21 Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions

Organic KNOWLEDGE TOOLS

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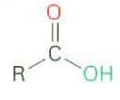
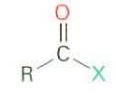
Online homework for this chapter may be assigned in *Organic OWL*.

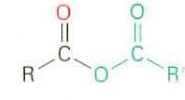
Closely related to the carboxylic acids and nitriles discussed in the previous chapter are the **carboxylic acid derivatives**, compounds in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in a substitution reaction. Many kinds of acid derivatives are known, but we'll be concerned primarily with four of the more common ones: **acid halides**, **acid anhydrides**, **esters**, and **amides**. Esters and amides are common in both laboratory and biological chemistry, while acid halides and acid anhydrides are used only in the laboratory. **Thioesters** and **acyl phosphates** are encountered primarily in biological chemistry. Note the structural similarity between acid anhydrides and acyl phosphates.



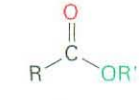
Carboxylic acid



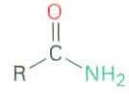
Acid halide (X = Cl, Br)



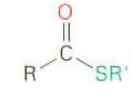
Acid anhydride



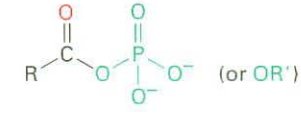
Ester



Amide



Thioester



Acyl phosphate

The chemistry of all acid derivatives is similar and is dominated by a single reaction—the nucleophilic acyl substitution reaction that we saw briefly in *A Preview of Carbonyl Compounds*.

Sean Duggan

WHY THIS CHAPTER?

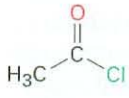
Carboxylic acid derivatives are among the most widespread of all molecules, both in laboratory chemistry and in biological pathways. Thus, a study of them and their primary reaction—nucleophilic acyl substitution—is fundamental to understanding organic chemistry. We'll begin this chapter by first learning about carboxylic acid derivatives, and then we'll explore the chemistry of acyl substitution reactions.

21.1 Naming Carboxylic Acid Derivatives

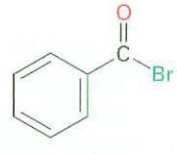
Acid Halides, RCOX

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to draw structures of acyl derivatives based on their IUPAC names.**

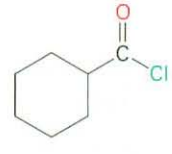
Acid halides are named by identifying first the acyl group and then the halide. The acyl group name is derived from the carboxylic acid name by replacing the *-ic acid* ending with *-yl* or the *-carboxylic acid* ending with *-carbonyl*, as described previously in Section 20.1 and shown in Table 20.1 on page 753. For example:



Acetyl chloride



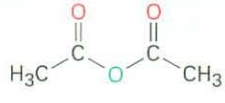
Benzoyl bromide



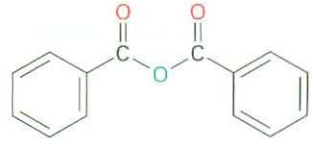
Cyclohexanecarbonyl chloride

Acid Anhydrides, RCO_2COR'

Symmetrical anhydrides of unsubstituted monocarboxylic acids and cyclic anhydrides of dicarboxylic acids are named by replacing the word *acid* with *anhydride*.



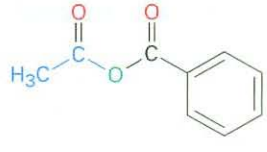
Acetic anhydride



Benzoic anhydride

Succinic anhydride

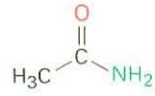
Unsymmetrical anhydrides—those prepared from two different carboxylic acids—are named by citing the two acids alphabetically and then adding *anhydride*.



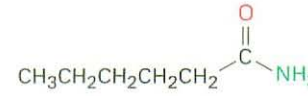
Acetic benzoic anhydride

Amides, $RCONH_2$

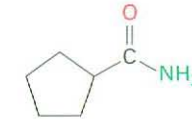
Amides with an unsubstituted $-NH_2$ group are named by replacing the *-oic acid* or *-ic acid* ending with *-amide,* or by replacing the *-carboxylic acid* ending with *-carboxamide.*



Acetamide

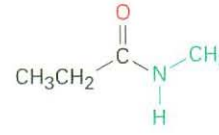


Hexanamide

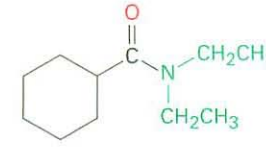


Cyclopentane-carboxamide

If the nitrogen atom is further substituted, the compound is named by first identifying the substituent groups and then the parent amide. The substituents are preceded by the letter *N* to identify them as being directly attached to nitrogen.



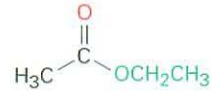
***N*-Methylpropanamide**



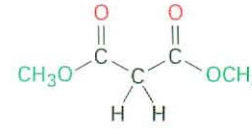
***N,N*-Diethylcyclohexanecarboxamide**

Esters, RCO_2R'

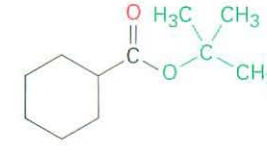
Esters are named by first identifying the alkyl group attached to oxygen and then the carboxylic acid, with the *-ic acid* ending replaced by *-ate.*



Ethyl acetate



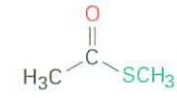
Dimethyl malonate



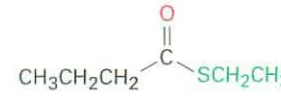
***tert*-Butyl cyclohexane-carboxylate**

Thioesters, $RCOSR'$

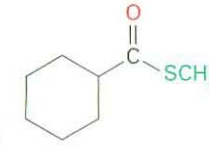
Thioesters are named like the corresponding esters. If the related ester has a common name, the prefix *thio-* is added to the name of the carboxylate; acetate becomes thioacetate, for instance. If the related ester has a systematic name, the *-oate* or *-carboxylate* ending is replaced by *-thioate* or *-carbothioate;* butanoate becomes butanethioate and cyclohexanecarboxylate becomes cyclohexane-carbothioate, for instance.



Methyl thioacetate



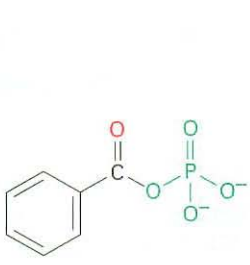
Ethyl butanethioate



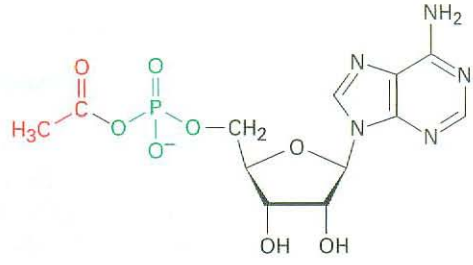
Methyl cyclohexane-carbothioate

Acyl Phosphates, $RCO_2PO_3^{2-}$ and $RCO_2PO_3R'^-$

Acyl phosphates are named by citing the acyl group and adding the word *phosphate*. If an alkyl group is attached to one of the phosphate oxygens, it is identified after the name of the acyl group. In biological chemistry, acyl adenosyl phosphates are particularly common.



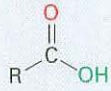
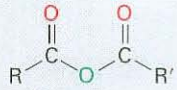
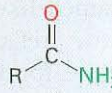
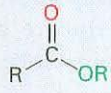
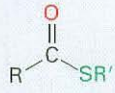
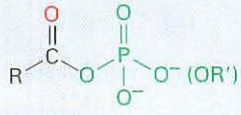
Benzoyl phosphate



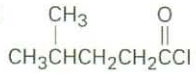
Acetyl adenosyl phosphate

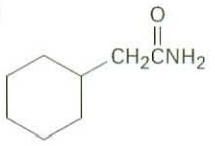
A summary of nomenclature rules for carboxylic acid derivatives is given in Table 21.1.

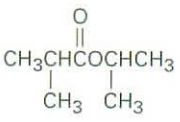
Table 21.1 Nomenclature of Carboxylic Acid Derivatives

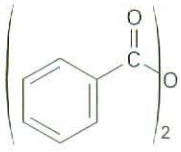
Functional group	Structure	Name ending
Carboxylic acid		*-ic acid (-carboxylic acid)*
Acid halide		*-oyl halide (-carbonyl halide)*
Acid anhydride		*anhydride*
Amide		*-amide (-carboxamide)*
Ester		*-ate (-carboxylate)*
Thioester		*-thioate (-carbothioate)*
Acyl phosphate		*-yl phosphate*

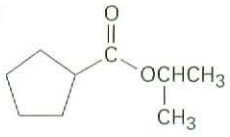
Problem 21.1 Give IUPAC names for the following substances:

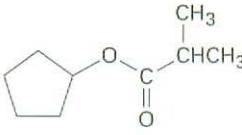
(a) 

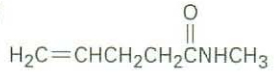
(b) 

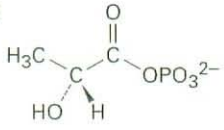
(c) 

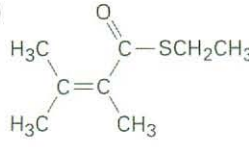
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

Problem 21.2 Draw structures corresponding to the following names:

(a) Phenyl benzoate
(b) *N*-Ethyl-*N*-methylbutanamide
(c) 2,4-Dimethylpentanoyl chloride
(d) Methyl 1-methylcyclohexanecarboxylate
(e) Ethyl 3-oxopentanoate
(f) Methyl *p*-bromobenzenethioate
(g) Formic propanoic anhydride
(h) *cis*-2-Methylcyclopentanecarbonyl bromide

21.2 Nucleophilic Acyl Substitution Reactions

ThomsonNOW Click *Organic Interactive* to **learn to predict the course of an acyl transfer reaction by examining reactants and leaving groups.**

The addition of a nucleophile to a polar C=O bond is the key step in three of the four major carbonyl-group reactions. We saw in Chapter 19 that when a nucleophile adds to an aldehyde or ketone, the initially formed tetrahedral intermediate either can be protonated to yield an alcohol or can eliminate the carbonyl oxygen, leading to a new C=Nu bond. When a nucleophile adds to a carboxylic acid derivative, however, a different reaction course is followed. The initially formed tetrahedral intermediate eliminates one of the two substituents originally bonded to the carbonyl carbon, leading to a net **nucleophilic acyl substitution reaction** (Figure 21.1).

The difference in behavior between aldehydes/ketones and carboxylic acid derivatives is a consequence of structure. Carboxylic acid derivatives have an acyl carbon bonded to a group −Y that can leave as a stable anion. As soon as the tetrahedral intermediate is formed, the leaving group is expelled to generate a new carbonyl compound. Aldehydes and ketones have no such leaving group, however, and therefore don't undergo substitution.

