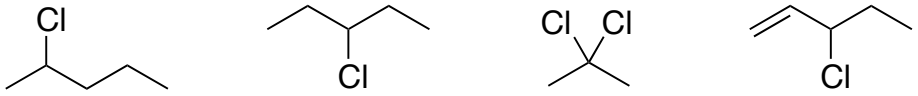
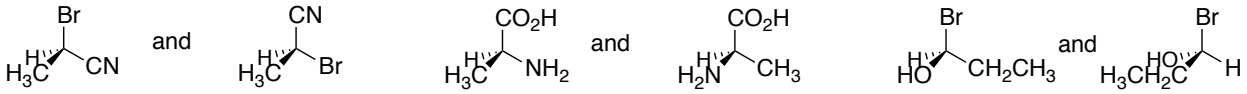
CHAPTER 5: STEREOCHEMISTRY

Identifying Chiral Carbons and Chirality.

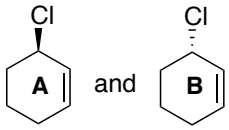
Which molecules contain chiral carbons? Mark the chiral carbons with an asterisk.



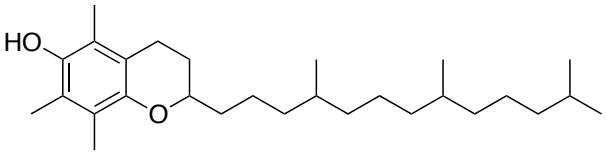
Without determining stereochemical configuration (R or S), can you determine which of the following pairs of molecules are the same, and which are enantiomers?



For molecules that have only one chiral atom, there can only be two possible isomers (below, left). If you count the number of chiral atoms and solve for 2^n, where n = # chiral atoms, this will tell you how many stereoisomers are possible for any given molecule. For example, $2^1 = 2$.



only two possible stereoisomers are possible for 3-chlorocyclohexene



1. Identify the chiral carbons
2. How many possible stereoisomers are can you have for this molecule?

Is molecule **A** optically active? _____

Is molecule **B** optically active? _____

Can you predict the optical rotation of **A** or **B**? _____

If you were to consider an equal mixture (1:1) of both **A** and **B**, could you predict the optical rotation of the mixture? _____

What is the name for this kind of mixture? _____

Naming Chiral Centers - The *R,S* System. Since we cannot assign D (or +) or L (or -) to an enantiomer simply based on its structure, another naming system must be used to distinguish between stereoisomers. After all, we can't name both these molecules 2-chloropentane.

2-chloropentane?

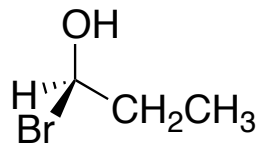
The Cahn-Ingold-Prelog priority rules are in place to specify an *absolute configuration* around a chiral center (carbon, in these examples).

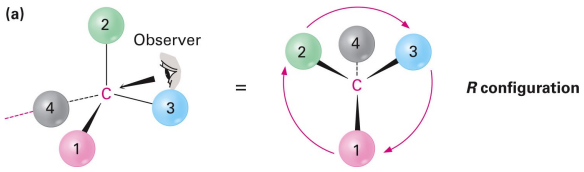
Cahn-Ingold-Prelog Priority Rules

Rule 1:

- Look at the four atoms (not group of atoms) directly attached to the chiral atom, and rank them according to atomic number, where 1 is the highest and 4 is the lowest priority.
- With the lowest priority group pointing away, look at the remaining 3 groups in a plane.
- From highest to lowest priority, clockwise is designated *R*, counterclockwise is designated *S*.

Is this *R* or *S*?

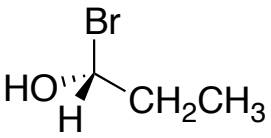


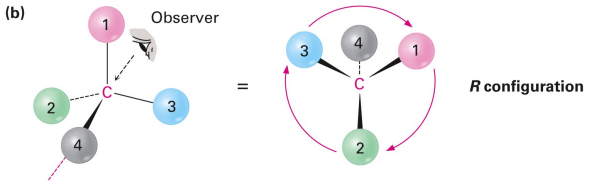


Rule 2:

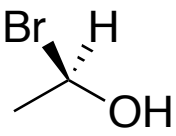
- If the lowest priority group is facing TOWARD you, rather than away from you, continue the standard method for determining *R* and *S*, but REVERSE the ending result. Alternatively, you can simply put your eye where it needs to be in order for the lowest priority group to be facing away from you - which is how the middle and right images are drawn, below.

