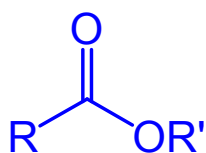


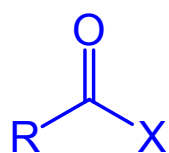
## 14. Derivatives of Carboxylic Acids (text 15.1 – 15.7)

### A. Structure and Nomenclature

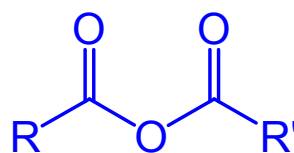
- We're interested in four derivatives, each of which has a group bonded to an acyl carbon:



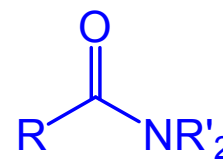
ester



acyl halide

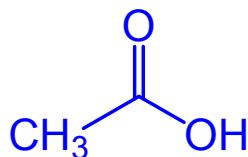


anhydride

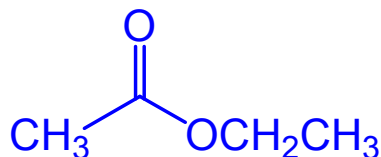


amide

- The names of the derivatives come from the carboxylic acid. For esters, change **ic acid** to **ate**, preceded by the name of the alkyl group on the ester alcohol group.

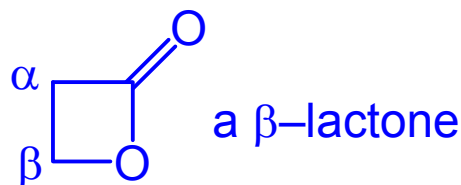
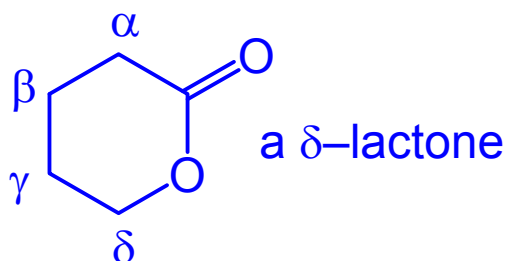


acetic acid

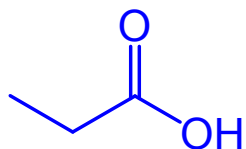


ethyl acetate

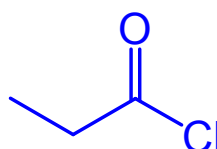
- Cyclic esters are **lactones** and are designated using Greek letters ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ , etc.), depending on the number of carbon atoms that the ester oxygen is from the carbonyl.



- For acid halides, change **ic acid** to **yl halide**.

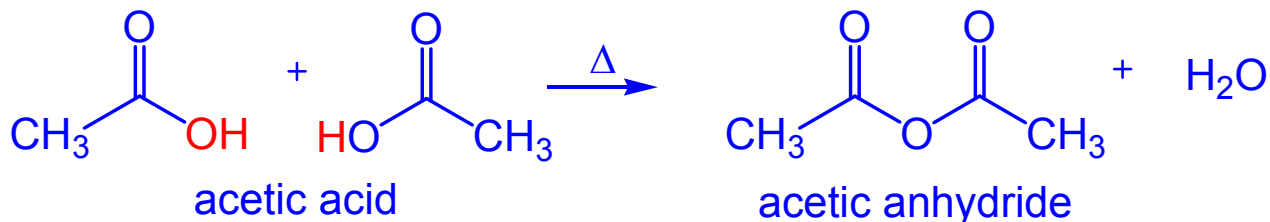


propanoic acid

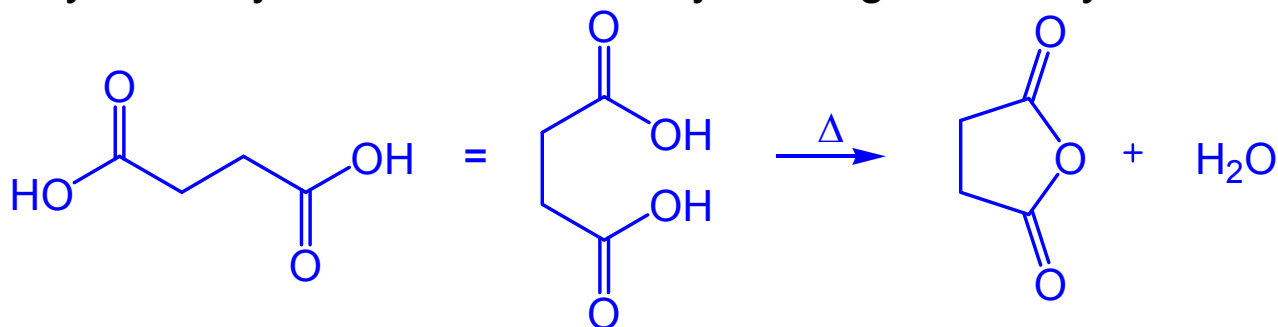


propanoyl chloride

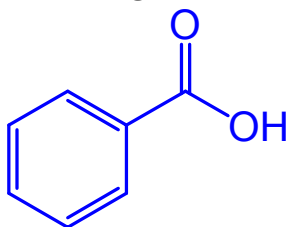
- For symmetrical anhydrides, change **acid** to **anhydride**. Anhydrides are usually formed by coupling two carboxylic acids with the loss of water (hence the name anhydride)



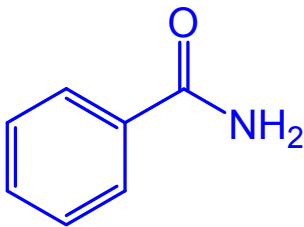
- Cyclic anhydrides are formed by heating dicarboxylic acids.



