

# Organic Chemistry, *Fourth Edition*

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## Chapter 22 Lecture Outline

Prepared by Layne A. Morsch  
The University of Illinois - Springfield

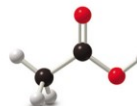
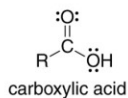
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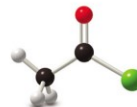
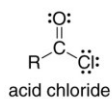
## Carboxylic Acid Derivatives

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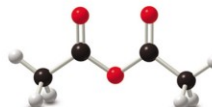
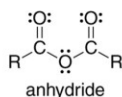
Z = OH



Z = Cl



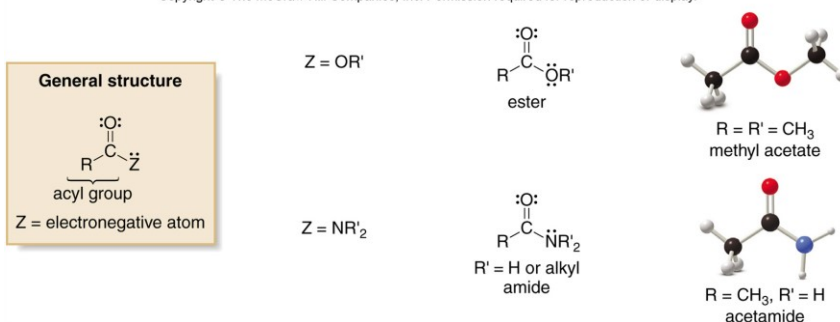
Z = OCOR



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# Carboxylic Acid Derivatives

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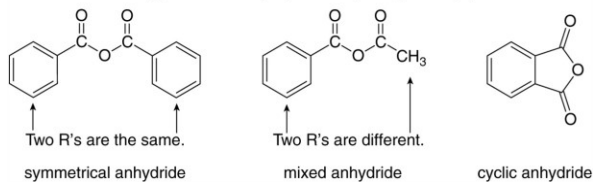


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## Anhydrides and Amides

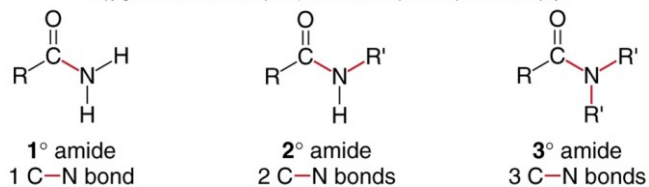
### Types of anhydrides:

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### Types of amides:

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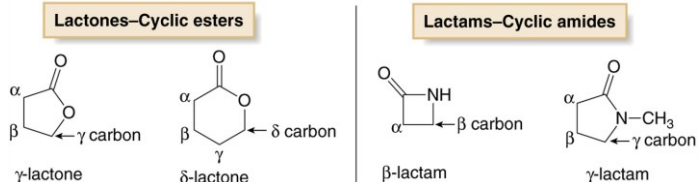


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# Lactones, Lactams and Nitriles

## Cyclic esters and amides:

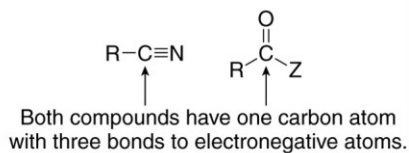
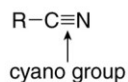
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## Nitriles:

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### General structure—Nitriles

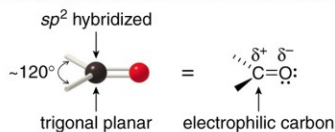


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## Structural Features of the Carbonyl Group

The two most important features of the carbonyl group are:

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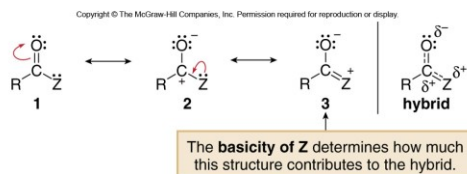


- The carbonyl carbon is  $sp^2$  hybridized and trigonal planar, making it relatively uncrowded.
- The electronegative oxygen atom polarizes the carbonyl group, making the carbonyl carbon electrophilic.

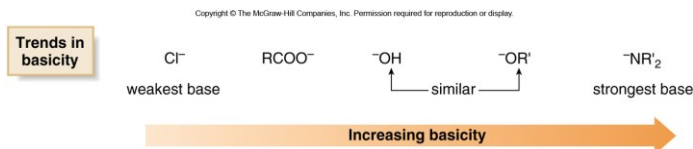
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## Resonance of Carboxylic Acid Derivatives

- Three resonance structures stabilize carboxylic acid derivatives (RCOZ) by delocalizing electron density.
- The more resonance structures 2 and 3 contribute to the resonance hybrid, the more stable RCOZ is:

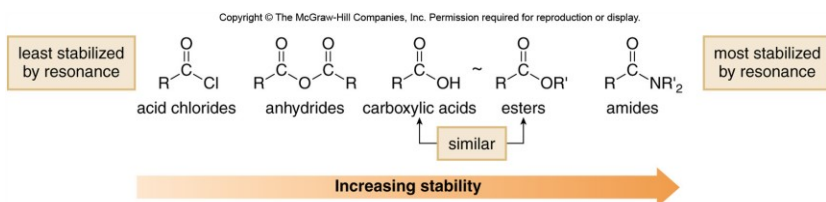


- The more basic Z is, the more it donates its electron pair, and the more resonance structure 3 contributes to the hybrid.





## Stability of Carboxylic Acid Derivatives

- Because the basicity of Z determines the relative stability of the carboxylic acid derivatives, the following stability order results:



- In summary, as the basicity of Z increases, the stability of RCOZ increases because of added resonance stabilization.

**Table 22.1**  $pK_a$  Values of the Conjugate Acids (HZ) for Common Z Groups of Acyl Compounds (RCOZ)

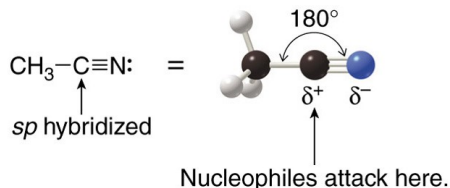
	Structure	Leaving group (Z <sup>-</sup> )	Conjugate acid (HZ)	$pK_a$	
Increasing basicity of Z 	<b>RCOCl</b> acid chloride	$\text{Cl}^-$	HCl	-7	 Increasing acidity of HZ
	<b>(RCO)<sub>2</sub>O</b> anhydride	$\text{RCOO}^-$	RCOOH	3-5	
	<b>RCOOH</b> carboxylic acid	$\text{OH}^-$	$\text{H}_2\text{O}$	15.7	
	<b>RCOOR'</b> ester	$\text{OR}'^-$	$\text{R}'\text{OH}$	15.5-18	
	<b>RCONR'<sub>2</sub></b> amide	$\text{NR}'_2^-$	$\text{R}'_2\text{NH}$	38-40	

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## Resonance of Carboxylic Acid Derivatives

- The structure and bonding of nitriles is very different from that of other carboxylic acid derivatives, and resembles the C–C triple bond of alkynes.

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- The carbon atom on the  $\text{C}\equiv\text{N}$  group is  $sp$  hybridized, making it linear with a bond angle of  $180^\circ$ .
- The triple bond consists of one  $\sigma$  and two  $\pi$  bonds.

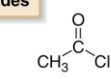
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## Nomenclature—Acid Chlorides

- For acyclic acid chlorides: change the suffix *-ic acid* of the parent carboxylic acid to the suffix *-yl chloride*; or
- When the  $\text{-COCl}$  group is bonded to a ring: change the suffix *-carboxylic acid* to *-carbonyl chloride*.

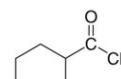
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### Naming acid chlorides



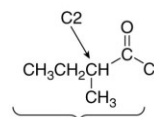
derived from acetic acid

acetyl chloride



derived from cyclohexanecarboxylic acid

cyclohexanecarbonyl chloride



derived from 2-methylbutanoic acid

2-methylbutanoyl chloride

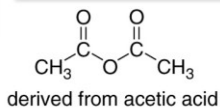
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## Nomenclature—Anhydrides

- Symmetrical anhydrides are named by changing the acid ending of the carboxylic acid to the word *anhydride*.
- Mixed anhydrides, which are derived from two different carboxylic acids, are named by alphabetizing the names for both acids and replacing the word *acid* with the word *anhydride*.

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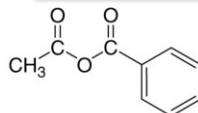
### Symmetrical anhydride



derived from acetic acid

acetic anhydride

### Mixed anhydride



derived from acetic acid and benzoic acid

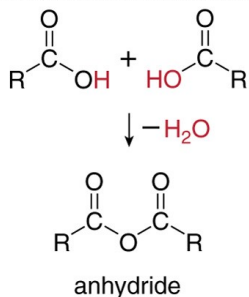
acetic benzoic anhydride

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## Composition of Anhydrides

- Anhydride means without water.
- Removing one molecule of water from two molecules of carboxylic acid forms an anhydride.

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## Nomenclature—Esters

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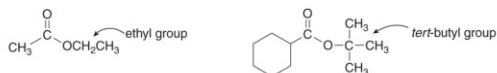
**How To** Name an Ester (RCO<sub>2</sub>R') Using the IUPAC System

**Example** Give a systematic name for each ester:



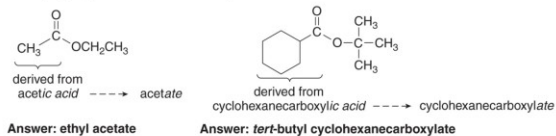
**Step [1]** Name the R' group bonded to the oxygen atom as an alkyl group.

- The name of the alkyl group, ending in the suffix *-yl*, becomes the *first* part of the ester name.



**Step [2]** Name the acyl group (RCO-) by changing the *-ic acid* ending of the parent carboxylic acid to the suffix *-ate*.

