

1.9: Carboxylic Acid Derivatives- Interconversion

Structures of Carboxylic Acid Derivatives

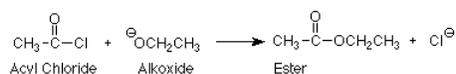
Last time we completed our study of the reactions of aldehydes and ketones, compounds in which a carbonyl group is bonded either to carbons or hydrogens. The typical reaction pattern for these compounds was addition, with a nucleophile adding to the carbonyl carbon and an electrophile adding to the carbonyl oxygen. Today we'll look at carboxylic acid derivatives. This group of compounds also contains a carbonyl group, but now there is an electronegative atom (oxygen, nitrogen, or a halogen) attached to the carbonyl carbon. This difference in structure leads to a major change in reactivity. Here we find that the reactions of this group of compounds typically involve substitution of the electronegative atom by a nucleophile. Before looking at that reaction in detail, though, let's see what kind of compounds we're talking about.

Name	Structure	Found or Used In:
Carboxylic Acid	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$	Vinegar, Cream of Tartar
Ester	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}'$	Fats, Cell Membranes
Amide	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NHR}'$	Nylon, Proteins
Acyl Chloride	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Cl}$	Synthesis of Carboxyl Derivatives
Acid Anhydride	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$	Synthesis of Carboxyl Derivatives

Notice that each of these functional groups has either an oxygen, a nitrogen, or a halogen attached to the carbonyl carbon.

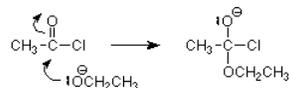
Substitution by Addition-Elimination

The typical reactions of these compounds are substitutions -- replacing one of these heteroatoms by a another atom. Here's an example:



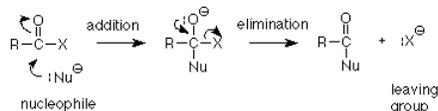
The chlorine of the acyl chloride has been replaced by the OCH_2CH_3 , more specifically by the oxygen atom of that group. This type of reaction, in which an atom or group is replaced by another atom or group, is called a substitution reaction.

We can begin to connect this reaction type with what we have seen earlier by thinking about the mechanism. We notice that the O^- end of the group (called an alkoxide) which is doing the substituting is very much like the oxygen in an OH^- . Since we've seen the OH^- act as a nucleophile when it attacked the electrophilic carbon of a carbonyl group, let's begin by seeing what happens if we use the same approach here.



The first step is familiar from aldehyde and ketone chemistry. The nucleophilic oxygen uses its electrons to make a new bond to the electrophilic carbonyl carbon while the pi bond's electrons move to the carbonyl oxygen. We've made the necessary oxygen-carbon bond. In the next step, the pi bond is reformed, and the carbon-chlorine bond is broken. This is a new type of step, and it happens when breaking this bond is eased by the electron pair being attracted to an electronegative atom such as oxygen, nitrogen or a halogen. This step is called an elimination. The overall substitution process occurs by an addition-elimination mechanism which begins with a nucleophilic addition to the carbonyl group and finishes with the departure of an atom with the bonding pair of electrons. This atom or group is called a "leaving group."

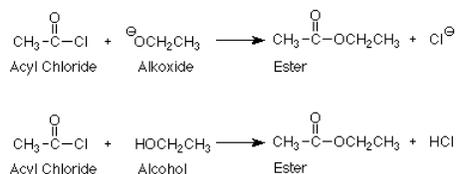
Here's a general statement of the mechanism:



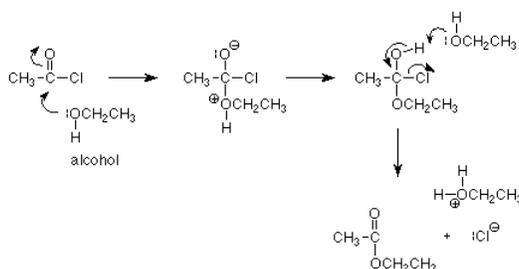
As we look at some specific examples, keep this pattern in mind. There will be some elaborations on it, but we will always find an addition step in which the nucleophile attacks and an elimination step in which the leaving group leaves.

Esters - Preparation and Mechanisms

The conversion of acyl chlorides to esters is more commonly carried out by using an alcohol rather than an alkoxide (RO⁻).

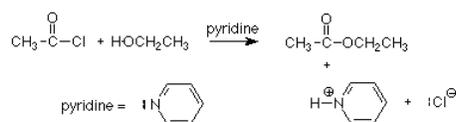


The mechanism of this reaction starts just the same way the earlier one did; the first step is attack of the nucleophile at the carbonyl carbon. In this instance, the nucleophile is an unshared electron pair on a neutral oxygen atom. The intermediate formed in this step rapidly shifts a proton (H⁺) to the O⁻. Such transfers of protons between oxygen atoms or nitrogen atoms are fast. (These intermediates are called "tetrahedral intermediates" since carbonyl carbon has been changed to a tetrahedral geometry and an sp³ hybridization.)

