



CHEMISTRY 2600

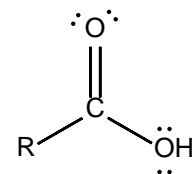
Topic #7: Reactions of Carboxylic Acid Derivatives

Fall 2018

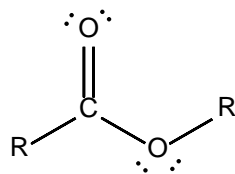
Dr. Susan Findlay

Carboxylic Acid Derivatives

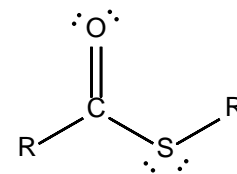
- Carboxylic acid derivatives are frequently grouped together because the carbonyl carbon has the same oxidation state, so they can be interconverted via substitution reactions.
- The most common carboxylic acid derivatives include:



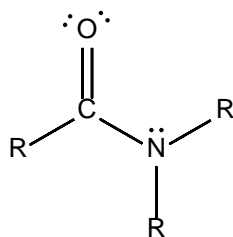
carboxylic acid



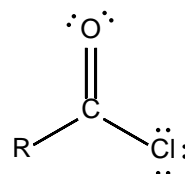
ester



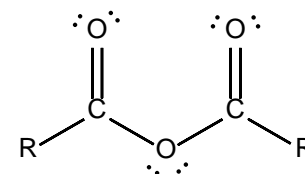
thioester



amide



acid chloride



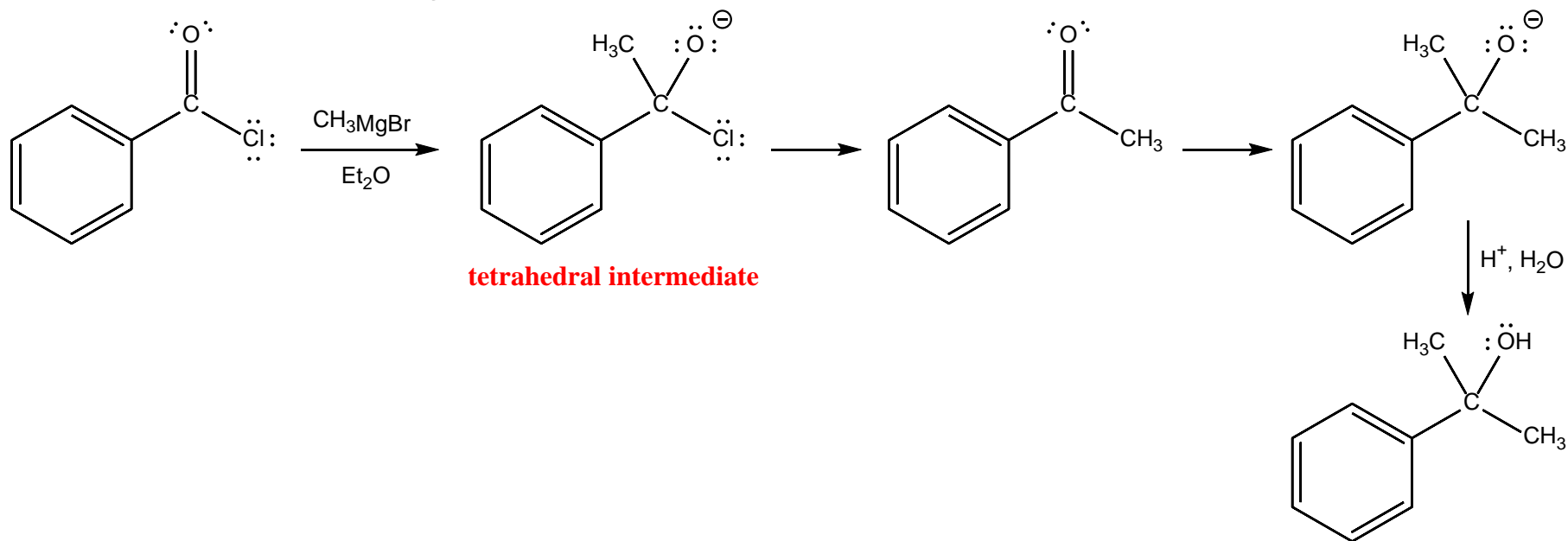
anhydride

For these examples, note that

- R groups may be carbon-based or hydrogen. R groups in the same molecule are not necessarily the same.
- R' groups must be carbon-based. If they were hydrogen, that would change the functional group.

