Isomerism and Stereochemistry

Isomerism

Isomers are
- Compounds that have the same molecular formula but different structures
- Very important in chemistry, but especially important in the chemical reactions that take place in living organisms - the shape is as important as the functional groups present!
- Classified according to type

**Isomerism and Stereochemistry**
*(McMurry chapter 9)*

**Isomers**
Compounds with same molecular formula different structures

- **Constitutional Isomers**
  Differ in the nature sequence of bonding

- **Stereoisomers**
  Contain the same sequence of atoms and bonds but differ in the three dimensional arrangement of atoms

- **Conformational Isomers**
  Differ by rotation about single bonds. Conformers rapidly interconvert at room temperature

- **Configurational Isomers**
  All stereoisomers that are not conformers. Interconversion requires the breaking and reforming of bonds

So far, DIASTEROISOMERS
Isomerism and Stereochemistry

Example of constitutional isomers:

1-butene

2-butene

Example of conformational isomers:

(sawhorse representations)

Eclipsed staggered

Examples of configurational isomers:

(Z) -

(E) -

1,2-dimethyl cyclobutane

cis-

trans-

Question: Classify the following pairs of isomers as constitutional, conformational or configurational (diastereomers):

CH₃CH₂COOH

HOCH₂CH₂CHO

Cl

Cl

Cl

Cl

H

H

H

H

Cl

Cl

H

H

H

H


Sub-classes of *configurational* isomers:

Note: these definitions apply when we are comparing two structures!

**Configurational Isomers**

*All stereoisomers that are not conformers.*

Interconversion requires the breaking and reforming of bonds.

**Enantiomers**

Stereoisomers which are *non-superimposable mirror images of each other.*

**Diastereomers**

Stereoisomers which are *not mirror images of each other.*

Note: "*diastereomer*" and "*diastereoisomer*" are equivalent terms.
Chirality in Organic Chemistry

• An object (such as a molecule!) is chiral if it is not superimposable upon its mirror image.

• The two non-identical mirror image compounds are called enantiomers.

• With a few important exceptions, enantiomers have identical physical and chemical properties.

We will look at three separate areas:

• Structures of chiral compounds
• Samples of chiral compounds
• Reactions of chiral compounds

Structures of Chiral Compounds: Stereogenic Centres
(also known as "stereocentres" or "chiral centres")

• A stereogenic centre is an sp³ hybridised carbon with four different groups attached to it.

Example:

A chiral molecule usually contains one or more stereogenic centres. In these molecules there is no plane of symmetry.

(Plane of symmetry - a mirror plane that cuts a molecule in half, so that one half of the molecule is the mirror reflection of the other half)

If a molecule contains a stereocentre, its mirror image is non-superimposable, i.e. it is a chiral molecule.
Compounds which lack stereogenic centres are **achiral**

Example:

An **achiral** molecule is identical with its reflection and contains a plane of symmetry.
Question: Identify with an asterisk (*) the stereogenic centres in the following molecules:
Samples of chiral compounds: *optical activity*

As we noted a little earlier, enantiomers generally have identical physical and chemical properties. Here are the important exceptions:

- Enantiomers differ in the way in which they interact with *other chiral molecules*.
- Enantiomers differ in the way in which they interact with *plane polarised light*.

The interaction of chiral molecules with plane polarised light:

(Plane polarised light consists of waves oscillating in only one plane.)

- All chiral compounds (enantiomers) rotate the plane of polarised light to some extent - this is why they are called *optically active*.
- We use an instrument called a *polarimeter* to measure the *sign* and *magnitude* of the rotation. It is not possible to predict these two values by looking at the structure - it must be measured experimentally.
- A sample of one enantiomer rotates the plane of polarised light with the *same magnitude* but in the *opposite direction* to the other enantiomer.

**Physical Properties - Optical activity**

Amount of rotation $\alpha$ is a characteristic of the enantiomer.

Rotation in a *clockwise* direction is labelled (+) and rotation in a *counter-clockwise* direction is labelled (-).

- [Image of limonene structures]
  - (+)-limonene: odor in oranges
  - (-)-limonene: odor in lemons
A mixture of equal amounts of the two enantiomers will give no net rotation and is called a **racemic mixture**.

