Chapter 17. Carbonyl Compounds I
Nucleophilic Acyl Substitution

- Carbonyl compounds: compounds containing C=O group.
1. Class I carbonyl compounds: Carboxylic acids and derivatives containing a group (–OH, -X, -OR, -NHR, -O(CO)R), which can be replaced by a nucleophile.
2. Class II carbonyl compounds: Carbonyl compounds containing a group that can not be replaced by a nucleophile: aldehyde and ketone.
- The acyl groups of Class I carbonyl compounds are attached to weaker bases than are the acyl groups of Class II carbonyl compounds. The –H of an aldehyde and the alkyl or aryl (-R or –Ar) group of a ketone are too basic to be replaced by another group.

17.1 Nomenclature of Carboxylic acids and carboxylic Acid Derivatives

- Carboxylic acids
1. Replace "e" of alkane with "oic acid"
2. Number the carbonyl carbon as 1.
3. When the carboxylic group is a functional group, it is called a "carboxyl group"
- Acyl Halides: replace the "ic acid" of carboxylic acids with "yl halides"
- Acid anhydride (loss of water from two molecules of a carboxylic acids)
1. Symmetrical anhydride: replace "acid" of a carboxylic acid with "anhydride"
2. Mixed anhydride: state the names of both acids in alphabetical order, followed by "anhydride"
- Esters
1. The name of the group attached to the carbonyl oxygen is stated first, and replace "ic acid' with "ate"
2. In case of salts, the cation is named first.
3. Lactons (cyclic esters): a Greek designates the length of the carbon chain.
- Amides
1. Primary amides: replace "oic acid" of a carboxylic acid with "amide"
2. If there is a substituent to the nitrogen, the name of the substituent goes first, followed by the name of the amide.
3. Lactams: cyclic amides

17.2 The Structure of carboxylic acids and Carboxylic acid Derivatives

- Both the carbon and oxygen of the carbonyl group are sp^2 hybridized, so the structure is trigonal planar.
- Carboxylic acid derivatives have two resonance structures.

17.3 Physical Properties of carbonyl Compounds

- Carbonyl compounds have the following relative boiling points: amide > carboxylic acid > nitrile >> ester ~ acyl chloride ~ aldehyde ~ ketone.
- The boiling points of the ester, acyl chloride, ketone, and aldehyde are lower than boiling point of the alcohol with a comparable molecular weight because the molecules of those carbonyl compounds are unable to form hydrogen bonds with each other.
- Carboxylic acids have relatively high b.p. because they form intermolecular hydrogen bonds, giving them larger effective molecular weights.
- Amides have the highest boiling points, because they have dipole-dipole interactions since the resonance contributor with separated charges contributes significantly to the overall structure of the compound.
- Carboxylic acid derivatives are soluble in solvents such as ethers, chlorinated alkanes, and aromatic hydrocarbons.

17.4 Naturally Occurring carboxylic Acids and Carboxylic Acid derivatives

- Because of their high reactivity, acyl halides and acid anhydride are not found in nature, but carboxylic acids are less reactive and are found in nature.
- Lactic acid is the compound responsible for the burning sensation felt in muscles during anaerobic exercise, and it is found in sour milk.
- Malic acid is responsible for the sharp taste of unripe apples and pears. As the fruit ripens, the amount of malic acid in the fruit decreases and the amount of sugar increases.
- Esters are also commonly found in nature. Many of the fragrances of flowers and fruits are due to esters.
- Amides are abundant in nature. Amino acids are linked together by amide bonds to form peptides and proteins. Caffeine and Peniciline G are other examples of amides.

17.5 How class I carbonyl Compounds React

- The carbonyl group is polar, because oxygen atom is more electronegative than carbon, so

the carbon is attacked by necleophiles (electrophile).

a tetrahedral intermediate
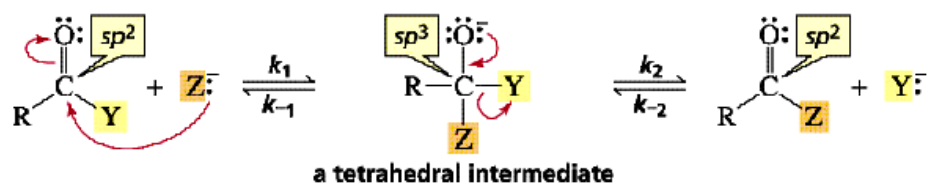
- When a nucleoiphile attacks the carbonyl carbon of a carboxylic acid derivative, the carbon-oxygen π bond breaks and a tetrahedral intermediate is formed. In general, a compound that has an sp^3 carbon bonded to an oxygen atom will be unstable if the sp^3 carbon is bonded to another electronegative atom. A lone pair on the oxygen reforms the π bond, and either Y^- or Z^- is expelled with its bonding electrons.

