Chapter 3
Stereoisomerism and Chirality
Chirality

- **Chiral**: Objects that are not superposable on their mirror images
- **Achiral**: Objects that lack chirality and are superposable on their mirror images
  - Objects have one or more elements of symmetry
  - **Plane of symmetry**: Imaginary plane passing through an object dividing it so that one half is the mirror image of the other half
  - **Center of symmetry**: A point so situated that identical components of an object are located on opposite sides and equidistant from that point along any axis passing through it
Isomers: same molecular formula, different compounds

- **Constitutional isomers** - Isomers with a different connectivity of atoms in their molecules

  - **Pentane** ($\text{C}_5\text{H}_{12}$) and **2-Methylbutane** ($\text{C}_5\text{H}_{12}$) and **1-Pentene** ($\text{C}_5\text{H}_{10}$) and **Cyclopentane** ($\text{C}_5\text{H}_{10}$)

- **Stereoisomers**: Isomers with the same connectivity but different orientations of their atoms in space
  - **Configurational isomers**: Isomers that differ by the configuration of substituents on an atom
  - **Stereocenter**: An atom about which exchange of two groups produces a stereoisomer
  - **Chiral center**: A tetrahedral atom, most commonly carbon, that is bonded to four different groups
    - All chiral centers are stereocenters, but not all stereocenters are chiral centers
Symmetry, Chirality, and Enantiomers

Ethanol is ACHIRAL

2-Butanol is CHIRAL
Some Important Vocabulary Words

- **Enantiomers**: stereoisomers that are non-superimposable mirror images
- **Chirality**: the property of having a non-superimposable mirror image

*How can I tell if a molecule is chiral?*

1. Does it have a stereogenic center?

Generalizations:

- If a molecule has 0 stereogenic centers, it is **achiral**.
- If a molecule has a single stereogenic center, it is **chiral**.
- If a molecule has >1 stereogenic centers, we must consider another property.
How can I tell if a molecule is chiral?
2. Is there an internal plane of symmetry in the molecule?
• Any molecule that has a plane of symmetry will be **achiral**.
• Any molecules that lacks a plane of symmetry will be **chiral**.

For each of the following molecules, determine whether it is chiral or achiral. If it is chiral, draw its enantiomer.
Enantiomers - Example

• 2-Butanol
  • Has one stereocenter

• 2-Chlorobutane

• 3-Chlorocyclohexene
Atropisomers

- **Enantiomers that lack a chiral center** and differ because of hindered rotation
- Example - Substituted biphenyl
Which of the following statements about enantiomers is false?

1. They have identical melting points
2. They have identical boiling points
3. The magnitude of their specific rotations is identical
4. They have identical densities
5. They react at the same rate with optically active reagents
The $R, S$ system – naming chiral centers
R, S System - priority rules

1. Each atom bonded to the chiral center is assigned a priority based on atomic number
   - Higher the atomic number, higher the priority

2. If priority cannot be assigned as per the atoms bonded to the chiral center, look at the next set of atoms
   - Continue until a priority can be assigned
   - Priority is assigned at the first point of difference

3. Atoms participating in a double or triple bond are considered to be bonded to an equivalent number of similar atoms by single bonds

4. Do not assume that larger groups must always have higher priority
Assign priorities

(a) \(-\text{COH}\) and \(-\text{CH}\)

(b) \(-\text{C} = \text{C}\) and \(-\text{CH}_3\)

First point of difference along path of higher priority

Carboxyl group (higher priority)  Aldehyde group (lower priority)

Vinyl group (higher priority)  Isopropyl group (lower priority)
Naming Chiral Centers

1. Locate the chiral center, and identify its four substituents
   • Assign priority from 1 (highest) to 4 (lowest) to each substituent
2. Orient the molecule so that the group of lowest priority (4) is directed away from you
3. Read the three groups projecting toward you in order from highest priority (1) to lowest priority (3)
4. If the groups are read clockwise, the configuration is \( R \) (latin rectus)
   • If they are read counterclockwise, the configuration is \( S \) (latin sinister)
Assign an $R$ or $S$ configuration to the chiral center

Cl $>$ CH$_2$CH$_3$ $>$ CH$_3$ $>$ H

Cl $>$ CH = CH $>$ CH$_2$ $>$ H

OH $>$ CH$_2$COOH $>$ CH$_2$CH$_2$OH $>$ CH$_3$

(a) H Cl

(b) Cl H

(c) HO CH$_3$ CO OH

S

R

R
Naming Enantiomers: The R, S System

1. Rank the groups attached to the stereocenter in priority order - as for E & Z nomenclature of alkenes. The greater the atomic number, the greater the priority. Use the first point of difference where necessary.

2. Orient the molecule (re-draw if necessary) so that it is viewed with the lowest priority group is directed away from viewer (i.e. the bond to 4 is dashed).

3. Now trace the path 1 → 2 → 3 clockwise - (turning Right) - \((R)\)-enantiomer
counterclockwise - (turning Left) - \((S)\)-enantiomer

Assign \(R\) or \(S\) configurations to each of the following compounds:

\(\text{(R)-2-butanol}\)
\(\text{(S)-2-butanol}\)
Are Enantiomers Different?

• Roald Hoffmann (who shared the Nobel Prize for frontier molecular orbitals) wrote a wonderful book about chemistry titled *The Same and Not The Same*. His point was that much of chemistry involves substances that are the same in some respects, and not the same in others. Enantiomers are an excellent example:

  • A pair of enantiomers will generally have **identical physical properties**: - color, boiling point, melting point, solubility, etc.
  • A pair of enantiomers will generally have **different biological properties**: - taste, smell, toxicity, therapeutic action, etc.
  • A pair of enantiomers can exhibit the **same chemical reactivity OR different chemical reactivity**, depending on what they are reacting with (more on this later).

