Organic Chemistry, *Fourth Edition*

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Chapter 22
Lecture Outline

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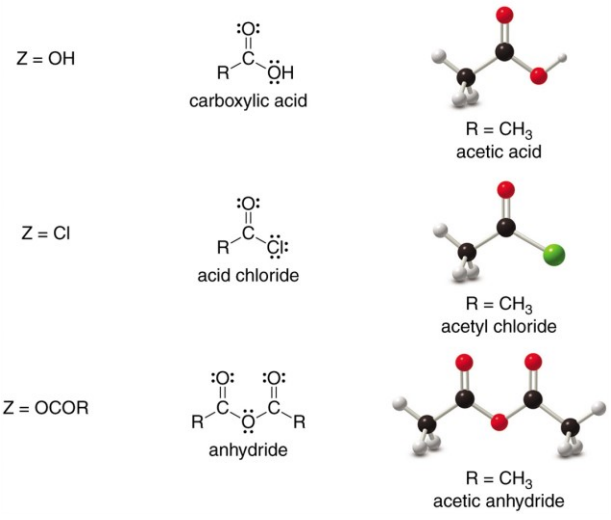
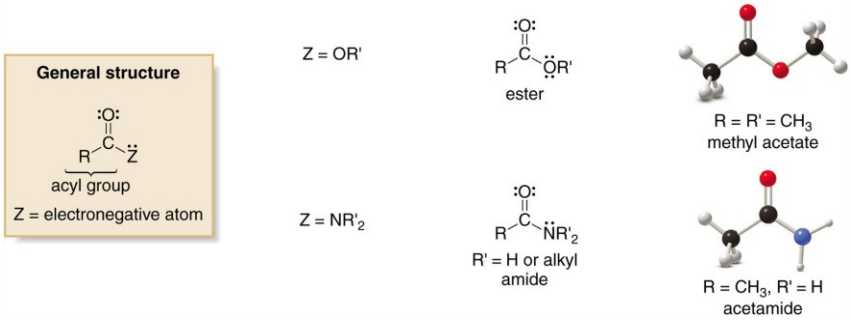
The University of Illinois - Springfield

Carboxylic Acid Derivatives



Carboxylic Acid Derivatives



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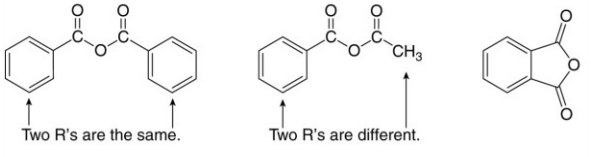
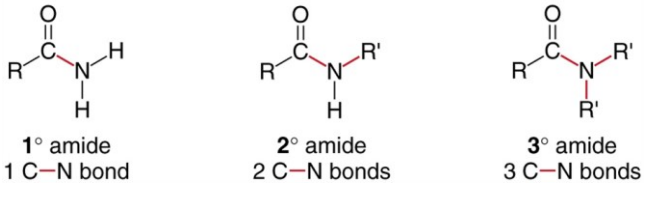
Anhydrides and Amides

Types of anhydrides:



Types of amides:



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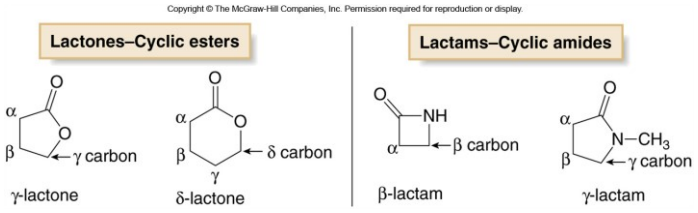
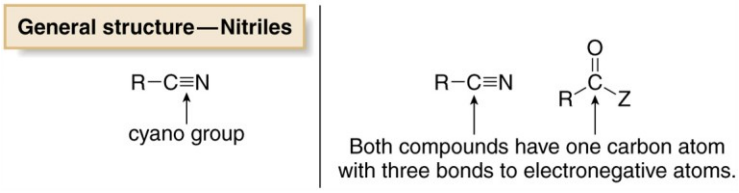
Lactones, Lactams and Nitriles

Cyclic esters and amides:



Nitriles:



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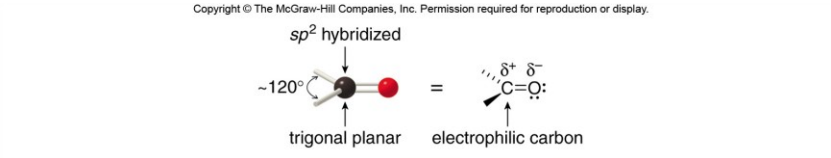
Structural Features of the Carbonyl Group

The two most important features of the carbonyl group are:



- 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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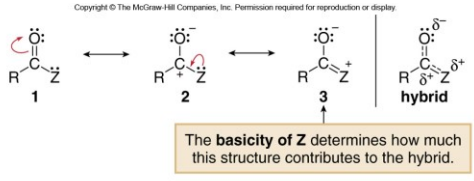
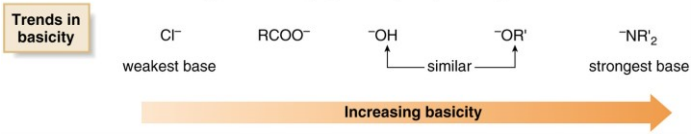
Resonance of Carboxylic Acid Derivatives

- **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:**

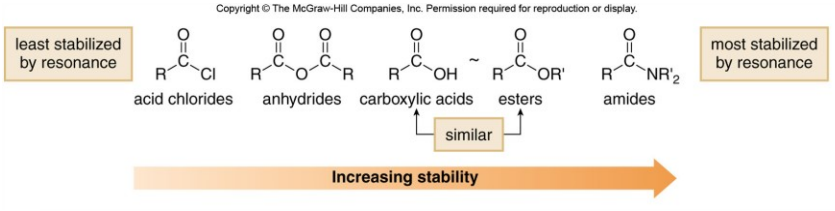


- The more basic Z is, the more it donates its electron pair, and the more resonance structure 3 contributes to the hybrid.



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^-)	Conjugate acid (HZ)	pK_a	
Increasing basicity of Z ↓	**RCOCl** acid chloride	Cl^-	HCl	−7	↑ Increasing acidity of HZ
	$(RCO)_2O$ anhydride	$RCOO^-$	RCOOH	3–5	
	RCOOH carboxylic acid	^-OH	H_2O	15.7	
	RCOOR' ester	$^-OR'$	R'OH	15.5–18	
	RCONR'$_2$ amide	$^-NR'_2$	R'_2NH	38–40	

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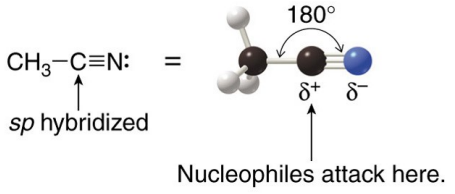
Resonance of Carboxylic Acid Derivatives

- **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.**



- **The carbon atom on the C≡N group is *sp* hybridized, making it linear with a bond angle of 180°.**
- **The triple bond consists of one σ and two π bonds.**

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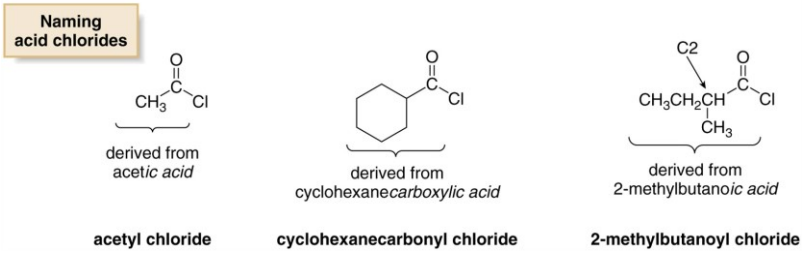
Nomenclature—Acid Chlorides

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



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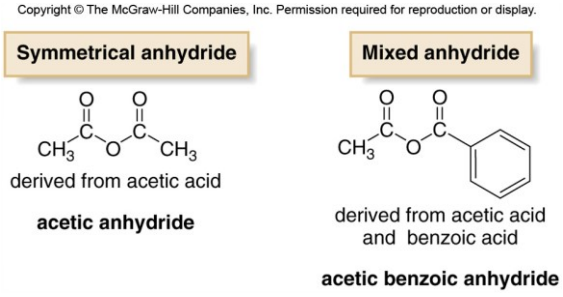
Nomenclature—Anhydrides

- **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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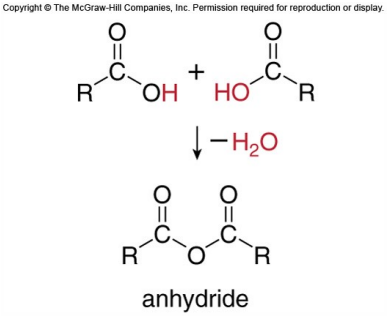
Composition of Anhydrides

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



anhydride

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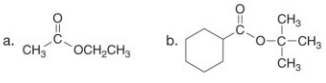
Nomenclature—Esters

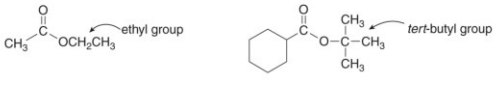
How To Name an Ester (RCO_2R') Using the IUPAC System

Example Give a systematic name for each ester:



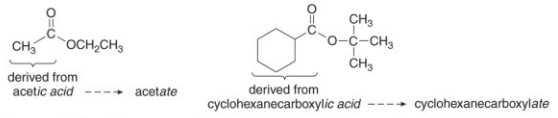
Step [1] Name the R' group bonded to the oxygen atom as an alkyl group.