Interconverting Carboxylic Acid Derivatives

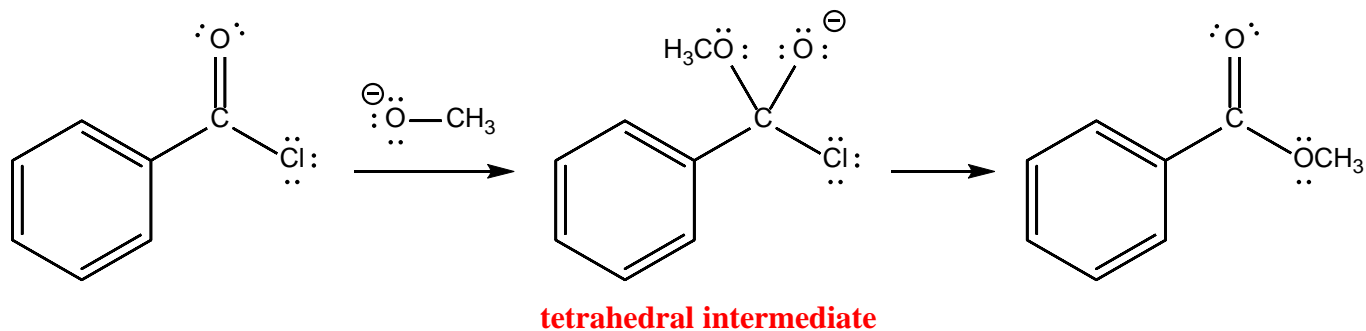
- When have seen what happens when a Grignard reagent attacks a carboxylic acid derivative such as an ester or acid chloride:



- A **tetrahedral intermediate** is formed as the nucleophile attacks the electrophilic carbon, breaking the weakest bond (the $\text{C}=\text{O}$ pi bond). If a leaving group is present, the $\text{C}=\text{O}$ pi bond reforms (*as shown above*), regenerating the carbonyl group.
- Similar reactions can also be used to interconvert carboxylic acid derivatives. Just change the nucleophile!

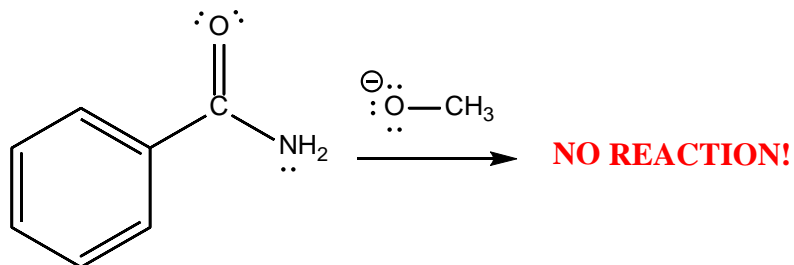
Interconverting Carboxylic Acid Derivatives

- What happens when we use methoxide instead:



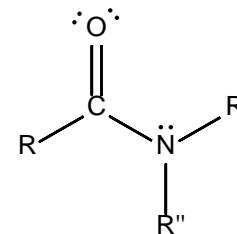
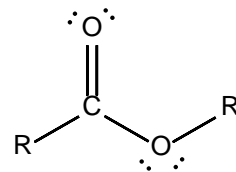
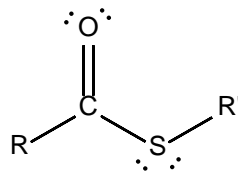
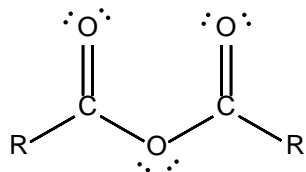
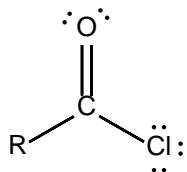
Again, a **tetrahedral intermediate** is formed as the nucleophile attacks the electrophilic carbon, breaking the weakest bond (the C-O pi bond). The C-O pi bond reforms, regenerating the carbonyl group.

