Molecular Models: Stereoisomers

Note:
No pre-laboratory summary is required for this experiment, but there are some topics you most probably need to review from 351 and you may want to start work on the activity. Half the questions are really review topics and the other half based on application to topics that relate directly to Chem 353. The laboratory time will be an opportunity to discuss and explore stereochemistry with your TA. If you know your “trouble spots” then the opportunity to help resolve them will be there for you to take advantage of.
Your grade for this laboratory is based on your answers to an individual quiz assigned at the end of the laboratory session. The assignment questions will be run under examination conditions.

Introduction
This activity is based on the use of molecular models to clarify important aspects related to stereoisomerism, a topic that will be fundamental to the discussion of alkene and alkyne chemistry. Molecular models are designed to reproduce molecular structures in three dimensions, allowing many subtle features concerning shapes of molecules (such as dipole moment, polarity, bond angle, symmetry, reaction stereochemistry) to become clearer. The correct use of molecular models can be a very valuable tool to an organic chemist, novice or expert.

In Chem 351 you studied conformational analysis where an important fundamental principle was that a molecule tends to position its atoms to give the arrangement with the lowest possible energy. This allows us to predict the shape of a molecule, and the subsequent physical and chemical properties to a very good approximation.

In this exercise you will learn how to use your model kit to help answer questions and investigate:

- aspects of isomerism
- conventions used in 2-D representations of 3-D molecules.
- chirality and chirality centers – R / S nomenclature
- enantiomers and diastereomers – E / Z and cis / trans designation
- plane of symmetry, superimposable mirror images, enantiomers
- meso compounds
- stereochemistry of reactions

In preparation you should review the following concepts and terms from Chem 35 and/or the etext

- alkanes, alkenes, isomerism
- E/Z, cis/trans and R/S nomenclature
- Newman projections, wedge-hash diagrams and Fischer projections
MOLECULAR MODELS

The shape of molecules results from the 3D arrangements of their constituent atoms, and as such are often difficult to visualise in terms of a two-dimensional diagram. For this reason chemists often make use of molecular structure models (either physical models or computer models). In addition to the qualitative appreciation of molecular structure, scale models can be used to make approximate quantitative measurements. For this experiment you should use your own set of models if you have them. Atoms are joined together by inserting the appropriate bond into the holes in the atoms. The single short rigid bond should be used to represent a single (σ) bond. Two curved pieces should be used to represent a double bond and three curved pieces to represent a triple bond.

There is an “online model kit” at https://chemagic.org/molecules/amini.html which might make a reasonable plan B. The easiest way to create a model in this online tool is to go to LOAD MODELS (left side, half way down) and then DRAW. This will open a familiar face, the same drawing tool we use in Moodle. Draw what you need to in the window and then “LOAD MODEL” (bottom left) which will create a 3D interactive model of the molecule you had drawn. This 3D model can then be used like a hand built model. Almost…

Sometimes more than one sensible structure may be drawn for a particular molecular formula. In this case the arrangement of atoms must be determined experimentally. The different arrangements are said to be “ISOMERS” of each other. The many different possible arrangements of the same set of atoms is the main reason for the enormous number (over a million) of known organic molecules. These different “isomeric” arrangements are possible since carbon has a singular ability to form very strong bonds with itself (as carbon chains or carbon rings), hydrogen atoms, or heteroatoms (especially with O and N). Depending on how the isomers differ, different classes of isomers are possible and importantly, this gives information about the expected relative reactivity of those types of isomers. Remember that isomerism is a pair wise relationship (i.e. it specifically describes the relationship of a pair of molecules, one molecule is an isomer of another). On the previous page is an “isomer tree” that helps highlight the different types of isomer and also how to recognise the differences, with some examples.
EXPERIMENTAL PROCEDURE

Work through the following tutorial exercises / questions using your model kit, text book etc. and record your answers, talking to your and checking with your TA as you work through them, there will (hopefully) be a Moodle self assessment version too to help you check your answers to most of the questions, but some you will need to show your drawings to your TA. At the end of the laboratory period, you will be given a hands on (i.e. use your models to help) Moodle assessment to be done individually.

