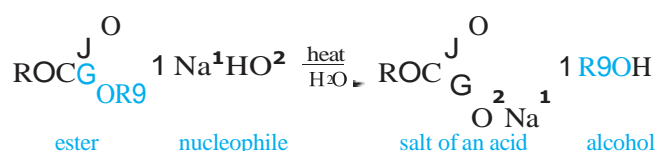


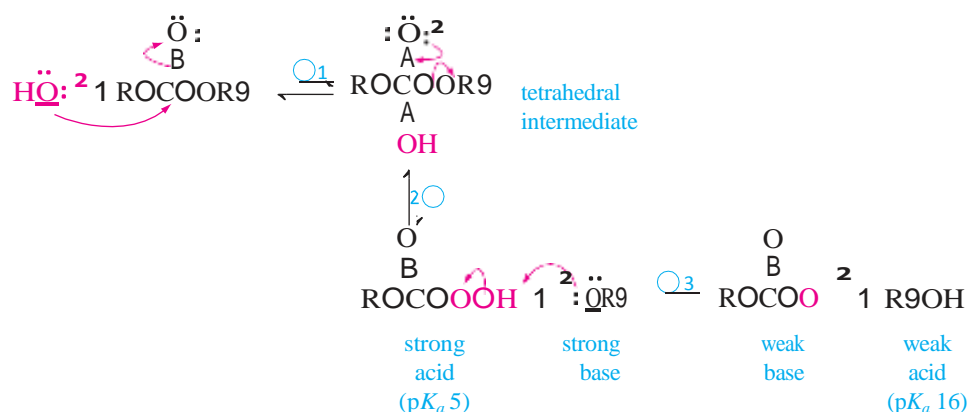
13 Saponification of Esters

Esters are commonly hydrolyzed with base. The reaction is called **saponification** (from the Latin *sapon*, soap) because this type of reaction is used to make soaps from fats (Chapter 15). The general reaction is as follows:

Saponification is the hydrolysis of an ester with a base.



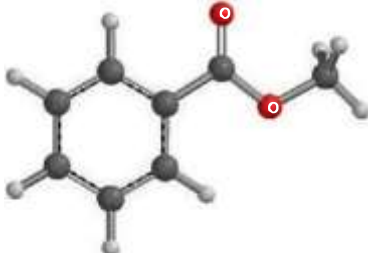
The mechanism is another example of a nucleophilic acyl substitution. It involves nucleophilic attack by hydroxide ion, a strong nucleophile, on the carbonyl carbon of the ester.



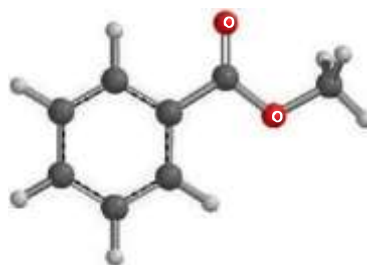
The key step is nucleophilic addition to the carbonyl group (step 1). The reaction proceeds via a tetrahedral intermediate, but the reactant and the product are trigonal. *Saponification is not reversible*; in the final step (3), the strongly basic alkoxide ion removes a proton from the acid to form a carboxylate ion and an alcohol molecule—a step that proceeds completely in the forward direction.

Saponification is especially useful for breaking down an unknown ester, perhaps isolated from a natural source, into its component acid and alcohol for structural determination.

PROBLEM Following eq. write an equation for the saponification of methyl benzoate.

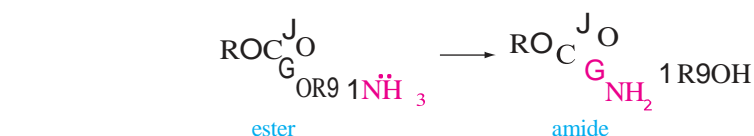


The image shows a ball-and-stick model of methyl benzoate. It consists of a benzene ring (a hexagon of six carbon atoms, each bonded to one hydrogen atom) attached to a carboxylate group. The carboxylate group is represented by a central carbon atom double-bonded to one oxygen atom and single-bonded to another oxygen atom, which is in turn single-bonded to a methyl group (a carbon atom bonded to three hydrogen atoms).

