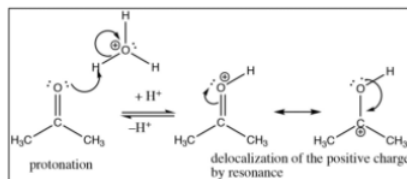
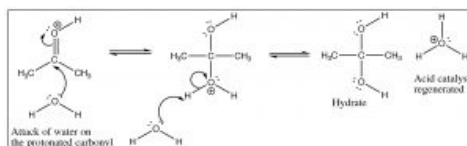


7.8: Reactions of Aldehydes and Ketones with Oxygen Nucleophiles

In contrast to the addition of hydrogen or carbon nucleophiles, the addition of oxygen and nitrogen nucleophiles is reversible under the conditions in which the reaction occurs. This is because (as we will see) the addition of an oxygen or nitrogen nucleophile results in a tetrahedral intermediate that can regenerate the carbonyl by expelling a leaving group. In contrast to the cases with carbon or hydrogen nucleophiles, oxygen and nitrogen nucleophiles can be good leaving groups. Typically, the reaction is catalyzed either by acid or base as discussed below. For example: in aqueous solution, most aldehydes and ketones will react with water to produce a hydrate.

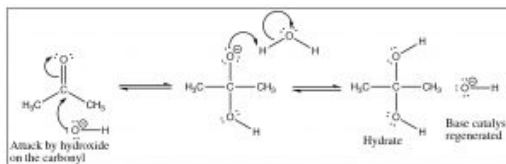


In acid, the first step is protonation of the carbonyl oxygen, the resultant positive charge is partially delocalized onto the carbon \rightarrow , which makes the carbonyl more susceptible to nucleophilic attack even by a relatively poor nucleophile such as water.



This reaction is completely reversible in aqueous solution, and if any aldehyde or ketone is dissolved in water there is always some equilibrium concentration of the hydrate. In fact, formaldehyde ($\text{H}_2\text{C}=\text{O}$) exists almost exclusively as the hydrate in aqueous solution, whereas most other aldehydes and ketones exist mainly in the carbonyl form. However, it is important to keep in mind that both forms are typically present, and therefore further reactions can proceed from either the hydrate or the carbonyl form.

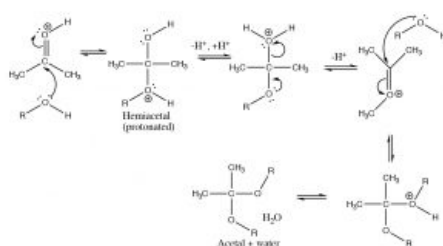
Base catalysis differs in that the first step is attack by the hydroxide (rather than water) on the carbonyl. Since hydroxide is more reactive than water, the carbonyl does not need to be activated by protonation. What the two mechanisms have in common is the rapid protonation/deprotonation reactions that take place in the intermediate steps. We have already seen this many times and with the reactions of aldehydes and ketones, it becomes more important to appreciate just how ubiquitous protonation and deprotonation are. By controlling the pH or the amounts of reactants or products we will see that it is possible to direct such reactions so that the product we desire is produced.



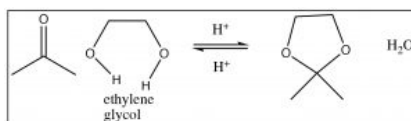
The hydrate is an example of a structure that will play a major part in our discussion of all carbonyl compounds—which we will refer to as the “tetrahedral intermediate.” In this tetrahedral form, the carbon is in the same *oxidation state* as the ketone (two bonds to oxygen) but in a different *hybridization state*, sp^3 for the hydrate and sp^2 for the carbonyl. In most cases, the $\text{C}=\text{O}$ bond (in the sp^2 hybridized form) is stronger (745 kJ/mol in a typical ketone) than two single $\text{C}-\text{O}$ bonds (2×358 kJ/mol) (in the sp^3 hybridized form), which explains why (when there is a low-energy stable leaving group) the tetrahedral intermediate that is formed by attack on the sp^2 carbon usually collapses back down to a $\text{C}=\text{O}$, expelling a leaving group at the same time. As we move forward, we will see the move from tetrahedral to $\text{C}=\text{O}$ many times, the difference in many of the reactions is which group will leave during this process.

If we change the solvent to an alcohol, we see that the same type of reaction occurs. The alcohol oxygen attacks the carbonyl carbon, but we find that the reaction proceeds further. The first product, formed by addition of one alcohol to the carbonyl is called a hemiacetal but then the reaction continues. Each step is reversible (with low activation energy), each protonation and deprotonation is reversible. All of the oxygens in the molecule can be protonated and deprotonated. When the OH group of the

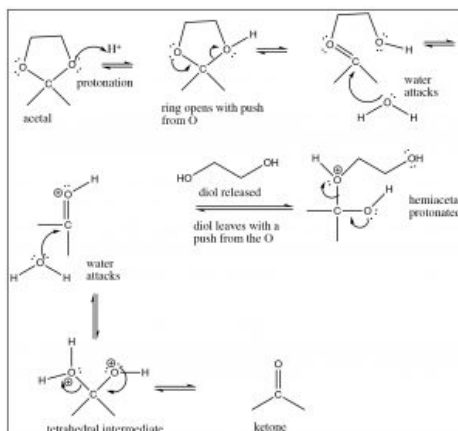
hemiacetal is protonated, it is turned into a good leaving group (H_2O) and the carbon undergoes another attack by an alcohol molecule. The end result is an acetal^[4] and water.



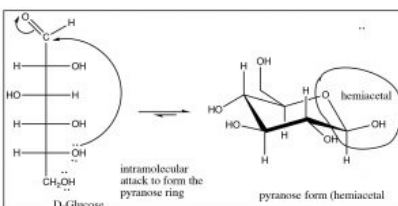
Since these reactions are reversible, you may be asking how we can control the reaction. In this case we can use Le Chatelier's principle: we can either add a lot of starting material or we can remove one of the products as it is formed. In this case, acetal formation is usually done using the alcohol as solvent, and the water that is formed is removed, so that the position of equilibrium is shifted over to produce the acetal. However, as we will see shortly, sometimes we want to regenerate the carbonyl compound, and this can be done by adding water (and acid catalyst) so that the equilibrium shifts back.



If we use a diol such as ethylene glycol ($\text{HOCH}_2\text{CH}_2\text{OH}$), the resulting cyclic acetal is formed. This is frequently used to protect carbonyl groups in more complex molecules, for example, if we wanted to do a reaction in another part of the molecule. Again, the carbonyl group is easily regenerated. The mechanism of hydrolysis is simply the reverse of the acetal formation, beginning with protonation, attack by water, and so on as shown below.



While this mechanism may look (a bit) complicated, in fact, each step is simple and we have seen similar things many times. The issue with these kinds of reactions is that all the oxygens are being protonated and deprotonated all the time.



Note that the ways that tetrahedral intermediates behave depends on which oxygen is protonated, and which nucleophile (water or alcohol) attacks the protonated acetal or ketone.

One common example of hemiacetal formation is the intramolecular cyclization of D-glucose to form a six-membered ring which contains a hemiacetal group (among many others). This case is actually a rare example of the tetrahedral form (hemiacetal) being more stable than the carbonyl form.

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