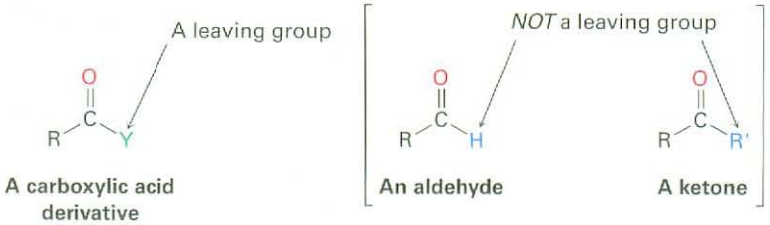
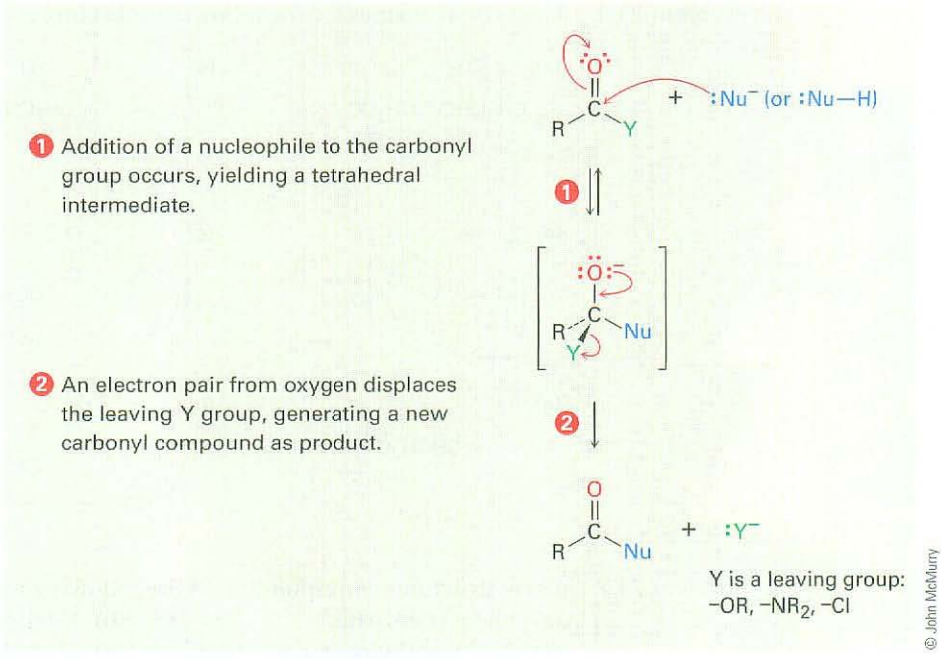


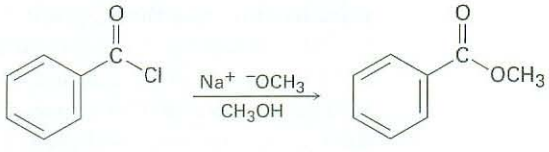
Figure 21.1 MECHANISM: General mechanism of a nucleophilic acyl substitution reaction.

ThomsonNOW Click *Organic Process* to **view animations showing chemistry of the acyl transfer process.**



The net effect of the addition/elimination sequence is a substitution of the nucleophile for the −Y group originally bonded to the acyl carbon. Thus, the overall reaction is superficially similar to the kind of nucleophilic substitution that occurs during an S_N2 reaction (Section 11.3), but the *mechanisms* of the two reactions are completely different. An S_N2 reaction occurs in a single step by backside displacement of the leaving group; a nucleophilic acyl substitution takes place in two steps and involves a tetrahedral intermediate.

Problem 21.3 Show the mechanism of the following nucleophilic acyl substitution reaction, using curved arrows to indicate the electron flow in each step:

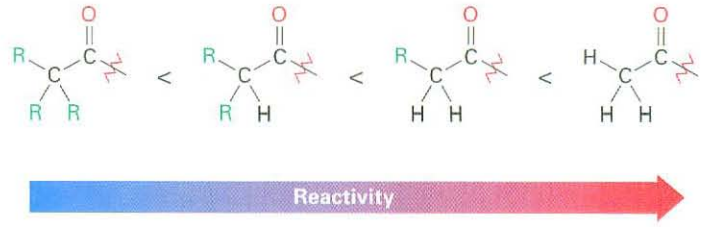


Relative Reactivity of Carboxylic Acid Derivatives

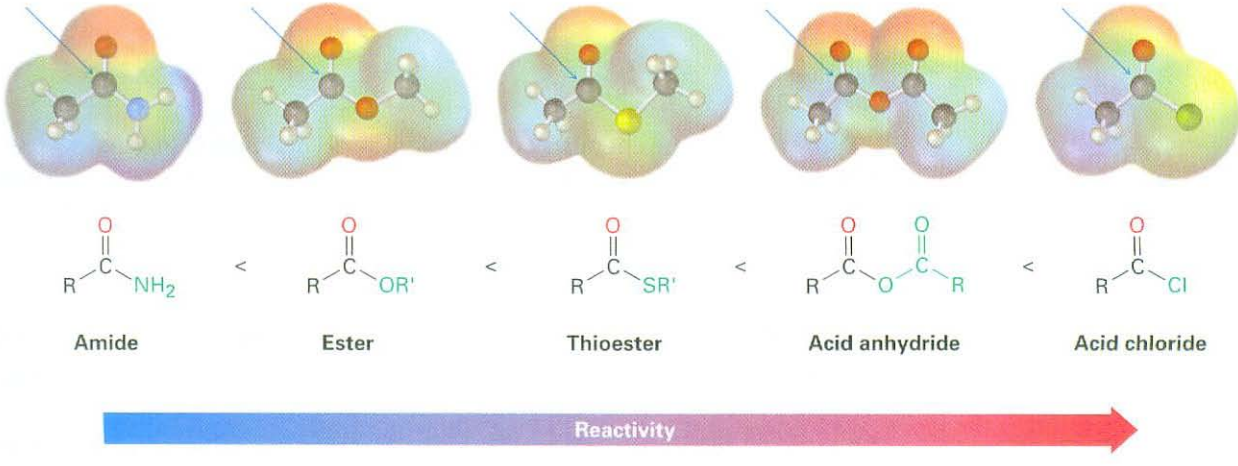
Both the initial addition step and the subsequent elimination step can affect the overall rate of a nucleophilic acyl substitution reaction, but the addition step is generally the rate-limiting one. Thus, any factor that makes the carbonyl group more reactive toward nucleophiles favors the substitution process.

Steric and electronic factors are both important in determining reactivity. Sterically, we find within a series of similar acid derivatives that unhindered,

accessible carbonyl groups react with nucleophiles more readily than do sterically hindered groups. The reactivity order is



Electronically, we find that strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon, whereas amides are the least reactive. Although subtle, electrostatic potential maps of various carboxylic acid derivatives indicate the differences by the relative blueness on the C=O carbons. Acyl phosphates are hard to place on this scale because they are not used in the laboratory, but in biological systems they appear to be somewhat more reactive than thioesters.



The way in which various substituents affect the polarization of a carbonyl group is similar to the way they affect the reactivity of an aromatic ring toward electrophilic substitution (Section 16.5). A chlorine substituent, for example, inductively *withdraws* electrons from an acyl group in the same way that it withdraws electrons from and thus deactivates an aromatic ring. Similarly, amino, methoxyl, and methylthio substituents *donate* electrons to acyl groups by resonance in the same way that they donate electrons to and thus activate aromatic rings.

As a consequence of these reactivity differences, it's usually possible to convert a more reactive acid derivative into a less reactive one. Acid chlorides, for instance, can be directly converted into anhydrides, thioesters, esters, and amides, but amides can't be directly converted into esters, thioesters, anhydrides, or acid chlorides. Remembering the reactivity order is therefore a way to keep track of a large number of reactions (Figure 21.2). Another consequence, as noted previously, is that only acyl phosphates, thioesters, esters, and amides are

commonly found in nature. Acid halides and acid anhydrides react with water so rapidly that they can't exist for long in living organisms.

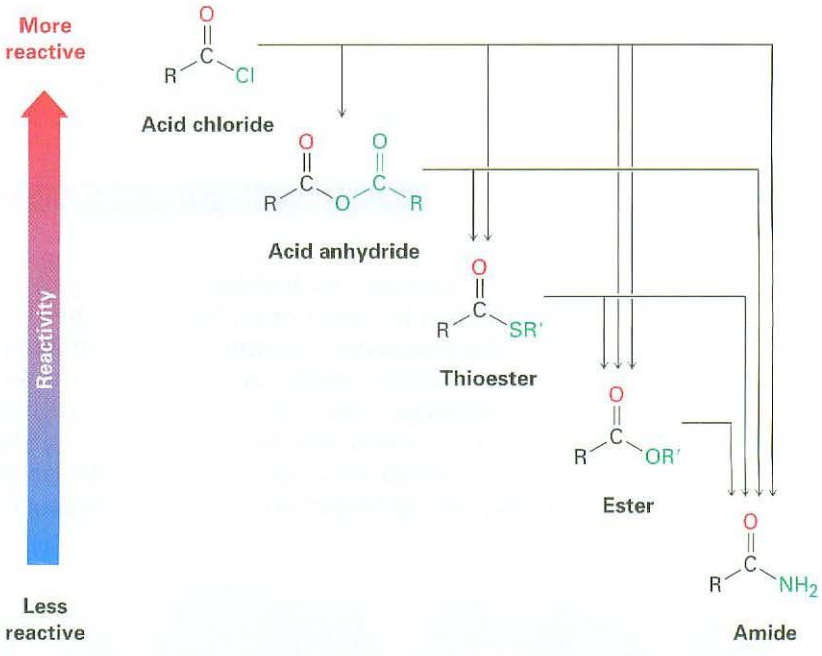


Figure 21.2 Interconversions of carboxylic acid derivatives. A more reactive acid derivative can be converted into a less reactive one, but not vice versa.

In studying the chemistry of carboxylic acid derivatives in the next few sections, we'll be concerned largely with the reactions of just a few nucleophiles and will see that the same kinds of reactions keep occurring (Figure 21.3).

- **Hydrolysis** — Reaction with water to yield a carboxylic acid
- **Alcoholysis** — Reaction with an alcohol to yield an ester
- **Aminolysis** — Reaction with ammonia or an amine to yield an amide
- **Reduction** — Reaction with a hydride reducing agent to yield an aldehyde or an alcohol
- **Grignard reaction** — Reaction with an organometallic reagent to yield a ketone or an alcohol

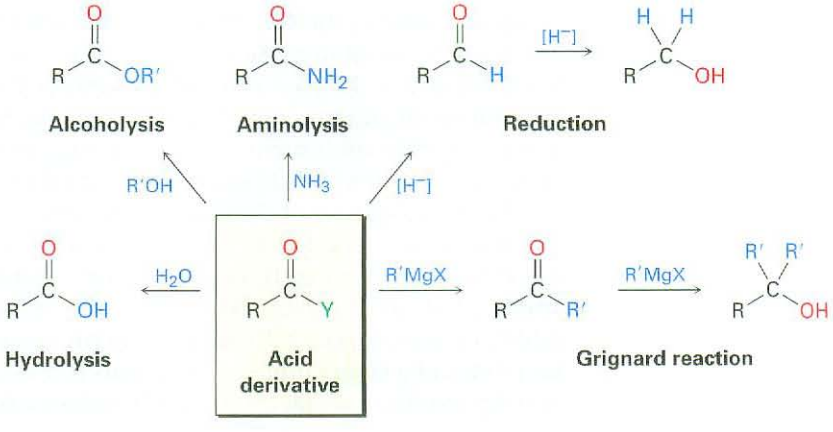
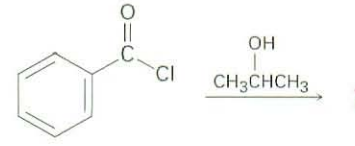


Figure 21.3 Some general reactions of carboxylic acid derivatives.

