

Organic Chemistry Unit #3: Chirality at Carbon Centres

Bring your model kits to class!

Objectives: by the end of this unit, you should be able to...

- Identify the chiral centres (stereocentres) present in the structure of an organic molecule
- Given a structure indicating the three dimensional arrangements of atoms, be able to label chiral centres as either *R* or *S* using the priority rules
- Given a series of structures of the same molecular formula, identify them as either constitutional (structural) isomers, stereoisomers (enantiomers), or the same
- Predict the total maximum number of stereoisomers that are possible for a molecule, given its structure

Summary of Concepts

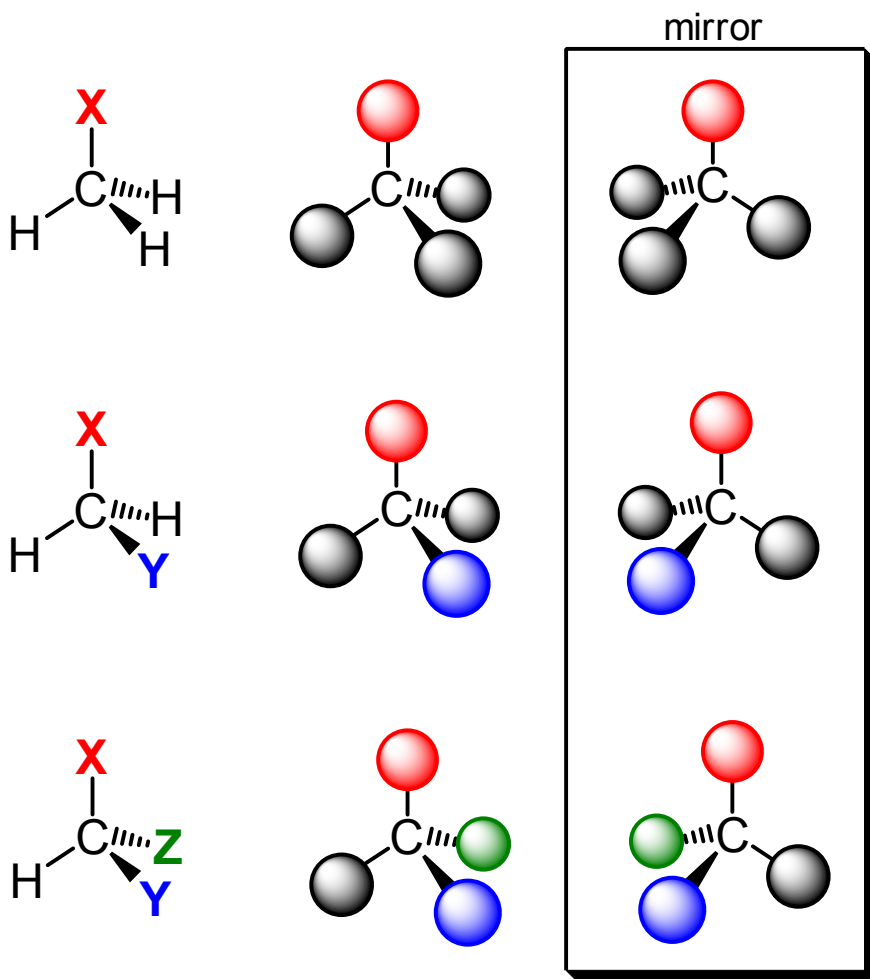
- **Constitutional isomers** are same-formula molecules that differ in the bonding sequence of the atoms.
- **Conformations** are momentary spatial orientations of molecular groupings caused by rotation around σ bonds.
- **Stereoisomerism** refers to molecules that have the same molecular formula **and** same bonding sequence, but have different, non-interconverting 3-D architectures.

Types of Stereoisomerism:

- ***cis-trans* isomerism**, as found in cycloalkanes
- **Geometric (*E/Z*) isomerism**, as found in alkenes
- **Chirality**, as found in virtually all biomolecules

