Chapter 5
Stereochemistry
The study of the 3-dimensional structure of molecules

Stereoisomers: have the same bonding sequence, but differ in the orientation of their atoms in space

Example: 2-butene

\[
\begin{array}{c}
\text{cis-2-butene} \\
\text{trans-2-butene}
\end{array}
\]

\[
\begin{array}{c}
\text{cis= both substituents (CH}_3\text{) are on the same side of the double bond} \\
\text{trans= both substituents (CH}_3\text{) are on opposite sides of the double bond}
\end{array}
\]
**Chirality and Enantiomers (5-2)**

✓ **Chiral objects**: are those that have right-handed and left-handed forms.

The chirality of an object can be determined by **looking at its mirror image**.
A chiral object has a mirror image that is different from the original object (it is non-superimposable).

Figure 5-1

Chiral

Achiral: object that is not chiral
Molecules can either be chiral or achiral

Figure 5-6
Chiral compound

Figure 5-7
Achiral compound
In **B**: the original molecule and its mirror image are non-superimposable (**no plane of symmetry**)

**Chiral**

In **A**: the original molecule and its mirror image are superimposable (**plane of symmetry**)

**Achiral**
Two molecules are said to be **superimposable** if they can be placed on top of each other and the **3-D position** of each atom on one molecule coincides with the **equivalent atom** on the other molecule.

Molecules that are **non-superimposable mirror images** are called: **Enantiomers**
Nomenclature of Asymmetric Carbon Atoms (5-3)

- For a carbon atom to be chiral, it must have 4 different substituents. In this case the carbon atom is called:
  - Chiral carbon
  - Chiral centre
  - Asymmetric carbon
  - Stereocentre

Figure 5-6
Asymmetric carbons are marked with an asterisk.

Figure 5-4
Generalizations

- If a compound has no chiral carbon, it is usually achiral

- If a compound has just one chiral carbon, it is always chiral

- If a compound has more than one chiral carbon, it may or may not be chiral
Rule of thumb:

Any molecule that has an internal plane of symmetry cannot be chiral, even though it may contain chiral carbon atoms.

Figure 5-3

* cis-1,2-dichlorocyclopentane (achiral) *

* trans-1,2-dichlorocyclopentane (chiral) *
Because enantiomers are actually 2 distinct molecules with different properties, a notation (nomenclature) system for naming configurations of chiral carbon atoms was proposed by:

Cahn-Ingold-Prelog

- It assigns a letter (R) or (S) to the chiral carbon
Procedure to assign “R” and “S”

- Assign a priority to each group attached to the chiral centre
  - 1) highest priority
  - 2) next highest
  - 3) next highest
  - 4) lowest priority
higher atomic # (or atomic mass) gets the highest priority (this is for the atom directly attached to the chiral carbon)

- Question:
  Assign the priorities for all the groups in this molecule.

\[
\text{CH}_3
\]
\[
\begin{array}{c}
\text{C} \\
\text{H} \\
\text{F} \\
\text{NH}_2
\end{array}
\]
In case of a tie, use the next atom along the chain as tie breaker

- Question:
  Assign the priorities for all the groups in this molecule.
Treat double and triple bond as if each were bonds to a separate atoms

\[
\begin{align*}
\text{R} & \text{C} &= \text{C} & \text{becomes} & \text{R} & \text{C} &= \text{C} & \text{H} \\
\text{break and duplicate} & & & & \text{C} & \text{C} \\
\text{R} & \text{C} &= \text{N} & \text{becomes} & \text{R} & \text{C} &= \text{N} & \text{H} \\
\text{break and duplicate} & & & & \text{N} & \text{C} & \text{C} & \text{C} \\
\text{R} & \text{C} &= \text{C} & \text{H} & \text{becomes} & \text{R} & \text{C} &= \text{C} & \text{H} \\
\text{break and duplicate} & & & & \text{C} & \text{C} \\
\text{R} & \text{C} &= \text{O} & \text{becomes} & \text{R} & \text{C} &= \text{O} & \text{H} \\
\text{break and duplicate} & & & & \text{O} & \text{C}
\end{align*}
\]
– Question:

Assign the priorities for all the groups in this molecule.
Using a molecular model or a 3-D drawing, place the group with the lowest priority in the back (pointing away from you).

