الكلية	العلوم
القسم	علوم الكيمياء
المادة باللغة الانجليزية	Organic chemistry
المادة باللغة العربية	الكيمياء العضوية
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عنوان المحاضرة باللغة الانجليزية	Carboxylic acids
عنوان المحاضرة باللغة العربية	الاحماض الكاربوكسيلية
رقم المحاضرة	4
المصادر والمراجع	Fundamental of organic chemistry, T. W. Craham Solomon
	Organic chemistry, 10th Ed, T. W. Craham Solomon & Craig B. fryhle
	Organic chemistry, 8th Ed, L. G. WADE JR

Carboxylic Acids and Their Derivatives

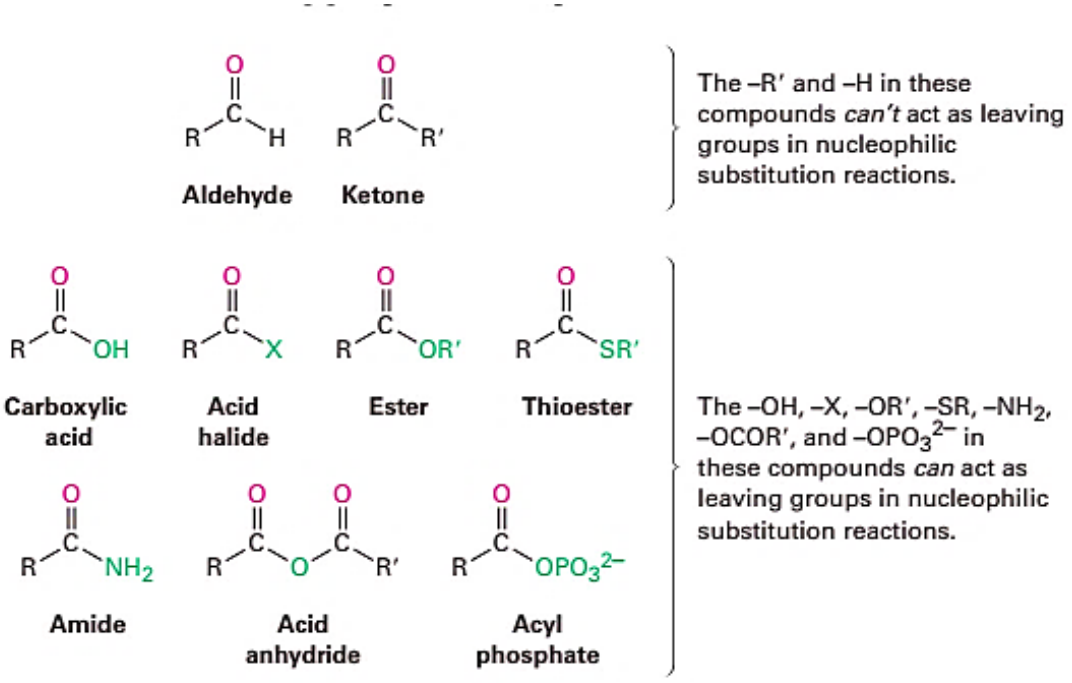
By : Wahaj Raed Abbas

Content

Introduction

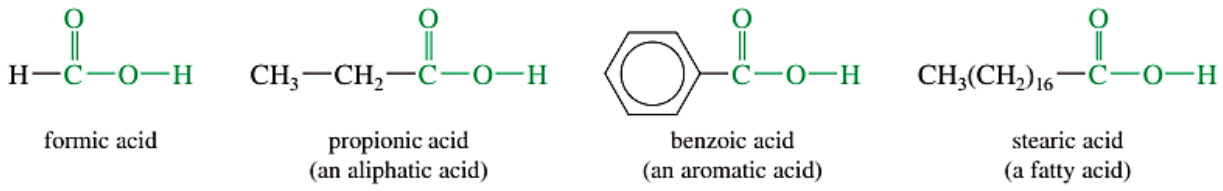
Compounds that contain an electronegative atom bonded to the carbonyl group. These

include carboxylic acids, acid chlorides, esters, and amides. Each of these compounds contains an electronegative atom (Cl, O, or N) capable of acting as a leaving group. Acid chlorides, esters, and amides are often called carboxylic acid derivatives, because they can be synthesized from carboxylic acids. Since each compound contains an acyl group (RCO^-), they are also called acyl derivatives.



1.1.Carboxylic acid

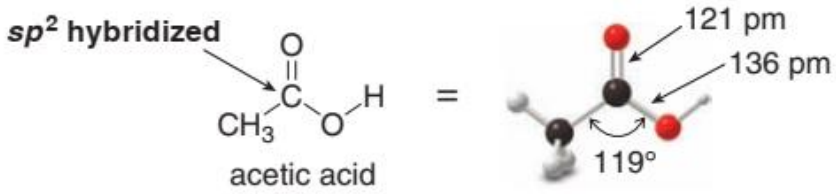
Compounds of a carbonyl group and a hydroxyl on the same carbon atom is called a carboxyl group. Compounds containing the carboxyl group are distinctly acidic and are called carboxylic acids (with -COOH moiety). These compounds are abundant in nature, where they are responsible for some familiar odors. Carboxylic acids are classified according to the substituent bonded to the carboxyl group. An aliphatic acid has an alkyl group bonded to the carboxyl group, and an aromatic acid has an aryl group.



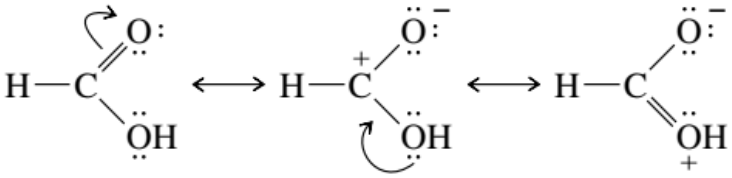
1.1.1. Structure and Bonding

Carboxylic acids are organic compounds containing a carboxy group (COOH). Although the structure of a carboxylic acid is often abbreviated as RCOOH or RCO_2H, keep in mind that the central carbon atom of the functional group is doubly bonded to one oxygen atom and singly bonded to another. The carbon atom of a carboxy group is

surrounded by three groups, making it sp^2 hybridized and trigonal planar, with bond angles of approximately 120°. The C = O of a carboxylic acid is shorter than its C – O.



Additionally, sp^2 hybridization of the hydroxyl oxygen allows one of its unshared electron pairs to be delocalized by orbital overlap with the π system of the carbonyl group. In resonance terms, this electron delocalization is represented as:

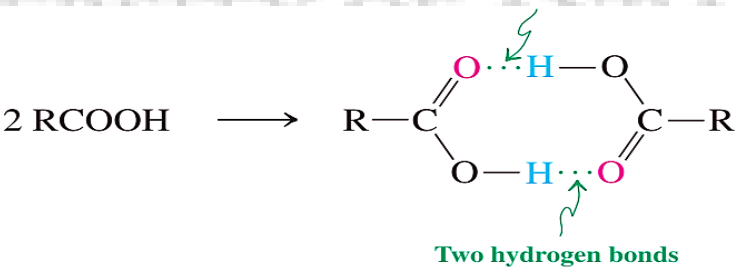


Lone-pair donation from the hydroxyl oxygen makes the carbonyl group less electrophilic than that of an aldehyde or ketone. Carboxylic acids are fairly polar, and simple ones such as acetic acid, propanoic acid, and benzoic acid have dipole moments in the range 1.7–1.9 D.

1.1.2. Physical properties

The melting points and boiling points of carboxylic acids are higher than those of hydrocarbons and oxygen-containing organic compounds of comparable size and shape and indicate strong intermolecular attractive forces.

Like alcohols, carboxylic acids are strongly associated because of hydrogen bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds. This strong hydrogen-bonding has a noticeable effect on boiling points, making carboxylic acids much higher boiling than the corresponding alcohols. Acetic acid, for instance, has a boiling point of 117.9 °C, versus 78.3 °C for ethanol, even though both compounds have two carbons.



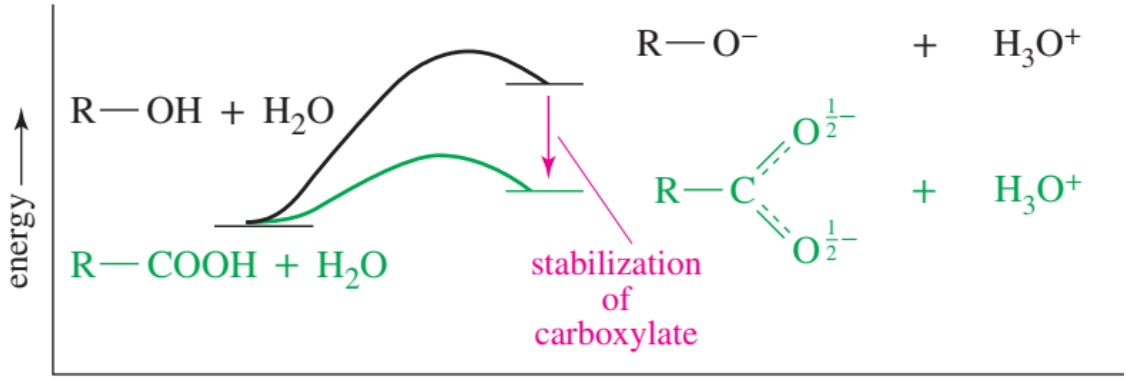
Carboxylic acids form hydrogen bonds with water, and the lower molecular-weight acids (up through four carbon atoms) are miscible with water. As the length of the

hydrocarbon chain increases, water solubility decreases until acids with more than 10 carbon atoms are nearly insoluble in water.

Carboxylic acids are very soluble in alcohols because the acids form hydrogen bonds with alcohols. Also, alcohols are not as polar as water, so the longer-chain acids are more soluble in alcohols than they are in water. Most carboxylic acids are quite soluble in relatively nonpolar solvents such as chloroform because the acid continues to exist in its dimeric form in the nonpolar solvent. Thus, the hydrogen bonds of the cyclic dimer are not disrupted when the acid dissolves in a nonpolar solvent.

