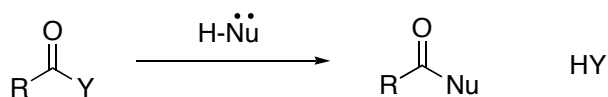


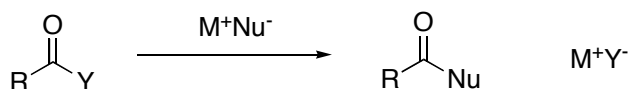
Carboxylic acids can be transformed into a variety of different derivatives in which the carboxyl -OH group has been replaced. These derivatives include acid halides, acid anhydrides, esters and amides, all which you have seen before.

The chemistry of the carboxylic acid derivatives is dominated by the nucleophilic acyl substitution reaction. Mechanistically, these substitutions take place by addition of a nucleophile to the carbonyl of the acid derivative, followed by expulsion of a polar leaving group from the tetrahedral intermediate as shown previously. This reaction can take place under acidic or basic conditions. Under acidic conditions, the lone pair of electrons on the nucleophile attacks the carbonyl group and eliminates the leaving group (Y) as HY. Under basic conditions, the nucleophile attacks the carbonyl group and eliminates the leaving group as Y<sup>-</sup> (either directly or with protonation by solvent). The Y<sup>-</sup> group may then form a salt with the metal.

Acidic conditions

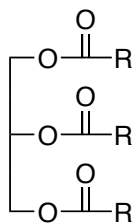


Basic conditions



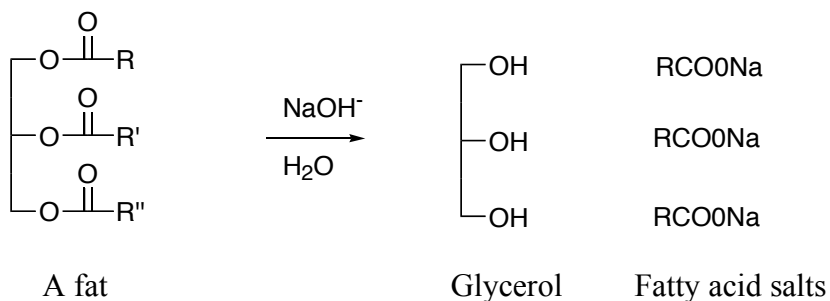
## Esters and Fats

Lipids are the naturally occurring organic molecules isolated from cells and tissues by extraction with non-polar organic solvents. Lipids are classified into two different categories: those like fats and waxes, which contain ester linkages and can be hydrolyzed, and those like cholesterol and other steroids, which don't have ester linkages and can't be hydrolyzed.



Animal fat, an ester  
(R = long hydrocarbon chains)

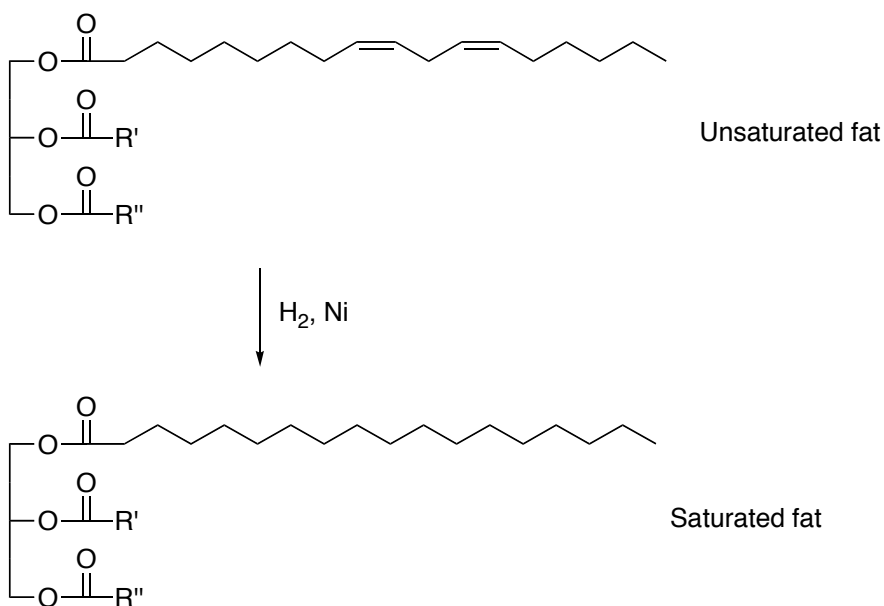
Animals fats and vegetable oils are the most widely occurring lipids. Although they appear different (animals fats like butter and lard are solid, and vegetable oils like corn and peanut oil are liquid), their structures are closely related. Chemically, a major portion of fats and oils are triacylglycerols (also called triglycerides), triesters of glycerol and three long chain fatty acids. Hydrolysis of a fat or oil with aqueous NaOH yields glycerol and three fatty acid salts as shown below (the mechanism will be discussed later).