Look at the molecule along the bond from the chiral centre to the lowest priority group.
Draw an arrow going from the first priority group to the second and third.

If the arrow follows a **clockwise rotation**: notation “R”

If the arrow follows a **counterclockwise rotation**: “S”
When the lowest priority group is not located in the back, a rotation may be needed in order to facilitate the determination of the configuration.
Question:
Predict the configuration.
 Tricks:

It is often difficult to rotate an entire molecule. In this case, use either of the two tricks below.

(A) if you look through the 4 to C priority bond (ie the opposite to what you should do), simply reverse your answer since you are looking at the mirror image of the original molecule.

Looking through 4-C, a S configuration is obtained….therefore, the correct answer is the mirror image of this one, ie: R
(B) Or you can use your right (R) or left (S) hand to determine the configuration. Use your thumb to point through the C-4 bond, the tip of your other fingers are now the arrow head. If you use your right hand = R configuration, left hand = S configuration.

Using your left hand, your fingertips
Go from 1 to 3 (wrong hand)

With your right hand, the fingertips
Go from 1-2-3 (correct).

R configuration
Practice Questions

What is the configuration of the chiral centers in the following compounds?
What is the configuration of the chiral centers in the following molecules?
Optical Activity (5-4)

✎ Chiral compounds have a physical property that other compounds do not have:

✎ Optical activity: it is the ability of chiral molecules to rotate the plane of polarized light.

✎ Molecules that can rotate the plane of polarized light are: Optically active

Instrument used is: Polarimeter

Figure 5-13
Rotations of the plane that are clockwise are:

Dextrorotatory and (+)

Rotations of the plane that are counterclockwise are:

Levorotatory and (-)

NOTE: These signs and terms have nothing to do with “R” and “S” notations
Specific Rotation

symbolized by (α): measure of optical activity. This is a physical property.

\[
[\alpha]_{\lambda} = \frac{\alpha}{l \times c}
\]

- \( \alpha \) = rotation observed
- \( c \) = concentration of the sample (in g/mL)
- \( l \) = length of the cell (in decimeter)
- \( T \) = temperature
- \( \lambda \) = wavelength of light source

Depends on:
- concentration of sample
- Path length of the cell used
- Temperature
- Wavelength of light source
Practice Question

The observed rotation of 2.0g of a compound in 50mL of solution in a polarimeter tube of 20cm long is +13.4°. What is the specific rotation of the compound?
What would be the optical rotation of the enantiomer of this compound?
**Racemic mixtures (5-6)**

Suppose we have an equal amount of

- (++)-2-butanol \([\alpha]_D = 13.5^\circ\)
- (–)-2-butanol \([\alpha]_D = -13.5^\circ\)

✓ The observed optical rotation for this mixture will be zero

✓ An equal mixture of 2 enantiomers is called:

“racemic mixture” or “racemate” and it is optically inactive
Enantiomeric excess (ee) (5-7)

This is the measure of optical purity

✓ If a mixture is neither a racemate nor an optically pure compound, the optical purity must be determined

\[
\text{optical purity} = \text{ee} = \frac{[\text{experimental rotation}]}{[\text{rotation of pure enantiomer}]} \times 100
\]
Practice Question

A mixture of (+)-2-butanol and (-)-2-butanol gives an optical rotation of 9.54°. What is the optical purity of the mixture?
If you know the amounts of each compounds present in the mixture, it is not necessary to know the optical rotation of the pure enantiomer in order to calculate the ee.

\[
\text{ee} = \left| \frac{R - S}{R + S} \right| = \left| \frac{(+) - (-)}{(+) + (-)} \right|
\]
Example

A mixture is composed of 6g of (+)-2-butanol and 4g of (-)-2-butanol. What is the ee of the mixture?

\[
ee = \frac{6 - 4}{6 + 4} = 20\%
\]

Example 2

What is the ee of a mixture made of R/S = 5/1?

\[
ee = \frac{5 - 1}{5 + 1} = 67\%
\]
Practice Question

(+) - Mandelic acid has a specific rotation of +158°. What would be the observed specific rotation of the following mixtures?