- 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.



Answer: ethyl acetate **Answer: *tert*-butyl cyclohexanecarboxylate**

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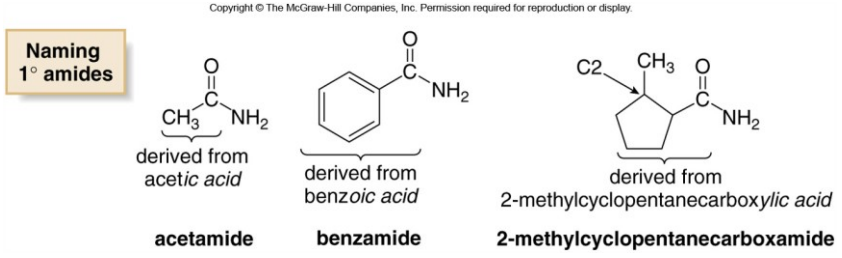
Nomenclature—Amides

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



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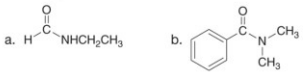
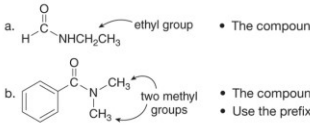
How To Name a 2° or 3° Amide

Example Give a systematic name for each amide:

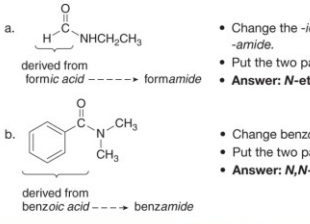


Step [1] Name the alkyl group (or groups) bonded to the N atom of the amide. Use the prefix "*N*-" preceding the name of each alkyl group.

- 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

- **$CH_3CH_2CH_2CN$ is butanenitrile, not propanenitrile.**

Figure 22.1

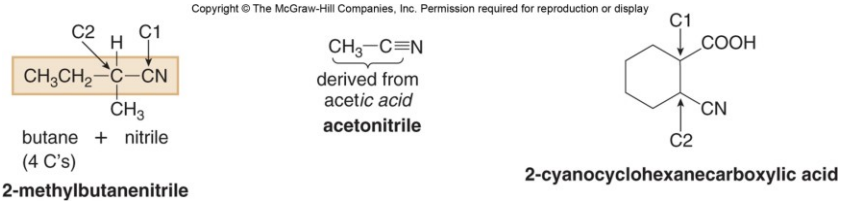

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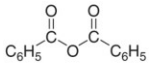
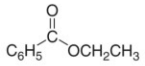
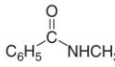
Table 22.2 Summary: Nomenclature of Carboxylic Acid Derivatives and Nitriles

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

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Intermolecular Attractions

- **Nitriles also have dipole-dipole interactions, because they have a polar C≡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

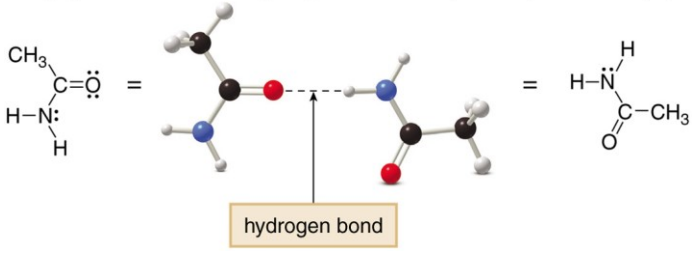

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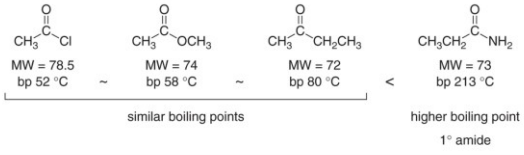
Table 22.3 Physical Properties of Carboxylic Acid Derivatives

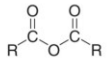
Property	Observation
Boiling point and melting point	• Primary (1°) and 2° amides have *higher* boiling points and melting points than compounds of comparable molecular weight. • The boiling points and melting points of other carboxylic acid derivatives are similar to those of other polar compounds of comparable size and shape. 
Solubility	• Carboxylic acid derivatives are soluble in organic solvents regardless of size. • Most carboxylic acid derivatives having ≤ 5 C's are H_2O soluble because they can hydrogen bond with H_2O (Section 3.4C). • Carboxylic acid derivatives having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent.

Key: MW = molecular weight

Spectroscopic Properties—IR

- **Like all carbonyl compounds, carboxylic acid derivatives have a strong C=O absorption between 1600 and 1850 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 cm^{-1}.**
  2. **An N–H bending absorption at ~1640 cm^{-1}.**
- **As the carbonyl π 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.**

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

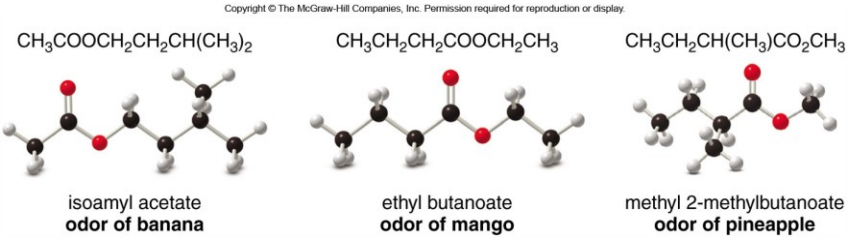
	Compound type	Structure (RCOZ)	Carbonyl absorption ($\tilde{\nu}$)	
Increasing basicity of Z	acid chloride		~1800	Increasing $\tilde{\nu}$ of absorption
	anhydride		1820 and 1760 (2 peaks)	
	ester		1735–1745	
	amide	 R' = H or alkyl	1630–1680	

Spectroscopic Properties—NMR

- **Protons on the α 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}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}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.**

Interesting Esters and Amides

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



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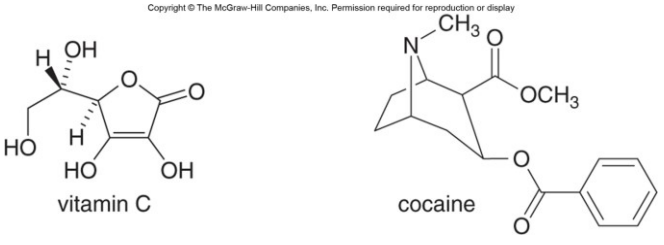
Biologically Active Esters

- **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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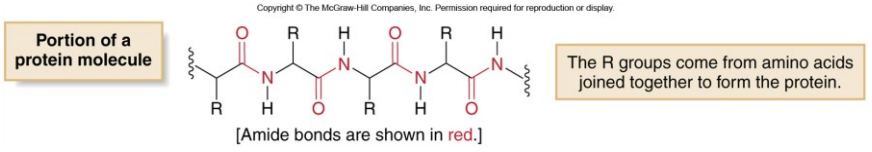
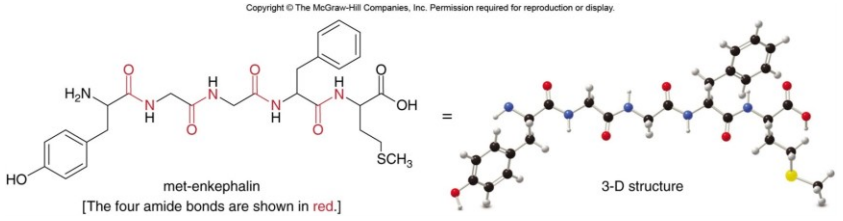
Proteins—Polyamides

