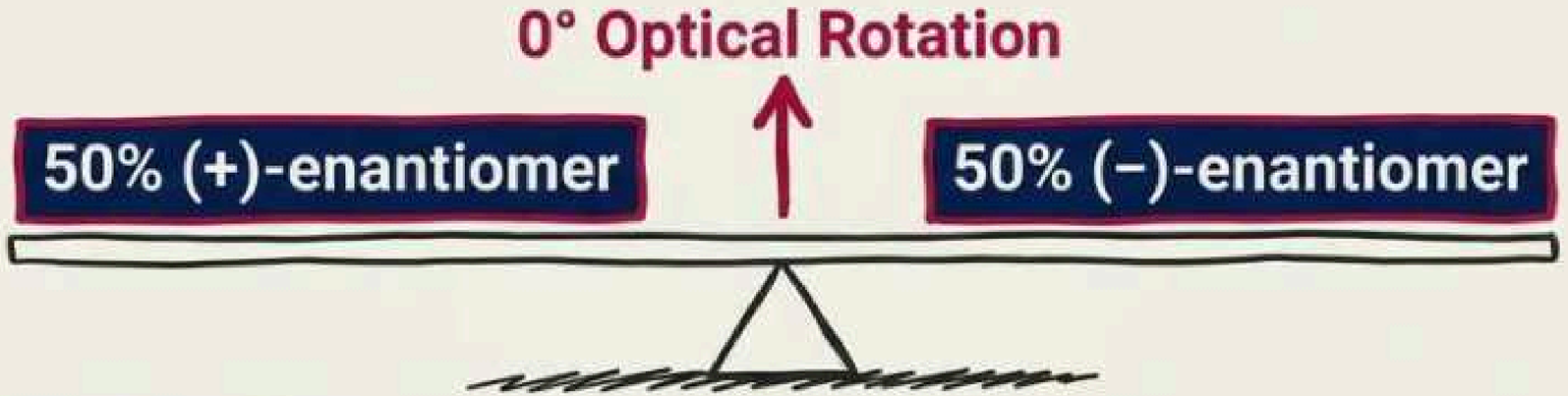



**S** (Sinister / Left)

These letters describe geometry only.
They do not tell you the direction of optical rotation (+ or -).

¶4.8

# Racemic Mixtures & Optical Balance




## Reaction Flow

Achiral starting materials + Achiral reagents → Racemic Mixture

(Both mirror-image paths are equally likely).

**ee (Enantiomeric Excess)**

$$= \left| \% \text{ Enantiomer A} - \% \text{ Enantiomer B} \right|$$

**A racemic mixture shows no optical activity because the opposing rotations perfectly cancel each other out.**

# Scaling Complexity: Diastereomers

¶ 4.9

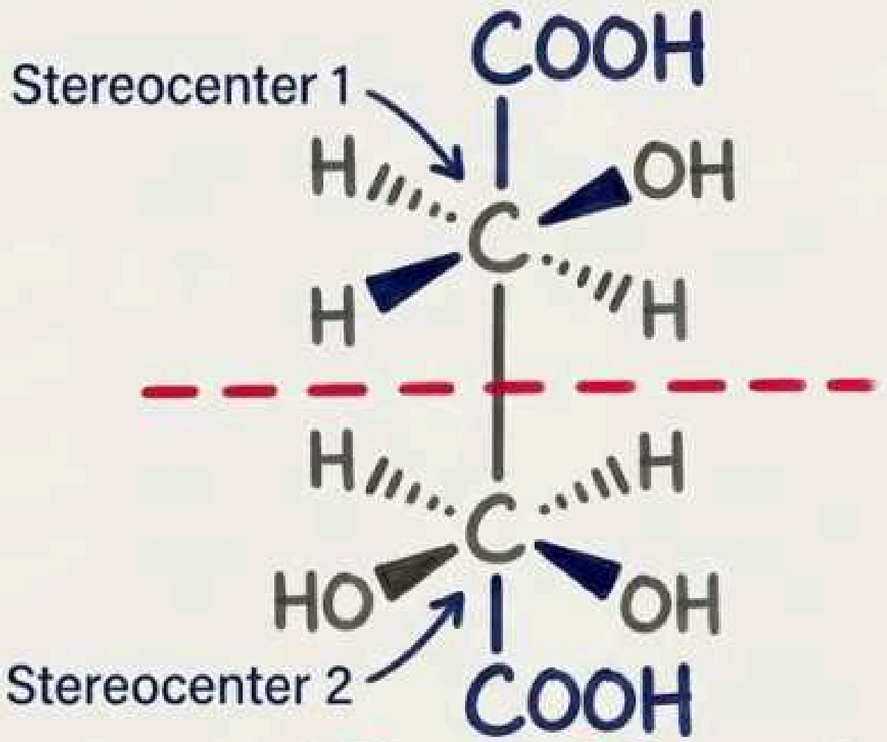
**The $2^n$ Rule:** A molecule with *n* stereocenters has up to $2^n$ stereoisomers.

