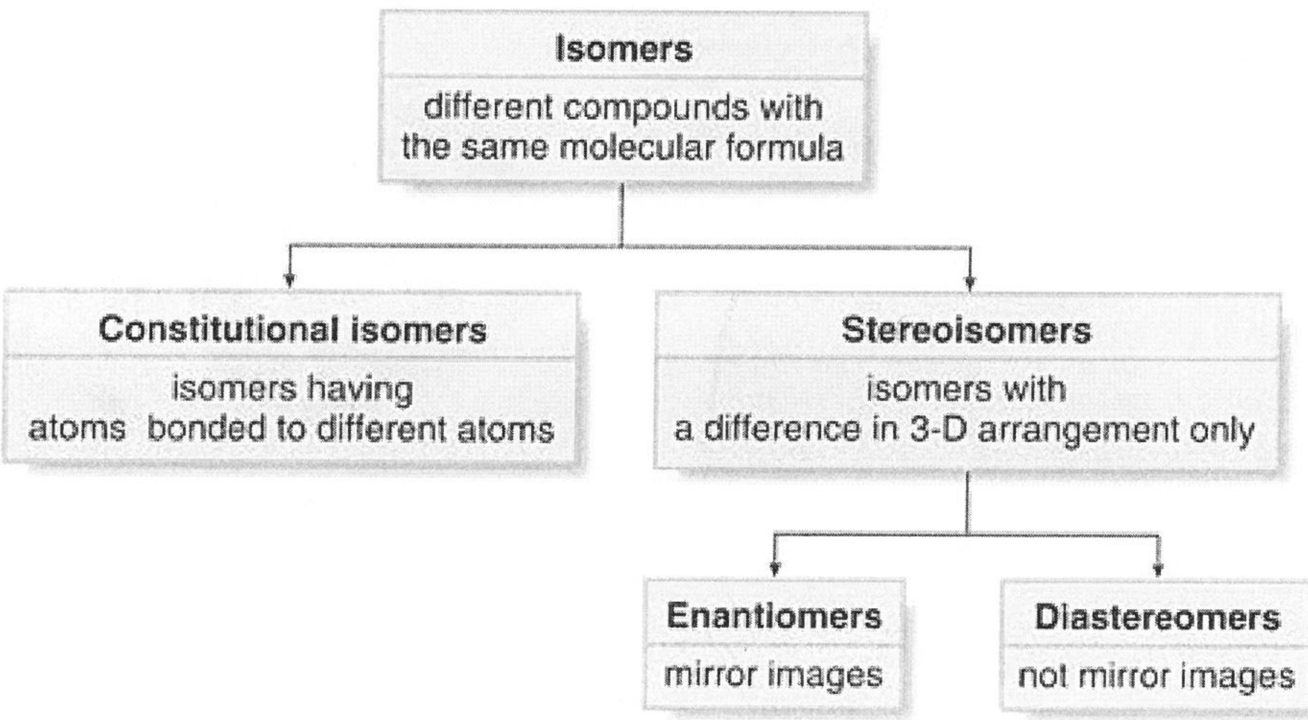
# Chapter 3: Stereochemistry & Chirality

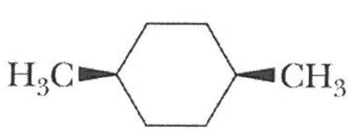
1. **Chiral & Achiral Compounds - Identifying Stereocenters**
2. **Assigning R & S configurations**
3. **Diastereomers - Molecules with two or more stereocenters**
4. Properties of Stereoisomers & Optical Activity

Of course I would want you to do all the problems at the end of the chapter, but your doing the following problems would be a bare minimum: 3.20-22, 3.26, 3.30, 3.31, 3.34, and 3.36. Be sure to practice all the R and S problems within the chapter reading since there are not enough at the end of the chapter.

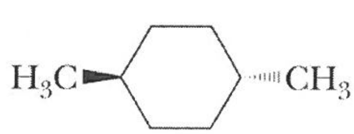
## Stereoisomers – WHERE DO THEY FIT INTO THE BIG PICTURE?




Configurational isomers (*cis,trans* isomers)

