ORGANIC CHEMISTRY - A "CARBONYL EARLY" APPROACH

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1.1: Carbonyl Group - Notation, Structure, and Bonding

Introduction

Organic chemistry is the chemistry of the element carbon. The compounds formed from carbon and a few other elements (O, N, P, S and H) form the chemical basis for living systems. Most therapeutic drugs are organic compounds. Organic polymers, whether obtained from nature or by synthetic means, are extremely important economic materials. These include plastics, rubber, glues, starch, cotton, and wood, as well as the proteins we must have in our diet.

Why is it called "organic" chemistry? Historically, when chemists discovered the Law of Definite Proportions at the beginning of the 19th century, it appeared that this law did not apply to the various compounds they had isolated from plant and animal sources. Carbon compounds can be so complex that the ratios of elements in them did not appear to be simple numbers. For example, ordinary table sugar has the molecular formula $C_{12}H_{22}O_{11}$, not the kind of simple ratio seen with the oxides of copper, Cu_2O or CuO, for example. Chemists imagined that organic compounds were held together by a mysterious "vital force".

The beginning of the end of the "vital force" hypothesis is generally considered to be Friedrich Wöhler's synthesis of urea in 1828. He started with lead cyanate, which is about as "dead" as any chemical can be, and ammonium hydroxide or chloride, also "dead", which generated ammonium cyanate, $NH_4^+OCN^-$ (empirical formula CH_4N_2O) (still "dead"). When he heated the ammonium cyanate, he got urea, H_2NCONH_2 (molecular formula also CH_4N_2O, but atoms arranged differently). Urea is just what the name sounds like, a major ingredient in urine, and was thought at the time to be a purely "organic" chemical. Other syntheses of "organic" compounds from "inorganic" materials soon convinced chemists that organic compounds obeyed the same laws of chemistry as other chemicals.

Although chemists gave up the "vital force" hypothesis at least 150 years ago, a shadow of it lingers on in the popular notion that "natural" organic materials are somehow safer or more healthful than synthetic chemicals. This popular notion ignores the fact that we would not know, for example, what vitamin C is if we could not find out its molecular structure, synthesize it, and show that the synthetic material is in every way identical with the vitamin C that the famous Hungarian chemist Szent-Gyorgy (pronounced "Saint-George") first isolated from Hungarian peppers. This bit of popular culture also ignores the toxicity of nicotine, strychnine, pufferfish toxin, and botulism toxin, the last of which is the most poisonous chemical known. You might even call the AIDS virus an "organic chemical", since it has a known chemical structure, though its ability to reproduce itself in the human body (and to undergo rapid molecular evolution to defeat immune response or chemical inhibitors) makes it far more sinister than a mere poison.

You will be learning and applying the principles which govern the structure of organic compound and relating your understanding of structure to the reactions--the changes in structure--which happen when specific portions of organic compounds interact with other chemical substances. We will spend the first several weeks of the semester looking at a group of organic compounds which share a common structural element--the carbonyl group.

Structural Principles

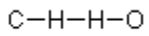
First, though, we need to review a few structural characteristics of the carbon atom. These are ideas which were part of your general chemistry courses, but it will help if we briefly restate them.

1. Carbon is tetracovalent. That means that a carbon atom typically makes four bonds to other atoms and that these bonds are covalent--formed by sharing an electron pair between the two atoms joined by the bond. Such arrangements provide eight valence electrons for a carbon atom, so that it's electronic configuration is like that of the very stable noble gas neon. Similarly, hydrogen forms one covalent bond, oxygen two, and nitrogen three.
2. Carbon can form multiple covalent bonds. That is, a single carbon atom can form a double (to C, O or N) or triple (to C or N) bond to another atom. A double bond would involve two electron pairs between the bonded atoms and a triple bond would involve three electron pairs.
3. Bonds between carbon and atoms other than carbon or hydrogen are polar. That is, in a bond between carbon and oxygen or nitrogen the electrons are closer to the more electronegative element (oxygen or nitrogen) than to the carbon, so the carbon has a slightly positive charge. (Fluorine is the most electronegative element, and the elements close to fluorine in the periodic table are also quite electronegative.)

4. Bonds between one carbon atom and another and between a carbon and a hydrogen are non polar. That is, the electron pair forming the bond is quite evenly shared by the atoms.
5. We can predict the geometry of the bonds around an atom by using the idea that electron pairs and groups of electron pairs (such as in double or triple bonds) repel each other (Valence Shell Electron Pair Repulsion--VSEPR--Theory).

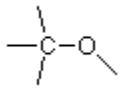
Representing Structures

Now, let's apply some of these ideas to a small organic compound, formaldehyde. The molecular formula (composition by element) of formaldehyde is CH_2O. If we interpret this literally, reading from left to right, we get something like this (bonds are indicated by lines):

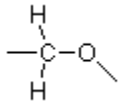


If we check this against our understanding of how many bonds each atom should form, we find that the carbon has one bond where we expect four, the hydrogens have two bonds instead of one, and the oxygen has only one instead of the expected two bonds.

A better approach is to draw four bonds to carbon and then think how the hydrogens and the oxygen might be linked to the carbon. If we connect the carbon and oxygen by a single bond, we get:



Here the lines which don't connect to more than one atom represent unused valences. We have four such unused valences and only two hydrogens to use them, so we'd be stuck with something like (there are other possibilities, but none based on this skeleton that work well):



If we remember the possibility that carbon and oxygen can make a double bond, we can check out a skeleton like:

Now we have two unused valences and two hydrogens to connect to them, so by doing so we arrive at this structure for formaldehyde.

> The structural unit made up of a carbon joined by a double bond to oxygen is known as a **carbonyl group** (often represented as "C=O"). We will spend the next several weeks on the chemistry of this group as it is found in somewhat different structural situations

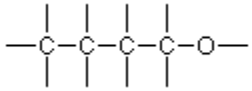
We can learn from this process that converting a molecular formula to a structure is best done by working the atoms which can form more than one bond first, then checking each trial skeleton against the typical numbers of bonds for a particular atom. Those that pass that test can be further tested by balancing the number of unused valences against the remaining atoms so as to come out even.

More Carbons

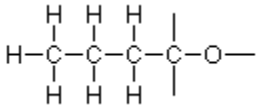
Let's look at a more complex case, one with several carbon atoms. As you will learn from studying the section on isomerism in Brown (Section 3.2), a molecular formula is not enough to specify the structure of an organic compound which includes more than three carbons. We need information about which atoms, particularly carbons, nitrogens and oxygens, are connected to each other. This is often represented in a **condensed** formula like:

$$CH_3CH_2CH_2CHO$$

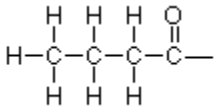
To take a more detailed look at the structure of this compound, we need to expand its representation. (See Brown, Section 3.4) As we have learned to do, we begin by ignoring the hydrogens and focusing on the carbons and the oxygen to arrive at a skeleton. A trial skeleton might be (where the unused valences are again shown as lines that connect to only one atom):



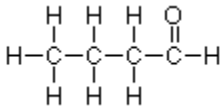
If we compare this skeleton to the condensed formula above, the left end carbon seems to be associated with three hydrogens in the condensed formula and there are three unused valences on the left end carbon as shown in the skeleton, so that matches well. Similarly, the two middle carbons have two hydrogens each, and there are two unused valences on each of those carbons in the skeleton. If we match all these up we arrive at:



The right end carbon and the oxygen are troublesome, though. We have only one hydrogen left and there are three unused valences to deal with. We've seen this situation before when we were working on formaldehyde and we can use the same idea here, so that we try a double bond between carbon and oxygen. That gives us this skeleton:

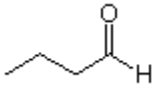


Adding the final hydrogen, we arrive at this expanded structure:



Bond-Line Structures

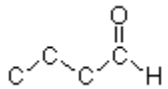
It is often inconvenient to show all the carbons and hydrogens in detail, especially since we will learn soon that the parts of a molecule which are made up of only carbon and hydrogens joined by single bonds do not play a significant role in the reactions of that molecule. (These portions of the molecule are known as "R-groups.") We can represent these atoms and how they are connected by using an abbreviated structural type known as a bond-line structure. Such a structure for the compound we just worked with is shown below:



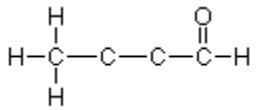
In a bond-line structure, carbons are shown by the "empty" ends of lines and by junctions (corners) between lines. Letters at the end of a line represent atoms of the designated heteroatom (Heteroatoms are atoms other than carbon or hydrogen. Hydrogen

is often shown where necessary for clarity.) Double or triple bonds are represented by two or three parallel lines joining the same two atoms. Hydrogens are added as needed to fill up the remaining unused valences.

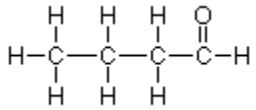
We can "flesh out" the skeleton above by first filling in the carbons at the corners and "empty" ends:



Then we count how many bond each carbon has showing, and add enough hydrogens to each carbon to bring its number of bonds up to four. (For other atoms like oxygen or nitrogen which can make more than one bond, hydrogens are added as needed to arrive at an appropriate number of bonds.) For example, the left end carbon has one bond showing, so we need to add three hydrogens:

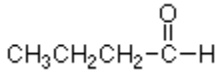


Continuing in the same way with the middle carbons, each of which has two bonds showing, we arrive at the final expanded structure:



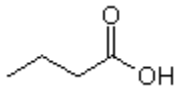
Notice that we didn't need to do anything to the right end carbon (the "carbonyl" carbon) or the oxygen, since these atoms already have the appropriate number of bonds showing.

Sometimes we'll represent a molecule by showing its R-groups in a condensed fashion and its reactive parts (functional groups, see next lecture) in an expanded fashion:



All these representations are useful, but we will commonly use the stick or line representation because it is economical to draw. You should practice converting between stick or line structures, condensed structures, expanded structure and the structures which show R-groups in condensed way and functional groups expanded. Try it with these examples:

A. $CH_3CH_2COCH_3$

B. 

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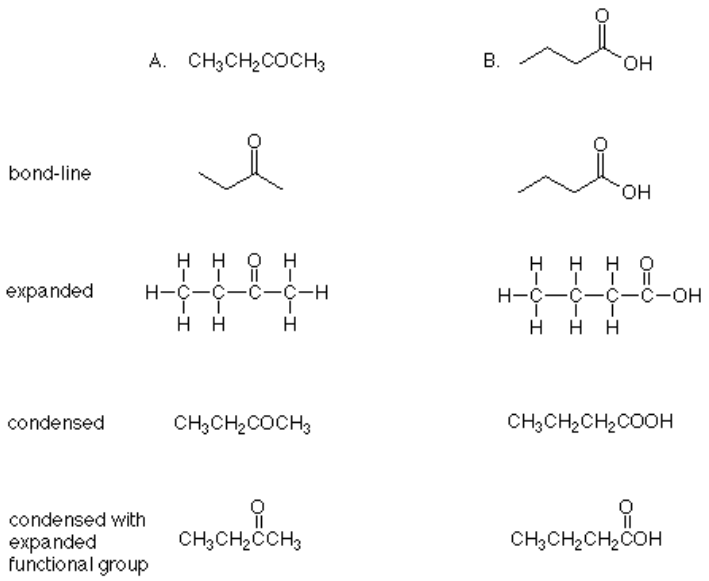
1.2: Functional Groups, Hybridization, Naming

Representation Answers

First, let's look at the various structural representations you were asked to develop for the molecules given at the end of the last lecture. Here they are:



Compare your answers with these representations. Please see me if there are puzzles.

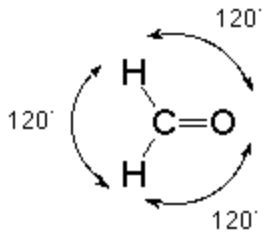
Naming

Naming organic compounds is a necessity, and the names of large molecules can be fairly complex. The rules are simple - but picky. You can learn the basics of these rules by studying on your own using the appropriate sections in Brown. The principles are outlined in Section 3.5. The application of these rules to aldehydes and ketones are discussed in Section 11.2. Study these, practice applying them by doing problems, and bring up puzzles in class for discussion. There will be naming questions on the exams, so you will profit by working on naming. These questions will not tackle complex examples.

Shape

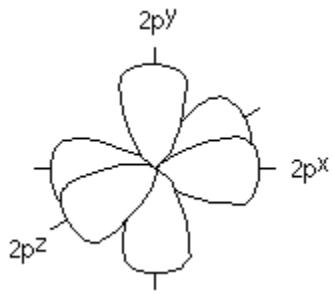
Now let's look at the carbonyl group so as to understand why it is a site for chemical reactivity. We'll start by examining its geometry, specifically the bond angles around the carbon atom. We'll use formaldehyde as our example:

In the context of VSEPR theory we notice that there are three groups of electrons associated with that carbon, two single bonds to hydrogen and one double bond to oxygen. The best way for these clusters of negative charge to be as far apart from each other so as to minimize their mutual repulsion is to adopt bond angles of approximately 120°:



Such an arrangement is given the name "**trigonal**."

The problem with this is that if we think of the orbitals used by the valence electrons of a carbon atom, they are the 2s and 2p orbitals. You will remember that the 2p orbitals are arranged at 90° angles from each other.



This doesn't fit the 120° bond angles we need for our carbonyl group.

Hybridization

Fortunately, the theory of quantum mechanics tells us that we can mix the 2s and 2p orbitals in suitable proportions without violating the mathematical rules of differential equations. If we mix the 2s orbital and two of the 2p orbitals in this way, the resulting orbitals are pointed at from each other. Orbitals formed in this way are called **hybrid** orbitals and the process is called **hybridization**. These particular hybrid orbitals are called sp^2 orbitals since they are made by hybridizing one "s" orbital and two "p" orbitals and they have the appropriate geometry for a trigonal carbon atom such as is found in the carbonyl group. (See Section 1.14 in Atkins and Carey for the same ideas applied to the doubly bonded carbons in ethylene.)

To summarize these connections, when we see a carbon involved in a double bond, its geometry will be **trigonal**, with 120° bond angles, and it will have **sp^2 hybridization**. In a shorthand way trigonal and sp^2 are synonyms.

Bonding

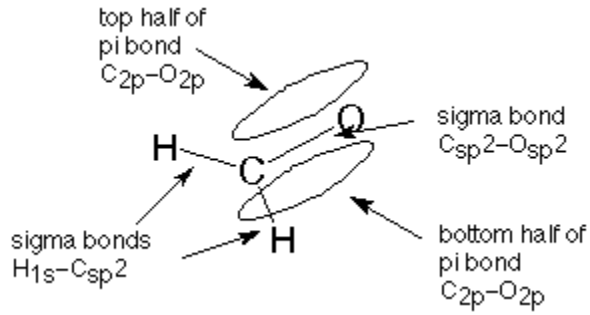
The sp^2 hybrid orbitals formed in this fashion form single bonds. In the case of formaldehyde, each bond to hydrogen is formed by overlap between the sp^2 hybrid orbitals on the carbonyl carbon and 1s orbitals on the hydrogen. This forms what is called a **molecular orbital**, one which involves atomic orbitals from two or (less commonly) more atoms. When two electrons, usually one from each atom, occupy this molecular orbital, we have a covalent bond. This bond is referred to as a *sigma* bond since it is shaped like a cylinder (hot dog) and the letter sigma is the first letter of the greek word for cylinder.

In a similar way, one of the bonds beween the carbon and the oxygen is formed by overlap of an sp^2 hybrid orbital from carbon and a similar orbital from oxygen. (The oxygen orbital is also an sp^2 hybrid orbital, but we will not pursue that.) This is also a sigma bond. What about the second carbon-oxygen bond?

When we discussed the hybridization process earlier, you may have wondered what happened to the carbon 2p orbital which wasn't used to form the sp^2 hybrid orbital. It is still there, and it is used to make the second bond to oxygen. It overlaps with a similar 2p orbital from the oxygen atom to form what is called a *pi* bond. The term pi is used because half of this bond extends above the plane of all three sigma bonds and half extends below that plane. The first letter of the greek word for plane is pi. The

pi molecular orbital can be visualized as a hot dog bun, which would lead us to visualize the double bond as a complete hot dog. One bond is a sigma bond, represented by the sausage, and the other is a pi bond, represented by the bun.

This description of the bonding in formaldehyde can be represented this way (see also Figure 11.1 in Atkins and Carey):



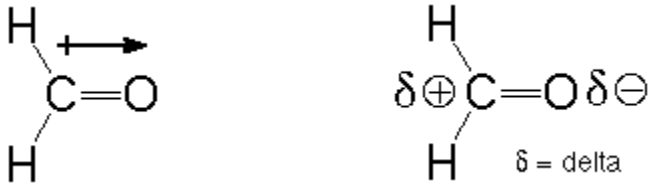
Similar representations apply to the double bonded carbons in ethylene (Atkins and Carey, Section 1.14) and to carbons involved in one double bond wherever they are found.

Reaction Sites

Why does this bonding scheme make the carbonyl group a reactive group, a functional group? There are three things involved here, at least one of which is seen in every functional group.

First, notice that the pi bond is above and below the plane of the sigma bonds. That means that the electrons in this bond (the pi electrons) are not located between the positively charged carbon and oxygen nuclei, but are instead above and below a line joining them. The pi electrons are farther away from the nuclei and are less strongly held to them than are sigma electrons. These pi electrons are consequently easier to move into a different location than are sigma electrons. If they are moved so as to make a new bond involving another atom, the pi bond has been broken, the structure has changed, and a reaction has occured. The short statement: pi bonds are easier to break than sigma bonds. We'll look at several examples in the next few lectures.

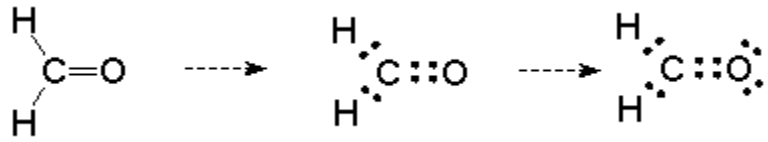
Second, both carbon-oxygen bonds are polar (see Atkins and Carey, Sections 1.5 and 11.2). That means that the electrons in both bonds are more strongly attracted to the more electronegative oxygen atom than the less electronegative carbon. This results in an oxygen which is slightly negatively charged and a carbon which is slightly positively charged. An atom which has an electron pair to donate (a Lewis base) will be attracted the electron-poor carbon and will show a tendency to make a new bond there. An atom which is deficient in electrons (a Lewis acid) will correspondingly be attracted to the electron-rich oxygen and show a tendency to bond there. We can indicate this polarity using the symbol +-->, where the arrow points towards the more negative end. We can also use the greek letter delta to describe a small amount (much less than an electron's worth) of charge:



The short statement: polar bonds are places where reactions occur.

Third, there are unshared pairs of electrons (Lewis base structural sites) on the oxygen. This can be seen if we take our expanded structure for formaldehyde and convert it to a Lewis dot structure by replacing each line with two dots to represent electrons:

This picture is incomplete. The oxygen does not have a full octet and should not be neutral in a formal charge sense. We can correct this by showing the two unshared pairs on the oxygen atom. Doing so represents the full octet and the formally neutral oxygen, and most importantly, tells us that the oxygen is a Lewis base.



We will then expect that the oxygen will be the site of reaction with Lewis acids. This reinforces the conclusion we arrived at on the basis of polarity.

For contrast, consider that the "R-group" parts of molecules are made of carbons and hydrogens which are connected by sigma bonds. The carbons are sp^3 hybridized (Atkins and Carey, Section 1.12) and cannot make pi bonds. Carbon and hydrogen have very similar electronegativity, so the sigma bond between them is not at all polar. All the electrons associated with the carbon and hydrogen atoms are involved in bonding, and each has a completely occupied valence shell. There are no unshared pairs or vacancies, so neither atom will behave as a Lewis acid or base.

To put these ideas into action, go through the functional groups listed inside the front cover of Atkins and Carey (ignore the alkanes). Each group is reactive for one or more of the reasons listed above. List the reasons for each group, and be ready to discuss any puzzling issues in class.

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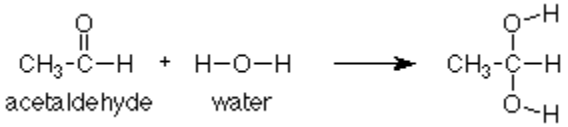
1.3: Additions- Electrophilic and Nucleophilic

Addition of Water

Last time we listed three reasons to expect that the carbonyl (C=O) group would be a functional group, a reactive part of the molecule. All of these reasons were connected with the way electrons are distributed in the group. This makes sense because reactions involve making and breaking bonds. Bonds are electrons, so making and breaking bonds will change the location of electrons. Functional groups are the places where changing the location of electrons can happen fairly easily, which means that the distribution of electrons in a functional group is a key to its reactivity.

We need a specific example to make these ideas useful. We'll begin with the addition of water to a carbonyl group, specifically the aldehyde carbonyl group in acetaldehyde. The overall reaction (from reactants to products) is:



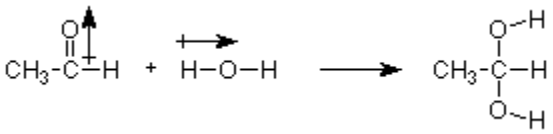
This type of reaction is known as an addition reaction. The name fits, because the product is the sum (or adduct) of the reactants. Addition reactions occur typically with functional groups which include *pi* bonds. Functional groups which include pi bonds are called *unsaturated* functional groups because some of the atoms in them have fewer than the maximum number of sigma bonds. For contrast, those which have no pi bonds do have the maximum number (four for carbon) of sigma bonds and are called *saturated*. (Take another look at the table of functional groups inside the front cover of Brown and note which ones are unsaturated.)

As we study more addition reactions of unsaturated functional groups during the semester, we'll notice that the pi bond in the reactant is typically broken. In the product we find that there are now two groups or atoms attached where the pi bond had been. In our instance, the pi bond between carbon and oxygen has disappeared and the hydrogen from water has added to the oxygen while the OH group from water has added to the carbon.

We can also notice that nothing happened to the CH_3 group. It is saturated so it lacks a pi bond and cannot undergo an addition reaction. It is unreactive and is simply carried along from the reactant to the product.

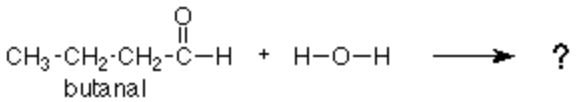
Polarity Matching

Let's probe a little deeper into this reaction. Does it make sense that the OH group from water attaches to the carbon of the carbonyl? Does is make sense that the H from water attaches to the oxygen of the carbonyl? Let's look at the polarity of these materials.

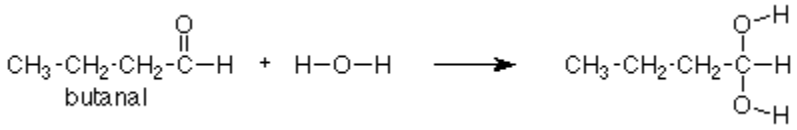


We notice that the *positive* (carbon) end of the carbonyl dipole becomes attached to the *negative* (oxygen) end of the OH dipole. Put another way, the electron-rich oxygen of water attacks the electron-poor carbon of the carbonyl group. Much of what we will learn in organic chemistry can be related to this idea, and we will develop it in more detail later in this lecture.

We noticed earlier that the CH_3 group was not involved in any bond breaking or bond making. In this respect, it is very much like the "spectator ion" which did nothing in an inorganic reaction. These groups are caled "R-groups." Since these groups do not change in a reaction, we should focus our attention on the groups which do, the functional groups. For example, let's predict what the product of the following reaction would be:

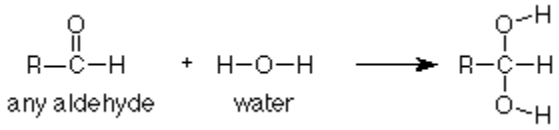


We might remember that the carbonyl group of acetaldehyde (above) adds water, the similar carbonyl group of butanal (below) should do so as well. We would look again at the acetaldehyde reaction, notice where the OH and H go, and put the OH and H in the same positions on the carbonyl group of butanal. We would get the following answer:



General Reaction

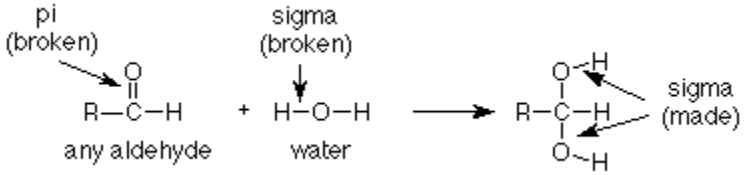
Notice again that the $CH_3CH_2CH_2$ group didn't change and is merely copied from the reactant to the product. It helps immensely to think of this reaction as a reaction of the carbonyl group, not of the whole compound. In that way we can focus our attention on the part of the molecule which reacts and regard the rest as carried along for the ride. To express this in symbols, we can write the following equation which says that addition of water is a general reaction of the carbonyl group which occurs to any aldehyde.



"R" is a "stand-in" for any group which might be attached to an aldehyde carbonyl. If a specific case tells us that R = CH_3, then the complete equation is the first one we looked at (acetaldehyde). If a question tells us that R = $CH_3CH_2CH_2$, as the butanal question did above, then we can use our general"R" reaction (directly above) and just replace "R" with $CH_3CH_2CH_2$ whereever we see "R." This means that instead of learning every reaction of every compound, we only need to learn the reactions of the functional groups and how to apply them to specific cases as needed.

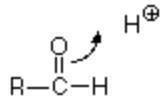
Mechanism

Now that we know something about how to use general ("R") reactions to tackle specific cases, let's turn to another question. How does this reaction take place? What sequence of events results in the breaking of the C-O pi bond and the O-H bond in water and the making of a new C-O sigma bond and a new O-H sigma bond?

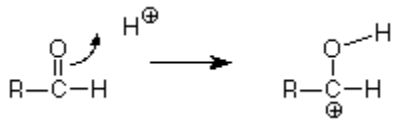


Some experimental observations will help. We find that the addition of water to an aldehyde is rather slow if the solution is neutral (pH = 7, neither acidic nor basic), and that it is much more rapid if acid or base is added. In fact, the more acid or base is added, the faster the reaction goes. The acid or base is not used up, so what we are seeing is that the acid or base is acting as a catalyst.

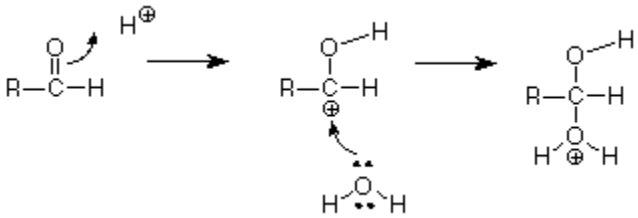
Let's look at the acid catalyized case first and ask how an H^+ might play a role in this reaction. Where would an H^+ attack the carbonyl group? From our analysis of the C=O structure, we'd expect the electron-poor H^+ to attack electrons on the electron rich oxygen of the C=O group. Since we need to break the pi bond, let's have the electrons of the pi bond move to make a new bond between O and H.



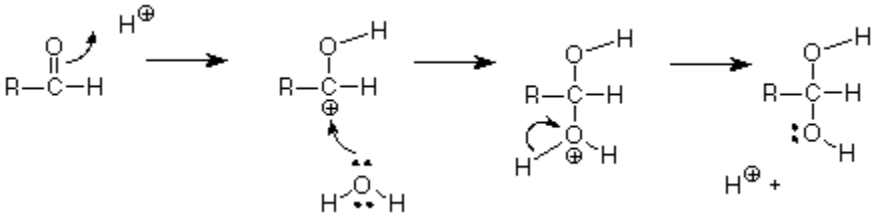
We symbolize that shift of electrons from between the carbonyl carbon and the carbonyl oxygen by drawing a curved arrow leading from the pi bond location to the new bond location between the carbonyl oxygen and the H^+. That arrow can be interpreted to mean that the carbon loses one electron (one half of one pair) and the hydrogen gains one electron. The oxygen neither gains nor loses electrons since the electron pair stays connected to it. The outcome of this transaction is:



Keeping score, we have broken the carbon-oxygen pi bond, and we have made the new carbon-hydrogen sigma bond. We still have to make another bond, and the positively charged carbon atom with only three bonds looks like a reactive place. We need to make a bond between that carbon and the oxygen of water, but where do we get the electron pair needed to make that bond? The carbon is a poor candidate, so let's look at the oxygen. When we're looking for electrons to make a bond, we should consider unshared pairs. These are typically found on atoms like oxygen and nitrogen, although we don't usually draw them in unless we need them. Does such a pair exist on the oxygen of water? If we do our electron calculations carefully, the answer is yes, and that pair attacks the positively charged carbon atom. (Water is acting as a Lewis base, an electron pair donor, and the carbon is acting as a Lewis acid, and electron pair acceptor. The carbon has only six electrons in its sigma bonds and has a vacancy for an electron pair. Check the formal charge to verify this.)



This makes the final carbon-oxygen bond. What remains (if we compare this structure with our product) is to break the final carbon hydrogen bond. Doing so, with that bond's electrons becoming an unshared pair on oxygen, gives us an H^+ to replace the one which started the reaction so that the catalytic H^+ is not used up. This sequence of steps by which the breaking and making of the requisite bonds is accomplished is called a **mechanism**.

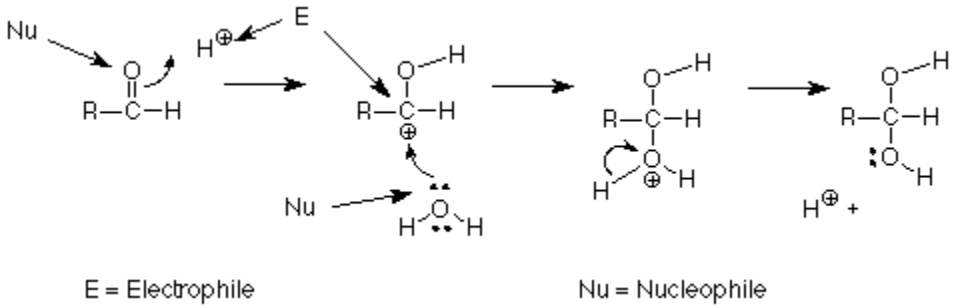


If we summarize, another way to describe this is to say that the Lewis acid H^+ attacks the electron pair of the carbon-oxygen pi bond. The positively charged carbon (carbocation) which results is also a Lewis acid and is attacked by the unshared pair of the oxygen of water, acting as a Lewis base. Finally the Lewis acid H^+ is regenerated by cleavage of the oxygen-hydrogen bond in much the same way as H_3O^+ serves as a source of H^+

Electrophile-Nucleophile

The terms Lewis acid and Lewis base are useful, but when we are talking about making and breaking bonds to carbons, we find that two other terms are more general. We use the term **electrophile** to designate atoms or groups which form bonds by using

electron pairs from another atom. The positively charged carbon above is an example. It is attacked by the oxygen of water, using the oxygen's unshared pair. We use the term **nucleophile** to designate the atom or group which donates the electrons to make such a new bond to carbon. In our example, the oxygen atom is serving as a nucleophile. Another way to say this is that nucleophiles make bonds using their own electron pairs. Electrophiles make bonds using the electron pairs of nucleophiles. We can identify those roles in our mechanism as follows:



A summary of the reactivity of the carbonyl group is that *electrophiles attack the oxygen; nucleophiles attack the carbon*. We will find this to be a very useful way to organize what we learn about many other reactions of carbonyl groups.

Exercise 1.3.1

Now, use these principles to work out a mechanism for the base catalyzed addition of water to a carbonyl group. Some suggestions: categorize the OH^{--} as a nucleophile or electrophile. Remember to break the pi bond to avoid having five bonds to carbon. Keep track of changes in the charge on particular atoms.

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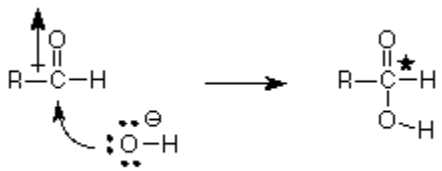
1.4: Acetal Formation, Mechanism, Resonance

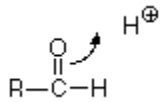
Base-Catalyzed Hydration

Last time I left you with a problem, "what is the mechanism for the base catalyzed addition of water to a carbonyl group?" Let's go through that and see how it goes.

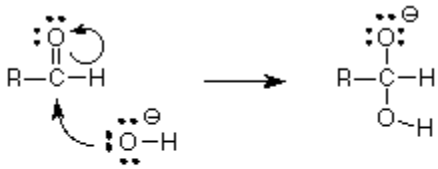
First let's check out the electronic structure of the OH^-. If we find unshared pairs we can say that the OH^- is a **Lewis base** and a **nucleophile**. That would tell us that an electron pair is ready to be used to make a new bond. Then we have the question of where that bond will go. In the carbonyl group, we know that the carbon is the more positive end of the C=O dipole, so let's try to make our new bond there.



This seems to be the right place to make the bond, but if we do that, the carbonyl carbon has five bonds (*). That means ten electrons in the valence shell, so it doesn't happen. We must find a way to reduce the number of bonds to four. We can think back to the mechanism we worked out for the acid catalyzed addition of water. In that mechanism we broke the pi bond by using its electrons to make a new bond to H^+.



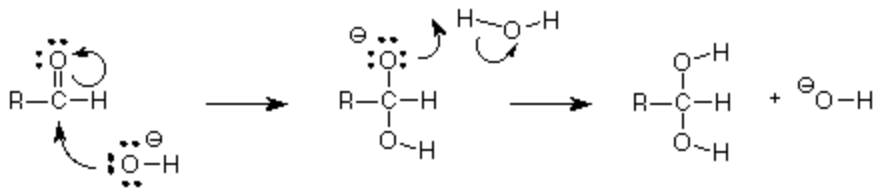
Let's look into the possibility that the C=O pi bond breaks as the C-O sigma bond forms. After all, the electrons in the pi bond are farther from the nuclei than those in a sigma bond, so they should be easier to push around.



(We have shown all the unshared pairs on each oxgyen atom in this example. Normally, we will only show those pairs which are involved in the bonds being broken or made.)

Another way to say this is that the pi bond is weaker than the sigma bond, so it takes less energy to break it. The energy required to break the pi bond comes from making the new sigma bond to the OH^-. (In the acid catalyzed case, the new bond which is being formed is the bond beween the carbonyl oxygen and the H^+. *Breaking old bonds is usually assisted by the formation of new bonds.*

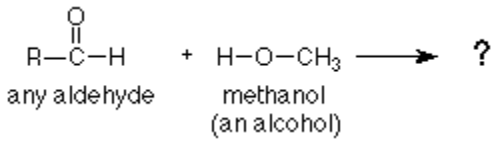
We finish this mechanism by making the only bond which is left to do, the O-H bond.



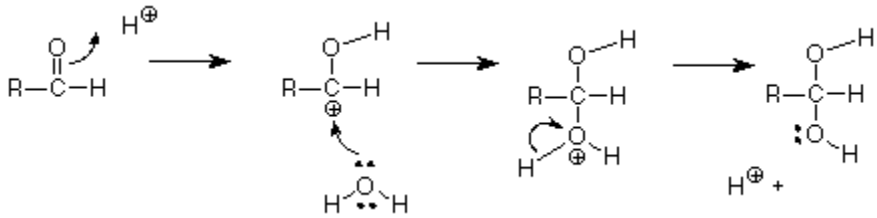
Here again, the breaking of one bond is assisted by the formation of another bond. Also, this mechanism makes a new OH^- to replace the one which was used in the first step, consistent with the observation that the reaction is base catalyzed, which means that the OH^- is not used up.

Hemiacetal Formation

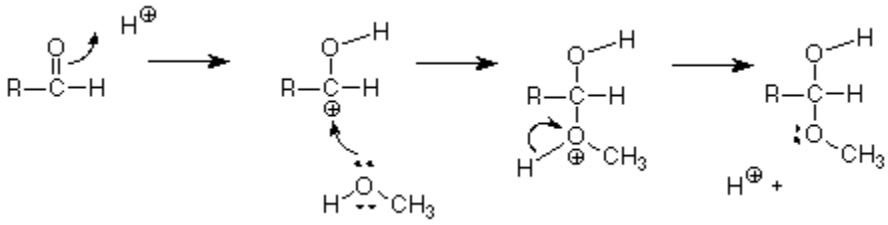
Now let's use what we know about the acid catalyzed addition of water to make a prediction of what will happen when we mix an aldehyde with an alcohol and add a drop or two of an acid catalyst.



We want to use our mechanism to predict the structure of the product. Recall the mechanism of acid-catalyzed addition of water



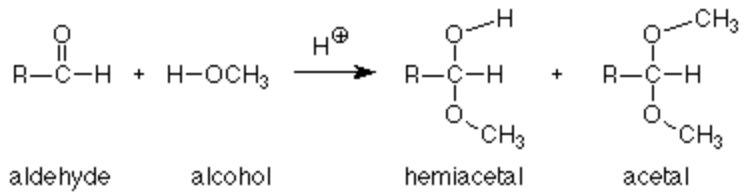
If we follow closely the bonding changes that happen around the water oxygen, we notice that one of the hydrogens always stays attached. That bond doesn't break. That bond could just as well be a C-O bond as is the situation in an alcohol. What would happen if we just replaced water by methanol in the mechanism for acid-catalyzed hydration?



Indeed, the same mechanism seems to work just fine. The OH group in methanol is a nucleophile just like the OH group in water. Another way to say this is that the functional group of water is the same as the functional group of any alcohol, an OH group. If we learn a reaction for one alcohol, it will work very much the same way for any other alcohol - often including water as the smallest possible alcohol.

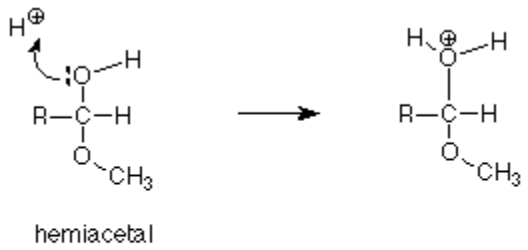
Acetal Formation

When we do the experiment to test our prediction, we find that yes, the product we have predicted is formed. But, we also find another product, one which hadn't been predicted.

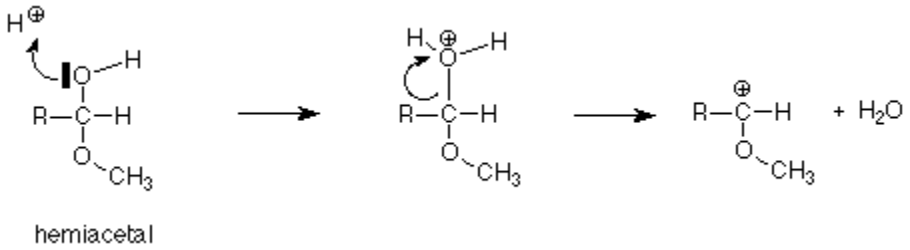


(The new product is called an acetal. The one we predicted is called a hemiacetal.) Since the hemiacetal seems to be about halfway to the acetal, we'll explore converting the hemiacetal into the acetal.

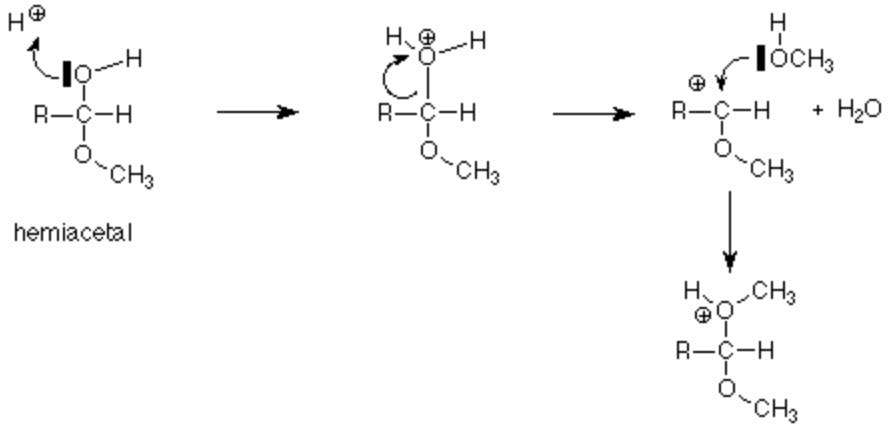
If we look closely at the differences between these two products, we see that to do this, we need to replace the OH group of the hemiacetal with the OCH_3 group of the acetal. (We can rule out the seemingly simpler alternative of replacing the H with the CH_3 because isotopic labelling experiments show that the O-CH_3 bond is not broken and the bond between the central carbon and the OH oxygen is broken.) This reaction is also acid catalyzed, so we may begin by making a bond between H^+ and the OH oxygen, using the Lewis base electrons of the oxygen (electron pairs are often symbolized by bars).



In the next step the bond between the central carbon and the oxygen we have just broken is broken. This produces water and leaves the central carbon atom with only three bonds and a vacancy in its valence shell. A formal charge calculation tells us that this atom is also positively charged, but it is the electron pair vacancy which is more important.

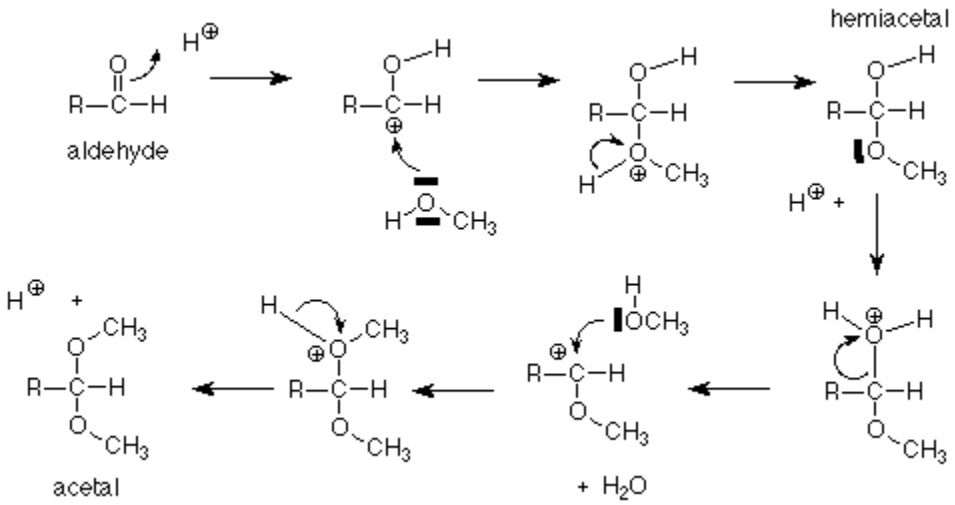


The central atom is consequently an electrophile, open to making a bond with a nucleophile. The nucleophile is the oxygen of another molecule of methanol, whose unshared electron pair becomes the new carbon oxygen bond.



It remains to break the bond between the hydrogen and the positively charged oxygen which produces the acetal and replaces the H^+ to regenerate the catalyst.

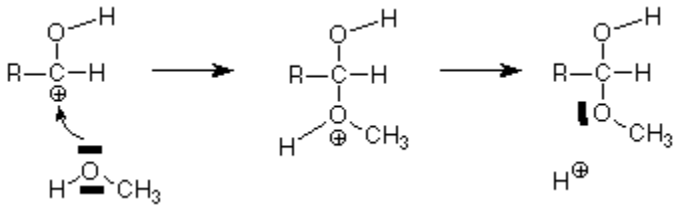
Just to have the whole process in one place, here's the full mechanism from the aldehyde through the hemiacetal to the acetal:



Some Principles

There are a couple of general ideas we can extract from what we did in working out this mechanism.

Charge and Reactivity: Let's contrast two positively charged molecules we found in this mechanism, one with three bonds to oxygen and one with three bonds to carbon.



Both molecules are positively charged, and formal charge calculations tell us where that charge is. But there is an important difference in their structures and that difference makes an important difference in their reactions.

The positively charged cation (we call it a carbocation) with three bonds has only six electrons in its valence shell. It is an

electrophile. It makes a fourth bond using electrons from a nucleophile (the methanol oxygen atom here).

The positively charged oxygen (we call it an oxonium ion) has three bonds and an unshared pair. It has a complete octet in its valence shell. It needs no more electrons so it makes no more bonds. It is not an electrophile. Its reaction is to break a bond, keeping the electrons, by dropping off an H^+.

This distinction is important. The charge alone does not tell us what to expect. It does provide a means of determining whether a positively charged atom has a vancancy or not. From that we can decide whether a such an atom is an electrophile -- ready to accept electrons to make a bond -- or not.

ROH as Nucleophile: Notice that whenever we used an alcohol (general formula, ROH) as a nucleophile, the order of the steps was:

1. Reaction of the unshared pair on oxygen to form a new covalent bond. The oxygen gets a positive charge.
2. Then an H^+ is lost from the positively charged oxygen (oxonium ion).

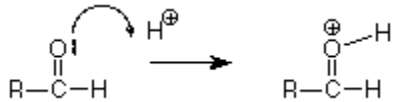
Students often wonder why we don't reverse the order so that the H^+ comes off first to make RO^-, which would then act as the nucleophile. This does not happen because the reaction is occuring in an acidic solution. A srong base like RO^- (about as basic as OH^-) would be immediately consumed by reaction with the acid and would not survive. The alcohol (weaker base, about as basic as water) is the solvent, so there are many alcohol molecules surrounding the carbocation. This makes its reaction with an alcohol rather than RO^- (called an alkoxide ion) very likely.

Intermediates: The aldehyde, the methanol, the hemiacetal, and the acetal are all stable molecules. They can be isolated and studied over a period of time. All the other molecules in this mechanism are much less stable. They have relatively high energies and thus short lifetimes. When they are formed, they react quickly. The main clue to this in their structures is that they have unusual bonding patterns such as three bonds to carbon (with a positive charge) instead of four, or three bonds to oxygen instead of two. Such molecules are called reactive intermediates; reactive because their unusual bonding pattern suggest that a change in bonding will happen, and intermediates because they appear between the reactants and the products.

Resonance

To finish up, let's return to one of our carbocation intermediates. Recall that we began thinking about acid catalyzed reactions of aldehydes by using a C-O pi bond to supply the electrons to make a new bond with H^+.

There is an alternative. We could also think about using one of the unshared electron pairs on the oxygen atom.



Let's compare the two molecules we obtain in this way.

Notice first that the "connectivity" of these two structures is identical. That is, each atom is connected to exactly the same atoms in one structure as it is in the other. Then, notice that the only difference is in the location of an electron pair. On the left, an electron pair is shown as unshared on the oxygen. On the right, that pair is shown as making a pi bond.

When two (or more) structures differ only in the location of electrons, without changing which atoms are bonded to which other atoms, those structures are different ways of describing a single molecule. The symbols differ, but there is only one molecule being described. The notation for this is to connect the two structures by a double headed arrow, which does not imply equilibrium. (We can use the curved arrow symbol to keep track of the formal electron motions.)

This situation is called resonance. When resonance is involved the real structure (called a resonance hybrid) is more stable than any of the formal (called contributing) structures we might draw. This is called resonance stabilization.

Often, I will only draw one structure and expect that you will recognize that resonance is involved and know what other structures might be included in describing the resonance hybrid. The structure presented will be the one which most directly connects to the reaction being described.

We will use resonance many more times during the semester, so there will be many opportunities to clarify your understanding.

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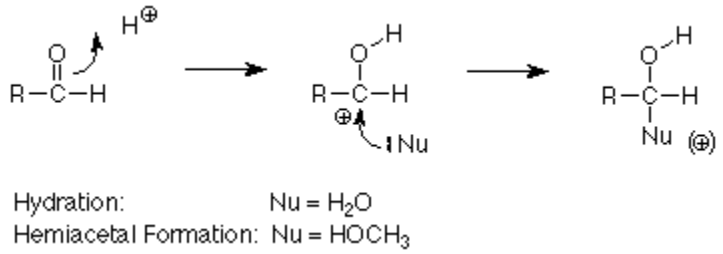
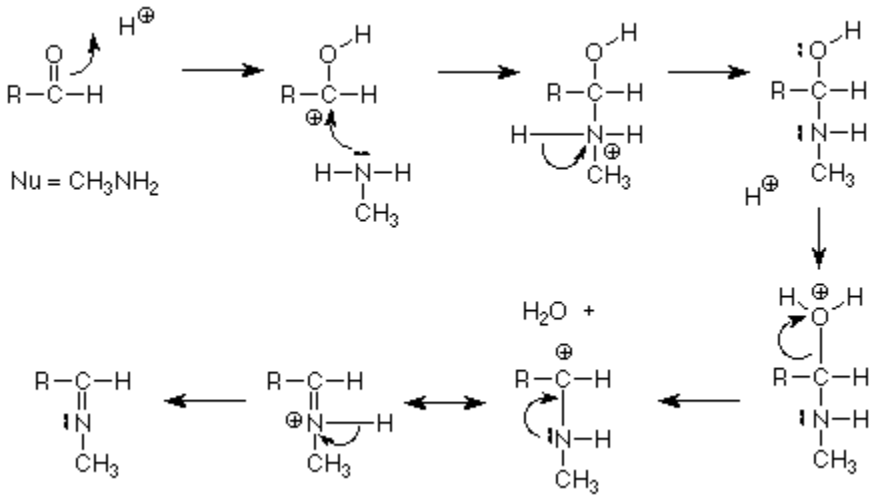
1.5: Nitrogen Nucleophiles - Imine Formation

Imine Formation

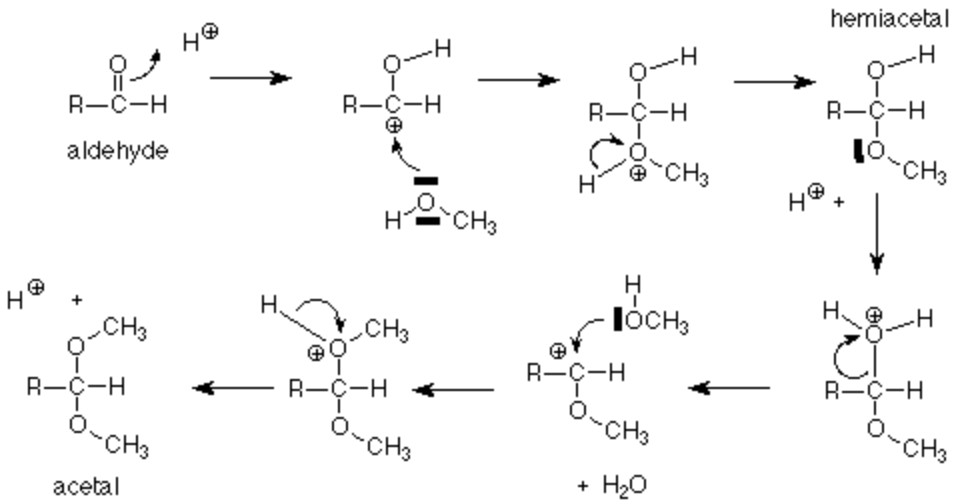
Last time We looked at the formation of a hemiacetal and an acetal from an aldehyde and an alcohol. In both this case and the previous case in which we added water to an aldehyde, the first steps involved acid-catalyzed addition of a nucleophile to the carbonyl carbon of an aldehyde.



In many of the biological reactions of carbonyl groups the nucleophile is a nitrogen atom. The eventual outcome is different, so let's take a look at the details. The specific molecule as an example of a nitrogen nucleophile is methylamine. What happens if Nu = CH_3NH_2? Here's the complete mechanism.



Compare this mechanism to that for the formation of an acetal.



If we compare the individual steps in these mechanisms, we notice that they are very similar up until the last steps. Let's describe them in general terms:

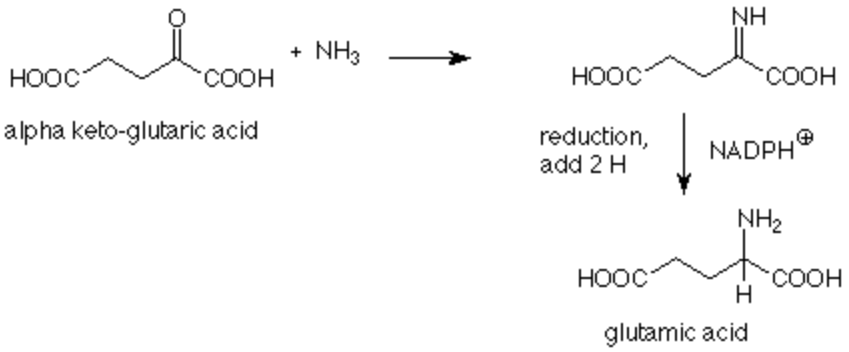
1. Formation of a bond between the carbonyl oxygen and H^+.
2. Attack of the nucleophile (N: or O:) on the electrophilic carbonyl carbon.
3. Loss of an H^+ from the now positively charged N or O atom.
4. Formation of a bond between the OH oxygen and H^+.
5. Cleavage of the bond between the now positively charged H_2O and the central carbon atom. This forms a resonance stabilized intermediate.
6. Here the patterns diverge. With methylamine as the nucleophile, the nitrogen is still bonded to another hydrogen, which can be lost as H^+. This forms a carbon-nitrogen double bond and the nitrogen forms its normal three covalent bonds. With oxygen from the alcohol as the nucleophile, there isn't an O-H bond to break at this point, so the reaction continues with a second molecule of alcohol reacting. Another way to say this is that forming three covalent bonds to oxygen results in a charged reactive molecule which doesn't persist.

We can learn from this that when a nucleophile adds to a carbonyl group in an aldehyde or ketone, it always adds to the electrophilic carbonyl carbon. What happens next depends on the structure of the nucleophile. If there are two hydrogens on its nucleophilic atom, it will eventually lose them with the formation of a double bond between the nucleophilic atom and the carbonyl carbon.

[A question -- Water has two hydrogen atoms. What happens if you apply the pattern just discussed to water and an aldehyde? Does this provide a pathway for exchange of oxygen between water and the aldehyde? What would happen if this were done with water labeled with Oxygen-18?]

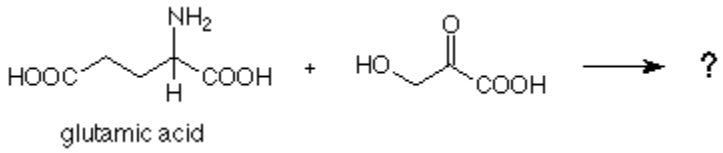
Biological Example

There is a biological example of this reaction. In the metabolic synthesis of amino acids (we'll study these later, they're the components of proteins) the key molecule is glutamic acid. This is formed from a ketone (alpha keto-glutaric acid) by a two step process, the first of which is the reaction of the ketone carbonyl with ammonia to generate a carbon-nitrogen double bond. This double bond is then "reduced" (more about this later) by the addition of two hydrogen atoms to form glutamic acid. [In this description we have ignored the details of the carboxylic acid groups.]



You may wish to work through the mechanism of the first step of this example using the pattern above. Notice also that even though the carboxylic acid groups at the end of the carbon chains in these molecules are functional groups by any structural definition, they don't react here. We can learn from this that a reaction needs both the right functional group and the right circumstances to occur.

Another biological example is part of the process by which nitrogen atoms are transferred from glutamic acid to other carbonyl-containing molecules in the formation of other important amino acids. Here is an example of the reactants:



What do you anticipate that the product of this reaction would be? Base your answer on the fact that a carbon-nitrogen bond needs to be formed and that we have a pattern for what happens when a nitrogen nucleophile reacts with a carbonyl group. The completion of this process, which is called transamination, involves several other steps and will be covered when you take Biochemistry.

Cyanohydrin

If we look back over the reactions we've studied, we can see some consistent patterns emerging in the addition reactions of carbonyl groups.

1. The carbonyl carbon is electrophilic. Nucleophiles add there.
2. If acid is present, the first step is attack of H^+ at the oxygen atom. The nucleophile adds to the carbonyl carbon, which is now quite electrophilic, in the second step of the reaction.
3. If acid is not present, the first step is the reaction of the nucleophile with the carbonyl carbon, a process in which the carbonyl oxygen becomes negatively charged. This step is followed by attachment of an H^+ to that oxygen.
4. Later steps, which depend upon the structure of the nucleophile, determine whether the overall reaction is addition or replacement of the oxygen by the nucleophilic atom.

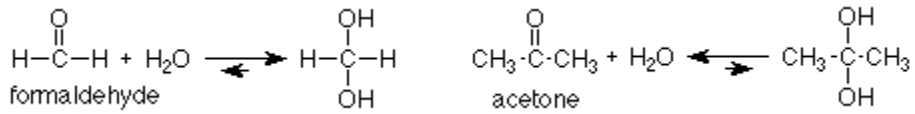
Equilibrium

Now that we have learned several reactions, we can take a look at two general questions:

1. What controls whether a reaction proceeds to the left or to the right? In other words, what controls the equilibrium constant for a reaction?
2. What controls whether a reaction goes rapidly or slowly? In other words, what controls the kinetics of a reaction?