WORKED EXAMPLE 21.1 ***Predicting the Product of a Nucleophilic Acyl Substitution Reaction***

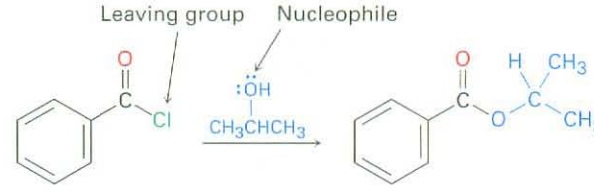
Predict the product of the following nucleophilic acyl substitution reaction of benzoyl chloride with 2-propanol:



Benzoyl chloride

Strategy A nucleophilic acyl substitution reaction involves the substitution of a nucleophile for a leaving group in a carboxylic acid derivative. Identify the leaving group (Cl^- in the case of an acid chloride) and the nucleophile (an alcohol in this case), and replace one by the other. The product is isopropyl benzoate.

Solution



Benzoyl chloride Isopropyl benzoate

Problem 21.4 Rank the compounds in each of the following sets in order of their expected reactivity toward nucleophilic acyl substitution:

(a) CH_3CCl, CH_3COCH_3, CH_3CNH_2

(b) CH_3COCH_3, $CH_3COCH_2CCl_3$, $CH_3COCH(CF_3)_2$

Problem 21.5 Predict the products of the following nucleophilic acyl substitution reactions:

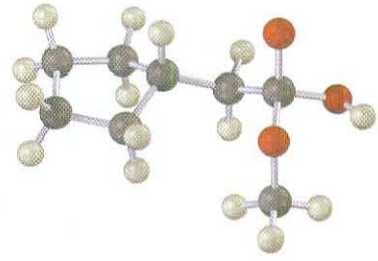
(a) H_3C–C(=O)–OCH_3 $\xrightarrow[H_2O]{NaOH}$?

(b) H_3C–C(=O)–Cl $\xrightarrow{NH_3}$?

(c) H_3C–C(=O)–O–C(=O)–CH_3 $\xrightarrow[CH_3OH]{Na^+ {}^-OCH_3}$?

(d) H_3C–C(=O)–SCH_3 $\xrightarrow{CH_3NH_2}$?

Problem 21.6 The following structure represents a tetrahedral alkoxide ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product.

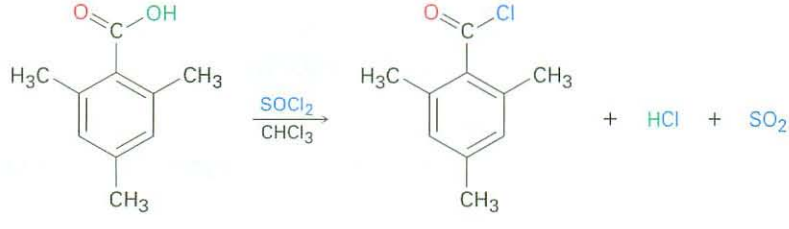


21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

The direct nucleophilic acyl substitution of a carboxylic acid is difficult in the laboratory because —OH is a poor leaving group (Section 11.3). Thus, it's usually necessary to enhance the reactivity of the acid, either by using a strong acid catalyst to protonate the carboxyl and make it a better acceptor or by converting the —OH into a better leaving group. Under the right circumstances, however, acid chlorides, anhydrides, esters, and amides can all be prepared from carboxylic acids.

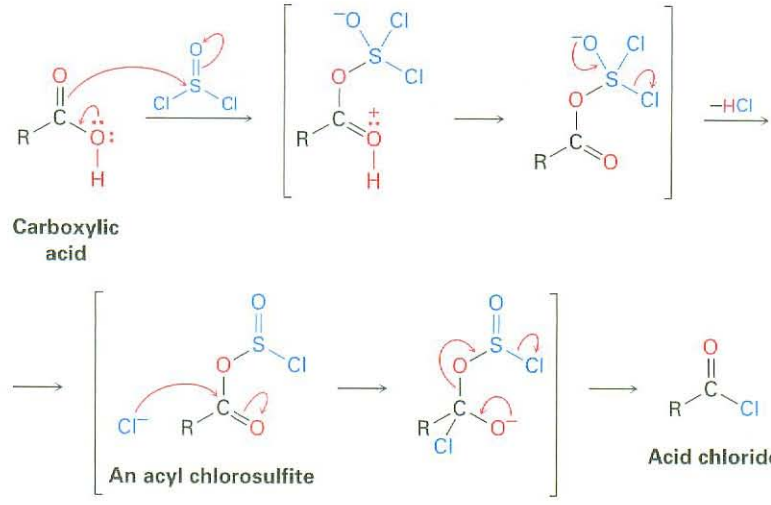
Conversion of Carboxylic Acids into Acid Chlorides

Carboxylic acids are converted into acid chlorides by treatment with thionyl chloride, $SOCl_2$.



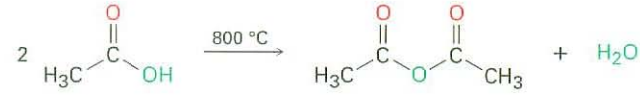
2,4,6-Trimethylbenzoic acid **2,4,6-Trimethylbenzoyl chloride (90%)**

The reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into a chlorosulfite intermediate, thereby replacing the —OH of the acid with a much better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion. You might recall from Section 17.6 that an analogous chlorosulfite is involved in reaction of an alcohol with $SOCl_2$ to yield an alkyl chloride.



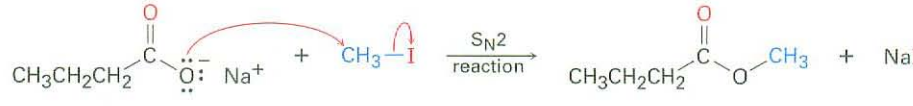
Conversion of Carboxylic Acids into Acid Anhydrides

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



Conversion of Carboxylic Acids into Esters

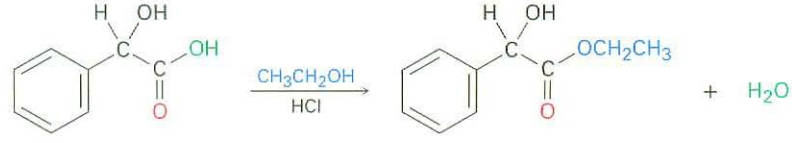
Perhaps the most useful reaction of carboxylic acids is their conversion into esters. There are many methods for accomplishing the transformation, including the S_N2 reaction of a carboxylate anion with a primary alkyl halide that we saw in Section 11.3.



Emil Fischer

Emil Fischer (1852–1919) was perhaps the finest organic chemist who has ever lived. Born in Euskirchen, Germany, he received his Ph.D. in 1874 at the University of Strasbourg with Adolf von Baeyer. He was professor of chemistry at the universities of Erlangen, Würzburg, and Berlin, where he carried out the research on sugars and purines that led to his receipt of the 1902 Nobel Prize in chemistry. During World War I, Fischer organized the German production of chemicals for the war effort, but the death of two sons in the war led to his depression and suicide.

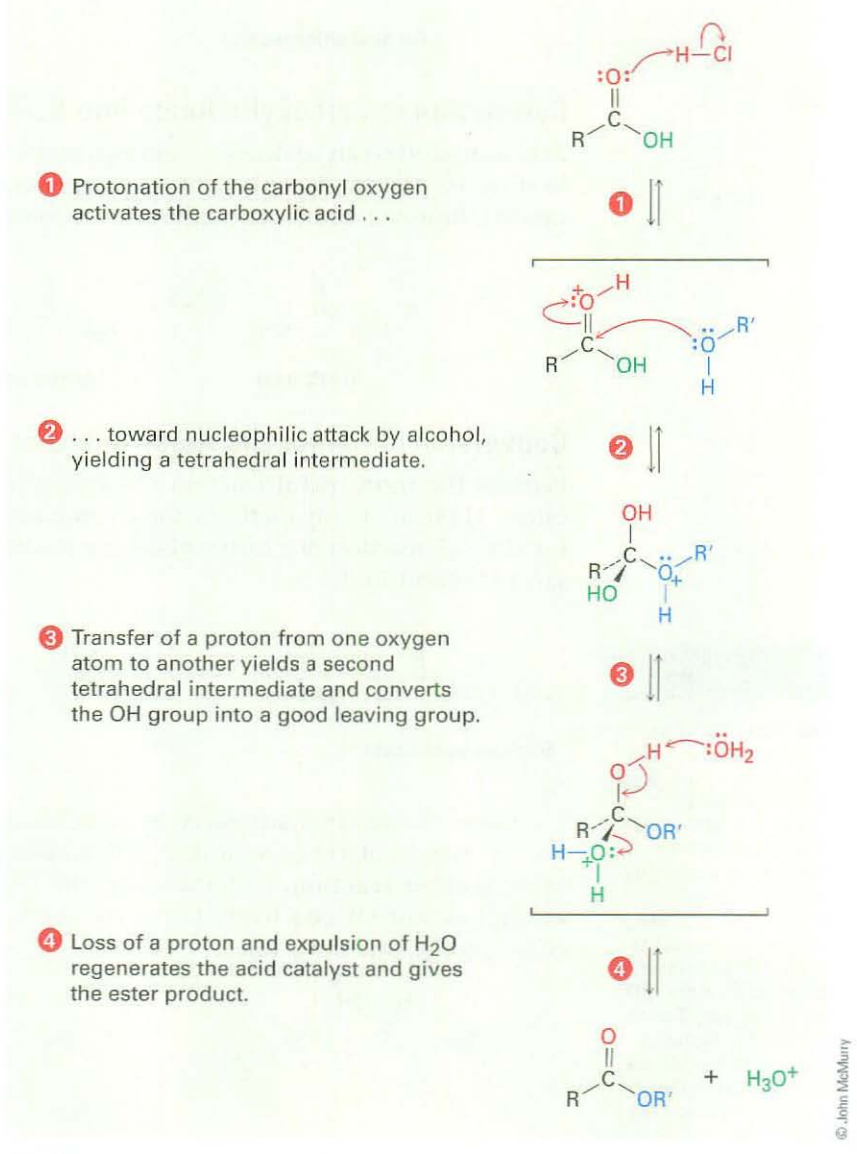
Esters can also be synthesized by an acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol, a process called the **Fischer esterification reaction**. Unfortunately, the need to use an excess of a liquid alcohol as solvent effectively limits the method to the synthesis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



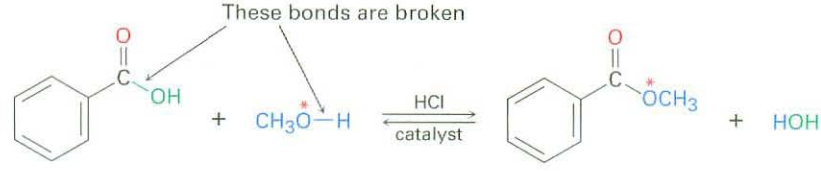
The mechanism of the Fischer esterification reaction is shown in Figure 21.4. Carboxylic acids are not reactive enough to undergo nucleophilic addition directly, but their reactivity is greatly enhanced in the presence of a strong acid such as HCl or H_2SO_4. The mineral acid protonates the carbonyl-group oxygen atom, thereby giving the carboxylic acid a positive charge and rendering it much more reactive. Subsequent loss of water from the tetrahedral intermediate yields the ester product.