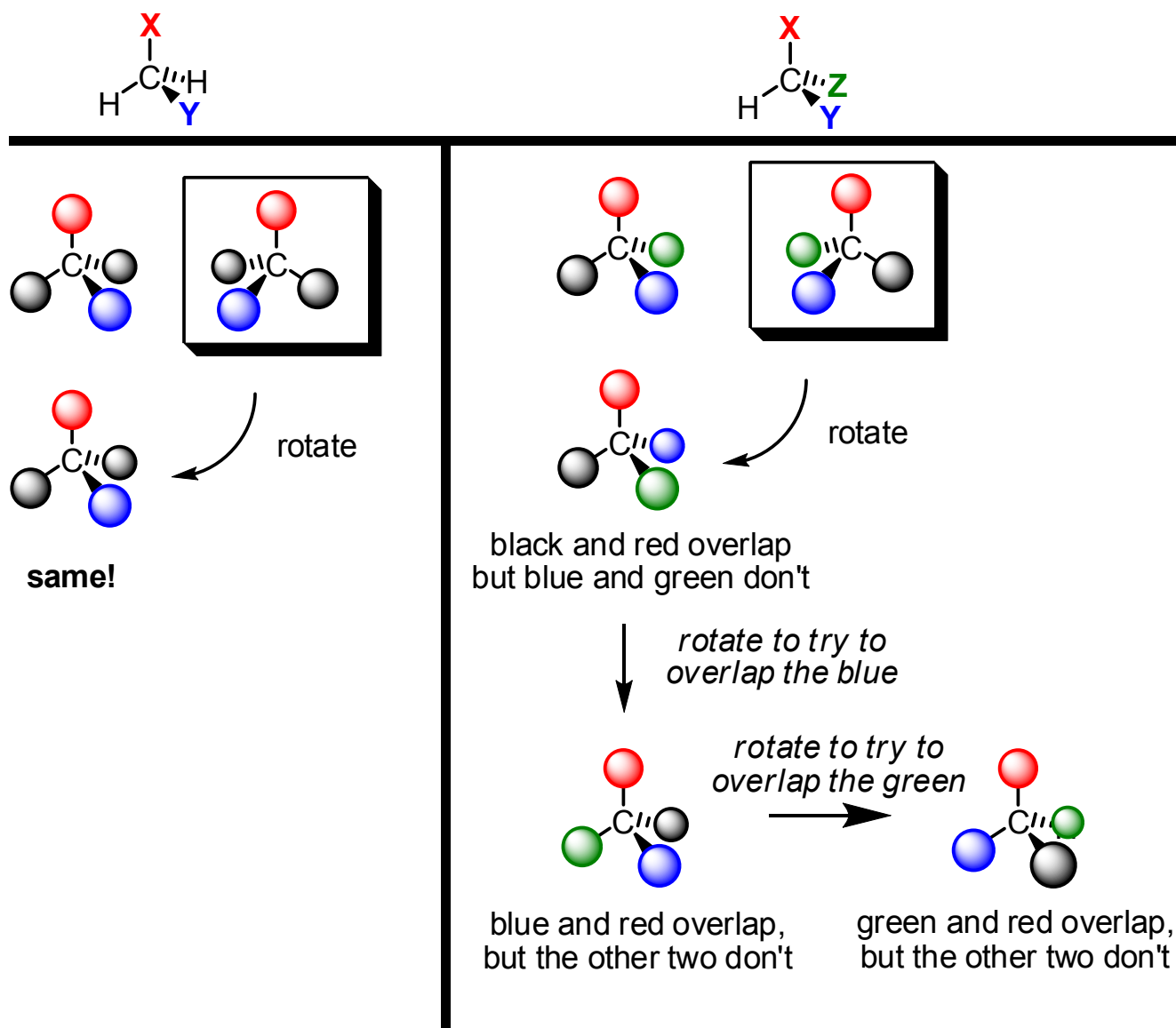
A. Chiral Molecules

- Build the three molecules in the centre column below, as well as their mirror images, exactly as shown. The mirror images are the reflections of the centre molecules.



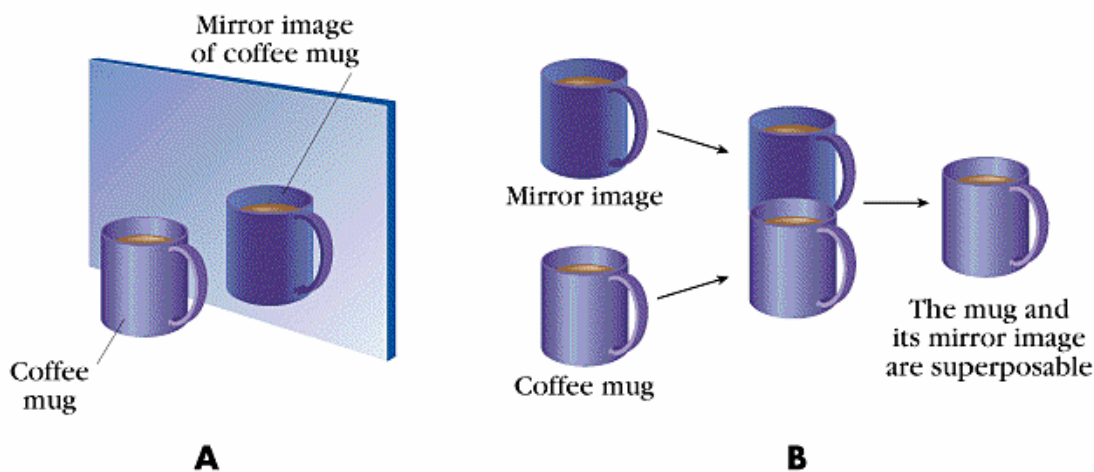
- The models of CH_3X and the CH_2XY are identical to those of their mirror images. Each model and its respective mirror image are superimposable, and it is possible to lay one on top of the other and match the groups.
- However, CHXYZ and its mirror image are not superimposable. The two molecules are not the same!

- As shown below, it can be seen for CH_2XY that the two models can overlap completely. In contrast, it is impossible to overlap the two models of CHXYZ . Two groups will match up, but the other two will not.