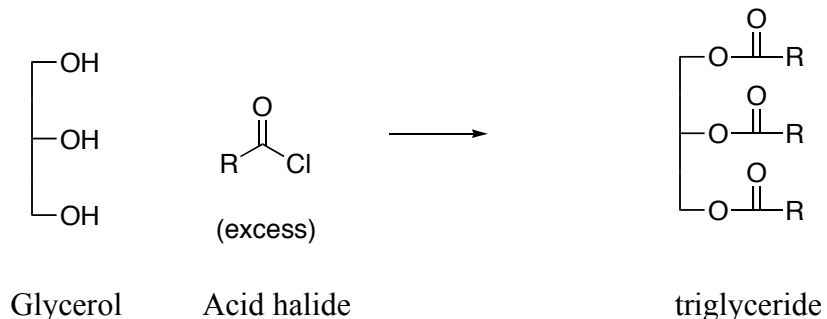
The fatty acids that are obtained after hydrolysis are often un-branched and contain an even number of carbon atoms between 12 and 20. If there are double bonds present, they are usually in the Z (cis) configuration. Usually the three fatty acids of a specific triglyceride are not the same and are in fact a complex mixture. There are about 40 different fatty acids that occur naturally.

Unsaturated fatty acids generally have a lower melting point than their saturated counterparts, a trend that holds true for triglycerides as well. Since vegetable oils generally have a higher proportion of unsaturated to saturated fatty acids than animal fats, they have lower melting points and therefore are oils at room temperature. The difference is due to the structure. Saturated fats have a uniform shape and can easily pack together in a crystal lattice. Unsaturated fats have double bonds, which produce “bends” and “kinks” in the hydrocarbon chains, making crystal formation difficult. The general trend is that the more double bonds there are, the harder it is for the molecules to crystallize and the lower the melting point of the oil.

The double bond in vegetable oils can be reduced by catalytic hydrogenation to produce saturated or partly saturated fats as shown below. The other two fatty acid chains are shown as R groups to simplify the drawing. Margarine, and solid cooking fats such as lard, are produced by hydrogenating soybean, peanut, or cottonseed oil until the proper consistency is obtained. A large problem with hydrogenating the cis double bonds in fatty acids are that the double bond sometimes isomerizes to the trans (E) configuration to produce what is known as trans fats.

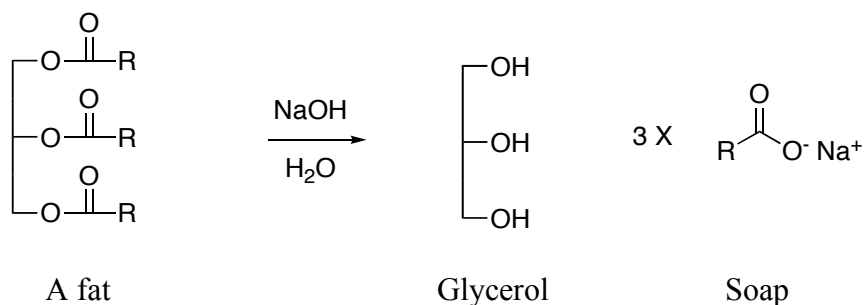


Triglycerides can also be synthesized by the addition of an acid halide with glycerol as shown below. The acid halide is added in excess (xs) to ensure complete conversion of the glycerol.



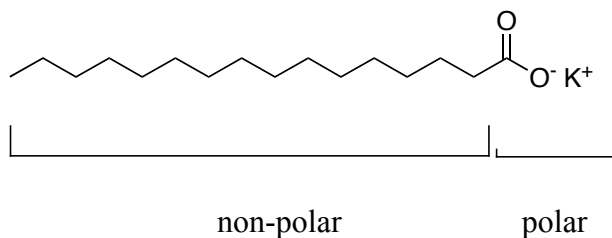
## Soap

Soap is a mixture of the sodium or potassium salts of the long chain fatty acids produced by the hydrolysis (saponification) of animal fat with alkali. Wood ash or pot ash, was used as a source of alkali until the mid 1800's, when NaOH became commercially available. Potash is formed from burnt plant material and consists of mainly potassium carbonate ( $\text{K}_2\text{CO}_3$ ) and potassium hydroxide (KOH).

