

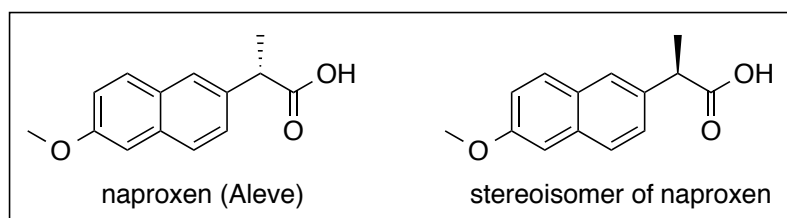
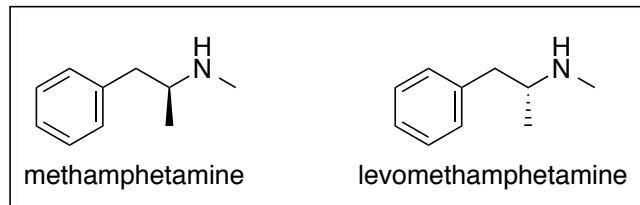
9. Stereochemistry: Introduction to Using Molecular Models

The first part of this document reviews some of the most important stereochemistry topics covered in lecture. Following the introduction, a number of exercises are presented. During lab, you should work through as many of the exercises as possible. You will need a molecular model kit to aid you in completing the exercises.

A. Introduction

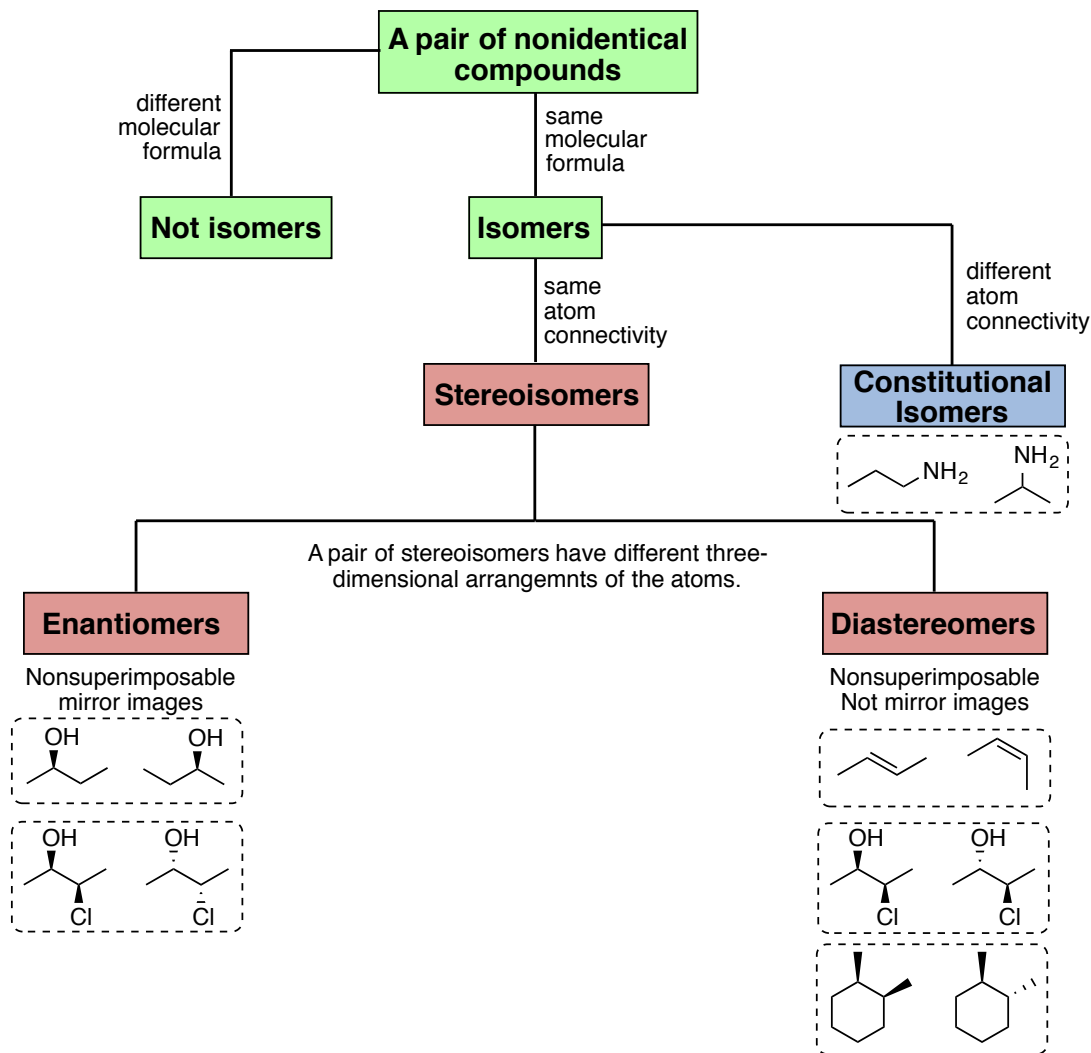
It is very important to understand stereoisomers and the different properties associated with the different stereoisomers of a molecule. Understanding stereochemistry will allow you to understand the three-dimensional nature of molecules and the reactions that they undergo.