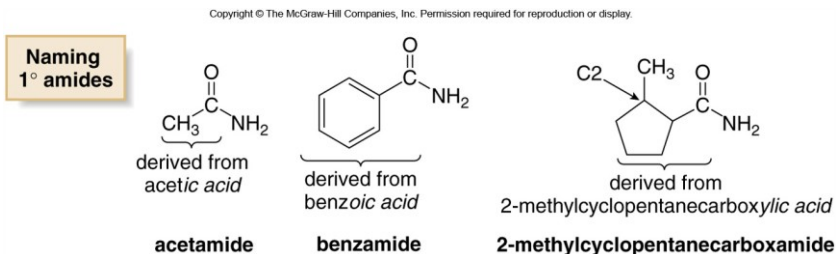
- The name of the acyl group becomes the *second* part of the name.



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# Nomenclature—Amides

- All 1° amides are named by replacing the *-ic acid*, *-oic acid*, or *-ylic acid* ending with the suffix **amide**.

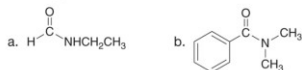


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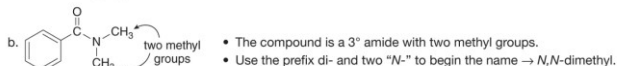
**How To** Name a 2° or 3° Amide

**Example** Give a systematic name for each amide:

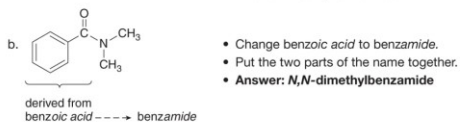
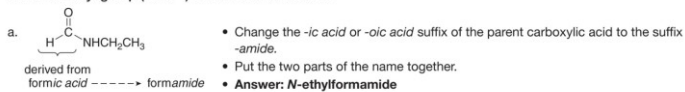


**Step [1]** Name the alkyl group (or groups) bonded to the N atom of the amide. Use the prefix “N-” preceding the name of each alkyl group.

- The names of the alkyl groups form the first part of each amide name.
- For 3° amides, use the prefix **di-** if the two alkyl groups on N are the same. If the two alkyl groups are different, **alphabetize** their names. One “N-” is needed for each alkyl group, even if both R groups are identical.



**Step [2]** Name the acyl group (RCO–) with the suffix *-amide*.



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## Nomenclature—Nitriles

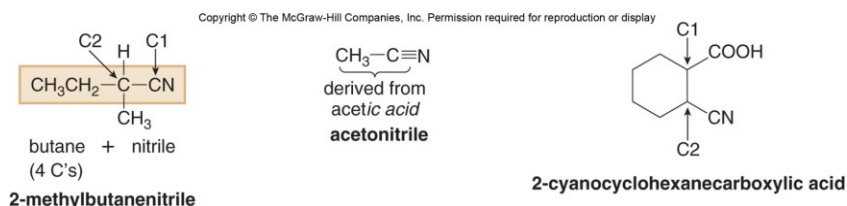
- In contrast to the carboxylic acid derivatives, nitriles are named as alkane derivatives.
- Find the longest chain that contains the CN and add the word nitrile to the name of parent alkane.
- Number the chain to put CN at C1, but omit this number from the name.
- Common names of nitriles are derived from the names of the carboxylic acid having the same number of carbon atoms by replacing the *-ic acid* ending of the carboxylic acid with the suffix *-onitrile*.
- When the CN is named as a substituent it is called a cyano group.

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## Nomenclature—Nitriles


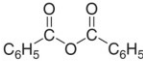
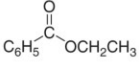
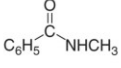
- $\text{CH}_3\text{CH}_2\text{CH}_2\text{CN}$  is butanenitrile, not propanenitrile.

Figure 22.1



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**Table 22.2** Summary: Nomenclature of Carboxylic Acid Derivatives and Nitriles

Compound	Name ending	Example	Name
acid chloride	<b>-yl chloride</b> or <b>-carbonyl chloride</b>		benzoyl chloride
anhydride	<b>anhydride</b>		benzoic anhydride
ester	<b>-ate</b>		ethyl benzoate
amide	<b>-amide</b>		<i>N</i> -methylbenzamide
nitrile	<b>-nitrile</b> or <b>-onitrile</b>	$C_6H_5-C\equiv N$	benzonitrile

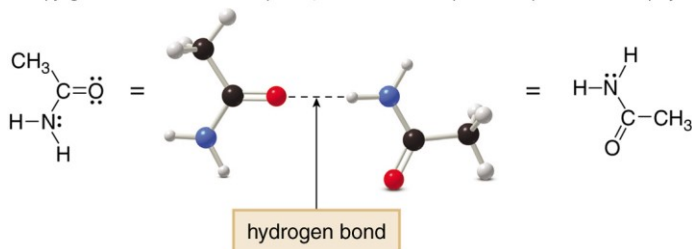
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## Intermolecular Attractions

- Nitriles also have dipole-dipole interactions, because they have a polar  $C\equiv N$  group.
- Because they contain one or two N–H bonds, 1° and 2° amides are capable of intermolecular hydrogen bonding and will have substantially higher melting and boiling points.

**Figure 22.2**  
Intermolecular hydrogen  
bonding between two  
amide molecules

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**Table 22.3** Physical Properties of Carboxylic Acid Derivatives

Property	Observation
Boiling point and melting point	<ul style="list-style-type: none"> <li>Primary (1°) and 2° amides have <i>higher</i> boiling points and melting points than compounds of comparable molecular weight.</li> <li>The boiling points and melting points of other carboxylic acid derivatives are similar to those of other polar compounds of comparable size and shape.</li> </ul> <div style="text-align: center; margin: 10px 0;"> <p style="margin: 0;"> <math>\text{CH}_3\text{C}(=\text{O})\text{Cl}</math>      <math>\text{CH}_3\text{C}(=\text{O})\text{OCH}_3</math>      <math>\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{CH}_3</math>      <math>\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{NH}_2</math>  MW = 78.5      MW = 74      MW = 72      MW = 73  bp 52 °C      bp 58 °C      bp 80 °C      bp 213 °C  <span style="display: inline-block; width: 300px; border-top: 1px solid black; margin-top: 5px;"></span> similar boiling points      higher boiling point  <span style="display: inline-block; width: 100px; border-top: 1px solid black; margin-top: 5px;"></span> 1° amide </p> </div>
Solubility	<ul style="list-style-type: none"> <li>Carboxylic acid derivatives are soluble in organic solvents regardless of size.</li> <li>Most carboxylic acid derivatives having <math>\leq 5</math> C's are H<sub>2</sub>O soluble because they can hydrogen bond with H<sub>2</sub>O (Section 3.4C).</li> <li>Carboxylic acid derivatives having <math>&gt; 5</math> C's are H<sub>2</sub>O insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H<sub>2</sub>O solvent.</li> </ul>

Key: MW = molecular weight





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## Spectroscopic Properties—IR

- Like all carbonyl compounds, carboxylic acid derivatives have a strong C=O absorption between 1600 and 1850  $\text{cm}^{-1}$ .
- Primary (1°) and 2° amides have two additional absorptions due to N–H bonds:
  1. One or two N–H stretching peaks at 3200–3400  $\text{cm}^{-1}$ .
  2. An N–H bending absorption at  $\sim 1640$   $\text{cm}^{-1}$ .
- As the carbonyl  $\pi$  bond becomes more delocalized, the C=O absorption shifts to lower frequency.
- Conjugation shifts a carbonyl absorption to lower frequencies.
- For cyclic carboxylic acid derivatives, decreasing ring size shifts a carbonyl absorption to higher frequencies.

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**Table 22.4** IR Absorptions for the Carbonyl Group of Carboxylic Acid Derivatives

Compound type	Structure (RCOZ)	Carbonyl absorption ( $\bar{\nu}$ )
acid chloride		~1800
anhydride		1820 and 1760 (2 peaks)
ester		1735–1745
amide	 R' = H or alkyl	1630–1680

Increasing basicity of Z

Increasing  $\bar{\nu}$  of absorption

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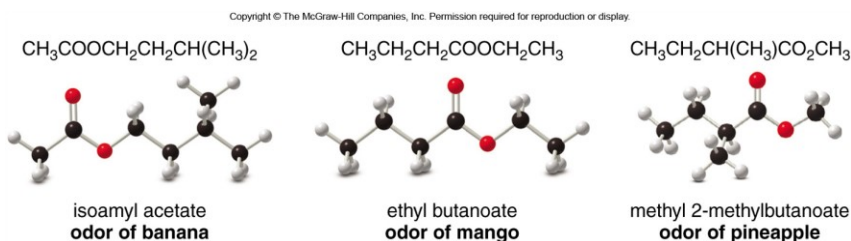
## Spectroscopic Properties—NMR

- Protons on the  $\alpha$  carbon to the carbonyl absorb at 2–2.5 ppm.
- The N–H protons of 1° and 2° amides absorb at 7.5–8.5 ppm.
- In their  $^{13}\text{C}$  NMR spectra, carboxylic acid derivatives give a highly deshielded peak at 160–180 ppm due to the carbonyl carbon.
  - This is somewhat upfield from the carbonyl absorption of aldehydes and ketones, which occurs at 190–215 ppm.
- Nitriles give a peak at 115–120 ppm in their  $^{13}\text{C}$  NMR spectrum due to the  $sp$  hybridized carbon.
  - This is further downfield than the signal due to the  $sp$  hybridized carbon of an alkyne which occurs at 65–100 ppm.

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## Interesting Esters and Amides

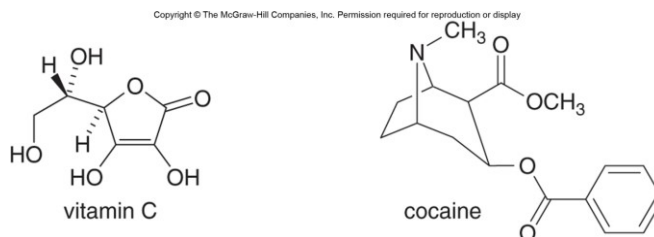
- Many low molecular weight esters have pleasant and very characteristic odors.