1. CONFORMATIONAL ISOMERISM

Carbon of sp³ hybridisation forms four single bonds and therefore the carbon atom is situated at the centre of a tetrahedron. Construct an ethane molecule with the medium straight bonds and confirm that each of the carbon atoms are at the centre of a tetrahedron.

\[
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} - \text{C} - \text{C} - \text{H} \\
\text{H} \\
\end{array}
\]

ethane

The molecule is flexible; grasp one carbon atom and rotate around the C-C bond. View the molecule along the C-C axis and rotate the C-C bond about 360°. The relative positions of the hydrogen atoms on the different carbon atoms are constantly changing, and every different relative arrangement is called a "CONFORMATION" or they can be described as "CONFORMATIONAL ISOMERS" or "CONFORMERS". There are two extreme conformations, and these have important names.

staggered conformation
eclipsed conformation

It is often useful to inspect the conformational interactions between groups on adjacent atoms by viewing along the C-C bond.

2. REPRESENTATING THE 3-D SHAPE OF MOLECULES

There are three common representations that are used to represent the 3D shapes of molecules. These are:

(a) wedge - hash diagram
(b) Newman projection
(c) Fischer projection

The ability to interpret the diagrams and interconvert them is an important and valuable skill.

(a) the wedge-hash diagram is probably the most widely used diagrammatic representation of three-dimensional molecules. It is based using the ideas of perspective.
As an example, the staggered conformation of ethane would be represented as:

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

Remember that at room temperature the rotation about the C-C bond takes place many thousands of times per second, however the different conformations do not have identical energies. When drawing wedge hash diagrams, it is important to make sure that the atoms look like they have the appropriate hybridisation geometry, i.e. in the diagram above, the C atoms look tetrahedral. For sp\(^3\) systems, one way to do this is to draw the diagram such that the wedge and the hash are adjacent to each other and the two bonds in the plane are also adjacent to each other (as shown by the arrows in the diagram below).

(b) A "Newman Projection" is drawn by looking directly along a particular bond in the system and arranging the substituents symmetrically around the atoms at each end of that bond. The protocol requires that groups attached to the front carbon intersect at the centre of the circle; those attached to the rear carbon project only as far as the edge of the circle.

(c) the Fischer projection is commonly used to represent sugars as they provide a quick way of representing multiple stereocenters. Fischer projections are typically drawn with the longest chain oriented vertically and with the more highly oxidised C at the top. These representations are typically used for molecules that contain chirality centers, which are then represented as simple crosses.
They can be derived by considering the more accurate 3D representation using wedges and assuming
the convention that all the horizontal lines represent bonds coming out of the plane of the paper and
vertical lines represent bonds going behind the plane of the paper. Here we see the Fischer projection
(left) and corresponding wedge-hash diagram of the simplest carbohydrate, glyceraldehyde. An example
with multiple stereocenters is shown below.

4. STEREOCHEMISTRY / NOMENCLATURE OF ALKENES
Alkenes contain sp² carbon atoms joined in a double bond. Construct an ethene molecule using the long
flexible bonds and satisfy yourself it is planar. Try to rotate the molecule about the C=C bond; this is only
possible if you break the π-bond. This restricted rotation means that longer chain or substituted alkenes
can exist as two isomers, e.g. 2-butene:

For example, due to the lack of rotation about the C=C bond it is possible to construct THREE
DIFFERENT dichloroethenes.

The “Z” prefix indicates that the two groups of higher priority according to the Cahn-Ingold-Prelog
Rules** (see notes at the end) are situated on the same side (Ger. Zusammen = together) of the double
bond. Conversely, “E” (Ger. Entgegen = opposite) indicates these groups are across from each other.
Only in the very simplest cases does Z correspond to cis and E to trans. Make a model of the Z isomer
and then convert this to the E isomer. Note that in order to do this, a chemical bond must be broken, so
they are not conformation isomers.
The two isomers have the same atoms bonded to each other, but in a different spatial arrangement, so
they are called STEREOISOMERS. In this case, interconversion requires that bonds are broken. This
general kind of isomerism is called CONFIGURATIONAL ISOMERISM and this type specifically is E/Z, or
GEOMETRIC ISOMERISM. These molecules are quite different and have different physical and
chemical properties. This is in complete contrast to CONFORMATIONAL ISOMERS which are different
stereoisomers of the SAME molecule, achieved by rotation about C-C single bonds.
Construct models of the two stereoisomers of each of 2-butene and 2-bromo-2-butene.

1) On a diagram, show each structure and assign the stereochemistry as (i) cis or trans, and (ii) E or Z.