In biological systems, the three-dimensional structure of a molecule has a profound impact on how it interacts with the biomolecules in a living system. Consider the examples shown below. Methamphetamine, an illegal street drug, is a potent psychostimulant while its stereoisomer, levomethamphetamine, is the active components in certain decongestants such as the Vicks vapor inhaler. Another example is the nonsteroidal anti-inflammatory drug (NSAID) naproxen, which is sold under the trade name Aleve. Naproxen is sold as a single stereoisomer because the other stereoisomer is a liver toxin and has no anti-inflammatory properties.



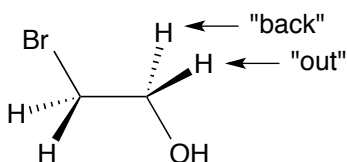
The above examples show that different stereoisomers have serious impacts on the human body. For this reason, it is important that chemists be able to recognize and understand the stereochemistry of organic molecules. Additionally, this information is necessary so that specialized reactions or purification protocols can be devised to prepare or isolate a single stereoisomer selectively. This is especially important when other stereoisomers of a molecule have adverse or even toxic effects.

B. Classification of Isomers



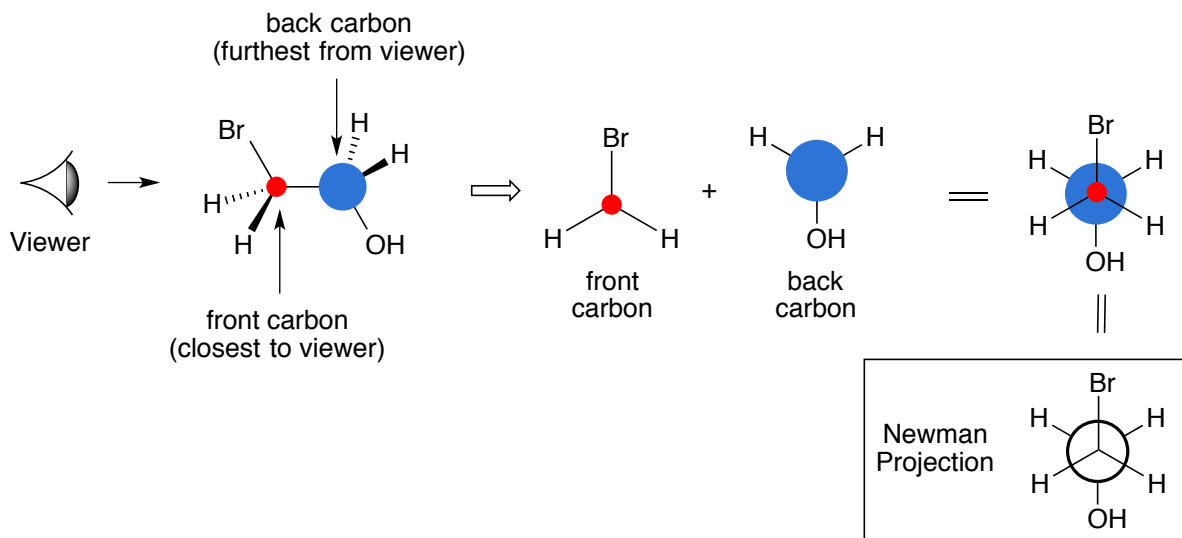
C. Conformations of Acyclic Alkanes

Dash and Wedge Drawings: An atom connected to a carbon using a bold wedge indicates that the atom is coming out of the plane of the page towards you. An atom connected to a carbon using a dash (or hash) indicates that the atom is going back into the page away from you. Atoms connected by single lines indicate that those atoms lie in the plane of the page.