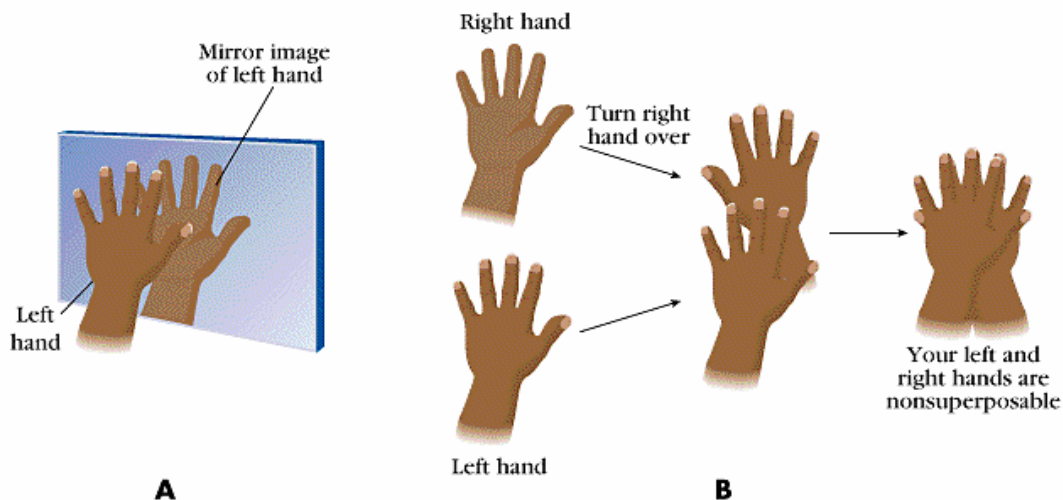


- Two molecules that have the same molecular formula, the same bonding sequence, but are non-superimposable mirror images of each other are **stereoisomers**.
- They are called a pair of **enantiomers**.

- Molecule CHXYZ is an example of a **chiral molecule**. The two molecules that are related by being mirror images of each other are known as **enantiomers**.
- Molecules CH_3X and CH_2X are **achiral**. Their respective mirror images are superimposable, so they are identical.
- Chiral objects have no plane of symmetry. Likewise, an achiral object (non-chiral object) has a plane of symmetry.
- **All chiral objects are not superimposable on their mirror images, as they have no plane of symmetry.** Likewise, achiral objects are superimposable on their mirror images.
- For example, coffee mugs are achiral. They have a plane of symmetry, since they can be cut into two vertical halves. So, they can be superimposed on their mirror images.

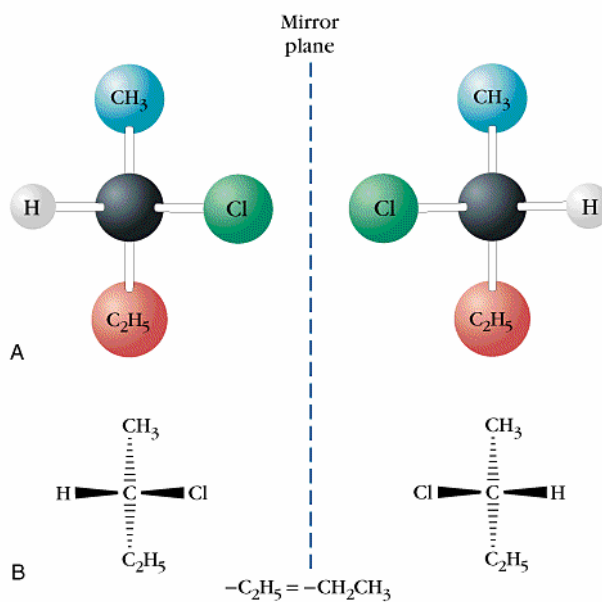


However, our left hand is not superimposable on our right hand, its mirror image. The two sides of our hands are not the same (no plane of symmetry).



- The same principles apply to molecules. Achiral molecules can be superimposed on their mirror images, while chiral ones cannot.
- 2-Chlorobutane is chiral and not superimposable on its mirror image.
- Carbon #2 is bonded to four different substituents:

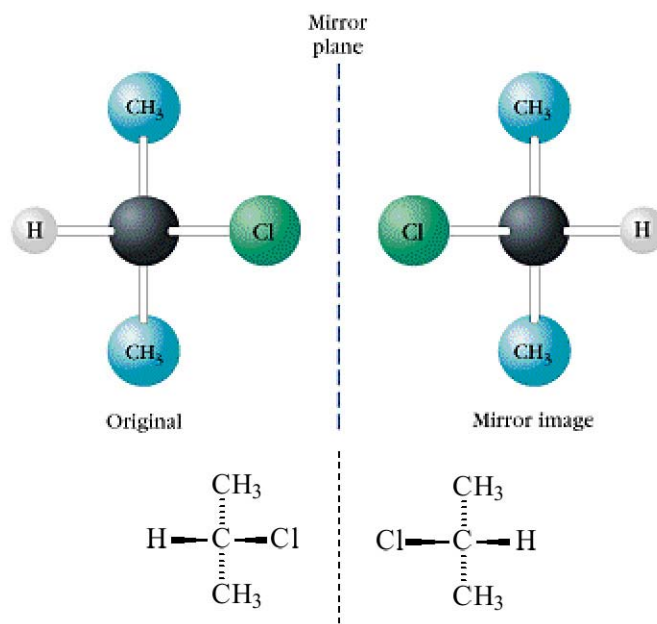
H, Cl, CH₃, and CH₂CH₃



- However, 2-chloropropane is achiral so it is superimposable on its mirror image.