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





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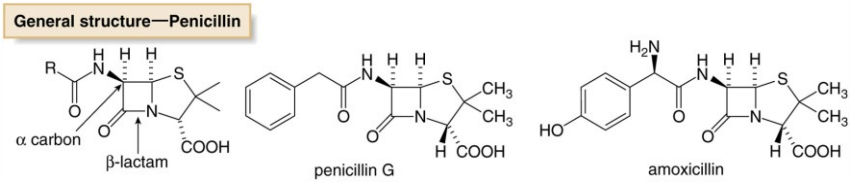
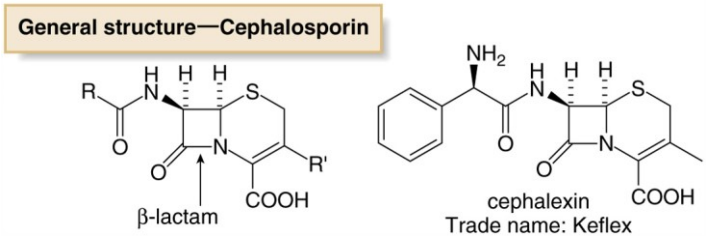
Useful Drugs Containing Lactams





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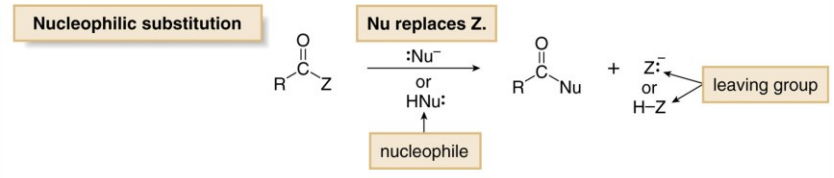
Nucleophilic Acyl Substitution

- **Nucleophilic acyl substitutions 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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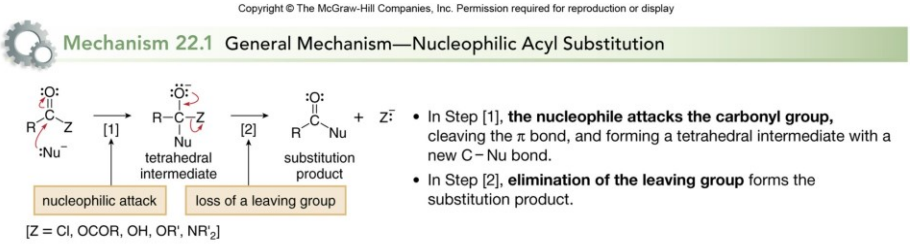
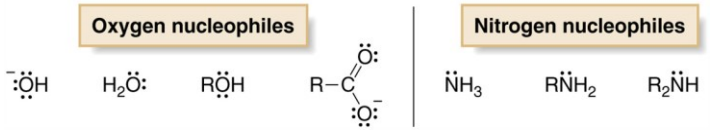
Mechanism of Nucleophilic Acyl Substitution



- **Other nucleophiles that participate in this reaction include:**



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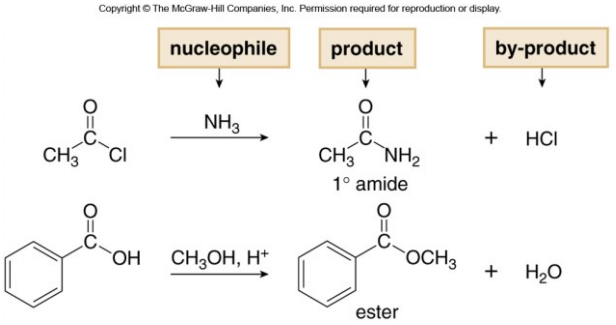
Drawing Products of Nucleophilic Acyl Substitution

[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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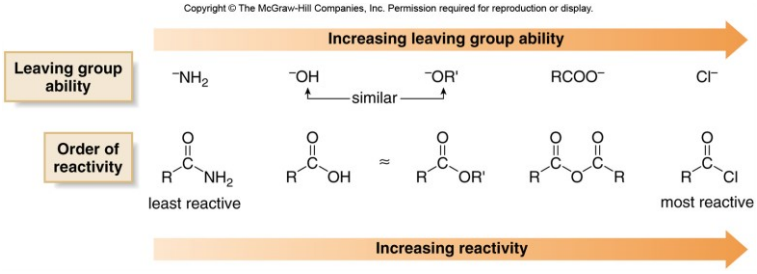
Reactivity Related to Leaving Group Ability



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

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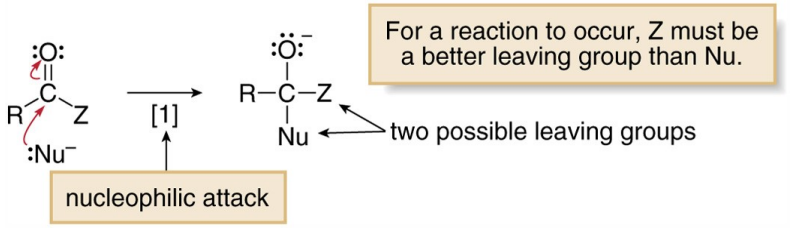
Comparing Leaving Group and Nucleophile

- **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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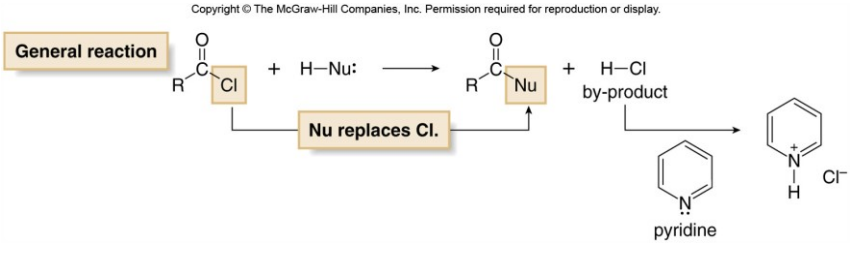
General Reactions of Acid Chlorides

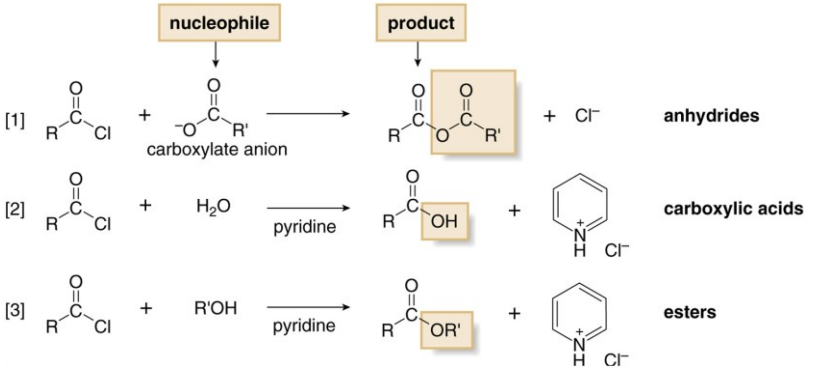
- **Since acid chlorides have the best leaving group of acid derivatives, they react readily with a wide range of nucleophiles to form nucleophilic substitution products.**
- **HCl is usually formed as a by-product.**
- **A weak base like pyridine is added to the reaction mixture to remove the strong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



34

Reactions of Acid Chlorides and Oxygen Nucleophiles

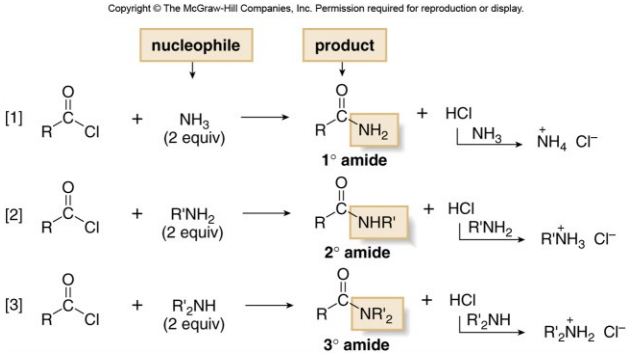
- **Acid chlorides react with oxygen nucleophiles to form anhydrides, carboxylic acids, and esters.**