The answer to the first question is simple in principle, but difficult to predict in practice. Rather, we commonly look at the outcomes of similar reactions and decide what factors seem to be important in explaining those outcomes. In doing so, it is important to examine the situation for contrasts -- what's different between the cases we are examinining -- and for similarities -- what's the same between the cases we are examining.

For example, if we look at the addition of water to formaldehyde, we find that almost all of the formaldehyde has been reacted when equilibrium is reached. The equilibrium constant is quite large, much greater than one. In contrast, if we look at the same reaction with acetone (2-propanone), we find that only a very small fraction of the acetone has reacted to add water. (This is so regardless of whether the reaction is catalyzed by acid or base. Remember that catalysts do not change the position of equilibrium.) We can symbolize these statements by making the arrow pointing towards the predominant product larger.

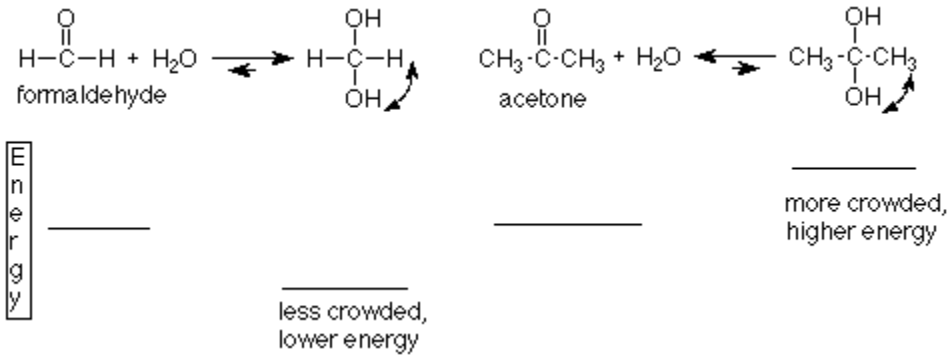


What might be responsible for the change in equilibrium behavior? The important idea here is that at equilibrium, more stable (lower energy) molecules predominate. We have to look at the changes in structure between reactants and products *and* the changes in structure between our two cases to understand what changes the relative energies of the molecules involved. Changes which raise a molecule's energy will reduce its concentration at equilibrium. Changes which raise a molecule's energy will increase its concentration at equilibrium.

Steric Effects

In working out such explanations we ignore things that are the same in the cases we are examining. For instance, the bonds made and the bonds broken are the same whether the reaction involves formaldehyde or acetone. The change which does occur in this reaction can be described as a change in the geometry of the carbonyl carbon as it adds water. In the reactant, it is trigonal, with 120° bond angles and sp^2 hybridization. After water is added, the same carbon is tetrahedral with 109.5^o bond angles and sp^3 hybridization. This change in bond angle means that the groups attached to the carbon atom are closer together after water is added than before, so the electrons in those groups repel each other more in the product than in the reactant. The stronger this repulsion the higher the energy of such a molecule.

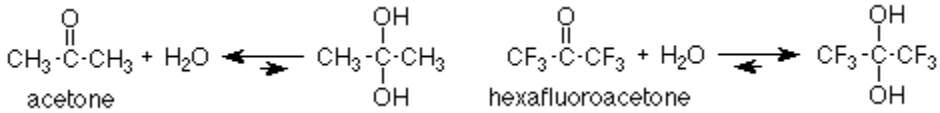
The most obvious structural difference between the formaldehyde and acetone cases is that in formaldehyde, the atoms attached to the carbonyl carbon are hydrogens, which are about as small as atoms get. In the same location in acetone, we have methyl (CH_3 groups, which are considerably larger. Pushing the larger methyl groups closer together in the product of adding water to acetone requires more energy that pushing hydrogens close together in the formaldehyde case. Consequently, the equilibrium is much less favorable for the addition of water to acetone.



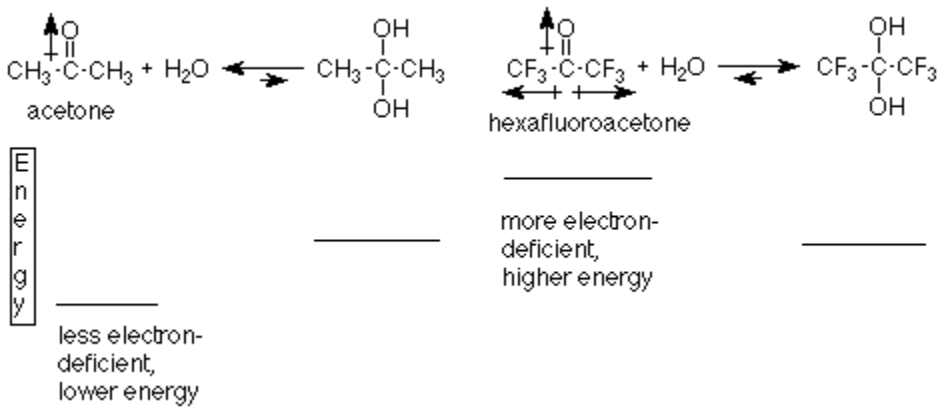
This kind of explanation uses *steric* effects, effects on a reaction which arise from the *size* of atoms or groups.

Polar Effects

Another important explanation of changes in equilibrium constant lies in *polar* effects. This can be seen in the following example:



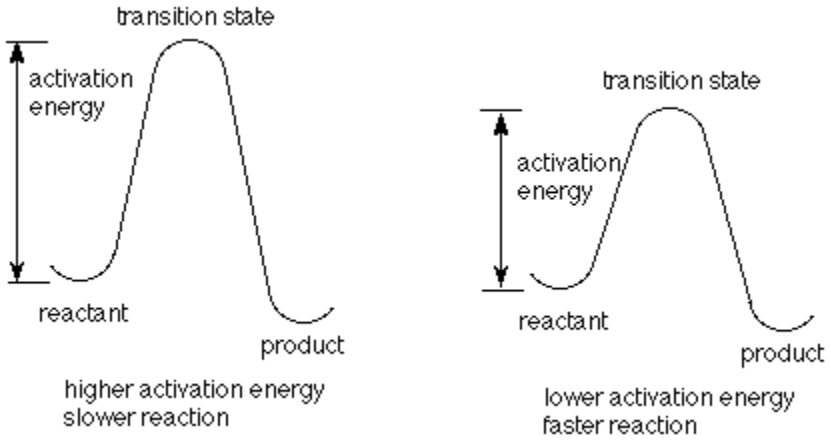
Why is hexafluoroacetone more completely hydrated than acetone? Since a trifluoromethyl group (CF_3) is about the same size as a methyl (CH_3 group, steric effects are not involved. The structural difference between these two cases is the electronegativity difference between H and F. Consider that the carbonyl carbon is already somewhat electron deficient since it is associated with the more electronegative oxygen and two of its valence electrons are relatively far away in a pi orbital. When the electronegativity of six fluorine atoms is included in hexafluoroacetone, it becomes even more electron deficient. This raises its energy in comparison to that of acetone, so there is less of it at equilibrium. On the product side of the reaction, no pi bonds are involved, so the polar effect on energy is less pronounced.



We will use steric and polar effects to explain how energies change in a reaction and between reactions. Keep in mind that steric effects involve changes in size between comparable situations, and polar effects involve changes in electronegativity or similar electronic characteristics.

Rates - Activation Energy

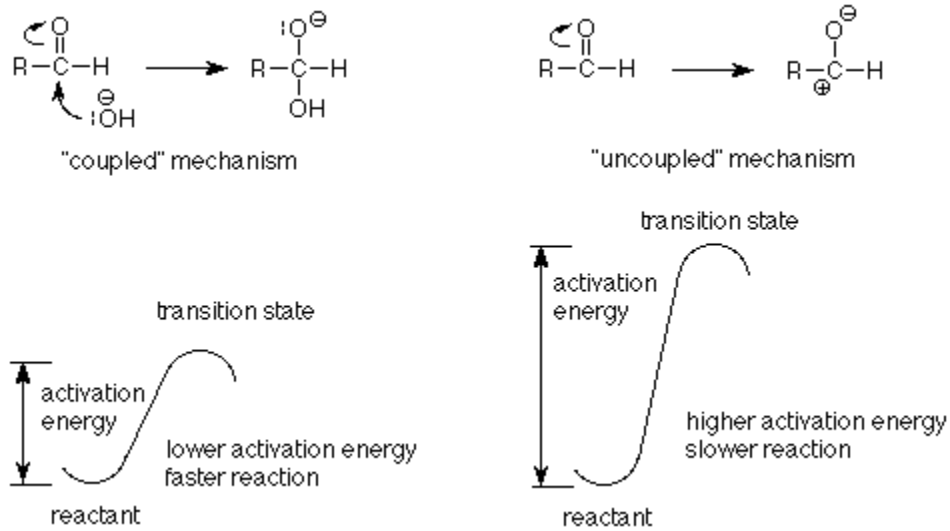
Next, let's take up the question of what makes a reaction faster or slower. Several variables are involved here. If two molecules must collide (such as hydroxide ion and formaldehyde for example) then higher concentrations of either make collisions more frequent and the reaction more rapid. If we raise the temperature, most reactions go faster. These are variables can be studied by experiments in which concentrations and temperatures are changed and the number of moles of product formed in a given time is measured. From such experiments we can obtain a measure of the reaction's *activation energy*. The activation energy is the energy which must be put into a collision of two reacting molecules in order for the reaction step to occur. If the activation energy is high, few molecules collide with enough energy to react and the reaction is slow since few molecules of reactant become product in a given time interval. If the activation energy is low, many molecules collide with enough energy and become product in a given time interval. The following diagram illustrates these points.



A molecular collision which packs enough energy for the molecules to reach the top of the hill -- the *transition state* -- makes product. If the transition state has a lower energy, then the activation energy is lower and the more molecules will collide with the necessary energy; more molecules will become product. Since higher temperatures produce more energetic conditions, we have

an explanation for the fact that reactions go faster at higher temperatures.

It follows that if we are to understand why one reaction is faster than another, we have to think about how structural differences between one reaction and another influence the relative energy of the transition states and thus the activation energies. The following two reactions are the first steps of possible mechanisms for the hydration of an aldehyde.



In the "coupled" mechanism to the left, the bond between carbonyl oxygen and the carbonyl oxygen is broken at the same time as the bond between the OH^- group and the carbonyl carbon is formed. Bond breaking requires an energy input -- it is moving electrons away from a stable position -- while bond making produces an energy output. If the energy required for breaking the C=O pi bond can come largely from the energy released by making the new C-O sigma bond, the overall energy of the transition state will be lowered, the activation energy is lower and the reaction is faster..

Contrast this with the "uncoupled" mechanism at the right. Here the C=O pi bond is being broken without the energy input from a forming C-O sigma bond. The transition state is much higher in energy than that for the coupled mechanism. This mechanism has a prohibitively high activation energy, so the reaction without base is very slow. Adding base allows the coupled reaction mechanism to proceed over its much lower energy transition state. Look back over the mechanisms we have examined. Are bond breaking processes commonly coupled with bond breaking processes? One of the reasons for the dramatic success of enzymes in making reactions go very fast is that they use the energy of forming bonds very efficiently to drive bond breaking.

We'll find that explaining faster and slower reactions by looking at what happens to transition state energies to be very useful. I hope you'll use opportunities for questions to clarify these ideas in your own mind.

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1.6: Addition of Organometallics - Grignard

Review of Reactivity

Last time we looked at a reaction in which a new carbon-carbon bond was made. Today, we'll look at another such reaction, one which is generally quite useful for synthesis, the assembly of larger carbon structures from smaller molecules.

First, let's look back over the reactions we've studied. We see some consistent patterns emerging in the addition reactions of carbonyl groups.

1. The carbonyl carbon is electrophilic. Nucleophiles add there.
2. If acid is present, the first step is attack of H^+ at the oxygen atom. The nucleophile adds to the carbonyl carbon, which is now quite electrophilic, in the second step of the reaction.
3. If acid is not present, the first step is the reaction of the nucleophile with the carbonyl carbon, a process in which the carbonyl oxygen becomes negatively charged. This step is followed by attachment of an H^+ to that oxygen.
4. Later steps, which depend upon the structure of the nucleophile, determine whether the overall reaction is addition or replacement of the oxygen by the nucleophilic atom.

Let's think a bit about the relationship between the presence of acid and the sequence of events. Remember that nucleophiles and Lewis bases react in the same way, by using an unshared electron pair to make a new bond. It isn't a surprise that molecules which are good (strong) Lewis bases are also good (strong) nucleophiles. Hydroxide ion (OH^-) is a strong base, as are most compounds which share the $-O^-$ functional group. It is also a strong nucleophile, which we see in its unassisted reaction with a carbonyl carbon in the base-catalyzed addition of water.

It is tempting to think that we could set up a really fast reaction if we used both acid to attack the carbonyl oxygen with H^+, which would make the carbonyl carbon really electrophilic, and base to attack the carbon with the strong nucleophile OH^-. This sounds really attractive, but it doesn't work. What we've forgotten with this idea is that significant concentrations of acid and base can't exist in the same solution because they neutralize each other. We have to conclude that in acidic solutions, only weak bases like water can exist (the conjugate strong bases like those which include $-O^-$ functional group would be neutralized to give -OH groups). Such weak bases are also weak nucleophiles and need the increased electrophilic character which comes when the carbonyl oxygen is attached to an H^+. This is the pattern we saw when weak nucleophiles like water and alcohols reacted in acid-catalyzed addition of water and in acetal/hemiacetal formation.

Another way to look at this is to say that if a strong nucleophile is to be used we must stay away from acidic solutions. We've seen this pattern both in the base-catalyzed addition of water and in the formation of a cyanohydrin. Addition of acid would have destroyed the nucleophiles (converted OH^- to H_2O and CN^- to HCN) in these cases.

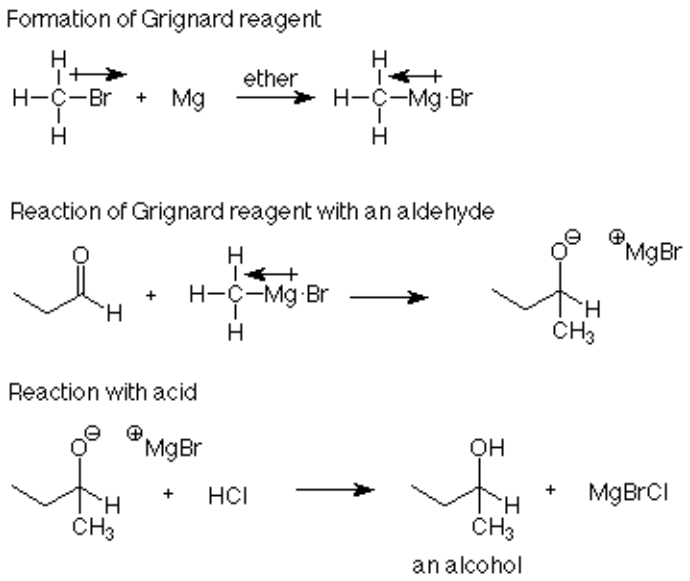
Grignard Reagent

We saw that the cyanide ion is a useful nucleophile and that its addition to a carbonyl group makes a carbon-carbon bond. Making carbon-carbon bonds is the central concern in organic synthesis, so it is important to find other compounds in which a carbon atom serves as a nucleophile. Let's think a bit about what that might mean.

A nucleophile needs to have a pair of electrons to donate in order to make a new covalent bond. A carbon nucleophile would need to have an unshared pair or a bonding pair in which the polarity of the bond was such that the carbon was a strongly negative end of the dipole. That would imply that the carbon should be bonded to an atom which is less electronegative than carbon itself. A quick glance at the periodic table suggests that the bond will have to be between carbon and a metal. While there are many metals, we will look at only one, magnesium.

In the early part of the 20th century, Victor Grignard, a French organic chemist (the French pronunciation of his name can be approximated as "greenyard") studied the reactions of bromoalkanes with magnesium metal. When he carried out these reactions in solutions with ether, he found that the magnesium dissolved, heat was released and the solution turned dark gray. If he added a

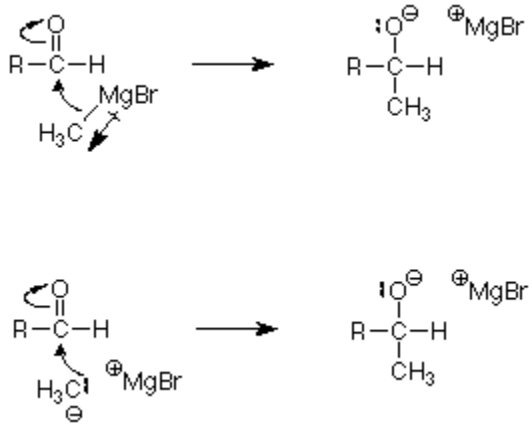
ketone or aldehyde to this mixture, heat was again evolved and a light gray precipitate was formed. When he finished the reaction by adding aqueous acid to the mixture, he found that he had made an alcohol in which the carbon to which the bromine atom had been attached had now become bonded to the carbonyl carbon. The process is outlined as follows:



Since we have learned that the carbonyl carbon of aldehydes reacts as an electrophile, we must conclude that the carbon which started out attached to the bromine is behaving as a nucleophile. This can be understood if the magnesium is inserted between the bromine and the carbon, making a carbon magnesium bond which would be polarized so that the carbon is the negative end of the dipole. A compound with a carbon-magnesium bond is called a Grignard reagent. The details of the insertion of the magnesium atom into the carbon-bromine bond are not well understood, nor is the exact structure of the Grignard reagent itself. However, the reactivity of this reagent is symbolized effectively by the formula given.

Addition to Carbonyl Group

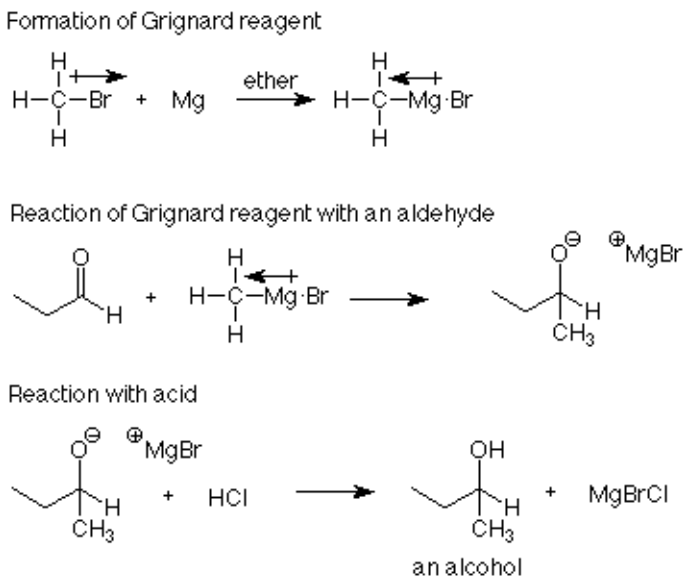
Let's look at the reaction of the Grignard reagent with the carbonyl carbon in a little more detail.



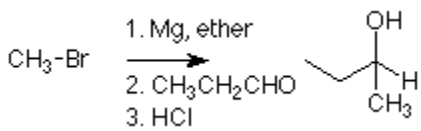
In the top reaction, the nucleophilic electron pair is shown as coming from the carbon-magnesium sigma bond, which is strongly polarized so that the electrons are much closer to the carbon. This makes the carbon nucleophilic. In the bottom reaction, the depiction of this bond is taken to an ionic extreme in which the electron pair is shown as entirely belonging to the carbon, which emphasizes the carbon's nucleophilic character. In this picture, the magnesium ion is "in the neighborhood" rather than being covalently bonded to the carbon. Such an extreme picture is probably and exaggeration, but it does emphasize the consideration of the attacking carbon as a nucleophile.

The picture of a carbon bearing an unshared electron pair also tells us that such a carbon would be a very strong base, much stronger than needed to take an H^+ from water to generate the weaker base OH^-. A practical consequence of this is that Grignard reagents must be kept dry, away from even the slightest traces of moisture, lest they be destroyed by reaction with water.

Now let's examine how we can use this overall reaction in synthesis. First, for economy in notation, let's develop a shorthand for the preparation of a Grignard reagent, its addition to a carbonyl group, and the reaction of that product with acid to make an alcohol. Here's the longhand version (repeated):



Now here's the shorthand version:



The shorthand version is interpreted to mean that

1. First we react bromomethane with magnesium metal using ether as a solvent. When this reaction is complete --
2. Second we add propanal (CH_3CH_2CHO) to this solution. After the second reaction is complete --
3. Third we add HCl to neutralize the O_- and make the alcohol.

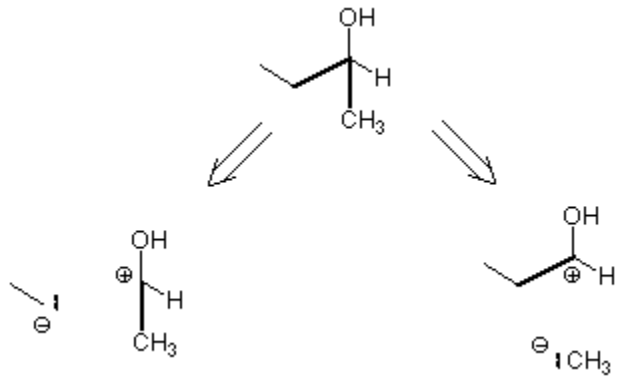
This represent a sequence of events in carried out in the laboratory. In each numbered step all the reactants present are allowed to react before the next reaction is started. At the completion of each numbered step, the product could (in principle) be isolated and stored to be used later. In practice the high reactivity of water with Grignard reagents makes this very difficult, so it is not done.

This way of describing a sequence of laboratory events must not be confused with the sequence of steps which we used to describe a mechanism. When describing a mechanism we are tracing the path of single molecule at a time. At a given time, very few molecules are actually reacting; most are "resting" as either reactants which haven't gotten enough energy to proceed or products which have finished passing through the series of mechanistic steps. Usually, context will tell you which type of interpretation is meant. If you are in doubt, please ask.

Thinking from Products to Reactants

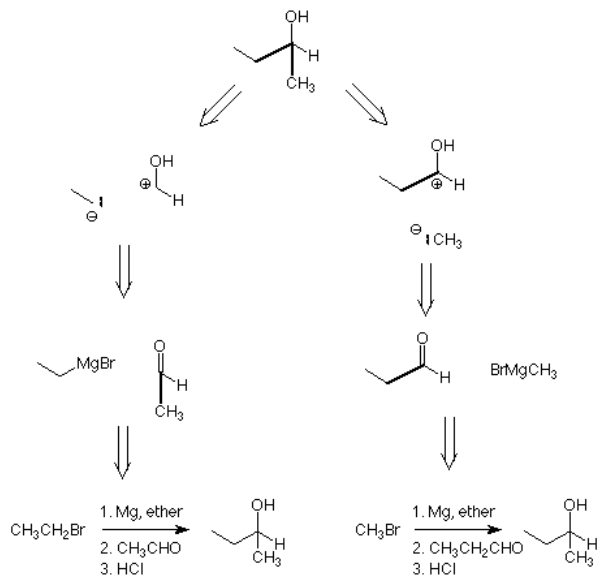
Now, lets see how the addition of a Grignard reagent can be used in synthesis. If we look at the product of our shorthand description and remember that the addition of a Grignard reagent makes a new carbon-carbon bond in which one of the carbons is attached to an OH group, we can see that there are two such bonds (thicker and longer in the drawing) in our product molecule.

Either is a candidate for being formed in the addition of the Grignard reagent. We can imagine the reagents needed for this to happen by simply erasing either of those bonds and examining what we get.



We remember that the bond came from an unshared electron pair on the Grignard reagent, and that the carbonyl carbon is electrophilic, so we show the appropriate charges. The structures we show here are not those of real molecules, but they serve to tell us which parts play what roles in the reactions. (The double-line arrows represent the direction of our thinking, not the direction of the actual reaction.)

In this way we arrive at a sketch of the reactants needed, which we need to turn into real reagents. We do this by remembering that the electrophilic carbon is provided by the carbonyl carbon and that the nucleophilic carbon comes from the Grignard reagent and then writing down what that tells us.



We finish up by placing the formation of the necessary Grignard reagent, its addition to the appropriate carbonyl compound, and the hydrolysis of the addition product in the appropriate sequence. This whole thought process is called "retrosynthetic analysis," but it is more simply regarded as *thinking backward from a goal to a process which will get you there*. It's a useful skill in organic chemistry and in many other areas.

If we do a few of these problems, we notice a pattern. If the carbonyl compound is formaldehyde, in the product there will be only one bond between the carbon attached to the OH group and another carbon (from the Grignard reagent). There will be two bonds between the OH-bearing carbon and hydrogens (from formaldehyde). Such an alcohol is called a primary alcohol, because the OH-bearing carbon is bonded to only one other carbon atom.

Similarly, if an aldehyde other than formaldehyde is used, the OH-bearing carbon in the product is bonded to two other carbons, and the alcohol formed is called secondary. Carrying this process one step further, the reaction of a ketone with a Grignard reagent gives a tertiary alcohol.

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1.7: Oxidation and Reduction, alpha-C-H acidity

Last time we saw how a nucleophilic addition of a carbon atom to the carbonyl carbon could be carried out through the use of a Grignard reagent. This time we'll look at oxidations and reductions of carbonyl groups and at the acidity of the alpha hydrogen atom

Symbolizing Oxidations & Reductions

We'll start by recalling what the terms "oxidation" and "reduction" meant in inorganic chemistry. Oxidation is usually used to describe a process in which electrons are removed from a molecule or atom. Here's an example:

$$Fe^{2+} \rightarrow Fe^{3+} + e^{-} \tag{1.7.1}$$

This is interpreted to mean that a ferrous (+2) ion has been oxidized to a ferric (+3) ion by the removal of one electron (e^{-}). Similarly, reduction is used to describe a process in which electrons are added to a molecule or atom. An example might be:

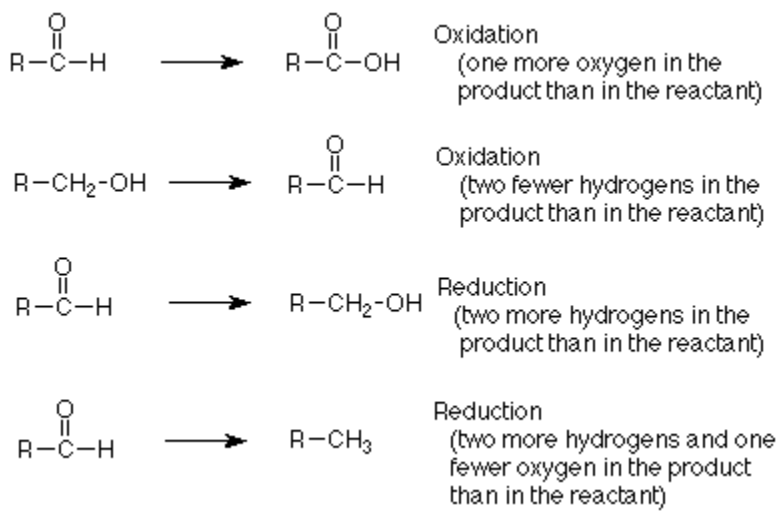
$$Cr^{6+} + 3e^{-} \rightarrow Cr^{3+} \tag{1.7.2}$$

We would interpret this to mean that a chromium atom in oxidation level six is being reduced to chromium in oxidation level three by the addition of three electrons. Using these symbols we can keep track of the oxidation levels of atoms as electrons are added or removed. Keep in mind that these equations are "half reactions" and they don't indicate where the electrons come from or where they go.

There are important areas of biochemistry (photosynthesis, oxidative phosphorylation) where this symbolism for oxidation and reduction is very useful, but for most of organic chemistry where molecules have many atoms, keeping track of oxidation levels this way is cumbersome and not very useful. Instead, we will use the following definitions:

- Oxidation means the addition of oxygen to a molecule or the removal of hydrogen from a molecule.
- Reduction means the addition of hydrogen to a molecule or the removal of oxygen from a molecule.

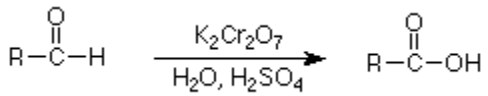
Let's look at some examples:



What about a reaction in which both oxygen and hydrogen are added or subtracted. If the ratio is one oxygen to two hydrogens (in other words, water), neither oxidation or reduction is happening. *Addition or removal of water does not involve, by itself, an oxidation or a reduction reaction*. The addition of water to an aldehyde to form a hydrate does not involve oxidation or reduction. You may wish to look at the formation of an acetal or hemiacetal in this way. If the **net change** in the number of hydrogens and oxygens comes out to be a ratio of two hydrogens to one oxygen, neither oxidation nor reduction is involved.

Oxidizing Agents

Now, let's turn to what we have to do to make an oxidation reaction go. If we return to the example we had earlier, we are trying to figure out what reagent to add to an aldehyde in order to oxidize it to a carboxylic acid. Such a reagent is called an oxidizing agent. Experiments have shown that there are many such reagents, but one which is commonly and effectively used for this purpose is chromic acid (H_2CrO_4). This reagent is prepared *in situ* (in the reaction mixture) by mixing a strong acid such as $H_2SO_4$and a sodium or potassium salt of the chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) ion. The reaction and the necessary reagents are shown as follows:

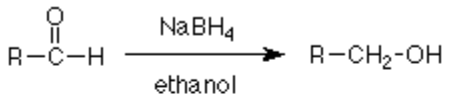


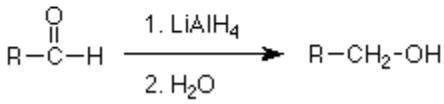
If a question asks for a reagent which will carry out a reaction, it is necessary to answer with a specific reagent. That means that you will need to develop a personal list of reagents and what they do. Both chromate and dichromate ions contain Cr^{VI}, so we recognize them as potential oxidizing agents based on the ability of Cr^{VI} to absorb electrons (and be reduced). Similarly, $KMnO_4^-$ (permanganate) ions contain Mn^{VII} and are good oxidizing agents for many organic reactions.

A final point: most of the reactions we have illustrated for aldehydes also work with ketones. We have made note of the generally less favorable equilibrium constant for additions to ketones, but the additions of water, alcohols, amines, cyanide and Grignard reagents all proceed to measurable extents with ketones. This is not so with oxidation. To oxidize a ketone would require breaking a carbon-carbon bond between the carbonyl carbon and a carbon bonded to it. Mechanisms to do this involve such high activation energies that they do not occur to any practical extent.

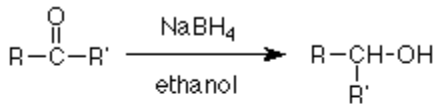
Reducing Agents

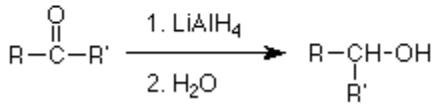
What about reduction? Similarly, there are specific reagents for the reduction of aldehydes and ketones to alcohols. (See Brown, Sec. 11.10B). Two important ones are sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$). Their use is illustrated in the following two examples.





Since there is no carbon-carbon bond breaking which occurs in these reactions, we might expect that these reagents would also reduce ketones to alcohols. That is indeed the case, as seen in these examples.





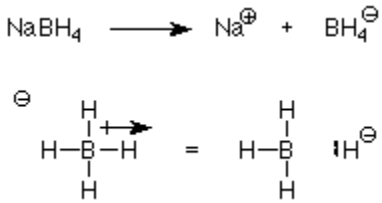
If we compare the outcome of reduction of aldehydes to that of reduction of ketones, we notice that aldehydes produce primary alcohols while ketones produce secondary alcohols. This give us an alternate method to the Grignard addition for making these types of compounds. (*Now would be a good time to make a personal list of reactions which produce alcohols, together with the necessary reagents and the specific structural types involved.*)

Mechanism of Reduction

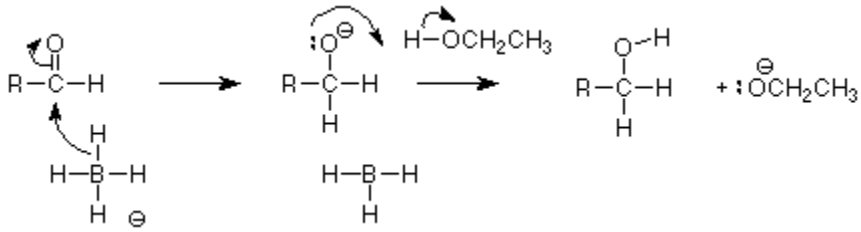
The comparison of these reduction reactions with the Grignard addition suggests another important point. In these reductions, hydrogen atoms are added to the carbonyl carbon and to the carbonyl oxygen. Since there is no hint of acid present, these reactions resemble base-catalyzed addition of water, addition of HCN, and the addition of a Grignard reagent rather than acid catalyzed reactions. We may expect them to begin with the attack of a nucleophile at the carbonyl carbon. In order to arrive at the observed product, the effective nucleophile has to be $:H^-$, just as in the addition of a Grignard reagent, the nucleophile was effectively $:R^-$. We justified that statement for the Grignard reagent by examining the carbon-magnesium bond and arguing that it was very strongly polarized so that the carbon effectively controlled the bonding pair of electrons, making it behave like $:C^-$. Can we do something similar for the hydrogen in sodium borohydride or lithium aluminum hydride?

First, we need to realize that sodium borohydride is a salt which is made up of a sodium cation (Na^+) and a borohydride anion (BH_4^-) The sodium ion plays no important role in the reaction, so we will ignore it (ions like sodium and potassium are seldom directly involved in reactions. They are present merely to maintain charge balance so that stable compounds can be added to reaction mixtures. They are often called spectator ions.) The borohydride ion is the important player in this process, and it is the B-H bond that we want to examine.

A quick glance at the periodic table to review electronegativities tells us that both boron and aluminum are metals with relatively low electronegativities. Each is less electronegative than carbon, and since hydrogen has about the same electronegativity as carbon we can conclude that the B-H bond is polarized with the boron positive and the hydrogen negative. This is very similar to the way we understood the electronic situation in a Grignard reagent, so we conclude that the B-H bond effectively serves as a source of hydride ion ($:H_-$). This is summarized below.



With this information and the addition of a Grignard reagent as a pattern, we can arrive at the following mechanism for the reduction of an aldehyde by sodium borohydride.

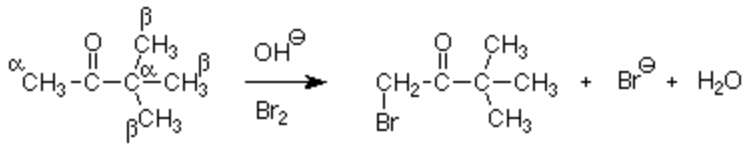


Notice the familiar pattern: Attack by a nucleophile at the carbonyl carbon, followed by protonation of the carbonyl oxygen.

The same mechanism applies to the reduction of ketones by sodium borohydride and to reactions of carbonyl groups with lithium aluminum hydride. In the latter case, lithium aluminum hydride is itself highly reactive with water, so the water is added after the lithium aluminum hydride has reacted.

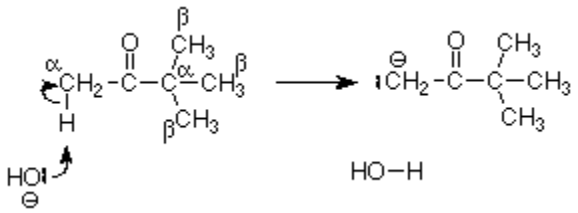
Enolate Ions

We have one major topic in carbonyl chemistry to introduce -- the reactions which occur at the carbon attached to the carbonyl carbon. This carbon is called the alpha-carbon. Here's an example of such a reaction.

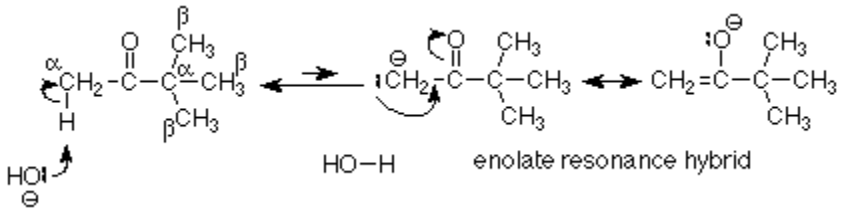


We can pick out several important features of this reaction from this example. First, there are two alpha carbons, but only one undergoes a reaction. That one (on the left) is attached to a hydrogen in the reactant. Second, we notice that there is no reaction at the beta-C-H bonds. Reactivity is restricted to the C-H bond on a carbon directly to the carbonyl carbon. **This type of reaction requires an alpha-C-H bond.** In a sense, the presence of the carbonyl group next to this C-H bond makes it a functional group.

Now to consider a mechanism. Our mechanism must account for the formation of a carbon-bromine bond and an oxygen-hydrogen bond (in water) and the cleavage of a carbon-hydrogen bond (alpha) and a bromine-bromine bond. It must also suggest a role for the OH^-. so let's begin by speculating that the hydroxide ion acting as a base makes a bond to the alpha-hydrogen. This process is coupled to the breaking of the alpha-C-H bond, whose electrons are then transferred to the alpha-carbon.

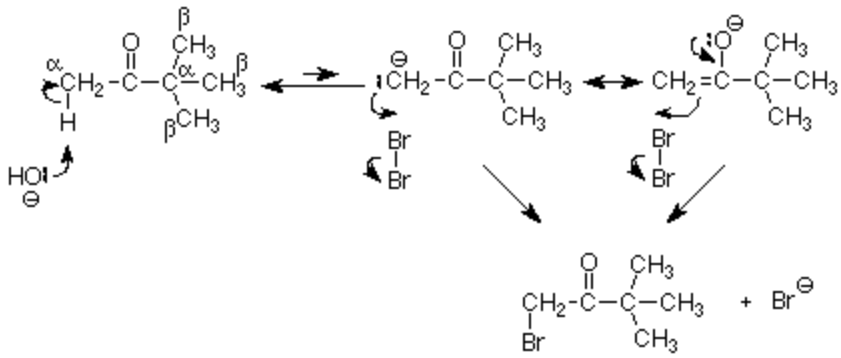


This is striking, because we are proposing that the alpha-hydrogen is acidic enough to be removed by a base no stronger than OH^-. This is certainly not true of other C-H bonds, and it is only true here to the extent that the equilibrium constant for this step is very small. There is very little of the product of this step at equilibrium (we'll call this product an enolate, for reasons which will make more sense a bit later). What is it about an enolate ion which allows it to be made at all. Put another way, why is the enolate ion stable enough to be formed, while a similar ion made from another C-H bond isn't. When we're looking for reasons of stability, resonance is one of the ideas we should explore. Since this process requires the carbonyl group next door, that resonance should involve the carbonyl group.



Sure enough, if we move electrons as indicated by the curved arrows, we find an alternative resonance structure. This structure has the energetic advantage that the unshared electron pair is on the oxygen (the more electronegative atom) rather than the carbon. And, the resonance itself contributes to lowering the energy of the enolate, which makes it stable enough for a little of it to be formed at equilibrium. It is important to re-emphasize that none of this can happen if the carbonyl group is not next door to reactive C-H bond.

The alpha carbon in the enolate is all set up to behave as a nucleophile, providing a pair of electrons to make a new bond to a molecule of bromine. This requires that the bromine-bromine bond be broken at the same time. Notice that either resonance structure can be used to deliver the needed pair of electrons to make the carbon-bromine bond. This is necessarily so, since the two resonance structures are alternate descriptions of the same resonance hybrid.



Bromine is behaving as an electrophile, not because it has a vacancy in a valence orbital, but because it can simulate such a vacancy by breaking a bond. This reminds us of the behavior of the pi bond in a carbonyl group when it reacts with a nucleophile at the carbon atom.

Example 1.7.1:

There are some questions that are routinely asked, so let's take them up here.

1. Why does the OH^- attack the alpha C-H bond rather than the carbonyl carbon?
    1. It attacks both, but the attack at the carbonyl carbon leads to the hydrate - the product of addition of water. This certainly occurs, but it leads nowhere since the hydrate is present in very small quantities at equilibrium for ketones and most aldehydes.
2. Why does the reaction with molecular bromine take place at the carbon only? After all, there is a potentially nucleophilic unshared electron pair on oxygen as well.
    1. Reaction can take place at the oxygen, but the compound formed with a covalent bond between two rather electronegative elements is less stable than the one which results from reaction at the alpha-carbon.

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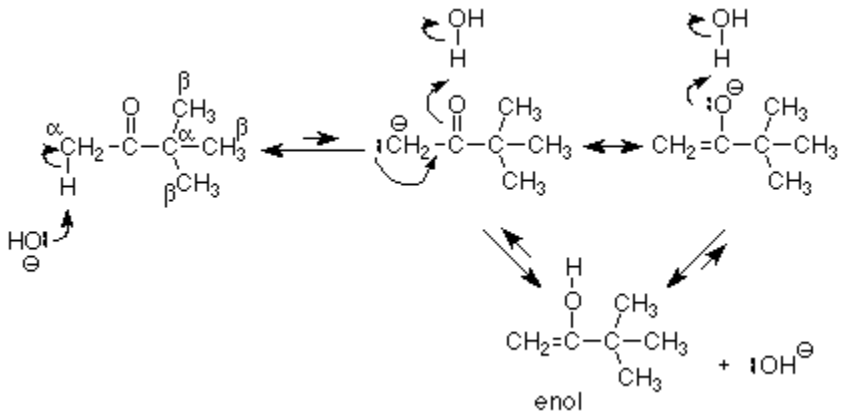
1.8: Enolates, Aldol Condensation, Synthesis

Last time we worked through the reagents which oxidize aldehydes to carboxylic acids and the reagents which reduce aldehydes to primary alcohols and ketones to secondary alcohols. We also learned how enolate ions can be formed by the removal of an alpha hydrogen atom and how these enolate ions can act as nucleophiles toward bromine.

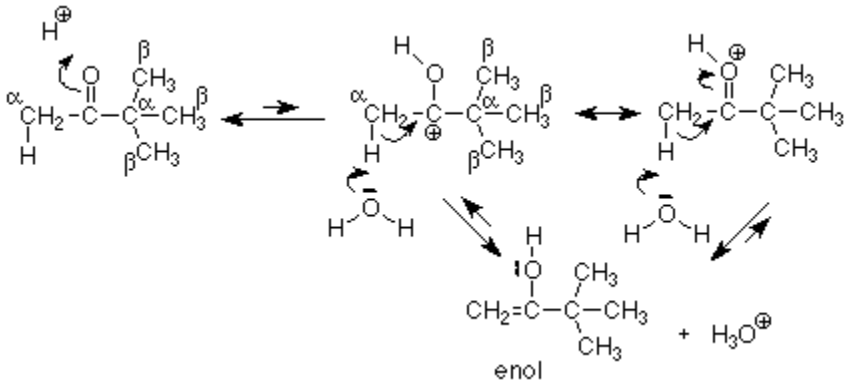
Enols

What happens if we leave out bromine? The alternate electrophile is effectively a H^+ from water. It can react either at the alpha carbon (which bears some electron density) or at the oxygen (which also is a basic site). The first reaction just reverses the formation of the enolate, but the second reaction makes a new structure, an enol. Since either reaction produces an OH^- ion, either reaction is catalyzed by base.



Notice that the product of this mechanism, an enol, is an **isomer** of the original ketone. It is not a resonance structure, because there is no OH bond in the ketone, so the two structures are differ in how they are connected, and resonance structures may not be that different. Notice also that this is an equilibrium between isomers. Isomers that are in equilibrium with each other are called **tautomers**. This situation is called keto-enol tautomerism (the same term is used when the carbonyl component is an aldehyde.) Generally, there is very little enol in equilibrium with the keto tautomer, and we will generally write an enol structure when we need it.

Since addition of water was catalyzed by both acid and base, we can ask whether keto-enol tautomerism can also be catalyzed by acid. We know what the first step must be, because an H^+ must react with the carbonyl oxygen. This moves electrons away from the carbonyl carbon, which in turn attracts electrons from it's immediate neighborhood, particularly the alpha C-H bond. This bond is thus susceptible to attack by the weakly basic water molecule (there's very little hydroxide ion in an acidic solution) to form the enol.



Of course, since a catalyst cannot change the position of equilibrium, the amount of the enol tautomer formed is small whether the reaction is acid catalyzed or base catalyzed.

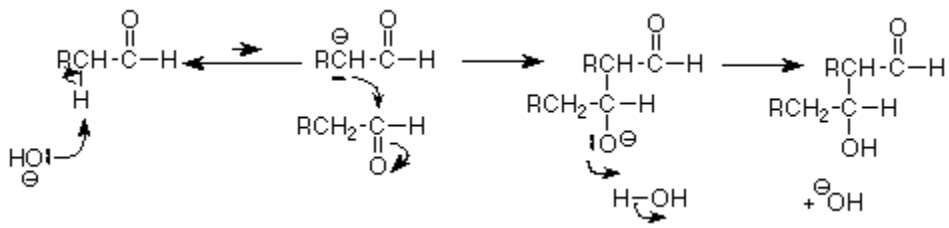
The term "enol" is a combination of the "ene" ending typical for alkenes (compounds with C=C double bonds) and the "ol" ending typical for alcohols. The anion derived from an enol has the ending "ate" appended as is the case for many polyatomic anions (consider sulfate as an example).

Aldol Addition

One way to describe what we have just done is to say that we have worked out a way to make the alpha-carbon of a carbonyl compound into a carbon nucleophile. Earlier we found that the carbon nucleophile of a Grignard reagent was very important as a synthetic tool. Can we use this alpha-carbon nucleophile similarly? To some extent, the answer is yes. There are a few restrictions:<

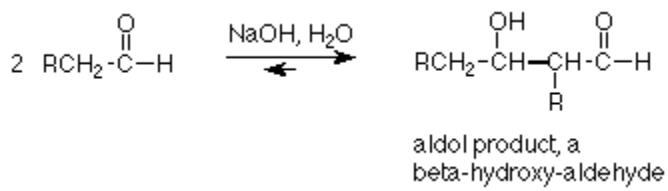
1. To use the strongest nucleophile we can form at the alpha carbon, we will use base catalysis so as to make enolate ions.
2. Since there is little enolate ion at equilibrium, we will use the more reactive carbonyl compound -- an aldehyde, rather than a ketone.

The mechanistic pattern is as follows:



The first step forms the enolate ion. The second step makes a carbon-carbon bond by nucleophilic attack of the enolate alpha-carbon on the carbonyl carbon of a second molecule of the aldehyde. The third step places a proton on the now negatively charged oxygen and regenerates the basic catalyst.

Let's look at the overall reaction and relate the structure of the product to that of the reactant.



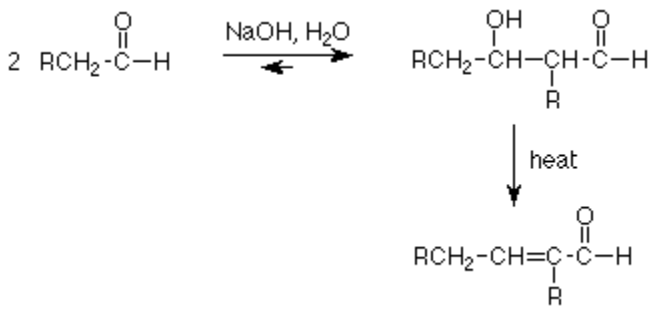
Two molecules of an aldehyde combine so that the alpha-carbon of one becomes attached to the carbonyl carbon of the other. The carbonyl oxygen becomes an alcohol group, located on the beta carbon (relative to the remaining carbonyl group) of the product. The overall reaction is an equilibrium, as we would expect since all steps in our mechanism are equilibria. The equilibrium favors aldol product when the carbonyl group is an aldehyde, but does not for ketones.

If we are seeking to use the aldol addition for synthetic purposes, we look for the characteristic beta-hydroxy-aldehyde arrangement of functional groups. Then we check to see that the R-groups are in fact identical. If these criteria are met, then we can work backwards to the needed aldehyde by mentally breaking the "thick" bond -- the one which was formed in the actual addition step. That gives us our reactant. Incidentally, the term aldol stems from the "ald" of aldehyde and the "ol" of alcohol.

Aldol Condensation

The particular example we have discussed is capable of one more reaction. If we heat the aldol addition product, it usually loses a molecule of water to make a double bond between the alpha and beta carbons of the former aldol. This is a dehydration reaction, and it is also an example of an **elimination** reaction. An elimination reaction is the structural opposite of an addition reaction,

and we'll look at typical mechanisms for these reactions later



Notice that this elimination reaction requires that the alpha carbon of the aldol product have attached a hydrogen. Since that carbon already lost one hydrogen in forming the enolate intermediate essential to the aldol addition, it must have had two hydrogens in the original aldehyde. The product of this second reaction is called an alpha-beta-unsaturated aldehyde (unsaturated because of the carbon-carbon double bond), and the overall reaction is called an aldol condensation. The term condensation is used to describe a reaction in which two molecules combine to form a larger product with the loss of a molecule of water.

The key structural feature of a molecule which might be made by way of an aldol condensation is the carbon-carbon double bond between the alpha and beta carbons of an aldehyde. If a synthetic target has that feature, we need to check to see if the R-groups are identical. If so, we can make that molecule by the aldol condensation.

In your later biochemical studies you will find that carbon-carbon bonds are often made (in photosynthesis for example) by enzymatically catalyzed aldol additions. The reverse reaction is also common (called a retro-aldol reaction), particularly in glycolysis, the metabolism of glucose.

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1.9: Carboxylic Acid Derivatives- Interconversion

Structures of Carboxylic Acid Derivatives

Last time we completed our study of the reactions of aldehydes and ketones, compounds in which a carbonyl group is bonded either to carbons or hydrogens. The typical reaction pattern for these compounds was addition, with a nucleophile adding to the carbonyl carbon and an electrophile adding to the carbonyl oxygen. Today we'll look at carboxylic acid derivatives. This group of compounds also contains a carbonyl group, but now there is an electronegative atom (oxygen, nitrogen, or a halogen) attached to the carbonyl carbon. This difference in structure leads to a major change in reactivity. Here we find that the reactions of this group of compounds typically involve substitution of the electronegative atom by a nucleophile. Before looking at that reaction in detail, though, let's see what kind of compounds we're talking about.

Name	Structure	Found or Used In:
Carboxylic Acid	$R-\overset{O}{\overset{\|\|}{C}}-OH$	Vinegar, Cream of Tartar
Ester	$R-\overset{O}{\overset{\|\|}{C}}-OR'$	Fats, Cell Membranes
Amide	$R-\overset{O}{\overset{\|\|}{C}}-NHR'$	Nylon, Proteins
Acyl Chloride	$R-\overset{O}{\overset{\|\|}{C}}-Cl$	Synthesis of Carboxyl Derivatives
Acid Anhydride	$R-\overset{O}{\overset{\|\|}{C}}-O-\overset{O}{\overset{\|\|}{C}}-R$	Synthesis of Carboxyl Derivatives

Notice that each of these functional groups has either an oxygen, a nitrogen, or a halogen attached to the carbonyl carbon.

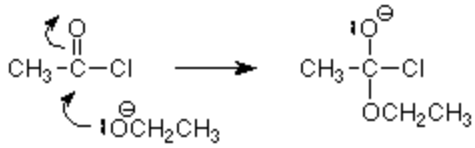
Substitution by Addition-Elimination

The typical reactions of these compounds are substitutions -- replacing one of these heteroatoms by a another atom. Here's an example:

$$\underset{\text{Acyl Chloride}}{CH_3-\overset{O}{\overset{\|\|}{C}}-Cl} + \underset{\text{Alkoxide}}{{}^{\ominus}OCH_2CH_3} \longrightarrow \underset{\text{Ester}}{CH_3-\overset{O}{\overset{\|\|}{C}}-OCH_2CH_3} + Cl^{\ominus}$$

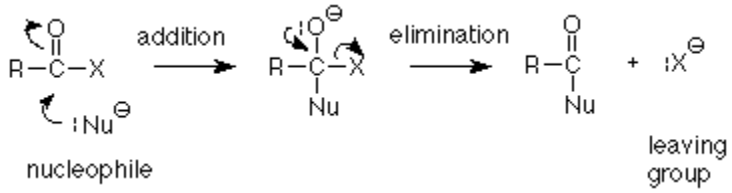
The chlorine of the acyl chloride has been replaced by the $^-OCH_2CH_3$, more specifically by the oxygen atom of that group. This type of reaction, in which an atom or group is replaced by another atom or group, is called a substitution reaction.

We can begin to connect this reaction type with what we have seen earlier by thinking about the mechanism. We notice that the O^- end of the group (called an alkoxide) which is doing the substituting is very much like the oxygen in an OH^-. Since we've seen the OH^- act as a nucleophile when it attacked the electrophilic carbon of a carbonyl group, let's begin by seeing what happens if we use the same approach here.



The first step is familiar from aldehyde and ketone chemistry. The nucleophilic oxygen uses its electrons to make a new bond to the electrophilic carbonyl carbon while the pi bond's electrons move to the carbonyl oxygen. We've made the necessary oxygen-carbon bond. In the next step, the pi bond is reformed, and the carbon-chlorine bond is broken. This is a new type of step, and it happens when breaking this bond is eased by the electron pair being attracted to an electronegative atom such as oxygen, nitrogen or a halogen. This step is called an elimination. The overall substitution process occurs by an addition-elimination mechanism which begins with a nucleophilic addition to the carbonyl group and finishes with the departure of an atom with the bonding pair of electrons. This atom or group is called a "leaving group."

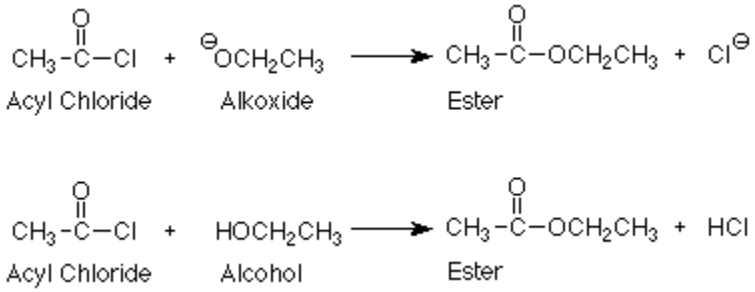
Here's a general statement of the mechanism:



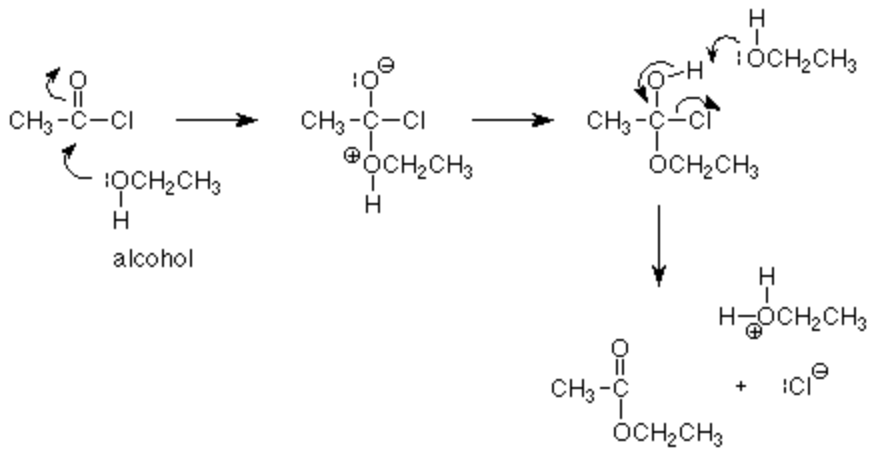
As we look at some specific examples, keep this pattern in mind. There will be some elaborations on it, but we will always find an addition step in which the nucleophile attacks and an elimination step in which the leaving group leaves.

Esters - Preparation and Mechanisms

The conversion of acyl chlorides to esters is more commonly carried out by using an alcohol rather than an alkoxide (RO^-).

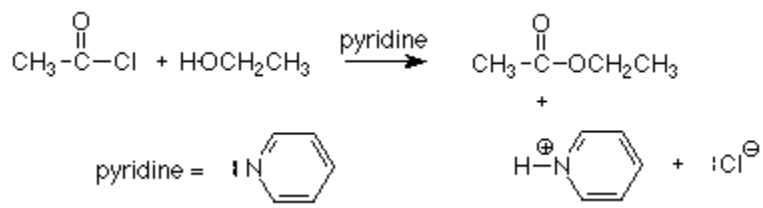


The mechanism of this reaction starts just the same way the earlier one did; the first step is attack of the nucleophile at the carbonyl carbon. In this instance, the nucleophile is an unshared electron pair on a neutral oxygen atom. The intermediate formed in this step rapidly shifts a proton (H^+) to the O^-. Such transfers of protons between oxygen atoms or nitrogen atoms are fast. (These intermediates are called "tetrahedral intermediates" since carbonyl carbon has been changed to a tetrahedral geometry and an sp^3 hybridization.)