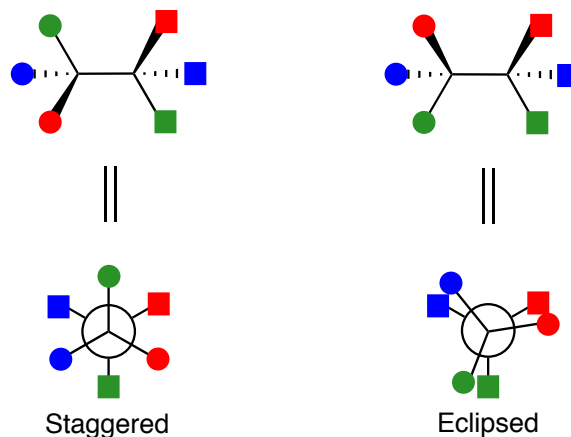


The connected atoms Br-C-C-O all lie in the plane of the page.

Newman Projections: The viewer looks along a bond connected by two carbon atoms (a front carbon and a back carbon). Each carbon has one group either pointing straight up or straight down. The other two groups are pointing up or down and to the left and right. In the example below, the front carbon has a bromine that points straight up, a hydrogen that points down and to the left, and a hydrogen that points down and to the right.

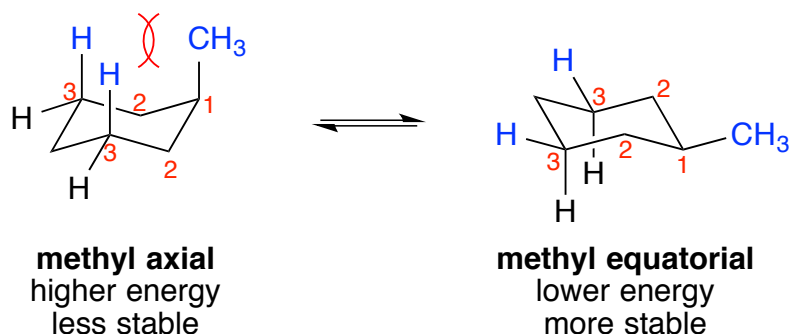


Newman projections can be used to show the conformations about a single bond in a molecule. Some conformations are higher in energy while others are lower in energy. Newman projections help up analyze the relative energies of the various conformations. Newman projections may be either staggered or eclipsed. In the eclipsed conformation, the three groups on the front carbon are directly in front of the three groups on the back carbon. To make the eclipsed structure easier to visualize, the groups on one of the carbons are skewed slightly so that the other eclipsed groups can be seen.

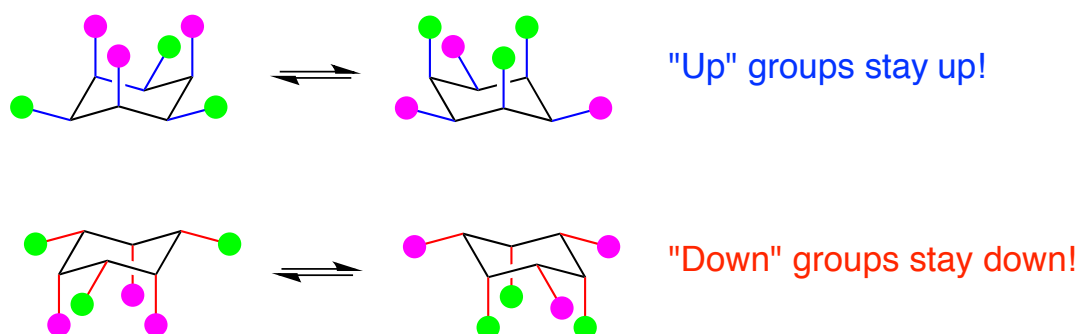


D. Conformations of Cyclohexane

The three-dimensional structure of cyclohexane is best represented by drawing cyclohexane in the chair form. Cyclohexane undergoes rapid interconversion between two chair conformers via a chair interconversion (ring flip). Substituents in the axial orientation suffer from unfavorable 1,3-diaxial interactions; therefore, the chair conformation that puts the larger group(s) in the equatorial position is energetically preferred.

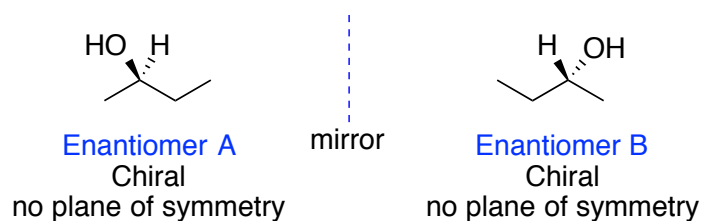


During the chair interconversion, axial substituents become equatorial and equatorial substituents become axial. It should be noted, however, that substituents that are pointing “down” below the ring stay “down” and substituents that point “up” above the ring stay “up” during the ring interconversion.