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## Biologically Active Esters

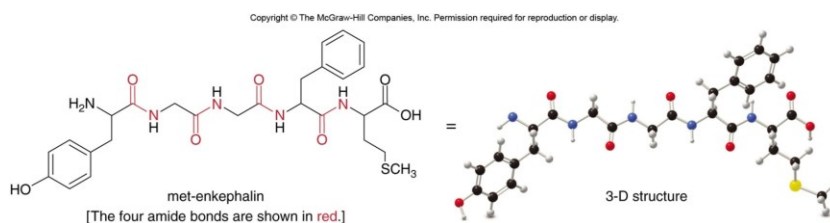
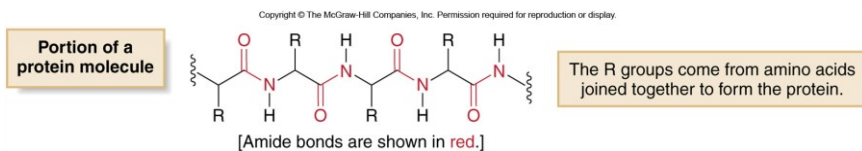
- Vitamin C (ascorbic acid) is a water-soluble vitamin that contains a five-membered lactone ring.
  - Vitamin C is synthesized in plants.
  - Humans do not have the necessary enzymes to make it, so we must obtain it from our diet.
- Cocaine is an addictive stimulant obtained from the leaves of the coca plant.



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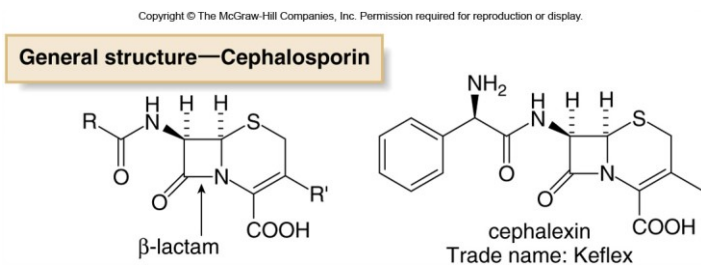
# Proteins—Polyamides

Proteins are an important group of naturally occurring amides, consisting of polymers of amino acids joined together by amide linkages.



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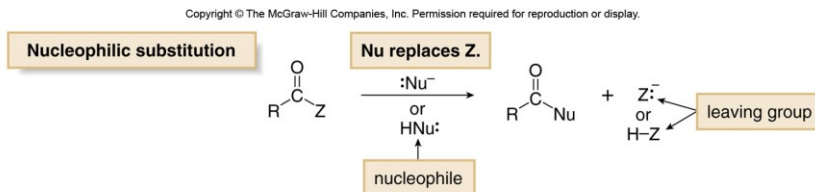
# Useful Drugs Containing Lactams



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# Nucleophilic Acyl Substitution

- Nucleophilic acyl substitution is the characteristic reaction of carboxylic acid derivatives.
- This reaction occurs with both negatively charged nucleophiles and neutral nucleophiles.



- Carboxylic acid derivatives (RCOZ) react with nucleophiles because they contain an electrophilic, unhindered carbonyl carbon.
- Substitution occurs, *not* addition, because carboxylic acid derivatives (RCOZ) have a leaving group Z on the carbonyl carbon.

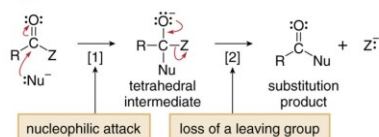
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## Mechanism of Nucleophilic Acyl Substitution

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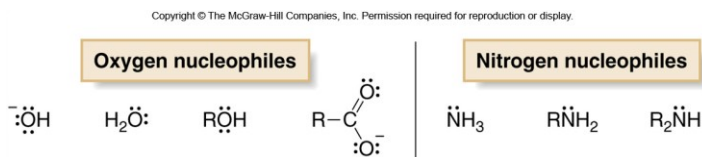
### Mechanism 22.1 General Mechanism—Nucleophilic Acyl Substitution



- In Step [1], the nucleophile attacks the carbonyl group, cleaving the  $\pi$  bond, and forming a tetrahedral intermediate with a new C–Nu bond.
- In Step [2], elimination of the leaving group forms the substitution product.

[Z = Cl, OCOR, OH, OR', NR'<sub>2</sub>]

- Other nucleophiles that participate in this reaction include:



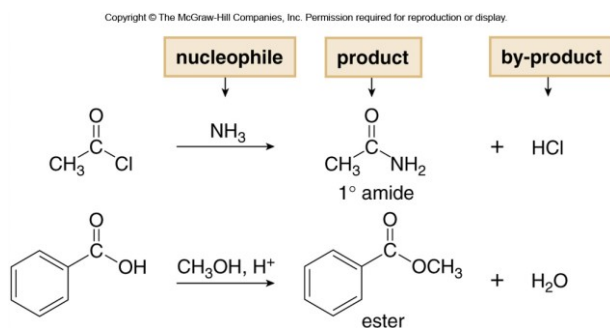
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## Drawing Products of Nucleophilic Acyl Substitution

[1] Find the  $sp^2$  hybridized carbon with the leaving group.

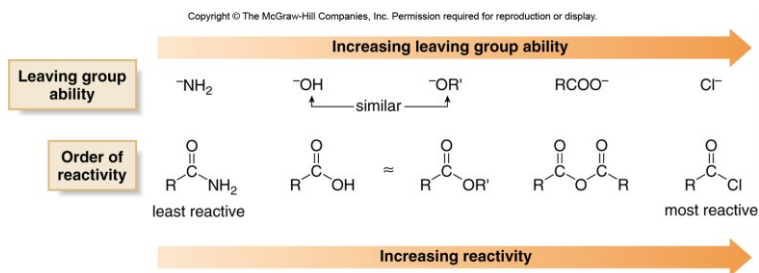
[2] Identify the nucleophile.

[3] Substitute the nucleophile for the leaving group. With a neutral nucleophile, the proton must be lost to obtain a neutral substitution product.



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## Reactivity Related to Leaving Group Ability



- Based on this order of reactivity, more reactive compounds can be converted into less reactive ones.
- The reverse is not usually true.

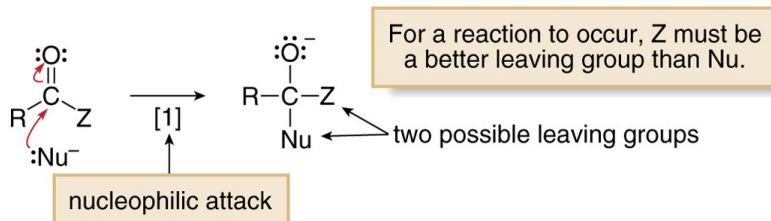
32



## Comparing Leaving Group and Nucleophile

- **Nucleophilic addition to a carbonyl forms a tetrahedral intermediate with two possible leaving groups, Z or Nu.**
- **Whichever group is a better leaving group will be eliminated.**

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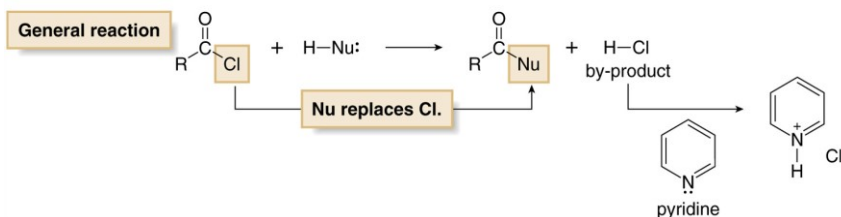


33

## General Reactions of Acid Chlorides

- **Since acid chlorides have the best leaving group of acid derivatives, they react readily with a wide range of nucleophiles to form nucleophilic substitution products.**
- **HCl is usually formed as a by-product.**
- **A weak base like pyridine is added to the reaction mixture to remove the strong acid (HCl), forming an ammonium salt.**

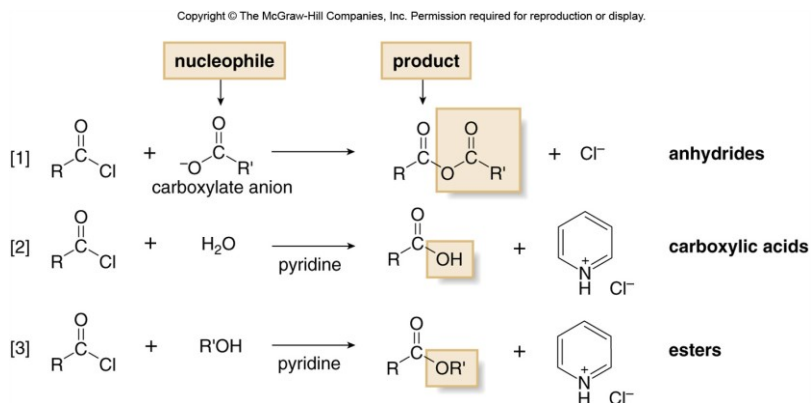
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## Reactions of Acid Chlorides and Oxygen Nucleophiles

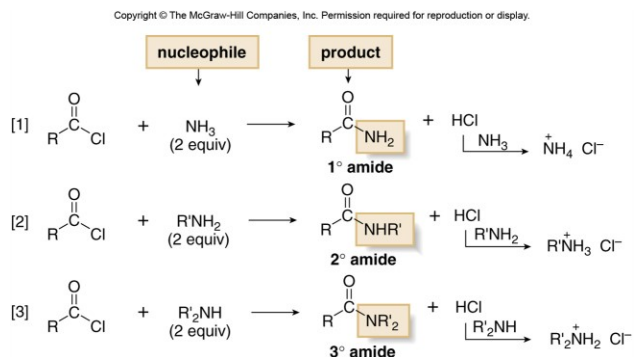
- Acid chlorides react with oxygen nucleophiles to form anhydrides, carboxylic acids, and esters.