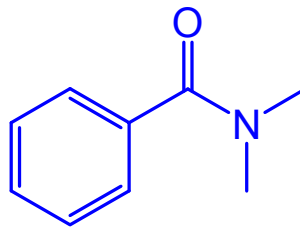
- For amides change **oic acid** or **ic acid** to **amide**. If the amide N has groups other than H, their attachment to the nitrogen is designated by the prefix **N**.



benzoic acid

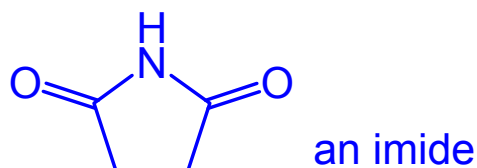
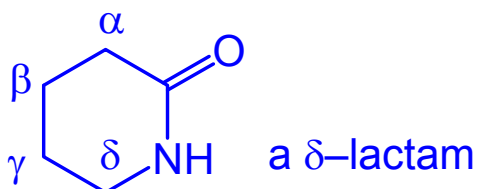


benzamide



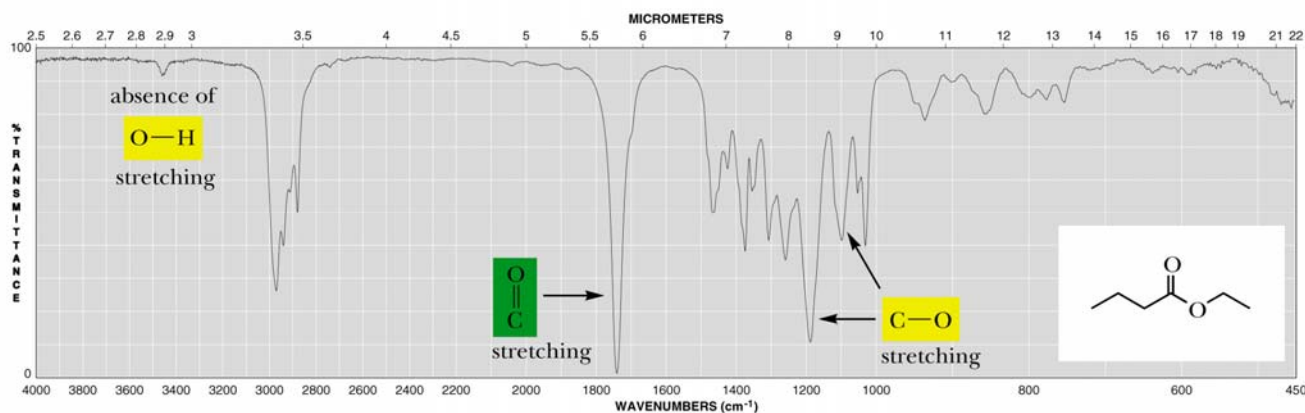
N,N-dimethylbenzamide

- Cyclic amides are called **lactams**. When two acyl groups form amide bonds to the same N atom (like an anhydride), we get an **imide**. Designate with Greek letters.

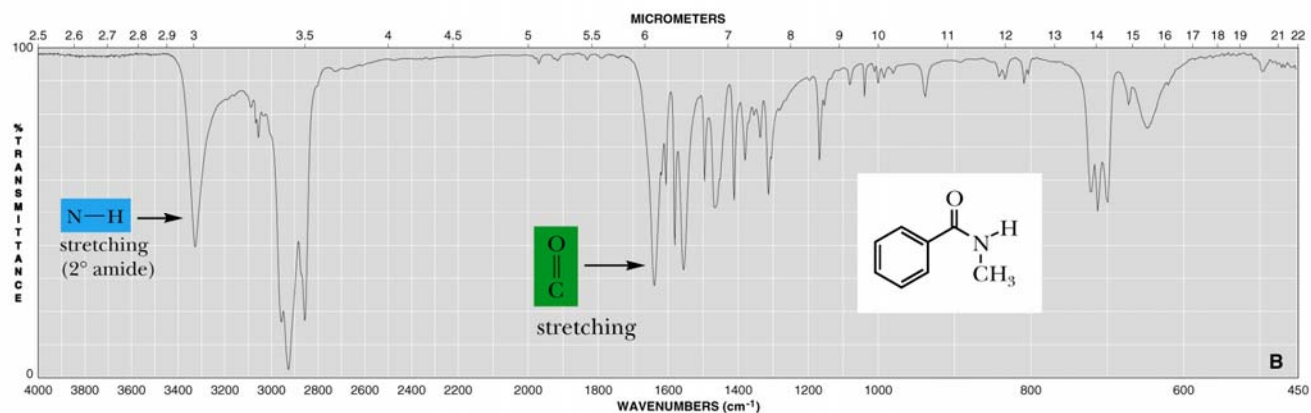


## B. Spectroscopy

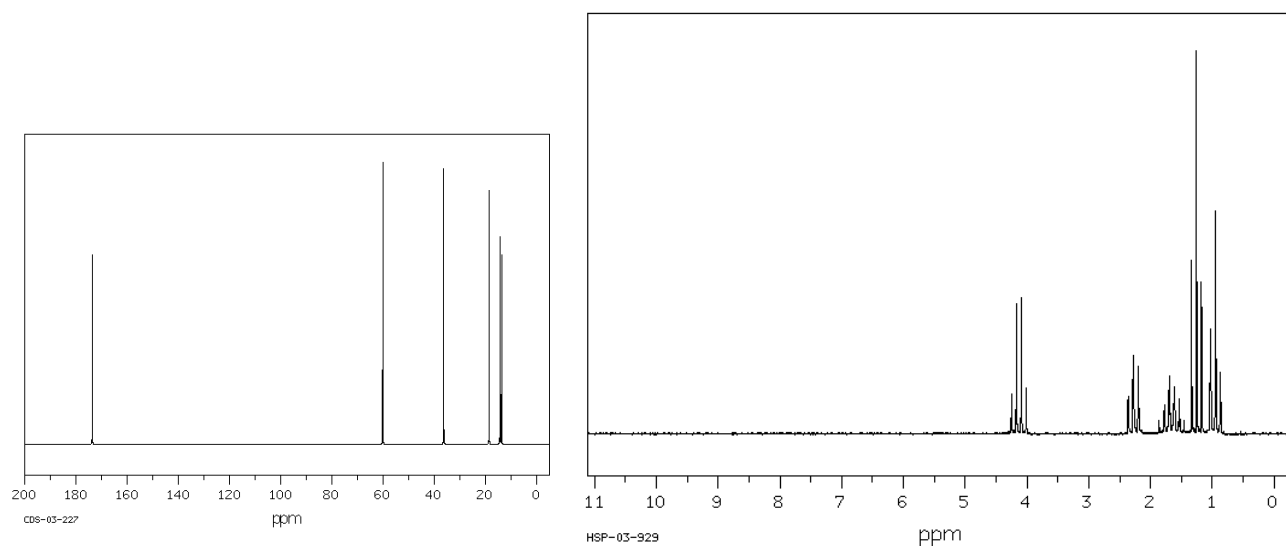
- All acid derivatives contain a strong C=O stretch near the  $1630 - 1800 \text{ cm}^{-1}$  region.
- Esters also have two peaks due to the C–O stretch around  $1050$  and  $1250 \text{ cm}^{-1}$ . e.g. ethyl butanoate