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

Figure 21.4 MECHANISM: Mechanism of Fischer esterification. The reaction is an acid-catalyzed, nucleophilic acyl substitution of a carboxylic acid.

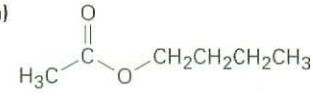


Evidence in support of the mechanism shown in Figure 21.4 comes from isotope-labeling experiments. When ^{18}O-labeled methanol reacts with benzoic acid, the methyl benzoate produced is found to be ^{18}O-labeled but the water produced is unlabeled. Thus, it is the C–OH bond of the carboxylic acid that is broken during the reaction rather than the CO–H bond and the RO–H bond of the alcohol that is broken rather than the R–OH bond.

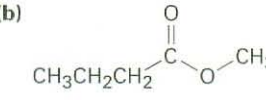


Problem 21.7 How might you prepare the following esters from the corresponding acids?

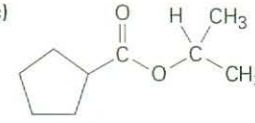
(a)



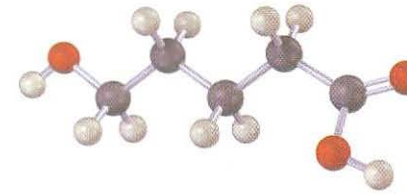
(b)



(c)



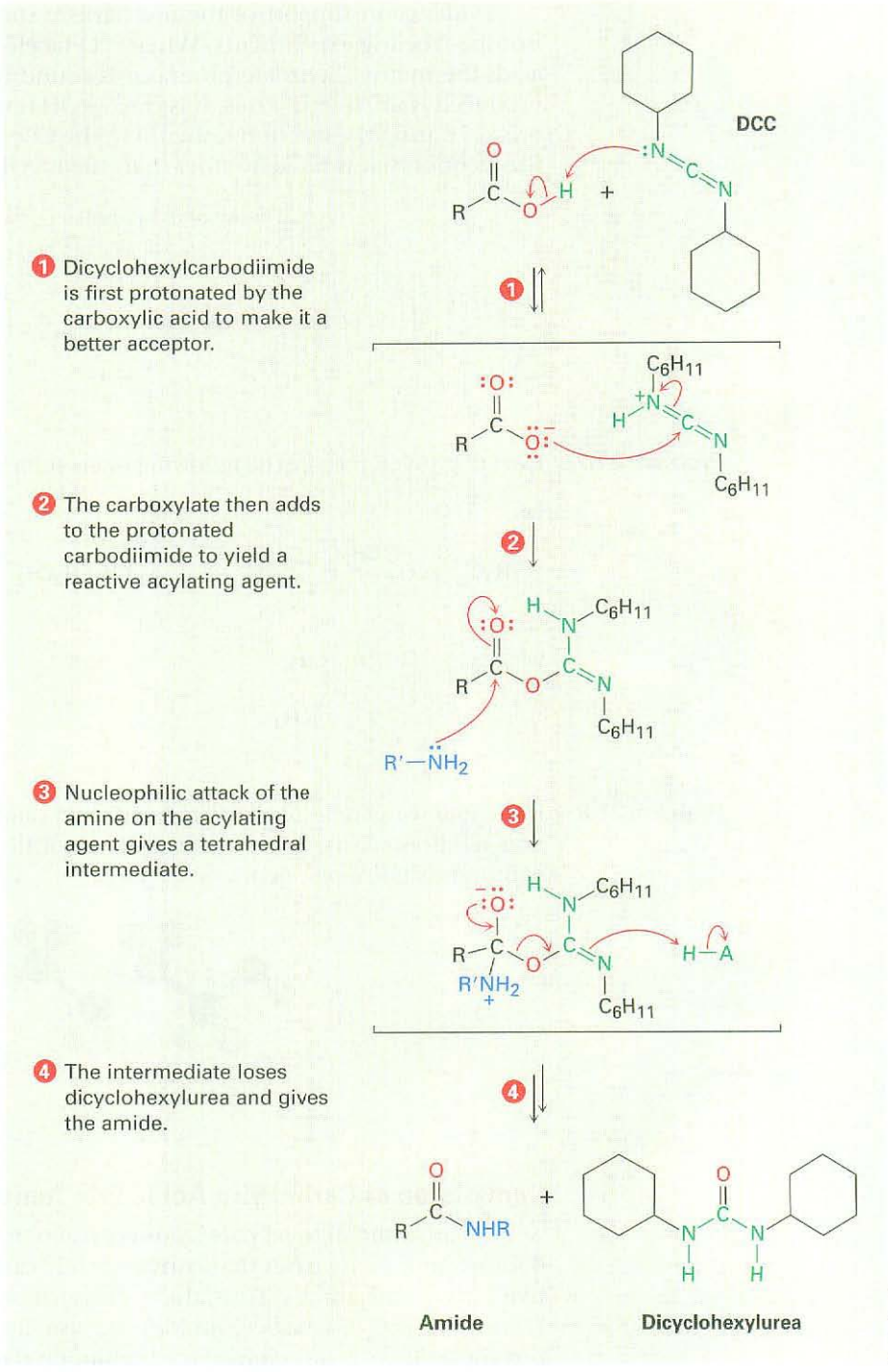
Problem 21.8 If the following molecule is treated with acid catalyst, an intramolecular esterification reaction occurs. What is the structure of the product? (*Intramolecular* means within the same molecule.)



Conversion of Carboxylic Acids into Amides

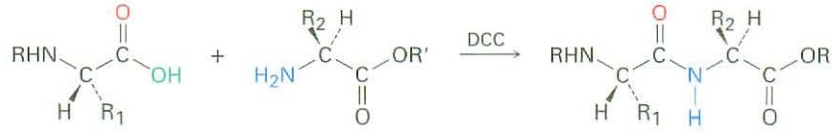
Amides are difficult to prepare by direct reaction of carboxylic acids with amines because amines are bases that convert acidic carboxyl groups into their unreactive carboxylate anions. Thus, the –OH must be replaced by a better, nonacidic leaving group. In practice, amides are usually prepared by treating the carboxylic acid with dicyclohexylcarbodiimide (DCC) to activate it, followed by addition of the amine. The acid first adds to a C=N bond of DCC, and nucleophilic acyl substitution by amine then ensues, as shown in Figure 21.5. Alternatively, and depending on the reaction solvent, the reactive acyl intermediate might also react with a second equivalent of carboxylate ion to generate an acid anhydride that then reacts with the amine.

Figure 21.5 MECHANISM: Mechanism of amide formation by reaction of a carboxylic acid and an amine with dicyclohexylcarbodiimide (DCC).



We'll see in Section 26.7 that this DCC-induced method of amide formation is the key step in the laboratory synthesis of small proteins, or *peptides*. For instance, when one amino acid with its NH_2 rendered unreactive and a second

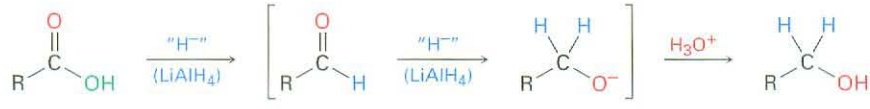
amino acid with its $-CO_2H$ rendered unreactive are treated with DCC, a dipeptide is formed.



Amino acid 1 **Amino acid 2** **A dipeptide**

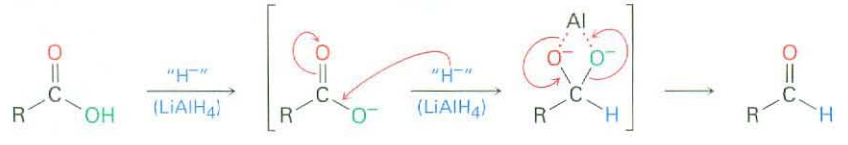
Conversion of Carboxylic Acids into Alcohols

We said in Section 17.4 that carboxylic acids are reduced by $LiAlH_4$ to give primary alcohols, but we deferred a discussion of the reaction mechanism at that time. In fact, the reduction is a nucleophilic acyl substitution reaction in which $-H$ replaces $-OH$ to give an aldehyde, which is further reduced to a primary alcohol by nucleophilic addition. The aldehyde intermediate is much more reactive than the starting acid, so it reacts immediately and is not isolated.



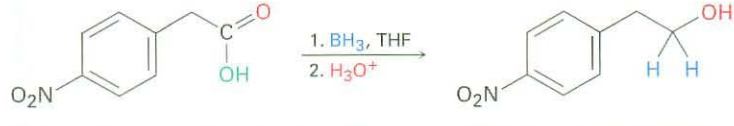
A carboxylic acid **An aldehyde (not isolated)** **An alkoxide ion** **A 1° alcohol**

Because hydride ion is a base as well as a nucleophile, the actual nucleophilic acyl substitution step takes place on the carboxylate ion rather than on the free carboxylic acid and gives a high-energy *dianion* intermediate. In this intermediate, the two oxygens are undoubtedly complexed to a Lewis acidic aluminum species. Thus, the reaction is relatively difficult, and acid reductions require higher temperatures and extended reaction times.



A carboxylic acid **A carboxylate** **A dianion** **An aldehyde**

Alternatively, borane in tetrahydrofuran (BH_3/THF) is a useful reagent for reducing carboxylic acids to primary alcohols. Reaction of an acid with BH_3/THF occurs rapidly at room temperature, and the procedure is often preferred to reduction with $LiAlH_4$ because of its relative ease and safety. Borane reacts with carboxylic acids faster than with any other functional group, thereby allowing selective transformations such as that shown below on *p*-nitrophenylacetic acid. If the reduction of *p*-nitrophenylacetic acid were done with $LiAlH_4$, both nitro and carboxyl groups would be reduced.



***p*-Nitrophenylacetic acid** **2-(*p*-Nitrophenyl)ethanol (94%)**

Biological Conversions of Carboxylic Acids

The direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur in biological chemistry. As in the laboratory, *the* acid must first be activated. This activation is often accomplished in living organisms by reaction of the acid with ATP to give an acyl adenosyl phosphate, or *acyl adenylate*. In the biosynthesis of fats, for example, a long-chain carboxylic acid reacts with ATP to give an acyl adenylate, which then reacts by subsequent nucleophilic acyl substitution of a thiol group in coenzyme A to give the corresponding acyl CoA (Figure 21.6).