| | Enantiomers | Diastereomers |
|---|---|---|
| Mirror Image? | Yes (Mirror Images) | No (Not mirror images) |
| Melting Point | Same | Different |
| Boiling Point | Same | Different |
| Solubility | Same | Different |
| Separation Method | Hard to separate | Easily separated via ordinary crystallization |

**Diastereomers are stereoisomers that are not mirror images of one another.**

# The Meso Exception: When Symmetry Overrides Math

¶ 4.10




$2^2 \neq 4$ isomers

(Only 3 isomers exist for tartaric acid)

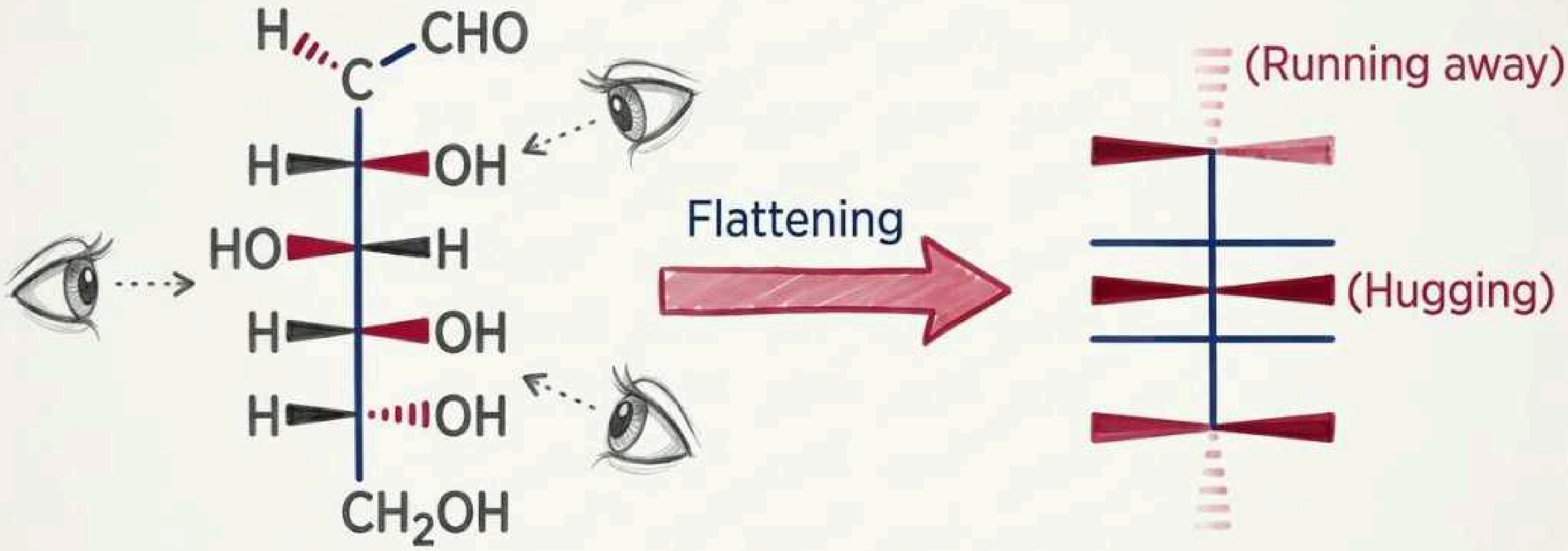
Internal Plane of Symmetry

**Meso Compound:** A molecule with stereocenters that is identical to its mirror image due to an internal plane of symmetry.

Meso compounds are optically inactive.