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## Reactions of Acid Chlorides and Amines

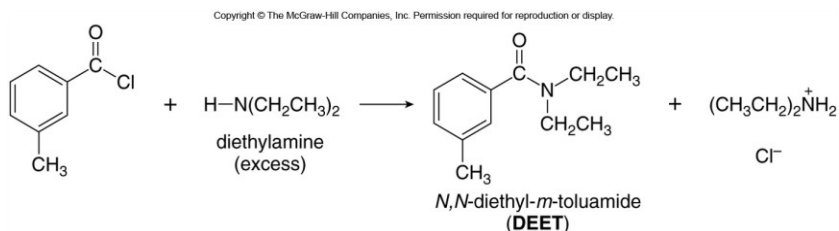
- Acid chlorides also react with ammonia, and 1° and 2° amines to form 1°, 2° and 3° amides, respectively.
- Two equivalents of  $\text{NH}_3$  or amine are used.
- One equivalent acts as the nucleophile to replace  $\text{Cl}$ , while the other reacts as a base with the  $\text{HCl}$  by-product to form an ammonium salt.



36

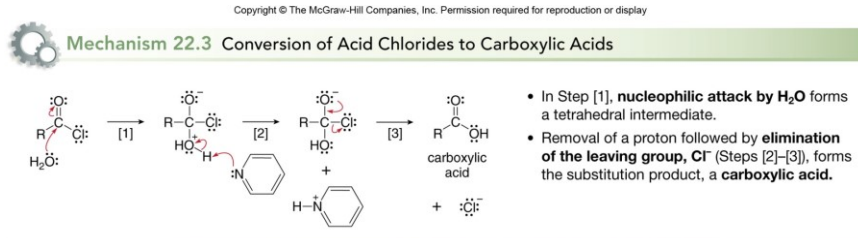
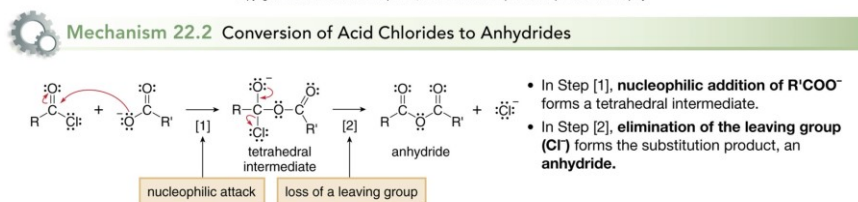
# Amide Formation

- As an example, reaction of an acid chloride with diethylamine forms the 3° amide *N,N*-diethyl-*m*-toluamide, popularly known as **DEET**.
- DEET is the active ingredient in the most widely used insect repellents, and is effective against mosquitoes, fleas, and ticks.



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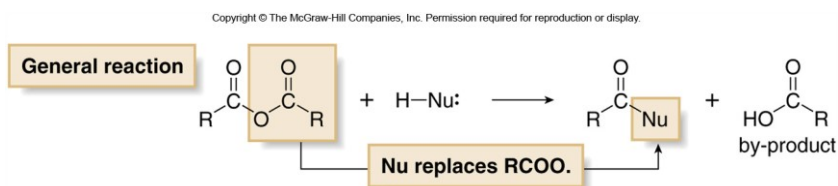
# Mechanisms of Acid Chloride Substitutions



38

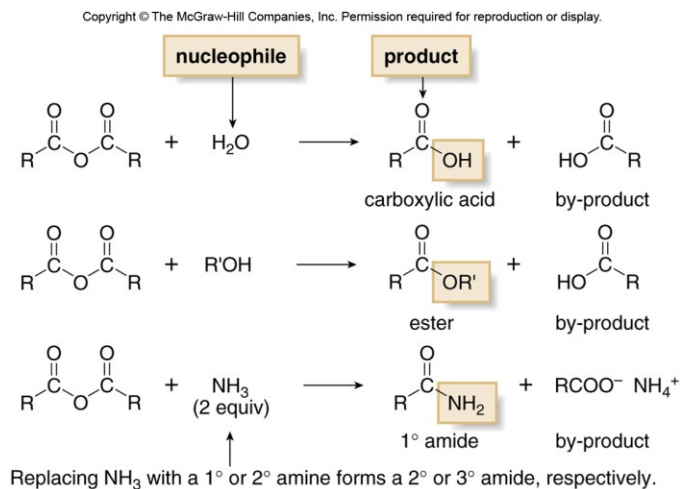
## General Reaction of Anhydrides

- Anhydrides are somewhat less reactive than acid chlorides, but still readily react with most nucleophiles.
- Nucleophilic attack occurs at one carbonyl group, while the second carbonyl becomes part of the leaving group.



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## Reactions of Anhydrides



40

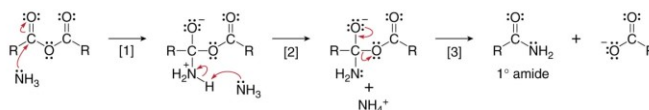
## Mechanism of Anhydride Substitution

- Besides the usual steps for nucleophilic addition and elimination of the leaving group, the mechanism involves an additional proton transfer.

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### Mechanism 22.4 Conversion of an Anhydride to an Amide



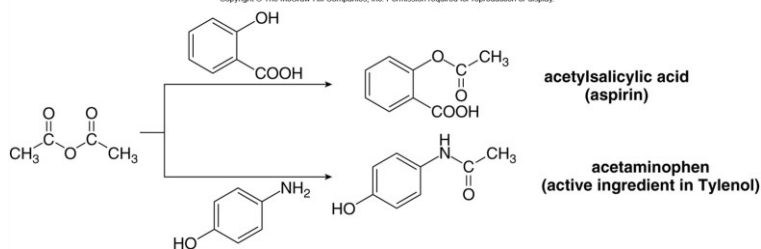
- In Step [1], **nucleophilic attack by  $\text{NH}_3$**  forms a tetrahedral intermediate.
- Removal of a proton followed by **elimination of the leaving group,  $\text{RCOO}^-$**  (Steps [2]–[3]), forms the substitution product, a **1° amide**.

41

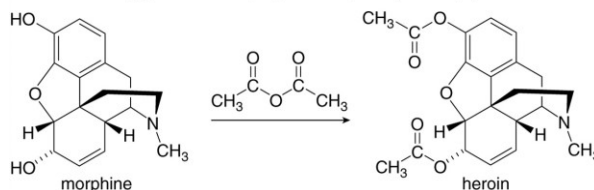
## Anhydrides Use in Acetylation Reactions

- Reactions that result in the transfer of an acetyl group are known as **acetylations**.

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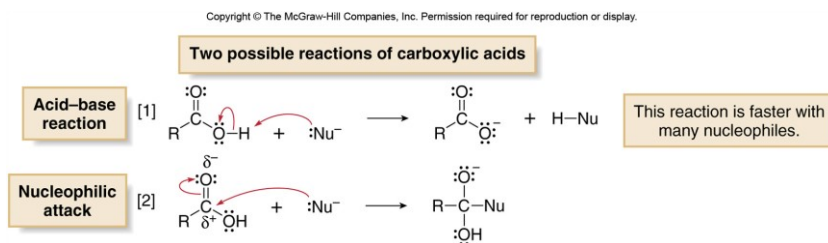
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## General Reactions of Carboxylic Acids

- Nucleophiles that are also strong bases react with carboxylic acids by removing a proton first, before any nucleophilic substitution reaction can take place.

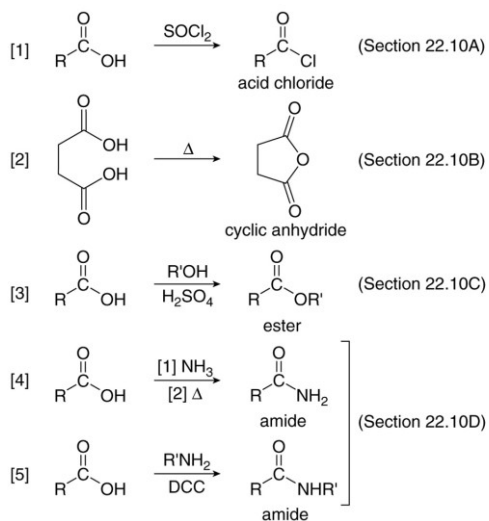


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## Acyl Substitution Reactions of Carboxylic Acids

Figure 22.3

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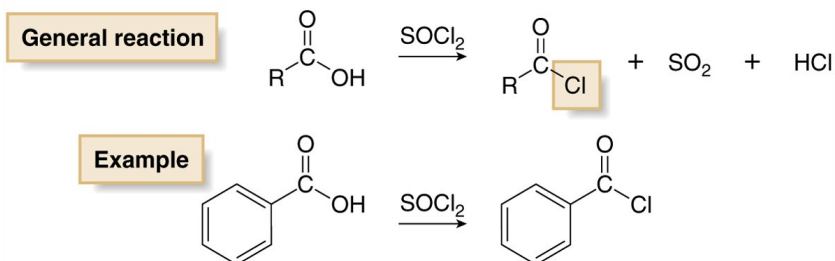


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# Formation of Acyl Halides

- Treatment of a carboxylic acid with **thionyl chloride (SOCl<sub>2</sub>)** affords an acid chloride.
- This is possible because thionyl chloride converts the OH group of the acid into a better leaving group, and because it provides the nucleophile (Cl<sup>-</sup>) to displace the leaving group.

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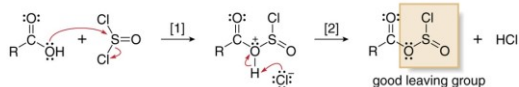
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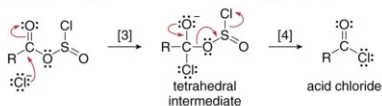
## Mechanism 22.5 Conversion of Carboxylic Acids to Acid Chlorides

**Steps [1] and [2]** Conversion of the OH group into a good leaving group



- Reaction of the OH group with SOCl<sub>2</sub> forms an intermediate that loses a proton in Step [2]. This two-step process converts the OH group into OSOCl, a **good leaving group**.