35

Reactions of Acid Chlorides and Amines

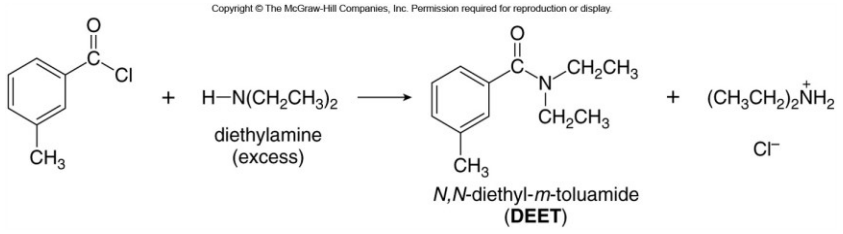
- **Acid chlorides also react with ammonia, and 1° and 2° amines to form 1°, 2° and 3° amides, respectively.**
- **Two equivalents of NH_3 or amine are used.**
- **One equivalent acts as the nucleophile to replace Cl, while the other reacts as a base with the HCl by-product to form an ammonium salt.**



36

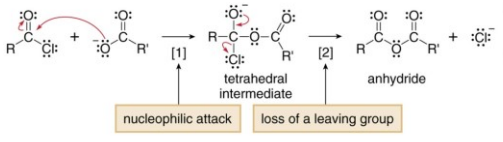
Amide Formation

- **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.**



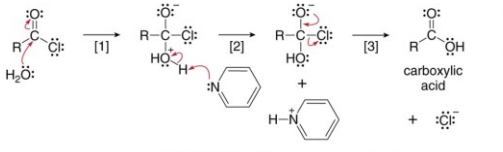
Mechanisms of Acid Chloride Substitutions

Mechanism 22.2 Conversion of Acid Chlorides to Anhydrides



- In Step [1], **nucleophilic addition of R'COO⁻** forms a tetrahedral intermediate.
- In Step [2], **elimination of the leaving group (Cl⁻)** forms the substitution product, an **anhydride.**

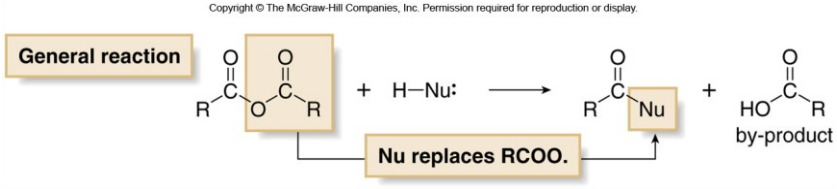
Mechanism 22.3 Conversion of Acid Chlorides to Carboxylic Acids



- In Step [1], **nucleophilic attack by H_2O** forms a tetrahedral intermediate.
- Removal of a proton followed by **elimination of the leaving group, Cl⁻** (Steps [2]–[3]), forms the substitution product, a **carboxylic acid.**

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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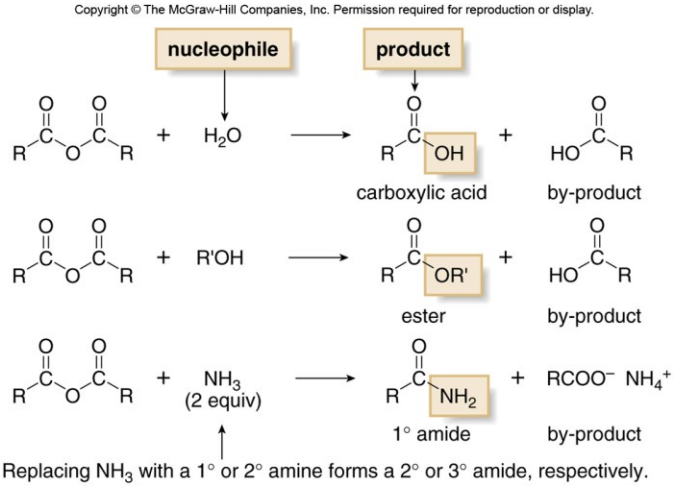
Reactions of Anhydrides



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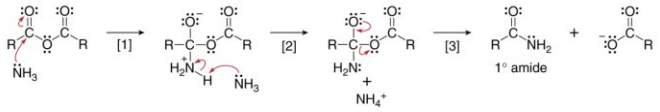
Mechanism of Anhydride Substitution

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

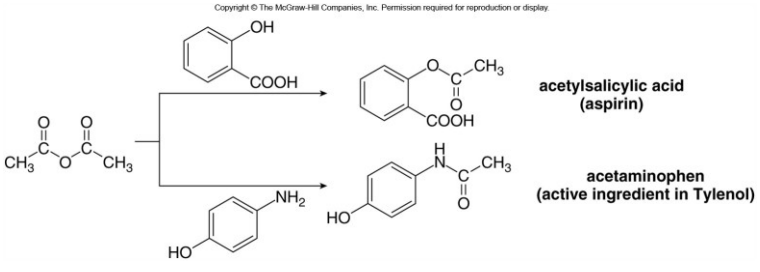
Mechanism 22.4 Conversion of an Anhydride to an Amide

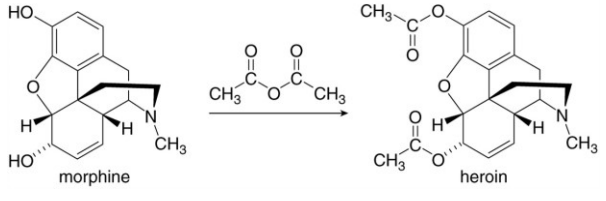


- In Step [1], **nucleophilic attack by NH_3** forms a tetrahedral intermediate.
- Removal of a proton followed by **elimination of the leaving group, $RCOO^-$** (Steps [2]–[3]), forms the substitution product, a **1° amide.**

Anhydrides Use in Acetylation Reactions

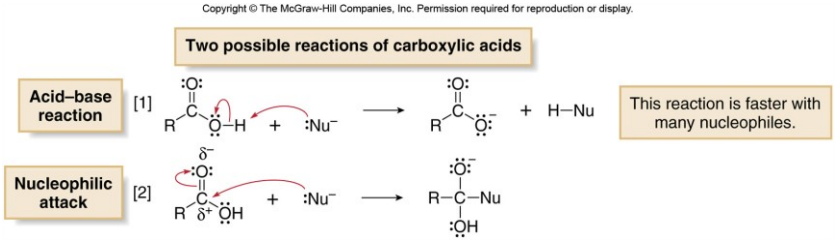
- **Reactions that result in the transfer of an acetyl group are known as acetylations.**





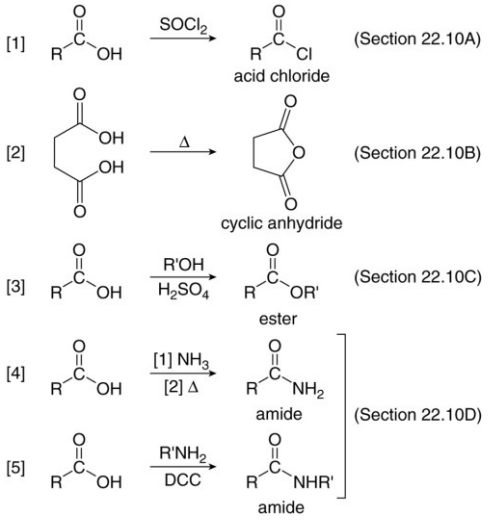
General Reactions of Carboxylic Acids

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



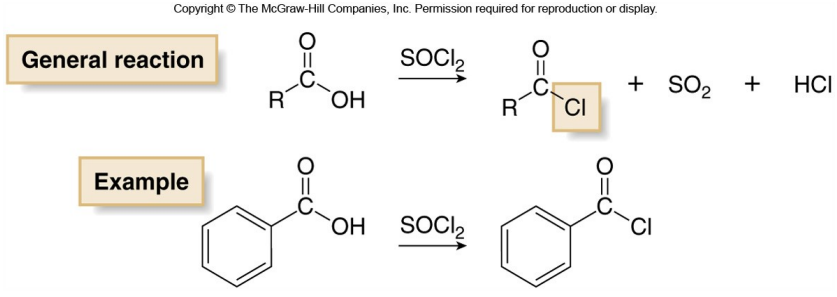
Acyl Substitution Reactions of Carboxylic Acids

Figure 22.3



Formation of Acyl Halides

- **Treatment of a carboxylic acid with thionyl chloride ($SOCl_2$) 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^-) to displace the leaving group.**



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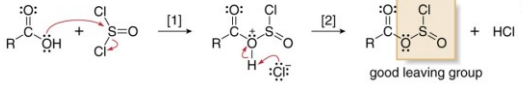
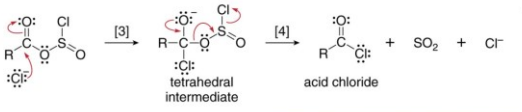
Mechanism 22.5 Conversion of Carboxylic Acids to Acid Chlorides

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



- Reaction of the OH group with $SOCl_2$ 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^- and loss of the leaving group** ($SO_2 + Cl^-$) forms the acid chloride.