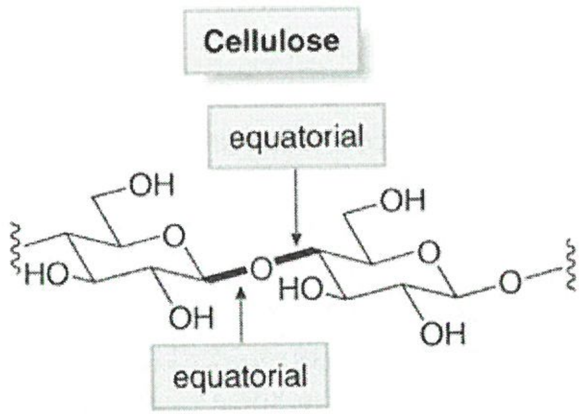



and

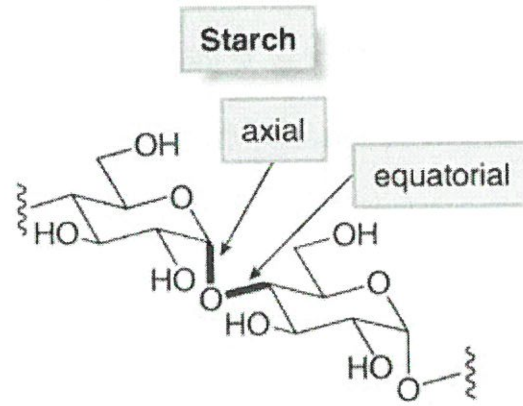



***cis*-1,4-Dimethylcyclohexane** ***trans*-1,4-Dimethylcyclohexane**

# Does stereoisomerism matter chemically?

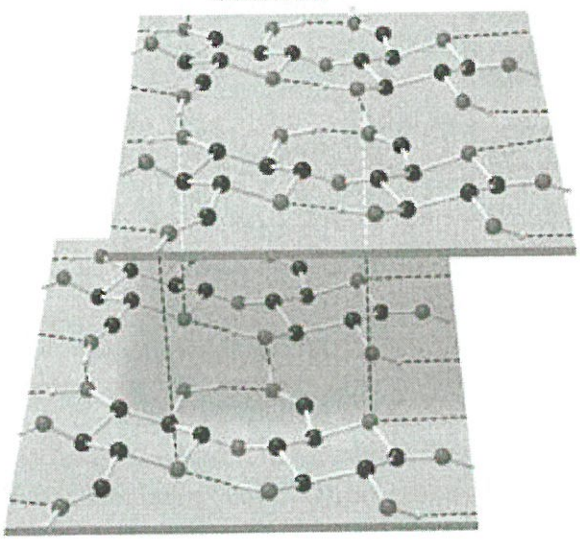



two equatorial bonds

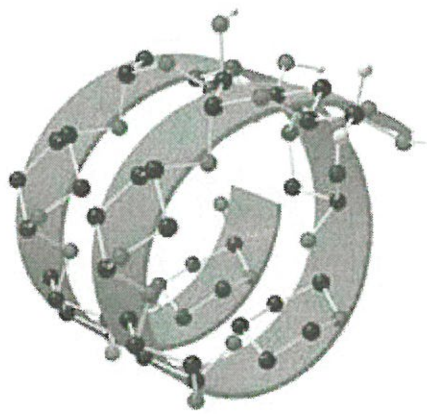


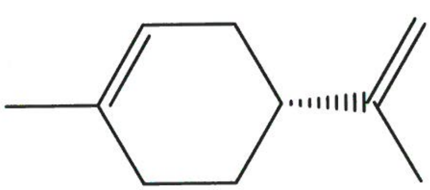

one axial, one equatorial bond

Cellulose

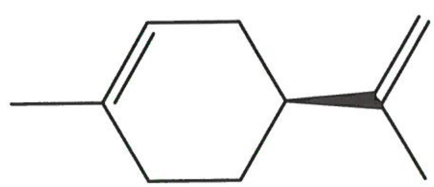


Starch





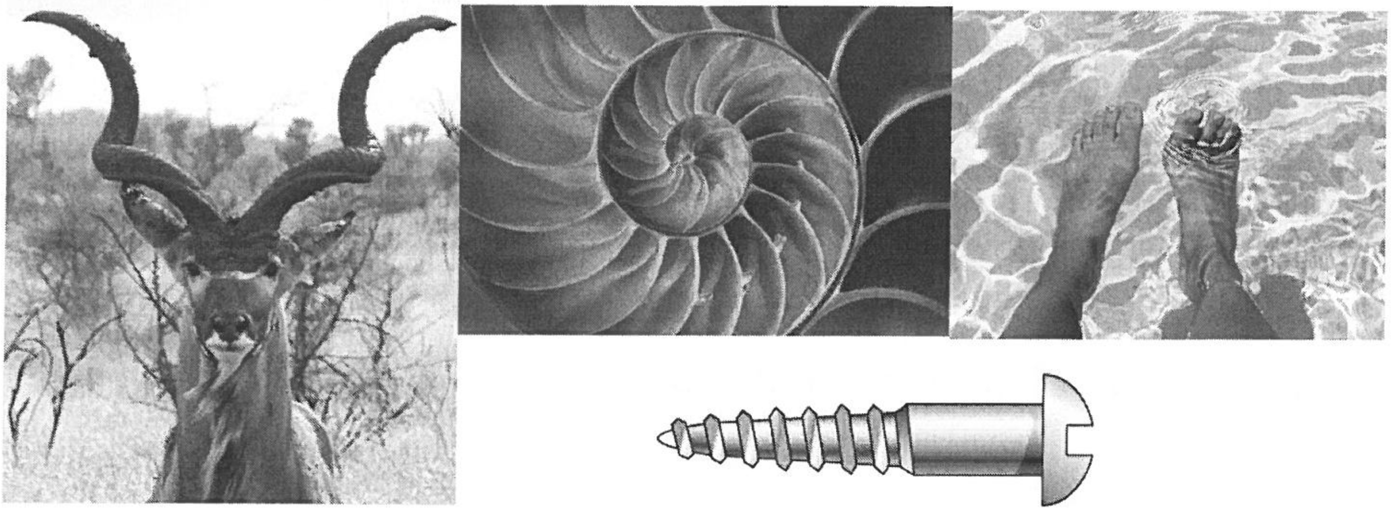
(R)-limonene
Orange smell



(S)-limonene
Lemon smell

# 1. Chiral & Achiral Compounds

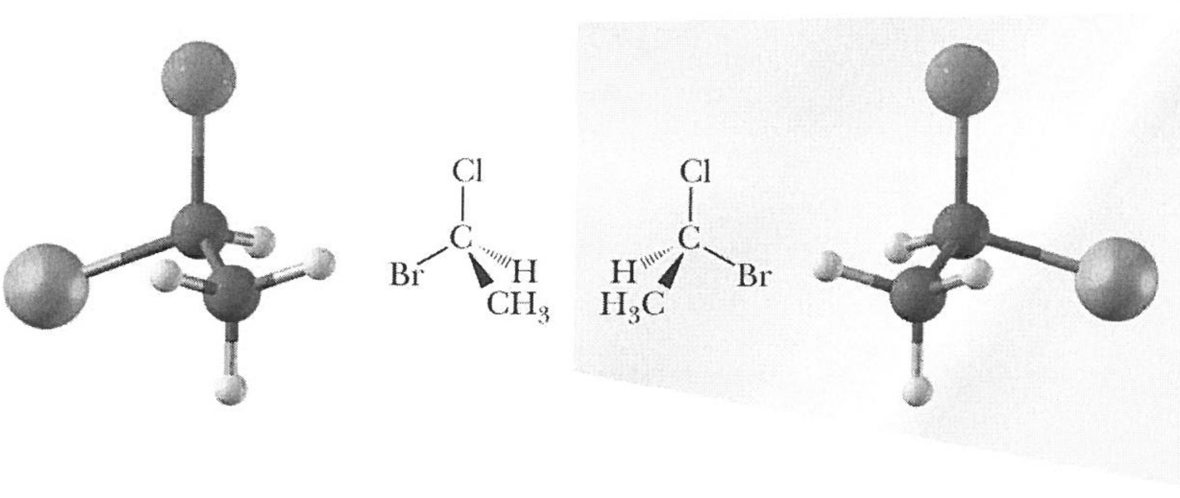
**Chirality** is encountered in a host of everyday examples where asymmetry exists:



**Chiral** = molecules that are non-superimposable on their mirror image

A simplified rule applies to tetrahedrally-bonded carbon, *where all four substituents are different*, the carbon is a called ***stereocenter* = *chiral center***.