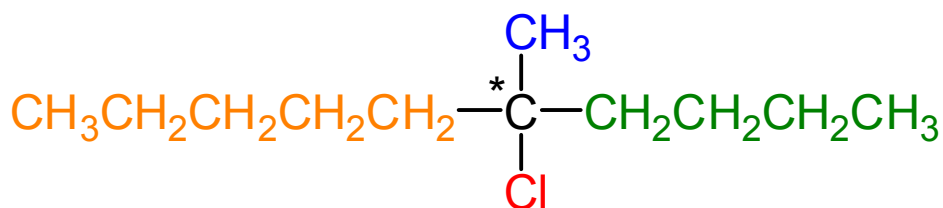
i.e. Its mirror image is identical.

- Carbon #2 is bonded to four substituents, two of which are identical (CH₃).



- The most common source of chirality in a molecule is a stereocentre, usually a carbon bonded to four different groups (substituents).
 - An atom bonded to four different groups in a tetrahedral geometry is called a **stereocentre** or a **chiral centre**.
- Identifying stereocentres in a complex molecule requires practice. It is not always clear that 4 different groups are bonded to a given carbon, as the differences do not have to be on just the adjacent carbon (recall when we were using rules to assign *E/Z* to alkenes).

- Example: the difference between the green and the orange groups is not noticed until four carbons away, but the two groups are still considered to be different.



substituents on C:

CH₃

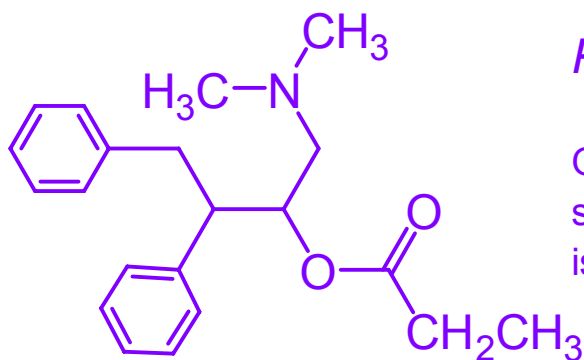
Cl

CH₂CH₂CH₂CH₃

CH₂CH₂CH₂CH₂CH₃

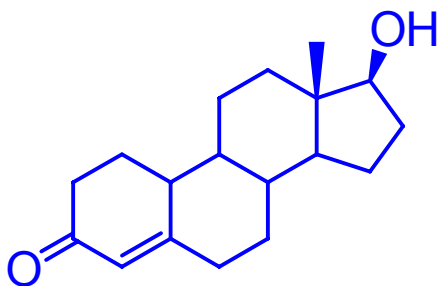
- Enantiomers are isomers that do not interconvert at room temperature. They are different compounds! Because they share the same bonding sequence, the same formula, and the same number and type of functional groups, **their chemistry is exactly the same**, EXCEPT (discussed later):
 - The two enantiomers have different effects on the rotation of plane-polarized light.
 - They react differently with other chiral compounds (this is the very important in biochemistry).

- Practice: Indicate all the chiral carbons in the following molecules by labelling them with a ★



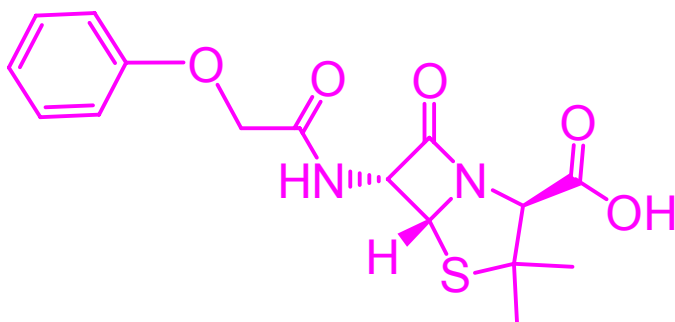
Propoxyphene

One stereoisomer is a cough suppressant, but its enantiomer is an analgesic



Nandrolone

An anabolic steroid used to build muscle mass in athletes. Subject of the major league baseball scandal.

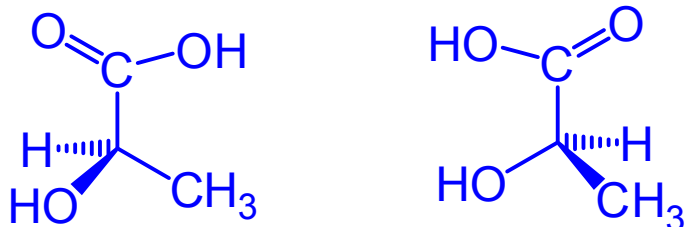


Penicillin V

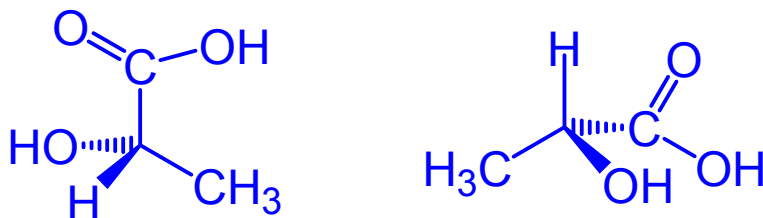
Used to treat throat and mouth infections