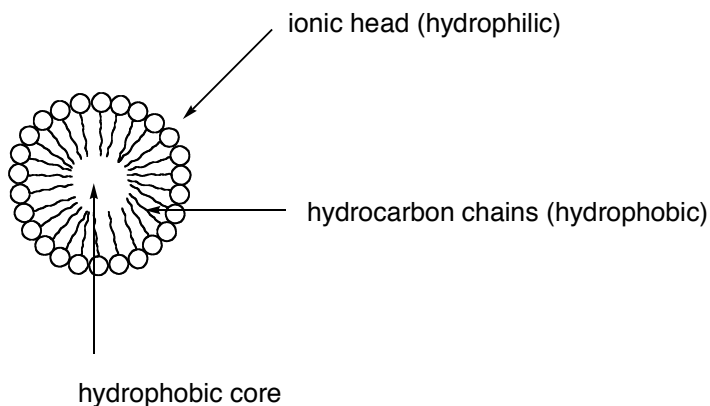


Crude soap curds contain glycerol and excess alkali as well, but the soap can be purified by boiling with water and adding NaCl to precipitate the pure sodium carboxylate salts. The salts are collected, perfume is added and the substance is pressed into bars for household use.

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.

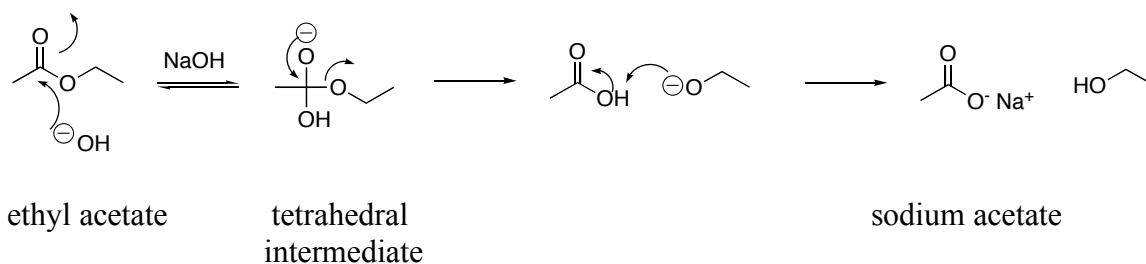


When soaps are dispensed into water, the long hydrocarbon chain clusters together in a tangled hydrophobic ball, while the ionic heads on the surface of the cluster stick out into the water layer. These spherical clusters are known as micelles and are shown below. The ball depicts the ionic head (polar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



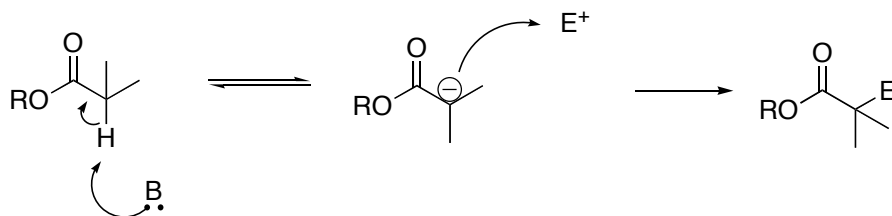
## Mechanism of Saponification (Ester hydrolysis)

Ester hydrolysis in basic solution is called saponification, after the Latin *sapo*, meaning “soap”. Ester hydrolysis occurs through the typical acyl substitution pathway as shown below, in which the hydroxide ion is the nucleophile that adds to the ester carbonyl group to give a tetrahedral intermediate. Loss of the alkoxide ion then gives the carboxylic acid, which is immediately deprotonated by the alkoxide ion to give the carboxylate salt.



## Reaction at the $\alpha$ -Carbon

Alpha substitution reactions of esters occur at the position next to the carbonyl group, and involve the substitution of an  $\alpha$ -hydrogen atom with some other group through an enolate intermediate. Just like in ketones, the  $\alpha$ -hydrogen's of an ester are acidic ( $\text{pK}_a \sim 25$  compared to  $\text{pK}_a \sim 20$  for ketones) and undergo similar reactions. The general reaction scheme involves deprotonation of the  $\alpha$ -hydrogen to give the enolate, which is stabilized through resonance. The enolate then attacks an electrophile to complete the substitution in a similar way to ketones.