- Whether Y^- or Z^- is expelled depends on their relative basicities. The weaker the base, the better it is as a leaving group.

- Nucleophilic acyl substitution: a nucleophile has replaced the substituent that was attached to the acyl group in the reactant.

- The product depends on the basicity of the substituent attached to the carbonyl carbon.

1. If the incoming nucleophile is a weaker base than the group attached to the carbonyl carbon, the product will be the starting material(Fig. a).

2. If the incoming nucleophile is a stronger base than the group attached to the carbonyl carbon, the product will be the substitution product (Fig. b).

3. If the incoming nucleophile and the group attached to the acyl group have similar basicity, mixture of the starting material and the product will be formed (Fig. c).
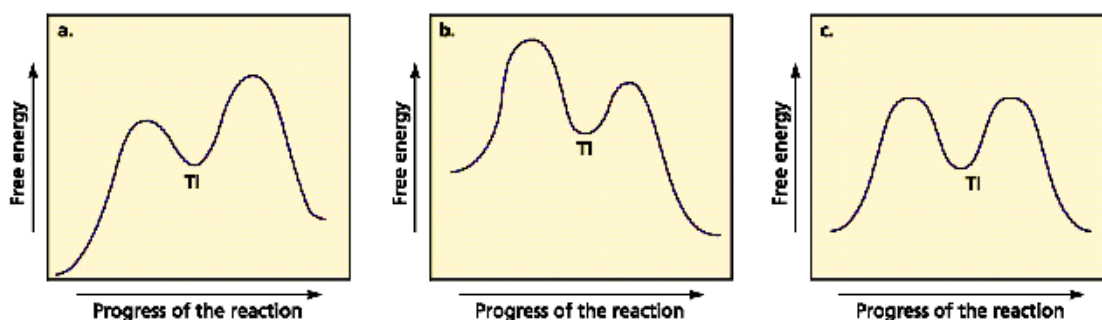
- Mechanism

1. In the first step, the incoming nucleophile attacks the carbonyl carbon and breaks the π bond to form a tetrahedral intermediate.

2. Then, the lone pair electrons in oxygen reform the π bond.

- When a filled orbital and an empty orbital overlap, the result is a molecular orbital that is more stable than either of the overlapping orbitals (Fig. 16.3).

- In aldehydes or ketones, there is no good leaving group, so nucleophilic addition reaction occurs.

17.6 Relative Reactivities of Carboxylic acids and Carboxylic Acid derivatives

- The reactivities of carboxylic acid derivatives depend on the basicity of the leaving group attached to the carbonyl carbon: the weaker the base, the easier it leaves *in the second step of the reaction.*
- Relative basicities: $X^- < \,^-OCOR < \,^-OR < \,^-NHR$
- Relative reactivities: acyl halide > acid anhydride > ester > amide
- A weak base facilitates *the first step of the reaction*
1. A weaker base is a more electronegative base: that is, it is better able to accommodate its negative charge. Thus, weaker bases are better at withdrawing electrons inductively forming the carbonyl carbon. Electron withdrawal increases the carbonyl carbon's susceptibility to nucleophilic attack.
2. The weaker the basicity of a nuclephile(Y), the smaller is the contribution from the resonance contributor with a positive charge on Y. The less the carboxylic acid derivatives are stabilized by electron delocalization, the more reactive it will be.
3. Since a weak base does not share its electrons, a weak base makes the carbonyl compound less stable.
4. A weak base attached to the acyl group will make the second step of the nucleophilic acyl substitution reaction easier because weak bases are easier to eliminate when the tetrahedral intermediate collapses.
- Carboxylic acid derivatives can be converted into the less reactive derivatives, but not vice versa.

