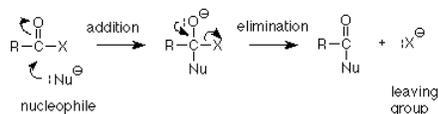


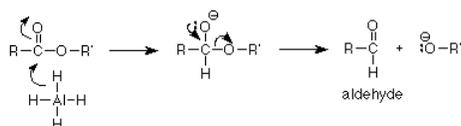
## 1.11: Fats, Fatty Acids, Detergents

### Biosynthesis of Fats

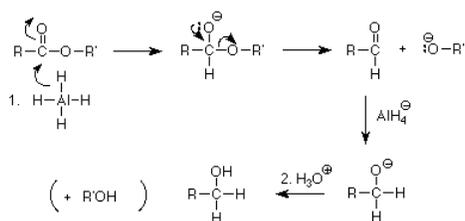
We've seen that carboxylic acid derivatives react with nucleophiles to give substitution products in which the leaving group is replaced by the attacking nucleophile.



This same pattern describes the first steps in the reaction of esters with lithium aluminum hydride and Grignard reagents, but in both cases the reaction proceeds further because the first product formed also reacts with the reagent. For an example, let's look at the reduction of an ester with lithium aluminum hydride.

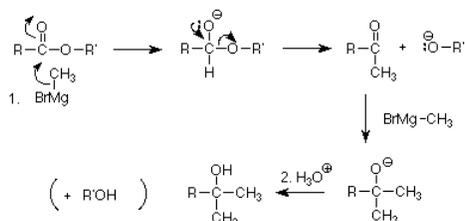


When the "hydride ion" ( $\text{H}^-$ ) from lithium aluminum hydride replaces the  $\text{OR}'$  group of the ester, an aldehyde is formed. We've already seen that an aldehyde is reduced by lithium aluminum hydride, so it comes as no surprise that the aldehyde is immediately reduced to a primary alcohol. In fact, the aldehyde is more electrophilic than the ester, so as soon as a few molecules of aldehyde are formed, they are attacked by the hydride in preference to the ester. The reaction is completed by the later addition of aqueous acid to protonate the  $\text{O}^-$  atoms.



The result is that esters are reduced by lithium aluminum hydride to primary alcohols in which the ester carbon has become the alcohol carbon. Sodium borohydride is not reactive enough to carry out this reduction. This is a useful way to make primary alcohols.

A very similar process occurs when an ester reacts with a Grignard reagent. Remember that the Grignard reagent serves as a source of carbon nucleophiles. We can use the same pattern as worked for the lithium aluminum hydride reduction by replacing the "H:" with the "C:" from the Grignard reagent. Here's an example in which the Grignard reagent is methylmagnesium bromide:



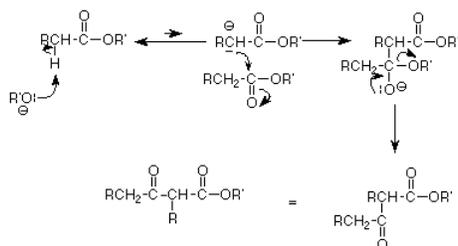
Here the first product is a ketone in which the  $\text{OR}'$  group of the ester has been replaced by the alkyl group of the Grignard reagent. This ketone is immediately attacked by another molecule of the Grignard reagent. After neutralization with aqueous acid the product is an alcohol in which the two identical groups attached to the alcohol carbon are from the Grignard reagent. If the R group of the ester is a carbon group this will be a tertiary alcohol.

In both these cases, we've combined a the general pattern for carboxylic acid derivatives, substitution of the nucleophile in place of the leaving group, with a pattern which applies to aldehydes and ketones, to arrive at "double" reaction. The first part is substitution

and the second part is addition. We can't stop the reaction halfway, because aldehydes and ketones are more reactive than esters, so the aldehydes and ketones gobble up the reagent faster than the esters.

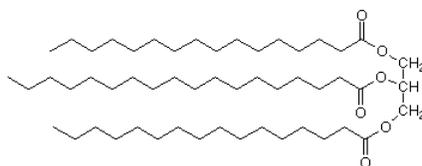
We spent some time on the aldol condensation when we were studying aldehydes, and we learned that the alpha C-H bonds of aldehydes and ketones can be attacked by base to form enolates. The same thing can occur with esters, although we need to be very specific about the identity of the base we use -- it needs to be the same as the OR' (alcohol derived) portion of the ester. (That will make a bit more sense later).

