Learning Guide for Chapter 6 - Stereochemistry

I. Stereoisomers containing C=C p 1
II. Introduction to chirality - compounds with one stereoisomer - p 5
   Chirality
   Recognizing chiral compounds
   Labeling stereocenters as R or S
III. Compounds with two or more stereoisomers - p 9
   Diastereomers and meso compounds
   Fischer projections
IV. Physical properties of chiral compounds - p 14
   Melting point, boiling point, etc
   Biological environments
   Optical activity
   Separation of enantiomers
   Determination of stereochemical correlation

I. Stereoisomers containing C=C

What do two compounds which are constitutional isomers have in common? How are they different?
   same molecular formula
   different bonding sequence

Give the molecular formula and one constitutional isomer for each of the following compounds.

   \[ \text{C}_7\text{H}_{14} \]

   \[ \text{C}_7\text{H}_{16} \]

   Are these compounds constitutional isomers of each other? no - different formula

What do two compounds which are stereoisomers have in common? How are the different?
   same molecular formula
   same bonding sequence
   different shape
   stereoisomers can only occur under certain conditions

Draw line structures for two different molecules with the condensed structure shown.

   \[ \text{CH}_3\text{CH}=\text{CHCH}_3 \]

   make models!
What keeps these two compounds from being the same?

\[ \text{draw a picture of sigma and pi bonds} \]

they can't rotate around the C=C

Why aren't these two structures the same as the ones above? What relationship do they have?

\[ \text{staggered} \quad \text{eclipsed} \]

two conformations of the same compound

can rotate around C-C bond

Draw a constitutional isomer, a stereoisomer, and a conformation of the following compound.

\[
\begin{array}{ccc}
\text{constitutional} & \text{stereoisomer} & \text{conformation} \\
\text{isomer} & & \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{same formula?} & \text{yes} & \text{yes} \\
\text{same bonding sequence?} & \text{no} & \text{yes} \\
\text{same shape?} & \text{no} & \text{no} \\
\text{same compound?} & \text{no} & \text{yes} \\
\end{array}
\]

How many stereoisomers are possible for a compound containing a C=C? two max

Do all compounds containing a C=C have stereoisomers? no

How many stereoisomers does the following compound have? Why?

\[ \text{only one} \quad \text{H's on one side are the same} \]

How can you tell if a compound with a C=C will have a stereoisomer?

look at both sides of the C=C; both groups must be different from each other
Determine whether or not the compounds below will have a stereoisomer, and for those that will, draw it.

yes \[ \text{CH}_3 \)'s the same

no H's the same, ring the same also

yes can't switch because of the ring!

no

What is a stereocenter?

carbon - switch two substituents, get a new compound

new compound! #2 carbon is a stereocenter

#2 and #3 are both stereocenters

same thing - not an isomer (can just turn over)

Can a compound containing a C=C have only one stereocenter?

no - it must either have 2, or none
When can we use cis and trans to label the two stereoisomers?

when there is only one substituent on each side of the C=C

Which of these is cis, and which is trans?

- trans
  - opposite sides
- cis
  - same side
  - this is an older system

Why can't cis and trans be used on the following compound?

more than one group on each side - can't tell what to compare

In the following examples, the #1 substituent has priority over the #2 substituent. Which is E and which is Z?

<table>
<thead>
<tr>
<th>E</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>(2)</td>
</tr>
</tbody>
</table>

Label the following as E or Z and explain why.

- If they were the same all the way out, then what? no stereochemistry
II. Introduction to Chirality

What does it mean to say that an object is chiral? What about achiral?

chiral - its mirror image is different from the original object
achiral - its mirror image is the same as the original object

Many everyday objects are chiral. Consider the following. Are they chiral or achiral? Is the mirror image of the object the same, or different?

<table>
<thead>
<tr>
<th>Object</th>
<th>Chirality</th>
</tr>
</thead>
<tbody>
<tr>
<td>hand</td>
<td>chiral</td>
</tr>
<tr>
<td>spoon</td>
<td>achiral</td>
</tr>
<tr>
<td>fork</td>
<td>achiral</td>
</tr>
<tr>
<td>knife</td>
<td>achiral</td>
</tr>
<tr>
<td>(unless is has an edge)</td>
<td></td>
</tr>
<tr>
<td>socks</td>
<td>achiral</td>
</tr>
<tr>
<td>shoes</td>
<td>chiral</td>
</tr>
<tr>
<td>scissors</td>
<td>chiral</td>
</tr>
<tr>
<td>gloves</td>
<td>chiral</td>
</tr>
<tr>
<td>nail</td>
<td>achiral</td>
</tr>
<tr>
<td>screw</td>
<td>chiral</td>
</tr>
<tr>
<td>DNA helix</td>
<td>chiral</td>
</tr>
<tr>
<td>folding student desk</td>
<td>chiral</td>
</tr>
</tbody>
</table>