17.7 General Mechanism for Nucleophilic Acyl Substitution reactions

- All carboxylic acid derivatives undergo nucleophilic acyl substitution reaction by the same mechanism.
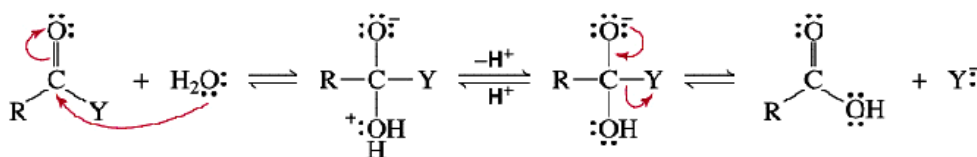
- The nucleophile attacks the carbonyl carbon, forming a tetrahedral intermediate. When the tetrahedral intermediate collapses, the weaker base is eliminated.

- If the nucleophile is neutral, the mechanism has an additional step. A proton is lost from the tetrahedral intermediate formed in the first step, resulting in a tetrahedral intermediate equivalent to the one formed by negatively charged nucleophiles. This tetrahedral intermediate expels the weaker of the two bases.

17.8 Reactions of Acyl Halides

- Acyl halide is the most reactive on carboxylic acid derivatives because the halide is the best leaving group.

mechanism for the conversion of an acyl chloride into an ester
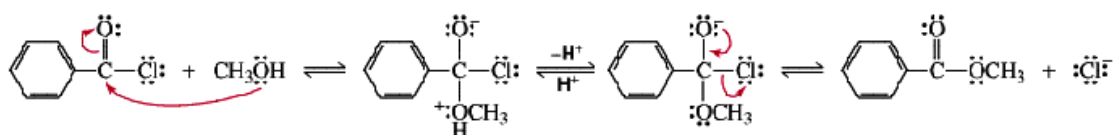
- Acyl halides react with carboxylate ions to form anhydrides, with alcohols to form esters, with water to form carboxylic acids, and with amines to form amides.
- The reaction of an acyl chloride with ammonia or with a primary or secondary amine forms an amide and HCl. The acids generated in the reaction will protonate unreacted ammonia or unreacted amine, so the protonated amines cannot react with the acyl chloride. Therefore, the reaction must be carried out with twice as much ammonia or amine as acyl chloride so that there will be enough amine to react with all the acyl halide.

17.9   Reactions of Acid anhydrides

- Acid anhydrides do not react with halide anions, but react with alcohols to form esters, with water to form two equivalents of carboxylic acids, and with amines to form amides.

17.10 Reactions of Esters

- The reactions of esters to form acids (hydrolysis) or different esters (alcoholysis) are very slow, so it needs catalysts (acid or base).
- The tetrahedral intermediate formed form a reaction of an ester with water has both an RO^- leaving group and a HO^- leaving group.
- **Transesterification reaction**: an ester reacts with an alcohol to form a new ester and a new alcohol.
- The rate of transesterification can be increased by H^+ or by the conjugate base (RO^-) of the

reactant alcohol.

- Phenyl esters are more reactive than alkyl esters, because phenolate ions are weaker bases than alkoxide ions.
- Esters react with amine to form amides. A reaction with an amine that converts one compound into two compounds is called aminolysis. The aminolysi of an ester requires only one equivalent of amine, because the leaving group of an ester (RO^-) is more basic than the amine, so the alkoxide on picks up the proto generated in the reaction.
- The rate of the reaction of an ester with an amine can't be increased by H^+ or by RO^-.