**Chemical Properties**

We live in an asymmetric world!

- The enantiomers of a chiral molecule behave in an identical way when reacting with an *achiral* reagent (e.g. the two enantiomers of 2-butanol are oxidized at the same rate with $\text{H}^+/\text{Cr}_2\text{O}_7^{2-}$ to give 2-butanone).
- But they may react quite differently to one another towards another chiral compound.

**Examples**

Our smell and taste receptors are chiral and so may differentiate between enantiomers

- *limonene* (odor in oranges)
- *odor in lemons*
- *asparagine* (bitter)
- *sweet*

Pharmaceuticals are often sold as a mixture of the two enantiomers:

- *ibuprofen*
There have been cases in which the two enantiomers have very different effects in the body:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

*thalidomide*

\[
\begin{align*}
\text{mild sedative} & \quad \text{extreme teratogen}
\end{align*}
\]

Can also be written omitting the H at the stereogenic centre:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

*thalidomide*

\[
\begin{align*}
\text{mild sedative} & \quad \text{extreme teratogen}
\end{align*}
\]

**General Rule:** if an ACHIRAL molecule is converted to a CHIRAL molecule then the product will be a *racemic mixture* (50% R enantiomer and 50% S enantiomer).

Example:

1. 

\[
\begin{align*}
\text{O} & \quad 1. \text{NaBH}_4 \\
\text{CH}_3 & \quad 2. \text{H}^+ / \text{H}_2\text{O}
\end{align*}
\]

Why?
**Structures Of Chiral Compounds: Nomenclature**

(McMurray 9.5)

**Describing the absolute configuration of a stereogenic centre**

It is very important to know which of the two possible enantiomers you are dealing with. Use the \((R)\)- and \((S)\)- descriptors to name enantiomers.

- A stereogenic centre of **one** possible absolute configuration
- A stereogenic centre of the **other** possible absolute configuration

This enantiomer has an absolute configuration designated as \((S)\)-

This enantiomer has an absolute configuration designated as \((R)\)-
Describing the **absolute configuration** of a stereogenic centre

**How to do it:**
1. Assign the 4 groups in order of "priority" (1st, 2nd, 3rd and 4th).
2. Classify the 3D arrangement of the 1st, 2nd, 3rd and 4th priority groups as either (R)- or (S)-.

1. **Assigning priorities - the sequence rules** (compare E/Z alkene nomenclature):

   (i) The higher the atomic number, the higher the priority.
   
   i.e.  I > Br > Cl > OH > NH₂ > CH₃ > H

   (ii) If two atoms attached to the stereogenic centre are the same, move down the chain to the next atoms and compare their atomic numbers.
   
   i.e. HOCH₂⁻ > H₂NCH₂⁻ > CH₃CH₂⁻
   (since O > N > C)

   (iii) Expand multiple bonds to give the same number of single bonds to that atom.

   i.e artificially replicate them as though they are all singly bound, eg.

   hence:
   
   \[ \text{–COOH} > \text{–CHO} > \text{–CH₂OH} \]

   \[ \text{C(O,O,O)} \quad \text{C(O,O,H)} \quad \text{C(O,H,H)} \]
Describing the absolute configuration of a stereogenic centre \((continued)\)

2. Classify the 3D arrangement of the 1st, 2nd, 3rd and 4th priority groups as either \((R)\)- or \((S)\)-

(i) Rotate the molecule to place the lowest (4th) priority group \(\text{behind}\) the plane of the page.

(ii) Pass over the 1st, 2nd and 3rd priority groups \(\text{in this order}\)!
If you went in a \(\text{clockwise}\) direction, the stereogenic centre has the \((R)\)- \text{configuration}.
If you went in an \(\text{anticlockwise}\) direction, the stereogenic centre has the \((S)\)- \text{configuration}.

\[
\begin{array}{c}
\text{behind page!} \\
\text{behind page!}
\end{array}
\]

Question: Assign the configurations of the following stereogenic centres:
Give the constitutional formula of the following compounds:

(i) $(R)$-1-bromo-2-methylbutane

(ii) $(S)$-2-bromo-2-phenylacetic acid

(iii) $(R)$-2,3-dimethyl-1-pentene
What if the lowest priority group is not pointing behind the plane??