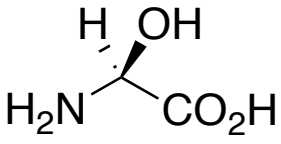
Is this *R* or *S*?

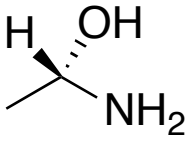




Assign *R* or *S* to the chiral carbons in each example:

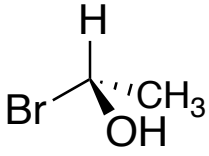


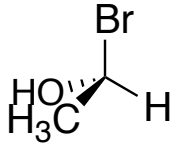




- If the lowest priority group is neither facing away from you or toward you (like below), adjust your perspective so it IS pointing away from you.

Assign *R* or *S* to the following:





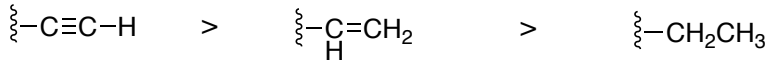
Rule 3:

- If a decision on priority cannot be reached by ranking the first atoms from the chiral atom, compare the second, third, or fourth atoms until a priority can be assigned.

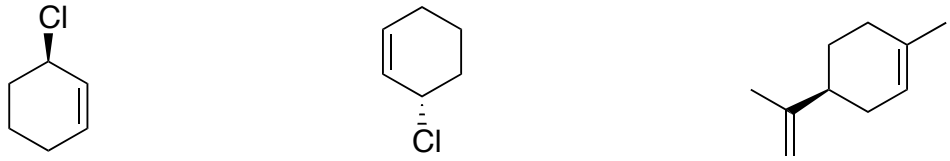
Which is (*R*)-2-chloropropane and which is (*S*)-2-chloropropane?

Rule 4:

- In most cases, it is safe to presume that atoms with a greater number of bonds are of a higher priority when compared to the *same* atom with less bonds, for example:

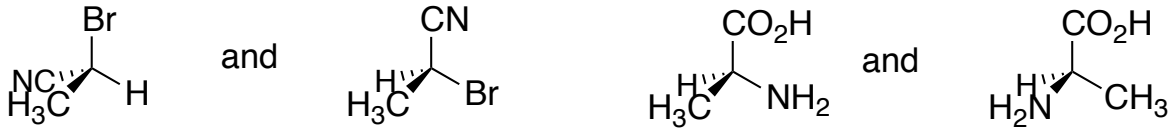


Try assigning the configuration of the chiral carbons below:

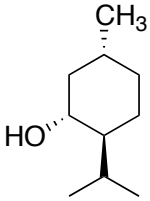


Let's Practice:

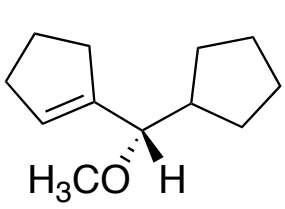
Assign (*R*) or (*S*) to the molecules below. Are the pairs the same or are they enantiomers?

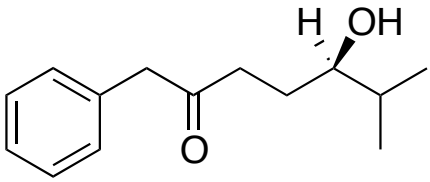


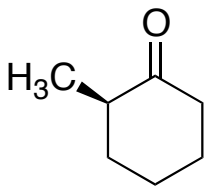
Assign (*R*) or (*S*) configurations to the chiral carbons in the following isomer of menthol:

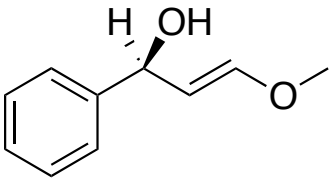


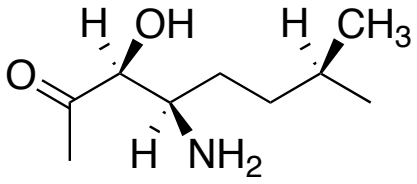
Assign (*R*) or (*S*) configurations to the chiral carbons in the following molecule:





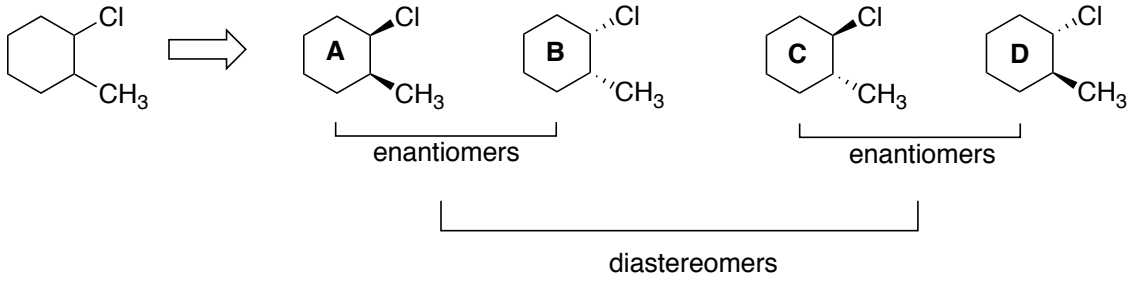






Molecules With Multiple Chiral Atoms.

1-chloro-2-methylcyclohexane has four possible stereoisomers ($2^2 = 4$); they are:



A and **B** are enantiomers and **C** and **D** are enantiomers, but "diastereomer" describes the relationship of **A** or **B** with **C** or **D**.

Using IUPAC rules, **A** is now named (1*R*,2*S*)-1-chloro-2-methylcyclohexane. You try naming **B** through **D**.

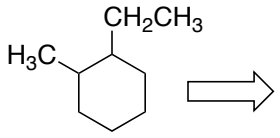
A: _(1*R*,2*S*)_____-1-chloro-2-methylcyclohexane

B: _____-1-chloro-2-methylcyclohexane

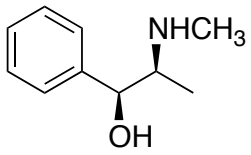
C: _____-1-chloro-2-methylcyclohexane

D: _____-1-chloro-2-methylcyclohexane

We predict four stereoisomers for the example below. Draw them, assign (*R*) and (*S*) to the chiral atoms, then determine which are enantiomers and which are diastereomers.



The levorotatory isomer of epinephrine, below, has profound effects on the cardiovascular system. Draw (+)-epinephrine (remember, enantiomers have exactly the opposite stereochemistry).

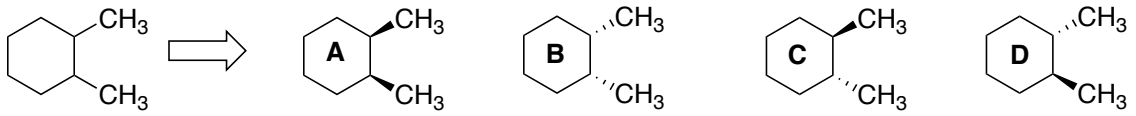


(-)-Epinephrine

What can you say with certainty about the optical rotation of (+)-epinephrine?

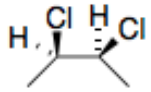
What can you say with certainty about the biological properties of (+)-epinephrine?

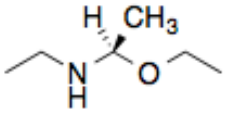
Meso Compounds. Some molecules that have chiral carbons do not obey the "2^n" rule. For example, consider the following four structures of 1,2-dimethylcyclohexane

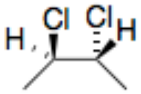


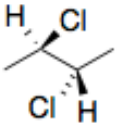
Although **C** and **D** are enantiomers, **A** and **B** are the same; hence, although *trans*-1,2-dimethylcyclohexane is chiral, c*is*-1,2-dimethylcyclohexane is not - and it carries a unique name: *meso*. A molecule that is *meso* has more than one chiral carbon, but *is not chiral*. So ultimately, 1,2-dimethylcyclohexane only has three different stereoisomers; **A** is meso, and is a diastereomer of **C** and **D**, while **C** and **D** are enantiomers of each other.

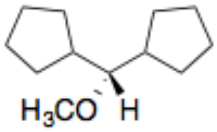
Can you identify which of the following are meso compounds? Look for symmetry.

