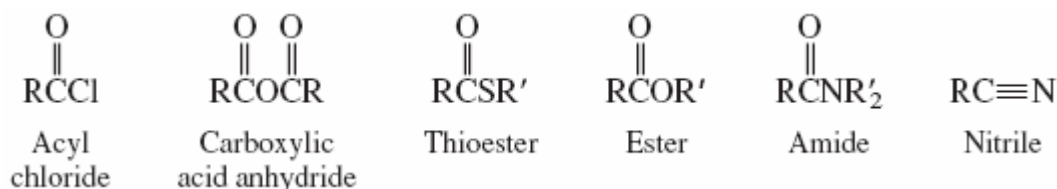


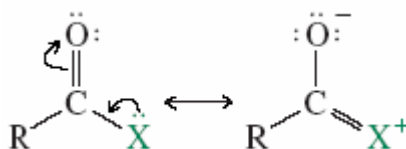
Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution

SUMMARY

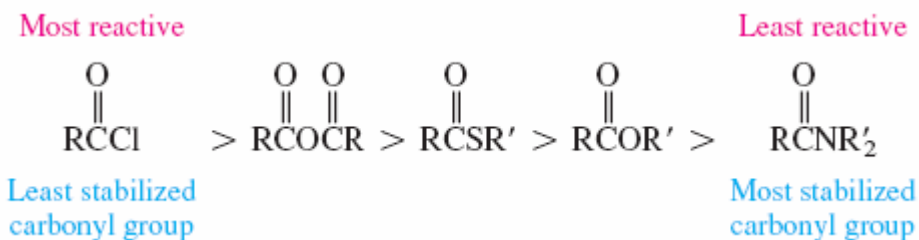
Section 20.1 This chapter concerns the preparation and reactions of *acyl chlorides*, *acid anhydrides*, *thioesters*, *esters*, *amides*, and *nitriles*. These compounds are generally classified as carboxylic acid derivatives, and their nomenclature is based on that of carboxylic acids.



Section 20.2 The structure and reactivity of carboxylic acid derivatives depend on how well the atom bonded to the carbonyl group donates electrons to it.

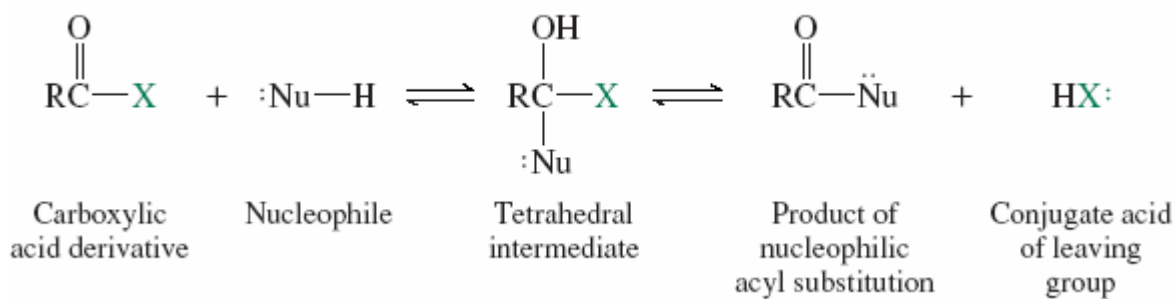


Electron-pair donation stabilizes the carbonyl group and makes it less reactive toward nucleophilic acyl substitution.

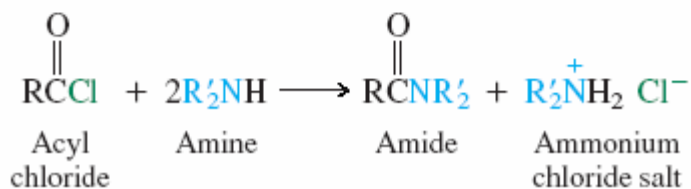
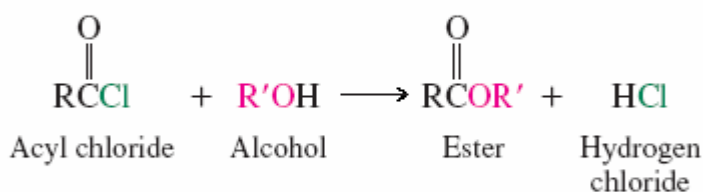
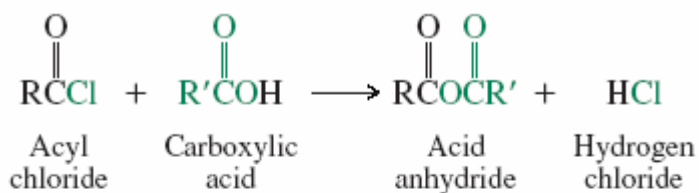