Tetris shapes

- achiral
- chiral
- achiral
- chiral

Striped quilt triangles

- chiral
- chiral
- achiral

How can a molecule be chiral?

most common way - asymmetric carbon: 4 different groups

Using models, make the compound below. Then construct its mirror image

Are they the same (are they superimposable)? no
What is the relationship between these two compounds?

![Chemical structures](image)

- same molecular formula
- same bonding sequence
- different shape
- non-superimposable mirror images
- enantiomers (type of stereoisomer)

Are the central carbon atoms stereocenters?

- yes - switching any two substituents gives the other enantiomer

Construct the compound below, and its mirror image.

![Chemical structures](image)

- mirror image - same compound

Are these compounds superimposable? yes
Is the original compound chiral? no
Does the original compound have an enantiomer? no

How can you determine if a molecule is chiral?

1) Is the mirror image superimposable? yes - achiral
   no - chiral
   
   only completely reliable test

![Chemical structures](image)

- chiral
- enantiomers
- same compound
2) Is there a plane of symmetry in the molecule?

Yes - molecule is achiral.
No - molecule is probably chiral.

There are other, rarer kinds of symmetry that can also make the molecule achiral.

3) How many asymmetric carbons are in the molecule?

None - molecule is probably not chiral.
One - molecule is chiral.
Two or more - molecule is chiral unless there is a plane of symmetry.

more about molecules with more than one stereocenter shortly

Which of the following molecules are chiral? Which have planes of symmetry? Where are the asymmetric carbons? Where are the stereocenters?
How are enantiomers labeled?

1) Prioritize the groups
2) Rotate so that the last priority group is pointed away.
3) Look at the 1-2-3 direction.
   - clockwise - R
   - counterclockwise - S

S  when last group is already back, you're set

use overhead of clock!

R  when last group is forward, you're looking at it from behind
go 1-2-3, then reverse

S = when last group is in the plane of the page,

use models!
at 1st glance it looks R

Practice:

S  R  R  R  S

How is this label included in the name?

(S)-3-methylhexane

(1S,2R)-1-ethyl-2-methyl-cyclopentane

(cis)-1,4-dimethylcyclohexane

could be

(or a mixture of both!)
III. Compounds with two or more stereocenters

Consider the following compound. How many stereocenters does it have? How many stereoisomers could it have?

2 stereocenters
4 possible stereoisomers

Which stereoisomers are enantiomers? non-superimposable mirror images

all stereocenters are opposite RS-SR
RR-SS

Which stereoisomers are diastereomers? non-superimposable, not mirror images

one stereocenter is the same, the other opposite RR-RS
RR-SR
SS-SR
SS-RS

Next, consider the following compound. How many stereocenters does it have? How many stereoisomers does it have?

2 stereocenters
4 possible stereoisomers only 3 are different

Enantiomers? RR-SS Diastereomers? RS-RR RS-SS
What is the difference between the following compounds?

- achiral (plain of symmetry)
  - no stereocenters - not meso

- achiral (plain of symmetry)
  - 2 stereocenters - meso

Consider the following compound. How many stereocenters does it have? How many stereoisomers does it have?

- 2 stereocenters
- not asymmetric - can't assign R or S
- 4 possible stereoisomers
- only 2 are different

Enantiomers? none  Diastereomers? cis-trans
All of the isomers we have seen so far can be related as follows:

**Isomers**

same molecular formula

- **constitutional isomers**
  different connectivity

- **stereoisomers**
  same connectivity, different shape

- **enantiomers**
  non-superimposable mirror images

- **diastereomers**
  not mirror images
  2 or more stereocenters
  or cis/trans

Classify the following compounds as identical, enantiomers, diastereomers, meso, or constitutional isomers.

- **identical**

- **enantiomers**

- **diastereomers**

- **meso**
Fischer Projections

When are Fischer projections useful? showing multiple stereocenters biological molecules like sugars

Draw a Fischer projection of the following molecule: 1) main C chain up and down most oxidized C at the top 2) substituents left or right

right/left = coming forward up/down = going away

Convert the following Fischer projection to a line structure.