- If there are two equivalent groups on the same carbon, that carbon CANNOT be a stereocenter.




**Achiral** = a species with no chiral center - **achiral compounds** have a plane or center of symmetry somewhere…

**We will discuss in a moment that chiral carbons have two forms – R & S**

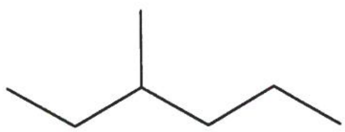
## Are all molecules chiral? How do you identify a chiral compound?

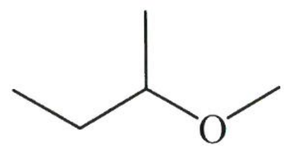
(We will only focus on the chirality around carbon for this discussion.)

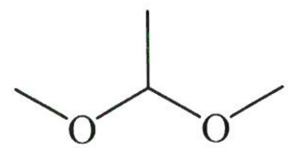
- The most common cause of chirality in organic molecules is a tetrahedral carbon with 4 different substituents attached to it.

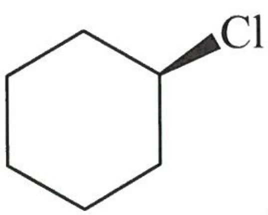
- If you find a carbon with four different groups attached to it, it is called a ***stereocenter***, or chiral center.