Can you assign the *R* and *S* designations to these enantiomers of carvone? Do you remember the rule for multiple bonds?
Optical Activity of Enantiomers

- Enantiomers rotate the plane of polarized light equally in opposite directions.

  ![Diagram of polarized light](image)

  - If the plane has **rotated clockwise**, the compound is **dextrorotatory or (+)**
  - If the plane has **rotated counterclockwise**, the compound is **levorotatory or (-)**
  - ... and we can incorporate this into the name: *(S)-(+)-2-butanol*

**Note:** (+) and (-) are physical properties and CANNOT be determined by the structure or by correlation with R/S. They are properties of the entire molecule.
Detecting Chirality - Plane-Polarized Light

• Light oscillating in only a single plane
  • Ordinary light consists of waves vibrating in all planes perpendicular to its direction of propagation

• **Optically active**: Refers to a compound that rotates the plane of plane-polarized light

• Vector sum of left and right circularly polarized light that propagates through space as left- and right-handed helices
  • Each component interacts in an opposite way with chiral molecules
    • Results in each member of a pair of enantiomers rotating the plane of polarized light in an opposite direction
Detecting Chirality - Polarimeter

- Device for measuring the ability of a compound to rotate the plane of polarized light

1) Sample tube filled with solvent is placed in the polarimeter; 2) Analyzing filter is adjusted so that the field is dark, position of the analyzing filter is taken as 0°; 3) When a solution of an optically active compound is placed in the sample tube, some light passes through the analyzing filter, optically active compound has rotated the plane of polarized light from the polarizing filter so that it is now no longer at an angle of 90° to the analyzing filter; 4) Analyzing filter is then rotated to restore darkness in the field of view.
What would happen to the polarized light if it is passed through a solution of (R)-2-butanol?

What about a mixture composed of equal amounts of both (S)-2-butanol and (R)-2-butanol? Such a 50-50 mixture of enantiomers is called racemic mixture or a racemate.

Standard form for reporting optical rotation.
Specific Rotation

- Observed rotation of the plane of polarized light when a sample is placed in a tube 1.0 dm in length and at a concentration of 1 g/mL
  - For a pure liquid, Concentration is expressed in grams per milliliter (g/mL)

\[
\text{Specific rotation} = \left[ \alpha \right]_\lambda^T = \frac{\text{Observed rotation (degrees)}}{\text{Length (dm) \times Concentration (g/mL)}}
\]

- A solution is prepared by dissolving 400 mg of testosterone, a male sex hormone, in 10.0 mL of ethanol and placing it in a sample tube 10.0 cm in length
  - The observed rotation of this sample at 25°C using the D line of sodium is +4.36°
  - Calculate the specific rotation of testosterone

- Concentration of testosterone is 400 mg/10.0 mL = 0.0400 g/mL
- Length of the sample tube is 1.00 dm
- Inserting these values in the equation for calculating specific rotation gives

\[
\text{Specific rotation} = \frac{\text{Observed rotation (degrees)}}{\text{Length (dm) \times Concentration (g/mL)}} = \frac{+4.36°}{1.00 \times 0.0400} = +109
\]
Mixtures of Enantiomers: Racemates and Purity

• What would happen to polarized light if it passed through a mixture composed of equal amounts of both enantiomers of a compound? Such a 50-50 mixture of enantiomers is called a racemic mixture or a racemate.

• For any other mixture of enantiomers, we can characterize the mixture by measuring its optical rotation. We define the optical purity or enantiomeric excess (e.e.) as:

\[
\text{optical purity} = \text{e.e.} = \frac{\text{observed specific rotation}}{\text{specific rotation of pure enantiomer}} = (\% \text{ major enantiomer}) - (\% \text{ minor enantiomer})
\]

Optical purity is numerically equal to enantiomeric excess, but is experimentally determined.
Example:

A sample of (S)-(+-)-monosodium glutamate (MSG) has an observed specific rotation of $+19.2^\circ$.

\[ [\alpha]^D_{20} = +24 \quad \text{known specific rotation of pure enantiomer} \]

What is the optical purity of the sample? What is the composition of the mixture?
Problems

• One commercial synthesis of naproxen gives the enantiomer shown in 97% enantiomeric excess
  • Naproxen is the active ingredient in Aleve and a score of other over-the-counter and prescription nonsteroidal anti-inflammatory drug preparations
  a. Assign an $R$ or $S$ configuration to this enantiomer of naproxen
  b. What are the percentages of $R$ and $S$ enantiomers in the mixture?
Which of the following statements about chirality and optical activity is false?

1. If a solution shows optical activity, it must have a compound present whose mirror image is not superposable on the compound itself.
2. Molecules with a plane of symmetry will show no optical activity.
3. The angle of rotation of plane-polarized light depends on how many chiral molecules the light interacts with while passing through the sample.
4. Enantiomers will always have opposite signs of optical rotation.
5. The R enantiomers are dextrorotatory.
Which of the molecules given below are achiral?

1. A and C
2. A and E
3. B and C
4. B and D
5. D and E
Test yourself now

• For each of the following molecules, identify whether the molecule is chiral or achiral. For molecules that are chiral, assign $R$ or $S$ configurations to each stereocenter, and draw the enantiomer of the molecule.