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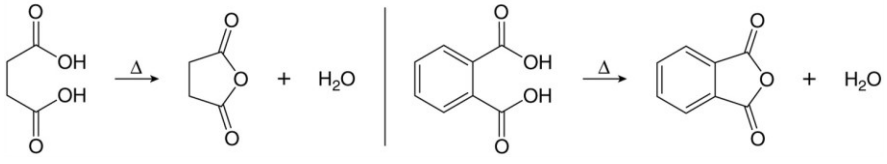
Dehydration of Carboxylic Acids

- **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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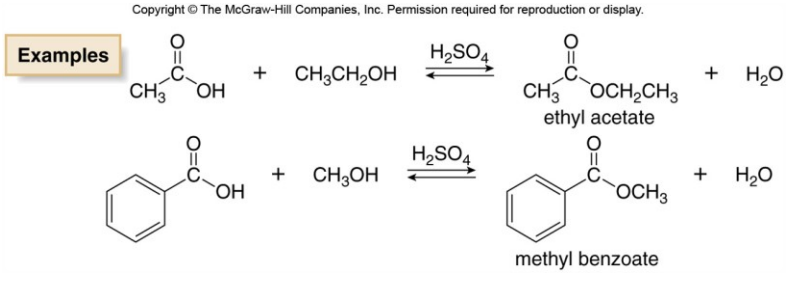
Fischer Esterification of Carboxylic Acids

- **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.**



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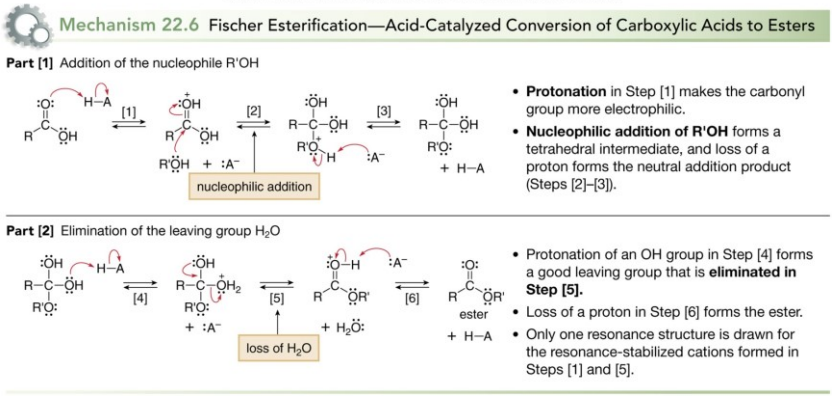
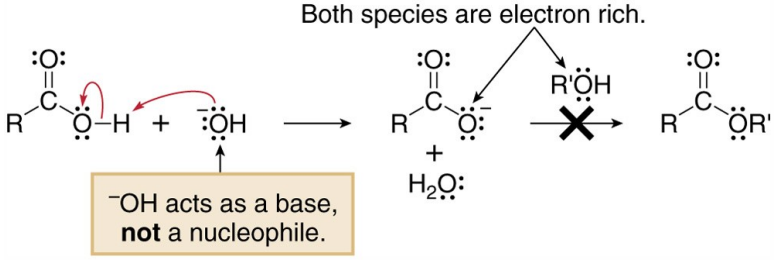


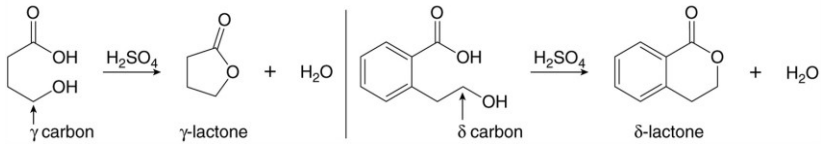
No Base Catalysis of Fischer Esterification

- **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.**



Intramolecular Fischer Esterification

- **Intramolecular esterification of γ- and δ-hydroxy carboxylic acids forms five- and six-membered lactones.**



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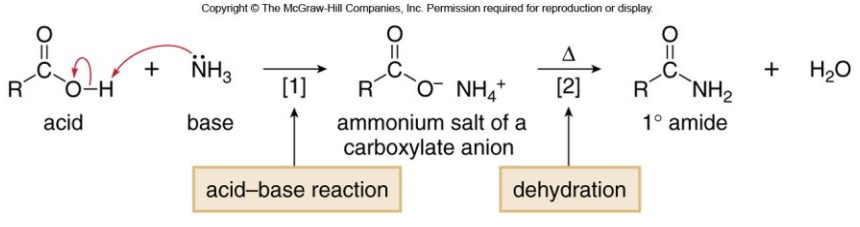
Amide Formation from Carboxylic Acids

- **Carboxylic acids cannot be converted into amides by reaction with 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°C) dehydrates the resulting ammonium salt of the carboxylate anion to form an amide, although the yield can be low.**



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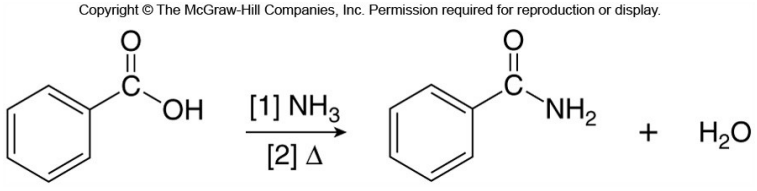
Amide Formation from Carboxylic Acids

- **The overall conversion of RCOOH to $RCONH_2$ requires two steps:**
  - **[1] Acid–base reaction of RCOOH with NH_3 to form an ammonium salt.**
  - **[2] Dehydration at high temperature (>100°C).**



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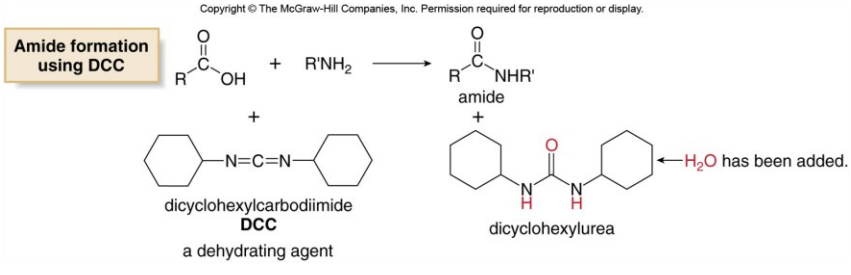
DCC in Amide Formation

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



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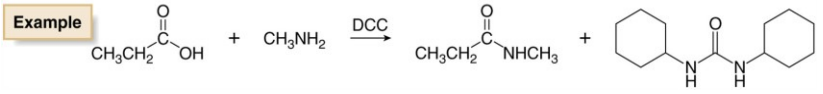
DCC in Amide Formation

- **DCC is a dehydrating agent.**
- **The dicyclohexylurea by-product is formed by adding the elements of H_2O to DCC.**
- **DCC promotes amide formation by converting the carboxy group OH group into a better leaving group.**



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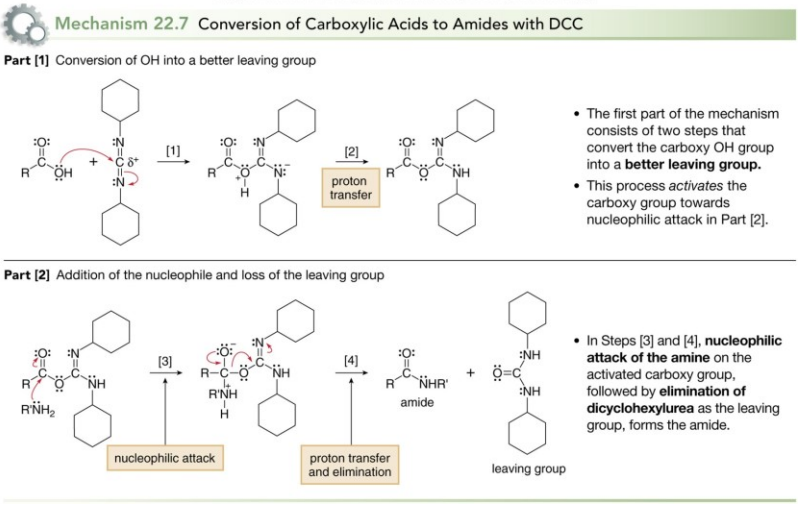