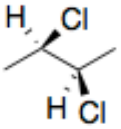


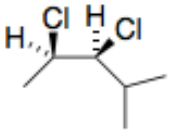


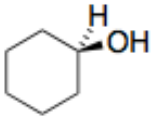


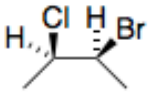


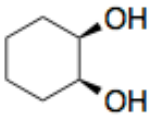


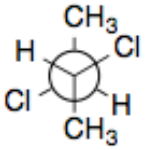


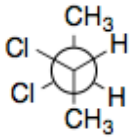






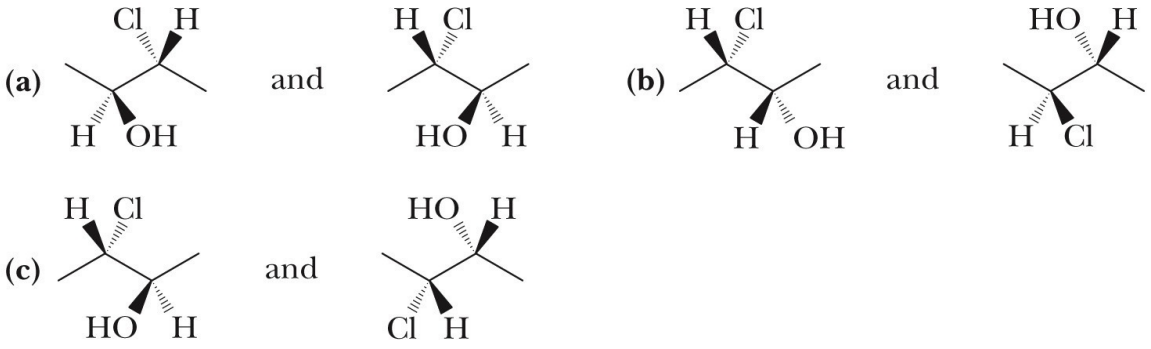






Are the molecules within each set, below, identical, enantiomers or diastereomers?

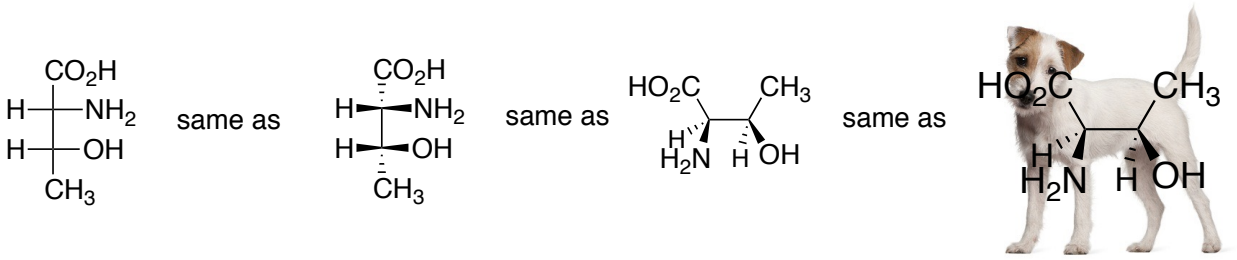
If you find these difficult by simply looking at the molecules and comparing their shape, start by assigning (*R*) and (*S*) to the chiral atoms - this may simplify the task.



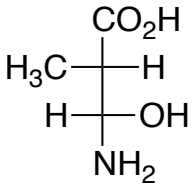
Fischer Projections. Molecules depicted this way are all drawn with the assumption that the horizontal bonds are coming toward you and the vertical bonds are going away from you - like this:

Fischer Projection

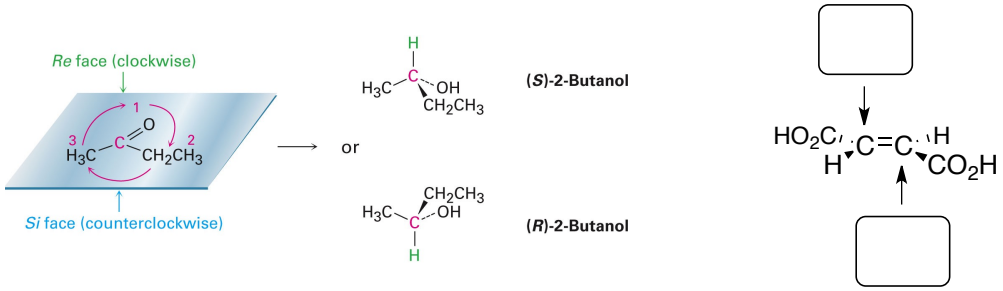
If that representation is still a little foreign, you can convert this to a molecular representation you might recognize by pretending that you're looking at the underside of a dog. The horizontal bonds are the four legs, and are coming toward you, and the vertical bonds are the head and tail, going away from you. Simply pick up the dog and put it on its feet. No joke - it works!