Why are the OH's all on the right in the Fischer projection, but some up and some down on the line structure?

line structure - staggered have to rotate to change between them Fischer projection - eclipsed

Which shows the relationship between the stereocenters better? Fischer projection

Which is the more stable conformation? line structure

What is the relationship between the following molecules?

enantiomers all stereocenters opposite diastereomers some opposite some the same
same - meso
plane of symmetry
two stereocenters

enantiomers
all stereocenters opposite

Label each stereocenter as R or S:

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

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

Label each of the following molecules as D or L:

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

D-glucose  L-glucose  D-mannose  L-mannose

enantiomers  diastereomers  enantiomers

What is the relationship between the first two molecules? What about the second two? What about the middle two?

Since D and L only give the stereochemistry of one stereocenter, how can you tell what the rest are?

each set of enantiomers has a different name

D, L just tells you which of the pair it is
IV. Physical Properties of Chiral Compounds

Regular physical properties

What are some of the physical properties that we regularly talk about with organic compounds?

*melting point, boiling point, solubility, density, color, etc*

How are the properties of enantiomers related? they are the same

How are these properties of diastereomers related? they are different

What is the relationship of the pairs of compounds below? What would you predict about their physical properties?

- **constitutional isomers - different**
  - bp 196°C
  - bp 176°C

- **diastereomers - different**
  - mp -105°C
  - mp -139°C

- **enantiomers - same**
  - bp 175°C
  - bp 175°C

- **diastereomers - different**
  - mp 158°C
  - mp 256°C

Why is the odor of a compound an exception to this?

receptors in your nose are chiral - can detect different enantiomers

- **S-carvone**
  - (caraway seed)

- **R-carvone**
  - (spearmint)

What areas of chemistry are strongly influenced by stereochemistry? Why?

*biochemistry, pharmaceuticals*

*biological molecules are often chiral - amino acids, nucleotides, carbohydrates, neurotransmitters, hormones*
Optical Activity

How is plane polarized light different from ordinary light?

- ordinary light - light waves in all planes
- polarized light - light waves in only one plane

How do you obtain plane polarized light?

- put ordinary light through a filter

What would happen if you put two polarizing filters together and then turned them at right angles?

- no light would get through

Why do polarizing sunglasses work?

- reflected light (glare) is polarized - filter blocks it out

What happens when polarized light passes through a solution containing chiral molecules?

- it rotates the plane of the light waves - show overhead

What is this called? optical rotation - angle that the plane is rotated

How is it measured? using a polarimeter

What factors affect the optical rotation? Which is the most useful? How do we eliminate the effect of other factors?

- structure - this is what we are interested in
- concentration - standard concentration - 1 g/ml
- distance traveled - path length - standard path length - 1 dm (10 cm)
- temperature - always measure at 25°C
- wavelength of light - always use the same wavelength (D line of sodium)

The optical rotation of a compound measured under these conditions is called:

- specific rotation - $[\alpha]$ - there are tables where you can look these up
We can use a different concentration or path length and correct for them using what equation? Why does this work?

\[ \alpha = [\alpha] \times c \times l \quad \text{optical rotation is directly proportional to } c \text{ and } l \]

The specific rotation of (S)-2-butanol is -13.5°. If a sample is made by dissolving 6 g of the compound in 40 ml of solvent, and a 2 cm cell was used to measure the optical activity, what angle of rotation will be observed?

\[ [\alpha] = -13.5^\circ \]

\[ c = 6 \text{ g} / 40 \text{ ml} \quad \alpha = (-13.5^\circ)(6/40)(0.2) = -0.405^\circ \]

\[ l = 0.2 \text{ dm} \]

If given an observed rotation, how could you figure out the specific rotation?

\[ [\alpha] = \alpha / cl \]

What is the relationship between the following molecules? How would their melting points and specific rotations be related?

<table>
<thead>
<tr>
<th>enantiomers</th>
<th>diastereomers</th>
<th>enantiomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>same mp</td>
<td>different mp</td>
<td>same mp</td>
</tr>
<tr>
<td>opposite [\alpha]</td>
<td>different [\alpha]</td>
<td>opposite [\alpha]</td>
</tr>
</tbody>
</table>

![Chemical structures](https://via.placeholder.com/150)

\[
\begin{align*}
D\text{-erythrose} & : [\alpha] = -14.5^\circ, \text{ mp } = 164^\circ\text{C} \\
L\text{-erythrose} & : [\alpha] = +14.5^\circ, \text{ mp } = 164^\circ\text{C} \\
D\text{-threose} & : [\alpha] = -21.5^\circ, \text{ mp } = 137^\circ\text{C} \\
L\text{-threose} & : [\alpha] = +21.5^\circ, \text{ mp } = 137^\circ\text{C}
\end{align*}
\]

What can you tell about R and S vs. + and - rotations? What can't you tell?