Note that the first step in Figure 21.6—reaction of the carboxylate with ATP to give an acyl adenylate—is itself a nucleophilic acyl substitution on *phosphorus*. The carboxylate first adds to a P=O bond, giving a five-coordinate phosphorus intermediate that expels diphosphate ion as leaving group.

21.4 Chemistry of Acid Halides

Preparation of Acid Halides

Acid chlorides are prepared from carboxylic acids by reaction with thionyl chloride ($SOCl_2$), as we saw in the previous section. Similar reaction of a carboxylic acid with phosphorus tribromide (PBr_3) yields the acid bromide.

Reactions of Acid Halides

Acid halides are among the most reactive of carboxylic acid derivatives and can be converted into many other kinds of compounds by nucleophilic acyl substitution mechanisms. The halogen can be replaced by −OH to yield an acid, by −OCOR to yield an anhydride, by −OR to yield an ester, or by $-NH_2$ to yield an amide. In addition, the reduction of an acid halide yields a primary alcohol, and reaction with a Grignard reagent yields a tertiary alcohol. Although the reactions we'll be discussing in this section are illustrated only for acid chlorides, similar processes take place with other acid halides.

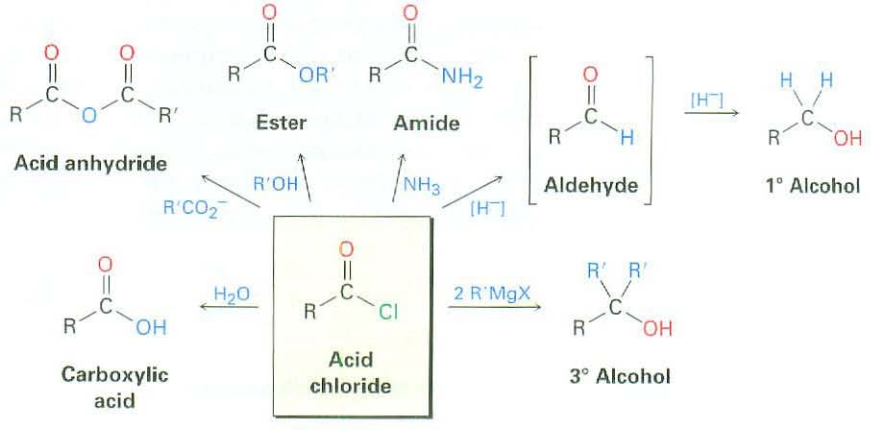
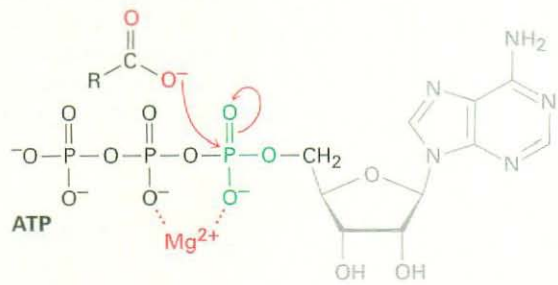
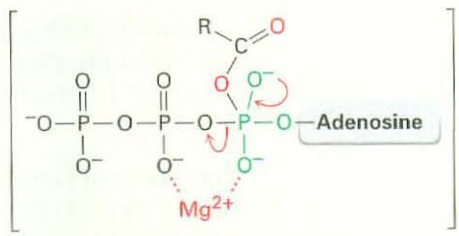


Figure 21.6 MECHANISM: In fatty-acid biosynthesis, a carboxylic acid is activated by reaction with ATP to give an acyl adenylate, which undergoes nucleophilic acyl substitution with the –SH group on coenzyme A. (ATP = adenosine triphosphate; AMP = adenosine monophosphate.)

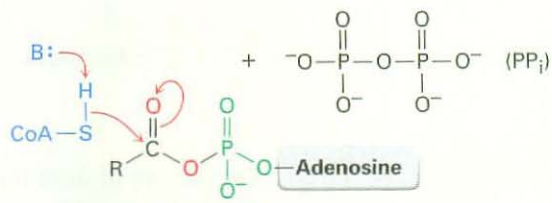


1. ATP is activated by coordination to magnesium ion, and nucleophilic addition of a fatty acid carboxylate to phosphorus then yields a pentacoordinate intermediate . . .



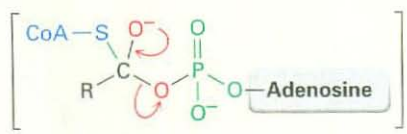
Pentacoordinate intermediate

2. . . . which expels diphosphate ion (PP_i) as leaving group and gives an acyl adenosyl phosphate in a process analogous to a nucleophilic acyl substitution reaction.

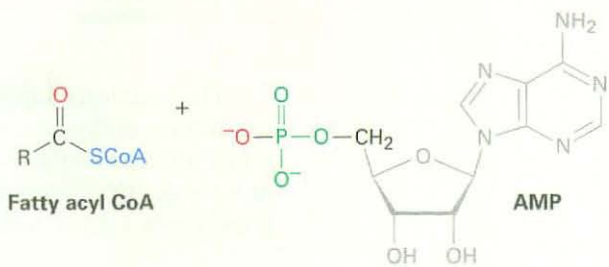


Acetyl adenosyl phosphate (acyl adenylate)

3. The –SH group of coenzyme A adds to the acyl adenosyl phosphate, giving a tetrahedral alkoxide intermediate . . .

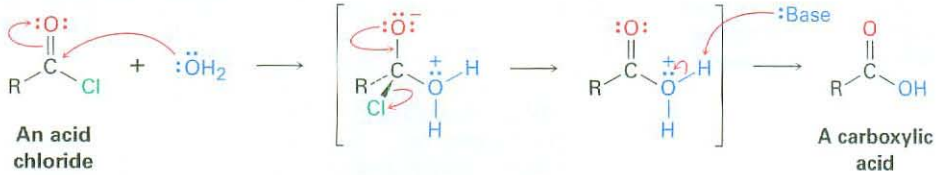


4. . . . which expels adenosine monophosphate (AMP) as leaving group and yields the fatty acyl CoA.



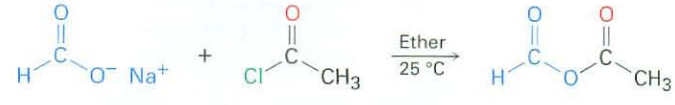
Fatty acyl CoA AMP

Conversion of Acid Halides into Acids: Hydrolysis Acid chlorides react with water to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution process and is initiated by attack of water on the acid chloride carbonyl group. The tetrahedral intermediate undergoes elimination of Cl^- and loss of H^+ to give the product carboxylic acid plus HCl.

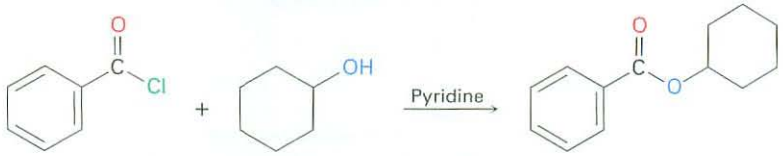


Because HCl is generated during the hydrolysis, the reaction is often carried out in the presence of a base such as pyridine or NaOH to remove the HCl and prevent it from causing side reactions.

Conversion of Acid Halides into Anhydrides Nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion gives an acid anhydride. Both symmetrical and unsymmetrical acid anhydrides can be prepared in this way.

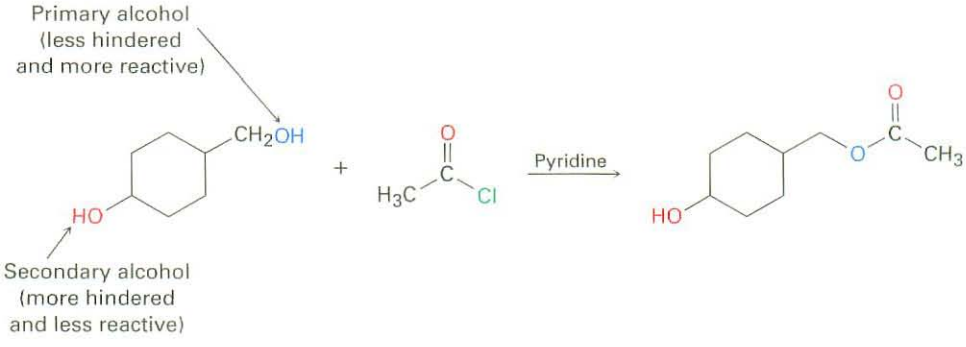


Conversion of Acid Halides into Esters: Alcoholysis Acid chlorides react with alcohols to yield esters in a process analogous to their reaction with water to yield acids. In fact, this reaction is probably the most common method for preparing esters in the laboratory. As with hydrolysis, alcoholysis reactions are usually carried out in the presence of pyridine or NaOH to react with the HCl formed.



The reaction of an alcohol with an acid chloride is strongly affected by steric hindrance. Bulky groups on either partner slow down the reaction considerably, resulting in a reactivity order among alcohols of primary > secondary > tertiary. As a result, it's often possible to esterify an unhindered alcohol selectively in the presence of a more hindered one. This can be important in complex syntheses

in which it's sometimes necessary to distinguish between similar functional groups. For example,



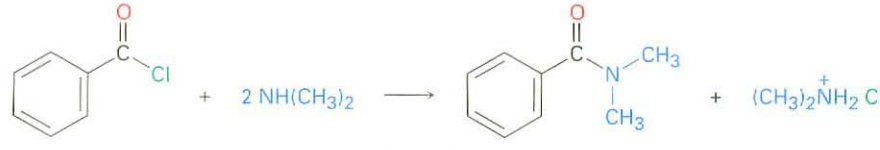
Problem 21.9 How might you prepare the following esters using a nucleophilic acyl substitution reaction of an acid chloride?

(a) $CH_3CH_2CO_2CH_3$ (b) $CH_3CO_2CH_2CH_3$ (c) Ethyl benzoate

Problem 21.10 Which method would you choose if you wanted to prepare cyclohexyl benzoate—Fischer esterification or reaction of an acid chloride with an alcohol? Explain.

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

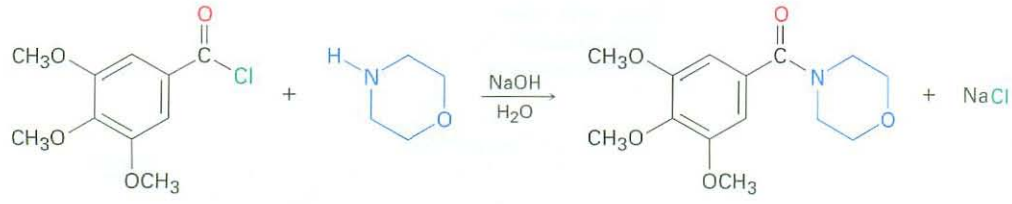
2-Methylpropanoyl chloride **2-Methylpropanamide (83%)**



Benzoyl chloride ***N,N*-Dimethylbenzamide (92%)**

Because HCl is formed during the reaction, two equivalents of the amine must be used. One equivalent reacts with the acid chloride, and one equivalent reacts with the HCl by-product to form an ammonium chloride salt. If, however, the amine component is valuable, amide synthesis is often carried out using 1 equivalent of the amine plus 1 equivalent of an inexpensive base such as NaOH. For example, the sedative trimetozine is prepared commercially by

reaction of 3,4,5-trimethoxybenzoyl chloride with the amine morpholine in the presence of one equivalent of NaOH.