**Steps [3] and [4]** Substitution of the leaving group by Cl

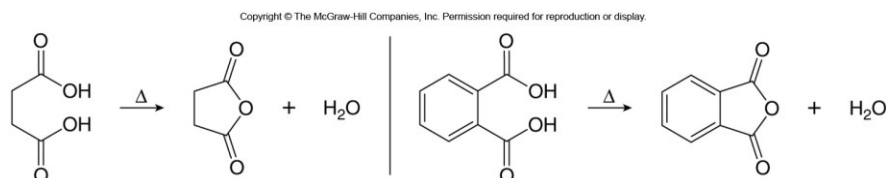


- **Nucleophilic attack by Cl<sup>-</sup> and loss of the leaving group** (SO<sub>2</sub> + Cl<sup>-</sup>) forms the acid chloride.

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## Dehydration of Carboxylic Acids

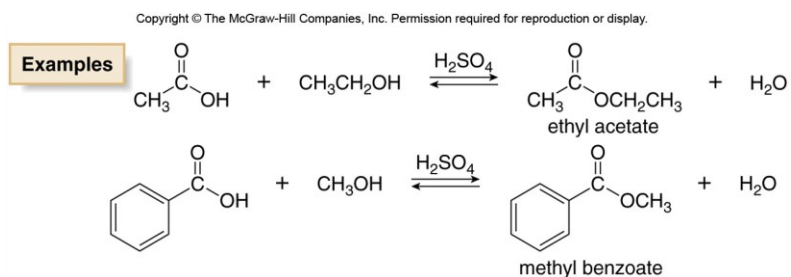
- Although carboxylic acids cannot readily be converted into anhydrides, dicarboxylic acids can be converted to cyclic anhydrides by heating to high temperatures.
- This is a dehydration reaction because a water molecule is lost from the diacid.



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## Fischer Esterification of Carboxylic Acids

- Treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst forms an ester.
- This reaction is called a **Fischer esterification**.
- The reaction is an equilibrium, so it is driven to the right by using excess alcohol or by removing water as it is formed.



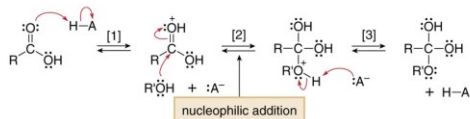
48





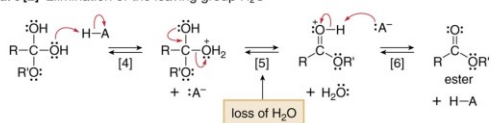
### Mechanism 22.6 Fischer Esterification—Acid-Catalyzed Conversion of Carboxylic Acids to Esters

**Part [1]** Addition of the nucleophile R'OH



- **Protonation** in Step [1] makes the carbonyl group more electrophilic.
- **Nucleophilic addition of R'OH** forms a tetrahedral intermediate, and loss of a proton forms the neutral addition product (Steps [2]–[3]).

**Part [2]** Elimination of the leaving group H<sub>2</sub>O



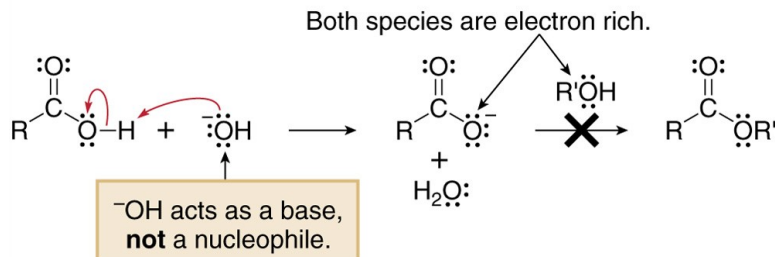
- Protonation of an OH group in Step [4] forms a good leaving group that is **eliminated in Step [5]**.
- Loss of a proton in Step [6] forms the ester.
- Only one resonance structure is drawn for the resonance-stabilized cations formed in Steps [1] and [5].

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## No Base Catalysis of Fischer Esterification

- Esterification of a carboxylic acid occurs in the presence of acid but not in the presence of base.
- Base removes a proton from the carboxylic acid, forming the carboxylate anion, which does not react with an electron-rich nucleophile.

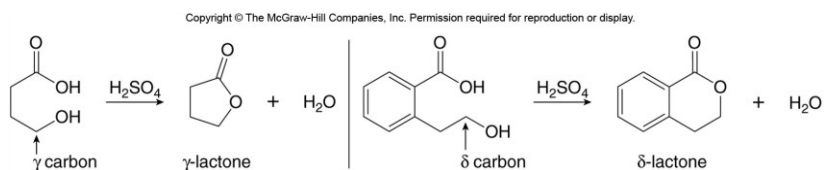
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## Intramolecular Fischer Esterification

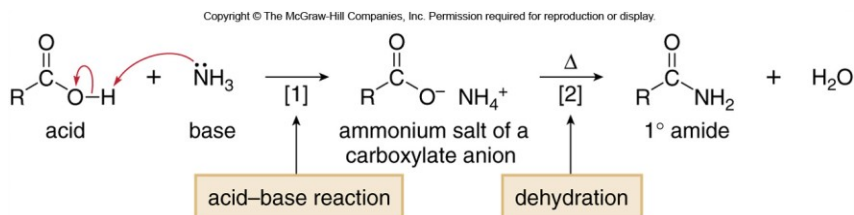
- Intramolecular esterification of  $\gamma$ - and  $\delta$ -hydroxy carboxylic acids forms five- and six-membered lactones.



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## Amide Formation from Carboxylic Acids

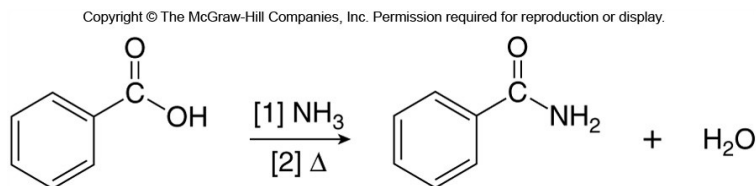
- Carboxylic acids cannot be converted into amides by reaction with  $\text{NH}_3$  or an amine because amines are bases, and undergo an acid–base reaction to form an ammonium salt before nucleophilic substitution occurs.
- However, heating the ammonium salt at high temperature ( $>100^\circ\text{C}$ ) dehydrates the resulting ammonium salt of the carboxylate anion to form an amide, although the yield can be low.



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## Amide Formation from Carboxylic Acids

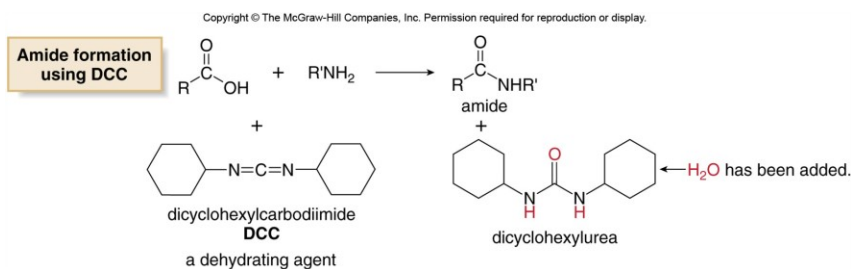
- The overall conversion of  $\text{RCOOH}$  to  $\text{RCONH}_2$  requires two steps:
  - [1] Acid–base reaction of  $\text{RCOOH}$  with  $\text{NH}_3$  to form an ammonium salt.
  - [2] Dehydration at high temperature ( $>100^\circ\text{C}$ ).



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## DCC in Amide Formation

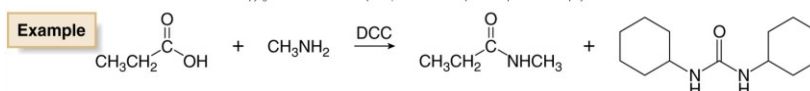
- A carboxylic acid and an amine readily react to form an amide in the presence of **dicyclohexylcarbodiimide (DCC)**, which is converted to the by-product dicyclohexylurea by the course of the reaction.



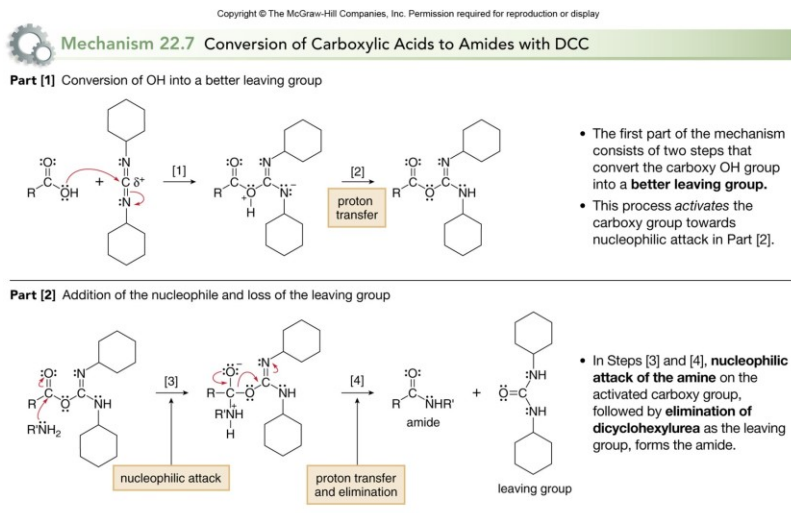
54

# DCC in Amide Formation

- DCC is a dehydrating agent.
- The dicyclohexylurea by-product is formed by adding the elements of H<sub>2</sub>O to DCC.
- DCC promotes amide formation by converting the carboxy group OH group into a better leaving group.



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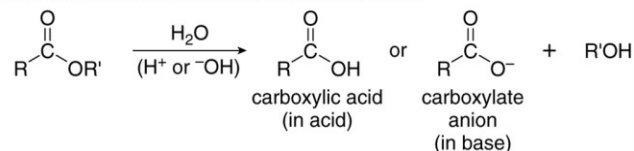


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# Reactions of Esters

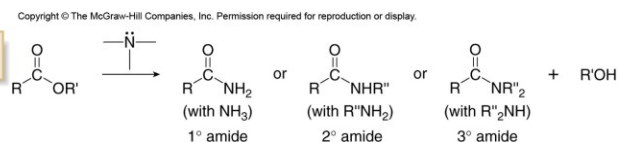
- Esters are hydrolyzed with water in the presence of either acid or base to form carboxylic acids or carboxylate anions, respectively.

