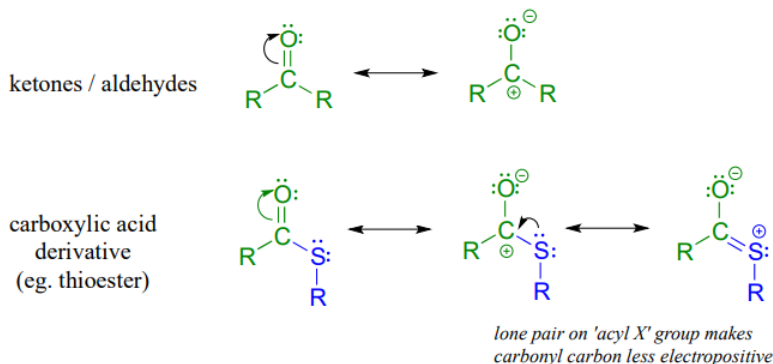


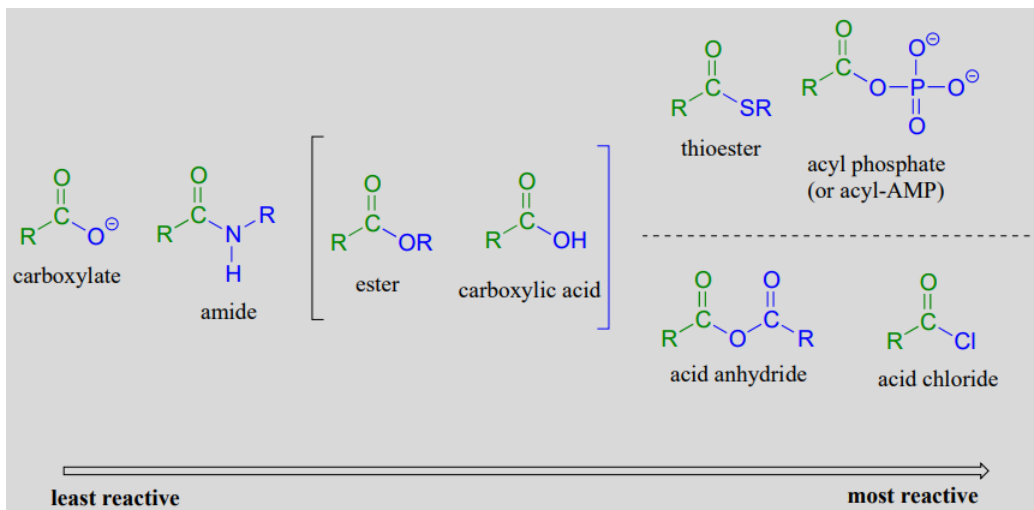
## 11.4: The Relative Reactivity of Carboxylic Acid Derivatives

In carboxylic acid derivatives, the partial positive charge on the carbonyl carbon is stabilized by electron donation from nonbonding electrons on the adjacent heteroatom, which has the effect of decreasing electrophilicity.



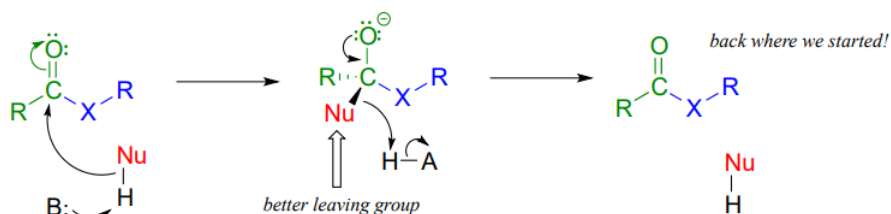
Among the carboxylic acid derivatives, carboxylate groups are the least reactive towards nucleophilic acyl substitution, followed by amides, then carboxylic esters and carboxylic acids, thioesters, and finally acyl phosphates, which are the most reactive among the biologically relevant acyl groups. Acid anhydrides and acid chlorides are laboratory reagents that are analogous to thioesters and acyl phosphates, in the sense that they too are highly reactive carboxylic acid derivatives. Section 11.8 near the end of this chapter includes information about the chemistry of these two reagents.

Relative reactivity of carboxylic acid derivatives:



The reactivity trend of the carboxylic acid derivatives can be understood by evaluating the basicity of the leaving group (acyl X group) - remember from section 8.4 that weaker bases are better leaving groups. A thioester is more reactive than an ester, for example, because a thiolate ( $\text{RS}^-$ ) is a weaker base and better leaving group than an alkoxide ( $\text{RO}^-$ ). Recall from chapter 7 that the  $pK_a$  of a thiol is about 10, while the  $pK_a$  of an alcohol is 15 or higher: a stronger conjugate acid means a weaker conjugate base.

In general, if the incoming nucleophile is a weaker base than the 'acyl X' group that is already there, it will also be the better leaving group, and thus the first nucleophilic step will simply reverse itself and we'll get the starting materials back:



In general, acyl substitution reactions convert higher energy carboxylic acid derivatives into derivatives of lower energy. Thioesters, for example, are often converted directly into carboxylic esters in biochemical reactions, but not the other way around. To go 'uphill' - from a carboxylate to a thioester, for example, requires the 'coupling' of the uphill reaction to an energetically favorable reaction. We will see how this works in the next section.

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