The first step in such a reaction is strictly analogous to making an enolate from an aldehyde. This is followed by attack of the nucleophilic alpha carbon of the enolate on the carbonyl carbon of a second molecule of the ester. Again, this is strictly analogous to the situation in the aldol reaction, and it has resulted in a nucleophilic addition to the carbonyl carbon. As is typical for carboxylic acid derivatives, the next step is loss of the leaving group, so that the carbonyl group which has been added to shows up as a ketone. (Since the newly-formed ketone is in a beta position relative to the ester functional group these compounds are called beta-keto-esters.) This overall reaction is called the Claisen condensation after Ludwig Claisen, a prominent German organic chemist of the late 19th and early 20th centuries.



While this reaction is of considerable use for synthesis in organic chemistry, we are going to turn our attention to the involvement of this pattern in the biological synthesis of fatty acids.

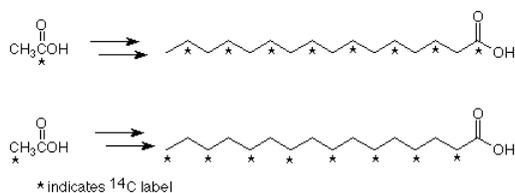
First we need to know something about the structures of fats. Fats are esters in which the OR' (alcohol) portion of the molecule is the trihydroxy compound, glycerol (HOCH<sub>2</sub>CHOHCH<sub>2</sub>OH). There are three carboxylic acid portion in these molecules since each glycerol molecule can be esterified with a different carboxylic acid. They are consequently called triacylglycerols or triglycerides. These carboxylic acids typically have long hydrocarbon chains of fourteen to twenty carbons (including the carbonyl carbon). These chains are typically unbranched and, most strikingly, they contain even numbers of carbon atoms. The carboxylic acids obtained by hydrolysis of fats are called fatty acids.



Since most carbons in fats are completely reduced (maximum number of hydrogens, no oxygens), the oxidation of fats produces substantial quantities of energy, about double the energy per gram as is obtained from the more oxidized carbohydrates and proteins. Fats are thus used for long-term energy storage in organisms.

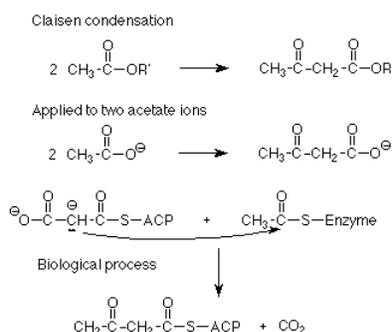
The observation that fatty acids have even numbers of carbons in them provides a clue as to the mechanism of their biological synthesis. The most obvious idea is that fatty acids are built up two carbons at a time, which would mean that each fatty acid would have to have an even number of carbons. A common two carbon molecule in biochemistry is acetic acid. (At the near acid/base neutrality which prevails in biological systems, acetic acid is present as its conjugate base, acetate ion).

This speculation was verified by feeding organisms with radioactively labeled (<sup>14</sup>C) acetate. The radioactive label appeared in the fats. More specifically, if the <sup>14</sup>C was placed in the carbonyl carbon of the acetate, it appeared in the odd numbered locations in the fatty acid. If it was placed in the methyl carbon of the acetate, it appeared in the even numbered carbons in the fatty acid.



This is interpreted to mean that the fatty acid is built up two carbons at a time. Each two carbon unit is added by reacting the alpha carbon of one acetate unit with the carbonyl carbon of the next -- exactly the pattern which we see in the Claisen condensation.

Of course, there is much more to the process than this, but the key bond forming step has the same pattern as the Claisen condensation. That is, attack by nucleophilic carbon atom at the carbonyl carbon of an ester, which is followed by loss of the alcohol portion of the ester as a leaving group. In the the biological reaction, the esters have sulfur in them rather than oxygen and are attached to enzymes or other proteins, and the nucleophilic carbon is flanked by not one but two carbonyl groups. Nevertheless, the underlying pattern is the same.