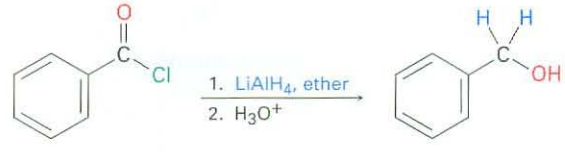
3,4,5-Trimethoxybenzoyl chloride **Morpholine** **Trimetozine (an amide)**

Problem 21.11 Write the mechanism of the reaction just shown between 3,4,5-trimethoxybenzoyl chloride and morpholine to form trimetozine. Use curved arrows to show the electron flow in each step.

Problem 21.12 How could you prepare the following amides using an acid chloride and an amine or ammonia?

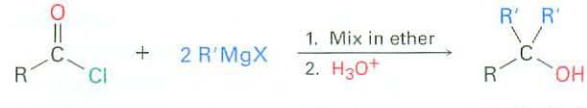
(a) $CH_3CH_2CONHCH_3$ (b) *N,N*-Diethylbenzamide (c) Propanamide

Conversion of Acid Chlorides into Alcohols: Reduction Acid chlorides are reduced by $LiAlH_4$ to yield primary alcohols. The reaction is of little practical value, however, because the parent carboxylic acids are generally more readily available and can themselves be reduced by $LiAlH_4$ to yield alcohols. Reduction occurs via a typical nucleophilic acyl substitution mechanism in which a hydride ion ($H:^-$) adds to the carbonyl group, yielding a tetrahedral intermediate that expels Cl^-. The net effect is a substitution of $-Cl$ by $-H$ to yield an aldehyde, which is then immediately reduced by $LiAlH_4$ in a second step to yield the primary alcohol.



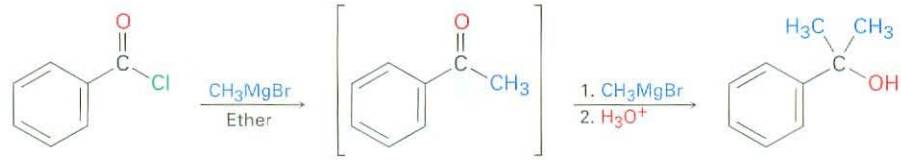
Benzoyl chloride **Benzyl alcohol (96%)**

Reaction of Acid Chlorides with Organometallic Reagents Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same.



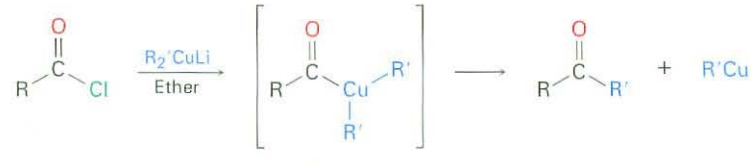
Acid chloride **3° Alcohol**

The mechanism of this Grignard reaction is similar to that of $LiAlH_4$ reduction. The first equivalent of Grignard reagent adds to the acid chloride, loss of Cl^- from the tetrahedral intermediate yields a ketone, and a second equivalent of Grignard reagent immediately adds to the ketone to produce an alcohol.



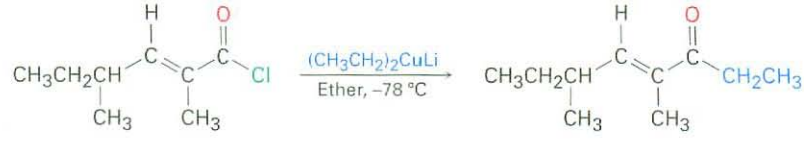
Benzoyl chloride — **Acetophenone** *(NOT isolated)* — **2-Phenyl-2-propanol** (92%)

The ketone intermediate can't usually be isolated because addition of the second equivalent of organomagnesium reagent occurs too rapidly. A ketone *can*, however, be isolated from the reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $Li^+ R_2Cu^-$. The reaction occurs by initial nucleophilic acyl substitution on the acid chloride by the diorganocopper anion to yield an acyl diorganocopper intermediate, followed by loss of R'Cu and formation of the ketone.



An acid chloride — **An acyl diorganocopper** — **A ketone**

The reaction is generally carried out at −78 °C in ether solution, and yields are often excellent. For example, manicone, a substance secreted by male ants to coordinate ant pairing and mating, has been synthesized by reaction of lithium diethylcopper with (*E*)-2,4-dimethyl-2-hexenoyl chloride.

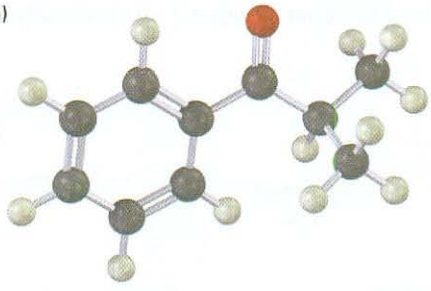


2,4-Dimethyl-2-hexenoyl chloride — **4,6-Dimethyl-4-octen-3-one (manicone, 92%)**

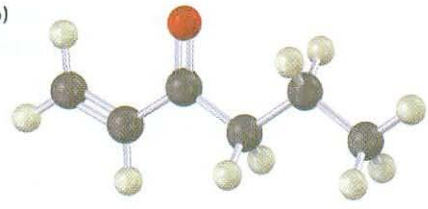
Note that the diorganocopper reaction occurs only with acid chlorides. Carboxylic acids, esters, acid anhydrides, and amides do not react with lithium diorganocopper reagents.

Problem 21.13 How could you prepare the following ketones by reaction of an acid chloride with a lithium diorganocopper reagent?

(a)



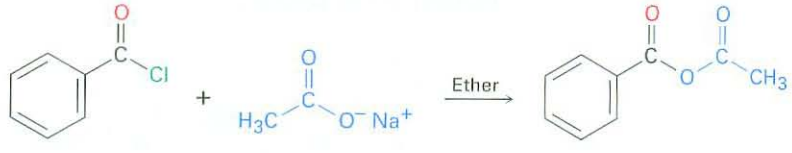
(b)



21.5 Chemistry of Acid Anhydrides

Preparation of Acid Anhydrides

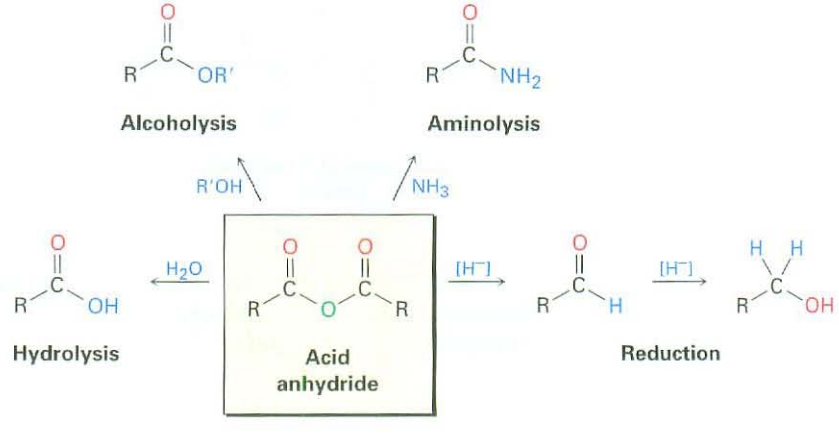
Acid anhydrides are typically prepared by nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion, as we saw in Section 21.4. Both symmetrical and unsymmetrical acid anhydrides can be prepared in this way.



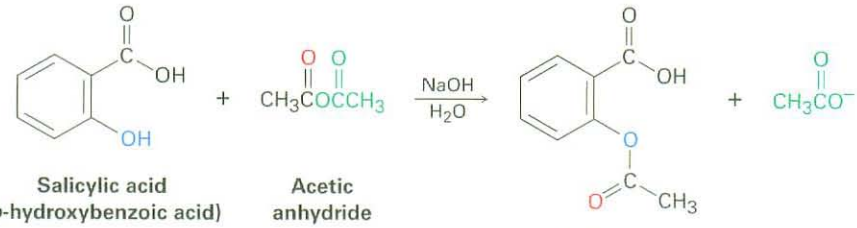
Benzoyl chloride **Sodium acetate** **Acetic benzoic anhydride**

Reactions of Acid Anhydrides

The chemistry of acid anhydrides is similar to that of acid chlorides. Although anhydrides react more slowly than acid chlorides, the kinds of reactions the two groups undergo are the same. Thus, acid anhydrides react with water to form acids, with alcohols to form esters, with amines to form amides, and with $LiAlH_4$ to form primary alcohols. Only the ester and amide forming reactions are much used, however.

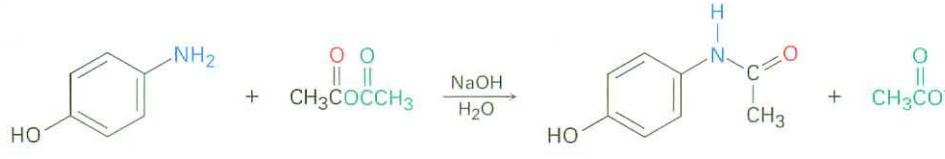


Conversion of Acid Anhydrides into Esters Acetic anhydride is often used to prepare acetate esters from alcohols. For example, aspirin (acetylsalicylic acid) is prepared commercially by the acetylation of *o*-hydroxybenzoic acid (salicylic acid) with acetic anhydride.



Salicylic acid (*o*-hydroxybenzoic acid) **Acetic anhydride** **Aspirin (an ester)**

Conversion of Acid Anhydrides into Amides Acetic anhydride is also commonly used to prepare *N*-substituted acetamides from amines. For example, acetaminophen, a drug used in over-the-counter analgesics such as Tylenol, is prepared by reaction of *p*-hydroxyaniline with acetic anhydride. Note that the more nucleophilic $-NH_2$ group reacts rather than the less nucleophilic $-OH$ group.

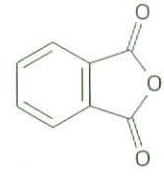


***p*-Hydroxyaniline** **Acetic anhydride** **Acetaminophen**

Notice in both of the previous reactions that only "half" of the anhydride molecule is used; the other half acts as the leaving group during the nucleophilic acyl substitution step and produces acetate ion as a by-product. Thus, anhydrides are inefficient to use, and acid chlorides are normally preferred for introducing acyl substituents other than acetyl groups.

Problem 21.14 Write the mechanism of the reaction between *p*-hydroxyaniline and acetic anhydride to prepare acetaminophen.