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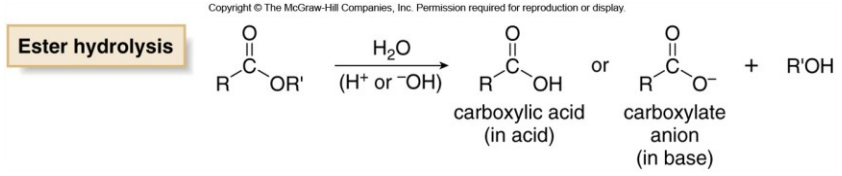
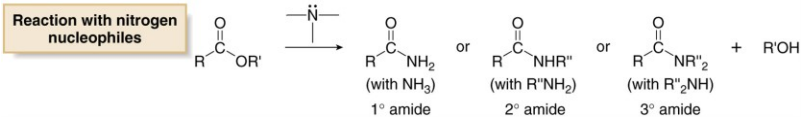
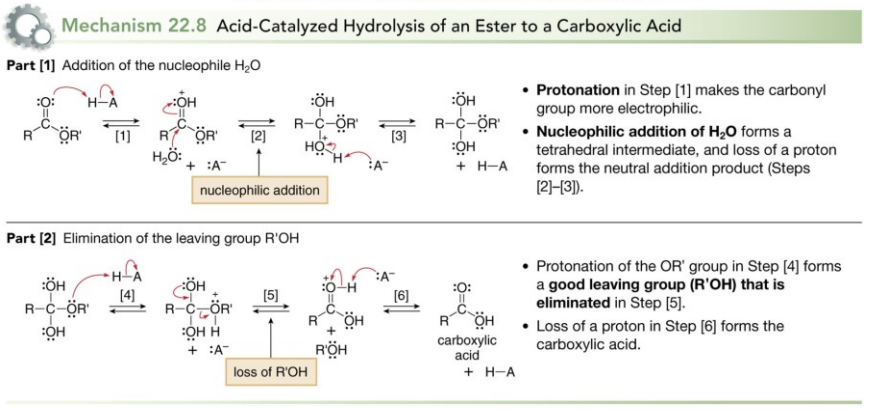
Reactions of Esters

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



- **Esters react with NH_3 and amines to form 1°, 2°, or 3° amides.**

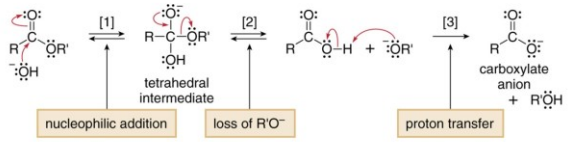




Base Hydrolysis of Esters

- **Basic hydrolysis of an ester is also called saponification.**

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



- Steps [1] and [2] result in **addition of the nucleophile,** ⁻OH, followed by **elimination of the leaving group, ⁻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 (⁻OR') is a strong base, so an **acid–base reaction** occurs in Step [3] to form the carboxylate anion.

- **Hydrolysis is base promoted, <u>not</u> base catalyzed, because the base (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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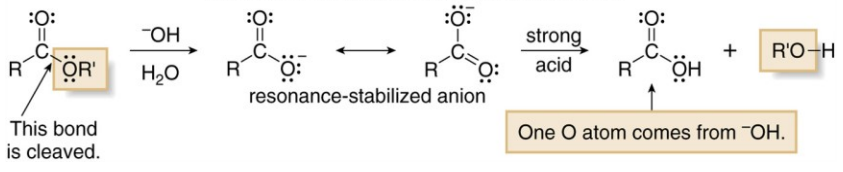
Basic Hydrolysis of Esters

- **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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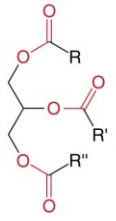
Lipid Hydrolysis

- 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.



R groups have 11–19 C's.
[Three ester groups are labeled in red.]

triacylglycerol
the most common type of lipid

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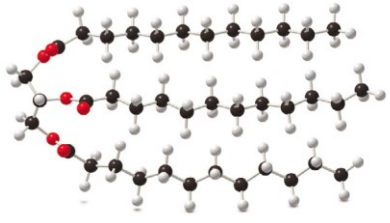
Structure of a Saturated Triacylglycerol

Figure 22.4



- 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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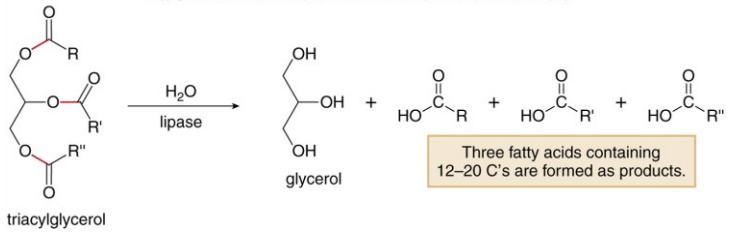
Lipid Hydrolysis

- 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 CO_2 and H_2O, as well as nearly twice as much energy as an equal amount of carbohydrate.



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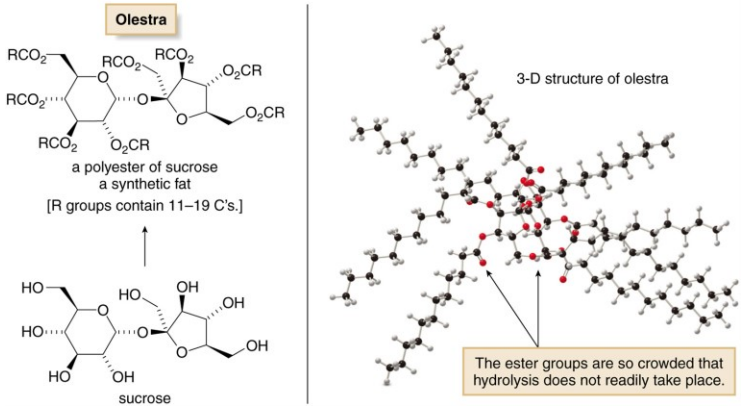
Fat Substitutes

- 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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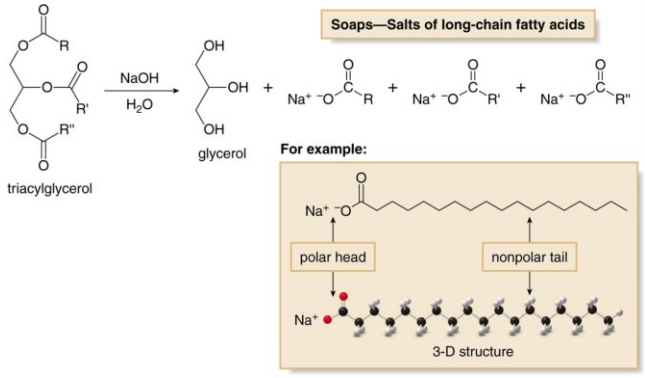
Soap Formation

- **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.**



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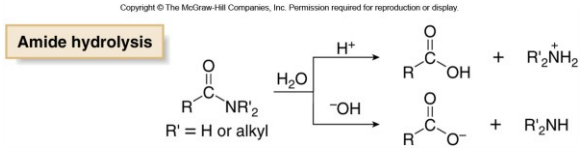
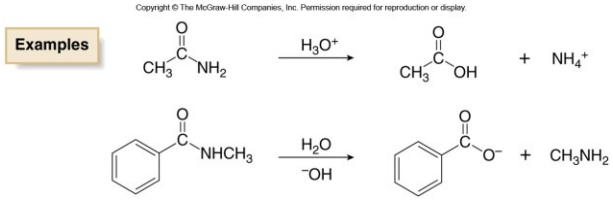
Reactions of Amides

- **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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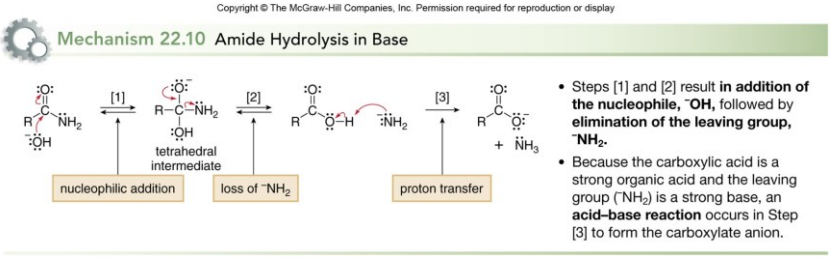
Amide Hydrolysis

- **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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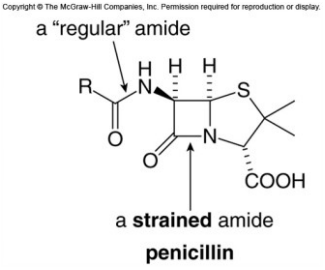
β-Lactam Antibiotics