Need to rotate the molecule in space to put the lowest priority group pointing behind the plane of the board so that sequence rules can be applied.

In 2-dimensions this can be done by applying the following rules:

- swap any two groups in 2D until you convert structure 1 into structure 2
- add up the total number of changes required
  
  ODD number (1 or 3) then you have a pair of enantiomers
  EVEN number (2 or 4) then you have the same compound.

EXAMPLES: Are the following A/B pairs the same compound or a pair of enantiomers?

\[
\begin{array}{ccc}
\text{A} & \text{B} \\
\begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{CH}_3 \\
\text{Cl}
\end{array} & \begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{H}_3\text{C} \\
\text{Cl}
\end{array}
\end{array}
\]

\[
\begin{array}{ccc}
\text{A} & \text{B} \\
\begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{CH}_3 \\
\text{CH}_2\text{CH}_3
\end{array} & \begin{array}{c}
\text{CH}_3\text{CH}_2 \\
\text{H} \\
\text{H}_3\text{C} \\
\text{Ph}
\end{array}
\end{array}
\]
NOTE: The Sequence Rules are also used to assign priorities and name alkenes \((E), (Z)\) nomenclature for alkenes

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\]

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

Give the full systematic name of the compound shown below:

\[
\begin{align*}
\text{H} & \quad \text{H} \quad \text{Cl} \\
\text{H}_3\text{C} & \quad \text{H} \quad \text{CH}_3
\end{align*}
\]
Samples of chiral compounds: optical activity revisited

As we noted earlier, a sample of one enantiomer rotates the plane of polarised light with the same magnitude but in the opposite direction to the other enantiomer.

What if we have mixtures of two enantiomers?
• A 50:50 mixture of two enantiomers is called a racemic mixture.
• Like achiral compounds, racemic mixtures do not rotate the plane of plane polarised light.
• There is no connection between the direction of optical rotation (+)/(-) and (R)/(S).

Reactions involving chiral compounds

The vast majority of biologically-important compounds (proteins, enzymes, nucleic acids, carbohydrates, fats, hormones, neurotransmitters, vitamins, medicines of all kinds, etc. etc.) are chiral organic molecules.

Your body can be viewed as simply a gigantic chemical factory, carrying out reactions/interactions involving (mainly chiral) organic molecules.

It is, therefore, of the utmost importance that we are able to understand how chiral organic molecules are generated, in which form they are produced (as a single enantiomer or as a mixture of the two enantiomers).

Let's look at a simple reaction that generates a chiral compound...
Electrophilic addition of bromine to propene

- Recall that these reactions occur by 2 discrete steps.

\[
\text{step 1: } H\text{C}=\text{C}H + Br\text{Br} \rightarrow \text{Br-Br}^+ \rightarrow \text{Br-Br}^+ + \text{H}_3\text{C}^+\text{H} \\
\text{step 2: } \text{Br-Br}^+ \rightarrow \text{Br-Br}^+ \rightarrow \text{Br-Br}^+ + \text{H}_3\text{C}^+\text{H} 
\]

- Br approach to carbocation from above
- Br approach to carbocation from below

A carbocation
**Fischer Projections**

- In order to simplify the presentation of chiral molecules, a system devised by Emil Fischer and originally used in sugar chemistry, is useful.

- The compound \((R)-(+)-\text{glyceraldehyde}\) and its enantiomer \((S)-(-)-\text{glyceraldehyde}\) can be represented in **Fischer projections** as shown below.

![Fischer projections](image)

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} & \quad \text{CHO} & \quad \text{CHO} \\
\text{H} \text{C} \text{OH} & \quad \text{H} \text{O} \text{H} & \quad \text{HO} \text{C} \text{H} & \quad \text{HO} \text{H} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

\((R)-(+)-\text{glyceraldehyde}\)

or D\((+)-\text{glyceraldehyde}\)

\([\alpha]_{D}^{20} + 11^\circ\)

\((S)-(-)-\text{glyceraldehyde}\)

or L\((-)-\text{glyceraldehyde}\)

\([\alpha]_{D}^{20} -11^\circ\)