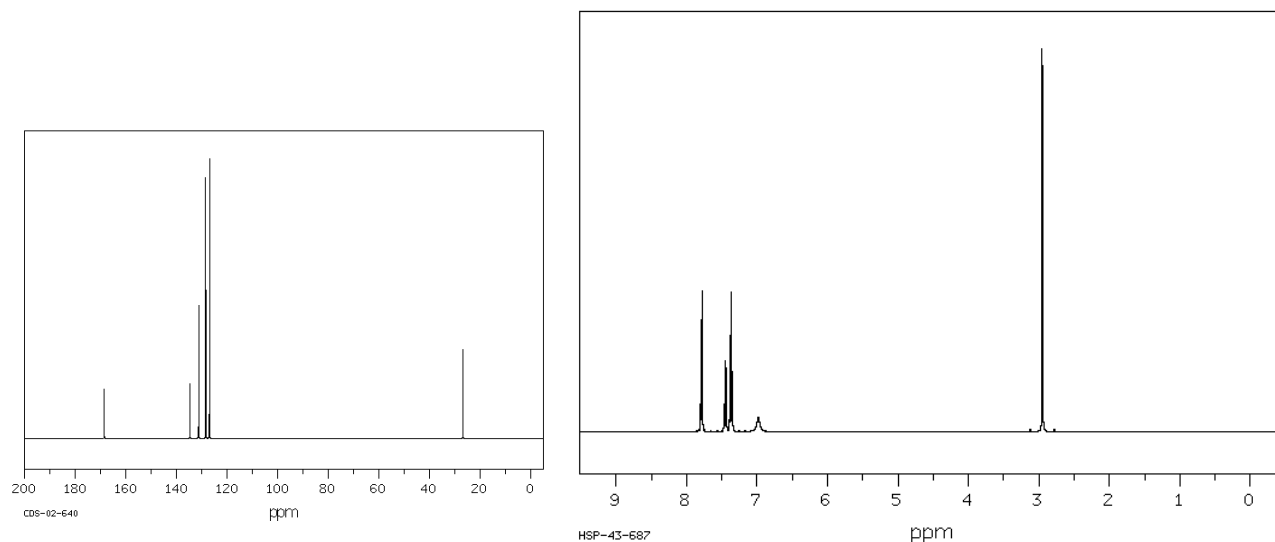
- Amides have a C=O stretch near  $1650\text{ cm}^{-1}$  and the usual N–H peaks near  $3330$ . e.g. *N*-methylbenzamide.



- Carbon- and proton-NMR spectra of ethyl butanoate



- Carbon- and proton-NMR spectra of *N*-methylbenzamide

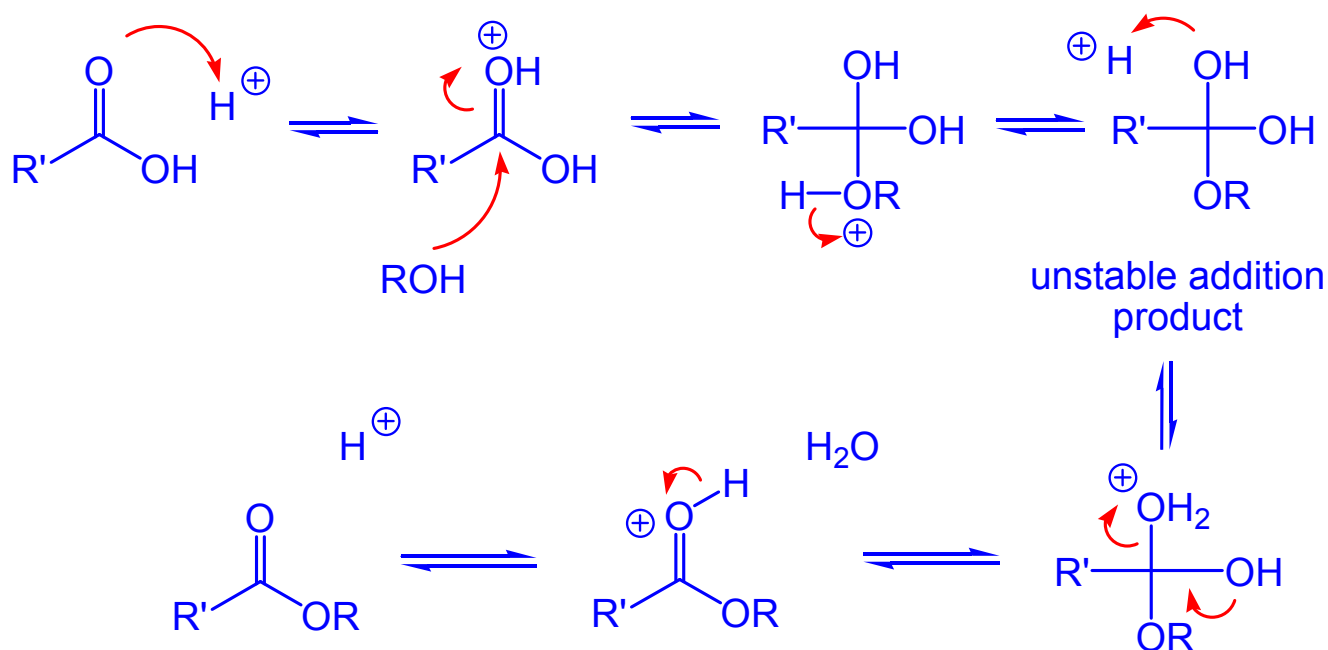


### ***C. Preparation***

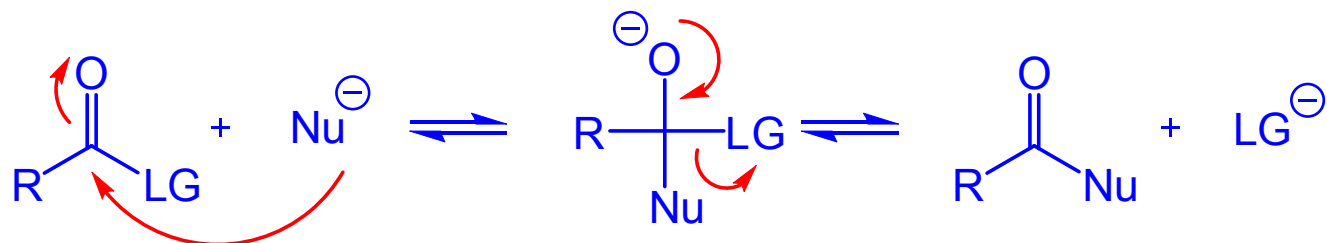
- Esters from Fischer esterification (last chapter).
- Acid chlorides from the reaction of acids with  $\text{SOCl}_2$  (last chapter). Acid chlorides are the most reactive of the four derivatives, so they are used to make the other derivatives.

