ORGANIC CHEMISTRY I



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Organic Chemistry I

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Licensing

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CHAPTER OVERVIEW

1: Introduction to Organic Chemistry

1.1: Line Angle Notation as the Language of Chemical Structure

1.2: Using Chemical Arrows

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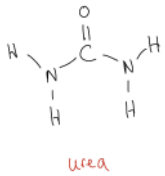
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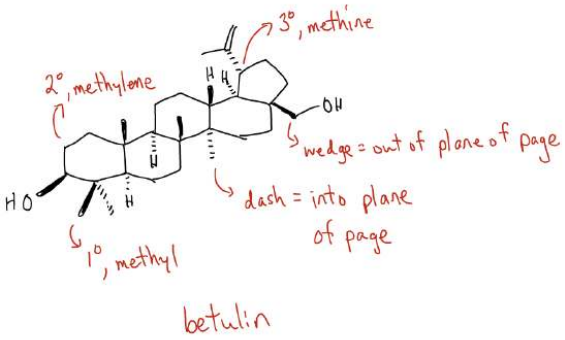
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1.1: Line Angle Notation as the Language of Chemical Structure

Organic chemistry has often been defined as the chemistry of life or the chemistry of carbon-containing compounds. But this is actually a misnomer. The term “organic” emanated from the misconception that organic compounds were always related to life processes. We know now, however, that carbon-containing molecules can be produced by processes not involving living organisms. For example, molecules can be made from scratch in the research lab. Friedrich Wöhler was the first to synthesize an organic molecule (urea) from inorganic components. This was regarded as a true breakthrough in the field and provided direct evidence against the doctrine of **vitalism** – that living things are governed by different principles than non-living entities.



So, what is organic chemistry, then? After all, Wöhler’s synthesis of urea took place in 1828! A wise man once said that this particular branch of chemistry can be defined as “knowing how to make a molecule and knowing when you’ve made it.” I first want to introduce you to some conventions in the field because organic chemistry is a language. We communicate information about molecules and reactions in a certain way. Consider the molecule betulin, which is present in the bark of the white birch tree at a concentration as much as 30% by dry weight. We draw betulin, which is a small molecule with a molecular weight <500 g/mol, as such:



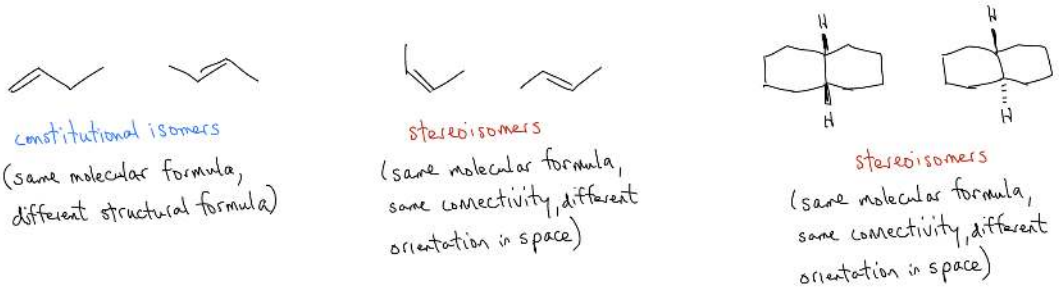
So, what does this all mean?

1. any corner of a polygon or branchpoint of any chain is a carbon atom.
2. no H atoms attached to C are drawn, unless they depict **stereochemistry**.
3. all H atoms attached to heteroatoms (ex. O, N, P, S, etc.) are shown (quick question: what kinds of heteroatoms are in betulin?).
4. one line connecting atoms is a single bond; two lines = double bond; three lines = triple bond (quick question: what kinds of bonds are in betulin?).
5. any end of a chain is a $–CH_3$ group (quick question: how many CH_3 groups in betulin?).
6. dashes and wedges indicate whether an atom or group is coming out of the plan of the page or into the plane of the page.
7. 1° (primary carbon) = one other carbon attached; 2° (secondary carbon) = two other carbons attached; 3° (tertiary) = three other carbons attached); 4° (quaternary) = four other carbons attached.
8. Methyl = CH_3, Methylene = CH_2, Methine = CH.

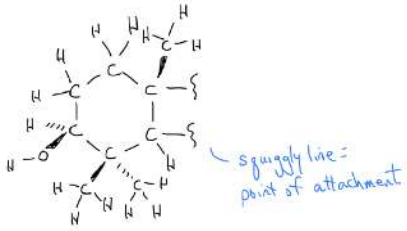
Given this depiction, one might think that organic molecules are flat – but don’t fall into this trap. Remember that carbon atoms have three different types of geometry:

sp = linear sp^2 – trigonal planar sp^3 – tetrahedral

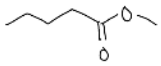
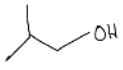
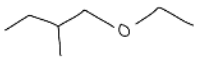
Only two of these geometries are flat – sp carbons are linear and rod-like and sp^2 carbons are flat and trigonal. On the other hand, tetrahedral carbons have three-dimensionality, which means that the atoms or groups attached to carbon occupy a certain region in space. A specific orientation of atoms or groups in space is a molecular property known as **stereochemistry**. In betulin, this is depicted with a dash or wedge. **Stereoisomers** have the same *constitution* (same atoms connected to the same atoms), but different orientation in space. You may recall that constitutional isomers have the same molecular formula, but different structural formulas. Stereoisomers have the same molecular formula, same structural formulas (connectivity), but different orientation of atoms/groups in space.



We call this shorthand for drawing organic molecules **line-angle notation**. Consider the alternative, that is if we were to draw out every single atom, as in the first ring of betulin shown below. Even with line-angle notation, we are limited, so if we really want insight into the structure of a molecule, we should build a model!

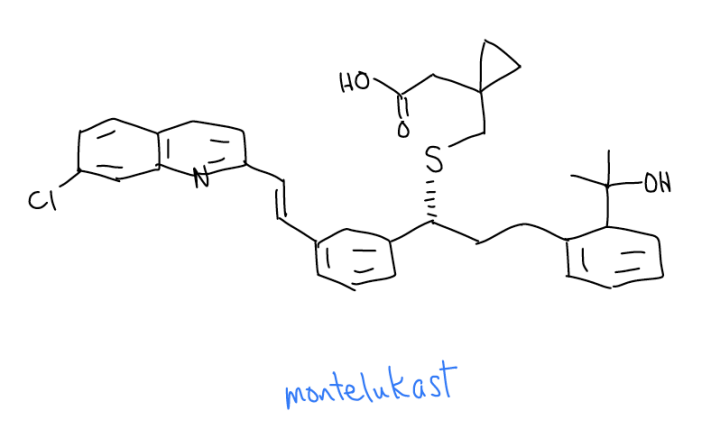


Line-angle notation can also be converted into condensed formulas in simple cases (does not apply for cyclic systems). Condensed formulas are “read” in line-angle structures from left to right carbon-by-carbon, taking into account heteroatoms and branching groups through the use of parentheses. For example:

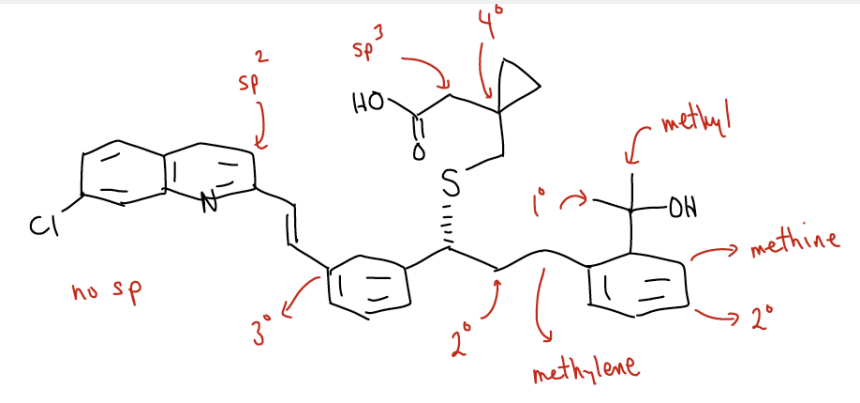
line-angle notation	condensed formula
	$CH_3CH_2CH_2CH_2CO_2CH_3$
	$(CH_3)_2CHCH_2OH$
	$CH_3CH_2(CH_3)CHCH_2OCH_2CH_3$

Biomedical Spotlight

Montelukast is the active ingredient in the asthma drug that is sold under the brand name Singulair™. Its chemical structure shows the rich diversity in architecture of organic molecules. See if you can identify sp, sp^2, sp^3 carbon atoms, 1°, 2°, 3°, and 4° carbon atoms, and methyl, methylene, and methine C-H bonds.



Solution:



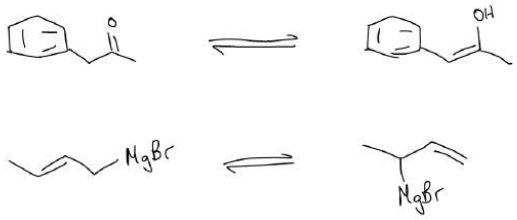
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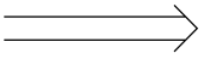
1.2: Using Chemical Arrows

The other common convention in organic chemistry is the use of arrows. Beware – not all arrows are created equal! Different types of arrows mean different things. Let's go through each of them:

1. This is a **reaction** arrow depicting conversion of one molecule to another: starting materials or substrates are drawn before the arrow; reagents and conditions are drawn above and below the arrow; products of the transformation are drawn to the right of the arrow.

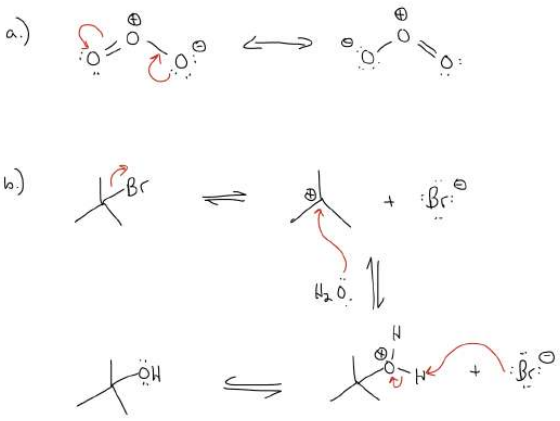
2.  This is an **equilibrium** arrow: two species on either side of the arrow are in equilibrium with each other, with a defined equilibrium constant (K_{eq}). This does not mean that they are in equal amounts; it simply means that the rate of change between the two is constant. Equilibrium species involve the movement of atoms and involve bond breaking/bond forming events. This arrow designates that these species can be interconverted and that the forward direction is reversible. Some common example are below:



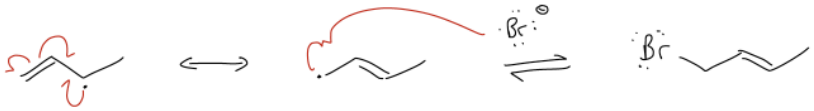
3.  This is a **retrosynthetic** arrow: the species before the arrow (normally more complicated) is synthesized from the species after the arrow (normally less complicated). The target molecule can be made by one or more steps. We use this type of arrow to plan syntheses of more complex molecules in the forward direction by detaching the more complex molecule in strategic ways.

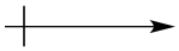


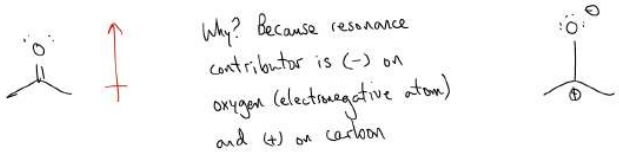
4.  This is a **curved (curly) double-headed arrow**: it is used to depict the movement of a *pair of electrons* from one place to another. It can be used to draw electron flow through a π system (a), or for electron flow in reactions (b). In the latter, known as a mechanism, arrows are always drawn from a pair of electrons (either a lone pair or bonding electrons) toward another atom/group.



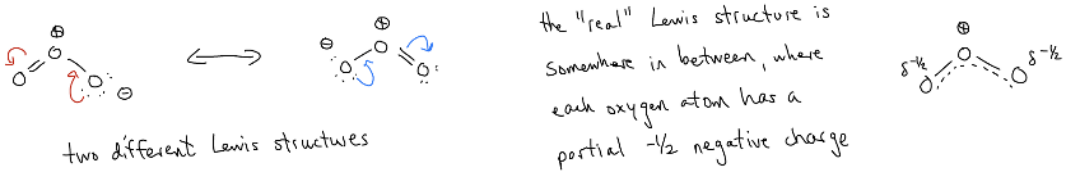
5.  This is a **curved (curly) single-headed arrow**: it is used to depict the movement of a *single electron* from one place to another, either in resonance or in a mechanism.



6.  This is a **dipole moment arrow**: it depicts the direction of polarity, from partial positive charge to partial negative charge.



7. This is a **resonance arrow**: it indicates that the real Lewis structure for a molecule is an average between the two. We use resonance arrows because our two-dimensional depiction of organic structures (that is, Lewis structures using line-angle notation) does not allow us to account for the **<u>movement of electrons</u>** through a π network. Take the example of ozone:



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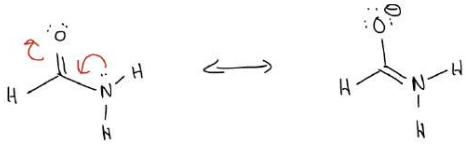
1.3: Resonance

Resonance involves the delocalization of electrons throughout an extended network of π bonds (double and triple bonds). This occurs because it is lower in energy to distribute charge over multiple atoms. Thus, the electrons on the negatively charge terminal oxygen lie in an atomic p orbital that can overlap with the adjacent π system so that there is optimal orbital mixing – this is lower in energy! As a rule, any lone pair that sits adjacent to a π system and can delocalize into this π system will do so from an atomic p orbital on an atom that is sp^2-hybridized.



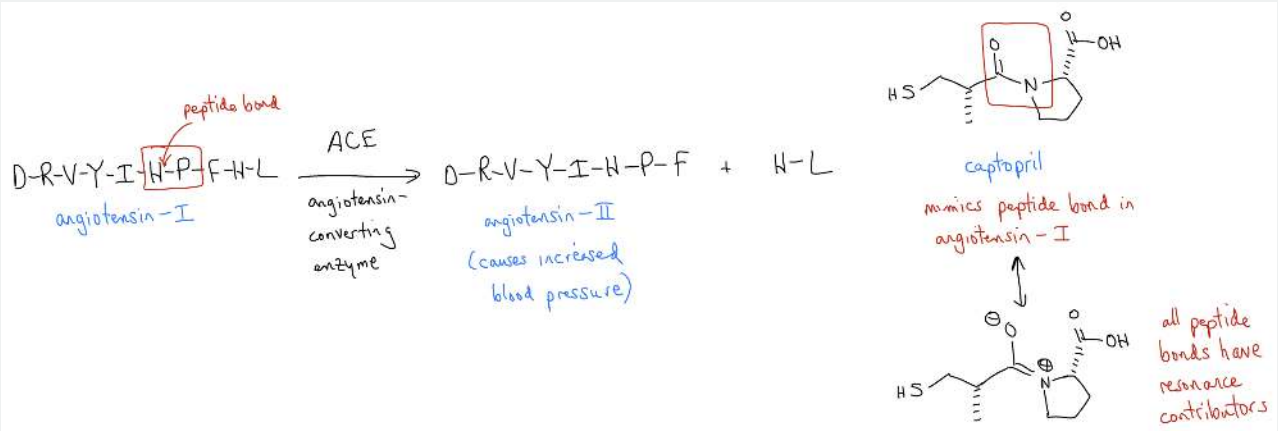
The Lewis structures we draw using line-angle notation are defective because they localize electrons. However, electrons like to be arranged in ways that are most stable and the resonance arrow can account for this. Be careful, though, because a resonance arrow does not mean the structures are interconverting (like equilibrium) – they are not! There is only a single structure that accounts for all resonance contributors, which happens to lie intermediate between all of them.

We call each of the Lewis structures on each side of a resonance arrow a **resonance contributor**, or **resonance form**. If a molecule is symmetrical, then the true structure is exactly in between the two forms. However, this is not always the case. Electronegativity can control which resonance form will predominate. For example, take the molecule formamide. The resonance contributor which has charge separation is a major contributor because the negative charge is on oxygen, a more electronegative atom.



Biomedical Spotlight

Captopril™ is a blood pressure-lowering drug discovered by Bristol-Myers-Squibb in 1977. It works by preventing the enzyme ACE (angiotensin-converting enzyme) from cleaving its peptide substrate angiotensin-1 into angiotensin-2, the latter which results in increased blood pressure. A key feature of this drug is the amide bond (shown in red), which mimics the peptide bond between histidine (H) and proline (P) in the natural peptide. All peptides have resonance contributors where the lone pair on the nitrogen is resonance delocalized into the carbonyl group, leaving negative charge on the oxygen atom. Captopril has this same resonance contributor, which allows it to mimic the natural peptide angiotensin-1, inhibiting ACE from performing its function, and resulting in lower blood pressure in diseased patients.



Adapted from Hallelujah Moments, by Eugene Cordes, 2014

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1.4: Acids and Bases

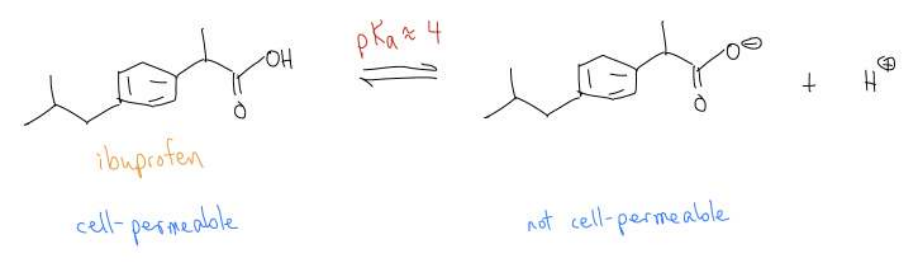
You should be familiar with acids and bases from general chemistry, where attention was given to calculations of pH, percent ionization, buffers, etc. All of the acids and bases in general chemistry were soluble in water, but many of the acids and bases we use in organic chemistry are not soluble in water, but are much more soluble in organic solvents. As such, there is a larger pK_a range that we can use in chemical reactions.

So, what are the factors that influence pK_a and lead to an expansion of the dynamic range of acidity?

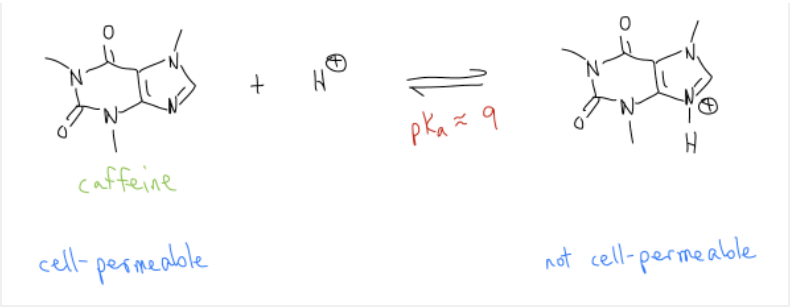
1. Bond strength
2. Electronegativity
3. Hybridization
4. Hyperconjugation (σ-donation)
5. Polarizability
6. Resonance delocalization
7. Inductive effects

Biomedical Spotlight

Quanitifying the absorption, distribution, metabolism, and excretion (ADME) of drugs in an important step in the drug discovery process. If a drug cannot reach its target due to poor absorption or distribution, then the drug will not be able to treat disease. Likewise, if a drug is metabolized or excreted too quickly, it will also be unable to perform its function. Understanding the acid-base chemistry of drugs is critical to improving ADME, and ultimately human health and well-being. Consider what happens when one ingests a drug in pill form. It almost immediately encounters the acidic environment (pH ~ 2) of the stomach. The pill starts to dissolve and secretory enzymes begin to break down the pill into its active components. At this stage, some drugs pass through the stomach mucosa and into the bloodstream for distribution to the appropriate tissues. This process is dependent on the pK_a's of the functional groups in the molecule. In the case of ibuprofen, the carboxylic acid functional group is rather acidic (pK_a ~ 4) because the deprotonated (and negatively charged) form is resonance stabilized. In water at pH = 7, almost all of the ibuprofen exists in its deprotonated form. However, under the acidic conditions of the stomach (again, pH ~2), ibuprofen will exist in its neutral, protonated form. This will give it an ability to cross a nonpolar biological membrane and into the bloodstream towards its target.



Some drugs cannot pass through the stomach mucosa due to a difference in pK_a of the functional groups in the molecule. Take caffeine, as an example. The lone pairs on the nitrogen atoms are weakly basic. In the acidic environment of the stomach, they will become protonated (pK_a ~ 9). The protonated form, now positively charged, will not be able to cross a nonpolar biological membrane into the bloodstream. So, it stays in the digestive tract until it reaches the intestines. The intestines are much more basic than the stomach, resulting in a shift of the acid-base equilibrium towards the deprotonated form once again. There will now be enough neutral species present to pass through a nonpolar biological membrane and into the bloodstream, where it can be distributed to the appropriate tissues and perform its function.



Understanding trends in acids and bases and their impact on pK_a is an important skill to master in organic chemistry because it can often predict how molecules react.

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1.5: Guiding Principles of Organic Chemistry

Finally, there are a few guiding principles that you should be familiar with as you journey through organic chemistry:

1. (+) and (-) charges are attracted to each other and like charges repel
    a. **Nucleophiles** (literally “nucleus loving”) are normally (–) charged species or those with a lone pair that are “looking” for a “nucleus” (aka, something electron deficient)
    b. **Electrophiles** (literally “electron loving”) are normally (+) charged species or those with an empty orbital that are willing to “accept” a pair of electrons (aka, something electron rich)
2. Electronegative atoms hoard electrons
3. Atoms love having filled outer shells, which is more stable (octet rule)
    a. How many bonds do the atoms C, N, O, F, and H make to other things? How many lone pairs on each atom?
4. Electrons like to have space to move around
    a. **Resonance** can move electrons through π systems
    b. **Polarizability** is the “squishiness” of an atom, or how diffuse it is. For example, I^- is more stable than Br^- because electrons can better spread out on the larger I atom.
5. Unstable compounds are higher in energy, and are thus more reactive
6. H^+ atoms can be added or removed fairly easily, which can have a big impact on reactivity

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CHAPTER OVERVIEW

2: Bonding in Organic Molecules

2.1: Lewis and Valence Bond Models

2.2: Molecular Orbital Theory

2.3: Bonding in Symmetrical Hydrocarbons

2.4: Bonding in Unsymmetrical Systems

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2.1: Lewis and Valence Bond Models

There are several models of bonding in organic molecules that have, at one point in their history, achieved scientific consensus. Each of them has their own pitfalls, but they are all useful to organic chemists, even today.

Lewis model – sharing of two electrons by more than one atom can permit each atom to have a stable closed-shell electron configuration, aka octet rule: in forming bond, atoms either gain, lose, or share electrons (depending on the electronegativity of the atoms that make up the bond) to achieve a stable electron configuration characterized by eight valence electrons:

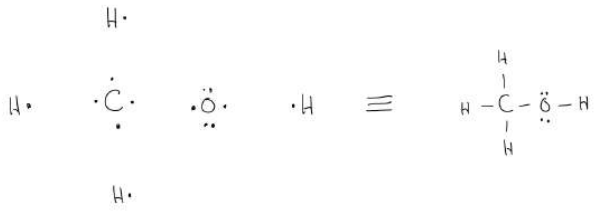
- gain/loss of electrons results in ionic bonding
- sharing of electrons results in covalent bonding

atom	# valence electrons	# electrons needed for octet	# bonds made to other atoms	# lone pairs
H	1	1 (duet)	1	0
C	4	4	4	0
N	5	3	3	1
O	6	2	2	2
F	7	1	1	3
Li	1	7	(loses an electron to generate octet)	0

Lewis dot structures:

CH_4O C + (4 x H) + O =

4 + (4 x 1) + 6 = 14 electrons

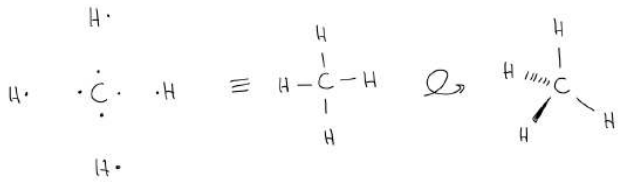


Other examples: CH_5N, C_2H_6O, CH_6N^+ (*quick question*: can you draw the Lewis structure for these molecules?)

So, what do Lewis structures look like in three dimensions? We use **Valence Shell Electron Pair Repulsion** (VSEPR) to predict geometries. In essence, an electron pair, existing either in a bond or as an unbounded lone pair, associated with an atom will lie as far away from the atom's other electron pairs as possible. An example is CH_4, or methane:

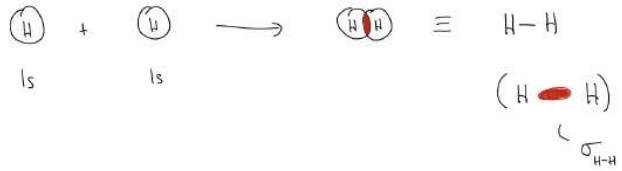
CH_4 C + (4 x H) =

4 + (4 x 1) = 8 electrons



What is the simplest way to arrange an atom containing four identical substituents? A **tetrahedron**, of course. We say the geometry of methane is tetrahedral with bond angles of 109.5°. Other geometries include H_2O (bent, 105°), NH_3 (trigonal pyramidal, 107°), BF_3 (trigonal planar, 120°), CH_2O (trigonal planar, 120°), and CO_2 (linear, 180°). Can you draw the Lewis structures for these molecules?

Valence Bond model – 2nd generation response to the Lewis model, which is convenient but not the whole picture. In summary, electrons have wave-particle duality, so we can describe bonding as an interaction between waves. When two waves overlap in-phase, they reinforce each other to create a new wave, or chemical bond. The best example is molecular hydrogen. When the electrons in two 1s orbitals overlap, a new orbital is created that is known as a σ orbital, or σ bond.



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2.2: Molecular Orbital Theory

Molecular Orbital Theory – 3rd generation model in response to limitations of valence bond model that help describe reactivity. Just as electrons occupy atomic orbitals, electrons in molecules (namely, in chemical bonds) occupy molecular orbitals. Molecular orbitals are described as combinations of atomic orbitals, known as the **linear combination of atomic orbitals**:

Rule #1: for every *n* atomic orbitals, one will create *n* molecular orbitals. So, if you start with a 1s orbitals of H and another 1s orbital of H and combine them to form a chemical bond, you will generation *two* molecular orbitals overall. We call these the bonding (σ) and antibonding (σ^*) orbitals, derived from in-phase and out-of-phase overlap of the wavefunctions, respectively. The σ bond is lower in energy than the 1s atomic orbital and the σ^* is higher in energy than the 1s atomic orbital.

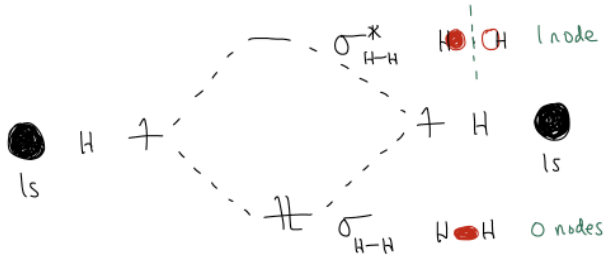
Rule #2: these two new molecular orbitals will have different energies. The lowest molecular orbital (σ) will have zero nodal planes and each successive orbital thereafter will have an additional nodal plane.

Rule #3: the coefficients, C_1 and C_2, represent the contribution of each atomic orbital to the overall wavefunction:

- bonding orbital: $\sigma = C_1\Psi_1 + C_2\Psi_2$
- antibonding orbital: $\sigma^* = C_1\Psi_1 - C_2\Psi_2$

In symmetrical molecules, C_1 and C_2 will be the same, but this will rarely occur in more complicated systems. The size of the coefficient will tell you which side of the bond has the bigger lobe for that orbital. In addition, the squares of the coefficients will always equal one (that is, $(C_1)^2 + (C_2)^2 = 1$) and both wavefunctions will contribute one net orbital (that is, bonding$(C_1)^2$ + antibonding$(C^1)^2 = 1$).

Let's take the example of H_2. Just as in the valence bond model, when two atomic orbitals overlap in-phase, we get net bonding (σ), but when they overlap out-of-phase, we get destructive interference and a nodal plane results (σ^*).



Given the **molecular orbital diagram** above, can you draw one for H_2^+?

When two atomic orbitals combine, the bonding orbital is lower in energy (s → σ) and you fill in the electrons from lowest energy to highest energy. What this tells us, then, is that in H_2, there is **net bonding** between the H atoms. Convince yourself that the bond order is one. Now, say we were to fill the σ^* orbital with an electron. By doing so, the bond order will decrease to ½ and the σ bond will weaken. Add two electrons, and the σ bond will break completely (bond order = 0). This is why molecular orbital theory is so important – it gives us an entry into reactivity. It allows us to break bonds!

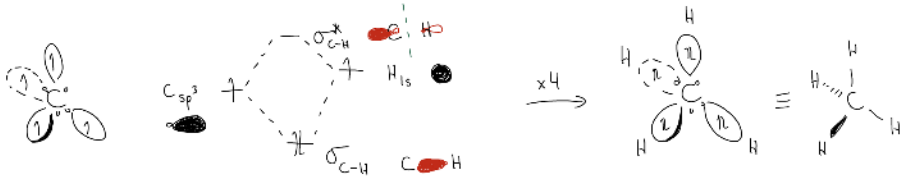
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2.3: Bonding in Symmetrical Hydrocarbons

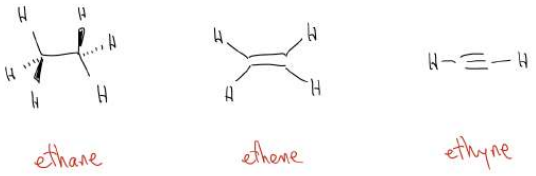
Consider, now, a molecular orbital diagram for the tetrahedral molecule methane, CH_4. In order to describe the bonding, let us remember what types of atomic orbitals exist on carbon alone. According to Lewis theory, carbon has four valence electrons: two occupy the 2s orbital and one each occupy the $2p_x$ and $2p_y$ orbitals. When we mix all four atomic orbitals, we produce four sp^3-hybridized atomic orbitals of equal energy, but slightly different shape.



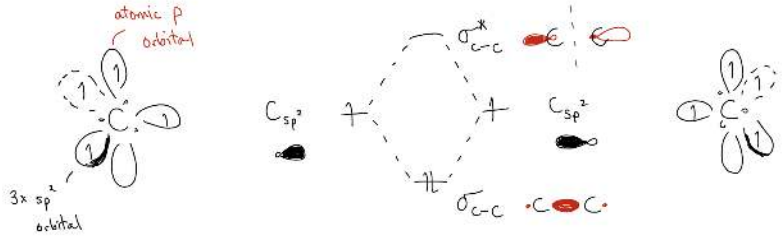
Our net result is a carbon atom that looks like this, which has tetrahedral geometry:



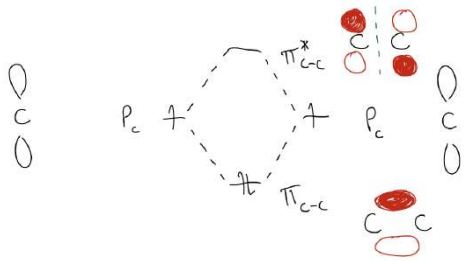
If we now overlap each sp^3 orbital with a 1s orbital from a H atom, we get 8 new orbitals: 4 new bonding σ_{C-H} and 4 new antibonding σ^*_{C-H}. What about bonding in systems with higher oxidation states? For example, how can we describe the C-C bonding in ethane vs. ethene vs. ethyne?



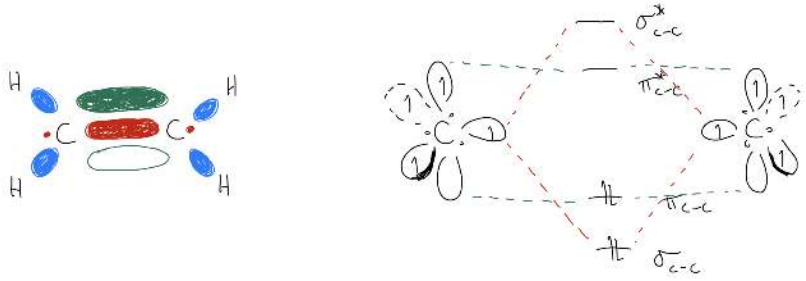
Ethene: carbon atom is sp^2-hybridized ($3sp^2$ + 1 atomic p)



Overlap occurs between two sp^2 orbitals to form a σ bond, but also between the two atomic p orbitals (p → π).



π orbitals are higher in energy than σ orbitals because there is weaker overlap (recall that σ bonds results from head-on overlap). Let's put it all together, then:

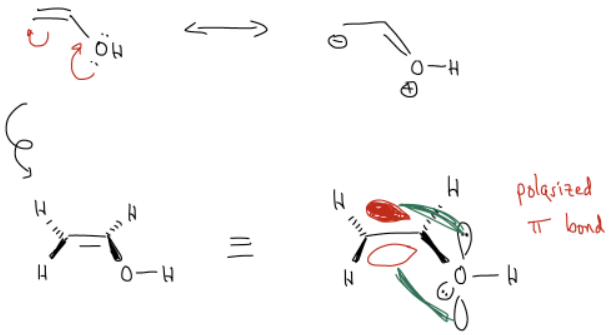


When we draw an orbital diagram, we normally only draw the bonding orbitals. However, it will be important later to know where the antibonding orbitals lie. Also, don't forget the bonds made from carbon to hydrogen. Unlike in methane, where an sp^3 orbital and a 1s orbital overlapped to give a σ bond, we will now overlap an sp^2 orbital with a 1s orbital to give a σ bond.

How about ethyne?



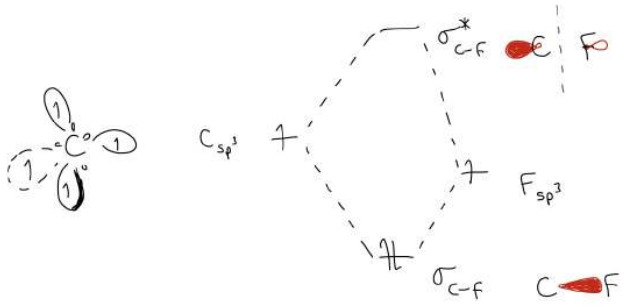
What happens when a heteroatom is attached to a π system? Well, the coefficients C_1 and C_2 change. We can see this from resonance structures that we can draw – any atom that has a formal charge will have a larger coefficient in the bonding π orbital.



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2.4: Bonding in Unsymmetrical Systems

What about unsymmetrical systems, in which the two atoms are not identical? Again, the coefficients C_1 and C_2 will change. Consider CH_3F:



Since F is the electronegative, the bonds are polarized (unequal). Thus, F likes having a higher electron density around it, so the σ bond is skewed and no longer symmetrical. By analogy, the exact opposite is true for the σ^*.

Let's return to betulin for a moment. Take a minute to look at its structure and think about how complex it would be if we drew molecular orbitals for every bond. That's why we draw molecules using line-angle notation, a short-hand of the Lewis model of bonding. You just need to recognize where it comes from.

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CHAPTER OVERVIEW

3: Simple Hydrocarbons

3.1: Nomenclature

3.2: Conformations of Acyclic Hydrocarbons

3.3: Conformations of Substituted Hydrocarbons

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3.1: Nomenclature

Nomenclature

How do we name organic compounds? There are two ways

1. common name – colloquial name $CHCl_3$ = chloroform
2. IUPAC – "official" international naming system of International Union of Pure and Applied Chemistry $CHCl_3$ = trichloromethane

For starters, we need to know how to describe the atoms and bonds that are depicted using line-angle notation. We use a specific language to describe how many carbons are in a molecule and what kinds of functional groups are in a molecule. Watch the video below for a crash course on this language, which will be followed up with more complicated nomenclature.

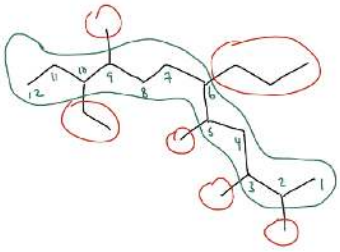


Now that you know simple alkane nomenclature and various functional groups, we can begin to discuss more complicated systems.

1. Branched alkanes C_nH_{2n+2} = suffix -ane

a) identify the longest contiguous chain
b) number the chain; start with a substituent group occupying the lowest number possible
c) locate the substituents, give them a number
d) alphabetize
e) if more than one of the same substituent, use following prefixes: 2 = di; 3 = tri; 4 = tetra, 5 = penta; 6 = hexa; 7 = hepta; 8 = octa; 9 = nona; 10 = deca

Example:



12 carbons = dodecane

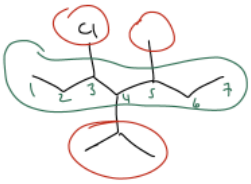
2,3,5,9-tetramethyl

6-propyl

10-ethyl

Name: 10-ethyl-2,3,5,9-tetramethyl-6-propyldodecane

Example:

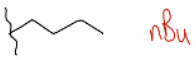


IUPAC name: 3-chloro-4-(1-methylethyl)-5-methylheptane

Common name: 3-chloro-4-isopropyl-5-methylheptane

Other common groups (IUPAC names):

nBu = normal butyl (butyl)



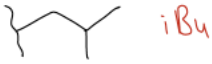
tBu = tertiary butyl (1,1-dimethylethyl)



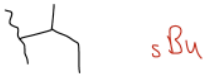
iPr = isopropyl (1-methylethyl)



iBu = isobutyl (2-methylpropyl)



sBu = secondary butyl (1-methylpropyl)

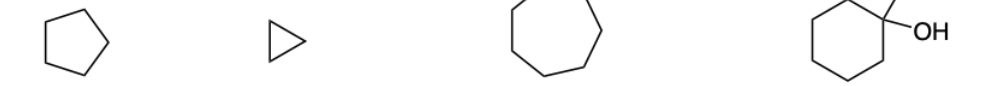


2. Cycloalkanes C_nH_{2n}

a) count number of carbons in the ring

b) add prefix “cyclo” to the alkane chain

Examples:



cyclopentane cyclopropane dimethylcycloheptane 1-propylcyclohexanol

In cycloalkanes, there are often stereoisomers that arise:



cis = same side trans = opposite sides

cis-2-methylcyclopentanol *trans*-2-methylcyclopentanol

3. Bicycloalkanes – a fused or bridged cycloalkane that requires 2 bonds to be broken to become acyclic

a) count # of carbons in the bridged system (do NOT include substituents)
b) add prefix “bicyclo” to parent chain
c) identify bridgehead carbons (ring fusion centers) and count # of intervening carbons in each bridge
d) insert [#.#.#] in between “bicyclo” and parent chain
e) number around the largest ring first, then next largest ring, etc.
f) when two rings are the same size, number ring with substituent first

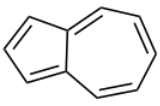
Examples:



camphor
(1,7,7-trimethylbicyclo[2.2.1]heptan-2-one)



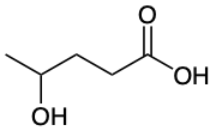
bicyclo[2.2.2]octane



bicyclo[5.3.0]deca-1,3,5,7,9-pentaene

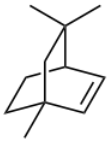
4. Functional groups

If more than one functional group exists, the base or parent name will depend on its priority rank.

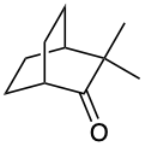


IUPAC name: 4-hydroxypentanoic acid (*not* 4-carboxy-2-butanol - carboxylic acid has higher priority than alcohol!)

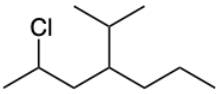
Let's have some practice. What is the IUPAC name for the following molecules?



1,5,5-trimethylbicyclo[2.2.2]oct-2-ene



3,3-dimethylbicyclo[2.2.2]octan-2-one



2-chloro-4-(1-methylethyl)heptane

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3.2: Conformations of Acyclic Hydrocarbons

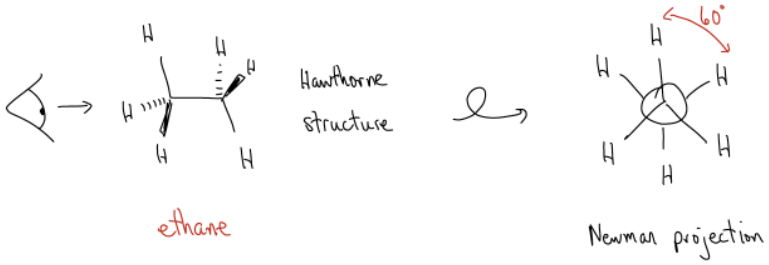
As we have mentioned previously, organic molecules exist in three dimensions. But the Lewis structures we draw are also not static – at room temperature (and even low temperature), molecules tumble, their bonds vibrate, and atoms rotate. Not all of these types of motion are the same in energy. **Conformational analysis** is a study of the energetics of **rotational isomers**, or **conformers**, that occur upon rotation of a single (σ) bond.

Conformations are different spatial arrangements of a molecule that are generated by rotation about single bonds. One molecule may have many different conformations. Some may be low in energy, others high. Some may be required for reactivity, while others may be completely inert. So, it is important to understand how conformations influence the properties of a molecule.

There are primarily two types of conformations we will be worried about here: a) conformations of acyclic hydrocarbons; and b) conformations of substituted hydrocarbons.

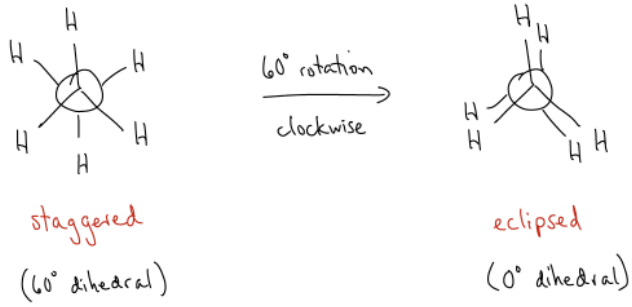
A. Conformations of acyclic hydrocarbons

Let's consider ethane. One way of depicting ethane is by drawing all of the hydrogens and attaching some perspective, as in the Hawthorne structure (saw-horse) shown. If we look down the barrel of the C-C bond, what do we see?