- **Aside:** These are examples highlighting the common problems that are encountered when comparing structural representations of molecules, or when manipulating models

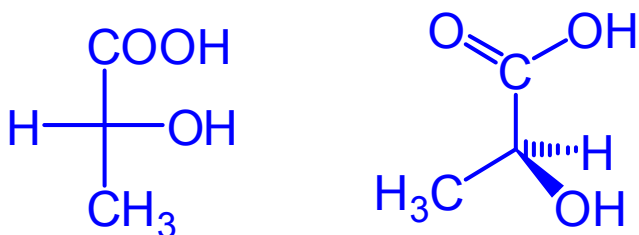
- How are these two structures of lactic acid related?



- How about these two molecules?

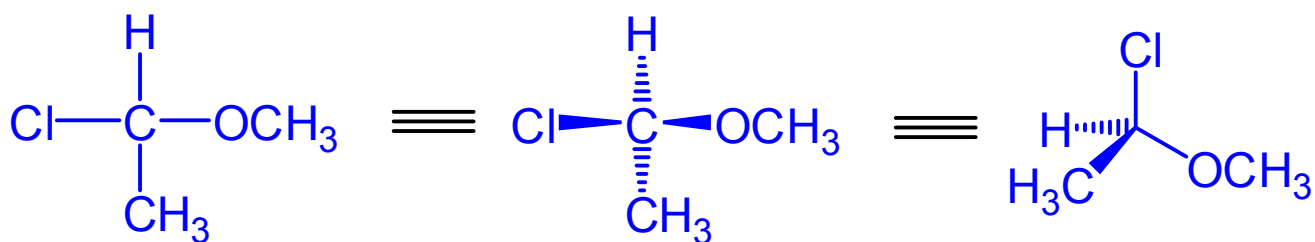


- And these?



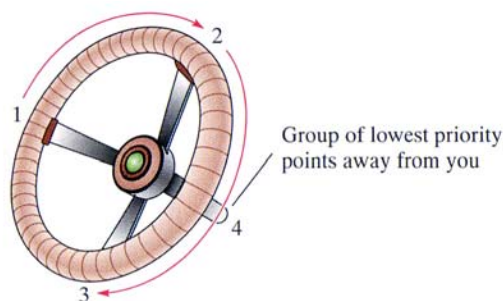
B. R and S Designation of Enantiomer Configuration

- We use the *R and S convention* to specify the absolute 3D configuration of stereocentres, which are commonly marked in structures as ★.
- The convention assigns a priority order to the substituents on the stereocentre according to the *same priority rules we examined when looking at the E/Z convention in alkenes*.
- Example on assigning priorities:



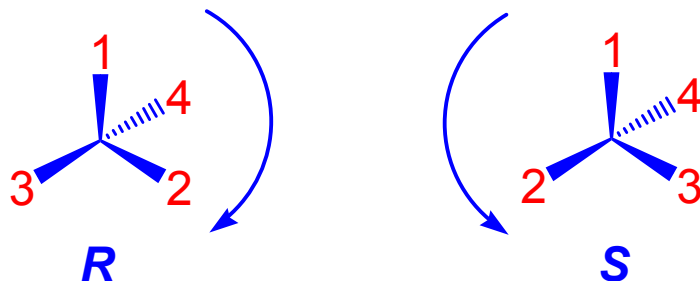
- Using the priority assignments, we can assign an *R* or *S* configuration label to the molecule as follows:

1. Draw the molecule with the lowest-priority group (#4) behind the plane (dash), with the remaining three in a steering wheel arrangement.

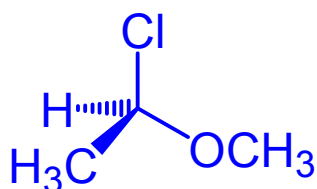


2. Draw an arrow going from the highest priority group (#1) to the second-highest (#2), and the third-highest (#3).

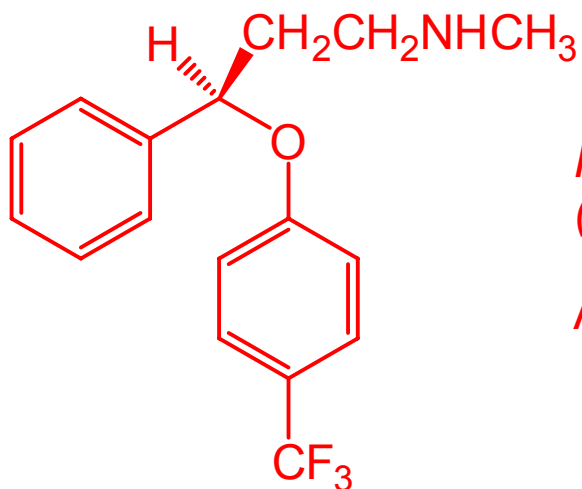
- If the steering wheel is rotated in the direction of the arrow and the car turns left, the absolute configuration is *S* (sinister = counterclockwise).
- If rotation of the steering wheel in the arrow direction makes the car turn right, the absolute configuration is *R* (rectus = clockwise).



