**Properties of Carboxylic Acids**

Since carboxylic acids are structurally related to both ketones and aldehydes, we would expect to see some similar structural properties. The carbonyl carbon of carboxylic acids is sp^2 hybridized with an approximate bond angle of 120°. The electronegative oxygen also make the carbonyl carbon partially positively charged and susceptable to nucleophilic attack.

Carboxylic acids with more than six carbons are only slightly soluble in water, but alkali metal salts of carboxylic acids are often quite water soluble because of their ionic nature. Other carboxylic acid derivatives, such as acid chlorides, anhydrides, and esters, are quite insoluble in water. Acid chlorides and anhydrides react with water, as we will see later. Some amide derivatives are also soluble in water.

Like alcohols, carboxylic acids are strongly associated because of hydrogen bonding. Most carboxylic acids can exist as cyclic dimers held together by two hydrogen bonds, which are represented by the dashed lines.
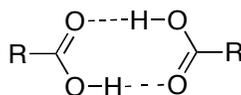

cyclic dimer

This strong hydrogen bonding has a noticeable effect on boiling points, making carboxylic acids much higher boiling than the corresponding alcohols >100°.

Dissociation of Carboxylic Acids

As the name implies, carboxylic acids are acidic. They therefore react with bases such as sodium hydroxide to give metal carboxylate salts. Like other Bronsted-Lowry acids discussed in previous courses, carboxylic acids dissociate slightly in dilute aqueous solution to give H_3O^+ ($H^+ + H_2O$) and carboxylate anions, $RCOO^-$. The carboxylate anion is stabilized by resonance where the negative charge is delocalized over both oxygen atoms. Remember that we use a double-headed arrow only when electrons are being moved (resonance forms) and not when atoms are moving.
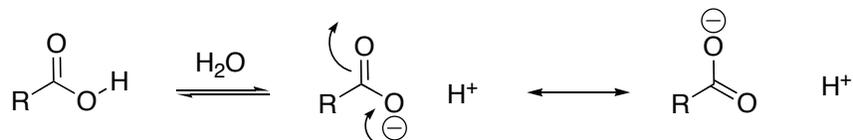
As with all acids, we can define an acidity constant K_a which equals the concentration of the carboxylate salt multiplied by the concentration of (H^+) divided by the concentration of the carboxylic acid.

$$K_a = \frac{[RCOO^-][H^+]}{[RCOOH]}$$

For most carboxylic acids, K_a is approximately 10^{-5}. Acetic acid, for example, has $K_a = 10^{-4.5}$, which corresponds to a pK_a of 4.5 ($pK_a = -\log K_a$). In practical terms, K_a values near 10^{-5} mean that only about one part in 100,000 is dissociated, as opposed to 100% dissociation found with strong mineral acids such as HCl and H_2SO_4.

Substituent Effects on Acidity

The pK_a value of a carboxylic acid is quite different when it is substituted. Since the dissociation of a carboxylic acid is an equilibrium reaction, any factor that stabilizes the carboxylate anion relative to the undissociated carboxylic acid will drive the equilibrium toward increased dissociation and result in increased acidity. For example, an electron-withdrawing group attached to the carboxyl should inductively withdraw electron density, thereby stabilizing the carboxylate anion and increase acidity. An electron-donating group would conversely do the opposite.

Electronegative substituents, such as halogens, make the carboxylate anion more stable by inductively withdrawing electrons. Fluoroacetic acid and trifluoroacetic acid are both stronger acids than acetic acid because they stabilize the carboxylate anion by inductively withdrawing electron density.


pKa = 4.5   pKa = 2.6   pKa = 0.2
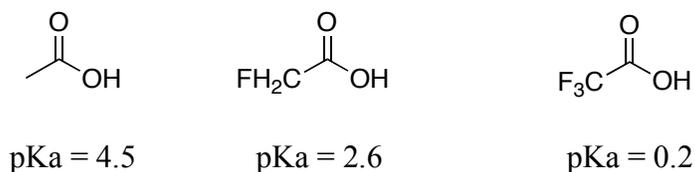
Preparation of Carboxylic Acids

You have already seen most of the methods for the preparation of carboxylic acids so here is a review.

Oxidative cleavage of an alkene with aqueous $KMnO_4$ gives a carboxylic acid if the alkene has at least one vinylic hydrogen.