This drawing is known as a **Newman projection**. Is this a stable conformation? Why, yes it is. All of the H atoms are as far apart from each other as possible. The conformation in which the dihedral angle (HCCH) is 60° is called the **staggered** conformation.

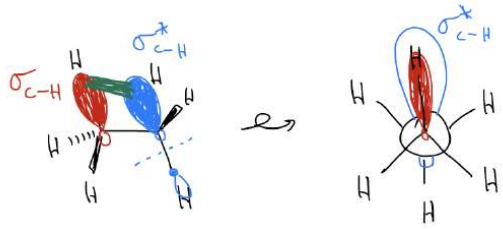
Now, what if we were to rotate the rear carbon 60° clockwise without rotating the front carbon? What changes would we see? Draw the Newman projection:



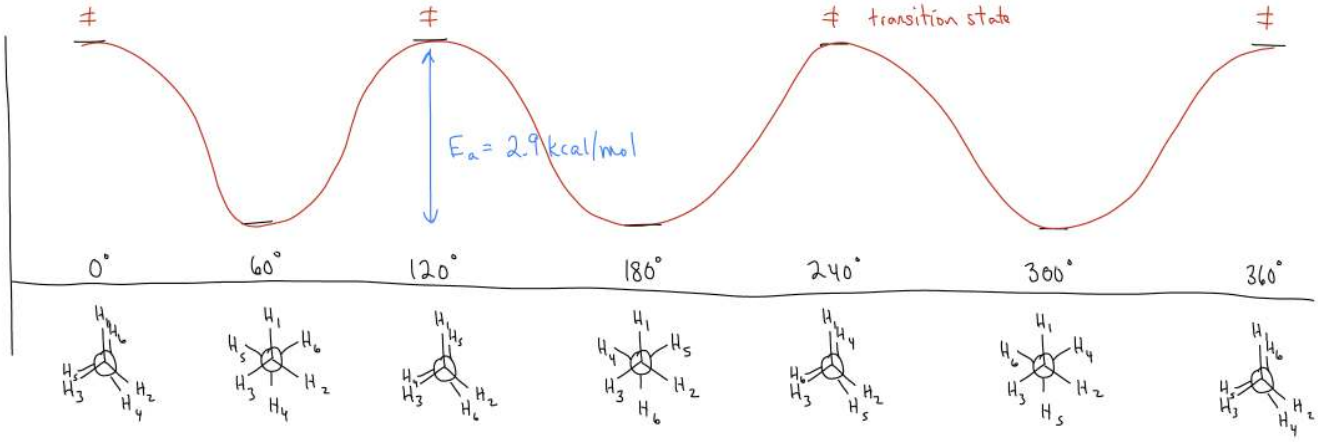
In this conformation, known as the **eclipsed** conformation, the dihedral angle is now 0°. This conformation is higher in energy than the staggered conformation by 2.9 kcal/mol. But, why is it higher? There are two reasons, both of which are electronic in nature:

1. There is electron repulsion, known as **torsional strain**, between the overlapping electrons clouds of the two σ_{C-H} bonds. Like charges repel, so when they are close together, there is an increase in energy.

2. In the staggered conformation, electrons can delocalize from the σ_{C-H} into the σ^*_{C-H}. This is known as **hyperconjugation**, or what I'm going to call σ**-donation**. This delocalization does not exist in the eclipsed conformation. Electrons from the σ_{C-H} are aligned correctly for overlap through space with the σ^*_{C-H}, which leads to stabilization (think about it as electrons liking to be spread out more).



How would this look if we drew a potential energy diagram? As we've said, the difference in energy between the eclipsed and staggered conformations is 2.9 kcal/mol, which is the activation energy (E_a) required to proceed from one staggered conformation to the closest eclipsed conformation. Since there are three eclipsed conformations, we can say that each σ_{C-H} eclipsing interaction is approximately 0.9-1.0 kcal/mol. At room temperature, there is more than enough energy to overcome this barrier. The point of maximal potential energy, known as the **transition state**, is a transient species. It is fleeting and we cannot detect it, so eclipsed conformations will always funnel into the next low energy conformation.

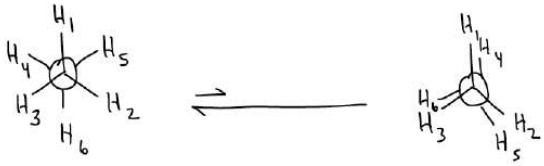


What does this energy different tell you about the relative distribution of conformations of ethane? In other words, what is the ratio between the staggered and eclipsed conformations? Recall:

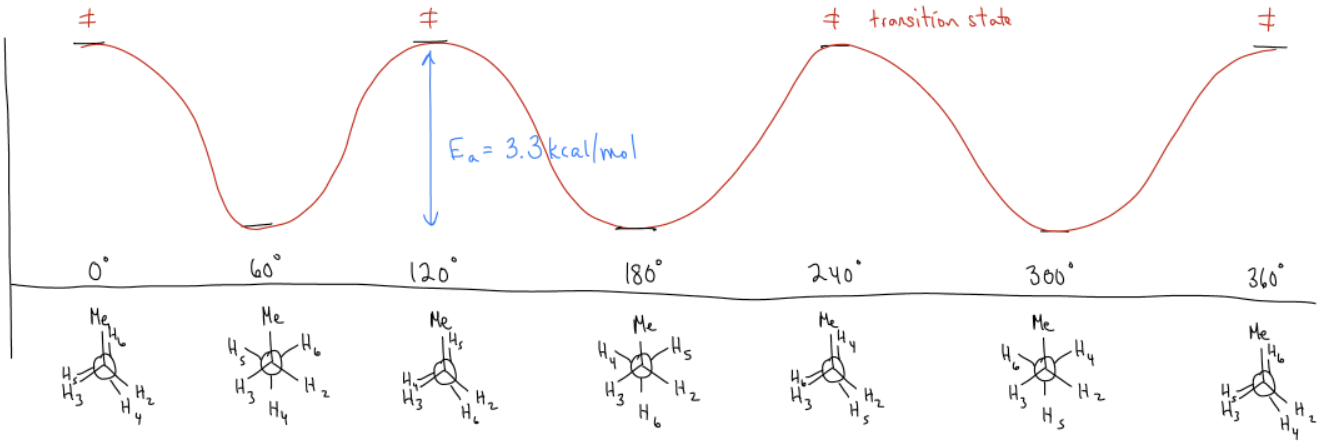
$\Delta G = - RT \ln K$

$1.9 \text{ kcal/mol} = - (1.986 \times 10^{-3} \text{ kcal/(K*mol)}) \times 298 \text{ K} \times \ln K$

$K = 0.007446$ therefore the ratio > 99:1



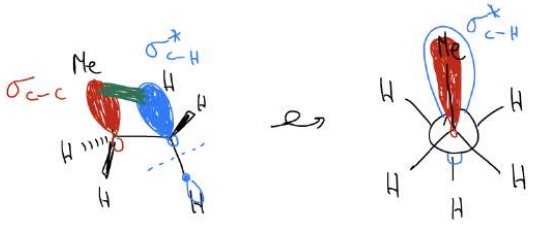
Let's now add one more level of complexity. Draw the most stable conformation of propane and rotate around the C-C bond to form a potential energy diagram:



The activation energy is now 3.3 kcal/mol! Why is it higher than ethane? Two principles continue to influence the conformation:

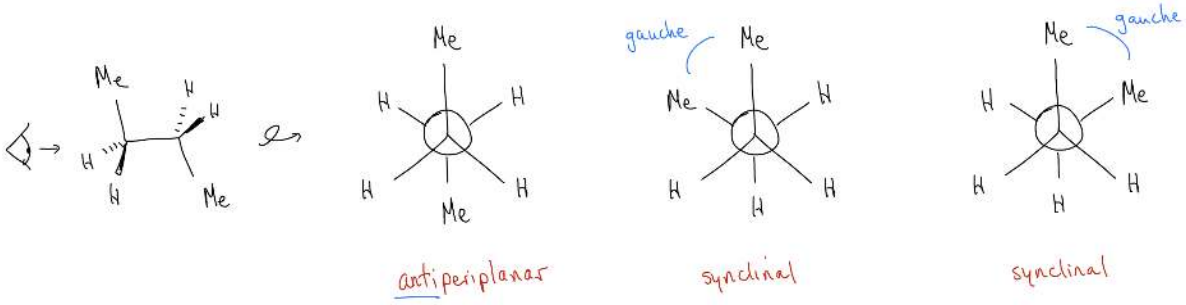
1. Torsional strain – now, it is between σ_{C-C} (which is a little longer) and σ_{C-H}.

2. Hyperconjugation (σ-donation) – now, the delocalization is between σ_{C-C} and σ^*_{C-H}. Since a σ_{C-C} bond is a slightly better donor than σ_{C-H}, there is a greater stabilization effect.

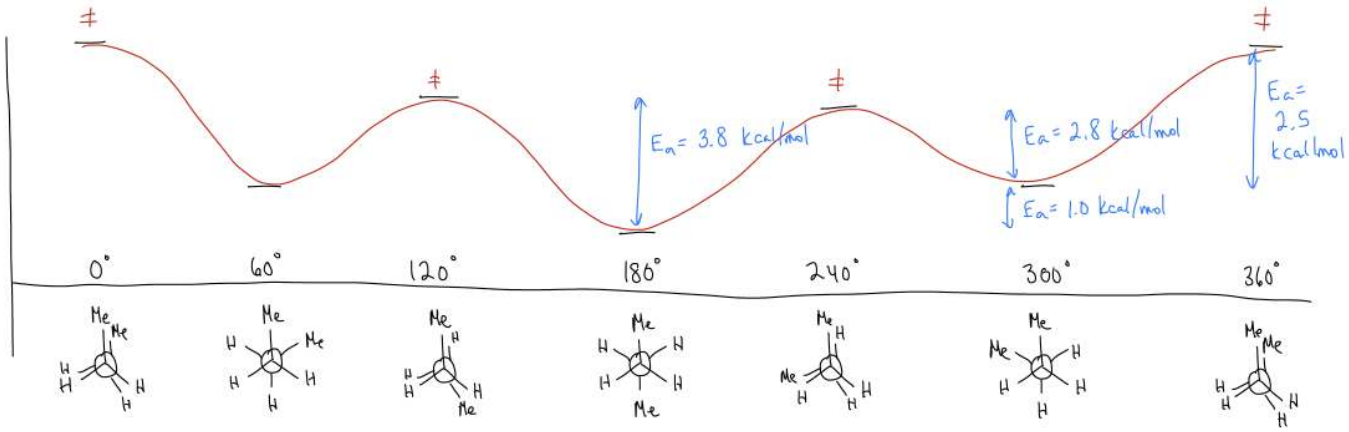


Because of these effects, the difference between the eclipsed and staggered conformers are maybe not as great as you would expect by adding a much bigger methyl group.

Let's now go one atom longer. Draw the three most stable conformations for butane:



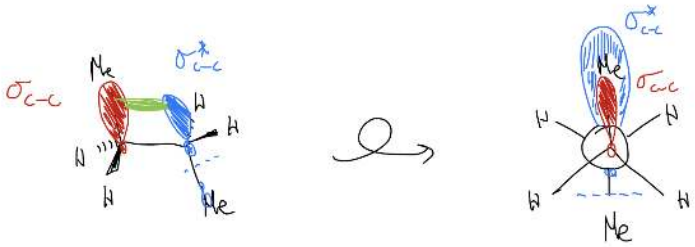
Did you notice that not all of the staggered conformations look the same? The conformation in which the dihedral angle between the methyl groups is 180° is called **antiperiplanar**, and we say that the methyl groups are **anti**. The conformation where the dihedral angle is 60° is called **synclinal**, and we say that the methyl groups are **gauche**. There are two synclinal conformations and one antiperiplanar conformation, all of which are staggered, and therefore low in energy. What would a potential energy diagram look like in this case?



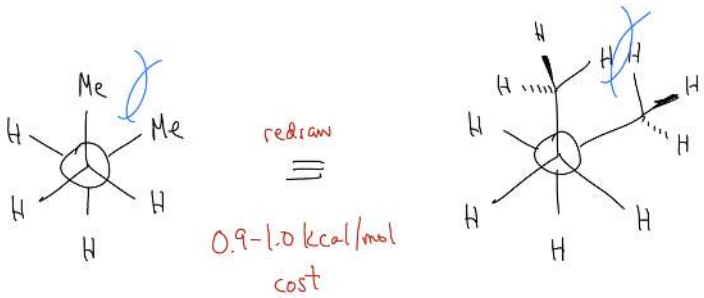
Notice that the energy differences between the various conformers are quite different this time. What accounts for this?

1. Torsional strain - now, it is between σ_{C-C} (which is a little longer) and both σ_{C-H} and σ_{C-C}.

2. Hyperconjugation (σ-donation) – now, one particular delocalization is between σ_{C-C} and σ^*_{C-C}. This is highly stabilizing since not only is a σ_{C-C} bond a slightly better donor than σ_{C-H}, but because the σ^*_{C-C} is lower in energy than the σ^*_{C-H} (consider the effects of electronegativity and bond length). Add up all of the other stabilizing effects, and the energy of the staggered conformations go down.



3. **Steric hindrance** - occurs when two groups are too close to each other. Their electron clouds overlap too much, creating electronic repulsion. This is different from torsional strain because the atoms themselves are bumping into each other, not just the bonds. This should explain why the antiperiplanar conformation is more stable (by about 0.9 kcal/mol) than the synclinal conformations. A **gauche interaction**, which is true steric strain, between methyl groups costs about 0.9 kcal/mol.



So, let's summarize our findings:

H/H eclipsed interactions = 0.9-1.0 kcal/mol per bond

H/CH_3 eclipsed interaction = 1.4 kcal/mol per bond

CH_3/ CH_3 eclipsed interaction = 2.4 kcal/mol per bond

CH_3/ CH_3 gauche interactions = 1.0 kcal/mol per bond

Look back at your potential energy diagrams to convince yourself that these values are accurate! What this all should mean is that in alkanes, the antiperiplanar staggered conformation will be the lowest in energy – this is why we draw alkanes in line-angle notation with a zig-zag! After all, the zig-zag is an antiperiplanar arrangement for the carbon skeleton.

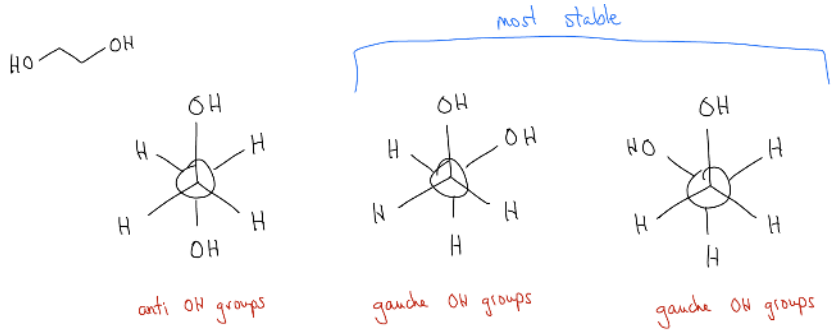
3.2: Conformations of Acyclic Hydrocarbons is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

3.3: Conformations of Substituted Hydrocarbons

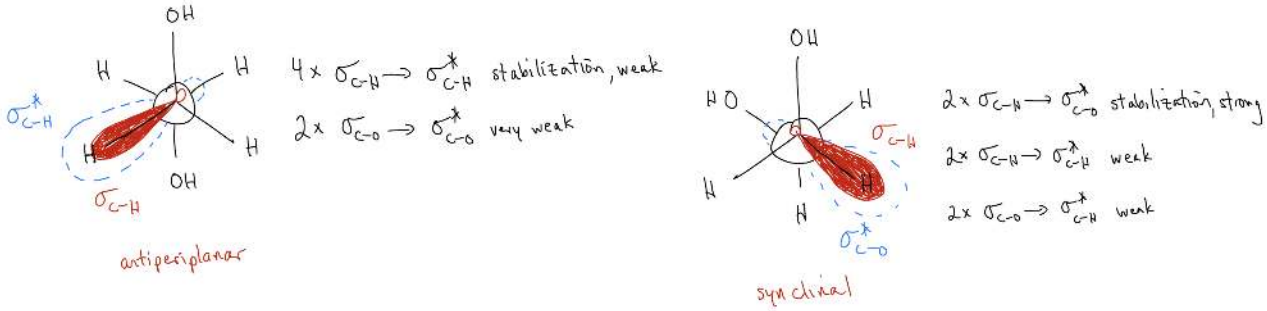
B. Conformations of substituted hydrocarbons

We have said that for straight chain or branched hydrocarbons, the most stable conformation will be staggered and preferably antiperiplanar (if not, at least minimizing gauche interactions). This is due primarily to three principles: torsional strain, σ-donation, and steric strain. It turns out that steric factors are not as strong as electron factors (torsional and σ-donation). Here's why:

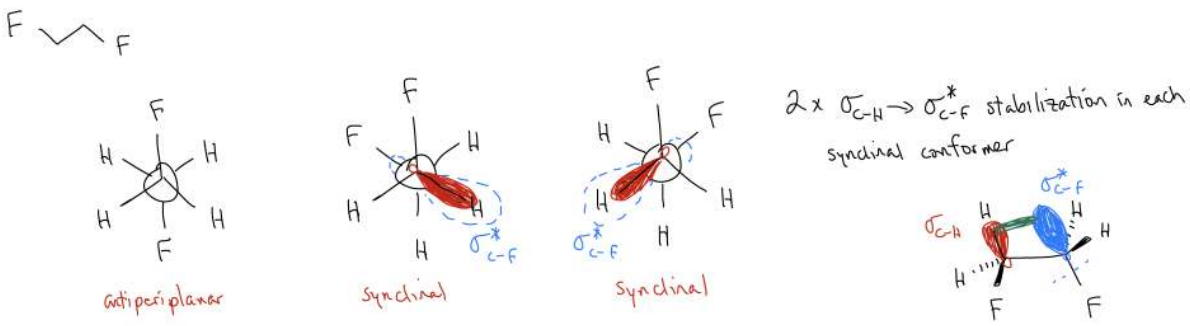
Consider the molecule ethylene glycol, a common component of antifreeze. Draw the three most stable conformations down the barrel of the C-C bond:



Which of these is more stable? It is actually the gauche conformations! While in the antiperiplanar conformation there is minimal steric clash, the delocalization of electrons between σ_{C-H} and σ^*_{C-H} is weak. However, in the two gauche conformations, the delocalization of electrons is between σ_{C-H} and a much lower energy σ^*_{C-O}. There are two such interactions and since σ^*_{C-O} is lower in energy due to electronegativity, this has a powerful stabilizing effect for the electrons in σ_{C-H} (they can delocalize into a much lower energy orbital). This cannot happen in the antiperiplanar conformation.

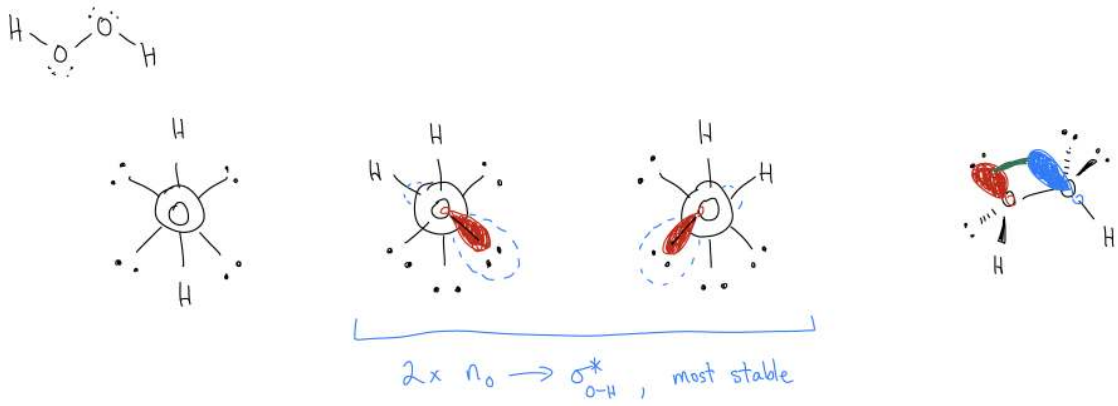


Here's another example. Draw the three most stable conformations for 1,2-difluoroethane and decide which is the most stable.



Again, there is better σ-donation between σ_{C-H} and σ^*_{C-F}. Overlap of these orbitals creates a new molecular orbital with even lower energy than before! This is called the gauche effect.

One more example, this time involving lone pairs. Draw the most stable conformations for hydrogen peroxide:



This time, the two gauche conformations have nonbonding electrons on oxygen (n_O) that can delocalize into a low lying antibonding orbital (σ^*_{O-H}). Nonbonding electrons are always higher in energy than σ electrons, so the maximum stabilization occurs in the gauche conformation again.

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CHAPTER OVERVIEW

4: Rings

4.1: Cyclohexane Ring Conformations
4.2: A-values and Equilibrium Ratios
4.3: Converting Between Chair Conformations
4.4: Other Ring Conformations
4.5: Fused Ring Systems

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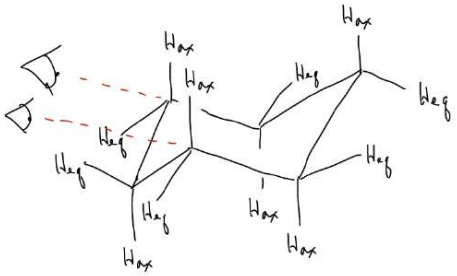
4.1: Cyclohexane Ring Conformations

Rings are ubiquitous in organic chemistry. Like their straight-chain cousins, they also have conformations. Due to their cyclic nature, however, they have fewer degrees of freedom because they cannot rotate completely about their σ bonds.

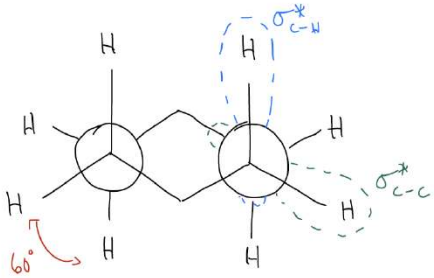
Let's start with the conformation of cyclohexane. Even though we draw cyclohexane like a hexagon on a page, cyclohexane itself is not flat. Because of the tetrahedral carbon atoms in the ring, each of the bond angles is 109.5°. This makes the cyclohexane ring pucker to give it three-dimensionality. We say that cyclohexane exists in a **chair conformation** in its most stable form. There are actually two chair conformations for cyclohexane - I like to arbitrarily call them the "**right-handed**" and "**left-handed**" chair conformations - which exist in equilibrium with each other. Since there is no substitution on the ring, the ratio of the left-handed and right-handed chair is equal to one.



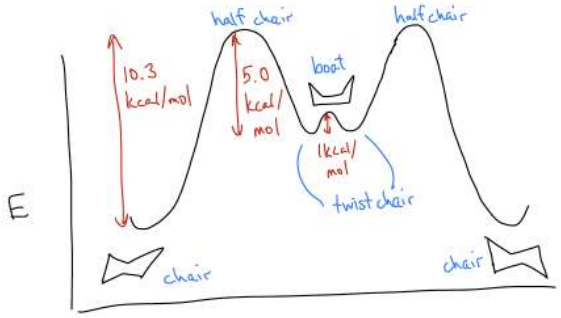
Each carbon atom in the ring has what are known as **axial** and **equatorial** substituents. Axial substituents point directly above and below the "plane" of the ring, while equatorial substituents form a circle around the "equator" of the ring. Notice that as you move around the ring, axial substituents alternate "up" and "down" if looking from the top ("bird's eye view"). Likewise for equatorial groups. This is best seen by building a model of cyclohexane and placing it into its chair conformation.

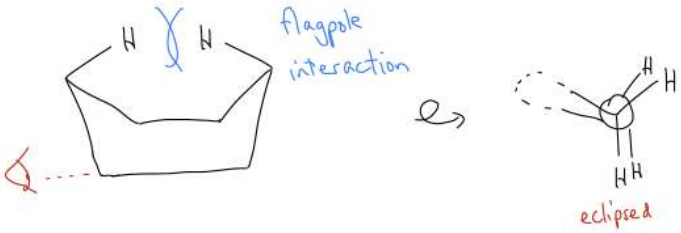


Why does cyclohexane adopt this conformation? Let's consider what happens when we look down the C_2-C_3 and C_6-C_5 bonds simultaneously. What you might notice is that the chair structure is in the staggered conformation – the dihedral angles are all 60° and there is maximum overlap between the various σ_{C-H} and $\sigma^*_{C-H}/\sigma^*_{C-C}$ orbitals. So, how would you convert from one chair to another, and why does it matter? Just like when converting between alkane conformers, we can draw a potential energy diagram that describes how one would convert between the right- and left-handed chair. At room temperature, an unsubstituted cyclohexane ring has enough energy to overcome several activation barriers, and proceeds through several intermediates and transition states.



Why is the boat conformation so high in energy? It turns out that there is a **flagpole interaction** between the H atoms on C_1 and C_4 that causes steric strain. If we look closer, however, we can also see an electronic argument that speaks to its higher energy. If we look down the C_2-C_3 or C_6-C_5 bonds, we see that all of the bonds are eclipsed. This increases the torsional strain of the molecule, driving up the energy compared to the chair conformation.



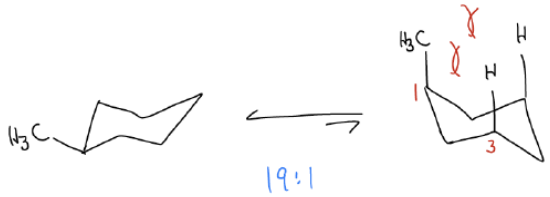


I want you to practice drawing *perfect* cyclohexane chair conformations, since we will come back to this conformation again and again throughout the semester.

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4.2: A-values and Equilibrium Ratios

So, why do we care about chair conformations? Well, most of the time things aren't as simple as cyclohexane. Usually, rings have substituents on them. It turns out that as soon as you put a substituent on the cyclohexane ring, you perturb the equilibrium. Consider the following:

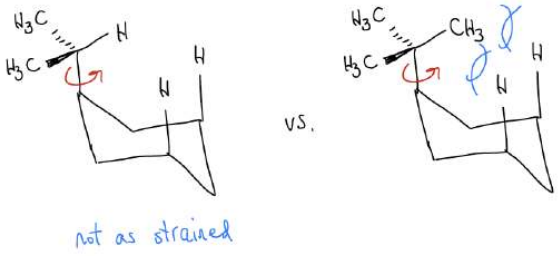


The difference in energy between the right- and left-handed chair is 1.7 kcal/mol. This means that the ratio of the chair structures where CH_3 is equatorial and axial, respectively, is 19:1 (in other words, favoring the CH_3 group in the equatorial position). This happens because a specific type of steric interaction known as a **diaxial interaction**. Axial substituents that are in a 1,3-relationship on a ring will prefer to be equatorial because they bump into each other when axial (but lie far apart when equatorial).

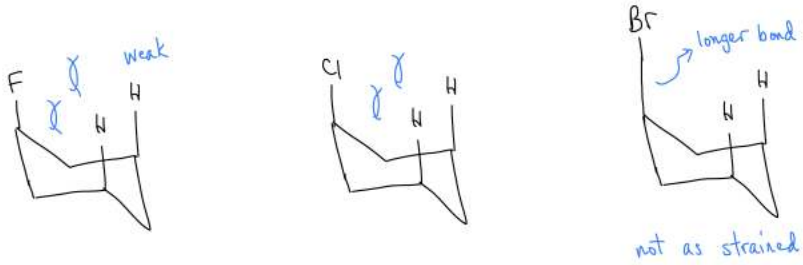
Can we quantify or predict these ratios? **A-values** tell you the energetic preference for a substituent in the equatorial position.

Group	A-value (kcal/mol)
Me	1.7
Et	1.8
iPr	2.2
tBu	5.0
F	0.24
Cl	0.53
Br	0.48
I	0.47

If we take a close look at these numbers, we see a few peculiarities. In the case of the hydrocarbons (Me, Et, iPr, tBu), we see that there is a slight increase in energy as one proceeds from Me to Et to iPr, but then there is a big jump in A-value for tBu. This happens because you can always rotate a Me, Et, or iPr group in a chair conformation so that a H atom points over the middle of the ring. For a tBu substituent, this cannot happen. One of the methyl groups of the tBu substituent will point over the ring and cause a lot of steric strain. This is called a **syn-pentane interaction**. It's like trying to fit 7 atoms in a space that geometrically can only fit 6!



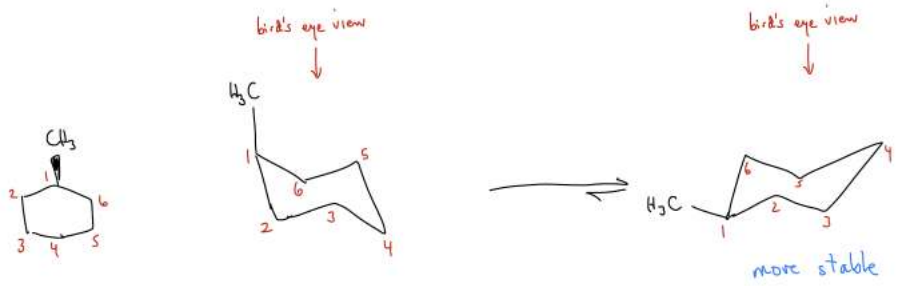
The trend in the A-values for the halogens is also counterintuitive. Chlorine is certainly bigger than fluorine, and indeed it has a higher A-value. But this does not hold true for the rest of the series. Br and I are bigger atoms, so one might expect that they have greater A-values. However, since the C-Br and C-I bonds are much longer, this effect is negated, and the A-value goes down.



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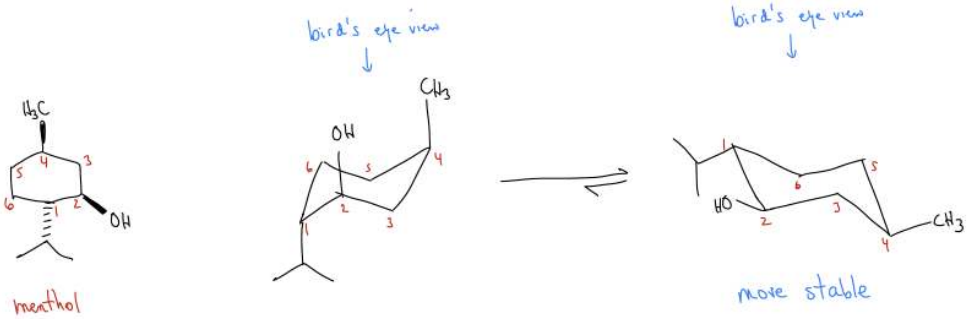
4.3: Converting Between Chair Conformations

How do you convert between one chair and another so that you can decide which chair will be more stable, or which side of the equilibrium will be favored? Essentially, you take the apex at C_1 and C_4 and bring them "down" and "up," respectively. When this occurs, what *was* axial now becomes equatorial and what *was* equatorial becomes axial. In *all* cases, a substituent that was marked by a wedge or a dash in a 2-D drawing will remain that way, but in the chair conformation, the wedge might means axial "up" instead of equatorial "up" depending on whether it is a right- or left-handed chair. In both cases, a "bird's eye view" will reinforce that the stereochemical orientation of a particular group has not changed.



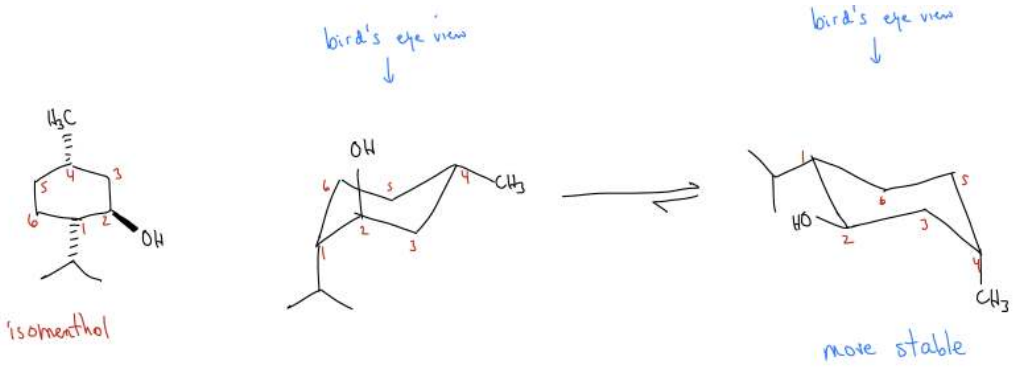
As an example, what is the most stable chair conformation for menthol?

1. First, draw one chair conformation (this can be done arbitrarily)
2. Number both the 2-D drawing AND the chair conformation clockwise or counterclockwise (stay consistent).
3. Place substituents on the ring in either axial or equatorial positions depending on how they are represented with dashes or wedges in the 2-D structure.
4. Perform the ring flip by moving C_1 and C_4 "down" and "up" respectively. Renumber the ring clockwise (or counterclockwise, staying consistent).
5. Decide which conformation is lower in energy based on A-values.

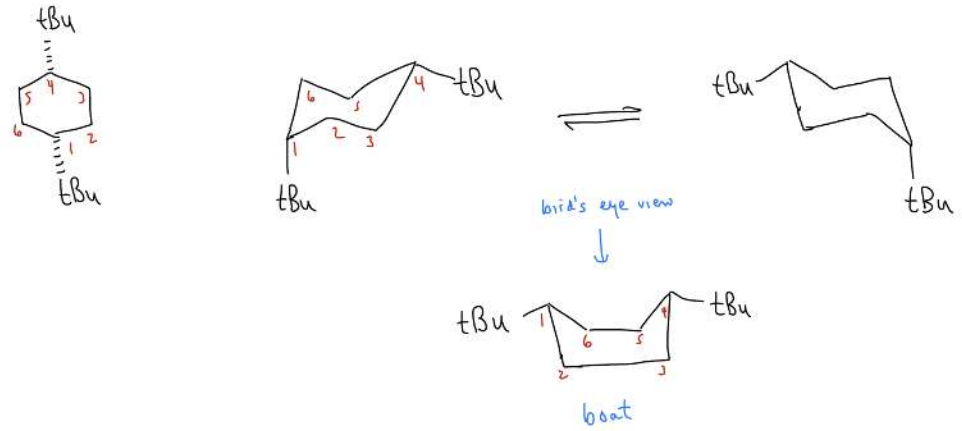


Since all substituents are equatorial in the left-handed chair, it is more stable.

Consider isomenthol, a diastereomer of menthol. What is the most stable conformation of isomenthol?



Consider 1,4-di-tert-butylcyclohexane. What is the most stable conformation of this molecule? You might notice that both conformations have one tBu group axial and the other equatorial. So, which one is favored? Neither! Here, the most stable conformation is no longer a chair, but rather the boat conformation. Since you can get both tBu substituents in an equatorial position, the boat conformation is more stable.



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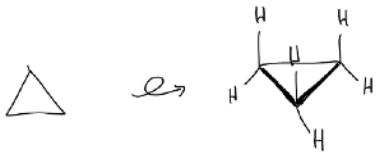
4.4: Other Ring Conformations

While cyclohexane-like rings are most common, there are certainly other types of rings besides **six-membered rings**. Cyclohexane is the most stable of all ring because each carbon atom has the ideal 109.5° bond angles for each tetrahedral atom. As you reduce the size of the ring, this angle decreases dramatically, leading to **angle strain**. Since this occurs in a ring, we call it **ring strain**. For a cyclohexane ring, there is no angle or ring strain. So if the idealized geometry is 109.5°, what happens in the other rings?

Cyclopropane

bond angles are forced to be 60°

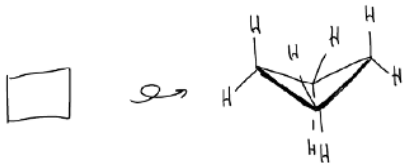
all C-H bonds eclipsed (torsional strain)



Cyclobutane

bond angles are forced to be roughly 90°

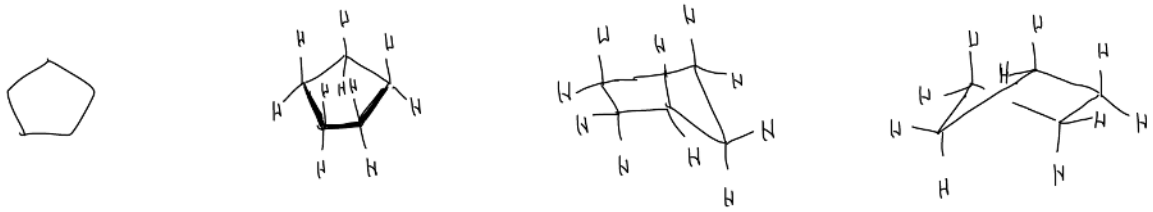
"puckered" conformation reduces eclipsing



Cyclopentane

bond angles are roughly 108°

three different conformations:



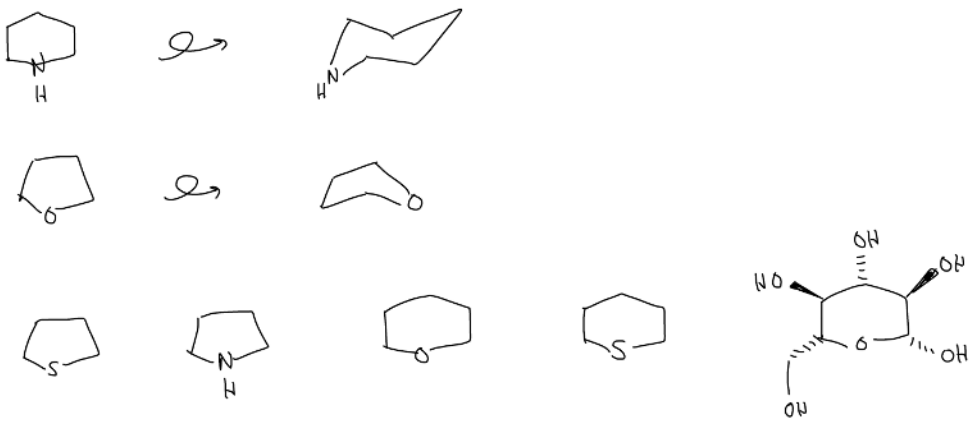
planar

envelope

half-chair

Heterocyclic rings

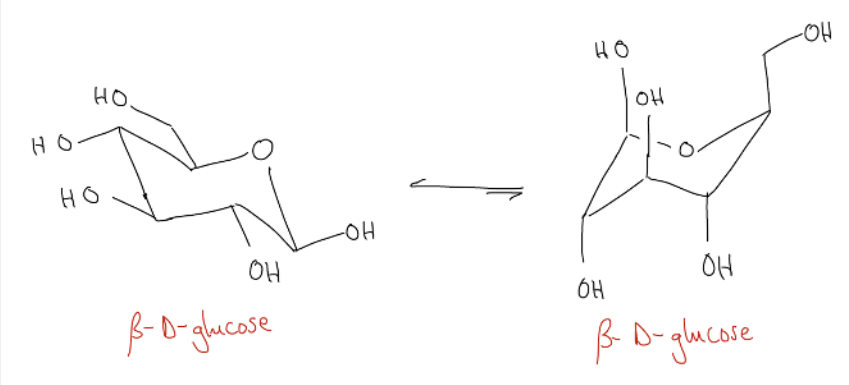
Another level of complexity is when heteroatoms are found in rings. These rings will adopt conformations similar to their well-known all-carbon counterparts.



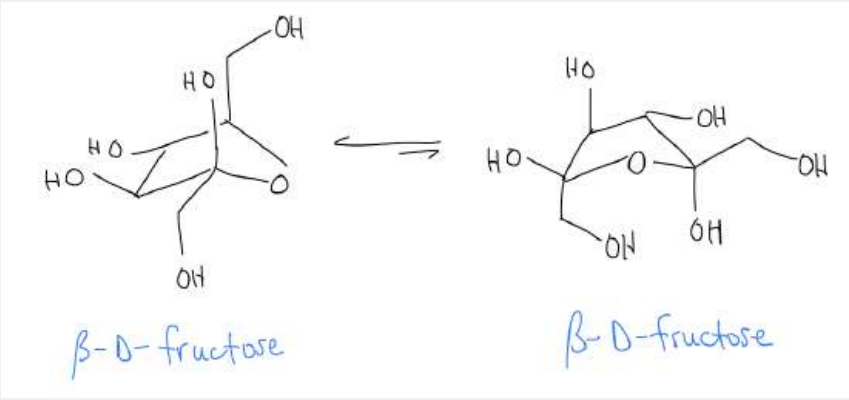
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Biomedical Spotlight

As we will see in the chapter on stereochemistry, carbohydrates can exist in both their straight-chain form and ring-like form. Under physiological conditions, the ring-like form predominates, and the rules for determining which ring conformer is most stable will still apply. Consider the ring conformations of the sugar glucose ($C_6H_{12}O_6$). Two chair conformations will result in which one of the carbon atoms has been replaced by an oxygen atom. However, we can still see the axial and equatorial substituents alternating around the ring. We know from our discussion of A-strain that substituents like to be equatorial, so the β-D-glucose form that contains more equatorial substituents will be more stable, shifting the equilibrium to the right.



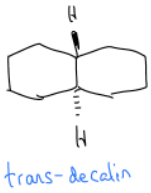
However, consider the example of fructose (also $C_6H_{12}O_6$), which also exists under physiological conditions in a ring-like conformation. This time, due to the connectivity of the molecule, a five-membered ring forms. The envelope conformation will predominate, and pseudo-axial and pseudo-equatorial substituents will alternate around the ring. In the case of β-D-fructose, the equilibrium will favor the envelope in which only two substituents are pseudoaxial.