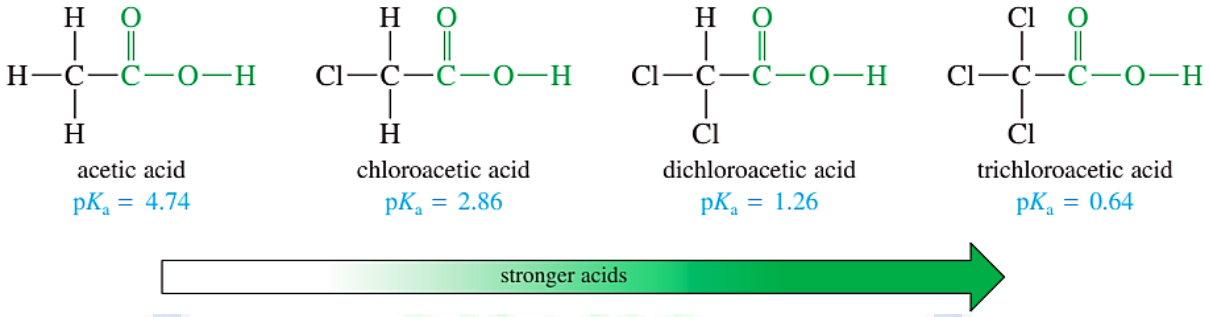
1.1.3. Acidity of carboxylic acids

A carboxylic acid may dissociate in water to give a proton and a carboxylate ion. The equilibrium constant for this reaction is called the acid-dissociation constant. Values of pKa are about 5 ($Ka = 10^{-5}$) for simple carboxylic acids. For example, acetic acid has pKa =4.7 ($Ka = 1.8 \times 10^{-5}$). Although carboxylic acids are not as strong as most mineral acids, they are still much more acidic than other functional groups we have studied. Dissociation of either an acid or an alcohol involves breaking an bond, but dissociation of a carboxylic acid gives a carboxylate ion with the negative charge spread out equally over two oxygen atoms, compared with just one oxygen in an alkoxide ion. This charge delocalization makes the carboxylate ion more stable than the alkoxide ion; therefore, dissociation of a carboxylic acid to a carboxylate ion is less endothermic than dissociation of an alcohol to an alkoxide ion. The carboxylate ion can be visualized either as a resonance hybrid or as a conjugated system of three p orbitals containing four electrons. The carbon atom and the two oxygen atoms are hybridized, and each has an unhybridized p orbital. Overlap of these three p orbitals gives a three-center molecular orbital system. There is half of a
bond between the carbon and each oxygen atom.



Any substituent that stabilizes the negatively charged carboxylate ion promotes dissociation and results in a stronger acid. Electronegative atoms enhance the strength of an acid by withdrawing electron density from the carboxylate ion. This inductive

effect can be quite large if one or more strongly electron-withdrawing groups are present on the a carbon atom. The magnitude of a substituent effect depends on its distance from the carboxyl group. Substituents on the carbon atom are most effective in increasing acid strength. More distant substituents have smaller effects on acidity, showing that inductive effects decrease rapidly with distance.



In conclusion, the factors effect the acidity are:

1- Resonance effects: A carboxylic acid is more acidic than an alcohol or phenol because its conjugate base is more effectively stabilized by resonance.

2- Inductive effects:

Electron-withdrawing groups, stabilize a conjugate base, making an acid more acidic. An electron-withdrawing group stabilizes a conjugate base by removing electron density from the negatively charged carboxylate anion.

Electron-donor groups, destabilize a conjugate base, making an acid less acidic. An electron-donor group destabilizes a conjugate base by donating electron density onto a negatively charged carboxylate anion.

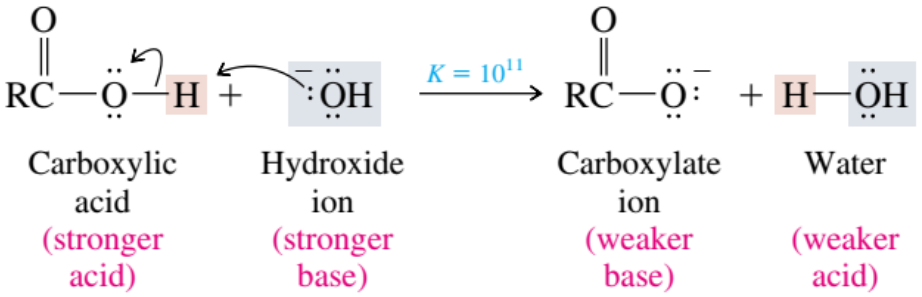
3- Substituted benzoic acids:

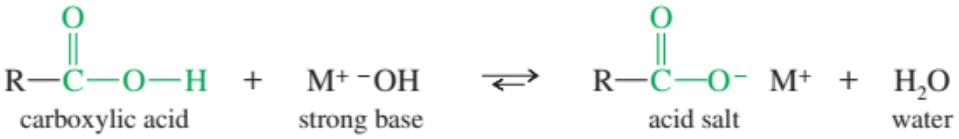
Electron-donor groups (D) make a substituted benzoic acid less acidic than benzoic acid.

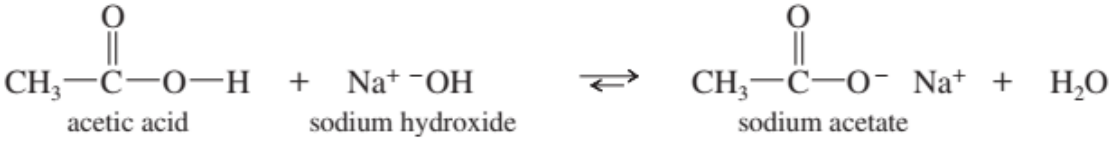
Electron-withdrawing groups (W) make a substituted benzoic acid more acidic than benzoic acid.

1.1.4. Salts of Carboxylic Acids

Carboxylic acids exhibit mildly acidic protons. Treatment of a carboxylic acid with a strong base, such as sodium hydroxide, yields a carboxylate salt. Because mineral acids are stronger than carboxylic acids, addition of a mineral acid converts a carboxylic acid salt back to the original carboxylic acid.



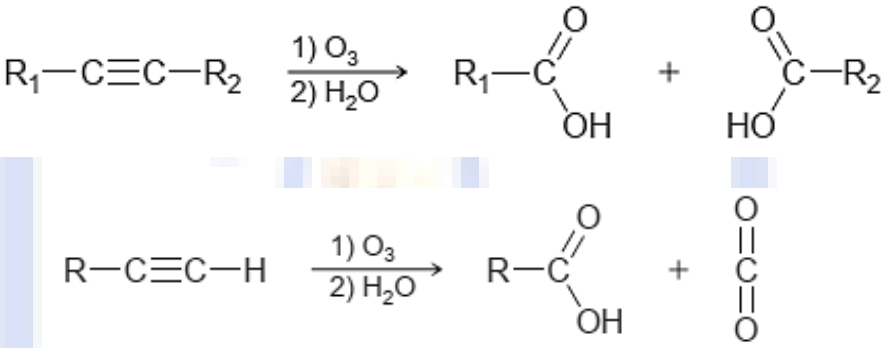




1.1.5. Preparation of Carboxylic Acids

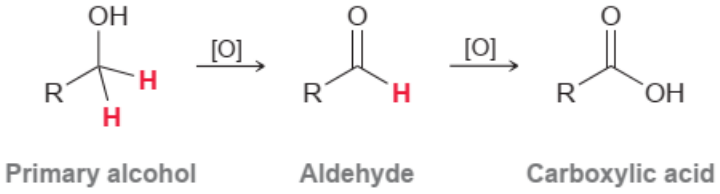
1.1.5.1. Oxidative Cleavage of Alkynes

When treated with ozone followed by water, alkynes undergo oxidative cleavage to produce carboxylic acids. When a terminal alkyne undergoes oxidative cleavage, the terminal side is converted into carbon dioxide.



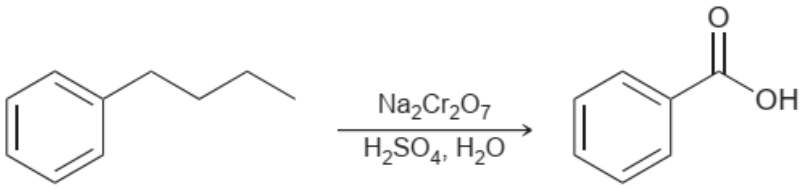
1.1.5.2. Oxidation of Alcohols

The outcome of an oxidation process depends on whether the starting alcohol is primary, secondary, or tertiary. Let's first consider the oxidation of a primary alcohol. Primary alcohols can be oxidized twice. The first oxidation produces an aldehyde, and then oxidation of the aldehyde produces a carboxylic acid.



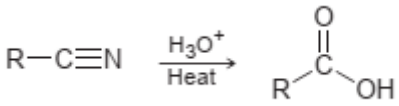
1.1.5.3. Oxidation of Alkylbenzenes

Any alkyl group on an aromatic ring will be completely oxidized to give benzoic acid, provided that the benzylic position has at least one hydrogen atom.



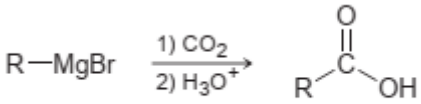
1.1.5.4. Hydrolysis of Nitriles

When treated with aqueous acid, a nitrile (a compound with a cyano group) can be converted into a carboxylic acid.