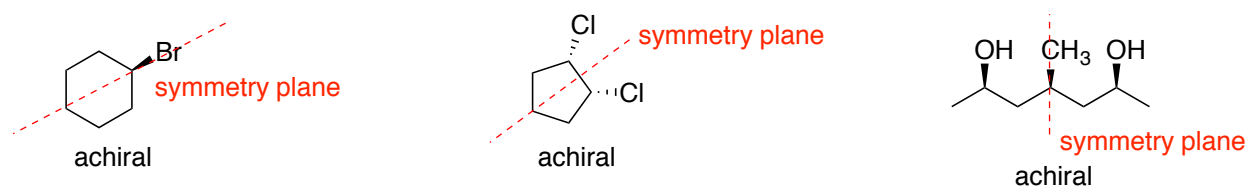


E. Chirality

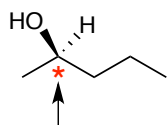
A molecule is chiral if it cannot be superimposed on its mirror image. A chiral compound will have two enantiomeric forms (a pair of enantiomers).



A molecule that contains a plane of symmetry will be superimposable on its mirror image and is thus achiral.

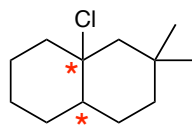


Most, but not all chiral molecules contain **asymmetric centers** (chiral centers). An atom, usually carbon, that contains four different groups attached to it is an asymmetric center.



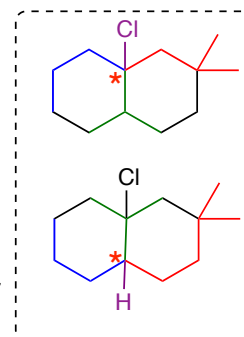
4 different things attached

- methyl group
- propyl group
- OH
- H



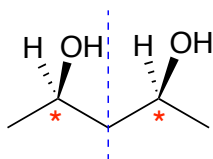
Two asymmetric centers

Sometimes you have to trace around to look for a point of difference in order to determine if you have 4 different groups.



F. Molecules with More than One Chiral Center

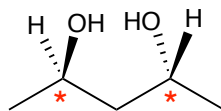
A molecule that contains one chiral center is a chiral molecule. A molecule that contains two or more chiral centers may or may not be chiral. If a molecule containing two or more chiral centers has a plane of symmetry, it is achiral and is called a **meso compound**.



Symmetry Plane

This compound has two asymmetric centers, however, it has a plane of symmetry. This plane of symmetry makes it achiral. This is by definition a meso-compound.

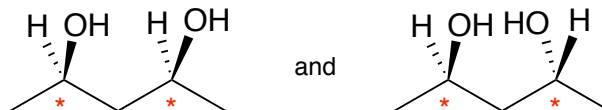
When there is no plane of symmetry, the molecule is chiral.



No Symmetry Plane

A Chiral Molecule

The two molecules above are stereoisomers. They have the same molecular formula and the same atom connectivity, but they are not superimposable and are not mirror images. These two molecules represent a pair of **diastereomers**.



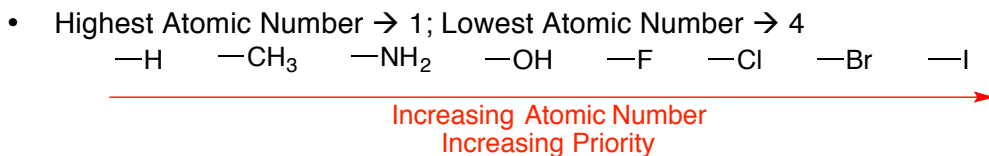
Diastereomers

G. R and S Assignment

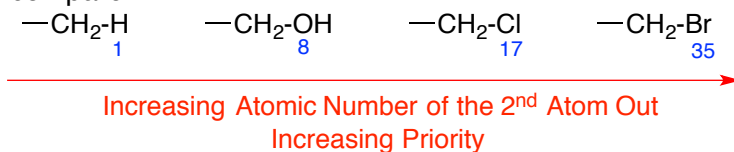
Chiral centers can be assigned an *R* or *S* configuration based on the arrangement of the four different groups around the chiral center. This allows one to name each enantiomer in a pair unambiguously as shown below for the two 2-chlorobutane enantiomers.



1. Look at the four atoms directly attached to the asymmetric center.
2. Prioritize these atoms based on atomic number



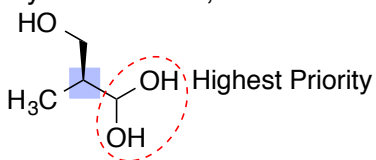
- If there is a tie between two or more groups, move out to the next atom in each chain and compare.