(a) 25% (-)-isomer and 75% (+)-isomer
(b) 50% (-)-isomer and 50% (+)-isomer
**Fisher Projections** (5-10)

looks like a cross with the **horizontal bonds** projecting out towards the viewer and the **vertical bonds** projecting away.

In Fisher projections, **only the central carbon atom** is in the plane.
Rules for drawing Fisher Projections

- Longest carbon chain is always vertical
- Most oxidized carbon is on top
- Rotation of $180^\circ$ do not change the molecule (must be kept in the plane)
Practice Question

Determine the configurations of the chiral centers in these compounds.
Draw the Fisher projections of the two enantiomers of:

Br
\[\text{OH}\]

Cl
\[\text{CH}_3\]
Diastereomers (5-11 to 5-13)

Summary of Isomerism

- **Isomers**: compounds with same molecular formula
  - **Structural Isomers**: different bonding sequence
  - **Configurational Isomers**: isomers containing chiral carbons
    - **Enantiomers**: non-superimposable mirror images
    - **Diastereomers**: not mirror images
  - **Geometric Isomers**: cis or trans isomers (by definition, geometric isomers are diastereomers)
  - **Stereoisomers**: different 3D arrangement of atoms
Diastereomers:
Configurational diastereomer with chiral centers must have at least 2 chiral carbons
✓ NOTE  diastereomers have at least 2 chiral carbons, one of which has the same configuration

![Structures of diastereomers](image)

enantiomers of *trans*-1,2-dimethylcyclopentane

*cis*-1,2-dimethylcyclopentane (achiral)

✓ Usually, the number of possible stereoisomers for a given molecule is equal to:  

\[ \# \text{ stereoisomers} = 2^n \]

where \( n \) = # of chiral carbons
✓ Practice Question

How many stereoisomers? Draw all possibilities.
Using the answer from the previous examples, pair the enantiomers and the diastereomers.
How many stereoisomers are expected? Can you draw them all? Can you pair them as enantiomers and diastereomers?
Exception

Sometimes this general rule does not give the exact number of stereoisomers

Example: 2,3-dibromobutane

- **Enantiomers**: (2R,3R) and (2S,3S)
- **Same Compound!**: (2R,3S) and (2S,3R)

The (±) diastereomer

The *meso* diastereomer

Mirror plane of symmetry

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Result: only 3 stereoisomers
2 enantiomers (optically active if pure)
1 diastereomer (always optically inactive since it is achiral)

This achiral diastereomer is called:
Meso diastereomer (compound)
Meso compounds

Are achiral compounds with chiral carbons. These compounds are also optically inactive.

enantiomers of trans-1,2-dimethylcyclopentane

cis-1,2-dimethylcyclopentane (achiral)
Practice Question

Which of the following compounds has a stereoisomer that is a meso compound?

(a) 2,4-dibromohexane
(b) 2,4-dibromopentane
(c) 2,4-dimethylpentane
(d) 1,3-dichlorocyclohexane
(e) 1,4-dichlorocyclohexane
(f) 1,2-dichlorocyclobutane
Study Problems

✓ 5-26 For each structure:

Star (*) the asymmetric atoms

assign a configuration (R or S)

label structure as chiral, achiral and meso
5-32

Calculate the specific rotation of the following sample taken at 25°C using the sodium D line. 1.0 g sample is dissolved in 20.0 mL of ethanol. Then 5.0 mL of this solution is placed in a 20.0 cm polarimeter tube. The observed rotation is 1.25° counterclockwise.
Draw all the stereoisomers of 1,2,3-trimethylcyclopentane and give the relationships between them.
5-33

(+)-Tartaric acid has a specific rotation of $+12.0^\circ$. Calculate the specific rotation of a mixture of 68% (+)-tartaric acid and 32% (-)-tartaric acid.
5-29

Convert the following Fisher Projections to perspective formulas.

\[
\begin{align*}
\text{CHO} \\
\text{H} & \quad \text{OH} \\
\text{CH}_2\text{OH} \\
\text{CH}_2\text{OH} \\
\text{H} & \quad \text{Br} \\
\text{H} & \quad \text{Cl} \\
\text{CH}_3
\end{align*}
\]