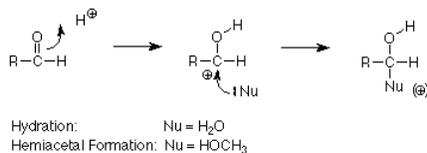


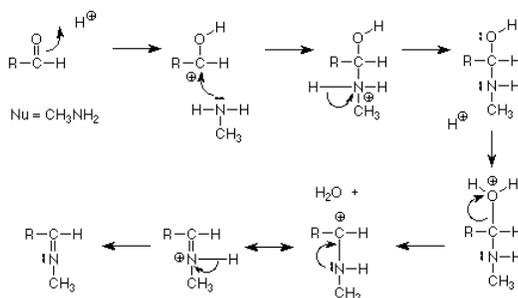
1.5: Nitrogen Nucleophiles - Imine Formation

Imine Formation

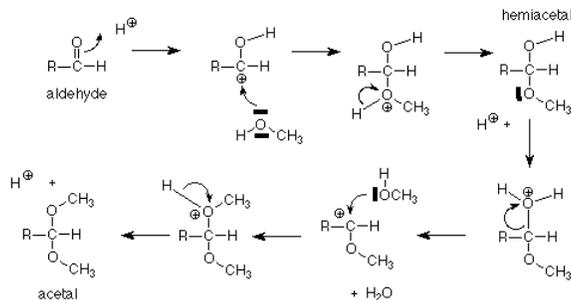
Last time we looked at the formation of a hemiacetal and an acetal from an aldehyde and an alcohol. In both this case and the previous case in which we added water to an aldehyde, the first steps involved acid-catalyzed addition of a nucleophile to the carbonyl carbon of an aldehyde.



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 = CH₃NH₂? 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 H₂O 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.

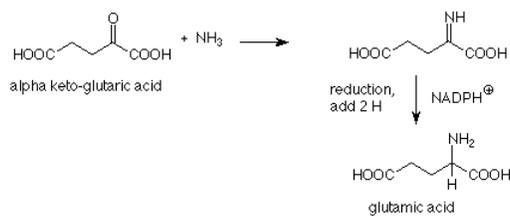
We can learn from this that when a nucleophile adds to a carbonyl group in an aldehyde or ketone, it always adds to the electrophilic carbonyl carbon. What happens next depends on the structure of the nucleophile. If there are two hydrogens on its

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?]

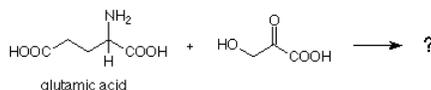
Biological Example

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.

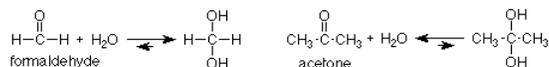
Equilibrium

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 examining -- 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.

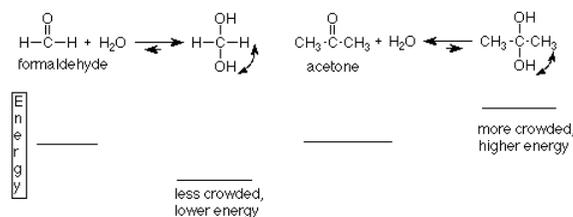


What might be responsible for the change in equilibrium behavior? The important idea here is that at equilibrium, more stable (lower energy) molecules predominate. We have to look at the changes in structure between reactants and products *and* the changes in structure between our two cases to understand 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 sp² hybridization. After water is added, the same carbon is tetrahedral with 109.5° bond angles and sp³ 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.

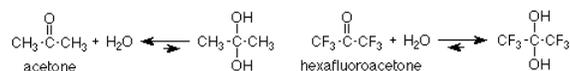
The most obvious structural difference between the formaldehyde and acetone cases is that in formaldehyde, the atoms attached to the carbonyl carbon are hydrogens, which are about as small as atoms get. In the same location in acetone, we have methyl (CH₃) groups, which are considerably larger. Pushing the larger methyl groups closer together in the product of adding water to acetone requires more energy than 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.

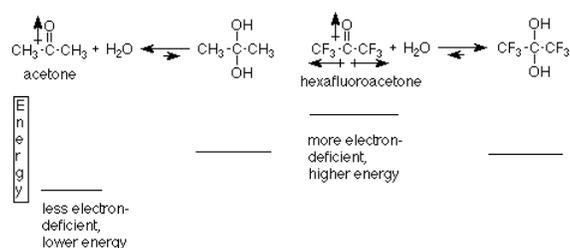
Polar Effects

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 (CF₃) is about the same size as a methyl (CH₃) 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

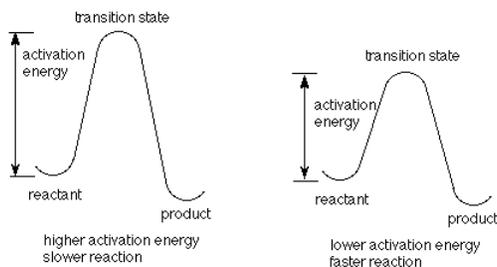
to that of acetone, so there is less of it at equilibrium. On the product side of the reaction, no pi bonds are involved, so the polar effect on energy is less pronounced.



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.

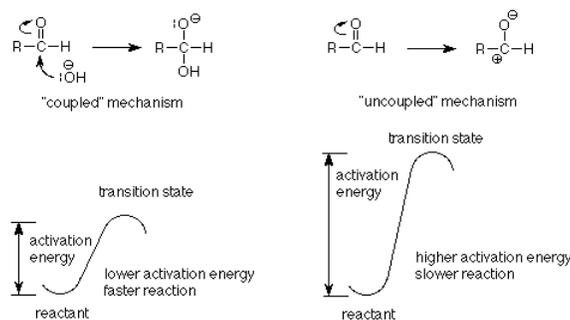
Rates - Activation Energy

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 $\text{C}=\text{O}$ pi bond can come largely from the energy released by making the new $\text{C}-\text{O}$ 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 $\text{C}=\text{O}$ pi bond is being broken without the energy input from a forming $\text{C}-\text{O}$ 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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