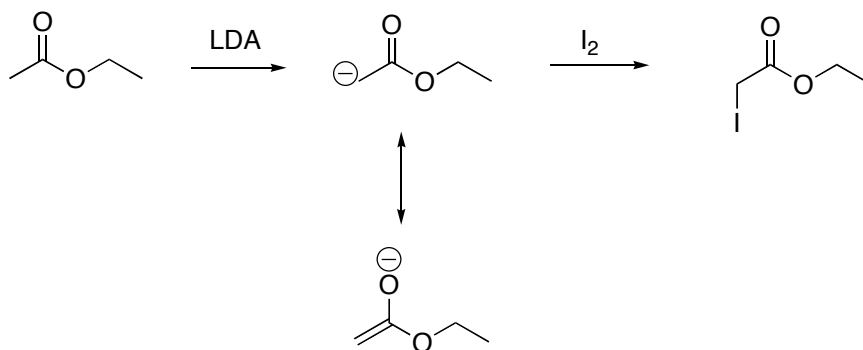


The difference in the pKa between ketones/aldehydes and esters is due to the oxygen attached to the carbonyl in the ester. The ester oxygen has the ability to donate electron density into the electron poor carbon of the carbonyl making it less reactive than the ketone. Amides also have this effect but more so as the amide nitrogen is better at electron donation than the ester oxygen. Amide functionalities are usually planar and often have restricted rotation as a result of this resonance effect.

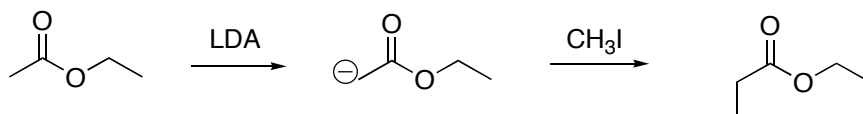


Since esters can undergo similar reactions to that of ketones, it is possible to halogenate, alkylate, acylate and do aldol reactions with esters. Below are examples of each of these reactions with an ester.

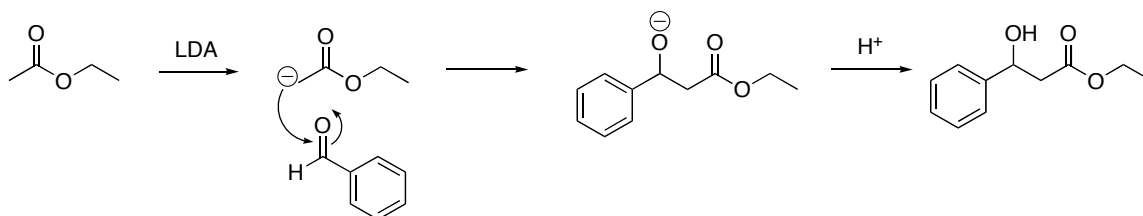
In the halogenation example below, ethyl acetate is first reacted with LDA to produce the resonance stabilized enolate intermediate. The enolate then reacts with the halogen ( $I_2$  in this case) to yield ethyl iodoacetate.



In the alkylation example below, ethyl acetate is first reacted with LDA to give the enolate, then added methyl iodide reacts to alkylate the  $\alpha$  position to yield ethyl propionate (ethyl propanoate).



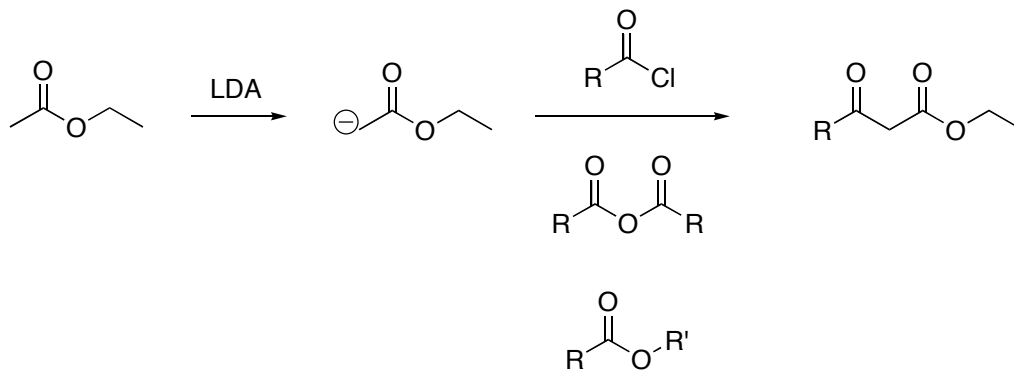
In the aldol example below, ethyl acetate is first reacted with LDA to produce the enolate, then benzaldehyde is added to give the deprotonated  $\beta$ -hydroxy ester. Upon protonation with acid, the  $\beta$ -hydroxy ester is formed.



ethyl acetate

$\beta$ -hydroxy ester

With acylation reactions, a variety of different reagents can be used including acid halides, anhydrides or esters. The general reaction scheme involves treatment of the ester with LDA to produce the enolate. Addition of an acylating agent such as an acid halide, anhydride or other activated ester then yields the acylated product.





An example is the acylation of ethyl acetate with benzoyl chloride. Ethyl acetate is first reacted with LDA to form the enolate, which is then added to benzoyl chloride to produce the tetrahedral intermediate. Elimination of the chloride anion then forms the  $\beta$ -keto ester product.