## Ester hydrolysis



- Esters react with  $\text{NH}_3$  and amines to form 1°, 2°, or 3° amides.

## Reaction with nitrogen nucleophiles



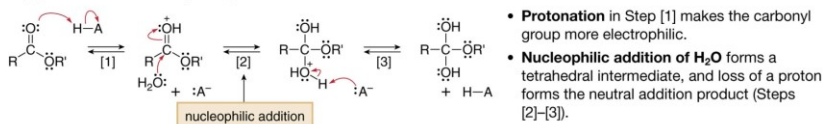
57

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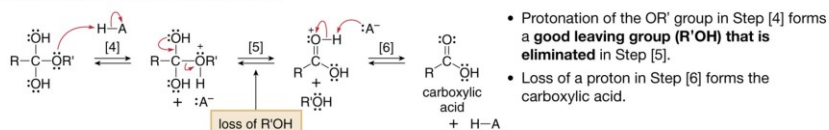


## Mechanism 22.8 Acid-Catalyzed Hydrolysis of an Ester to a Carboxylic Acid

### Part [1] Addition of the nucleophile $\text{H}_2\text{O}$



### Part [2] Elimination of the leaving group $\text{R}'\text{OH}$



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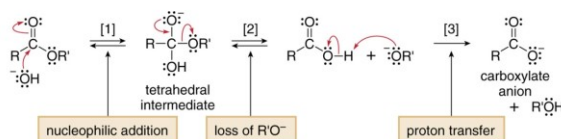
## Base Hydrolysis of Esters

- Basic hydrolysis of an ester is also called saponification.

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### Mechanism 22.9 Base-Promoted Hydrolysis of an Ester to a Carboxylic Acid



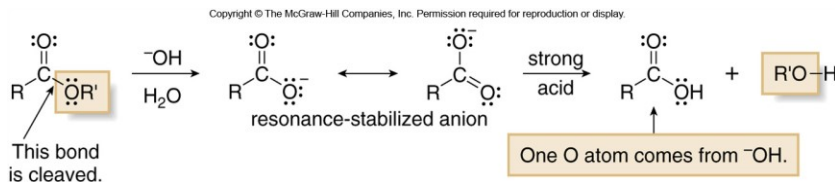
- Steps [1] and [2] result in **addition of the nucleophile**,  $\text{OH}^-$ , followed by **elimination of the leaving group**,  $\text{OR}'^-$ . These two steps, which form the carboxylic acid, are reversible, because the stability of the reactants and products is comparable.
- Next, the carboxylic acid is a strong organic acid and the leaving group ( $\text{OR}'^-$ ) is a strong base, so an **acid-base reaction** occurs in Step [3] to form the carboxylate anion.

- Hydrolysis is base promoted, not base catalyzed, because the base ( $\text{OH}^-$ ) is the nucleophile that adds to the ester and forms part of the product.
- It participates in the reaction and is not regenerated later.

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## Basic Hydrolysis of Esters

- The carboxylate anion is resonance stabilized, and this drives the equilibrium in its favor.
- Once the reaction is complete and the anion is formed, it can be protonated with strong acid to form the neutral carboxylic acid.

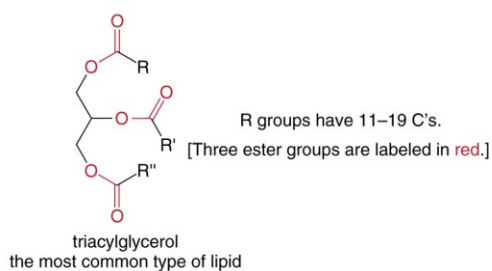


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# Lipid Hydrolysis

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- Each triacylglycerol is a triester, containing three long hydrocarbon side chains.
- Unsaturated triacylglycerols have one or more double bonds in their long hydrocarbon chains, whereas saturated triacylglycerols have none.

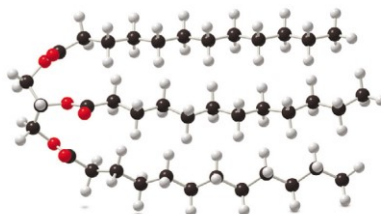


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## Structure of a Saturated Triacylglycerol

Figure 22.4

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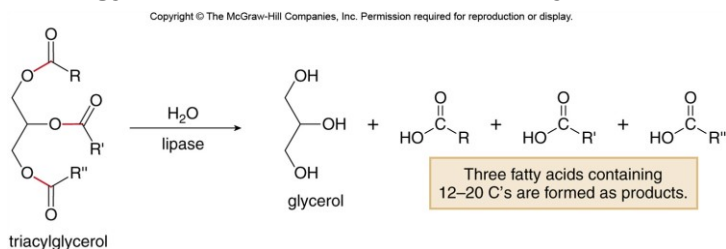


- This triacylglycerol has no double bonds in the three R groups (each with 11 C's) bonded to the ester carbonyls, making it a saturated fat.

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## Lipid Hydrolysis

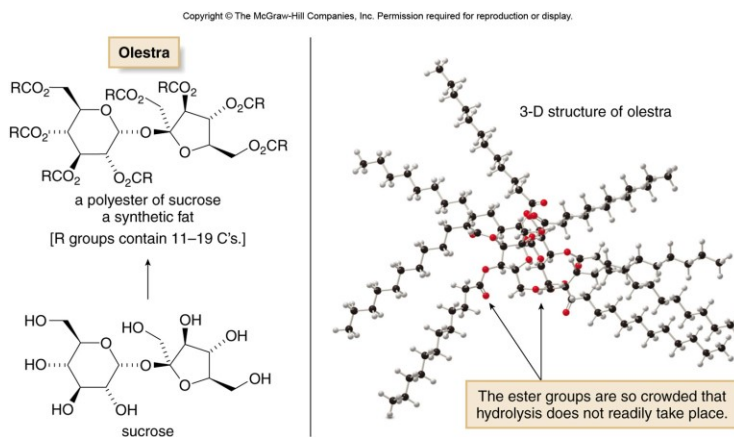
- The first step in the metabolism of a **triacylglycerol** is hydrolysis of the ester bonds to form glycerol and three fatty acids.
- The three bonds of the triacylglycerol drawn in red are cleaved in hydrolysis.
- In cells, this reaction is catalyzed by **lipases**.
- The fatty acids produced on hydrolysis are then oxidized, ultimately yielding  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , as well as nearly twice as much energy as an equal amount of carbohydrate.



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## Fat Substitutes

- One recent attempt to reduce calories in common snack foods has been to substitute “fake fats” such as **olestra** for triacylglycerols.

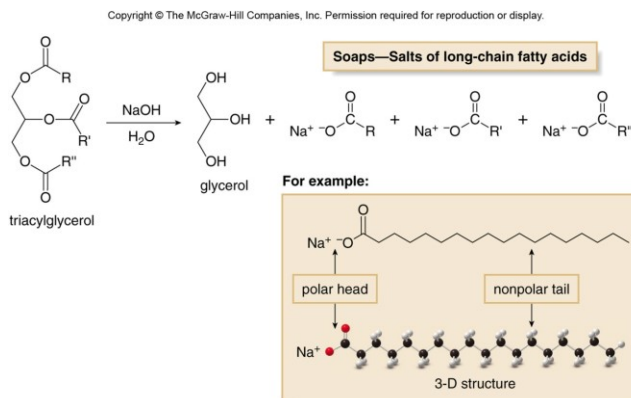


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# Soap Formation

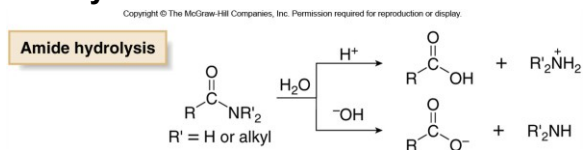
- Soap is prepared by the basic hydrolysis or **saponification** of a triacylglycerol.
- Heating an animal fat or vegetable oil with aqueous base hydrolyzes the three esters to form glycerol and sodium salts of three fatty acids.



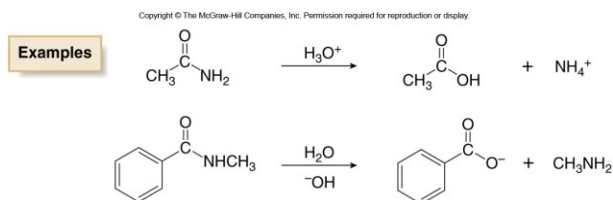
65

# Reactions of Amides

- Amides are the least reactive of the carboxylic acid derivatives.
- Amides are hydrolyzed in acid or base to form carboxylic acids or carboxylate anions.



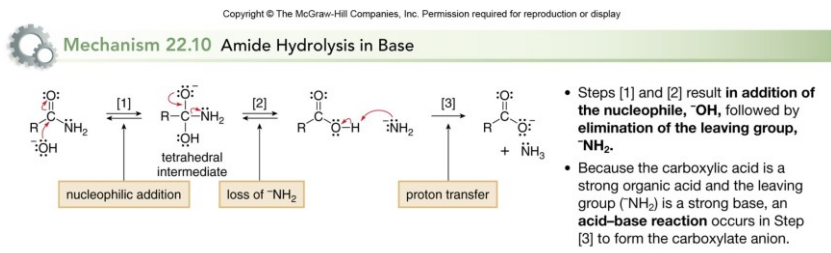
- In acid, the amine by-product is protonated as an ammonium ion, whereas in base, a neutral amine forms.



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## Amide Hydrolysis

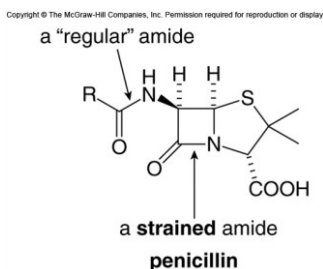
- The mechanism of amide hydrolysis in acid is exactly the same as the mechanism of ester hydrolysis in acid.
- The mechanism of amide hydrolysis in base has the usual two steps in the general mechanism for nucleophilic acyl substitution, plus an additional proton transfer.