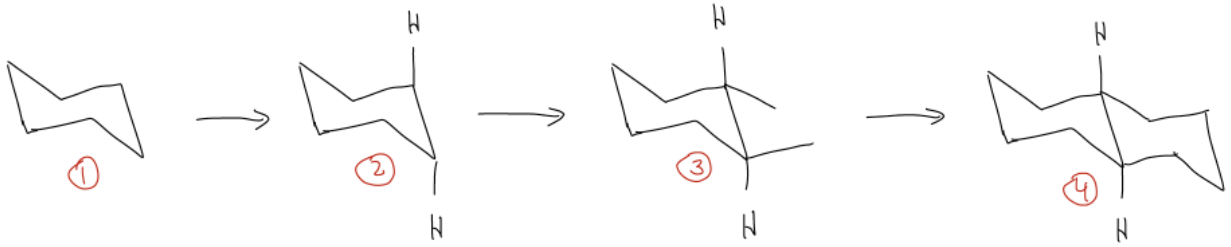
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4.5: Fused Ring Systems

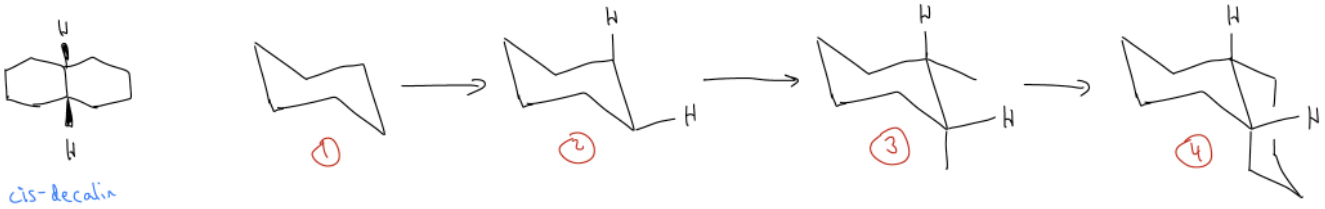
We have already discussed isolated ring systems, but what about rings that are fused with other rings – how might their conformations change? Well, nothing really changes except that the rings are fused. Fused rings still adopt the most stable ring conformations. In the case of six-membered rings, this would be the chair conformation. Consider the molecule *trans*-decalin, which is a set of fused six-membered rings where the hydrogen atoms at the ring fusion carbons are trans.



1. Start by drawing a chair conformation for one ring
2. Place the substituents on the ring fusion carbons, according to their stereochemistry depicted in the 2-D drawing
3. Finish the rest of the conformation

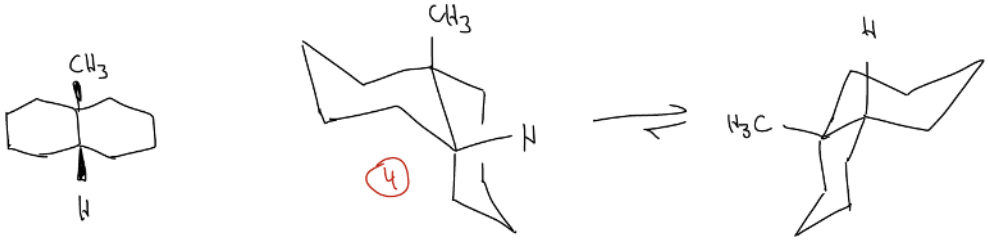


What about rings that are *cis*-fused? We follow the same set of steps. Consider *cis*-decalin:



Quick question: which of these two rings, *cis*- or *trans*-decalin is more stable? *Trans*-decalin, of course, because it places substituents farther away from each other. There are no gauche interactions in the *trans*-decalin.

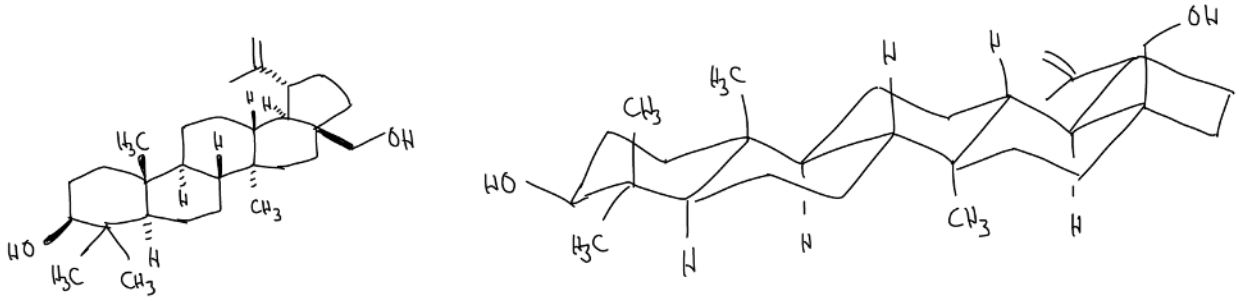
How would you perform a ring flip for a *cis*-decalin? We would need to do this in order figure out which conformation is most stable Let's take one example, shown below. This ring flip is hard to visualize, so build a model, do the ring flip, and then redraw what you see.



What about a ring flip for a *trans*-decalin? It can't be done - this conformation is locked! You can't move the two equatorial bonds axial, nor can you move the two axial substituents equatorial - this is a constraint of the system itself.

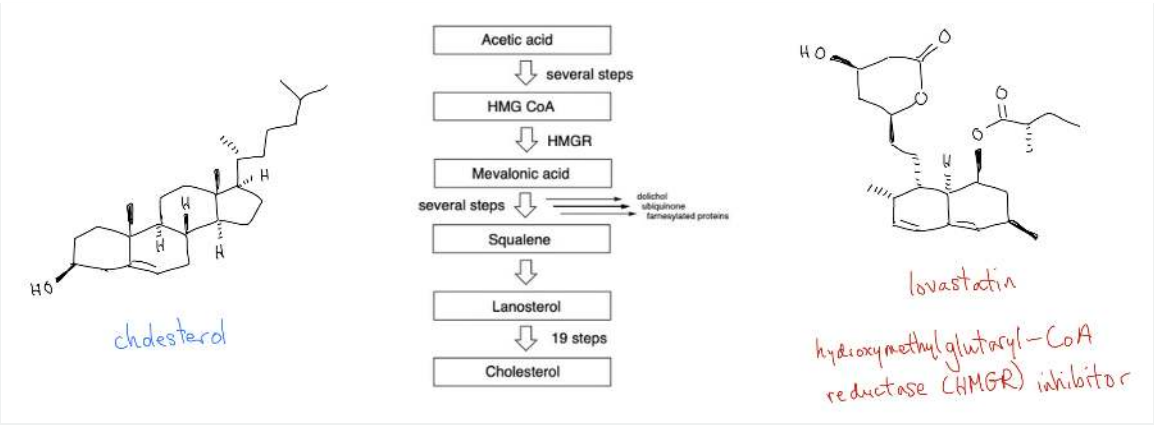
Putting all of this together means that we can draw conformations of complex polycyclic systems. Consider the first molecule you came across this semester, betulin:

1. Start with one of the 6-membered rings and work outward
2. Connect the rings in a systematic fashion as before!



Biomedical Spotlight

Steroids are polycyclic, fused hydrocarbons that play an important role in biological processes. The main sex hormones - estrogen and testosterone, for example - have similar structures that play a huge role in the development of male and female characteristics throughout the life cycle. Another important steroid is cholesterol, which is essential for health and well-being. Cholesterol is a major component of the phospholipid bilayer that give cells their structure and function, it is a precursors to the bile acids that aid in the digestion of fats, and it gets converted into many of the steroids needed for cell signaling and regulation (including estrogen and testosterone). But, like most small molecules, too much of it can be a problem. Elevated blood levels of cholesterol are linked to atherosclerosis (hardening of the arteries) and increased risk of heart attack and stroke. We get cholesterol from our diet, but it is also made endogenously. Decades ago, chemists identified the biosynthetic pathway for cholesterol. More than 30 steps are needed to make cholesterol from acetic acid, all of which involve carefully regulated enzymatic activity. In the 1970s, Merck saw an opportunity to use this pathway to solve a growing health problem. Merck scientists hypothesized that cholesterol levels could be reduced to acceptable levels by inhibiting the activity of the protein hydroxymethylglutaryl-CoA reductase (HMGR). This enzyme converts HMG-CoA to mevalonic acid, but it is the slowest enzyme in the 30-step sequence. Years of work were needed to identify a small molecule that could inhibit HMGR *in vitro*, reduce cholesterol levels in clinical patients, and be safe for human consumption. The result were the statin drugs, of which Merck's lovastatin (Mevacor™) is a leading member. The statins are multi-billion dollar drugs that have had an tremendous impact on reducing high cholesterol in patients, thereby significantly reducing heart disease and stroke as leading causes of premature death.



Adapted from Hallelujah Moments, by Eugene Cordes, 2014

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CHAPTER OVERVIEW

5: Analytical Methods for Structure Elucidation

5.1: The Physics of Nuclear Magnetic Resonance Spectroscopy

5.2: Determining the Number of Signals in NMR Spectroscopy

5.3: Factors That Influence NMR Chemical Shift

5.4: Infrared Spectroscopy

5.5: Mass Spectrometry

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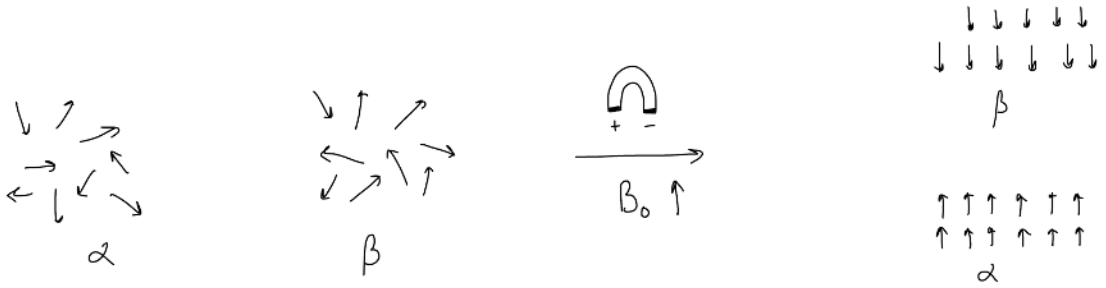
5.1: The Physics of Nuclear Magnetic Resonance Spectroscopy

Spectroscopy is the study of the interaction of matter with light, or energy form the electromagnetic spectrum. Since we cannot visually observe the atoms and bonds in a molecule, we must use indirect techniques to determine a molecule's identity. Spectroscopy allows us to infer clues into molecular structure based on the behavior of the molecules as they interact with different wavelengths of light. For example, microwave energy light causes molecules to tumble. Infrared wavelength light causes bonds to vibrate. Ultraviolet light causes electronic excitations. And on and on.

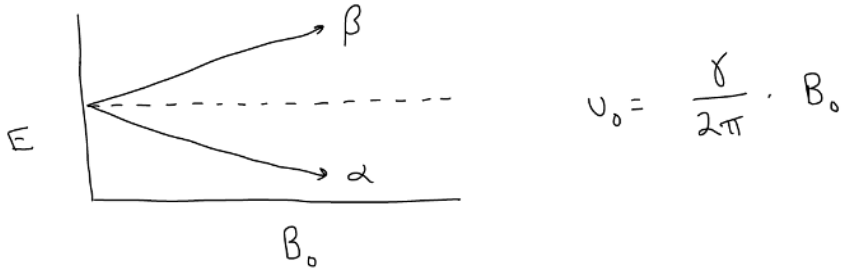
Nuclear magnetic resonance (NMR) spectroscopy is a tool that we use to elucidate molecular structure. It involves the absorption of low energy radiowaves. Radiowaves cause nuclear spin transitions, and NMR will detect what happens when this increase in energy is released in the presence of a magnetic field. This technology was the precursor for the development of the modern MRI machine.

In order to understand why this occurs, it is important to review a little physics. Just like an electron, inherent to any **nucleus** is a **spin quantum number** known as "I." I can be any integer, half-integer, or zero, but only nuclei that have non-zero spin quantum numbers are NMR-active (that is, we can see differences in their interaction with radiowaves). For all elements with even atomic numbers, I = 0. On the other hand, for the most useful nuclei in organic chemistry, we've luckily hit the jackpot - ^{1}H and ^{13}C nuclei have I = ½. For a given nucleus, the number of spin states is equal to 2I+1. So, for both ^{1}H and ^{13}C nuclei, the number of spin states is two: + ½ (or α) and – ½ (or β).

The most important feature of NMR is that in the absence of a magnetic field, all of the spin states are degenerate. The orientations of the spins are completely random and they are equal in energy. But since nuclei are themselves charged and moving, they possess angular momentum and thus generate a magnetic field. This causes the states to lose their degeneracy when a magnetic field is applied externally. Let's look at this pictorially. When no magnetic field is present, the α and β states are random and equal in energy. When an external magnetic field (B_o) is applied, the α state becomes slightly lower in energy than the β state. Each of the spins aligns with the magnetic field for α or against the magnetic field for β, and the number of spins in the α state is slightly greater than the β state (this is known as a Boltzmann distribution).



This is an important distinction and is the only reason why NMR works. If we were to plot energy versus the applied magnetic field, we see that as the magnetic field gets bigger, the difference between the α and β states gets bigger. This is known as **Ziemann splitting**. Absorption of the appropriate wavelength of light, then, will cause a spin to "flip" from the α state to the β state. For organic molecules, low energy radiowaves are energetic enough to promote this transition. The **Larmour equation** relates the frequency of this transition to the applied magnetic field:

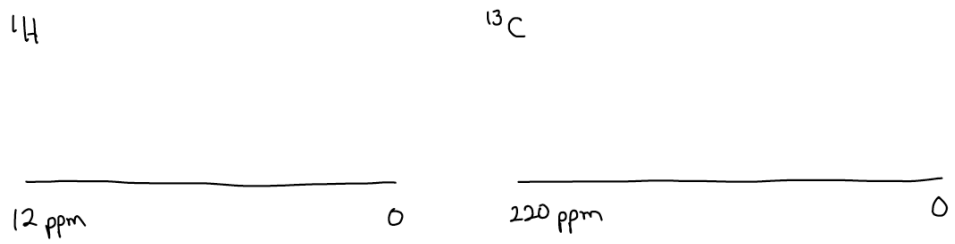


This frequency is different for each nucleus (conveniently for us, otherwise the signals would all overlap), with the distinguishing factor being the g value, which is the **magnetogyric ratio**, or how good a magnet a particular nucleus is. For example, the proton has a higher γ value than a carbon atom, so it's Larmour frequency is also larger.

Let's take a closer look at the Larmour equation and Ziemann splitting. Let's say we were to use an NMR spectrometer that has a 70.5 kG magnet. The frequency of light needed to promote an α to β spin flip for a proton would be 75 MHz. But what if you take a spectrum at a higher or lower field instrument? Or, perhaps more likely, what if you want to compare your spectrum to a spectrum reported in the literature that was taken on a 60 kG machine. We know that as the magnetic field changes, the Larmour frequency also changes, so in order to compare spectra, we instead use a relative scale known as the δ scale, or **chemical shift**. The δ scale is reported in parts per million and is equal to:

$$(\nu_i - \nu_{TMS})/n_o \times 10^6$$

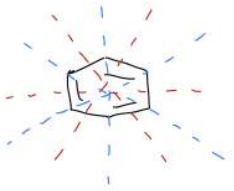
where the shifts are all reported relative to tetramethylsilane (TMS). ν_i is the frequency of the desired peak and ν_o is the idealized Larmour frequency. ν_{TMS} is obviously the frequency of the α to β spin flip for TMS. For the two most important nuclei, the chemical shift spectral width ranges from roughly 0-12 ppm for ^1H and 0-220 ppm for ^{13}C.



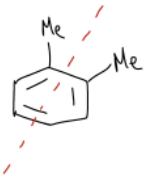
5.1: The Physics of Nuclear Magnetic Resonance Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

5.2: Determining the Number of Signals in NMR Spectroscopy

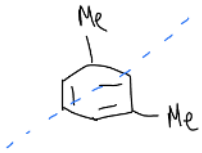
Let's take a look at how the structure of a molecule affects the number and type of peaks we see in the NMR spectrum. For simplicity, let's focus only on ^{13}C nuclei. The first thing we need to worry about is something known as **magnetic equivalency**. The total number of signals (or resonances) for a particular nucleus may not exceed the total number of those nuclei in the molecule, but it *may* be less. This happens when there is **symmetry** in the molecule, for example when there are **mirror planes** or **rotational axes**. Let's look at a few examples and determine how many ^{13}C signals would exist in an NMR spectrum. Benzene has the structure shown below. Since it has six carbon atoms, it's NMR spectrum could have a total of six signals maximum. However, there are lines of symmetry in this molecule – six of them to be exact – which causes each of the carbon atoms to become magnetically equivalent. Therefore, we only see one signal in the NMR spectrum for benzene. All of the ^{13}C nuclei in benzene are magnetically equivalent and share the same frequency.



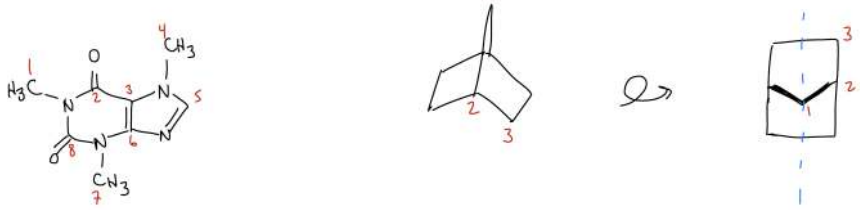
The next example is 1,2-dimethylbenzene. There are eight carbon atoms total, so the maximum number of signals is eight. However, there is a mirror plane through the center of the molecule. This reduces the number of signals in half because nuclei that are on either side of the mirror plane are magnetically equivalent. There are four signals total.



In 1,3-dimethylbenzene, there are still eight signals maximum, but this time there is a mirror plane that bisects the molecule in which two of the carbon atoms sit directly on the mirror plane. The total number of signals that we see is five because the nuclei that are *on* the mirror plane are unique.

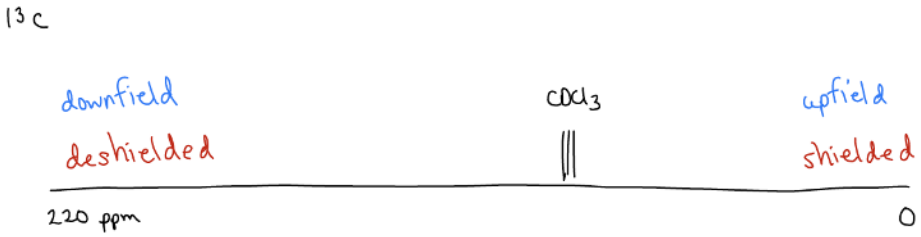


In certain cases, there is no element of symmetry. The molecule caffeine, for example, has eight carbons. There are no planes or axes of symmetry in caffeine, so we observe eight signals total. Finally, just because a molecule looks complex, such as bicyclo[2.2.1]heptane, does not mean that the ^{13}C NMR spectrum is overly complex. There are a total of seven carbon atoms in this molecule, but a plane of symmetry exists in the molecule directly through the center. Thus, we see only three carbon resonances in the NMR spectrum. This is much easier to see if you were to build a model and rotate it so that you are looking at the molecule from the front.



The same symmetry rules apply for ^{1}H nuclei. Go back and see if you can identify how many ^{1}H signals you would find in the ^{1}H NMR spectrum for each of the molecules above.

Another factor that affects any NMR spectrum is the chemical shift, which tells us about the electron density around a particular nucleus. This allows us to deduce the molecules' connectivity. The typical ^{13}C spectrum has a spectral width of 0-220 ppm. We normally dissolve our sample in deuterochloroform ($CDCl_3$), which will give its own signal at 77.0 ppm. The right hand side of the spectrum (or lower ppm) is called **upfield**, and nuclei in this region are considered **shielded**, while the left hand side of the spectrum (higher ppm) is called **downfield**. We say that nuclei in this region are **deshielded**.



The Larmour equation will take into account small changes in the local environment, which will change the resonant frequency ever so slightly. How does this happen? Well, shielding will occur because the local environment will reduce the full effect of the applied magnetic field. This happens when more electron density surrounds a particular nucleus. Shielding will shift nuclei upfield. Deshielding, on the other hand, will shift nuclei downfield, because now the nuclei are experiencing the full effect of the magnetic field, and perhaps even more. Nuclei that do not have a lot of electron density around them will thus be shifted downfield.

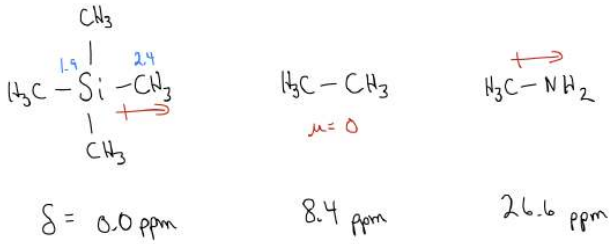
$$\nu_i = \frac{\gamma}{2\pi}(B_o - B_{local})$$

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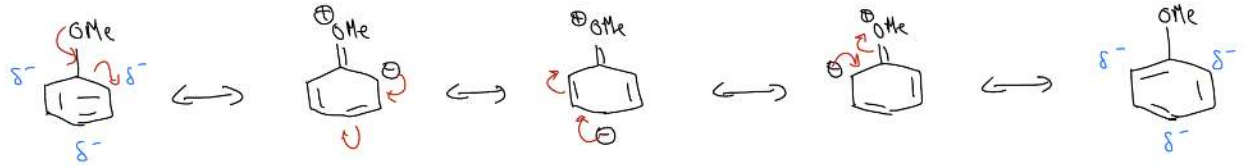
5.3: Factors That Influence NMR Chemical Shift

So, what kinds of structural factors influence downfield or upfield shifting?

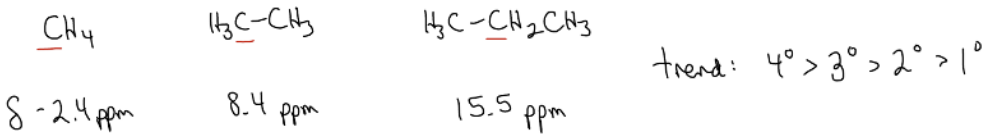
1. **Inductive effects**. Consider the molecules tetramethylsilane, ethane, and methylamine. The dipole moment of the C-Si, C-C, and C-N bonds are quite different and are based on electronegativity. We observe this effect in the NMR since TMS will have a shift at 0 ppm, ethane comes at 8.4 ppm, and methylamine is shifted downfield to 26.6 ppm. Thus, electronegative atoms will move the frequency downfield, but it is important to note that inductive effects only last for 1-2 bonds.



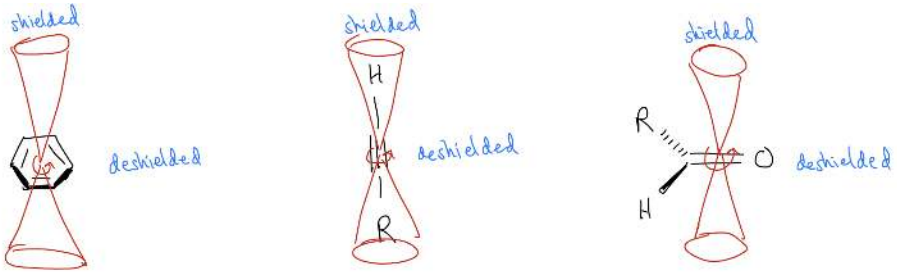
2. **Resonance**. In anisole (or methoxybenzene), the lone pairs on oxygen are delocalized into the aromatic ring. We can draw a resonance structure that places negative charge on one of the ring carbon atoms, and then draw two more resonance structures that place negative charge on alternating carbon atoms. The net result is that each of those carbons atoms will have a partial negative charge. This means there is more electron density at those positions. This has a shielding effect on the chemical shift, so these carbons will resonate more upfield.



3. **Substitution**. Methane, ethane, and propane have different chemical shifts for the carbon atoms. Increasing the substitution will shift the resonant frequency downfield. Thus, the trend is that quaternary carbons are most downfield, followed by tertiary, secondary, and primary, which is the most shielded and most upfield of the four.

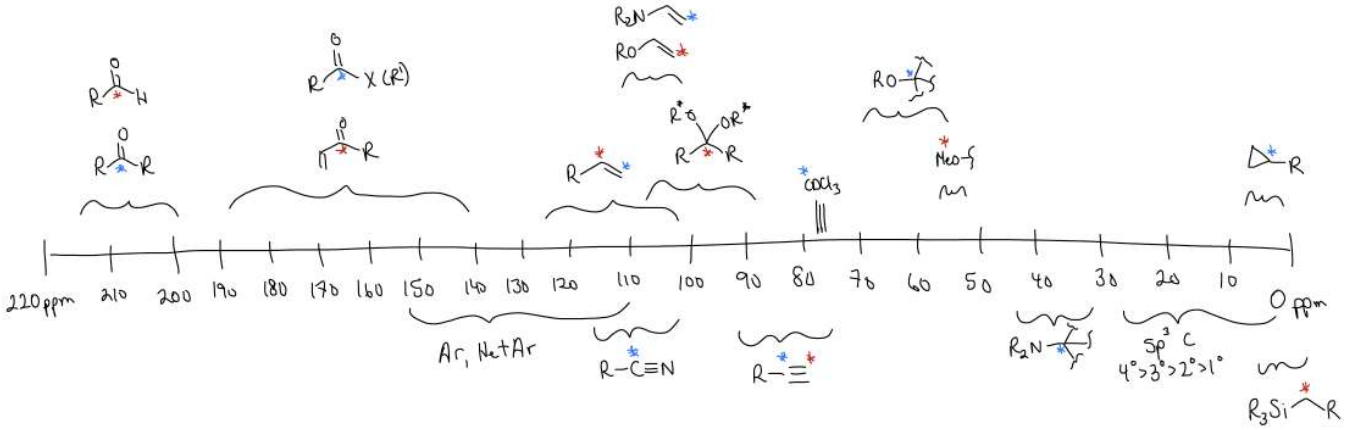


4. **Magnetic anisotropies**. Electron movement in bonds will create magnetic fields, which of course can change the local magnetic environment of a particular nucleus. Consider the molecule benzene. The electrons in the ring are fully delocalized and are moving in a circle around the ring. This creates a magnetic field itself, with two different zones, a **shielding zone** and a **deshielding zone**. Nuclei that are in the deshielding zone, such as the protons shown, will be shifted downfield. Any nucleus in the shielding zone will be shifted upfield. The same thing occurs for alkynes, and it is the reason why the methyl groups in this alkyne are shifted so far upfield. Another example is the ketone, whose carbon atoms lie in the deshielding zone, and are thus shifted more downfield.



Chemical Shift for ^{13}C:

Here are some common functional groups and their corresponding chemical shift ranges for the ^{13}C nucleus:



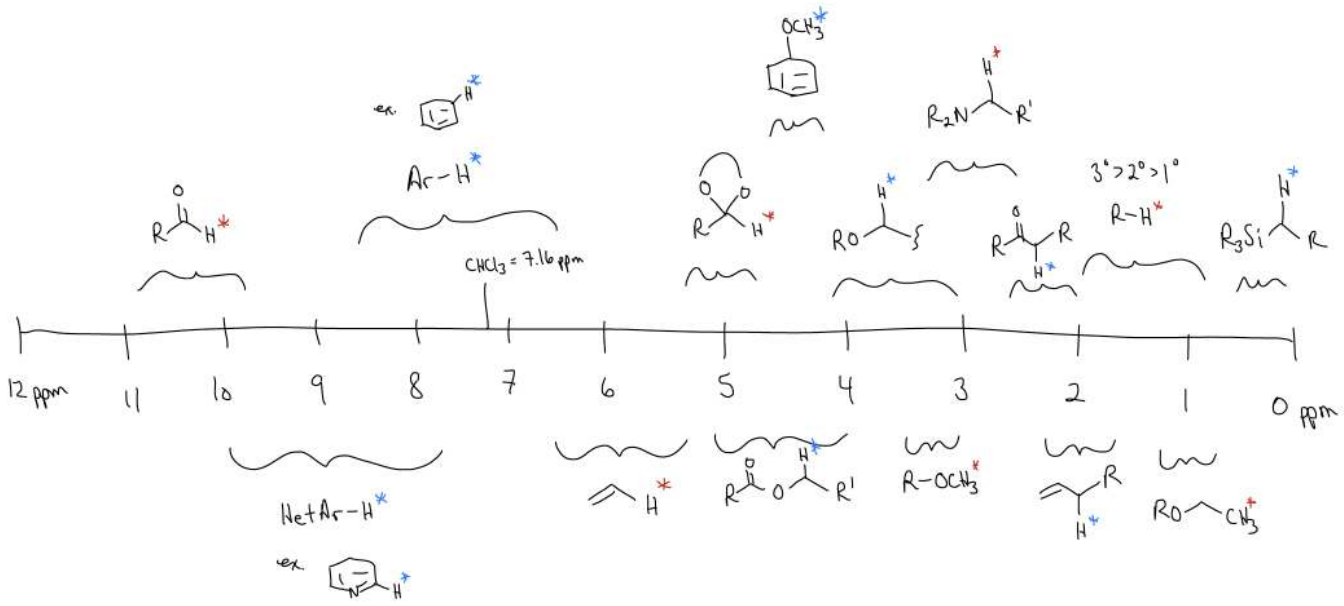
^{1}H NMR Spectroscopy

We've talked a lot about ^{13}C NMR (mainly because it is simpler than other nuclei), but there are a few key differences in ^{1}H NMR spectroscopy that make it indispensable for structure elucidation.

1. The natural abundance of ^{1}H is 99.9%, while the natural abundance for ^{13}C is 1.1%. This means you can run a ^{1}H spectrum in a matter of seconds, but it will take much longer to obtain a ^{13}C spectrum.
2. The magnetogyric ratio is greater for ^{1}H, so there is no overlap in the spectra.
3. **Integration** of peaks (area under the curve) corresponds directly to the number of ^{1}H nuclei with that chemical shift.
4. Proton indirect coupling reveals ***σ***-connectivity (we will cover this second semester)

Chemical Shift for ^{1}H:

Here are some common functional groups and their corresponding chemical shift ranges for the ^{1}H nucleus:



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5.4: Infrared Spectroscopy

Infrared Spectroscopy is used to characterize organic molecules by functional group. Since we cannot visually observe the atoms and bonds in a molecule, we use indirect techniques to determine the functional groups in a molecule.

Let's first talk about spectroscopy as a discipline within chemistry. Spectroscopy is the study of the interaction of matter with energy from the electromagnetic spectrum. In other words, it is the study of what happens to molecules in the presence of difference wavelengths of light. The electromagnetic spectrum in shown in Figure 5.4.1. High energy waves of light have short wavelengths and high frequencies. Examples of this kind of light include x-rays and gamma rays. On the opposite end of the spectrum are radio waves, which have long wavelengths, low frequencies, and low energies. Interaction of different wavelelengths of light have an impact on the behavior of molecules. Radiowaves, for example, cause nuclear spin transitions. Microwaves cause molecules to tumble. Infrared light, which is now higher in energy, causes bonds to vibrate. Visible light gives molecules color. Finally, ultraviolet light causes electronic transitions.

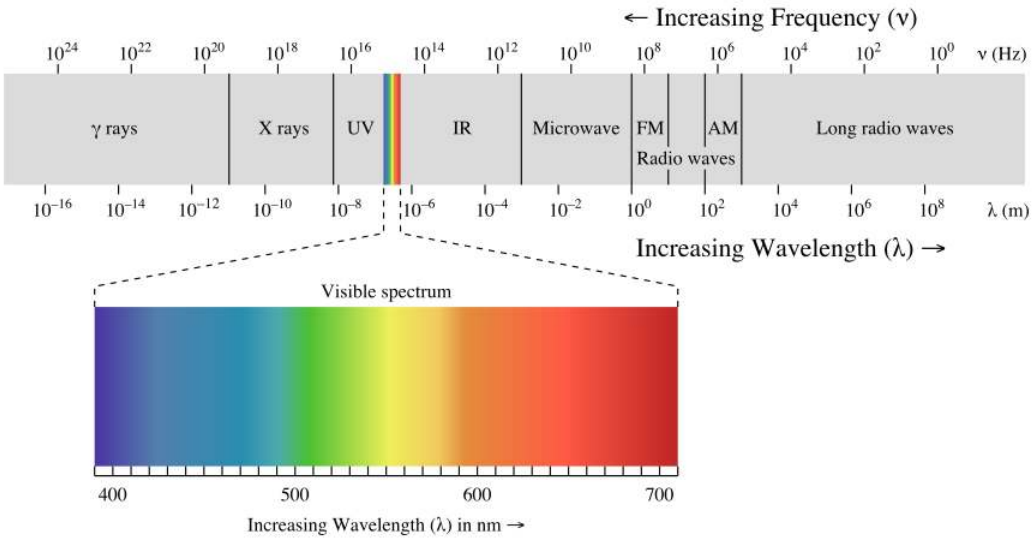


Figure 5.4.1: The electromagnetic spectrum. (CC BY-NC-SA; Brittany Stadler via LibreTexts)

Infrared light causes molecular vibrations. Certain bonds will absorb at specific wavelengths, which will give us information on the strength of the bond and which functional groups are present. An example of an infrared spectrum is shown in Figure 5.4.2. From this spectrum, we can deduce that this molecule contains at least two types of bonds: C-H and C=O. The x-axis is in wavenumbers. A wavenumber is defined as the reciprocal of wavelength. You may recall that energy is equal to Planck's constant times the speed of light (c), divided by the wavelength. Substituting for wavelength, we can also obtain E = hc * wavenumber. A wavenumber is really just the number of cycles of a wave in 1 cm. If one wanted to convert from wavenumbers to wavelength (in this case microns), the equation is simply wavenumbers = 10,000/microns. The y-axis is the percent transmittance (which is the opposite of absorbance (1/A)). When reporting peaks in an infrared spectrum, we use a qualitative approach, where s is an intense peak, m is a moderately sized peak, and w is a weak peak.

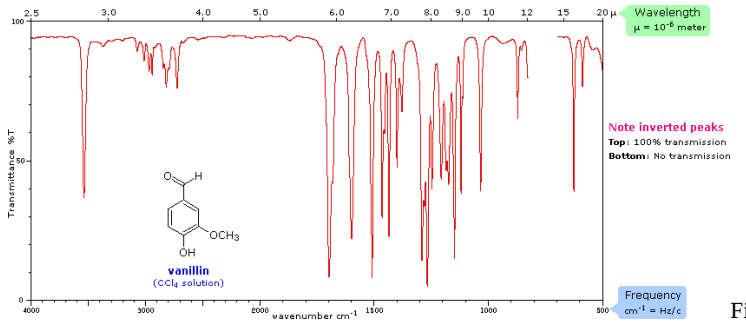


Figure **5.4.2**: Infrared spectrum of vanillin. (CC BY-NS-SA; Delmar Larsen via LibreTexts)

Let's now talk about the theory of IR spectroscopy by considering a spring. If we have a block and a ball connected by a spring in a vacuum and we were to pull them apart, the spring would stretch. The spring now has a high tension and high potential energy. If we then released both structures, the ball and block would bounce back and forth until they came to rest. Thus, a restoring force inherent in the spring would bring the ball and block back to an equilibrium state. Likewise, if we pushed the two together, the spring would compress and the distance between the block and ball would shorten. Again, the spring at this stage would have high tension and high potential energy, such that when you released the block and ball, they would vibrate back and forth until they are at rest. This same analogy can be used for chemical bonds. Instead of a block and a ball connected by a spring, we have two atoms connected by a bond.

So, what kinds of molecular vibrations are there? Well, if we were to extend our analogy of the spring, we would have a diatomic molecule that upon excitation with infrared light would causes stretching of the bond, and then the movement back and forth of each atom. This is called a stretching vibration. In a molecule containing three atoms, there are several modes of vibration, as described in Figure 5.4.3. When both bonds lengthen and shorten at the same time, we call this a symmetric stretching vibration. When one bond shortens and the other lengthens, this is called asymmetric stretching. In the same molecule, there are two types of bending vibrations (scissoring and rocking). Infrared light can cause the bond angle between the atom to decrease, and then increase as it reaches back to equilibrium. In a complex molecule, many types of bonds will be undergoing these vibrations, all at different frequencies and intensities, so the spectra can become quite complicated. But there are a few factors that determine where the vibrational frequency will lie.

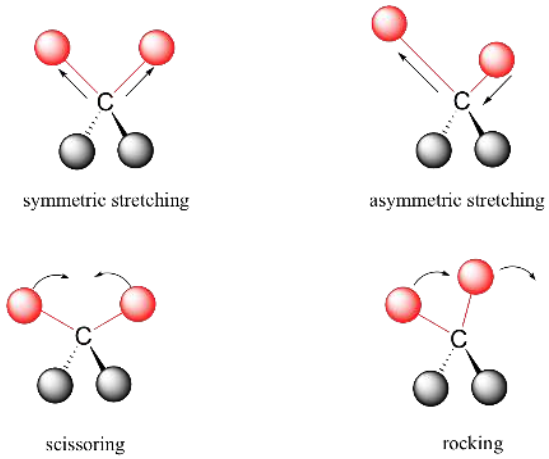


Figure **5.4.3**: Types of vibrational modes. (CC BY-NC-SA; Layne A. Morsch via LibreTexts)

Vibrational frequencies are determined by the type of vibration, the strength of the bond, the masses of the atoms, and by electronegativity. The first factor is the type of vibration. If we were to consider the C-H stretch versus the CH_2 bend, we see that the stretching vibration occurs at higher frequency. This tells us that stretching vibrations require more energy than bending vibrations.

The strength of the bond or bond order also has an impact on frequency. Consider a bond order of 1, we can have C-C, C-O, and C-N single bonds, with frequencies in the range of 1300-800 cm^{-1}. Using the same atoms, but with a bond order of two, a C=C double bond, C-O double bond, and C-N double bond vibrate much higher, at 1900-1500 cm^{-1}. Triple bonds, which are stronger than both

double and single bounds, vibrate at even higher frequencies, roughly 2300-2000 cm^{-1}. Thus, we can conclude that stronger bonds require more force to compress or stretch, which means that they will also vibrate faster than weaker bonds. Thus, frequency increases as bond strength increases. A third factor is the masses of the atoms. If we consider the C-H versus C-D stretch, we see that the C-H stretch is much more energetic than C-D. Hydrogen is a small atom and can vibrate much faster than large atoms. We see this hold true for other atoms bound to hydrogen as well. O-H, N-H, and C-H bonds have high vibrational frequencies. Thus, heavier atoms vibrate more slowly than lighter atoms, so frequency increases as weight decreases.

The final parameter is electronegativity. While electronegativity does not affect frequency, it does effect the intensity of the peak. This is because bond polarity effected absorption intensity. For example, C-C single and double bonds are either weak or moderate in intensity, while C-O single and double bonds are quite strong. This is because as infrared light causes stretching vibrations, bond dipoles will change. If a C=O double bond lengthens, the bond dipole will be stronger. This increases the intensity of the IR band.

Finally, we need to discuss where to find specific bands for functional groups in an IR spectra and develop a strategy for interpreting such data. We can divide the IR spectra into four regions, roughly 4000-2800, 2800-1900, 1900-1200, and 1200-400 cm^{-1}. The first region, above 2800, is characteristic of X-H bonds, or bonds to hydrogen. Triple bonds come at slightly lower frequency, followed by double bonds, and finally single bonds. This final region can be very complex and there are often peaks that overlap. Another name for this region is the fingerprint region.

In the X-H region we have C-H, N-H, and O-H bonds at the frequencies shown. These stretches are correlated to the energies of the respective bonds. Thus, the O-H bond has the highest frequency since it is the strongest bond. One important feature of this region is that alcohols and carboxylic acids can be easily detected because hydrogen bonding causes band broadening. Extensive hydrogen bonding will cause the width of the O-H band to increase. What was roughly 100 cm^{-1} in width is now as much as 600 cm^{-1} in width.

The triple bond region is home to alkynes, at around 2200-2100 cm^{-1}, and nitriles, which are slightly higher. The difference between these two is that a strong bond dipole exists for nitriles due to the electronegativity of N, causes strong bands for nitriles, but weak or moderate bands for alkynes. The double bond region is complex and many types of double bonds exist, such as C=O, C=C, N=O, and C=N. What is most informative is the C=O, also known as the carbonyl functional group. The carbonyl is common to many types of functional groups and their vibrational frequencies come at specific regions of the spectrum, as shown.

Finally, the C-X region is home to single bond vibrations. The problem with this region is its overall complexity. There are so many single bonds in a molecule that this region of the IR spectrum is difficult to interpret. However, just like a fingerprint is unique to each person, the fingerprint region of the IR is unique to each molecule.

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5.5: Mass Spectrometry

A final technique in structure elucidation is mass spectrometry, which allows us to measure the mass of an ion via a mass-to-charge (m/z) ratio.

The basic schematic of a mass spectrometer is shown in Figure. 5.5.1:

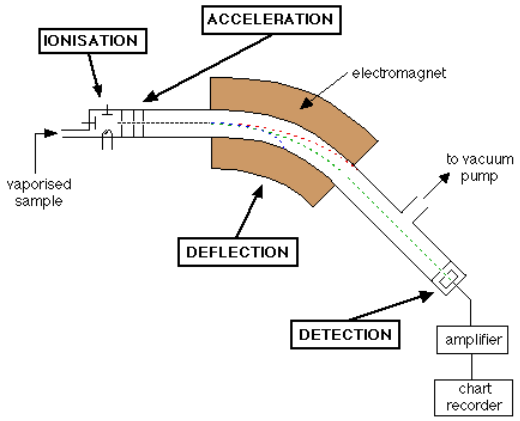


Figure **5.5.1**: Basic diagram of a mass spectrometer. (CC BY-NC-SA; Jim Clark via LibreTexts)

There are four main components:

1. **Ionization**: After injection of a sample and vaporization via the sample inlet, the sample is ionized by one of several mechanisms.
2. **Acceleration**: The vaporized beam of ions is accelerated so that they have the same energy
3. **Deflection**: In the mass analyzer (an electromagnet), the ions are sorted according to their size (m/z).
4. **Detection**: Ions finally strike a plate and generate a current

The type of mass spectrometer is normally determined by the mechanism of ionization:

Electron Impact (EI) - high energy electrons (6700 kJ/mol) are bombarded at a neutral molecule. The resulting high energy radical cation can break apart into smaller fragments (this is called **fragmentation** - the **molecular ion** (M^+) breaks down into small **daughter peaks**). Because electron impact is a high energy technique, one often does not see the molecular ion M^+, only daughter peaks due to rapid fragmentation.