## D. Reactions of Acid Derivatives

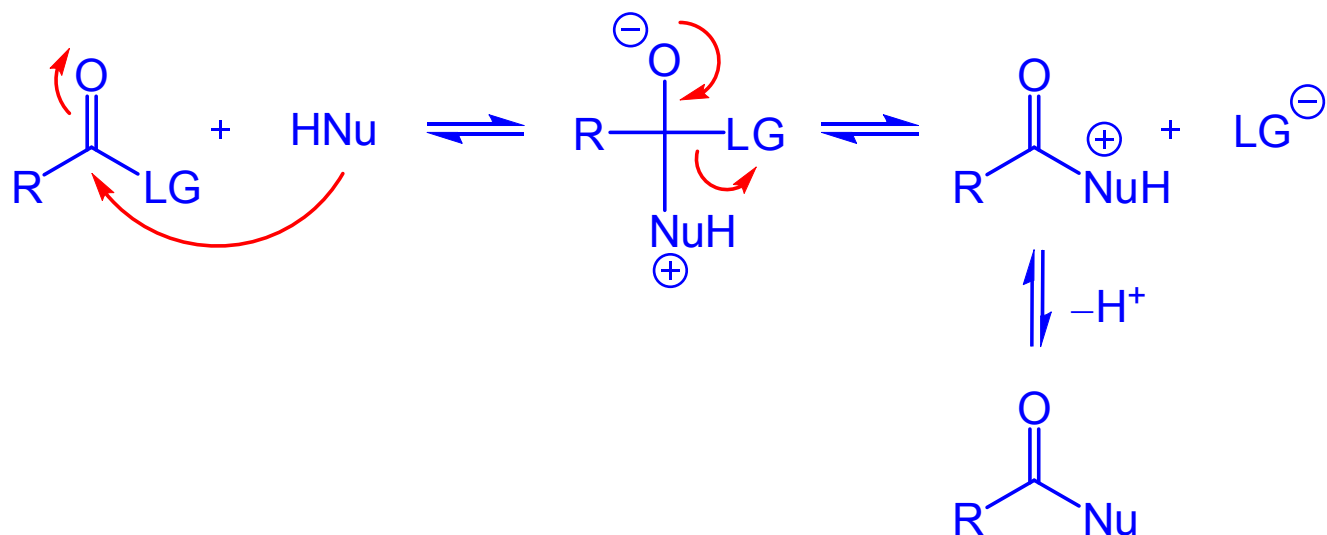
- The derivatives can be interconverted to one another, and all can be converted back to the parent carboxylic acid by the same type of substitution mechanism that converts acids to esters (**nucleophilic acyl substitution**).
- The mechanism involves the addition of a nucleophile to the acyl group, followed by the elimination of a leaving group. The mechanism varies depending on whether the reaction is occurring under acidic, basic, or neutral conditions.
- All mechanisms for the acid-catalyzed nucleophilic acyl substitution of other derivatives are similar to that of the Fischer esterification, except with a different nucleophile and/or leaving group.



- Under basic conditions, the nucleophile is negatively charged. Note that under basic conditions, there are no cations. Similarly, there are no anions under acidic conditions.



- Acid derivatives that are very reactive can react even in the absence of acid or base. In this case, the nucleophile is usually uncharged, and a deprotonation step occurs after the leaving group is expelled.

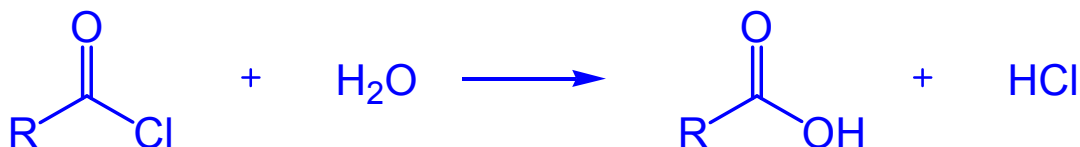


## Hydrolysis to carboxylic acids

- All acid derivatives react under proper conditions with water to form carboxylic acids, a reaction called **hydrolysis**.

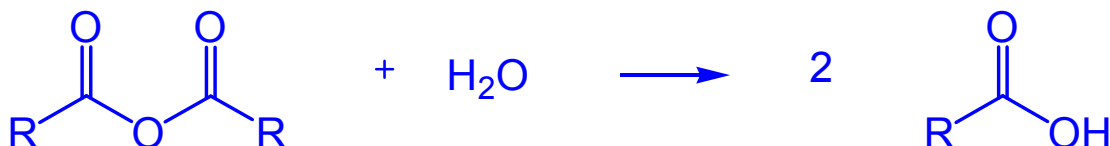
### a. Acid chlorides (most reactive)

- Acid chlorides are very reactive – no catalyst needed.



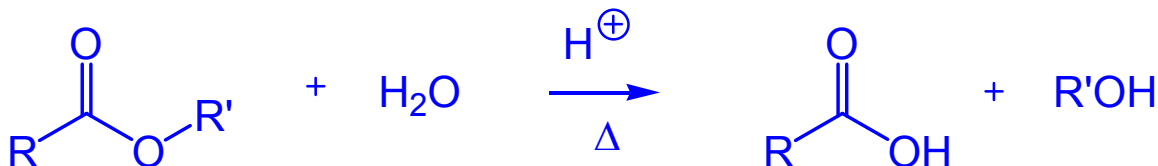
### b. Anhydrides (2<sup>nd</sup> most reactive)

- Anhydrides also react rapidly with water, but slower than acid halides. No catalyst is needed, but can be helpful.



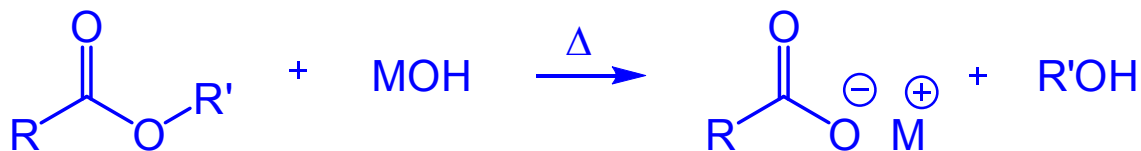
### c. Esters (third most reactive)

- Esters need to be heated to the boiling point of water for hydrolysis, and must be done under acidic or basic pH.
- Acid catalysis forms carboxylic acid as the product.





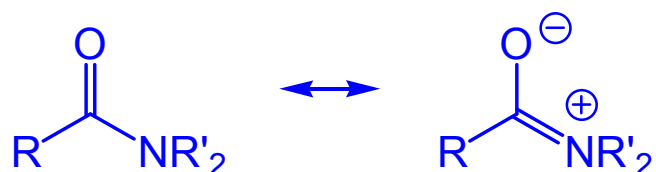
- In base, the acid formed reacts with the base to form the carboxylic acid salt. So, an equimolar amount of base is required to hydrolyze esters.



- Base hydrolysis gives good yields, since the salt usually precipitates out of solution. This reaction is used in soap-making and is termed *saponification*.

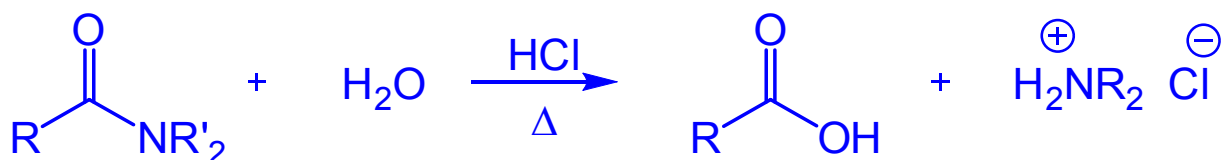
*d. Amides (least reactive)*

- Amides are the least reactive of the derivatives, because the carbon-nitrogen bond is strengthened by resonance stabilization.

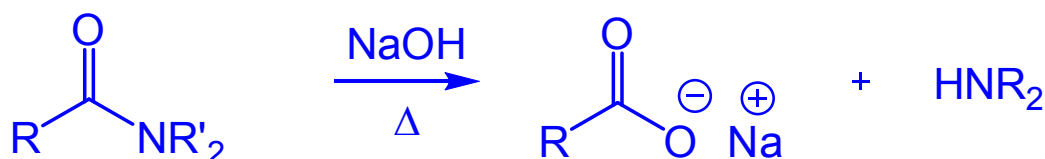


- Note that resonance is not significant in esters and anhydrides because O is more electronegative than N (*i.e.* O contributes its electron pair less readily). Resonance is not significant in acid chlorides because Cl is electronegative and is much larger.
- Because amides are so stable, higher temperatures are required for hydrolysis.

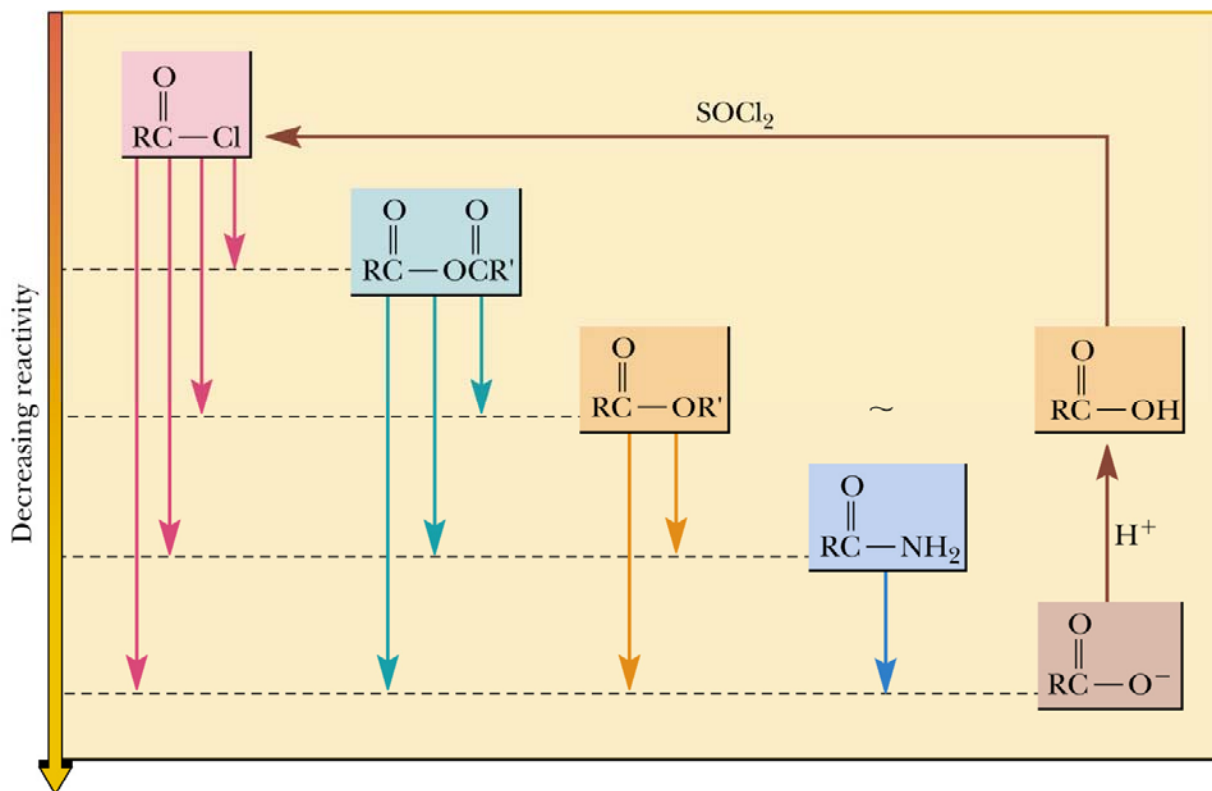
- In acid hydrolysis, the liberated amine reacts with the acid to form a salt, which drives the reaction to completion.



- In base hydrolysis, the base reacts with the acid product to form a salt, again driving the reaction to completion.



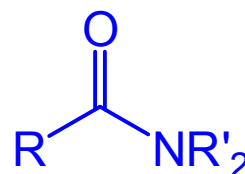
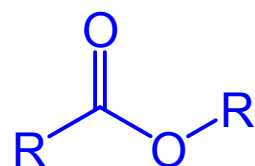
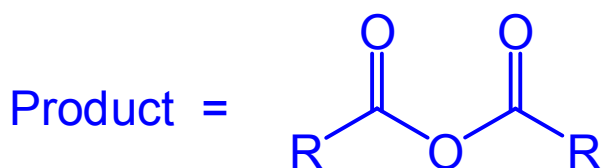
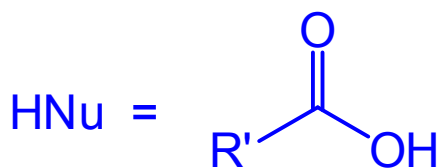
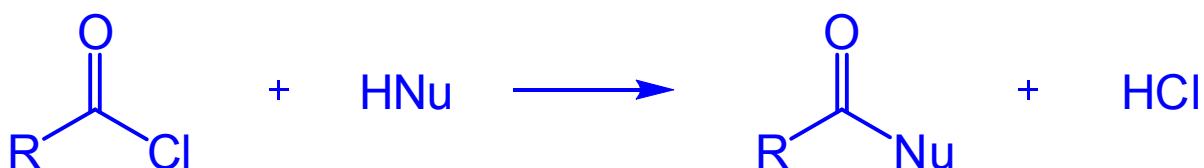
- The reactivity of the four acid derivatives towards hydrolysis reveals their *general order of reactivity*: **acid halide** > **anhydride** > **ester** > **amide**.



- Each derivative can be converted to one lower on the reactivity list. Acid halides are easily converted to others.
- The groups of lowest reactivity (carboxylic acids and their carboxylate anions) need to be first converted to acid halides before conversion to other derivatives can be accomplished.
- These reactions are summarized below.

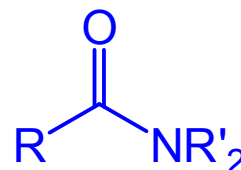
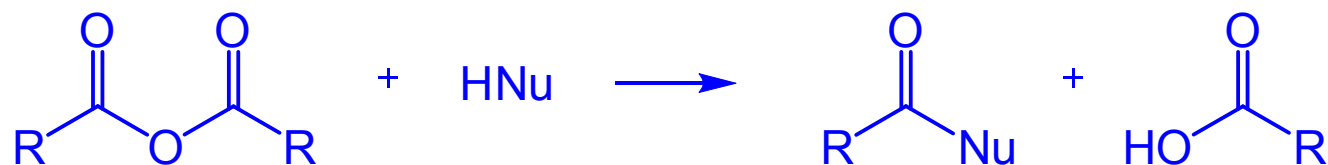
### Acid chlorides

- These are the most reactive and are a chemist's choice for preparing other acid derivatives.



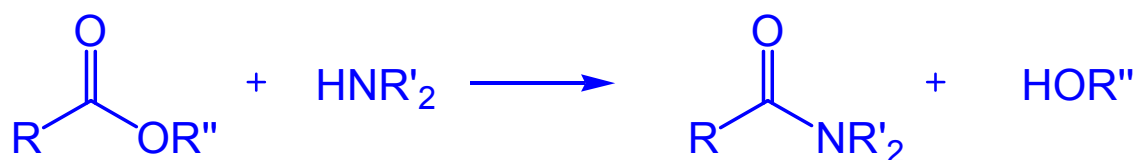
## Anhydrides

- Anhydrides can be converted to amides and esters.



## Esters

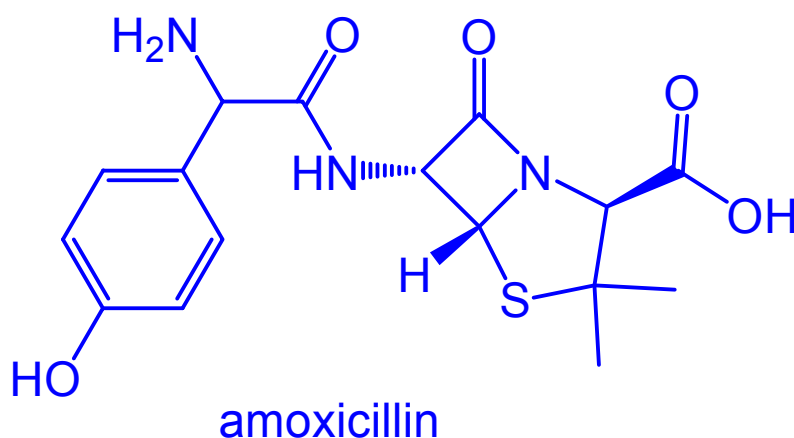
- Esters can only be converted to amides



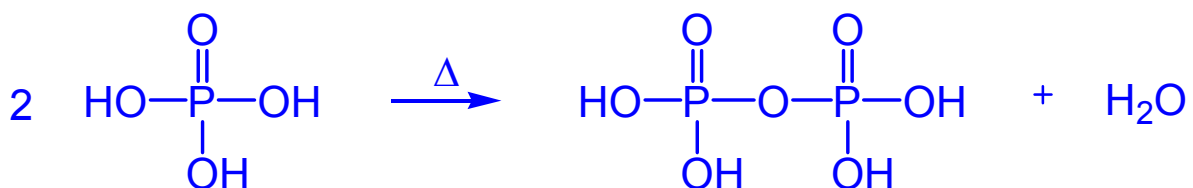
- Note: we will not look at the reduction of esters (textbook section 15.8) or Grignard reactions with esters (15.9).