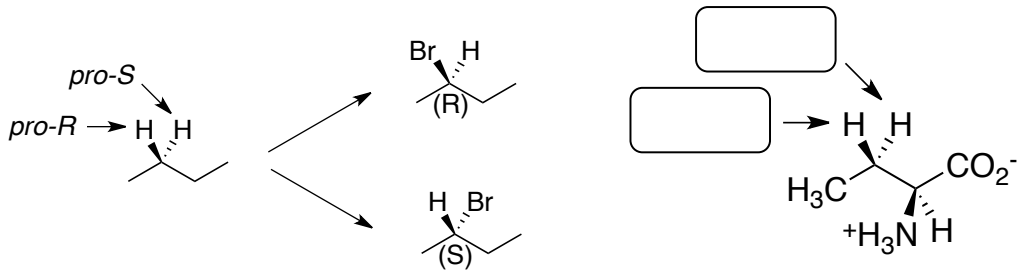
To assign chirality to atoms in molecules that are drawn in a Fischer projection, you can either simply imagine the horizontal/vertical bonds forward/back (the easier way to do it) or stand the dog up on its feet. Which ever method works for you - give it a try. Assign (*R*) or (*S*) to the chiral carbons in the following molecule:



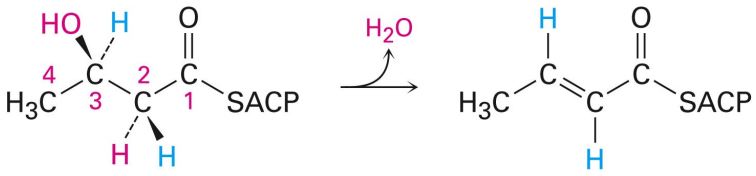
Prochirality. Some molecules that are NOT chiral can have *prochiral* atoms if adding a fourth atom can create asymmetry. *Re* and *Se* are used to describe the face of a planar molecule such as this ketone to indicate the rotation from highest to lowest priority (left). From the perspective of viewing the alkene (right) in the plane of the paper, each of the two prochiral carbons can be labeled *Re* or *Se* - give it a try:



Prochirality can also describe hydrogen atoms attached to achiral carbons. In the following example, if the *pro-R* hydrogen was replaced with a higher priority atom, the resulting absolute configuration would be (*R*). You try:



Question 5.61 from text: One of the steps in fatty-acid biosynthesis is the dehydration of (*R*)-3-hydroxybutyryl ACP to give *trans*-crotnyl ACP. Does the reaction remove the pro-*R* or pro-*S* hydrogen from C2?



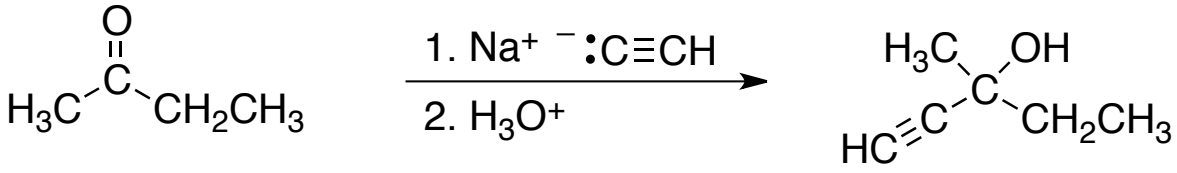
(*R*)-3-Hydroxybutyryl ACP **_trans_-Crotonyl ACP**

Question 5.70 from the text: (*S*)-1-Chloro-2-methylpentane undergoes light-induced reaction with Cl_2 to yield a mixture of products, among which are 1,4-dichloro-2-methylbutane and 1,2-dichloro-2-methylbutane.

(a) Write the reaction, showing the correct stereochemistry of the reactant

(b) One of the products is optically active, but the other is optically inactive. Which is which?

Question 5.76 from the text: Ketones reaction with sodium acetylide to give alcohols. For example, the reaction of sodium acetylide with 2-butanone yields 3-methyl-1-pentyn-3-ol.



(a) Is the product chiral?

(b) Assuming that the reaction takes place with equal likelihood from the *Re* and *Si* faces of the carbonyl group, is the product optically active? Explain.

Most chiral nitrogens are unstable and readily interconvert their stereochemistry spontaneously to form racemic mixtures. This process can be slowed to maintain the stereochemistry of the nitrogen atom in which of the following ways?

(a) Increasing the pH of the solution
(b) Decreasing the size of the functional groups on the nitrogen
(c) Increasing the temperature of the solution
(d) Increasing the steric hinderance of the functional groups on the nitrogen