- We can also see that this reaction would not have worked if we replaced the acid chloride with an amide. Why not?



Interconverting Carboxylic Acid Derivatives

- We can use the leaving group's basicity as a measure of how reactive a carboxylic acid group is to this type of substitution:
 - Acid Chlorides (Cl^- leaves; pK_a of HCl is ___)
 - Anhydrides (RCO_2^- leaves; pK_a of RCO_2H is ___)
 - Thioesters (RS^- leaves; pK_a of RSH is ___)
 - Esters (RO^- leaves; pK_a of ROH is ___)
 - Amides (R_2N^- leaves; pK_a of R_2NH is ___)
 - Carboxylic Acids cannot undergo this type of reaction directly. They tend to be deprotonated instead.

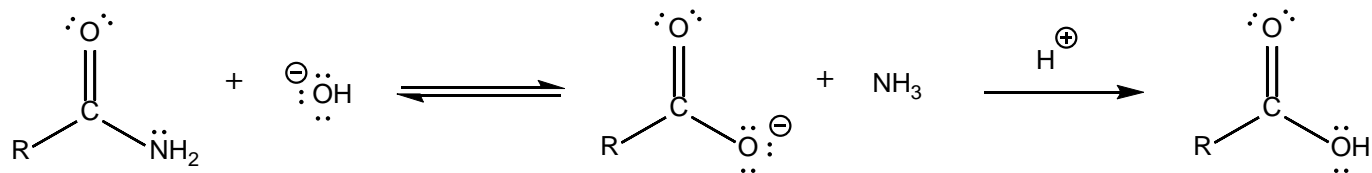


most electrophilic

least electrophilic

Interconverting Carboxylic Acid Derivatives

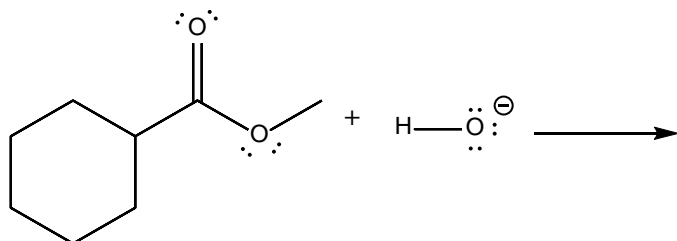
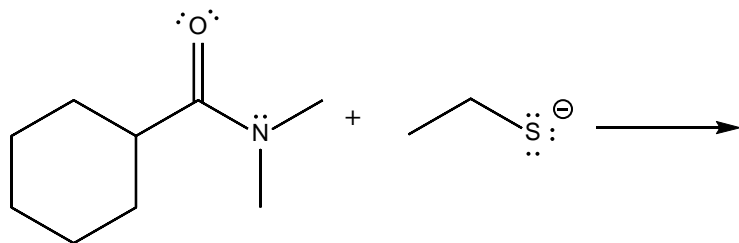
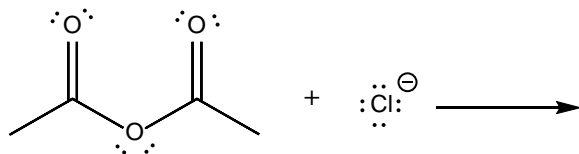
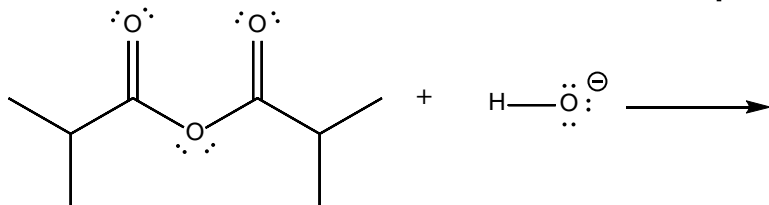
- As a general rule, we can only displace a better leaving group with a poorer leaving group (and better nucleophile). So, you can make an ester by reacting an acid chloride with RO^- but you cannot make an acid chloride by reacting an ester with Cl^- .
- Carboxylic acids are a special case. The nucleophilicity of HO^- is similar to that of RO^- but if you add a lot of hydroxide and heat, you can use Le Châtelier's principle to push the reaction forward slowly. So you can even react amides with HO^- to give the corresponding carboxylate salt (which can later be protonated to give the carboxylic acid):



What pushes the equilibrium forward in the first step?