- Therefore....

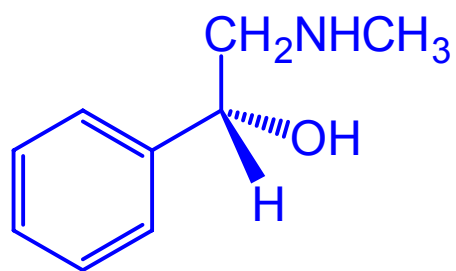


- Practice: what is the *R* and *S* configuration of the following?



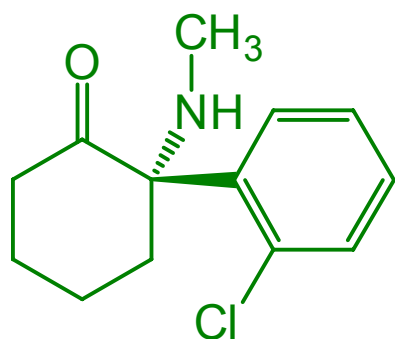
Fluoxetine
(Prozac)

Antidepressant



Epinephrine
(adrenalin)

Hormone that
dilates airways and
increases heart rate

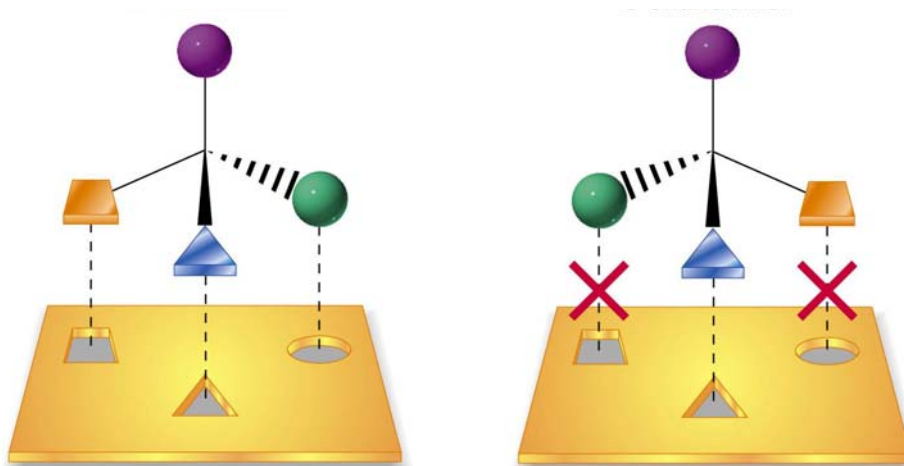


Ketamine

Anesthetic

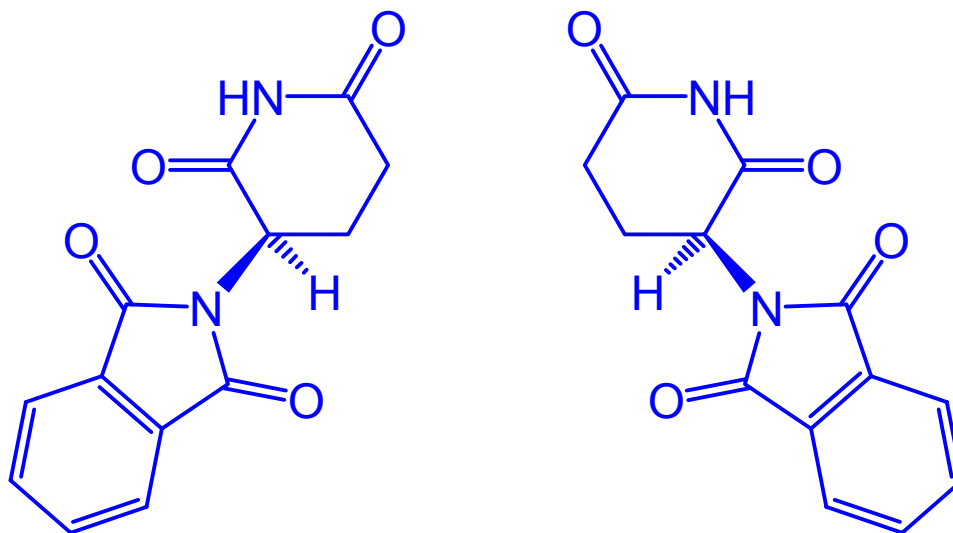
C. Chirality in Biomolecules

- Most physiologically active biomolecules are enantiomerically pure (only one stereoisomer is active), and only this pure enantiomer undergoes a chemical reaction.
- This is because the *in vivo* synthesis of biomolecules, as well as their reactions, are catalyzed by proteins called enzymes. Enzymes create stereocentres in a spatially controlled way, so that only one enantiomer can form. Likewise many biological processes will only interact with a single enantiomer.