Chemical Ionization (CI) - a cloud of high energy methane (CH_4) gas and a source of protons (H^+ ions) transfer a proton to a small molecule to generate a molecular ion $[M+H]^+$ (observed in the mass spectrum at a m/z ratio of M+1).

Electrospray ionization (ESI) - the most common technique droplets of a small molecule in solvent are created via an aerosol from the sample inlet. Normally, the solvent contains a proton source which protonates basic sites on the small molecule. As the solvent shell evaporates, a charged small molecule results.

Matrix-Assisted Laser Desorption Ionization (MALDI) - a sample is mixed with a chemical matrix and deposited on a plate to dry and crystallize. In a vacuum chamber, the plate is pulsed with a laser that ionizes and desorbs ions, which are now in the gaseous state, usually $[M+H]^+$ or $[M+Na]^+$.

Isotopic patterns

The natural abundance of certain isotopes can be useful in structure elucidation. For example, we can tell if a molecular ion has a chlorine or bromine atom in it just by loking at the isotopic pattern of the molecule ion or daughter peaks. To do this, we need a **high resolution mass spectrum** (HRMS). HRMS is necessary for accurate mass determination, and we use the following exact masses:

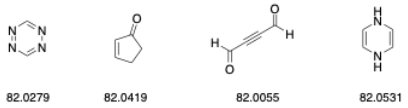
$^{12}C = 12.000000$ amu

$^{1}H = 1.007825$ amu

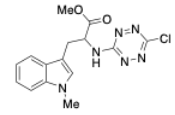
$^{16}O = 15.99491$

$^{14}N = 14.00307$

For calculating the mass-to-charge ratio of an ion, just add up all of the masses of the atoms in the ion using these values. Since these values are extremely accurate, only a handful (or maybe only one) of molecules can have that exact mass, down to an accuracy of less than 10 ppm. For example, we can distinguish each of the molecules below, which have a molecular weight of 82 g/mol, via HRMS (using EI).



Getting back to isotopic patterns, we see that for the following molecule, there are two molecular ions because the natural abundance of chlorine is ^{35}Cl (75%) and ^{37}Cl (25%). Thus, is you have a sample of the molecule, 75% of it will have ^{35}Cl atoms and 25% of it will have ^{37}Cl atoms. You will see both bypes of species in a mass spectrum in a 3:1 ratio separated by two mass units.



Other typical patterns in mass spectra are when bromine atoms appear. Here, one observes peaks that are two mass units apart and equal in intensity. This is because ^{79}Br and ^{81}Br are naturally abundant in a 1:1 ratio.

Let's see what would happen if there were multiple halogen atoms, as in CH_2Cl_2 (MW = 85 g/mol).

Peak 1: m/z 84 = $CH_2{}^{35}Cl{}^{35}Cl$ = (0.75)*(0.75) = 56.25 = 56.25%

Peak 2: m/z 86 = 37.5%

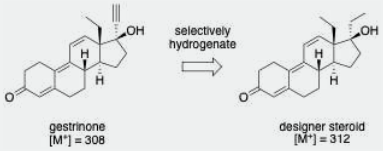
(second chlorine is ^{37}Cl) = $CH_2{}^{35}Cl{}^{37}Cl$ = (0.75)*(0.25) = 18.75 = 18.75%

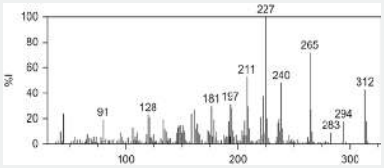
(first chlorine is ^{37}Cl) = $CH_2{}^{37}Cl{}^{35}Cl$ = (0.75)*(0.25) = 18.75 = 18.75%

Peak 3: m/z 88 = $CH_2{}^{37}Cl{}^{37}Cl$ = (0.25)*(0.25) = 6.25 = 6.25%

Biomedical Spotlight

The United States Anti-Doping Agency (USADA) is the nation's premier non-profit organization charged with upholding the ideal of fair play by ensuring that athletic competitions are free from performance-enhancing drugs. In 2003, USADA was sent a syringe containing an unknown substance from an anonymous coach who claimed that there had been rampant use of a designer steroid among track and field athletes. In what then came widely known as the BALCO scandal, this same substance was implicated in Major League Baseball players, including Barry Bonds. A sample from the syringe was tested for all 70 steroids that are banned by USADA, but no matches were found. However, the mass spectrum had remarkable similarity to a known anabolic agent, gestrinone. In fact, the daughter peaks from electron impact ionization mass spectrometry (EI-MS) for a sample of the designer steroid completely matched that of gestrinone. However, the molecular ion for the designer steroid differed by 4 amu (EI-MS shown below). By using chemical intuition, anti-doping scientists were able to conclude that gestrinone had been partially and selectively hydrogenated to produce an ethyl group from the terminal alkyne. This new molecule had performance-enhancing capabilities, but had previously escaped detection. The new molecule, now known as tetrahydrogestrinone (THG), was quickly banned by the World Anti-Doping Agency.





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CHAPTER OVERVIEW

6: Alkenes

6.1: Cahn-Ingold-Prelog Convention

6.2: Bonding, Stereoisomerism, and Stability

6.3: Electrophilic Addition

6.4: Acid-Catalyzed Hydration

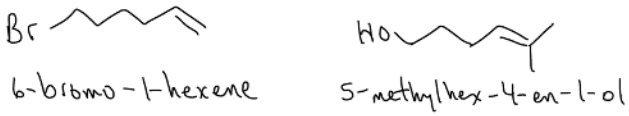
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6.1: Cahn-Ingold-Prelog Convention

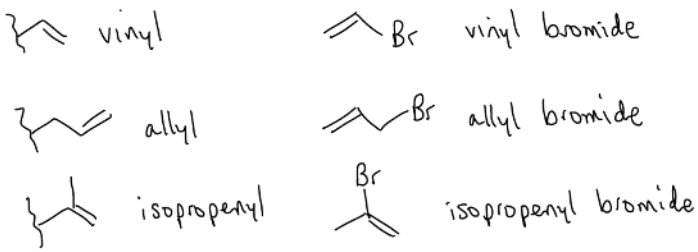
Alkenes are hydrocarbons that contain a C=C double bond. We name them similarly to alkanes, but use the suffix –ene instead of –ane. We normally indicate the position of the double bond with a number. For example, 2-butene (or but-2-ene) and 1-butene (or but-1-ene) have different structures.



When substituents are placed along the chain, the priority rules much be followed. Alkenes are higher priority than halides, but lower priority than alcohols, for example. So:



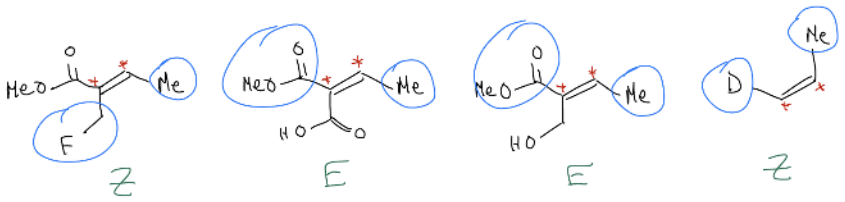
There are three other groups that contain a C=C double bond which have common names:



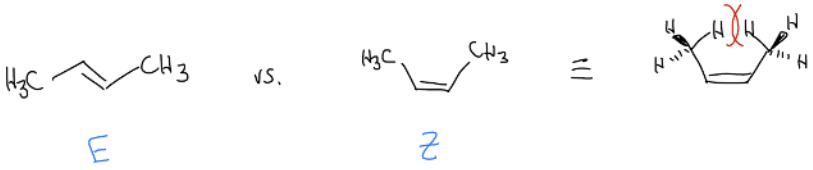
E/Z nomenclature of alkenes

The Cahn-Ingold-Prelog convention dictates that we assign priority to the various groups attached to the alkene in order to distinguish between isomers. We use the prefixes *E*- (for entgegen, German for “opposite”) to indicate that the two highest priority groups lie on opposite sides of the alkene, or *Z*- (for zusammen, German for “same”) to indicate that the two highest priority groups lie on the same side. This E/Z system of nomenclature assigns priority based on **atomic number**:

1. atoms that are directly attached to the alkene are assigned priority based on decreasing atomic number (highest atomic number = highest priority)
2. if two groups have the same atomic number, consider atomic mass (higher atomic mass = higher priority)
3. if two groups have the same atomic mass AND number, move along the chain to a different atom until there is a difference in priority
4. if two groups have the same atomic number AND atomic mass AND lie in the same position along the chain (say, -CH_2**O**H vs. –CH=**O**), but one of them is doubly bonded (such as C=O), then count that atom twice (as if it were attached to two oxygen atoms. But beware that this is not additive!)
5. if two highest priority groups are on the same side = *Z*, opposite sides = *E*. Note that we do not use the terms *cis* and *trans* when naming alkenes, only when indicating the relative position of groups.



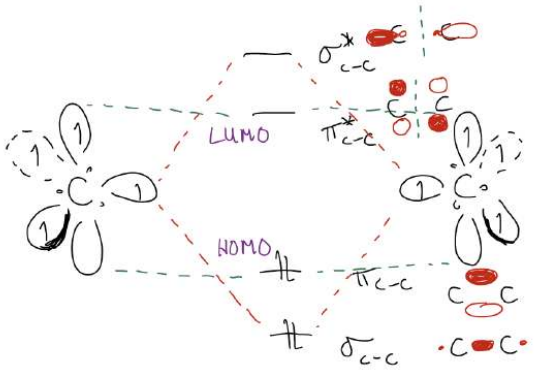
We call the *Z* and *E* isomers of the same compound **geometric isomers**, which is a class of stereoisomers known as **diastereomers**. These isomers do not have the same physical properties because they have different energies. In fact, *E*-but-2-ene is 0.7 kcal/mol more stable that *Z*-but-2-ene. There is a van der Waals interaction when two groups come into close contact, such as the cis methyl groups. This is **steric strain** that drives up the energy of the cis isomer.



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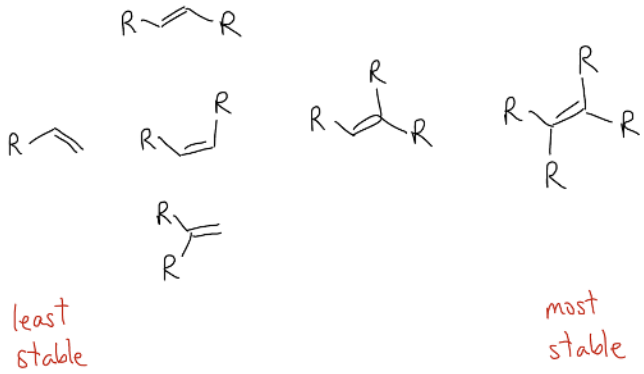
6.2: Bonding, Stereoisomerism, and Stability

So, why do alkenes exhibit stereoisomerism in the first place? Recall the molecular orbital description for a C=C double bond. The carbon atoms are sp^2 hybridized, which means that each carbon atom has 3 sp^2 orbitals and an atomic p orbital. In ethylene, the C=C double bond would look like this, in which there is net bonding between the carbon atoms (σ_{C-C}) AND above and below the plane of the molecule (π_{C-C}). There are four electrons total in the C=C bond, two in the σ_{C-C} and two in the π_{C-C}. We say that the π_{C-C} is the **highest occupied molecular orbital** (HOMO) and that the π^*_{C-C} is the **lowest unoccupied molecular orbital** (LUMO). The HOMO and LUMO are known as the **Frontier molecular orbitals**.

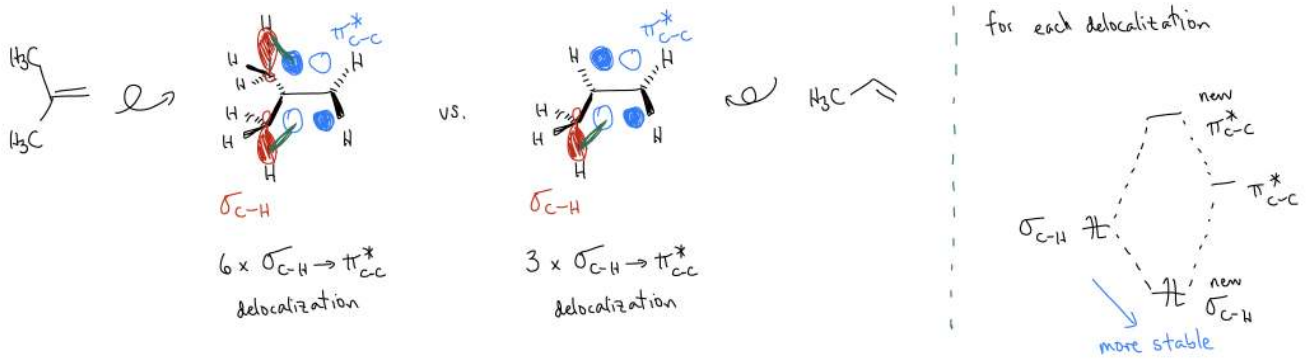


The double bond increases the bond strength by 62 kcal/mol to 145 kcal/mol (a σ_{C-C} bond has a bond strength of 83 kcal/mol). Since there is net bonding above and below the plane, there is no longer rotation about the central C=C bond. Thus, the creation of stereoisomers. Whether the two highest priority groups are on the same side or opposite sides will create different geometric isomers.

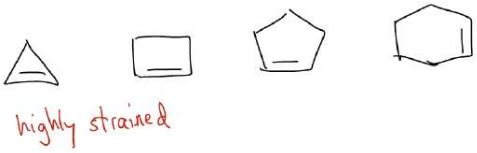
One other important feature of alkenes is their relative stability. Alkenes that are more highly substituted are more stable than less highly substituted alkenes. Monosubstituted alkenes are higher in energy than disubstituted alkenes, which are higher in energy than trisubstituted, and so on.



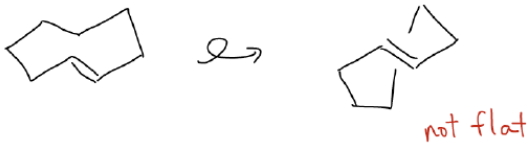
The reason for this is σ-donation. Let's consider 1-propene and 2-methyl-1-propene. We say that greater substitution stabilizes the molecule, which it does this through a-donation. Stability can be calculated by summing all of the bond enthalpies in the molecule. When σ_{C-H} and π^*_{C-C} orbitals mix, a new orbital is created which lowers the energy of the σ_{C-H}, making the alkene more stable overall. How does this happen? Well, remember that σ_{C-H} bonds are electron-donating. Since σ-donation occurs many more times in a disubstituted alkene than a monosubstituted alkene, there is greater stabilization of the σ_{C-H} bonds. There are six σ_{C-H} bonds that can donate in a disubstituted system, but only three σ_{C-H} bonds that can do so in a monosubstituted alkene.



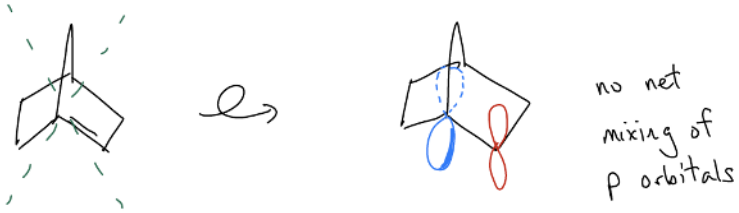
Besides steric strain and σ-donation, alkene stability can also be effected by ring strain. Placing a double bond in a ring alters the conformation and contributes to angle strain. Alkene carbon atoms that are sp^2 hybridized want to have bond angles of 120°, but when they are placed in a ring, sometimes they are forced to be much smaller. This increases the energy of the cycloalkene. Larger rings (7-, 8-, 9-, etc.) do not suffer from angle strain in the opposite sense (>120° bond angles) because the ring can distort its conformation to keep the alkene carbons at 120°.



All of the molecules above are *cis*-cycloalkenes. In *trans*-cycloalkenes, the strain is even greater. Because *trans*-substituted groups are much farther apart, the smallest *trans*-cycloalkene possible is cyclooctene. Anything smaller than that is too strained.



Finally, we must consider alkenes in bicyclic systems. **Bredt's rule** states that you cannot have a double bond at a bridgehead carbon. The reason for this is that there is no overlap of atomic p orbitals to create a π_{C-C} bond. The atomic p orbital on the bridgehead is **orthogonal** to the atomic p orbital on the adjacent carbon, therefore there is no net bonding – the orbitals cannot mix because they are perpendicular to one another.

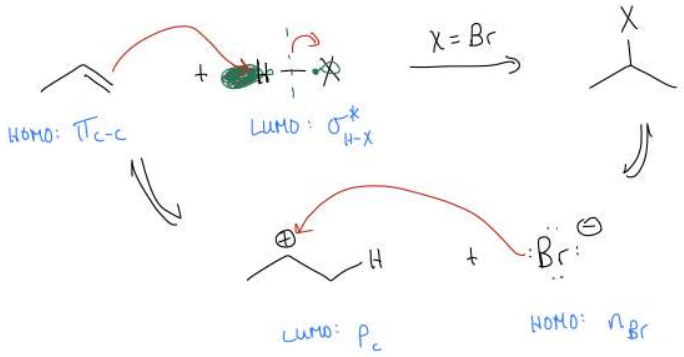


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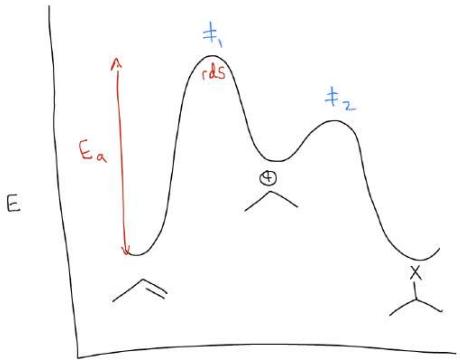
6.3: Electrophilic Addition

We said that the highest energy pair of electrons (or HOMO) in alkenes is the π_{C-C}. Thus, it should be the first thing to react in a chemical reaction. In an electrophilic addition, there is net addition of H-X across the π system. The π_{C-C} (HOMO) acts as the nucleophile in search for an empty orbital (LUMO). In the case of electrophilic addition, it finds that empty orbital in the form of a σ^*_{H-X} bond. The mechanism for electrophilic addition is a three-step process:

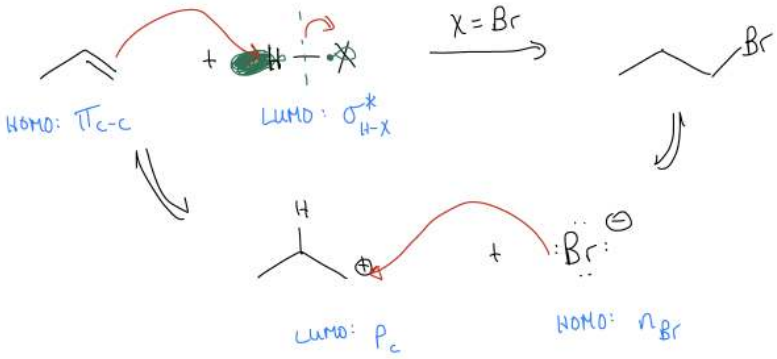
1. protonation of the double bond
2. formation of the carbocation
3. trapping of the atomic p orbital with X^-



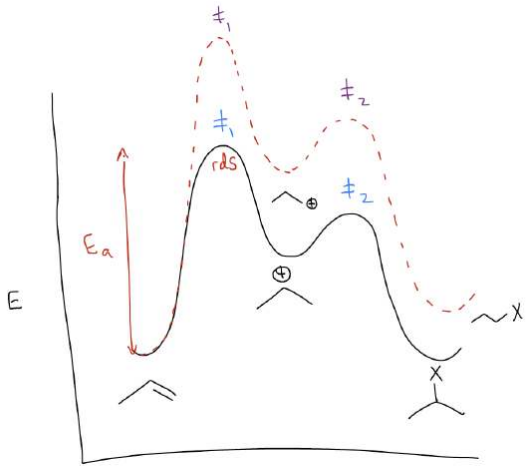
The **reaction energy diagram** (or **reaction coordinate diagram**) shows us that there is a larger activation barrier for the first set of arrows. Remember that a **transition state** is a local energy maximum that exhibits simultaneous bond-forming and bond-breaking events. In this case, the transition state brings together the alkene and the H-X. Once the alkene is protonated, the reaction funnels into a slightly lower energy well. This is known as the carbocation. The next set of arrows (where n_X is the HOMO and atomic p is the LUMO) is also a high energy transition state, but slightly lower than the first. The net result is an isopropyl halide as product. Recall that the rate determining step of this reaction is simply the step that contains the highest energy barrier. In this case, it is the protonation step, before the carbocation is even formed. Nothing after that event matters to the overall rate of the reaction.



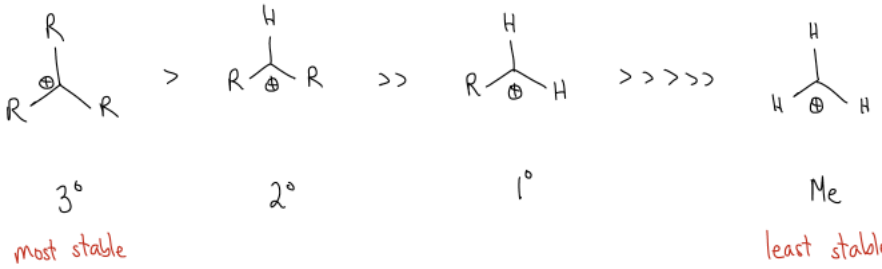
You might be thinking about this reaction and wondering why we protonated the alkene the way we did. We certainly could have protonated the central carbon, leaving the positive formal charge on the terminal position. The difference would be that we would create a 1^o carbocation vs. a 2^o carbocation. If we were to draw the mechanism, it would look quite similar. The only difference is the position of the protonation, and the location of the nucleophilic attack of X^-.



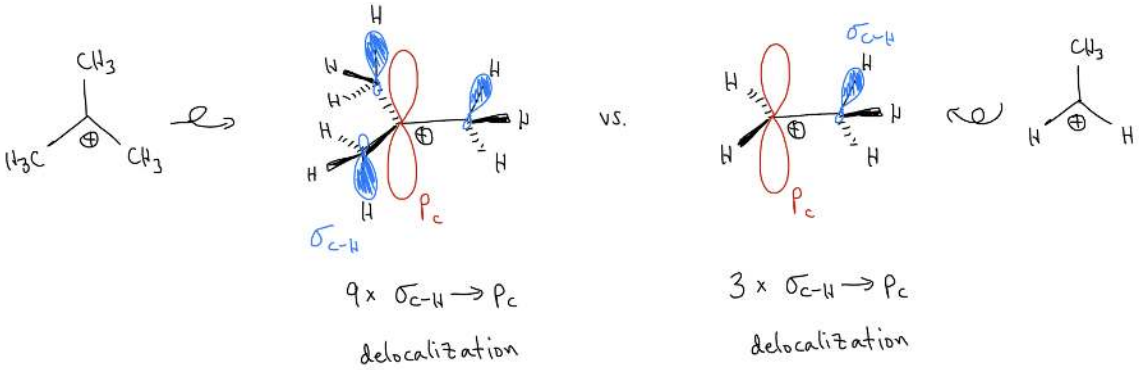
The reaction coordinate diagram would also look similar, with two key differences.



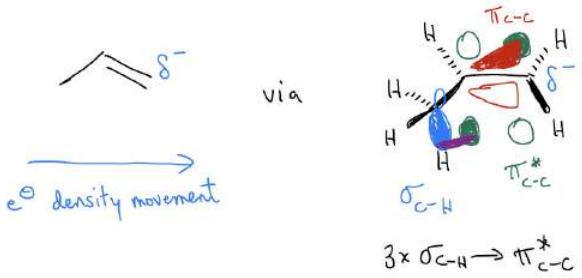
The first key difference is that the 1° carbocation is higher in energy than the 2° carbocation. If we extrapolate, we would see that the trend is that 3° carbocations are the most stable.



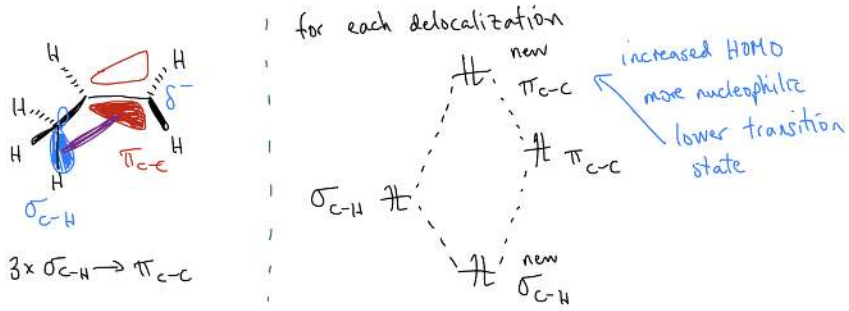
So, what accounts for this difference in stability? Again, our good friend σ-donation is at it again. Consider the following two carbocations. In the first carbocation, we have σ_{C-H} bonds that can delocalize into the atomic p orbital. This stabilizes the positive charge at that carbon atom. For a 3° carbocation, this type of σ-donation occurs nine times. In a 1° carbocation, it only occurs three times. Thus, there is a much greater effect with greater substitution.



Along these lines, we must consider why the protonation occurs on the terminal carbon in the first place. After all, it is the transition state that determines the initial bond-formation to the proton – it has nothing to do with carbocation formation because that occurs later in the mechanism. Let's take a look at the molecular orbital description of 1-propene and see if we can account for this **regiochemistry**. There are two possible **regioisomers** that can form in this reaction: isopropyl halide and *n*-propyl halide. **Regiochemistry** is a property of reactions that asks us to determine *which* of two possible sites will react. To confirm the regiochemical outcome of this reaction, let us recall the σ-donation that occurs in the alkene. 1-Propene is not a symmetrical system, so we should not expect that the p system is symmetrical. It should be polarized to one or the other side. Because there is σ-donation between the σ_{C-H} bonds and the π^*_{C-C}, partially populating this orbital will shift electron density to the right (think of it as partially breaking the π_{C-C} bond, with electrons continuing to move along the chain). Thus, we should have electron density depositing on the terminal carbon. We say that the π_{C-C} bond is polarized towards the terminal carbon. It has greater electron density and will have a greater coefficient in the wavefunction. Since it has greater electron density, it is slightly more negatively charged and is bigger, which helps decrease the energy of the transition state – you get much better orbital overlap under these conditions.



While this explains the regiochemistry of the electrophilic addition, you still might not understand why the transition state leading to the 1° carbocation is higher in energy. Thus, the second key difference in the reaction coordinate diagram is that the height of the first transition state is much greater for the formation of the 1° carbocation. This can also be explained by σ-donation. This time, mixing between the σ_{C-H} orbitals and the π_{C-C} will create two new molecular orbitals in which the π_{C-C} increases in energy. This makes more highly substituted alkenes more reactive than less highly substituted alkenes – the HOMO is higher in energy and more reactive. In the transition state, this matters because now the two reactants don't require as much kinetic energy to react. In essence, they're already preprogrammed to find each other quicker. This takes less energy, driving down the energy of the transition state.



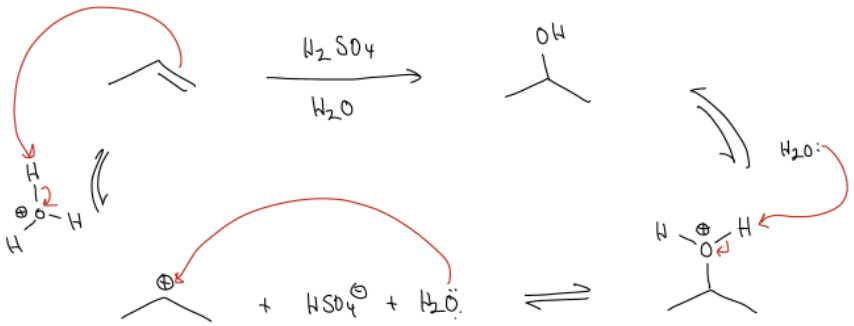
In summary, σ-donation has the effect of both decreasing the energy of the carbocation AND the initial transition state. Another truism is that more highly substituted alkenes are both more stable AND more reactive. This might seem counterintuitive, but remember that these are two very different things. Stability is a thermodynamic phenomenon, while reactivity is a kinetic phenomenon. It happens that both things are working in concert in this reaction to give you the same product, but it doesn't always have to be this way.

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6.4: Acid-Catalyzed Hydration

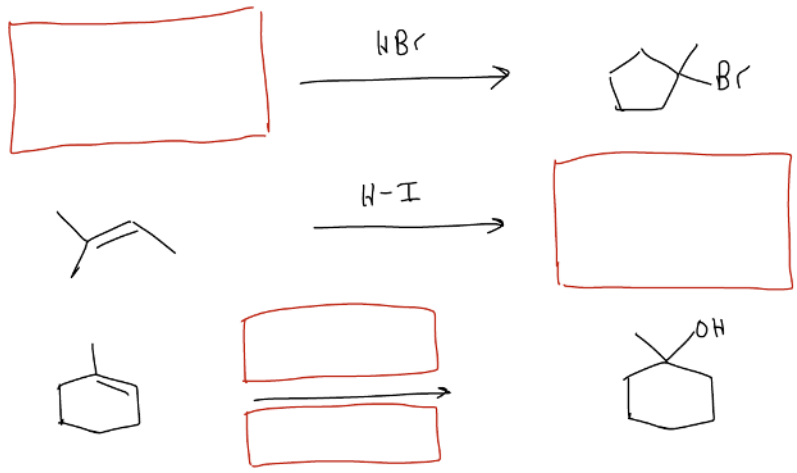
A slight variant of the electrophilic addition of H-X across a double bond is the acid-catalyzed addition of H_2O across a double bond, also known as an **acid-catalyzed hydration**. The mechanism has a few key differences, but overall looks quite similar.

The first step is protonation of the alkene (by H_2SO_4) at the less highly substituted carbon to give the more highly substituted (thus, more stable) carbocation. In the next step, the nonbonding pair of electrons on H_2O will act as a nucleophile to attack the empty atomic p orbital on carbon. When this happens, a bond forms between the oxygen and the carbon. This species is overall positively charged. To get rid of the charge, remember that protons can be removed (or added) very easily. Thus, proton transfer occurs. Some weak base (either H_2O or HSO_4^-) can attack the proton via its σ^*_{H-O} orbital, breaking the σ_{H-O} bond and moving the electrons up onto oxygen as a lone pair. The net result is the regeneration of the acid (hence, why it's a catalyst) and the formation of the alcohol product.



Synthesis

You are now at a point where you can begin to make molecules of greater complexity. So far, you have a simple starting material (an alkene) that can be reacted with two different types of reagents (H-X or H_2SO_4/H_2O) to give two different functional groups (alkyl halide and alcohol, respectively. The mechanism is exactly the same for this reaction – electrophilic addition. You should now be comfortable enough to draw the mechanism for both reactions, but also be able to predict the product, reagents, or starting materials of this transformation when the other two are provided. This will be a common theme as we work through more and more reactions.



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CHAPTER OVERVIEW

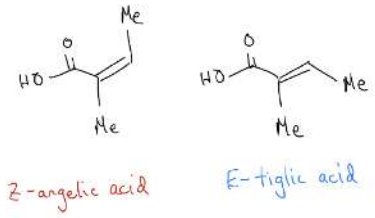
7: Stereochemistry

7.1: The Fundamentals
7.2: Chirality
7.3: Absolute Configuration
7.4: Fisher Projections
7.5: Determining Numbers of Stereoisomers
7.6: Creating Chiral Centers
7.7: Resolution

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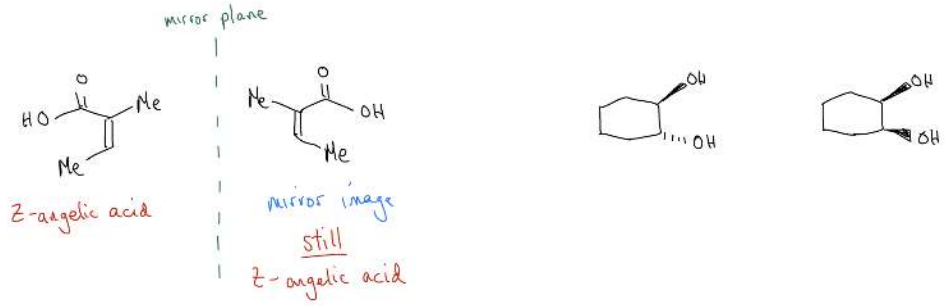
7.1: The Fundamentals

We have said many times before that stereochemistry is the study of molecules that have a different orientation in space. **Stereoisomers** arise when molecules with the same constitution (same atoms attached to the same atoms) differ in their orientation of those atoms in three-dimensional space. We have come across stereoisomers before in the form of double bond isomers, or **geometric isomers**.

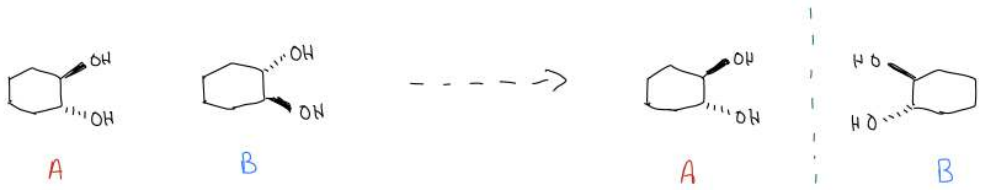


The E and Z isomers have a different orientation of the atoms attached to the double bond. Their *E*/*Z* nomenclature is determined by the priority of each group attached to the double bond, based on atomic number. Geometric isomers fall under a larger umbrella of stereoisomers called **diastereomers**. Diastereomers are stereoisomers that are *not* mirror images and *not* superimposable. So, they are non-superimposable, non-mirror images of each other. Z-angelic acid and E-tiglic acid are neither mirror images of each other, nor can they be superimposed on one another (that is, laid on top of each other so that all of the atoms and bonds match), so they are considered diastereomers. If they were superimposable on their mirror image, they would be the same compound!

The two molecules below, while mirror images, can superimpose on one another, so they are identical (and therefore *not* diastereomers). Another example of diastereomers would be the *cis*/*trans* isomers of substituted rings. cis-1,2-Cyclohexanediol and trans-1,2-cyclohexanediol are diastereomers because they are not mirror images and they cannot be superimposed.



Let's now compare the following molecules. Are they mirror images? Are they superimposable?



Species that are nonsuperimposable mirror images are another class of stereoisomers called **enantiomers**. Enantiomers exist everywhere in nature. Your hands, for example, are enantiomeric – they are mirror images but cannot be superimposed. While diastereomers are different compounds with different energies and physical properties (mp, bp, NMR, IR, refractive index, etc.), enantiomers have identical physical properties because they have the same energy. The *only* physical property that is different between enantiomers is the ability to rotate plane polarized light or circularly polarized light. Hold this thought for a moment while we discuss a few more terms.

Suppose that we have the enantiomers **A** and **B** from above. If we had a sample that contained 100% enantiomer **A**, we say that the sample is **enantiopure**. If we had a sample that contained 100% enantiomer **B**, we say that it is also enantiopure. If we had a

sample that contained 95% of isomer **A** and 5% of isomer **B**, we say it is **enantioenriched** in **A**. The **enantiomeric excess (ee)** of this sample, defined as the difference between the major and minor enantiomer, would be 90%. However, if we had a sample that contained 50% **A** and 50% **B**, we have what is known as a **racemic mixture (or racemate)**. The enantiomeric excess of a racemic mixture is 0.

Now, let's go back to our discussion of enantiomers' ability to rotate plane or circularly polarized light. For a sample that is 100% **A**, plane-polarized light passing through a sample will rotate (refract) by some value, let's say +X (although it could be –X). The enantiopure sample of molecule **B** will rotate plane-polarized light by the same value, but in the *opposite* direction, –X. We call this the **optical rotation** of the sample, or α, which is measured by a **polarimeter**. Note that the optical rotation's sign and magnitude are completely random (that is, nor correlation between structure and + or –), but for a pair of enantiomers, they will ALWAYS be equal in magnitude and opposite in sign.

The **specific rotation** is a standardized way of reporting optical rotation, which can vary from instrument to instrument. We did the same kind of thing for chemical shift in NMR. When comparing values in the literature, always compare the specific rotation values:

$$[\alpha]_D^T = \frac{\alpha}{c \cdot l}$$

[α] = optical rotation obtained directly from the polarimeter
T = temperature
D = designation for the light source, normally a Na arc lamp.
c = concentration in g/mL
l = path length, normally in dm (10 cm).

What happens when we measure the optical rotation of a sample that is not enantiopure, but rather only enantioenriched? For example, if the optical rotation for an enantiopure sample of **A** is 10°, what is the optical rotation for a sample that is 95% **A** and 5% **B**? Well if the optical rotation values for enantiomers are equal and opposite, then the portion of light that is rotate to one side by the 5% **B** should be offset by the rotation in the opposite direction by 5% **A**. This leaves an excess of 90% **A**. What this means, then, is that the optical rotation of the mixture should be a fraction of the value for enantiopure **A** (this assumes that the concentration of the sample we are measuring is the same as that obtained for pure **A**). Indeed, the optical rotation should be:

$$(0.9)(10^\circ) = 9^\circ$$

enantiomeric excess expressed as a fraction

optical rotation of pure enantiomer

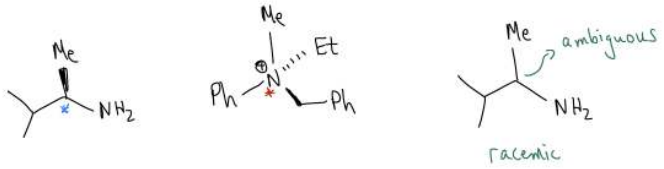
optical rotation of mixture

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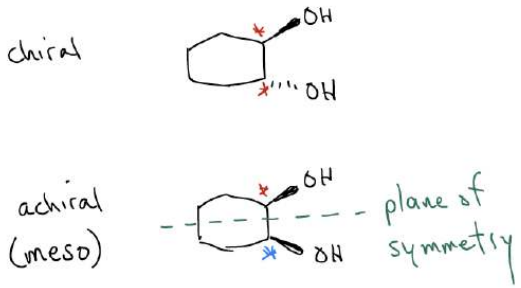
7.2: Chirality

Chirality is a subset of stereochemistry that deals with molecules that rotate plane-polarized light, which is different from stereoisomers that cannot do so, such as geometric isomers. A molecule is considered **chiral** if it can rotate plane-polarized light, and will always possess a nonsuperimposable mirror image. The most common examples of chiral molecules are those that contain a **stereocenter** (there are others that do not fall into this category – we will discuss these later).

A **stereogenic center (stereocenter, or chiral center)** is a tetrahedral atom that contains four different groups attached. This means that the molecule itself has a nonsuperimposable mirror image, or enantiomer. For example, the molecule on the left below has a stereogenic carbon atom. Likewise, the molecule in the middle has a chiral nitrogen atom. The molecule on the right is the same as the molecule on the left, yet no stereochemistry has been provided to us, so we can assume that the chirality is ambiguous and it is a 1:1 mixture of enantiomers (racemic mixture).

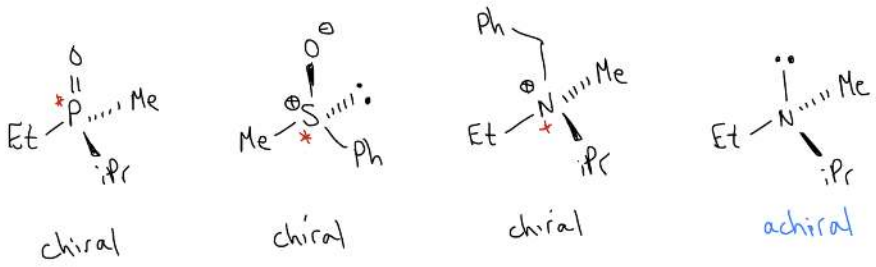


A molecule that contains a stereocenter *can* be considered chiral, but this is not always the case. Consider again the following two molecules. These molecules are diastereomers because they are nonsuperimposable non mirror image isomers, but only one of them is chiral. Each molecule contains two stereocenters, however, only the molecule on the left is chiral because it does not have an internal plane of symmetry. Stated another way, the internal plane of symmetry in the second molecule would cancel the rotation of plane-polarized light. The top half of the molecule would rotate the molecule in one direction while the bottom half of the molecule (since it is a mirror image) would rotate it the opposite way. Think of it like having a racemic mixture in the same molecule. The optical rotation is zero and we say that this molecule is achiral (not chiral). It has stereocenters, but the molecule as a whole will not rotate plane polarized light. These types of molecules, which have stereocenters that generate an internal plane of symmetry, are called **meso compounds**. Another example of a meso compound is a molecule that has an **inversion center** (center of symmetry). For example, a molecule can be achiral if when you rotate it 180° and then flip it, you get the same compound. It is as if the center of the molecule is a point of symmetry.



Chirality Beyond Carbon Stereocenters

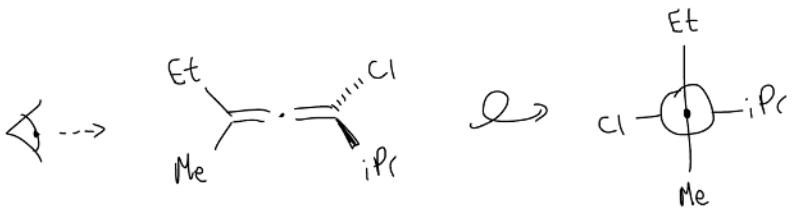
Chirality exists outside the traditional description of four different groups attached to a tetrahedral carbon atom. Other chiral centers include P-, N-, and S-containing molecules, as shown below. Each of these has a nonsuperimposable mirror image, so they are chiral.