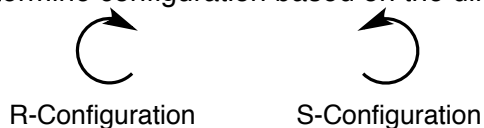
- Atoms with a double or triple bond are treated as having two (or three) bonds to phantom atoms.



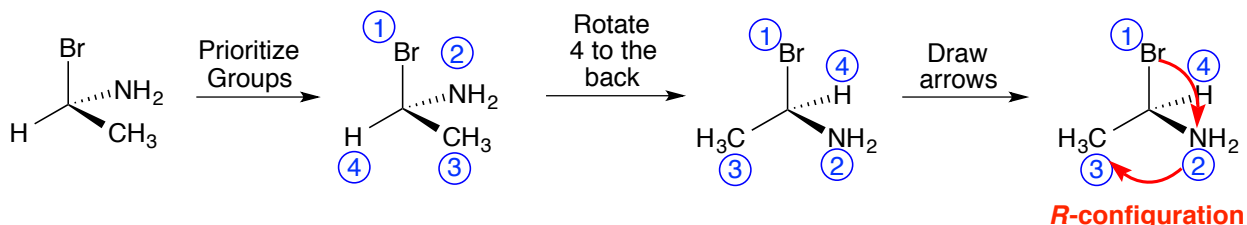
- When two carbons have substituents of the same priority, but one has more of the priority substituents, this carbon is given priority.



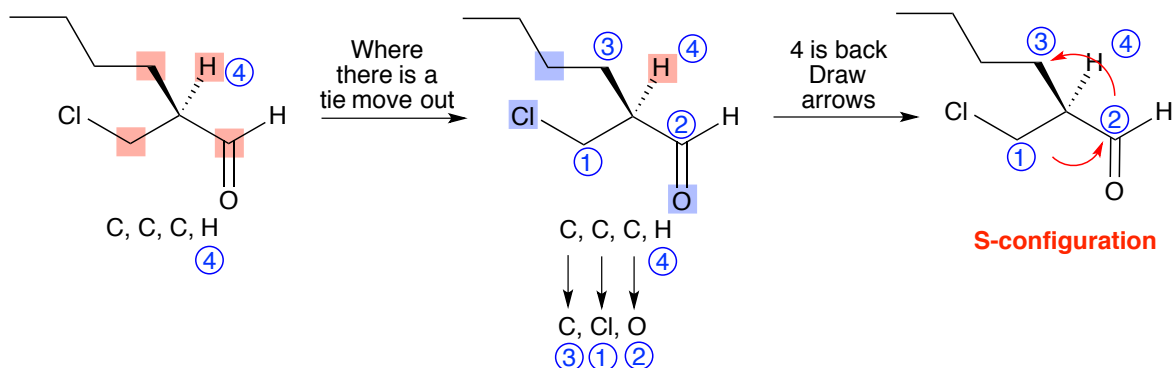
3. Orient molecule so that the lowest priority group (group 4) is pointing to the back.
4. Draw a curved arrow from group 1 → 2 and from 2 → 3.
5. Determine configuration based on the direction of the curved arrows.



Example 1:

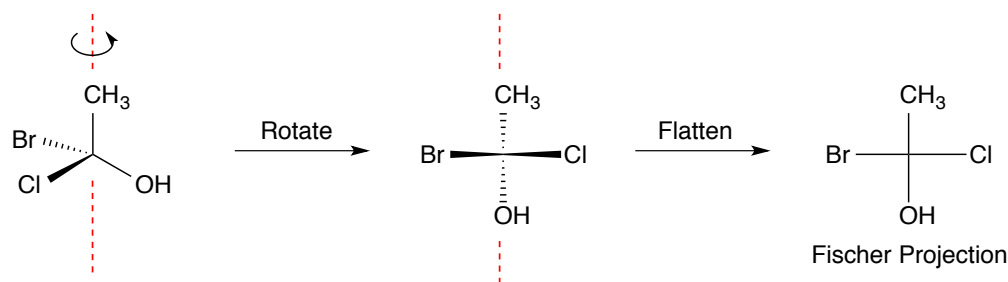


Example 2:

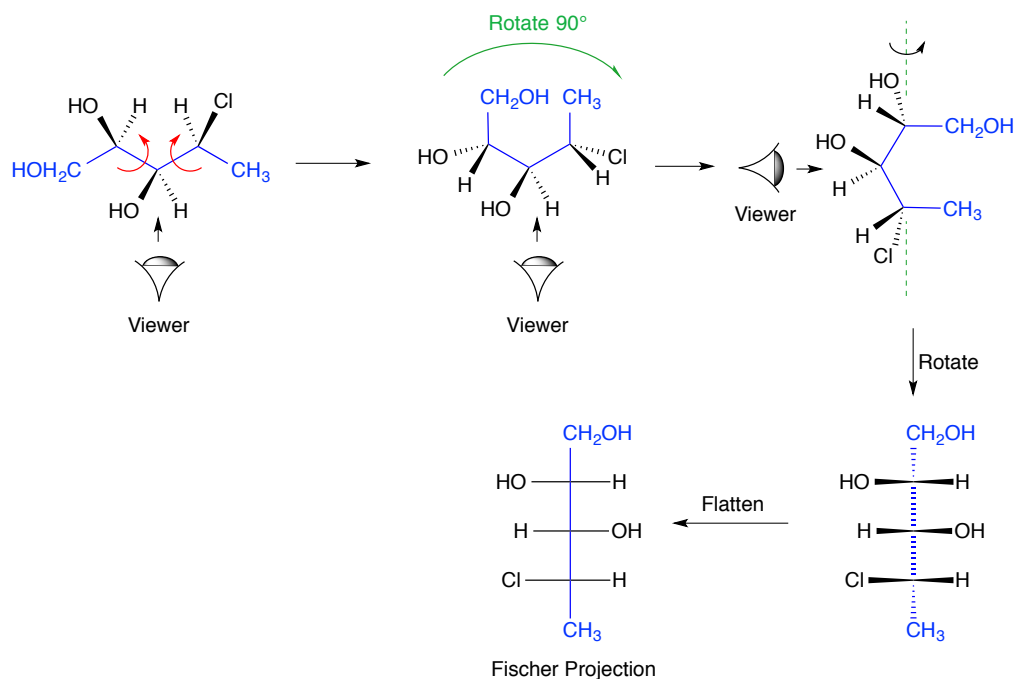


H. Fischer Projections

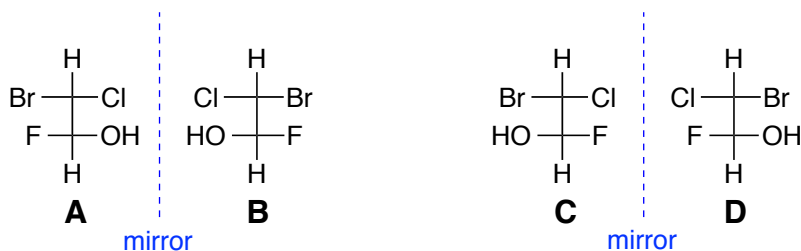
Fischer projections are another drawing style that is used to represent the three-dimensional structure of acyclic molecules. Each cross in a Fischer projection typically represents a chiral center. By definition, in a Fischer projection, the horizontal bonds are considered to be coming out of the page while the vertical bonds are considered to be going back into the page.



To convert a molecule with more than one chiral center into a Fischer projection, you must first identify the main backbone that will be the vertical axis in the Fischer projection (highlighted in blue in the example below). Next you must rotate the bonds so that the vertical axis is pointing away from the viewer. Basically, the main carbon backbone is positioned such that it curves away from the viewer. Next, to get the main chain in a vertical orientation, the entire molecule is then rotated 90° to the right. This representation can then be rotated around an axis to put the vertical groups back and the horizontal group out. Finally, flattening the molecule gives the Fischer projection.



Stereoisomers can be represented easily using Fischer projections. In the example below, **A** and **B** represent a pair of enantiomers as does **C** and **D**. **A** and **C**, **A** and **D**, **B** and **C**, and **B** and **D**, all represent pairs of diastereomers because they are non-superimposable and are not mirror images.



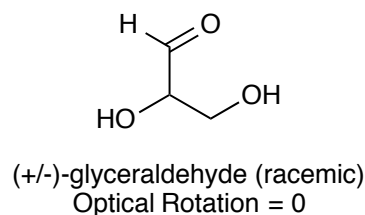
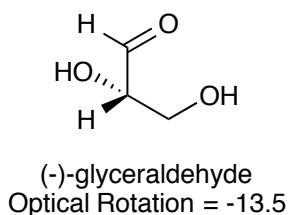
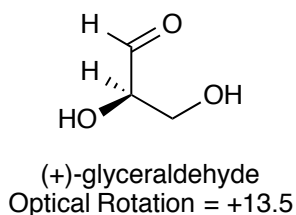
A few rules regarding Fischer projection that will be explored further in the exercises are as follows:

1. Fischer projections may be turned 180°.
2. Fischer projections may not be turned 90°.
3. Fischer projections may not be lifted from the page and flipped over.
4. The three groups at the top or bottom of a Fischer projection may be simultaneously rotated either clockwise or counterclockwise without changing the stereochemistry of the molecule.