17.11 Acid-Catalyzed Ester Hydrolysis and Transesterification

- The rate of hydrolysis of esters can be increased by either acid or HO^-.
- Keep in mind the followings:
  1. In an acid-catalyzed reaction, all organic intermediates and products are positively charged or neutral; negatively charged organic intermediates and products are not formed in acidic solutions.
  2. In a reaction in which HO^- is used to increase the rate of the reaction, all organic intermediate and products are negatively charged or neutral.
- Mechanism for normal ester hydrolysis
1. In the first step, the carbonyl oxygen is protonated by acid.
2. In the second step, the nucleophile (H_2O) attacks the protonated carbonyl group to form a tetrahedral intermediate. Te resulting protonated tetrahedral intermediate is in equilibrium with its nonprotonated form. Either the OH or the OR group of tetrahedral intermediate II can be protonated. Because the OH and OR groups have approximately the same basicity, both tetrahedral intermediate I and tetrahedral intermediate III are formed. The relative amount of the three intermediates depends on the pH of the solution ad the pKa values of the protonated intermediates.
3. The tetrahedral intermediate can eliminate H_2O to form the starting material or eliminate CH_3OH to form a carboxylic acid. When tetrahedral intermediate I collapses, it expels H_2O in preference to CH_3O^- because H_2O is a weaker base forming an ester. When tetrahedral intermediate III collapses, it expels CH_3OH rather than HO^- because CH_3OH is a weaker base forming the carboxylic acid. Tetrahedral intermediate II s less likely to collapse, because both HO^- and CH_3O^- are strong bases.
- Consequently, when the reaction has reached equilibrium, both ester and carboxylic acid will be present in approximately equal amounts. Excess water will force the equilibrium to the right.

mechanism for acid-catalyzed ester hydrolysis


tetrahedral intermediate I

tetrahedral intermediate II
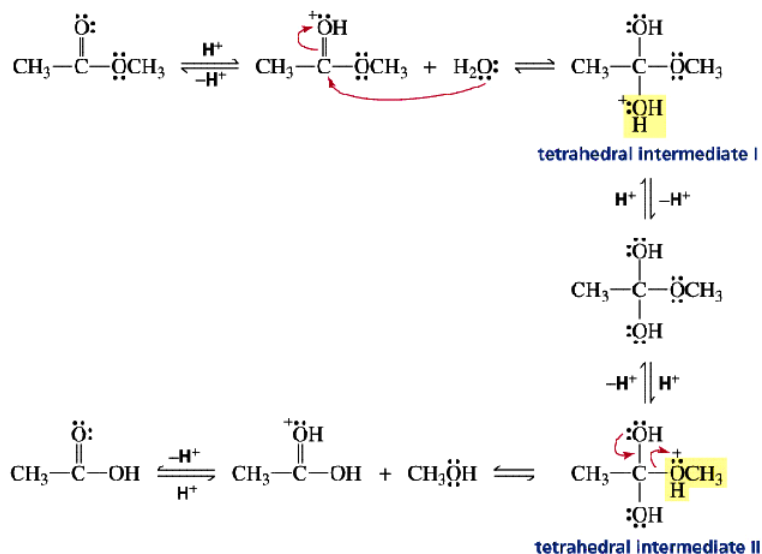
- The acid increases the rate of ester hydrolysis by the following reasons.
1. H^+ protonates the carbonyl oxygen atom and the protonated carbonyl group will be attacked by a nucleophile easily, because a positively charged oxygen is more electron withdrawing than a neutral oxygen
2. H^+ decreases the basicity of the leaving group, so it is easier for the leaving group to leave.
- Esters with tertiary alkyl groups undergo hydrolysis much more rapidly than do other esters because they hydrolyze by a completely different mechanism-one that does not involve formation of a tetrahedral intermediate. It goes through S_N1 reaction.
- Transesterification is also catalyzed by acid. The nucleophile is ROH instead of HO.

17.12 Hydroxide-Ion-Promoted Ester Hydrolysis

- OH^- increases the rate of ester hydrolysis by the following reasons.
1. OH^- is a better nucleophile than H_2O.
2. Hydroxide ion increases the rate of collapse of the tetrahedral intermediate because a smaller fraction of the negatively charged tetrahedral intermediate becomes protonated in a basic solution. A negatively charged oxygen can more readily expel the very basic leaving group (RO^-) because the oxygen does not develop a partial positive charge in the transition state.
- The final products are the carboxylate ion and methanol because CH_3O^- is more basic than CH_3COO^-.
- The final product in basic condition is carboxylate ion, which are not easily attacked by

nucleophiles. Therefore, the hydroxide-ion-promoted hydrolysis of an ester is not a reversible reaction.