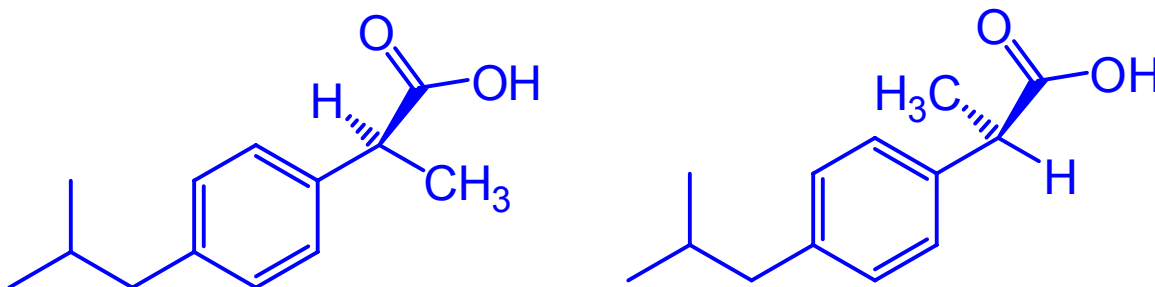


- Drug companies often sell drugs as racemic mixtures, provided clinical trials show that the non-active enantiomer has little unwanted side effects.
- However, the two enantiomers of a drug can sometimes affect the body differently, sometimes badly. Nowadays, drugs usually need to be prepared in the enantiomerically pure form (one enantiomer) in order to be approved for use.
- Examples....
- Thalidomide has one stereocentre.

- This drug was widely prescribed as a sedative and anti-nausea drug to pregnant women (in part to help with morning sickness) in Europe and Canada in the 1960's.
- Unfortunately, this drug was sold as a mixture of the *R* and *S* forms. The *R* form had the desired anti-nausea properties but, unknown at the time, the *S* form acted as a teratogen and an anti-abortion drug. It caused thousands of serious birth defects in the children born to women who took this drug during pregnancy.
- Interestingly, this drug was not approved in the USA, where a chemist noted that there were an unusual number of birth defects in the babies of mother rats given the medication.
- Which one is *R*, and which is *S*?

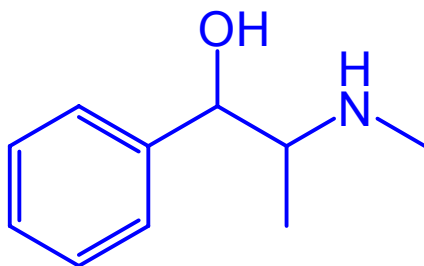


- Ibuprofen (Advil and Motrin) also has one stereocentre.
 - It is sold as a 1:1 mixture of the *R* and *S* forms. A 1:1 mixture of two enantiomers is called a **racemic mixture**.
 - Only the *S* enantiomer acts as an anti-inflammatory and as an analgesic (pain killer). The *R* enantiomer is inactive and harmless.
 - Which one of the structures below is the active *S* form?

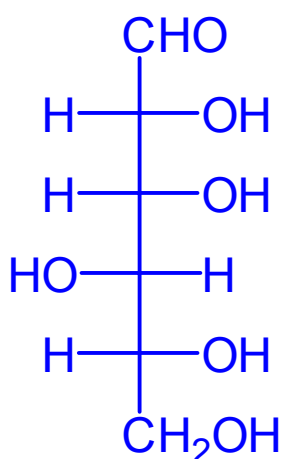


D. Molecules with Two or More Stereocentres

- Large organic molecules can have two, three, four, or up to hundreds of chiral centres!
- For example, ephedrine is a common bronchodilator and decongestant that has received plenty of attention in the past year. Locate its two stereocentres.



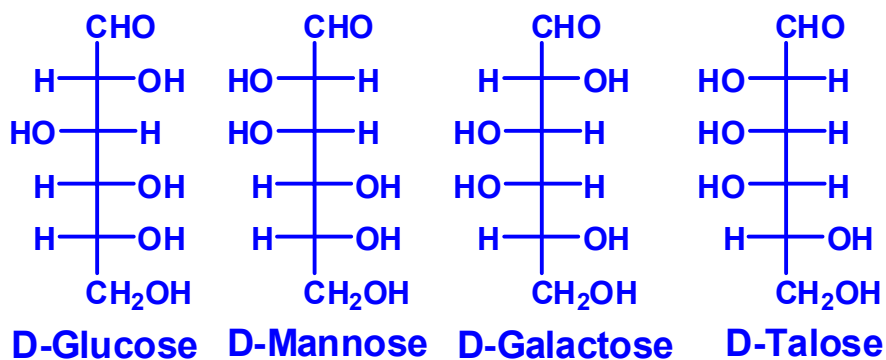
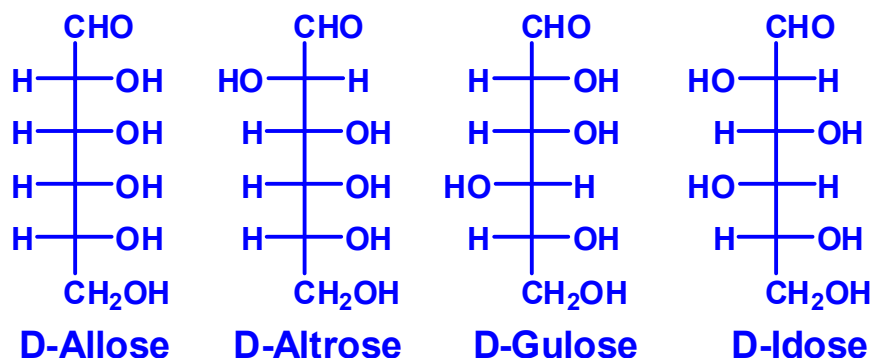
- Since there are two stereocentres, four different combinations of *R/S* labels are possible.
 - *R,R*
 - *S,S*
 - *R,S*
 - *S,R*
- Therefore, a molecule with 2 stereocentres will have **up to** $2^n = 2^2 = 4$ possible stereoisomers (n = the number of stereocentres). **Compounds with n chiral centres will have a maximum of 2^n stereoisomers.**
- The sugar D-glucose, shown below, belongs to a family of sugars known as the six-carbon aldehyde sugars. Its structure is shown below. Find its stereocentres.