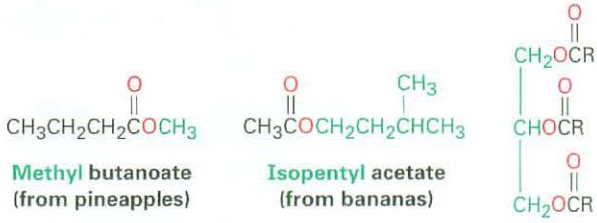
Problem 21.15 What product would you expect from reaction of 1 equivalent of methanol with a cyclic anhydride, such as phthalic anhydride (1,2-benzenedicarboxylic anhydride)? What is the fate of the second "half" of the anhydride?



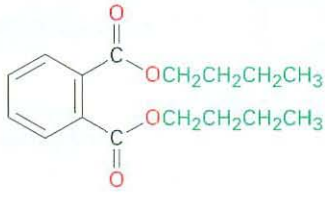
Phthalic anhydride

21.6 Chemistry of Esters

Esters are among the most widespread of all naturally occurring compounds. Many simple esters are pleasant-smelling liquids that are responsible for the fragrant odors of fruits and flowers. For example, methyl butanoate is found in pineapple oil, and isopentyl acetate is a constituent of banana oil. The ester linkage is also present in animal fats and in many biologically important molecules.



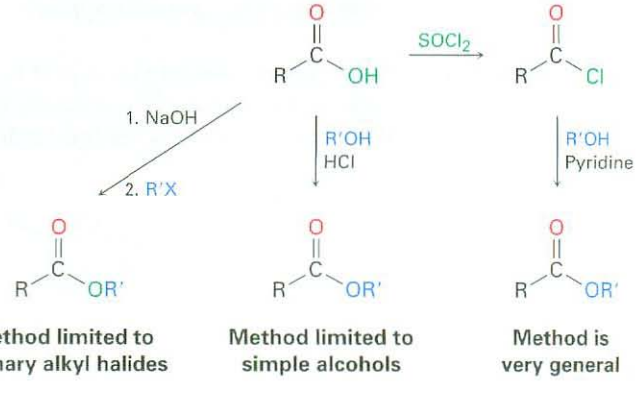
The chemical industry uses esters for a variety of purposes. Ethyl acetate, for instance, is a commonly used solvent, and dialkyl phthalates are used as plasticizers to keep polymers from becoming brittle. You may be aware that there is current concern about possible toxicity of phthalates at high concentrations, although a recent assessment by the U.S. Food and Drug Administration found the risk to be minimal for most people, with the possible exception of male infants.



Preparation of Esters

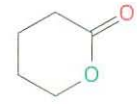
ThomsonNOW Click *Organic Process* to view an animation of the steps involved in Fischer esterification.

Esters are usually prepared from carboxylic acids by the methods already discussed. Thus, carboxylic acids are converted directly into esters by S_N2 reaction of a carboxylate ion with a primary alkyl halide or by Fischer esterification of a carboxylic acid with an alcohol in the presence of a mineral acid catalyst. In addition, acid chlorides are converted into esters by treatment with an alcohol in the presence of base (Section 21.4).



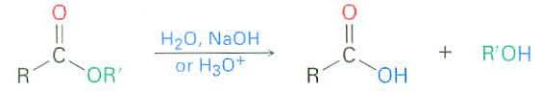
Reactions of Esters

Esters undergo the same kinds of reactions that we've seen for other carboxylic acid derivatives, but they are less reactive toward nucleophiles than either acid chlorides or anhydrides. All their reactions are equally applicable to both acyclic and cyclic esters, called **lactones**.



A lactone
(cyclic ester)

Conversion of Esters into Carboxylic Acids: Hydrolysis An ester is hydrolyzed, either by aqueous base or by aqueous acid, to yield a carboxylic acid plus an alcohol.



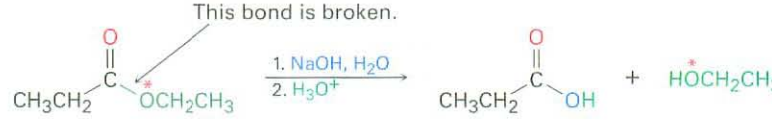
Ester Acid Alcohol

ThomsonNOW Click *Organic Process* to **view an animation of the steps involved in base-catalyzed ester hydrolysis.**

Ester hydrolysis in basic solution is called **saponification**, after the Latin word *sapo*, meaning "soap." As we'll see in Section 27.2, soap is in fact made by boiling animal fat with base to hydrolyze the ester linkages.

Ester hydrolysis occurs through a typical nucleophilic acyl substitution pathway in which hydroxide ion is the nucleophile that adds to the ester carbonyl group to give a tetrahedral intermediate. Loss of alkoxide ion then gives a carboxylic acid, which is deprotonated to give the carboxylate ion. Addition of aqueous HCl in a separate step after the saponification is complete then protonates the carboxylate ion and gives the carboxylic acid (Figure 21.17).

The mechanism shown in Figure 21.7 is supported by isotope-labeling studies. When ethyl propanoate labeled with ^{18}O in the ether-like oxygen is hydrolyzed in aqueous NaOH, the ^{18}O label shows up exclusively in the ethanol product. None of the label remains with the propanoic acid, indicating that saponification occurs by cleavage of the C–OR′ bond rather than the CO–R′ bond.

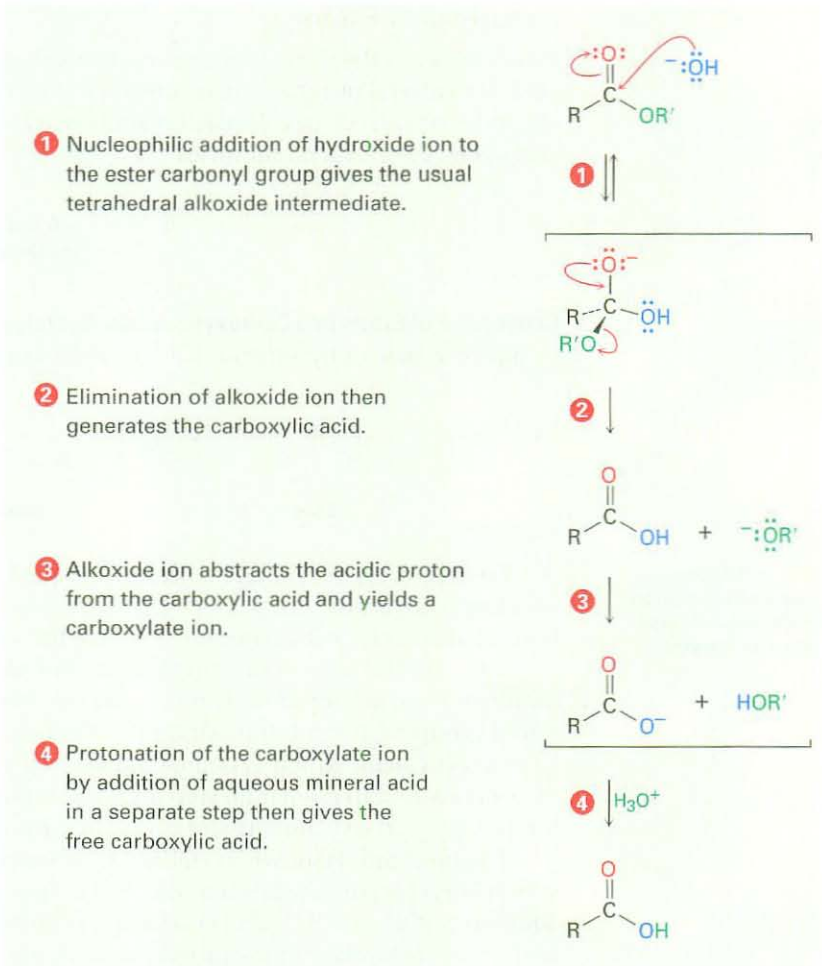


ThomsonNOW Click *Organic Process* to **view an animation of the steps involved in acid-catalyzed ester hydrolysis.**

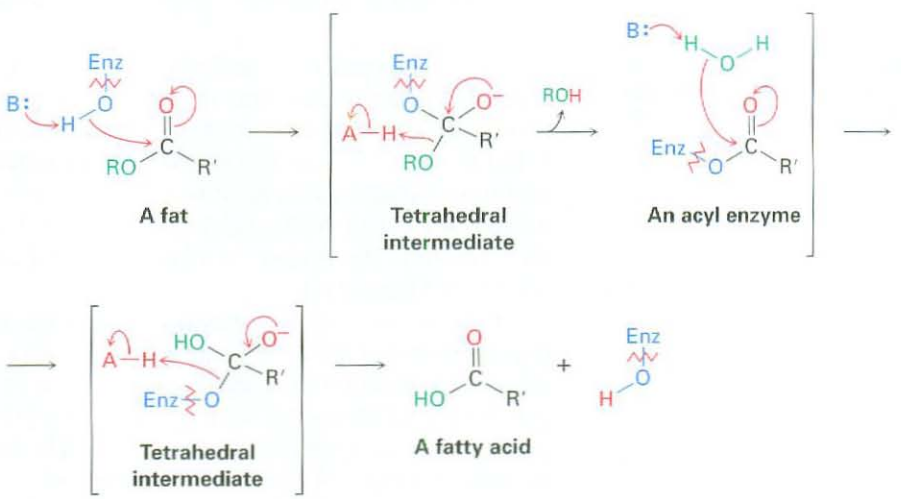
Acid-catalyzed ester hydrolysis can occur by more than one mechanism, depending on the structure of the ester. The usual pathway, however, is just the reverse of a Fischer esterification reaction (Section 21.3). The ester is first activated toward nucleophilic attack by protonation of the carboxyl oxygen atom, and nucleophilic addition of water then occurs. Transfer of a proton and elimination of alcohol yields the carboxylic acid (Figure 21.8). Because this hydrolysis reaction is the reverse of a Fischer esterification reaction, Figure 21.8 is the reverse of Figure 21.4.