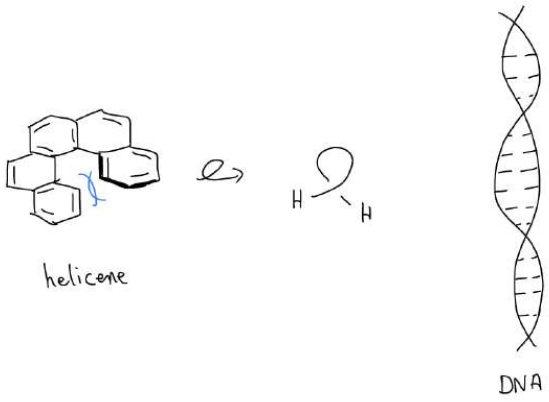
It should be noted that amines (containing three different groups AND a lone pair) are *not* chiral because at room temperature, the trigonal pyramidal geometry inverts rapidly, giving you a racemic mixture. However, phosphines (containing three different groups AND a lone pair) *are* chiral because they do *not* invert at room temperature. The barrier to pyramidalization is too high, so single enantiomers can be isolated.

Other molecules can be chiral even though they may not even contain a stereocenter. But they still satisfy the definition of having nonsuperimposable mirror images, so they are still chiral!

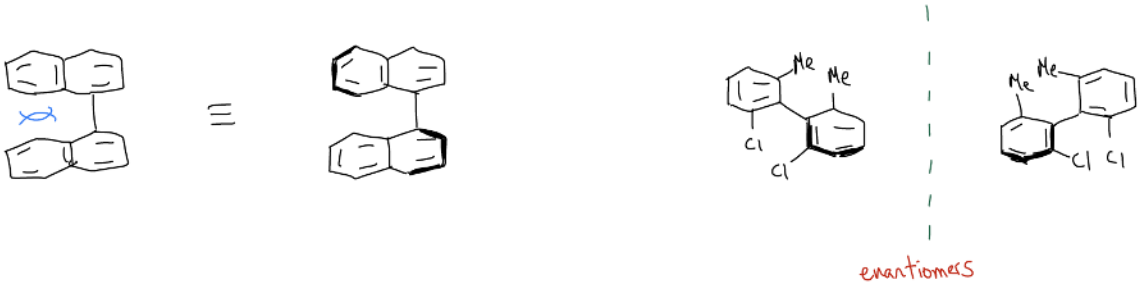
1. **allenes** have a form of chirality known as **axial chirality**. In these molecules, it is as if the central sp-hybridized carbon contains "four" different groups attached.



2. **helicenes** are hydrocarbons that twist. Similarly, the DNA double helix twists with a certain "handedness," so it is also chiral.

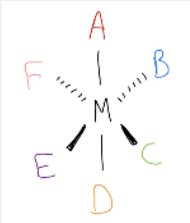


3. **atropisomers** occur when there is hindered rotation about a s-bond. This is another type of axial chirality.

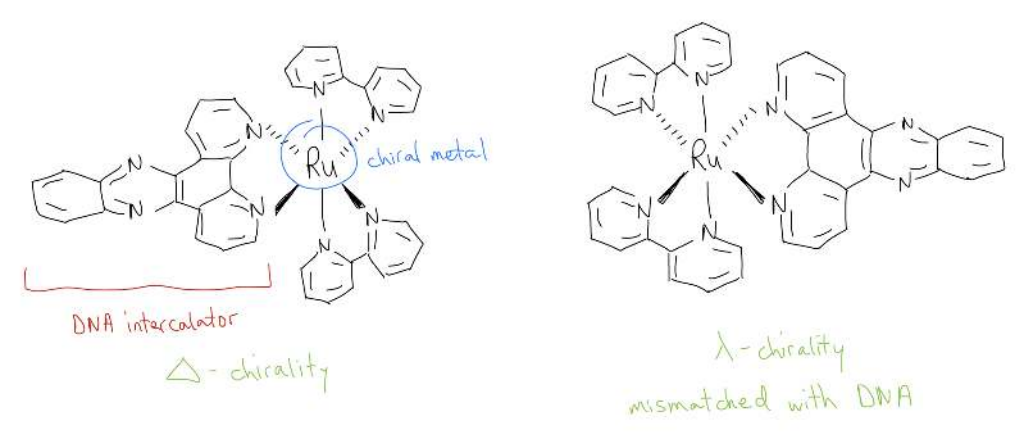


Biomedical Spotlight

Transition metals also have the potential for chirality, but given their expanded coordination numbers, many more stereoisomers can result. Take, for example, an octahedral complex that contains six different monodentate ligands. One can arrange these ligands to give 32 unique stereoisomers!



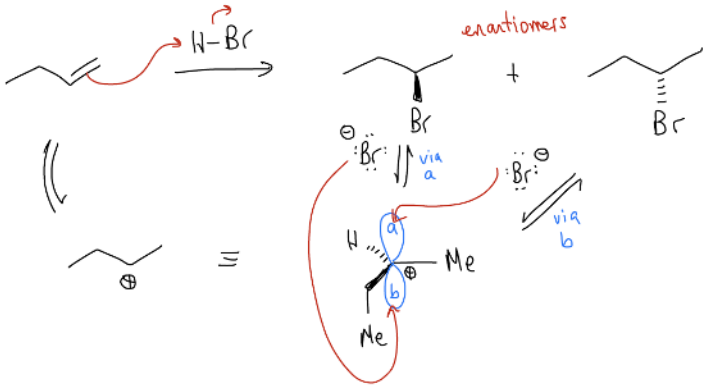
This rich stereochemical diversity can be harnessed to selectively bind DNA. Consider the ruthenium-based polypyridyl complexes pioneered by Jacqueline Barton. These molecules contain three different bidentate ligands surrounding an octahedral ruthenium center. The planar nature of one of the ligands is capable of inserting into the base pairs of DNA and causing the DNA helix to unwind. Since DNA is chiral itself (a helicene with a right-handed twist!), only one of the two enantiomers will bind to DNA with sufficient strength. Convince yourself that the two molecules below are enantiomers of one another (that is, that they are non-superimposable mirror images of one another).



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7.3: Absolute Configuration

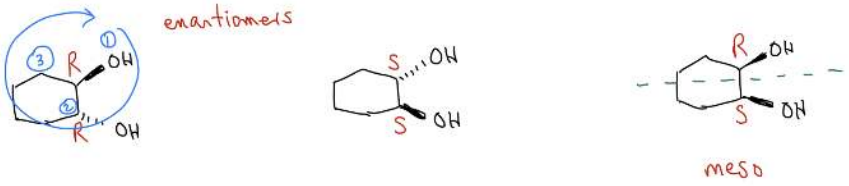
Let's recall the electrophilic addition reaction that we learned about before. In this reaction, protonation gives a carbocationic intermediate that has an empty atomic p orbital. Since the atomic p orbital lies above and below the plane of the trigonal planar carbon, there is equal chance of attack of the nucleophile from the top or bottom face. If we look at the products that result from these two scenarios, we should notice that attack on one face gives one enantiomer, while attack on the other gives the mirror image. We say that the carbocation (which is achiral) has two **enantiotopic faces**, meaning if it is attacked, it will give one enantiomer or the other. Because there is equal chance of attack from the top and bottom faces, the energy barrier to form each enantiomer is identical, so a racemic mixture of enantiomers results.



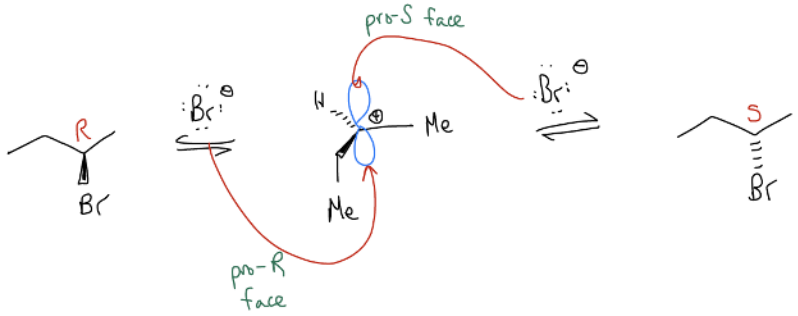
So, how do we communicate if we have one enantiomer or the other? Just as in the naming of alkenes, we use the Cahn-Ingold-Prelog convention, which is based on the atomic number of the attached groups.

1. Rank the groups attached to a stereocenter based on atomic number (1 = highest priority, 4 = lowest priority)
2. Rotate the molecule (USE A MODEL KIT!) so that the lowest priority group faces away from you.
3. Draw a circle from the highest priority group to the next highest priority to the next highest priority (ignoring the lowest priority group).
4. If your rotation is **clockwise**, we say that it is an *R* stereocenter (a little mnemonic – a steering wheel rotates **clockwise** to steer right = R); if the rotation is **counterclockwise**, we that it is an *S* stereocenter.

The *R* and *S* designations are what we call the **absolute configuration**. This is different from **relative configuration**, which are things like *cis* and *trans*. Both of the following compounds have a trans relative configuration, but they have the exact opposite absolute configurations. These are enantiomers. Reflection of a chiral center through a plane of symmetry will convert from one absolute configuration to the other (as is the case with the meso compound on the right).



If we go back to our electrophilic addition reaction, remember that the second step is the **stereochemistry-determining step**. Attack of the atomic p orbital from one face will give you the *R* enantiomer, while attack of the other face will give you the *S* enantiomer. We say that these two faces of the atomic p orbital are **pro-*R*** and **pro-*S***, respectively.

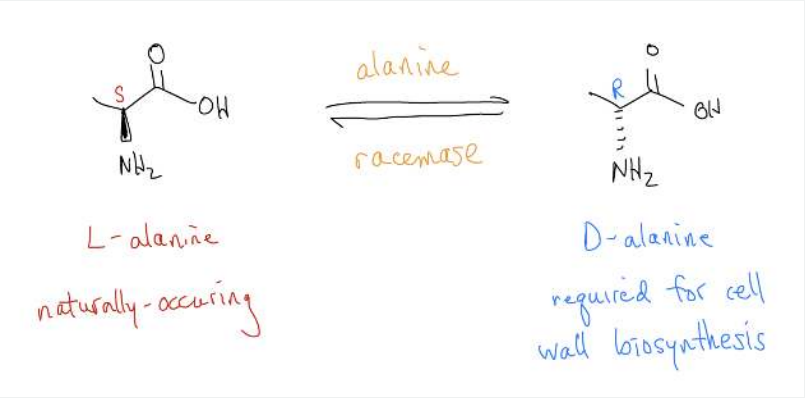


Biomedical Spotlight

Absolute configuration (R/S) assigns the stereochemical arrangement of groups around individual stereocenters according to the rules of the Cahn-Ingold-Prelog convention. In biochemistry, there is an additional nomenclature system that you may come across that is a bit antiquated. The Fischer-Rosanoff convention assigns entire molecules (not individual stereocenters) as D/L (dextrorotatory/levorotatory) based on the relative orientation of the substituent groups when compared to the enantiomers of the biomolecule glyceraldehyde. Compounds that arrange the substituent groups in the same way as (+)-glyceraldehyde are given the designation D, while compounds that arrange the substituent groups in the same way as (–)-glyceraldehyde are given the designation L.

Why is all of this important? Because you will often see D/L designations in the literature to describe amino acids, sugars, and other small molecules. For example, there is both D-(+)-glucose and L-(–)-glucose. But be careful, the D/L designations have no correlation to optical activity (+/–), and correspond to the molecule as a whole (saying nothing about individual stereogenic centers). For example, the D- and L-forms of ribose are D-(–)-ribose and L-(+)-ribose, respectively.

One important example of D/L-designations and its relation to absolute configuration comes from microbiology. Cells in the animal kingdom have phospholipid bilayer-derived membranes, but microorganisms like bacteria have an additional shell of protection known as cell walls. Cell walls are composed of densely-packed carbohydrate-peptide conjugates. This peptidoglycan cell wall is largely made up of the L-amino acids, with two exceptions. Bacteria require D-alanine and D-glutamate for cell wall biosynthesis. This is striking since most of the living world is homochiral, incorporating only small molecules with the L-configuration that exist naturally. As such, bacteria have evolved a mechanism to convert L-alanine into D-alanine using an enzyme, alanine racemase. This enzyme binds the naturally-occuring L-alanine (with corresponding S absolute configuration) and converts it into D-alanine (inverting the stereocenter into its R absolute configuration).



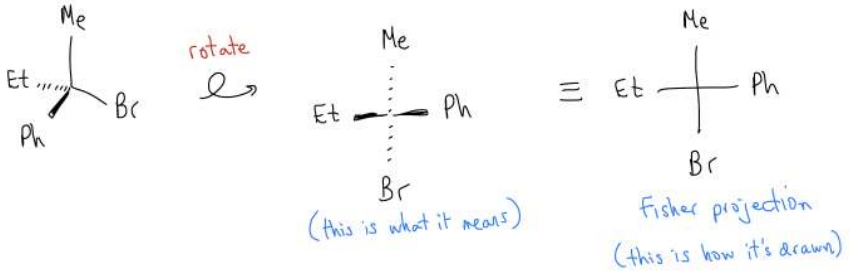
Adapted from Hallelujah Moments, by Eugene Cordes, 2014

One might think that exploiting this pathway as a mechanism for creating new antibiotics would be viable, since creating an inhibitor of alanine racemase would have no effect on human health. Merck devised an antibiotic research program to test this hypothesis. However, creating a small molecule that could inhibit alanine racemase and be safe was a problem that could not be overcome, and the project was abandoned.

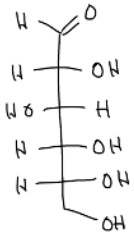
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7.4: Fisher Projections

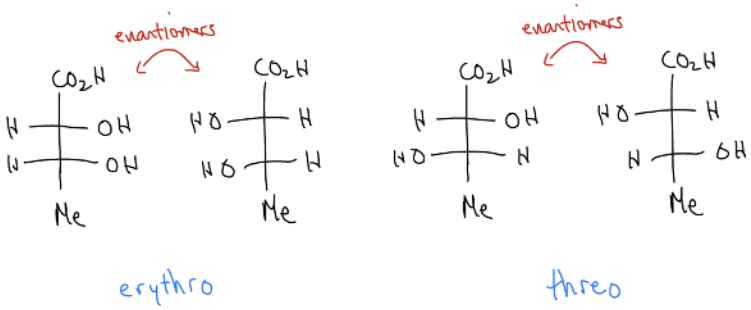
Another way of representing chiral molecules is via a **Fisher projection**.



In order to designate *R* and *S* from Fisher projections, it is best to build a molecular model and then assign the absolute configuration. Fisher projections are often used for depicting sugars. For example, glucose has the structure below. Quick question: how many stereocenters does glucose have? What are the *R*/*S* configurations?



Another convention that we use in Fisher projections is to describe the relative configuration of the respective groups with the designations *erythro* and *threo*. When two groups are on the same side of a Fisher projection, we say they are *erythro*; when the groups are on opposite sides, we say they are *threo*.

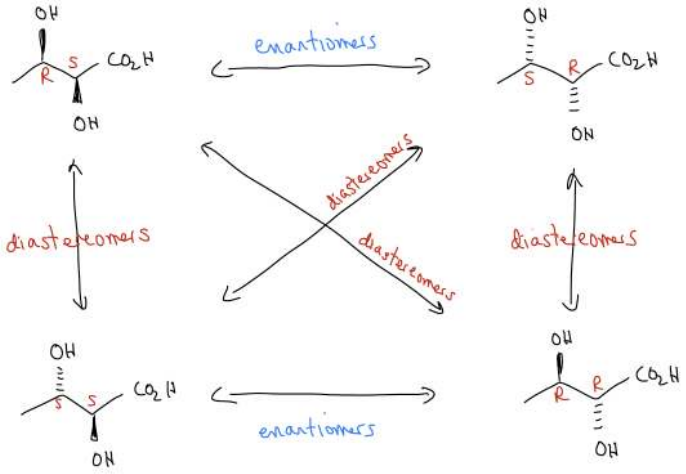


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7.5: Determining Numbers of Stereoisomers

Let's take a step back and consider a molecule that contains multiple stereocenters. If a molecule has one chiral center, we say there are two enantiomers. If a molecule has two stereocenters, there should be four *possible* stereoisomers. If a molecule has three stereocenters, there should be a maximum of eight stereoisomers. So, the maximum number of stereoisomers for a particular constitution is 2^n, when n is the number of chiral centers. You should proceed with caution, however, because some stereoisomers may be meso and therefore identical to other isomers. This will reduce the overall number of possible isomers.

In summary, for a molecule with two chiral, non-racemic, non-meso stereocenters, there are four possible isomers – two pairs of enantiomers. As a general rule, when comparing stereoisomers, if one stereocenter changes *R*/*S* designation and the other stays the same, they are diastereomers. For enantiomers, *all* stereocenters must change.

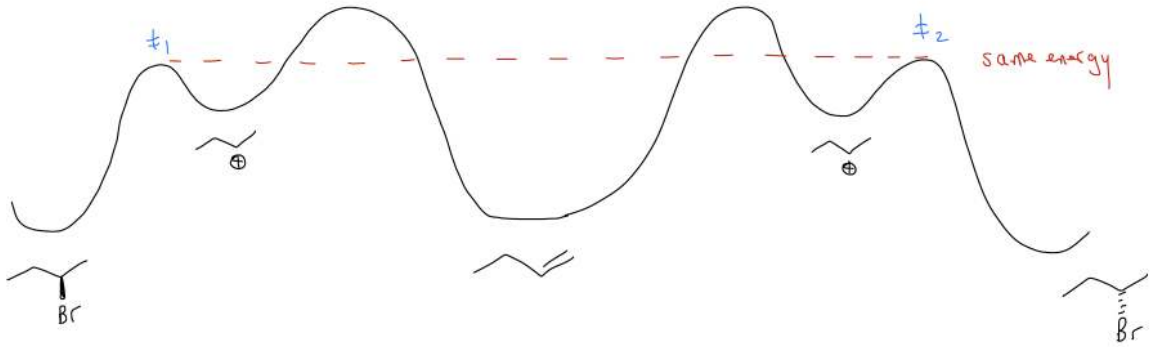




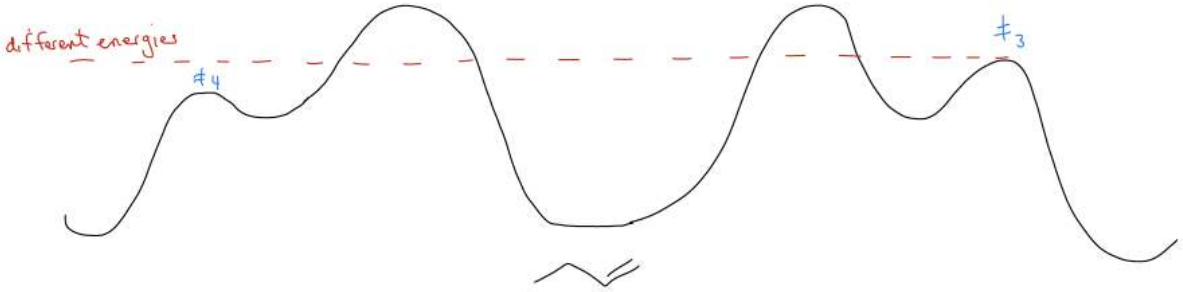
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7.6: Creating Chiral Centers

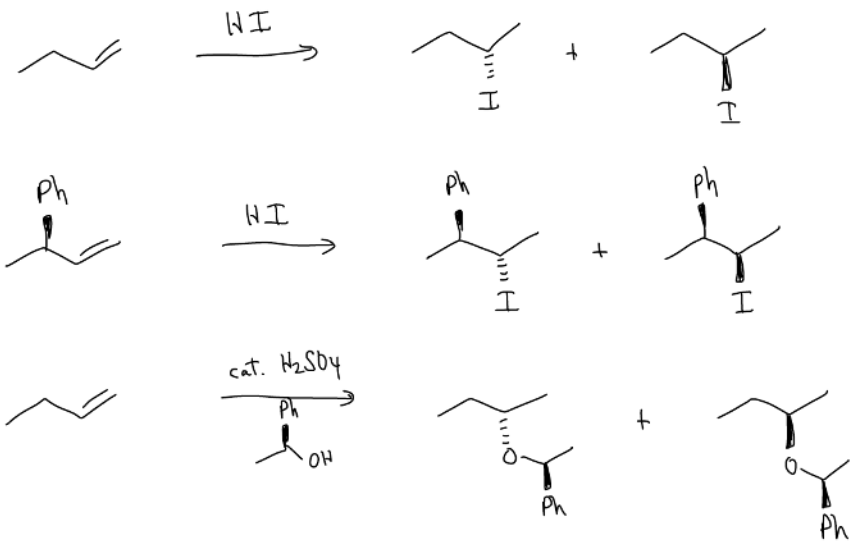
You may be wondering how we create chiral centers. So far, we have only come across one reaction, the electrophilic addition, which we've said will lead to a racemic mixture of enantiomers. This is because the transition state of the stereochemistry-determining step is the same in energy for formation of both enantiomers. In other words, $\Delta G^{\neq 1} = \Delta G^{\neq 2}$, so $\Delta\Delta G^{\neq} = 0$. Enantiomeric transition states are mirror images of one another and equal in energy. In the starting material, we say that each face of the double bond is enantiotopic.



But, what if we changed our system so that the transition state energies were not equal? Well, the only way to do that is to make the transition state **diastereomeric** instead of **enantiomeric**. Then and only then will attack of one face be preferred over the other. In this case, $\Delta G^{\neq 3} > \Delta G^{\neq 4}$, so one pathway (4) is easier to overcome than the other.



You are not familiar with any reactions in which this can occur, but consider the following variations on the electrophilic addition reaction. Would these examples have enantiomeric or diastereomeric transition states? Are the products enantiomers or diastereomers? By changing either the starting material or reagent to become chiral itself, we can create non-racemic stereocenters.

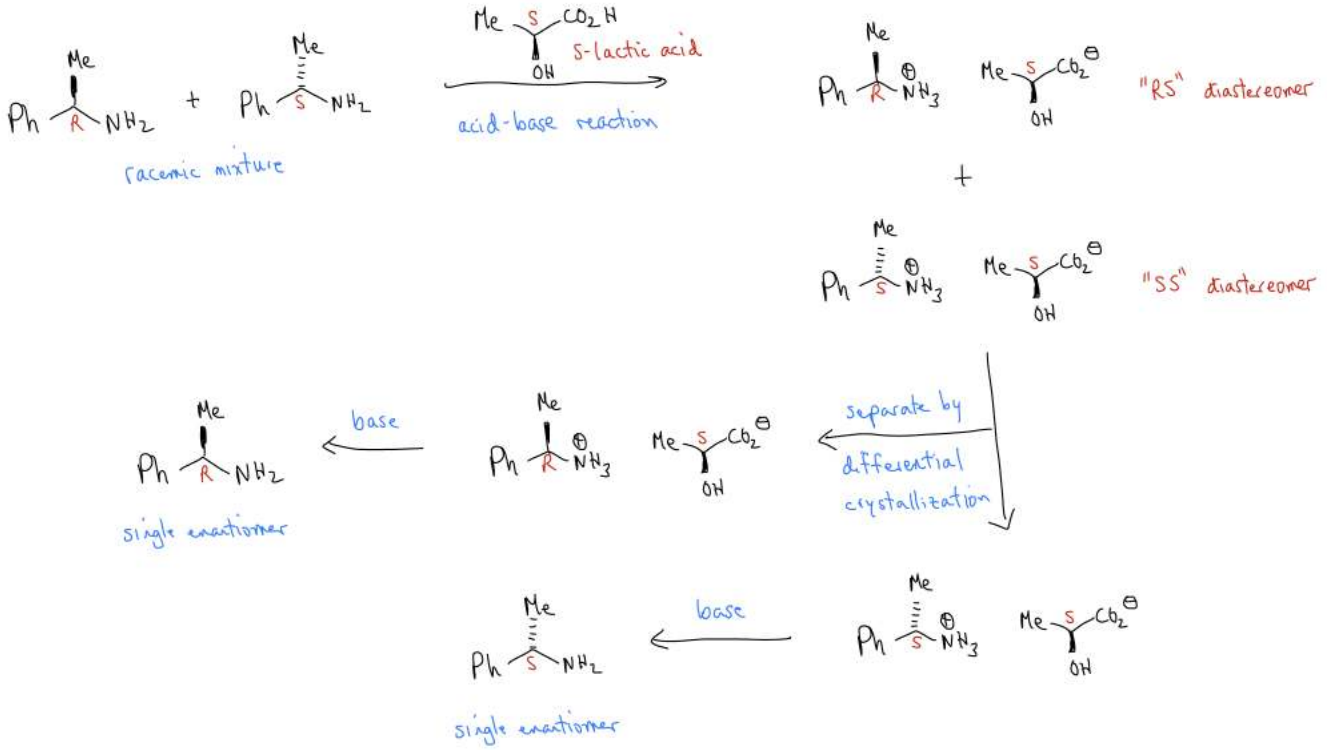


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7.7: Resolution

Finally, we have said that enantiomers are equal in energy and have similar physical properties. One interesting question you might ask is: we are composed of chiral molecules, so how did chirality come into being in the first place. As in, evolutionarily? This is a large area of research, for which we do not have answers for, because we know that we cannot create chirality from achiral material. A similar, more practical consideration is: once we make a racemic mixture, how do we separate the enantiomers into enantiopure samples?

A **resolution** is the separation of a racemic mixture into its respective enantiomers. Since enantiomers are identical, they must first be converted into diastereomers, which have different energies and are easy to separate. The strategy here is to use acid-base chemistry to create diastereomeric salts that have differential solubility. One diastereomer will crystallize while the other will remain soluble. Simple filtration will provide a means of physical separation.



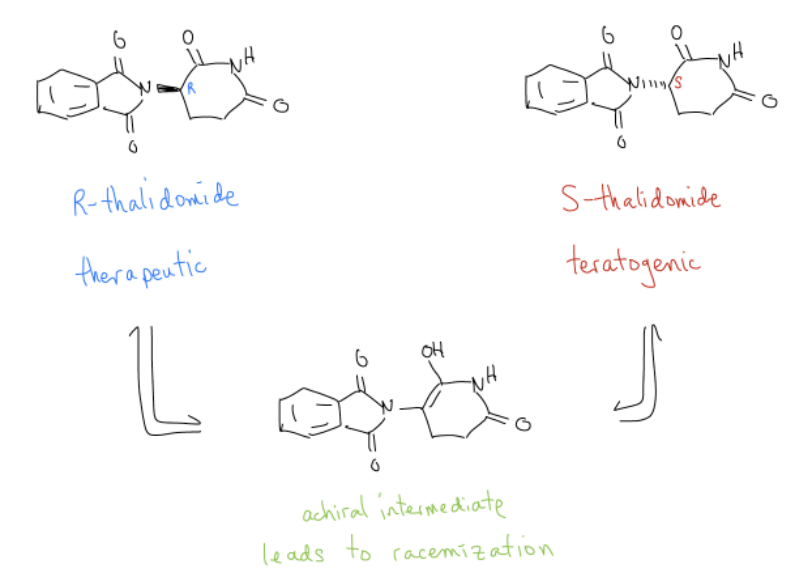
Other types of resolutions include **enzymatic resolutions**, where an enzyme preferentially binds one enantiomer and performs a chemical reaction on it, or **chiral chromatography**, where selective adhesion of one enantiomer to a chiral stationary phase allows separation of isomers.

Biomedical Spotlight

Living organisms have evolved to be mostly homochiral, meaning that the carbon stereocenters have a single, consistent stereochemistry. Because proteins, nucleic acids, and carbohydrates have a single handedness, it should come as no surprise that the interaction of these large macromolecules with the enantiomers of chiral small molecules are different. In essence, diastereomeric pairs of protein and racemic small molecule are created that should have different energies. This is important when considering the interaction of these drugs with macromolecules in live tissue. If one enantiomer binds tightly and the other one doesn't, would it not make more sense to develop a synthesis in which only a single enantiomer is created. Furthermore, what if one enantiomer had therapeutic effects and the other enantiomer was unsafe? In this case, would the development of a drug as a racemic mixture be ethical?

Believe it or not, these stereochemical considerations are more recent that one might imagine. The Food and Drug Administration (FDA), which governs the regulation of the pharmaceutical industry, only issued guidelines regarding the stereochemistry of drug-like molecules in 1992. These guidelines require that any drug that is chiral must be developed as a single enantiomer with defined absolute configuration and that the stereochemistry of the drug be monitored for degradation, metabolism, or even racemization/interconversion. If a drug is prepared and marketed as a racemic mixture, enough testing is required to demonstrate that the individual enantiomers do not cause any harm. As a result of these guidelines, most drugs are developed as single enantiomers from the beginning.

One famous (and sad) example of the need for more regulation in drug development is the story of thalidomide. Thalidomide is on the "List of Essential Medicines" that is compiled the World Health Organization. It was primarily prescribed as a treatment for morning sickness in the late 1950's, but has recently been used to treat multiple myeloma and leprosy. When it first became popular in West Germany to treat nausea in pregnant women, it was marketed and sold as a racemic mixture. While the R-enantiomer is the bioactive form, the S-enantiomer turned out to be teratogenic, meaning it resulted in severe birth defects including limb deformities. Furthermore, it was discovered that the the two enantiomers readily interconvert under biological conditions due to the highly acidic proton adjacent to the carbonyl, so development of a single enantiomer drug was not viable. As a result, physicians prescribe this drug with extreme caution, and only to those patients who are not pregnant or plan to become pregnant.



While tragic, this story was one of the reasons for the passage of the Kefauver-Harris Drug Amendments Act of 1962 that required drug makers to demonstrate the safety and efficacy of the drugs they manufacture. Thalidomide was further made famous by the song "We Didn't Start the Fire," by Billy Joel, who sang about the "children of thalidomide" in 1989.

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CHAPTER OVERVIEW

8: Substitution Reactions

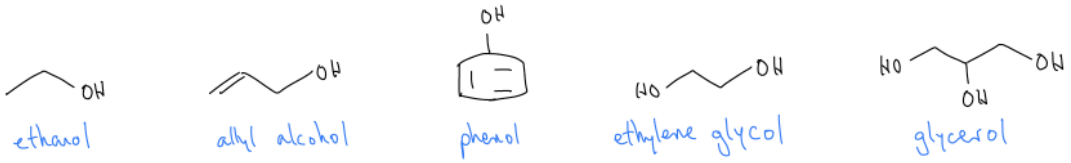
8.1: Substituted Alkanes
8.2: Polarity, Acidity, and Solubility
8.3: The Basics of Determining Mechanism
8.4: Nucleophilic Substitution - 1st Order
8.5: Nucleophilic Substitution - 2nd Order
8.6: Converting Alcohols into Better Leaving Groups
8.7: Peculiarities in Substitution Chemistry

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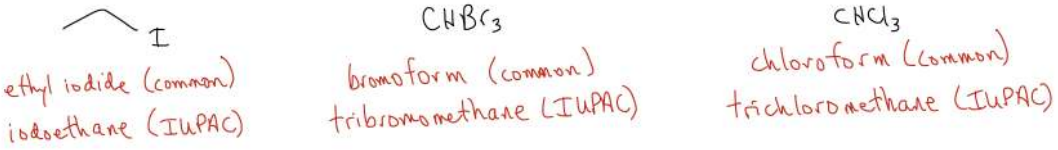
8.1: Substituted Alkanes

Functional groups are common in organic chemistry and similar functional groups will have similar physical and/or reactive properties. Many of these functional groups can be made via substitution reactions, or are the starting materials for substitution reactions.

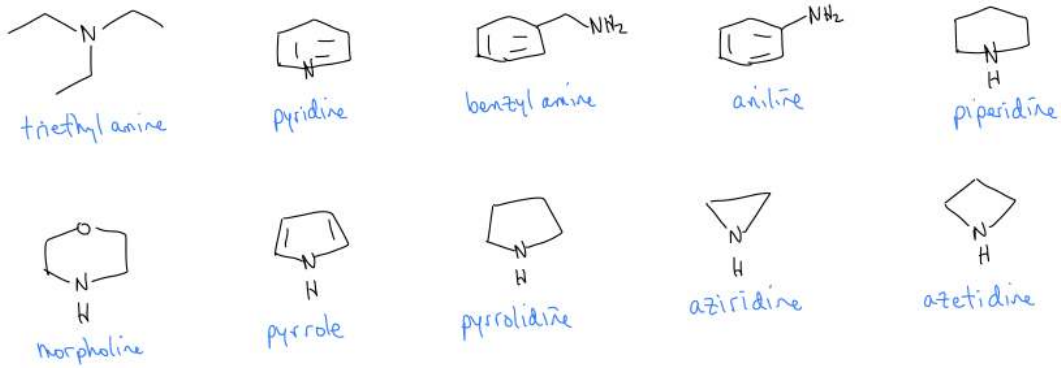
Alcohols = R-OH (suffix –ol)



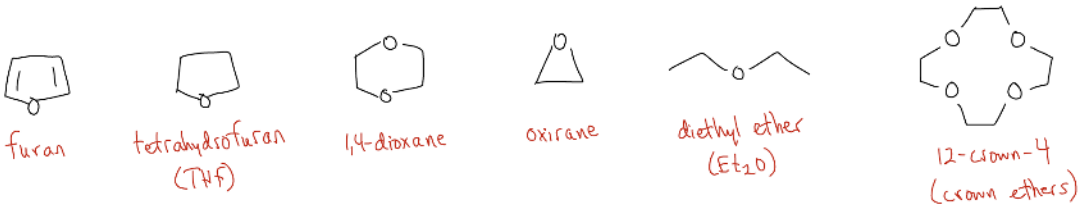
Alkyl halides – R-X



Amines – R-NH_2 (primary), R_2NH (secondary), R_3N (tertiary), R_4N^+ (ammonium)



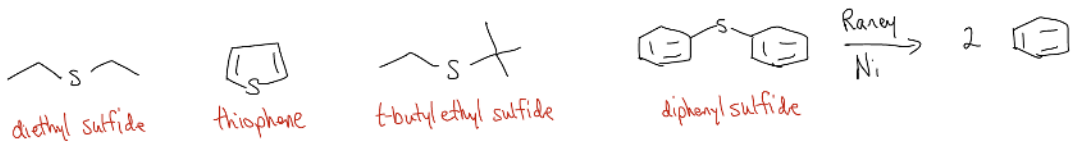
Ethers – R-O-R'



Thiols (mercaptans) – R-SH



Sulfides – R-S-R’



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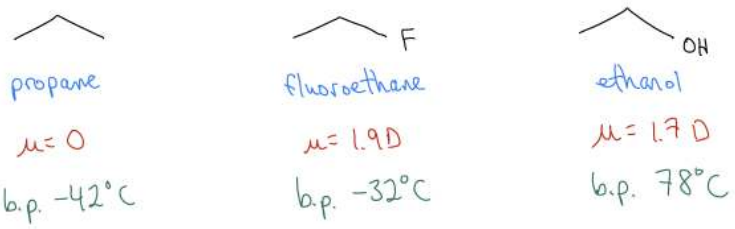
8.2: Polarity, Acidity, and Solubility

Substituted alkanes are polar molecules compared to hydrocarbons, but the intermolecular forces between them are quite unique.

1. **induced dipole-induced dipole** – temporary dipole moments result in weak attraction, but can accumulate (only available in hydrocarbons)

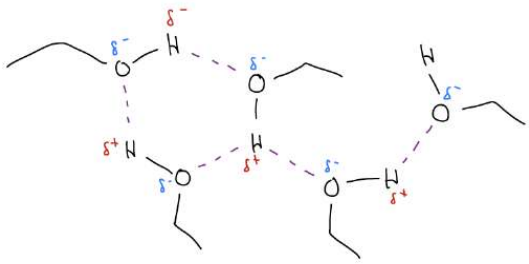
2. **dipole-induced dipole** – polar region of one molecule alters the electron distribution in a nonpolar region of another to produce an induced dipole that results in weak attraction

3. **dipole-dipole** – mutual attraction between the positively-charged region ((δ^+) of one molecule and the negatively-charged region (δ^- of another; generally quite strong



These data suggest another unusually strong intermolecular force.

4. **hydrogen bonding** – notice that ethanol has a slightly acidic proton (pKa = 16.2), meaning there is a partial (δ^+ on the hydrogen atom. This can interact with the lone pairs (δ^-) on the oxygen atom to generate a hydrogen bond.



Hydrogen bonds are usually ~5 kcal/mol and exist whenever there is a hydrogen atom bound to an electronegative atom (ie. N, O, S) and a lone pair. Thus, hydrogen bonding can occur in amines, thiols, and alcohols. Hydrogen bonding is also what makes life possible – the 3-D structures of DNA/RNA, proteins, and carbohydrates all have hydrogen bonding.

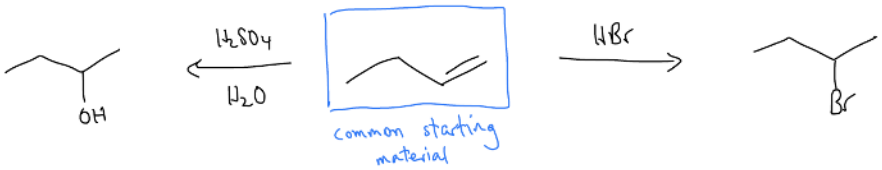
The types of intermolecular forces a molecule has will also dictate its solubility in a solvent. Those molecules that can hydrogen bond will dissolve in solvents that can also hydrogen bond – hence, the phrase “like dissolves like.” In the same vein, very nonpolar hydrocarbons will only dissolve in other nonpolar solvents. This happens because the solvation shell will stabilize the molecule. An appropriate choice of solvent is important for an efficient substitution reaction.

- **protic solvents** – contain a labile proton; very polar (ex. MeOH, EtOH, H_2O)
- **aprotic solvents** – do not contain a labile proton; can be polar (THF, DMF, DMSO) or nonpolar (CH_2Cl_2, EtOAc, hexanes)

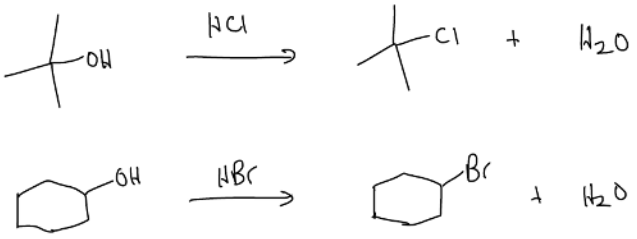
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8.3: The Basics of Determining Mechanism

By now, you've been exposed to only a few chemical reactions whereby a simple starting material is converted into a more complex product. Take, for example, the electrophilic addition reaction. In this reaction, an alkene is converted into the more highly substituted alcohol (or alkyl halide) by reaction with water and an acid like H_2SO_4 or H_3PO_4 (or a mineral acid like HCl, HBr, and HI). The mechanism is protonation of the alkene (π_{C-C} = HOMO) at the less highly substituted carbon atom of the alkene to form a stable carbocation, which then gets trapped by a nucleophile (followed by deprotonation, if applicable).

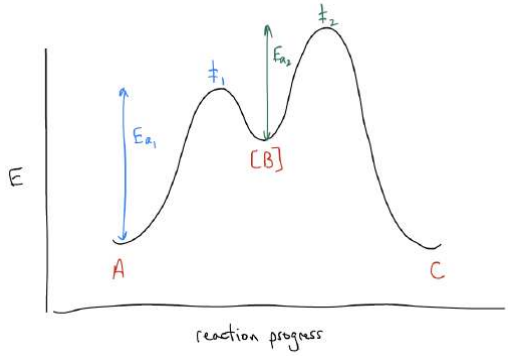


As you will come to appreciate soon, there is often more than one way to make a particular molecule. For example, there is another method of making an alkyl halide that does not use an alkene as the starting material. The reaction between an alcohol and an inorganic acid (hydrogen halide) results in a chemical reaction that generates an alkyl halide and water. Each of the reactants (alcohol and HX) has an impact on the reactivity (how well the reaction works).



So, how does this reaction work? We are making and breaking bonds in the process, so how could we draw a set of curly arrows that would get us from starting material to product? We have come across this type of thinking before. It involves a description of the step-by-step pathway from starting material to product. This is known as the **mechanism**. Mechanisms are based on experimental evidence and can never be proven (however, mechanisms CAN be disproven). One may be able to think of a variety of ways of constructing curly arrows in a reaction mechanism, but understanding whether they are reasonable is more important. Say, for example, you wanted to get from New York to Los Angeles within 24 hours. There are a variety of ways you can get there (car, train, plane), a variety of routes to take, etc. But if you told me that you arrived by boat, I'd think you were crazy. The same thing happens with organic reaction mechanisms – we must always be checking ourselves to see if everything makes sense.

The reaction we just described is known as an **S_N1 reaction**, which stands for **nucleophilic substitution, 1st order**. What this means is that the rate of the reaction is dependent only on the presence of one molecule in the rate determining step, hence 1st order. The rate determining step, or slowest step, involves only one molecule, and the energy required to get this one molecule to make or break bonds is the largest (compared to the other individual bond forming/breaking events). Potential energy diagrams are useful in thinking about reaction mechanisms. Consider the following generic reaction: A → [B] → C, where A is starting material, B is an intermediate, and C is a product. A point of maximum potential energy is known as a **transition state**. The difference in energy between an energy well and a transition state is called the **activation energy**. If the energy level of the products is lower than that of the reactants, we say that the reaction is **exothermic** (vice versa for **endothermic**). The intermediate B is very high in energy and normally cannot be detected because it is so transient. Transition states are not stable structures and cannot be detected because they involve both bond-making and bond-breaking events. According to the **Hammond postulate**, they resemble the energy well that is closest in energy. So, for TS #1 and TS #2, they look mostly like intermediate B. The rate of this reaction depends on the height of the highest transition state and everything that comes before. So, the rate will depend on the structure and concentration of B, in this case.



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8.4: Nucleophilic Substitution - 1st Order

Let's now consider what is happening in an S_N1 reaction:

Step 1: Many organic reactions are acid-base reactions. In this reaction, we have an acid (HCl, $pK_a = -8$). Quick question: do we have a base that we can protonate easily? In other words, is there a pair of electrons that can grab a proton and move the reaction forward?



In the first step, the lone pairs on the alcohol pick up a proton from HCl. The HOMO in this step is n_O and the LUMO is σ^*_{H-Cl}. The right hand side of the equation is favored because the pK_a of the protonated alcohol is approximately –1.7.