Oxidation of an alkylbenzene derivative with $KMnO_4$ gives a substituted benzoic acid derivative. Both primary and secondary alkyl groups can be oxidized but tertiary groups cannot.
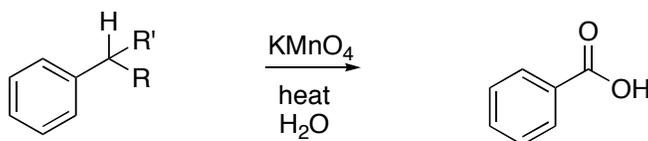
Oxidation of primary alcohols and aldehydes yields carboxylic acids when oxidized with $KMnO_4$ H_2CrO_4 or Jones reagent (CrO_3, H_2O, H_2SO_4). The oxidation of primary alcohols proceeds via an aldehyde intermediate, which is further oxidized to the carboxylic acid.
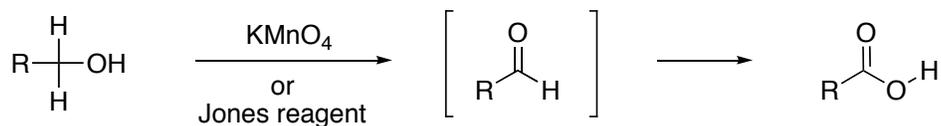
The haloform reaction converts a methyl ketone into a carboxylate salt plus a haloform (chloroform, $CHCl_3$; bromoform, $CHBr_3$; or iodoform, CHI_3) and is the qualitative test for methyl ketones.
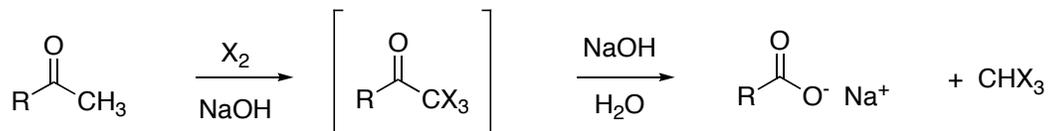
Hydrolysis of Nitriles

Nitriles, R-CN, can be hydrolyzed by strong, hot, aqueous acid or base to yield a carboxylic acid. Starting with an alkyl cyanide (nitrile) and treatment with either acid or base will yield an intermediate amide, which is further converted to the carboxylic acid and ammonia.
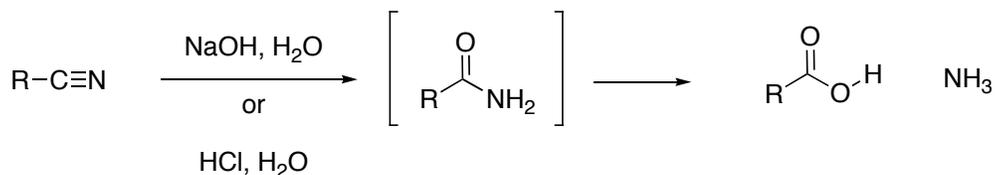

alkyl cyanide (nitrile)   amide

Carboxylation of Grignard Reagents

Another method of preparing carboxylic acids is by reacting a Grignard reagent with CO_2 to yield a metal carboxylate, which is protonated with acidic treatment. This carboxylation is usually carried out by either pouring the Grignard reagent over dry ice (solid CO_2) or by bubbling CO_2 through the Grignard reagent solution.
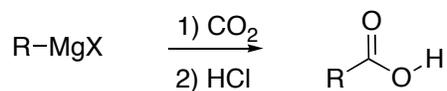

Grignard reagent

The mechanism of Grignard carboxylation is similar to that of other Grignard reactions. The organomagnesium halide adds to a C=O bond of carbon dioxide in a typical nucleophilic addition reaction. Protonation with acid then gives the carboxylic acid.
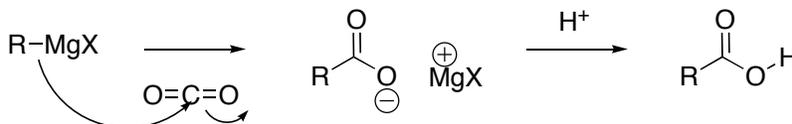
**General Reaction of any Carboxylic Acid Derivative with a Weak Nucleophile**

The chemistry of carboxylic acid derivatives is dominated by the nucleophilic acyl substitution reaction. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative, followed by expulsion of a leaving group from the tetrahedral intermediate. These reactions takes place in both acidic, and basic environments and have slight mechanistic differences. These reactions are also reversible with weak nucleophiles.