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## $\beta$ -Lactam Antibiotics

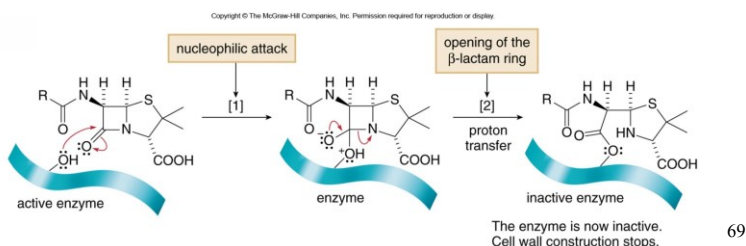
- **Penicillin** and related  $\beta$ -lactams kill bacteria by a nucleophilic acyl substitution reaction.
- All penicillins have an unreacted side chain and a very reactive amide that is part of a  $\beta$ -lactam.
- The  $\beta$ -lactam is more reactive than other amides because it is part of a strained, four membered ring that is readily opened with nucleophiles.



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## The Mechanism of Action of $\beta$ -Lactam Antibiotics

- Bacterial cell walls are composed of carbohydrates linked together by peptide chains containing amide linkages formed by the enzyme glycopeptide transpeptidase.
- A nucleophilic OH group of the glycopeptide transpeptidase enzyme cleaves the  $\beta$ -lactam ring of penicillin by a nucleophilic acyl substitution reaction.
- The reaction causes covalent modification of the enzyme, thus inactivating it and halting cell wall construction killing the bacterium.



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**Table 22.5** Summary of the Nucleophilic Substitution Reactions of Carboxylic Acids and Their Derivatives

Starting material	Product				
	RCOCl	(RCO) <sub>2</sub> O	RCOOH	RCOOR'	RCONR' <sub>2</sub>
[1] RCOCl	→ -	✓	✓	✓	✓
[2] (RCO) <sub>2</sub> O	→ X	-	✓	✓	✓
[3] RCOOH	→ ✓	✓	-	✓	✓
[4] RCOOR'	→ X	X	✓	-	✓
[5] RCONR' <sub>2</sub>	→ X	X	✓	X	-

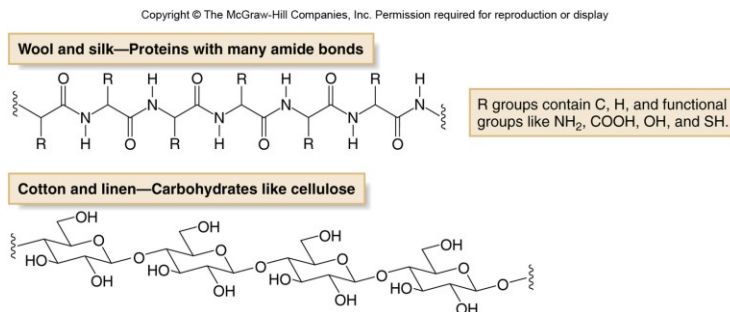
Table key: ✓ = A reaction occurs.  
X = No reaction occurs.

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# Natural Fibers

- Natural fibers are obtained from either plant or animal sources
- Fibers like wool and silk are proteins obtained from animals.
- Cotton and linen are derived from carbohydrates having the general structure of cellulose.

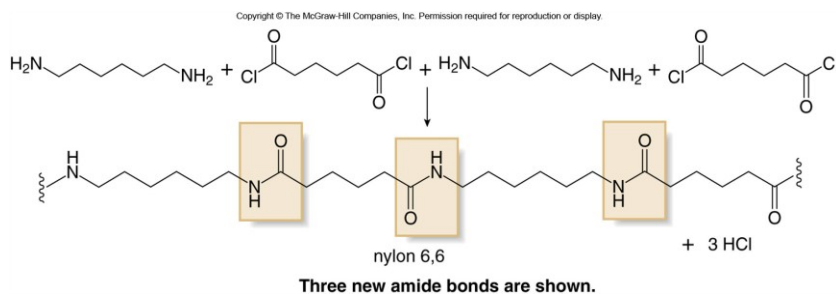
Figure 22.4



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## Synthetic Fibers: Nylon—A Polyamide

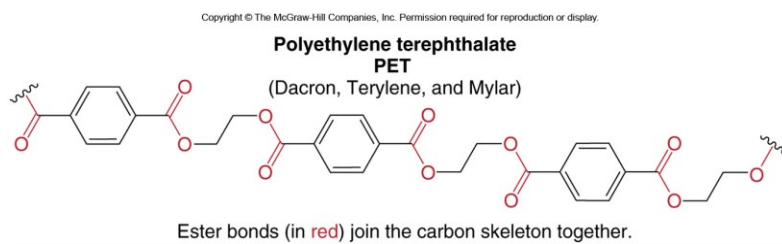
- There are a number of synthetic polyamides (nylons), but the most well known is **nylon 6,6**.
- Nylon 6,6 can be synthesized from two six-carbon monomers which react together to form new amide bonds.
- Nylon is a **condensation polymer** because a small molecule (in this case, HCl) is eliminated during its synthesis.



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## Synthetic Fibers: Polyesters

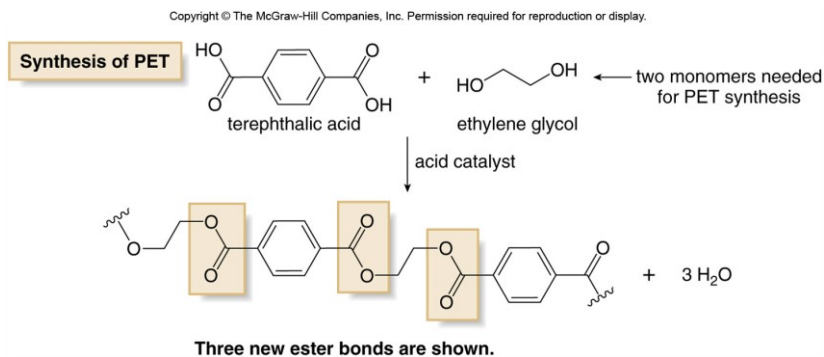
- The most common polyester is **polyethylene terephthalate (PET)**, which is sold under a variety of trade names (Dacron, Terylene, and Mylar), depending on its use.



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## Synthesis of Polyesters

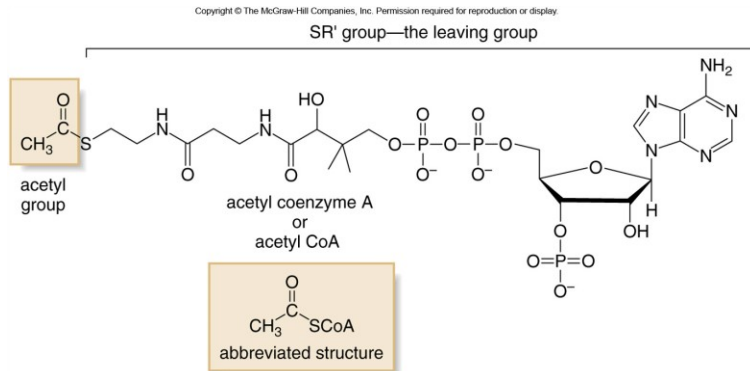
- One method of synthesizing a polyester is by acid-catalyzed esterification of a diacid with a diol (**Fischer esterification**).



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# Biological Acylations

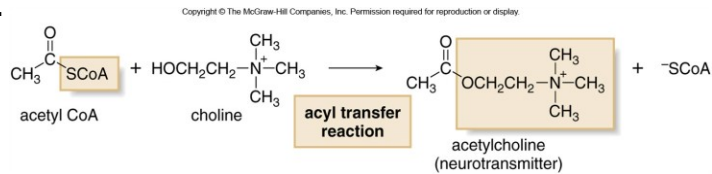
- In cells, acylations occur with the sulfur analogue of an ester (a thioester).
- The most common ester is **acetyl coenzyme A (acetyl CoA)**.



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# Acyl Transfer Reactions

- An example of a biological acyl transfer reaction is the formation of the neurotransmitter acetylcholine from choline and acetyl CoA.

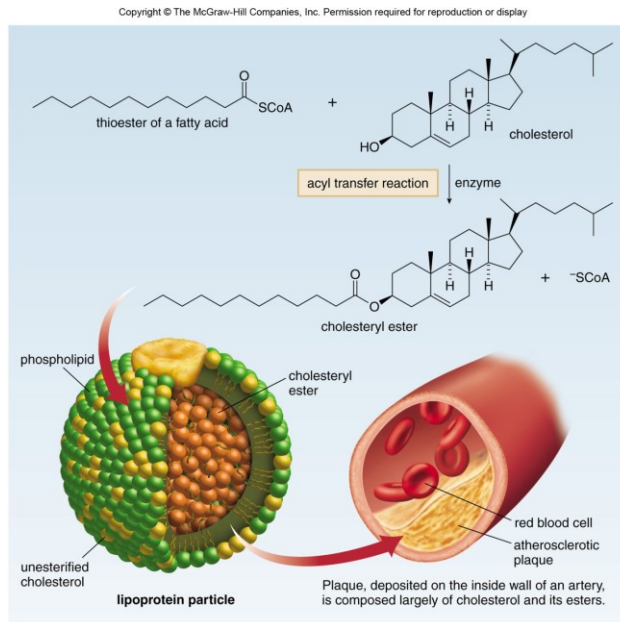


- Other important acyl transfer reactions include the reaction of thioesters of fatty acids with cholesterol, forming cholesteryl esters.
- These esters are the principal form in which cholesterol is stored and transported in the body.
- It is carried in the blood stream in particles that also contain proteins and phospholipids.
- These particles are classified by their density: **low density lipoproteins (LDL)** and **high density lipoproteins (HDL)**.