5. OPTICAL ISOMERS: ENANTIOMERS and DIASTEREOMERS

There is a further spatial relationship between atoms in molecules that we must consider, and it is a very subtle one. OPTICAL ISOMERISM arises as a result of the arrangement of substituents in space most commonly at a tetrahedral center.

Build two models of CH₂ClBr. Position the two molecules of CH₂ClBr such that they are 'reflected' through an imaginary mirror that runs between them. Try putting one molecule 'on top' of the other such that all the atoms line up.

2) Is CH₂ClBr superimposable on its mirror image?

3) Therefore, is CH₂ClBr chiral or achiral?

4) Does interchanging any two atoms (Cl, Br, or H’s) create a new molecule?

Looking at only one of the models for now, note the plane of symmetry that bisects the C, Cl and Br atoms. This molecule has an internal plane of symmetry and because of this, it is superimposable on its mirror image.

Now take a black, tetrahedral C atom and add a white, an orange, a purple and a green piece to the C to make a simple tetrahedral molecule, CHClBrF. Now ignore this first model and make as many other models as you can from your model kit (4 or 5 minimum: cooperate with another group if you need to). Now compare them all. Separate them into distinguishable types. You should have only two groups, all those within a group are superimposable on each other and they are all mirror images of all those in the other group.

Superimposable means that two models can be placed side by side in such a way that they look identical (i.e. they can be superimposed in each other).

Non-superimposable means that when two models are placed side by side, they can always be distinguished.

Enantiomers are non-superimposable mirror images.

Compare the structures you built and make sure you understand the principle of superimposability. CHClBrF is chiral, has no internal plane of symmetry, and forms a pair of enantiomers.

5) What happens when any pair of substituents within these structures are interchanged? (i.e. remove one substituent and switch it with another then see if it belongs to the original group or the other group)
Build each of the following structures and its mirror image, then check for superimposability: bromochloromethane, 2-chloropropane, 2-chlorobutane, and 2,3-pentadiene.

6) Which of the structures listed above have non-superimposable mirror images?

The most common scenario that leads to this type of isomerism arises if four different groups are attached to a central atom, then two different molecules can exist depending on the 3D-sequence in which the four groups are attached. The center with the four groups different groups attached is the CHIRALITY CENTER. The relationship between these two different molecules is they are non-superimposable and mirror images of each other and they are given the name OPTICAL ISOMERS or ENANTIOMERS*. If the four groups are different there is no element of symmetry (mirror plane, rotation axis, inversion center) in the molecule and the central atom is termed an asymmetric atom. The reason for the term OPTICAL ISOMERS is that most physical and chemical properties of these isomers are identical. However, they have a different effect on a beam of plane polarised light, hence their name. Molecules with no asymmetric atom have no effect - they are optically inactive. One other difference has considerable biochemical significance - optical isomers typically react at different rates with another optically active compound (such as an enzyme).

The absolute configuration of chirality centers are assigned as R or S according to the Cahn-Ingold-Prelog Rules** (see notes at the end). It is also possible the test the relationship of optical isomers by checking the absolute configurations (i.e. R- and S- designations). A pair of enantiomers have the opposite configurations are all the chirality centers.

7) Assign the absolute configuration to each of the chirality centers in each of the following structures:

* The term enantiomer comes from the Greek enantios - opposite.
8) For the following structures, identify a pair of conformational isomers, a pair of enantiomers, a pair of diastereomers and any meso compounds.

Build a model of the isomer of the 1,2-dibromo-1,2-dichloroethane system shown below and its mirror image.

9) Are these structures superimposable on each other?

10) Are there any chirality centers? If so assign the configurations.

11) Do they have any symmetry elements (mirror planes, rotation axes, inversion center)?

This type of compound is a special type of stereoisomer, known as a MESO compound. Note the special relationship of the asymmetric centers. To be considered to be a MESO compound a molecule MUST have two (or more) chiral centers and is superimposable on its mirror image – if there are NO chirality centers (e.g. CH₂BrCl) the molecule is NOT considered to be MESO.

Keep the last two models and now build the isomer shown below, and its mirror image.

12) Are these two new models superimposable on each other or either of the other isomers of 1,2-dibromo-1,2-dichloroethane you have built?

13) Are there any chirality centers? If so assign the configurations.

14) Do they have any symmetry elements (mirror planes, rotation axes, inversion center)?

What you have just worked through covers a slightly different type of stereoisomers. Stereoisomers that are non-superimposable mirror images are ENANTIOMERS (opposite configurations are all chirality centers). Stereoisomers that are not enantiomers are DIASTEREOMERS (have different configurations at some, but not all, chirality centers).