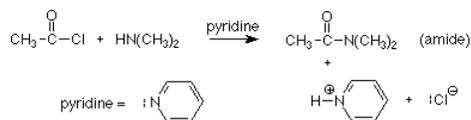


The tetrahedral intermediate loses HCl in a single step, one in which the H⁺ is transferred to a second molecule of alcohol and the Cl comes off as Cl⁻. It is important to notice that the neutral alcohol oxygen serves as the nucleophile. The O-H bond is not broken until after the C-O bond is formed. There is never any alkoxide in this reaction. Indeed, an alkoxide ion could not survive in the strongly acidic (HCl) solution. This pattern, neutral nucleophile attacks first, then the proton is removed, is very common for neutral nucleophiles and must be followed.

This is a practical and useful method for making esters, but it does make the strong acid HCl, which is often troublesome. A more practical variation is to add a weak base such as pyridine to react with the HCl and neutralize it. This gives us a procedure for making esters from acyl chlorides which uses the following reaction statement:



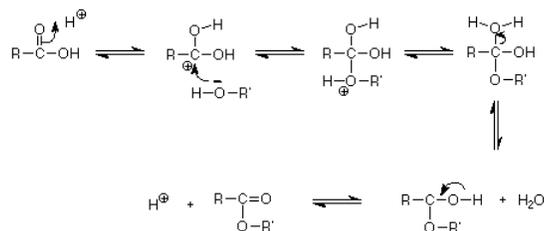
A similar procedure is used to make amides from acyl chlorides and amines (the amine must have at least one hydrogen attached to the nitrogen).



Acyl chlorides are the most reactive carboxylic acid derivatives. The electronegative chlorine atom pulls electrons toward it in the C-Cl bond, which makes the carbonyl carbon more electrophilic. This makes nucleophilic attack easier. Also, the Cl⁻ is an excellent leaving group, so that step is also fast. Because of their reactivity, acyl chlorides are easily converted into esters and amides and are thus valuable synthetic intermediates. They are made from carboxylic acids by this reaction (Atkins & Carey, Sec 12:10):



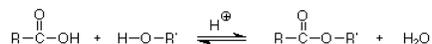
In the mechanism we just looked at, the key steps (attack of a nucleophile and departure of a leaving group) were accompanied by steps in which protons moved from one location to another. Such proton transfers are very common in acid catalyzed reactions. Here's the mechanism for the acid catalyzed formation of an ester from a carboxylic acid and an alcohol:



Notice that the nucleophilic attack is preceded by protonation of the carbonyl oxygen. We've seen this step before in the acid-catalyzed additions of nucleophiles to carbonyl groups. Its purpose is to increase the reactivity of the carbonyl carbon as an electrophile, so that it can be easily attacked by the alcohol oxygen. After nucleophilic attack, there is a proton transfer. Its purpose is to make one of the OH groups (either will do) into a good leaving group, water.

Think back to the addition of alcohols to aldehydes to produce hemiacetals. The two mechanisms start off identically. Compare them in detail, and work out the reasons for the different outcome.

Notice that each step in this mechanism is presented as an equilibrium. That means that the whole reaction represents an equilibrium in which significant amounts of carboxylic acid and alcohol co-exist with ester and water.

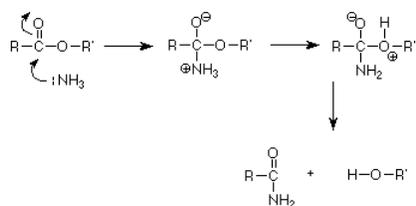


This allows us to push the reaction one way or the other by controlling concentrations, particularly of water. If we remove water from the reaction mixture, more ester is formed because carboxylic acid and alcohol react to replace the water we have removed. The resulting formation of ester is called Fischer esterification.

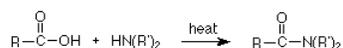
If we add water to the reaction mixture, equilibrium is restored by the production of more carboxylic acid and alcohol. This is called acid catalyzed ester hydrolysis.

Amides - Preparations

Esters can also react with amines or ammonia to form amides. This reaction doesn't involve acid catalysis, so the first step is nucleophilic attack at the carbonyl carbon. Proton transfer follows and loss of the alcohol portion of the ester.



This gives us two ways to make amides, this one from esters and the earlier one from acyl chlorides. Here's a third and very direct way to make amides, by heating carboxylic acids and amines together.



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