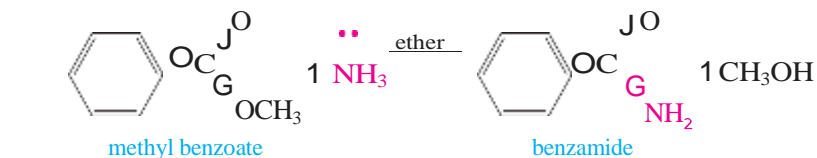


Ammonolysis of Esters

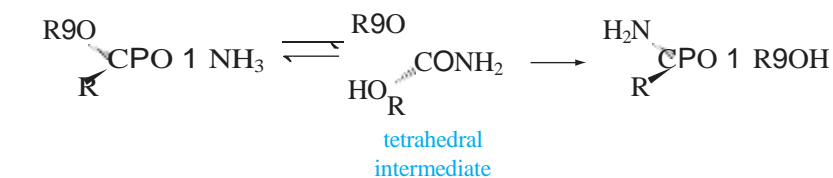
Ammonia converts esters to amides.



For example,



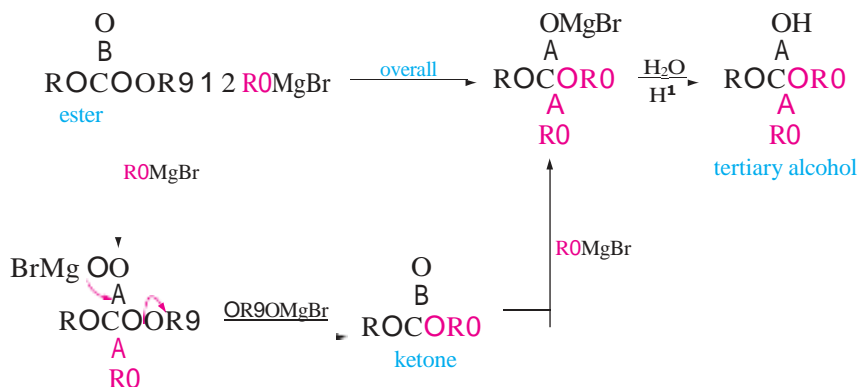
The reaction mechanism is very much like that of saponification. The unshared electron pair on the ammonia nitrogen initiates nucleophilic attack on the ester carbonyl group.



PROBLEM The first step in eq. really involves two reactions, *addition* of ammonia to the carbonyl carbon to form an ammonium alkoxide followed by a *proton transfer* from the nitrogen to the alkoxide oxygen. Illustrate this process with equations using the arrow-pushing formalism. The second step in eq. 10.26 also involves two steps, *elimination* of an alkoxide (R^2O^-) followed by deprotonation of the hydroxyl group. Write a detailed mechanism for these steps.

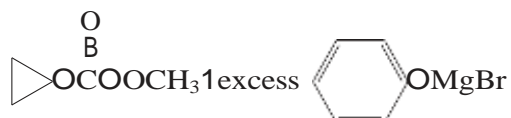
15 Reaction of Esters with Grignard Reagents

Esters react with two equivalents of a Grignard reagent to give tertiary alcohols. The reaction proceeds by *irreversible* nucleophilic attack of the Grignard reagent on the ester carbonyl group. The initial product, a ketone, reacts further in the usual way to give the tertiary alcohol.



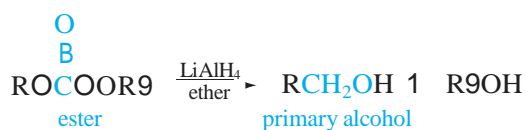
This method is useful for making tertiary alcohols in which at least two of three alkyl groups attached to the hydroxyl-bearing carbon atom are identical.