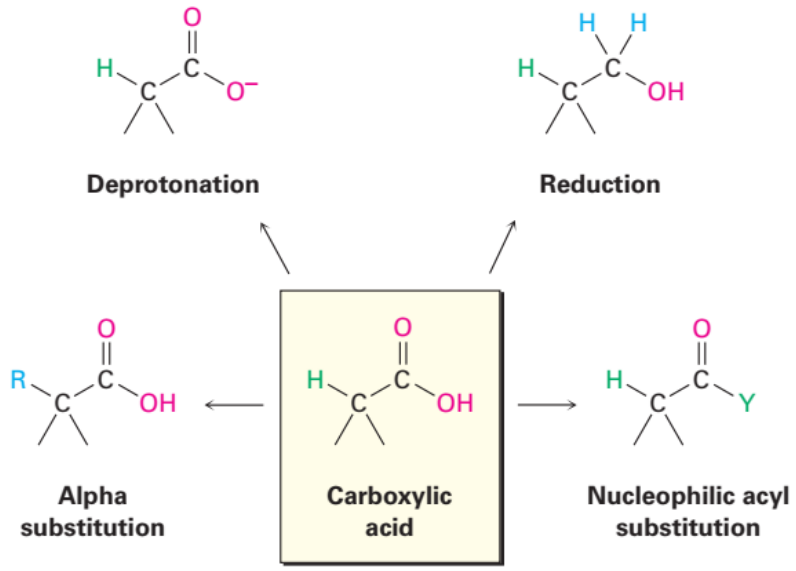
1.1.5.5. Carboxylation of Grignard Reagents

Carboxylic acids can also be prepared by treating a Grignard reagent with carbon dioxide.

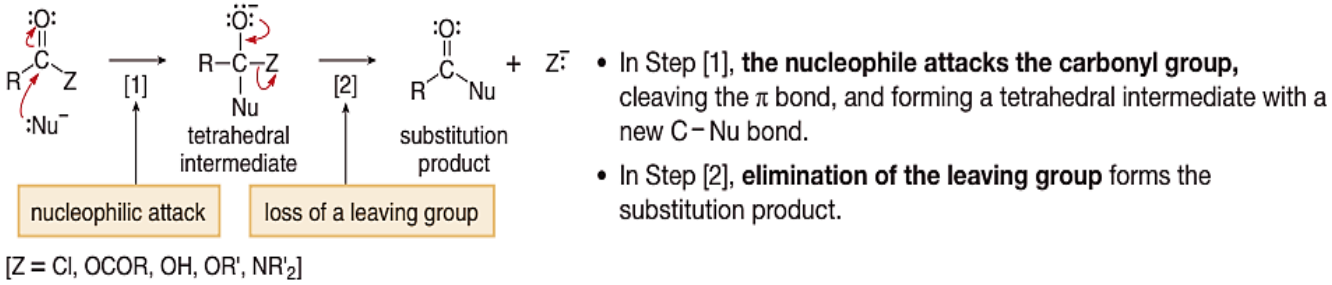


1.1.6. Reaction of Carboxylic Acid

Carboxylic acid undergoes nucleophilic substitution reaction. The carbonyl group in carboxylic acids shows reactivity similar to that in aldehydes and ketones: It is subject to attack by nucleophiles at carbon and electrophiles at oxygen. However, the presence of the carboxy OH group in the structure adds another dimension to the chemical function of carboxylic acids: Just as in alcohols, this OH may be converted into a leaving group. As a result, after nucleophilic addition to the carbonyl carbon takes place, the leaving group may depart, resulting in a net substitution process and a new carbonyl compound. This section introduces this process and the general mechanisms by which it takes place. This type of reactivity is observed in the carboxylic acids and the carboxylic acid derivatives, substances with the general formula RCOL (L stands for leaving group).



General Mechanistic Pattern for an Addition–Elimination Sequence

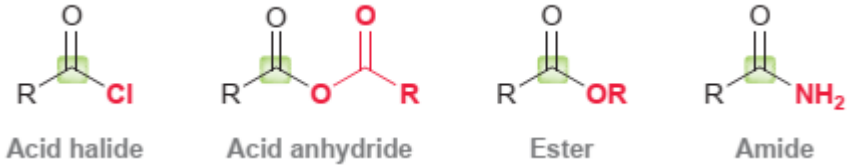


1.1.6.1. Redaction of Carboxylic Acids

Carboxylic acids are reduced to alcohols upon treatment with lithium aluminum hydride. An alternative method for reducing carboxylic acids involves the use of borane (BH_3).

1.1.6.2. Convert Carboxylic Acid to It Is Derivative

Carboxylic acids also undergo many other reactions that do not involve a change in oxidation state. Nucleophilic acyl substitution is the most common method for interconverting these derivatives. Replacement of the OH group with a different group (Z) does not involve a change in oxidation state if Z is a heteroatom (Cl, O, N, etc.). Compounds of this type are called carboxylic acid derivatives, and they will be the focus of the remainder of this chapter. The four most common types of carboxylic acid derivatives are shown below.



1.1.6.3. Spectroscopy

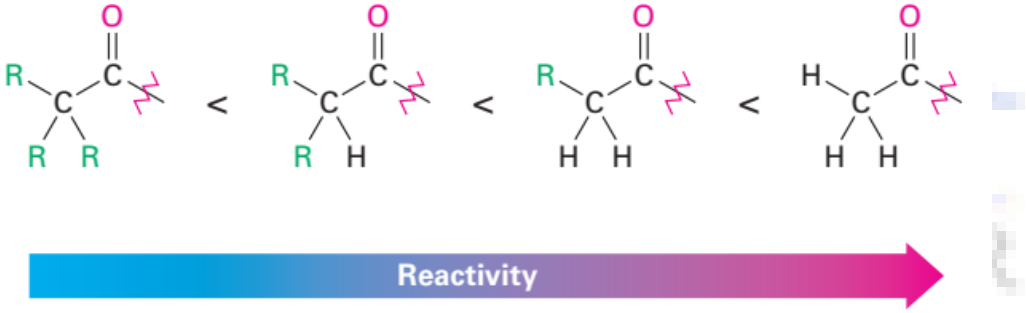
1.1.6.4.

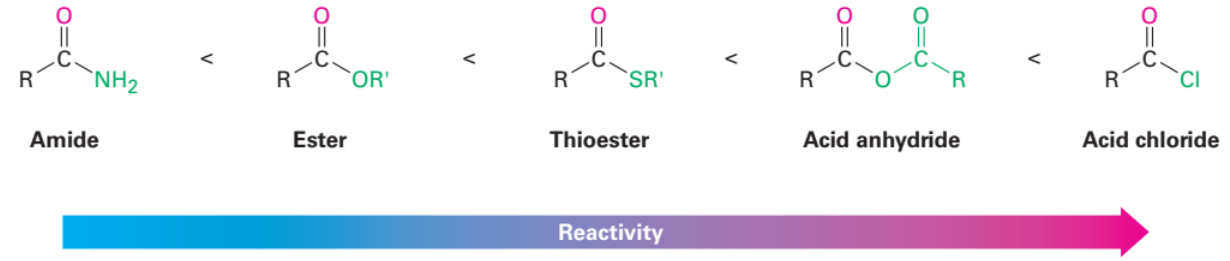
H-NMR: Carboxylic acid protons are the most deshielded protons we have encountered, absorbing between δ= 10-13 ppm. Depending on the solvent and the concentration, this acid proton peak may be sharp or broad, but it is always unsplit because of proton exchange. The protons on the carbon atom absorb between δ= 2-2.5 ppm in about the same position as the protons on a carbon atom alpha to a ketone or an aldehyde.

IR: O-H stretch, usually very broad (strongly H-bonded), at 3400–2400 cm^{-1}. C=O stretch, broad, occurs at 1730 –1700 cm^{-1}. C-O stretch occurs in the range 1320 –1210 cm^{-1}

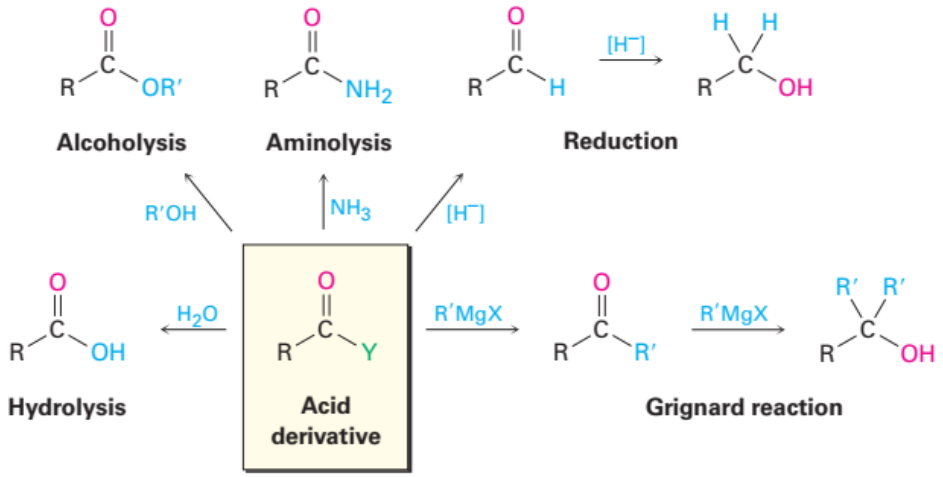
1.2. Carboxylic acid derivative

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. Electronically, the 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. The reactivity order is





General reaction of acids derivative

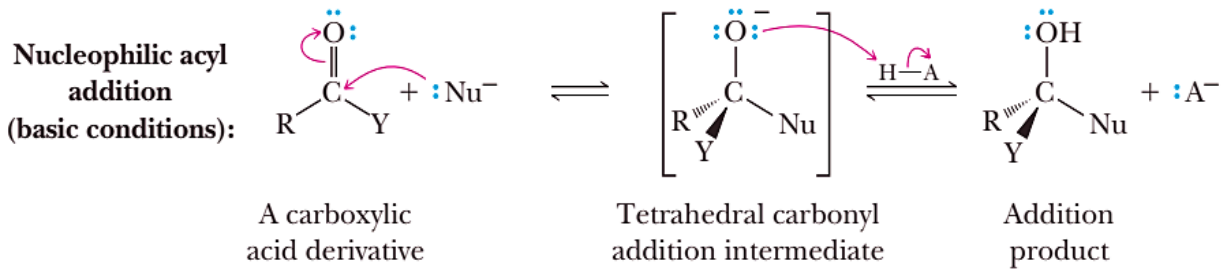


1.2.1. Characteristic Reactions

In this and subsequent sections, we examine the interconversions of various carboxylic acid derivatives. All these reactions begin with formation of a tetrahedral carbonyl addition intermediate (make a new bond between a nucleophile and an electrophile).

