MOLECULAR MODELS : STEREOISOMERS AND OPTICAL ACTIVITY

NOTE: Bring your model kit and a calculator to your scheduled laboratory session.

There is no pre-laboratory quiz or summary required for this experiment. However, before your scheduled laboratory session, you should review 351 and 353 stereochemistry lectures and start working through the content. The laboratory period will run more like a tutorial, it's "open book", you can work in groups and ask your TA about any of the concepts you don't understand or that you need further clarity on.

BRING YOUR MODEL KIT and a PRINTED COPY OF THIS DOCUMENT. Remember that model kits are allowed tools during CAL activities, assignments and examinations.

This laboratory activity is assessed based on an online Moodle "molecular models" graded activity (45 min. time limit) that is to be completed before your next in-person laboratory session.

INTRODUCTION

This activity is based on the of molecular models to clarify important aspects related to stereoisomerism and optical activity etc. Stereochemistry is 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 (*i.e*. the most stable). This allows us to predict the shape of a molecule, and the subsequent physical and chemical properties to a very good approximation.

This exercise is an opportunity to ensure that you know 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
- optical activity and optical purity
- stereochemistry of reactions

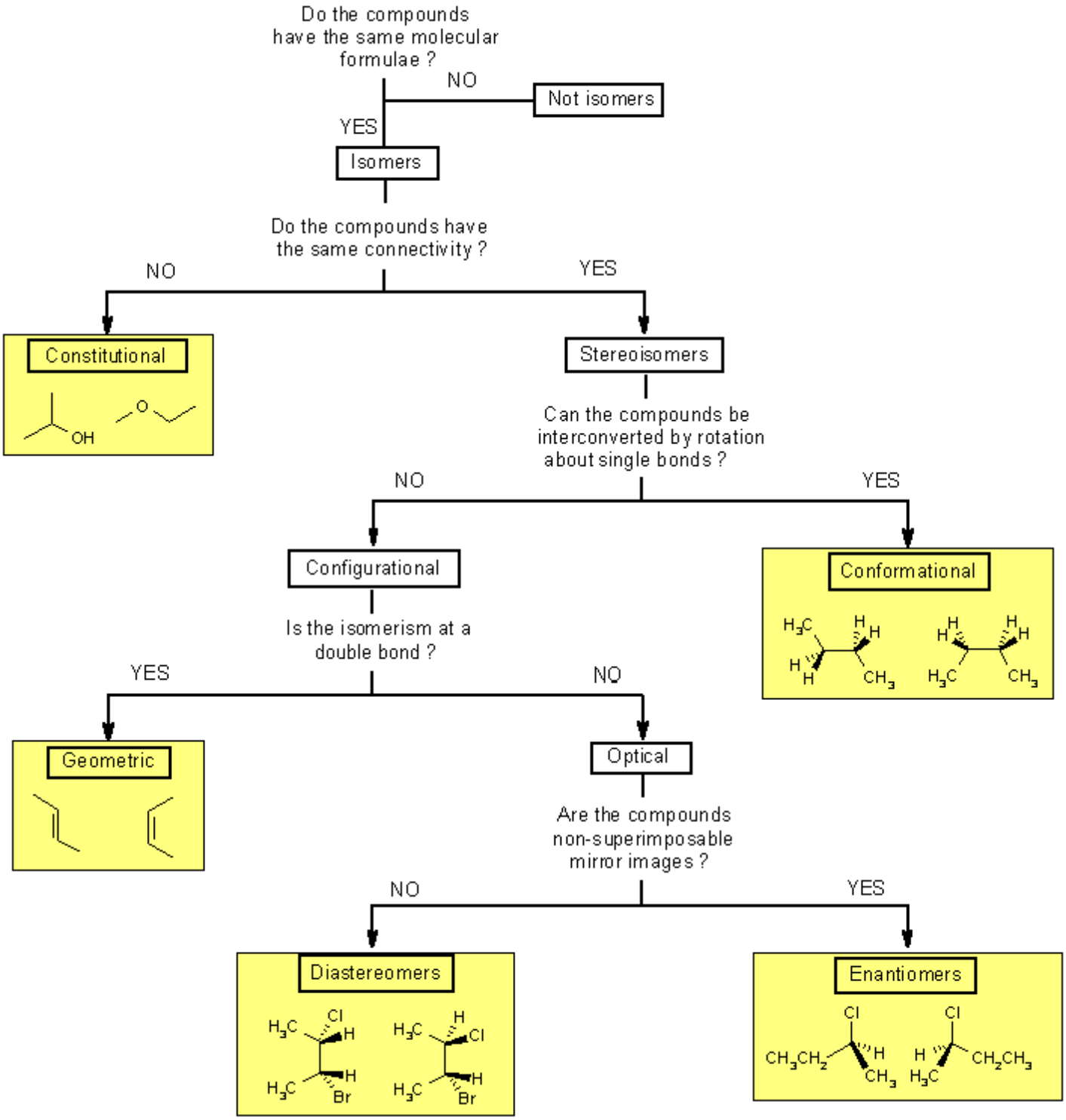
In preparation you should review the following concepts and terms from Chem 351 and/or the etext