## E. Biological Connections

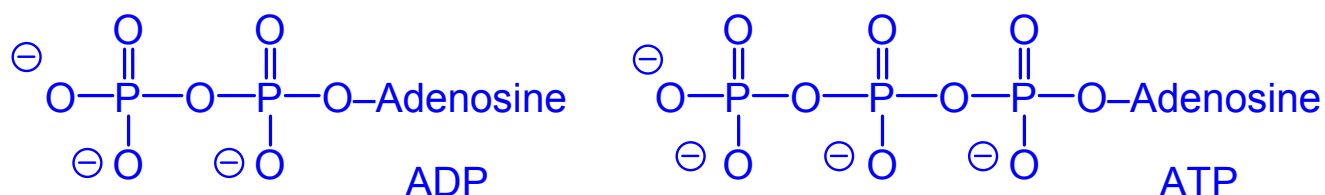
- The chemistry of acid derivatives is vital to the understanding of many biological disciplines, including biochemical pathways and pharmaceutical drugs.
- For example, all antibiotics in the penicillin family are beta-lactams. Bacteria that are resistant to the penicillins contain the enzyme beta-lactamase, which hydrolyzes the beta-lactam ring, rendering the drug useless.



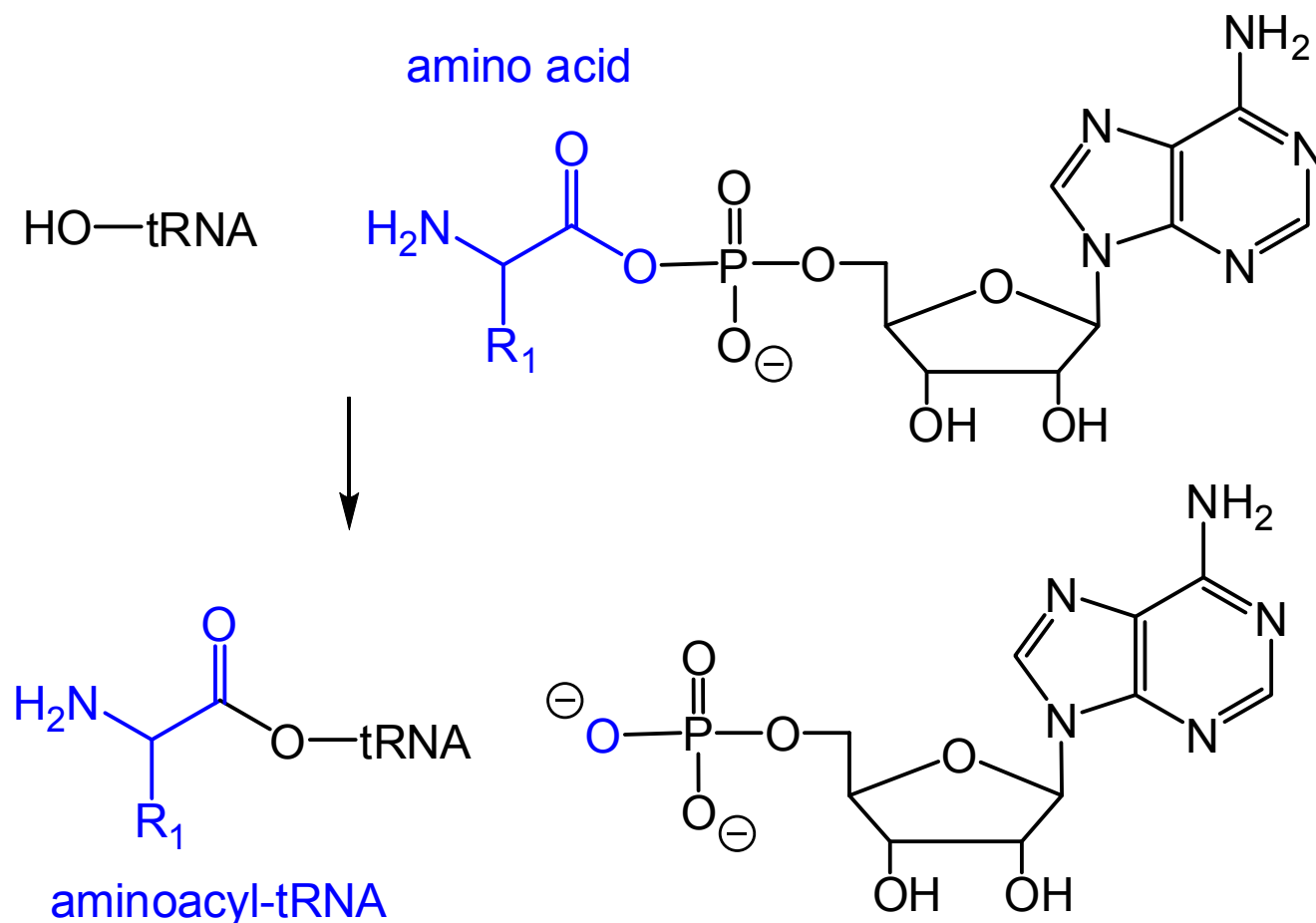
- The acid derivatives found in a biological system are often variations of the four acid derivatives, but they nonetheless undergo the same chemical reactions and have similar trends in reactivity.
- Anhydrides of phosphoric acids (known as phosphoric anhydrides) can be made in the lab by the dehydration of phosphoric acid. The product is pyrophosphoric acid.



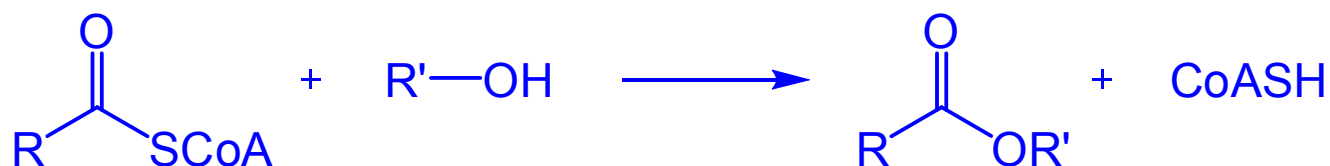
- Pyrophosphate is a key component of ADP and ATP. The hydrolysis of one phosphoric anhydride yields 30.5 kJ/mol.