I. Physical Properties of Stereoisomers

Enantiomers. Most physical properties of pair of enantiomers are identical. Enantiomers have identical melting points, boiling points, densities, and IR spectra. One physical property, however, is different. Enantiomers rotate plane-polarized light equally, but in opposite directions. For example, one enantiomer of glyceraldehyde rotates plane-polarized light 13.5 degrees in the clockwise direction (+13.5 °) while the other enantiomer rotates plane-polarized light 13.5 degrees in the counterclockwise direction (-13.5 °). This rotation of plane-polarized light brought about by interaction of the light with a chiral substance is called **optical rotation**. Individual enantiomers of a chiral substance are each said to be **optically active**. If two enantiomers of a

chiral substance are present in a 1:1 ratio, the mixture is said to be **racemic**. Because the optical rotations of the two enantiomers cancel out in a racemic mixture, its optical rotation is zero and the mixture is optically inactive. A racemic mixture is typically characterized by the (+/-) notation.



Achiral molecules do not rotate plane polarize light and are characterized as **optically inactive**.

Diastereomers. Unlike enantiomers, diastereomers are stereoisomers that are not mirror images of one another. Diastereomers have different physical and chemical properties. Diastereomers have different boiling points and can thus potentially be separated by distillation. Additionally, chromatography such as GC or TLC can be used to separate diastereomers.

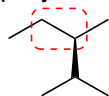
J. Lab Exercises

Conformations of Acyclic Alkanes

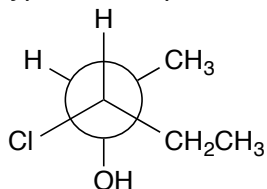
- Build a molecular model of pentane. Viewing along the C2-C3 bond, rotate your bonds in order to make the following conformations. Draw each of these conformations in your notebook.
 - Staggered, anti
 - Staggered, gauche
 - Eclipsed

Of the three conformations, which is the most stable? Least Stable?

- Build a molecular model of the compound shown below. Viewing along the indicated bond, rotate the bonds in the molecule to make the most stable conformation. Draw the Newman projection for this most stable conformation in your notebook.

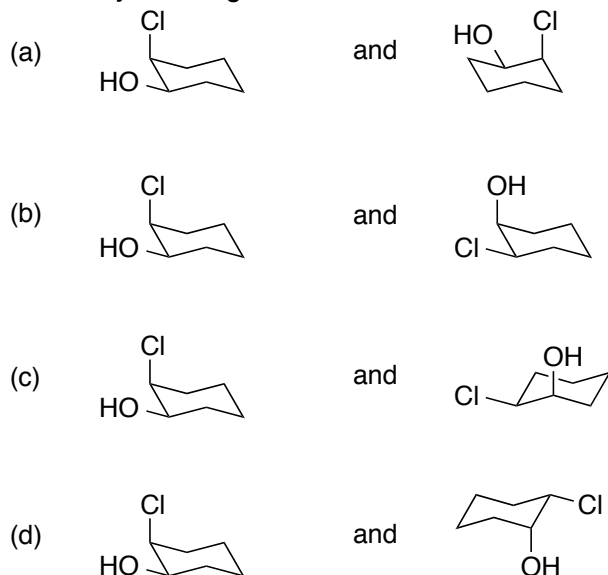


- Build a molecular model of the compound shown below. Look at the molecule from multiple directions in order to see the perspective of the Newman projection and the perspective for a typical 3D representation. Draw a bond-line structure of this molecule in your notebook.



Conformations of Cycloalkanes

- Build molecular models of cyclobutane and cyclopentane.
 - What are the approximate bond angles in each?
 - See if you can find the torsional strain that is present in cyclobutane.
 - Take your model of cyclopentane and twist the atoms so that you make an envelope shape. Can you see how this envelope shape helps relieve torsional strain?
- Build a molecular model of methylcyclohexane.
 - Look at the molecule from the side and see if you can identify the chair structure. You may need to twist the atoms and bonds a bit to get a correct chair.
 - In this structure is your methyl group axial or equatorial?
 - Move the atoms in the model to make the boat conformation. Can you see why the boat conformation is higher in energy than the chair?
 - Move the atoms again to convert the boat to the other chair conformation. Is the methyl in this conformation axial or equatorial?
 - In the conformation that has the methyl axial, see if you can identify the 1,3-diaxial interactions.
- Build models of *cis*-3-methylcyclohexanol and *trans*-3-methylcyclohexanol. Look at both chair conformation of each. Draw these chair conformations in your notebook.
 - Which conformation for each molecule is the most stable?
 - Which isomer of 3-methylcyclohexane do you think is overall more stable? Explain.
- Build models of each pair of chair cyclohexanes below. Compare the two models in each set and determine whether they are identical or stereoisomers. You are allowed to do a ring-flip to see if you can get the molecules to match.



