

Nuggets of Knowledge for Chapter 6 – Stereochemistry
Chem 2310

I. Introduction to Stereochemistry

- Definitions:
 - Isomer – compounds with the same molecular formula.
 - Constitutional isomer – compounds with the same molecular formula but with a different bonding sequence.
 - Stereoisomer – compounds with the same molecular formula and the same bonding sequence, but with a different shape that cannot be changed by rotating around single bonds.
 - Stereocenter – an atom which, if two of the substituents are switched, results in a different compound.
 - Conformation – one possible arrangement of a molecule, which can be changed by rotating it around a single bond.
- Stereoisomers are only possible in certain situations. One of these is in compounds containing a C=C. This occurs because the pi bond prevents the molecule from rotating around that bond, creating the possibility of two different shapes, but the same bonding sequence.
 - A compound containing a C=C only has the possibility of having two different stereoisomers, not more than two.
 - Not all compounds with a C=C have two stereoisomers. Only those that have two different substituents on both sides of the double bond will have two different shapes.
 - All compounds containing a C=C which have two stereoisomers will also have two stereocenters.
- Since stereoisomers are different compounds, they must be labeled so that you can tell which is which.
 - When there is only one substituent on each carbon of a C=C, the labels cis and trans can be used to show which is which. This is an older system, but is still in common use for simple compounds.
 - If the two substituents are on opposite sides of the C=C, the compound is trans; if they are on the same side, the compound is cis.
 - If there is more than one substituent on either side of a C=C, then they must be prioritized.

- If the two highest priority substituents are on opposite sides of the C=C, then the compound is labeled E; if they are on the same side of the C=C, then the compound is labeled Z.
- When prioritizing substituents, use the following rules:
 - First, look at the atomic mass of the atom attached to the C=C. Give higher priority to the atom of highest atomic mass.
 - If the atoms have the same atomic mass, look at all atoms attached to them. Order them from largest to smallest atomic mass, and consider them one by one. Give higher priority to the one that has the higher mass first.
 - If all three atoms attached to the first atom are the same, continue to the next atom.

II. Introduction to Chirality

- Definitions:
 - Chiral – a compound which has a mirror image that is different from the original (has an enantiomer). This is a property of a molecule (or any other physical object, for that matter).
 - Achiral – a compound whose mirror image is identical to the original (doesn't have an enantiomer).
 - Enantiomer – compounds which are non-superimposable mirror images of each other. This is a relationship between two molecules.
 - Plane of symmetry – an imaginary plane dividing a molecule in half such that both halves are the same.
 - Asymmetric carbon – a carbon with four different groups attached to it.
- There are three ways to determine if a molecule is chiral.
 - 1 – Superimposable mirror image: If the mirror image is not superimposable, the molecule is chiral. If the mirror image is superimposable, the molecule is achiral. This is the only completely reliable test.
 - 2 – Plane of symmetry: If there is a plane of symmetry in the molecule, it is achiral. If there is not a plane of symmetry, the molecule is probably chiral (but there are other more rare kinds of symmetry that might render it achiral).

- 3 – Asymmetric carbons: If there are no asymmetric carbons in the molecule, it is probably not chiral (but might be under unusual circumstances). If there is only one asymmetric carbon in the molecule, it is chiral. If there are two or more asymmetric carbons in the molecule, it is chiral unless there is a plane of symmetry.
- Since enantiomers are different compounds, they must also be labeled so that we can tell them apart.
 - First, prioritize all four groups on the asymmetric carbon, using the same rules as applied to compounds containing C=C.
 - Second, rotate the molecule so that the last group is pointing away from you.
 - Third, determine the direction going from highest to lowest priority of the first three groups.
 - If the direction is clockwise, the molecule is labeled R.
 - If the direction is counterclockwise, the molecule is labeled S.
- When naming compounds, use (R)- or (S)- at the beginning if there is only one stereocenter.
 - If there are two or more, include the number of the carbon: (2R,4S).
 - Cis and trans on rings may only be used for compounds which are not chiral.
 - Please note: chiral compounds are not always written with their stereochemistry showing. If the direction of the bonds is not specified, it could represent either enantiomer, and the R or S of that carbon cannot be determined.

III. Compounds with two or more stereocenters

- When a compound has more than one stereocenter, it can have up to 2^n stereoisomers, where n is the number of stereocenters.
- Definitions:
 - Diastereomer – compounds which are stereoisomers, but not enantiomers; they have different shapes but are not mirror images of each other.
 - This includes two kinds of compounds: those with C=C, and compounds with two or more stereocenters in which one is the same and one is different.
 - Meso compound – a compound which contains stereocenters, but in a symmetrical arrangement so that the compound is not chiral.

- Isomer tree – all of the types of isomers can be organized into the following tree:
 - Isomers – have the same molecular formula
 - Constitutional isomers – have the same molecular formula, but different bonding sequence
 - Stereoisomers – have the same molecular formula, the same bonding sequence, but different shape (that can't be changed without breaking a bond).
 - Enantiomers – non-superimposable mirror images (all stereocenters must be opposite).
 - Diastereomers – non-superimposable, not mirror images; (C=C, or some stereocenters different, others the same).
- Fischer projections are often used to show the stereochemistry of compounds with multiple stereocenters.
 - They are especially useful for biological molecules such as carbohydrates and amino acids.
- To draw a Fischer projection:
 - The main carbon chain is drawn as a straight line going from the most oxidized carbon at the top. This is like the backbone of the molecule.
 - The most oxidized carbon is the one that has the most bonds to an electronegative atom (usually oxygen). These are often aldehyde, abbreviated CHO, or carboxylic acids, abbreviated COOH.
 - The substituents on the main carbon chain are drawn coming straight out to the left and the right of the main chain. Sometimes, the hydrogen atoms are not shown (just as in line structures). Electron pairs are not usually shown.
 - For each atom, the bonds going up and down (the backbone) are understood to be going away from you. The bonds going left and right (the substituents) are understood to be coming towards you.
- When changing line structures to Fischer projections, substituents going forward will alternate going right and left. This is because the line structure is shown in the staggered conformation (which is the most likely position for the molecule to be in), but the Fischer projection is shown in the eclipsed conformation (which is a high energy position, but useful for showing the relationship between the stereocenters).
- Molecules shown in the Fischer projection follow the same rules as molecules shown as line structures.

- If there is a plane of symmetry, the molecule is achiral, and if there are two or more stereocenters, it is meso.
- If all stereocenters are opposite, they are enantiomers; if some stereocenters are the same and some are opposite, they are diastereomers.
- To assign R or S to each stereocenter, prioritize the groups. If the lowest priority group is pointing backwards, take the 1-2-3 position. If it is pointing forwards, take the reverse of the 1-2-3 position.
- Molecules in the Fischer projection are also labeled using “D” and “L.” This is an older system, but is still in common use for many biological molecules.
 - To label a molecule as D or L, look at the last stereocenter (furthest from the most oxidized carbon). If the highest priority substituent is on the right, it is D. If the highest priority substituent is on the left, it is L.

IV. Physical Properties of Chiral Compounds

Regular physical properties

- Chiral compounds can be characterized by physical properties such as melting and boiling points, solubility, density, color, and so on.
 - In general, the properties of two compounds which are enantiomers will be the same.
 - For compounds which are diastereomers, these properties will be different.
- One simple exception to this is odor. The receptors in your nose are chiral, and can therefore detect the difference between some enantiomers.
 - The main reason that chiral compounds are of interest is that nearly all biological molecules are chiral, including amino acids, sugars, nucleotides, neurotransmitters, hormones, etc. Receptors on cells are shape selective, and will react with one enantiomer of a compound differently from the other. Both biochemistry and pharmaceuticals are therefore deeply involved in the chirality of molecules.

Optical Activity

- Another important difference between the physical properties of enantiomers is how they react with plane polarized light.
 - Light from a source such as the sun or a lamp includes light waves in which are oriented in all possible planes. Plane polarized light, often simply called polarized light, is light in which has been filtered so that it only contains light waves in one plane.

- A polarizing filter has tiny slits which only allow the light in that plane to pass through.
 - Reflected light is usually polarized. Polarized sunglasses contain a polarizing filter at a right angle to the reflected light, which is why they are good at cutting down on glare.
- When chiral molecules interact with polarized light, they shift the angle of the plane of the light waves. This angle is called the optical rotation.
 - This angle change is measured by a polarimeter, and is called the optical rotation. If the angle is positive, then the plane has rotated in the clockwise direction, while a negative number indicates the counterclockwise direction.
 - The optical rotation for a solution depends upon several factors.
 - The structure of the molecule.
 - The concentration of the solution.
 - The distance the light travels through the solution, called the path length.
 - The temperature of the solution.
 - The wavelength of the light.
 - Since we are most interested in the effect of the structure of the molecule, we need to eliminate the effects of other factors.
 - The effect of temperature of the solution is eliminated by always measuring the optical rotation at 25°C.
 - The effect of different wavelengths of light is also eliminated by always using the D line of sodium (a specific frequency given off by excited sodium atoms).
 - The optical rotations of different chiral compounds at a standard concentration of 1.0 g/ml and standard path length of 1.0 decimeter have been measured and recorded – this is called the specific rotation for that compound, and has the symbol $[\alpha]$.
 - To use a different concentration or path length, we use an equation: $\alpha = [\alpha] c l$, where α is the optical rotation that we have measured.
- The specific rotations of two enantiomers always have the same number, but are opposite in sign. Diastereomers, however, have no relationship between their rotations.
- There is no relationship between whether a molecule is R or S, and whether it will have a positive or negative rotation. R or S are conventions that we have invented to label enantiomers, so they don't tell us about how they will interact with polarized light.

- The only thing you can tell is that if the R enantiomer of a compound has a positive rotation, the S enantiomer will have a negative rotation, and vice versa.
- A solution which rotates the plane of polarized light is said to be optically active.
 - A solution of one enantiomer of a chiral compound will always be optically active – this is called an enantiomerically pure solution. A solution of an achiral molecule (such as a meso compound) will always be optically inactive.
 - Equal mixtures of two enantiomers will be optically inactive, as the rotations will exactly cancel each other. Such a solution is called a racemic mixture.
 - Racemic mixtures are very common in synthesis. Since both enantiomers are of equal energy, they are formed in equal amounts. Drugs are often sold as racemic mixtures.
 - Unequal mixtures of two enantiomers will have a rotation proportional to the amount of each enantiomer.
 - Two different values are used to describe this proportion:
 - The percent optical purity (% o.p.) is the rotation of the mixture over the rotation of the pure enantiomer. This describes how much the optical rotation is reduced by the presence of the other enantiomer.
 - The percent enantiomeric excess (% e.e.) difference is the amount of the two enantiomers over the total amount, which is the same as saying the difference between the percentage of the two enantiomers.
 - The % o.p. And the % e.e. come out to the same value for a given mixture. This is because the % e.e. measures how much of the dominant enantiomer is left after the amount that is racemic is canceled out.

Separation of Enantiomers

- Enantiomerically pure compounds can be obtained from three sources:
 - Isolating them from nature: Many chiral compounds exist as pure enantiomers in nature, manufactured by plants and animals.
 - Separation of enantiomers: In most cases, when a chiral compound is synthesized in the laboratory, a racemic mixture is formed. These enantiomers can sometimes be separated to give enantiomerically pure compounds – this is called resolution of enantiomers.

- Since enantiomers have identical physical properties, they can't be separated using techniques like filtering, distillation, chromatography, recrystallization, and so on. Instead, they must be temporarily converted to diastereomers, which have different physical properties, separated, and then converted back to the original enantiomers.
- Stereoselective reactions: In some cases, a reaction can use a chiral, enantiomerically pure reagent to cause one of the enantiomers to be formed in greater amounts than the other. Ideally, this ratio can be maximized to over 99% of the desired enantiomer.
 - We will discuss stereoselective reactions in chapter 7.

Determination of Stereochemical Correlation

- There is no way to determine whether a compound has a positive or negative rotation by looking at the structure of the compound. This can only be determined by physically measuring the optical activity.
 - In some compounds, the R is positive and the S is negative, while in others the S is positive and the R is negative.
- It is also impossible to determine whether a compound is R or S by looking at a physical sample of a compound. This can only be determined by looking at the structure of the compound on paper.
- It is therefore difficult to determine whether the enantiomer that measures a positive rotation matches the R or the S structure of that compound.
- The task of matching up positive and negative rotations with R or S structures for a pair of enantiomers is called stereochemical correlation. For many years, organic chemists were not able to do this, until finally a method was developed in 1951.
 - First, a pure sample of either one of enantiomers must be obtained.
 - Second, its optical rotation is measured to determine if it is positive or negative.
 - Third, the solution is slowly evaporated to form large, pure crystals.
 - Fourth, x-ray crystallography is performed on the crystal. This allows the three dimensional shape of the molecules to be determined.
 - Finally, the stereochemistry of the molecules is determined from the three dimensional shape.
- This process of obtaining a crystal and doing x-ray crystallography is very difficult and time-consuming (it was only with the advent of computers that it became possible to do one in less than a year).
 - Fortunately, once the stereochemical correlation is known for one compound, it can be used to obtain others. The molecule is changed in a predictable way, so that the three dimensional structure is still known, and then the optical rotation is measured.