Chapter 6

Principles of Stereochemistry

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Chapter 6 Overview

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• 6.10 Conformational Stereoisomers
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Stereoisomers

- Compounds that have the same connectivity, but a different arrangement of atoms in space
- An early example of this was E vs Z alkene isomers

Molecular models are essential for this chapter!

6.1 Enantiomers, Chirality, and Symmetry
Enantiomers and Chirality

**Chirality** (Greek “hand” or “handedness”)

- Construct the mirror image of a molecule
- If the mirror image is **congruent** (i.e., superimposable) with the original structure it is **achiral**
6.1 Enantiomers, Chirality, and Symmetry
Enantiomers and Chirality

- If the mirror image is non-congruent with the original structure it is chiral
- Molecules that are non-congruent mirror images are enantiomer

- Some macroscopic chiral objects include hands, screws, baseball gloves
6.1 Enantiomers, Chirality, and Symmetry
Asymmetric Carbon

Many chiral molecules contain one or more asymmetric carbons.

An asymmetric carbon is a carbon to which four different groups are attached.

An asterisk is a convention used to denote an asymmetric carbon.

6.1 Enantiomers, Chirality, and Symmetry
Stereocenters

- An atom at which the interchange of two groups gives a stereoisomer
- Also known as a stereogenic atom
- An asymmetric carbon is a type of stereocenter
Chirality and Symmetry

- Chiral molecules lack a certain type of symmetry
- Symmetry types include: lines, points, and planes
Nomenclature of Enantiomers

• Apply the same Cahn-Ingold-Prelog priority rules used to determine $E$ and $Z$ for alkenes
• Assign priorities to each of the groups
• View along the asymmetric carbon to the lowest priority group ($C^* \rightarrow #4$)
• Assign CW or CCW for $#1 \rightarrow #2 \rightarrow #3$
• CW = $R$ (rectus, Latin “proper”)
• CCW = $S$ (sinister, Latin “left”)

6.2 Nomenclature of Enantiomers: The $R,S$ System
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A stereoisomer is named by indicating the configuration of each asymmetric carbon before the systematic name.
I Properties of Enantiomers

Å Enantiomers share identical physical properties (m.p., b.p., n_D, density, heats of formation, etc.)

Å ...except for their interaction with plane-polarized light
6.3 Physical Properties of Enantiomers: Optical Activity
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Optical Activity

Å If the sample rotates the plane of polarized light CW → dextrorotatory (+)

Å If the sample rotates the plane of polarized light CCW → levorotatory (-)

Å Optical rotation (α) is a quantitative measure of optical activity

Å α = [α]cl

Å [α] = specific rotation; c = concentration; l = path length
Optical Activity of Enantiomers

Å Enantiomers rotate plane-polarized light in equal, but opposite directions

Å The sign of optical rotation is unrelated to $R$ and $S$ configuration of a compound
Racemic Mixtures

Â A mixture containing *equal amounts* of two enantiomers

Â *Racemates* typically have different physical properties from that of the pure enantiomers
Racemic Mixtures

- The process of forming a racemate from a pure enantiomer is called racemization.
- The separation of a pair of enantiomers is called enantiomeric resolution.
How does one determine the configuration of a new, enantiomerically pure compound?

Recall optical rotation does not reveal R and S

X-ray crystallography (anomalous dispersion) can be used if the compound is crystalline

The most common approach is to use stereochemical correlation
Stereochemical Correlation

Apply reactions that do not break any of the bonds to the asymmetric carbon

Caution!: Priorities may have changed

6.5 Stereochemical Correlation
Diastereomers

Additional stereoisomers are possible when a molecule has *two or more* asymmetric carbons.

Stereoisomers that are not enantiomers are called **diastereomers**.

Diastereomers are *not* mirror images.

Diastereomers *differ in all their physical properties*.

*6.6 Diastereomers*
Diastereomers

6.6 Diastereomers
6.6 Diastereomers and Enantiomers
Properties of Stereoisomers

6.6 Diastereomers

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Specific rotation at 25 °C, degrees mL g⁻¹ dm⁻¹</th>
<th>Melting point, °C</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2S,3R)</td>
<td>+15</td>
<td>150 – 151</td>
<td>Enantiomers</td>
</tr>
<tr>
<td>(2R,3R)</td>
<td>-15</td>
<td>150 – 151</td>
<td>Enantiomers</td>
</tr>
<tr>
<td>(2S,3R)</td>
<td>+21.5</td>
<td>155 – 156</td>
<td>Diastereomers</td>
</tr>
<tr>
<td>(2R,3S)</td>
<td>-21.5</td>
<td>155 – 156</td>
<td>Diastereomers</td>
</tr>
<tr>
<td>Racemate of</td>
<td></td>
<td>117 – 123</td>
<td></td>
</tr>
<tr>
<td>(2S,3R) and (2R,3R)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Racemate of</td>
<td></td>
<td>165 – 166</td>
<td></td>
</tr>
<tr>
<td>(2S,3R) and (2R,3S)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.6 Diastereomers
Meso Compounds

Å Meso compounds have two or more asymmetric carbons and are achiral
Å They are not optically active
Å They possess an internal mirror plane
Meso Compounds

A molecule with \( n \) stereocenters, can exist as \( 2^n \) stereoisomers.