# Fischer Projections (Emil Fischer, 1890s)

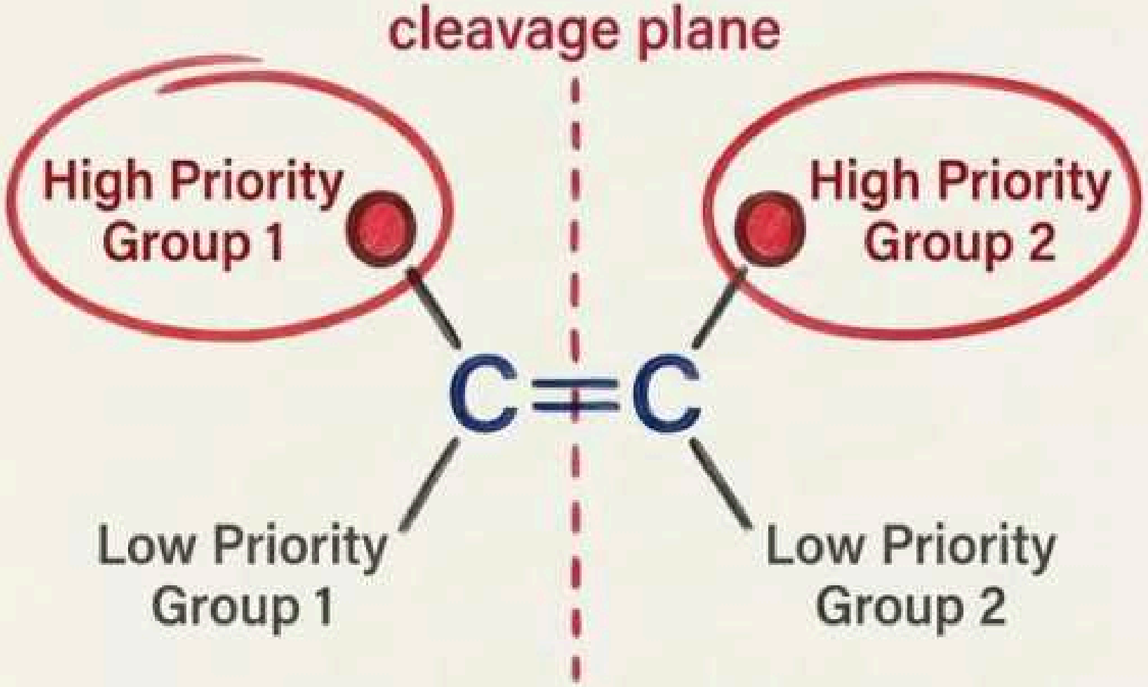
¶ 4.11




The essential drawing tool for molecules with several stereocenters in a row, like sugars and amino acids.

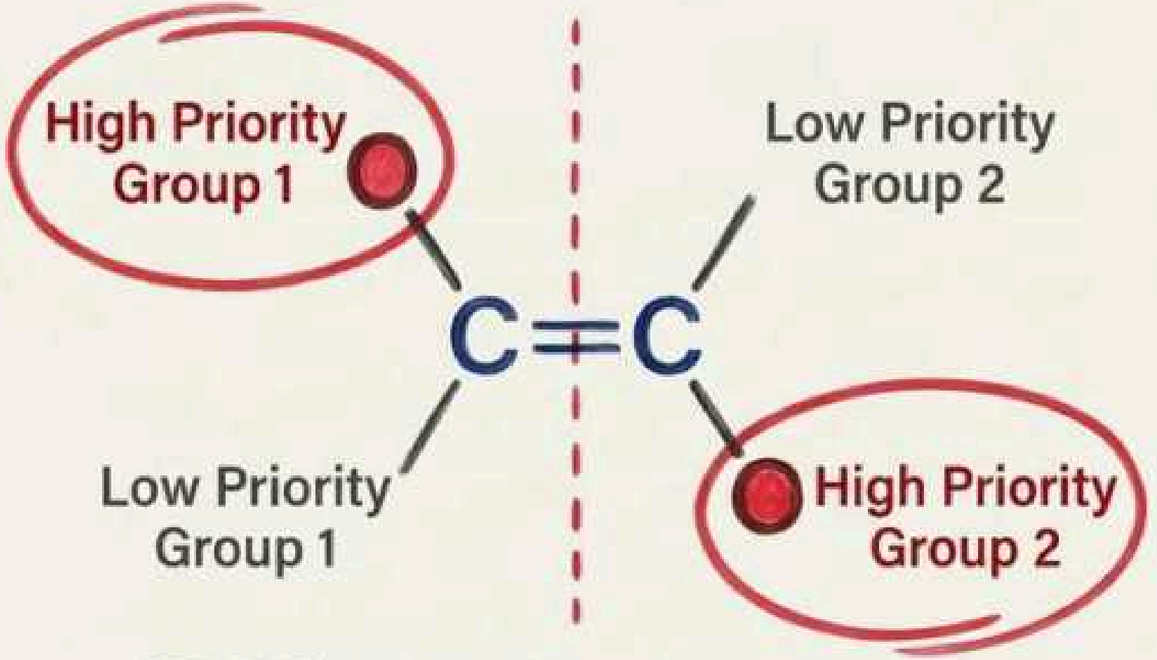
# Rigid Barriers: *E* and *Z* Stereoisomers