- **Penicillin and related β-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 β-lactam.**
- **The β-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 β-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 β-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.**

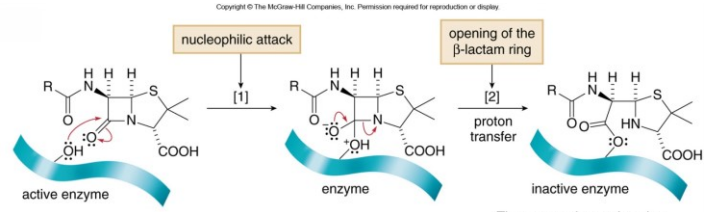

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Table 22.5 Summary of the Nucleophilic Substitution Reactions of Carboxylic Acids and Their Derivatives

Starting material		Product: RCOCl	$(RCO)_2O$	RCOOH	RCOOR'	$RCONR'_2$
[1] RCOCl	→	–	✓	✓	✓	✓
[2] $(RCO)_2O$	→	✗	–	✓	✓	✓
[3] RCOOH	→	✓	✓	–	✓	✓
[4] RCOOR'	→	✗	✗	✓	–	✓
[5] $RCONR'_2$	→	✗	✗	✓	✗	–

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

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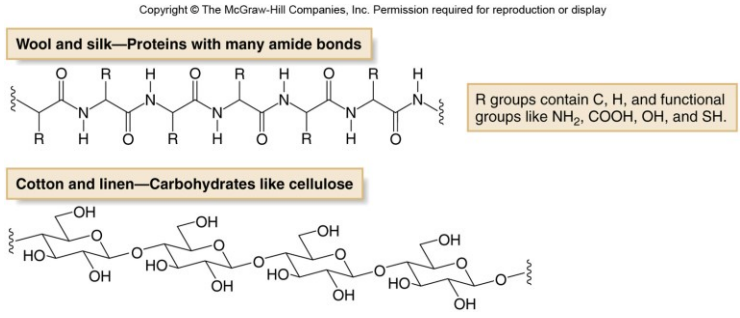
Natural Fibers

- **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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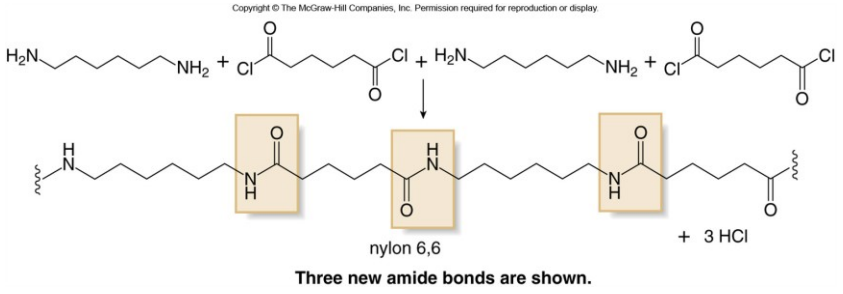
Synthetic Fibers: Nylon—A Polyamide

- **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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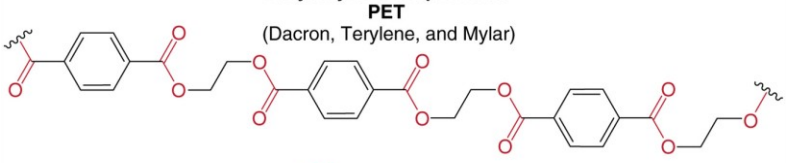
Synthetic Fibers: Polyesters

- **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.**

Polyethylene terephthalate
PET
(Dacron, Terylene, and Mylar)



Ester bonds (in red) join the carbon skeleton together.

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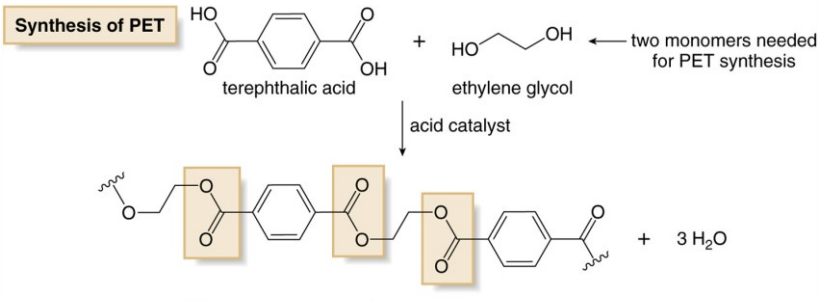
Synthesis of Polyesters

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

Synthesis of PET



Three new ester bonds are shown.

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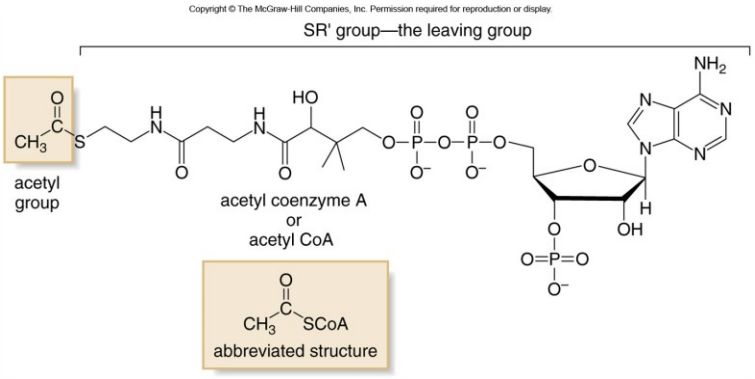
Biological Acylations

- 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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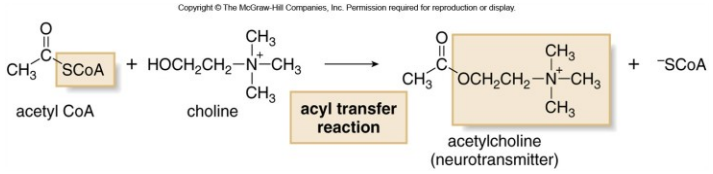
Acyl Transfer Reactions

- 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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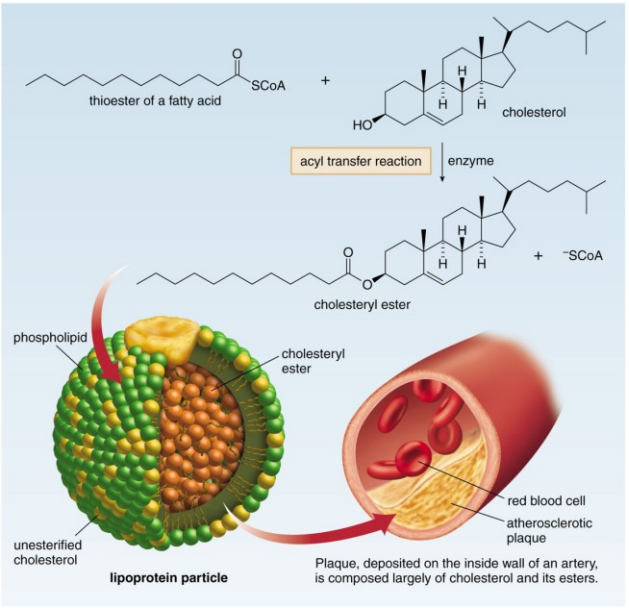
Cholesteryl Esters and LDL Particles

Figure 22.6



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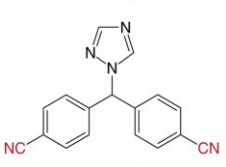
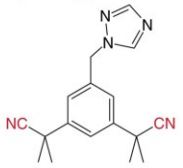
Structure and Formation of Nitriles

- **Nitriles have the general structural formula RC≡N.**
- **Two useful biologically active nitriles are letrozole and anastrozole.**

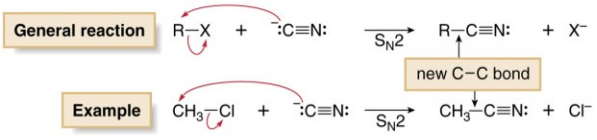


Generic name: letrozole
Trade name: Femara



Generic name: anastrozole
Trade name: Arimidex

- **Nitriles are prepared by S_N2 reactions of unhindered methyl and 1° alkyl halides with ^-CN.**



