Chapter 4: Stereochemistry
Consider two of the compounds we produced while finding all the isomers of \( \text{C}_7\text{H}_{16} \):

- 2-methylhexane
- 3-methylhexane

2-methylhexane is superimposable with its mirror image.
Consider two of the compounds we produced while finding all the isomers of $C_7H_{16}$:

2-methylhexane is superimposable with its mirror image.
Introductor To Stereochemistry

Consider two of the compounds we produced while finding all the isomers of $C_7H_{16}$:

- Compounds that are not superimposable with their mirror image are called **chiral** (in Greek, chiral means "handed") 3-methylhexane is a chiral molecule.

- Compounds that are superimposable with their mirror image are called **achiral**. 2-methylhexane is an achiral molecule.

- An atom (usually carbon) with 4 different substituents is called a **stereogenic center** or **stereocenter**.
Two compounds that are non-superimposable mirror images (the two "hands") are called enantiomers.
Introduction To Stereochemistry

**Structural (constitutional) Isomers** - Compounds of the same molecular formula with different connectivity (structure, constitution)

2-methylpentane  
3-methylpentane

**Conformational Isomers** - Compounds of the same structure that differ in rotation around one or more single bonds

**Configurational Isomers** or **Stereoisomers** - Compounds of the same structure that differ in one or more aspects of stereochemistry (how groups are oriented in space - enantiomers or diastereomers)

3-methylhexane  
3-methylhexane

We need a a way to describe the stereochemistry!
The CIP System Revisited

1. Rank each substituent attached to the stereocenter according to the CIP priority system (1 = highest, 4 = lowest)

```
Me  H
3  4
```
```
H  Me
4  3
```

2. "View" the compound with the lowest priority substituent pointing away from you

```
Me  H
3  4
```
```
Pr  H4
2  1
```
```
Pr  Et
1  2
```
```
H  Me
4  3
```
```
H  Me
4  3
```
```
H  Me
4  3
```
```
H  Me
4  3
```

3. Draw a circular arrow from connecting substituents 1–3 from highest to lowest priority. If the arrow moves clockwise, the stereocenter is labeled (R) [this stands for rectus]. If the arrow moves counterclockwise, then the stereocenter is labeled (S) [this stands for sinister].

```
Me  H
```
```
Et  Pr
1  2
```
```
Pr  Et
1  2
```
```
H  Me
```
```
H  Me
```
```
H  Me
```

(S)-3-methylhexane  counterclockwise  clockwise  (R)-3-methylhexane
The CIP System Revisited
The CIP System Revisited

(R)-2-fluorobutane

(S)-3-tert-butylcyclohexene

(S)-4-bromo-2-methyl-1-pentene

(R)-2-hydroxy-2-methyl-butanal
Properties of Chiral Molecules

Chiral objects can only be "recognized" as chiral by another chiral object

Carvone

Which is (S) and which is (R)? [Your nose can tell!]

Properties of Chiral Molecules

*Chiral objects can only be "recognized" as chiral by another chiral object*

Which is (S) and which is (R)? [Your nose can tell!]

(R)   

(S)
Properties of Chiral Molecules

*Chiral objects can only be “recognized” as chiral by another chiral object*

(R)-carvone [odor of spearmint]  
(S)-carvone [odor of caraway seed]
**Multiple Stereocenters**

1 stereocenter: 2 stereoisomers

- (S)-3-methylhexane
- (R)-3-methylhexane

2 stereocenter: 4 stereoisomers

- 3(S), 4(S)-3-chloro-4-methylhexane
- 3(R), 4(S)-3-chloro-4-methylhexane
- 3(S), 4(R)-3-chloro-4-methylhexane
- 3(R), 4(R)-3-chloro-4-methylhexane
Multiple Stereocenters

What about these relationships?

Stereoisomers that are not enantiomers (non-superimposable mirror images) are called diastereomers.
Multiple Stereocenters

For any compound, the maximum number of stereoisomers is \(2^n\) where \(n\) is the number of stereocenters.
Multiple Stereocenters

How many stereoisomers for 3,4-dimethylhexane?

- (3S,4S)-3,4-dimethylhexane
- (3R,4R)-3,4-dimethylhexane

The same compound! (superimposable)

enantiomers
Meso Compounds

3,4-dimethylhexane has 3 stereoisomers!

meso-3,4-dimethylhexane
meso-3,4-dimethylhexane
(3S,4S)-3,4-dimethylhexane
(3R,4R)-3,4-dimethylhexane

A Meso Compound (achiral)

Enantiomers (chiral)
The best way to identify a meso compound is to prove that it is superimposable with its mirror image. However, a quick test is to see if it contains a plane of symmetry:

*Compounds containing a plane of symmetry are achiral!*

*No plane of symmetry*
The Isomers of $C_3H_4Cl_2$, Revisited
The Isomers of $\text{C}_3\text{H}_4\text{Cl}_2$, Revisited