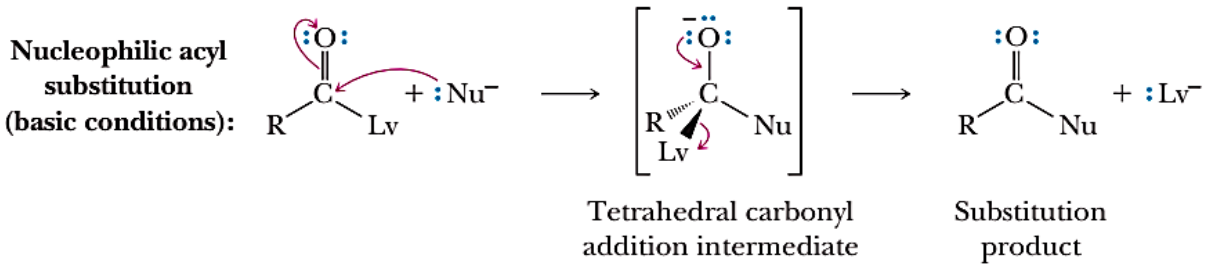
Nucleophilic Acyl Addition

The first step of this reaction is exactly analogous to the addition of alcohols to aldehydes and ketones. This reaction can be carried out under basic conditions, in which a negatively charged nucleophile adds directly to the carbonyl carbon. The tetrahedral carbonyl addition intermediate formed then adds a proton from a proton donor, HA. The result of this reaction is nucleophilic acyl addition.

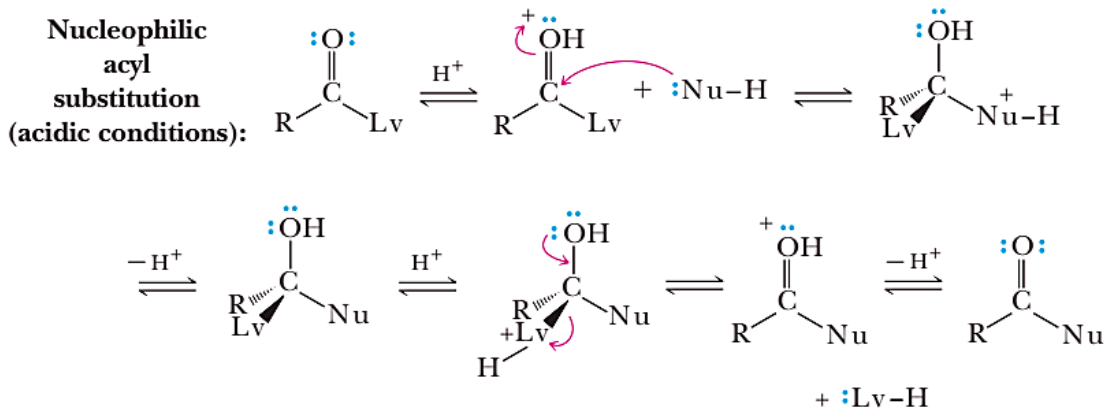


Nucleophilic Acyl Substitution

For functional derivatives of carboxylic acids, the fate of the tetrahedral carbonyl addition intermediate is quite different from that of aldehydes and ketones; the intermediate collapses to expel the leaving group (Lv) and regenerate the carbonyl group (break a bond to give stable molecules or ions). The result of this addition-elimination sequence is nucleophilic acyl substitution.



The four carboxylic acid derivatives we study in this chapter have a leaving group, that can leave as a relatively stable anion or as a neutral species. Neutral molecules commonly serve as nucleophiles in this reaction, mainly when it is carried out under acid-catalyzed conditions. When these reactions are catalyzed by acid, protonation precedes nucleophilic attack, and similarly protonation precedes leaving group departure.



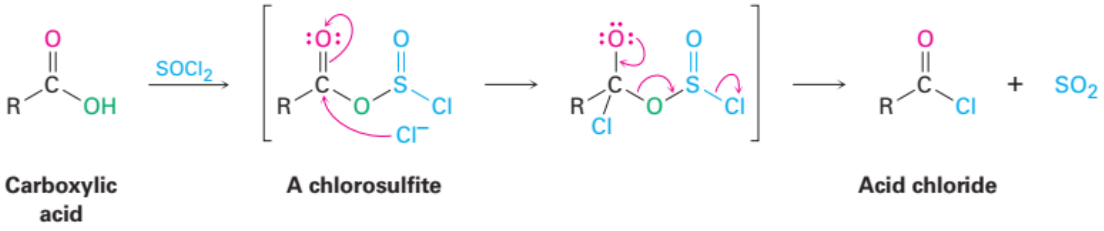
1.2.2. Acid Chloride

Halide ions are excellent leaving groups for nucleophilic acyl substitution. Therefore, acyl halides are useful intermediates for making acid derivatives. In particular, acid chlorides (acyl chlorides) are easily made and are commonly used as an activated form of a carboxylic acid. Acid chlorides react with a wide range of nucleophiles, generally through the addition–elimination mechanism of nucleophilic acyl substitution. The best reagents for converting carboxylic acids to acid chlorides are thionyl chloride and oxalyl chloride because they form gaseous by-products that do not

contaminate the product. Oxalyl chloride is particularly easy to use because it boils at 62 °C and any excess is easily evaporated from the reaction mixture.

1.2.2.1. Conversion of Carboxylic Acids into Acid Chlorides

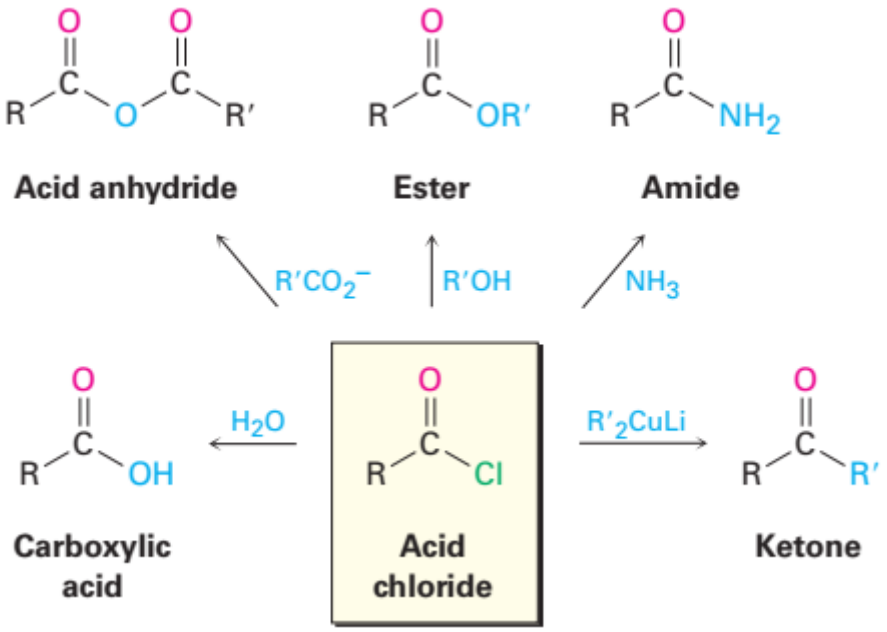
In the laboratory, carboxylic acids are converted into acid chlorides by treatment with thionyl chloride, $SOCl_2$. The reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into an acyl chlorosulfite intermediate, thereby replacing the OH of the acid with a much better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion. Similar reaction of a carboxylic acid with phosphorus tribromide (PBr_3) yields the acid bromide.



Carboxylic acid **A chlorosulfite** **Acid chloride**

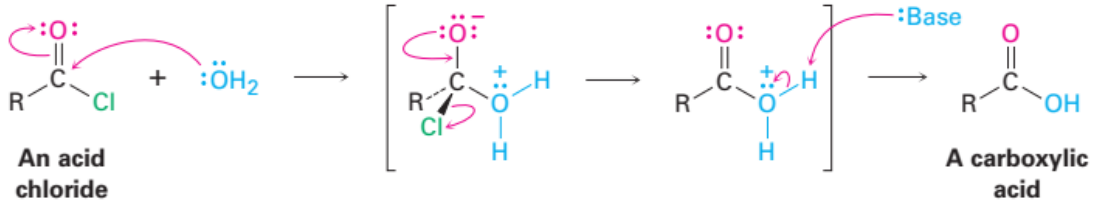
1.2.2.2. Reactions of Acid Halides

Acid halides are among the most reactive of carboxylic acid derivatives and can be converted into many other kinds of compounds by nucleophilic acyl substitution mechanisms. The halogen can be replaced by -OH to yield an acid, by -OCOR to yield an anhydride, by -OR to yield an ester, by -NH2 to yield an amide, or by R′ to yield a ketone. In addition, the reduction of an acid halide yields a primary alcohol, and reaction with a Grignard reagent yields a tertiary alcohol. Although the reactions we'll be discussing in this section are illustrated only for acid chlorides, similar processes take place with other acid halides.



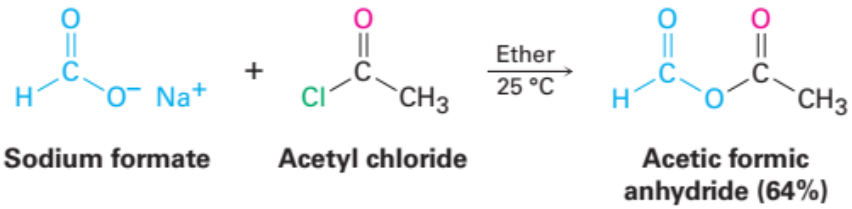
Conversion of Acid Halides into Acids: Hydrolysis

Acid chlorides react with water to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution process and is initiated by attack of water on the acid chloride carbonyl group. The tetrahedral intermediate undergoes elimination of Cl^- and loss of H^+ to give the product carboxylic acid plus HCl. This reaction creates the very strong acid HCl (H_3O^+ and Cl^-). Chemists commonly add a weak base, such as pyridine, to neutralize the acid that is created.