Under basic conditions, the anionic nucleophile will attack the carbonyl of the carboxylic acid derivative to form the tetrahedral intermediate. This intermediate will then displace the leaving group (shown as Y) to yield the substituted carboxylic acid and the Y anion. If the Y anion is quite basic (e.g. amide anion $R_2N:^-$ or alkoxide/hydroxide anion RO^-) it will leave only as a neutral species after protonation of the nitrogen or oxygen.
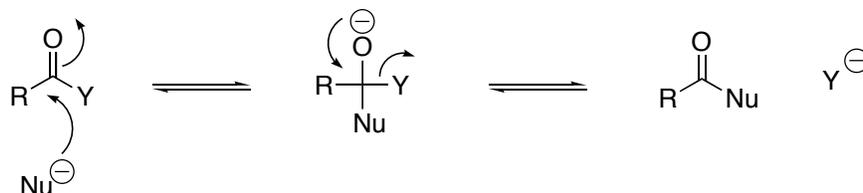
tetrahedral intermediate

Under acidic condition, a lone pair of electrons from the nucleophile will attack the protonated carbonyl group of the carboxylic acid derivative to form a positively charged tetrahedral intermediate. Loss of a proton then yields the neutral species. The intermediate then displaces the leaving group, which is protonated to yield the substituted carboxylic acid and the protonated leaving group.
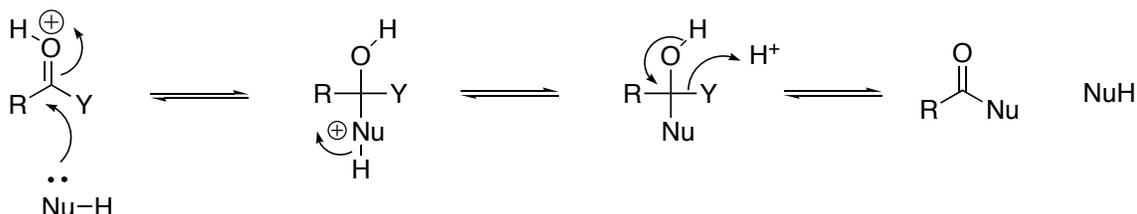
Preparation of Acid Chlorides

Acid chlorides are prepared from carboxylic acids by reaction with thionyl chloride (SOCl$_2$) by a mechanism we will not discuss now.

Hydrolysis of Acid Chlorides

Acid chlorides react under acidic or basic conditions to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution. Acid halides, anhydrides, esters and amides react in a similar fashion under these hydrolysis conditions. Under basic conditions, the hydroxide anion attacks the carbonyl group of the acid chloride to yield a tetrahedral intermediate reversibly, which then displaces the chloride irreversibly to yield the carboxylic acid. Since we are under basic conditions, the base will deprotonate the acid to yield the carboxylate salt. The displacement step of the reaction is irreversible because the chloride is a far better atom to stabilize a negative charge than the oxygen.
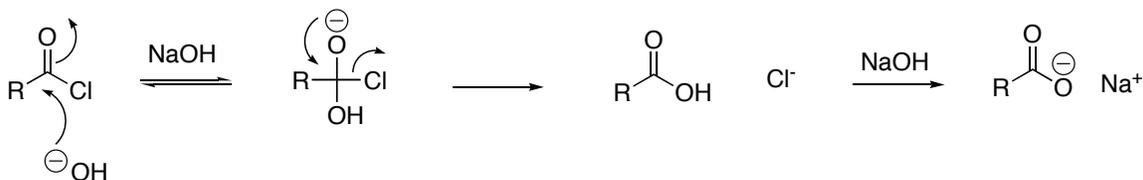
Under acidic conditions, the protonated carbonyl group of the acid chloride is attacked by water to yield the tetrahedral intermediate, which is then deprotonated to become a neutral species. The intermediate then displaces the chloride anion to yield the carboxylic acid. Once again the displacement step of the reaction is irreversible due to the reasons given above.
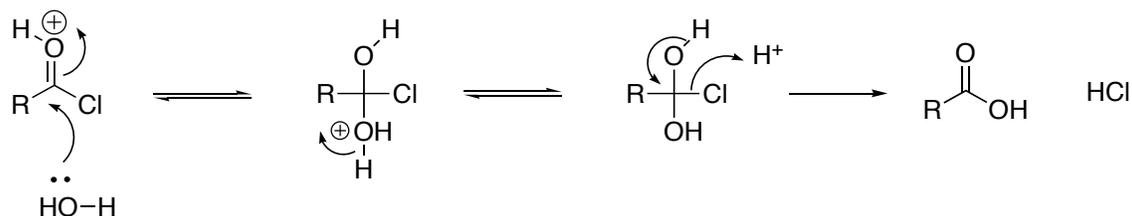
## Reactivity of Carboxylic acid Derivatives