Fischer projection of glucose

- The six-carbon aldehyde sugars have four stereocentres, hence a maximum of $2^4 = 16$ stereoisomers. One of these, D-glucose, is the most common one found in nature.

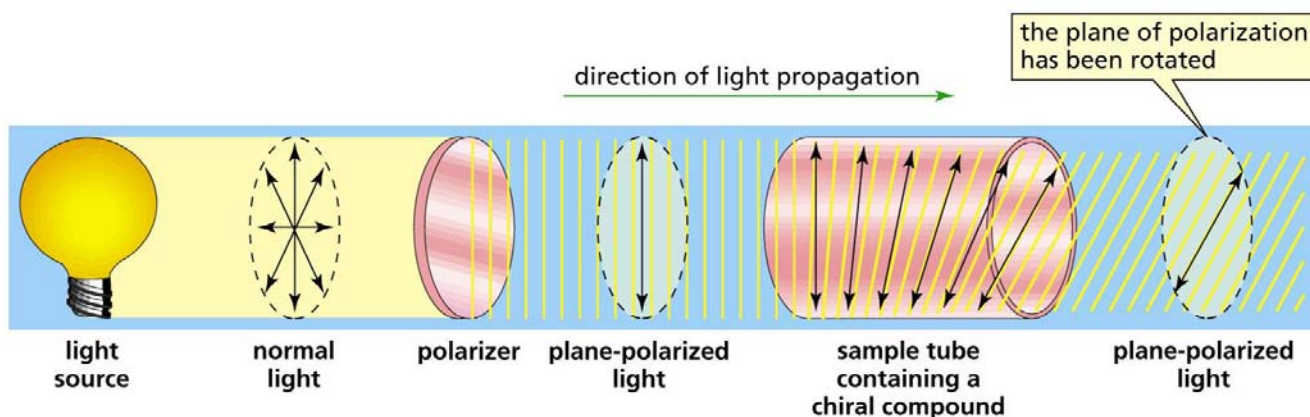
- There are another 7 sugars of the D series, shown below.



- Each one of these D sugars has an enantiomer, which carries the L prefix (L-glucose, L-allose, etc.), giving a grand total of 16 stereoisomers.

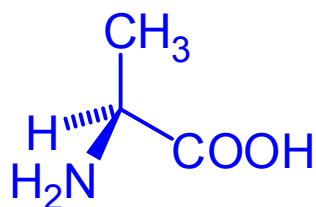
E. Plane-Polarized Light and Optical Activity

- If normal light or sunlight is passed through a plane-polarizing filter (such as polarized sunglasses), the light rays all vibrate in the same plane.
- When plane-polarized light is passed through a solution of a pure enantiomer of a chiral compound, the plane of polarization is *rotated* to the right by one enantiomer, and to the left by the other enantiomer.

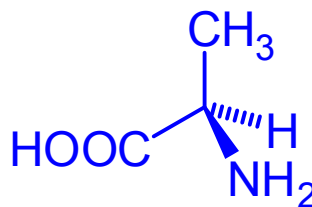


- The enantiomer rotating light to the right was termed the "+" enantiomer. Similarly, the one rotating light to the left was termed the "-" enantiomer.
- In the old days, before advanced chemical instrumentation were available to determine stereochemical configuration, chiral molecules were simply called *optical isomers*. Achiral molecules had no effect on light.

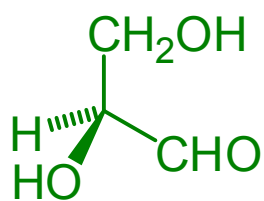
- Students taking other courses, such as biology and biochemistry, will also encounter the D and L notation. That notation is based on how a Fischer projection is drawn.
 - **D/L**, **+/-**, and **R/S** have nothing in common! They are simply different ways of identifying enantiomers of chiral molecules.
- Examples: the amino acid alanine, and glyceraldehyde, the simplest sugar.



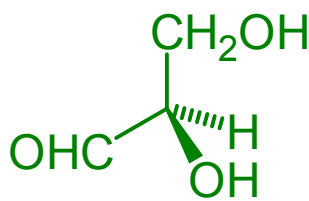
(+)-alanine
L-alanine
S-alanine



(-)-alanine
D-alanine
R-alanine



(-)-glyceraldehyde
L-glyceraldehyde
S-glyceraldehyde



(+)-glyceraldehyde
D-glyceraldehyde
R-glyceraldehyde