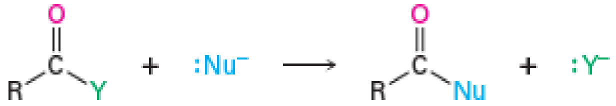
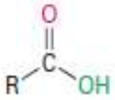
Carboxylic Acid Derivatives:
Naming and Physical Properties

Dr. Ayad Kareem
Department of Pharmaceutical Chemistry, Collage of Pharmacy
Al-Mustansiriyah University (2020-2021).

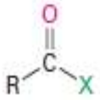
Closely related to the carboxylic acids discussed in the previous chapter are the **carboxylic acid derivatives**, compounds in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in the nucleophilic acyl substitution reaction that we saw briefly in the *Preview of Carbonyl Chemistry:*



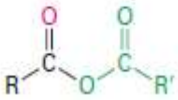
Many kinds of acid derivatives are known, but we'll be concerned primarily with four of the more common ones: **acid halides**, **acid anhydrides**, **esters**, and **amides**. Acid halides and acid anhydrides are used only in the laboratory, while esters and amides are common in both laboratory and biological chemistry. In addition, carboxylic acid derivatives called **thioesters** and **acyl phosphates** are encountered primarily in biological chemistry. Note the structural similarity between acid anhydrides and acyl phosphates.



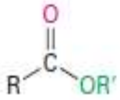
Carboxylic acid



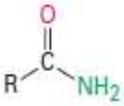
Acid halide
(X = Cl, Br)



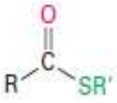
Acid anhydride



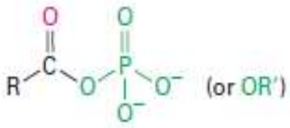
Ester



Amide



Thioester

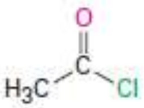


Acyl phosphate

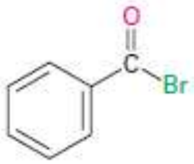
Naming Carboxylic Acid Derivatives

Acid Halides, RCOX

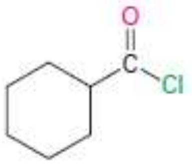
Acid halides are named by identifying first the acyl group and then the halide. The acyl group name is derived from the carboxylic acid name by replacing the ***-ic acid*** or ***-oic acid*** ending with ***-oyl,*** or the -*carboxylic acid* ending with ***-carbonyl***. To keep things interesting, however, IUPAC recognizes eight exceptions for which a ***-yl*** rather than an ***-oyl*** ending is used: formic (formyl), acetic (acetyl), propionic (propionyl), butyric (butyryl), oxalic (oxalyl), malonic (malonyl), succinic (succinyl), and glutaric (glutaryl).



Acetyl chloride



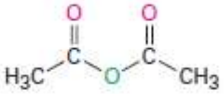
Benzoyl bromide



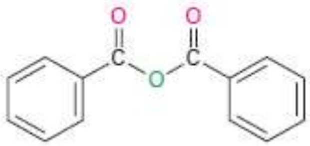
Cyclohexanecarbonyl chloride

Acid Anhydrides, RCO_2COR'

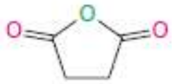
Symmetrical anhydrides of unsubstituted monocarboxylic acids and cyclic anhydrides of dicarboxylic acids are named by replacing the word ***acid*** with ***anhydride.***



Acetic anhydride

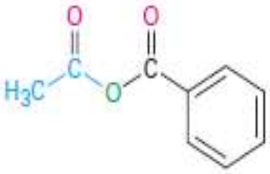


Benzoic anhydride



Succinic anhydride

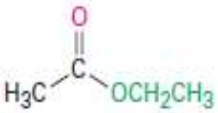
Unsymmetrical anhydrides those prepared from two different carboxylic acids are named by listing the two acids alphabetically and then adding ***anhydride.***

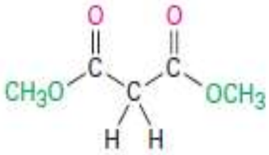


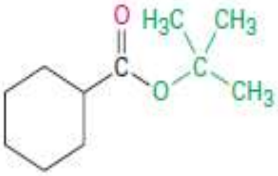
Acetic benzoic anhydride

Esters, RCO_2R'

Esters are named by first identifying the alkyl group attached to oxygen and then the carboxylic acid, with the ***-ic acid*** ending replaced by ***-ate.***


Ethyl acetate

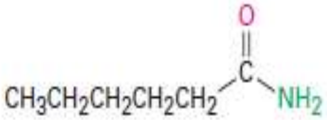

Dimethyl malonate

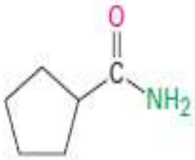

tert-Butyl cyclohexane-carboxylate

Amides, $RCONH_2$

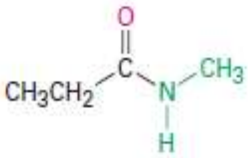
Amides with an unsubstituted **$-NH_2$** group are named by replacing the ***-oic acid*** or ***-ic acid*** ending with ***-amide***, or by replacing the ***-carboxylic acid*** ending with ***-carboxamide.***

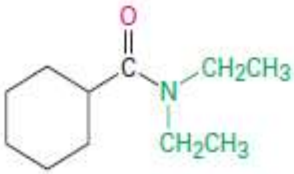

Acetamide


Hexanamide


Cyclopentane-

If the nitrogen atom is further substituted, the compound is named by first identifying the substituent groups and then the parent amide. The substituents are preceded by the letter ***N*** to identify them as being directly attached to nitrogen.


N-Methylpropanamide


N,*N*-Diethylcyclohexanecarboxamide

A summary of nomenclature rules for carboxylic acid derivatives is given in **Table 21-1**.

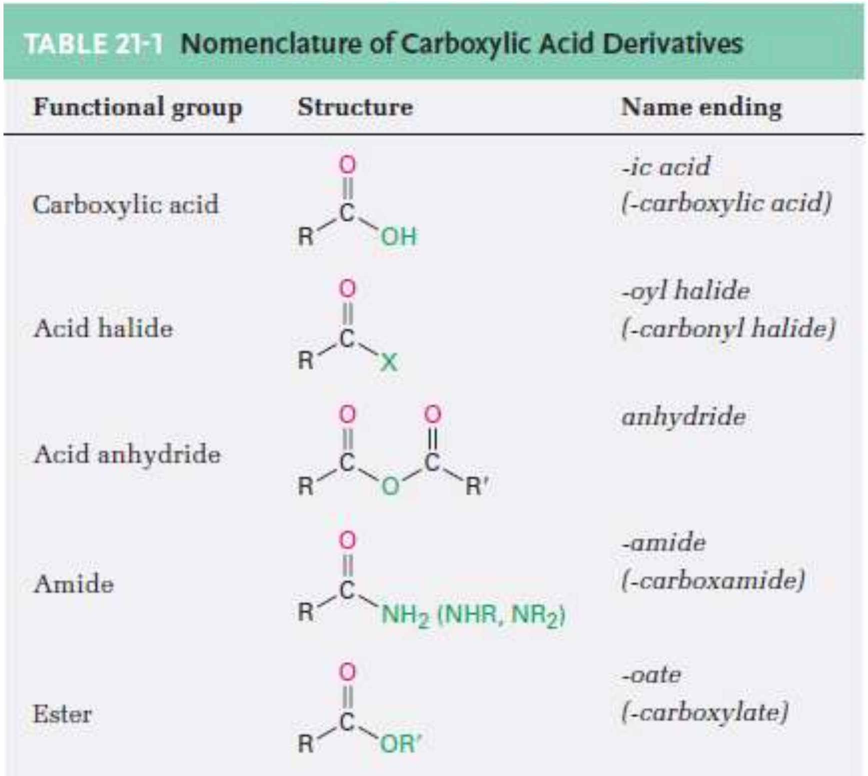


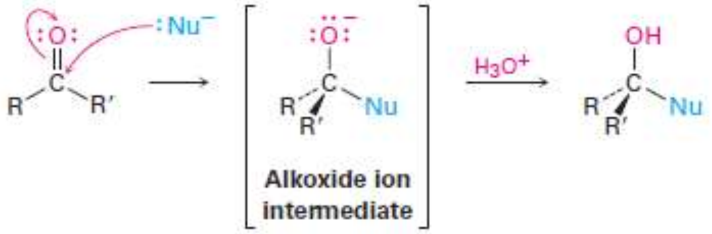
TABLE 21-1 Nomenclature of Carboxylic Acid Derivatives

Functional group	**Structure**	**Name ending**
Carboxylic acid	$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OH}$	*-ic acid* *(-carboxylic acid)*
Acid halide	$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}X}$	*-oyl halide* *(-carbonyl halide)*
Acid anhydride	$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}R'}$	*anhydride*
Amide	$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}NH_2\ (NHR,\ NR_2)}$	*-amide* *(-carboxamide)*
Ester	$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OR'}$	*-oate* *(-carboxylate)*

Nucleophilic Acyl Substitution Reactions

When a nucleophile adds to a carboxylic acid derivative, however, a different reaction path is taken. The initially formed tetrahedral intermediate eliminates one of the two substituents originally bonded to the carbonyl carbon, leading to a net **nucleophilic acyl substitution reaction (Figure 21-1)**. The difference in behavior between aldehydes/ketones and carboxylic acid derivatives is a consequence of structure. Carboxylic acid derivatives have an acyl carbon bonded to a group **-Y** that can act as a leaving group, often as a stable anion. As soon as the tetrahedral intermediate is formed, the leaving group is expelled to generate a new carbonyl compound. Aldehydes and ketones have no such leaving group, however, and therefore don’t undergo substitution.

(a) Aldehyde or ketone: nucleophilic addition



(b) Carboxylic acid derivative: nucleophilic acyl substitution

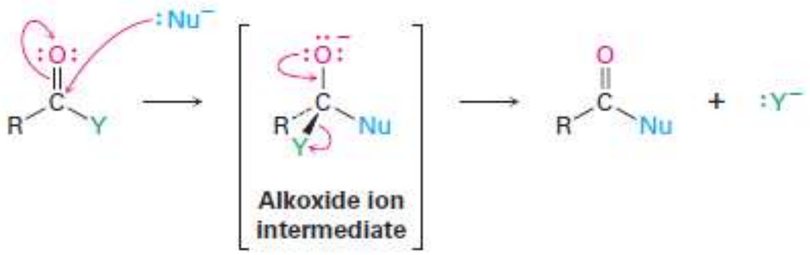
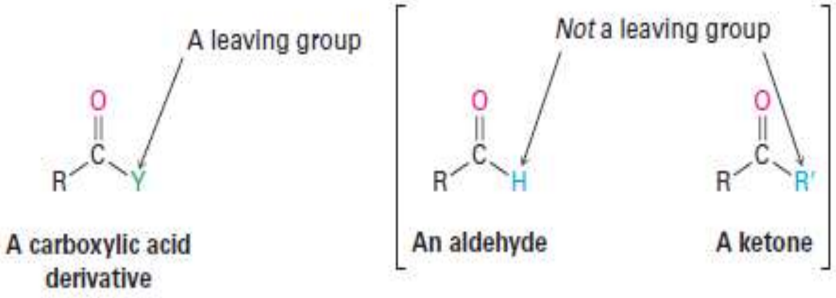


Figure 21-1 the general mechanisms of nucleophilic addition and nucleophilic acyl substitution reactions. Both reactions begin with addition of a nucleophile to a polar **C=O** bond to give a tetrahedral, alkoxide ion intermediate. **(a)** The intermediate formed from an aldehyde or ketone is protonated to give an alcohol, but **(b)** the intermediate formed from a carboxylic acid derivative expels a leaving group to give a new carbonyl compound.

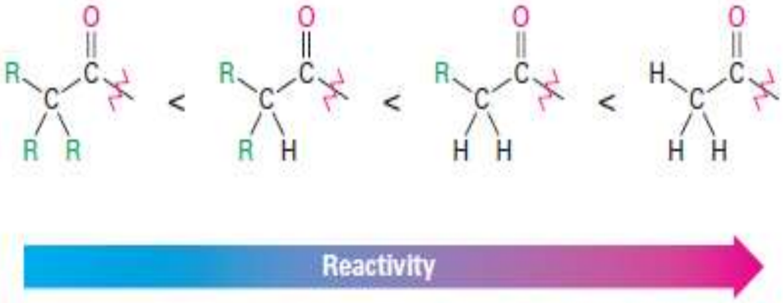


The net effect of the addition/elimination sequence is a substitution of the nucleophile for the **-Y** group originally bonded to the acyl carbon. Thus, the overall reaction is superficially similar to the kind of nucleophilic substitution that occurs during an S_N^2 reaction, but the mechanisms of the two reactions are completely different. An S_N^2 reaction occurs in a single step by backside displacement of the leaving group, while a nucleophilic acyl substitution takes place in two steps and involves a tetrahedral intermediate.

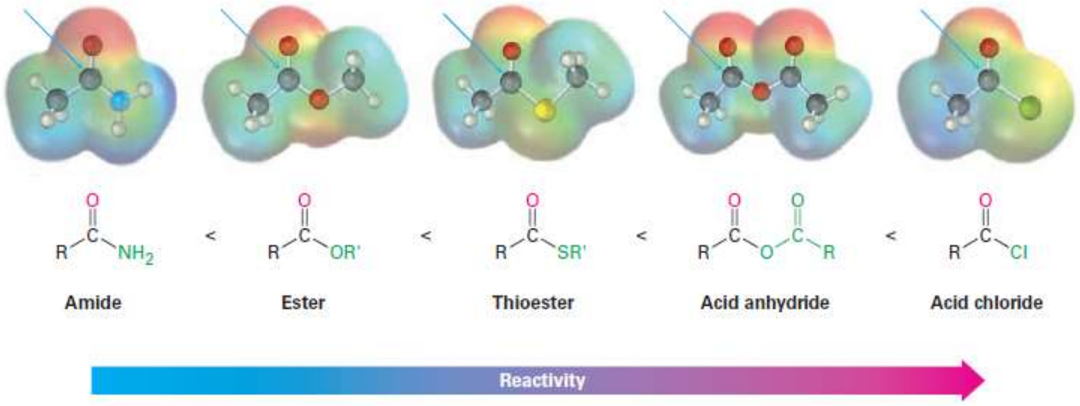
Relative Reactivity of Carboxylic Acid Derivatives

Both the initial addition step and the subsequent elimination step can affect the overall rate of a nucleophilic acyl substitution reaction, but the addition is generally the rate-limiting step. Thus, any factor that makes the carbonyl group more reactive toward nucleophiles favors the substitution process. Steric and electronic factors are both important in determining reactivity.

Sterically, we find within a series of similar acid derivatives that unhindered, accessible carbonyl groups react with nucleophiles more readily than do sterically hindered groups. The reactivity order is



Electronically, we find that strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon, whereas amides are the least reactive. Although subtle, electrostatic potential maps of various carboxylic acid derivatives indicate these differences by the relative blueness on the C=O carbons. Acyl phosphates are hard to place on this scale because they are not often used in the laboratory, but in biological systems they appear to be somewhat more reactive than thioesters.



The way in which various substituents affect the polarization of a carbonyl group is similar to the way they affect the reactivity of an aromatic ring toward electrophilic substitution. A chlorine substituent, for example, inductively withdraws electrons from an acyl group in the same way that it withdraws electrons from and thus deactivates an aromatic ring. Similarly, amino, methoxyl, and methylthio substituents donate electrons to acyl groups by resonance in the same way that they donate electrons to, and thus activate, aromatic rings.

As a consequence of these reactivity differences, it's usually possible to convert a more reactive acid derivative into a less reactive one. Acid chlorides, for instance, can be directly converted into anhydrides, thioesters, esters, and amides, but amides can't be directly converted into esters, thioesters, anhydrides, or acid chlorides. Remembering the reactivity order is therefore a way to keep track of a large number of reactions **(Figure 21-2)**. Another consequence, as noted previously, is that only acyl phosphates, thioesters, esters, and amides are commonly found in nature. Acid halides and acid anhydrides react so rapidly with water that they can't exist for long in living organisms.

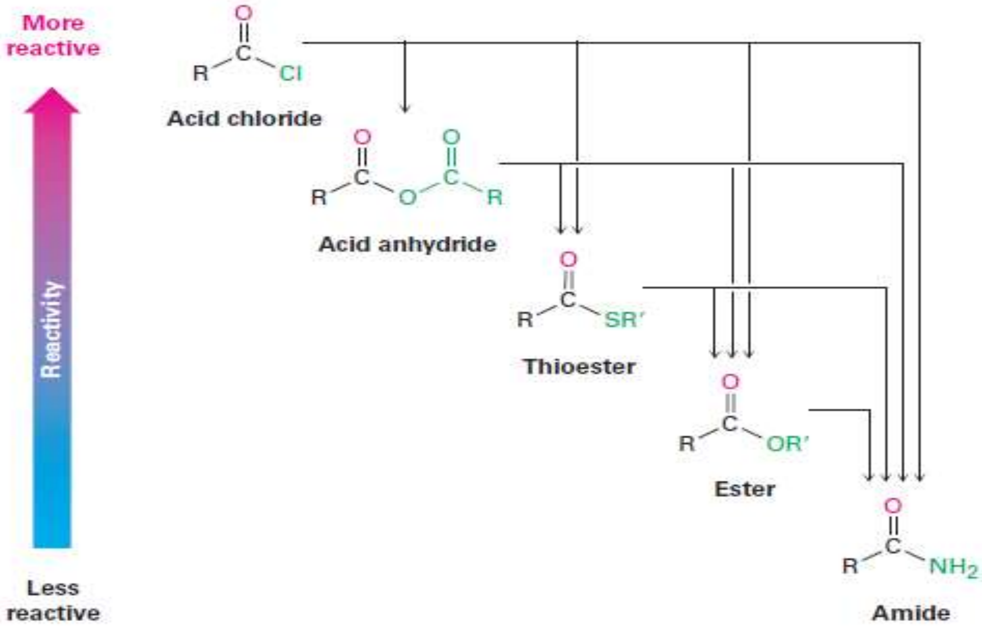


Figure 21-2 interconversions of carboxylic acid derivatives. A more reactive acid derivative can be converted into a less reactive one, but not vice versa.

In studying the chemistry of carboxylic acid derivatives in the next few sections, we'll be concerned largely with the reactions of just a few nucleophiles and will see that the same kinds of reactions tend to occur (Figure 21-3).

- **Hydrolysis** Reaction with water to yield a carboxylic acid
- **Alcoholysis** Reaction with an alcohol to yield an ester
- **Aminolysis** Reaction with ammonia or an amine to yield an amide
- **Reduction** Reaction with a hydride reducing agent to yield an aldehyde or an alcohol
- **Grignard reaction** with an organometallic reagent to yield a ketone or an alcohol

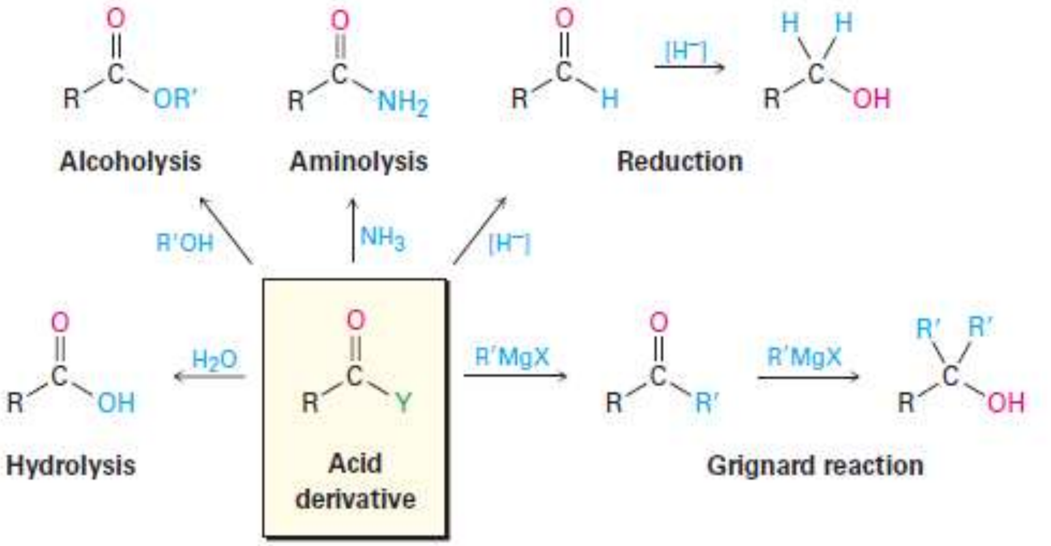


Figure 21-3 some general reactions of carboxylic acid derivatives.