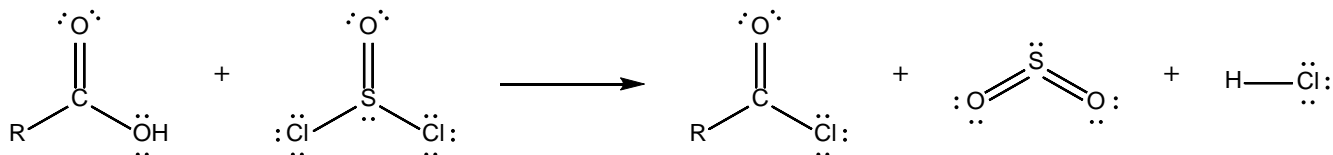
Interconverting Carboxylic Acid Derivatives

- Which of the following reactions would you expect to work well? For those that will, draw the products.

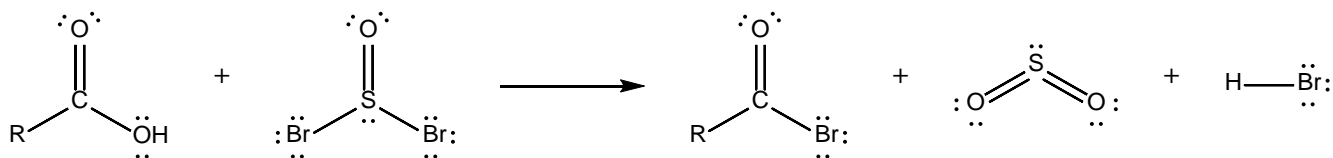


Making Acid Chlorides

- Since acid chlorides are among the most reactive carboxylic acid derivatives, they are popular choices as starting materials. They can be readily prepared from carboxylic acids and react with a wide variety of nucleophiles.
- To make an acid chloride from a carboxylic acid, just add thionyl chloride (SOCl_2):



Similarly, thionyl bromide (SOBr_2) can be used to make acid bromides:





Making Acid Chlorides

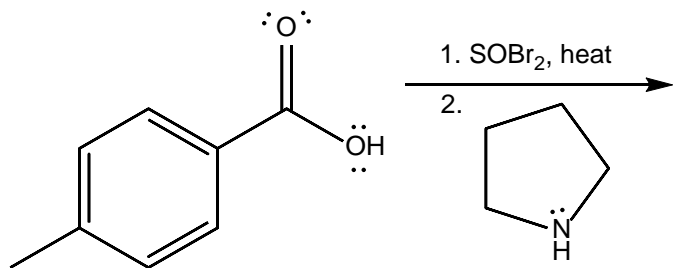
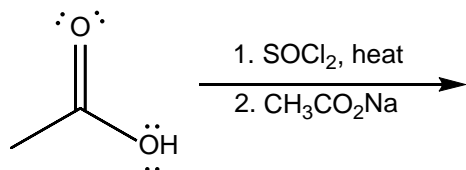
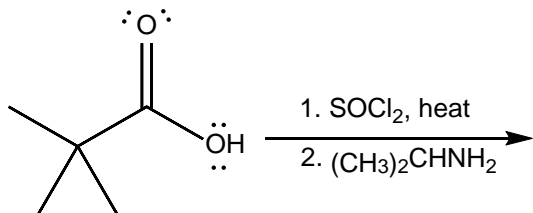
- First, the carboxylic acid attacks the SOCl_2 :

- Then the chloride ion produced attacks the adduct:

- Finally, there is a rearrangement, breaking the adduct into the acid chloride and two gases (SO_2 and HCl):

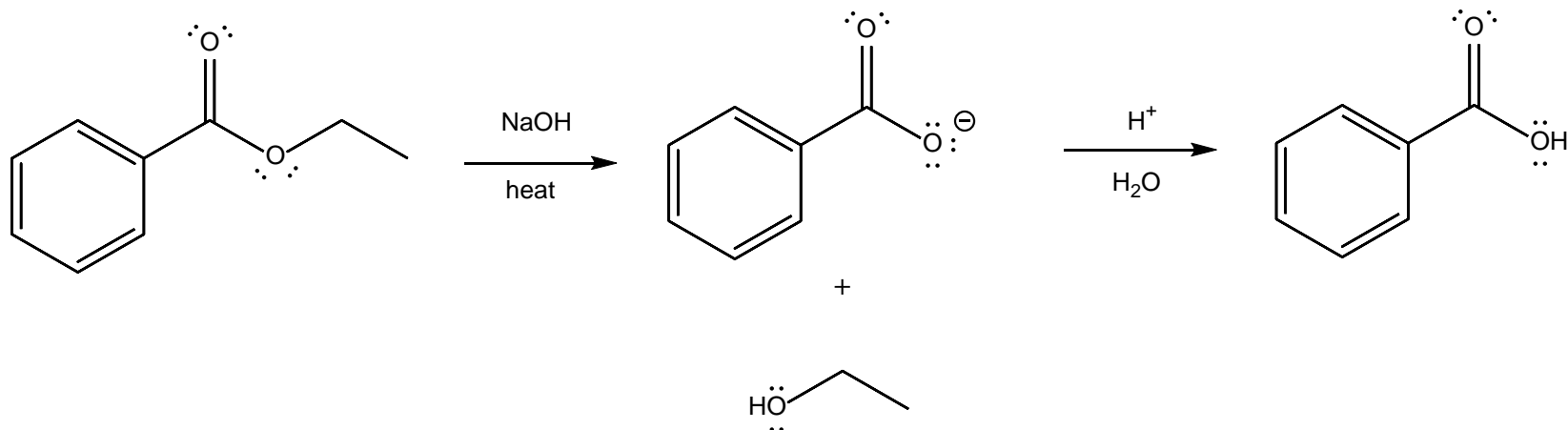
Making and Reacting Acid Chlorides

- Draw the products of each of the following reaction sequences:



Making Carboxylic Acids from Esters

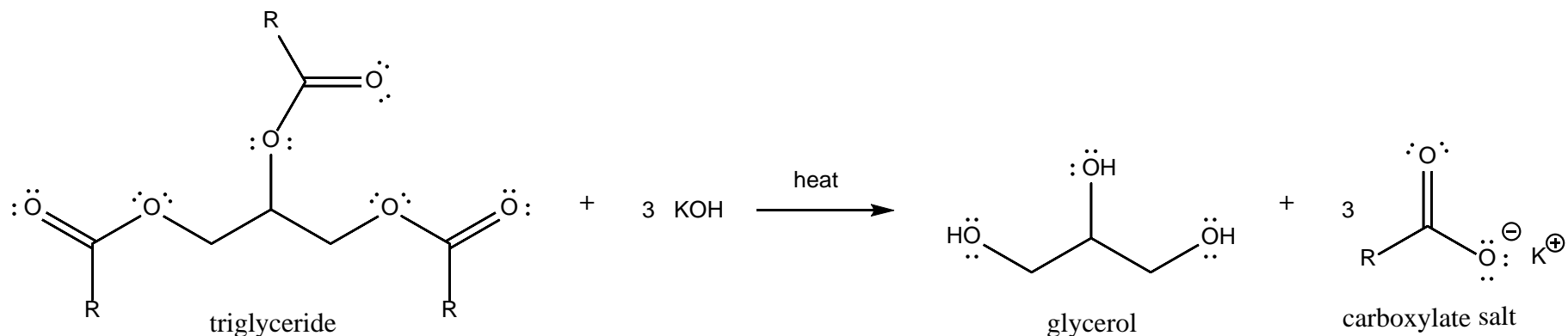
- Esters are less reactive than acid chlorides, but more abundant in nature. As such, they are important starting materials in organic synthesis. If necessary, an ester can be converted to a carboxylic acid – which can then be converted to the acid chloride.
- Reaction of an ester with hydroxide is called a **saponification** (“soap making”) reaction:



- Acidic work up is necessary if you wish to obtain the carboxylic acid rather than a carboxylate salt.