mechanism for hydroxide-ion-promoted hydrolysis of an ester
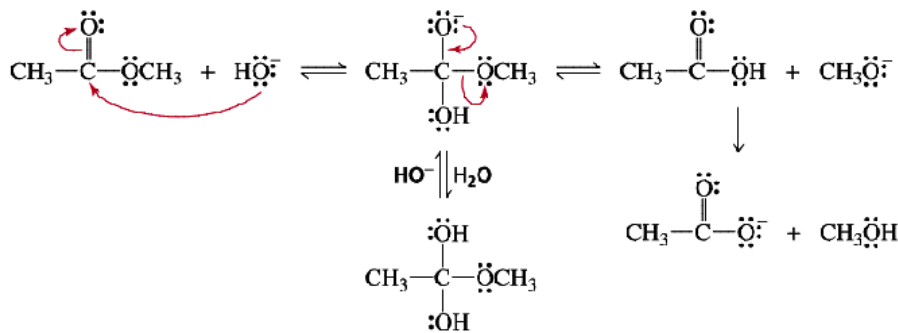
- In this reaction, base is consumed as a reagent, so the base is not a catalyst. Therefore, this reaction is called "hydroxide-ion-promoted ester hydrolysis".
- Only hydrolysis reactions can be promoted by hydroxide ion.
- The evidence for the existence of tetrahedral intermediate: ^{18}O labeling experiment. Myron investigated the hydroxide-ion-promoted hydrolysis of ethyl benzoate, with the carbonyl oxygen of ethyl benzoate labeled with ^{18}O. When he isolated ethyl benzoate from an incomplete reaction mixture, he found that some of the ester was no longer labeled. If the reaction undergoes by one step direct-displacement mechanism, all the isolated ester would have remained labeled because the carbonyl group would not have participated in the reaction. If the mechanism involved a tetrahedral intermediate, some of the isolated ester would no longer be labeled because some of the label would have been transferred to the hydroxide ion.

17.13 How the Mechanism for Nucleophilic Acyl Substitution Reactions Was Confirmed
- The intermediate is tetrahedral, which is very unstable. Then how do we know we have this species as an intermediate?
- How do we know it does not go through concerted reaction (one step)?
- Myron Bender used ^{18}O: some of the esters were no longer labeled. If it goes through one-step reaction, esters must be labeled.

17.14 Soaps, Detergents, and Micelles

- Soaps are sodium or potassium salts of fatty acids. They are obtained when fats or oils are hydrolyzed under basic conditions (used oil + NaOH solution).
- Fatty acids: long-chain unbranched carboxylic acids.

- Saponification: the hydrolysis of an ester in a basic solution.
- Long-chain carboxylate ions do not exist as individual ions in aqueous solution. Instead, they arrange themselves in spherical clusters called micelles.
- The attractive forces of hydrocarbon chains for each other in water are called hydrophobic interaction, not hydrophobic attraction.
- Soap has cleansing ability because nonpolar oil molecules, which carry dirt, dissolve in the nonpolar interior of the micelle and are carried away with the soap during rinsing. Because the surface of the micelle is negatively charged, the individual micelles repel each other instead of clustering to form larger aggregates.
- While micelles with sodium and potassium cations are dispersed in water, micelles with calcium and magnesium cations form aggregate and form a precipate, which is called soap scum.
- To avoid the formation of soap scum, synthetic soaps, detergents, are developed. They are the salts of benzene sulfonic acids.
- Compounds that lower the surface tension of water are called surfactants. Lowering the surface tension enables the soap or detergent to penetrate the fibers of a fabric, thus enhancing its cleaning ability.

17.15 Reactions of Carboxylic Acids

- The basic form of carboxylic acid (carboxylate anion) does not undergo nucleophilic acyl substitution reactions because the negatively charged carboxylate ion is resistant to nucleophilic attack.
- Carboxylic acids react with alcohols to form esters. The reactions must be carried out in an acidic solution, not only to catalyze the reaction but also to keep the carboxylic acid in its acidic form so that it will react with the nucleophile.
- Since the tetrahedral intermediate formed in this reaction has two potential leaving groups of approximately the same basicity, the reaction must be carried out with excess alcohol to drive it toward products.
- Fischer esterification reaction: reaction of carboxylic acid with excess amount of alcohol in the presence of acid catalyst.
- Carboxylic acids do not undergo nucleophilic substitution reactions with amines.