Nucleophilic acyl substitution reactions usually take place in two steps: addition of the nucleophile and elimination of a leaving group. Although both steps can affect the overall rate of the reaction, it is generally the first step that is rate-limiting. Therefore any factor that makes the carbonyl group of the carboxylic acid derivative more easily attacked will favor the reaction.

Electronically, polarized acid derivatives are attacked more readily than less polar ones. Thus, acid chlorides are more reactive than anhydrides, which are more reactive than esters, which are more reactive than amides. This is due to the electronegative group, such as chlorine, polarizing the carbonyl group more strongly than an alkoxy group (ester) or an amino group (amide).

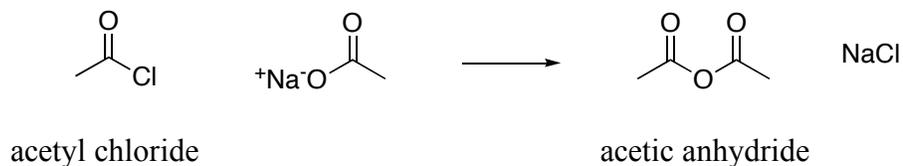
Less Reactive   More Reactive
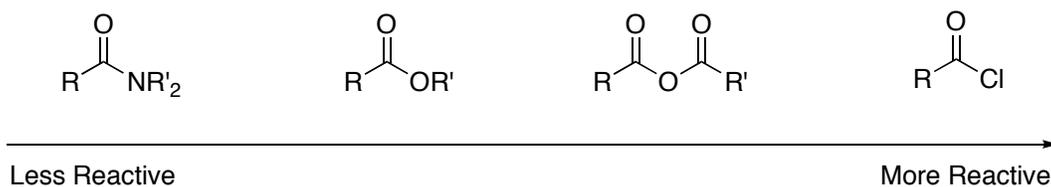
An important factor of the observed reactivity order is that it is possible to transform a more reactive acid derivative into a less reactive one. Acid chlorides for example can be converted into anhydrides, ester and amides but amides cannot readily be converted into esters, anhydrides or acid chlorides directly.

