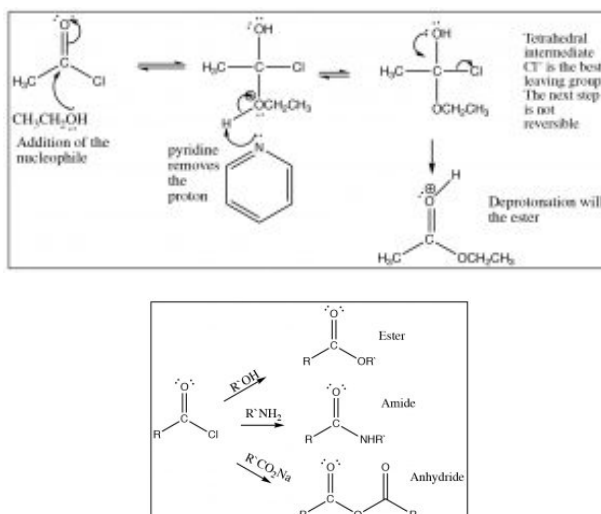


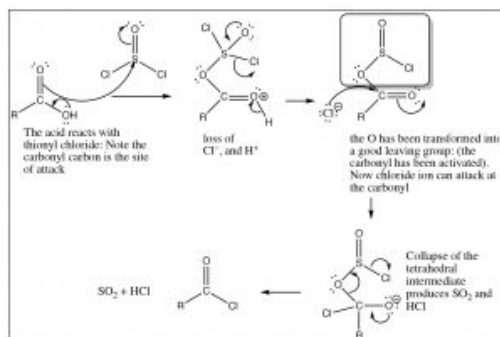
## 7.1: Interconversion of Acids and Derivatives- Predicting Outcomes

As we have just seen, esters can be made from carboxylic acids and vice versa: we can control the outcome of the reaction by using Le Chatelier's principle. This is because the tetrahedral intermediate contains only oxygen leaving groups and the reactants and products are of similar stability. However, if we react a derivative such as an acid chloride with an oxygen nucleophile, we see that the resulting reaction tends not to be reversible. It is possible to go from the acid chloride to the carboxylic acid (with  $\text{H}_2\text{O}$  nucleophile), to the ester (with an alcohol nucleophile), or to the amide (with an amine nucleophile). The reverse reaction is not feasible because 1) the tetrahedral intermediate, for either the forward or the reverse reaction, now has different leaving groups as shown below and 2) the acid chloride is highly reactive (it is destabilized by inductive withdrawal) and the reaction is unlikely to reverse under typical reaction conditions.



The tetrahedral intermediate reacts to produce the carbonyl by expelling chloride, which is the best leaving group. It is, therefore, difficult to get this reaction to reverse. In fact, the acid chloride can be used to produce all the other acid derivatives, and carboxylic acids. Reaction of acid chlorides with amines will produce amides and, with a carboxylate anion, will produce acid anhydrides as shown. In each case chloride is the best leaving group when the tetrahedral intermediate collapses, and the more stable product is formed.

You may now be asking yourself if acid chlorides are such good reactants, how can we make them in the first place? We cannot use chloride ion to do a nucleophilic addition/elimination on any other acid derivative, so how can we get around that problem? The answer is to introduce an even better leaving group into the molecule. One example is the reaction of carboxylic acids with thionyl chloride ( $\text{SOCl}_2$ ). The sulfur in thionyl chloride is highly susceptible to nucleophilic attack—much more so than the carbonyl—because of all the electronegative groups attached to it. The first step is attack by the carboxylic acid oxygen on the  $\text{SOCl}_2$ , as shown below.



The intermediate that is formed has an excellent leaving group (in the shadowed box). In effect, we have activated the carbonyl and made it more reactive. Attack of chloride ion can now proceed and the reaction will move forward because we have a better leaving group than chloride. The tetrahedral intermediate now collapses and, at the same time, the leaving group decomposes to give  $\text{SO}_2$

and hydrogen chloride<sup>[10]</sup>, both of which are gases that are expelled from the reaction mixture which drives the reaction towards products (Le Chatelier's principle).

In this reaction, we have seen a very important and powerful idea: we have been able to drive a reaction forward to produce a thermodynamically unfavorable product by producing a highly reactive intermediate. We encountered simpler examples earlier: for example, protonating an alcohol or preparing a tosyl derivative to transform OH into a good leaving group. In this case, the reaction is messy and toxic (it's no fun at all to do this reaction in a laboratory), but biological systems use this strategy to bring about thermodynamically unfavorable reactions. As we will discuss later in the course, substrate reactants can be activated by this same strategy of making an OH into a good leaving group that then leads to the formation of a product that could not be produced under normal circumstances. For example, the formation of sucrose from glucose and fructose proceeds using such a (enzyme-catalyzed) strategy. In this case, activation involves the activation of an OH group by coupling with ATP.

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