Chapter 5: Stereoisomerism - three-dimensional arrangement of atoms (groups) in space

5.1 Overview of Isomerism

**Isomers**: different chemical compounds with the same formula

*Constitutional isomers*: same formula, but different connectivity of atoms (or groups)

![Different types of isomers](image)

**Stereoisomers**: molecules with the same connectivity but different spatial arrangement of atoms (groups)

![Stereoisomers examples](image)

5.2 Introduction to Stereoisomerism

*Enantiomers*: non-superimposable mirror image isomers.

Enantiomers are related to each other much like a right hand is related to a left hand.

Enantiomers have identical physical properties, e.g., bp, mp, etc.

Chirality (derived from the Greek word for hand). Enantiomers are said to be chiral.

![Hand images](image)
**Chirality Center.** Chiral molecules most commonly contain a carbon with four different groups; the carbon is referred to as a chiral center, or asymmetric center, or stereogenic center, or stereocenter.

5.3 Designating Configuration Using the Cahn-Ingold-Prelog System – Assigning the Absolute Configuration

1a. Look at the four atoms directly attached to the chiral carbon atom and rank them according to decreasing atomic number.

priority of common atoms: I > Br > Cl > S > P > F > O > N > C > H

1b. If the two atoms attached to the chiral carbon are identical (designated A and B below), look at all the atoms directly attached to the identical atoms in questions (designated A-1, A-2, A-3 and B-1, B-2, B-3). Assign priorities to all these atoms based on atomic number (1 is the highest priority, 3 the lowest).
1c. Compare the highest priority atoms, i.e., compare A-1 with B-1. If A-1 is a higher priority atom than B-1, then A is higher priority than B. If A-1 and B-1 are the same atom, then compare the second highest priority atoms directly bonded to A and B (A-2 with B-2); if A-2 is a higher priority atom than B-2, then A is higher priority than B. If A-2 and B-2 are identical atoms, compare A-3 with B-3.

1d. If a difference still cannot be found, move out to the next highest priority group (A-1 and B-1 in the diagram) and repeat the process.

1e. Multiple bonds are considered equivalent to the same number of single bonded atoms.

2a. Orient the molecule so that the lowest priority atom is in the back (away from you). Look at the remaining three groups of priority 1–3. If the remaining three groups are arranged so that the priorities 1 → 2 → 3 are in a clockwise fashion, then assign the chiral center as R (“rectus” or right). If the remaining three groups are arranged 1 → 2 → 3 in a counterclockwise manner, then assign the chiral center as S (“sinister” or left).

2b. Or use the “Hand Rule.” Orient the lowest priority group up. Point your thumb in the direction of the lowest priority group. If you need to use your right hand so that your fingers point in the direction of the group priorities in the order 1 → 2 → 3, then the stereogenic center is assigned R (“rectus” or right). If your left hand is required so that your fingers point in the direction of the group priorities 1 → 2 → 3, the the stereogenic center is assigned S (“sinister” or left).
You must be able to draw tetrahedral carbons properly!!

In the plane of the paper and in the same plane as the tetrahedral carbon (adjacent position off the tetrahedral carbon)

Dash: projecting behind the plane of the paper away from you

Dash and Wedge are on adjacent position off the tetrahedral carbon

Wedge: projecting out of the plane of the paper toward you

LINEAR ALKANES: You should draw the carbon backbone in the plane of the paper, and draw substituents either coming towards you (with wedges) or going away from you (with dashes). Note that each carbon should look like a tetrahedron.

Correct 😊

Incorrect 😞

Interchanging any two groups inverts the stereochemistry. Switch the lowest priority group to the desired position. Then switch the other two groups. The “double-switch” does not change the stereochemistry.

5.4 Optical Activity – samples enriched in one enantiomer will rotate plane polarized light and are said to be optically active. The optical rotation is dependent upon the substance, the sample concentration, the path length through the sample, temperature, and the wavelength of light.
 Plane polarized light: light that oscillates in only one plane

α: angle (# of degrees) plane polarized light is rotated by an optically active sample. Expressed in degrees.

Enantiomers will rotate plane polarized light the same magnitude (α) but in opposite directions (+ or -)

90% (+) + 10% (-) will rotate light 80% of pure (+)
75% (+) + 25% (-) will rotate light 50% of pure (+)
50% (+) + 50% (-) will be optically inactive

50:50 mixture of enantiomers (+/-): racemate or racemic mixture

Each individual molecule may be chiral; however, the bulk property of the substance is achiral (if it is in an achiral environment).