PROBLEM Using eq. as a guide, write the structure of the tertiary alcohol that is obtained from

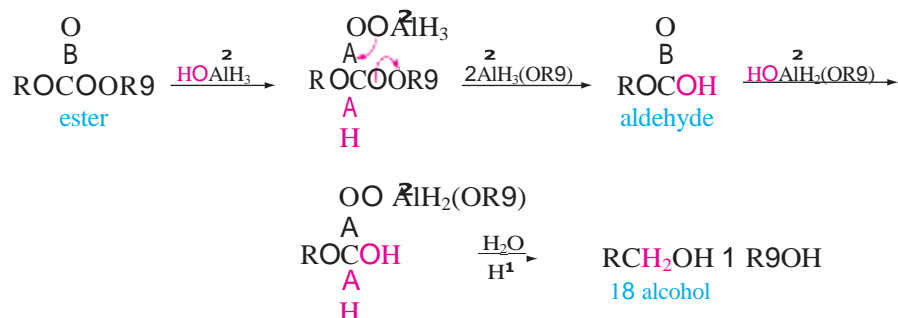


16 Reduction of Esters

Esters can be reduced to primary alcohols by lithium aluminum hydride (LiAlH_4).

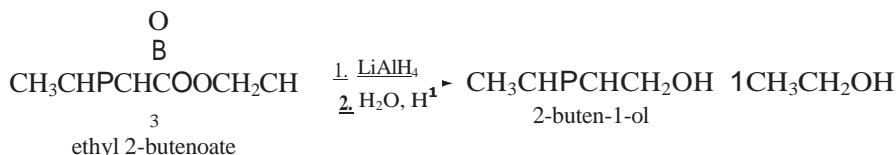


The mechanism is similar to the hydride reduction of aldehydes and ketones



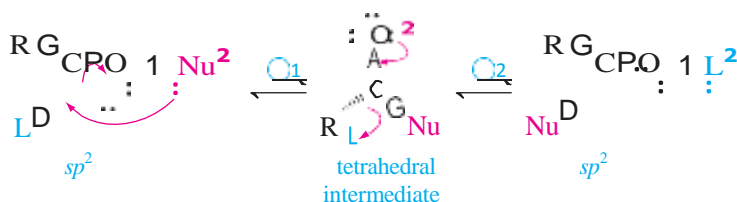
The intermediate aldehyde is not usually isolable and reacts rapidly with additional hydride to produce the alcohol.

Thus, with LiAlH_4 , it is possible to reduce the carbonyl group of an ester without reducing a C^C bond in the same molecule. For example,



1 The Need for Activated Acyl Compounds

As we have seen, most reactions of carboxylic acids, esters, and related compounds involve, as the first step, nucleophilic attack on the carbonyl carbon atom. Examples are Fischer esterification, saponification and ammonolysis of esters, and the first stage of the reaction of esters with Grignard reagents or lithium aluminum hydride. All of these reactions can be summarized by a single mechanistic equation:

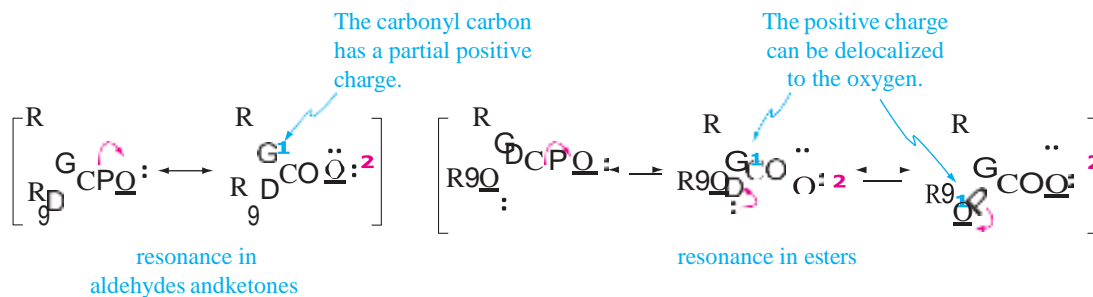


The carbonyl carbon, initially trigonal, is attacked by a nucleophile Nu^- to form a tetrahedral intermediate (step 1). Loss of a leaving group L^- (step 2) then regenerates the carbonyl group with its trigonal carbon atom. The net result is the replacement of L by Nu.

Biochemists look at eq. in a slightly different way. They refer to the overall reaction as an **acyl transfer**. The acyl group is transferred from L in the starting material to Nu in the product.