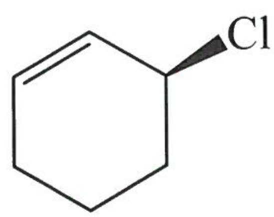
**Are the following compounds chiral? (Look for a plane of symmetry/similar groups)**

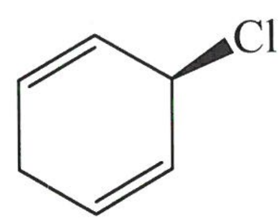


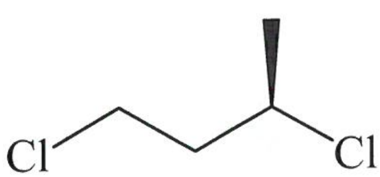


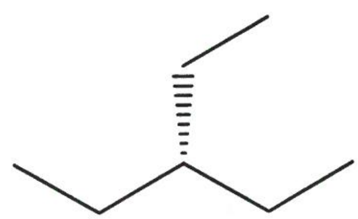



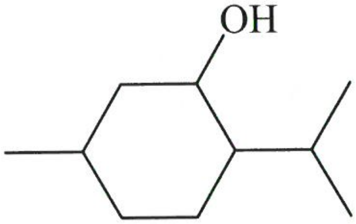



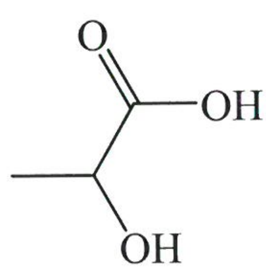



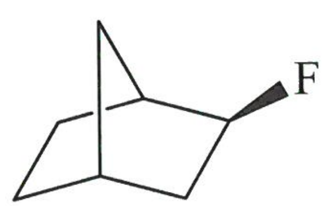



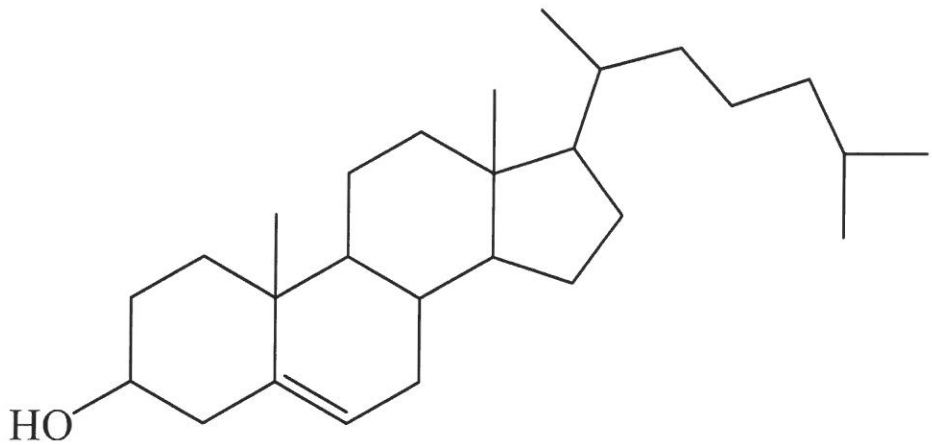





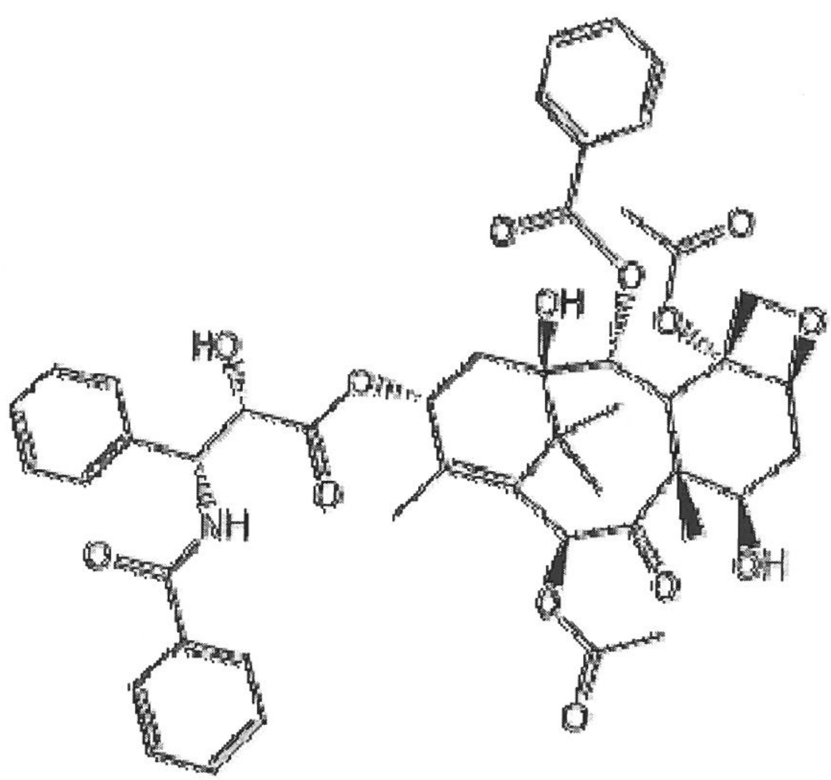



# Q: Identify all the stereocenters in the following molecules.

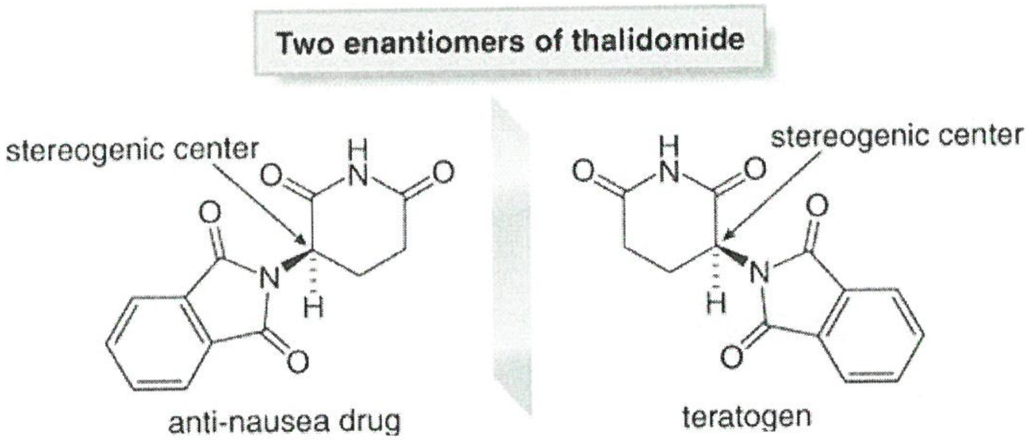



**CHOLESTEROL**




**TAXOL-** Taxol, a potent anticancer natural product (with activity against a number of leukemias and solid tumors in the breast, ovary, brain, and lung in humans) was isolated from the bark of the pacific yew in 1971.

# Thalidomide – an example of enantiomers having different properties




- **Thalidomide** was released in 1956 as a mild sedative used to treat nausea in pregnant women. (Withdrawn from the market in 1961 once it was discovered thalidomide was a human teratogen.)