Making Carboxylic Acids from Esters

- If, on the other hand, you want to make soap, the carboxylate salt is your target:



In soap making, R is an alkyl chain (typically 15-25 carbon atoms long). It may include double bonds (if an unsaturated fat was used).

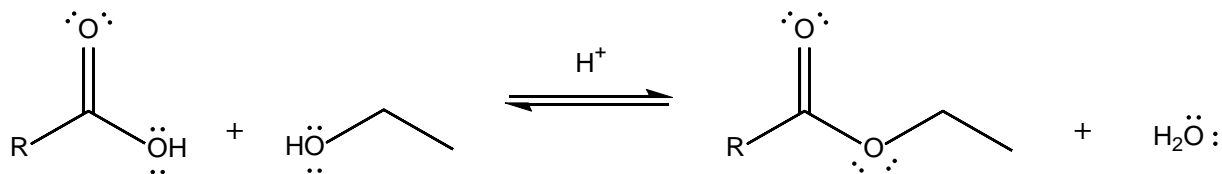


Making Esters from Carboxylic Acids

- When making a carboxylic acid from an ester, we take advantage of the acidity of the carboxylic acid, deprotonating it to give an insoluble carboxylate salt. Since the salt precipitates out of solution, Le Châtelier's principle drives the reaction forward even though HO^- and RO^- are about equally basic.
- Unfortunately, that doesn't help us if we wish to do the reverse reaction: making an ester from a carboxylic acid. In fact, we cannot make an ester from a carboxylic acid under basic conditions. Why not?

Making Esters from Carboxylic Acids

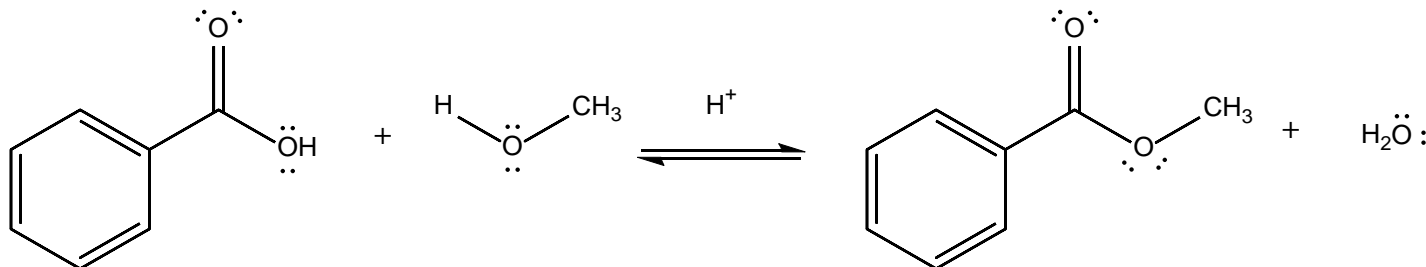
- We therefore have to use acidic conditions to make an ester from a carboxylic acid. Alcohols are not good enough nucleophiles to attack neutral carboxylic acid groups, so we need the acid to activate the carbonyl group in the carboxylic acid and make it more electrophilic before the alcohol will attack:



- This is known as a Fischer esterification.
- Since the alcohol and water are comparable nucleophiles, and the carboxylic acid and ester are comparable electrophiles, we must again use Le Châtelier's principle to drive the reaction forward. How?