Unlike enantiomers, DIASTEREOMERS typically have different chemical and physical properties, a factor that often makes them much easier to separate and purify.
15) What is the relationship of last two structures you built to the previous two?
(Note: to convert one enantiomer to the other or to a diasteromer requires bond breaking and hence these types of molecules are configurational isomers).

APPLICATION TO REACTIONS

You don’t need to know anything about the reactions ahead of time to answer these questions. The examples are self-contained and your focus should be on the stereochemistry and working with the structures so that you are able to address stereochemistry in reactions.

First, here are a couple of examples of the types of questions you will need to be able to answer (they are from past examinations). We don’t expect that you can answer them yet:

EXAMPLE 1

Cis-2-butene reacts with Br₂ to give the products according to the scheme shown below. Note that the two Br atoms are added to opposite faces of the alkene (for reasons that will be discussed in lectures). You might want to build models of X, Y and Z.
16) What is the relationship between the two products X and Y?

17) Draw a Newman projection of the conformation shown of product X.

18) Draw a wedge-hash diagram of the conformation of product X where the Br atoms syn to each other.

19) Draw a Fischer projection of product X.

20) Do X and Y have any chirality centers? If so, assign them as R/S.

21) Is product Z (below) the same as either X or Y? If not, then can Z be formed from cis-2-butene based on the scheme shown above? If not which alkene is required in order that Z is formed?

22) Build a mirror image of Z and check to see if it is superimposable on the original model of Z. What do you find? What type of structure is Z?

23) Does Z have any chirality centers? If so, assign them as R/S.

24) Does Z have any symmetry elements (mirror planes, rotation axes, inversion center)?

25) Predict which stereoisomer of 2-butene is the starting material of the reaction shown above that generates product V.

**Key issue**

When deducing the stereochemistry of starting materials for reactions it is important to draw the product in the conformation in which it is formed and then work backwards.

26) Draw a wedge-hash diagram of the product V in the conformation in which it is formed where the two Br atoms are anti to each other. Now think about removing the two Br atoms and reforming the
While paying attention to the stereochemistry of the two methyl groups. Does this change your prediction of the stereochemistry of the 2-butene (starting material)?

**EXAMPLE 2**

\[
\text{Br} \quad \text{C} \quad \text{C} \quad \text{OH} \quad \text{base} \quad \text{H}_3\text{C} \quad \text{C} \quad \text{C} \quad \text{CH}_3
\]

The starting material here is a halohydrin. When treated with a suitable base, it can undergo an intramolecular Williamson ether synthesis to give a cyclic ether (this 3 membered ring is also known as an epoxide). These types of reactions are usually SN2.

27) What type of stereochemical issues are associated with an SN2 process?

28) Build models of the product epoxide. How many stereoisomers are there?

29) Predict which stereoisomer is the product of the reaction shown above.

**Key Issue....**

When predicting the stereochemistry of products of reactions it is important to draw the starting material in the conformation in which it reacts and pay attention to the stereochemistry of the reaction.

30) Draw a wedge-hash diagram of the starting material halohydrin in the reactive conformation. Now think about how the reaction would occur paying attention to the stereochemistry of the two methyl groups. Does this change your prediction of the stereochemistry of the product?

**Useful References**

1. Organic Chemistry etext ch 7

**Cahn-Ingold-Prelog Rules**

See also [http://www.chem.ucalgary.ca/courses/351/ornom/stereo/stereo-01.html](http://www.chem.ucalgary.ca/courses/351/ornom/stereo/stereo-01.html)

For the purposes of assigning priorities to groups in order to differentiate geometric isomers at double bonds, and the absolute configuration at a chirality centre, there exist a set of arbitrary criteria. Priority is based on:

1. atomic number of atom attached (for isotopes, use higher atomic weight);
(2) If 2 or more identical atoms are attached to the chirality centre consider the three atoms attached, in turn and in decreasing atomic number (remember to open up and ‘ghost’ atoms for multiple bonds). Then,

(a) For **chirality centres** - view the centre with lowest group directly away from you (hold that group in a clenched fist), are the remaining 3 groups in descending order of priority in a clockwise (R) or counterclockwise (S) configuration?

(b) For **double bonds** - are the higher priority groups on same side (Z) of double bond, or on opposite (E) sides?