- As little as one dose could cause a significant birth defect.
- Over 10,000 infants were born with birth defects to women who ingested thalidomide during pregnancy.
- In 1998, it was rereleased for leprosy selling over $300M in sales.

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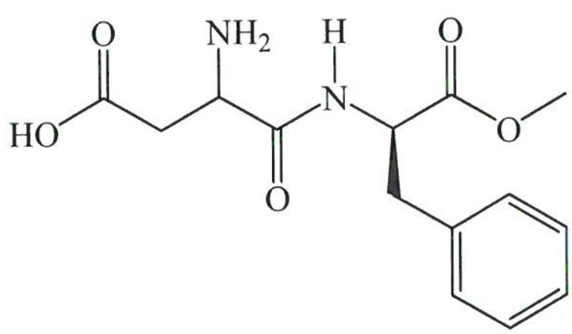
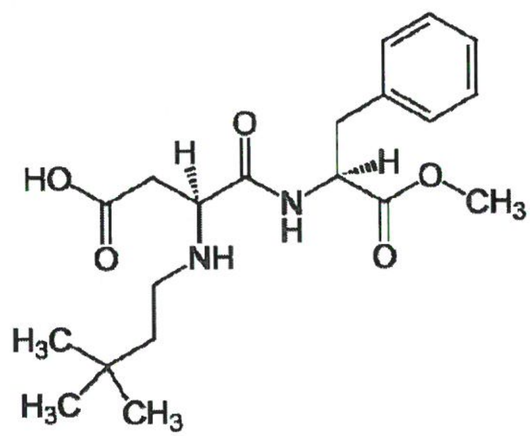
**Aspartame**® is a sweetening agent (Equal) that is more than a 180 times sweeter than sucrose. Only the R-enantiomer is desired as the S-enantiomer does not have the correct shape to fit the binding site of the 'sweetness' receptors on the tongue. **Neotame** (NutraSweet) is between 7,000-13,000 times sweeter than sucrose.



**Aspartame**



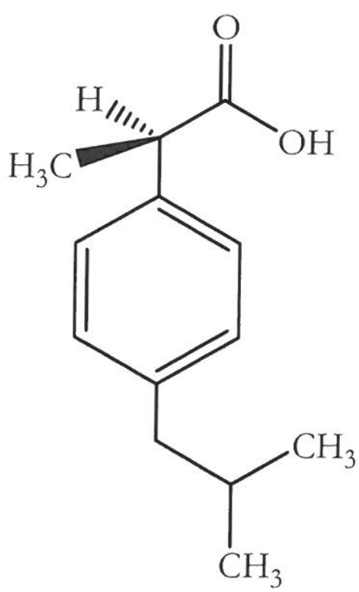
**Neotame**

## So, how common is chirality?

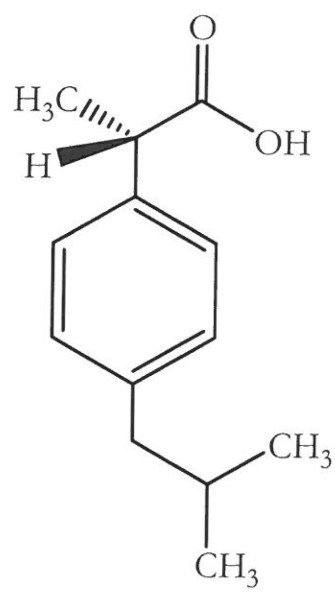
## Chirality in your everyday life…

### Ibuprofen

- **R** – enantiomer is relatively "inactive" in the body
- **S** – enantiomer is 160 times more active as a pain killer!