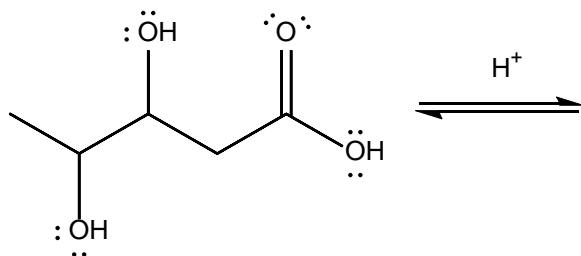
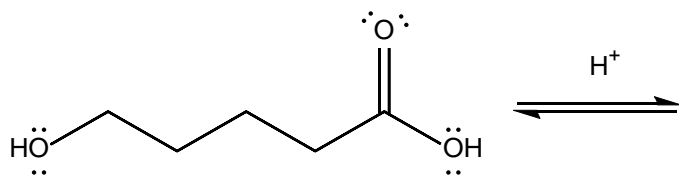
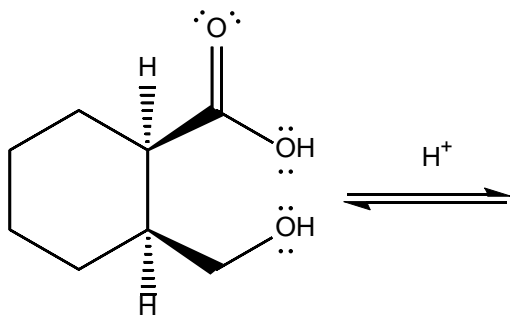
Making Esters from Carboxylic Acids

- A Fischer esterification may look like an ordinary substitution reaction, but it still goes through a **tetrahedral intermediate**. Remember that S_N2 reactions can only occur at tetrahedral carbon atoms; they CANNOT occur at carbonyl groups!



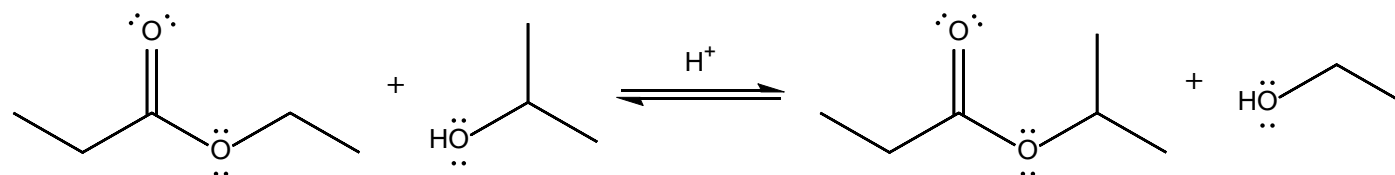
Making Esters from Carboxylic Acids

- If the alcohol and carboxylic acid are both in the same molecule, the product of an esterification will be a **lactone** (a cyclic ester).
What are the products of the following reactions:



Making Esters from Other Esters

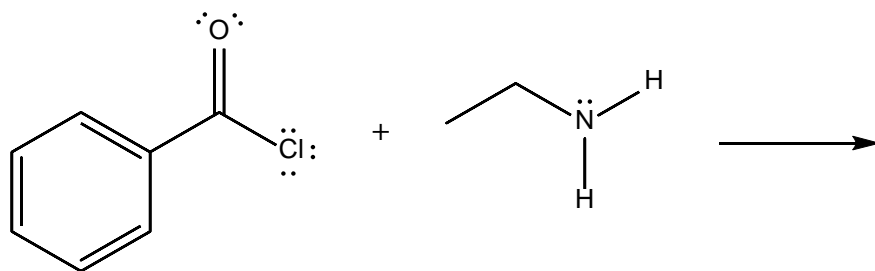
- We can perform **transesterification** reactions in a similar way:



- Again, we need to promote the forward reaction over the reverse reaction. How can we do that?

Making Amides from Acid Chlorides or Esters

- Unlike alcohols and water, amines are good enough nucleophiles that they can attack most carboxylic acid derivatives without being deprotonated by base (and without needing acid to protonate the carbonyl group).



Making Amides from Acid Chlorides or Esters

- Reaction of an ester with an amine (or NH_3) is termed **ammonolysis** since the amine breaks – or “lyses” – the ester.