Conversion of Acid Halides into Anhydrides

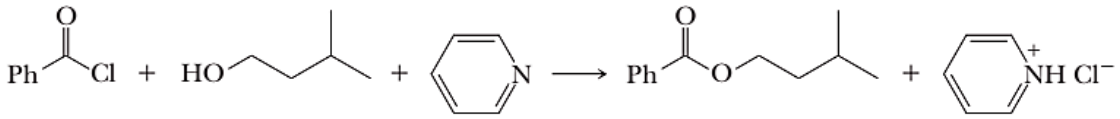
Nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion gives an acid anhydride. Both symmetrical and unsymmetrical acid anhydrides can be prepared.



Sodium formate **Acetyl chloride** **Acetic formic anhydride (64%)**

Conversion of Acid Halides into Esters: Alcoholysis

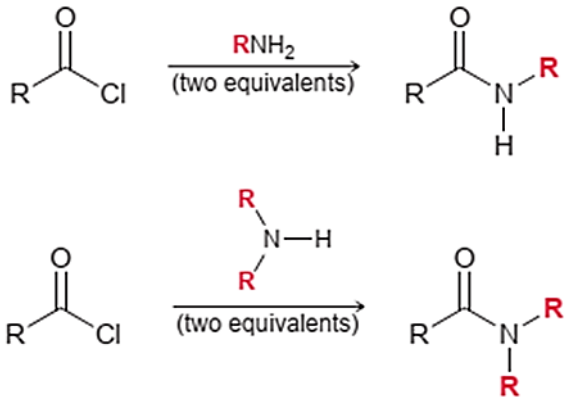
Acid chlorides react with alcohols to yield esters in a process analogous to their reaction with water to yield acids. In fact, this reaction is probably the most common method for preparing esters in the laboratory. As with hydrolysis, alcoholysis reactions are usually carried out in the presence of pyridine or NaOH to react with the HCl formed. reactivity order among alcohols of primary > secondary > tertiary. As a result, it's often possible to esterify an unhindered alcohol selectively in the presence of a more hindered one.



Benzoyl chloride **3-Methyl-1-butanol (Isoamyl alcohol)** **Pyridine** **3-Methylbutyl benzoate (Isoamyl benzoate)** **Pyridinium chloride**

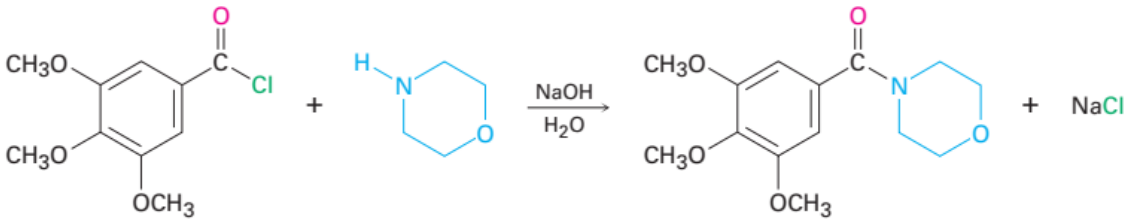
Conversion of Acid Halides into Amides: Aminolysis

Acid chlorides react rapidly with ammonia and amines to give amides. As with the acid chloride-plus-alcohol method for preparing esters, this reaction of acid chlorides with amines is the most commonly used laboratory method for preparing amides. Both monosubstituted and disubstituted amines can be used, but not trisubstituted amines (R_3N).



Because HCl is formed during the reaction, 2 equivalents of the amine must

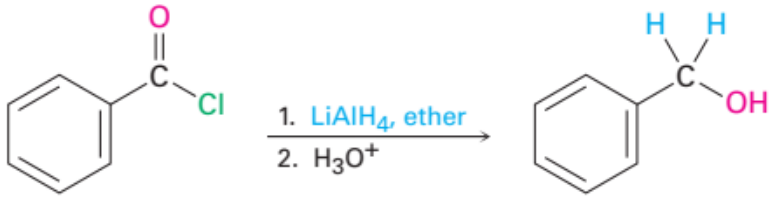
be used. One equivalent reacts with the acid chloride, and one equivalent reacts with the HCl by-product to form an ammonium chloride salt. If, however, the amine component is valuable, amide synthesis is often carried out using 1 equivalent of the amine and 1 equivalent of an inexpensive base such as NaOH.



3,4,5-Trimethoxybenzoyl chloride **Morpholine** **Trimetozine (an amide)**

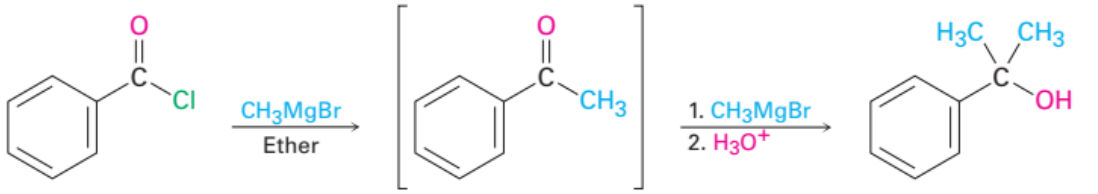
Conversion of Acid Chlorides into Alcohols (Reduction and Grignard Reaction)

Acid chlorides are reduced by $LiAlH_4$ to yield primary alcohols. Reduction occurs via a typical nucleophilic acyl substitution mechanism in which a hydride ion ($H:^-$) adds to the carbonyl group, yielding a tetrahedral intermediate that expels Cl^-. The net effect is a substitution of Cl^- by H^- to yield an aldehyde, which is then further reduced by $LiAlH_4$ in a second step to yield the primary alcohol.



Benzoyl chloride **Benzyl alcohol (96%)**

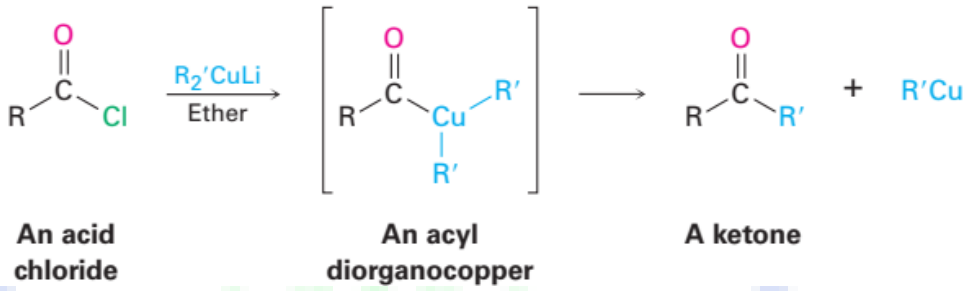
Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same. The mechanism of the reaction is similar to that of $LiAlH_4$ reduction. The first equivalent of Grignard reagent adds to the acid chloride, loss of Cl^- from the tetrahedral intermediate yields a ketone, and a second equivalent of Grignard reagent immediately adds to the ketone to produce an alcohol.



Benzoyl chloride **Acetophenone *(Not isolated)*** **2-Phenyl-2-propanol (92%)**

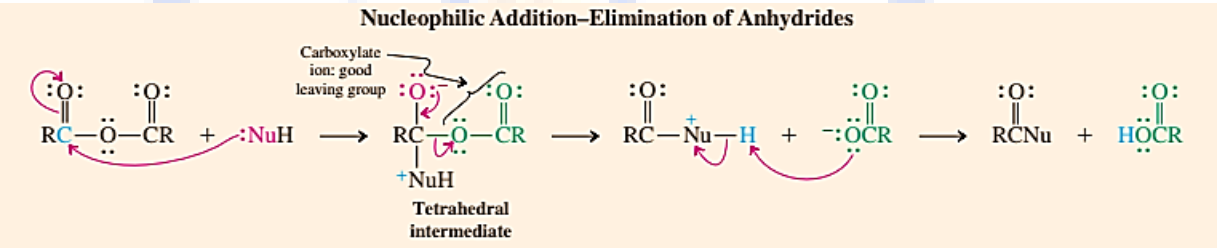
Conversion of Acid Chlorides into Ketones: Diorganocopper Reaction

The ketone intermediate formed in during the reaction of an acid chloride with a Grignard reagent can't usually be isolated because addition of the second equivalent of organomagnesium reagent occurs too rapidly. A ketone can be isolated from the reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $Li^+ R_2Cu^-$.



1.2.3. Acid Anhydrides

The reactions of carboxylic anhydrides with nucleophiles, although less vigorous, are completely analogous to those of the acyl halides. The leaving group is a carboxylate instead of a halide ion.

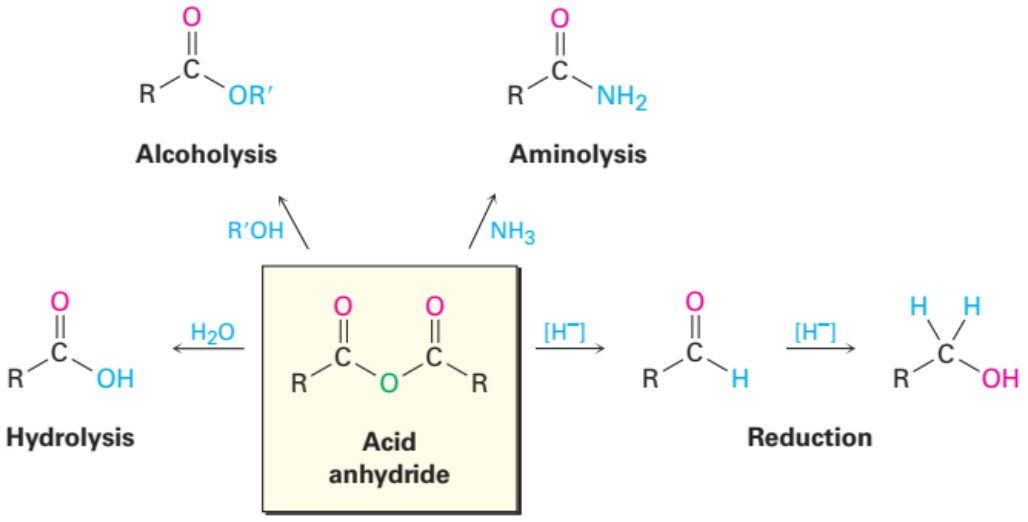


1.2.3.1. Conversion of Carboxylic Acids into Acid Anhydrides

Acid anhydrides can be derived from two molecules of carboxylic acid by heating to remove 1 equivalent of water. Because of the high temperatures needed, however, only acetic anhydride is commonly prepared this way.