Step 2: At this point, we must consider where we are going – we need to form a C-Cl bond. Is there a way to do this? Certainly, and there are actually two ways:

(a)

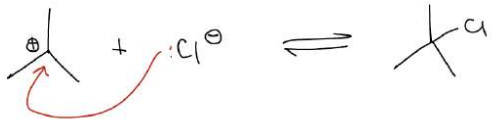


(b)

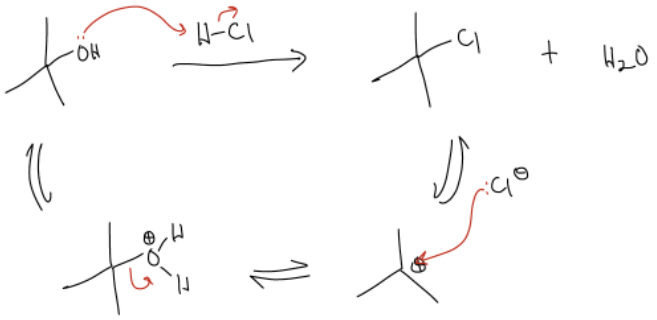


Which one is correct? If I told you that step 2 was the rate determining step of an S_N1 reaction, which one must it be? Well, if the rate is 1st order, then the rate determining step must involve only one molecule. So, it must be (b).

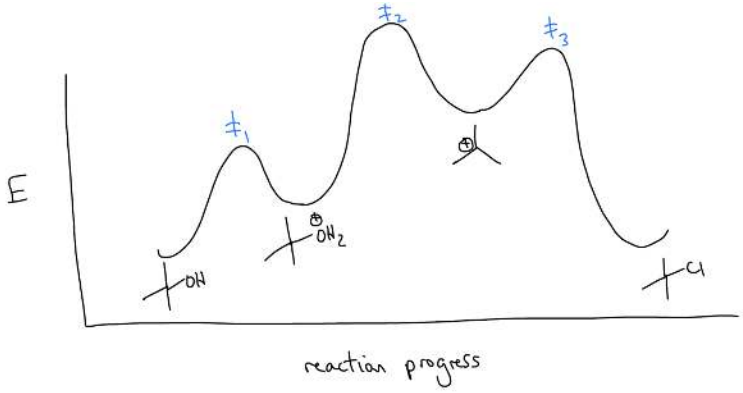
Step 3: At the end of step 2, we will have generated an intermediate that is highly reactive (a carbocation). What happens next is that the **nucleophilic** chloride (Cl^-) reacts with the **electrophilic** carbocation and forms a new bond. The HOMO is the n_{Cl} and the LUMO is the atomic p orbital on carbon.



Now we have the product! Let's put everything together into one mechanistic diagram:



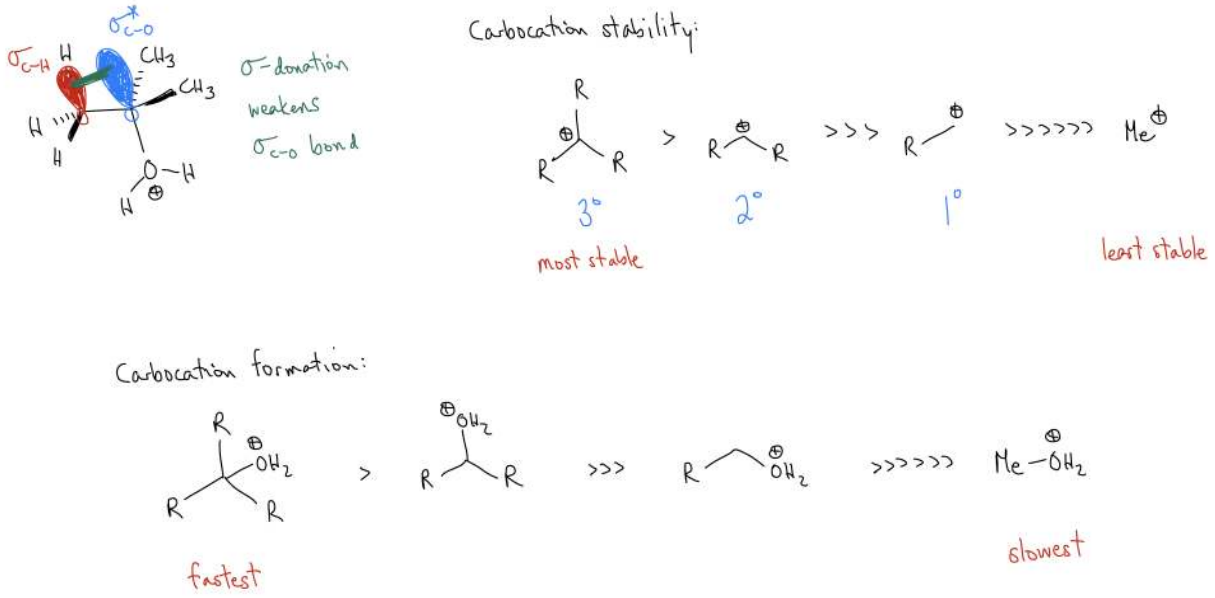
What would the potential energy diagram of an S_N1 reaction look like?



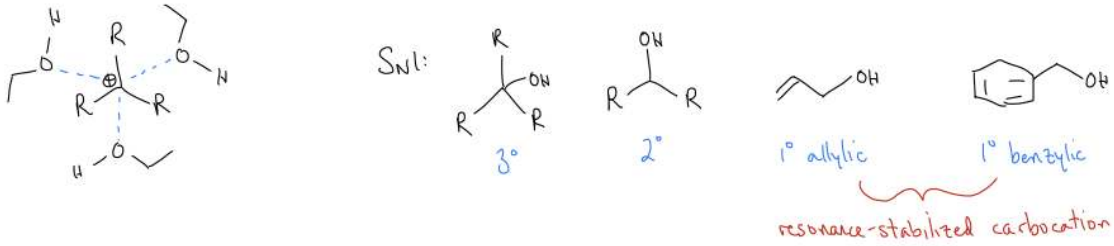
The rate of the reaction should be dependent on only one molecule (remember, 1st order), and indeed TS #2 is the highest in energy. It is dependent on all of the steps that come before it. What this also means is that the rate is *independent* of the concentration of Cl^- (increasing Cl^- has no effect on rate).

So, what does effect the rate? The rate of the reaction depends on the formation of the carbocation. There are two factors that contribute to this. The first is that using a stronger acid can accelerate the protonation step. This depends on the pK_a of the inorganic acid. For example, hydroiodic acid ($pK_a = –10.0$) is stronger than hydrobromic acid ($pK_a = –9.0$), so the protonation step should be faster. The conjugate base, in this case iodide (I^-), is more stable because it is more polarizable than bromide and better able to stabilize the negative charge.

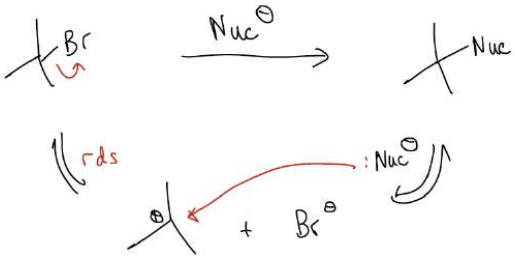
The second factor that contributes to the rate of formation of the carbocation is less intuitive, but involves the structure of the starting material itself. The rate of formation of the carbocation matches the stability of the carbocation, but remember that *stability* and *reactivity* are two different phenomena. **Stability** is a **thermodynamic phenomenon**, and we have said before that more highly substituted carbocations are more stable because of s-donation. **Reactivity** is a **kinetic phenomenon**, which states that carbocations that are more highly substituted are formed faster. The reason for this also has to do with s-donation, but this time it occurs in the transition state (TS #2 from above). Remember that the transition state for an S_N1 reaction has a bond-breaking event that involves one species. By increasing the substitution on this molecule/ion, the energy needed to overcome this transition state is lowered (it's an easier hill to go over). Tertiary alcohols form tertiary carbocations faster than secondary alcohols form secondary carbocations (assuming they've been protonated). Increased substitution lowers this transition state maximum because the increased σ-donation is weakening the σ_{C-O} bond. Why? Because there is delocalization from $\sigma_{C-C}/\sigma_{C-H}$ into the σ^*_{C-O}. Since more σ-donation will populate the σ^*_{C-O} to a greater extent, the bond will lengthen/weaken, lowering the energy needed to break the bond entirely.



So, to review, the rate of an S_N1 reaction is faster when a stronger acid is used, and also faster when the starting material is more highly substituted. In general, S_N1 reactions occur only for tertiary and secondary alcohols, which can generate stable carbocations. Primary alcohols do not undergo S_N1 reactions, with the exception of allylic/benzylic alcohols (which form resonance-stabilized primary carbocations – quite stable!). And finally, the solvent for S_N1 reactions is normally a polar, protic solvent like H_2O, MeOH, or EtOH. The reason for this is that polar, protic solvents stabilize the charged carbocation formed during the course of the reaction.



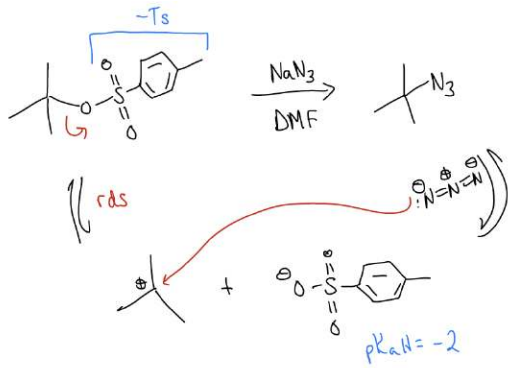
There are other types of S_N1 reactions that do not involve substitution of alcohols. The mechanism is quite similar, but eliminates the protonation step entirely. In order for this to happen, the starting material must be tertiary or secondary (or benzylic/allylic) and have a good **leaving group**. A leaving group is a functional group that "leaves" during the rate-determining step to generate the carbocation. For example, in *tert*-butyl bromide, we can generate the *tert*-butyl carbocation if the σ_{C-Br} bond breaks to give a carbocation and Br^-. We say that the leaving group is "good" because Br^- is stabilized (polarizable). The more σ-donation there is, the more the σ^*_{C-Br} is populated, and the faster the leaving group leaves. Remember that this is a bond-breaking event which involves only one molecule, so it is still 1st order.



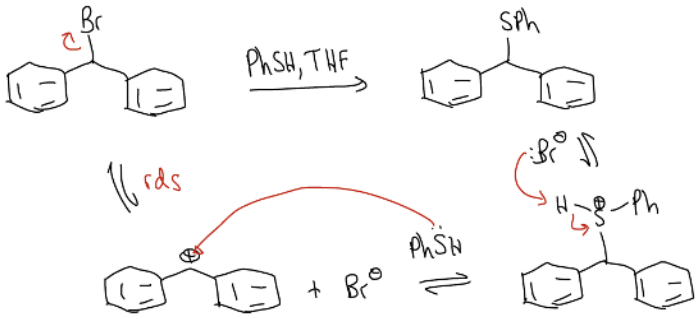
The leaving group ability of a functional group will depend on the pK_a of its conjugate acid. The stronger the conjugate acid, the better leaving group ability of that particular group. For substitution reactions, the leaving group ability cut-off point is a conjugate acid pK_a of 4. Thus, OH^- is never a good leaving group because the pK_a of water is 15.7. This is why we protonate alcohols in the first S_N1 mechanism you learned – protonation turned a good leaving group (OH^-, pK_aH = 15.7) into a much better leaving group (H_2O, pK_aH = –1). Several common leaving groups are listed below:

Let's do a few examples. What is the mechanism of these reactions?

1.

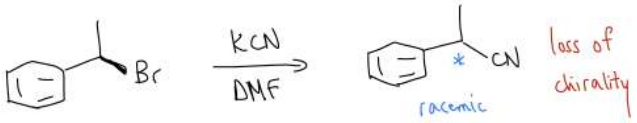


2.

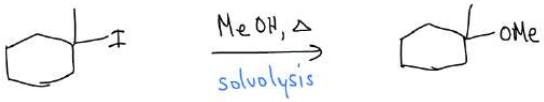


Draw the starting material, reagents, or products of the following reactions:

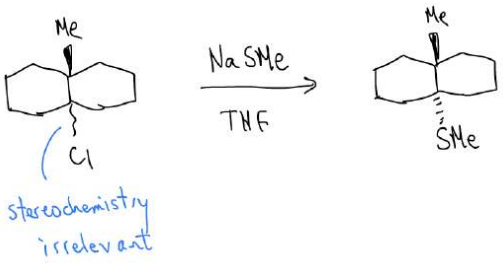
1.



2.



3.

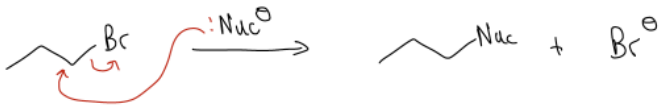


So, to summarize, substituted alkanes (alkyl halides, sulfonates, etc.) that have good leaving group can participate in S_N1 reactions. The solvent for these reactions is normally polar and aprotic (DMF or THF). Alcoholic solvents are not suitable because they can themselves act as nucleophiles (unless one is performing a solvolysis reaction, in which you WANT an alcoholic solvent which acts as your nucleophile). DMF and THF are used because the inorganic salts that are often the source of the nucleophile need to be dissolved in something polar because they are charged.

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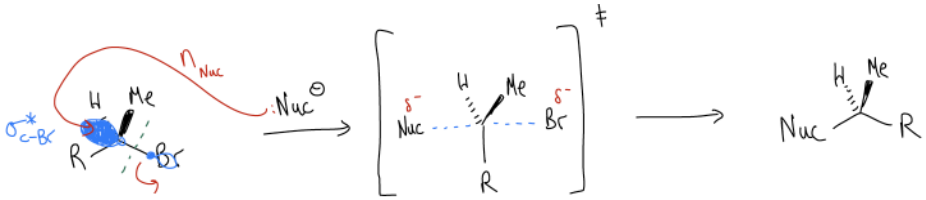
8.5: Nucleophilic Substitution - 2nd Order

The S_N2 reaction is nucleophilic substitution, 2nd order. It is still a substitution reaction, but this time the rate-determining step involves two molecules. S_N2 reactivity is normally reserved for primary (or sometimes secondary) carbon atoms, which cannot form a stable carbocation. Instead, the formation of the σ_{C-Nuc} bond and the breaking of the σ_{C-LG} bond occur at the same time in what is known as a **concerted mechanism**. The reaction is 2nd order because the rate of the reaction is dependent on the concentration of both the nucleophile AND the structure of the starting material.

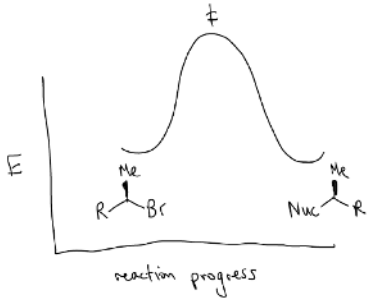


rate = k [nucleophile][alkyl bromide]

What are the orbital interactions involved in an S_N2 reaction? For an S_N2 to occur, the nucleophile must be able to populate the σ^*_{C-X}, where X is a good leaving group ($pK_aH < 4$). This means that the nucleophile must approach exactly 180° opposite of the direction of the leaving group, which is where the larger lobe of the σ^*_{C-X} lies. We call this **backside attack**. Since it is concerted, bond forming and bond breaking events occur simultaneously.

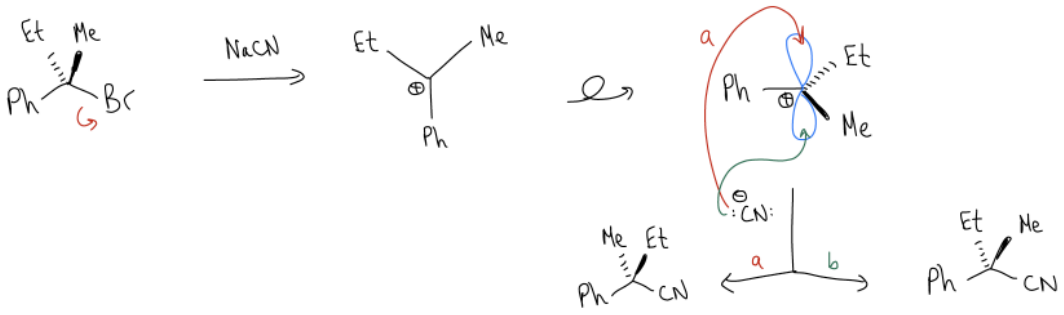


If we look at the potential energy diagram of an S_N2 reaction, we notice that it is quite different than an S_N1 reaction. There is no carbocation intermediate, but rather the rate-determining step involves a transition state that is pentacoordinate – both the nucleophile and electrophile are involved. This is why it's 2nd order.



S_N2 reactions have a very different stereochemical outcome than S_N1 reactions. An S_N2 reaction is **stereospecific**, which means that according to the mechanism, only one stereoisomer is possible. In the example above, the stereochemistry is inverted (**inversion of configuration**). This happens because of the concerted mechanism and the direction of σ^*. Think of it like the sp^3-carbon "flipping" like an umbrella in the wind.

Compare this result to the S_N1 reaction, where the **stereochemical consequence** is not inversion, but rather **racemization**:



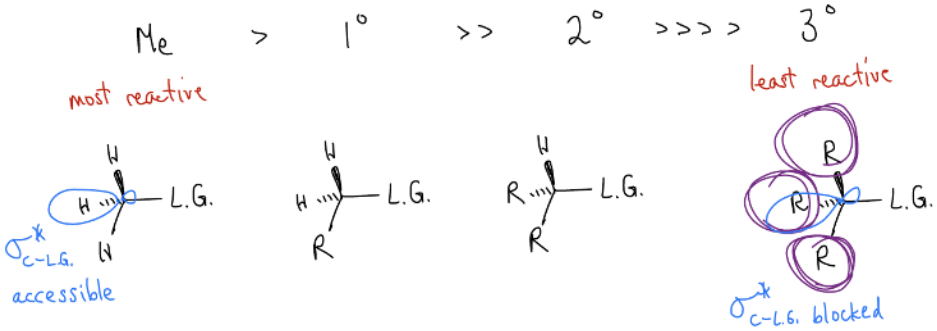
Let's think through the various factors that effect the S_N2 reaction.

1. **Nucleophilicity** – good nucleophiles are **polarizable**; much like their ability to delocalize charge over larger volumes, they also have better orbital overlap with empty σ^* orbitals. Good nucleophiles are often big and diffuse, and you will sometimes hear them describes as being soft (squishy like a pillow). Nucleophilicity does NOT correlate with basicity. Strong bases are tiny, point charges on electronegative atoms. Common nucleophiles are as follows:

Excellent	Good	Fair	Poor
CN^-, RS^-, I^-, RSH	RO^-, Br^-, N_3^-, RNH_2, NO_2^-	Cl^-, $CH_3CO_2^-$ (AcO^-), ROH	H^-, NH_2^-

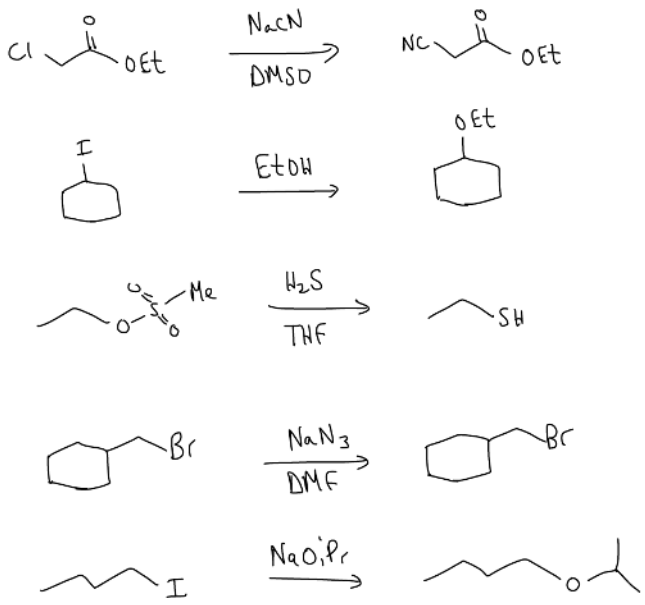
2. **Leaving group ability** – much like S_N1, the leaving group ability correlates with the pK_a of the conjugate acid, which must be less than 4.

3. **Clear trajectory** – the nucleophile must be able to attack the σ^*. If this orbital is blocked by bulky groups, the reaction won't occur. In fact, in some cases, the reaction will proceed by S_N1 instead. S_N2 reactions do not happen for tertiary carbons because the σ^*_{C-LG} is inaccessible because of the steric bulk of the tertiary center; an S_N1 reaction will occur instead.



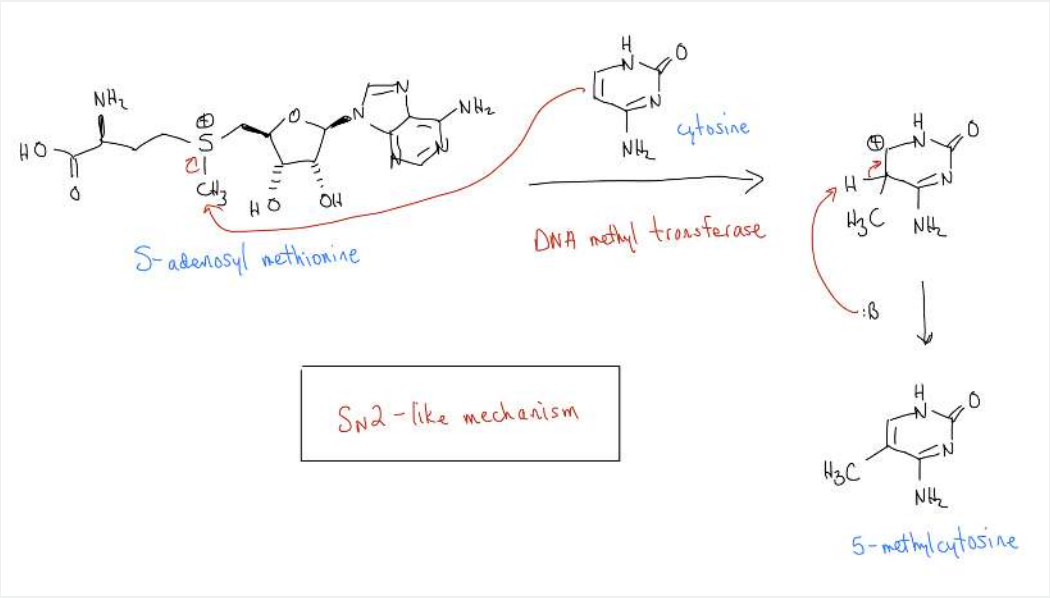
4. **Reaction conditions** –solvents for S_N2 should be polar, aprotic (DMF, DMSO) because these solvents normally help to dissolve inorganic salts. Because there is no charged intermediate (carbocation), alcoholic solvents or other protic solvents will inhibit the reaction. This is because these solvents will aggregate/solvate the nucleophilic anions. Nonpolar solvents (THF, dioxane, MeCN, hexanes) can also be used.

Examples:



Biomedical Spotlight

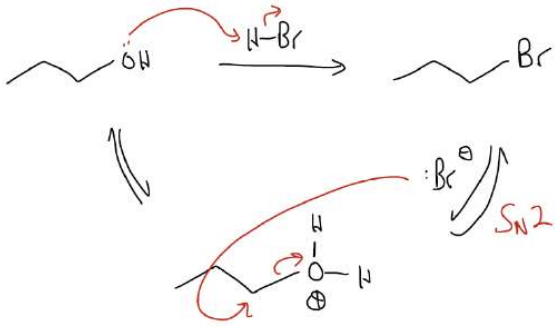
Even though methyl iodide is a common reagent in organic chemistry, it is far too reactive in biological systems to be useful. In fact, it is so reactive that it will readily alkylate one's DNA, causing mutations that can cause disease. Methylation in biological systems is still an important biochemical pathway, but it is highly regulated (methyl groups can be added and removed by enzymes fairly easily). The source of the methyl group, however, is a small molecule known as *S*-adenosyl methionine (SAM). SAM is generated by the union of the amino acid methionine with the nucleobase adenine. Since methionine has a methylthioether functional group, it becomes electrophilic at carbon when activated by adenine (notice the positive charge on sulfur - this makes the methyl group highly electrophilic). As a result, S_N2-like mechanism can occur between nucleobases like cytosine. This reaction, whereby a methyl group is transferred to a substrate in S_N2 fashion, is catalyzed by a DNA methyl transferase and is the main source of methylation events in biological systems. But SAM is far less toxic to living organisms!



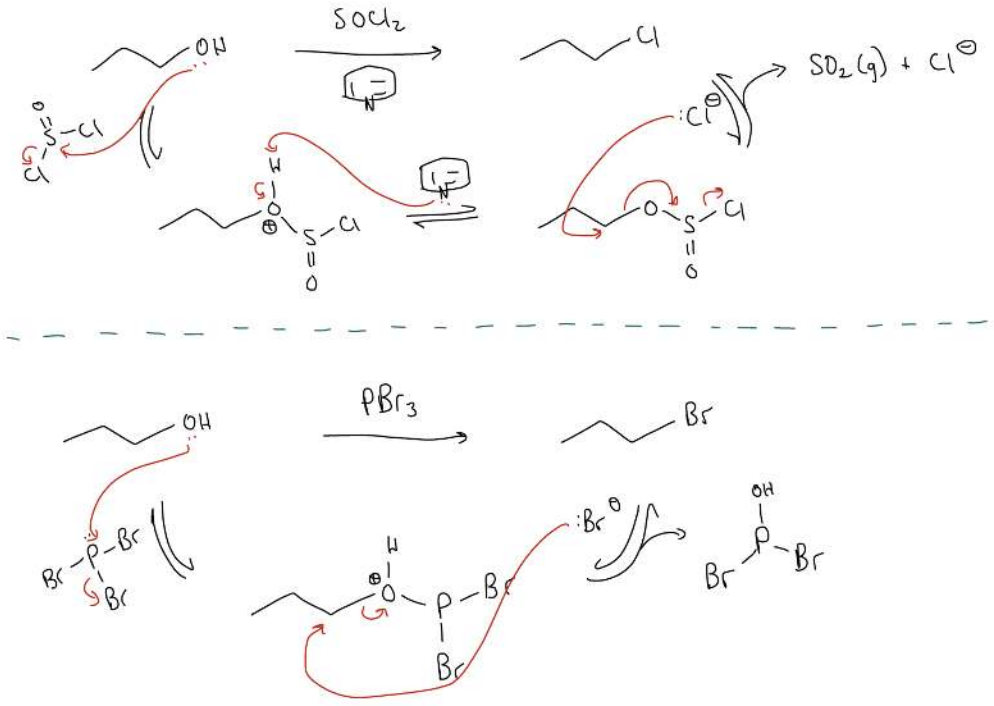
8.5: Nucleophilic Substitution - 2nd Order is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

8.6: Converting Alcohols into Better Leaving Groups

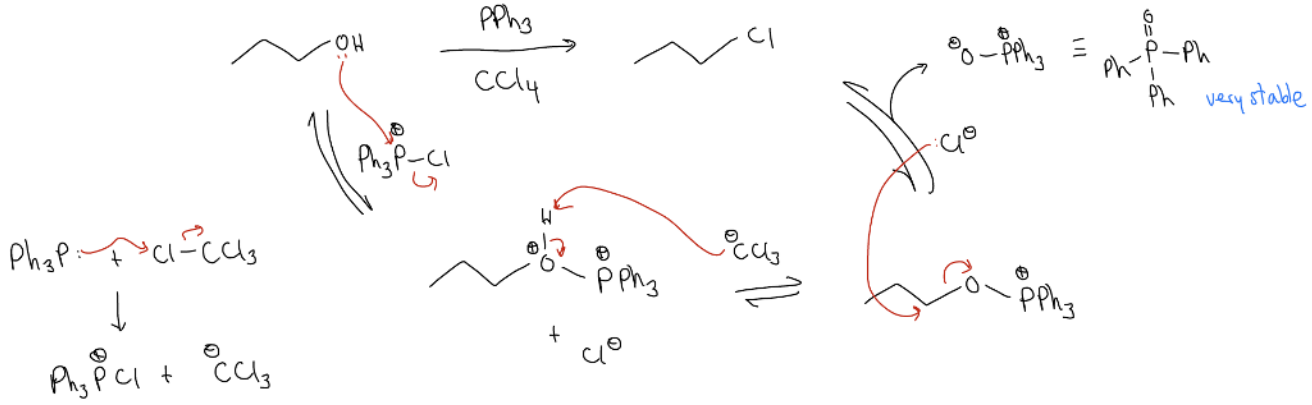
One of the key features of the S_N2 reaction is that it is useful for substitution of primary (or secondary) carbon atoms. You've come across examples above where the leaving group is mostly a halide or sulfonate anion. Recall that conditions for substitution of an alcohol involve protonation of the alcohol first, then loss of water as a leaving group to generate a carbocation. The same holds true for primary alcohols: protonation of the alcohol occurs in the first step, but then loss of water occurs at the same time as nucleophilic attack. Since two things are involved in the rate-determining step, we say that it is S_N2.



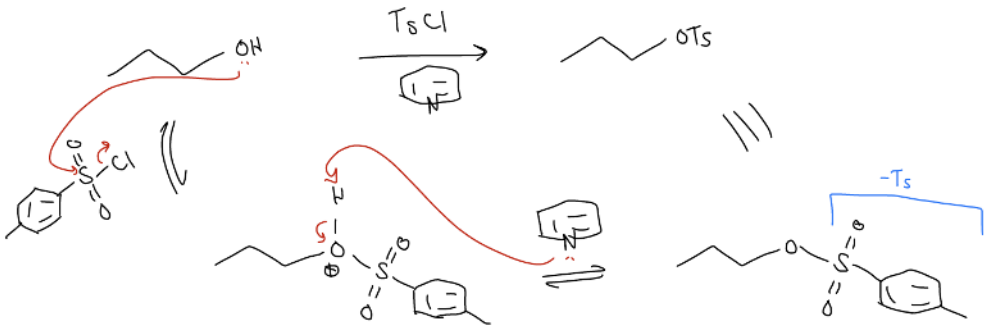
Along the same lines, there are other ways of making alkyl halides from alcohols. These reactions involve converting an alcohol into a better leaving group, much like when we take an alcohol and protonate it to make it into a better leaving group. The reagents we use for this are thionyl halides in pyridine (SOX_2, where X = halide) or phosphorus trihalides (PX_3, where X = halide). You'll notice in the mechanisms for each reaction below that the rate-determining step is an S_N2 reaction.



A similar type of reaction involves treating an alcohol with triphenylphosphine and carbon tetrahalide, according to the mechanism below:



The reactions above form very reactive intermediates in situ that have "**super leaving groups**" capable of attack by halides. The resulting alkyl halides can then be isolated and used in subsequent reactions to build more complex structures. But halides are not the only type of leaving group that we can use for substitution reactions. How would you make alkyl sulfonates? One can prepare sulfonates by reacting alcohols with sulfonyl chlorides. In the mechanism of this reaction, the alcohol attacks the sulfur center like an S_N2 reaction, displacing chloride. Normally, this reaction is performed in the presence of a base (Et_3N, pyridine) that then removes the proton to generate the product.



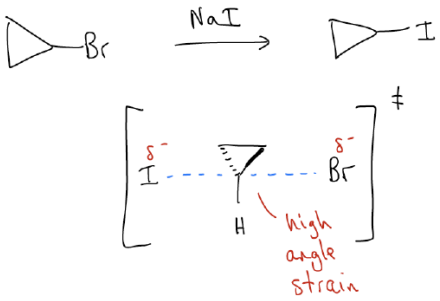
8.6: Converting Alcohols into Better Leaving Groups is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

8.7: Peculiarities in Substitution Chemistry

Finally, there are a few important features and/or exceptions that occur for substitution reactions, whether S_N1 or S_N2:

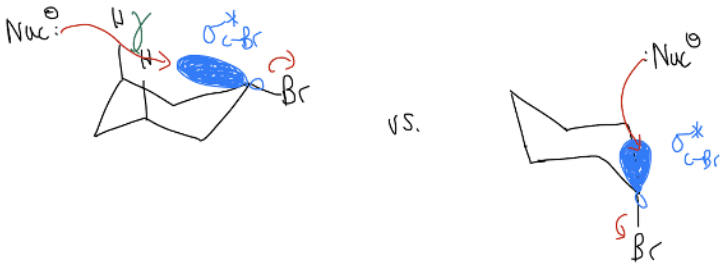
Substitution of small rings

Small rings are notoriously slow S_N2 substrates. Why? Recall that the transition state for an S_N2 reaction involves the formation of a pentacoordinate intermediate. The carbon atom in this intermediate will need to adopt a planar geometry, with bond angles of 120°. Because cyclopropyl rings have considerable angle strain (forced to be 60°), their rates of S_N2 will be much slower. They cannot adopt this geometry very easily, and the transition state energy will be incredibly high.



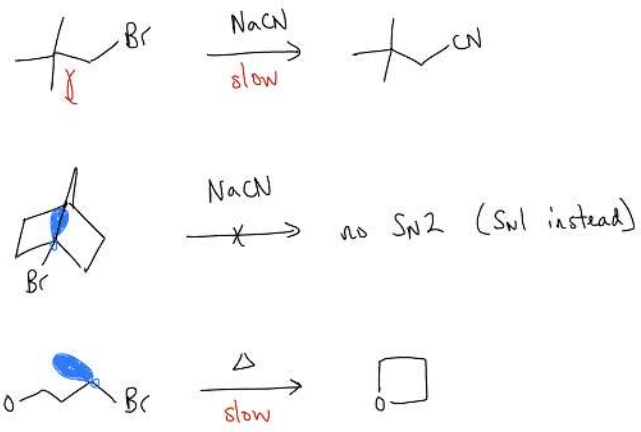
Substitution of cyclohexyl derivatives

By contrast, when cyclohexane rings have a leaving group attached, substitution can occur, but only in a particular conformation. When the leaving group occupies an equatorial position, the σ^*_{C-X} is positioned over the inside of the ring. When a nucleophile approaches, it must pass through the center of the ring, where it is blocked by eclipsing hydrogens, and occurs more slowly. If the leaving group is axial, the S_N2 reaction can occur, even though the conformation itself is higher in energy.



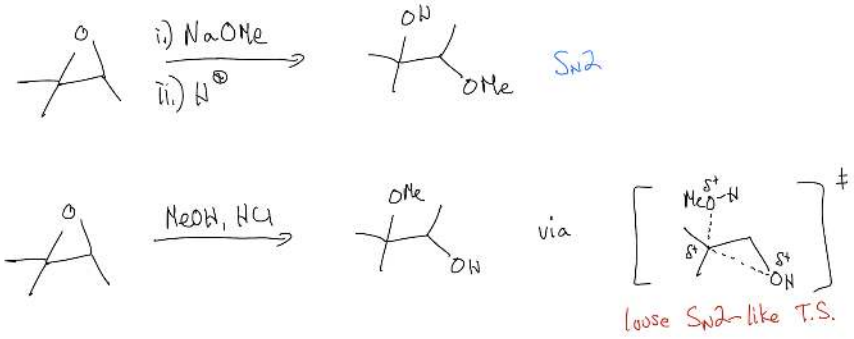
Proper overlap of orbitals

For an S_N2 reaction, proper orbital overlap of the incoming nucleophile and the σ^*_{C-X} is needed. If this orbital is blocked, or otherwise inaccessible, the reaction will not occur. This can happen for neopentyl systems, bicyclic systems, or intramolecular substrates.



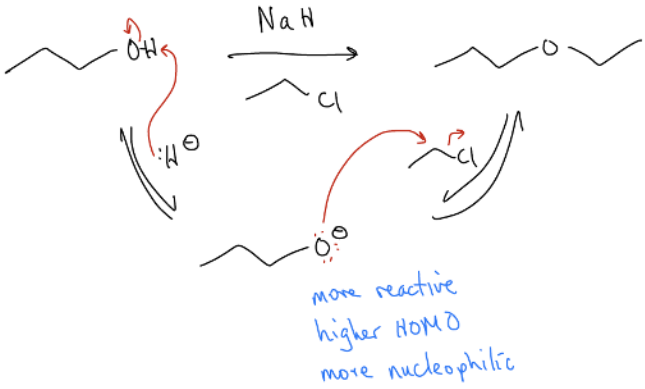
Substitution of epoxides

Nucleophilic substitution that results in the opening of **epoxides** (three-membered rings containing oxygen) can have different regiochemical outcomes depending on the reaction conditions. Under basic or neutral conditions, the nucleophile will attack via S_N2 at the less highly substituted carbon atom. Under acidic conditions, the oxygen will protonate and then undergo an S_N2-like reaction at the more highly substituted center via a loose transition state. This results in the opposite regiochemistry.



Deprotonation of weak nucleophiles

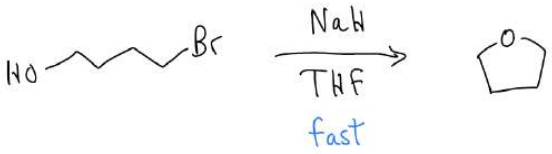
Weak nucleophiles like alcohols and water can be made more nucleophilic by deprotonation. This increases the HOMO of the nucleophile (increase in energy of nonbonding electrons). In some mechanisms, if a base is present, it is likely to deprotonate the acidic proton of the nucleophile to generate a more reactive species.



The reaction between an alkoxide (conjugate base of an alcohol) and an alkyl halide or sulfonate results in an S_N2 reaction that forms an ether. This is known as a **Williamson ether synthesis**, which is the first **named reaction** that you have come across. Name reactions are important reactions in organic chemistry that are described by the person who discovered them.

Intramolecular substitution

Reactions between electrophile and nucleophile can occur between two different exogenous species, but can also occur within the same molecule. **Intramolecular reactions** are faster than intermolecular reactions because there is very little entropic cost – the starting material is preorganized to react.



S_N1/S_N2 competition

Secondary carbons will undoubtedly exhibit features of both S_N1 and S_N2 reactivity. While S_N1 reactivity is normally reserved for tertiary carbons, and S_N2 reactivity for primary carbons, there is considerable overlap for secondary carbons. Using different reaction conditions can normally force one or the other mechanism.

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CHAPTER OVERVIEW

9: Elimination Reactions

9.1: First Order Eliminations

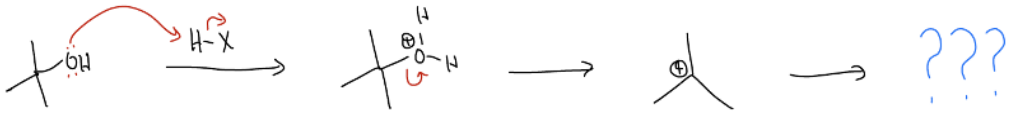
9.2: Second Order Eliminations

9.3: Rearrangement of Carbocations

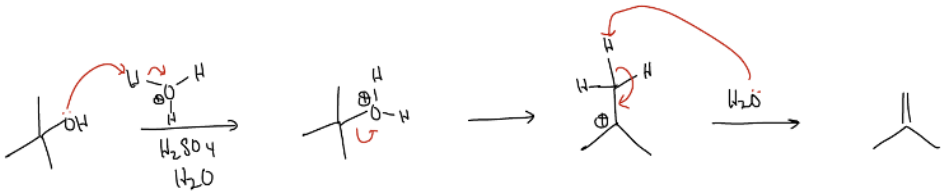
9: Elimination Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

9.1: First Order Eliminations

Recall the S_N1 reaction that occurs between alcohols and hydrogen halides. The first step in the reaction involves protonation of the alcohol to form an **oxonium ion**. We say that H_2O will leave ($pK_a < 4$) to generate a carbocation. At this point, we said that if there was a halide ion in the mixture, it would react to give an alkyl halide. This *assumes* that the halide ion is sufficiently reactive enough to form that σ_{C-X} bond. What would happen if the anion wasn't very nucleophilic?

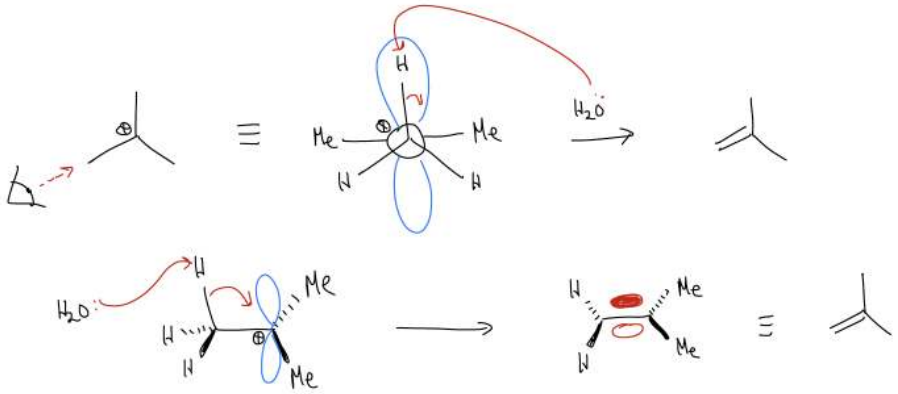


In this case, the carbocation would still form, but would react via a different set of curly arrows to give a different product. We call this reaction an **elimination reaction** because H_2O is eliminated to give an alkene.