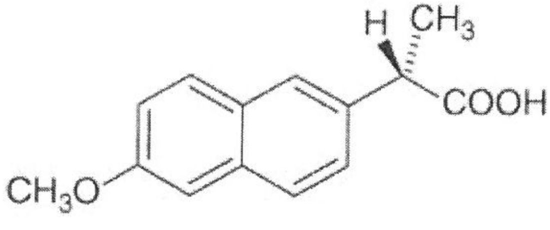



R - enantiomer

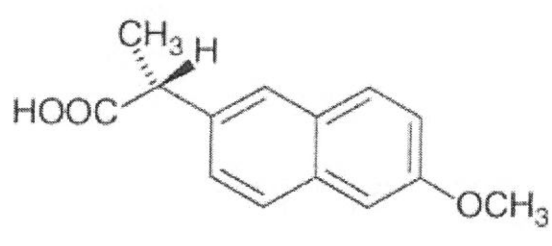



S - enantiomer

### Naproxen Sodium

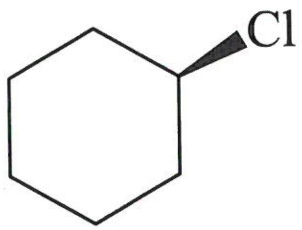


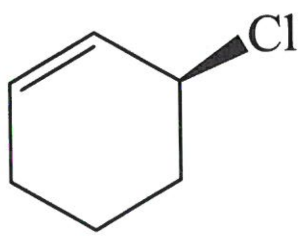

**(*S*)-naproxen**
anti-inflammatory agent

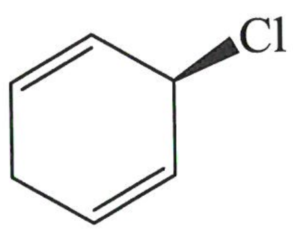


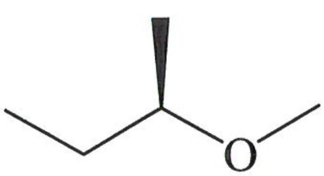

**(*R*)-naproxen**
liver toxin

# Let's practice drawing mirror images and testing for superimposability



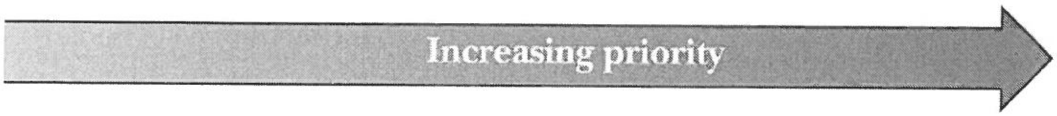



## 2. Assigning R & S stereocenters

### A. Assign priority to the four atoms attached to the stereocenters.

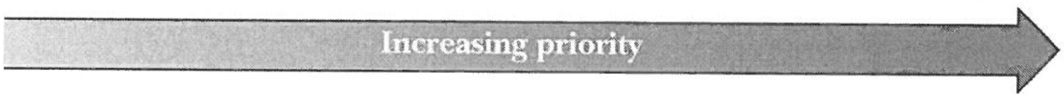
a. Each atom is assigned a priority based on atomic number. Heavier isotopes get higher priority.

| (1) | (6) | (7) | (8) | (16) | (17) | (35) | (53) |
|---|---|---|---|---|---|---|---|
| —H, | —$CH_3$, | —$NH_2$, | —OH, | —SH, | —Cl, | —Br, | —I |

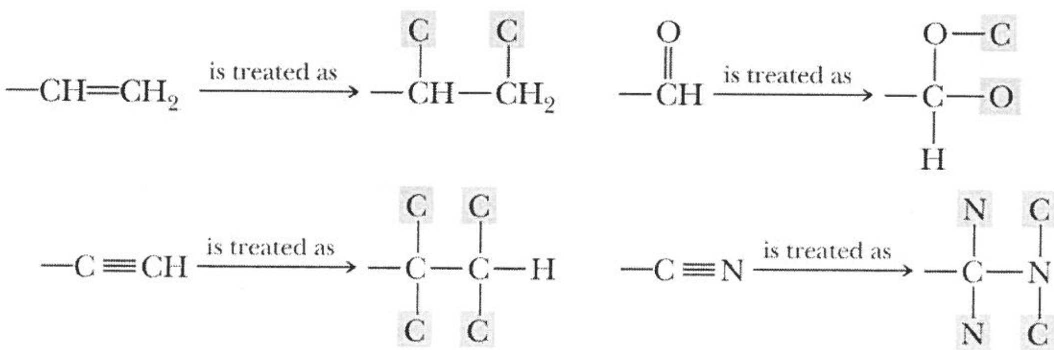



b. If priority cannot be assigned based solely on atomic number, then look at the next atom attached. Priority is assigned by the first point of difference.