Nitrogen is a better electron-pair donor than oxygen, and amides have a more stabilized carbonyl group than esters and anhydrides. Chlorine is the poorest electron-pair donor, and acyl chlorides have the least stabilized carbonyl group and are the most reactive.

Section 20.3 The characteristic reaction of acyl chlorides, acid anhydrides, esters, and amides is **nucleophilic acyl substitution**. Addition of a nucleophilic reagent :Nu-H to the carbonyl group leads to a tetrahedral intermediate that dissociates to give the product of substitution:



Section 20.4 Acyl chlorides are converted to acid anhydrides, esters, and amides by nucleophilic acyl substitution.



Examples of each of these reactions may be found in Table 20.1.

Section 20.5 Acid anhydrides are less reactive toward nucleophilic acyl substitution than acyl chlorides, but are useful reagents for preparing esters and amides.

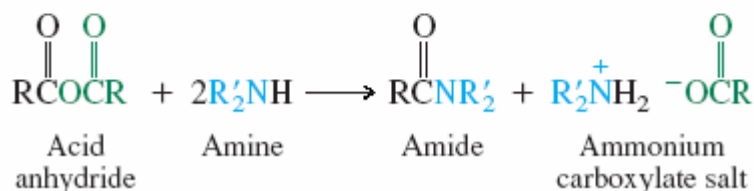
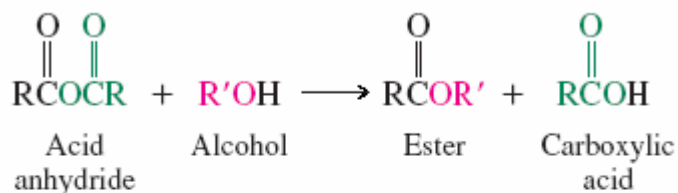
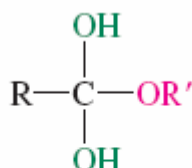


Table 20.2 presents examples of these reactions.

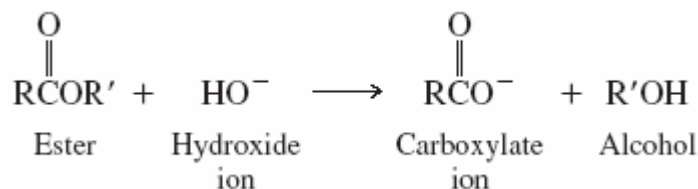
Section 20.6 Esters occur naturally or are prepared from alcohols by Fischer esterification or by acylation with acyl chlorides or acid anhydrides (see Table 20.3).

- Section 20.7 Esters are polar and have higher boiling points than alkanes of comparable size and shape. Esters don't form hydrogen bonds to other ester molecules so have lower boiling points than analogous alcohols. They can form hydrogen bonds to water and so are comparable to alcohols in their solubility in water.
- Section 20.8 Esters react with Grignard reagents and are reduced by lithium aluminum hydride (Table 20.4).
- Section 20.9 Ester hydrolysis can be catalyzed by acids and its mechanism (Mechanism 20.3) is the reverse of the mechanism for Fischer esterification. The reaction proceeds via a tetrahedral intermediate.

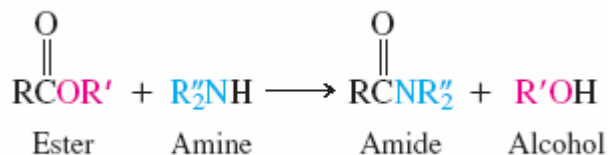


Tetrahedral intermediate
in ester hydrolysis

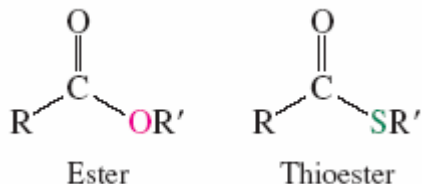
- Section 20.10 Ester hydrolysis in basic solution is called *saponification* and proceeds through the same tetrahedral intermediate (Mechanism 20.4) as in acid-catalyzed hydrolysis. Unlike acid-catalyzed hydrolysis, saponification is irreversible because the carboxylic acid is deprotonated under the reaction conditions.