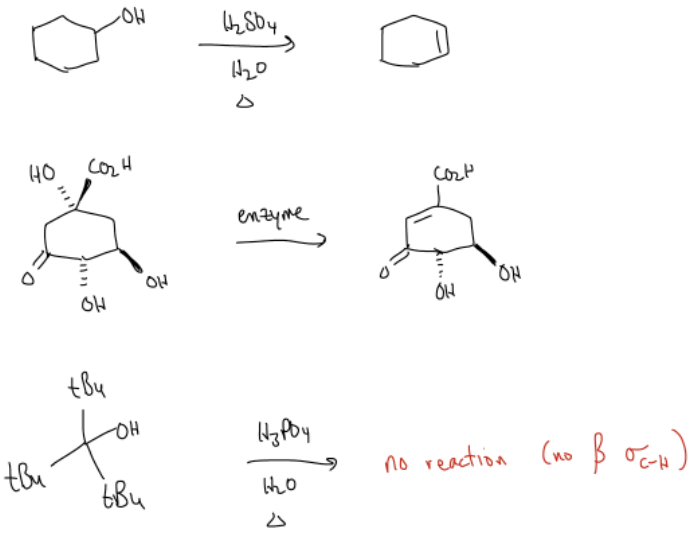


Here, sulfuric acid acts as the proton source, but the hydrogen sulfate anion is too weak of a nucleophile to form a σ_{C-O} bond. Instead, H_2O acts as a base rather than a nucleophile and deprotonates an acidic proton, placing its electrons into a newly formed π_{C-C} bond. This reaction is called an E_1 reaction. Much like the S_N1 reaction, the rate-determining step is the formation of the carbocation.

Let's view this reaction from the perspective of a Newman projection:

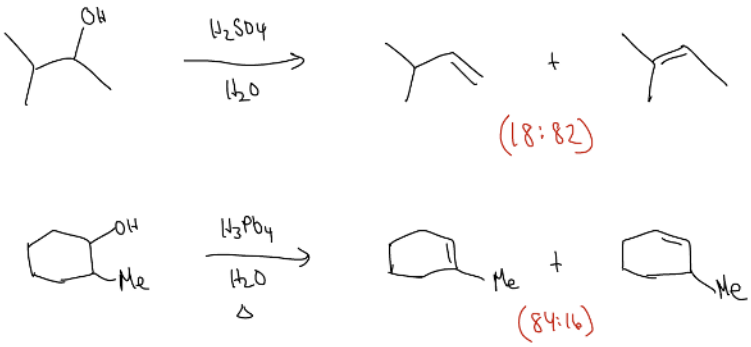


The σ_{C-H} bond is perfectly aligned with the two lobes of the atomic p orbital so that upon deprotonation, the electrons can overlap with the empty atomic p orbital and form a new π_{C-C} bond. Thus, in order for an E_1 reaction to occur, a σ_{C-H} bond *must* be able to overlap with an atomic p orbital. The conformation of a molecule must allow this (σ_{C-C} and σ_{C-X} will not eliminate). Let's look at a few examples:

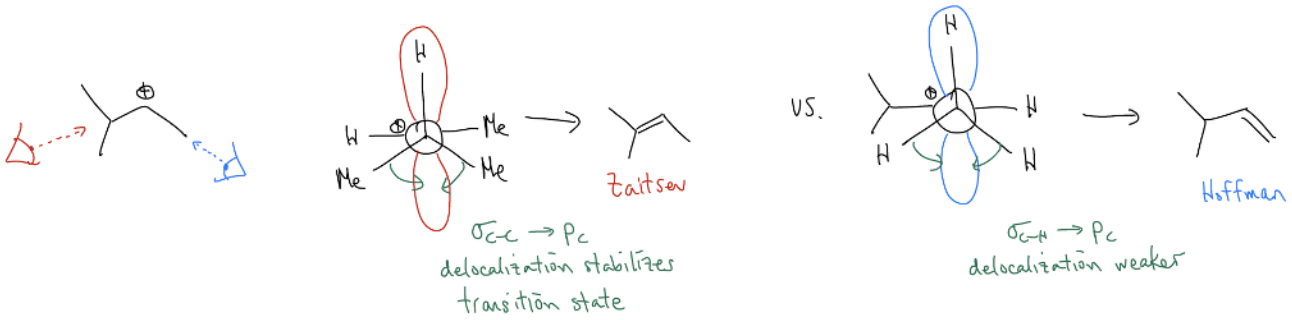


This might sound pretty straightforward, but there are two things that we need to worry about in an E_1 reaction:

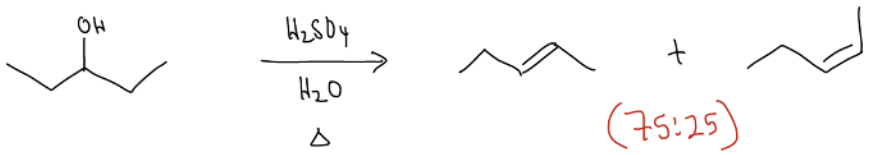
1. **Regioselectivity** – if there is more than one functional group that can react, we must ask ourselves which one will react. This is the **regiochemistry** of the reaction. If one **regioisomer** forms predominantly, we sat that the reaction is **regioselective**. In the case of the E_1 reaction, say that you have several σ_{C-H} bonds that overlap with the empty atomic p orbital. How do you know which one to deprotonate? Deprotonation to give the more highly substituted alkene product of an E_1 reaction will generate the **Zaitsev product**, while deprotonation to give the less highly substituted alkene product will generate the **Hoffman product**. **Zaitsev's rule** states that the more highly substituted alkene will form predominantly. There are ways to favor the Hoffman product, which we will encounter later.



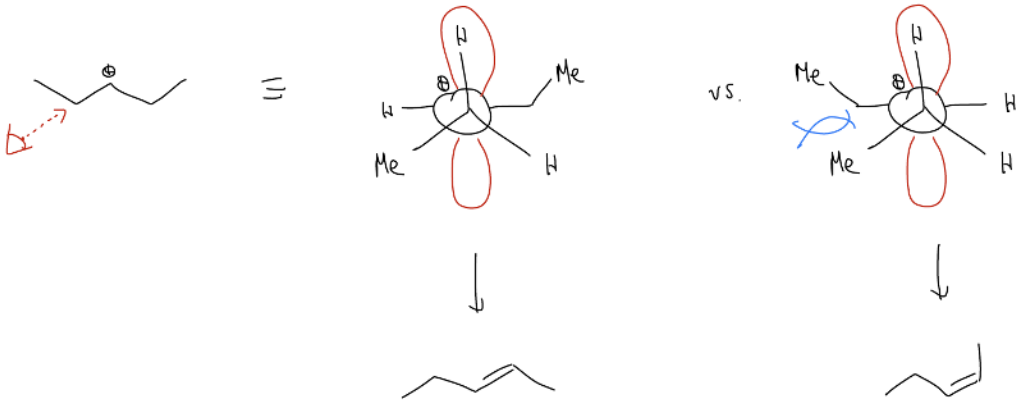
Zaitsev's rule occurs because the transition state energy is stabilized (lower) due to an increase in σ-donation, even if statistically there are fewer σ_{C-H} bonds. This means that the **regiochemistry-inducing step** is under **kinetic control** – the height of the transition state is more important. It just so happens that the thermodynamically more stable product (think, more highly substituted alkene) also forms. But remember that thermodynamics and kinetics are different things.



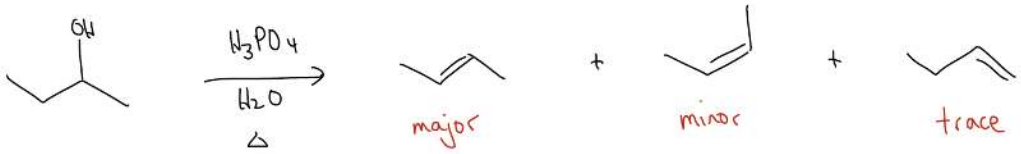
2. **Stereoselectivity** – if more than one stereoisomer can be produced in a reaction, we must ask ourselves which one will be the major product. It is possible that deprotonating a single proton in an E_1 reaction could give more than one product that are themselves geometric isomers (diastereomers).



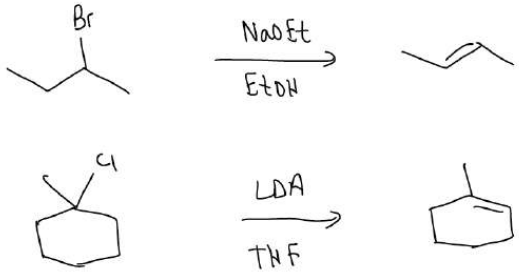
We can rationalize the selectivity by looking at the mechanism. Let's skip forward to the formation of the carbocation, which is the rate-determining step. Everything thereafter is fast, but the energy of the transition state will determine which stereoisomer you get. Therefore, the deprotonation is also the **stereochemistry-inducing step**. There are two different conformations which have overlap between a σ_{C-H} and the atomic p orbital. Deprotonation of these hydrogens will give either the *E* or *Z*-alkene. One conformation has a gauche interaction which increases the energy of the transition state because of steric strain. This would be the unflavored deprotonation leading to the *Z*-alkene. In the other conformation, the two biggest groups are on opposite sides, so this would lead to the *E*-alkene. Again, the stereochemistry is controlled by the energy of the transition state (**kinetic control**), but happens to lead to the more stable product.



If we combine the effects of regioselectivity and stereoselectivity, we should be able to predict the major product from the following reaction:



The E_1 reaction can also occur for tertiary and secondary alkyl halides. In this case, a strong base is needed to perform the deprotonation, but all of the other rules still apply. There must be overlap between at σ_{C-H} and the atomic p orbital, Zaitsev's rule is followed, and the reaction is stereoselective. The rate depends, again, on the leaving group ability and structure of the alkyl halide (hence, first order): rate = k [alkyl halide].

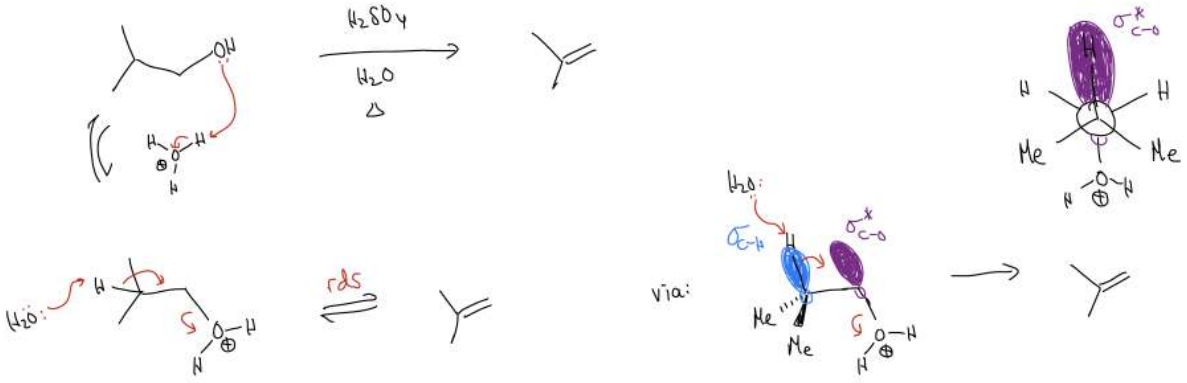


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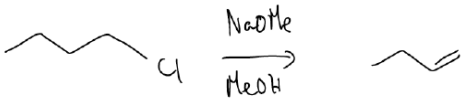
9.2: Second Order Eliminations

It should be no surprise that E_1 occurs mainly for secondary and tertiary carbons, since the mechanism proceeds through a carbocationic intermediate. For primary carbons, formation of the carbocation does not occur, but elimination still occurs to give an alkene product. This time, the mechanism is different. An E_2 elimination proceeds in a concerted manner (similar to S_N2). The reaction is called a **dehydration**.

The deprotonation, formation of the π bond, and release of H_2O all occur in the same step. This step is rate-determining and involves two molecules, so it is second order. Since these curly arrows must occur simultaneously, there are specific restrictions as to what conformations will provide product. In order for correct orbital alignment to occur, the β-proton and H_2O must be **antiperiplanar**, allowing for alignment of the σ_{C-H} and σ^*_{C-O}. Protonation of the oxygen makes the σ^*_{C-O} even lower in energy.



While E_2 reactions are certainly possible with alcohols, the more synthetically useful way to make alkenes is by **dehydrodehalogenation**. Contrary to E_1/E_2 with alcohols (acidic conditions, heat), this reaction occurs under basic conditions at lower temperature.



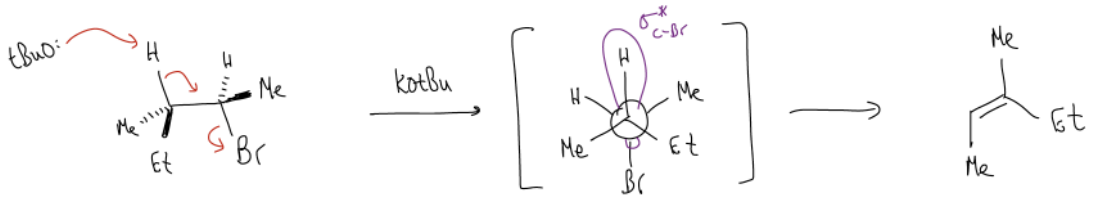
All of the same rules of **stereoelectronic control** apply for E_2:

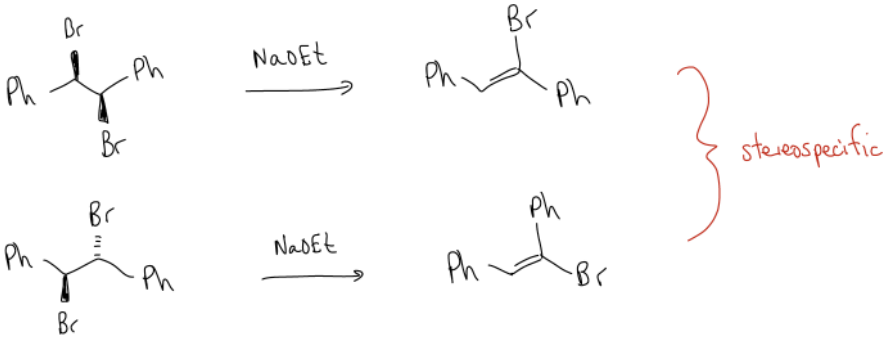
1. Deprotonation of a β-proton must occur antiperiplanar to the halide.
2. σ_{C-H} and σ^*_{C-X} must overlap properly.
3. Zaitsev's rule is followed
4. The reaction is **stereospecific** (stereochemistry of the product is determined by the mechanism) and **stereoselective** (two possible products, more stable one is favored).

So, what determines how fast this reaction goes? Well, if the rate-determining step involves both the base AND the alkyl halide, then making each of these more reactive will increase the rate so that: rate = k [base] [alkyl halide]. The factors effecting rate are:

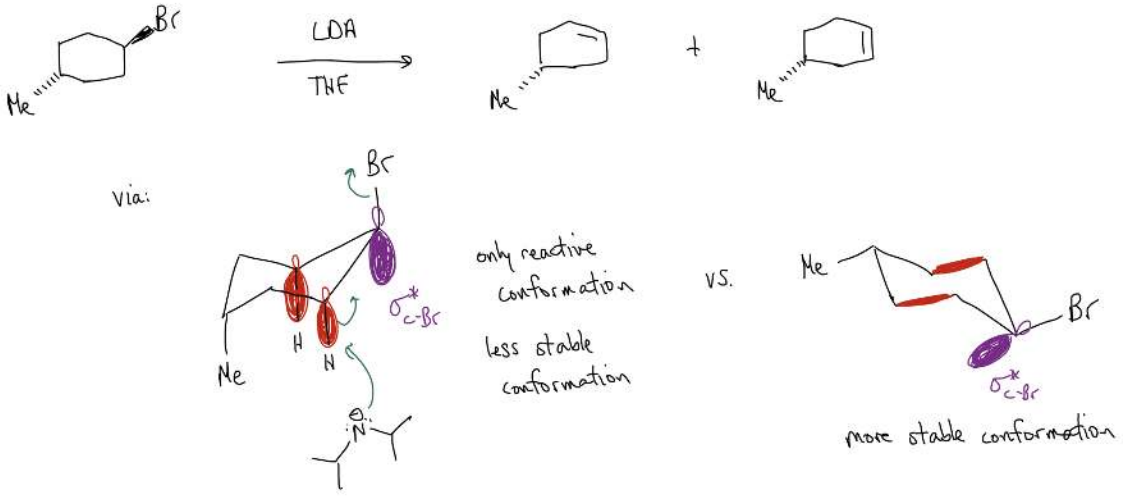
1. leaving group ability – again, the pK_aH of the leaving group must be < 4.
2. structure of alkyl halide – primary and secondary only
3. strength of the base – stronger bases increase the rate

The most common strong bases are LDA (lithium diisopropylamide, pK_aH = 42), $NaNH_2$ (sodium amide, pK_aH = 38), NaH (sodium hydride, pK_aH = 36), KOtBu (potassium tert-butoxide, pK_aH = 18), NaOMe (sodium methoxide, pK_aH = 15). Bulky bases will favor the Hoffman product in both E_1 and E_2 because during the deprotonation, the formation of the more highly substituted alkene is more sterically encumbered.





One consequence of these factors can be seen in the elimination of cyclohexyl halides. We know that substituted cyclohexanes exist in two different chair conformations, but in only one of them is there proper orbital overlap to give the alkene. This might not necessarily be the most **stable conformation**, but it is indeed the **reactive conformation**. A general rule is that the leaving group must be in an axial position in order for an E_2 reaction to occur.



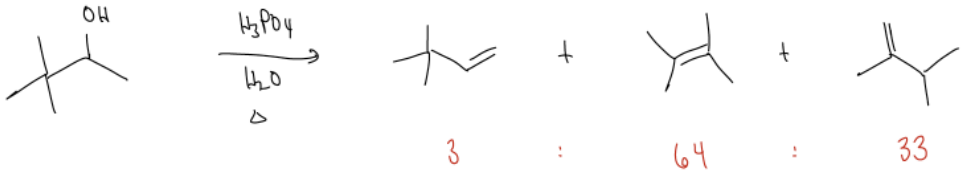
This has an important effect on the product observed, as shown in the example below:



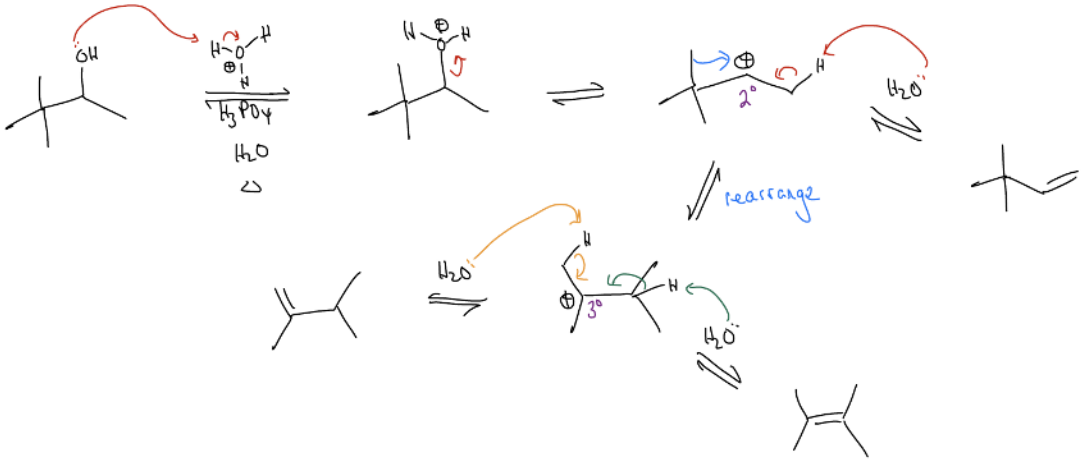
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9.3: Rearrangement of Carbocations

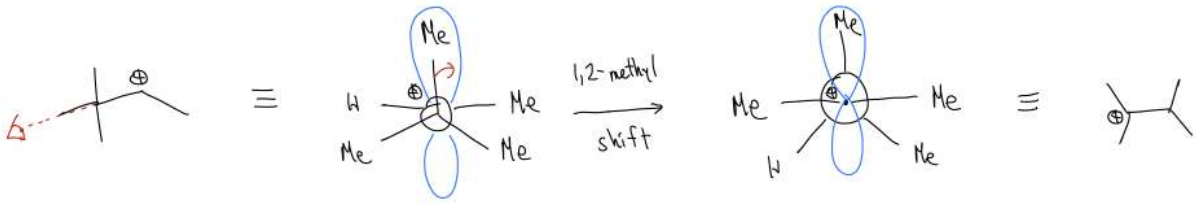
Often, dehydrohalogenation or dehydration reactions result in the formation of several products. For example, while we may be able to justify the formation of the first product in the following reaction, can we draw arrows to produce the other two? Well, this would involve σ_{C-C} bond cleavage, or rearrangement of the carbon skeleton.



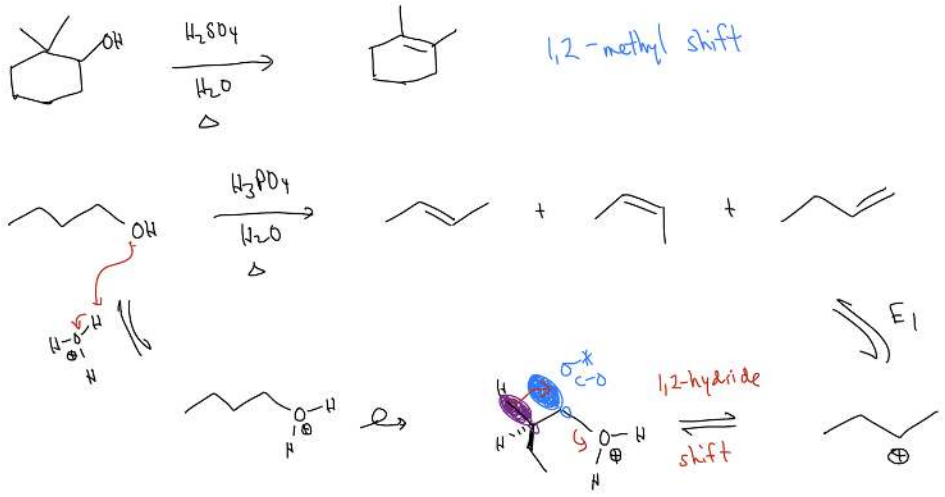
Rearrangements occur when the formation of a carbocation results in a reorganization of the σ-framework to generate a more stable carbocation. This occurs when σ-donation goes "too far" and the σ bond is actually broken.



Let's take a look at the rearrangement step via a Newman projection. A σ_{C-C} bond is overlapping with the atomic p orbital. This weakens the σ_{C-C} bond so much that it actually breaks and moves over (1,2-methyl shift) to generate a new carbocation, which can then proceed to undergo other things (substitution or elimination reactions).

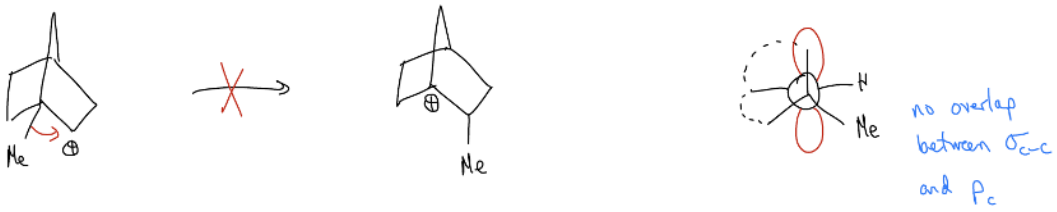


Normally, rearrangements occur because these shifts (1,2-methyl, 1,2-hydride, 1,2-alkyl, etc..) result in a more stable carbocation.

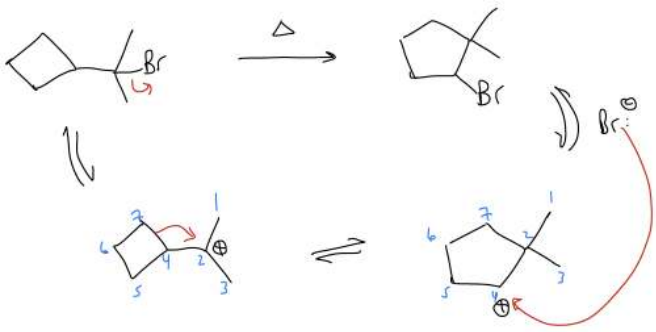


There are some special cases of rearrangements that we must be aware of:

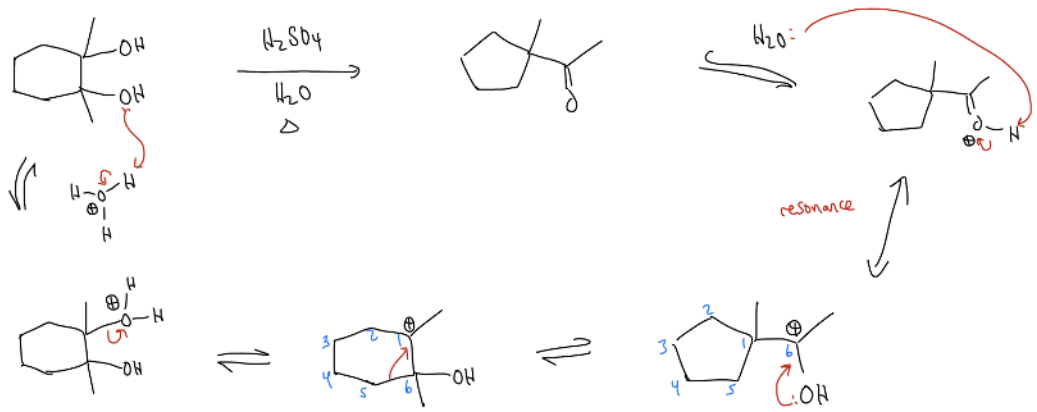
Improper orbital alignment - σ_{C-H} and σ_{C-C} bonds that aren't aligned properly with an atomic p orbital will not migrate, even if a more stable carbocation would result.



Ring expansions - σ_{C-C} bonds can migrate to form larger, more stable rings that relieves ring strain. This is known as a **Wagner-Meerwein shift**.



Ring contraction - σ_{C-C} bonds can migrate to form smaller rings. The best example of this is the **pinacol rearrangement**. The driving force for this reaction is the formation of a C=O bond (the carbocation resulting from the rearrangement is resonance-stabilized).



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CHAPTER OVERVIEW

10: Addition Reactions of Alkenes

10.1: Hydrogenation

10.2: Concerted Cycloadditions

10.3: Polymerization Reactions

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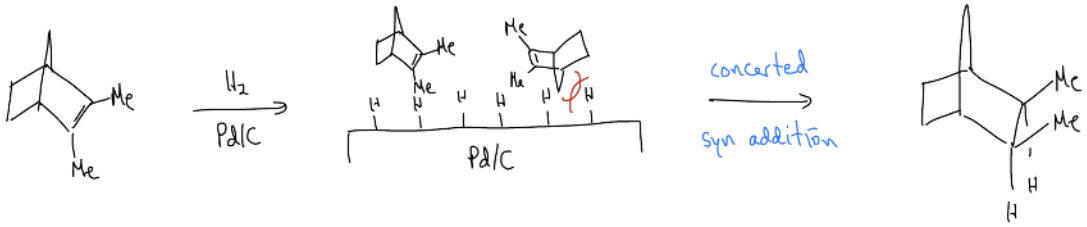
10.1: Hydrogenation

Let's take a step back again and talk about the **electrophilic addition** reaction. Alkenes can undergo electrophilic addition reactions to give substituted alkanes such as alcohols, alkyl halides. In the mechanism of this reaction, the π_{C-C} bond is the HOMO, which reacts with the σ^*_{H-X} to become protonated and generate a carbocationic intermediate that is the most stable. We've said that this happens because unsymmetrical alkenes have π_{C-C} wavefunctions that are polarized due to imbalanced σ-donation. This makes the carbon that is less highly substituted more negatively charged (δ^-) and the more highly substituted alkene carbon more positively charged (δ^+). Thus, the proton becomes attached to the less highly substituted carbon, generating the more stable carbocation. We call this **Markovnikov regioselectivity**. However, if the less stable carbocation is formed, we call it **anti-Markovnikov regioselectivity**. This will be important moving forward, especially when trying to synthesize complex molecules.



You might imagine that there are a variety of other LUMOs that the alkene can react with (not just σ^*_{H-X}). In this section, we will discuss other reactions of alkenes that use the π_{C-C} as the HOMO. These reactions are (for the most part) concerted mechanisms, so there is no carbocation formed. But you must still pay special attention to the regiochemical (Markovnikov vs. anti-Markovnikov) and stereochemical (racemization, inversion, retention, but also cis/trans isomerism) outcomes.

Hydrogenation of alkenes results in the formation of an alkane directly from an alkene using hydrogen gas and a catalyst. It is a formal addition of H_2 across the double bond. A catalyst (Pd/C, PtO_2, Ni^0) is needed to weaken the σ_{H-H} bond, and the reaction is normally heterogeneous (occurs on a surface). The reaction is **stereospecific** since hydrogen is added in a concerted fashion from the same face of the alkene, without any opportunity for bond rotation. This is known as a **syn addition**.



In the example above, we also get a **stereoselective** reaction since the bridgehead carbon is hindering attack of one face of the π_{C-C} bond. The other side is not blocked, so it can interact with the activated catalyst.

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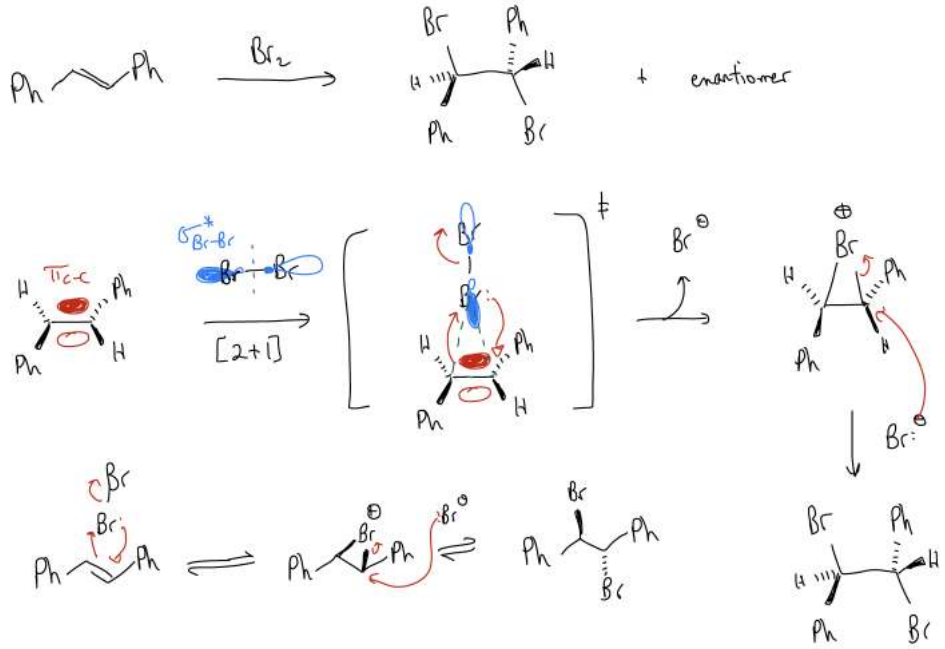
10.2: Concerted Cycloadditions

A **concerted cycloaddition** is a reaction in which electron flow occurs in a circle or ring-like form, when bond-making and bond-breaking are simultaneous. The nature of the electrophile will dictate the size of the ring that forms and what functional group transformations will occur. For example, a [2+1] cycloaddition involves a 3-membered ring transition state where two atoms of the ring come from the alkene substrate (HOMO, nucleophile) and one atom of the ring comes from the electrophile. We will now go through each of these examples.

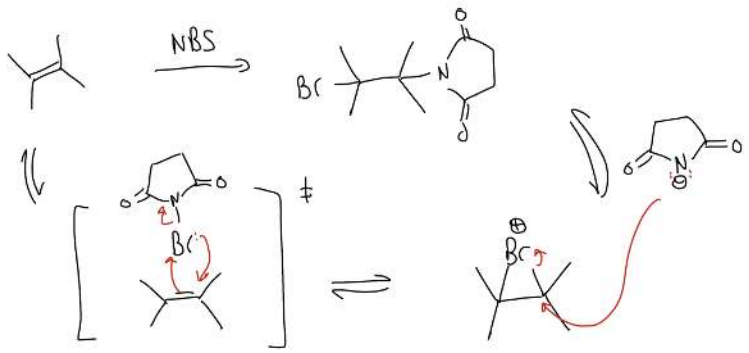
A. **[2+1] cycloadditions**

1. **Halogenation**

The **bromination reaction** involves formal addition of Br_2 across the double bond. The mechanism is a [2+1] cycloaddition followed by an S_N2 reaction.

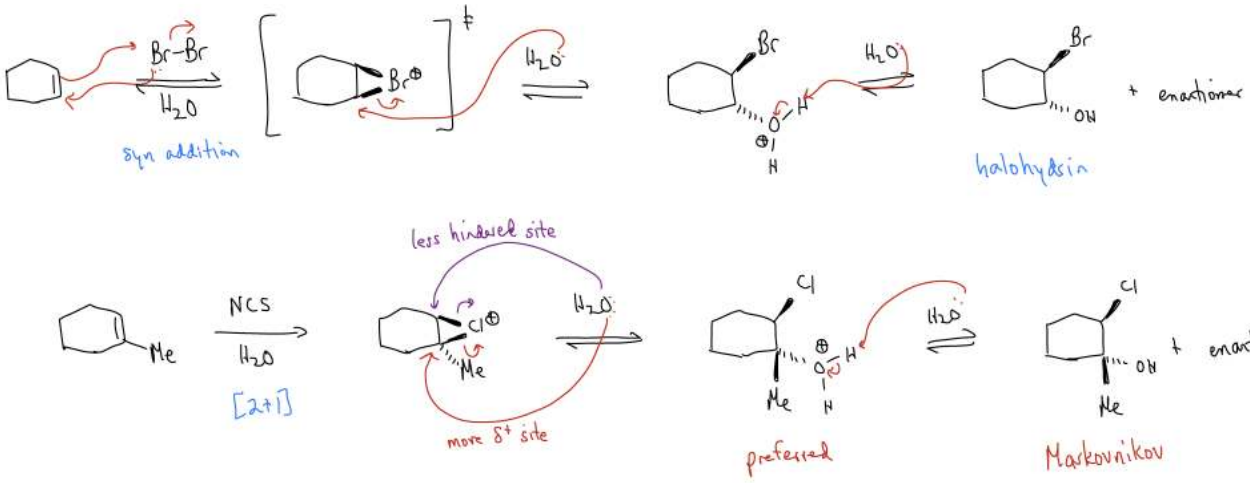


In the first step, the π_{C-C} (HOMO) acts as a nucleophile and populates the σ^*_{Br-Br}, breaking the σ_{Br-Br} bond. At the same time, the lone pairs (n_{Br}) will form a bond with the other carbon atom. We say that the bromine is now **bridged**, and the net result is a **bromonium ion**. There is equal bond formation between both carbon atoms. Notice that there is NEVER formation of a carbocation. The reaction is concerted and the addition of bromine is stereospecific. In the second step, bromide (Br^-) will perform an S_N2 reaction by attacking the σ^*_{C-Br}. The net result (also stereospecific) is that there is **anti addition** across the double bond to give a *trans* dibromide. The fact that we get one product tells us that it is a concerted reaction. If it was not a concerted process and the bridged bromonium ion opened up, then we would get multiple products (from rotation about the s bond), such as the *syn* dibromide. Bromination of alkenes is a good method of testing a sample for the presence of double bonds because the brown color of Br_2 will disappear upon reacting with alkenes to give a dibromide. Another method of bromination is with N-bromosuccinimide (NBS). There are other electrophiles that will perform similar mechanisms but give different functional groups: Cl_2, NCS, I_2, and NIS. In the case of chlorination, there is some stereochemical leakage (some competing halonium ion ring opening), and in the case of iodination, it can only be done intramolecularly.



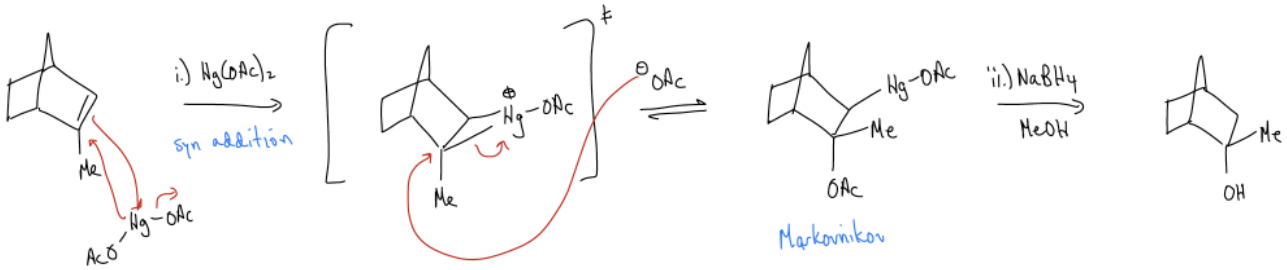
2. **Halohydrin formation**

If a halogenation reaction is performed in H_2O (or some other nucleophilic solvent), a **halohydrin** can form. The stereochemical outcome is critical. Since the halonium ion must be cis, and S_N2 reaction give the trans product stereospecifically. The regiochemical outcome could be described in two ways: attack of the halonium ion at the less sterically hindered site, or attack at the site that is more δ^+. All halohydrins form with Markovnikov regioselectivity because H_2O will attack at the site that is more δ^+.



3. **Oxymercuration**

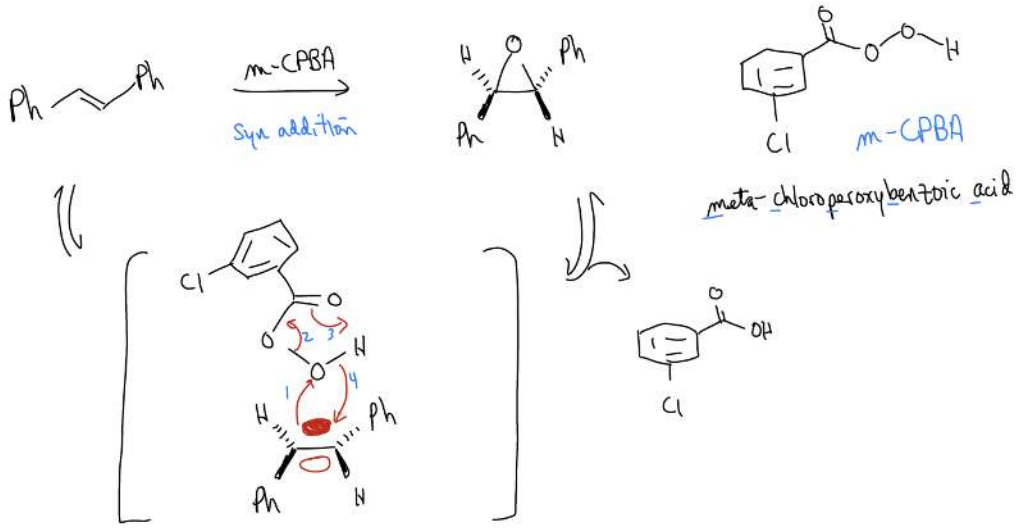
The reaction between an alkene and a mercury(II) salt is known as an **oxymercuration**. The mercurium ion also bridges, and is opened up by the acetate anion. Removal of the mercury can be accomplished by treating the reaction in a workup step with $NaBH_4$ in methanol. This will replace the σ_{C-Hg} with a σ_{C-H} bond.



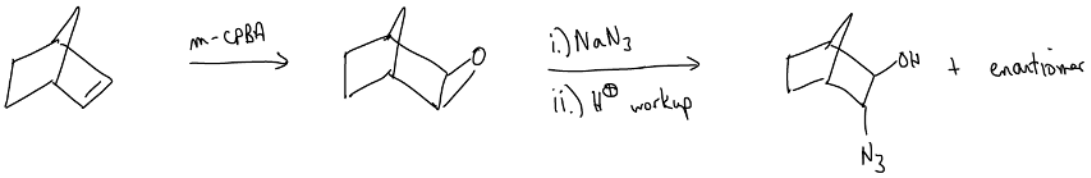
4. **Epoxidation**

The reaction between an alkene and a peroxyacid is known as an **epoxidation**. The product of the reaction is an epoxide, a three-membered ring containing oxygen. The reaction is stereospecific and takes advantage of the low-lying σ^*_{O-O} bond. Just like in

halogenation, a bridged system results, but this time it is not charged. The most common reagent for this is *meta*-chloroperoxybenzoic acid (*m*CPBA).

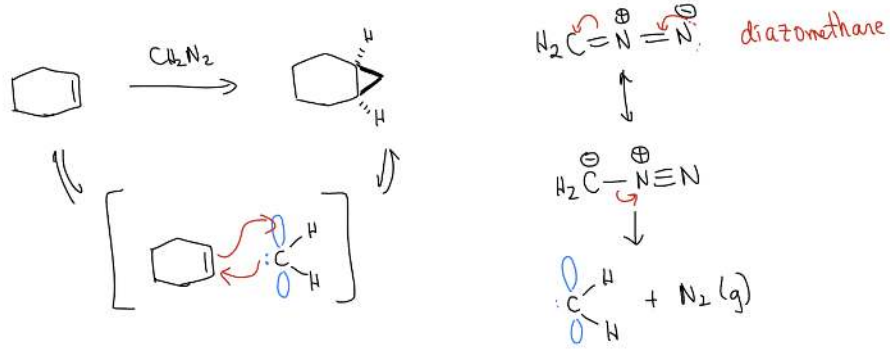


Epoxides are quite useful synthetic intermediates, since they readily open via S_N2.