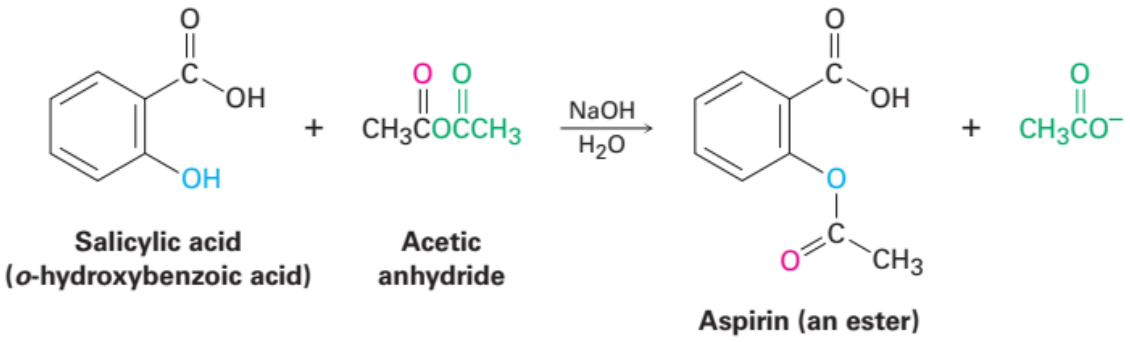
1.2.3.2. Chemistry of Acid Anhydrides

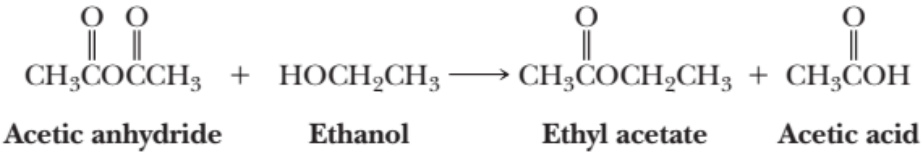
The chemistry of acid anhydrides is similar to that of acid chlorides, although anhydrides react more slowly. Thus, acid anhydrides react with water to form acids, with alcohols to form esters, with amines to form amides, and with $LiAlH_4$ to form primary alcohols. Only the ester and amide forming reactions are commonly.

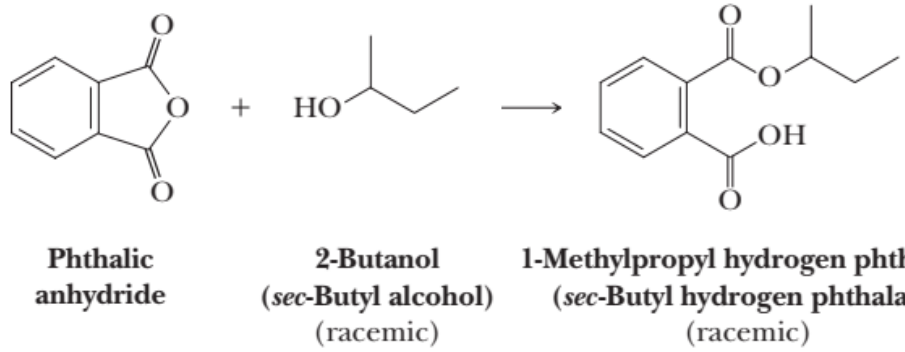


Conversion of Acid Anhydrides into Esters

Acetic anhydride is often used to prepare acetate esters from alcohols. For example, aspirin (acetylsalicylic acid) is prepared commercially by the acetylation of o-hydroxybenzoic acid (salicylic acid) with acetic anhydride.

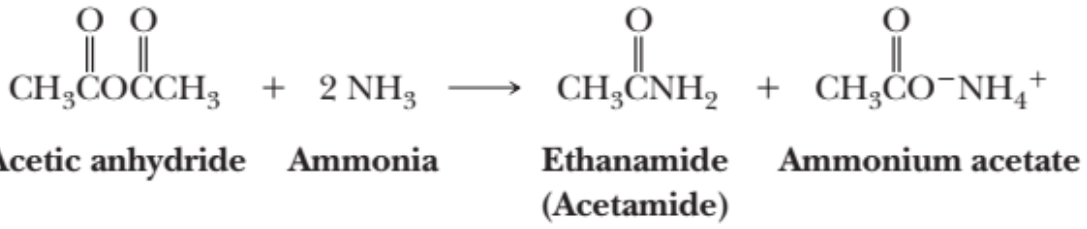


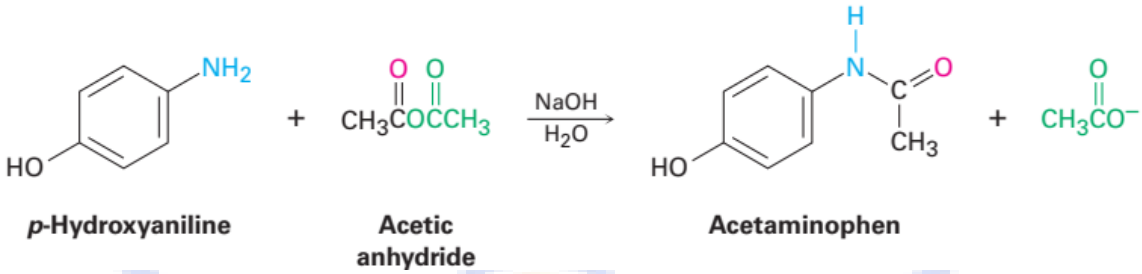




Conversion of Acid Anhydrides into Amides

Acetic anhydride is also commonly used to prepare N-substituted acetamides from amines. Only the more nucleophilic -NH_2 group reacts rather than the less nucleophilic -OH group.



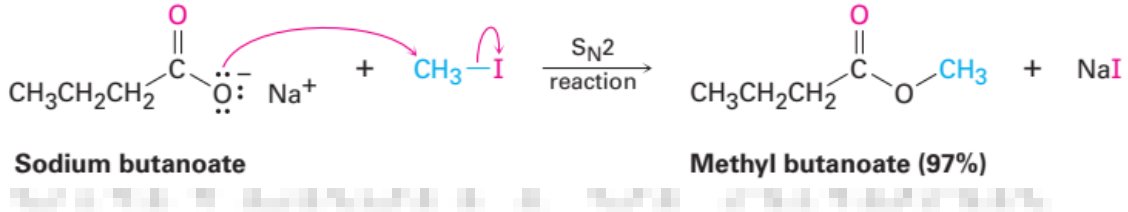


1.2.4. Ester

constitute perhaps the most important class of carboxylic derivatives. They are particularly widespread in nature, contributing especially to the pleasant flavors and aromas of many flowers and fruits. Esters undergo typical carbonyl chemistry but with reduced reactivity relative to that of either acyl halides or carboxylic anhydrides.

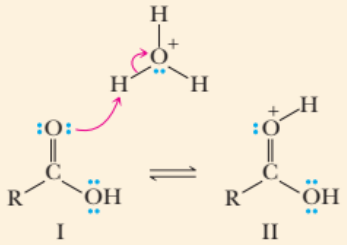
1.2.4.1. Conversion of Carboxylic Acids into Esters

Perhaps the most useful reaction of carboxylic acids is their conversion into esters. There are many methods for accomplishing the transformation, including the S_N2 reaction of a carboxylate anion with a primary alkyl halide .



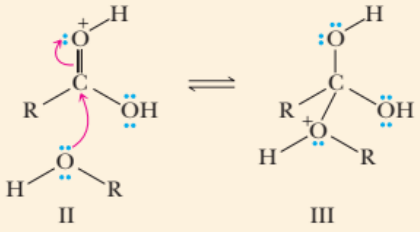
Esters can also be synthesized by an acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol, a process called the Fischer esterification reaction. Unfortunately, the need to use an excess of a liquid alcohol as solvent effectively limits the method to the synthesis of methyl, ethyl, propyl, and butyl esters.

Step 1: **Add a proton.** The reaction begins with protonation, which increases the electrophilicity of the carboxylic acid carbonyl carbon.



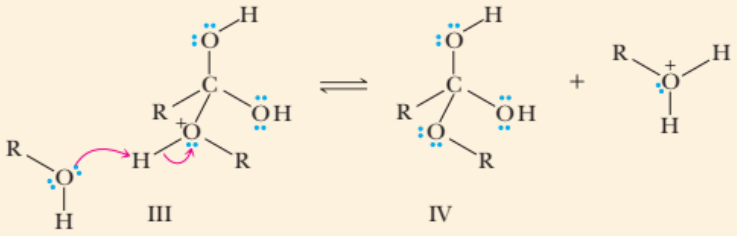
I II

Step 2: **Make a new bond between a nucleophile and an electrophile.** The alcohol adds to the carbonyl carbon atom.



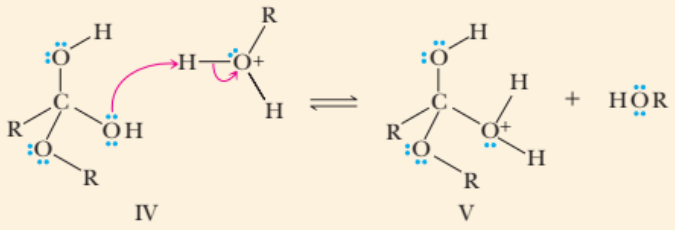
II III

Step 3: **Take a proton away.** Deprotonation gives a tetrahedral addition intermediate.