This number is reduced if a meso compound is present among the possibilities.

2,3-Butanediol possesses two stereocenters = \( 2^n = 2^2 = 4 \) possible stereoisomers.
Stereoisomers of 2,3-Butanediol

6.7 Meso Compounds
Stereoisomers of 2,3-Butanediol

Two of the stereoisomers are the same

Hence, there are only three stereoisomers of 2,3-butanediol

6.7 Meso Compounds
Stereoisomers of 2,3-Butanediol

An internal plane of symmetry is present

6.7 Meso Compounds
Stereoisomers of 2,3-Butanediol

A Relationship among the 2,3-butanediol stereoisomers

6.7 Meso Compounds
Resolution of Enantiomers

Resolution: The separation of a racemate into pure enantiomers

Enantiomers have identical m.p., b.p., and solubility making separation a non-trivial task

Diastereomers have different physical properties, however

Temporary conversion of a racemate into a mixture of diastereomers is the best strategy
Resolution of Enantiomers

**Resolving agent:** An enantiomERICALLY pure chiral compound used to form diastereomers from a racemic mixture

**A common method is diastereomeric salt formation**

![Chemical reaction diagram](image-url)
By this method a racemic mixture of an amine may be resolved with a chiral carboxylic acid.

Two diastereomeric salts are formed.

**Diastereomeric Salts**

6.8 Enantiomeric Resolution
Diastereomeric Salts

These salts have different physical properties.

The \( (S,R,R) \)-diastereomer is less soluble in methanol and can be selectively crystallized.
Diastereomeric Salts

Each pure enantiomer may then be recovered by decomposition of the salt with base.

\[ 2\text{NaOH} + \text{Ph-C-CH}_3-\text{C}-\text{C}-\text{H}_2-\text{H}_2\text{O} + \text{CO}_2^- + \text{Ph-CH}_3-\text{C}-\text{C}-\text{H}_2-\text{H}_2\text{O} \rightarrow \text{Ph-CH}_3-\text{C}-\text{C}-\text{H}_2-\text{H}_2\text{O} + \text{CO}_2^- \text{Na}^+ + 2\text{H}_2\text{O} \]

\[ pK_a = 9.5 \quad \text{salt} \]

\[ \text{insoluble in water} \]

\[ \text{soluble in water} \]

6.8 Enantiomeric Resolution
Asymmetric carbon atoms are unnecessary for chirality

That is, some chiral compounds contain no asymmetric atoms

By definition, an object is chiral if it is not congruent with its mirror image
Each compound contains \textit{three carbon stereocenters} (shown in magenta)

6.9 Chiral Molecules without Asymmetric Atoms
6.9 Chiral Molecules without Asymmetric Atoms

Each stereocenter can be verified by *interchanging any two groups* bound to it.

This interchange gives the other enantiomer.
**Conformational enantiomers**: Enantiomers interconverted by a conformational change

Butane contains no stereocenters, but it can exist as a pair of conformational enantiomers.
Conformational diastereomers:
Diastereomers that are interconverted by a conformational change

The anti conformation of butane is achiral and is a diastereomer of either one of the gauche butanes

Hence, anti-butane and either one of the gauche-butanes are conformational diastereomers
Despite the chirality of select conformers of butane, it is not optically active.
The isolation of an individual chiral conformer is not possible even at very low temperatures.
A molecule is achiral if we can find one achiral conformation.

6.10 Comformational Stereoisomers
Asymmetric Nitrogen

Amines with an asymmetric nitrogen atom have the potential for chirality

However, these two enantiomers cannot be resolved due to inversion of the lone pair

6.10 Comformational Stereoisomers
6.10 Comformational Stereoisomers
Newman projection:

(one conformation of (2S,3S)-2,3-pentanediol)
Informational Representations

A Sawhorse projection:

6.11 Drawing Structures that Contain Three-Dimensional Information
Conformational Representations

A Line-and-wedge structure:

6.11 Drawing Structures that Contain Three-Dimensional Information
History of Stereochemistry

The first chemical substance in which optical activity was observed was quartz (1815).

The first observation of enantiomeric forms of the same compound involved tartaric acid.

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{OH} \\
\text{C} & \quad \text{CH} \\
\text{C} & \quad \text{OH}
\end{align*}
\]

\text{tartaric acid}
History of Stereochemistry

Pasteur meticulously separated the “left-” and “right-handed” forms of a tartaric acid double salt via microscope (1848)

Note: The first resolution occurred by hand!
Van’t Hoff suggested that the arrangement of the four groups around carbon is key to the origin of enantiomerism (1874)

The ideal of tetrahedral carbon was promoted with other possibilities having been ruled out

6.12 The Postulation of Tetrahedral Carbon