- can tell: if R is + S is -; if R is - S is +
- why?

- can't tell: if R will be + or -
What does it mean to say a solution is optically active?

it rotates the plane of polarized light - has an \( \alpha \)

Would a solution of the following compound(s) be optically active?

a) \[ \text{chiral molecule - yes} \]

b) \[ \text{achiral molecule - no} \]

c) \[ \text{meso compound, achiral - no} \]

d) \[ \text{racemic mixture - no (exactly cancel)} \]

could we use grams? yes - same MW

e) \[ \text{3 mol of racemic - yes} \]

some left over

f) \[ \text{diastereomers, won't cancel - yes} \]

Why are racemic mixtures common?

both compounds have the same energy, formed in the same amounts.

If a solution has 40\% optical purity, what does this mean?

the optical rotation has been reduced by 40\% by having some of the other enantiomer

If a pure enantiomer has an optical rotation of 20°, what rotation will a solution have which has a 40\% optical purity?

\( 8° \)

What equation describes this? \( \% \text{o.p.} = \text{rotation of solution} \)

rotation of pure enantiomer
What proportion of enantiomers will give you a 40% optical purity?

\[
\text{% o.p.} = \text{% e.e.} = \%R - \%S \\
70\% - 30\% = 40\%
\]

Take 3 mol of R, 7 mol of S

\[
\frac{3 + 7}{10} = 40\% \text{ e.e.}
\]

6g of racemic mixture
4g of excess R enantiomer

If the specific rotation of (S)-2-butanol is 13.75°, and a mixture of (R)- and (S)-2-butanol has a rotation of -6.75°, what is the optical purity of the solution? What is the % e.e.?

What percentage of the two isomers is present?

\[
\begin{align*}
\frac{-6.75^\circ}{13.5^\circ} &= .5 \\
\text{% o.p.} &= 50\% \\
\text{% e.e.} &= 50\%
\end{align*}
\]

75\% - 25\% = 50\%

since S is + and mixture is -, must be 75\% R, 25\% S

Separation of Enantiomers

Where do enantiomerically pure compounds come from?

1. many found in nature
2. separation of enantiomers (resolution)
3. stereoselective reactions (Ch 7)

Why can't enantiomers be separated by operations like chromatography, distillation, etc?

same physical properties

What must be done to separate them?

turn them into diastereomers - now they will have different properties
Consider the following example:

1. 
   - (R)-2-butanol
   - (S)-2-butanol
   - 
   - same properties

2. 
   - (R, R)-tartaric acid
   - H$_2$SO$_4$
   - react with R, R compound
   - (R)-2-butyl (R, R)-tartrate diastereomers
   - (S)-2-butyl (R, R)-tartrate diastereomers

3. 
   - separate using physical properties

4. 
   - (R)-2-butanol + (R, R)-tartaric acid
   - remove tartaric acid

5. 
   - (S)-2-butanol + (R, R)-tartaric acid
   - enantiomerically pure compounds!
Determining the stereochemical correlation

What does it mean to determine the stereochemical correlation for a pair of enantiomers?

- match up R and S structures with + and - rotations

Why is this difficult?

- you can't tell by looking at the structure whether it is + or -

<table>
<thead>
<tr>
<th>+ tartaric acid</th>
<th>- tartaric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOH</td>
<td>COOH</td>
</tr>
<tr>
<td>H—OH</td>
<td>H—OH</td>
</tr>
<tr>
<td>HO—H</td>
<td>HO—H</td>
</tr>
<tr>
<td>COOH</td>
<td>COOH</td>
</tr>
<tr>
<td>2R, 3R</td>
<td>2S, 3S</td>
</tr>
</tbody>
</table>

What method has been developed?

1 - get a pure sample
2 - measure its rotation
3 - evaporate to get a crystal
4 - do x-ray crystallography to get 3D structure
5 - see if structure is R or S

Once the stereochemical correlation of one compound has been discovered, how can it be used to determine another without x-ray crystallography?

- change molecule in a predictable way (structure still known), measure rotation

\[ \text{substrate} \xrightarrow{1. \text{BH}_3} \xrightarrow{2. \text{H}_2\text{O}_2} \text{product} \]