¶ 4.12




**Z** (from German *zusammen*, meaning together)

Correlates to older “cis”.



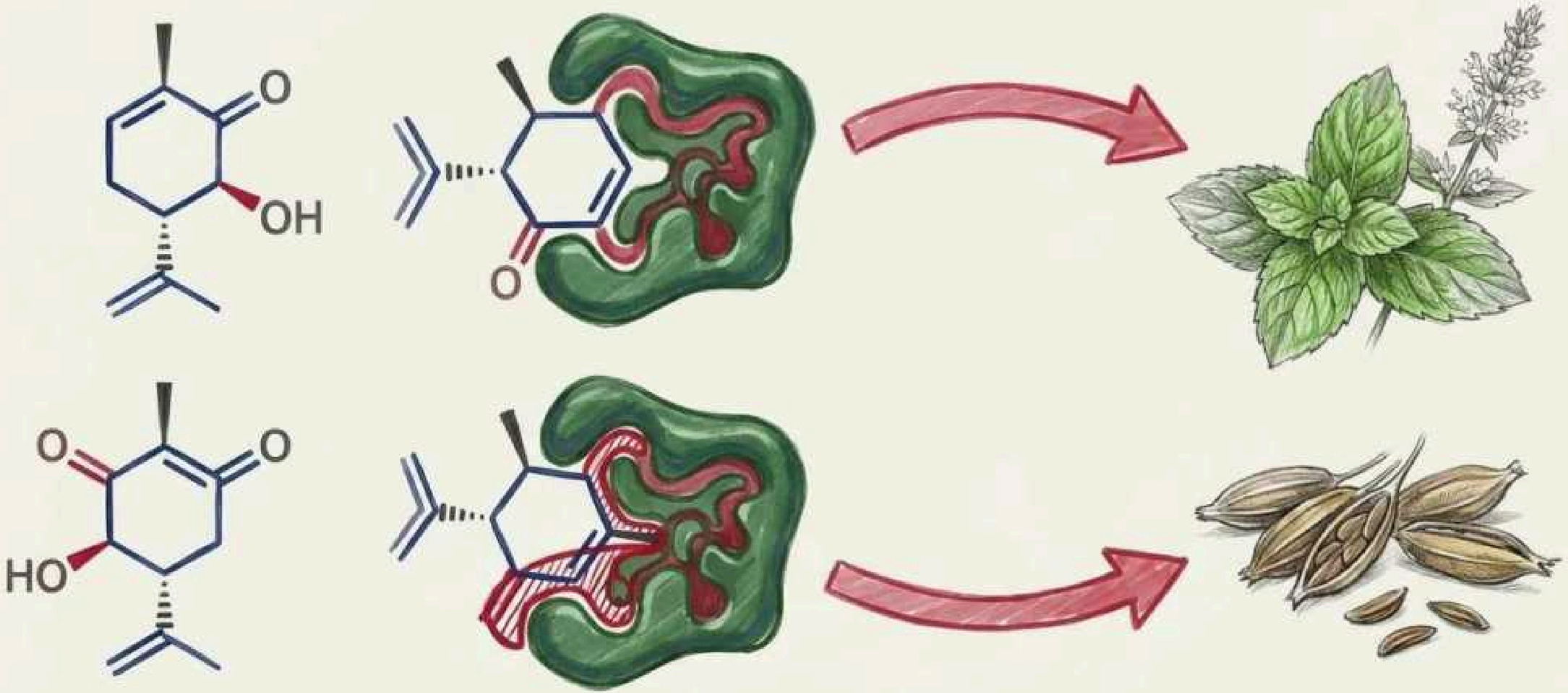

**E** (from German *entgegen*, meaning opposite)

Correlates to older “trans”.