**Rules**

1. Arrange atoms of carbon skeleton in a vertical line with the carbon of the most oxidized functional group at the top.

2. Horizontal lines represent substituents on the chiral carbon(s).

3. Horizontal lines project upwards

4. Vertical lines project downwards

This gives rise to two series of compounds

- **D series**: functional group on the penultimate carbon is on the **RIGHT**
- **L series**: functional group on the penultimate carbon is on the **LEFT**

- **The D/L nomenclature is used with Fischer projections and is the convention used in naming sugars and amino acids.**
Compounds With More Than One Stereogenic Centre

• **Diastereomers** are configurational isomers which are *not* mirror images of one another.

\[ \text{CH}_3 \quad \text{CH}_3 \]
\[ \text{C} \quad \text{C} \quad \text{OH} \]
\[ \text{H} \quad \text{H} \quad \text{OH} \]
\[ \text{CH}_3 \quad \text{CH}_3 \]

**NB**
- a normal line (——) represents a bond in the plane;
- a dashed line (-----) represents a bond behind the plane; and
- a heavy line (——) or wedge (        ) represents a bond in front of the plane of the paper.

Consider C\(_4\)H\(_8\)O\(_4\) :

4 possible stereoisomers: erythrose and threose

-can have (R)- or (S)- configuration at each of the stereocentres:

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

D-(-)-erythrose  L-(+)-erythrose  D-(-)-threose  L- (+)-threose

Relationship between erythroses and threoses??
**Meso Stereoisomers**

- simplification occurs when the 2 chiral carbons have the same substituents

eg., oxidation of (+)/(-) erythrose and threose gives tartaric acid

It turns out that there are only THREE stereoisomers for this structure - two of the four possible structures are identical!

This comes about because one half of the structure has the same atoms and bonds as the other half (ie. it is symmetrical and has a **plane of symmetry**)

*Plane of symmetry - a mirror plane that cuts a molecule in half, so that one half of the molecule is the mirror reflection of the other half.*

(a) m.p. 210-212 °C  
[\(\alpha\)]\(\text{D}^{20}\) O °

(b) m.p. 170-172 °C  
[\(\alpha\)]\(\text{D}^{20}\) + 12.4 °

(c) m.p. 170-172 °C  
[\(\alpha\)]\(\text{D}^{20}\) - 12.4 °
• **Meso-compounds** contain two or more stereogenic centres **and** a plane of symmetry - i.e. the mirror images are superimposable (i.e. identical)

• *Meso*-compounds are always achiral.

there are 4 ways that tartaric acid can occur: (+)-tartaric acid, (-)-tartaric acid, *meso*-tartaric acid and racemic (+)/(-) tartaric acid (m.p. 206°C)

Which of the following isomers is the *meso*-isomer?
Predicting the Number of Possible Stereoisomers

**maximum** number of stereoisomers \(2^n \times 2^y\)

- \(n = \) number of stereogenic centres
- \(y = \) number of sites for \((E)/(Z)\) isomers

**** Check for plane of symmetry!
For possible meso-somers, **subtract 1** ****

Examples:

- menthol
- vitamin A
- cholesterol
- LSD
Stereoisomerism: Summary

What to look for...

Configurational Isomers

*All stereoisomers that are not conformers.*
Interconversion requires the breaking and reforming of bonds.

Diastereomers

Stereoisomers which are *not mirror images of each other.*

Enantiomers

Stereoisomers which are *non-superimposable mirror images of each other.*

- alkene $E/Z$ configurational isomers
- cycloalkane $cis/trans$ configurational isomers
- structures with *more than one* stereogenic centre
- structures with *one or more* stereogenic centres

To determine the relationship between two structures, we must know the configurations of the stereocentres.

Finally, keep on the lookout for *meso*-compounds!

Questions:

1. Identify the configuration ($R$ or $S$) of the stereogenic centre in each of the following molecules:

   \[
   \begin{align*}
   & \text{CH}_3 \ \text{C}^1 \ \text{H} \ \text{F} \\
   & \text{HO} \ \text{C}^1 \ \text{H} \ \text{H} \\
   & \text{HO} \ \text{C}^1 \ \text{H} \ \text{F} \\
   & \text{H}_3 \ \text{C}^1 \ \text{C} = \text{CH}_2 \\
   & \text{H}_3 \ \text{C}^1 \ \text{CH}_2 \ \text{CH}_3 \\
   & \text{H}_3 \ \text{C}^1 \ \text{C} = \text{CH}_2
   \end{align*}
   \]

2. Give the structure of the following compounds:

   $(R)$-2-methyl-3-pentanol \hspace{1cm} $(S)$-1-phenylethylamine \hspace{1cm} $(2R,3S)$-2,3-dihydroxybutane
Questions (continued):

3. Which of the following structures represent meso-compounds?

![Structures](image)

Biologically Active Chiral Compounds

- Note that two enantiomers often have remarkably different biological activities.