Regardless of how we consider the reaction, one important feature that can affect the rate of both steps is the nature of the leaving group. *The rates of both steps in a nucleophilic acyl substitution reaction are enhanced by increasing the electron-withdrawing properties of the leaving group.* Step 1 is favored because the more electronegative L is, the more positive the carbonyl carbon becomes, and therefore the more susceptible the carbonyl carbon is to nucleophilic attack. Step 2 is also facilitated because the more electronegative L is, the better leaving group it becomes.

In general, esters are *less* reactive toward nucleophiles than are aldehydes or ketones because the positive charge on the carbonyl carbon in esters can be delocalized to the oxygen atom. Consequently, the ester is more stable and less prone to attack.



Now let us examine some of the ways in which the carboxyl group can be modified to *increase* its reactivity toward nucleophiles.

18 Acyl Halides

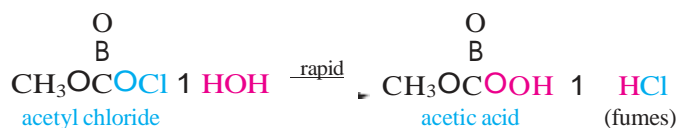
Acyl halides are among the most reactive of carboxylic acid derivatives. *Acyl chlorides* are more common and less expensive than bromides or iodides. They can be prepared from acids by reaction with thionylchloride.



The mechanism is similar to that for the formation of chlorides from alcohols and thionyl chloride. The hydroxyl group is converted to a good leaving group by thionyl chloride, followed by a nucleophilic acyl substitution in which chloride is the nucleophile (compare with Sec. 7.10). Phosphorus pentachloride and other reagents can also be used to prepare acyl chlorides from carboxylic acids.



Acyl halides react rapidly with most nucleophiles. For example, they are rapidly hydrolyzed by water.

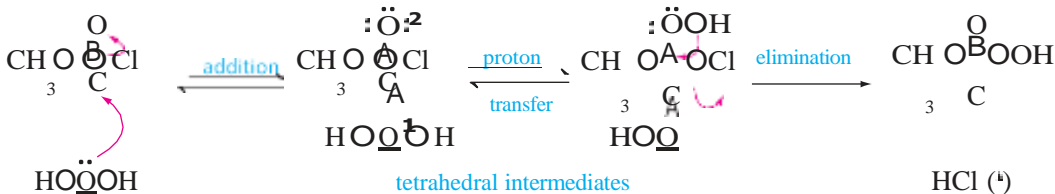


For this reason, acyl halides have irritating odors. Benzoyl chloride, for example, is a lachrymator (tear gas).

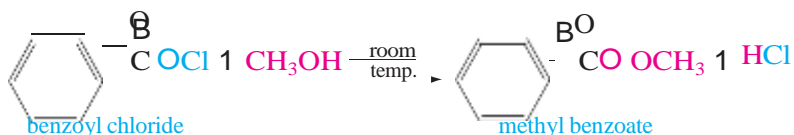
EXAMPLE

Write a mechanism for the reaction shown in eq.

Solution Nucleophilic addition of water to the carbonyl group, followed by proton transfer and elimination of HCl from the tetrahedral intermediate, gives the observed products.



Acyl halides react rapidly with alcohols to form esters.



Indeed, the most common way to prepare an ester *in the laboratory* is to convert an acid to its acid chloride, then react the latter with an alcohol. Even though two steps are necessary (compared with one step for Fischer esterification), the method may be

preferable, especially if either the acid or the alcohol is expensive. (Recall that Fischer esterification is an equilibrium reaction and must often be carried out with a large excess of one of the reactants.)

PROBLEM Rewrite eq. 10.32 to show the preparation of benzoyl chloride.

PROBLEM Explain why acyl halides may be irritating to the nose.

PROBLEM Write a mechanism for the reaction shown in eq. 10.35.

Acyl halides react rapidly with ammonia to form amides.



acetyl chloride acetamide

The reaction is much more rapid than the ammonolysis of esters. Two equivalents of ammonia are required, however—one to form the amide and one to neutralize the hydrogen chloride.

Acyl halides are used to synthesize aromatic ketones, through Friedel–Crafts acylation of aromatic rings (review Sec. 4.9.d).

PROBLEM 10.25 Devise a synthesis of 4-methylphenyl propyl ketone from toluene and butanoic acid as starting materials.