17.16 Reactions of Amides

- Amides can be converted into carboxylic acids in the presence of acid catalyst at high

temperature.

- MO theory can explain why amides are unreactive: The filled nonbonding orbital containing nitrogen's lone pair electrons overlaps the empty $\pi *$ antibonding molecular orbital of the carbonyl group. This stabilizes the lone pair, making it less reactive, and raise the energy of the $\pi *$ orbital of the carbonyl group, making it less able to react with nucleophiles (Fig. 16.5).

17.17 The Hydrolysis of Amides Is Catalyzed by Acids

- How does the acid catalyze hydrolysis?
1. Protonation of carbonyl oxygen increase the susceptibility of the nucleophilic attack.
2. Protonation in the tetrahedral intermediate makes the NH_2 group (leaving group) better leaving group.
- Why an amide cannot be hydrolyzed without a catalyst?: In the uncatalyzed reaction, the amide is not protonated. So water, a very poor nucleophile, must attack a neutral amide that is much less susceptible to nucleophilic attack than a protonated amide would be. In addition, the NH_2 group of the tetrahedral intermediate is not protonated in the uncatalyzed reaction, so HO^- is the group expelled from the tetrahedral intermediate- because HO^- is a weaker base than $-NH_2^-$ which reforms the amide.
- Hydroxide-ion-promoted hydrolysis:
1. OH^- is better nucleophile than H_2O.
2. The product from the hydrolysis of amides is a carboxylate anion, which is not reactive toward nucleophiles.

17.18 The Hydrolysis of an Imide: A Way to Synthesize Primary Amines

- *Gabriel synthesis*: convert alkyl halides into primary amines
1. In the first step, a base removes a proton from the nitrogen of phthalimide.
2. The resulting nucleohpile reacts with an alkyl halide in S_N2 manner to form N-substituted phthalimide, which is catalyzed to phthalic acid and primary ammonium ion
3. This reaction is applicable only for the preparation of primary amines.

17.21 How Chemists Activate Carboxylic Acids

- Since carboxylic acids are not reactive, it is no easy to synthesize their derivatives from carboxylic acids through substitution reaction.

- Carboxylic acids can be converted into acyl halides by using $SOCl_2$, PCl_3, and PBr3.
- The resulting acyl halides transform to other derivatives.
- Carboxylic acid derivatives in biological system: acyl phosphate (mixed anhydride of a carboxylic acid and phosphoric acid), acylpyrophosphate (mixed anhydride of a carboxylic acid and pyrophosphoric acid), acyl adenylate (mixed anhydride of a carboxylic acid and adenosine monophosphate), and thioester.
- Acyl phosphates are formed by nucleophilic attack of a carboxylate ion on the ɣ-phosphorous of ATP. Attack of a nucleophile on the P=O group breaks a phosphoanhydride bond, so an intermediate is not formed. It is an S_N2 reaction with an adenosine pyrophosphate leaving group.
- The carbonyl carbon of a thioester is more susceptible to nucleophilic attack than is the carbonyl carbon of an oxygen ester because there is less electron delocalization onto the carbonyl oxygen when Y is S than when Y is O. There is less electron delocalization because there is less overlap between the 3p orbital of sulfur and the 2p orbital of carbon, compared with the amount of overlap between the 2p orbital of oxygen and the 2p orbital of carbon. In addition, a thiolate ion is a weaker base and therefore a better leaving group than an alkoxide ion.
- The first step in converting a carboxylic acid into a thioester is to convert the carboxylic acid into an acyl adenylate. The acyl adenylate reacts with CoASH to form the thioester.
- Acetylcholine, an ester, is one example of a carboxylic acid derivative that cells synthesize using acetyl-CoA.

17.23 Dicarbpoxylic Acids and Their Derivatives

- Although the two carboxyl groups of a dicarboxylic acid are identical, the two pKa values are different because the protons are lost one at a time and therefore leave from different species.
- A COOH group withdraws electrons and therefore increases the stability of the conjugate base that is formed when the first COOH group loses a proton, so increases its acidity (Table 17.2).
- Dicarboxylic acids readily lose water when heated if they can form a cyclic anhydride with a five- or six-membered ring.