Three-Dimensional Structures of Drugs


- Chiral drugs are sometimes sold as one enantiomer (pure S- or R-drug) because potency is better, less side-effects, etc.
  - Some enantiomers are also metabolized better than other
- **Chiral** = a molecule is chiral when it is asymmetric and it's mirror images are not superimposable
  - **Your hands are chiral. You cant place one on top of the other where the thumbs and pink line up unless you flip one hand!**
- **Enantiomer** = two molecules that are mirror images of one another
- A molecule has a **chiral center** when four different groups are attached to a carbon atom
- 30% of drugs are sold as racemates
  - **Racemate** = Both enantiomers make up the drug product
  - **Racemic switch** = when a drug sold as a racemic mix is patented and sold as a single enantiomer
    - Ex.) Cetirizine (Zyrtec) is a racemate, while Levocetirizine (Xyzal) is the R-enantiomer of cetirizine
- **Eutomer** = the more potent isomer
- **Distomer** = the less potent isomer
  - Basically an impurity. Can sometimes cause toxicity
  - Teratogen = drug that can cause birth defects if taken during pregnancy
- **Eudismic ratio** = ratio of potencies of enantiomers
  - Activity of eutomer/ activity of distomer
Cahn Ingold Nomenclature: Hey remember Orgo! Yea I tried to repress it too. NO MORE. So when trying to determine if something is (S) or (R) you number the groups around the chiral center (red dot) based on the next atom with the highest atomic number. In this case, the chiral center leads to another carbon in all directions. Ok, so then it’s based on number of bonds. Double bonds take precedence over single. So now we are between the nitrogen heterocycle and the aromatic ring with the chlorine. Since the nitrogen has a higher atomic number and it’s closer to the chiral center than the chlorine is, that group is ranked as number 1. Next would be the ring with the chlorine on it, since this is also a double bond which ranks higher than the single bond to the right of the chiral center. That makes the group to the right, the last ranked. Now draw a circle going from 1 to 3. If the circle is clockwise, this means this is an (R)-isomer. If the circle is counter-clockwise, this means this is an (S)-isomer. HOWEVER. This is ONLY TRUE when the hydrogen is pointing AWAY FROM THE PLANE (the dashed line). In this case, the hydrogen is on a wedge so it’s pointing towards us. You simply switch the isomer then to the (S)-isomer.

The number in front of the R/S (ex. 2S, 3R) just refers to which chiral center you are dealing with. The numbering is based off how you number carbons in a chain (if you forgot this, the numbering starts on the side of the chain closest to the first substituent or double/triple bond)
Factors that make up 3D Structures of Drugs

1. Bond length
2. Bond angles: sp (180°) vs. sp2 (120°) vs. sp3 (109°)
3. Conformation (torsional angle) = conformation about a single bond

![Chemical structure]

Ex.) Because of resonance, this sp³ bond that would normally be around 109° is distorted because there is a barrier to rotation. This can affect drug binding, etc.

4. Hybridization
5. Charges
6. Size and nature of R group – hydrophobic, flexible, aromatic, polar

Terms to Know

**Structure** = complete arrangement of all atoms of a molecule in space

**Constitution** = nature and number of atoms, types of bonds, and manner in which they are connected = connectivity

![Constitutional isomers C₃H₈O]

**Configuration** = spatial arrangement of atoms that distinguishes molecules of the same constitution other than distinction due to differences in conformation. Can only be changed by breaking bonds. Examples are (R)- and (S)- isomers
**Conformation** = spatial arrangement of atoms in molecule of given constitution and configuration. Can be changed by single-bond rotation. Examples are cis/trans or E/Z conformers.

Ex) (R)- vs. (S)- isomers

Even though it looks like you can just rotate the bonds to get the other isomer, if you rotate the methyl group you would also have to rotate the hydrogen and it would be pointing toward you, which would essentially keep the same isomer because the naming is reversed. So you MUST break the bond and swap the ethyl and the methyl groups to get the other isomer.

Ex) cis vs. trans conformers
Formula same; constitution different

Constitution same; configuration different

Configuration same; conformations different
Isomers

- **Constitutional Isomers** = Same number of atoms with different connectivity
- **Conformational Isomers** = Same connectivity of atoms but different arrangement of atoms in space

Ex) Constitutional isomers:

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

and

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

- same # of atoms but different connectivity

4 carbons
8 hydrogens
one oxygen

Ex) Conformational isomers:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{C} \\
\text{F} & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{H} \\
\text{Br} & \quad \text{H}
\end{align*}
\]

- flip 180°
- rotate C1 120° clockwise
- same

Ex) Stereoisomers / Conformational Isomers

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

vs.

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

- These are actually enantiomers because they are mirror images of each other. If you put a mirror behind the first molecule, you get molecule 2 as the mirror image. Hint: Just flip dashes and wedges and see if you get same molecule as #2. They are non-superimposable

Ex) Diastereomers

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

vs.

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

- Stereoisomers that are not enantiomers. They have same chiral centers, but are not mirror images. Are still non-superimposable
Ex) Meso Compounds = have chiral centers but are achiral

- HINT: if your have chiral centers with a plane of symmetry, they will be meso
- Flip the molecule 180° and see if you get the meso structure.

• To tell if enantiomers or diastereomers:
  - If we have opposite configurations (dash vs. wedge) at all chiral centers = enantiomers.
  - If we have opposite configurations at some chiral centers = diastereomers.

1 and 2 are enantiomers
1 and 3 are diastereomers
2 and 4 are diastereomers
1 and 4 are diastereomers

• Another meso example: HINT - if you have same substituents on two diff. carbons, may be hint you have a meso structure. For example...

