Reactivity of Carboxylic acid Derivatives



Example: Acid chloride to anhydride

Since an acid chloride is more reactive than an anhydride, treatment of acetyl chloride with carboxylate salt of acetic acid (sodium acetate) will give acetic anhydride and sodium chloride.



Example: Acid chloride to ester

An acid chloride is more reactive than an ester, therefore treatment of acetyl chloride with methanol will yield methyl acetate and HCl.



Example: Acid chloride to amide

Another example is the conversion of acetyl chloride to acetamide. An acid chloride is more reactive than an amide, therefore treatment of acetyl chloride with ammonia will yield acetamide.



Example: Hydrolysis of acid chlorides



Hydrolysis can occur under either basic or acidic conditions. Under acidic conditions (shown below), the protonated carbonyl group of the acid chloride is attacked by water to yield a tetrahedral intermediate, which is then deprotonated to become a neutral species. The intermediate then displaces the chloride anion to yield the carboxylic acid.



In each of the above examples, the reverse reaction will NOT proceed

Alkaloids

Nitrogen-containing compounds from plant sources are referred to as alkaloids. The study of alkaloids provided much of the growth of organic chemistry in the nineteenth century and still remains a growing area of research. One particular group of alkaloids are the morphine alkaloids.



Morphine

Derivatives of morphine were synthesized to try to separate the addictive properties from the analgesic properties. One of the first such derivatives involved the treatment of morphine with acetyl chloride to yield an acetylated derivative of morphine. This compound was found to be 1000x better of an analgesic and was referred to as the "hero" compound. This compound was also found to be 1000x more addictive than morphine and is commonly known as heroin.



However, the above reaction does not really work (very slow) with \mathcal{A}_{OH} \mathcal{A}_{OCH_3} and it does not with \mathcal{A}_{NH_2}

Example: Ergotamine



This structurally complicated molecule is called ergotamine. It is a mycotoxin produced by fungi *Claviceps paspalii* and it causes constriction of blood vessels. It is the cause for the disease St. Anthony's Fire in the middle ages through contamination on rye.

When ergotamine is treated with acid/water, what is the functional group that will react with the left side of the structure?



At the left hand of the structure, there is an amide functionality. When treated with acid in water, the amide is hydrolyzed to carboxylic acid.

In 1938, Albert Hofmann, as part of a large research program searching for medically useful ergot alkaloid derivatives, discovered/synthesized LSD.



Note that acid cannot go directly to amide. Amine and acid will for an unreactive salt. It must go through the acid halide intermediate before being finally converted to amide.

Example: Reserpine



The molecule above is reserpine. It is isolated from Indian snake root (*Rauwolfia* serpentina) and was found to reduce blood pressure. It is also used to treat schizophrenia. However, it causes suicidal depression.

Although it is a big molecule, you should be able to calculate its formula and molecular weight, as well as identify all of its functional groups. Be able to identify stereogenic centres.



When it is allowed to react with ammonia, the esters are converted to amides. Since there are two ester functional groups in this molecule, there would be two amides formed as products. The groups that react are highlighted in the starting material.



Hydrolysis of Esters



The hydroxide anion attacks the carbonyl carbon in the first step, and a tetrahedral intermediate is formed. This process is reversible (so if the negative charge on oxygen comes down and kicks out the OH group instead of ethoxide in the second step, we get the starting material again).

In the second step, the ethoxide anion (in protonated form = ethanol) is ejected and carboxylic acid is formed. However, under the basic conditions, the proton on the carboxylic acid is abstracted by the anion to form carboxylate anion and ethanol.

The pKa for acetic acid is 4.5, whereas the pKa of ethanol is 17. Ethoxide is a stronger base, therefore it will deprotonate the acetic acid to give acetate.

The process of hydrolyzing esters with base is called **saponification**. Saponification refers to the process of making soap. When you accidentally pour NaOH in your hand, you feel your hand has a soapy feeling. What occurs is that the fat (triglycerides) in your hand are getting hydrolyzed.



glycerol triester = triglyceride This one is a glycerol triester of octadecanoic acid



glycerol triester of oleic acid

Soaps act as cleansers because the two ends of the molecule are very different. The sodium carboxylate end of the long chain fatty acid is ionic and therefore hydrophilic (water-loving). As a result, it tries to dissolve in water. The long chain hydrocarbon on the other hand, is non-polar and hydrophobic (water-fearing). It therefore tries to avoid water and dissolve in grease. The net effect is that soaps are attracted to both water and greases are therefore valuable cleansers.



When soaps are dispensed into water, the long hydrocarbon chain clusters together in a tangled hydrophobic ball, while the ionic heads on the surface of the cluster stick out into the water layer. These spherical clusters are known as micelles and are shown below. The ball depicts the ionic head (polar end) of the fatty acid (carboxylate salt) whereas the chain represents the hydrocarbon chain (non-polar end).

Soap works because it has a polar 'head' which interacts with water, and an alkyl nonpolar 'tail' which can interact with compounds that are non-polar such as grease. Many of these molecules come together to form a micelle, where the polar heads face outward to the water, while the tails point inward. This allows the grease to be dispersed and washed away.



Above is a micelle with some greasy material dissolved in the interior. The circles represent the polar heads (the –COO⁻), while the lines represent the non-polar tails (the alkyl chain).