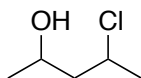
- Build models of *cis*-1,2-dichlorocyclopentane and *trans*-1,2-dichlorocyclopentane.
 - Identify the chiral centers in each.
 - Classify each molecule as chiral or achiral. If you have trouble deciding, build models of the mirror images and see if they are superimposable.

Enantiomers and Diastereomers

9. Build a model of CH_2BrCl . Next, build a model of the mirror image of your first molecule. How are these models related?

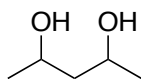
10. Build a model of CHBrClF . Next, build of model of the mirror image of your first molecule. How are these molecules related?

11. Consider the molecule shown below.



- How many stereoisomers are possible? *Recall: the maximum number of stereoisomers is equal to 2^n , where n = number of stereogenic centers.*
- Draw each of the possible stereoisomers.
- Identify pairs of enantiomers and pairs of diastereomers.
- Build a model of the stereoisomer that has both the OH group and the Cl pointing out. Also, build a model of the mirror image of this molecule.
- Do your two molecules represent enantiomers? Are they chiral?

12. Consider the molecule shown below.



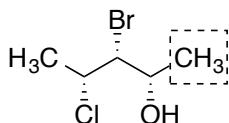
- How many stereoisomers are possible?
- Draw each of these stereoisomers.
- Identify pairs of enantiomers and pairs of diastereomers.
- Build a model of the stereoisomer that has both OH groups pointing out. Also, build a model of the mirror image of this molecule.
- Do your two molecules represent enantiomers? Are they chiral?

Fischer Projections

13. Build a model of 1-bromo-1-chloroethane.

- Draw a 3D representation of this molecule in your notebook.
- Assign an R/S configuration to your molecule.
- Draw four different, but correct Fischer projections for this molecule.
- Build a model of the other enantiomer and draw a Fischer projection of this molecule in your notebook.

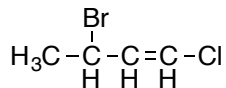
14. Build a model of the molecule shown below.



- Rotate the bonds of your molecule so that five-carbon chain of the molecule is curved away from the viewer. This will make up the vertical backbone of your Fischer projection.
- Placing the boxed CH_3 at the top, try to visualize flattening out your molecule to form a Fischer projection.
- Draw the Fischer projection in your notebook.
- Draw the enantiomer of your Fischer projection.
- Assign R/S configurations to each chiral center.

Alkenes and Stereoisomerism

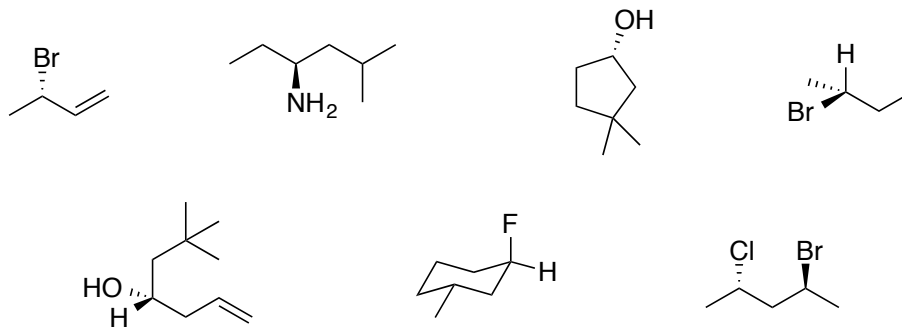
15. Build two different models of 2-butene. This is a four-carbon chain with a double bond between carbons 2 and 3.
- These two models are stereoisomers. What is their relationship? Enantiomers, diastereomers, something else?
 - Classify the two models as cis- and trans-
16. Build a model of the compound shown below.



- Draw the 3D representation that you built in your notebook.
- Draw the enantiomer of this molecule.
- Draw a diastereomers of this molecule.
- How many stereoisomers are possible for this molecule.
- How many chiral (asymmetric) centers are present?
- How many stereogenic centers are present?

Assigning R and S Configuration

17. Assign the R/S configuration to each chiral center below. If you have difficulty, try building a molecule.



Symmetry and Chirality

18. Identify all chiral centers in each molecule below. Determine whether each molecule is chiral or achiral. If the achiral molecules are meso, classify them as such.