3 and 4 have opposite absolute configuration at both chiral centers = enantiomers

1 and 2 have opposite configurations at both chiral centers, however they have a plane of symmetry so they are meso.

This is not the same structure as 3. It's mirror image so it's an enantiomer.

1 and 2, however they have a plane of symmetry so they are meso
Symmetry

- The different symmetry elements you should be familiar with are:
  - Plane of symmetry
  - Center of symmetry
  - Axis of symmetry

Plane of symmetry

- Divides a molecule so that points on one side of the plane are equivalent to points on the other side of the plane → Molecules must be achiral

Center of Symmetry

- Point from which any line drawn through the molecule encounters an identical environment in either direction from the center of symmetry
  - Molecules with center of symmetry must be achiral
Axis of Symmetry

- Axis which rotates molecules around 360°/n such that the new position is indistinguishable from the old one
  - If molecule has only axis of symmetry with no other symmetry elements, it must be **chiral**. Otherwise it may or may not be chiral
Practice symmetry problems

1. Circle the molecules that possess a horizontal mirror plane ($\sigma_h$).

2. Circle the molecules that possess an inversion center ($i$).

Answers on next page
Answer Key

1.) 2, 3
2.) 1, 3
Newman Projections

\[ \text{H}_3\text{C} - \text{CH}_3 \]

- Staggered conformation: more stable
- eclipsed conformation: less stable

Example: Butane, looking down C2

Ball and stick model looking down C8

\[ \text{CH}_3 \]

- anti-conformation: most stable

Newmans:

- rotate 120°: gauche-conformation, less stable
- rotate 60°: eclipsed, least stable

How to draw Newman when given wedges/dashes

If carbon is at top of peak (\(\wedge\))
- If group on wedge it goes right on the Newman and if on dash goes left on the Newman. This is actually the same strategy if carbon is at bottom (\(\wedge\)).
- So this Newman would be...

When we say something is anti, we are talking about the respective positions of two big groups on the Newman. When we talk about staggered/eclipsed we refer to the relative angles of all the atoms on one carbon (the front) with respect to the atoms on the back carbon.
Enantiomorphic = non-superimposable mirror image objects. Does not refer to the whole molecule, just segments of it

- Meso compound is achiral but has two or more enantiomorphic groups

Enantiopure = contains only one enantiomer

Racemic mixture = has equal amounts of both enantiomers

Optically active = compound has the ability to rotate plane of polarized light

- If the compound has a chiral center it will be optically active unless there is a plane or center of symmetry
- Levorotatory = rotates the plane of light left (designated “l” or “-“)
- Dextrorotatory = rotates the plane of light right (designated “r” or “+”)

Properties of Enantiomers

- Enantiomers can’t be distinguished by how they interact with achiral molecules or by physical properties EXCEPT how they rotate plane polarized light
- Enantiomers DO interact differently with other chiral molecules
- Enantiomers have different activities and can even antagonize each other to cancel out the overall activity
- Using one enantiomer only (remember the name for that... ENANTIOPURE) usually lowers side effects
  - What is the more potent isomer called?
  - What is the less potent (usually causes side effects) isomer called?
- Sometimes racemates are used because they work together to have a stronger overall effect
  - Ex.) Both isomers cause vasodilation by different mechanisms
**L/D Nomenclature**

- Naming molecules based off the placement of the hydroxyl at the penultimate carbon relative to D-glyceraldehyde

**Answers: eutomer, distomer**

**Tips for figuring out if L or D:**

If the penultimate carbon is on a “valley” the -OH will be to the right on the Fischer projection, and the molecule will be D- (as seen in image above)

If the penultimate carbon is on a “peak” the -OH will be to the left on the Fischer projection, and the molecule will be L-

**Numbering carbons:**

```
  CHO
  -C- #1
  -C- #2
  -C- #3
  OH
R - C - R
  R
```

**NOTE:**
L ≠ l
D ≠ d

**Z/E Geometry of Double Bonds**

- Naming system used for configuration around a double bond
- Different groups take precedence based on same rules used for Cahn Ingold naming
- If the two groups with highest priority are on the same side of the double bond → designated “Z”
  - They are on “Z same side”
- If two groups with highest priority are on opposite sides of the double bond → designated “E”

![Z/E Geometry of Double Bonds Diagram]

**Cis/Trans Naming of Heterocycles**

- If both high priority atoms are pointing the same direction (both are UP or both are DOWN), considered cis
- If each high priority atoms are pointing in different directions (one is UP and one is DOWN), considered cis

![Cis/Trans Naming of Heterocycles Diagram]

**Cis/Trans Naming:**
- The red bonds are all pointing down
- The black bonds are all pointing up
- Priority is given based on same principles for Cahn-Ingold naming
Epimers

- Stereoisomers that differ by only one stereocenter
  - If they are epimers they MUST also be diastereoisomers
  - See above for help with identifying diastereoisomers

Number of Stereoisomers

- Equal to $2^n$ where $n=$number of stereocenters
  - NOTE: will be less than this if the molecule is meso
  - Must include E/Z centers as well (double bonds with substituents)

Stabilization of Structures

1. Amide bonds

2. Ester bonds
   a. Trans much more stable than cis
   b. May need to use Newman projections to see if groups are trans or cis to each other

3. Cyclic Compounds
   a. 6 membered rings – Chair conformation more stable than half-chair or boat
      i. Equatorial ligands more stable than axial
a. 5 membered rings – Half chair and envelope are the most stable conformation
   ii. Can convert between one another with relative ease = conformational flux