- Section 20.11 Esters react with amines to give amides.



- Section 20.12 Thioesters have a less-stabilized carbonyl group than esters, and their reactions are characterized by more negative values of DG[‡].



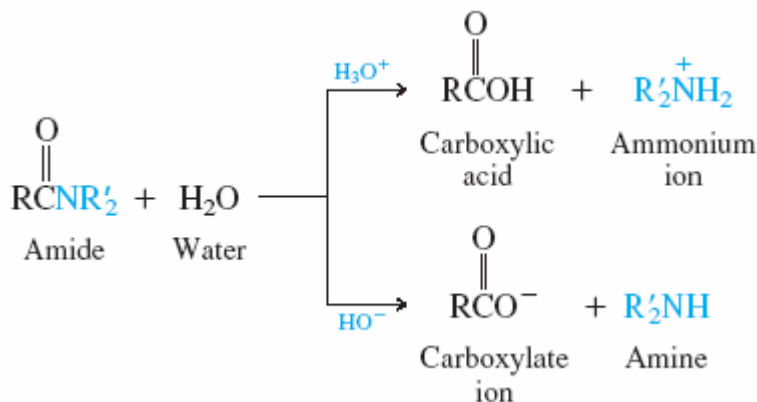
Although the rates of hydrolysis of thioesters and esters are similar, thioesters are more reactive toward nucleophilic acyl substitution by amines. Acetyl coenzyme A is a thioester involved in many biological nucleophilic acyl substitutions.

- Section 20.13 Amides having at least one NH unit can form intermolecular hydrogen bonds with other amide molecules. Compounds of this type have higher melting and boiling points than comparable compounds in which NH bonds are absent. Hydrogen bonding in amides influences the conformations of proteins.

Amides are normally prepared by the reaction of amines with acyl chlorides, anhydrides, or esters.

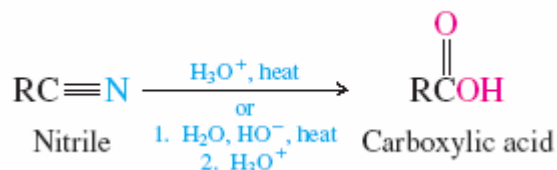
Section 20.14 Lactams are cyclic amides.

Section 20.15 Like ester hydrolysis, amide hydrolysis can be achieved in either aqueous acid or aqueous base. The process is irreversible in both media. In base, the carboxylic acid is converted to the carboxylate anion; in acid, the amine is protonated to an ammonium ion:

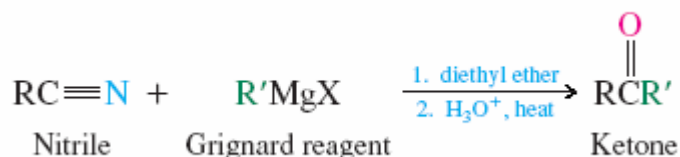


Section 20.16 Nitriles are prepared by nucleophilic substitution ($\text{S}_{\text{N}}2$) of alkyl halides with cyanide ion, by converting aldehydes or ketones to cyanohydrins (Table 20.6), or by dehydration of amides.

Section 20.17 The hydrolysis of nitriles to carboxylic acids is irreversible in both acidic and basic solution.



Section 20.18 Nitriles are useful starting materials for the preparation of ketones by reaction with Grignard reagents.



Section 20.19 Acyl chlorides, anhydrides, esters, and amides all show a strong band for C=O stretching in the infrared. The range extends from about 1820 cm^{-1} (acyl chlorides) to 1690 cm^{-1} (amides). Their ^{13}C NMR spectra are characterized by a peak near $\delta 180$ for the carbonyl carbon. ^1H NMR spectroscopy is useful for distinguishing between the groups R and R' in esters ($\text{RCO}_2\text{R}'$). The protons on the carbon bonded to O in R' appear at lower field (less shielded) than those on the carbon bonded to C=O.