**Double bonds block rotation. The Cahn-Ingold-Prelog priorities determine E or Z placement in complex cases.**

# Handedness in Biology

¶ 4.13




Living systems are chiral. Enzymes and receptors are built from chiral amino acids, causing them to respond completely differently to two enantiomers.

(Secondary example: Limonene – *R* is orange, *S* is pine)

# The Stakes of Medicine: Thalidomide

¶ 4.14




*R*-thalidomide
(thought to be safe sedative)

*S*-thalidomide
(harmful, birth defects)

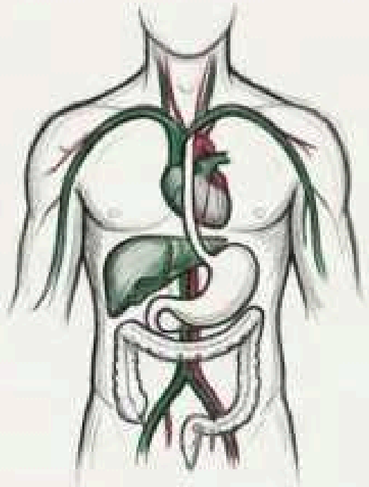
Sold in the late 1950s for morning sickness. The tragedy revealed that even if given as a pure enantiomer, the two forms interconvert within the human body. This led regulators to require far stricter stereoisomer testing for all new drugs.

# Modern Pharmacology: Single Enantiomers

¶ 4.15

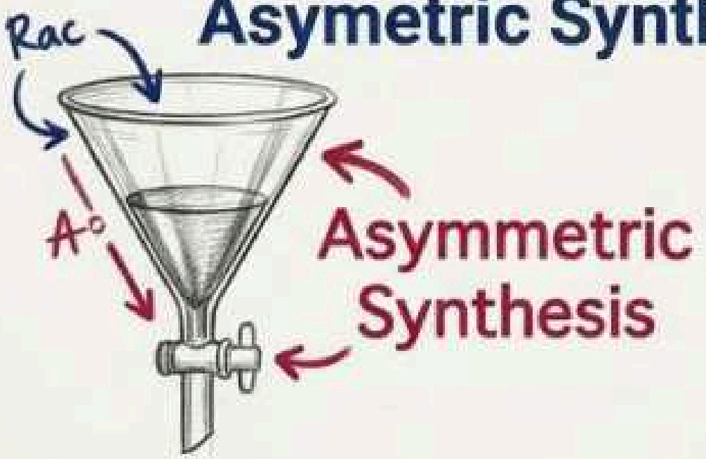
## The Body as a Filter

Racemic Ibuprofen (50/50 mix)



Body converts inactive form into the active painkiller.

## Asymetric Synthesis






Outputs pure Esomeprazole (the single S form of omeprazole, a stomach-acid drug).

Making a single enantiomer from scratch is an immense challenge. William Knowles, Ryoji Noyori, and Barry Sharpless shared the 2001 Nobel Prize in Chemistry for pioneering asymmetric synthesis.

# The Resolution Pathway

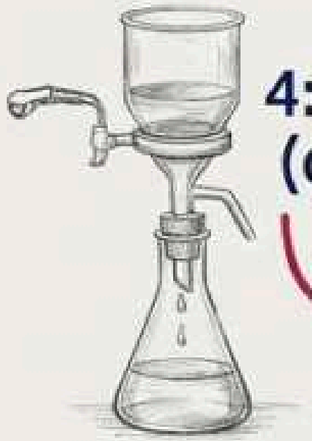
¶ 4.16

Step 1:  Racemic mixture (A + B)

2: Add a Pure Enantiomer reagent (C)

3: Reaction yields Diastereomers (AC + BC)

Different physical properties!



4: Separation (crystallization/physical sorting)