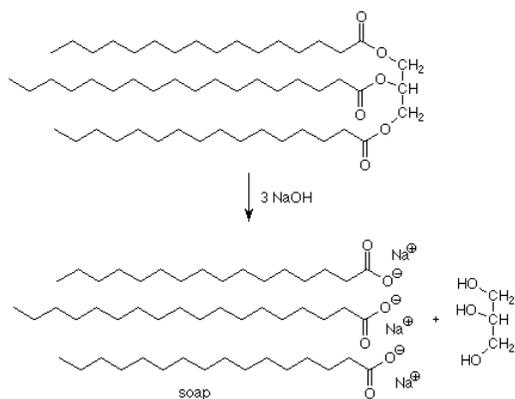
The biological Claisen condensation we have looked at is followed by further biochemical steps which replace the carbonyl oxygen with two hydrogens. The four carbon ester which is thus produced is attacked at its carbonyl carbon by another molecule of the carbon nucleophile and the cycle continues.

It is important to realize that biological chemistry uses the same mechanisms that we use in the laboratory. Organic reaction mechanisms underlie all of biochemistry, particularly metabolism.

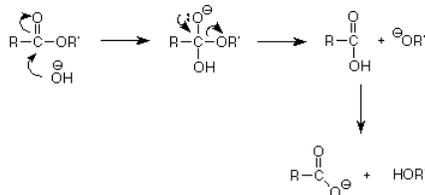
## Saponification and Soaps

Next, we'll look at a reaction of fats which is of great economic importance. Nobody knows when the first soap was made, but it was very important in the Middle Ages and early industrial period because it was used to wash out wool fat from wool in preparation for dyeing and spinning. It was too expensive in those times to use for general cleanliness. The general availability of soap has led to a rise in standards of cleanliness and a corresponding rise in general health.

Soap is made by treating fats with a strong solution of lye (NaOH). The ester functional groups are hydrolyzed releasing its alcohol portion as glycerol and the acid portions as the a mixture of the sodium salts of the fatty acid. The glycerol is water soluble and is separated from the fatty acid salts. These are nearly insoluble in water, and are washed and compressed into a cake -- soap.

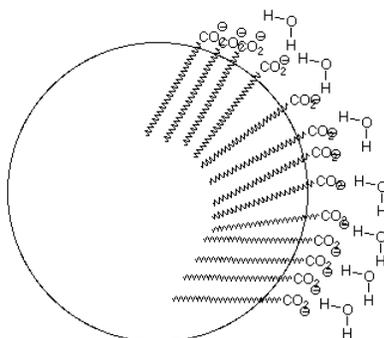


The mechanism of this reaction, which is called saponification) can be illustrated more easily on a simple ester than a fat. It follows the normal pattern for a carboxylic acid derivative and the first step is analogous to base-catalyzed hydration of aldehydes -- attack of the nucleophile hydroxide ion at the carbonyl carbon atom. This is followed by the usual departure of the leaving group (in this case, the  $\text{OR}'$  of the ester). Since the  $\text{OR}'$  is more basic than  $\text{RCOO}'$ , the last step is a neutralization reaction. (The last step will make more sense after next time.)

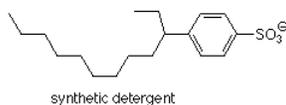


## Detergent Structure

To finish up, we need to look at how soaps work and how that relates to their structures. Soaps are "bridge" molecules. Their long hydrocarbon chains are very much like oils, so they mix well with oils. In fact, we can say that the chains of soap dissolve in oils. At the same time, their ionic heads are polar enough to dissolve in water. If we imagine a small globule of oily material which has dissolved a bunch of soap molecules, we can see that the polar ionic heads will stick out (insoluble in oil) at the surface. These polar bumps on the surface attract water molecules, so that the oily glob is coated with water molecules that are held there by the ions. The glob is now ready to be washed away in water. Since much of the dirt we hope to get rid of is held in place by oily films, removing the oils removes the dirt.



The structural requirements for a soap (or more generally, for a detergent) are a long hydrocarbon tail (12 or more carbons) and a polar (often ionic) head. In synthetic detergents, the hydrocarbon tail is usually formed by linking several ethylene molecules together and attaching this to a benzene ring. The polar part is derived by covalently bonding the sulfur of a sulfate ion to the benzene ring. We'll learn more about the chemistry of making these later. If there are few branches on the hydrocarbon tail, the synthetic detergent will be biodegradable, an important characteristic.



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