| (1) | (6) | (7) | (8) | (17) |
|---|---|---|---|---|
| —$CH_2$—H | —$CH_2$—$CH_3$ | —$CH_2$—$NH_2$ | —$CH_2$—OH | —$CH_2$—Cl |



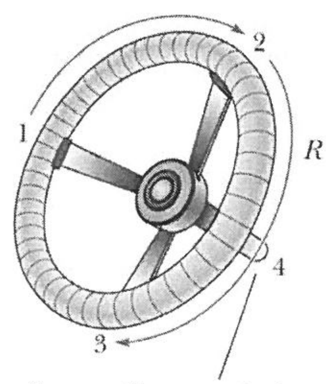

c. Atoms participating in multiple bonds are considered to be bonded to the equivalent number of similar atoms by a single bond.




### B. Orient the molecule in space so that the lowest priority is directed away from you.

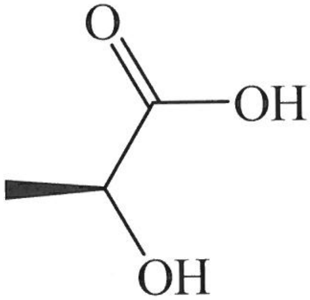
### C. "Read" the groups projected toward you in order from highest to lowest.

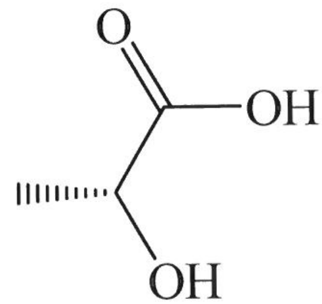
- **Groups in a clockwise fashion → R**
  (R stands for Latin, *rectus* = correct)
- **Groups in a counterclockwise fashion → S**
  (S stands for Latin *sinister* = left)

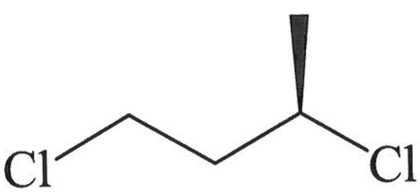


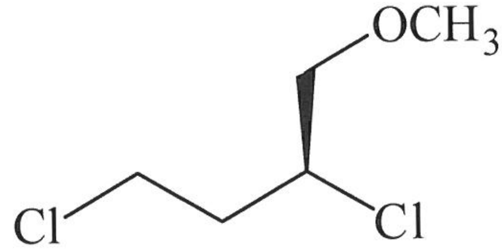
Group of lowest priority points away from you

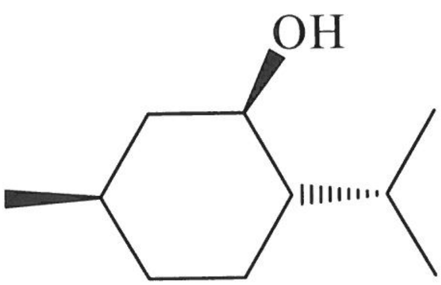
# Practice assigning R or S configurations:

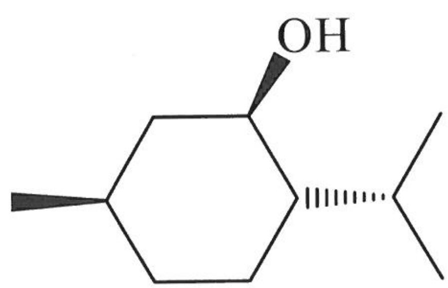


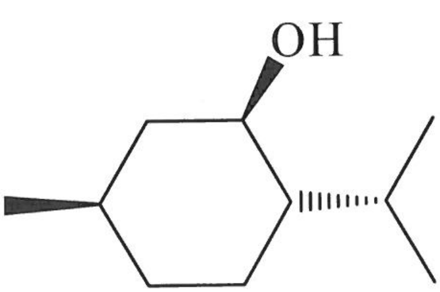



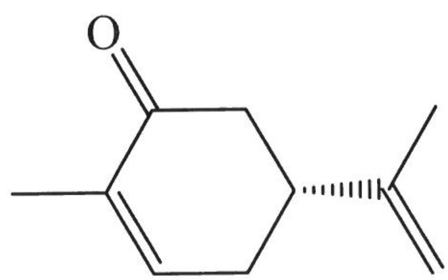



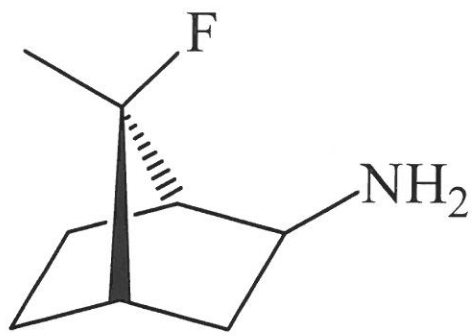



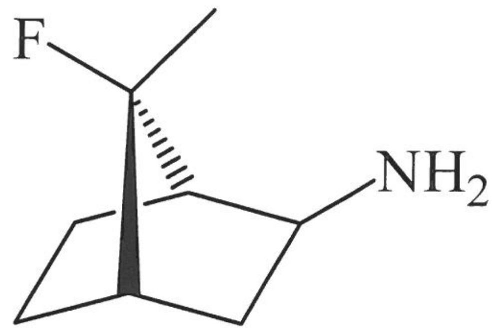



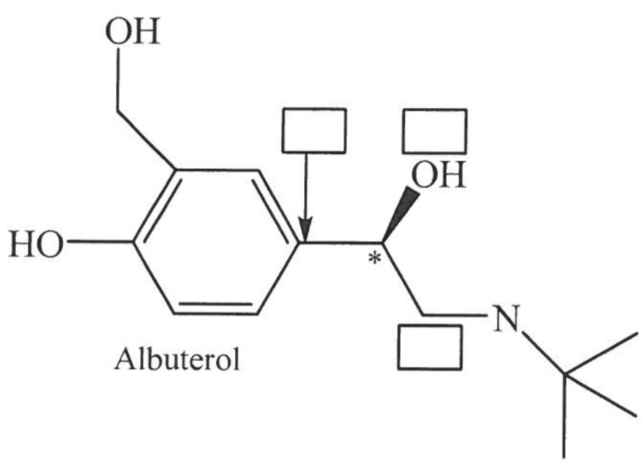
**Practice assigning R or S configurations:**

What if the 4[th] priority is **IN** the plane of the paper? Then what do you do?

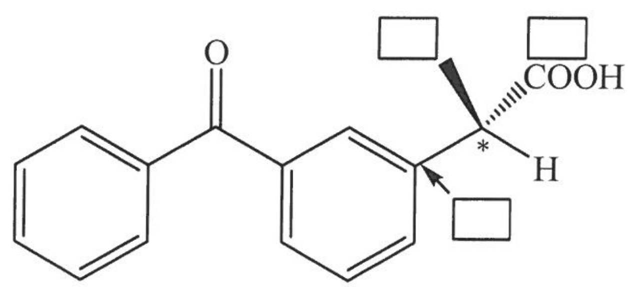


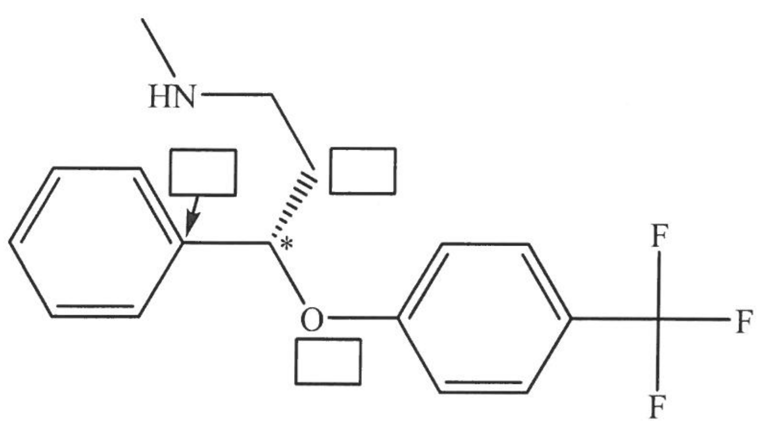

**More practice:**




Albuterol




Ketoprofen




**Fluoxetine**

## 3. Diastereomers -- Molecules with TWO or MORE stereocenters

"How many different configurations can one obtain with more than one chiral center in a molecule?"

- The possible number of stereoisomers for any molecule is ___________.

**<u>Chymotrypsin</u>** – **digestive enzyme** found in intestines and secreted by the pancreas of mammals that catalyze the hydrolysis of proteins during digestion.

- It has 251 stereocenters, with $2^{251}$ possible stereoisomers! But only one is synthesized and utilized in mammals!

**Diastereomer** = stereoisomers that are not enantiomers (mirror images of each other). Diastereomers are pairs of isomers that have opposite configurations at one or more of the chiral centers but are not mirror images of each other.

Diastereomers can have different physical properties and different reactivity.