The chart below will help you remember the reactivity order and the possible transformations. The reactivity of a carboxylic acid is approximately between an anhydride and an ester. The carboxylate salt is the least reactive but is easily converted to the carboxylic acid with acidic treatment. Using the chart, the carboxylic acid can easily be converted to the acid chloride by treatment with thionyl chloride (SOCl$_2$). The acid chloride can then be converted to a less reactive derivative such as an anhydride, ester or amide. As seen from the chart, an anhydride can be directly converted to an ester or an amide. An ester can be directly converted to an amide. Each of these derivatives can be converted back to the carboxylic acid or carboxylate salt by either acid or base hydrolysis. Using the chart, an amide cannot be directly converted to an acid chloride. First the amide must be hydrolyzed to the carboxylic acid by acid or base, then reacted with thionyl chloride to yield the acid chloride.
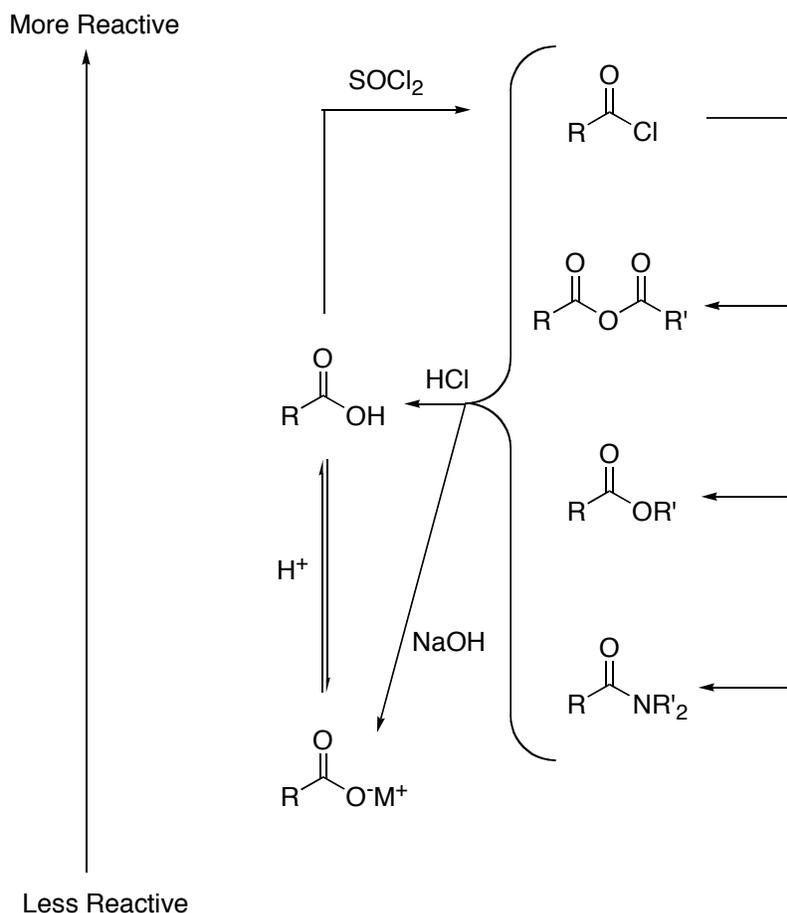
An example is the conversion of acetyl chloride to acetic anhydride. Since an acid chloride is more reactive than an anhydride, treatment of acetyl chloride with carboxylate salt of acetic acid (sodium acetate) will give acetic anhydride and sodium chloride.

acetyl chloride   acetic anhydride

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

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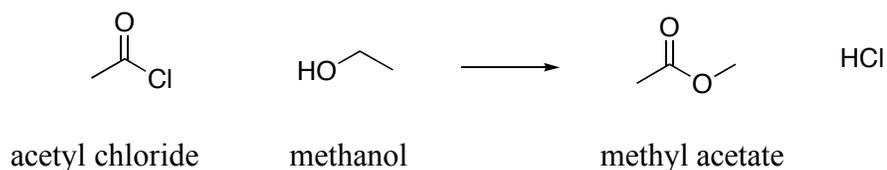
Another example is the conversion of acetyl chloride to acetamide. An acid chloride is more reactive than an amide, therefore treatment of acetyl chloride with ammonia will yield acetamide.

acetyl chloride   ammonia   acetamide
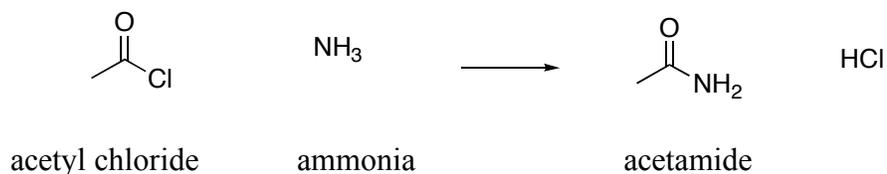
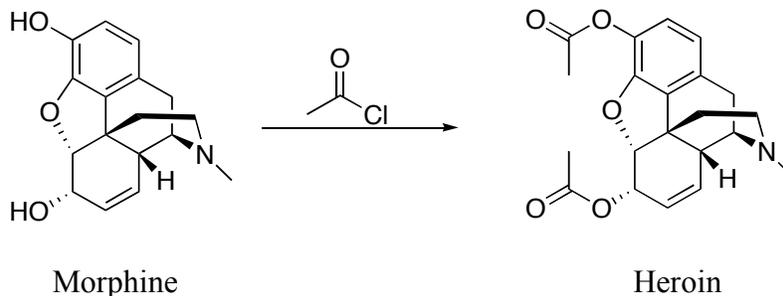In each of the above examples, the reverse reaction will NOT proceed

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.
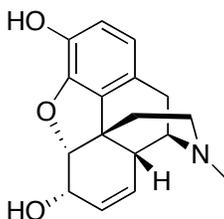
Morphine

Morphine was the first alkaloid isolated in pure form from the poppy. Morphine has addictive properties and is also an analgesic (pain killer). Therefore 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.

Morphine   Heroin