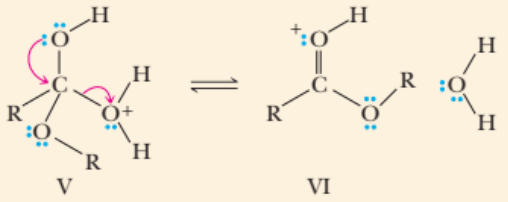
III IV

Step 4: **Add a proton.** Placing a proton on an —OH converts it to $—OH_2^+$; this process allows the much better leaving group water to depart.



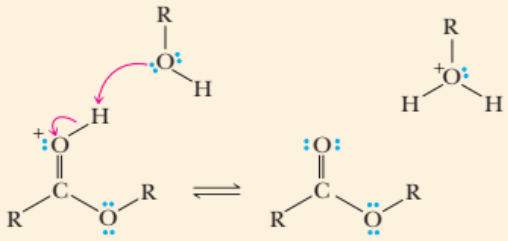
IV V

Step 5: **Break a bond to give stable molecules or ions.** Water departs as a leaving group.



V VI

Step 6: **Take a proton away.** A final deprotonation gives the ester product and regenerates the acid catalyst.



VI VII

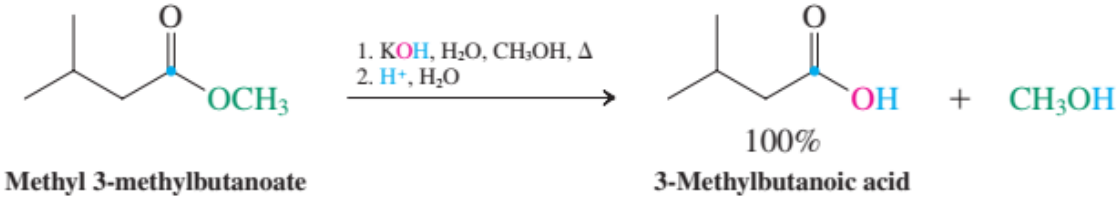
The net effect of Fischer esterification is substitution of an -OH group by -OR′. All steps are reversible, and the reaction typically has an equilibrium constant close to 1. Thus, the reaction can be driven in either direction by choice of reaction conditions. Ester formation is favored when a large excess of alcohol is used as solvent, but carboxylic acid formation is favored when a large excess of water is present.

1.2.4.2. Reaction of Ester

Esters hydrolyze to carboxylic acids

Esters undergo nucleophilic substitution reactions by means of addition – elimination pathways, albeit with reduced reactivity relative to halides and anhydrides. Thus, catalysis by acid or base becomes a frequent necessity. For example, esters are cleaved to carboxylic acids and alcohols in the presence of excess water and strong acid, and the reaction requires heating to proceed at a reasonable rate. The mechanism of this transformation is the reverse of acid-catalyzed esterification. As in esterification, the acid serves two purposes: It protonates the carbonyl oxygen to make the ester more reactive toward nucleophilic attack, and it protonates the alkoxy oxygen in the tetrahedral intermediate to make it a better leaving group. Strong bases also promote ester hydrolysis through an addition – elimination mechanism. The base (B) converts the poor nucleophile water into the negatively charged and more highly nucleophilic hydroxide ion.

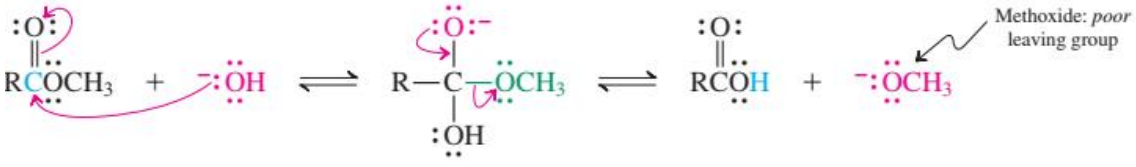
Example of Ester Hydrolysis Using Aqueous Base



Methyl 3-methylbutanoate **3-Methylbutanoic acid**

Mechanism of Base-Mediated Ester Hydrolysis

Step 1. Addition–elimination



Tetrahedral intermediate

Step 2. Deprotonation

Carboxylic acid **Methoxide (Strong base)** **Carboxylate ion**

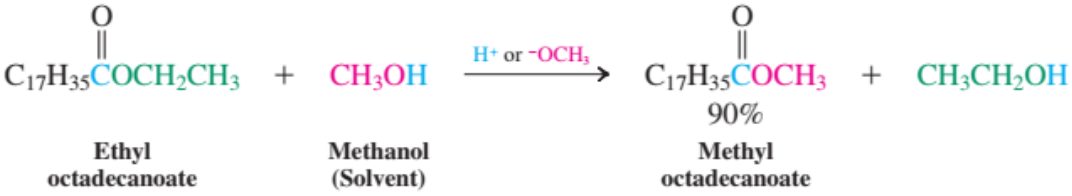
Favorable acid-base reaction of step 2 drives equilibrium of step 1

Transesterification

Esters react with alcohols in an acid- or base-catalyzed transformation called transesterification. This allows for the direct conversion of one ester into another without proceeding through the free acid. Like esterification, transesterification is a reversible reaction. To shift the equilibrium, a large excess of the alcohol is usually employed, sometimes in the form of solvent.

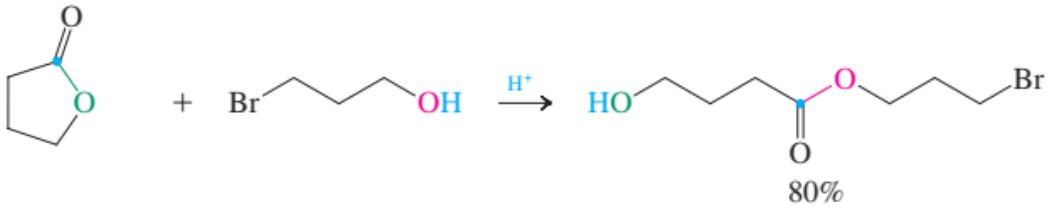
The mechanisms of transesterification by acid and base are analogous to the mechanisms of the corresponding hydrolyses to the carboxylic acids. Thus, acid-catalyzed transesterification begins with protonation of the carbonyl oxygen, followed by nucleophilic attack of the alcohol on the carbonyl carbon. In contrast, under basic conditions the alcohol is first deprotonated, and the resulting alkoxide ion then adds to the ester carbonyl group.

Conversion of an Ethyl Ester into a Methyl Ester



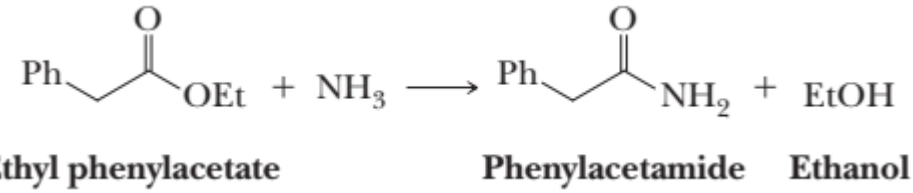
Lactones are opened to hydroxy esters by transesterification.

Conversion of a Lactone into an Open-Chain Ester



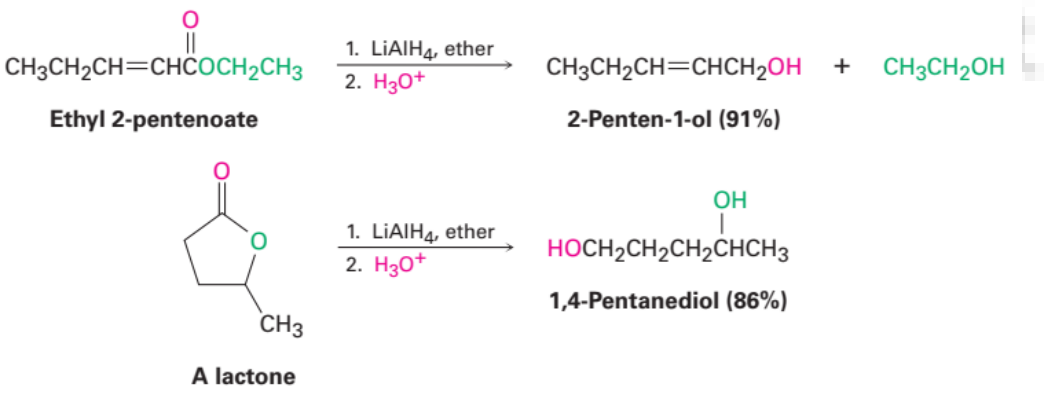
Conversion of Esters into Amides: Aminolysis

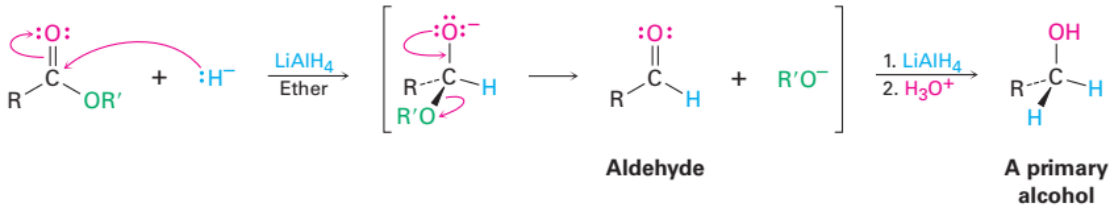
Esters react with ammonia and amines to yield amides. The reaction is not often used, however, because it's usually easier to prepare an amide by starting with an acid chloride.