Specific Rotation $[\alpha]_D$: a standardized value for the optical rotation

$$[\alpha]_D^T = \frac{\alpha}{l \cdot c}$$

α = optical rotation in degrees
l = path length in dm
c = concentration of sample in g/mL
T = temperature in °C
λ = wavelength of light, usually D for the D-line of a sodium lamp (589 nm)
The specific rotation is a physical constant of a chiral molecule. The \([\alpha_D]\) may also depend upon solvent, therefore the solvent is usually specified.

\[
\text{for alanine: } \quad [\alpha_D] = +14.5^\circ \text{ (c 10, 6N HCl)}
\]

An optically pure substance consists exclusively of a single enantiomer. Optical purity of an optically active substance is expressed as the enantiomeric excess:

\[
ee = \frac{\text{(observed } \alpha)}{\text{(}\alpha\text{ of the pure enantiomer})} \cdot 100
\]

5.5 Stereoisomeric Relationships: Enantiomers and Diastereomers

**Isomers**: different chemical compounds with the same formula

- *Constitutional isomers*: same formula, but different connectivity of atoms (or groups)
- *Stereoisomers*: same connectivity but different spatial arrangement of atoms (groups)

**Enantiomers**: non-superimposable, mirror image isomers

**Diastereomers**: non-superimposable, non-mirror image isomers
Diastereomeric relationships occur when more than one chiral center is present in a molecule.

Enantiomers must have the opposite stereochemistry (configuration) at all chiral centers.

In general, enantiomers have identical physical properties except optical rotation (which is equal in magnitude but opposite in sign). Diastereomers may have completely different physical properties.

Maximum number of stereoisomers = \(2^n\).

where \(n\) = number of structural units capable of stereochemical variation. Structural units include chiral centers and cis and/or trans double bonds.

Cholesterol: eight chiral centers

\(2^8 = 256\) possible stereoisomers

(only one of which is naturally occurring)
5.6 Symmetry and Chirality

Monarch butterfly: bilateral symmetry = mirror symmetry

Whenever winds blow butterflies find a new place on the willow tree
-Basho (~1644 - 1694)

Point (center) of symmetry

Mirror symmetry & axis (6 fold) of symmetry

Molecules are not chiral if they contain a plane of symmetry: a plane that cuts the molecule in half so that one half is the mirror image of the other half. Molecules (or objects) that possess a mirror plane of symmetry are superimposable on their mirror image and are termed achiral.

Achiral

Chiral

Not a symmetry plane

Chiral center (stereogenic, asymmetric)
Meso Compounds: molecules that contain chiral atoms but are achiral because they also possess a plane of symmetry.

\[
\begin{align*}
\text{meso (achiral)} & \quad \text{chiral} \\
\end{align*}
\]

5.7 Fischer Projections - representation of a three-dimensional molecule as a flat structure. A tetrahedral carbon is represented by two crossed lines:

\[
\begin{align*}
\text{vertical line is going back behind the plane of the paper (away from you)} & \quad \equiv \\
\text{horizontal line is coming out of the plane of the page (toward you)} & \\
\text{carbon} & \quad \text{substituent}
\end{align*}
\]

\( (\mathcal{R})-(+)\)-glyceraldehyde

\( (\mathcal{S})-(-)\)-glyceraldehyde
Manipulation of Fischer Projections

1. Fischer projections can be rotated by 180° (in the plane of the page) only!

   ![Fischer projections](image)

   180° rotation preserves stereochemistry.

2. A 90° rotation inverts the stereochemistry and is illegal!

   ![Fischer projections](image)

   90° rotation inverts stereochemistry.

   ![Correct conventions](image)

   Correct conventions for Fischer projections.
2. If one group of a Fischer projection is held steady, the other three groups can be rotated clockwise or counterclockwise.

Assigning \( R \) and \( S \) Configuration to Fischer Projections
1. Assign priorities to the four substituents according to the Cahn-Ingold-Prelog rules
2. Perform the two allowed manipulations of the Fischer projection to place the lowest priority group at the top or bottom.
3. If the priority of the other groups 1→2→3 is clockwise then assign the carbon as \( R \), if the priority of the other groups 1→2→3 is counterclockwise then assign the center as \( S \).
Fischer projections with more than one chiral center:

- mirror images (enantiomers)
- mirror images (enantiomers)
- non-mirror image (diastereomers)

5.8 Conformationally Mobile Systems

1,2-dimethylcycloheane and the gauche conformation of butane are chiral; however, . . . .

The chair-chair interconversion converts one enantiomer to the other.

The gauche conformation of butane is chiral

Rotation about the C2-C3 bond converts one chiral conformation into its enantiomer.
5.9 Resolution of Enantiomers - a process of separating a racemate into pure enantiomers.

Crystallization

Chiral resolving agents. The enantiomers of the racemate must be temporarily converted into diastereomers.

Chapter 6 Chemical Reactivity and Mechanisms

6.1 Enthalpy (ΔH) - the heat (energy) exchange between the reaction and its environment at constant pressure

Bond breaking processes require heat from the environment.

*Homolytic*: symmetrical bond breaking process

*Heterolytic*: unsymmetrical bond breaking processes

Bond dissociation energy (ΔH°) – energy required for homolytic cleavage of a covalent bond. Table 6.1 (p. 238)

Heat of reaction (ΔH°) - total enthalpy change bond during a reaction. ΔH°_products − ΔH°_reactant = ΔH°_reaction