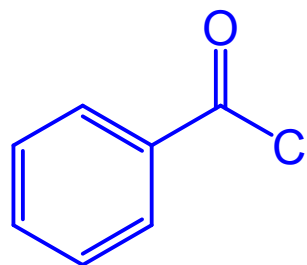
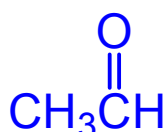
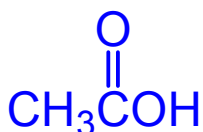
- It is also possible to have mixed anhydrides. For example, when amino acids are attached to transfer RNA, they are first linked to AMP as a mixed anhydride. The mixed anhydride is subsequently converted to an ester.



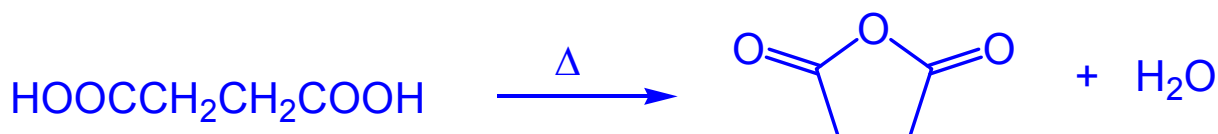
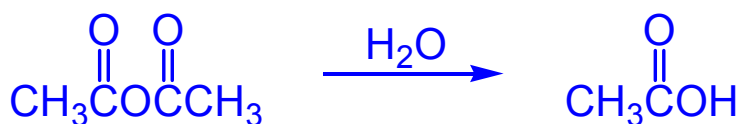
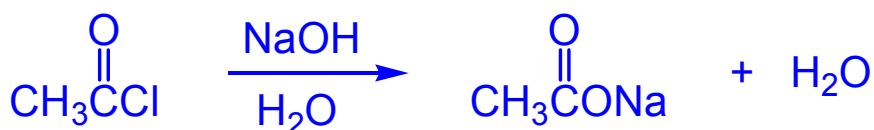
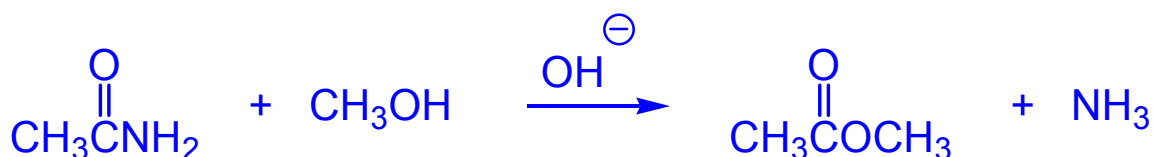
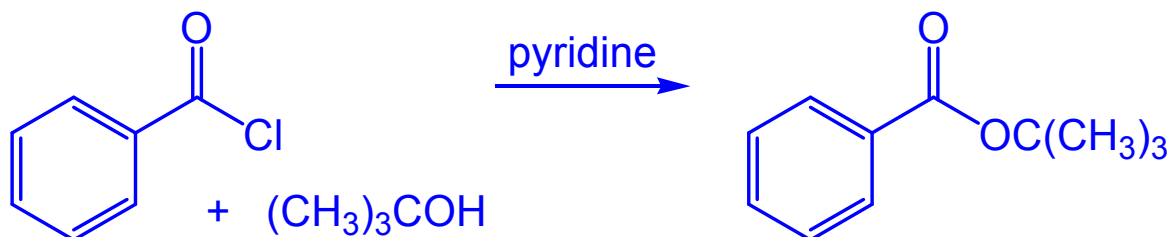
- Perhaps the most important acid derivative in a biological system is the thioester. Thioesters are frequently used to biosynthesize regular (oxygen) esters, which are found in molecules such as triglycerides (fats and oils).



- Pages covered: Chap. 15, 430 – 446.
- Problems: Chap. 12: 29, 31, 36. Chap. 15: 13, 14, 16, 17, 20, 25, 26, 37.
- 2005: 42, 45, 46, 49      2006: 42 – 44  
2007: 42 – 44      2008: 42 – 44
- Past test questions: Which one of the following does not react with aniline?

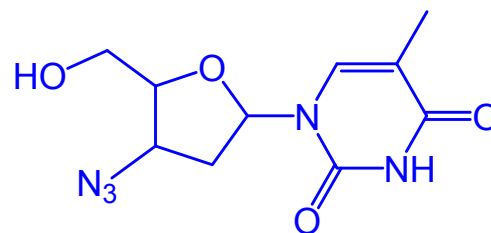


- Which one of the following reactions does NOT give a good yield of the product shown?



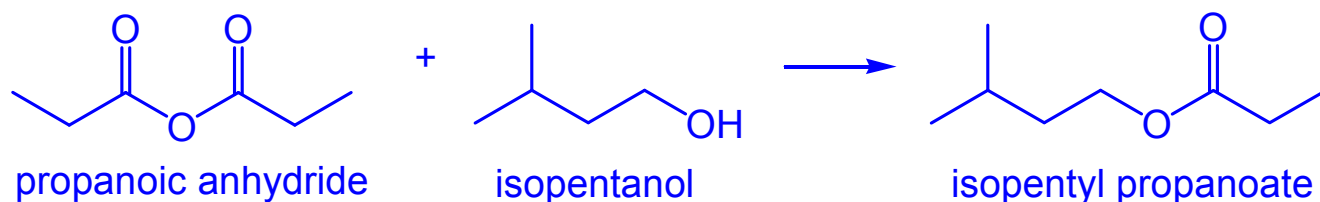
- Which statement about the antiviral drug AZT is wrong?

- It contains three carbon stereogenic centres
- It contains a conjugated alkene?
- It contains one or more amide groups
- It contains one or more hemiacetal groups
- It contains a tertiary N atom





- MCAT questions: Isopentyl propanoate is one of the primary components in pineapple odour. Use the synthesis reaction shown to answer the subsequent questions.



- The synthesis is catalyzed by an acid. What does the acid do in the first step of the synthesis?
  - Activate the electrophile by protonating the anhydride
  - Activate the nucleophile by protonating the anhydride
  - Activate the electrophile by protonating the alcohol
  - Activate the nucleophile by protonating the alcohol
- Which of the following reagents would be more reactive with isopentanol?
  - Propanoic acid
  - Propanoyl chloride
  - Methyl propanoate
  - Propyl acetate
- The methyl groups of isopentyl propanoate appear in the proton NMR spectrum as
  - Two singlets
  - A doublet and a triplet
  - A triplet and a quartet
  - A doublet and a multiplet