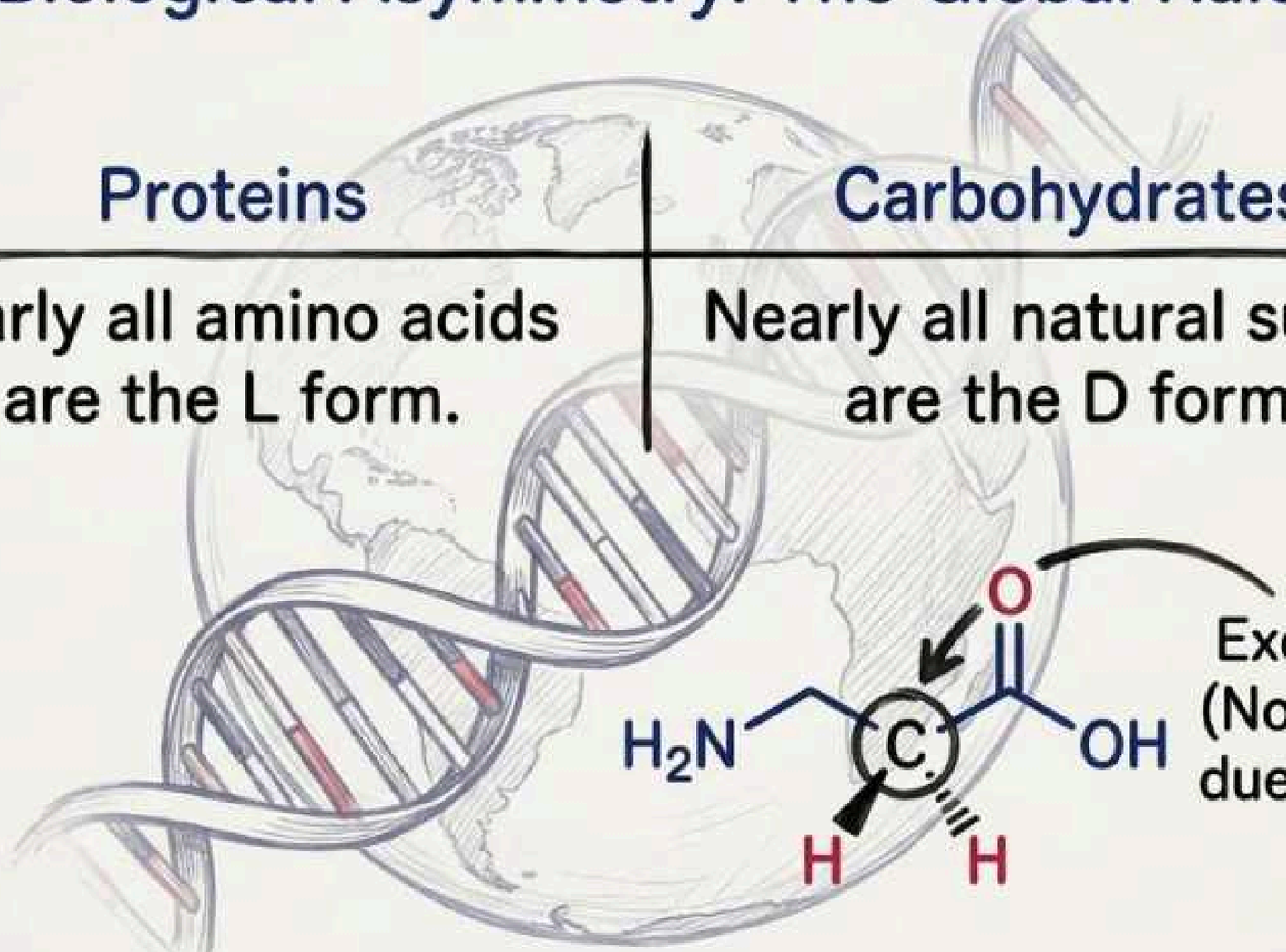
5:  Recovery of pure enantiomers (A) and (B)

Pasteur's hand-sorting was the first resolution. Today, we temporarily turn enantiomers into diastereomers to separate them, then recover the pure targets.

# Biological Asymmetry: The Global Rule

¶ 4.17

| Proteins | Carbohydrates |
| --- | --- |
| Nearly all amino acids are the L form. | Nearly all natural sugars are the D form. |




Exception: Glycine (Not a stereocenter due to two identical hydrogens).

Life chose one hand early in evolution and kept it. This is why a drug molecule of the wrong hand fits a biological receptor poorly, or not at all.

# Lecture Synthesis: The Grammar of Stereochemistry

¶ 4.18

| | |
|---|---|
| Chirality | Stereocenter bonded to 4 different groups. Mirror images are enantiomers. |
| Nomenclature | R and S system names the 3D geometry; optical rotation (+/-) measures the physical reality. |
| Diastereomers | Stereoisomers that are NOT mirror images (different physical properties). |
| Meso | Molecules with stereocenters that remain symmetric and achiral. |
| Impact | Biological handedness dictates drug and flavor interactions. |

Next: Lecture 5 — Reactions where stereochemistry decides the result.