The image contains chemical structures of various isomers of $\text{C}_3\text{H}_4\text{Cl}_2$. The structures include both single and double bond isomers, as well as cyclopropane derivatives.
Racemic Mixtures

A 50:50 mixture of 2 enantiomers is called a **racemic mixture** or a **racemate**.
**Racemic Mixtures In Medicine**

\[ \text{HO-CH}_3 \text{CH}_3 \ \text{CH}_3 \ \text{O} \ \text{H} \quad \text{HO-CH}_3 \text{CH}_3 \ \text{CH}_3 \ \text{O} \ \text{H} \]

(S)-ibuprofen (active)  \quad  (R)-ibuprofen (inactive)

**Advil** Tablets

Prescribed worldwide from 1957-1961 for morning sickness and as a sleep aid

\[ \text{N} \ \text{NH} \ \text{O} \ \text{O} \ \text{O} \ \text{O} \ \text{H} \quad \text{N} \ \text{NH} \ \text{O} \ \text{O} \ \text{O} \ \text{O} \ \text{H} \]

(R)-Thalidomide (analgesic)  \quad  (S)-Thalidomide (teratogenic)
Optical Rotation and Polarimetry

Chiral molecules will rotate polarized light:

monochromatic light source
randomly oriented light

optical polarizer - only allows "vertical" light to pass through

optical polarizer - only allows "horizontal" light to pass through

detector
**Optical Rotation and Polarimetry**

The maximum signal will be obtained if the second polarizer is rotated to match the light rotation:

- **Monochromatic light source**
- **Randomly oriented light**
- **Optical polarizer** - only allows "vertical" light to pass through
- **Chiral material**
- **Optical polarizer** - only allows "horizontal" light to pass through
- **Detector**
The amount (in degrees) that a chiral material will rotate light is called the **optical rotation**. Different chiral molecules will have optical rotations that vary in direction and size of the optical rotation. Enantiomers will always have equal optical rotations but in opposite directions.

The **optical purity** of a substance can be measured by comparing the optical rotation of the sample to the known optical rotation of a single enantiomer of that compound. Optical purity is usually reported in percent **enantiomeric excess (\%ee)**.

\[
\%ee = \frac{\text{sample rotation}}{\text{single enantiomer rotation}} \times 100
\]

Enantiomeric excess is the % of the sample that is non-racemic. For example, 80% ee means that there is 90% of one enantiomer and 10% of the other.
Vocabulary

• **(R) or (S):** identifies the configuration of a stereocenter using the CIP priority system

• **d- or (+):** indicates that a (chiral) compound rotates light in a clockwise direction (this has no correlation with S or R)

• **l or (-):** indicates that a (chiral) compound rotates light in a counterclockwise direction (this has no correlation with S or R)

• **dl or (+/-) or rac-:** indicates a racemate
Resolution of Enantiomers

(R)-compound X
(S)-compound X

react or somehow associate with:
(R)-compound Y

(S)-compound X......(R)-compound Y
(R)-compound X......(R)-compound Y

Separate by some technique (chromatography, crystallization, distillation, etc.)

(S)-compound X......(R)-compound Y
(R)-compound X......(R)-compound Y

single diastereomer

somehow remove compound Y

(S)-compound X
(R)-compound X

single diastereomer

single enantiomer

single enantiomer

Single enantiomer

mixture of 2 diastereomers

racemic mixture of enantiomers
Resolution of Enantiomers

$\text{(S)}$-2-chloropropionic acid

\[
\begin{align*}
\text{(S)}-2\text{-chloropropionic acid} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH}
\end{align*}
\]

$\text{(R)}$-2-chloropropionic acid

\[
\begin{align*}
\text{(R)}-2\text{-chloropropionic acid} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH}
\end{align*}
\]

$\text{(R)}$-$\alpha$-methylbenzylamine

\[
\begin{align*}
\text{(R)}-\alpha\text{-methylbenzylamine} & \quad \text{H}_2\text{NCH}_2\text{C}_6\text{H}_4\text{CH}_3 \\
\text{H}_2\text{NCH}_2\text{C}_6\text{H}_4\text{CH}_3 & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{H}_2\text{NCH}_2\text{C}_6\text{H}_4\text{CH}_3 & \quad \text{Me}_2\text{CCH}_2\text{COOH}
\end{align*}
\]

The $R,S$-diastereomer of the salt

\[
\begin{align*}
\text{The } R,S\text{-diastereomer of the salt} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH}
\end{align*}
\]

The $R,R$-diastereomer of the salt

\[
\begin{align*}
\text{The } R,R\text{-diastereomer of the salt} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH}
\end{align*}
\]

$\text{(S)}$-2-chloropropionic acid

\[
\begin{align*}
\text{(S)}-2\text{-chloropropionic acid} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH} \\
\text{acidify} & \quad \text{Me}_2\text{CCH}_2\text{COOH}
\end{align*}
\]
Chirality Without Stereocenters

There is hindered rotation around this bond!
Chirality Without Stereocenters

Why is 1,3-dimethylallane (1,3-dimethyl-2,3-pentadiene) chiral?