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

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 a page or screen. 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 model kit if you have one. 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.

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 (about 9 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 next page is an “isomer tree” that helps highlight the different types of isomer and can be used to define the type if isomeric relationship of a pair of molecules.

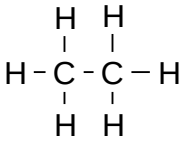

Do the compounds have the same molecular formulae ?
NO
Not isomers
YES
Isomers
Do the compounds have the same connectivity ?
NO
YES
Constitutional
OH
O
Stereoisomers
Can the compounds be interconverted by rotation about single bonds ?
NO
YES
Configurational
Conformational
Is the isomerism at a double bond ?
YES
NO
Geometric
Optical
Are the compounds non-superimposable mirror images ?
NO
YES
Diastereomers
Enantiomers
Cl
Br
CH3CH2
CH2CH3

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. Your grade for this laboratory activity is based an online Moodle assignment to be completed in the two days after the end of the laboratory session.

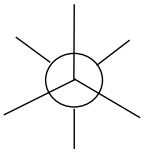
1. CONFORMATIONAL ISOMERISM

Carbon of sp^3 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.

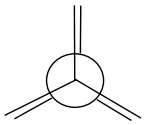


ethane

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 in 2D. These are:

(a) wedge - hash diagram

(b) Newman projection

(c) Fischer projection

Each is based on certain “rules” and the ability to interpret the diagrams and interconvert them is an important and valuable skill.

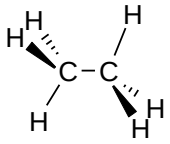
(a) the **wedge-hash diagram** is probably the most widely used diagrammatic representation of three-dimensional molecules. It is based using the ideas of perspective.

bond in the plane of the paper

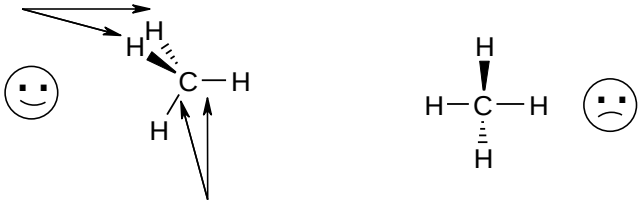
bond projecting behind the plane of the paper

bond projecting in front of the plane of the paper

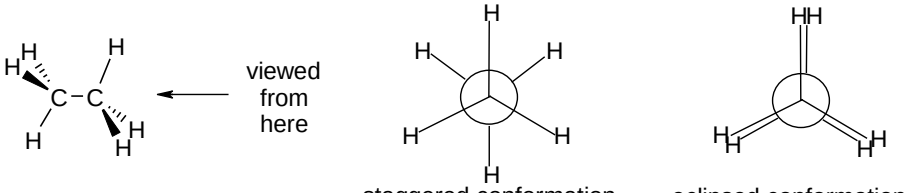
As an example, the staggered conformation of ethane would be represented as:



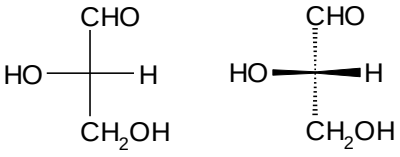
Remember that at room temperature the rotation about the C-C bond takes place many thousands of times per second, however the different conformations do not have identical energies (351). When drawing wedge hash diagrams, it is important to make sure that the atoms look like they have the appropriate hybridisation geometry, *i.e*. in the diagram above, the C atoms look tetrahedral. Moral "draw it like it is". 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).



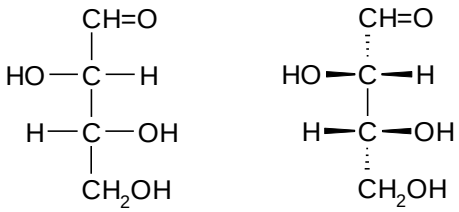
(b) A "**Newman Projection**" is drawn by looking directly along a particular bond in the system and arranging the substituents symmetrically around the atoms at each end of that bond. The protocol requires that groups attached to the front carbon intersect at the centre of the circle; those attached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



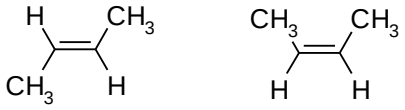
They can be derived by considering the more accurate 3D representation using wedges and assuming the



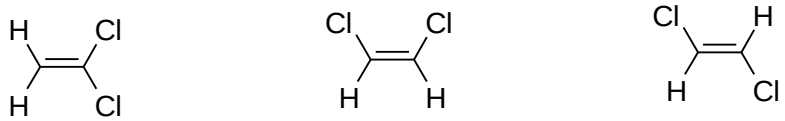
convention that all the horizontal lines represent bonds coming out of the plane of the paper and vertical lines represent bonds going behind the plane of the paper. Here we see the Fischer projection (left) and corresponding wedge-hash diagram of the simplest carbohydrate, glyceraldehyde. An example with multiple stereocenters is shown below.

4. STEREOCHEMISTRY / NOMENCLATURE OF ALKENES

Alkenes contain sp^2 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.



1,1-dichloroethene (Z)-1,2-dichloroethene (E)-1,2-dichloroethene

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 CH_2ClBr. Position the two molecules of CH_2ClBr 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 CH_2ClBr **superimposable** on its mirror image?*

3) *Therefore, is CH_2ClBr 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 (this means that the molecules are the same and can't be distinguished).

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 (the same) and each of those are 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, they are the same (*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 exists as 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)*

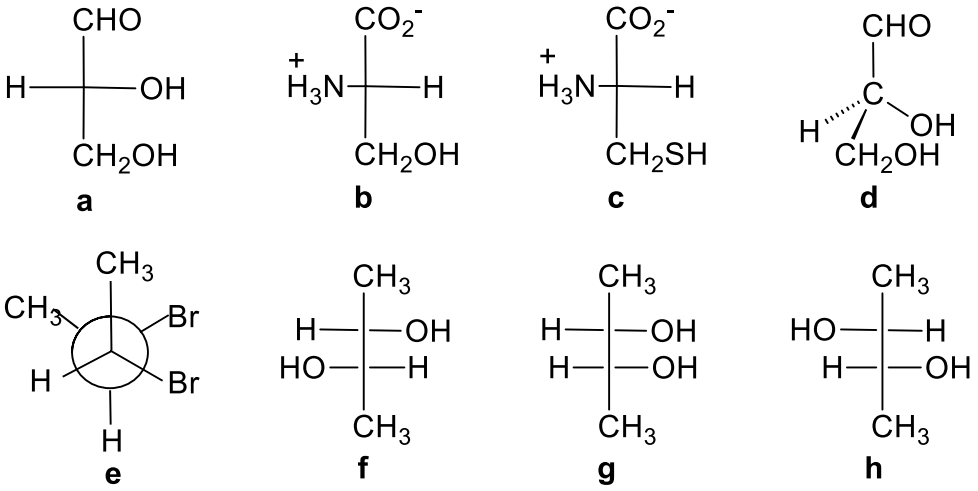
Build each of the following structures and its mirror image, then check for superimposability: bromochloromethane, 2-chloropropane, 2-chlorobutane, and 2,3-pentadiene.

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

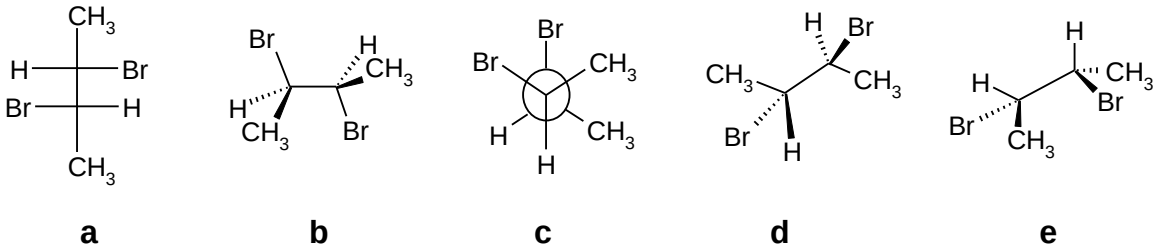
The most common scenario that leads to this type of isomerism arises if four different groups are attached to a central tetrahedral atom, then two different molecules can exist depending on the 3D-sequence in which the four groups are attached. The center with the four groups different groups attached 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 chirality center 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 either R or S according to the Cahn-Ingold-Prelog Rules** (351 nomenclature, 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:*

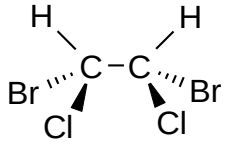


8) *For the following structures, identify a **pair** of conformational isomers, a **pair** of enantiomers, a **pair** of diastereomers and any meso compounds.*



[*] The term enantiomer comes from the Greek enantios - opposite.

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



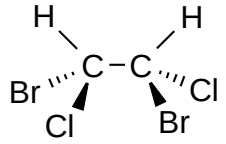
9) *Are these structures superimposable on each other?*

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*. CH_2BrCl) 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 (because they are different molecules), a factor that often makes them much easier to separate and purify.

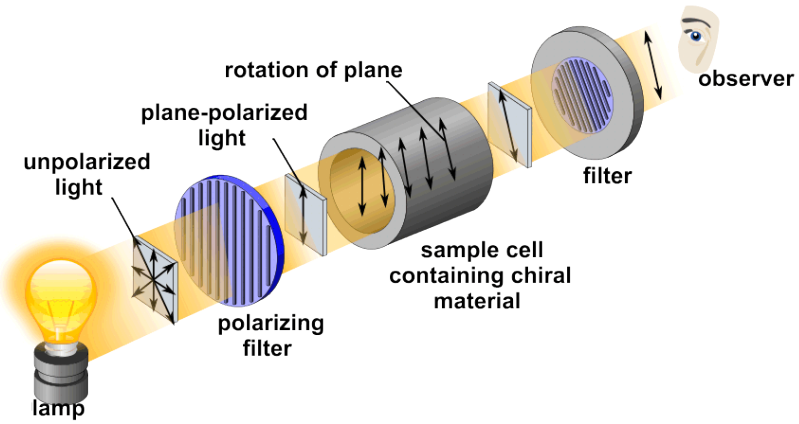
15) *What is the relationship of last two structures you built to the previous two?*

(Note: to convert one enantiomer to the other or to a diasteromer requires bond breaking and hence these types of molecules are configurational isomers).

MM.10

OPTICAL ACTIVITY and OPTICAL PURITY

"Optical isomers" are the subtype of stereoisomers that interact with plane polarized light because the molecules contain chirality centers (handedness). Optical isomers can be further subdivided into "enantiomers" and "diastereomers" depending on the stereochemical relationship between the structures. Chiral molecules interact with plane polarized light and cause the rotation of that polarization plane with enantiomers rotating the plane to the same extent but in opposite directions. This rotation can be measured using a polarimeter (see lecture content) to measure the observed rotation, α.



$$[\alpha]^{T}_{\lambda} = \frac{\alpha}{L\ c}$$

$[\alpha]$ = specific rotation
T = temperature of measurement
λ = wavelength used
α = observed rotation
L = path length in dm
c = sample concentration in g / mL

The observed rotation, α, depends of the structure, the concentration of the sample and the optical path length and therefore, the observed rotation is "corrected" to allow for those effects to give the specific rotation, $[\alpha]_D$ which is reported and can be checked in the literature. This is like correcting boiling point to sea-level.

Observed rotation depends on the concentration of an individual enantiomer present in the solution:
Single (pure) enantiomer = maximum magnitude rotation = optically pure = 100% optical purity
Racemic mixture = 50:50 mixture of enantiomers = zero optical rotation (because they cancel out, optically inactive) = 0% optical purity

Optical purity of a mixture (%) = 100 x , $[\alpha]_D$ (sample) / , $[\alpha]_D$ (pure enantiomer)

In simple cases (a mixture of enantiomers), optical purity equates to the enantiomeric excess (e.e.) which is how much more of one enantiomer there is than the other:

ee% = 100 ([major enantiomer] - [minor enantiomer]) / ([major enantiomer] + [minor enantiomer])

Optical purity = % enantiomeric excess = % (major enantiomer) - % (minor enantiomer)

Therefore, in principle, measuring the optical activity of a mixture of enantiomers allows one to measure the optical purity of a sample.

Collect together 10 black atoms and 5 red atoms. Think of the red atoms as being the +ve enantiomer and the black atoms as being the -ve enantiomer. In terms of optical rotation, the rotation to a +ve red will cancel out the rotation of a -ve black, and we can think of each piece as having a "unit of rotation".

Questions :

Take 5 red and 5 black atoms to make a "mixture". Remove pairs made of +ve red and -ve black (i.e. pairs that cancel each other out).

16) *What are you left with ? How much net rotation is there ? What optical purity does this correspond to ? (how many pieces are you left with compared to the 10 that you started with?)*

Now repeat the process using 6 black and 4 red.

17) *What are you left with ? How much net rotation is there ? What optical purity does this correspond to ?*

Now repeat the process using 8 black and 2 red.

18) *What are you left with ? How much net rotation is there ? What optical purity does this correspond to ?*

19) *If a sample of 1g of (S)-2-butanol in 10 mL of solvent, in a 10 cm polarimeter cell has an observed rotation of +1.35°, then what is the $[\alpha]_D$ of (R)-2-butanol ?*

20) *If a sample of a mixture of (R)-(-)- and (S)-(+)-2-butanol has a specific rotation of – 6.75°.*

a. What is the % optical purity ?

b. What is the % enantiomeric excess ?

c. What % of the (R) enantiomer is present ?

21) *If a sample of a mixture of (R)-(-)- and (S)-(+)-2-butanol has a specific rotation of – 8.1°.*

a. What is the % optical purity ?

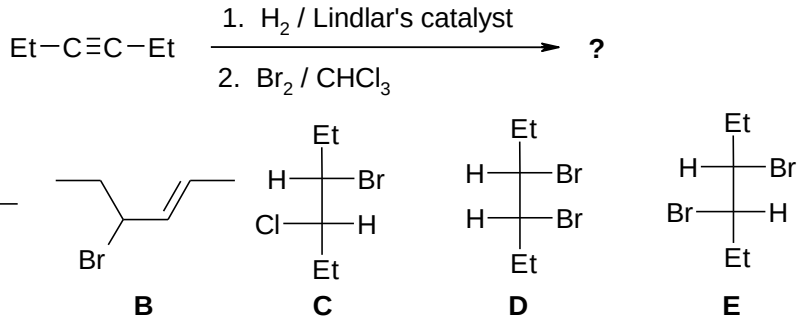
b. What is the % enantiomeric excess ?

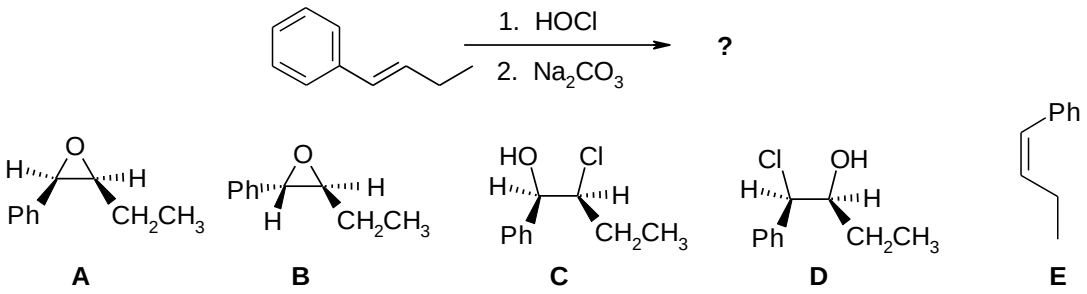
c. What % of the (R) enantiomer is present ?

APPLICATION OF STEREOCHEMISTRY TO REACTIONS

You don't need to know anything about the reactions ahead of time to answer these questions. The examples are all 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**.**

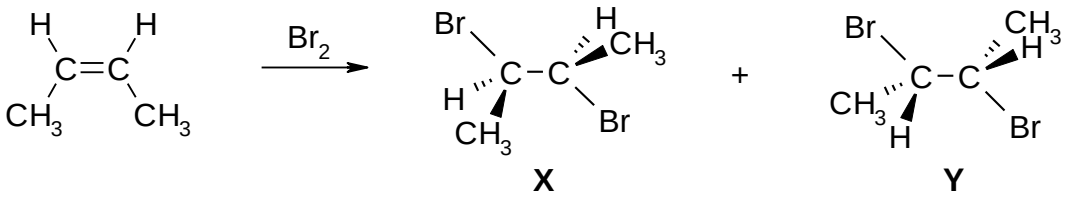
First, here are a couple of examples of the types of questions you will need to be able to answer (they are from past Chem 353 examinations). We don't expect that you can answer them at this time, but you will need to be able to do so in the near future:





EXAMPLE 1

Cis-2-butene reacts with Br_2 to give the products according to the scheme shown below. Note that the two Br atoms are added to opposite faces of the alkene. Since the two Br atoms are introduced at 180 degrees with respect to each other, this is referred to as an ANTI addition. The reasons why this is an anti addition will be discussed in lectures. If they were added on the same face of the alkene at 0 degrees with respect to each other it would be a SYN addition. You might want to build models of **X**, **Y** and **Z**.



X **Y**

22) *What is the relationship between the two products **X** and **Y** ?*

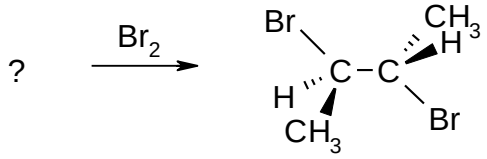
23) *Draw a Newman projection of the conformation shown of product **X**.*

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

25) *Draw a Fischer projection of product **X**.*

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

27) *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 ?*

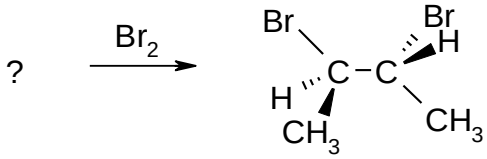


Z

28) *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** ?*

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

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



V

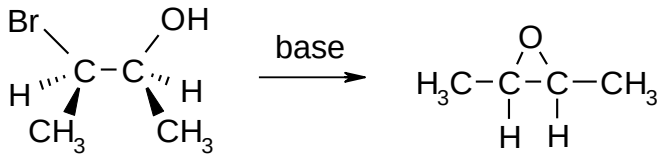
31 *Predict which stereoisomer of 2-butene is the starting material of the reaction shown above that generates product **V**.*

Key issue

When deducing the stereochemistry required of a starting materials for a reaction it is important to draw the product in the **conformation in which it is formed** and then work backwards from there to deduce the required stereochemistry of those starting materials.

32) *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 C=C 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



an epoxide

The starting material here is an example of what can be referred to as a 1,2-halohydrin. When treated with a suitable base (commonly Na_2CO_3 or NaOH) it can undergo a process that is very similar to what would be an intramolecular Williamson ether synthesis (Chem 351) to give a cyclic ether (this 3 membered ring is also known as an epoxide). These types of reactions are usually SN2 in character.

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

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

35) *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.

36) *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
2. E.L. Eliel, and S.H. Wilen, in "Stereochemistry of Organic Compounds", Wiley, New York, 1994, or E.L. Eliel, "The Stereochemistry of Organic Compounds", McGraw-Hill, New York, 1962.
3. R.S. Cahn, C.K. Ingold and V. Prelog, Experientia, 12, 81 (1956).

** **Cahn-Ingold-Prelog Rules**

See also https://www.chem.ucalgary.ca/courses/351/orgnom/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 ?