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## Cholesteryl Esters and LDL Particles

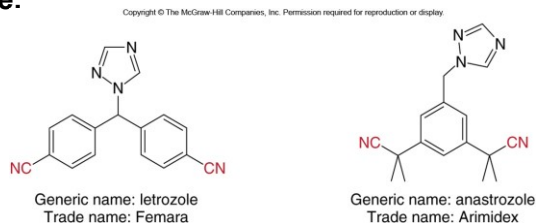
Figure 22.6



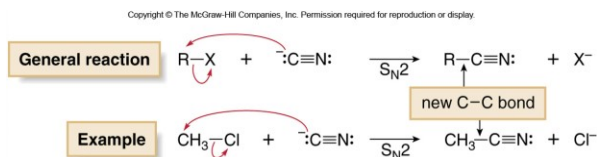
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## Structure and Formation of Nitriles

- Nitriles have the general structural formula  $RC\equiv N$ .
- Two useful biologically active nitriles are letrozole and anastrozole.



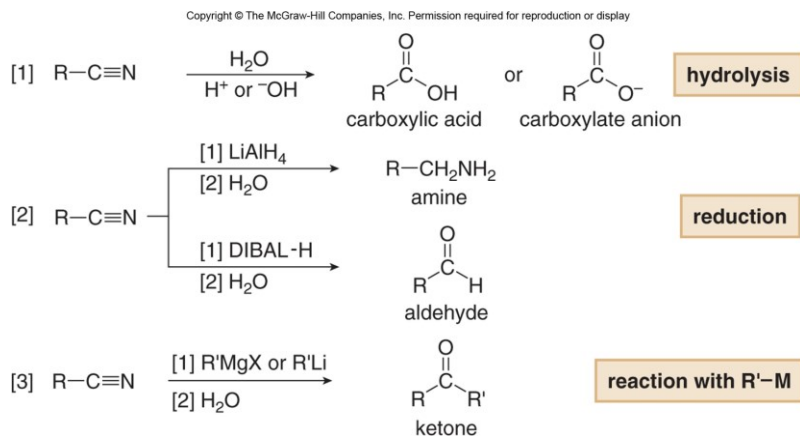
- Nitriles are prepared by  $S_N2$  reactions of unhindered methyl and  $1^\circ$  alkyl halides with  $^-CN$ .



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## Reactions of Nitriles

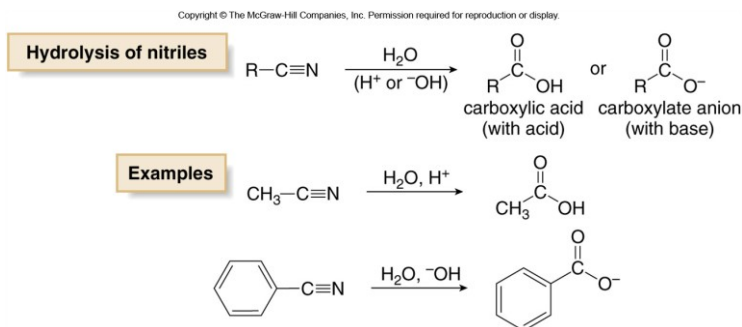
- Nitriles will react with water, hydride and organometallics.



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## Hydrolysis of Nitriles

- Nitriles are hydrolyzed with water in the presence of acid or base to yield carboxylic acids or carboxylate anions.
- In this reaction, the three C-N bonds are replaced by three C-O bonds.

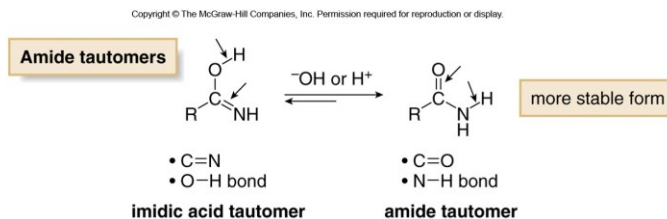


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## Amide Tautomers

- The mechanism of this reaction involves formation of an amide tautomer.
- Two tautomers can be drawn for any carbonyl compound, and those for a 1° amide are as follows:

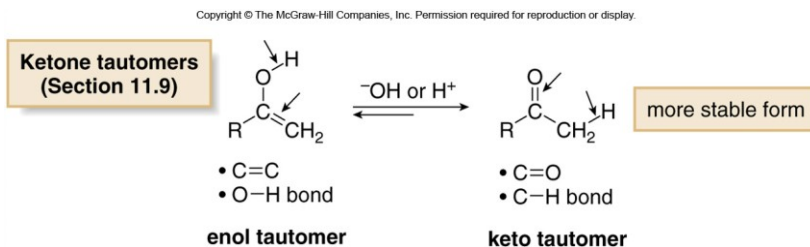


- The amide form is the more stable tautomer, having a C=O and an N-H bond.
- The imidic acid tautomer is the less stable form, having a C=N and an O-H bond.

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## Keto-Enol Tautomers

- The **imidic acid** and amide tautomers are interconverted by treatment with acid or base, analogous to keto-enol tautomers of other carbonyl compounds.

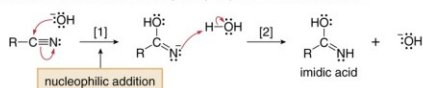


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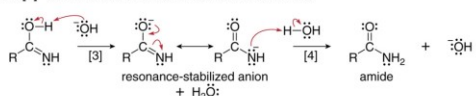
### Mechanism 22.11 Hydrolysis of a Nitrile in Base

**Part [1]** Addition of the nucleophile ( $\text{OH}^-$ ) to form an imidic acid



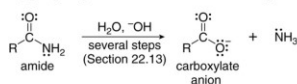
- Nucleophilic attack of  $\text{OH}^-$  followed by protonation forms an imidic acid.

**Part [2]** Tautomerization of the imidic acid to an amide



- Tautomerization occurs by a two-step sequence—**deprotonation followed by protonation**.

**Part [3]** Hydrolysis of the  $1^\circ$  amide to a carboxylate anion



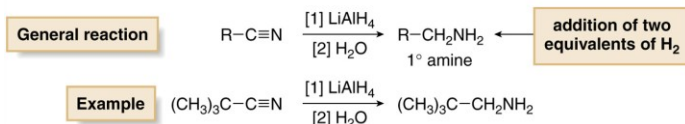
- Conversion of the amide to the carboxylate anion occurs by the multistep sequence detailed in Section 22.13.

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## Reduction of Nitriles

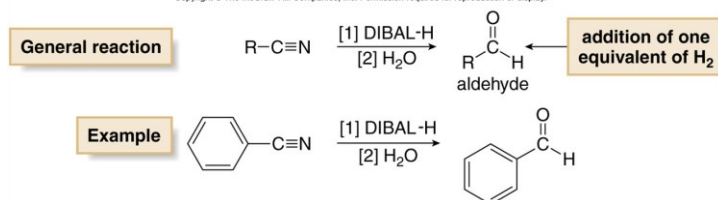
- Treatment of a nitrile with  $\text{LiAlH}_4$  followed by  $\text{H}_2\text{O}$  adds two equivalents of  $\text{H}_2$  across the triple bond, forming a  $1^\circ$  amine.

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- Treatment of a nitrile with a milder reducing agent such as DIBAL-H followed by water forms an aldehyde.

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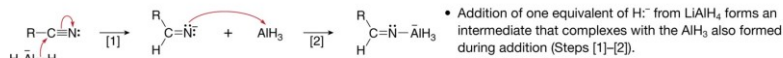
# Nitrile Reduction Mechanisms

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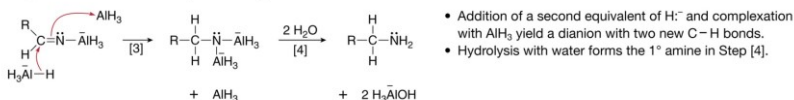


## Mechanism 22.12 Reduction of a Nitrile with LiAlH<sub>4</sub>

**Part [1]** Addition of one equivalent of hydride



**Part [2]** Addition of a second equivalent of hydride



- With LiAlH<sub>4</sub>, two equivalents of hydride are sequentially added to yield a dianion which is then protonated with H<sub>2</sub>O to form an amine.

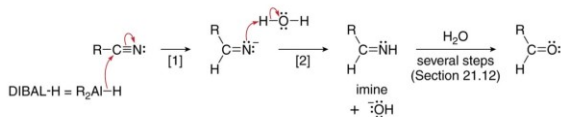
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# Nitrile Reduction Mechanisms

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## Mechanism 22.13 Reduction of a Nitrile with DIBAL-H

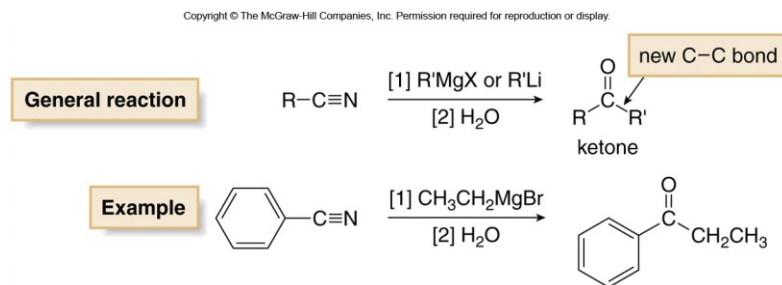


- With DIBAL-H, nucleophilic addition of one equivalent of hydride forms an anion which is protonated with water to generate an imine.
- The imine is then hydrolyzed in water to form an aldehyde.

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## Reduction of Nitriles with Organometallics

- Both Grignard and organolithium reagents react with nitriles to form ketones with a new C–C bond.

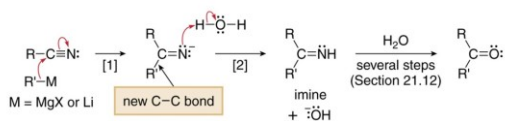


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## Organometallic Reduction Mechanism

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**Mechanism 22.14** Addition of Grignard and Organolithium Reagents (R–M) to Nitriles



- The reaction occurs by nucleophilic addition of the organometallic reagent to the polarized C–N triple bond to form an anion, which is protonated with water to form an imine.
- Water then hydrolyzes the imine, replacing the C=N with C=O.
- The final product is a ketone with a new C–C bond.

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