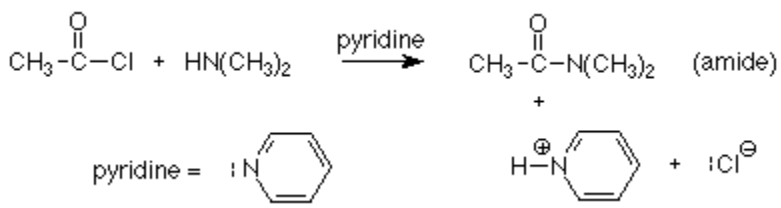


The tetrahedral intermediate loses HCl in a single step, one in which the H^+ is transferred to a second molecule of alcohol and the Cl comes off as Cl^-. It is important to notice that the neutral alcohol oxygen serves as the nucleophile. The O-H bond is not broken until after the C-O bond is formed. There is never any alkoxide in this reaction. Indeed, an alkoxide ion could not survive in the strongly acidic (HCl) solution. This pattern, neutral nucleophile attacks first, then the proton is removed, is very common for neutral nucleophiles and must be followed.

This is a practical and useful method for making esters, but it does make the strong acid HCl, which is often troublesome. A more practical variation is to add a weak base such as pyridine to react with the HCl and neutralize it. This gives us a procedure for making esters from acyl chlorides which uses the following reaction statement:

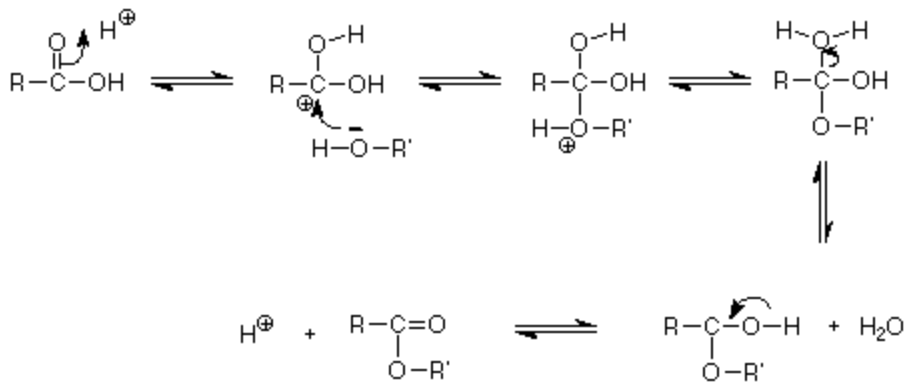


A similar procedure is used to make amides from acyl chlorides and amines (the amine must have at least one hydrogen attached to the nitrogen).



Acyl chlorides are the most reactive carboxylic acid derivatives. The electronegative chlorine atom pulls electrons toward it in the C-Cl bond, which makes the carbonyl carbon more electrophilic. This makes nucleophilic attack easier. Also, the Cl^- is an excellent leaving group, so that step is also fast. Because of their reactivity, acyl chlorides are easily converted into esters and amides and are thus valuable synthetic intermediates. They are made from carboxylic acids by this reaction (Atkins & Carey, Sec 12:10):

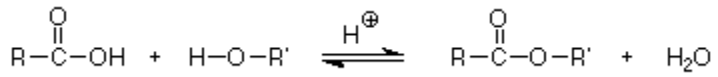
In the mechanism we just looked at, the key steps (attack of a nucleophile and departure of a leaving group) were accompanied by steps in which protons moved from one location to another. Such proton transfers are very common in acid catalyzed reactions. Here's the mechanism for the acid catalyzed formation of an ester from a carboxylic acid and an alcohol:



Notice that the nucleophilic attack is preceded by protonation of the carbonyl oxygen. We've seen this step before in the acid-catalyzed additions of nucleophiles to carbonyl groups. Its purpose is to increase the reactivity of the carbonyl carbon as an electrophile, so that it can be easily attacked by the alcohol oxygen. After nucleophilic attack, there is a proton transfer. Its purpose is to make one of the OH groups (either will do) into a good leaving group, water.

Think back to the addition of alcohols to aldehydes to produce hemiacetals. The two mechanisms start off identically. Compare them in detail, and work out the reasons for the different outcome.

Notice that each step in this mechanism is presented as an equilibrium. That means that the whole reaction represents an equilibrium in which significant amounts of carboxylic acid and alcohol co-exist with ester and water.

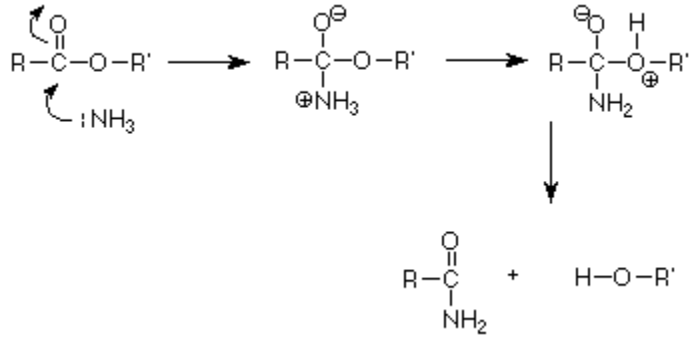


This allows us to push the reaction one way or the other by controlling concentrations, particularly of water. If we remove water from the reaction mixture, more ester is formed because carboxylic acid and alcohol react to replace the water we have removed. The resulting formation of ester is called Fischer esterification.

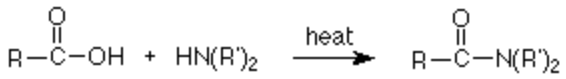
If we add water to the reaction mixture, equilibrium is restored by the production of more carboxylic acid and alcohol. This is called acid catalyzed ester hydrolysis.

Amides - Preparations

Esters can also react with amines or ammonia to form amides. This reaction doesn't involve acid catalysis, so the first step is nucleophilic attack at the carbonyl carbon. Proton transfer follows and loss of the alcohol portion of the ester.



This gives us two ways to make amides, this one from esters and the earlier one from acyl chlorides. Here's a third and very direct way to make amides, by heating carboxylic acids and amines together.



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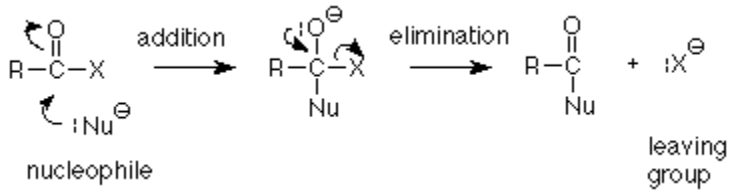
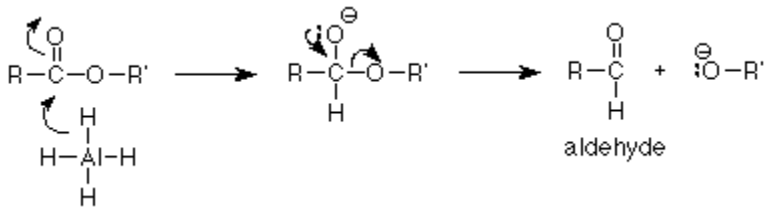
1.10: Carboxylic Acid Derivatives - Alpha Carbon Reactions

Reduction of Esters - Lithium Aluminum Hydride

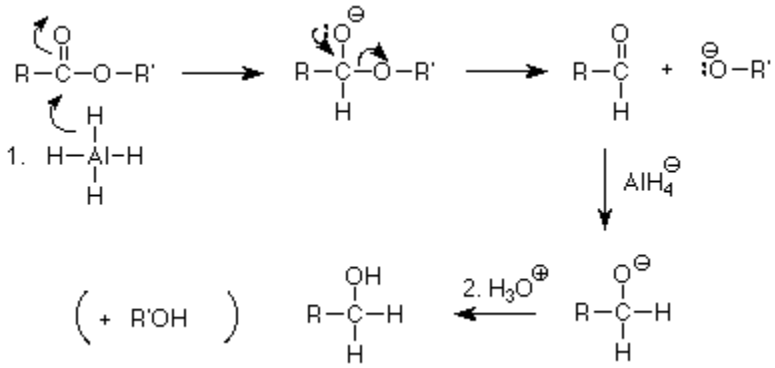
We've seen that carboxylic acid derivatives react with nucleophiles to give substitution products in which the leaving group is replaced by the attacking nucleophile.



This same pattern describes the first steps in the reaction of esters with lithium aluminum hydride and Grignard reagents, but in both cases the reaction proceeds further because the first product formed also reacts with the reagent. For an example, lets look at the reduction of an ester with lithium aluminum hydride.



When the "hydride ion" ($H:^-$) from lithium aluminum hydride replaces the OR' group of the ester, an aldehyde is formed. We've already seen that and aldehyde is reduced by lithium aluminum hydride, so it comes as no surprise that the aldehyde is immediately reduced to a primary alcohol. In fact, the aldehyde is more electrophilic than the ester, so as soon as a few molecules of aldehyde are formed, they are attacked by the hydride in preference to the ester. The reaction is completed by the later addition of aqueous acid to protonate the O^- atoms.

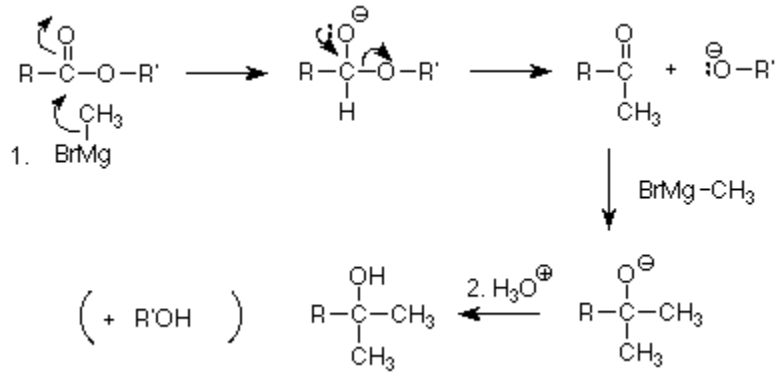


The result is that esters are reduced by lithium aluminum hydride to primary alcohols in which the ester carbon has become the alcohol carbon. Sodium borohydride is not reactive enough to carry out this reduction. This is a useful way to make primary alcohols.

Reaction of Esters with Grignard Reagents

A very similar process occurs when an ester reacts with a Grignard reagent. Remember that the Grignard reagent serves as a

source of carbon nucleophiles. We can use the same pattern as worked for the lithium aluminum hydride reduction by replacing the "H:-" with the "C:⁻" from the Grignard reagent. Here's an example in which the Grignard reagent is methylmagnesium bromide:



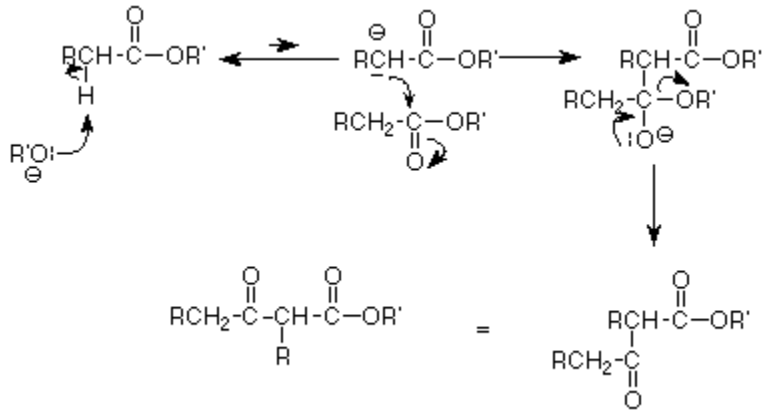
Here the first product is a ketone in which the OR' group of the ester has been replaced by the alkyl group of the Grignard reagent. This ketone is immediately attacked by another molecule of the Grignard reagent. After neutralization with aqueous acid the product is an alcohol in which the two identical groups attached to the alcohol carbon are from the Grignard reagent. If the R group of the ester is a carbon group this will be a tertiary alcohol.

In both these cases, we've combined a the general pattern for carboxylic acid derivatives, substitution of the nucleophile in place of the leaving group, with a pattern which applies to aldehydes and ketones, to arrive at "double" reaction. The first part is substitution and the second part is addition. We can't stop the reaction halfway, because aldehydes and ketones are more reactive than esters, so the aldehydes and ketones gobble up the reagent faster than the esters.

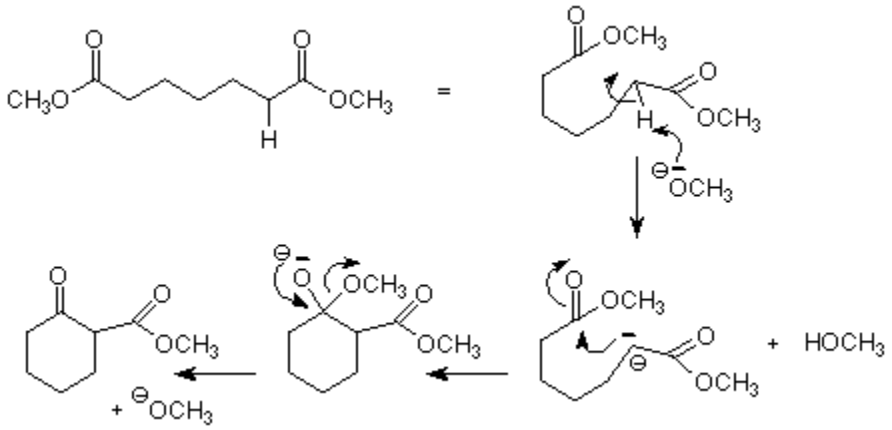
Claisen and Dieckmann Condensations

We spent some time on the aldol condensation when we were studying aldehydes, and we learned that the alpha C-H bonds of aldehydes and ketones can be attacked by base to form enolates. The same thing can occur with esters, although we need to be very specific about the identity of the base we use -- it needs to be the same as the OR' (alcohol derived) portion of the ester. (Consider what would happen if the base and the OR' group were different. The base would attack the carbonyl carbon and would replace the OR' group. A new and unwanted product would appear. If the base is the same as the OR' group, attack by the base on the carbonyl carbon results in no net change and keeps the reaction simpler.)

The first step in such a reaction is strictly analogous to making an enolate from an aldehyde. This is followed by attack of the nucleophilic alpha carbon of the enolate on the carbonyl carbon of a second molecule of the ester. Again, this is strictly analogous to the situation in the aldol reaction, and it has resulted in a nucleophilic addition to the carbonyl carbon. As is typical for carboxylic acid derivatives, the next step is loss of the leaving group, so that the carbonyl group which has been added to shows up as a ketone. (Since the newly-formed ketone is in a beta position relative to the ester functional group these compounds are called beta-keto-esters.) This overall reaction is called the Claisen condensation after Ludwig Claisen, a prominent German organic chemist of the late 19th and early 20th centuries.



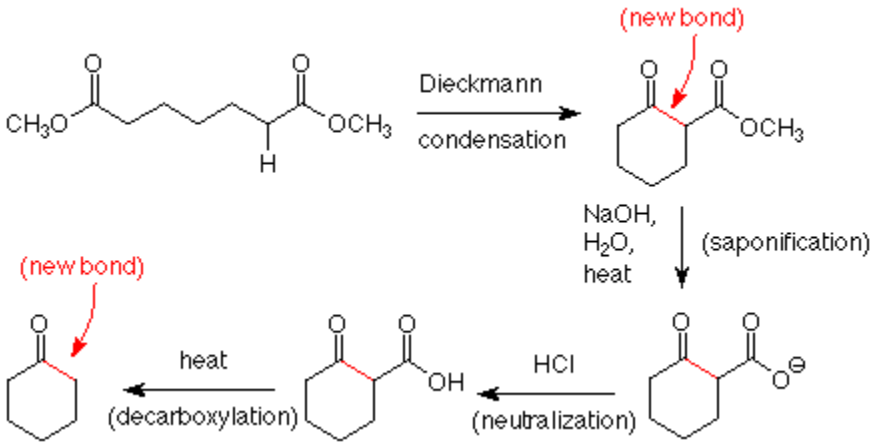
When there are two ester groups on the same carbon chain (a **diester**), the enolate formed at the alpha carbon atom of one ester group can react with the carbonyl carbon of the other ester group.



The resulting Claisen condesation makes a ring of carbon atoms. If this ring has five or six carbons in it, it forms readily. This (*intramolecular* variation of the Claisen condensation is called the Dieckmann condensation. Since many organic compounds which occur in nature have five or six membered rings, the Dieckmann condensation has been widely used in synthesis.

Decarboxylation and Ketone Synthesis

Notice that both the Claisen condensation and its Dieckmann condensation variant make a compound we can call a *beta-keto-ester*, that is, an ester with a keto group on the carbon two atoms away from the carbonyl carbon. Such beta-keto-esters can be hydrolyzed to beta-keto-acids by base-promoted hydrolysis (saponification) and acidification. The beta-keto-acids readily lose a molecule of carbon dioxide when heated to form a ketone. This means that a Dieckmann or Claisen condensation can be followed by a hydrolysis-decarboxylation step to form a ketone. This gives us a way to make ketones. Notice that the new carbon-carbon formed in this sequence is one which joins a carbonyl carbon to one of its alpha carbons. Here's an example of the use of this synthetic sequence of reactions to make cyclohexanone:



We'll look at some of the details of the saponification reaction next time.

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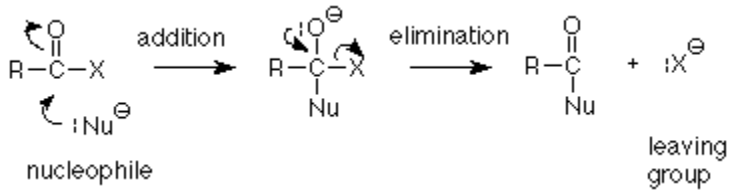
1.11: Fats, Fatty Acids, Detergents

Biosynthesis of Fats

We've seen that carboxylic acid derivatives react with nucleophiles to give substitution products in which the leaving group is replaced by the attacking nucleophile.



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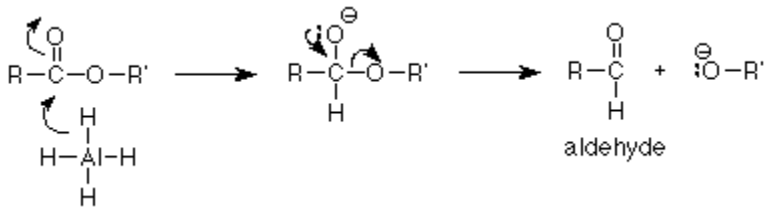

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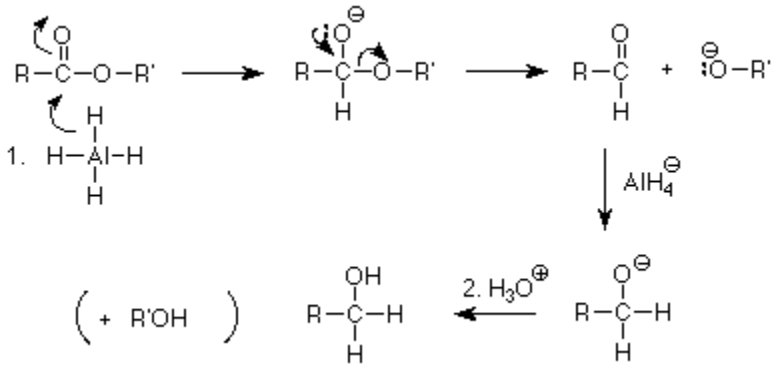

The result is that esters are reduced by lithium aluminum hydride to primary alcohols in which the ester carbon has become the alcohol carbon. Sodium borohydride is not reactive enough to carry out this reduction. This is a useful way to make primary alcohols.

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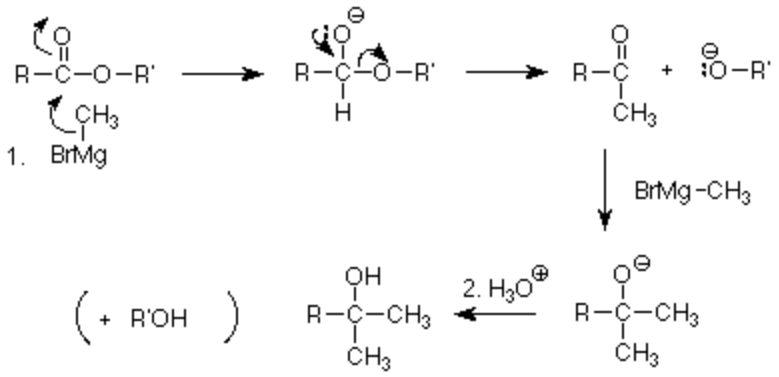

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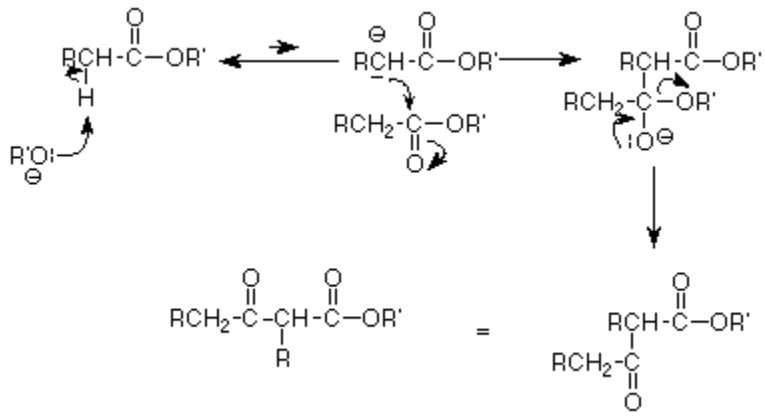
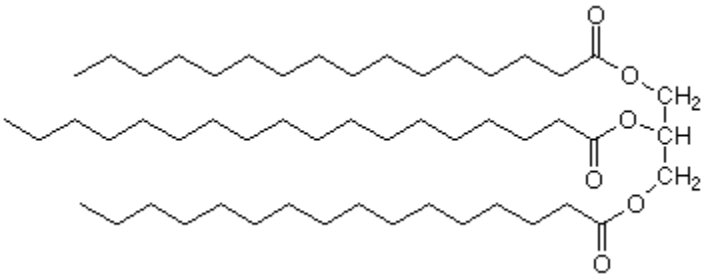
The first step in such a reaction is strictly analogous to making an enolate from an aldehyde. This is followed by attack of the nucleophilic alpha carbon of the enolate on the carbonyl carbon of a second molecule of the ester. Again, this is strictly analogous to the situation in the aldol reaction, and it has resulted in a nucleophilic addition to the carbonyl carbon. As is typical for carboxylic acid derivatives, the next step is loss of the leaving group, so that the carbonyl group which has been added to shows up as a ketone. (Since the newly-formed ketone is in a beta position relative to the ester functional group these compounds are called beta-keto-esters.) This overall reaction is called the Claisen condensation after Ludwig Claisen, a prominent German organic chemist of the late 19th and early 20th centuries.



While this reaction is of considerable use for synthesis in organic chemistry, we are going to turn our attention to the involvement of this pattern in the biological synthesis of fatty acids.

First we need to know something about the structures of fats. Fats are esters in which the OR' (alcohol) portion of the molecule is the trihydroxy compound, glycerol ($HOCH_2CHOHCH_2OH$). There are three carboxylic acid portion in these molecules since each glycerol molecule can be esterified with a different carboxylic acid. They are consequently called triacylglycerols or triglycerides. These carboxylic acids typically have long hydrocarbon chains of fourteen to twenty carbons (including the carbonyl carbon).

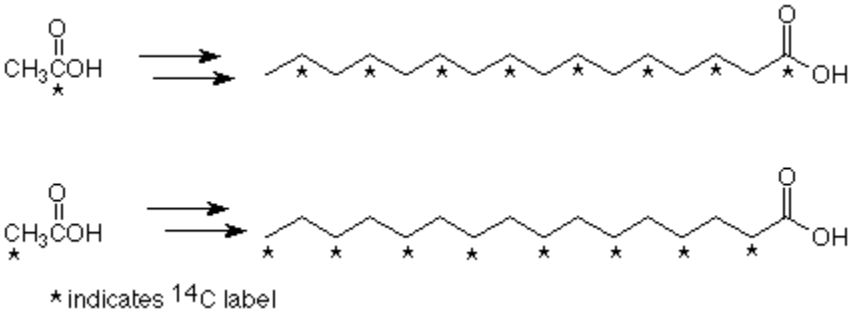
These chains are typically unbranched and, most strikingly, they contain even numbers of carbon atoms. The carboxylic acids obtained by hydrolysis of fats are called fatty acids.



Since most carbons in fats are completely reduced (maximum number of hydrogens, no oxygens), the oxidation of fats produces substantial quantities of energy, about double the energy per gram as is obtained from the more oxidized carbohydrates and proteins. Fats are thus used for long-term energy storage in organisms.

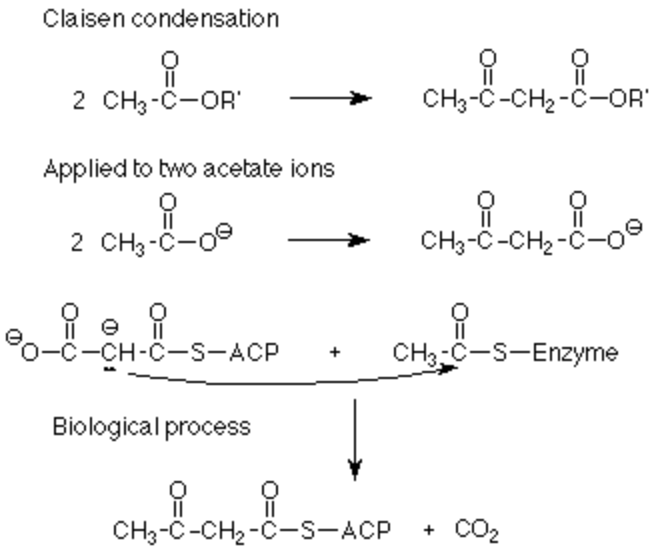
The observation that fatty acids have even numbers of carbons in them provides a clue as to the mechanism of their biological synthesis. The most obvious idea is that fatty acids are built up two carbons at a time, which would mean that each fatty acid would have to have an even number of carbons. A common two carbon molecule in biochemistry is acetic acid. (At the near acid/base neutrality which prevails in biological systems, acetic acid is present as it conjugate base, acetate ion).

This speculation was verified by feeding organisms with radioactively labeled (^{14}C) acetate. The radioactive label appeared in the fats. More specifically, if the ^{14}C was placed in the carbonyl carbon of the acetate, it appeared in the odd numbered locations in the fatty acid. If it was placed in the methyl carbon of the acetate, it appeared in the even numbered carbons in the fatty acid.



This is interpreted to mean that the fatty acid is built up two carbons at a time. Each two carbon unit is added by reacting the alpha carbon of one acetate unit with the carbonyl carbon of the next -- exactly the pattern which we see in the Claisen condensation.

Of course, there is much more to the process than this, but the key bond forming step has the same pattern as the Claisen condensation. That is, attack by nucleophilic carbon atom at the carbonyl carbon of an ester, which is followed by loss of the alcohol portion of the ester as a leaving group. In the the biological reaction, the esters have sulfur in them rather than oxygen and are attached to enzymes or other proteins, and the nucleophilic carbon is flanked by not one but two carbonyl groups. Nevertheless, the underlying pattern is the same.



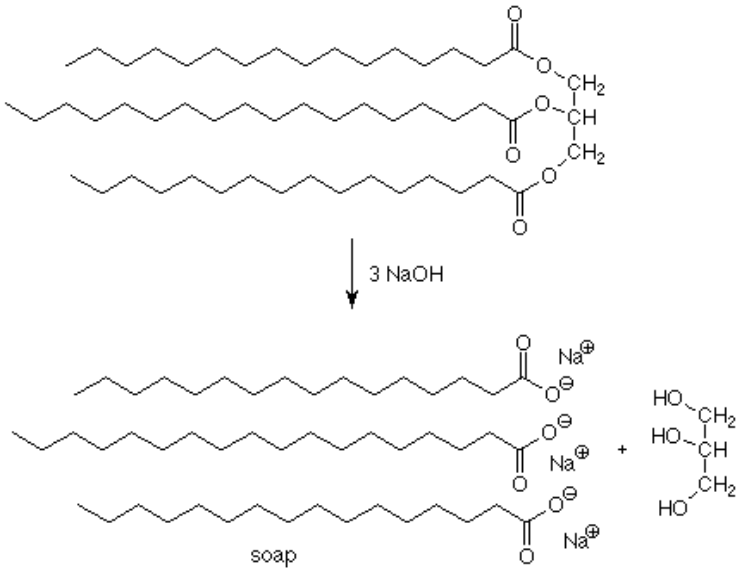
The biological Claisen condensation we have looked at is followed by further biochemical steps which replace the carbonyl oxygen with two hydrogens. The four carbon ester which is thus produced is attacked at its carbonyl carbon by another molecule of the carbon nucleophile and the cycle continues.

It is important to realize that biological chemistry uses the same mechanisms that we use in the laboratory. Organic reaction mechanisms underlie all of biochemistry, particularly metabolism.

Saponification and Soaps

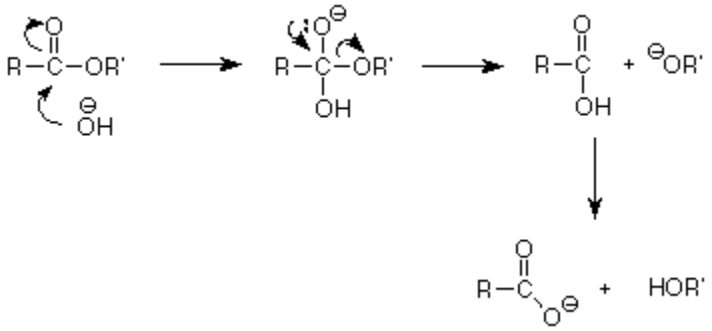
Next, we'll look at a reaction of fats which is of great economic importance. Nobody knows when the first soap was made, but it was very important in the Middle Ages and early industrial period because it was used to wash out wool fat from wool in preparation for dyeing and spinning. It was too expensive in those times to use for general cleanliness. The general availability of soap has led to a rise in standards of cleanliness and a corresponding rise in general health.

Soap is made by treating fats with a strong solution of lye (NaOH). The ester functional groups are hydrolyzed releasing its alcohol portion as glycerol and the acid portions as the a mixture of the sodium salts of the fatty acid. The glycerol is water soluble and is separated from the fatty acid salts. These are nearly insoluble in water, and are washed and compressed into a cake -- soap.



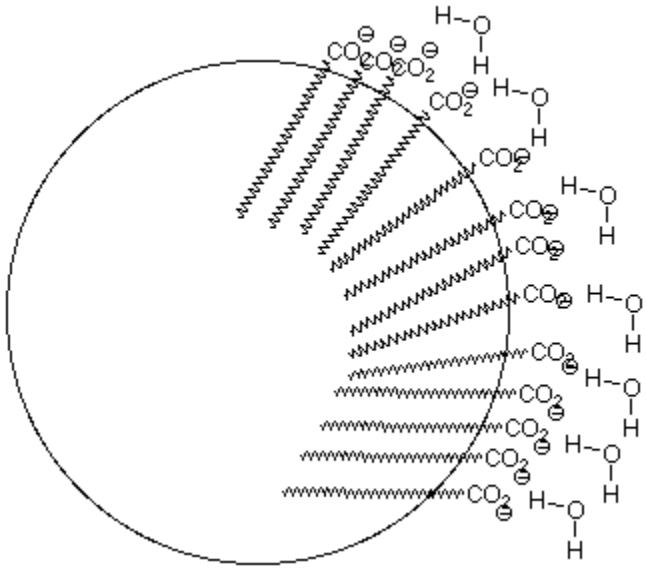
The mechanism of this reaction, which is called saponification) can be illustrated more easily on a simple ester than a fat. It

follows the normal pattern for a carboxylic acid derivative and the first step is analogous to base-catalyzed hydration of aldehydes -- attack of the nucleophile hydroxide ion at the carbonyl carbon atom. This is followed by the usual departure of the leaving group (in this case, the OR'^- of the ester). Since the OR'^- is more basic than $RCOO^-$, the last step is a neutralization reaction. (The last step will make more sense after next time.)

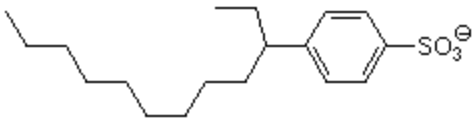


Detergent Structure

To finish up, we need to look at how soaps work and how that relates to their structures. Soaps are "bridge" molecules. Their long hydrocarbon chains are very much like oils, so they mix well with oils. In fact, we can say that the chains of soap dissolve in oils. At the same time, their ionic heads are polar enough to dissolve in water. If we imagine a small globule of oily material which has dissolved a bunch of soap molecules, we can see that the polar ionic heads will stick out (insoluble in oil) at the surface. These polar bumps on the surface attract water molecules, so that the oily glob is coated with water molecules that are held there by the ions. The glob is now ready to be washed away in water. Since much of the dirt we hope to get rid of is held in place by oily films, removing the oils removes the dirt.



The structural requirements for a soap (or more generally, for a detergent) are a long hydrocarbon tail (12 or more carbons) and a polar (often ionic) head. In synthetic detergents, the hydrocarbon tail is usually formed by linking several ethylene molecules together and attaching this to a benzene ring. The polar part is derived by covalently bonding the sulfur of a sulfate ion to the benzene ring. We'll learn more about the chemistry of making these later. If there are few branches on the hydrocarbon tail, the synthetic detergent will be biodegradable, an important characteristic.



synthetic detergent

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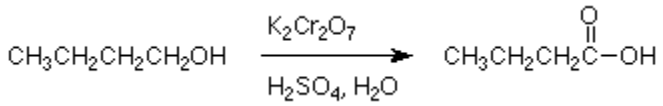
1.12: Carboxylic Acids

Oxidation of Primary Alcohols

There are two types of reactions which can make carboxylic acids. We will look first at those that depend upon oxidation of groups from a lower oxidation level (fewer oxygens, more hydrogens). Then we'll see that there are reactions which make a carbon carbon bond on the way to making a carboxylic acid.

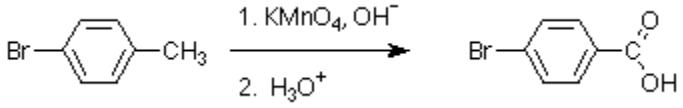
As you might suspect, carboxylic acids can be made by oxidizing groups which are less oxidized. The most important of these is the primary alcohol group. A typical reaction is:



We recognize the oxidizing agent, potassium dichromate, as the same reagent that was used in oxidizing aldehydes to carboxylic acids. Chromium is in oxidation level six in dichromates and it is reduced to oxidation level three in this process. The details of the reduction of chromate are complex, and we will not be concerned with them. The oxidation of aldehydes also produces carboxylic acids, but since aldehydes are less readily made than carboxylic acids, this process is not used much.

Oxidation of Side Chains on Aromatic Rings

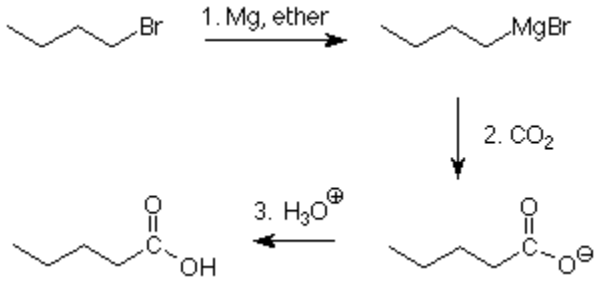
Another oxidative process seems at first not to involve a functional group. Alkyl groups (usually methyl groups) attached directly to an aromatic ring are also oxidized to carboxylic acids. Since the methyl group contains only sigma C-H bonds, it doesn't look like a likely place for reaction. It is influenced by the neigboring aromatic ring, though, so reaction does occur. This is somewhat like the special reactivity of the alpha C-H bonds of a ketone or aldehyde. Here's an example:



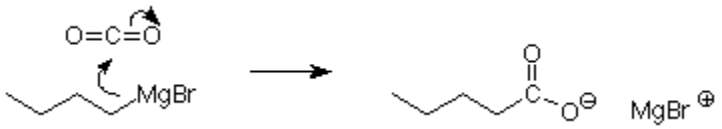
Remember, this reaction **requires** the presence of an aromatic ring next to the alkyl group which is to be oxidized. Any carbons beyond the first one are lost in this process, which is one of the few reactions which breaks a carbon-carbon bond.

Making a Carbon-Carbon Bond

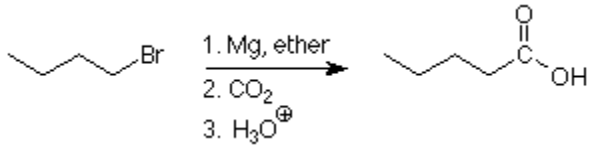
There are two reaction sequences which make carbon-carbon bonds on the way to carboxylic acids. The first is another use of the Grignard reagent. Remember that Grignard reagents react with carbonyl compounds to make alcohols. While we don't usually think of it that way, carbon dioxide is a a carbonyl compound (O=C=O). If a Grignard reagent is used to deliver a nucleophilic carbon atom to the carbonyl carbon of the carbon dioxide, we get a carboxlic acid (after quenching with aqueous acid).



The attack of the Grignard reagent on the carbon dioxide is directly analogous to the same step in reactions of other carbonyl compounds:

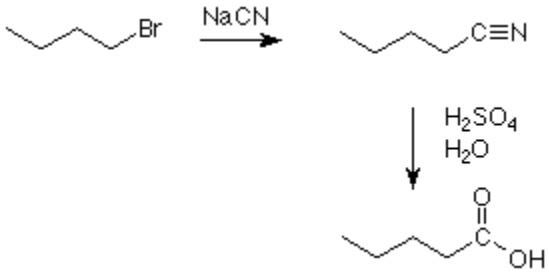


Here's the entire sequence presented in the more compact format we used for Grignard additions earlier:



Notice that the product has one more carbon than the bromoalkane we started with, and that this carbon is in a carboxylic acid group.

There is also another way to make a new carbon-bond and wind up with a carboxylic acid. If we have a primary alkyl halide (primary means that the carbon which is bonded to the halogen is bonded to only one other carbon atom, it's other two bonds are to hydrogen), we can react it with sodium cyanide. The cyanide ion will replace the halogen, and this makes a new carbon-carbon bond. The product is called a nitrile. Its carbon-nitrogen triple bond can be hydrolyzed with aqueous acid to produce a carboxylic acid. The sequence is as follows (normally, the nitrile is isolated and then hydrolyzed in a separate reaction):

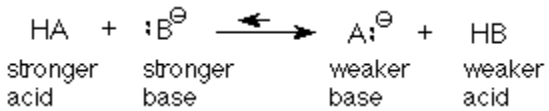


We won't look at the details of the mechanisms of either of these reactions now. You might usefully speculate about the hydrolysis of the nitrile. You could begin by thinking of the C-N triple bond as being like a carbonyl group. After all, it does include a pi bond between carbon and an electronegative atom, much like the pi bond in a carbonyl group.

Acid and Base Strengths

The remaining issue with carboxylic acids is to understand why they are acidic. We can experience their acidity by tasting vinegar -- which is a dilute solution of acetic acid in water. The Lowry-Bronsted model of acids is useful for this. Let's refresh our memories on this model and on the interpretation of the term pK_a.

When we think about acids using the Lowry-Bronsted model, we think of a molecule which can donate a proton (H^+). A base is a molecule which can accept a proton (using the pair of electrons which are the defining feature of a Lewis base). Stronger acids donate protons readily to stronger bases. The products of this transaction are weaker acids and weaker bases. Here's the pattern.



Notice particularly that a strong acid is strong because it readily donates a proton. That means that its conjugate base (the base which remains after the proton is gone) is weak. After all, if the base were strong, it would grab the proton back and the acid couldn't give it away. When we describe an acid as strong, by saying that it has a small pK_a, we are also saying that its conjugate

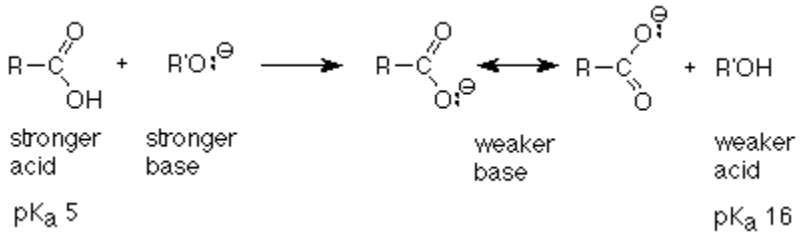
base is weak. HCl is a strong acid (pK_a -7). When we say that, we are also saying that Cl^- is a weak base. The conjugate base of an acid whose pK_a is small or negative is a weak base. This means that we can use a pK_a table like Table 2.1 on p 43 of Brown to keep track of both acidity (strong acids have small or negative pK_a's) and basicity (weak bases come from strong acids with small or negative pK_a's).

Carboxylic Acid Acidity - Carboxylate Ion Basicity

This also means that we can restate the question "Why are carboxylic acids acidic?" to say "Why are the conjugate bases of carboxylic acids such weak bases?" To put this into context, notice that carboxylic acids have pK_a's of about 5, while water and alcohols have pK_a's of about 16. What makes the conjugate base (we'll call it a carboxylate ion) of a carboxylic acid so weak compared to a hydroxide (OH^-) or alkoxide (RO^-) ion?

As usual, we'll try to find our explanations in structure. There is one obvious difference between a carboxylate ion and an alkoxide ion. The carboxylate ion has two electronegative oxygens to only one for the alkoxide ion. These electronegative atoms would hold the electron pairs more tightly, which means that the electron pairs would be less available to make a bond to a proton. Less available electron pairs means a weaker base.

That accounts for some of the weakness of carboxylate ions as bases, but there's also a more subtle feature. Notice that we can move electrons between pi-bonding and unshared pair situations without changing the structure of the carboxylate ion. We recognize this as resonance and we recognize that it will lower the energy of a carboxylate ion compared to that of an alkoxide ion in which such resonance is not possible. Lower energy means more stable, more easily formed and less reactive, all of which adds up to a weaker base. Consequently the conjugate carboxylic acid is stronger than one whose conjugate base doesn't have the resonance possibility.



The somewhat paradoxical outcome of this is that carboxylic acids are stronger acids than alcohols because carboxylate ions, their conjugate bases, are weaker bases than alkoxides. This is due in large part to resonance stabilization of the carboxylate ions, which cannot happen in alkoxides.

This understanding of the structure of carboxylate ions also helps us understand how it is that when a Grignard reagent reacts with carbon dioxide, only one of the two carbonyl groups reacts. The product of this reaction is a carboxylate ion. It is resonance stabilized so the "real" structure is about halfway between the two resonance structures. That means that each C-O bond is halfway between a single and a double bond -- a bond and a half. Such a bond would be much less reactive than the double bond of a carbonyl group, so it isn't surprising that the Grignard reagent reacts with carbon dioxide in preference to the carboxylate ion.

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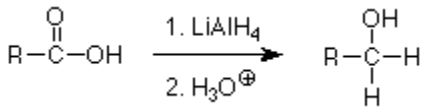
1.13: Alcohols

Making Alcohols

Here's a list of reactions we've already seen which make alcohols. The links will take you back to a previous lecture where the specific reactions are discussed.

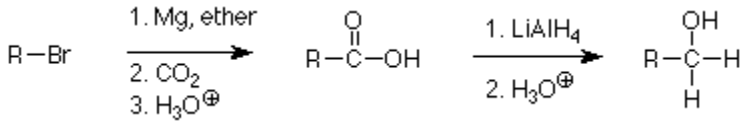
Reaction	Reactants	Product
Grignard Addition	Ketone, Grignard Reagent	Tertiary Alcohol
Grignard Addition	Aldehyde, Grignard Reagent	Secondary Alcohol
Grignard Addition	Formaldehyde, Grignard Reagent	Primary Alcohol
Hydride Reduction	Ketone, $NaBH_4$ or $LiAlH_4$	Secondary Alcohol
Hydride Reduction	Aldehyde, $NaBH_4$ or $LiAlH_4$	Primary Alcohol
Hydride Reduction	Ester, $LiAlH_4$	Primary Alcohol
Hydride Reduction	Carboxylic Acid, $LiAlH_4$	Primary Alcohol

The last reaction needs some further comment. Here's how we would do it:



The mechanism is similar to the mechanism for the reduction of esters by $LiAlH_4$, so we will not be concerned with the details. We can conclude that $LiAlH_4$ can be used to make a primary alcohol from either an ester or the corresponding carboxylic acid.

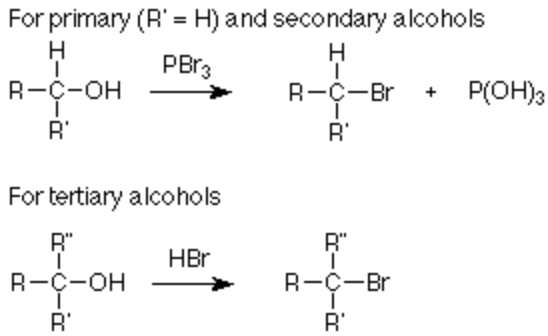
We can extend our understanding of the use of this reaction in synthesis by asking "How could we make the carboxylic acid we need for this reaction?" One particularly important way to do that, important because it makes a carbon-carbon bond, is to make a carboxylic acid by use of the addition of a Grignard reagent to carbon dioxide.



This combination gives us a two step way to convert an alkyl halide (RBr) to a primary alcohol with the addition of one more carbon to the chain.

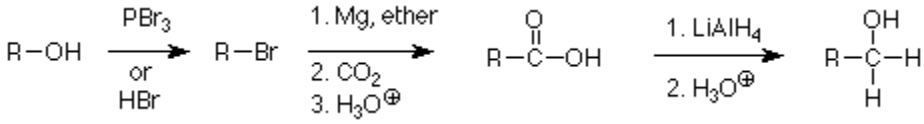
Alcohols to Alkyl Halides and Grignard Reagents

Of course, this raises the question: "Where do we get the RBr?" That takes us into the reactions of alcohols, because the most effective way to make alkyl halides is from alcohols. If we wish to make alkyl bromides, there are two reactions to consider.



If the alcohol is primary or secondary, the reagent of choice is phosphorous tribromide (PBr_3). If the alcohol is tertiary, we use hydrogen bromide (HBr) to ake the alkyl halide. The situation is similar if we wish to make an alkyl chloride. HCl is used for tertiary alcohols and $SOCl_2$ is used for primary and secondary alcohols. We'll take up the mechanisms of these reactions later. (If you wish to look ahead, see Chapter 7 in Brown.)

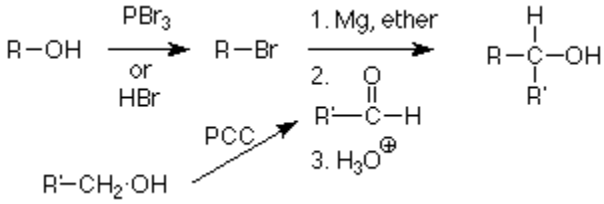
We now have an answer to the question of how to make alkyl bromides, so we can add another reaction to the beginning of the sequence we started with:



The alcohol product of this sequence can be used to make an alkyl halide to start a new sequence, which could be the starting point for a further sequence, etc. This makes alcohols extremely valuable synthetic reagents.

Including Aldehydes or Ketones

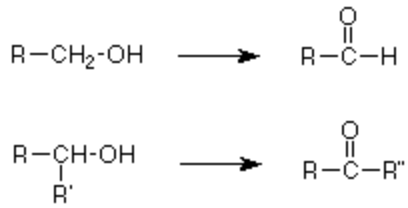
Suppose we used an aldehyde or ketone instead of carbon dioxide in such a sequence:



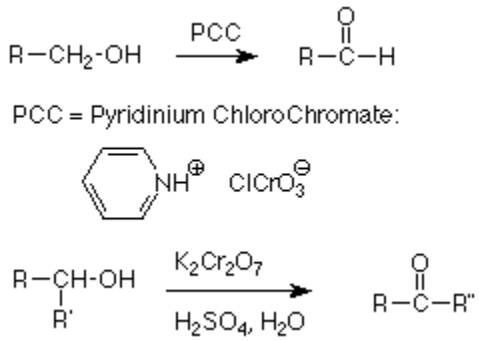
Here the product alcohol is produced directly rather than through a carboxylic acid. Notice that it is a secondary (from an aldehyde) or tertiary (from a ketone) alcohol, as we had seen when we looked at Grignard additions to aldehydes and ketones.

Oxidation of Alcohols to Aldehydes or Ketones

Since this has shown that one of the important components in a Grignard addition can be made from an alcohol, it seems natural to wonder whether the other major component, the aldehyde or ketone can be made from an alcohol. (We won't worry about how to make carbon dioxide -- there's plenty of it around.) The answer is yes, we can make an aldehyde or a ketone from an alcohol. The desired transformation is:



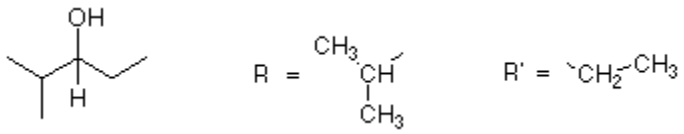
The products of these reactions have fewer hydrogens than the reactants, so these are oxidations. In the case of the ketone, further oxidation would require breaking a carbon-carbon bond to one of the R groups which is quite difficult. We can use chromic acid ($K_2Cr_2O_7$ - H_2SO_4). The situation with the aldehyde is more difficult, since we already know that the use of chromic acid will oxidize it to a carboxylic acid. It took considerable research to work out, but the reagent which works here is called pyridinium chlorochromate (PCC for short). Our synthetic reactions for the oxidation of alcohols are then:



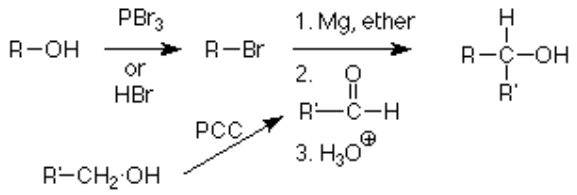
We can add the above reactions to our growing synthetic scheme.

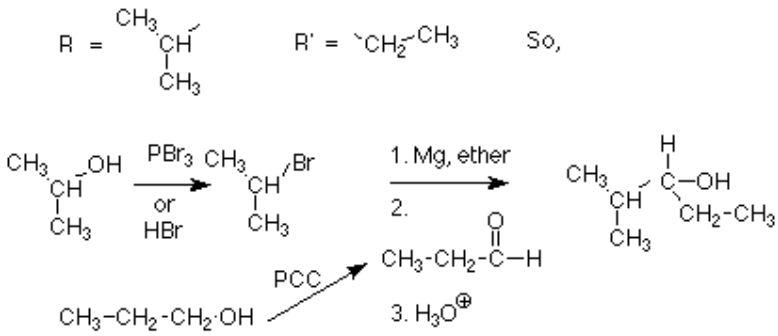
Since the product here is a secondary alcohol, the scheme could be carried onwards through its oxidation to a ketone and/or its conversion to an alkyl bromide, etc.

Let's apply this to a specific example. Suppose we wished to make this compound:



We can compare its structure to the general product of the scheme above and figure out what R and R' are. We then plug the specific identities of R and R' into the scheme to arrive at:





To summarize, since alcohols can be made into alkyl halides and can also be made into aldehydes and ketones, they are important starting points for carrying out a Grignard synthesis. As products of Grignard syntheses, they are also useful materials to begin a new cycle.

> The reactions we have looked at today have been those that affected the C-O bond of an alcohol. In making alkyl halides, we broke that bond and made a new bond between the carbon and a halogen. In oxidation, we added a pi bond to the C-O sigma bond of an alcohol.

Alcohols as Nucleophiles

We'll finish today by reminding ourselves of a couple of reactions of alcohols which use their unshared electron pairs, acting as nucleophiles, to make new bonds to carbonyl carbons.

Reaction	Alcohol Reacts With	Product
Hemiacetal Formation	Aldehyde	Hemiacetal
Ester Formation	Acyl Chloride	Ester

One thing to notice about these mechanisms is that the ushared electron pair is used to make the new bond **before** the O-H bond is broken. That's generally true unless there is a strong base present, something we'll take up next time.

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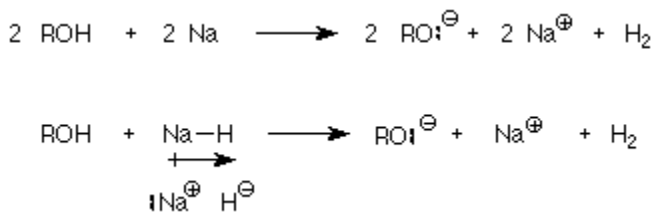
1.14: Ethers, Epoxides, Thiols

Alcohol Acidity - Making Alkoxide Ions

The acidity of alcohols is very comparable to that of water. That is, both water and most alcohols have pK_a's in the range of 15-16. As acids go, this makes them quite weak. Another way to say that the acidities of water and of alcohols are about the same is to say that the equilibrium constant for the following reaction is about 1.

$$H_2O + CH_3O^- \rightleftharpoons OH^- + CH_3OH \tag{1.14.1}$$

Of course, saying that water and alcohols have about the same acidity also means that hydroxide ion and alkoxide ions have about the same base strength. One practical consequence of this is that we can't completely convert an alcohol (ROH) to its conjugate base, the alkoxide (RO^-), by using hydroxide ion (HO^-) as the base because hydroxide ion isn't any stronger than a typical alkoxide ion. Instead there are two other reactions which work and which are commonly used

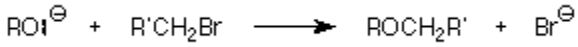


In the first of these, it is hard to see what is serving as the base which removes the H^+ from the alcohol. In a formal sense, two sodium atoms provide an electron each to make the new sigma bond in H_2, so perhaps it makes sense to call those electrons the strong base.

In the second reaction, the identity of the strong base is easier to see. In sodium hydride (NaH), the NaH bond is very strongly polarized, much more than the B-H bond in sodium borohydride, so that we can realistically regard it as an ionic compound (Na^+:H^-) so that the :H^- serves as the base. Since the hydrogen molecule (H_2) is such a weak acid that we never think of it as an acid, its conjugate base :H^- is a very strong base.

Making Ethers

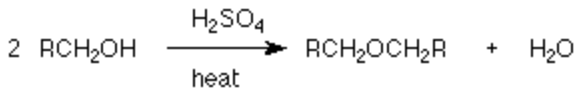
Now that we know about the acidity of alcohols and how to make alkoxide ions, their conjugate bases, we can ask "What are these alkoxide ions good for?" Since they are strong bases, we would also expect them to be good nucleophiles, and they are. We've seen their basic properties used in carrying out the Claisen condensation and occasional uses in other reactions with carboxylic acid derivatives, but their most direct use as synthetic reagents comes in their reactions with primary alkyl halides.



It is important to understand that this reaction only succeeds if the alkyl halide is primary. We'll take up the reasons for this later. Keep in mind that the most useful way to make an alkyl halide is from an alcohol, so that we could extend our reaction sequence by adding steps at the beginning to show how the alkoxide and the alkyl halide are made from alcohols:

The product of this reaction sequence is an ether, $ROCH_2R'$, so we have a synthetic method for making an ether from two alcohols, with the important restriction that one of the alcohols is primary.

There is also an acid catalyzed reaction which makes a symmetrical ether, one in which the two alkyl groups attached to the oxygen are identical. In this reaction a primary alcohol is heated with an acid catalyst (usually sulfuric acid). A molecule of water is lost and the ether is formed from two molecules of the alcohol.



Again, it is important to realize that this reaction can only be used on primary alcohols and that the ether produced this way is symmetrical.

Ethers as Solvents

Ethers are generally unreactive compounds. The C-O bond is polar, but breaking it is difficult. We will look at the reasons for this later.

The lack of reactivity of the ether functional group is one reason for the common use of ethers as solvents. A solvent has to dissolve the reactants to be useful, and it also must not react with the reactants present. In many cases, ethers meet these requirements well. They are fairly non-polar, since only the ether functional group contributes any polarity, so they dissolve most organic compounds easily. The unshared electron pairs on oxygen make them weak bases which allows them to dissolve some fairly polar reagents like Grignard reagents and lithium aluminum hydride. The lack of any acidic hydrogens, even those which are fairly weakly acidic like the OH hydrogens of alcohols, means that ethers are compatible with materials like Grignard reagents and lithium aluminum hydride which react with and are destroyed by alcohols. You will have seen ethers as solvents in many reactions.Two ethers which are commonly used as reaction solvents are:

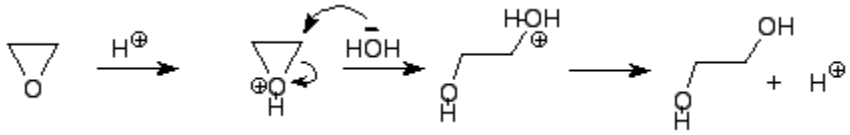
In lab, you also have used diethyl ether as a solvent for extractions. This takes advantage of ether's ability to dissolve most non-ionic organic compounds, its immiscibility (doesn't mix) with water, and the fact that ionic compounds are generally insoluble in diethyl ether. Since THF is miscible with water, it is not useful as an extraction solvent

Epoxides - Ring Strain

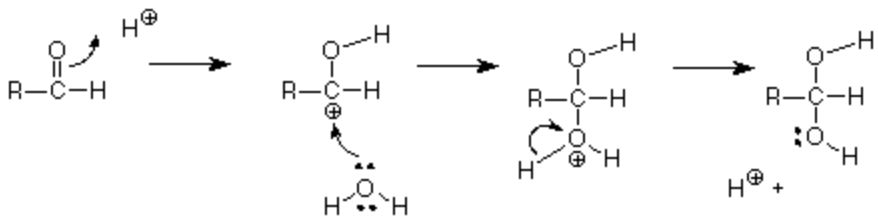
There is one type of ether which is quite reactive. The key structural feature of these ethers is that the oxygen atom is contained in a three-membered ring. Such ethers are called **epoxides**. The internal angles of such a ring will be near 60°, and this pushes the bonding electrons much closer together than the 109.5^{o} we would expect from the a VSEPR estimate or from sp^3 hybridization. Thus epoxides have high energies compared to "ordinary" ethers. One result is that epoxides are, in contrast to "ordinary" ethers, rather reactive compounds. Such rings are regarded as "strained" because the deviation of their bond angles from normal values leads to extra reactivity.

We'll look at two examples:

Acid-Catalyzed Hydrolysis: The name of this reaction recalls the acid-catalyzed hydration of ketones and aldehydes -- the first reaction we studied this semester. In fact, if we look at the mechanism of the acid catalyzed hydrolysis of the simplest epoxide:

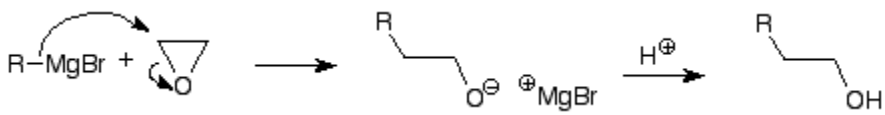


and compare it to the acid catalyzed hydration of an aldehyde:



we see that the steps in the two mechanisms are identical. In each case, the acidic H^+ adds to the oxygen atom. This pulls electron density away from the attached carbon atom, making it susceptible to attack by the weakly nucleophilic oxygen of water. A carbon-oxygen bond is broken, and the reaction is completed by regeneration of the H^+ catalyst. (We'll be in a position to look at the stereochemistry of this reaction in about three weeks).

The resemblance between these two mechanisms suggests that the reactions of epoxides are similar to those of carbonyl groups. More precisely, epoxide reactivity is intermediate between the reactivity of ethers (pretty unreactive) and carbonyl groups (reactive with selected reagents). Another example of this lies in the addition of Grignard reagents to epoxides. Again, we'll look at the simplest case (ethylene oxide), where there are no alkyl groups on the carbons of the epoxide.



Here again, we have a direct analogy with the reaction of an aldehyde or ketone with a Grignard reagent. As a synthetic reaction, this is best used with ethylene oxide, since complications are prevalent with more complex epoxide. The synthetic outcome of this reaction is to make a new primary alcohol which is two carbons longer than the Grignard reagent.

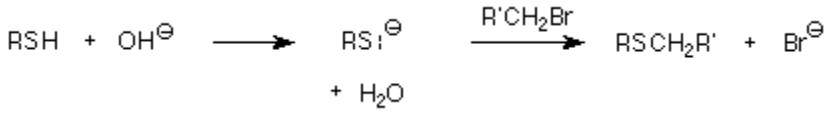
We'll defer discussion of the synthesis of epoxides until we look at the addition reactions of alkenes.

Thiols and Crosslinks

Our last topic for today is thiols -- the group of compounds in which the oxygen of an alcohol has been replaced by a sulfur. As one might expect given the close relationship between oxygen and sulfur in the periodic table, there are some similarities between alcohols and thiols. We will not examine the synthesis of thiols; rather, we'll look at some of their properties.

Perhaps the most obvious property of thiols, at least those which are small enough to be volatile, is their extremely disagreeable odor. This is understandable if we regard them as derived from hydrogen sulfide (rotten egg odor) in the same way that alcohols can be regarded as derived from water. Butanethiol ($CH_3CH_2CH_2CH_2SH$) is actually added to natural gas before it is distributed by pipeline so that the odor will signal the presence of a leak before it leads to dangerous concentrations of the gas. Chemists who work with thiols are careful to use them in the hood!

The SH group in a thiol is more acidic than the OH group in an alcohol. That means that the $RS:^-$ (thiolate ion) can be conveniently made by reacting a thiol (RSH) with hydroxide ion (OH^-). The thiolate ion is a good nucleophile, so it can react readily with a primary alkyl bromide to produce a thioether:



The SH group has important roles to play in biochemistry. We've seen how the sulfur serves as a leaving group in the Claisen-like reaction which makes the carbon-carbon bonds in fatty acid biosynthesis. This is quite general, since thioesters (the name for an ester containing a sulfur in the leaving group position) are very common in biochemical processes.

The thiol group is also important in the structure of proteins. Keep in mind that proteins are polyamides -- long chains of amino acids linked together by amide linkages. These chains can coil around and adopt a variety of shapes, some fairly straight and

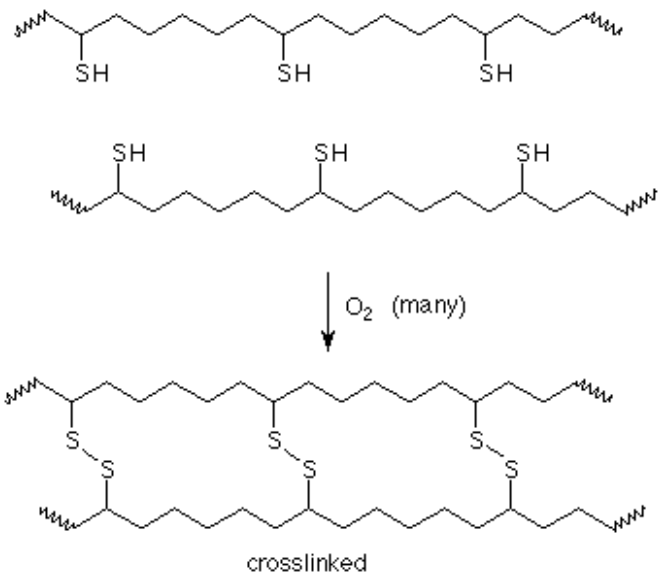
regular and others snarled like a tangled fishing line. For many purposes such as those in which proteins serve as enzymes (biochemical catalysts), it is essential that the protein have only one shape. Thiols contribute to maintaining that shape

The chemistry of this depends on the fact that the S-H bond can be oxidized by very mild oxidizing agents such as oxygen (O_2). This reaction produces a sulfur atom which has an unpaired electron. Two such sulfur atoms can join to produce a sulfur-sulfur bond. The reaction is outlined as follows:

$$2\ RSH + \tfrac{1}{2}O_2 \longrightarrow 2\ RS\cdot + H_2O \longrightarrow RS{-}SR$$

The new functional group is called a disulfide and the bond between the two sulfurs is called a disulfide bond.

If two polymer chains which include SH groups are positioned so those groups are close together, the oxidation reaction makes a link between the two chains, much like rungs link the side rails of a ladder. The new links are called crosslinks and the new structure is much more rigid than was the case with the flexible polymers prior to crosslinking.



The original process for the vulcanization of natural rubber (which involved heating the gummy natural material with sulfur) probably produced such crosslinks, although the details of the chemistry are different. In proteins the amino acid which provides the SH groups is cysteine ($HSCH_2CHNH_3^+COO^-$). The protein keratin, found in hair, skin and feathers, is rich in cysteine. Crosslinks through disulfide bonds formed by the mild oxidation of cysteine are important in maintaining the shape of these systems.

Home permanents work by controlling crosslinking. The first step is to apply a mild reducing agent which converts the disulfide bonds to two SH groups. The hair is "clamped" into the desired shape, then a mild oxidizing agent is added to form disulfide bonds between SH groups which have been moved close together in the new shape. These bonds "lock" neighboring keratin protein chains into the new shape, rendering it "permanent," at least until it grows out.

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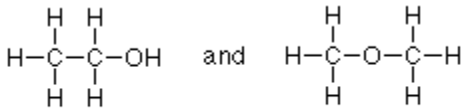
1.15: Chirality, Three Dimensional Structure

Isomerism

Let's begin by reminding ourselves of some of the ideas involved in the topic of isomerism. Structural understanding of organic chemistry begins with the statements that carbon makes four bonds and each carbon can bond to another carbon (the Kekule-Couper-Butlerov theory of organic structure). In even very small molecules (try C_2H_6O) this means that there is more than one way to connect the atoms. Each of these connection patterns represents a different compound. Here are two for C_2H_6O:



ethanol and dimethyl ether

There are two things to notice about this. First, the structural difference between the two molecules can be described in terms of "what's connected to what." For example, the oxygen in ethanol is connected to a CH_3CH_2 group and to a hydrogen while the oxygen in dimethyl ether is connected to two methyl groups. Connectivity is the key difference here. Second, and this is new, we can describe this connectivity quite nicely using just the usual two dimensions we can conveniently represent on paper, a chalkboard, or a computer monitor.

There are many types of organic compounds for which this description is inadequate. This is particularly true for compounds involved in biological processes such as sugars and amino acids (carbohydrates and proteins). For these compounds and many others we will need to use three dimensions in order to have an adequate description of the structure.

Chiral Objects

Let's look at some familiar objects so as to get a sense of when we will need to think about three dimensions. Consider the way in which a sock differs from a glove. It doesn't matter which foot you put a sock on, it will fit just as well. That certainly can't be said about a glove. A glove fits one hand much better than the other.

One quick way to differentiate between sock-like objects and glove-like objects is to ask whether an object is identical with its mirror image or not. Consider a pair of socks. One of the socks is a mirror image of the other (Think of holding one sock up to a mirror. What you see is identical to the other sock, and to the original sock.) Now consider a pair of gloves. The right glove is the mirror image of the left glove, but they are not identical. They can't be superimposed -- merged so they completely match. Objects like gloves which cannot be superimposed upon their mirror images are called *chiral*, from the Greek word for hand. Objects like socks which can be superimposed upon their mirror images are called *achiral*.

Now notice that we need three dimensions to describe the difference between a left glove and a right glove. If you hold up two gloves so that you are looking at the edge nearest the thumb, you notice that the difference lies in which way the thumb points. The rest of the glove can be pretty well described by a plane (two dimensions), just as a sock can be described by a plane, but the describing which way the thumb points requires a third dimension, out of the plane. Make up a list of your own of familiar objects and decide whether they are *chiral* or *achiral* by testing each for superimposability on its mirror image.

Stereogenic Centers

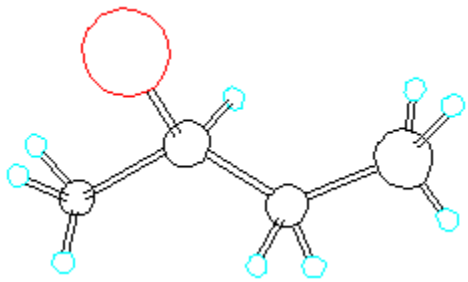
Now, how does this apply to molecules? You can satisfy yourself by playing with models that the following statement is true: **A molecule which contains one carbon which is directly bonded to four different groups or atoms is not superimposable on its mirror image.** Such a molecule is *chiral* just the same way that a glove is *chiral*and a carbon which is bonded to four different groups is called a *stereogenic center*. The lab for next week has a good example of a carbon bonded to four different atoms. You can move one of the two molecules to verify the mirror image relationship and you can check for superimposability.

So, if we wish to find out whether a candidate molecule is chiral or achiral, we check for stereogenic centers -- carbons which

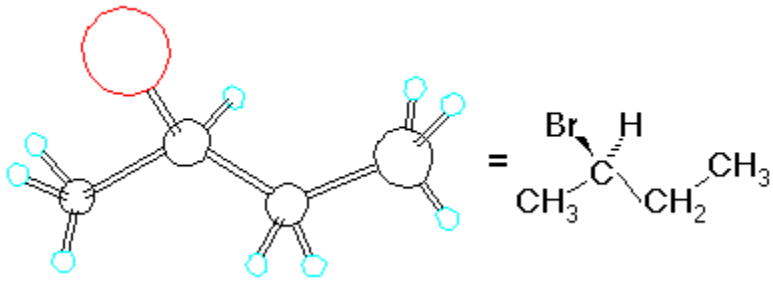
are bonded to four different groups or atoms. One question which always comes up at this point is "How different do the groups or atoms have to be?" If the groups have the same composition they are different if they are isomeric -- if they are connected differently. For example, propyl and iso-propyl are different.

Structural Representations

Once we've convinced ourselves that a stereogenic carbon atom makes a compound chiral, we need to think about how we will represent the three dimensional structures of these compounds when we are restricted to two dimensions. For example, the following sketch represents a 2-bromobutane. It is not superimposable upon its mirror image (see the three dimensional representations earlier).

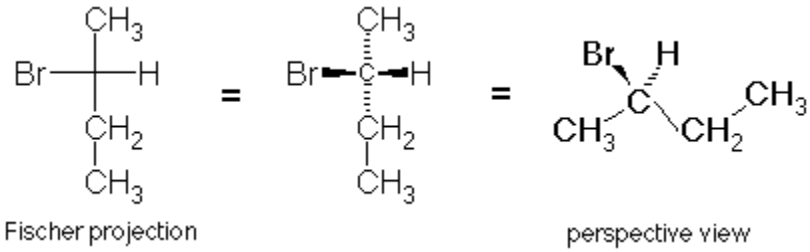


How do we represent this structure? There are two conventional representations. The first is called a "perspective view." In this view, bonds represented by solid wedges are taken to point toward the viewer (in front of the plane of the paper), bonds represented by dashed line wedges are taken to point away from the viewer (behind the plane of the paper, and bonds represented by ordinary straight lines are taken to lie in the plane of the paper. In a perspective view the 2-bromobutane above would be represented as:



The Br is in front of the plane, the H is behind it, and the methyl (to the left) and ethyl (to the right) groups are taken as being in the plane (at least the carbons of those groups).

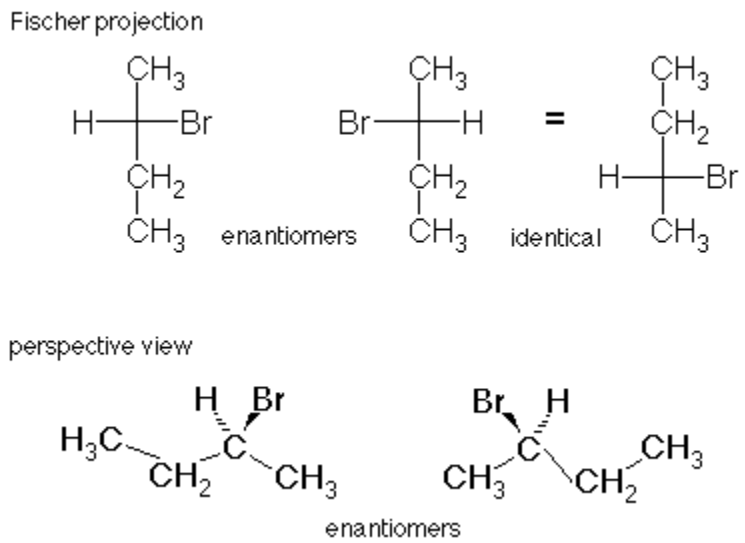
The other representation is known as the Fischer projection. This is a convention in which the stereogenic carbon atom is represented by the junction of two crossed lines. The horizontal line is taken to represent bonds which come from the carbon to an atom toward the viewer (in front of the plane) and the vertical lines are taken to represent a bond which goes from the carbon to an atom away from the viewer (behind the plane). This can be converted to a perspective view by drawing in the appropriate solid and dashed wedges:



The last "equals" sign says that the Fischer projection and the perspective view are representations of the same molecule. You may wish to verify this by imagining yourself as looking down from above the perspective view with the methyl group toward the top of your head. Can you see the wedge interpretation of the Fischer projection?

Because of the special meaning of horizontal and vertical lines in the Fischer projection, they can only maintain their meaning if we restrict manipulations to 180° rotations in the plane of the paper. You can demonstrate this for yourself by converting a Fischer projection to a perspective view, then rotating the Fischer projection by 90° and converting the new Fischer projection to another perspective view. The two perspective views are mirror images.

The term which describes the relationship between an object (molecule) and its non-superimposable mirror image is *enantiomeric*. An object and its non-superimposable mirror image are *entantiomers* of each other. If the object is superimposable on its mirror image, then there is really only one object and the term used is *identical*. These relationships are illustrated below:



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1.16: R/S Naming, Two or More Stereogenic Centers

Optical Activity

First, though, let's look at a property in which one enantiomer differs from another. Enantiomers are alike in all respects but one. They have the same melting point, the same boiling point and the same solubility in common solvents. The difference between the two enantiomers only shows up when we put them in a chiral environment. Our analogy with gloves can help here. In a pair of gloves, the left glove weighs the same as the right glove, it is the same size and typically the same color. It is made of the same material. The difference between them only shows up when we try one on. One fits the right hand better than the other. In this instance, the right hand is a chiral environment and the properties of the left and right gloves differ in that environment.

A specific "chiral environment" for molecules is provided by polarized light. The outcome of this is that if we pass a beam of polarized light through a solution of one enantiomer, the plane of that polarization will be rotated either to the left or the right. This phenomenon is called *optical activity*. If we do the same experiment, but use the other enantiomer (the mirror image of the first one) the plane of polarization will be rotated in the opposite direction. In either case, the amount of the rotation (the number of degrees in the angle between the plane of polarization before passage through the sample and the plane of polarization after passage through the sample) is the same but the directions are opposite.

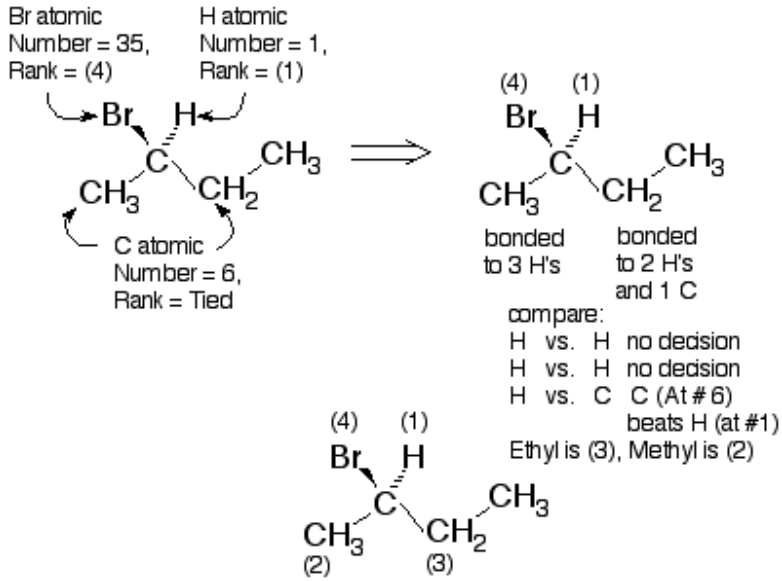
If the sample causes a rotation of the plane of polarization of the light in the clockwise direction (from the viewer's point of view) we say that the compound is dextrorotatory and we designate this by a plus sign in parentheses (+). Correspondingly, the terms for counter-clockwise rotation are levorotatory and (-).

R/S Naming

It has been possible to determine the *absolute configuration* of a chiral molecule since 1954. That is, we can know for a specific molecule which of the two mirror image structures is the one which represents the actual arrangement in three dimensions. We need a way to designate that information in the compound's name.

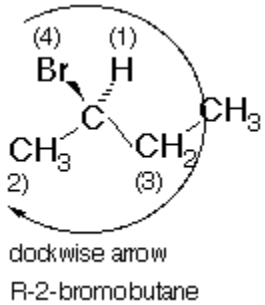
The system we use has two components. First we need to be able to list the four atoms or groups connected to the stereogenic carbon in a specific rank order. Then we need to have a way to distinguish the orientation of these groups or atoms in one enantiomer from the orientation in the other.

Ranking Groups or Atoms: We rank groups or atoms by the atomic number of the atom directly attached to the stereogenic carbon. The group or atom with the highest atomic number gets the highest rank number (4). In 2-bromobutane (below), this is bromine whose atomic number is 35. The lowest rank goes to hydrogen (atomic number one), so it gets rank number (1). That is fairly straightforward, but what do we do about the two carbons? They both have atomic numbers of six and are tied for ranking. The tie-breaker is to look next at the three atoms attached to each of these two carbons. We compare their atomic numbers until we find a difference. In 2-bromobutane one of these carbons is in a methyl group, so it is bonded to three hydrogens. The other "tied" carbon is carbon one of an ethyl group, so it is bonded to two hydrogens and a carbon. If we compare these two situations we find that there is no breaking the tie by comparing hydrogens, but the second carbon of the ethyl group has a higher atomic number than the hydrogen which is its competition on the methyl group. The tie is broken, the ethyl group has a higher (3) rank than the methyl group (2), so we have all of the atoms or groups attached to the stereogenic carbon ranked.



The "tie breaking" process can be extended to more complex situations. Study how it works for doubly bonded carbons in Section 4.3 (Rule 3) of Brown.

Orientation: Now that we have ranking for the four groups or atoms attached to the stereogenic carbon, we need to describe how they are oriented in space. We do this by turning our molecule so that the lowest (1) ranked atom or group is pointed behind the paper, away from us. Then we imagine a curved arrow which starts at the highest (4) ranked group, passes by the (3) group and ends at the (2) group. If this arrow points in a clockwise direction, we use the letter ***R*** (from Latin rectus) to describe the compound. If the arrow points counter-clockwise, we use the letter ***L*** (Latin sinistrus). These letters are prefixed to the IUPAC name of the compound, so our compound is *R*-2-bromobutane.



Practice this process using the problems in the text and bring up any questions in class. You can also practice with the on-line lab problems. Like other naming situations, it sometimes seems arbitrary and picky, but it isn't fundamentally hard. Practice is very necessary so that you can use the R/S system quickly and effectively.

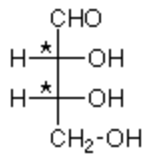
One last point about the R/S system and optical activity: There is no direct relationship between a compound's absolute configuration (designated by R or S) and its optical activity. Some R compounds have clockwise (+) rotations, some have counter-clockwise (-) rotations, and the same is necessarily true of S compounds.

Diastereoisomerism

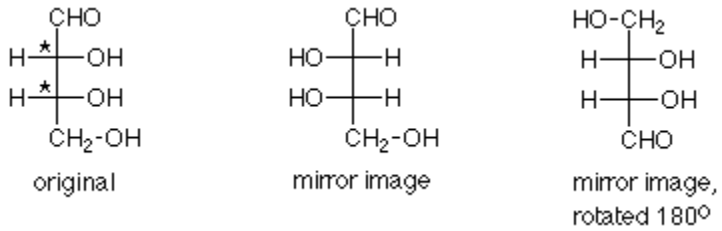
What happens if we have two (or more) stereogenic centers in the same compound?

Next time, we'll look at how these stereogenic atoms are included in naming, and then we'll go on to consider what complications arise if there are more than one stereogenic atom in a molecule. We'll use Fischer projections for this, since the next topic is sugars and Fischer projections are used routinely to describe sugar structures.

Let's take a compound with two stereogenic centers (designated with asterisks *):

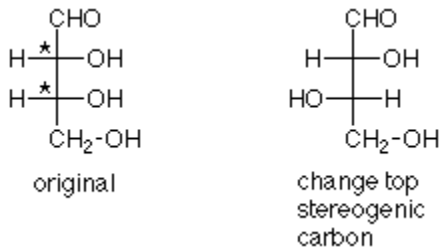


Does it have a mirror image? Yes. Is it superimposable on its mirror image? No. (Remember that we can rotate Fischer projections 180° in the plane of the paper.)

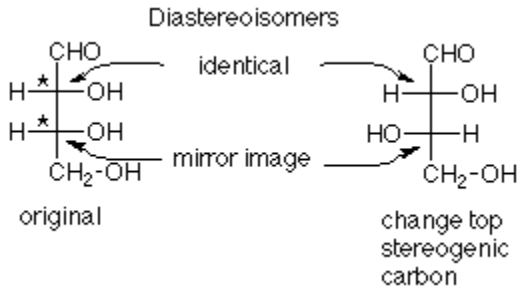


Notice that neither the mirror image nor the rotated mirror image is superimposable on the original structure. The original structure and its mirror image are enantiomers. Each will be optically active.

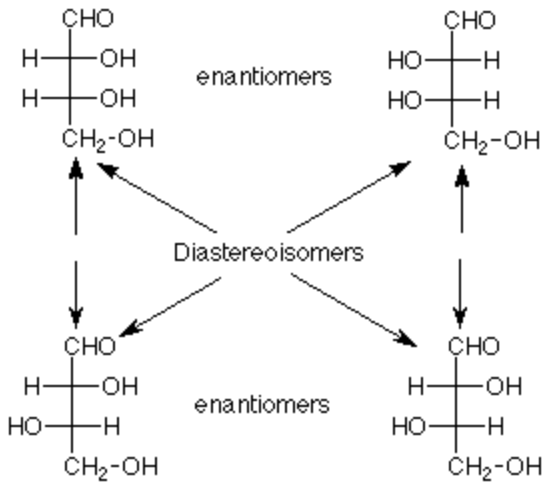
Now let's look at what the relationship would be if we did changed the configuration at one of the stereogenic carbon atoms, but left the other one alone.



There isn't a mirror image relationship here, and the structures are not superimposable. Neither of the terms "enantiomer" or "identical" applies. The compounds are isomers though, and since they are connected identically, they are stereoisomers. The word we use for this relationship is *diastereoisomeric*. Diastereoisomers may be recognized because they are connected identically, they have two (or more) stereogenic atoms and comparison of those atoms reveals that the relationship at one (or more) atom is identical and the relationship at the other (or more) atom is mirror-image.



Since the diastereoisomer we made by changing the top stereogenic carbon of our original compound is not superimposable upon its mirror image, it too is optically active and has a mirror image enantiomer. Here is the complete set of enantiomeric and diastereoisomeric relationships for this case:

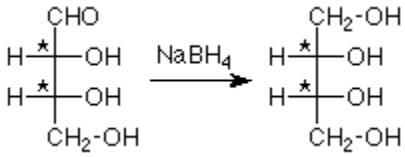


The horizontal relationships here are between enantiomers, compounds which are non-superimposable mirror images. The vertical and diagonal relationships are between diastereoisomers, stereoisomers which are neither identical nor mirror images.

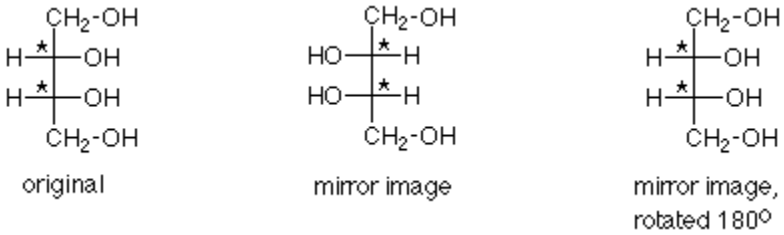
Diastereoisomers show differences in properties other than optical activity. They typically have different melting and boiling points and solubilities and they may show differences in how fast they react with other reagents. These differences are not usually as large as those shown by compounds which are not isomers. Here are some on-line problems on this topic

Meso Compounds

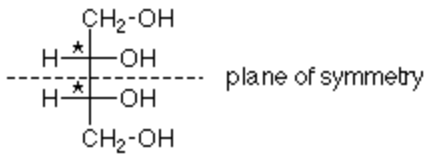
There is one more case to consider. What if the four atoms or groups bonded to one of the stereogenic atoms are the same as those bonded to the other. We can explore this in our example by considering what happens if we reduce the aldehyde (CHO) group with $NaBH_4$. The product is a primary alcohol ($-CH_2OH$) group, the same group as is at the bottom of this compound. The four atoms or groups attached to the top stereogenic carbon are the same as those attached to the bottom stereogenic carbon.



Now, let's test this molecule to see if it is superimposable upon its mirror image. As before, we make the mirror image and then we rotate it 180° in the plane of the paper. The original structure is identical to its mirror image, so we do not have enantiomers here. A compound like this is called a *meso* compound. Since it is superimposable upon its mirror image, it is not optically active, even though it has two (or more) stereogenic carbon atoms.

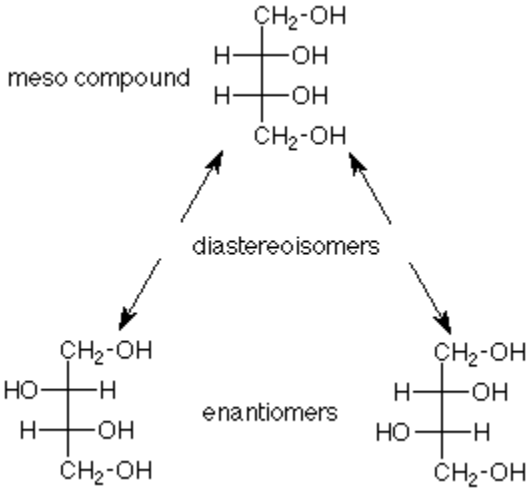


Another way to detect a meso compound is to look for a plane of symmetry within the molecule. This is particularly easy with Fischer projections, since what we have to do is to imagine a plane cutting the molecule precisely in two so that there is a bottom half and a top half. If the bottom half is the mirror image of the top half, we have a meso compound.



Meso compound, bottom half is mirror image of top half.

A meso compound will have diastereoisomers as well. We can generate these by changing one of the stereogenic carbons and then making its mirror image. The latter two compounds are enantiomers. Each is a diastereoisomer of the original meso compound.



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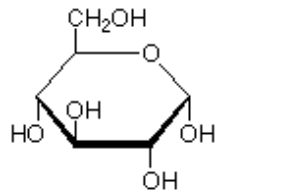
1.17: Carbohydrates- Monosaccharides

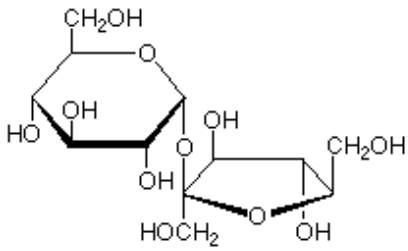
Mono-, Di-, and Polysaccharides

Sugars are small molecules which belong to the class of carbohydrates. As the name implies, a carbohydrate is a molecule whose molecular formula can be expressed in terms of just carbon and water. For example, glucose has the formula $C_6(H_2O)_6$ and sucrose (table sugar) has the formula $C_6(H_2O)_{11}$. More complex carbohydrates such as starch and cellulose are polymers of glucose. Their formulas can be be expressed as $C_n(H_2O)_{n-1}$. We'll look at them in more detail next time.

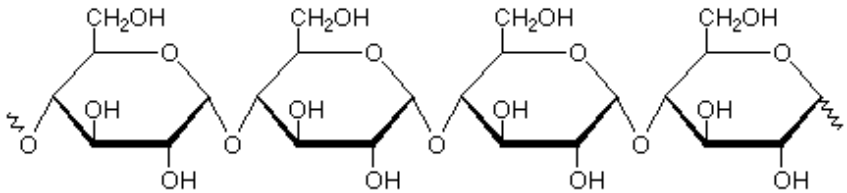
The difference between a monosaccharide and a disaccharide can be seen in the following example:



monosaccharide (glucose)

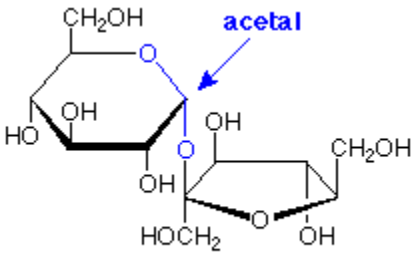


disaccharide (sucrose)

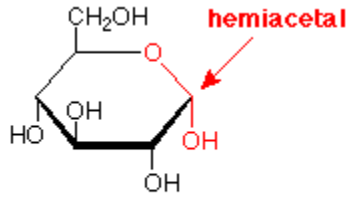


polysaccharide (amylose starch)

A quick glance tells us that a monosaccharide has just one ring, a disaccharide has two, and a polysaccharide has many. Beyond that, though, there's another important structural feature. Look at the disaccharide and focus on the oxygen which links the two rings together. The atom above it is connected to two oxygens, both of which are in ether-type situations. The carbon and these oxygens are in an acetal linkage. (The bonds are heavier and in blue.)



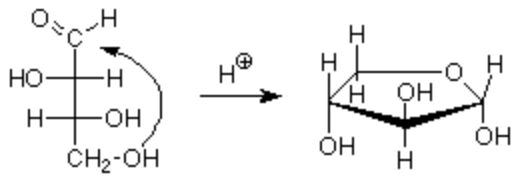
disaccharide (sucrose)



monosaccharide (glucose)

If we look at the corresponding location in the monosaccharide and ask what the functional group might be, we see that it is a hemiacetal. (Here the bonds are heavier and in red.) So, another way to describe the situation is that a monosaccharide has a single ring with a hemiacetal in it, a disaccharide has two rings linked by an acetal functional group, and a polysaccharide has many rings linked by many acetal functional groups. (Check this last statement against the polysaccharide structure above).

How about the "sugars" we saw last time with just 4 carbons. Why are they monosaccharides when there is no ring? If we consider that the OH group on the bottom carbon could form a hemiacetal with the aldehyde function, then we get a ring, and that structure fits our description of a monosaccharide.

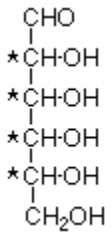


We'll take a more detailed look at the cyclic and non-cyclic structures of sugars shortly.

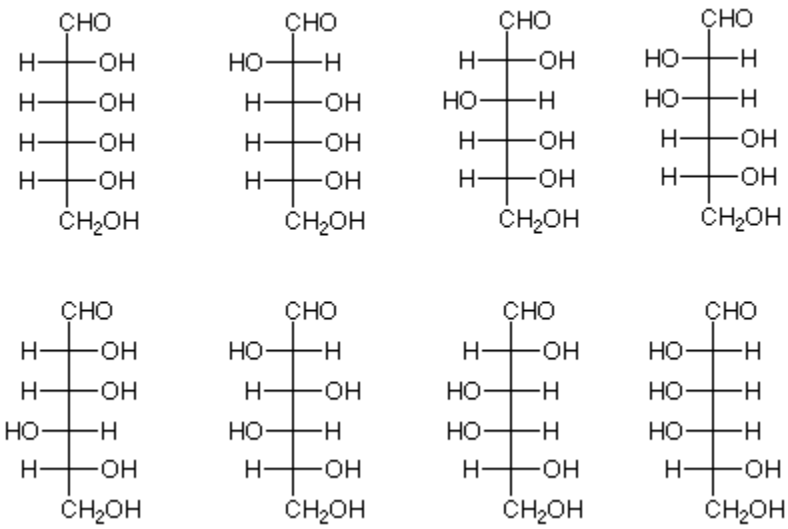
"Oses" and D-Sugars

Now let's see what aldotetrose means. Taking the name apart from right to left, the ending "ose" means a sugar, which may be a monosaccharide, a disaccharide or an oligosaccharide (a "short" polysaccharide). The middle part "tetr" means that our sugar has four carbons linked in a straight unbranched chain. Terms like "pent" for five carbons and "hex" for six carbons are also in common use. The beginning "aldo" means that there is an aldehyde in the compound. The alternative would be a ketone group, for which we would use the prefix "keto."

Glucose, the most common monosaccharide, is an aldohexose. We understand that to mean that it is a sugar having six carbons in a straight unbranched chain which ends in an aldehyde group. We can represent that structure in this fashion:



This structure includes four stereogenic carbon atoms (marked with an asterisk *). There are a total of sixteen stereoisomers possible. Eight of these are enantiomers of the other eight. The rest of the relationships are diastereoisomeric. Since the groups at the top and the bottom of the chain are not the same, there are no *meso* isomers. Eight of the isomers are shown here. The other eight are mirror images of these and may be readily drawn.



The question is "which of the sixteen stereochemical representations (Fischer projections, remember that each stereoisomer shown also has an enantiomer which is not shown) describes the absolute configuration of glucose? When Emil Fischer took up this problem about 100 years ago, he realized that there was no way to determine if glucose was one of the eight structures above or one of the unshown enantiomers. He made the assumption that it was one of the ones above so that he could work on the diastereoisomeric part of the problem, hoping that later work would resolve the question of which enantiomer best represented

glucose.

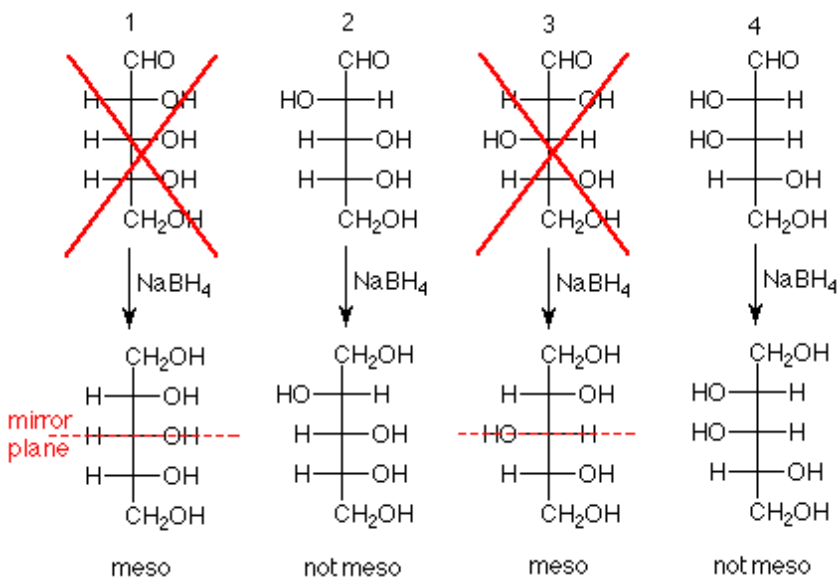
Fischer also developed the D/L system for specifying the structures of sugars. If the OH group on the stereogenic carbon farthest from the aldehyde group is to the right in the Fischer projection, then the compound is a D-sugar. All of the sugars in the figure above are D-sugars. If the OH group on the stereogenic carbon farthest from the aldehyde group is to the left in the Fischer projection, then the compound is an L sugar. The enantiomers of all the sugars in the figure above are L sugars. Fischer's assumption amounts to saying that glucose is a D-sugar. Later work resolved this issue, and Fischer was right.

Which D-aldohexose is Glucose?

How did Fischer determine which of the eight structures above was glucose? He had available samples of glucose and mannose, both aldohexoses, and arabinose, an aldopentose. He also learned how to reduce the aldehyde functional group to a primary alcohol. (We'll illustrate this with $NaBH_4$ to avoid learning a new reaction, but he used another reagent.) He developed a method for extending the carbon chain of an aldose (called the Kiliani-Fischer chain extension). He also had a polarimeter so he could determine whether a sample was optically active or not. Perhaps most importantly, he had a group of talented and dedicated students.

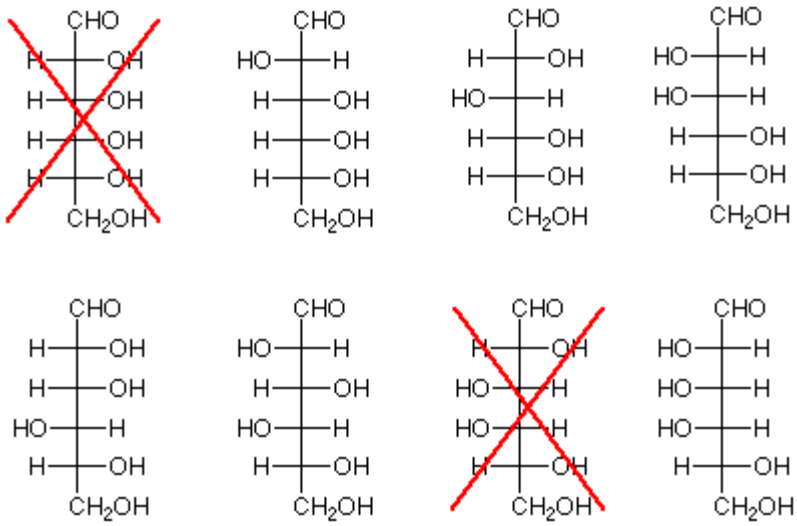
Now, some data.
Experimental result: When the aldehyde group of arabinose was reduced to a primary alcohol group, the product was optically active.

Conclusion: Arabinose has either structure 2 or 4 in the scheme below. This is because if arabinose were either 1 or 3, the product would have a plane of symmetry (mirror plane) and would be optically inactive.



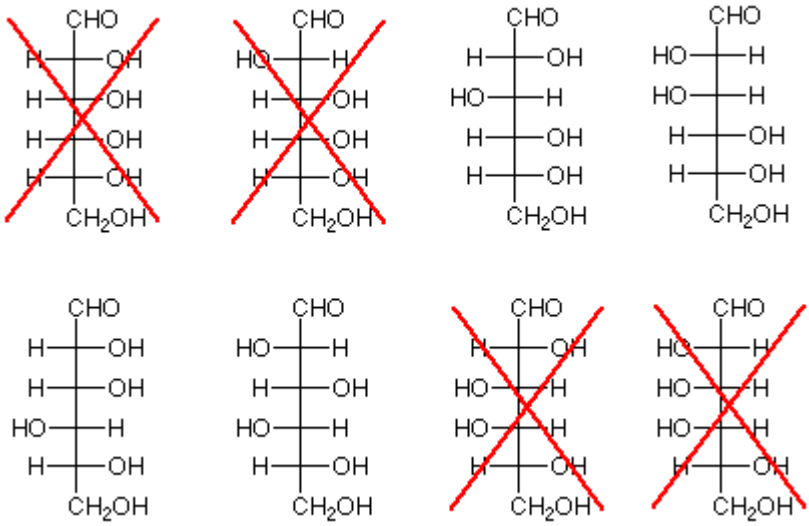
Experimental result: When the aldehyde group of glucose was reduced to a primary alcohol group, the product was optically active. The same result was obtained for mannose.

Conclusion: The structures "X'd" out below do not represent either glucose or mannose since the products from these structures would be meso compounds.

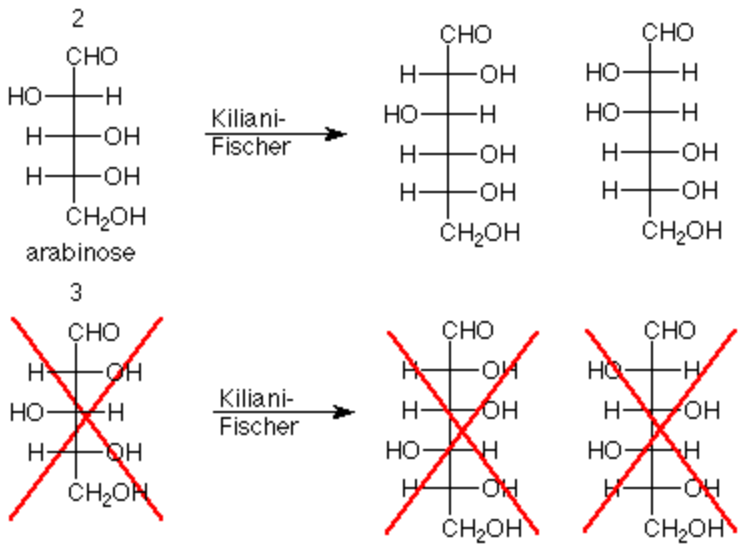


Experimental result: Kiliani-Fischer chain extension applied to arabinose produces glucose and mannose.

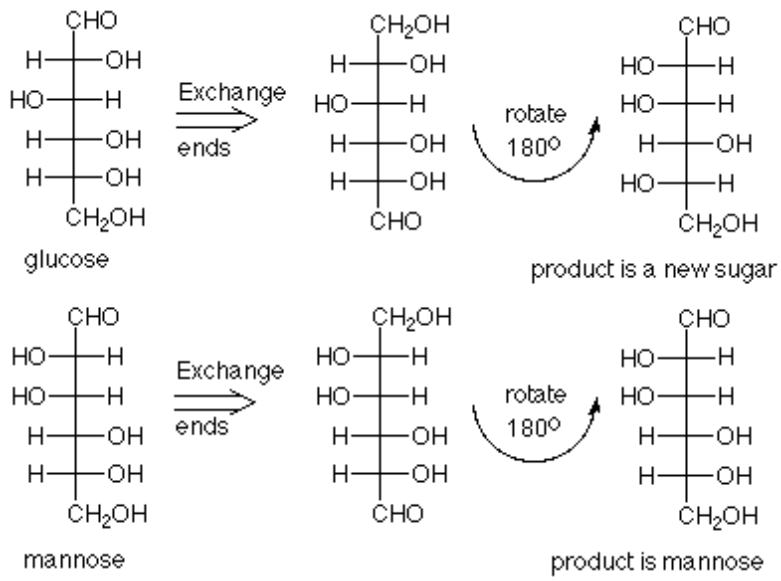
Conclusion: The bottom three stereogenic carbon atoms of glucose and mannose are have identical configurations to the three stereogenic carbon atoms of arabinose. This means that glucose and mannose differ only in the configuration of the stereogenic carbon atom nearest the aldehyde functional group. We can further conclude that if one member of a pair of aldohexoses (paired because their bottom three stereogenic carbons are identical) is ruled out, so is the other



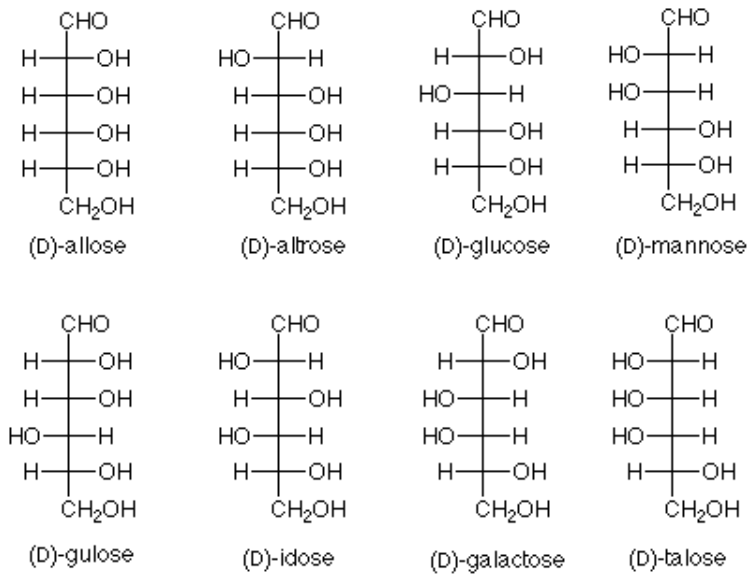
Now let's see what we have left. There are four structures remaining as candidates. They are on the right below. If we go back to the possibilities for arabinose, we find that the two on the top come from structure 2 for arabinose, which was a possibility, while the two on the bottom come from structure 3, which was ruled out earlier. The conclusion is that arabinose is represented by structure 2, and glucose and mannose are the two structures to its right.



But which is glucose and which is mannose? Fischer noticed that if reactions could be developed which changed the aldehyde group into a primary alcohol and the primary alcohol into an aldehyde (switch ends) one of these structures would give itself, and the other would give back a new L sugar. The reactions are complex and we will not look at them, but when the chemistry was applied to the sample called mannose, the product was mannose. When the chemistry was applied to the sample called glucose, a new sugar was formed.

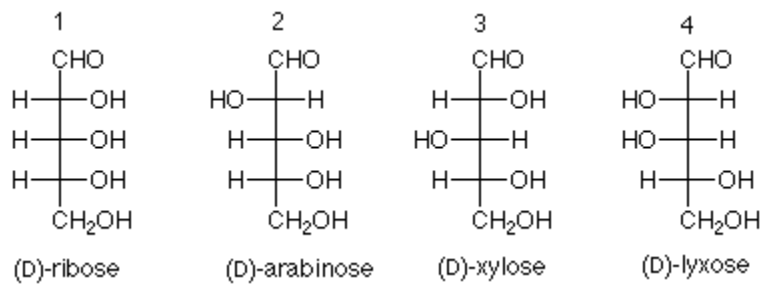


There was a great deal more to be done to confirm this conclusion and to synthesize the other six aldohexoses, but Fischer's exercise in logic and dedicated experimentation led to the conclusion that the eight D-aldohexoses are:



Notice that the new sugar which was produced from glucose by the "exchange ends" experiment is L-gulose. The names of the hexoses tell us which diastereoisomer we have; the D or L designation gives us which enantiomer we have.

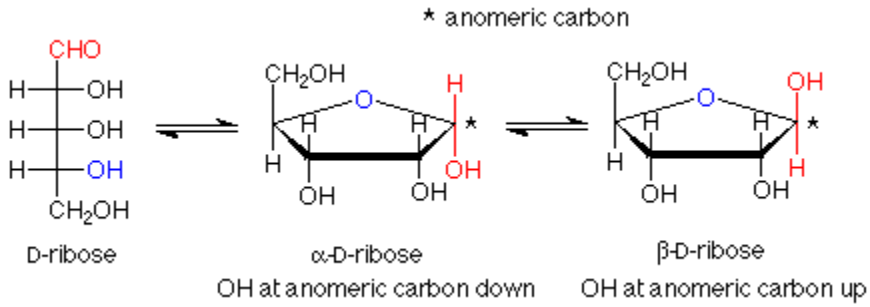
The corresponding names for the aldopentoses are:



Cyclic Structures - Anomers

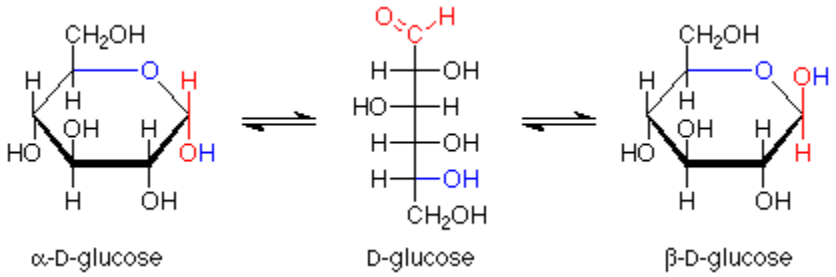
To finish today, we'll see what happens when a hemiacetal is formed between the aldehyde carbon and one of the OH groups on the chain. We'll look at two examples, ribose, which is a key component of RNA, and glucose because of its abundance. (You may wish to review the mechanism for hemiacetal formation.)

Since there are four OH groups in ribose, we could anticipate four different ring sizes. In three atom rings and four atom rings the bond angles are far from 109.5^{o}, so these rings are strained, have higher energies and are hard to form. Remember that there is an equilibrium between a hemiacetal and the aldehyde/alcohol it comes from, and that high energy materials don't persist at equilibrium. We are left with rings which have either five or six atoms in them. In the case of ribose the important ring (found in RNA) is the five membered ring.



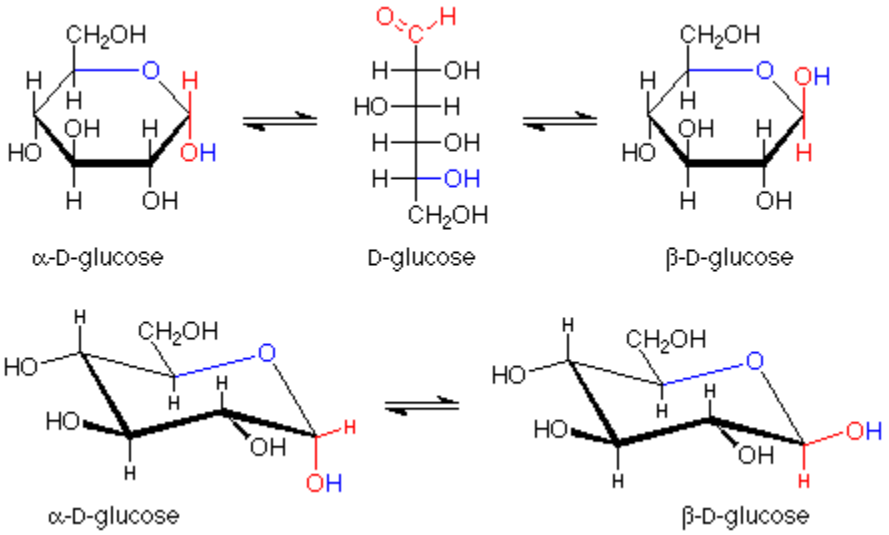
Notice that the carbon in the newly formed hemiacetal group is stereogenic. This means that there are two possible diastereoisomers for the cyclic structure. Usually both are formed, and they have a special name -- they are anomers of each other. The carbon between the two oxygens in the hemiacetal group is called the anomeric carbon. If the OH group is down (in a drawing with the ring oxygen to the rear center or right), the designation for that anomer is alpha. If the OH group is up, the designation is beta. Since the alpha and beta anomers are diastereoisomers, they have different properties; in particular, different optical activities. The term for a five atom sugar ring is "furanose."

Glucose usually makes hemiacetal cyclic structures with six atom rings, although five membered rings can also be formed when the six membered rings are precluded. Such six membered rings are named by the term "pyranose." The ring forms look like this, keeping in mind that alpha and beta anomers are also involved here:

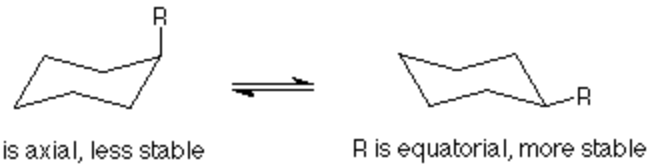


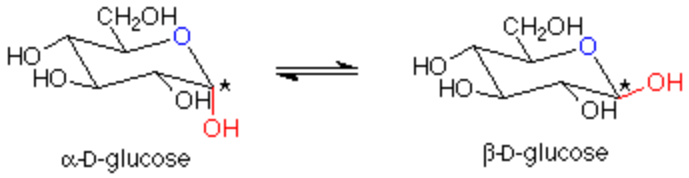
Again, we have an equilibrium between the open chain form and the two diastereoisomeric anomers.

There is one further point to be made about these glucopyranoses. The structure we have drawn for the ring is flat. The bond angles would be 120°, quite far from the normal tetrahedral value of 109.5^{o}. The atoms in the ring can have bond angles of about 109.5^{o} if the ring puckers as shown here:



Of course, molecules adopt these puckered shapes (called chair conformations from their resemblance to a rather wide lounge chair) automatically. You can review the material on **cyclohexane** for a more detailed analysis of this material. It has been established that in these chair conformations, the molecules have a lower energy if the larger substituents on the carbons are roughly in the plane of the ring itself. These positions are called "equatorial" to distinguish them from the other positions (roughly perpendicular to the ring, called "axial"). A compound which can have all of its larger substituents (everything is larger than hydrogen) in an equatorial position is more stable than one which cannot. beta-D-glucose has all of its substituents in equatorial positions, and is thus the most stable hexopyranose. It is also the most abundant.





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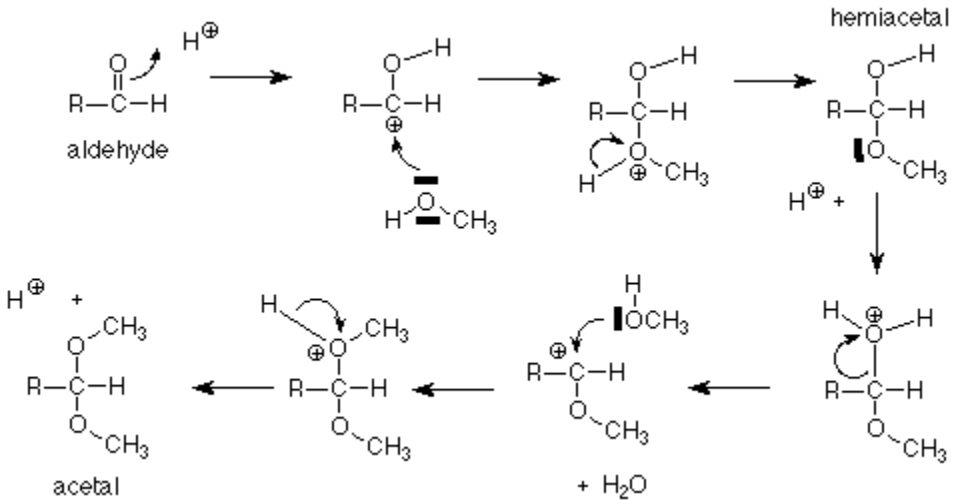
1.18: Glycosides, Disaccharides, Polysaccharides

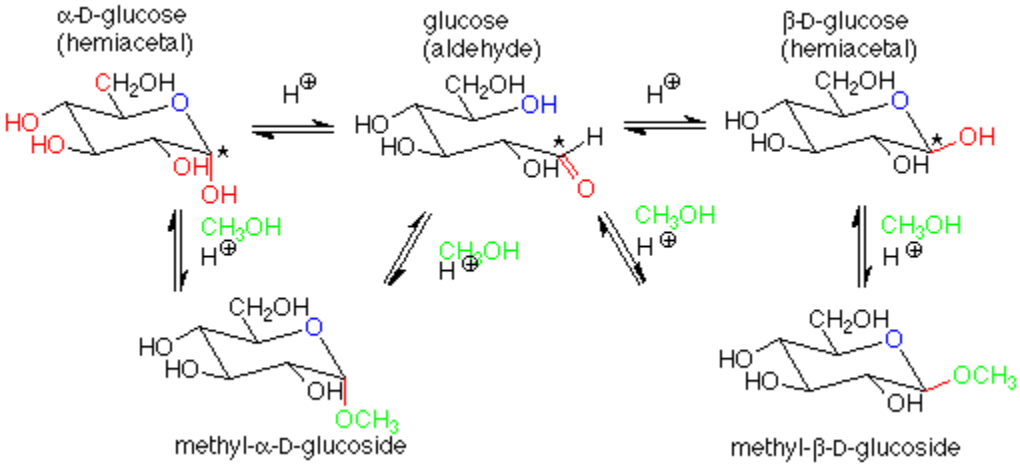
Glycosides

Last time we explored the structural characteristics of monosaccharides. We saw that the major stereochemical features of aldohexoses and aldopentoses are usefully described by Fischer projection formulas, but we learned that the structures of these compounds must also be understood as cyclic hemiacetals. Today we'll look in more detail at the chemistry of that hemiacetal linkage. In particular, we'll recall how hemiacetals are converted to acetals. We'll find that these acetal linkages are what holds di- and polysaccharides together.

Let's begin by remembering the reaction sequence which links aldehydes and alcohols, hemiacetals, and acetals.



For our purposes, the key feature is the conversion of a hemiacetal and an alcohol to an acetal, with the concurrent release of a molecule of water. If we apply this feature of the scheme to a solution of glucose in methanol (with a trace of acid catalyst included), we get:

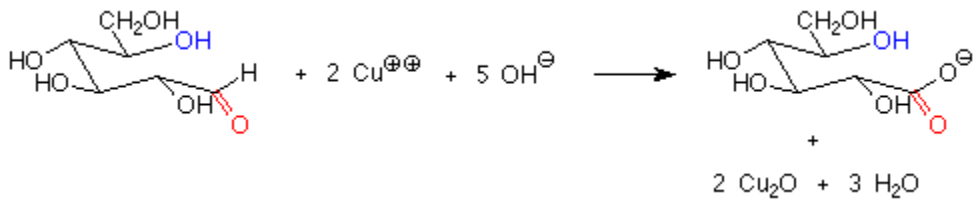


The acetal products are called "glycosides." If the sugar used is glucose, they are "glucosides." There are several reasonable mechanisms for these conversions and we will not look at them in detail. Keep in mind that the conversion between a hemiacetal and an acetal requires an acid catalyst. The conversion between an aldehyde and a hemiacetal is catalyzed either by base or by acid. Conditions can be arranged to produce either the alpha or beta stereochemistry in the glycoside.

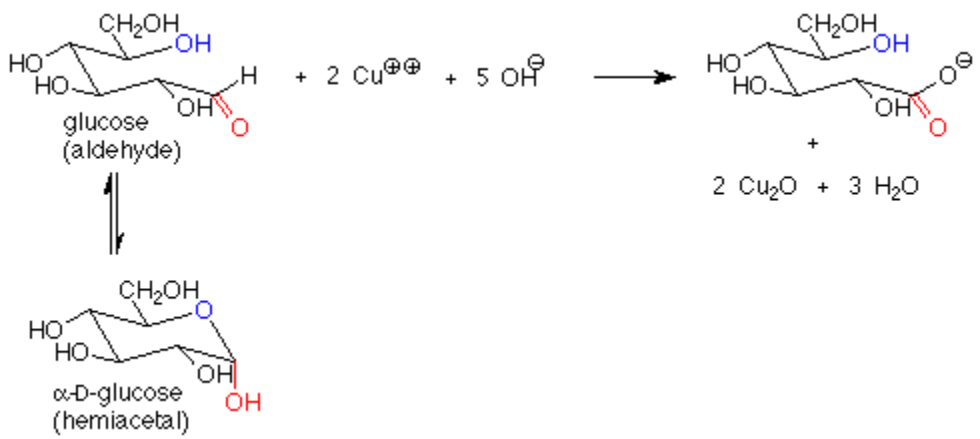
Glycosides are very common in nature. Besides the di- and polysaccharides we will look at later, it is very common for glucose (or other sugars) and an alcohol to form an acetal linkage. Often this improves the water solubility of the alcohol and makes it easier to excrete. This is the case with cholesterol:

Reducing and Non-Reducing Sugars

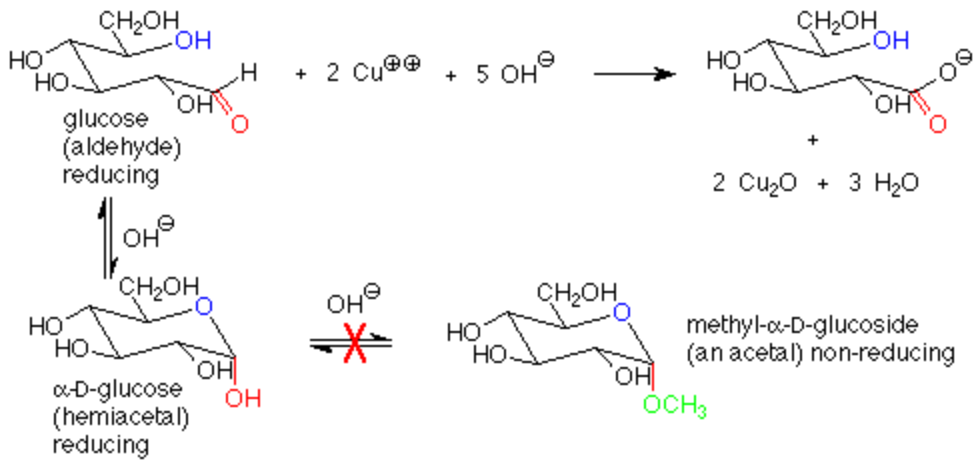
There is another important difference between the hemiacetal and acetal linkages in sugars and saccharides, and that is their reaction with mild oxidizing agents. Aldehydes are fairly easy to oxidize to carboxylic acids, while acetals (which have no carbonyl group) are quite difficult to oxidize. The oxidizing agents used in carbohydrate chemistry are typically copper(II) compounds which are reduced to copper(I) oxide. Sugars which are oxidized by these reagents are called reducing sugars because they reduce the copper(II) to copper(I).



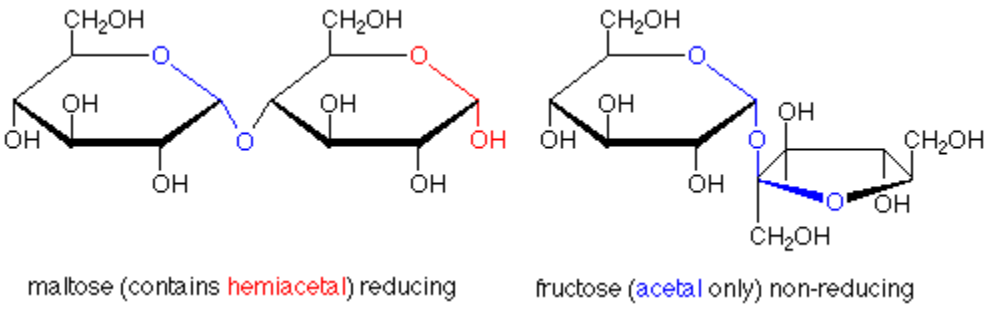
These reagents are used in basic solution, so that hemiacetals and aldehydes are in equilibrium. This means that the cyclic hemiacetal form of a sugar will produce an equilibrium amount of the open-chain aldehyde form, which will then reduce the copper(II) to copper (I) and give a positive test. A hemiacetal form is thus a reducing sugar.



In contrast, acetal forms (glycosides) are not reducing sugars, since with base present, the acetal linkage is stable and is not converted to the aldehyde or hemiacetal. The outcome is that in a reducing sugar the anomeric carbon is in an aldehyde or hemiacetal. In a non-reducing sugar, the anomeric carbon is in an acetal.

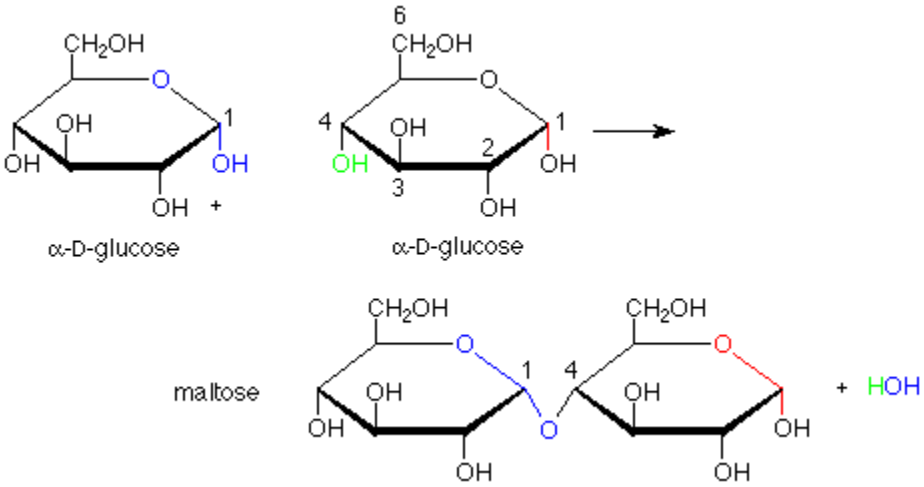


The characterization of sugars as reducing or non-reducing is gives useful clues as to their structures. Consider the disaccharides maltose and fructose. Maltose contains a hemiacetal functional group and is a reducing sugar. In fructose, both anomeric carbons are in acetal functional groups, so fructose is a non-reducing sugar.



Disaccharides

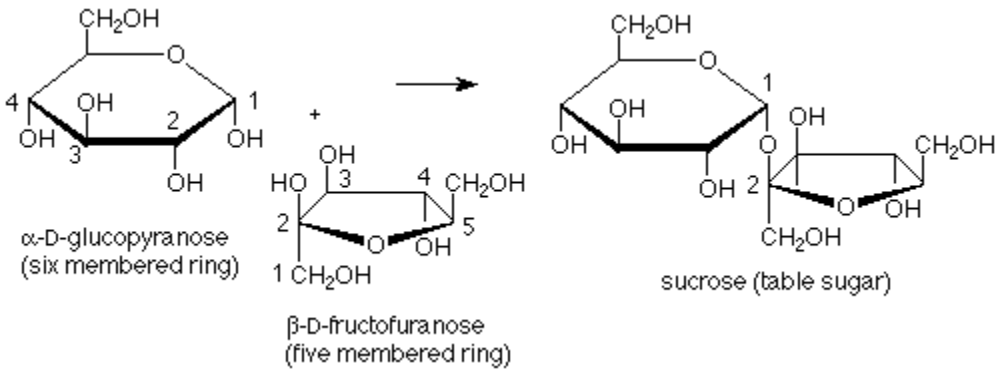
This brings us to the topic of disaccharides. The linkages between the monosaccharide ring units in disaccharides are acetal linkages. We can envision them as being made by the formation of an acetal from a hemiacetal and an alcohol. For this purpose, the hemiacetal includes the anomeric carbon of a monosaccharide and the alcohol role is played by a specific OH group of a second monosaccharide. The formation of maltose from two molecules of glucose is an example of this:



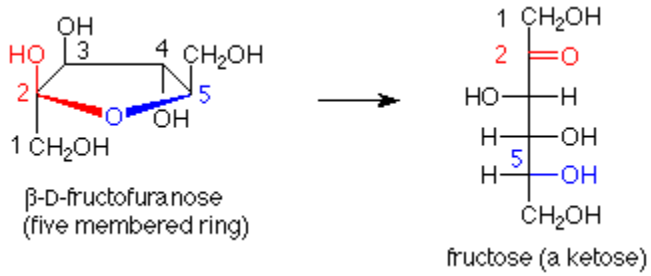
There are several intriguing features of this conversion. First, it is catalyzed by the enzyme *maltase*. The term "catalyzed" implies that enzyme speeds up the reaction in both directions, so that both formation and hydrolysis (conversion from acetal to

hemiacetal using a molecule of water) are faster with the enzyme. Enzymatic catalysis is usually also very specific. In this case, that specificity shows up in the fact that the new acetal linkage has the alpha configuration, not the beta (and correspondingly, maltase catalyzes the hydrolysis of an alpha linkage but does nothing to the beta linkage). Also, only the OH group on the number four carbon atom is used as the alcohol when others, such as the ones on carbons 1, 2, 3 and 6 might have been used. This suggests that the enzyme holds the two molecules of glucose in specific positions so that only the OH on carbon 4 of one glucose can reach the anomeric carbon of the other glucose.

Fructose provides an example of a disaccharide in which the acetal linkage joins the anomeric carbons of a glucose molecule to the anomeric carbon of a fructose molecule. In this case there is no hemiacetal functional group, so fructose is a non-reducing sugar. Also, here one of the rings has five members rather than six, showing that the cyclization of fructose from the open-chain form to the hemiacetal cyclic form uses the OH at carbon 5 and the carbonyl carbon 2.

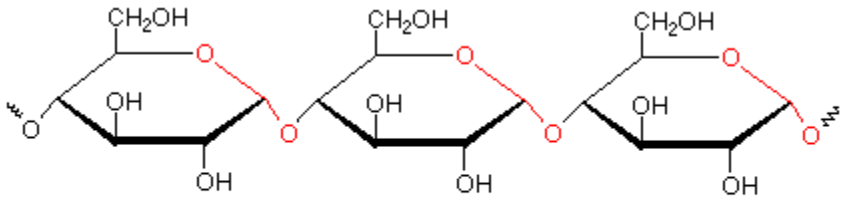


We can also look more carefully at fructose. In its cyclic form the anomeric (hemiacetal) carbon is involved in two carbon-carbon bonds. This means that when we open the molecule up to its open chain form the anomeric carbon becomes a keto carbonyl group. Fructose is thus an example of a *ketose*, a sugar in which the carbonyl group is a ketone rather than an aldehyde.



Polysaccharides

If we now return to our first look at polysaccharides, we can see that amylose starch is composed of many glucose monosaccharide units which are linked together by acetal functional groups involving the anomeric carbon of one glucose and the number four carbon of the next glucose. Repetition of this pattern many times gives the polymer.

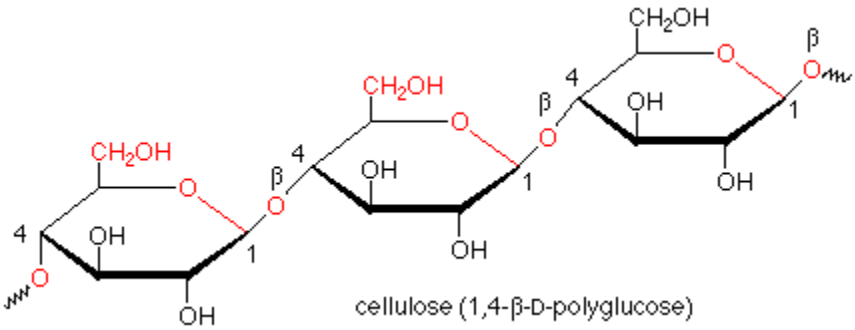


polysaccharide (amylose starch)

Amylose is a linear polymer with few branches. In amylopectin, another type of starch, there are branches which involve acetal

linkages through the oxygen on carbon 6. Glycogen, sometimes called animal starch, is a similar polymer found in animals as a storage medium for glucose. Glycogen is even more highly branched than amylopectin.

Hydrolysis of starch involves the cleavage of the acetal functional groups with the addition of a molecule of water for each acetal linkage and the production of many molecules of glucose. This is done by the enzymes called *glycosidases* which are found in saliva. These enzymes work only on alpha acetal linkages and do not attack beta linkages. Such beta linkages are found in cellulose. Since our glycosidases are unable to hydrolyze the beta linkages in cellulose, we cannot digest cellulose, even though it is also a polymer of glucose.



Of course, there are enzymes which hydrolyze the beta linkages in cellulose. Such enzymes are found in the bacteria which inhabit the stomachs of ruminants such as cattle and sheep, which makes cellulose digestible by ruminants. They are also found in fungi which rot wood.

The specificity of enzymes allows one monosaccharide, glucose, to be the building block for both starch, which we think of as a major source of energy in our foods, and cellulose, which we regard as a structural material in trees and a major component of paper. If we look at this in the context of the use of these materials in a plant, starch is found as a storage medium for glucose in seeds and tubers. It is used as a source of glucose both for energy and as a raw material for cellulose as the plant sprouts and enters its initial growth period. Enzymes specific for alpha linkages present in the sprouting plant hydrolyze the starch to glucose, as they do in the malting process used in beer and whisky production.

The cellulose produced as the plant grows is a major structural component of the plant. It must be quite stable if it is to serve that purpose, so enzymes specific for the alpha linkage do not attack its beta acetal functional groups and it is not readily hydrolyzed. The small stereochemical distinction between the alpha and beta linkages leads to very large consequences in the chemistry and function of starch and cellulose.

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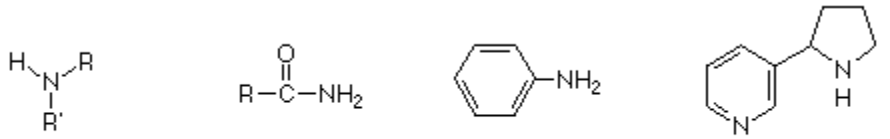
1.19: Amines- Structure and Synthesis

Structural Types

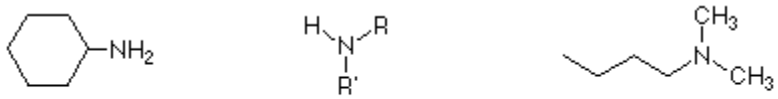
Last time we completed our study of carbohydrates. Now we are turning our attention to another important class of organic compounds, amines. Many important drugs are amines, the bases present in RNA and DNA are amines, and the fundamental building blocks of proteins are amino acids.

The functional group of an amine is the nitrogen atom connected by three sigma bonds to alkyl groups or hydrogen atoms. (Aryl groups - benzene rings - can also be connected to a nitrogen in amines, but we will not study these until later in the course.) The chemistry of amides is different enough from that of amines that they are normally not included among the amines. The nitrogen atom of an amine can also be included in a ring. Such amines are called "heterocycles." (Recall that nitrogen is a heteroatom -- not a carbon or a hydrogen.)



an amine (dialkyl) | an amide | an arylamine (for later) | a heterocyclic amine (nicotine)

Amines are classified as primary, secondary, or tertiary according to the number of carbons bonded directly to the nitrogen atom. Primary amines have one carbon bonded to the nitrogen. Secondary amines have two carbons bonded to the nitrogen, and tertiary amines have three carbons bonded to the nitrogen. The system is superficially similar to the way we have classified alcohols, but the important difference is that in alcohols we were counting bonds to the carbon which carried the OH group. For amines, we are counting the carbons bonded to the nitrogen.

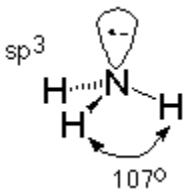


a primary amine | a secondary amine (general formula) | a tertiary amine

Since nitrogen has a normal valence of three, we can also conclude that there are two N-H bonds in primary amines and one N-H bond in secondary amines. In tertiary amines there are no N-H bonds.

Bonding, Shape and Hybridization

Now, let's look at the bonding around the nitrogen atom of an amine. First, we need to remember that the nitrogen, in addition to forming three sigma bonds, also carries an unshared electron pair. This means that there are four groups of electrons associated with the nitrogen. Mutual repulsion of these groups leads to a tetrahedral arrangment, much like that of a typical sp^3 carbon atom. This predicts a bond angle between the N-H bonds of 109.5^o which agrees pretty well with the observed value of 107° found in ammonia (which is the "smallest" amine, like water is the smallest alcohol).



Since the bonds connected to the nitrogen are shaped like a flattened pyramid, the arrangement is often called pyramidal. This

ignores the unshared electron pair, whose inclusion leads to the tetrahedral description and the corresponding understanding of the nitrogen's hybridization as sp^3. The example used to illustrate this is ammonia, but the nitrogen is also well described as having sp^3 hybridization primary, secondary and tertiary amines as well.

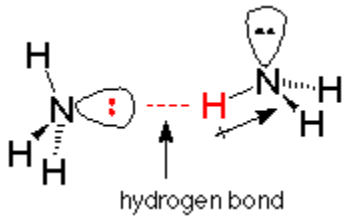
Hydrogen Bonds

The N-H bonds in amines are somewhat polar. As we might guess from considering electronegativities (estimated from positions in the periodic table), the N-H bond is more polar than the C-H bond and less polar than the O-H bond. This polarity shows up in a comparision of physical properties of amines and alcohols.

The simplest examples are water and ammonia. Water boils at 100°C, while ammonia boils at -33°C. This is interpreted to mean that it takes a good deal more energy to boil water than ammonia. Correspondingly, the forces between molecules of water (which resist separating them in the boiling process) are much stronger than those between molecules of ammonia. The most important of these forces is called the hydrogen bond.

The hydrogen bond is much weaker than a covalent bond. Breaking a hydrogen bond requires about 10% of the energy required to break a typical covalent bond. This is consistent with the fact that we can boil water without breaking any covalent bonds (the water molecules remain intact). Separation of one molecule from another only requires breaking the weaker hydrogen bonds.

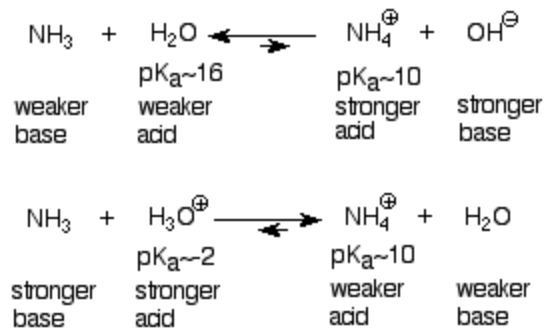
One useful picture of a hydrogen bond is electrostatic -- an attraction between the positive end of a dipole on one molecule and the negative end of a dipole on another. The more polar the molecules, the greater the degree of positive and negative charge associated with the dipoles, and the stronger the hydrogen bonds. In ammonia and water, the most concentrated and available negatively charged region is where the unshared electron pair is. The positively charged regions are the hydrogen ends of the N-H bonds. We can envision the hydrogen bond as a weak (compared to covalent bonds) attraction between the unshared electron pairs on of a nitrogen in one molecule and a hydrogen (covalently bonded to nitrogen) on another.



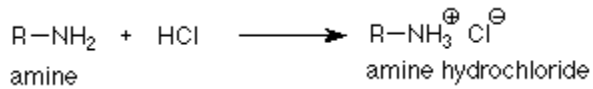
Hydrogen bonds are extremely important in the chemistry of the genetic code. As we will study later, the double strands of DNA are held together by hydrogen bonds. The replication of DNA depends on hydrogen bonds which selectively connect specific base pairs, as do the several steps by which the genetic message determines the specific order of amino acids in a protein.

Amines as Bases

The distinguishing chemical property of amines is that they are bases. This is a direct consequence of the presence of the unshared electron pair on the nitrogen, which makes them Lewis bases. The basic unshared electron pair is less tightly held by the nitrogen of an amine than the corresponding oxygen of an alcohol, which makes it more available to act as a base. Consequently amines (and ammonia) are more basic than alcohols (and water), and less basic than alkoxide (RO^-) and hydroxide (OH^-) ions. It is convenient to think about the base strength of amines and ammonia in terms of the pK_a of their conjugate acids, the ammonium ions. These ideas can be summarized in the following scheme, where we use water and ammonia as stand-ins for alcohols and amines:



As we have come to expect, these reactions go in the direction which consumes the stronger bases and acids and generates the weaker ones. Ammonium ions (pK_a ~10) are stronger acids than water (pK_a ~16, so water is produced when an ammonium ion is treated with hydroxide ion. Ammonium ions (pK_a ~10) are weaker acids than H_3O^+ (pK_a ~-2), so they are produced when amines are treated with aqueous solutions of strong mineral acids like sulfuric or hydrochloric acids. If the water is removed, there remains an ammonium salt which incorporates the negative counterion of the mineral acid (sulfate or chloride).

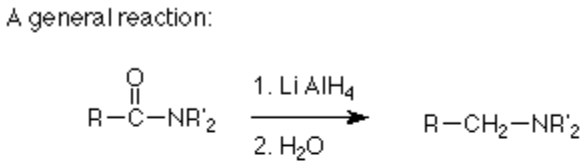


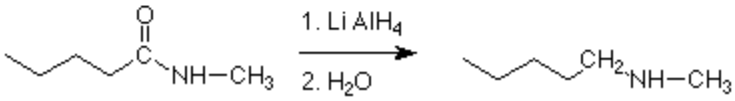
Since the basic properties of amines arise from the presence of the unshared electron pair on nitrogen, the strengths of primary, secondary and tertiary amines are quite similar. Aryl amines (those where the nitrogen is connected directly to an aromatic amine) weaker bases, but we will take that topic up later in the course.

Synthesis of Amines

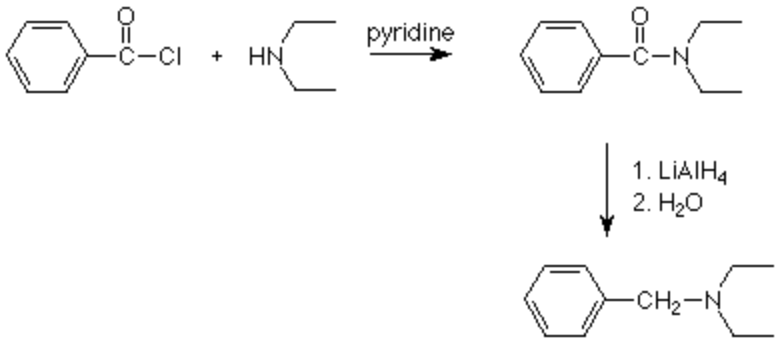
Our last topic for today is the synthesis of amines. While it is possible to make alkyl amines (an example which is a primary amine with a primary alkyl group) would be RCH_2NH_2) by reaction of a primary halide with ammonia, these reactions are seldom very practical.

The more practical approches to making alkyl amines involve reactions which are reductions. The first of these is a reaction of an amide with lithium aluminum hydride. The overall effect of this reaction is to replace the carbonyl oxygen of the amide with two hydrogens from lithium aluminum hydride. We will not discuss the mechanism, but it is likely that it begins with the familiar nucleophilic attack of the hydride ($H:^-$ of lithium aluminum hydride on the carbonyl carbon of the amide. (This reaction is discussed in Section 13.8B of Brown.)

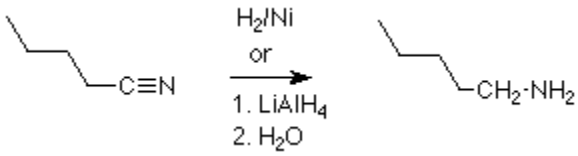




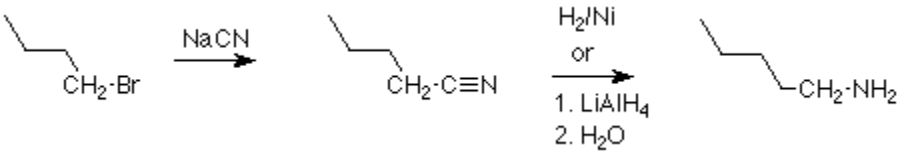
Notice that any other atoms or alkyl groups attached to the amide nitrogen are not changed. Since amides are commonly made by the reaction of acid chlorides with an amine, the two step sequence which begins with reacting an amine (or ammonia) with an acid chloride and follows with reduction of the amide using lithium aluminum hydride results in the substitution of an alkyl group on the nitrogen. Here's an example:



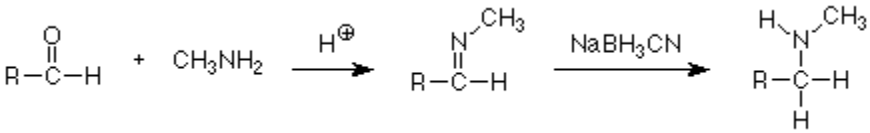
Another reductive synthesis of amines reacts a nitrile (RCN) with hydrogen in the presence of a catalyst which is very finely divided nickel. This reaction adds two molecules of H_2 to the triple bond of the nitrile, and produces a primary alkyl primary amine (RCH_2NH_2. Lithium aluminum hydride will also carry out this reduction.



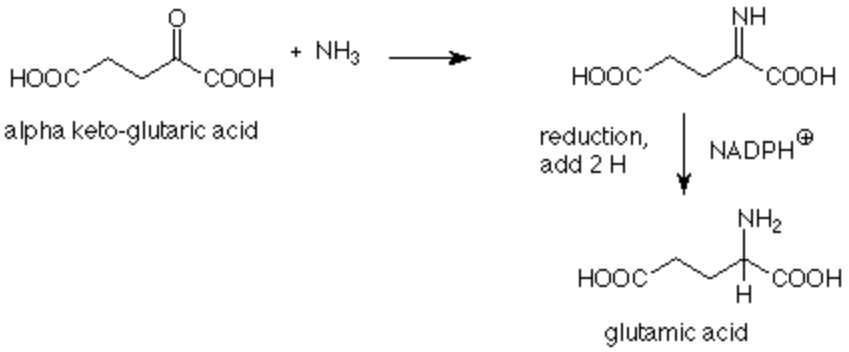
Recall that nitriles are commonly made by the reaction of primary alkyl halides with sodium or potassium cyanide, and we again have a two step sequence as in this example:



Finally, there is also a reductive method which involves a ketone or aldehyde carbonyl reaction. Early in the course we studied a reaction between primary amines and ketones or aldehydes which resulted in the replacement of the carbonyl oxygen by the nitrogen of the amine. Water was eliminated and the product was an imine.



If this reaction is carried out in a solution containing sodium cyanoborohydride ($NaBH_3CN$, a less reactive analog of sodium borohydride) the imine is reduced to an amine even though there is also a reducible carbonyl group in the reaction mixture. The formation of glutamic acid (from which the amino groups of all other amino acids arise by transamination) is a biological analog of this "reductive amination." Here the reducing agent is $NADPH^+$, one of several reducing agents which are common in biochemical reactions.



Again, we see that biochemical reactions use organic reaction mechanisms.

Contributors

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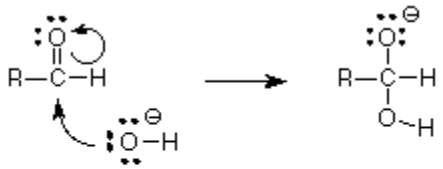
1.20: Amines- Reactions

Amines and Carbonyls - Imine Formation

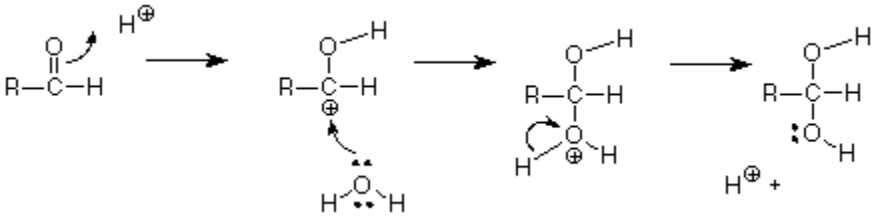
Last time we looked at the behavior of amines as bases, at their involvement in hydrogen bonds, and at the ways they can be synthesized. This time, we'll continue our study of amines by examining some of their reactions.

Let's begin reviewing reactions of amines with carbonyl compounds. When we first looked at aldehydes and ketones, we learned that the characteristic pattern of many reactions of the carbonyl group begins with the formation of a bond between the carbonyl carbon and an attacking nucleophile. The nucleophile provides the electrons to form the new bond and the pi bond of the carbonyl group is broken as it "gets out of the way." The electrons move from this pi bond onto what was the carbonyl oxygen. Here's an early example in which the nucleophile is an OH^- group.



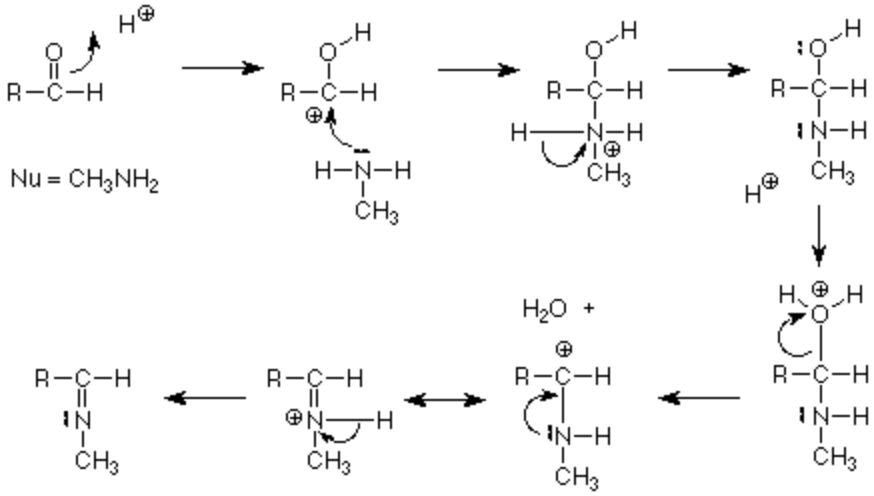
(We have shown all the unshared pairs on each oxgyen atom in this example. Normally, we will only show those pairs which are involved in the bonds being broken or made.)

This reaction step works because the OH^- group is a strong nucleophile (and a strong base) very capable of using one of its unshared pairs of electrons to make a new covalent bond. If a weak nucleophile is involved, like water, the reaction needs help in the form of acid catalysis. In this pattern, the H^+ begins the mechanism by making a bond with the carbonyl oxygen. The electrons which make this bond can be envisioned as coming from the carbonyl pi bond, which leaves a positive charge on the what was the carbonyl carbon.



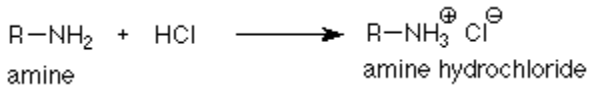
Once the pi electrons have been "gotten out of the way" by forming a new bond to the hydrogen, even a fairly weak nucleophile like water can us one of its unshared electron pairs to make a new bond to the former carbonyl carbon. The hydration reaction is completed by losing an H^+, which also keeps thing tidy by replacing the H^+ which was used to start the reaction.

The idea which emerges from this is that a strong nucleophile can attack directly, without help from an acid catalyst. For a weak nucleophile, an acid catalyst is needed so that the carbonyl carbon is prepared to share a pair of electrons as a new covalent bond. If we look at the mechanism of reaction between an aldehyde and an amine, we see how these factors balance. Here's the mechanism:



It is an experimental fact that this reaction -- imine formation -- is acid catalyzed. That suggests that the unshared pair of electrons on an amine nitrogen is not sufficiently nucleophilic to push the carbonyl pi electrons "out of the way" without help from an H^+ which breaks that pi bond in an earlier step. Since we know that an amine (pK_a of the conjugate acid ~ 10) is a weaker base than hydroxide or alkoxide ion (pK_a of the conjugate acid ~ 16), it makes sense that an amine would also be a weaker nucleophile than hydroxide ion. The weaker nucleophile would be more likely to need a little help from acid catalysis.

It's also an experimental fact that if we put in too much acid, the reaction stops. How do we make sense of this? The key is to remember that an amine is a base. (Yes, sometimes it's easy to forget that something is a base if we've gotten fixated on its nucleophilic behavior, but that's our problem, not the amine's problem.) Being a base means that an amine will react with an acid to form an ammonium ion.



For each molecule of amine which does this, the unshared electron pair has been used to make the N-H bond and is not available to act as a nucleophile. That molecule of amine has been "benched" and is not available to react with the carbonyl compound. If this happens to all of the amine molecules (we've added too much acid) the reaction has to stop since one of its reactants is gone.

What's the best compromise? We need some amine to make the reaction go, so we want to add fewer acid molecules than there are amine molecules. We need some acid, though because it is important both to "jump start" the reaction and to catalyze the removal of the water molecule later in the mechanism. It turns out that the fastest rate happens if we control the pH so that half of the amine molecules are available to act as nucleophiles and the other half are present as the conjugate acid (ammonium salt). The ammonium ion (RNH_3^+) actually serves as the acid catalyst since it is the strongest acid which can co-exist with the amine. (Any stronger acid would just react with the amine to make more ammonium ion.)

Amines and Carboxylic Acid Derivatives - Amide Formation

Now let's turn our attention to the reactions of amines with carboxylic acids and their derivatives. Again, the nitrogen serves as a nucleophile in making a new bond to the carbonyl carbon. The pi bond is broken to "make room for" the nitrogen's pair of electrons. This step is just like the attack of a nitrogen nucleophile on a carbonyl carbon in an aldehyde or ketone, but what happens next is different.

The structural difference between aldehydes and ketones on one hand and carboxylic acid derivatives on the other is that a carboxylic acid derivative has a "leaving group." Leaving groups are distinguished from alkyl groups or hydrogen atoms by having an electronegative atom bonded to the carbonyl carbon. Pertinent examples include the chlorine in an acyl chloride and the -OR' group in an ester. Since the bond between one of these groups and the carbonyl carbon is polarized so that the electrons are closer to the leaving group atom than to the carbonyl carbon, it is already somewhat ionic and can cleave more easily than a

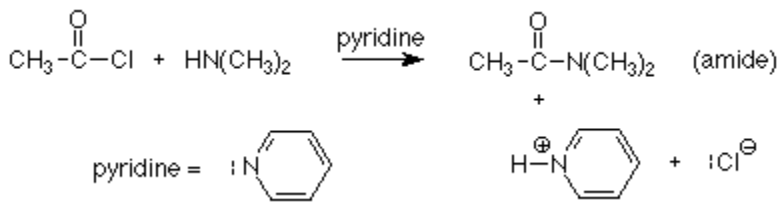
carbon-carbon or carbon-hydrogen bond. This pathway is not available to aldehydes and ketones, but it dominates the reaction of carboxylic acid derivatives. The overall result is that when an amine (or any nucleophile) reacts with a carboxylic acid derivative the outcome is that the amine replaces the leaving group (a hydrogen is lost from the amine nitrogen too). The overall reaction is a substitution.

Now let's recall some examples of the reaction of amines with carboxylic acid derivatives. The details here are usually designed to overcome the fact that carboxylic acids and esters (and amides too) are less reactive than aldehydes or ketones. This is due to the fact that the "leaving group" atom in these derivatives also is electron rich (one or more unshared electron pairs) which tends to make the carbonyl carbon less "accepting" of a nucleophile's attempt to add an electron pair to it. Thus successful reactions between amines and carboxylic acid derivatives need to overcome the rather low reactivity of the carbonyl carbon in these compounds.

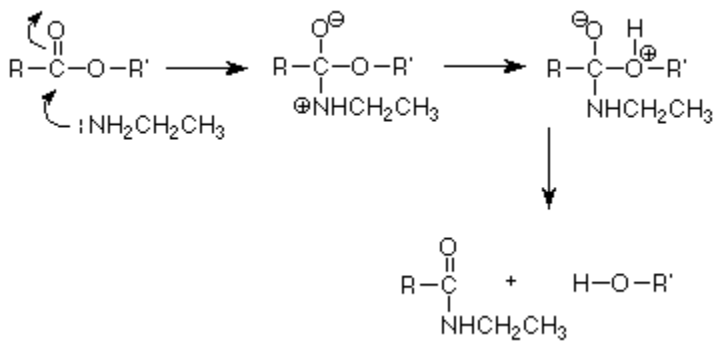
One very good way to do this is to put a very good leaving group in the carboxylic acid derivative. This is what is done with acyl chlorides.

We can get a sense of how good a leaving group might be by considering how strong a base is formed when the leaving group leaves. Remember that strong bases are difficult to form and weaker bases are easier to form. Chloride ion is the conjugate base of HCl, a very strong acid, so it is a very weak base and a very good leaving group.

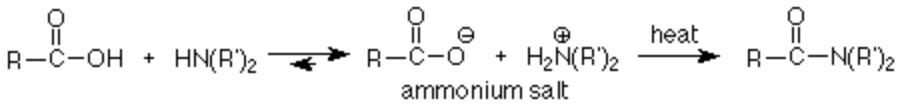
Once we have the acyl chloride with its very good leaving group, we can use a moderately effective nucleophile like an amine to get a satisfactory method for making amides.



How about reactions between amines and esters. Here, the reaction is accelerated by heating it moderately. Notice that a stronger base (amine) is used up and a weaker base (alcohol) is produced. Notice also that before the alcohol (leaving group) portion of the ester departs, it picks up an H^+ so that it can leave as the weak base alcohol (R'OH) rather than as the strong base alkoxide ion ($R'O^-$). Again, weaker bases make better leaving groups.



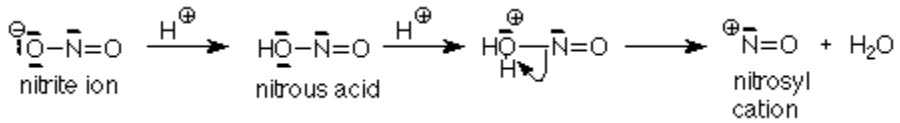
In the case of making amides from carboxylic acids, the difficulty comes because the carboxylic acid is a stronger acid (pK_a ~5) than the ammonium salt (pK_a ~10). The result is that there is very little amine and carboxylic acid at equilibrium. so there is very little nucleophile present. Also, the O^- in the carboxylic acid is a very poor leaving group. This reaction doesn't look promising at all, but it can be made to work by heating the ammonium salt strongly.



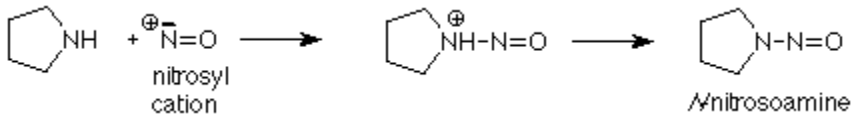
You may have noticed that we haven't tried acid catalysis of any of these reactions between amines and carboxylic acid derivatives. That's because any acid we add will react with the amine, so the strongest acid we can have in the reaction is the conjugate acid of the amine. That isn't a strong enough acid to "jump start" the lower reactivity carbonyl group of a carboxylic acid derivative.

Nitrosation - Nitroso Compounds and Diazonium Salts

Now to a reaction we haven't seen before. We will look at nitrosation because it follows on fairly naturally after the reactions of amines with carbonyl groups. Nitrosation reaction mechanisms begin with addition of a strong acid to sodium nitr**ite** ($NaNO_2$). Nitrous acid is formed, but it reacts further with acid to make water and the nitrosyl cation.

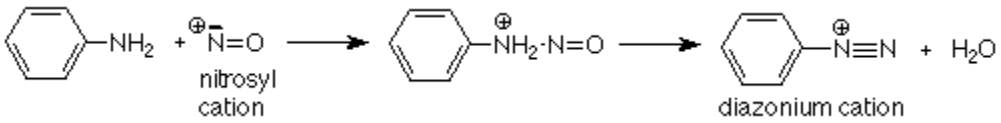


The nitrosyl cation is electron deficient. Its nitrogen has only three pairs of electrons in the valence shell, so it is a very good electrophile, very susceptible to attack by a nucleophile. When the nucleophile is a secondary amine, the product (after loss of an H^+ from the amine nitrogen) is called an *N*-nitrosoamine.



Some of these *N*-nitrosoamines have been shown to be carcinogenic in animals, so there is concern regarding the possibility that they may be formed when sodium nitrite (added to some meats to prevent botulism) reacts with acid in the stomach and amines present in the body. The beneficial effect of sodium nitrite in preventing botulism poisoning must be weighed against the potential hazard of *N*-nitrosoamine carcinogenesis. As with many dietary hazards, the longer term effects are difficult to determine.

When the amine is primary, its reaction takes a different course. We will look at an example where the R group is the phenyl group (a benzene ring), since that is the most important application of this reaction.



The aromatic diazonium ions produced by this reaction are stable enough to persist in a cold acidic aqueous solution. They are important as synthetic intermediates in the preparation of a variety of aromatic compounds, including dyes and photographic chemicals. We'll take a longer look at what we can do with these compounds when we study aromatic chemistry in a few weeks. In the meantime, keep this reaction in mind.

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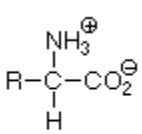
1.21: Amino Acids and Peptides

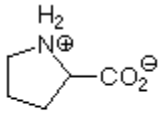
Amino Acids and Side Chain Structure

Last time we finished our examination of amines. Now we'll look at what happens when a carboxylic acid functional group and an amine functional group are in the same molecule. Our focus will be on the alpha amino acids, those in which the amino group is bonded to the alpha carbon -- the one next to the carbonyl group -- of the carboxylic acid. These are the basic building blocks of proteins and are the most important type of amino acid. While there are many other ways to link an amino group and a carboxylic acid group in a single molecule, we will concern ourselves only with the alpha amino acids.

There are 20 alpha amino acids commonly found in proteins. They are listed in Table 18.1 (p 503) in Brown. When the structures of these molecules are examined, it becomes clear that they share the common structural unit $RCH(NH_3^+)CO_2^-$ in which R can be either hydrogen (the amino acid is glycine) or one of 19 other possibilities. The one exception to this pattern is proline, in which the R group makes up part of a ring which also includes the amino group and the alpha carbon atom. Since the amino group in proline is involved in two carbon-nitrogen bonds, it is a secondary amino group.



generic amino acid
(primary amino group)



proline
(secondary amino group)

The table is further divided into groups according to the structure of the R group. (The R group is often called the "side chain.") If the R group is made up of only carbon and hydrogen (no heteroatoms), the side chain is regarded as non-polar since there is very little polarity associated with carbon-carbon and carbon-hydrogen bonds. These side chains are hydrophobic (water avoiding) in much the same way that the long hydrocarbon tail of a soap or detergent is hydrophobic. This will be important when we consider how the characteristics of proteins depend upon their folding patterns in an aqueous environment. There are heteroatoms in methionine (sulfur) and tryptophan (nitrogen) but the overall behavior of these amino acids suggests that these heteroatoms contribute very little polarity to the side chain. Side chains which contain more polar functional groups such as amide, alcohol and thiol provide locations for a polar water molecule to hydrogen bond. They are thus somewhat hydrophilic, like the OH groups in a sugar. These side chains are important in making a protein sufficiently water soluble to operate effectively inside a cell.

In two cases (aspartic acid and glutamic acid) the side chain includes a carboxylic acid group in addition to the one next to the amino group. These groups are ionized (present as the carboxylate anion) when the pH is near neutral (pH ~ 7). (We'll take up the acid-base behavior of amino acids shortly.)

Similarly, there are three amino acids whose side chains include an amino group. These amino groups are also ionized (present as the ammonium ion) at neutral pH. The ionized groups are quite polar, and like the ionized ends of soaps or detergents, they make the side chain quite hydrophilic.

Acid Base Chemistry

At neutral pH (around 7, the typical pH of most body fluids and the pH at which biochemical reactions usually happen) the amino groups in amino acids are protonated to make ammonium ions and the carboxylic acids are ionized to their conjugate bases (carboxylate ions). One way to look at this is to look at a water solution at pH = 7 as a large reservoir of acid whose pK_a is maintained at 7. If an acid with a pK_a lower than 7 (like a carboxylic acid, pK_a ~ 5) is dissolved in such a solution, it is the stronger acid and will transfer a proton to the solution and become the carboxylate ion. Thus when the pH is maintained at 7, carboxylic acids are ionized.

In the same way, when an amine (typical ammonium ion pK_a ~ 10) is dissolved in water which is held at pH = 7, the water is the stronger acid so the amine is protonated to make the weaker acid. Amines when held at pH = 7 are protonated to make ammonium ions. Practically, holding the pH at 7 means that the solution is buffered by the inclusion of weak acids and weak

bases in sufficient concentration so that the transfer of a few protons does not materially change the H^+ concentration.

We can use this idea at any pH. For example, if an amino acid is dissolved in water which is held at pH = 2, the solution is a stronger acid than the carboxylic acid which would be formed by transferring a proton to the carboxylate ion. The carboxylic acid (pK_a ~ 5) is formed as the weaker acid. Such a molecule would have only a positive charge from the ammonium ion. Similarly, in basic solution (pH > 11) the solution is a weaker acid than the ammonium ion, so the ammonium ion transfers a proton to the solution and becomes the amino group.

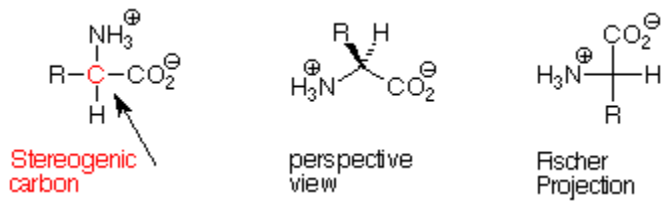
Since there are small variations in the specific pK_a values of amino and carboxylic acid groups in amino acids, the exact pH at which the predominant species is the zwitterion (the molecule with one positive ammonium ion and one negative carboxylate ion) varies somewhat. This pH is called the isoelectric point (pI) because it is the pH at which the amino acid is as likely to be attracted to a positive electrode as to a negative one. The pI values for the common amino acids are given in Table 18.2 (p 506 in Brown).

Notice that the acidic amino acids have low pI numbers. This makes sense because it will take a fairly strongly acidic solution to ensure that one of the carboxylate ions is protonated. Similarly, for basic amino acids the pI values are higher since it will take a fairly basic solution to ensure that one of the ammonium ions has lost a proton and the positive charge.

Stereochemistry

For all of the amino acids except glycine, the alpha carbon atom is a stereogenic carbon atom (four different groups attached). In two cases there is also another stereogenic carbon atom in the molecule. Only one of the two possible enantiomers is found in nature in the cases of the amino acids which include stereogenic carbon atoms. In all these cases the absolute configuration of the alpha stereogenic carbon is S.

It became possible to determine absolute configurations well after the stereochemical relationships between amino acids and sugars had been worked out. That work showed that if we orient a Fischer projection of an amino acid with the carboxylate ion group at the top and the R group at the bottom, we find that the ammonium ion is pointed to the left. For this reason the amino acids are considered to have the L configuration (opposite to the D configurations assigned to common sugars). You may wish to verify that that an L-amino acid is also an S amino acid.

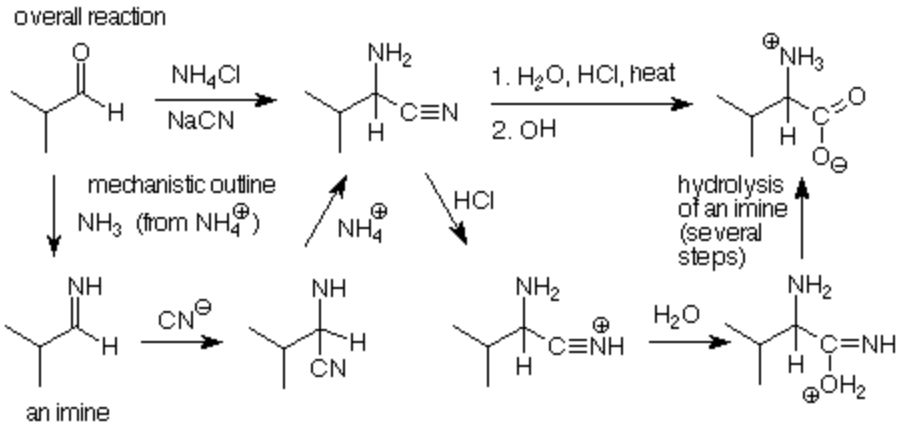


Amino acids are produced in living systems by biochemical pathways which involve multiple enzymes. The enzymes are proteins, themselves made up of L-amino acids so they provide a chiral environment in which only one of the two enantiomers is formed. Laboratory synthesis of amino acids typically does not involve a chiral environment, so equal amounts of the L- and D-amino acids are formed in typical laboratory syntheses. A mixture of equal amounts of enantiomers is called a *racemic* mixture.

Synthesis

Laboratory syntheses of amino acids are usually related to syntheses of amines and/or carboxylic acids. We'll take a look at one such synthesis, the Strecker synthesis. We won't look at it's mechanism in detail, but we will look for similarities with reactions we've seen before.

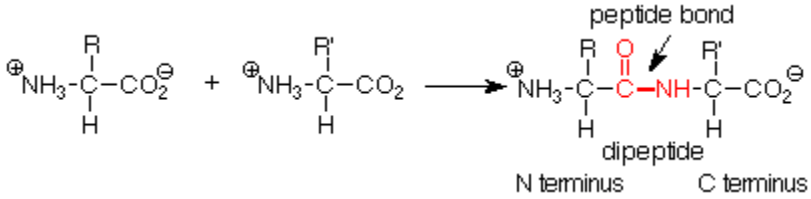
The reaction begins with imine formation from an aldehyde and ammonia. The acid catalysis required for this comes from ammonium chloride, a weak acid. An addition of hydrogen cyanide to the imine follows. This is analogous to the additions of nucleophiles to an aldehyde or ketone which we studied earlier. In this instance, the cyanide ion serves as the nucleophile.



The amino nitrile which results from these steps is purified and treated with aqueous HCl, followed by OH^-. This converts the nitrile to a carboxylate salt. We can put this reaction in context by thinking of the C-N triple bond as being much like a carbonyl group. That suggests that the electrophilic H^+ attacks the nitrogen, which is followed by a nucleophilic attack of water on the nitrile carbon. A C=N double bond remains, and it's reaction with water is the reverse of imine formation. The outcome is that the C=N double bond is hydrolyzed to a C=O double bond. Finally, neutralization with just enough base gives us the amino acid zwitterion.

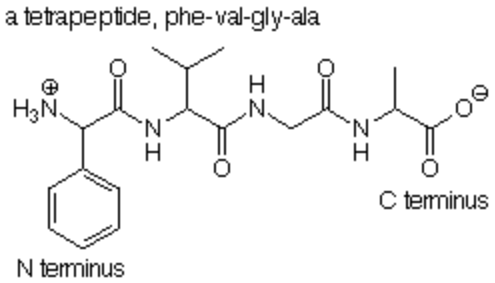
Peptides and the Peptide Bond

Now let's turn our attention to the way in which amino acids are linked together to form proteins. The key structural element here is the peptide bond. This is an amide linkage which joins the ammonium group of one amino acid to the carboxylate group of another by a new covalent bond. The O^- of the carboxylate is lost along with two H^+ ions from the ammonium group to form water. This is quite analogous to the formation of an amide by heating a carboxylic acid and an amine. The specific reaction conditions and processes required to do this may be (as we will see) quite sophisticated, but it helps to remember that what is being done is the joining of a carboxylate carbon and an ammonium nitrogen by a new C-N (peptide) bond.



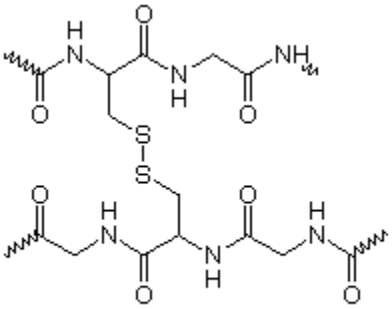
The new compound formed in this way is called a peptide. Our example is a dipeptide, formed from two amino acids. If a third amino acid is connected to the dipeptide by forming a new peptide bond at either the ammonium group or the carboxylate group of the dipeptide, we obtain a tripeptide, and so on. Polypeptides may have many amino acids. Polypeptides with more than 100 amino acids are considered to be proteins.

Since the amino acid whose carboxylic acid group participated in the formation of the peptide bond still has an ammonium group which contains a nitrogen atom, it is called the N terminus of the peptide. The N terminus is conventionally written to the left. Correspondingly, the amino acid which still has a free carboxylate group is called the C terminus and is written to the right. When the order of amino acids in a peptide is written out, it is conventional to write it left to right from the N terminus to the C terminus. The complete order of amino acids in a protein is called its sequence and is conveniently expressed by using the abbreviated names of the amino acids read from N to C terminus.

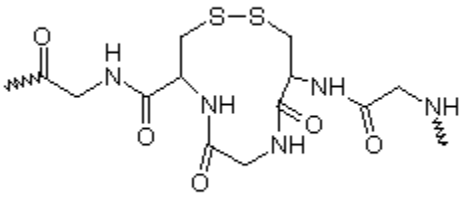


The sequence is held together by peptide bonds. As a part of an amide functional group, these bonds are difficult to break, so the sequence of a protein is quite stable. While there are many possible ways that a protein chain could be folded, the particular folding pattern adopted by the protein is completely determined by the its sequence.

In many cases the folding pattern is "locked in" by disulfide links. As we discussed when we were studying thiols, the presence of SH groups along a protein chain provides an opportunity for crosslinking between chains or the formation of loops within a chain. These disulfide bridges are important in holding the protein chain in a specific folding pattern.



disulfide crosslink



disulfide "loop"

A glance at Table 18.1 tells us that the SH groups necessary to make the disulfide links are found in the amino acid cysteine. Proteins which are stiff and used primarily for structural purposes (keratin in hair, skin and feathers, for example) usually have many disulfide links and thus have high contents of cysteine.

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1.22: Proteins

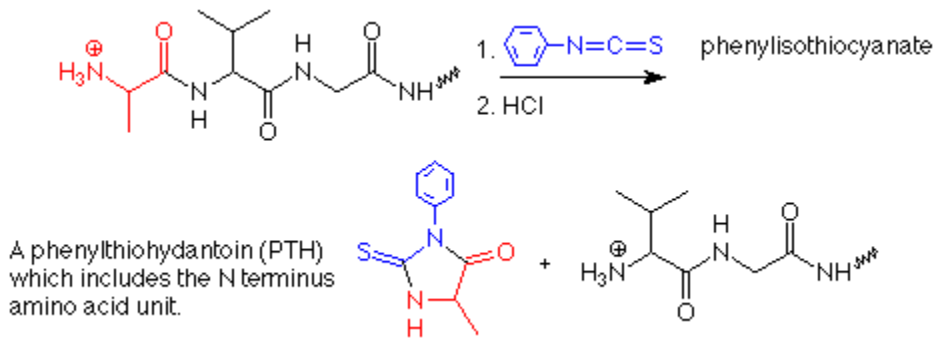
Sequencing a Peptide

Last time we looked at the structural characteristics of amino acids and the peptide bond which joins individual amino acids together to make proteins and peptides. We also learned about the sequence (order) in which amino acid units are joined in peptides. Today we'll study the ways in which the specific sequence of a peptide may be discovered and the methods which are used to synthesize such a peptide.

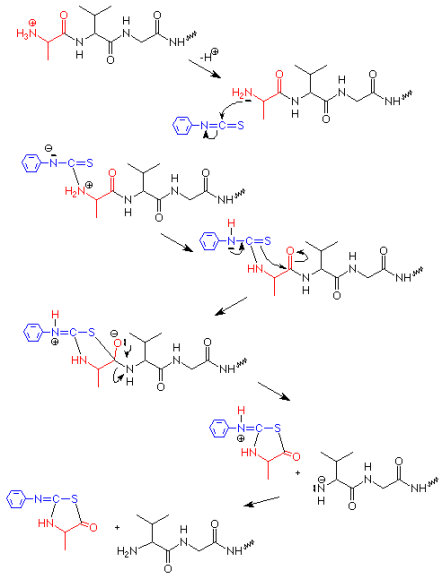
The first thing that is done in determining the sequence of a peptide is to find out which amino acids are present and in what ratios. This is much like beginning the process of determining the structure of an organic compound by determining the ratios of atoms such as carbon, hydrogen and oxygen. This is done by hydrolyzing the peptide bonds which hold the peptide together using HCl as an acid catalyst. (The mechanism is very much like acid catalyzed ester hydrolysis.)

This "amino acid analysis" tells us what the building blocks are in the peptide, but it tells us nothing about their sequence, the order in which they are joined. This information is lost when the peptide bonds which preserve that sequence are hydrolyzed. Even with as few as two amino acids, there are two possible sequences. Consider a dipeptide which amino acid analysis gives us **gly** and **ala**. Either of these could be the N terminus, so the dipeptide could be either **gly-ala** or **ala-gly**. Problem 18.6 in Brown gives you some experience with a pentapeptide, and things rapidly get more complex as the number of amino acid units in the peptide increases.

The next step is to determine which amino acids occupy the N terminus and C terminus positions in the peptide. N terminus determination is commonly done by a process called the Edman degradation. The chemistry is outlined as follows:



This reaction can be understood if we look for some analogies that will help us apply the patterns we used in the past. The -N=C=S group resembles a CO_2 (O=C=O) molecule in that the carbon atom is connected to two electronegative atoms by a double (sigma and pi) bond. We know from reacting Grignard reagents with CO_2 that the nucleophile attacks the carbon in CO_2, so we can expect the same type of pattern in the Edman degradation. The nucleophile is the free NH_2 group at the N terminus of the peptide, formed by loss of a proton from the $NH_3^+$to some unspecified base. As we have seen with other reactions of NH_2 groups, this step is followed by a proton shift.



The product of the addition of N and H to the C=N double bond has a nucleophilic sulfur atom located just in reach of the carbonyl carbon at the other end of the N terminal amino acid. Attack of this sulfur at that carbonyl group is followed by departure of the NH group of the next amino acid. This cleaves the peptide bond between the N terminal amino acid and the next amino acid. Further reshuffling of protons yields an isomer of the phenylthiohydantoin. This isomer is converted to the phenylthiohydantoin during the treatment with HCl and the phenylthiohydantoin is identified. Since the phenylthiohydantoin includes the R group of the N terminal amino acid, identification of the phenylthiohydantoin also identifies the N terminal amino acid.

The other product of the Edman degradation is also a peptide -- it is the original peptide minus the original N terminal amino acid. It now has a new N terminal amino acid, which was adjacent to the N terminal amino acid in the original peptide. The new peptide can also be subjected to Edman degradation. When this is done, we learn the identity of the second amino acid (from the N terminal end) of the original peptide and obtain again a peptide which is now two amino acids shorter than the original. In principle, repetition of this sequence would allow us to run successive Edman degradations, clipping off an N terminal amino acid with each degradation, and thus learn the entire sequence of of a peptide or protein. In practice, such a process is practical only for about 20 to 40 amino acids.

Since the laboratory steps in an Edman degradation are very repetitive -- the same thing is done at each cycle, it has been possible to automate this process. Computer controlled "protein sequenators" are common in biochemistry laboratories.

Overlapping Sequences

When peptides and proteins larger than 20 to 40 amino acid units are to be sequenced, they are first broken into smaller fragments either by chemical or enzymatic partial hydrolysis. Here's an example of how partial chemical hydrolysis might be used.

Angiotensin II

Amino acid analysis gives Arg, Asp, His, Ile, Phe, Pro, Tyr, Val.

Partial hydrolysis gives four fragments, which are sequenced by several cycles of Edman degradation as:

Asp-Arg-Val
Ile-His-Pro
Pro-Phe
Arg-Val-Tyr
Val-Tyr-Ile

The structure of Angiotensin II is then pieced together by looking for overlaps in these sequences. Fof example, we notice that the Arg-Val sequence occurs in two fragments, so we line those two fragments up with the Arg-Val pair aligned:

Asp-Arg-Val
Arg-Val-Tyr

Similarly, the Val-Tyr pair occurs twice, so we add it to the alignment.

Asp-Arg-Val
Arg-Val-Tyr
Val-Tyr-Ile

If we continue to look for these "overlaps," we can assemble the whole sequence.

Asp-Arg-Val
Arg-Val-Tyr
Val-Tyr-Ile
Ile-His-Pro
Pro-Phe

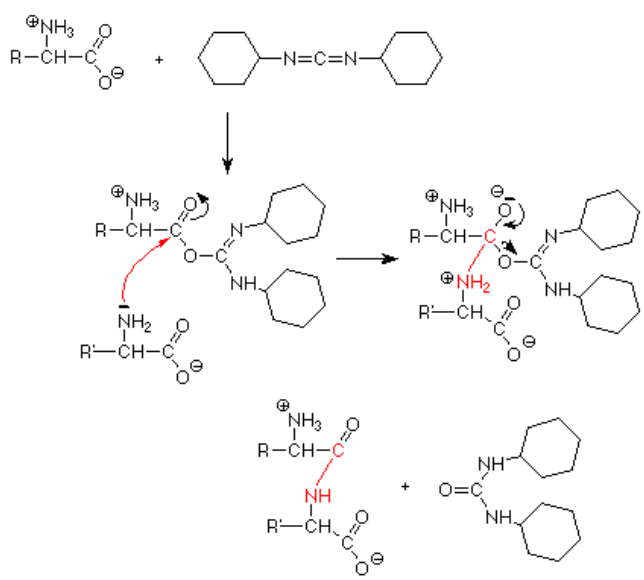
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

Of course, angiotensin II (a peptide involved in blood pressure regulation) is small enough that a protein sequenator could give its sequence directly, but the example illustrates the way fragments may be overlapped to give a complete sequence for a larger protein. The complete sequence of a protein is called its *primary structure*

Peptide Synthesis

When a sequence has been obtained for a peptide, attention can be turned to its synthesis. There are two issues to resolve in synthesizing a peptide. One is to develop a method for making the peptide bond which does not damage anything else in the peptide. This is called "coupling" the two amino acids. The other is to be sure that the amino acids are added to the peptide in the proper sequence.

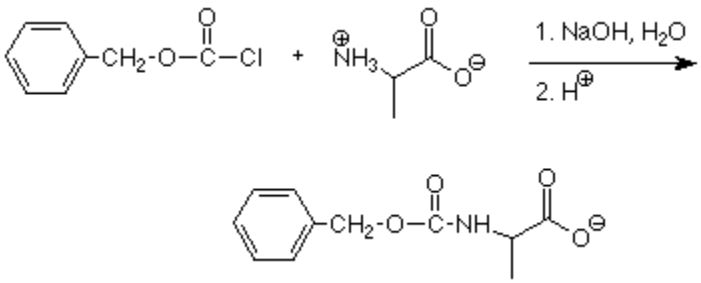
The key to the first issue is to convert the O^- an amino acid's carboxylate group into a better leaving group. We've seen something similar when we've converted an OH into a Cl as we made the reactive acyl chlorides. This is done by the use of a reagent called dicyclohexyl carbodiimide, or DCC for short. DCC works by bonding to the O_- and converting it to a good leaving group -- good because it has many electronegative atoms which can help stabilize the negative charge as it leaves. An amino acid which has a good leaving group is said to be "activated."



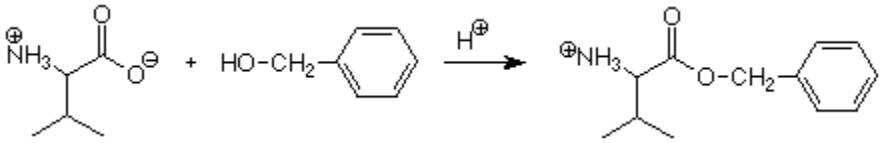
The actual coupling reaction occurs when the amino group of the amino acid "to the right" in the sequence attacks the carbonyl carbon of the "activated" amino acid and the DCC leaves with the oxygen it is bonded to. As usual, there are some proton shifts needed to tidy things up.

The second issue, adding amino acids in desired sequence, can be illustrated by considering the synthesis of a dipeptide such as Ala-Gly. If we simply mix equal quantities of glycine and alanine and run a DDC coupling reaction, we will get glycines reacting with glycines to give Gly-Gly, alanines reacting with alanines to give Ala-Ala, and glycines reacting with alanines in two ways to give Ala-Gly and Gly-Ala. This is a mess and it would be better to develop a more specific approach.

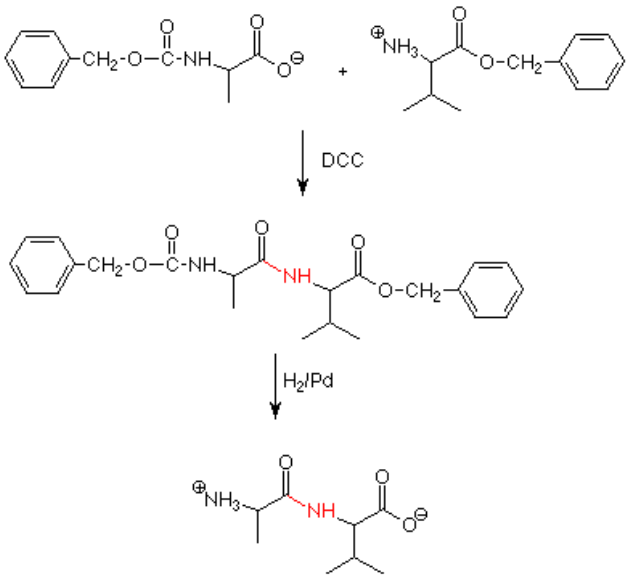
To do this we need to arrange things so that only one of the two carboxyl groups and only one of the two amino groups are free to engage in the coupling reaction. This is done by the use of protecting groups. If we make an amino group into an amide, it is much less reactive as a nucleophile. This can be done by reaction with an acid chloride.



Carboxyl groups are normally protected by conversion to a benzyl ester. This reaction is a Fischer esterification



After coupling, the protecting groups can be removed by hydrogenation.



This is a specific reaction in which only the bonds between the benzyl groups and the oxygens are broken, so the amide bond we have just made by coupling is not affected. (The carbonyl group on the formerly protected amino group is lost as CO_2.) More sophisticated protection schemes in which either the N protection or the O protection can be selectively removed have been developed.

In practice, proteins are now synthesized by molecular biological techniques in which the gene which encodes the sequence of

amino acids is isolated and used to direct the synthesis of the protein by a bacterium or a yeast.

Secondary, Tertiary and Quaternary Structure

When we are thinking of a peptide's sequence it is convenient to think of it as a chain which is stretched out, peptides are more commonly coiled (alpha helix, Brown p 518) or folded (beta sheet, Brown p 519). These shapes are called a peptide or protein's*secondary structure* and they are held in place primarily by hydrogen bonds. Recall that hydrogen bonds are much weaker than covalent bonds, but strong enough to resist rupture by mild temperatures. Hydrogen bonds are attractive interactions between the positive end of dipoles like the N-H and O-H bonds and negatively charged locations such as the unshared electron pairs on atoms like oxygen or nitrogen. In peptides it is commonly the N-H bonds of an amine and the oxygens of the carbonyl groups which participate in hydrogen bonds.

Regions of alpha helix or beta sheet are often combined by further folding patterns which make up a protein's *tertiary structure*. Structural proteins such as keratin or fibroin often have large regions of alpha-helix and make fibers. Enzymes are more often globular with hydrophilic amino acids on the outside and hydrophobic amino acids folded in towards the middle.

Individual proteins are often combined into clusters, which may include non-protein molecules such as heme (Fig 18.14, p 522 in Brown). Often such combinations are necessary so that the protein can carry out its biological function. Such clusters constitute the protein's *quaternary structure*.

Experiments have established that a protein's primary structure is enough, by itself, to determine how it will fold and combine with other proteins to make the appropriate secondary, tertiary and quaternary structures. It is not clear how this happens, and this is an area of active study.

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1.23: Nucleic Acids

Functions of DNA

Last time we examined how a the amino acid sequence of a peptide or protein might be discovered. We also learned how a chemical synthesis of a small peptide can be carried through.

Today we'll study the chemistry of the molecule which carries the information necessary for directing the biosynthesis of proteins and peptides. This is DNA, and we'll learn that the structure of DNA provides a very strong rationale for its function.

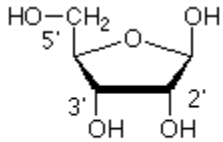
First, let's think a little about what a "molecule of heredity" needs to do. It must store an immense amount of information -- the directions for synthesizing all of the proteins necessary to for the successful functioning of a living organism. It must be able to transmit that information faithfully, with an extremely low error rate, to the protein synthesis system, to both daughter cells upon cell division, and to a future generation upon reproduction of the organism.

Prior to the discovery of the structure of DNA, there was much speculation regarding possible molecules which might meet these requirements. Proteins themselves were seriously considered as candidates, since they are stable, they can be large enough to hold a large amount of information, and they are certainly intimately involved in biology. The information might be encoded in the sequence of amino acids in a protein, much like information in a word is encoded in a sequence of letters. We might think of the amino acids as a 20 character alphabet, with which we could make a very large number of words, sentences, paragraphs, books, etc.

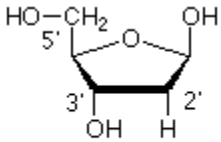
When the structure of DNA was established by James Watson and Francis Crick in 1953 it was immediately clear that it had the necessary characteristics to meet the specifications of a molecule of heredity. It is a polymer which can be extremely long. (The DNA in the single molecule which makes up a human chromosome is about 12 cm. long.) This provides the capacity to store large amounts of information. Like a protein this polymer backbone is carries an alphabet. In this case, the alphabet consists of only four letters, A, C, G, and T. Let's look at the details.

DNA Polymer Backbone

The polymer backbone is made up of two types of structure. One is a modification of the sugar ribose. The modification is that the OH group on the carbon next to the anomeric carbon has been replaced by a hydrogen. This is called 2-deoxy-D-ribose.

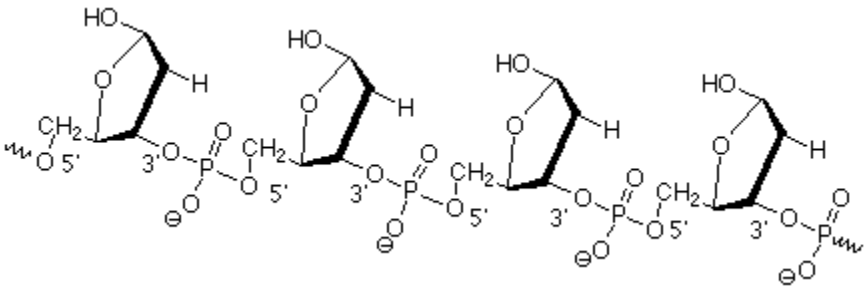


β-D-ribose



β-D-2-deoxyribose

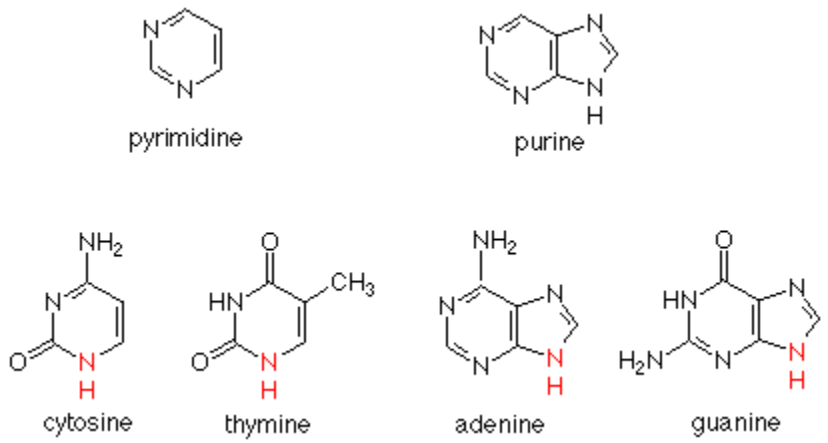
These 2-deoxyribose units are linked together by phosphate esters which link the 3' oxygen of one sugar with the 5' oxygen of the next. (The "primes" ' are there to differentiate atoms in the sugar ring from those in the bases, which we'll take up next.) This gives us a "backbone" for DNA which looks like this:



The "alphabet" molecules, A, C, G, and T, are attached to this backbone at the anomeric (1') carbons. Recall that these carbons are the ones where other groups can be attached by reactions such as those that convert hemiacetals to acetals. We'll next look at the structures of these molecules, which are called bases since they contain nitrogen atoms which make them mildly basic.

The Bases A, C, G, and T

Two ring structures are found in the bases. C (cytosine) and T (thymine) have a single six membered ring, called a pyrimidine ring. A (adenine) and G (guanidine) have two rings joined together. This unit is called a purine ring. C and T are called pyrimidine bases; A and G are called purine bases. Here are the structures:



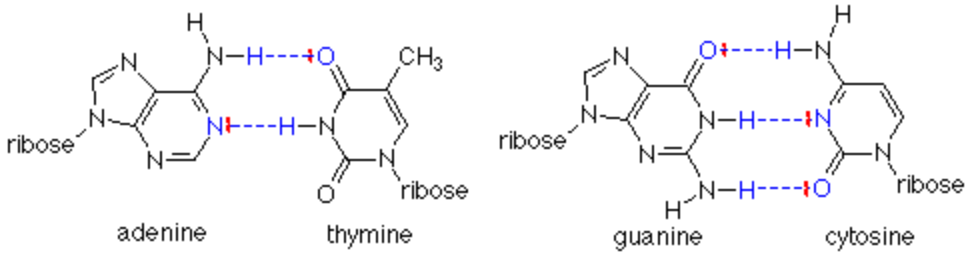
In each of these bases there is a secondary amine whose nitrogen forms a bond to the anomeric carbon of a deoxyribose in the DNA backbone. We can relate the chemistry of the formation of this linkage to the formation of a glycoside (acetal) from glucose (hemiacetal) and an alcohol. The difference is that in the current case the nucleophile is the secondary amine nitrogen of a base rather than the oxygen of an alcohol. An example of four bases attached in this way is:

The "word" here is CACT. Recall that the DNA backbone is very long, and it is clear that even with only a four letter alphabet, a great deal of information can be carried by DNA

Replication - Two DNA's from One

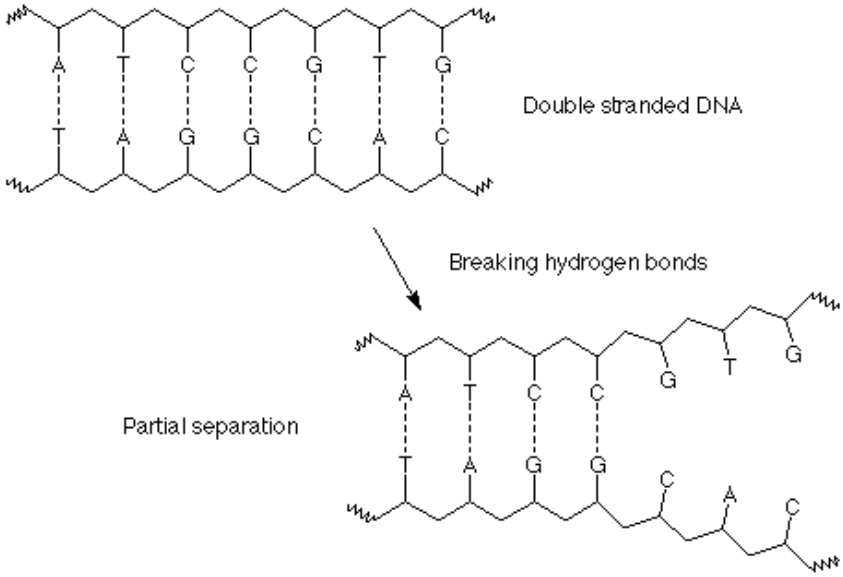
The next issue is transmission of the information to a daughter cell, to a succeeding generation, or to the protein synthesis machinery of a cell. The other key feature of the structure of DNA as discovered by Watson and Crick is that DNA molecules come in pairs, twisted together in the "double helix" (Figs. 19.8, 19.9; pp. 541,2 in Brown). Each of these molecules is a single long strand, held together by the covalent bonds along its backbone. The connections between the DNA strands are made by hydrogen bonds between the bases. Hydrogen bonds (as we learned when we studied amines) are much weaker than covalent bonds, but since there are many of them connecting the two DNA strands in the double helix, they serve very well to maintain that structure until there is a need for separation of the two chains.

Not only do the hydrogen bonds hold the chains together, they also are very specific in which bases are connected by the hydrogen bonds. Adenine (A) forms two hydrogen bonds only with thymine (T). Guanidine (G) forms three hydrogen bonds only with cytosine (C).

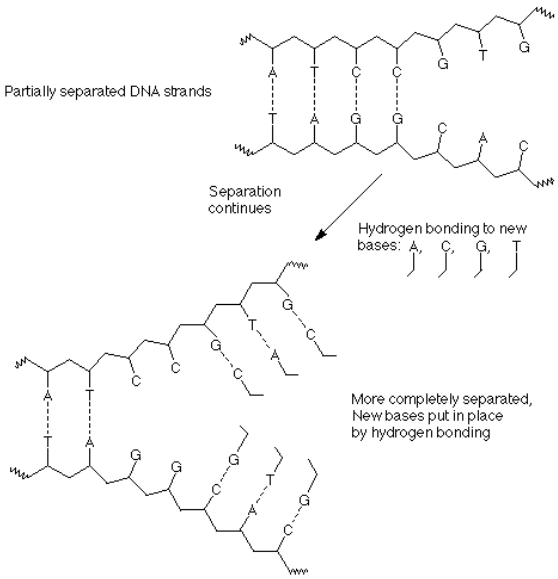


In each case, the hydrogen bond is formed between the positive hydrogen end of a polar N-H bond and a pair of electrons on either a nitrogen or a carbonyl oxygen. These "complementary" base pairs also have another important feature: a purine base (adenine or guanidine) always bonds to a pyrimidine base (cytosine or thymine). This means that the distance between the two strands is always the same (three rings and the hydrogen bonds). Hydrogen bonding between two purine bases, for example, would put four rings into the base pair, and the fit would be poor. You can try to put together other hydrogen bonding patterns, but these two are the ones which fit best.

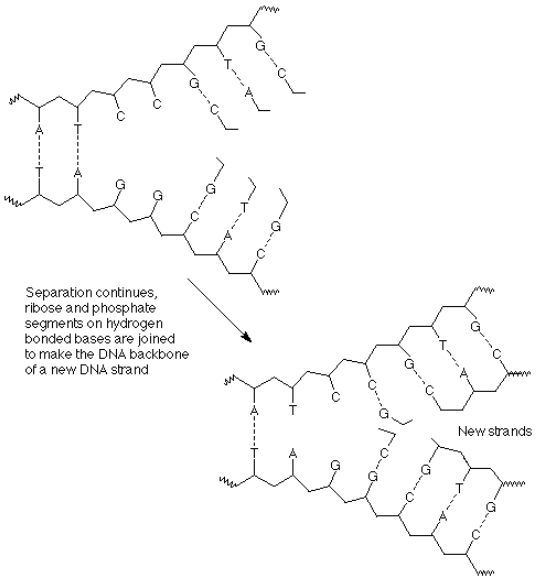
Watson and Crick realized that the specificity of this base pairing scheme was the key to replication of DNA and the transmission of information from one generation to the next. This is done in three steps. First the double helix is separated into the individual DNA strands by successively breaking hydrogen bonds between the base pairs.



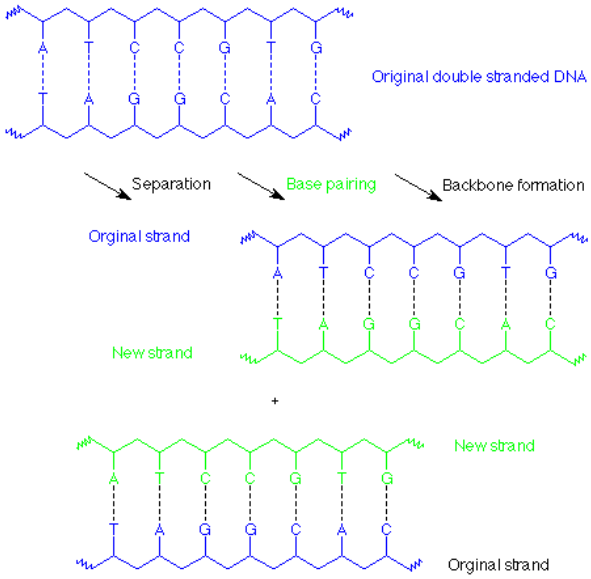
Second, as a segment of "unwound" DNA is exposed, bases from the solution encounter it, align with the complementary bases on the exposed DNA strands and form the proper base pairs, A with T and C with G. These bases are already joined to the necessary ribose and phosphate groups in molecules called nucleotides, so that as they line up in the proper arrangement, the materials for the formation of the backbone of a new polymer are in the proper locations.



Third, as separation and hydrogen bonding with new bases proceed, the individual nucleotides are joined together by the formation of new bonds between a phosphate of one nucleotide and the 3' OH group of the next nucleotide.



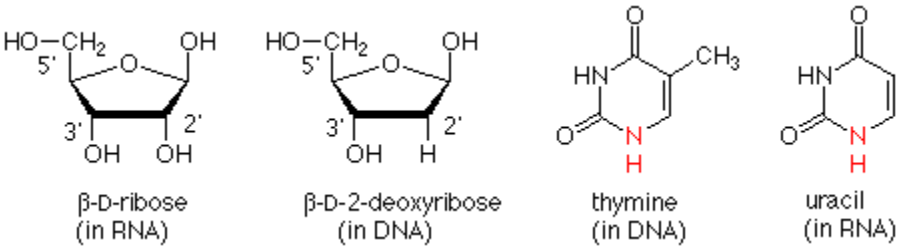
The outcome of these process is that each strand of the original DNA double helix has been used as a template upon which a copy of its former partner has been constructed. There are now two identical double helices which are the same as the original.



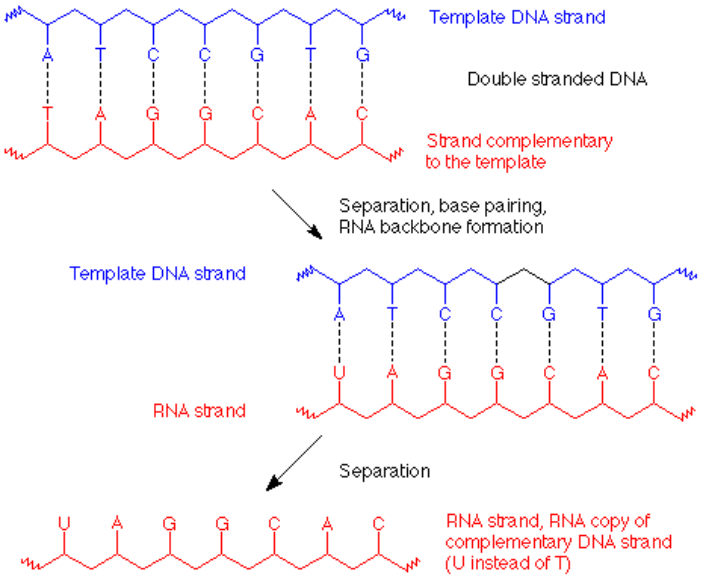
This is known as *replication*. In cell division each of these DNA copies would become part of one of the daughter cells. Each step in this process is assisted and controlled by enzymes, and there is also a "proofreading" function involved so that mismatched base pairs (such as an A-G pair) are excised and repaired.

Transcription and Translation - DNA to mRNA to Protein

There are two successive processes by which the information contained on a DNA strand is used to determine the amino acid sequence of a protein. In the first of these, called *transcription*, a copy of the DNA strand is made, but in this case the copy is RNA. There are two structural differences between DNA and RNA. In RNA the sugar is ribose (with the 2' OH group) while in DNA it is 2-deoxyribose (without the 2' OH group). Also, where T (thymine) would occur in DNA, U (uracil) occurs in RNA.



The transcription process by which a RNA copy is made is very similar to the process by which DNA replicates. In this case, only a partial unwinding of the DNA helix occurs, and the appropriate bases hydrogen bond to the separated DNA, U with A, C with G. The RNA nucleotides which are now lined up on the DNA template are then joined together to form the RNA strand, which is a copy of the DNA strand which was **not** the template, and is complementary to the strand which was used as a template.



In this way an RNA strand which carries the genetic message (called "messenger" or mRNA) to the protein synthesis machinery (called a ribosome) is made. Its base sequence specifies the amino acid sequence in the protein to be made. The codes for each amino acid use three bases in a row and are given in table 19.3 (p 547 of Brown). Since there are 64 ways to make three letter "words" (called codons) with a four letter alphabet, many amino acids are coded for by more than one "word."

In the ribosome, the codons on mRNA are matched with anticodons (A with U, G with C) on transfer RNA (tRNA) molecules. Each tRNA molecule carries the appropriate amino acid to the enzyme which links them together to make the protein. This process is called *translation*. We won't look at the linkage process in detail, but it does include protection and activation steps much like the chemical synthesis we studied earlier.

The information flow in the overall process is: Codon sequence in DNA determines codon sequence in mRNA. Codon sequence in mRNA determines the order in which tRNA molecules line up. The order of tRNA line-up determines the sequence in which amino acids are linked to make the protein.

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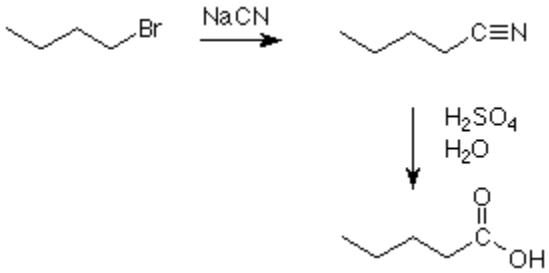
1.24: Nucleophilic Substitution, SN2, SN1

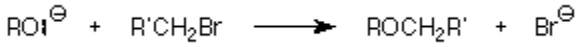
Recall Nucleophilic Substitution Examples

Today's topic takes us back to an important organic reaction mechanism. We've studied a few reactions which proceed by this mechanism. Now it's time to examine it in detail.

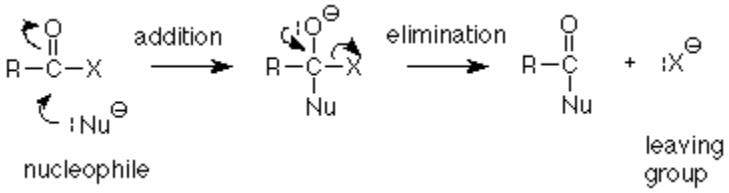
Let's begin by recalling a couple of reactions which occur with alkyl halides, but only work well when the alkyl halide is primary (the halogen is bonded to a carbon which is directly bonded to only one other carbon.) One such reaction involved cyanide ion and resulted in a nitrile which was then converted to a carboxylic acid:



Another similar reaction used an alkoxide (the conjugate base of an alcohol) and resulted in an ether. You may recall this as the Williamson ether synthesis:



In both of these examples the bond between the carbon and the halogen (usually bromine or chlorine) has broken and its pair of electrons has remained with the halide. If we compare what happens here with what happened with the chlorine in an acyl chloride, we recognize that in both situations the halide has behaved as a leaving group.



Similarly, we can focus our attention on the new bond that is being made. The electrons which form this bond in the product have come from the attacking reagent -- the cyanide in making a nitrile and the alkoxide in the Williamson ether synthesis. We recognize this behavior as that of a nucleophile, an atom or group which supplies a pair of electrons to form a new covalent bond. We've seen nucleophiles add to carbonyl carbons in both ketones and aldehydes and in carboxylic acid derivatives.

These reactions are known as *Nucleophilic Substitution Reactions,* substitution reactions because one atom or group has been substituted for another, and nucleophilic because the substituting atom or group has supplied the electrons for the new bond.

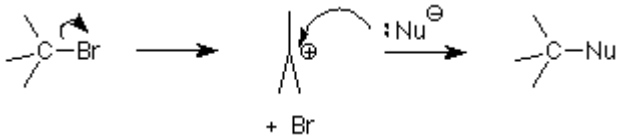
Possible Mechanisms

The typical reactions of carboxylic acid derivatives are also nucleophilic substitution reactions, but these are different. Remember that in the reactions of carboxylic acid derivatives there was first an addition to a the carbonyl group in which the carbon-oxygen pi bond was broken. This step was followed by one in which the leaving group departed and the carbon-oxygen pi bond was re-formed:

In alkyl halides this mechanism is not available since there is no carbon-oxygen pi bond to break and reform. This leaves us with

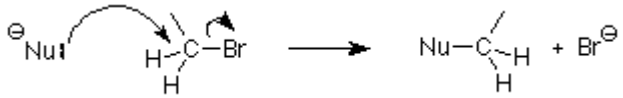
two possibilities:

1. The bond between the carbon atom and the leaving group breaks first. The carbon is left with six bonding electrons, an empty orbital, and a positive charge.

2. 

   In a second step, the nucleophile reacts to form a bond, much like the pattern which we saw in the acid catalyzed reactions of carbonyl groups. We'll study these reactions next time.

3. The bond between the carbon atom and the leaving group breaks at the same time as the bond between the nucleophile and the carbon atom is formed.

4. 

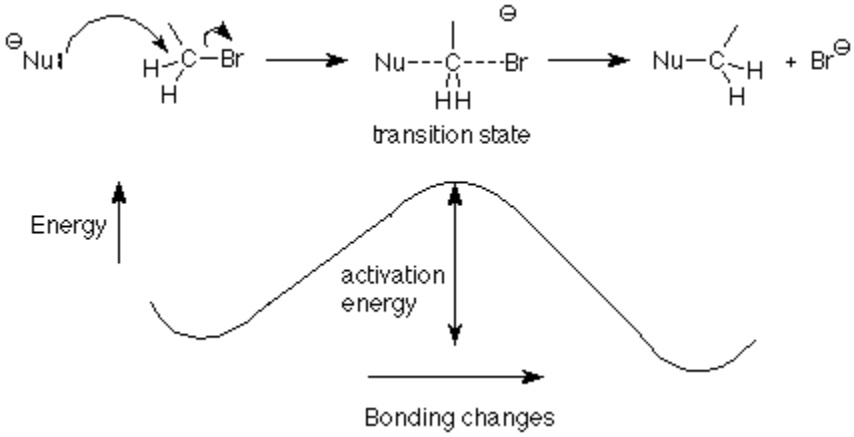
   There is only one step and it requires the nucleophile and the alkyl halide (also called the substrate) to collide for it to take place.

   (A third possibility, that the nucleophile attacks first to form an intermediate which later loses the leaving group, is not possible because the carbon in the intermediate would have ten bonding electrons and five bonds -- a very high energy situation.)

Today we'll consider the second of these possibilities. This mechanism is called an S_N2 mechanism; S for substitution, N for nucleophilic and 2 because two molecules collide at the critical point in the reaction.

S_N2 Mechanism

First, let's look at what happens in a little more detail. This is a one step reaction. In order for it to take place, the nucleophile must come close enough for bonding to begin to happen, but this also means that the carbon-halogen bond must begin to break. Both of these actions increase the energy of the combination - bond breaking requires energy as does overcoming the repulsion which results from moving the nucleophile's electron pair into close contact with the electrons in the carbon's bonding shell.



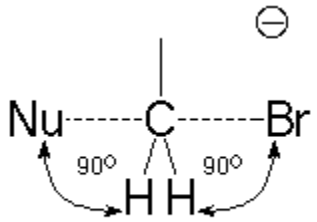
As the reaction process goes forward, the energy increases until a significant bonding begins to occur between the nucleophile and the carbon. This releases enough energy to balance the energy required to break the carbon-halogen bond. At this point. called a transition state, the energy is at a maximum. There is roughly a half bond between the nucleophile and the carbon and a half bond between the carbon and the halogen. Since the energy is at a maximum, any slight movement will cause it to decrease, either to go back to reactants or to go on to products. This picture of the transition state is the key to understanding

the characteristics of the S_N2 mechanism.

The energy required to boost the nucleophile and the alkyl halide to the transition state energy level is called the activation energy. It comes from the energy with which the molecules collide. If the activation energy is low, many collisions will provide enough energy and the reaction will be fast. If the activation energy is high, few collisions will provide enough energy and the reaction will be slow. Another way to say this is that slow reactions have high activation energies (and high energy transition states) and fast reactions have low activation energies (and low energy transition states). In order to understand what makes a reaction go slow or go fast, we examine the transition state to see what changes will increase or decrease its energy.

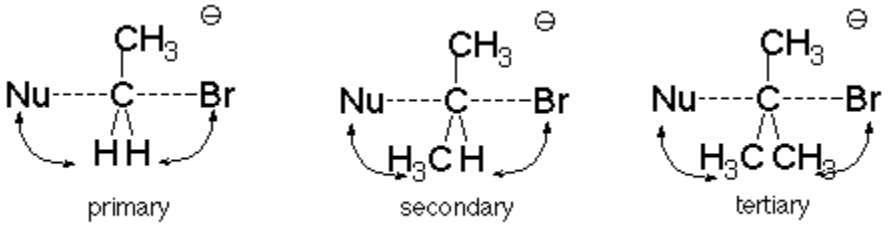
Effect of Alkyl Halide Structure

With this background, we can look back at the restriction that our examples of S_N2 reactions (nitrile and ether synthesis) only work well on primary alkyl halides. In the structure of the S_N2 transition state, there are 90° bond angles between the breaking bond to the leaving group and the three bonds which remain connected to the carbon as well as between the bond being made to the nucleophile and those same three bonds.



transition state

As long as the two of the groups attached to the carbon being attacked are small hydrogens, the repulsions which happen do not require much energy. If the groups attached to the carbon are larger, though, like methyl groups, the transition state energy increases, the activation energy increases, and the reaction becomes much slower.



primary secondary tertiary

transition states

This means that the reactivity order for alkyl halides in S_N2 reactions is:

methyl > primary > secondary > tertiary

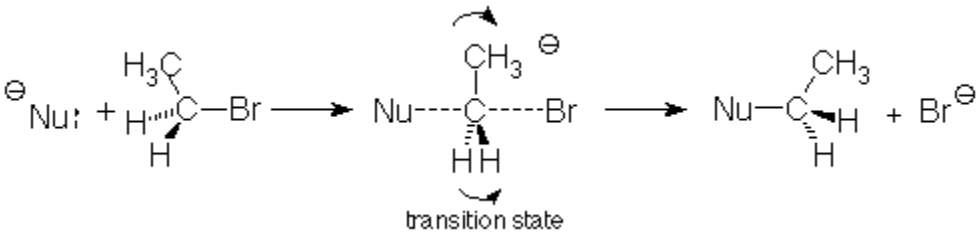
The practical outcome of this is that S_N2 reactions are generally reliable only when the alkyl halide is primary.

Stereochemical Inversion

The structural picture of the S_N2 transition state also accounts for another characteristic of S_N2 reactions. Notice that the nucleophile is bringing its bond-forming electrons into the transition state on the side of the carbon opposite to the position of the leaving group. We can understand this if we remember that the nucleophile and the leaving group are both electron rich atoms. We would expect them to repel each other and stay as far apart as possible while remaining connected by their half bonds to the central carbon atom.

The result of this is that the carbon atom is **inverted**. If we examine a three-dimensional picture of this, we can see that the three groups which remain connected to the carbon throughout the reaction move away from the entering nucleophile and towards the

position occupied by the departing leaving group.



If the nucleophile and the leaving group are both high in the ***R/S*** priority order, this means that an *R* alkyl halide gives an *S* product, and *vice-versa*. The term for this is *inversion of configuration* and it is an inherent and consistent characteristic of the S_N2 mechanism. If we know the configuration of the alkyl halide before reaction, we know that the configuration of the product will be the opposite. Conversely, if we determine that a nucleophilic substitution reaction proceeds with inversion of configuration, we conclude that its mechanism is S_N2.

Our picture of this reaction starts with a tetrahedral sp^3 carbon in the alkyl halide and ends with a tetrahedral sp^3 in the product. In the transition state the three bonds to carbon which don't react are approximately flat, it makes sense to regard the carbon atom as sp^2 hybridized at this point. One consequence of this is that the S_N2 mechanism is restricted to halides which are sp^3 hybridized at the reactive carbon. Carbons which are sp^2 hybridized at the halogen-bearing carbon do not react by this mechanism.

Kinetics, Alkyl Halide and Nucleophile Effects

Earlier we saw that the energy required to reach the transition state comes from the energy with which the nucleophile and the alkyl halide collide. The requirement for a collision also means that the frequency with which the nucleophile and the alkyl halide collide is important. This frequency is primarily controlled by concentration.

If the concentration of the alkyl halide is high, then there will be many opportunities for a nucleophile to collide with an alkyl halide molecule. The rate of the reaction will increase proportionately as the alkyl halide concentration is made higher. When this is the case the reaction is said to be first order in alkyl halide. Similarly an increase in the nucleophile concentration will result in a proportionate increase in the rate, so the reaction is also first order in nucleophile. Overall, the reaction is said to be second order. This can be summarized in the *rate equation*.

$$\text{Rate} = k[\text{RBr}][\text{Nu}^-]$$

It is the second order behavior (requirement for two molecules to collide in the critical transition state) which is designated by the "2" in S_N2

Since the bond between the carbon and the leaving group is being broken in the transition state, the weaker this bond is the lower the activation energy and the faster the reaction. This leads to the following reactivity order for alkyl halides

RI > RBr > RCl > RF

Practically, alkyl fluorides are not used for S_N2 reactions because the C-F bond is too strong. Often alkyl iodides are reactive enough to be difficult to store, so the the common choices for reactions are alkyl chlorides and alkyl bromides.

If we remember that the function of the nucleophile is to provide an electron pair to make a new bond, we can see a similarity between a nucleophile and a base. A Lewis base makes a new bond, typically to hydrogen, using its own electron pair. A nucleophile makes a new bond to carbon, using its own electron pair. As this suggests, good nucleophiles are typically strong bases. There are are other factors, but this is a good starting place and it reminds us to review base strengths, perhaps by reviewing Table 2.1 on p p 43 of Brown. Keep in mind that high pK_a numbers mean weak acids which have strong conjugate bases.

Next time we'll take a look at the other mechanism for nucleophilic substitution, the S_N1 mechanism. We'll also see how elimination reactions fit into this picture.

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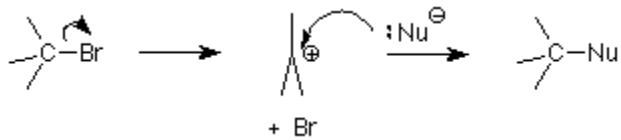
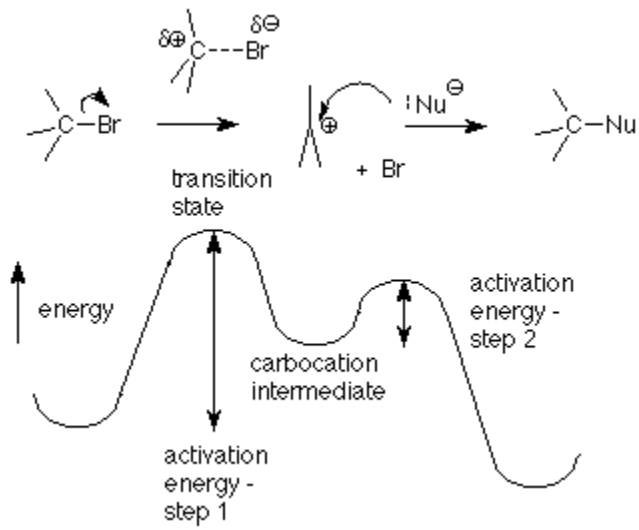
1.25: Elimination - E2 and E1

S_N1 Energy and Kinetics

Last time we saw an overview of the nucleophilic substitution mechanisms of alkyl halides. We examined one of these, the S_N2 mechanism in detail. Today we'll examine the other, the S_N1 mechanism, and then go on to look at elimination reactions, the major competition for substitutions. Here's the outline of the S_N1 mechanism:



Recalling what the "2" in S_N2 meant -- that the reaction was second order, two molecules had to collide to provide the activation energy needed to reach and pass through the transition state -- we can guess that the "1" in S_N1 means that only one molecule needs to be "activated" in order to reach the transition state. That molecule is the alkyl halide. The critical step in this mechanism is the first step, in which the bond between the carbon atom and the halogen leaving group is broken. The transition state for this step has the bond stretched far enough that the halide ion is balanced between leaving as a stable chloride or bromide ion or slipping back into a covalent bond.



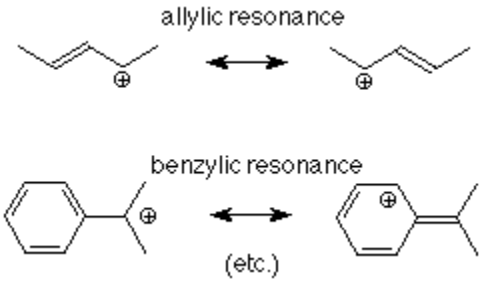
(The energy required to break this bond comes from random collisions with the solvent without the solvent reacting.) The activation energy for the first step is higher than for the second step, so the rate of the reaction is controlled by how many molecules get through the first step. Once a molecule is through the first step, it can react rapidly in the second step. We call the step which is slowest the "rate determining step." Notice that the rate determining step for this reaction doesn't involve the nucleophile. That means that changing the concentration of the nucleophile doesn't affect the rate. The only concentration which affects the rate is the concentration of the alkyl halide. We thus have a first order reaction:

$$\text{Rate} = k[RX]$$

This also means that the strength of the nucleophile -- its ability to use its electron pair to make a bond -- isn't important in determining how fast the reaction goes. It's not involved in the rate determining step, so it has no effect on the energy of that transition state.

Effect of Alkyl Group Structure

What does affect the energy of the rate determining transition state? If we examine its structure in more detail, we notice that there is considerable positive charge on the carbon atom and the carbon-halogen bond is nearly broken.



The nearly broken bond tells us that the effect of changing the halogen is the same as it was for the S_N2 reaction:

RI > RBr > RCl > RF

The substantial degree of positive charge on the carbon is important in explaining how the structure of the alkyl group affects the rate. A large number of experiments have established that the reactivity order for alkyl halides in the S_N1 mechanism is:

tertiary > secondary > primary > methyl

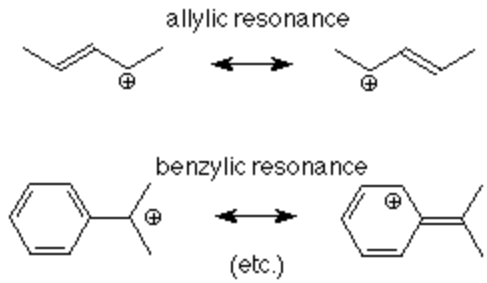
This is just the opposite of the order for the S_N2 reaction. The outcome of this contrast is that tertiary alkyl halides consistently use the S_N1 pathway. Primary and methyl alkyl halides use th S_N2 pathway. For secondary alkyl halides either pathway is possible, and we have to look at other information to make a decision.

The reactivity order tells us that the transition state for the S_N1 reaction of a tertiary alkyl halide has a lower energy than the transition state for a correspinding secondary alkyl halide. Perhaps the easiest way to understand this is to recognize that the transition state, with its substantial positive charge on carbon, is very much like the carbocation intermediate which is formed in the first step. Changes which make the carbocation intermediate, with its positively charged carbon, more stable will also make the transition state, with its nearly positively charged carbon, more stable.

The major thing which determines the energy of the carbocation intermediate is that it has only six electrons in its valence shell. It is an electrophile, a Lewis acid, and a seriously electron deficient molecule. The more electron density which can be shifted towards the positively charged carbon, the lower the energy. In a tertiary carbocation, there are three carbon atoms, each bonded to three other atoms, connected to the electron deficient carbocation carbon. This adds up to 18 electrons in the bonds adjacent to the carbocation, all of which can shift slightly to help neutralize the positive charge. Contrast this to the situation in a methy carbocation. Here there are no valence electrons other than the ones holding the hydrogens to the carbon, so there is a very poor supply of electrons to assist with lowering the energy of the carbocation.

While this discussion has focused on the carbocation intermediate with its full positive charge, the same principles apply in the case of the partial positive charge in the transition state. The more electrons there are in the near neighborhood, the more stable the transition state. There are more electrons available on the carbon atoms attached to a tertiarly carbocation center than there are on the hydrogens attached to a methyl carbocation center.

If there are pi bonds involved with a carbon attached to the carbocation carbon, the energy is reduced even more. Recall that pi electrons are less tightly bound than sigma electrons, so they are easier to move towards the electron deficiency. This can be symbolized in resonance terms:



The effect of this is that alkyl halides which have carbon-carbon pi bonds located one atom away from the carbon bearing the halogen are quite reactive in S_N1 reactions.

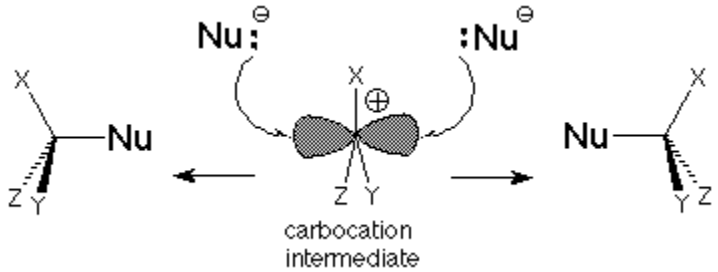
Stereochemical Outcome

The product of an S_N1 reaction is formed in the second step. This step starts with the carbocation intermediate, so let's look at its structure to see what we can learn from it. First, notice the distinction between an intermediate and a transition state. Remember that a transition state is at a maximum energy. Any slight change will cause it to fall from it's precarious perch and become either the product or the reactant of its step. In contrast, an intermediate is at an energy minimum so that most small changes only push it a little way up a hill from its lowest energy situation. It takes a substantial collision to provide it with the energy needed to reach a transition state so as to pass through and become a product. If the activation energy is fairly small, as it is with the second step of the S_N1 mechanism, the reaction may well be fast, but it doesn't occur with every small wiggle as it does with a transition state.

Another way to say this is that a transition state has a very, very short lifetime, while an intermediate may exist for micro- or milliseconds, which is a long time and provides opportunities for many collisions with other molecules.

One outcome of this is that the carbocation intermediate "lives" long enough for a nucleophile to approach it on either face of the molecule. The carbocation is flat with 120° angles between its three bonds. That means that it is trigonal like the carbon of a carbonyl group and is sp^2 hybridized. The "empty" orbital which we can associate with the electrophilic characteristics of the carbocation is a p orbital.

If the carbocation intermediate has the opportunity to engage in many collisions with potential nucleophiles, there is an equal chance that a nucleophile will attack at one lobe or the other of the p orbital. If there are three different groups attached to the carbocation center, the nucleophile will provide a fourth and generate a stereogenic carbon. Equal quantities of the two enantiomers will be expected so that the product mixture will not be optically active.

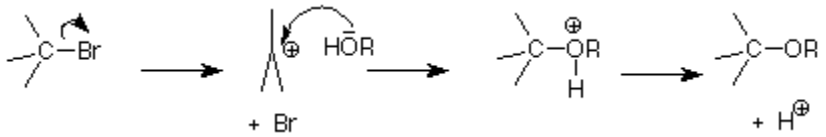


This is a somewhat idealized situation, since in practice the halide leaving group is "loitering" near one lobe of the p orbital. This makes reaction with the nucleophile easier on the other lobe, so there is usually some net inversion. The stereochemical oucome of the S_N1 is not as clearcut as that of the S_N2 mechanism's inversion, but it is still a distinguishing feature of the mechanism, one which can be used to decide which mechanism is operating in a particular reaction.

Solvolysis

The fact that the nucleophile is not involved in the rate determining step of an S_N1 reaction also means that it proceeds well with a relatively weak nucleophiles. When the nucleophile is also the solvent, the reaction is called "solvolysis." Solvents like water and

alcohols are particularly useful here, because they provide both a nucleophilic pair of electrons on the oxygen atom of the OH group and a fairly polar solvent which helps to stabilize the strongly polar transition state. The latter effect is much like the way in which a polar solvent dissolves a very polar substance like salt by surrounding its charged ions with polar solvent molecules.



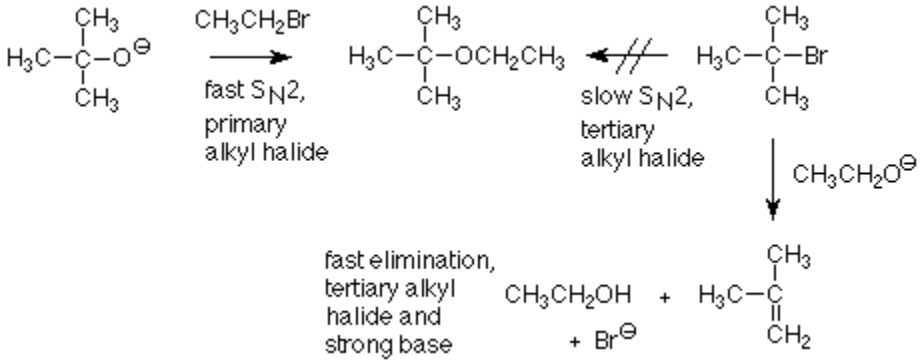
This process resembles the way in which an alcohol or water might attack the electrophilic carbon of a carbonyl group after an acid had added an H^+ to the oxygen. Remember that in these reactions the neutral nucleophilic atom attacks first; then the H^+ is lost.

A summary of the important differences between the S_N1 and S_N2 mechanisms is in Table 7.5 (Brown, p 189).

Competition with Elimination

One of the things we dealt with last time was the fact that nucleophiles are also Lewis bases. One outcome of this is that the same atom or group can attack a carbon in an S_N1 or S_N2 reaction -- behaving as a nucleophile -- or attack a hydrogen atom -- behaving as a Lewis base. The latter attack can lead to an elimination reaction. We will look at elimination reactions in more detail in a week or so, but we can usefully examine them as competitors for S_N1 and S_N2 reactions just now.

When we first learned about the Williamson ether synthesis, we learned that it works best when the alkyl halide is primary. We now understand that as a characteristic of the S_N2 mechanism -- primary alkyl halides react faster than secondary or tertiary alkyl halides. However, a patient person might suggest that even a slow S_N2 reaction might succeed if we were willing to wait a while. What defeats this strategy is that the alkoxide ion can also react as a base. This elimination reaction (an E_2 reaction for future reference) is fast enough that it uses up the secondary or tertiary alkyl halide long before the much slower S_N2 reaction produces any useful amount of product.

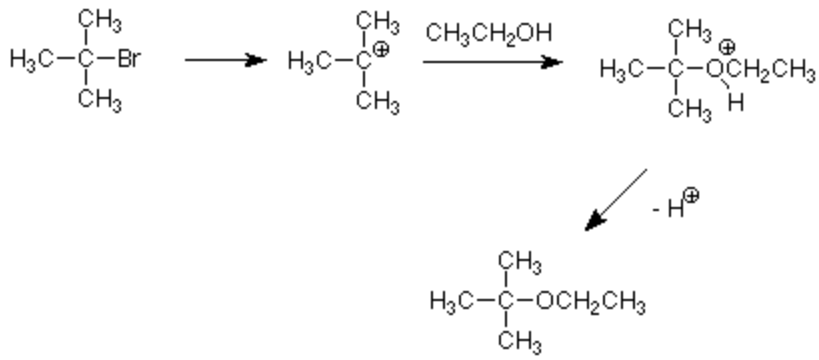


Elimination reactions are always potential competitors for substitution reactions. The key factors which alert us to situations favorable to eliminations are:

1. An alkyl halide which is slow in S_N2 reactions, i.e., tertiary and secondary alkyl halides.
2. The presence of a strong base like an alkoxide or hydroxide ion.

These conditions will typically produce much more elimination product (an alkene) than substitution product.

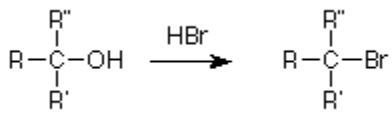
Can we use an S_N1 pathway to avoid this difficulty? Yes -- and the key here is that since the rate of an S_N1 reaction is not sensitive to the concentration or strenght of the nucleophile we can avoid the strong bases which promote elimination. Solvolysis of a tertiary alkyl halide using an alcohol as both nucleophile and solvent can make an ether very effectively.



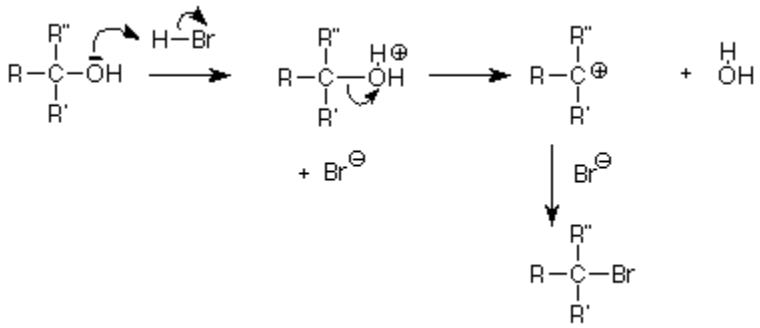
Of course, this is only possible when the desired nucleophile can be used as a solvent as is the case for alcohols and water.

S_N1 and S_N2 Reactions of Alcohols

To finish up today, let's revisit some reactions of alcohols and see if we can use the S_N1 or S_N2 pattern to understand them a little better. Recall that a useful method for making an alcohol into an alkyl halide was to treat the alcohol with the hydrogen halide, particularly when the alcohol was tertiary:



This looks like a nucleophilic substitution and since the alkyl group is tertiary, the S_N1 pathway through a carbocation intermediate looks like a good guess. We can also identify the nucleophile as the bromide ion (Br^-), but what about the leaving group? The obvious answer is that the OH^- serves as the leaving group, but this is worrisome since we would be making a strong base in the presence of an acid. The solution appears when we remember that the unshared electron pairs on the alcohol oxygen are also weak bases. They can accept a proton (H^+) from the strong acid HBr. When this is done, the leaving group is water, a weak base.



When the OH group of an alcohol is replaced by another nucleophile, we can be sure that the OH group is first converted to a good leaving group before the C-O bond is broken. That is the function of the H^+ in an acid, the SO_2 part of thionyl chloride and the phosphorus in PBr_3. We won't concern ourselves with the details of these processes, but we can notice that the need to make the OH group into a good leaving group is the same whether the reaction is S_N1 as we would expect for a tertiary alcohol or S_N2 as we would expect for a primary alcohol.

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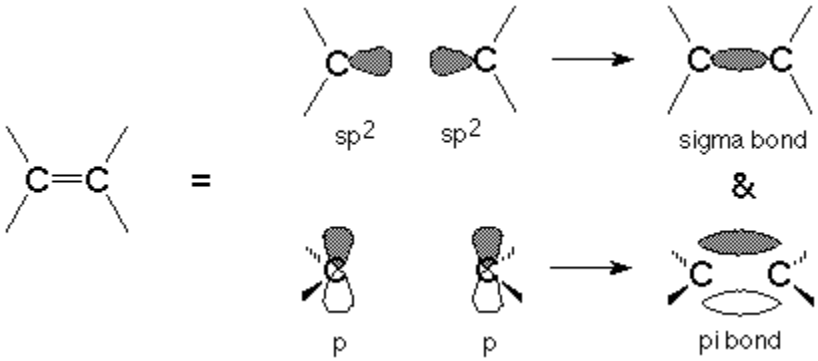
1.26: Alkenes and Alkyne Structure

Alkene Double Bond Structure

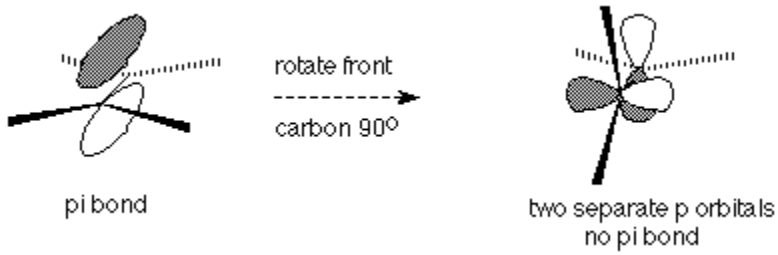
Today we'll begin by looking at the structural characteristics of alkenes, the products of elimination reactions. Then we'll return to the topic of elimination reactions and examine their reaction mechanisms in more detail.

The functional group of an alkene is the carbon-carbon double bond. In common with the double bond we studied at the beginining of the course (the carbon-oxygen double bond in the carbonyl group) this double bond consists of a sigma bond, viewed as "end to end" overlap between sp^2 hybridized orbitals on the carbon atoms, and a pi bond, viewed as "side to side" overlap between the p orbitals on the same carbon atoms.



Stereoisomerism

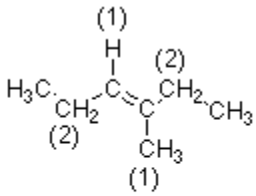
The presence of the pi bond in the alkene functional group has two important consequences. First, the reactions of alkenes are essentially the reactions of this pi bond. We'll look at these reactions in some detail next time. Second, the pi bond means that rotation of one end of the double bond relative to the other requires so much energy that it does not happen at ordinary temperatures. This is because such rotation would destroy the "side to side" overlap of the p orbitals which make up the pi bond and would effectively break the pi bond. Breaking bonds requires energy input.



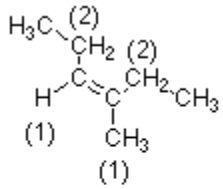
The result of this can be seen in the fact that there are two different substances which have the same "connectivity" structure and are both called 2-butene. (Alkene naming is treated in Section 5.2 of Brown). A sample of one of these compounds does not become the other, since to do so would require breaking the pi bond and there isn't enough energy available to do that. Since the difference is one of spatial arrangement, this is a type of stereoisomerism.

The absence of rotation about the double bond explains why there are two different 2-butene molecules. These differences must be reflected in the names given to the compounds. If there are two identical groups, one on each carbon involved in the double bond, then we can use the terms *cis* (which means that the two identical groups -- hydrogens or methyls in this case -- are on the same side of the double bond) or *trans* (means that the two identical groups are on opposite sides of the double bond).

This system breaks down when there are not identical groups on the two carbon atoms. In this type of situation we use a system which is derived from the same ranking rules we used in assigning **R** and **S** configurations to stereogenic carbon atoms. To use this system we look at each of the two doubly bonded carbons independently. For one carbon we examine the two groups or atoms which are connected to it by single bonds. We use the ranking rules to decide which of these groups or atoms has the higher ranking. Then weapply the same process to the second carbon atom. If the higher ranked group on one carbon is on the same side of the double bond as the higher ranked group on the other carbon, then the designation is **Z** (from the German word "Zusammen"). If the higher ranked group on one carbon is on the other side from the higher ranked group on the other carbon, the designation is **E** (from "Entgegen"). Here's an example:



groups ranked higher (2) are on opposite sides of the double bond:
E-3-methyl-3-hexene

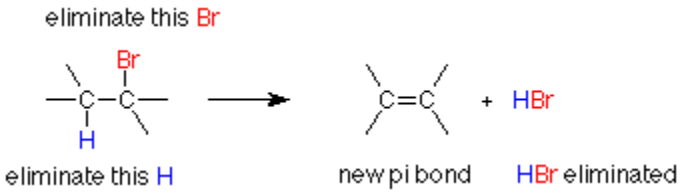


groups ranked higher (2) are on the same side of the double bond:
Z-3-methyl-3-hexene

Like all naming situations, you learn by doing problems, so do the naming problems listed in the internet syllabus and bring up points that need clarification. See Section 5.2C in Brown for further explanation.

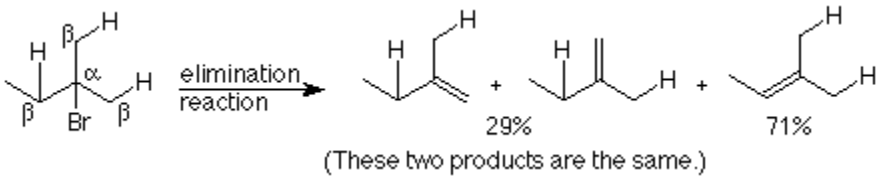
Elimination Reactions

Now let's turn our attention to making this double bond. The reactions which do this are called elimination reactions, because two atoms or groups are "eliminated" from an alkyl halide or alcohol so that the double bond can be formed. A formal example is:



Notice that the two atoms eliminated were attached to adjacent carbon atoms. This must be so if we are to make an new pi bond between those atoms. If the atom bearing the bromine is designated the alpha carbon atom, then the one next to it is a beta carbon atom. These eliminations are often called beta eliminations.

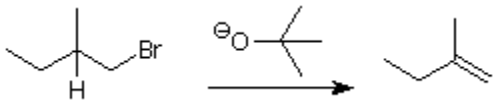
In many cases there are more than one beta carbon atom. This can lead to situations where more than one beta-elimination product is possible. Here's an example:



Notice that the major product is the one which has the most substituents (non-hydrogen atoms, in this case, methyl groups) attached to the doubly bonded carbons. This is generally the case, and it is called Zaitsev's rule after Alexander Zaitsev the 19th century Russian chemist who first proposed the general statement. *In elimination reactions the major product is the one in which*

the maximum number of substituents is attached to the doubly bonded carbons. (Notice that the carbon skeleton is not changed in this reaction.) Zaitsev's rule enables us to predict which of two or more possible beta-elimination products can be expected to predominate.

Often we can choose an alkyl halide such that only one beta-elimination product is possible. For example, if we wanted to make the "minor" product from the example above, we might choose the following approach:



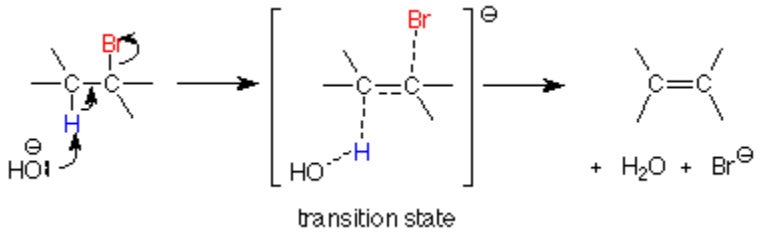
Here we've chosen an alkyl halide which has only one beta hydrogen, so it can give only one alkene in a beta-elimination reaction. We've also chosen a base which is bulky to slow down the competing substitution reaction.

The E_2 Mechanism - Dehydrohalogenation

The most important elimination reaction mechanisms are closely related to substitution mechanisms. The first one we'll study is called the E_2 mechanism, E for elimination and 2 for second order. In studying the S_N2 mechanism we learned that second order meant that the concentrations of both the alkyl halide and the nucleophile were important in determining the rate of the reaction.

rate = k[RX]{Nu]

We interpreted this to mean that the alkyl halide and the nucleophile must collide in order to form the transition state, which smoothly completes the reaction and becomes the product. The same interpretation occurs here. The important difference is that the reactant we considered to be a nucleophile attacking carbon in the S_N2 reaction is now acting as a base and attacking a beta hydrogen.



If we follow the curved arrow notation we see that formation of the O-H bond releases the C-H bonding electrons to begin to form the new C-C pi bond. The C-Br bond breaks at the same time to provide room for the new C-C pi bond to develop. All of these bonding changes occur in one step. The transition state (top of the energy hill) has three partial bonds in it. Since it includes both the alkyl halide and the base, it is consistent with the need for them to collide in order for the reaction to occur and with the second order kinetic behavior.

Since the transition state structure has a partial broken C-Br bond just like the partially broken C-Br bond in the S_N2 transition state, we expect that changing from one halide to another will produce the same change in rate that we saw for the S_N2 mechanism:

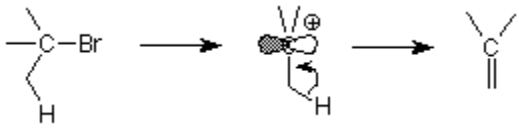
RI > RBr > RCl > RF

This is what is observed.

Since the base plays such an essential role in this mechanism, it is very likely that the elimination reactions we considered to be unwanted complications when we were studying S_N2 reactions were in fact E_2 reactions. Recall that we learned that these eliminations are most prevalent when we have strong base (essential for an E_2 mechanism) and a tertiary alkyl halide (which would make the competing S_N2 mechanism very slow). The combination would be good for a fast E_2 elimination and a slow S_N2 substitution and would predict lots of elimination product.

The E_2 mechanism is very closely related to the S_N2 mechanism. In much the same way, there is an E_1 mechanism which involves

the same first step and the same carbocation intermediate as the S_N1 mechanism. Here's the pattern:



Notice that the first step is identical to the first step in the S_N1: dissociation of a halide ion to form a carbocation. The E_1 mechanism continues by loss of a proton and the formation of a new pi bond. The first step determines how fast the reaction goes. The relative proportions of substistution and elimination product are determined by the relative rates of nucleophilic attack on the carbocation carbon (substitution by S_N1) or loss of the proton (elimination by E_1).

Since the rate of reactions proceeding by this mechanism is determined by the rate at which the carbocation is formed, the effect of changing alkyl group structure is the same as it was for the S_N1 mechanism. (Notice that a methyl halide only has one carbon and cannot make a double bond.)

tertiary > secondary > primary

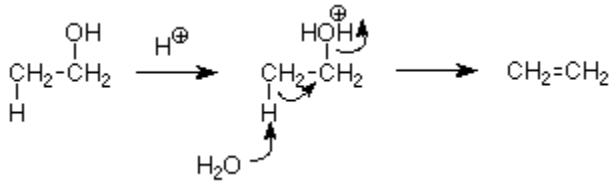
Notice that the rate of this reaction does not depend upon the base concentration. The base is not involved until after the carbocation is formed in the rate determining step. This means that the E_1 mechanism is likely to be used where no strong base is present.

The E_1 Mechanism - Dehydration

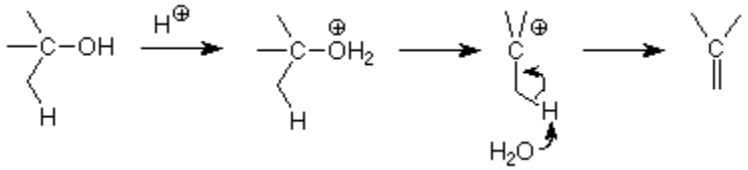
Alcohols can also be used to make alkenes by elimination reactions. We know that the OH^- group is a poor leaving group (it's a strong base and strong bases make poor leaving groups). To permit an alcohol to react by breaking the C-O bond, the OH group must first be changed into a better leaving group. This can be done using an acid to place a proton on the OH oxygen. This makes an H_2O of the OH, and since water is a much weaker base than OH_-, it is a much better leaving group.

Once the alcohol has been protonated, what happens next depends upon the alkyl group structure and what else is in the reaction mixture. If there are bromide or chloride ions present (perhaps because the acid used was HBr or HCl) then those bromide or chloride ions can serve as good nucleophiles and complete a substitution reaction. If we have used only a small, catalytic, amount of an acid such as sulfuric acid, then there is only a small amount of bisulfate ion present to act as a nucleophile. The reaction is more likely to result in elimination. One important factor in this outcome is heating the reaction. Alkenes have lower boiling points than alcohols, so once an alkene is produced, it boils out of the reaction mixture and is collected by distillation. Removing the alkene as it is formed protects it from other possible reactions.

If the alcohol is primary an elimination uses the E_2 pathway, primarily since forming primary carbocations is so slow. Ethylene can be made this way. Notice the close resemblance to the E_2 mechanism for alky halides, with the major difference that no strong base is involved here since a strong base cannot exist in an acid solution.



Secondary and tertiary alcohols are more likely to use the E_1 pathway. Here's a typical mechanism:



Like alkyl halide dehydrohalogenation (elimination), dehydration of alcohols follows Zaitsev's rule -- the more highly substituted alkene is the major product.

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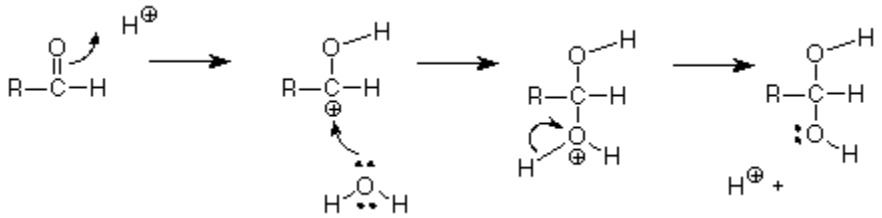
1.27: Electrophilic Additions

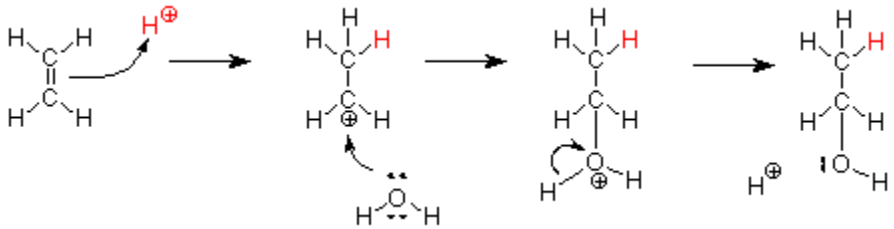
In the functional group of an alkene - the carbon-carbon double bond -- the most readily available electrons are those in the pi bond. They are farther from the nuclei than the electrons in a sigma bond, so they are more readily attracted to an electrophile if one approaches. Another way to say this is that the pi electrons are weakly nucleophilic. We'll begin by looking at a few reactions which begin with the attack of an electrophile on the pi part of the double bond.

First, let's briefly review a reaction of the carbonyl group with an electrophile. The acid catalyzed addition of water to an aldehyde is one such reaction discussed earlier. The mechanism is:



The first step is electrophilic attack on the carbonyl pi bond by the electrophilic, acid H^+. This step makes a carbocation, which is then attacked by the weak but very abundant nucleophile water. (*Do not use OH^- as the nucleophile. There is very little OH^- in an acidic solution!*) The final "mop-up" step gives the product and returns an H^+ to regenerate the catalyst.

Now let's apply this same mechanism to the addition of water to ethylene, the smallest alkene.

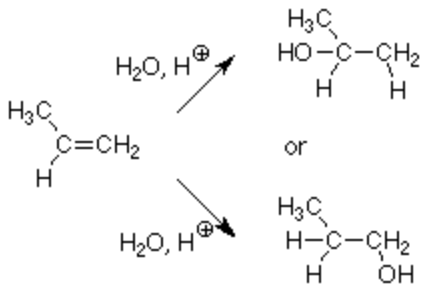


Notice that the steps are the same and that the last two steps (what happens to the carbocation) are the same steps which occured in the S_N1 hydrolysis (solvolysis in water) of an alkyl halide.

These steps -- first an electrophile attacks the pi bond to form a carbocation, second a nucleophile attacks the carbocation -- are the key steps in the most important reactions of alkenes, electrophilic addition reactions. The first step is the slow one, so it is the one which determines the rate of the reaction. This has very important consequences when we introduce a slight complication into the structure of the alkene.

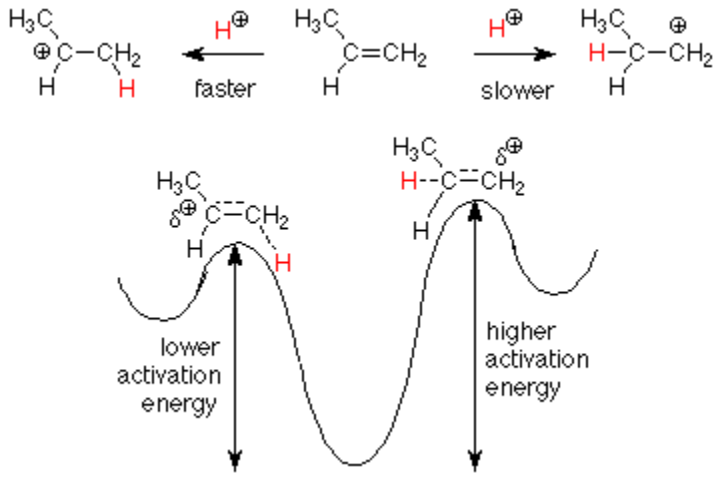
Orientation - Markovnikov's Rule

What happens if we apply this reaction to an alkene like propene? (Such an alkene is called "unsymmetrical" since the substitution patterns on the two alkene carbons are different.) There are two possible products since the OH could wind up on either the CH_2 carbon or the CH_3CH carbon.

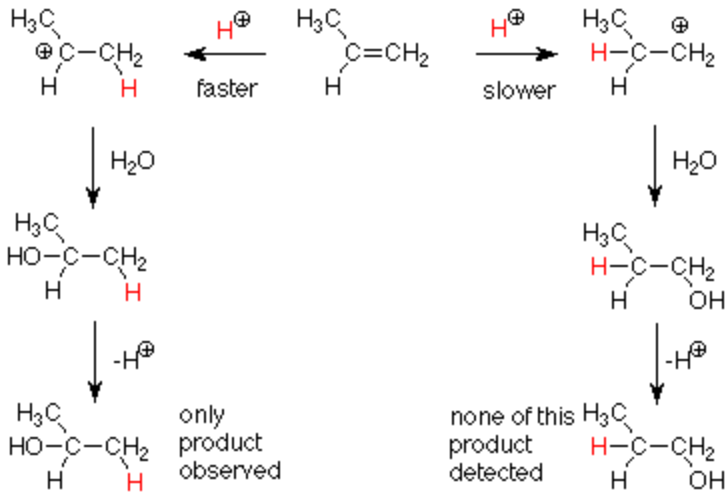


We may reasonably expect that the product which is formed fastest will be the one which predominates in the product mixture. In fact, if one product is formed more than 100 times faster than the other, it is the only product we will observe in a practical sense. This means that predicting which product is formed comes down to predicting which product is formed faster. In turn, this question becomes "which product is formed by a pathway with a lower activation energy?" We estimate relative activation energies by looking at transition state structures. The pathway with the lower energy transition state will be the faster pathway. It will produce more product in a given time than the slower pathway, so its product will be found in the greater amount.

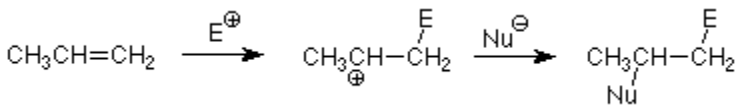
How do we make such a prediction? We know the mechanism, so we can apply it to the pathways which would lead to our potential products. Fortunately, the rates associated with these two pathways are determined by their first steps, so we need only concern ourselves with the activation energies for those steps.



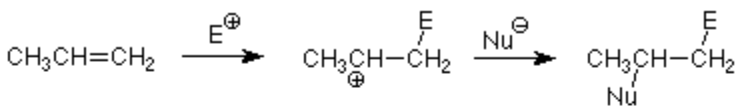
We know that a secondary carbocation (on the left) is more stable (has a lower energy) than a primary carbocation (on the right). We have explained this by saying that the the electrons in a methyl group are better at partially relieving the carbocation's electron deficiency than the relative lack of electrons around a hydrogen. Since the transition states for these two steps are also electron deficient partially formed carbocations, we would expect the same effects to prevail in the transition states. This tells us that the reaction to the left will have the lower activation energy and will occur faster. We then expect to see the product in which the attacking H^+ is attached to the less substituted carbon and the OH is attached to the more substituted carbon.

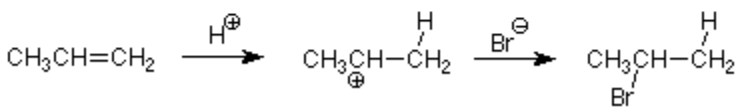


More generally, the electrophile attacks the less substituted carbon atom in the first step and the nucleophile attacks the more substituted product in the second step.



We can use this to predict which product will be formed in an electrophilic addition to an unsymmetrical alkene. All we have to do is identify the electrophile and the nucleophile in the compound which is adding. For example consider the addition of HBr. The HBr bond is polarized so that the H is positive and the Br is negative. The H^+ is thus the electrophile and the Br- is the nucleophile. Application of the pattern above gives us:

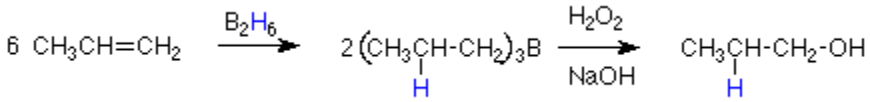




Historically, this pattern was observed by Vladimir Markovnikov in 1870, long before the mechanism was understood. The generalization that hydrogen adds to the carbon with the most hydrogens (another way to say what is in bold above) is known as Markovnikov's rule. Common applications include the additions of HBr and water (discussed above) and HCl.

Hydroboration-Oxidation

Notice that we cannot make a primary alcohol by adding water to any other alkene than ethylene by an electrophilic addition reaction as outlined above. An alternative reaction sequence which does achieve this result was developed about 40 years ago by H. C. Brown. It is outlined as follows.



We will focus our attention on the first step. We know the product of this step, so we can identify the atoms which are acting as the

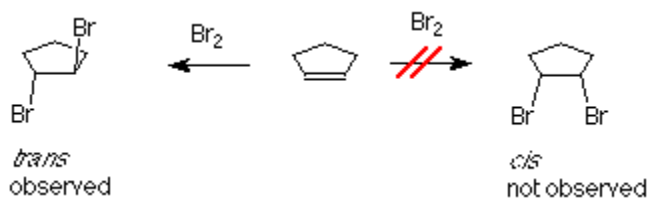
electrophile and the nucleophile. The boron adds to the least substituted carbon, so it is acting as the electrophile. The hydrogen adds to the most substituted carbon, so it is acting as the nucleophile. Does this make sense? We have seen the B-H bond act this way before in the reduction of ketones and aldehydes by BH_4^- (in sodium borohydride). There the hydrogen acted as a nucleophile and we explained that by saying that hydrogen is more electronegative than boron. We can understand the reaction of boron as an electrophile if we consider that B_2H_6 dissociates into two molecules of BH_3. A quick check of the electronic configuration of BH_3 shows that the boron has an empty 2p orbital, so BH_3 has the structural characteristics needed to qualify it as an electrophile.

Practically, the overall result of this reaction sequence is to add water to an alkene double bond in an orientation which is opposite to that predicted by Markovnikov's rule. For that reason it is referred to as an "anti-Markovnikov" addition. It is a powerful method for making primary alcohols and other alcohols where it is desired to locate the OH group on the less substituted carbon atom.

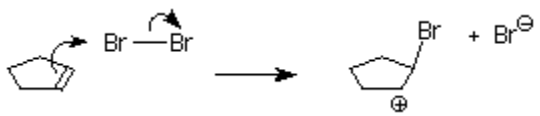
Halogen Addition

Halogen *molecules* such as Cl_2 and Br_2 also add to alkene double bonds. Here we need not be concerned with orientation since the two ends of the adding molecule are identical, but the electrophilic addition mechanism helps us understand another characteristic of this reaction, its stereochemistry.

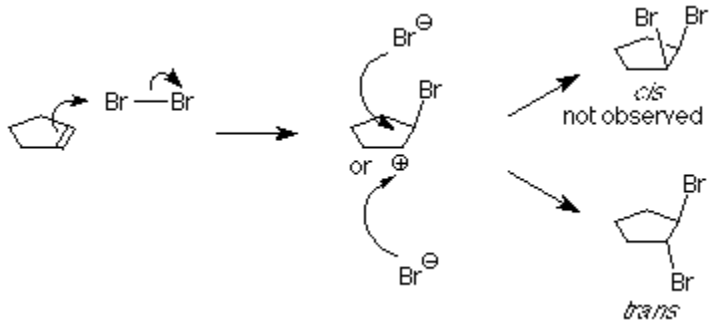
If bromine is added to cyclopentene, we might anticipate two products which differ in how the bromine atoms are geometrically related to each other. If the two bromines are on the same face of the ring, the compound is called *cis*. If they are on opposite faces, the compound is called *trans*. The experimental result is that only the *trans* product is formed.



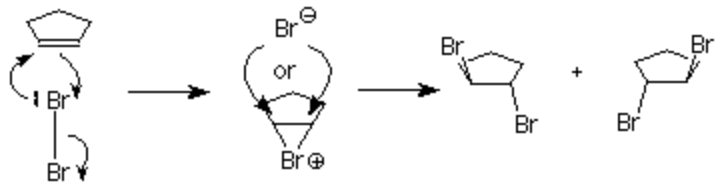
One of the bromine atoms is acting as an electrophile. If we apply the usual mechanism, it's first step it would go like this:



As we learned in our study of S_N1 reactions, carbocations are attacked by nucleophiles on both faces. If a carbocation is present in this system, we'd expect to find both the *cis* and *trans* products.



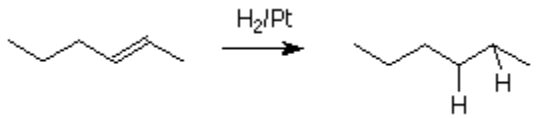
This is not what happens when the experiment is done, so we conclude that the carbocation is not present. Something else is happening, something which prevents the nucleophilic bromide ion from attacking the face of the carbocation which already is attached to the first bromine. We understand that by envisioning that the electrophilic bromine atom attaches itself to *both* alkene carbon atoms. One bond is made using the electrons from the pi bond, and the other is made using an unshared electron pair from the bromine. This results in a new ring formed from the bromine and the two alkene carbon atoms. It is called a "bromonium" ion.



Attack by the nucleophilic bromide ion on the bromine in this ring would only result in cyclopentene and bromine, so no reaction would occur. Attack by the bromide ion on the either of the alkene carbons would be like an S_N2 reaction. The attacked carbon would invert, and the product would have the *trans* configuration. (Notice that there are two such products, which are enantiomers, so we get a racemic mixture.)

Hydrogenation

There is another reaction of alkenes, hydrogenation, which deserves mention but which is not related to the electrophilic addition mechanism. Hydrogenation is the addition of molecular hydrogen ($H_2$2) to the alkene double bond. This converts a simple alkene into an alkane.



Hydrogenation reactions are carried out in the presence of a solid catalyst such as finely divided platinum (Pt) metal. The reaction occurs on the surface of the metal and involves temporary bonding of both the alkene and the hydrogen molecule to the atoms on the metal surface.

Hydrogenation is important in the conversion of highly unsaturated (many double bonds) fats to fats with fewer double bonds. This is done so that the product will have a higher melting point than the reactant and be more convenient as a dietary spread for bread. Also, the products are less susceptible to reaction with oxygen and do not turn rancid as rapidly.

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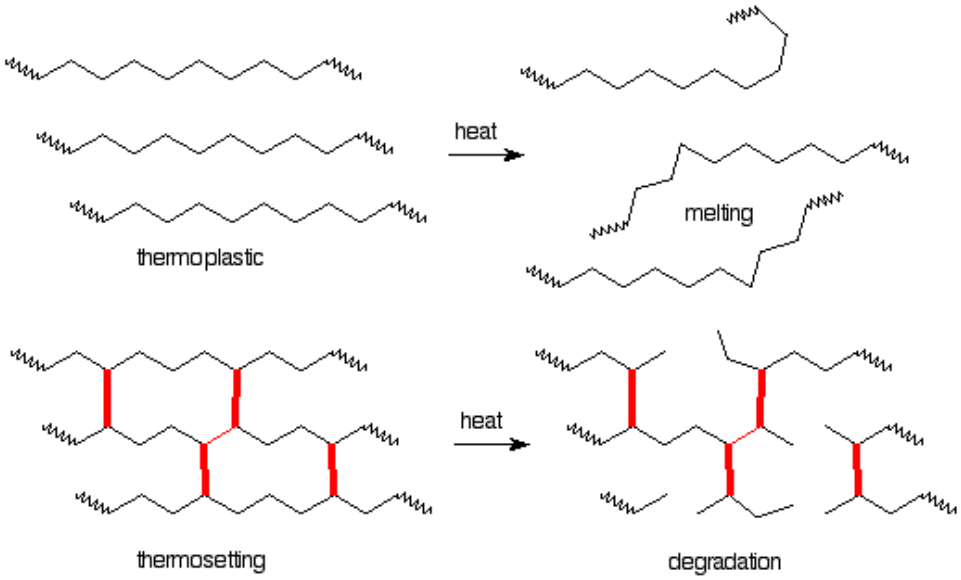
1.28: Polymers

Polymers - Structure and Response to Heat

Let's begin by noticing some important real-world characteristics of polymers. While they all contain molecules with very long chains, there are some important differences between the properties of different types of polymers. Most polymers are formed into the desired shapes after softening or melting by heating. Some, like the familiar polyethylene and polystyrene, may be melted and reshaped again and again. These are called *thermoplastic* polymers.

Others char or burn when reheated. These are called *thermosetting* polymers. Examples include Bakelite and vulcanized rubber. The structural difference between these polymers is that the thermosetting polymers have crosslinks between the chains and the thermoplastic polymers do not. When a thermoplastic polymer is heated the chains are free to move past each other making the sample less rigid and eventually melting it. This cannot happen with a thermosetting polymer, since its chains are locked together by the cross links. The energy from the heat must eventually go into breaking bonds which leads to decomposition of the polymer.

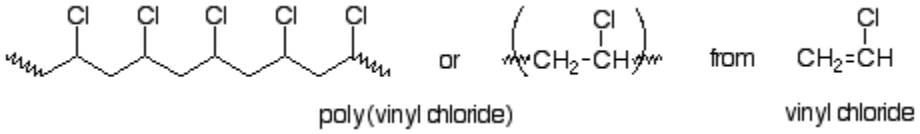
This schematic view suggests the difference:



We noticed crosslinking earlier when we saw how the disulfide crosslink formed by oxidation of the SH group in cysteine was important in maintaining protein structure.

Repeating Units and Monomers

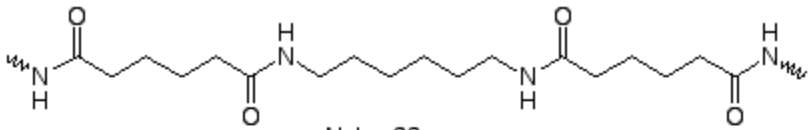
Since polymers are made by linking together many identical small molecules, there are repeating units in polymers. Here's an example, polyvinyl chloride, in which the repeating unit is -CH_2-CHCl-.



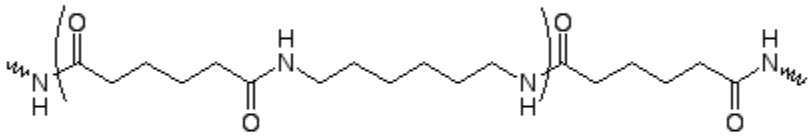
In poly(vinyl chloride) the repeating unit comes directly from the end-to-end linking of many vinyl chloride molecules. A molecule from which a polymer is made is called a monomer. Each vinyl chloride monomer molecule contributes a CH_2 group joined to a CHCl unit by a single bond. This single bond is a remnant of the double bond which joined those groups in the vinyl chloride molecule. This is just what happens in an addition reaction of an alkene. We'll see how an addition reaction leads to such polymers

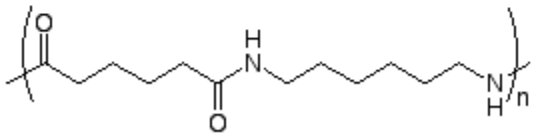
in a few paragraphs.

Repeating units can also be made from two monomers. Here's an example:



Nylon 66





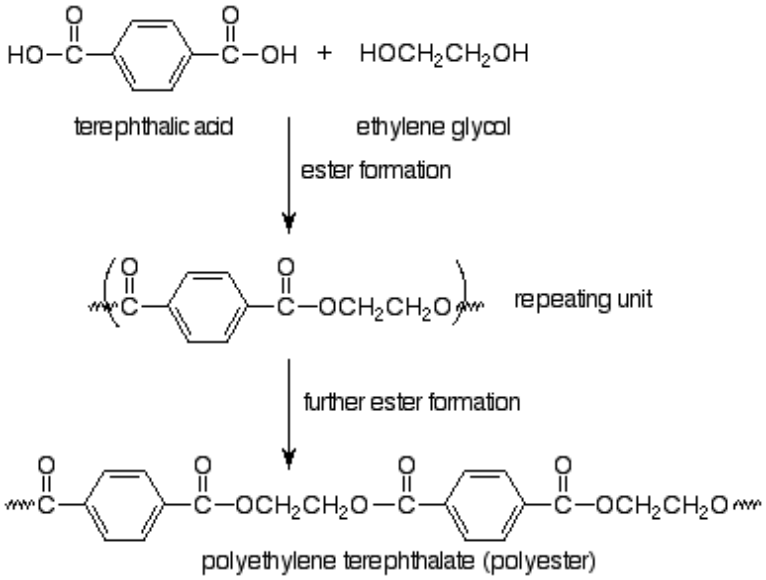
repeating unit

We notice that the repeating unit is linked to the rest of the chain by amide functional groups, and that the repeating unit contains an amide group. We can deduce the structrure of the monomers by imagining the compounds which might be used to make the amide group. In the industrial process these are a dicarboxylic acid (adipic acid) and a diamine (1,6-hexanediamine). These form a salt when dissoved in alcohol. The salt is heated at 250° under pressure to form the amide bonds. Nylon 66 is the result.

Step-Growth Polymers

Polymers formed in this way, where both ends of the growing chain have functional groups which can react with a monomer or with the appropriate functional group on another chain, are called step-growth polymers. Let's look at another step-growth polymer, but this time we'll look at the monomers and propose a structure for the polymer that would result.

The monomers are a dicarboxylic acid (terephthalic acid) and a dialcohol, also called a diol (ethylene glycol). We immediately recognize that these monomers can make an ester, so that we expect our polymer to be linked by ester functional groups. The resulting polymer is called polyethylene terephthalate and is the common polyester of plastic pop bottles and polyester fabrics.



Notice that in choosing how to represent the repeating unit in step-growth polymers we have picked the particular repeating unit (out of several possibilities) which is linked to the rest of the polymer through functional group bonds. In the case of Nylon, the functional group bond is an amide bond, so Nylon is a polyamide (in that way like a protein). The term polyester also puts our focus on the functional group which is made in the polymerization reaction. Step-growth polymerization involves normal functional group reactions. Polymers result because the monomers have two functional groups per molecule.

Chain-Growth Polymers

Polymers resulting from additions to alkenes are chain-growth polymers. In these processes each addition step results in a longer chain which ends in a reactive site. The mechanism of each addition step is the same, and each addition step adds another monomer to extend the chain by one repeating unit.

Each step in this polymer formation is an addition to an alkene. The mechanism is in most cases a *free radical* addition. In free radical reactions the pi pair of electrons separates. One of these electrons pairs with an electron from the attacking reagent to form a sigma bond with one of the alkene carbons. and the other electron remains attached to the other alkene carbon. (Curved arrows with only one "barb" on a point are used to follow the path of a single electron in the same way that "double-headed" arrows follow the path of an electron pair.) Intermedates with an unpaired electron are called free radicals, so this step can be described as adding a free radical to an alkene to lengthen the chain by two carbons and generate a new free radical. In its turn this new free radical can add to another molecule of monomer and continue the process.

A free radical (R·), with
and unpaired electron.
It comes from an
initiator which is used
to start the reaction

$R\cdot$

Addition to ethylene to form a new free radical,

$$R\cdot \quad CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2\cdot$$

Which adds to a second molecule of ethylene.

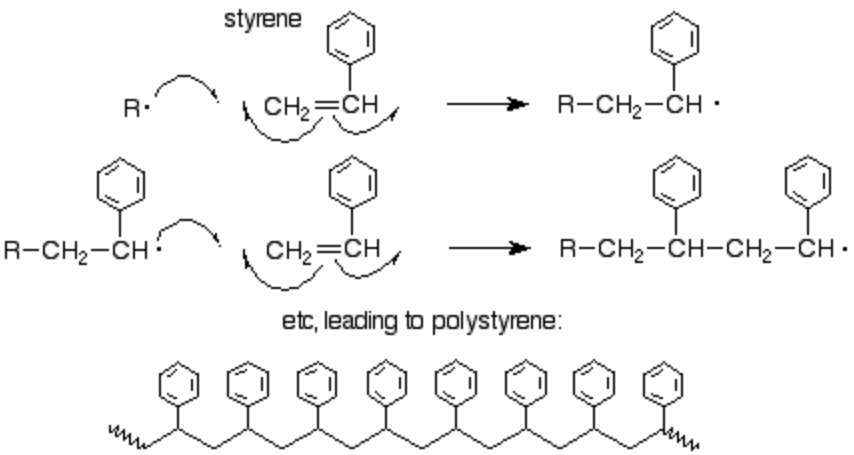
$$R{-}CH_2{-}CH_2\cdot \quad CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}CH_2\cdot$$

Repetition of this process leads to a growing chain of polyethylene.

$$R{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2\cdot$$

The most important monomers for this process are ethylene (which makes the polymer polyethylene) and substituted ethylenes like vinyl choride (polyvinyl chloride), styrene (phenylethylene, polystyrene), methyl methacrylate (Plexiglas), and acrylonitrile (cyanoethylene, acrylic fibers). Table 15.1, p 427 in Brown lists the structures of these monomers, from which you can deduce the structures of the polylmers.

We might ask about the orientation of attack of a radical on a substituted ethylene (vinyl) monomer. It has been shown that the orientation is the same as it is for an electrophilic addition, that is, the free radical attacks the less substituted of the two alkene carbons so as to produce the new free radical at the more substited carbon. Here's an example for styrene:



Other methods of polymerization are also known. The most important is the Ziegler-Natta polymerization which uses a combination of $TiCl_4$ and an alkyl aluminum compound such as $Al(CH_2CH_3)_3$. This process is discussed in more detail in Sec. 15.5B of Brown.

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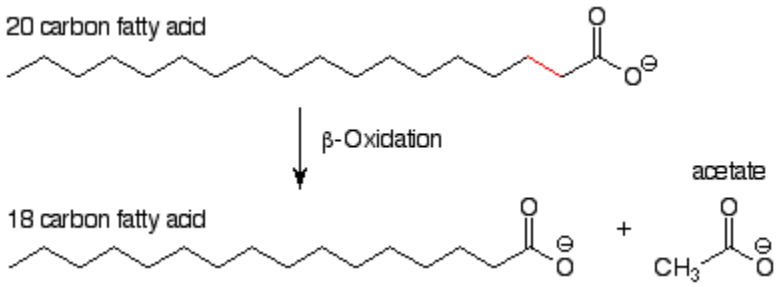
1.29: Metabolic Organic Reactions

Beta-Oxidation of Fatty Acids

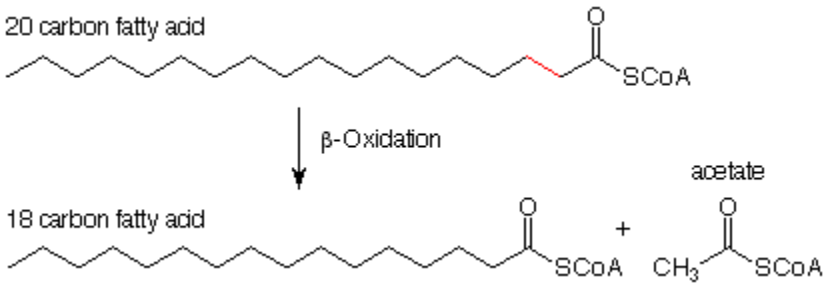
Today we're going to examine a selection of processes which occur in metabolism. We will focus on comparing these reactions to reactions we have already studied. In particular we will see that the reactions which break carbon-carbon bonds are just reverse versions of the aldol and Claisen condensations which we have studied earlier. Keep in mind that while we are looking for connections between these reactions and familiar organic reactions, all steps in these schemes are catalyzed by enzymes.

The two processes we are going to study are both *catabolic* processes, that is, they are processes that break down and oxidize larger molecules to produce smaller molecules and energy. The first, beta-oxidation, is a key part of the process by which fatty acids are broken down to acetate. [Acetate is the conjugate base of acetic acid. Since a neutral pH is more basic than the pK_a of acetic acid (~5), in neutral solution acetic acid is predominantly ionized and acetate is the major form present.] The overall scheme of beta-oxidation looks like this:

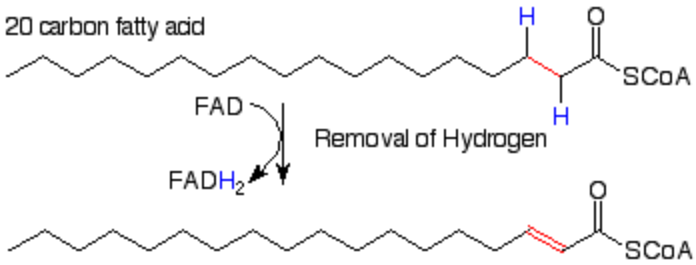


From this we can see that the outcome of a beta-oxidation "event" is that two carbon atoms are cleaved from a fatty acid. The bond broken is between the alpha and beta carbons. (This accounts for the term "beta-oxidation.") The gamma carbon shows up in the product as a carboxylic acid. This carboxylic acid, two carbons shorter than its "parent," can be shortened by another trip through the beta-oxidation process, with the production of another molecule of acetate and a new fatty acid, again two carbons shorter. That the reactions all occur at the carboxylic acid end of the molecule rather than at the CH_3 end is not surprising, since a fundamental idea of organic chemistry is that reactions occur at functional groups rather than elsewhere.

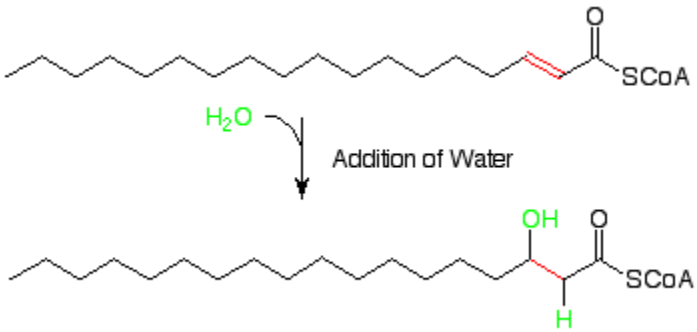
Prior to the commencement of the actual beta-oxidation cycle, the carboxylic acid end of the fatty acid is esterified with the SH group of coenzyme-A. This reaction is discussed in more detail in Sec 20.3A in Brown. Here is the scheme as it more realistically looks with the coenzyme-A included.



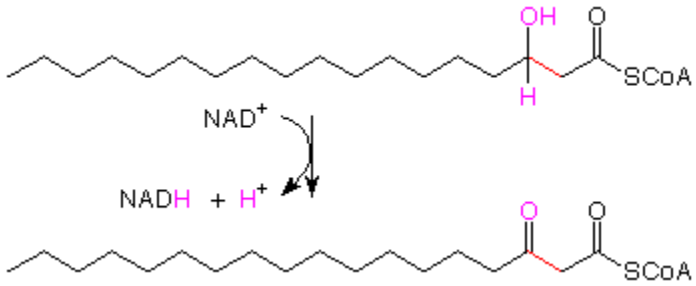
Now let's look at the individual reactions of this process. (Notice the slightly different notation scheme. The principal reactant and product are connected by a straight arrow. The necessary reagents and their byproducts are connected by a curved arrow.) The first reaction results in the removal of hydrogen atoms from the alpha and beta carbo atoms. Its effects are opposite to those of hydrogenation of a double bond. The removal of hydrogen atoms makes this an oxidation reaction. The oxidizing agent is a molecule called "FAD" (for flavine adenine dinucleotide). We'll look at its structure later.



Water is then added to the alkene pi bond which results from the first reaction. This is analogous to the addition of water to alkenes we studied recently. Since we know that a carbon alpha to a carbonyl group is a rather nuclophilic place (remember enolates?), it makes sense that the electrophilic hydrogen from water would add there and the nucleophilic OH would add at the beta carbon.

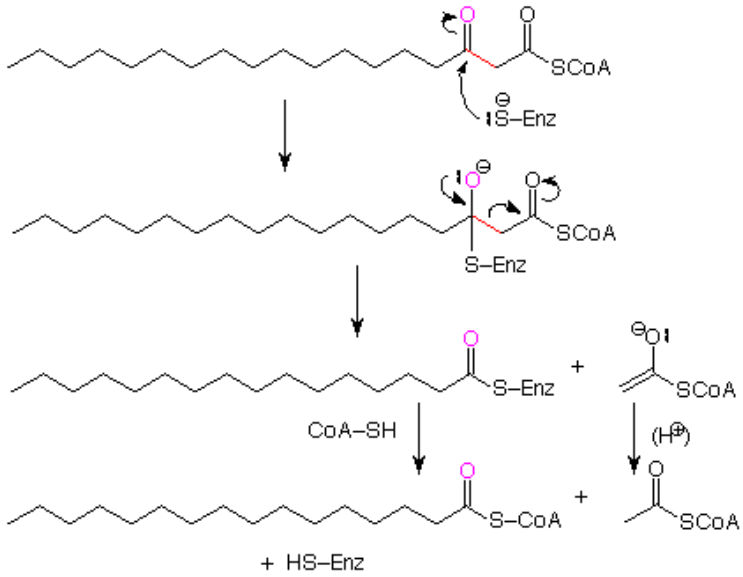


As soon as we see the third step,



we recognize the oxidation of a a secondary alcohol to a ketone. This is a reaction for which we used chromium-6 reagents earlier, but now the oxidizing agent is NAD^+ (nicotine adenine dinucleotide cation). The hydrogen attached to the OH-bearing carbon is transferred to the NAD^+, and the OH hydrogen comes away as an H^+.

The final step is the actual cleavage of the bond between the beta-carbon and the gamma carbonyl group. To put this in context, we have to think about it in reverse. When we do that, we see a pattern which is identical to the Claisen condensation.



The conclusion is that the final step in the beta-oxidation cycle is a reverse Claisen condensation. Like the Claisen condensation itself, this step is possible because the enolate ion obtained as the acetate fragment breaks away is stabilized by resonance. This enolate ion is neutralized by a proton source (acid). The shortened fatty acid is released from the enzyme as CoA?SH replaces the sulfur of the enzyme. This last step goes through a tetrahedral intermediate (not shown) as we would expect for a reaction which converts one carboxylic acid derivative to another.

The acetyl-coenzyme-A formed in this cycle enters the tricarboxylic acid cycle where it is oxidized to two molecules of CO_2. The NADH and $FADH_2$ produced in beta-oxidation and the tricarboxylic acid cycle enter a process called oxidative phosphorylation which results in the formation of ATP (adenosine triphosphate) for use in providing energy within the cell. We will not take up these latter processes, but they are an important part of a biochemistry course.

Glycolysis

Our next topic is glycolysis. This is the conversion of glucose to pyruvate. In the larger scheme of things the pyruvate produced is then converted to acetate, which like the acetate from beta-oxidation of fatty acids, enters the tricarboxylic acid cycle. Again, we will be looking at the reactions involved trying to find analogies in organic reactions we have studied. The chart in Fig 20.2 (p 571) in Brown lays out the whole scheme of glycolysis. Please refer to that chart to identify the reactions we are considering.

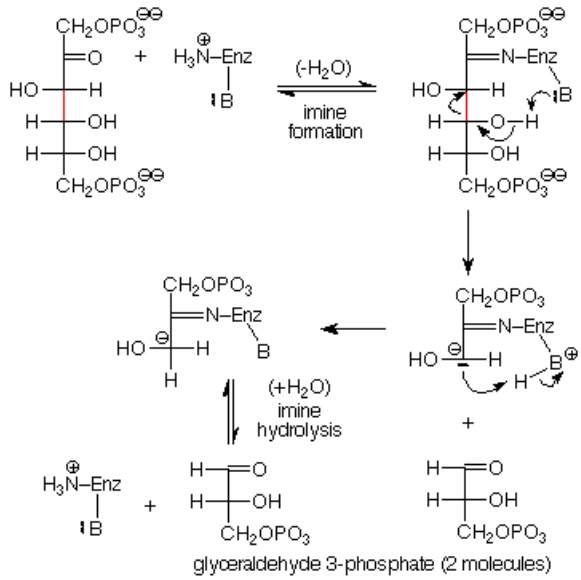
Reaction 1 is an esterification. It resembles the conversion of an alcohol to an ester by an acid chloride. In Reaction 1, ATP is used rather than an acid chloride, and the result is an ester of phosphoric acid rather than an ester of a carboxylic acid.

Reaction 2 is formally an internal oxidation-reduction reaction. The carbonyl group of glucose is reduced to a primary alcohol while the OH group at carbon-2 of glucose is oxidized to a ketone. The reaction goes through an enol as shown on p 572 of Brown.

Reaction 3 is similar to reaction 1, the formation of a phosphate ester (this is called a phosphorylation reaction).

Reaction 4 involves cleavage of a carbon-carbon bond and is the reaction in which the carbon skeleton changes from a six carbon chain to two three carbon chains. The first thing to notice is that the carbon-carbon bond broken joins a carbon which is alpha to a carbonyl group to one which is beta. This suggests that enol and enolate reactivity is going to be important. Like we did with the beta-oxidation of fatty acids, we can see a familiar reaction if we think about this one in the reverse direction, that is, look at it as a bond-making reaction rather than a bond-breaking reaction. If we ignore the groups which don't change, we can see that our reaction is a reverse aldol addition.

In more detail, the reverse aldol steps in this reaction are preceded by conversion of the carbonyl group of fructose 1,6-bisphosphate to an imine, and followed by the hydrolysis of that imine back to a carbonyl group and the amino group. The amino group is attached to the enzyme which catalyzes this reaction, and the formation of the imine helps anchor the fructose 1,6-bisphosphate molecule to the enzyme in the proper position to bring the bases and acids on the enzyme to the right location for the mechanism to go forward. The sequence of mechanistic steps is:



Reaction 5 converts dihydroxy acetone phosphate to glyceraldehyde 3-phosphate. This is like the reverse of reaction 2 in that it goes through an enol intermediate to oxidize an OH group to a carbonyl on one atom and reduce a carbonyl to an OH on the adjacent carbon. The sequence is on p 574 in Brown. At this point in glycolysis a glucose molecule has been converted to two molecules of glyceraldehyde 3-phosphate.

Reaction 6 is an oxidation of the aldehyde in glyceraldehyde 3-phosphate to a carboxylic acid. The odxidizing agent is NAD^+, which is reduced to NADH. The process also includes formation of an anhydride between the newly formed carboxylic acid and a molecule of monohydrogen phosphate ion. This anhydride is quite reactive (since phosphate is a stable anion, it's a good leaving group much like chloride) along the lines of an acid chloride.

Reaction 7 exploits the reactivity of this mixed anhydride by using it to transfer the phosphate to ADP. The resulting ATP is used as an energy source for many cell processes, so this step in glycolysis directly produces energy for the cell.

Reaction 8 shifts the phosphate group from the OH on carbon 3 to the OH on carbon 2. It is like an ester hydrolysis at one carbon and an esterification at the other.

Reaction 9 is a dehydration reaction. It resembles the dehydration of cyclohexanol to cyclohexene we did in lab, although the conditions in a cell are much milder since enzyme efficiencies make it unnecessary to employ strong acids and heat. The product is an enol phosphate (the phosphoric acid of a ketone).

Reaction 10 does two things. Like reaction 7 transfers a phosphate to ADP, making ATP, and it produces the enol form of pyruvate which rapidly equilibrates to the keto form.

If we add up all the balanced reactions, we find that one glucose molecule, two ADP molecules, two NAD^+ molecules, and two hydrogen phosphate molecules have been converted to two pyruvates, two ATP's, two NADH's and two hydronium ions.

Fates of Pyruvate

What happens to the pyruvate? This depends on the local conditions. In muscle tissue there may be a limited supply of oxygen (due to the demands of exercise outpacing the body's capacity to supply oxygen to the tissue). This means that the NADH produced in glycolysis not oxidized back to NAD^+. Glycolysis requires NAD^+, so it would stop and along with it production of energy in the form of ATP. This can be circumvented by lactate fermentation, which reduces pyrvate to lactate and oxidizes NADH to NAD^+. Energy production can continue until the build-up of lactate and acid as a result of this reaction (Brown, p 577) exhausts the muscle.

In yeasts in the absence of oxygen, fermentation to alcohol occurs. This is the basis of the fermentation processes which produce beverage alcohol in beer and wine. The byproduct is CO_2 which is responsible for the carbonation of beer and sparkling wines.

If the yeast is used in baking, the CO_2 expands the dough to produce the "rise" of bread dough. In this case the alcohol is the byproduct and it is largely driven off by the heat of baking. It is also responsible for much of the pleasant odor of baking bread.

If there is a good oxygen supply, pyruvate is oxidized to acetyl CoA and CO_2. As we have seen now several times, the oxidizing agent is NAD^+ which is reduced to NADH. This reaction is more complex than it looks at first glance, but we will leave those complexities for a biochemistry course.

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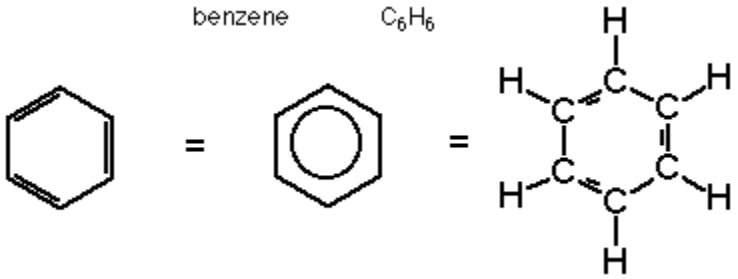
1.30: Aromatic Compounds

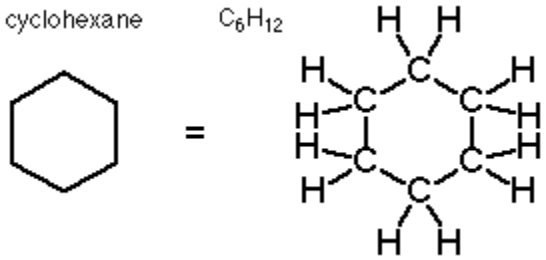
Symbols for the Benzene Ring

Today we'll find that resonance is very important in understanding both the structure and the reactions of aromatic compounds. First, let's take a look at the structural representations which distinguish aromatic compounds from those that aren't aromatic.

The most commonly encountered aromatic compound is benzene. The usual structural representation for benzene is a six carbon ring (represented by a hexagon) which includes three double bonds. Each of the carbons represented by a corner is also bonded to one other atom. In benzene itself, these atoms are hydrogens. The double bonds are separated by single bonds so we recognize the arrangement as involving conjugated double bonds. An alternative symbol uses a circle inside the hexagon to represent the six pi electrons. Each of these symbols has good and bad features. We'll use the three double bond symbol simply because it is also routinely used in the text.



Keep in mind that if the hexagon contains neither the three double bonds nor the circle, the compound is not aromatic. It is simply cyclohexane and there are two hydrogens on each carbon atom. This is easy to mistake when hurrying, so be careful when you are intepreting any structural formulas which include hexagons.



Kekule Structures

The structure with three double bonds was proposed by Kekule as an attempt to explain how a molecule whose molecular formula was C_6H_6 could be built out of carbons which make four bonds. The ring and the three double bonds fit the molecular formula, but the structure doesn't explain the chemical behavior of benzene at all well. Each of the double bonds would be expected to show the characteristic behavior of an alkene and undergo addition reactions, but this is not how benzene reacts.

In particular, we would expect a carbon-carbon double bond to react quickly with bromine to make a dibromo compound. This is what alkenes do very readily, and in fact it is a useful test for alkenes in the laboratory. Benzene does not react with bromine unless a very bright light or a strong catalyst is used, and then the reaction is not an addition reaction. We conclude that there is something quite unusual about the double bonds in benzene.

Kekule (thinking about this problem before bonds were understood as pairs of electrons) suggested that there are two forms of benzene which differ in the locations of the double bonds. His idea was that these were in rapid equilibrium, so rapid that there was never a fixed location for the double bond. One could say that an approaching bromine molecule could not "find" a double bond to react with.

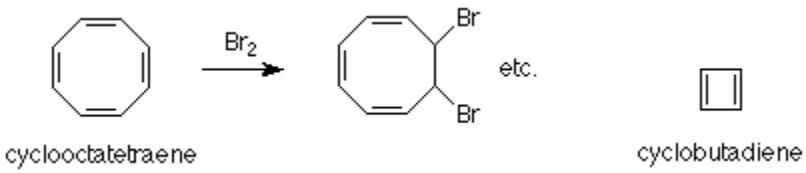
Resonance

There were several other structures proposed for benzene, but a much more satisfactory approach became possible when we began to understand that covalent bonds consist of pairs of electrons shared between atoms. The difference between the two structures Kekule envisioned (called Kekule structures) is only the difference between the locations of three pairs of electrons. This is exactly the type of situation where resonance must be involved. The hybrid or "average" of the two Kekule structures has one sigma bond and one-half of a pi bond between each two carbon atoms. Thus each carbon is joined to each of its neighbors by a one-and-half bond. Each bond in the benzene ring has the same number of electrons and is the same length. This picture is in complete accord with experiments which show that all carbon-carbon bonds in benzene are the same length, with no hint of shorter (double) or longer (single) bonds. It also helps explain why benzene does not undergo addition reactions: there are no simple pi bonds.

Recall that resonance has another important feature: when resonance is involved, the real structure is more stable than we would expect from any of the structures we write using the one line = two electrons symbolism. This extra lowering of energy, which for benzene is about one-third as much as making a typical covalent bond, is quite important in the reactions of benzene and other aromatic compounds. As we will see, reactions of the benzene ring almost always result in products which in which the benzene ring persists -- an outcome of its stability.

Huckel Rule

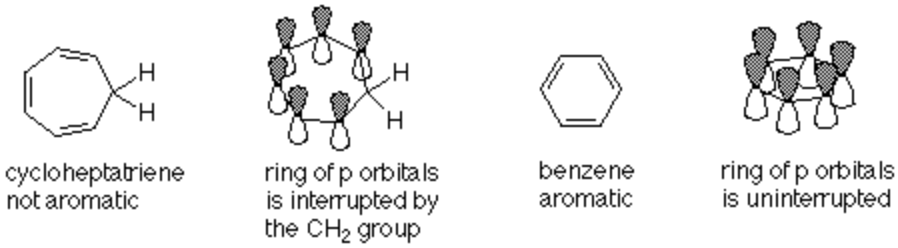
When resonance theory was first applied to understanding the structure of benzene, the key feature seemed to be a resonance hybrid of ring structures containing alternating single and double bonds. This immediately led to attempts to make and study compounds like cyclooctatetraene and cyclobutane. These compounds also have ring structures with alternating single and double bonds.



Cyclooctatetraene has been made, but it does not posess the properties of extra stability and resistance to addition reactions which distinquish aromatic compounds. It readily adds bromine, for example. Cyclobutadiene is extremely unstable -- one cyclobutadiene molecule reacts with another cyclobutadiene molecule instantaneously even at very low temperatures -- so it certainly does not act like an aromatic molecule and it has been called "antiaromatic" as a result.

It seems that there is more to being aromatic than simply a ring with alternating single and double bonds. After considerable development of the underlying theory, the pattern which has emerged is that aromatic characteristics are only expected when there is a ring of pi electrons in which the number of pi electrons is equal to **4n + 2** (where **n** is an integer, 0, 1, 2, etc.). (This is known as the Huckel rule after its discoverer.) We can check this against the compounds we have considered so far: Benzene has 6 pi electrons (two for each pi bond) which is the number we get from 4n + 2 if n = 1. Cyclooctatetraene has 8 pi electrons, and there is no integer "n" which will make 4n + 2 = 8. Cyclobutadiene has 4 pi electrons and also doesn't fit 4n + 2. There are many other examples which support Huckel's rule.

It is important to be sure that the ring of alternating single and double bonds is complete. If there is an sp^3 hybridized carbon in the ring, the conditions for aromatic character are not present, and we do not worry about checking for 4n + 2. Here's an example:

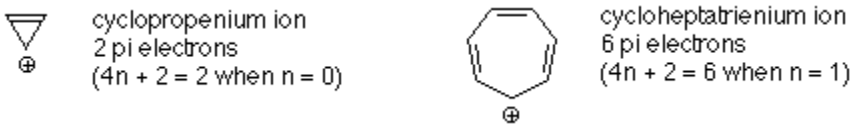


Another way to see this is to look at the p orbitals which combine to make the pi bonds. If these p orbitals combine to form an uninterrupted ring as is the case in benzene, then we can go ahead to use Huckel's rule to check for the proper number of pi electrons for aromatic character. If the ring of p orbitals is broken by a CH_2 (group or another tetrahedral carbon) with no p orbital, then the compound cannot be aromatic and we need not try to apply Huckel's rule.

The p orbitals which make up the unbroken p orbital ring can be associated with other atoms than carbon. Two examples are furan and pyrrole, in which two of the six electrons needed come formally from unshared electron pairs on oxygen.

Such an unshared pair can also come from a carbon atom, which will have to have a negative charge. An example of this is the cyclopentadienide ion which can be made by treating cyclopentadiene with a moderately strong base. Cyclopentadienide ion is sufficiently stabilized by its aromatic character that cyclopentadiene (its conjugate acid) has a pK_a of 16, close to that of water. Cyclopentadiene is a remarkably strong acid for a hydrocarbon because its conjugate base has the extra stability of an aromatic compound.

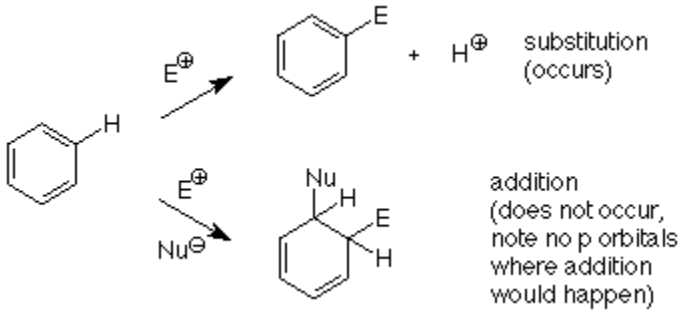
Extraordinarily stable cations can also be made if their structures are aromatic. Here are two:



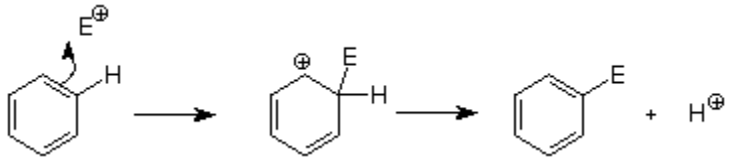
Notice that here the formally positively charged carbon atoms are sp^2 hybridized and have an empty p orbital which completes the cyclic arrangement of p orbitals.

Electrophilic Aromatic Substitution -- Mechanism

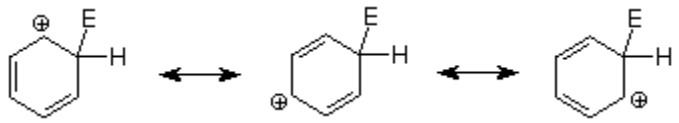
Let's finish up today by looking at the general mechanism for the characteristic reactions of aromatic compounds -- electrophilic aromatic substitution. The most important characteristics of these reactions follow directly from the stability of the aromatic ring. First, these reactions are typically catalyzed by strong electrophilic (Lewis acidic) catalysts like H_2SO_4, $AlCl_3$, and $FeCl_3$ which are required to overcome the stability of the aromatic ring. Second, these are substitution reactions since addition reactions would interrupt the p orbital ring and destroy the aromatic stability.



Even though the outcome of the attack of electrophiles on benzene is substitution rather than addition, the first step is the same as in electrophilic addition to alkenes -- attack of the electrophile on a pi bond and the formation of a new sigma bond between a carbon atom and the electrophile. The carbocation which is formed undergoes loss of the H^+ from the carbon which was attacked. The electrons from the C-H bond are returned to the aromatic pi electron ring and aromatic stability is restored.



Notice that the intermediate here is a carbocation, but it is not aromatic. The carbon bearing the hydrogen and the electrophile is sp^3 hybridized and has no p orbital to contribute to a cyclic p orbital system. The carbocation intermediate is somewhat resonance stabilized, though, by a resonance arrangement which is very similar to the one we saw in the addition of electrophiles to conjugated dienes.



This intermediate is a carbocation, and as we will see next time, its stability is important in determining how fast the reaction goes and (in benzene rings which bear substituents at one of the carbons) where the electrophile attacks. The key thing to recognize now is that the positive charge and the corresponding carbocation characteristics **only** appear at positions *ortho* and *para* relative to the point at which the electrophile attack. (Nomenclature is treated in Sec 6.3 of Atkins & Carey.) This will turn out to be quite important, so verify this for yourself.

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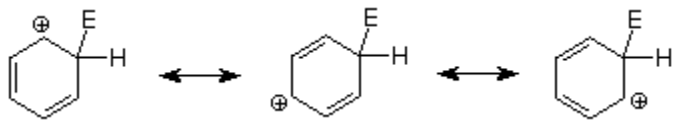
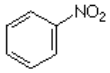
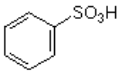
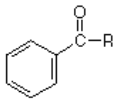
1.31: Electrophilic Substitution

Electrophiles and Products

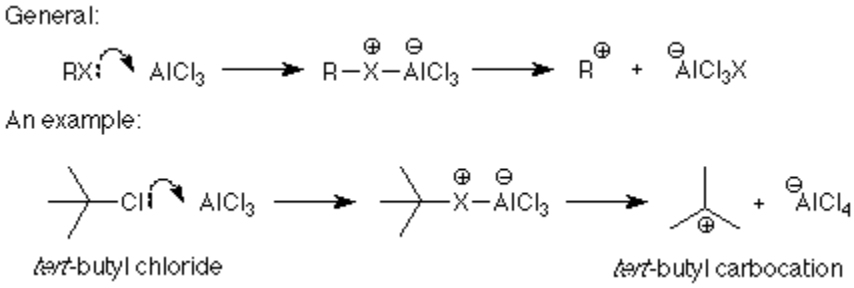
Let's begin by recalling the key steps in an electrophilic aromatic substitution mechanism.



An important feature of this mechanism is that we can identify the electrophile if we know the product because it is the atom or group which replaces the H^+. Conversely, if we know the electrophile, we can predict the structure of the product. The following table outlines these relationships in more detail for several reactions which follow the electrophilic aromatic substitution pathway.

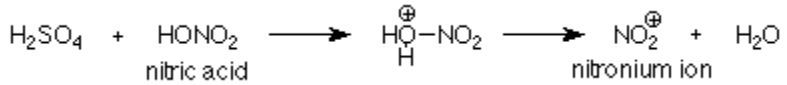
Reaction Name	Reagent	Catalyst	Electrophile	Product
Nitration	HNO_3	H_2SO_4	$NO_2^{\oplus}$	
Sulfonation	SO_3 (fuming sulfuric acid)	H_2SO_4	$HSO_3^{\oplus}$	
Halogenation (Bromination in this example)	Br_2	$FeBr_3$	$Br^{\oplus}$	
Friedel-Crafts Alkylation	RX (alkyl halide)	$AlCl_3$	$R^{\oplus}$	
Friedel-Crafts Acylation	$R-\overset{O}{\overset{\|\|}{C}}-Cl$	$AlCl_3$	$R-\overset{O^{\oplus}}{\overset{\|\|}{C}}$	

The connection between the electrophile and the product is clear from these examples. What is not clear is how the catalyst transforms the reagent into the electrophile. There are two patterns here. One applies when the electrophile is made by removing a halide ion from the reagent (halogenation and the two Friedel-Crafts reactions). The formation of a carbocation from an alkyl halide and aluminum trichloride is a typical example of the first process:



Notice that the role of the catalyst is to bond with the leaving group and make it into a better leaving group. This makes the formation of the electrophile (carbocation in this case) much easier so that there is more electrophile around to attack the benzene ring. Similar mechanisms are used in the halogenation and Friedel-Crafts acylation reactions.

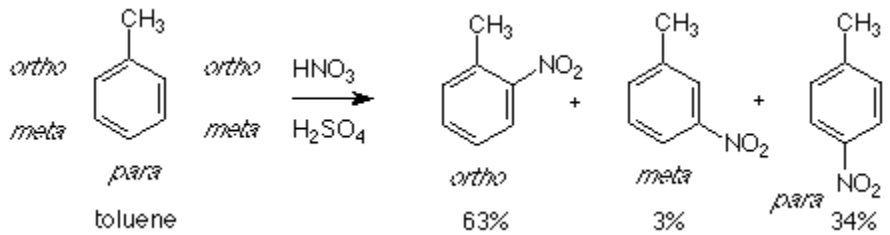
For sulfonation and nitration, the catalyst is sulfuric acid. Just as was the case in the S_N1 and S_N2 reactions of alcohols, the function of the acid is to protonate an unshared electron pair on oxygen. When the OH group of nitric acid is involved, the OH_2^+group which is formed is a good leaving group. Its departure makes the active electrophile:



To summarize, the function of the catalyst is to convert the reagent into a strong electrophile, which then attacks the pi electrons on the aromatic ring to make a new covalent bond. The reaction is completed by the loss of an H^+.

Ortho-Para Directive Effects

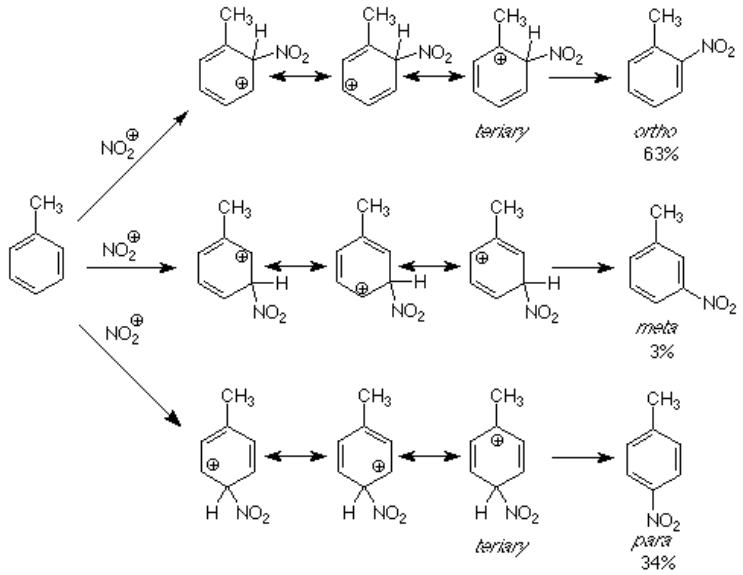
The reagent - catalyst - electrophile - product pattern works well when the aromatic compound is benzene itself, but things become more complicated when a substituted benzene (a molecule in which one of the hydrogens of benzene has been replaced by another atom or group) is used. There are three products which can arise in such a system. As an example let's look at toluene -- which is methyl benzene. We'll use nitration as our example of electrophilic aromatic substitution here.



Although there are five hydrogens available to be replaced on the benzene ring of toluene , two of those are directly adjacent (*ortho*) to the methyl group. Attack at either of these positions gives the same product. Similar considerations apply to the *meta* position. The result is that only three products are obtained. The actual distribution of these products shows that very little of the meta product is obtained. Instead almost all of the product consists of the *ortho* and *para* isomers. For this reason the methyl group is called an "ortho-para directing group." It "directs" the incoming electrophile to attack at the *ortho* and *para* positions relative to itself.

How does the methyl group exert this "directive" effect? We can begin to make sense of this by remembering that we explained Markovnikov's rule by considering that the product which is most abundant is formed fastest through a pathway which has the lowest activation energy. That lead us to a consideration of the relative energies of competing transition states and the use of intermediates as useful "stand-ins" for those transition states. We concluded that Markovnikov's rule is explained by the idea that the more abundant products are formed by pathways which go through lower energy intermediates.

If we apply the same reasoning to these directive effects, the question becomes "What makes the intermediates for the formation of *ortho* and *para* products more stable than those for *para* products? As usual, we will look for the answers by comparing the structures of the intermediates.

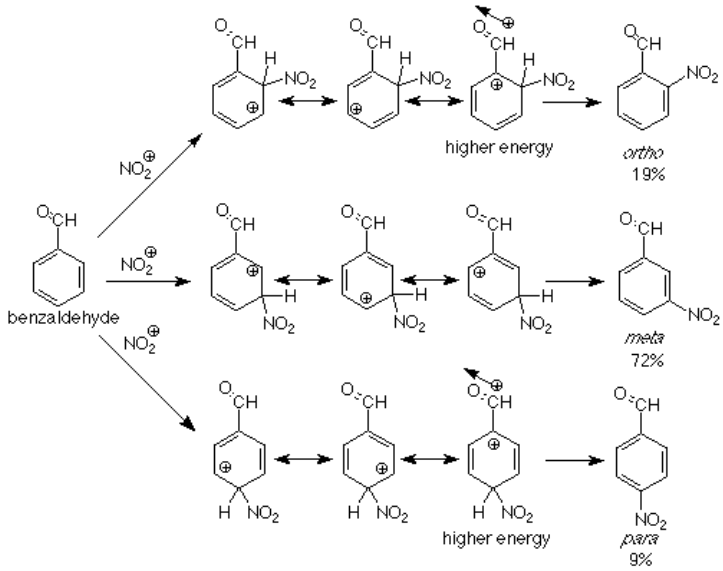


Each of the intermediates is described by resonance hybrid which includes three carbocations. However, for the intermediates leading to the *ortho* and *para* products, one of the contributing carbocationic structures is tertiary. This structure is more stable than the others because the electrons on the methyl group can directly stabilize the electron deficient carbocationic carbon. This stability is passed on to the resonance hybrid, which makes the intermediates for attack at the more stable than that for attack at the *meta* position. More stable intermediates mean lower energy transition states and faster reactions. A faster reaction means more product is formed through that pathway.

The result of this analysis is that groups which can donate electrons stabilize carbocations. Electrophilic attack will be faster at positions such that the carbocations produced have positive charges on carbons which are bonded to electron donating groups like methy groups. This occurs when attack happens at positions *ortho* and *para* to the electron donating group. Such electron donation happens with alkyl groups in general and when atoms like oxygen and amino-nitrogen are directly attacked to the ring. In the latter cases it is the unshared pair on the oxygen or nitrogen which helps reduce the energy of the electron deficient carbon atom. (See the figure at the bottom of p 165 in Atkins & Carey for an example.) Examine the *ortho-para* directing groups in Table 6.3 (p 162 of Atkins & Carey) and decide how each one acts as an electron donating group.

Meta Directive Effects

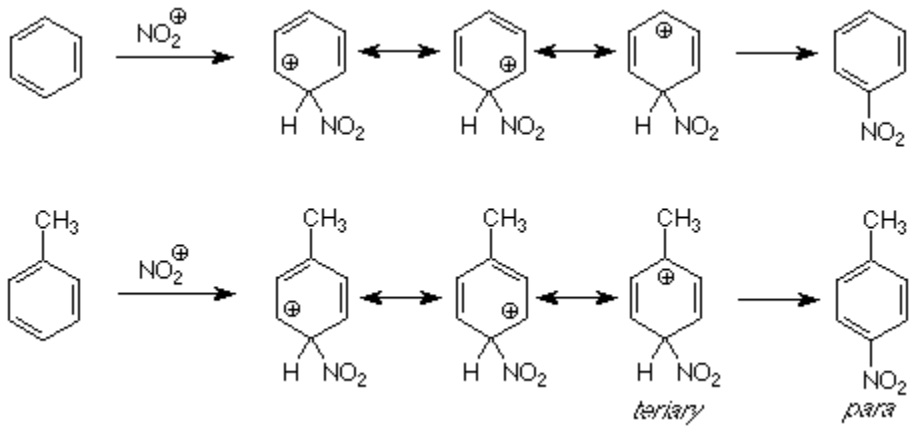
Can we extend this analysis to groups which are *meta* directing? Let's try an example. In the nitration of benzaldehyde the product mixture is 19% *ortho,* 72% *meta,* and 9% *para*. The aldehyde carbonyl group (and carbonyl groups in general) is a *meta*directing substituent. We'll look at the resonance structures of the intermediate for an explanation:



We see that attack at positions *ortho* and *para* to the carbonyl group places the positive charge directly adjacent to the positive end of the carbonyl group's dipole. The energy of such an intermediate will be higher than one in which the positive charge never approaches the carbonyl carbon, which is the case in the intermediate for *meta* attack. The consequence is that attack at the *meta* position is faster and more *meta* product is formed. Groups in which the atom directly attached to the benzene ring have a partial or complete positive charge tend to pull electrons toward themselves. Such groups are called electron withdrawing groups and are *meta* directing groups in electrophilic aromatic substitution. Look at the *meta* directing groups in Table 6.3 (p 162 in Atkins & Carey) and see if the preceding statement is borne out.

Activation and Deactivation

The underlying idea in the forgoing analysis of directive effects in electrophilic was understanding the relative rates of reaction when the competition was between different sites in the same molecule. This is termed intramolecular competition and it was also used in our understanding of Markovnikov's rule. We can also look at competition between molecules -- intermolecular competition -- using the same ideas, comparing the energies of intermediates in competing pathways. For example, let's imagine a reaction in which we mix toluene and benzene and then do a nitration. If we get more nitrotoluene (all three isomers) than nitrobenzene, the toluene has reacted faster than the benzene. We say that the methyl group "activated" the benzene ring. We understand this to mean that the methyl group lowered the energy of intermediates and transition states along the pathway to product as compared to the effect of a hydrogen (in benzene).



A comparision of the intermediates along the pathways from benzene and toluene to their respective products shows us the reason. (Only the *para* pathway is shown; the *ortho* pathway is similar.) The intermediate for attack *para* to the methyl group includes one resonance structure which is tertiary and thus is stabilized by the electron donating character of the methyl group.

There is no such structure in the intermediate for nitration of benzene, so the intermediate for toluene nitration is more stable and the reaction which goes through it is faster. We call the methy group (and alkyl groups in general) an "activating" group for electrophilic aromatic substitution.

Since the electron donating characteristics of the methyl group are responsible for both its activating properties and its *ortho-para* directing properties, we might suspect that *ortho-para* directing groups will also be activating groups. An examination of Table 6.3 (p 162, Atkins & Carey) shows that this is generally true. (The exceptions, the halogens, are treated in Section 6.10 of Atkins & Carey. We will not discuss them further)

This conclusion also suggests that *meta* directing groups will also be "deactivating" groups; that is, that benzene rings which carry a *meta* directing group will be less reactive than those which do not. Table 6.3 also bears this out. Both the *meta* directing characteristics and the deactivating characteristics are outcomes of the electron withdrawing nature of these groups and the consequent increase in the energy of electrophilic aromatic substitution intermediates when they are present.

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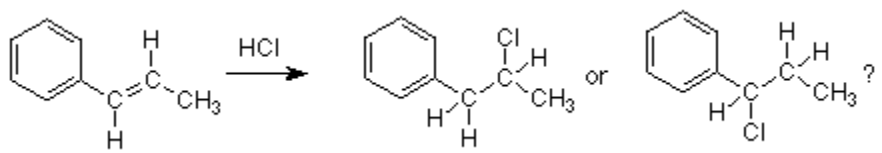
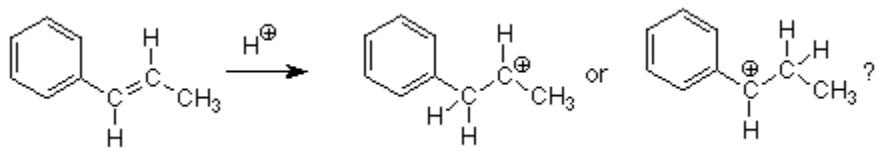
1.32: Side Chain Oxidations, Phenols, Arylamines

Carbocations Stabilized by Resonance

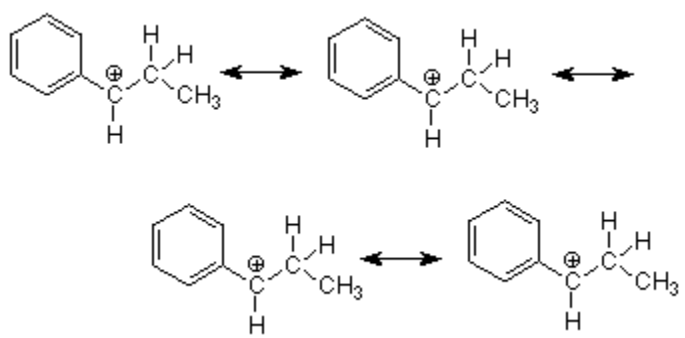
Let's begin by looking at the addition of HCl to an alkene in which one of the alkene carbons is directly attached to the benzene ring.



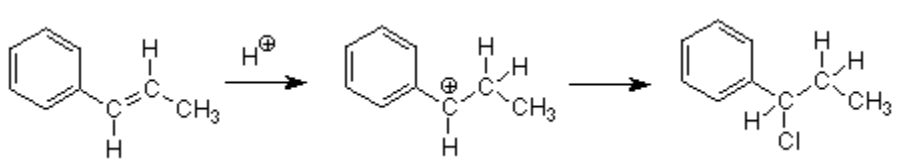
In this example each of the alkene carbons has the same number of hydrogens so the direct application of Markovnikov's rule is stymied. We find that we must go beyond Markovnikov's rule to its explanantion in terms of the relative stability of the two carbocations which might be formed. Here are the two carbocations which would be formed by the attack of H^+ on the alkene:



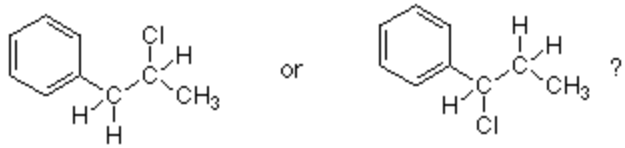
Which of these carbocations has the lower energy? Will the phenyl group donate electrons more effectively than the methyl group? The key thing to notice in answering these questions is that the pi electrons of the benzene ring are directly adjacent to the carbocation carbon in the structure on the left. This is reminiscent of the situation we saw in the addition of HCl to 1,3-butadiene where we encountered resonance stabilization of the carbocation by the pi electrons of the neighboring double bond. The same situation occurs here, and we can symbolize the resonance stabilization with the following resonance structures.



The effect of this resonance is to make the carbocation more stable when the charge and the electron deficiency are located on a carbon which is directly bonded to the phenyl group. Such a carbon is called a "benzylic" carbon. Since there is no such resonance stabilization available when a simple alkyl group is bonded to the carbocationic carbon, the benzylic carbocation is more stable, is formed faster, and the product formed from it is the only one we see.



With this background, we can quickly decide which of the two alkyl halides below will react faster by way of an S_N1 mechanism.



The more reactive alkyl halide is the one which give the more stable carbocation. The more stable carbocation (since both will be secondary carbocations) is the one where benzylic resonance is possible. (The resonance structures are given above.) Only the alkyl halide on the right will make a carbocation in which the carbocation carbon is directly attached to a phenyl group. Consequently we understand why the alkyl halide on the right is more reactive.

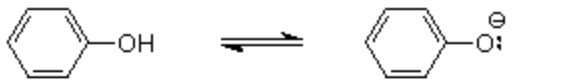
Bases Stabilized by Resonance

We've seen that benzylic carbocations are stabilized by resonance. What happens if the atom directly attached to the benzene ring has an unshared pair of electrons -- in other words, it is electron rich rather than electron poor. We can see the effects of this arrangement in the acid-base properties of phenols and aromatic amines.

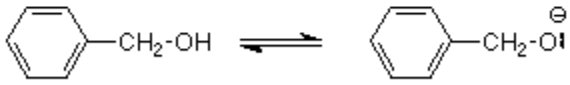
A phenol is an alcohol whose R group is a phenyl group. It is essential that the oxygen and the benzene ring be directly attached to each other. If there is a tetrahedral carbon between them, the compound is not a phenol but an alcohol.

a phenol an alcohol

An important difference between phenols and alcohols lies in their acidities. Recall that alcohols, like water, have pK_a's of about 16. Phenols in contrast typically have pK_a's of about 10, making them considerably stronger acids than alcohols. Since the stronger acid has the weaker conjugate base, we need to ask why a phenoxide (the conjugate base of a phenol) is weaker than an alkoxide (the conjugate base of an alcohol).

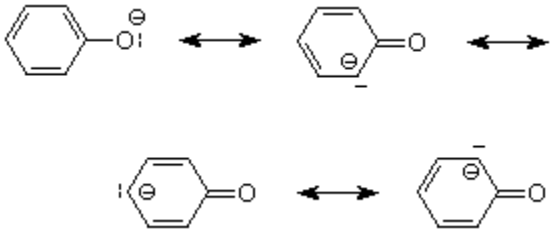


a phenol, pK_a ~ 10 a phenoxide



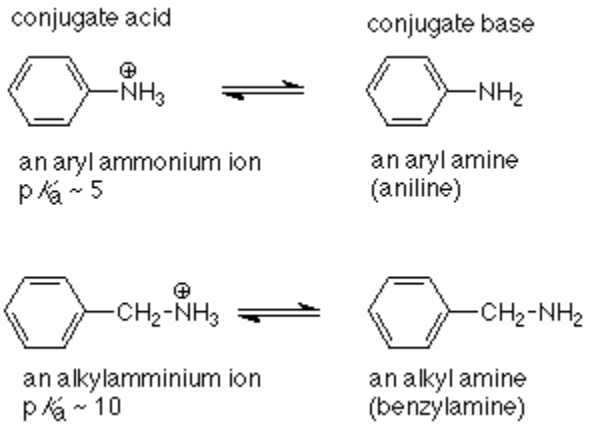
an alcohol, pK_a ~ 16 an alkoxide

Since it is the unshared electron pair which makes either of the bases a base, we can ask why the unshared electron pair on the phenoxide ion is less available to bond with a proton than the unshared electron pair on the alkoxide ion. Again, the reason is found in resonance.

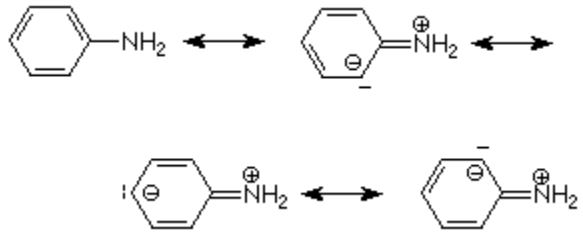


The resonance structures which improve the description of the phenoxide ion show that the electron pair on oxygen is partly moved into a pi bond position between the oxygen and the phenyl carbon it is attached to. To that extent the electron pair on a phenoxide ion is less available for attachment to a proton and the phenoxide ion is a weaker base than an alkoxide ion in which no such resonance is possible.

The same situation occurs in when an amino nitrogen is directly connected to an aromatic ring.



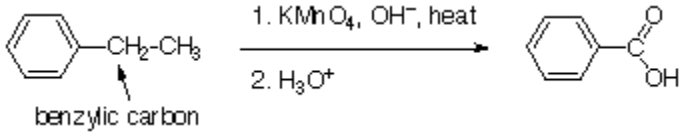
We see that the ammonium ion in which the nitrogen is directly attached to the phenyl group is a stronger acid than the one in which the nitrogen is attached to an sp^3 hybridized carbon atom. This means that the conjugate base, the aryl amine, in which the nitrogen is attached to the phenyl group is also weaker than its alkyl amine counterpart. This is understood by resonance between the unshared electron pair on nitrogen and the aromatic ring, only possible if the connection is direct, which makes the unshared electron pair less available to serve as a base.



The resonance possibilities for an aromatic group allow it to serve either as an electron donating substituent when the attached atom needs electrons (carbocation) or as an electron withdrawing substituent when the attached atom has an unshared pair to share (oxygen or nitrogen).

Side Chain Oxidation

There is another reaction which occurs at the atom directly attached to an aromatic ring. This is known as "side chain oxidation." When a compound which has an alkyl group directly attached to an aryl group is treated with a strong oxidizing agent like chromic acid, the benzylic carbon is oxidized to a carboxylic acid group which remains attached to the aryl group. Any other carbon-carbon bonds are broken. There is one further restriction -- the benzylic carbon must have a hydrogen attached.



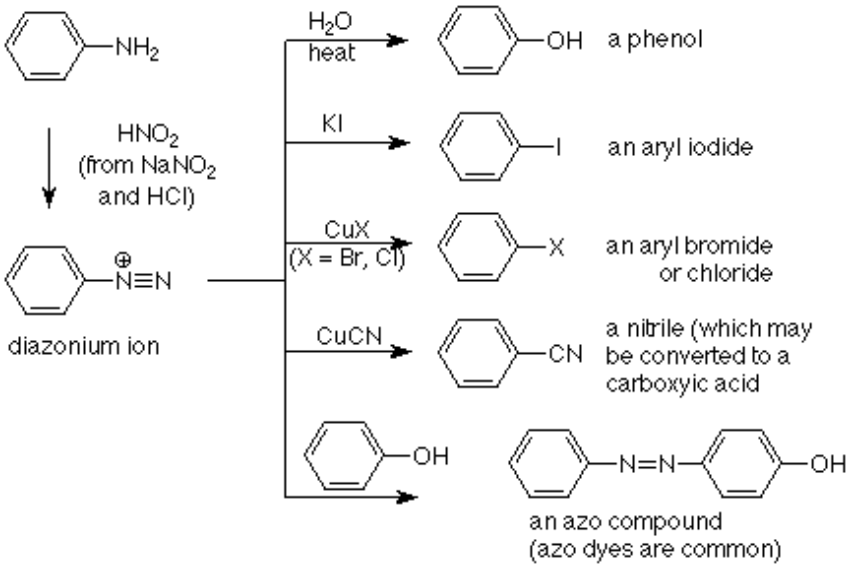
The mechanism of this reaction is obscure, but the fact that it specficially requires that there be a benzylic C-H bond suggests that breaking this bond is essential. Any intermediate that might be formed by breaking this bond will be stabilized by resonance with the aryl group, which provides an explanation for the specificity of attack at the benzylic position. Such reactions also occur in a biological context. Enzymes oxidize alkyl side chains on aromatic rings as part of making such compounds soluble enough

to be eliminated.

Diazonium Ions

When primary aryl amines are reacted with nitrous acid (HNO_2, generated from sodium nitrite ($NaNO_2$ and HCl) a reaction occurs which makes a new nitrogen-nitrogen triple bond. We will not be concerned with the mechanism, but the product (called a diazonium ion) is a valuable synthetic intermediate.

The diazonium ion is seldom isolated (diazonium ions can be explosive) so instead it is used in the solution it is made in. The N_2 group can be replaced by a variety of other groups and can also be an electrophile itself toward a sufficiently activated aromatic ring. The possibilities are outlined in the following chart:

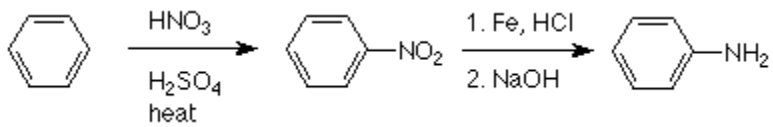


The first four reactions on this chart are examples of the replacement of the N_2 group by a nucleophile. These reactions provide a way to do nucleophilic substitutions on a carbon of an aromatic ring which are not possible by normal S_N1 and S_N2 mechanisms. The great stability of molecular nitrogen (N_2) makes it a very good leaving group, but the mechanisms of these reactions are not simple.

The last reaction in the table is one in which the diazonium group acts as an electrophile. It is not a particularly good electrophile, so it requires a reactive ring as a target. Such a ring needs to have a strong electron donating group like OH or NH_2 to increase its reactivity in an electrophilic aromatic substitution mechanism.

The product of the electrophilic coupling of a diazonium ion with a reactive aromatic ring includes a nitrogen-nitrogen double bond. These compounds are often intensely colored and are useful as dyes. A variety of other functional groups, often carrying ionic charges, may be included to make them stick tighter to cloth. Terms such as aniline dyes or azo dyes are often used to refer to these compounds.

Diazonium salts are versatile synthetic intermediate materials and we know that they are made from aniline or similar molecules. Where do aniline and its analogs come from? The most common route is by reduction of nitrobenzene or substituted nitrobenzenes. The usual reducing agent is tin (in the laboratory) or iron (in industrial practice) used in aqueous HCl solution. Since nitration is a commonly used route to nitrobenzene, the usual sequence for the production of aniline is:



The use of NaOH in the final step is to neutralize the HCl so that the basic amine (which would otherwise be in the form of its

conjugate acid ammonium ion) is non-polar enough to be extracted from the water.

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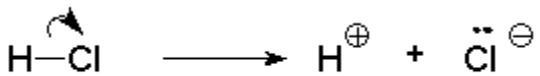
1.33: Radical Reactions

Homolytic Bond Cleavage -- Fishhook Symbols

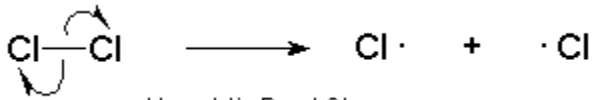
Last time we looked at how the benzene ring changes the reactivity of an atom or group to which it is directly attached. Today we'll finish presenting new material in the course by taking a brief look at reactions in which bond making and bond breaking events involve electrons moving singly rather than as pairs. To put this in perspective, lets recall how we envisioned the breaking of a covalent bond in the reactions we've encountered so far. The dissociation of HCl into H^+ and Cl^- is an example.



Heterolytic Bond Cleavage

We interpreted this to mean that the shared electron pair which formed the covalent bond between the hydrogen and the chlorine atoms moved together to become an unshared electron pair on chlorine. This is often called a "heterolytic" bond cleavage since in the products the electron pair is distributed quite unevenly. We have used the curved arrow symbol to show the origin and the destination of electron pairs in these steps. The reaction mechanisms we have worked with so far have all involved making and breaking bonds by processes like this in which pairs of electrons move together.

Now let's look at a bond cleavage in which each partner in the bond takes one electron of the bonding electron pair. The dissociation of molecular chlorine (Cl_2) is a good example. This occurs when Cl_2 is heated strongly or when it is illuminated by bright light.



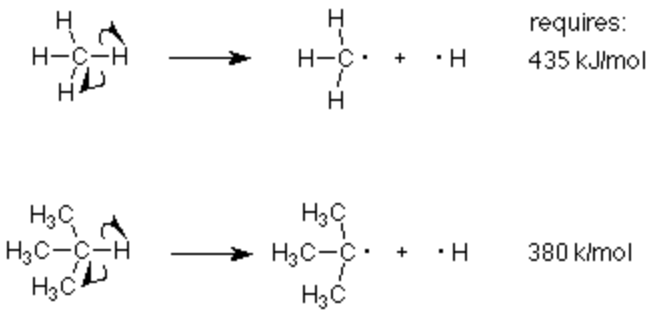
Homolytic Bond Cleavage

This is called "homolytic" bond cleavage since in the products the distribution of the electron pair is quite even. We use the "fishhook" (curved arrow with only one "barb" on the arrowhead) to show the motion of one electron. Such homolytic bond cleavages occur when the bond involved is not polar and there is no electrophile or nucleophile at hand to promote heterolytic patterns.

Bond Strength and Radical Energy

When a bond is made, the product has a lower energy than the reactants. It follows that breaking bonds requires energy. When the bond breaking process is homolytic there is no residual ionic attraction because there are no charges on the products, so the energy required to dissociate the bond is a good measure of how strong that bond is. Table 9.1 on page 237 of Atkins & Carey lists such "Bond Dissociation Energies."

A brief glance at this table shows us some interesting trends. First, all the halogen-halogen bonds (the Cl-Cl bond for example) are relatively weak. Carbon-carbon and carbon hydrogen bonds are stronger as are carbon-oxygen and hydrogen-oxygen bonds. Second, if we examine the trend in C-H bond dissociation energies as the structure of the alkyl group is changed, we notice that the strongest (435 kJ/mol) C-H bond is between the carbon of a methyl group and a hydrogen atom. The weakest (343 kJ/mol) is between the central carbon of a tertiary butyl group and a hydrogen atom.



We can interpret this to mean that the tertiary butyl free radical is more stable than the methyl free radical. (The term "free radical" or "radical" is used to mean an atom or group in which one of the bonding orbitals is occupied by a single electron. Radicals are normally uncharged.) That would explain why it is easier to break the tertiary C-H bond than the methyl C-H bond; the products from breaking the tertiary C-H bond are more stable.

Looking at the structures which would be formed by breaking the C-H bonds which lie between the methyl-H bond and the tert-butyl-H bond we can see that we have a familiar pattern. Just like carbocations, the order of stability of carbon free radicals is:

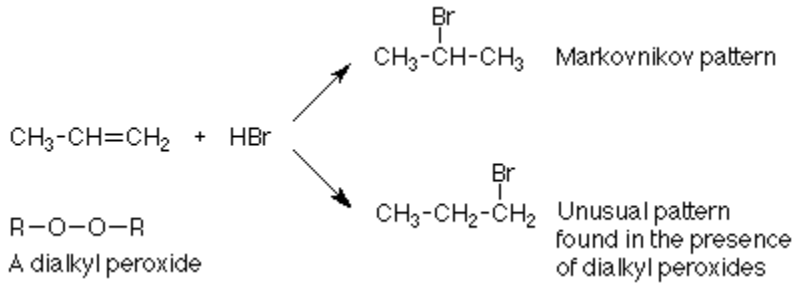
tertiary > secondary > primary > methyl

We have seen that intermediates which are more stable are also those which are formed most rapidly and that this fact often dominates the composition of product mixtures. Recall that this idea was the basis for our explanation of Markovnikov's rule and ofdirective and activation/deactivation effects in electrophilic aromatic substitution. The more stable intermediate (carbocation in those cases) was formed faster. More reaction occured through the faster pathway so the product mixture was dominated by the product formed through the more stable intermediate. In the next section we will see how this idea can be used to understand some free radical reactions.

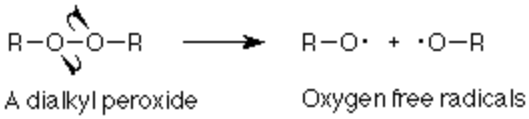
Radical Addition to Alkenes

We have made much of Markovnikov's rule. When we apply this rule to the addition of HBr to propene, we confidently predict that the product will be 2-bromopropane. It happens that occasionally considerable amounts of 1-bromopropane are formed. In fact it can happen that 1-bromopropane is the only product under some circumstances. This is puzzling and it tells us that something unusual is going on.

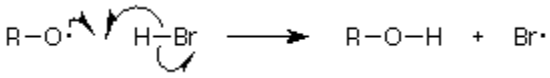
It took many experiments to pin down the details which control whether the reaction follows the Markovnikov pattern or the unusual course. It was eventually determined that the Markovnikov pattern is followed if the reagents are carefully purified just before they are used. The unusual pattern is followed if the reagents are "aged" before use. It was later learned that "aging" produces peroxides, compounds in which two alkyl groups or similar groups are joined through two oxygen atoms which share an O-O bond.



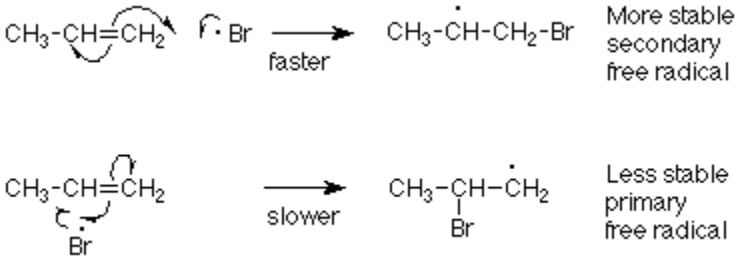
The O-O bond is weak (bond dissociation energy = 154 kJ/mol, much like the I-I bond) and it is non-polar so that we are not surprised that it breaks homolytically to give two oxygen free radicals.



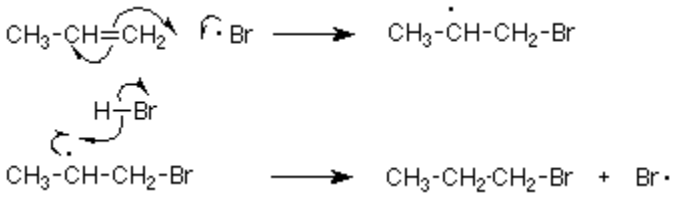
Next one of these oxygen free radicals reacts with HBr to give an alcohol (strong O-H bond) and a bromine atom radical.



These steps (called chain initiation steps for reasons we'll come to later) set the stage for the reaction with propene. The bromine atom radical can either attack propene's primary carbon to give a secondary free radical or propene's secondary carbon to give a primary free radical. We know that the secondary free radical is the lower energy intermediate and we know that reactions proceeding through lower energy intermediates are faster than those going through higher energy intermediates. We predict that attack of the bromine on the primary carbon to give the secondary free radical will be faster and the major product will be formed through this pathway.



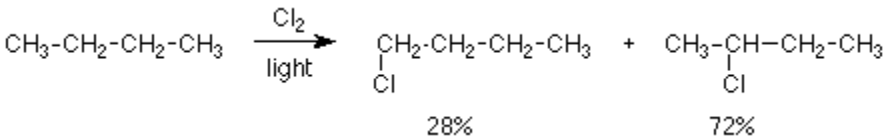
The reaction is completed when the secondary free radical reacts with another HBr molecule to produce the product -- 1-bromopropane -- and a new bromine atom.



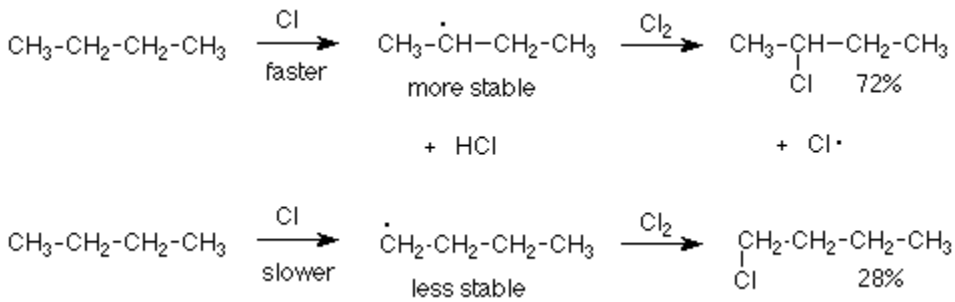
Notice that the second step regenerates a bromine atom which can begin a new cycle by attacking a fresh molecule of propene. The two steps together are called a chain reaction mechanism because a product of each one is a reactant of the other, creating a chain of events which stops when the reagents are used up. The sum of these two steps is an anti-Markovnikov addition of HBr to propene. While the outcome is different from the Markovnikov pattern we studied earlier, the underlying principle is the same: *We see the products of faster reactions, reactions which proceed by way of more stable intermediates.* In this instance the intermediates are free radicals and the secondary free radical is formed faster than the primary free radical. In the reactions which proceeded by way of carbocations (Markovnikov's rule) the more stable carbocation was formed.

Radical Substitution on Alkanes

There are also free radical mechanisms for substitution reactions of alkanes. These are of use for synthesis only in rather restricted cases, but the products we see are also controlled by competition in which the more stable intermediates are formed faster. An example is the chlorination of butane.



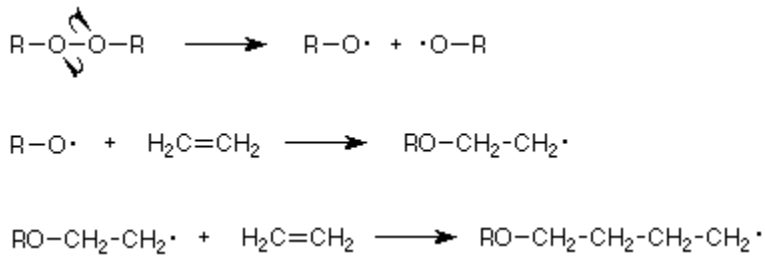
We see that a secondary hydrogen has been replaced by a chlorine more often than a primary hydrogen, even though there are six primary hydrogens and only four secondary hydrogens. This would make sense if the reaction mechanism went through a free radical, since we would expect a more stable secondary free radical to be formed faster (more often) than a less stable primary free radical. Such a mechanism would be:



Again the more abundant product is produced through the more stable (secondary) free radical rather than through the less stable (primary) free radical. Notice that this reaction is also a chain reaction, since the second step produces a chlorine atom which can react with another butane molecule to continue the chain. The reaction is initiated in this case by homolytic cleavage of the weak Cl-Cl bond by light to produce chlorine atoms.

Radical Polymerization

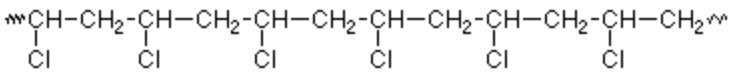
Finally, let's return to another application of free radical additions to alkenes. We saw earlier that the HBr adds to alkenes through a peroxide initiated free radical chain mechanism to produce an anti-Markovnikov product. The key step in this reaction was the addition of a bromine atom radical to the alkene to give the more stable of the two possible free radicals. Suppose that there was no HBr present. Then a carbon free radical, once formed, would have to react with an alkene to make a new carbon-carbon bond. Here's an example where ethylene is the alkene.



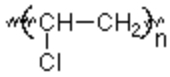
The new molecule would also be a free radical and could add to another molecule of ethylene. The product of that reaction would also be a free radical and could add to another molecule of ethylene, etc. The outcome is that the each reaction extends the growing chain by two carbons and produces a free radical intermediate at the end of the chain which can continue the reaction. In this way very long molecules are produced. These polymers such as polyethylene and polystyrene are produced in billion pound per year amounts and are very important commercial products.

Other polymerization reactions also are important, and Table 9.2 on p 251 of Atkins & Carey lists many of them. We can figure out the structure of the alkene from which the polymer was made by looking for the "repeating unit" in the polymer and thinking backwards to the alkene which was "added to" in making the polymer. Here's how it works for poly(vinyl chloride):

Poly(vinyl chloride)

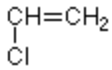


can be expressed as:



the repeating unit.

The monomer is:



vinyl chloride (1-chloroethene)

Since the repeating unit is formed by adding to each end of the double bond of the monomer, the structure of the monomer can be discovered by mentally cutting loose a repeating unit from the polymer and placing a double bond between its carbon atoms.

Contributors

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