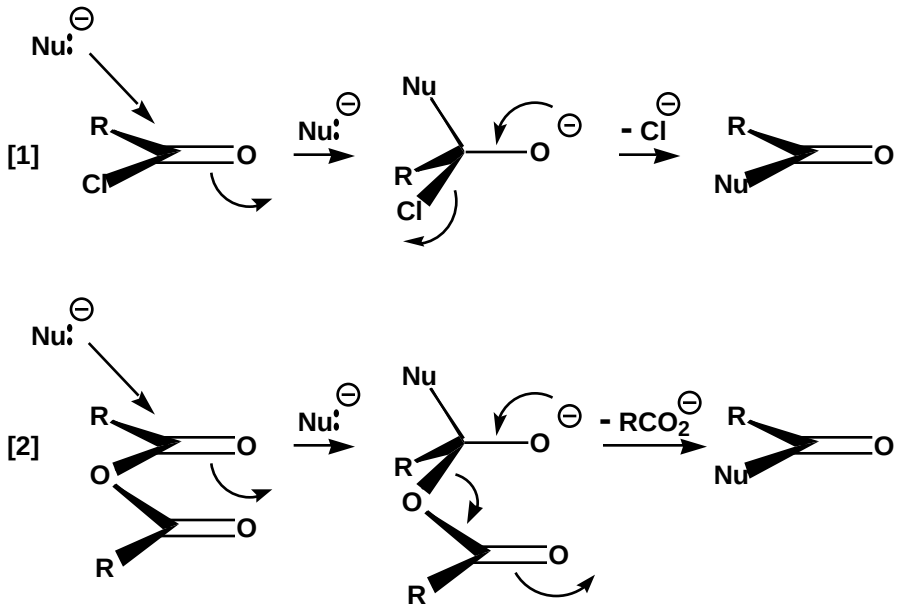
Text Related to Segment 19.01 ©2002 Claude E. Wintner

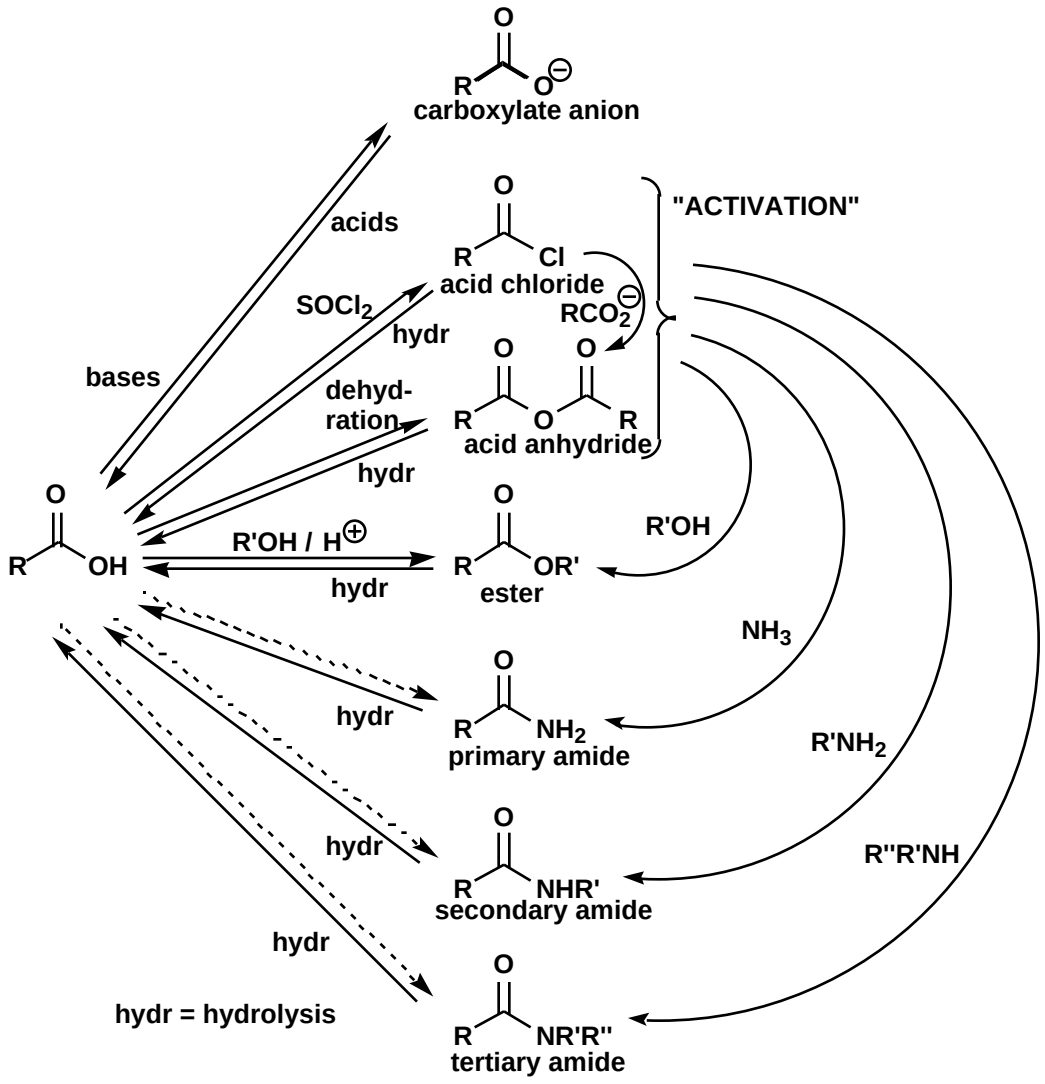
In a dichotomy that already has been introduced in Segment 16.04, aldehydes and ketones are the key players in the addition reactions of the previous section, while substitution is the rule for compounds having a leaving group attached to the carbonyl group. The common functionalities derived from carboxylic acids — acyl halides and anhydrides, esters and thioesters, and amides — all undergo substitution reactions. It is important to point out immediately that carboxylic acids themselves generally are impervious to attack by nucleophiles at the carbonyl carbon atom, and for a simple reason: as relatively strong acids, they immediately give up a proton in the presence of attacking nucleophiles (bases) such as we have been considering. This process generates a carboxylate anion, which is itself a nucleophile, a carrier of negative charge, and a species we have taken pains to label as well stabilized and lying at a relative energy minimum. Thus, we can expect carboxylates to be unreactive toward other nucleophiles.

Substitution is observed where there has been activation of a carboxylic acid by the transformation of its hydroxyl group to a functionality that no longer has a proton to give up, and is a good leaving group. Thus — to take as examples two standard specific cases which are effective in the laboratory — acid chlorides [1] have available as a leaving group the classical very weak base chloride ion, and acid anhydrides [2] contain the carboxylate anion itself built in for the same purpose:



nucleophilic attack on acyl halides and anhydrides results in substitution

The following figure summarizes a number of the most common types of substitution reaction at carbonyl carbon. When an acid chloride or acid anhydride is treated with an alcohol, an ester is the result, the nucleophilic oxygen atom of the alcohol providing the means for displacement. In like manner ammonia and primary and secondary amines lead to primary, secondary, and tertiary amides, respectively:



summary of substitution reactions at carbonyl carbon