Conversion of Esters into Alcohols:

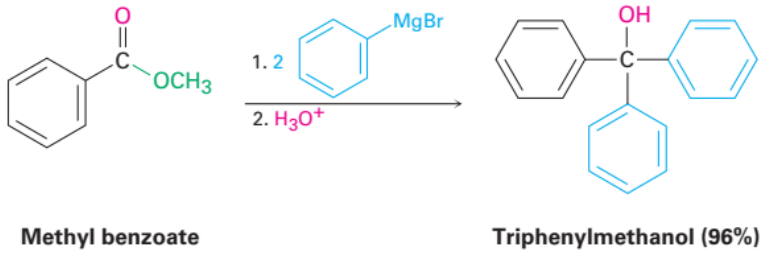
Reduction Esters are easily reduced by treatment with $LiAlH_4$ to yield primary alcohols.



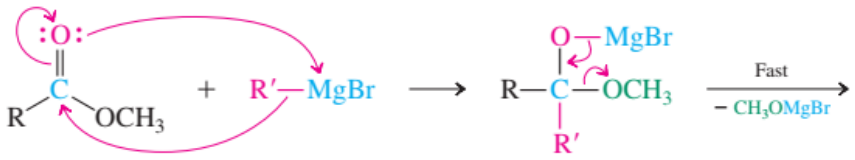


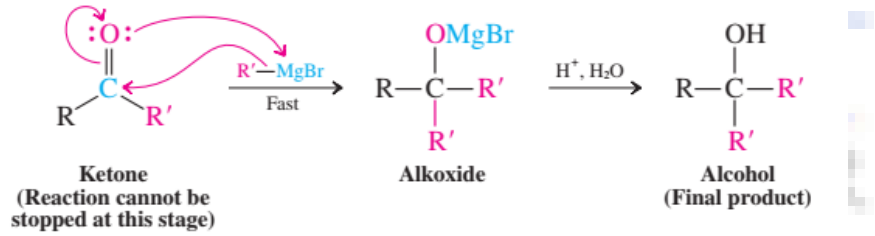
Conversion of Esters into Alcohols:

Grignard Reaction Esters react with 2 equivalents of a Grignard reagent to yield a tertiary alcohol in which two of the substituents are identical. The reaction occurs by the usual nucleophilic substitution mechanism to give an intermediate ketone, which reacts further with the Grignard reagent to yield a tertiary alcohol.



Mechanism of the Alcohol Synthesis from Esters and Grignard Reagents



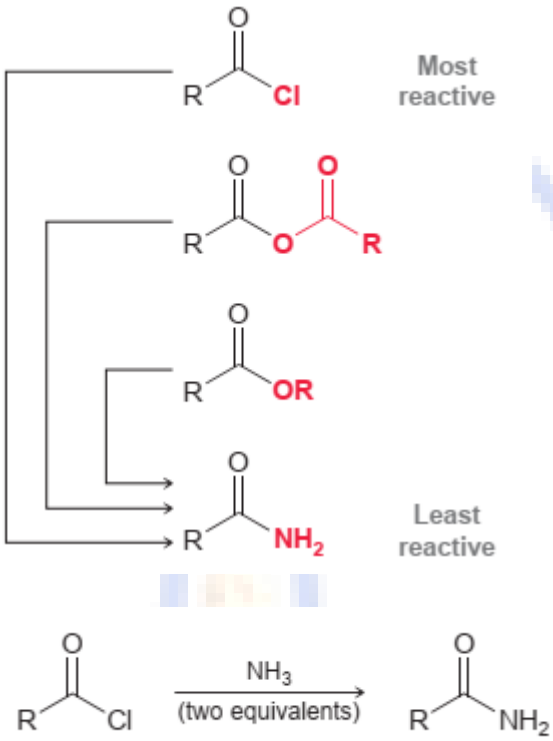


1.2.5. Amides

The amides are the least reactive of the carboxylic acid derivatives, in part because they are strongly stabilized by delocalization of the nitrogen lone pair.

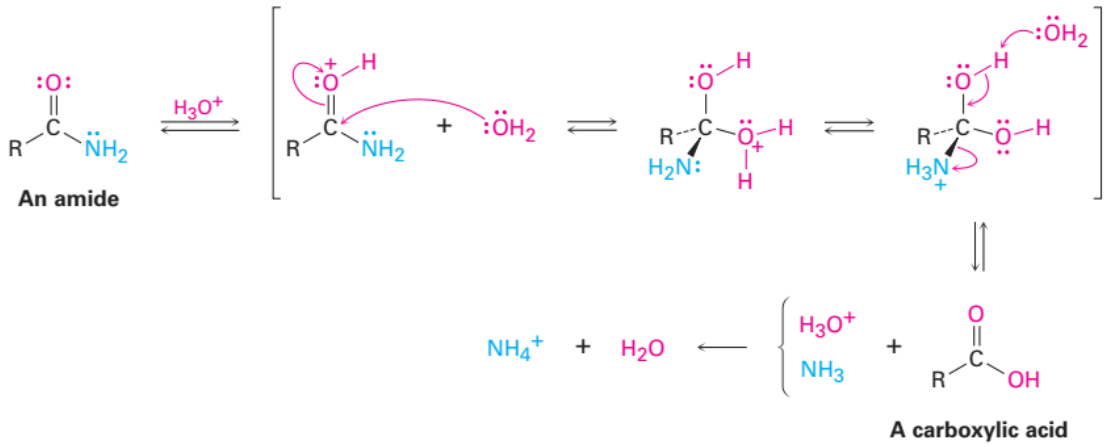
1.2.5.1. convert carboxylic acid derivatives to amide

Amides can be prepared from any of the carboxylic acid derivatives. Although they can be prepared in a variety of ways, amides are most efficiently prepared from acid chlorides.

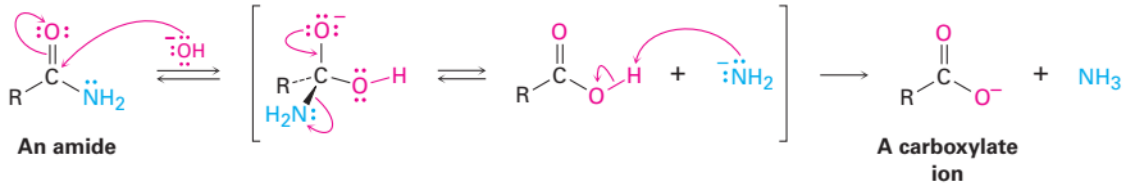


1.2.5.2. Reaction Of Amide

Conversion of Amides into Carboxylic Acids: Hydrolysis Amides undergo hydrolysis to yield carboxylic acids plus ammonia or an amine on heating in either aqueous acid or aqueous base. The conditions required for amide hydrolysis are more severe than those required for the hydrolysis of acid chlorides or esters, but the mechanisms are similar. Acidic hydrolysis reaction occurs by nucleophilic addition of water to the protonated amide, followed by transfer of a proton from oxygen to nitrogen to make the nitrogen a better leaving group and subsequent elimination. The steps are reversible, with the equilibrium shifted toward product by protonation of NH_3 in the final step.

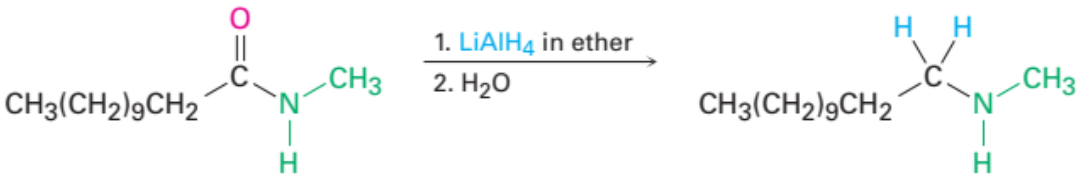


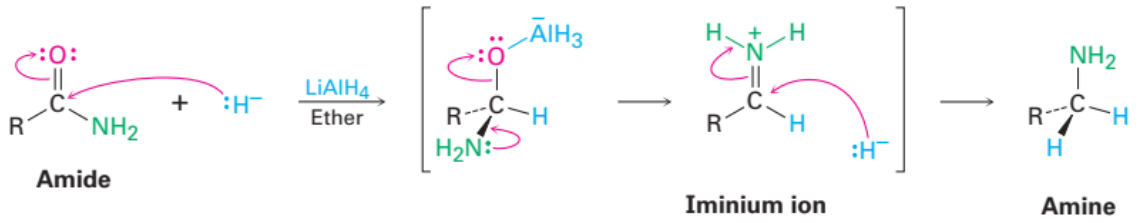
Basic hydrolysis occurs by nucleophilic addition of OH2 to the amide carbonyl group, followed by elimination of amide ion (-NH_2) and subsequent deprotonation of the initially formed carboxylic acid by ammonia. The steps are reversible, with the equilibrium shifted toward product by the final deprotonation of the carboxylic acid.



Conversion of Amides into Amines:

Reduction Like other carboxylic acid derivatives, amides can be reduced by $LiAlH_4$. The product of the reduction, however, is an amine rather than an alcohol. The net effect of an amide reduction reaction is thus the conversion of the amide carbonyl group into a methylene group (C=O → CH_2). This kind of reaction is specific for amides and does not occur with other carboxylic acid derivatives.





1.3. SPECTROSCOPY

IR:

Functional Group	Frequency	Comments
ketone	C=O, 1710 cm^{-1}	lower if conjugated, higher if strained (aldehydes 1725 cm^{-1})
acid	C=O, 1710 cm^{-1}; O—H, 2500–3500 cm^{-1}	lower if conjugated; broad, on top of C—H stretch
ester	C=O, 1735 cm^{-1}	lower if conjugated, higher if strained
amide	C=O, 1640–1680 cm^{-1}; N—H, 3200–3500 cm^{-1}	two peaks for R—CO—NH_2, one peak for R—CO—NHR′
acid chloride	C=O, 1800 cm^{-1}	very high frequency
acid anhydride	C=O, 1800 and 1750 cm^{-1}	two peaks
nitrile	C≡N, 2200 cm^{-1}	just above 2200 cm^{-1}

H-NMR: