Chapter 5

Stereochemistry: Chiral Molecules

Constitutional Isomers = same molecular formula, different connectedness
Stereoisomers = same molecular formula, same connectivity of atoms but different arrangement of atoms in space

Examples of Constitutional Isomers

<table>
<thead>
<tr>
<th>formula</th>
<th>constitutional isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₃H₈O</td>
<td>CH₃CH₂CH₂OH CH₃CH₃</td>
</tr>
<tr>
<td>C₄H₁₀</td>
<td>CH₃CH₂CH₂CH₃ CH₃CH₂CH₂CH₃</td>
</tr>
</tbody>
</table>

Constitutional Isomers - Review

Same molecular formula – different bond connectivities

Always different properties
Very different properties if different functional groups

Two types of stereoisomers

1. Enantiomers: stereoisomers whose molecules are nonsuperposable mirror images
2. Diastereomers: stereoisomers whose molecules are not mirror images of each other

Enantiomers and Chiral Molecules

- Chiral molecule - has the property of handedness
- Not superposable on its mirror image
- Can exist as a pair of enantiomers
- Pair of enantiomers
- A chiral molecule and its mirror image
- Achiral molecule
- Superposable on its mirror image

Mirror images = handedness

Left hand cannot be superimposed on the right hand
Mirror image = converts right hand into left

A chiral molecule: 2-butanol

I and II are mirror images of each other
I and II are not superposable and so are enantiomers

2-propanol is not chiral

B is mirror image of A, but is superimposable by 180° rotation

Everything has a mirror image, the question is whether it is superimposable

Chiral molecules and stereogenic centers

1. A molecule with a single tetrahedral carbon bonded to four different groups will always be chiral
2. Switching two groups at the tetrahedral center leads to the enantiomeric molecule
3. A molecule with more than one tetrahedral carbon bonded to four different groups is not always chiral

- Stereogenic center (stereo center)
  - An atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer
  - Carbons at a tetrahedral stereogenic center are designated with an asterisk (*)
- Example: 2-butanol

\[
\begin{align*}
\text{hydrogen} & \quad \text{hydroxyl} \\
\text{(methyl)} & \quad \text{(ethyl)} \\
\text{CH₃} & \quad \text{CH₂CH₃}
\end{align*}
\]

Tests for achirality

1. Draw mirror image. Is it superimposable?
2. Does the species have a bisecting plane of symmetry?
An imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other.

A molecule with a plane of symmetry cannot be chiral.

If any two groups on a C are identical, achiral.

Compounds with 4 different groups attached to one Carbon must be chiral unless a meso compound (2 stereocenters).

The binding specificity of a chiral receptor site for a chiral molecule is usually only favorable in one way.

Priorities are assigned as follows:
- Atoms directly attached to the stereogenic center are compared.
- Atoms with higher atomic number are given higher priority.

If priority cannot be assigned based on directly attached atoms, the next layer of atoms is examined.

Groups with double or triple bonds are assigned priorities as if their atoms were duplicated or triplicated.

The molecule is rotated to put the lowest priority group back:
- If the groups descend in priority (a, b, then c) in clockwise direction the enantiomer is R (rectus, right).
- If the groups descend in priority to counterclockwise direction the enantiomer is S (sinister, left).

Developed as the Cahn-Ingold-Prelog system (1956)

1. The four groups attached to the stereogenic carbon are assigned priorities from highest (a) to lowest (d).
2. Priorities are assigned as follows:
   - Atoms directly attached to the stereogenic center are compared.
   - Atoms with higher atomic number are given higher priority.
3. If priority cannot be assigned based on directly attached atoms, the next layer of atoms is examined.
4. The molecule is rotated to put the lowest priority group back.
   - If the groups descend in priority (a, b, then c) in clockwise direction the enantiomer is R (rectus, right).
   - If the groups descend in priority to counterclockwise direction the enantiomer is S (sinister, left).
5. Groups with double or triple bonds are assigned priorities as if their atoms were duplicated or triplicated.
**If lowest priority group is not in back: third option**

1. **Swap any two groups and then assign the opposite of the new priority**
   - This works because interchanging two groups automatically generates the enantiomer of the original

   ![Diagram of molecule transformation](image)

   Therefore: S

2. **Method 1: Rotate B to see if it will become superposable with A**

3. **Method 2: Exchange 2 groups to try to convert B into A**
   - One exchange of groups leads to the enantiomer of B
   - Two exchanges of groups leads back to B

   ![Diagram of molecule transformation](image)

   Identical with A

**Properties of Enantiomers**

- Enantiomers have almost all identical physical properties (melting point, boiling point, density)

<table>
<thead>
<tr>
<th>Physical Properties of (R) and (S)-2-Butanol</th>
<th>(R)</th>
<th>(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>boiling point</td>
<td>99.5°C</td>
<td>99.5°C</td>
</tr>
<tr>
<td>density (g/mL, 20°C)</td>
<td>0.808</td>
<td>0.808</td>
</tr>
</tbody>
</table>

- However enantiomers rotate the plane of plane-polarized light in equal but opposite directions
Enantiomers rotate the plane of plane-polarized light in equal but opposite directions.

Oscillation of the electric field of ordinary light occurs in all possible planes perpendicular to the direction of propagation.

If the light is passed through a polarizer only one plane emerges.

Properties of Enantiomers: Optical Activity

**Plane polarized light**

![Plane polarized light](image)

Reflected light is largely horizontally polarized.

**Plane polarized light oscillates in a single plane**

Like a rope thru a picket fence.

**Schematic of a Polarimeter**

An optically active substance (e.g., one pure enantiomer) will rotate the plane-polarized light.

- The amount the analyzer needs to be turned to permit light through is called the observed rotation $\alpha$.
- We need to calculate a standard value specific rotation $[\alpha]$

$$\alpha = \frac{\alpha}{c \cdot l}$$

where:

- $\alpha$ = the observed rotation
- $c$ = the concentration of the solution in grams per milliliter of solution (or density in g/mL for pure liquids)
- $l$ = the length of the tube (in decimeters (1 dm = 10 cm))

- If the analyzer is rotated clockwise the rotation is (+) and the molecule is dextrorotatory (D).
- If the analyzer is rotated counterclockwise the rotation is (-) and the molecule is levorotatory (L).

**Specific Rotation – a property of an enantiomer**

Specific rotation of enantiomers

- The specific rotation of the two pure enantiomers of 2-butanol are equal but opposite.

- There is no straightforward correlation between the R,S designation of an enantiomer and the direction [(+)] or [(-)] in which it rotates plane polarized light.
An example of specific rotation

A sample of compound A in chloroform (0.500 g/mL) at 25.0°C shows a rotation of +2.5° in a 1.0 decimeter cell. What is the specific rotation?

\[
[a]_\text{temp} = \frac{\alpha}{L \times C} = \frac{+2.5°}{1.0 \text{ dm} \times 0.50 \text{ g/mL}} = +5.0° \text{ dm}^{-1} \text{g/mL}^{-1}
\]

What is the observed rotation of A in a 0.5 dm cell?

\[
\alpha = [a] \times L \times C = 5.0° \text{ dm}^{-1} \text{g/mL}^{-1} \times 0.5 \text{ dm} \times 0.5 \text{ g/mL} = +1.25°
\]

What is the observed rotation if \(C = 0.050\) g/mL?

\[
\alpha = [a] \times L \times C = 5.0° \text{ dm}^{-1} \text{g/mL}^{-1} \times 1.0 \text{ dm} \times 0.050 \text{ g/mL} = +0.25°
\]

Enantiomeric Excess

A mixture of enantiomers may be enriched in one enantiomer. We can measure the enantiomeric excess (ee)

\[
\% \text{ Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100
\]

Example: The optical rotation of a sample of 2-butanol is +6.76°. What is the enantiomeric excess?

Enantiomeric excess = \(\frac{+6.76°}{+13.52°} \times 100 = 50\%
\)

The Synthesis of Chiral Molecules

Most chemical reactions which produce chiral molecules generate the racemic mixture (50%R, 50% S)

\[
\text{Butane (achiral molecules)} \quad + \quad \text{Hydrogen (achiral molecules)} \quad \text{but 50:50 mixture (R) and (S)}
\]

Enantioselective Synthesis

If all starting materials and reactants are achiral, the products will be achiral or racemic. If one of the reagents is chiral, as is common in biological systems, then the products may be chiral.

E.g.: picking out the left handed gloves from a racemic mixture of rights and lefts

\[
\text{5-chloro-2-pentanone (achiral)} \quad \text{enzymatic reduction} \quad \text{alcohol dehydrogenase} \quad \text{5-chloro-2-pentanol (99% ee)}
\]

Top and bottom faces of the ketone bond are different to handed reagents.
**Enantioselective Synthesis in the lab**

Synthetic chemists are designing chiral catalysts that mimic the enantioselectivity of enzyme-catalyzed reactions.

![Enantioselective Synthesis](image)

**Chiral Drugs and Pharmaceutical Companies**

Typically only one enantiomer of a drug is biologically active.

Preparation of only the desired enantiomer saves material, costs, and possible side effects.

![Chiral Drugs](image)

**Molecules with More than One Stereogenic Center**

Each new center may generate a potential pair of stereoisomers, so the theoretical number of possible stereoisomers is $2^n$.