![Thalidomide](image)  
*thalidomide*

* mild sedative  
* extreme teratogen

![Asparagine](image)  
*asparagine*

* bitter  
* sweet
Past Exam Questions:

(i) Clearly mark the stereogenic centre with an asterisk.

(iv) Name the functional groups a and b

\[
\begin{align*}
a &= \\
b &= 
\end{align*}
\]

(ii) List the substituents attached to the stereogenic centre in descending order of priority according to the sequence rules.

<table>
<thead>
<tr>
<th>highest priority</th>
<th>lowest priority</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(ii) Absolute stereochemistry of adrenaline? (R or S)

Past Exam Questions (continued):

\[
\begin{align*}
(a)-\text{citronellal} \\
\text{molecular formula?}
\end{align*}
\]

functional groups?

\[
\begin{align*}
a &= \\
b &= 
\end{align*}
\]

Is the structure shown a racemic mixture, the (R)-enantiomer or the (S)-enantiomer?
A recent estimate places the number of prescription and over-the-counter drugs marketed throughout the world at about 2000. Approximately one-third of these are either naturally occurring substances themselves or are prepared by chemical modification of natural products. Most of the drugs derived from natural sources are chiral and are almost always obtained as a single enantiomer rather than as a racemic mixture. Not so with the over 500 chiral substances represented among the more than 1300 drugs that are the products of synthetic organic chemistry. Until recently, such substances were, with few exceptions, prepared, sold, and administered as racemic mixtures even though the desired therapeutic activity resides in only one of the enantiomers. 

Spurred by a number of factors ranging from safety and efficacy to synthetic methodology and economics, this practice is undergoing rapid change as more and more chiral synthetic drugs become available in enantiomerically pure form.

Because of the high degree of chiral recognition inherent in most biological processes (Section 7.8), it is unlikely that both enantiomers of a chiral drug will exhibit the same level, or even the same kind, of effect. At one extreme, one enantiomer has the desired effect, and the other exhibits no biological activity at all. In this case, which is relatively rare, the racemic form is simply a drug that is 50% pure and contains 50% " inert ingredients." Real cases are more complicated. For example, it is the R enantiomer that is responsible for the pain-relieving properties of ibuprofen, normally sold as a racemic mixture. The 50% of racemic ibuprofen that is the S enantiomer is not completely wasted, however, because enzyme-catalyzed reactions in our body convert much of it to active (S)-ibuprofen.

A much more serious drawback to using chiral drugs as racemic mixtures is illustrated by thalidomide, briefly employed as a sedative and antinausea drug in Europe and Great Britain during the period 1959-1962. The desired properties are those of (R)-thalidomide. The (S)-thalidomide, however, has a very different spectrum of biological activity and was shown to be responsible for over 2000 cases of serious birth defects in children born to women who took it while pregnant.

![Thalidomide](image)

Basic research directed toward understanding the factors that control the stereochemistry of chemical reactions has led to new synthetic methods that make it practical to prepare chiral molecules in enantiomerically pure form. Recognizing this, most major pharmaceutical companies are examining their existing drugs to see which ones are the best candidates for synthesis as single enantiomers and, when preparing a new drug, design its synthesis so as to provide only the desired enantiomer. In 1992, the United States Food and Drug Administration (FDA) issued guidelines that encouraged such an approach, but left open the door for approval of new drugs as racemic mixtures when special circumstances warrant. One incentive to developing enantiomerically pure versions of existing drugs is that the novel production methods they require may make them eligible for patent protection separate from that of the original drugs. Thus the temporary monopoly position that patent law views as essential to fostering innovation can be extended by transforming a successful chiral, but racemic, drug into an enantiomerically pure version.