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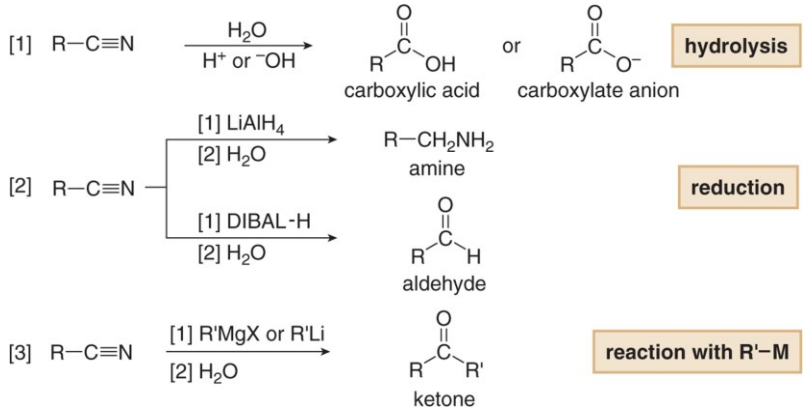
Reactions of Nitriles

- **Nitriles will react with water, hydride and organometallics.**



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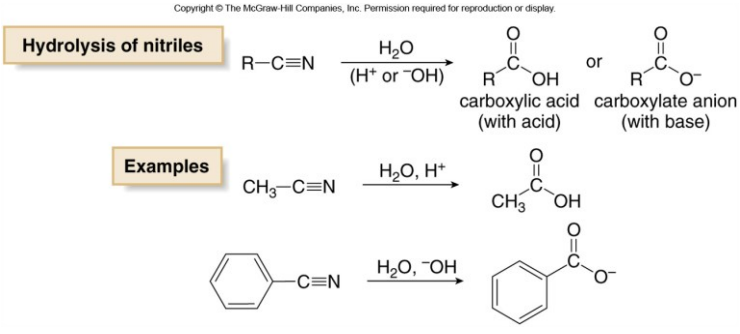
Hydrolysis of Nitriles

- **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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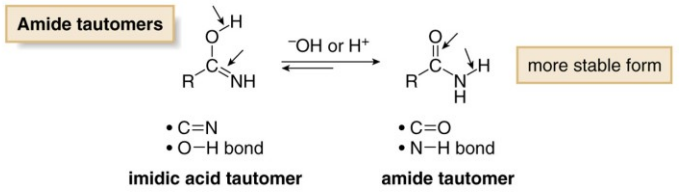
Amide Tautomers

- **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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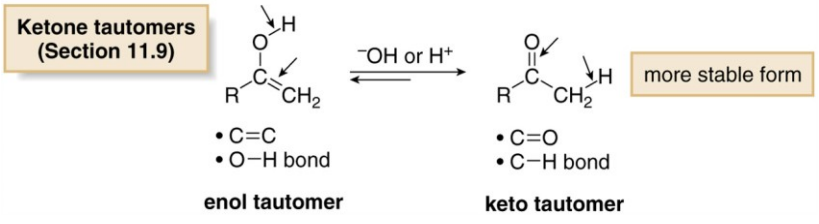
Keto-Enol Tautomers

- **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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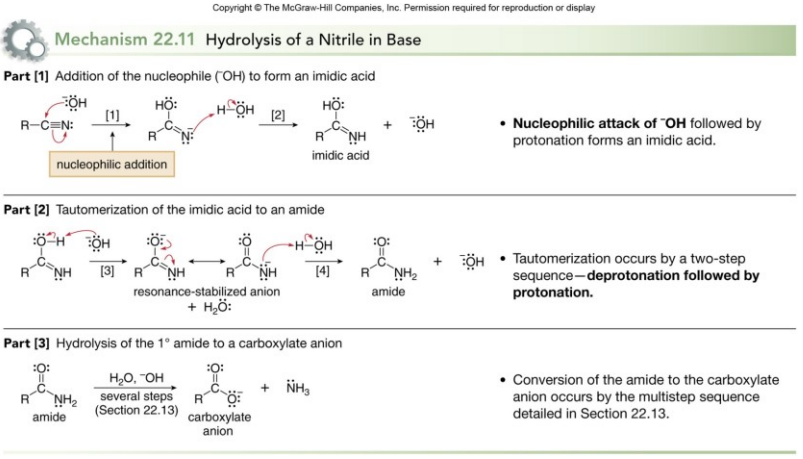
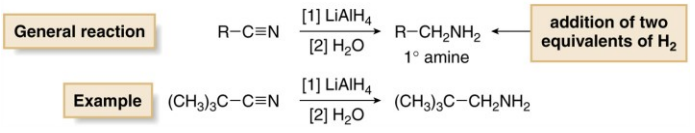
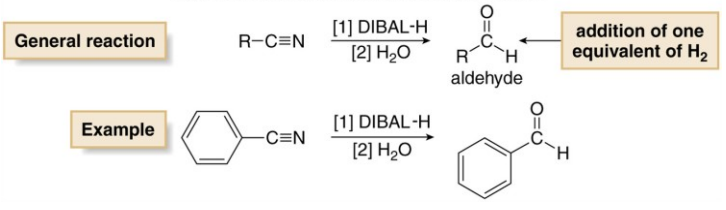


Reduction of Nitriles

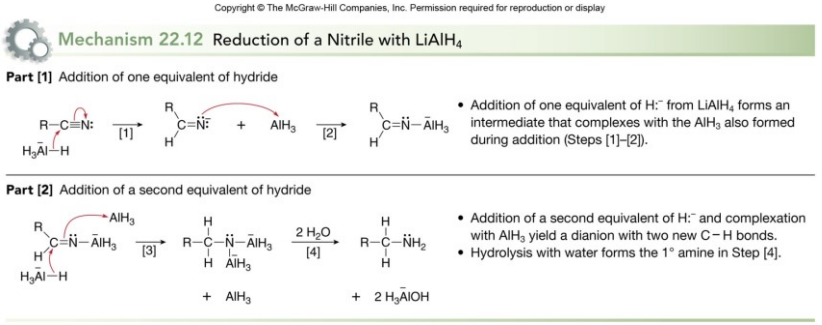
- **Treatment of a nitrile with $LiAlH_4$ followed by H_2O adds two equivalents of H_2 across the triple bond, forming a 1° amine.**



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

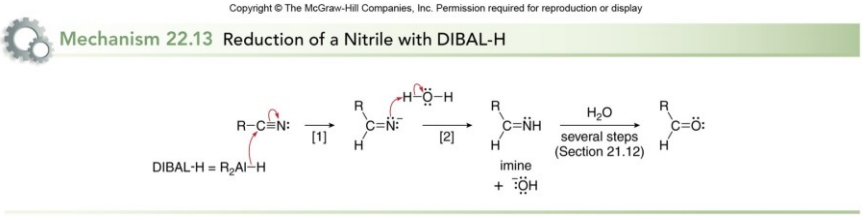


Nitrile Reduction Mechanisms



- **With $LiAlH_4$, two equivalents of hydride are sequentially added to yield a dianion which is then protonated with H_2O to form an amine.**

Nitrile Reduction Mechanisms

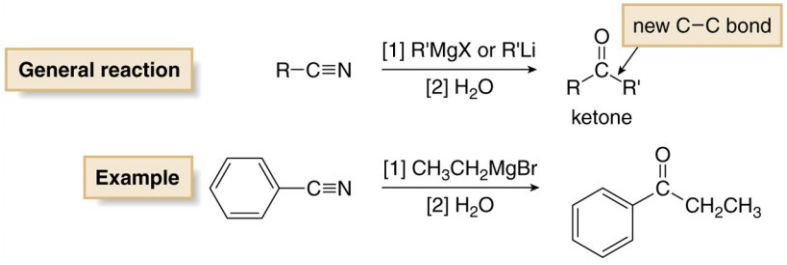


- **With DIBAL-H, nucleophilic addition of one equivalent of hydride forms an anion which is protonated with water to generate an imine.**

- **The imine is then hydrolyzed in water to form an aldehyde.**

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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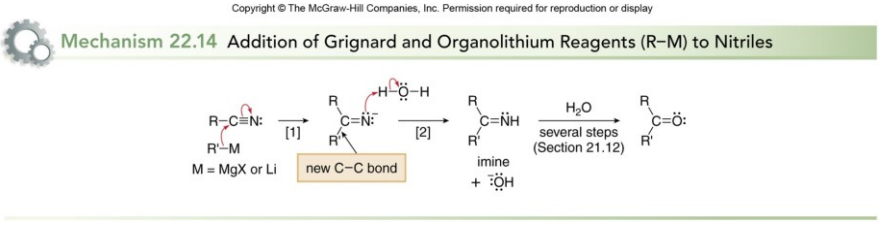
Organometallic Reduction Mechanism



- **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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