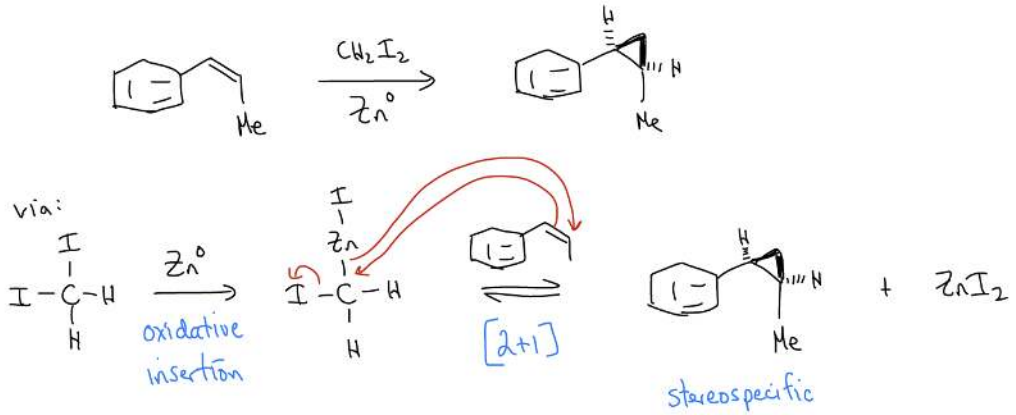


5. **Carbenes and Carbenoids**

Carbenes are another reactive intermediate in organic chemistry (in addition to anions, cations, and radicals of carbon). They are **divalent carbon** species that are overall neutral, meaning they must have both a lone pair and an empty atomic p orbital. These intermediates participate in [2+1] cycloaddition reactions with alkenes, much like *m*-CPBA, to give cyclopropanes. One example is the carbene formed when using diazo compounds, as shown below:



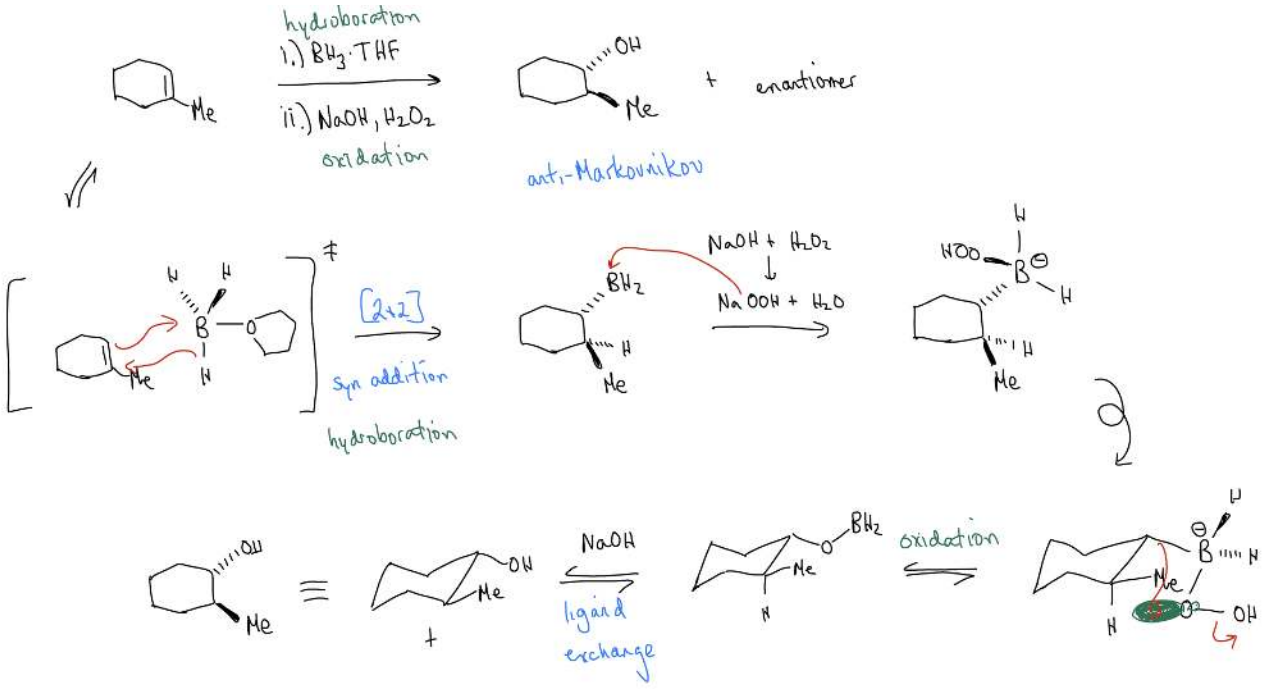
While there are some free carbenes, most reagents that have carbene-like reactivity are bound to a metal and are called **carbenoids**. One example is the **Simmons-Smith reaction**, which involves iodomethylzinc iodide.



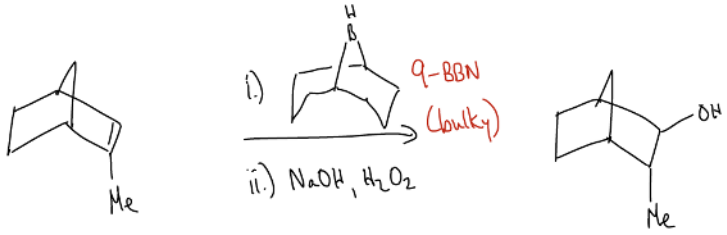
B. **[2+2] cycloadditions**

1. **Hydroboration/oxidation**

The mechanism of the two-step **hydroboration/oxidation** involves a 4-membered ring transition state in the first step. The addition of BH_3 across the double bond occurs so that the less highly substituted carbon is bound to boron. Because of this, when the σ_{C-B} bond is replaced with a σ_{C-O} bond in the product, we get the alcohol substitution on the less highly substituted carbon. Thus, this reaction has anti-Markovnikov regioselectivity (which is the exact opposite of a hydration reaction). The mechanism is found below:

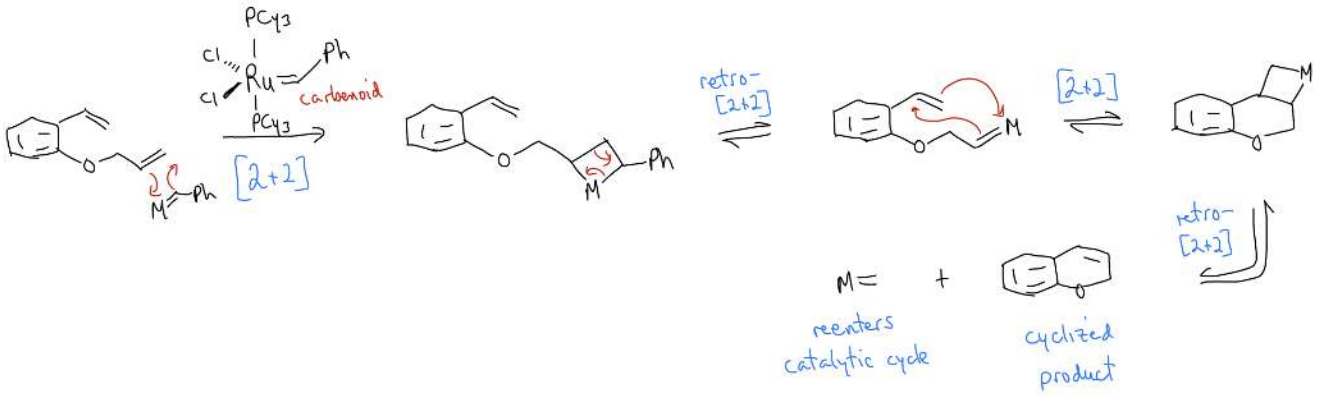


Why does the reaction occur with anti-Markovnikov regiochemistry? Consider the reacting orbitals: π_{C-C} (HOMO) and atomic p_B (LUMO). The carbon with the greatest electron density (coefficient in the wavefunction) is the less highly substituted carbon due to σ-donation. The most electron deficient orbital is the atomic p on boron, so that pairing gives you the best overlap. Steric factors also contribute to this regiochemistry, especially is the boron is attached to big groups, as in the example below:



2. **Olefin metathesis**

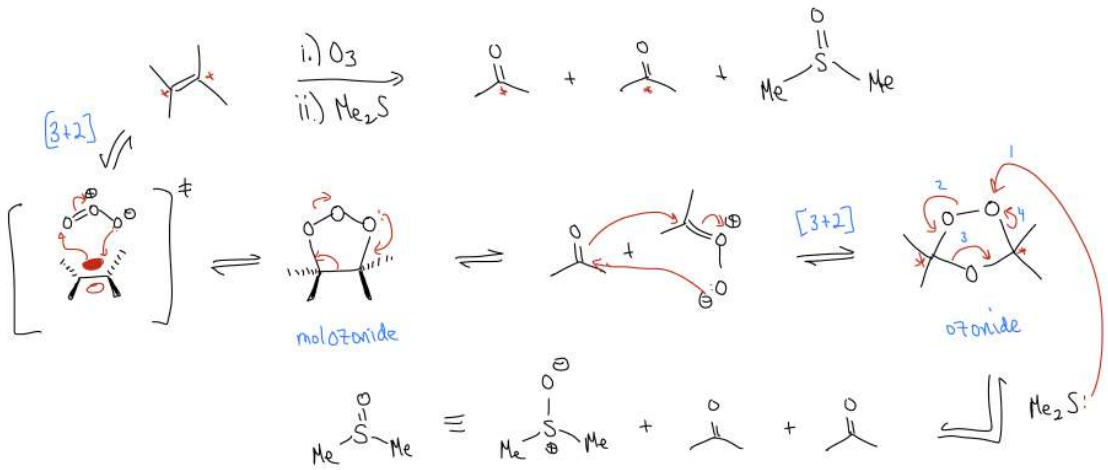
Another example of a [2+2] cycloaddition is the olefin metathesis reaction, which uses a complex of Ru, W, or Mo. These reactions are especially useful for forming larger rings from two alkenes. This reaction also makes use of a carbenoid intermediate.



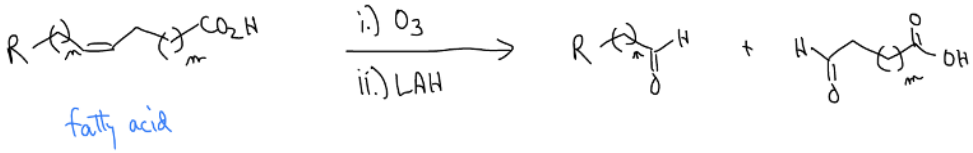
C. **[3+2] cycloadditions**

1. **Ozonolysis**

In an **ozonolysis reaction**, an alkene is converted into two different carbonyls (aldehydes or ketones, depending on the substitution pattern of the alkene). A 5-membered ring transition state brings together the alkene and ozone at low temperature to form an ozonide. This then breaks apart and rearranges to form a second ozonide. Workup with either dimethylsulfide (or $LiAlH_4$, commonly known as LAH) results in formation of two different carbonyls and dimethylsulfoxide. This is a convenient way of making aldehydes/ketones.

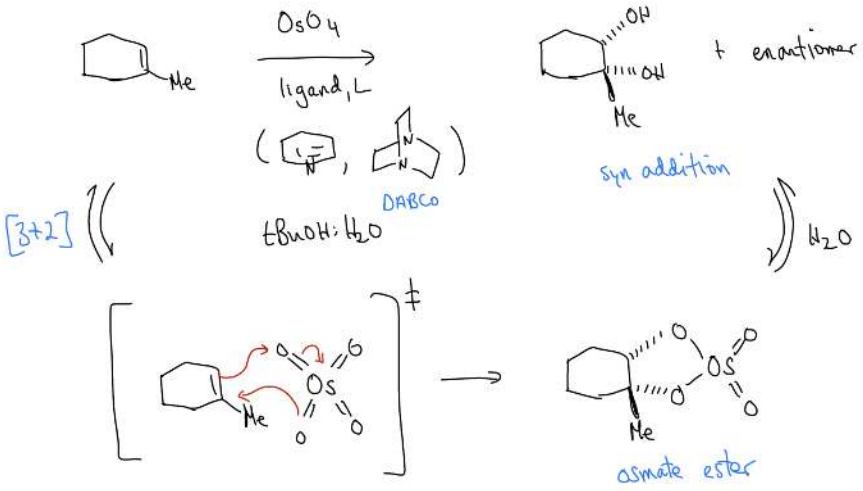


Ozonolysis is a convenient way of analyzing fatty acid content in food, since the lengths of the resulting carbonyls can be analyzed by mass spectrometry.

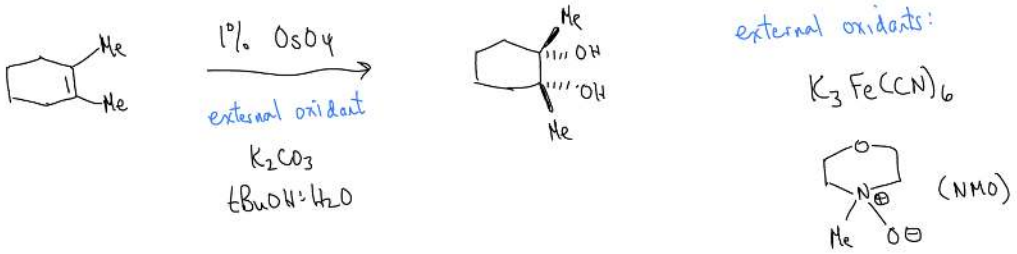


2. **Dihydroxylation**

In a **dihydroxylation reaction**, osmium tetroxide reacts with an alkene to form an **osmate ester,** which then hydrolyzes to give a *syn* diol. Because of the 5-membered ring transition state, the delivery of the two alcohol functional groups occurs from the same face of the alkene.



While this reaction can be performed stoichiometrically, it can also be performed catalytically if using a stoichiometric oxidant like $K_3Fe(CN)_6$ or N-methylmorpholine N-oxide (NMO).

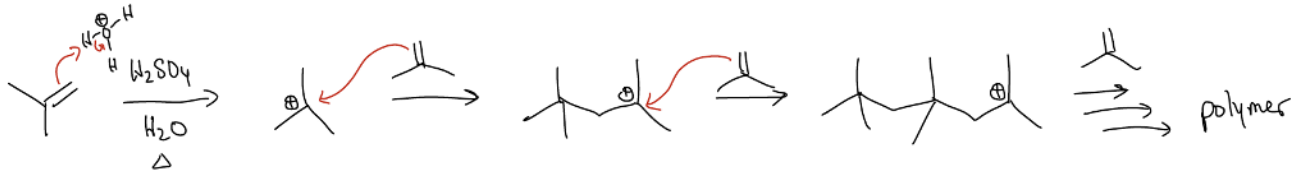


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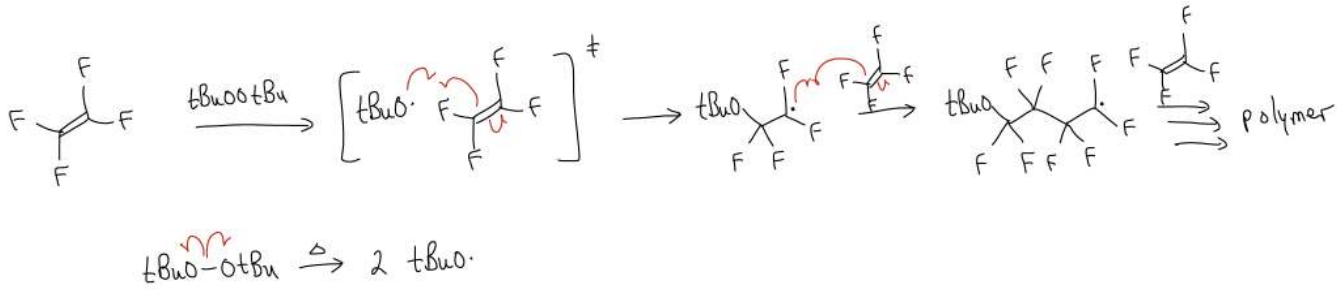
10.3: Polymerization Reactions

Polymerization can occur if a monomer reacts over and over again with other monomers to form very long chains. Polymers have important properties in materials science. Teflon, for example, is a polymer of tetrafluoroethylene and is used to coat frying pans and make them non-stick. **Polymerization** can occur using acid as a catalyst, or it can occur with a peroxide as a catalyst:

Acid-catalyzed:



Peroxide-catalyzed:



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CHAPTER OVERVIEW

11: Synthesis and Reactivity of Alkynes

11.1: Synthesis of Alkynes

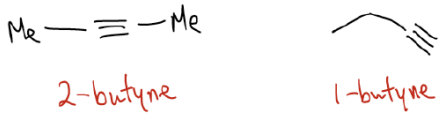
11.2: Alkyne Reduction and Electrophilic Addition

11.3: Cycloaddition Reactions of Alkynes

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11.1: Synthesis of Alkynes

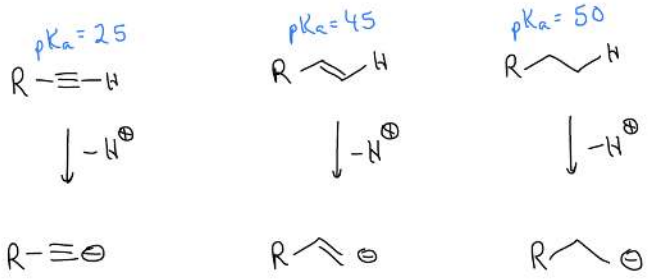
Alkynes are hydrocarbons that contain a C-C triple bond. We name them similarly to alkanes, but use the suffix –yne. As with alkenes, we indicate the position of the triple bond with a number. For example, 2-butyne would be different than 1-butyne. All other rules of IUPAC nomenclature apply to alkynes.



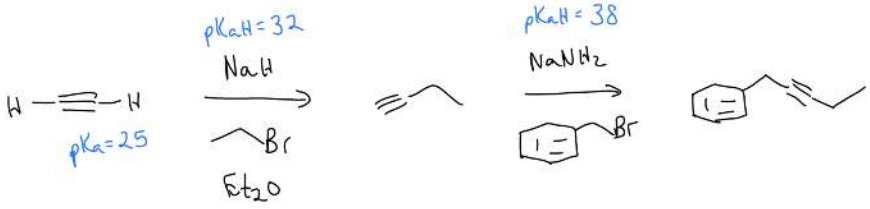
In a C-C triple bond, each of the carbon atoms is sp-hybridized, making the geometry of alkynes linear. Two sp-hybridized orbitals make σ bonds, while the two orthogonal atomic p orbitals make two π bonds that are also orthogonal to one another. These π bonds are equal in energy in alkynes. The HOMO is one of the π_{C-C} bonds, while the LUMO is one of the corresponding π^*_{C-C} bonds. Because of the requirement for a linear geometry, the number of cycloalkynes is limited to cyclootyne and larger due to angle/ring strain. The C-C triple bond is also shorter (120 pm) than the C=C double bond (134 pm), and thus also much stronger. The same rules for s-donation also apply – greater s-donation yields higher stability and greater nucleophilicity.

Synthesis of alkynes

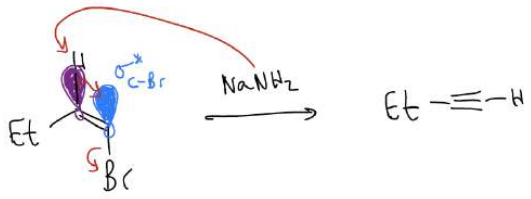
One of the easiest ways to make alkynes takes advantage of the acidity of the σ_{C-H} bond of **terminal alkynes**. Since the terminal carbon is sp-hybridized, it has 50% s character. Atoms with greater s character hold their electrons closer to the nucleus and are said to be more electronegative. This helps explain why alkynes are so much more acidic than either alkenes or alkanes.



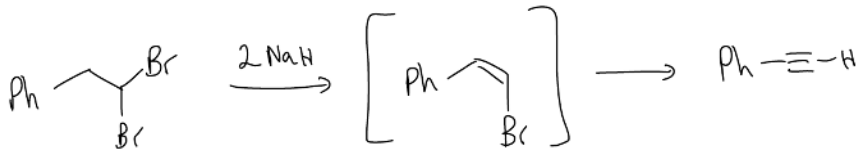
Since we can deprotonate alkynes, they can become nucleophilic. One good way to make substituted alkynes is to perform S_N2 reactions on acetylide anions. If acetylene were alkylated once, the product would be a terminal alkyne. Another alkylation would yield an **internal alkyne**.



Another good way of making alkynes is via elimination (E_2 only). Consider the following reaction. A stronger base like $NaNH_2$ is needed for this reaction, which is concerted (no carbocation forms because it is not stable). Proper orbital alignment is a requirement - σ_{C-H} and σ^*_{C-Br} must be overlapping. In this case, the newly formed π_{C-C} orbital is perpendicular to the existing one.

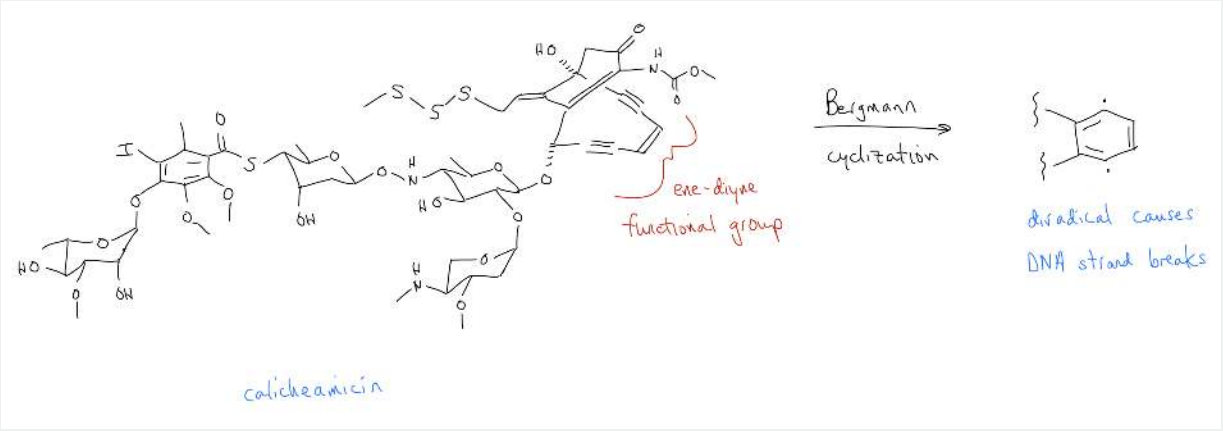


Additionally, if we take a dihaloalkane and treat it with two equivalents of base, the first elimination will give a vinyl halide that can then undergo dehydrohalogenation again to yield the alkyne.



Biomedical Spotlight

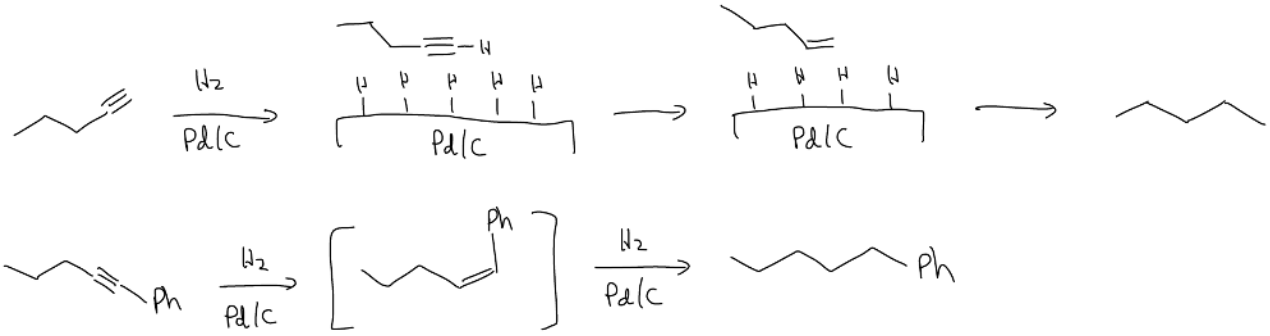
Calicheamicin is a natural product isolated from the *Micromonospora echinospora* bacterium. It is part of a potent class of natural products known as the enediyne antitumor antibiotics due to the presence of these functional groups in their structure. These molecules readily react with DNA. Calicheamicin can bind to the minor groove of DNA, where it becomes activated and then undergoes a Bergman cyclization to give a diradical benzene intermediate. This diradical then reacts with the deoxyribose backbone of DNA, ultimately causing double strand cleavage. While this reactivity makes it a useful molecule to treat cancer, this reaction is unspecific, so it happens in both cancerous and healthy cells. Fortunately, targeted immunotherapies have been developed that direct calicheamicin to solid tumors.



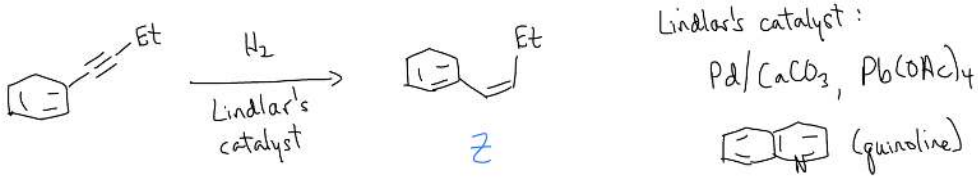
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11.2: Alkyne Reduction and Electrophilic Addition

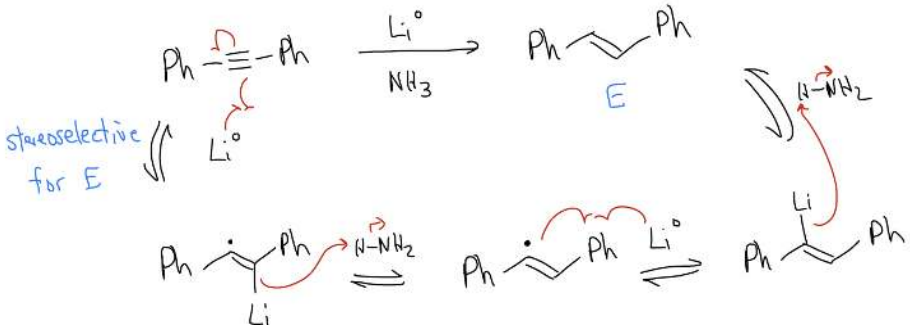
Alkynes react more readily under hydrogenation conditions (H_2, Pd/C, etc.) than alkynes. The heat of hydrogenation of acetylene is more than twice that of ethylene. This reaction is more exothermic and should make sense because π bonds are weaker than σ bonds and alkynes have more of the former and fewer of the latter. There is a problem however with the hydrogenation of alkynes. You might think that the product of the hydrogenation of an alkyne is an alkene, but remember that alkenes also react under these conditions to give alkanes. Thus, reduction of alkynes will proceed all the way to the alkane.



Is there a way to stop the hydrogenation halfway so that the alkene can be isolated? Of course, there is! **Lindlar's catalyst** is a deactivated catalyst that is unreactive towards alkenes. It is a combination of $Pd/CaCO_3$, $Pb(OAc)_4$, and quinoline that partially poisons the palladium enough that alkenes will not become hydrogenated. Since the mechanism of this reaction is still a concerted, syn-addition of H_2 across the triple bond, it is a good method of preparing *cis*-alkenes. This is in contract to the preparation of *cis*-alkenes via E_2, where they will be a minor product due to steric strain in the transition state.



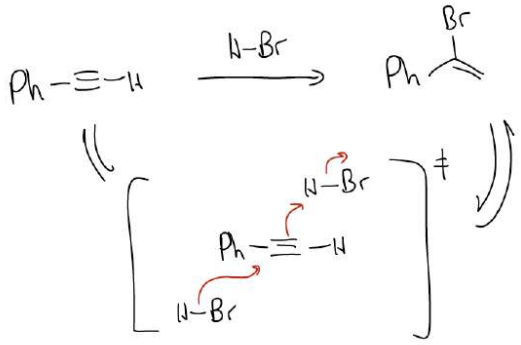
So, what about preparing *E*-alkenes from alkynes? This can be done by performing a dissolving metal reduction. The mechanism is quite different and involves one-electron transfer reactions, similar to the formation of the Grignard reagent. The initial one-electron transfer step is **stereoselective**, giving rise to the *E*-isomer. The reaction is a **dissolving metal reduction** since the metal actually dissolves as the reaction progresses.



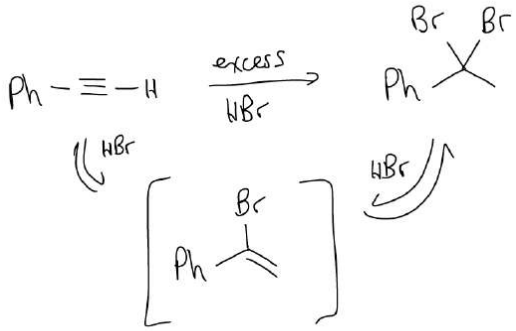
Let's now consider all of the other reactions of alkenes (where π_{C-C} is the HOMO) and how they might be applied to alkynes.

Electrophilic addition

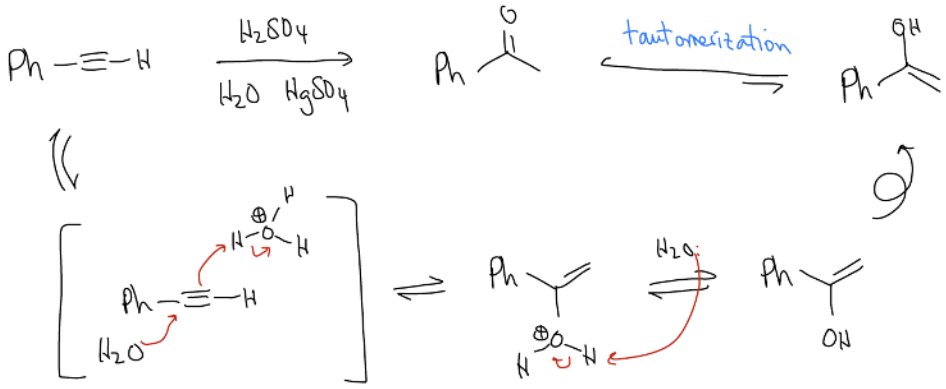
a. **Hydrohalogenation** - This will result in formation of a vinyl halide that is a Markovnikov addition of H-X across the triple bond. The terminal alkynyl carbon has the largest coefficient in the HOMO, so it is most nucleophilic. The rate of this reaction is third order, which suggests a different mechanism is operative. There is no formation of a vinyl carbocation, but rather two molecules of H-X are involved in the transition state. This mechanism is called an addition-electrophilic-termolecular (Ad_E3), and is still not quite well understood.



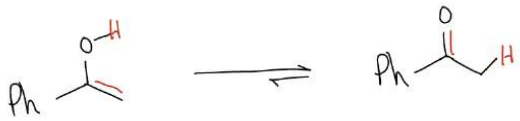
Vinyl halides are notoriously reactive, and in excess H-X, will react again via electrophilic addition to give a **geminal dihalide**, also via Markovnikov regiochemistry.



b. **Hydration** – This will result in formation of a ketone, formed by addition of water across the triple bond in a Markovnikov fashion. Normally, this proceeds via an Ad_E3 mechanism where water attacks the more highly substituted carbon while simultaneously protonating the less highly substituted carbon. Mercury(II) salts are commonly used in this reaction. The net result of the initial Ad_E3 mechanism is an **enol**, which rapidly **tautomerizes** to the **keto** form



Tautomerization is a consequence of resonance and occurs rapidly at room temperature. The keto form is more stable than the enol form, so hydration of alkynes is a good method of preparing ketones. In a retrosynthetic sense, be mindful that this is difficult to see because it is not readily apparent from the structure of the keto form that can come from an alkyne.



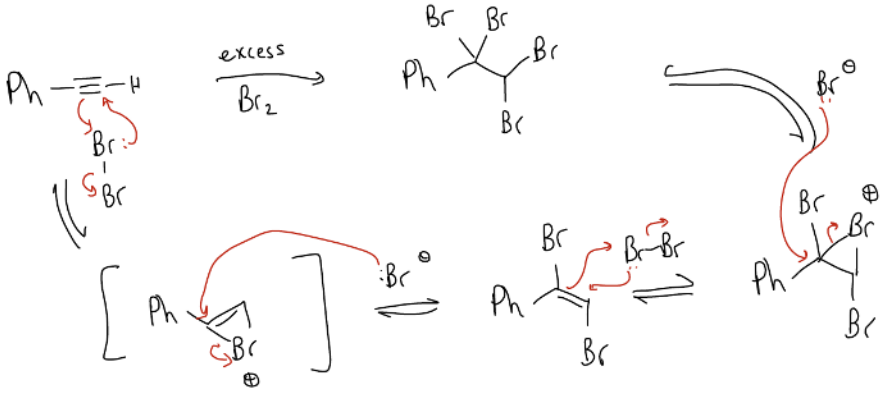
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11.3: Cycloaddition Reactions of Alkynes

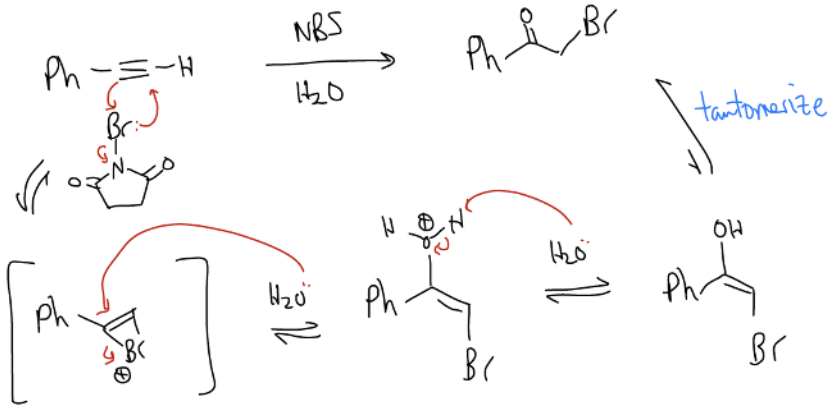
Let's now consider some of the other reactions of alkenes (where π_{C-C} is the HOMO) and how they might be applied to alkynes.

A. **[2+1] cycloadditions**

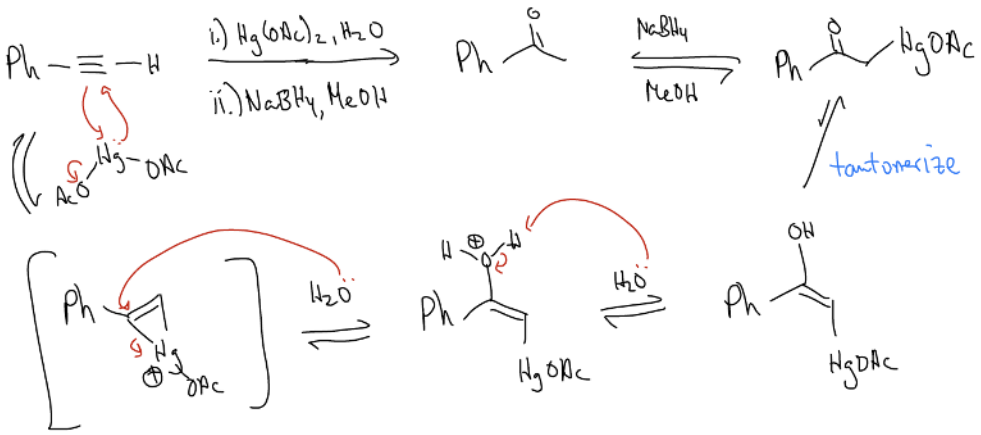
1. **Halogenation** – This will in formation of a tetrahalide, as shown below for a tetrabromide. The mechanism is quite complex but is thought to proceed via a [2+1] cycloaddition of the alkyne to give a bridged bromonium ion intermediate that contains a double bond – a *highly* reactive intermediate. Attack of the bromide on the more highly substituted carbon will generate a *trans*-dibromoalkene. Since this alkene is also reactive towards bromine, a second bromonium ion will form, followed by S_N2 to give the final tetrabromide product. It is very difficult to stop the reactive at the trans-dibromoalkene, even when one equivalent is used. Thus, we normally run this reaction in excess bromine.



2. **Halohydration** – This will result in the formation of an α-haloketone formed by addition of water and a halogen across the triple bond. Using NBS/H_2O as an example, initial formation of a bridged bromonium ion will occur via [2+1] cycloaddition. Attack of this species by water will generate an enol upon deprotonation. This enol will tautomerize to the keto form, which contains a bromide at the α-position. Thus, halohydration is a good method of creating an α-haloketone, which rapidly undergoes S_N2 chemistry.

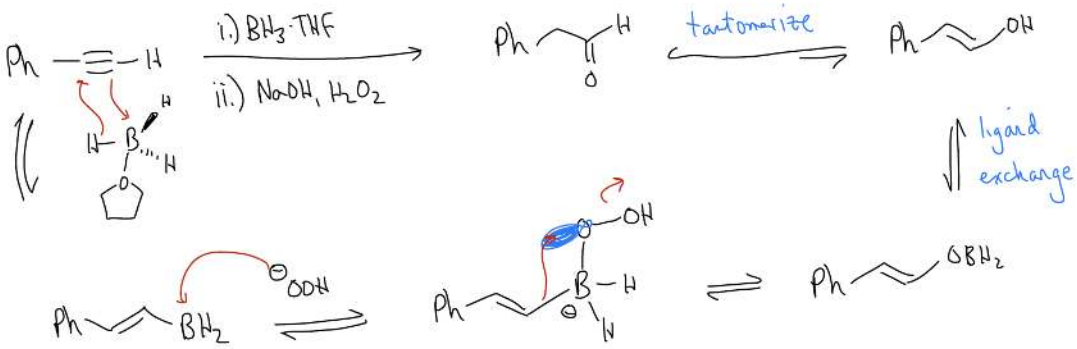


3. **Oxymercuration** – This will result in the formation of a ketone, formed by Markovnikov addition of water across the triple bond. Once again, formation of a mercurium ion will occur via a [2+1] cycloaddition. Water will then attack the σ_{C-Hg} orbital, resulting in formation of a enol upon deprotonation. Sodium borohydride ($NaBH_4$) will then reduce the σ_{C-Hg} bond to a σ_{C-H} bond. The enol will tautomerize to the keto form.



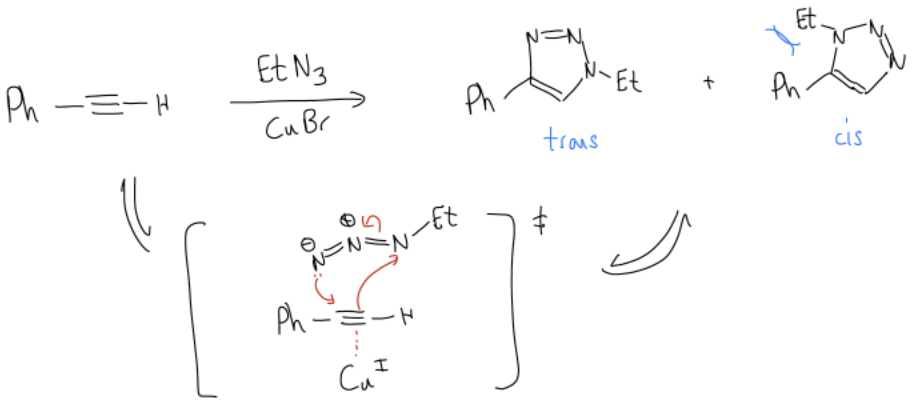
B. **[2+2] cycloadditions**

1. **Hydroboration/oxidation** – This will result in formation of a carbonyl on the less highly substituted carbon. In the case of an unsymmetrical internal alkyne, a ketone will result. In the case of a terminal alkyne, an aldehyde will result. Both products are formed by anti-Markovnikov [2+2] addition of σ_{B-H} across the triple bond. Much like hydroboration/oxidation of alkenes, this is a syn-addition. Oxidation of the σ_{C-B} bond with $NaOH/H_2O_2$ will generate an enol, which will tautomerize to the keto form.



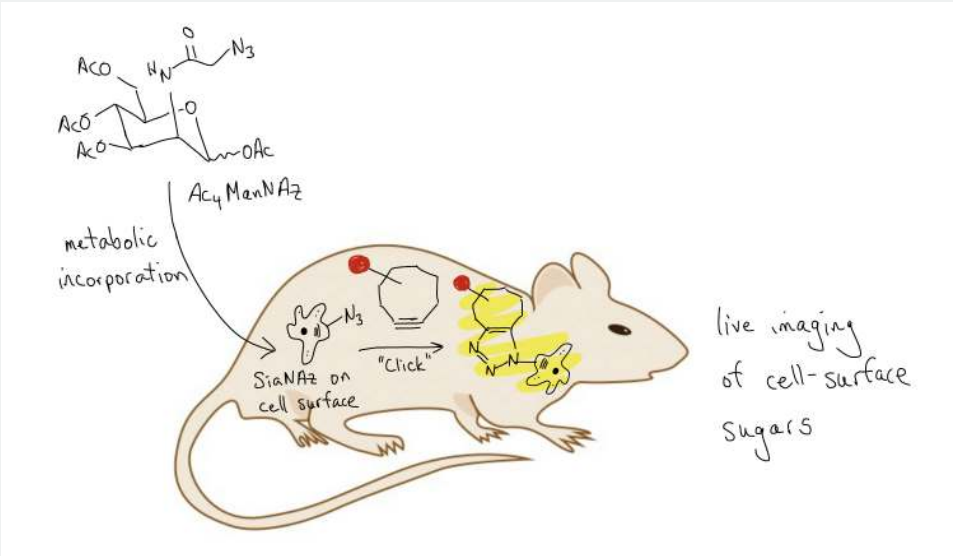
C. **[3+2] cycloadditions**

1. **"Click" chemistry** – This will result in formation of a triazole, where the "trans" regioisomer predominates. "Click" chemistry was popularized by K. Barry Sharpless as a convenient method of making heterocyclic rings. In this reaction, the alkyne participates in a [3+2] cycloaddition with organic azides. The reaction is catalyzed by Cu(I) salts. Formation of the trans-regioisomer predominates because the steric strain in the transition state is minimized when the largest groups are oriented away from one another.



Biomedical Spotlight

"Click" chemistry using azides and alkynes can be useful to create triazole heterocycles as a final target, but it can also be helpful for monitoring biological processes. The problem, however, is that copper is highly regulated in biological systems, and too much can be toxic to cells. Carolyn Bertozzi and coworkers published a study in 2010 (**PNAS**, *107* (5), 1821-1826) in which they took advantage of a cyclooctyne's inherent ring strain to facilitate triazole formation without the need for copper salts as additives. Bertozzi showed that a sugar that had been decorated with an azide group (Ac_4ManNAz) could be metabolically incorporated into the carbohydrates that lie on the cell-surface (SiaNAz). By then adding an exogenous cyclooctyne that had been tagged with an imaging agent, a "click" [2+3] cycloaddition could occur to give a triazole that is appended to the cell surface. This allowed the group to visualize the appearance, location, and metabolism of carbohydrates on the surface of cells in real time.



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