(May have fewer if symmetry elements are present)

![Molecules with More than One Stereogenic Center](image)

**Four stereoisomers of 2,3-dibromopentane**

- Relationship of 1 and 2 = enantiomers
  - Enantiomers: same properties, cannot be separated

- Relationship of 3 and 4 = enantiomers
  - Enantiomers: same properties, cannot be separated

- 1 and 3 (or 1 and 4) = diastereomers
  - Diastereomers: stereoisomers not mirror images of each other
  - Have different physical properties and can be separated

![Four Stereoisomers](image)

**Four stereoisomers of 2,3-dibromopentane**

- We cannot simply say that 1 is an enantiomer or a diastereomer

- Stereoisomerism refers to the relationship between two isomers

![Four Stereoisomers](image)

**Meso compounds**

Sometimes molecules with 2 or more stereogenic centers will have less than the maximum amount of stereoisomers.

![Meso compounds](image)
**Mesocompound are achiral**

- Because superposable on its mirror image
- Despite the presence of stereogenic centers
- Not optically active
- Has a plane of symmetry

Definition: a meso compound is a compound that is achiral despite having stereogenic centers

**Mesocompounds and Racemates**

Under achiral conditions, a synthesis of 2,3-dibromobutane may create:
- A and B in equal amounts (the racemate)
- C (the meso product)
- Some mixture of racemate (A/B) and meso compound C

**Naming Compounds with More than One Stereogenic Center**

Using same rules, assign each stereogenic center separately

**Example:** (2R, 3R)-2,3-dibromobutane

**Fischer Projections**

A 2-dimensional representation of chiral molecules
- Vertical lines represent bonds projecting behind the plane of the paper
- Horizontal lines represent bonds projecting out of the plane of the paper

**Relating Configurations of Stereogenic Centers**

If no bonds to the stereogenic carbon are broken, the reaction proceeds with retention of configuration

**Relative Configurations: (D)- and (L)-Glyceraldehyde**

The stereomers of Glyceraldehyde

Over 100 years ago, Fischer assigned the deuterioaldehyde (+) to a stereocenter, the configuration we call (R), and the deuteriomethyl (-) to a stereocenter was assigned the (S) configuration.

The labels Fischer assigned were called (D) and (L). Those assignments were a guess.
An Example: Relating (-)-Lactic Acid to (+)-Glyceraldehyde

\[(\text{+})\text{-glyceraldehyde} \xrightarrow{\text{oxidation}} \text{(-)-3-bromo-2-hydroxypropanoic acid} \]

This transformation shows that (+)-isoserine has the same absolute configuration as (-)-lactic acid.

(-)-lactic acid

For 1951 the absolute configurations were not known. Only these relative configurations were known from carefully designed chemical transformations linking the assignments to the configurations of the glyceraldehydes assumed by Emil Fischer.

1951, X-ray crystal structure of (+) tartaric acid showed Fischer made the right guess!

### Stereoisomerism of Cyclic Compounds

Consider 1,2-dimethylcyclopropane

Two stereogenic centers

Trans isomer has two enantiomers R,R and S,S

Cis isomer is a meso compound

1,3-dimethylcyclohexane

The trans and cis compounds each have two stereogenic centers

The cis compound has a plane of symmetry and is meso

The trans compound exists as a pair of enantiomers

Ring flip of (a) produces another (a), not the mirror image (b)

### Separation of enantiomers = resolution

Cannot be separated directly Why not?

Can be separated by chiral reagent which creates diastereomeric relationship

Racemic Form

Diastereomers (different properties)

R is a resolving agent. It is a single enantiomer such as R of a chiral compound.
**General Approach to Resolution**

Often use organic acids or bases which are found optically pure in nature.

Can form acid-base salts which usually assures a high melting point and the potential to separate by selective crystallization.

Easily regenerate starting acid or base.

![Quinine](image)

**(++)-2-phenylpropanoic acid**

- **(+,-)-2-phenylpropanoic acid (racemic form)**
- **(+)(-)-Salt**
- **(-)(-)-Salt**

**Diastereomers**

Separate by fractional crystallization.

**Resolution of a Carboxylic Acid**

![Resolution Diagram](image)

**Chiral Molecules without a tetrahedral carbon**

Some molecules begin a helical chirality by restricted rotation.

![Chiral Molecules](image)

**Chirality without tetrahedral atoms**

- **Atropoisomer:** conformational isomers that are stable.
  - ![Atropoisomer](image)
  - ![Atropoisomer](image)

- **Allenes:** contain two consecutive double bonds.
  - ![Allen](image)
  - ![Allen](image)