Ester hydrolysis is common in biological chemistry, particularly in the digestion of dietary fats and oils. We'll save a complete discussion of the mechanistic details of fat hydrolysis until Section 29.2 but will note for now that the reaction is catalyzed by various lipase enzymes and involves two sequential nucleophilic acyl substitution reactions. The first is a *transesterification* reaction in which an alcohol group on the lipase adds to an ester linkage in the fat molecule to give a tetrahedral intermediate that expels alcohol and forms an acyl

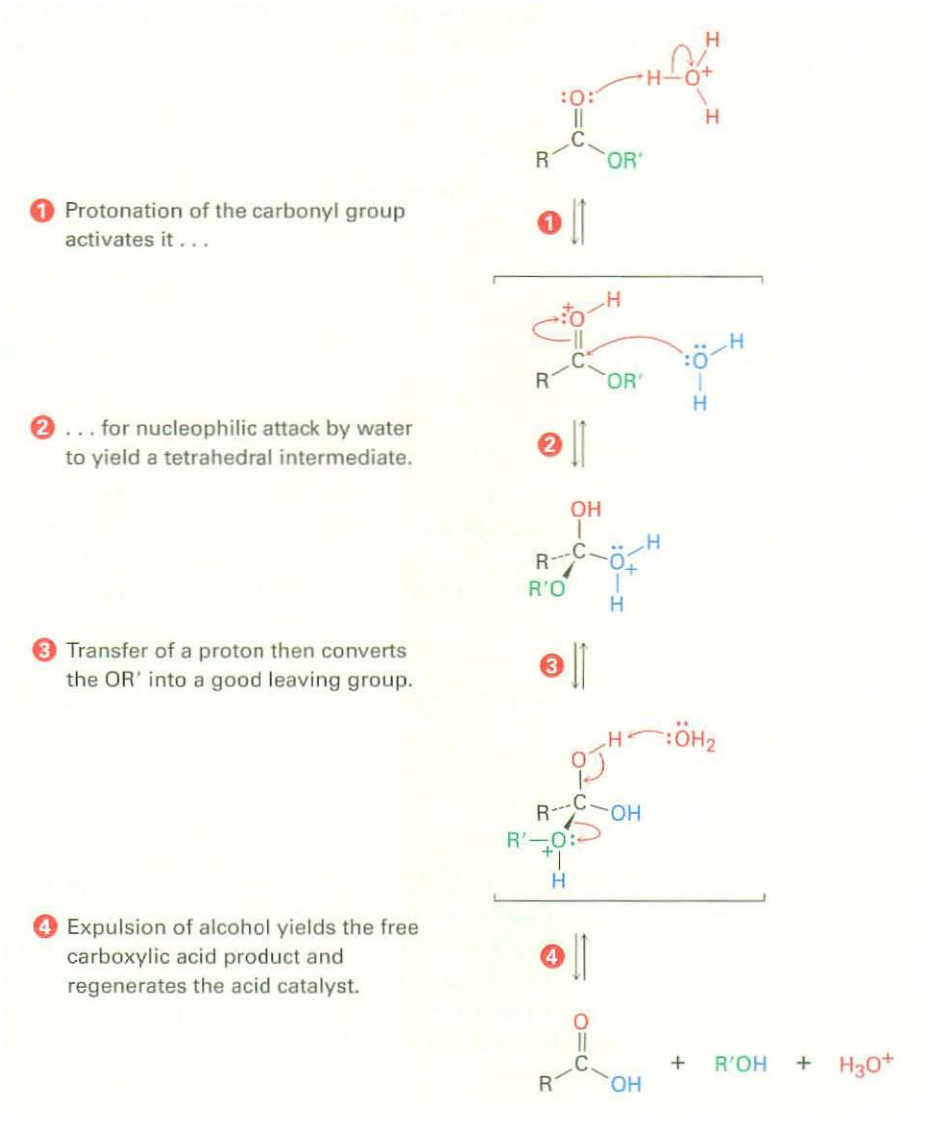
Figure 21.7 MECHANISM:
Mechanism of base-induced ester hydrolysis (saponification).



enzyme intermediate. The second is an addition of water to the acyl enzyme, followed by expulsion of the enzyme to give a hydrolyzed acid.

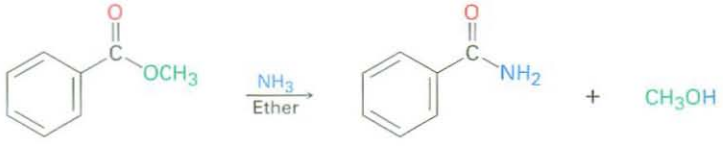


Active Figure 21.8
MECHANISM: Mechanism of acid-catalyzed ester hydrolysis. The forward reaction is a hydrolysis; the back-reaction is a Fischer esterification and is thus the reverse of Figure 21.4. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



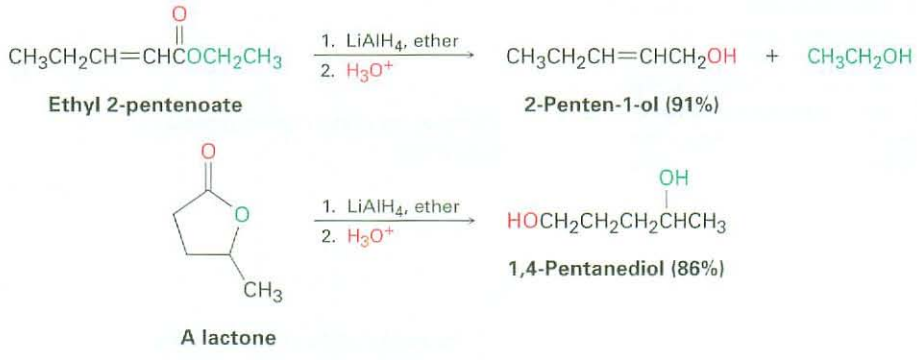
Problem 21.16 Why is the saponification of an ester irreversible? In other words, why doesn't treatment of a carboxylic acid with an alkoxide ion yield an ester?

Conversion of Esters into Amides: Aminolysis Esters react with ammonia and amines to yield amides. The reaction is not often used, however, because it's usually easier to start with an acid chloride (Section 21.4).

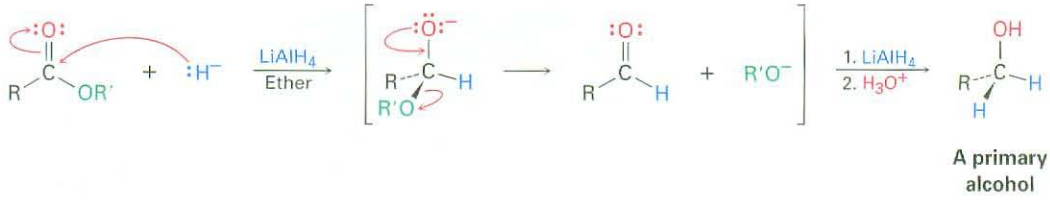


Methyl benzoate **Benzamide**

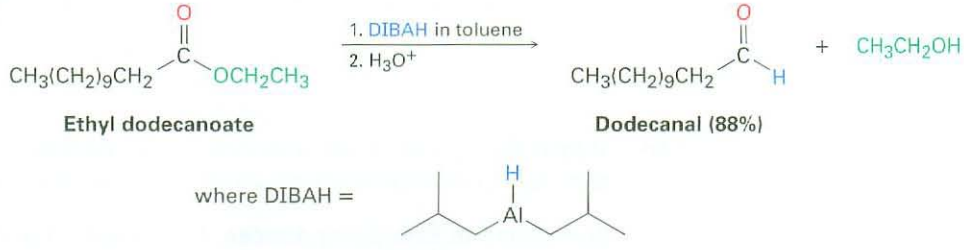
Conversion of Esters into Alcohols: Reduction Esters are easily reduced by treatment with $LiAlH_4$ to yield primary alcohols (Section 17.4).



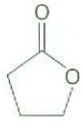
The mechanism of ester (and lactone) reduction is similar to that of acid chloride reduction in that a hydride ion first adds to the carbonyl group, followed by elimination of alkoxide ion to yield an aldehyde. Further reduction of the aldehyde gives the primary alcohol.



The aldehyde intermediate can be isolated if 1 equivalent of diisobutylaluminum hydride (DIBAH) is used as the reducing agent instead of $LiAlH_4$. The reaction has to be carried out at −78 °C to avoid further reduction to the alcohol. Such *partial* reductions of carboxylic acid derivatives to aldehydes also occur in numerous biological pathways, although the substrate is either a thioester or acyl phosphate rather than an ester.



Problem 21.17 What product would you expect from the reaction of butyrolactone with $LiAlH_4$? With DIBAH?

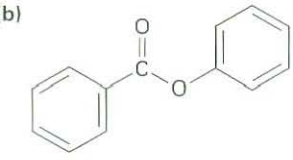


Butyrolactone

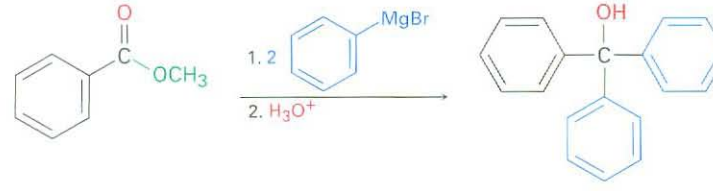
Problem 21.18 Show the products you would obtain by reduction of the following esters with $LiAlH_4$:

(a) $CH_3CH_2CH_2CH(CH_3)COCH_3$

(b)



Conversion of Esters into Alcohols: Grignard Reaction Esters and lactones react with 2 equivalents of a Grignard reagent to yield a tertiary alcohol in which two of the substituents are identical (Section 17.5). The reaction occurs by the usual nucleophilic substitution mechanism to give an intermediate ketone, which reacts further with the Grignard reagent to yield a tertiary alcohol.

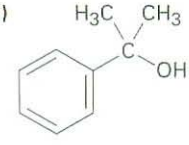


Methyl benzoate

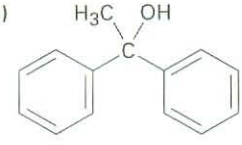
Triphenylmethanol (96%)

Problem 21.19 What ester and what Grignard reagent might you start with to prepare the following alcohols?

(a)



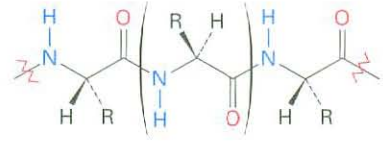
(b)



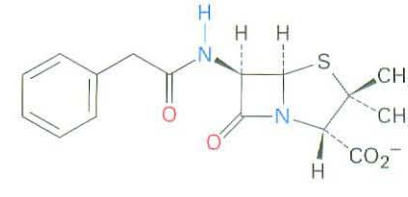
(c) $CH_3CH_2CH_2CH_2C(OH)(CH_2CH_3)CH_2CH_3$

21.7 Chemistry of Amides

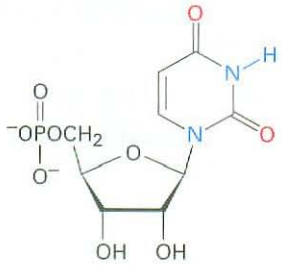
Amides, like esters, are abundant in all living organisms—proteins, nucleic acids, and many pharmaceuticals have amide functional groups. The reason for this abundance of amides, of course, is that they are stable to the conditions found in living organisms. Amides are the least reactive of the common acid derivatives and undergo relatively few nucleophilic acyl substitution reactions.



A protein segment



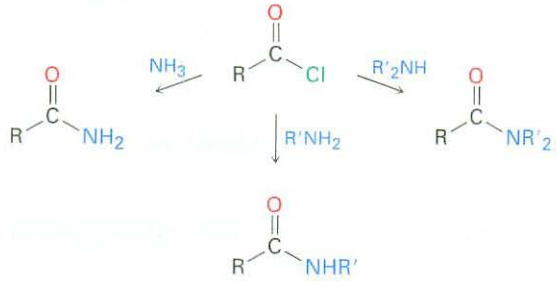
Benzylpenicillin (penicillin G)



Uridine 5′-phosphate (a ribonucleotide)

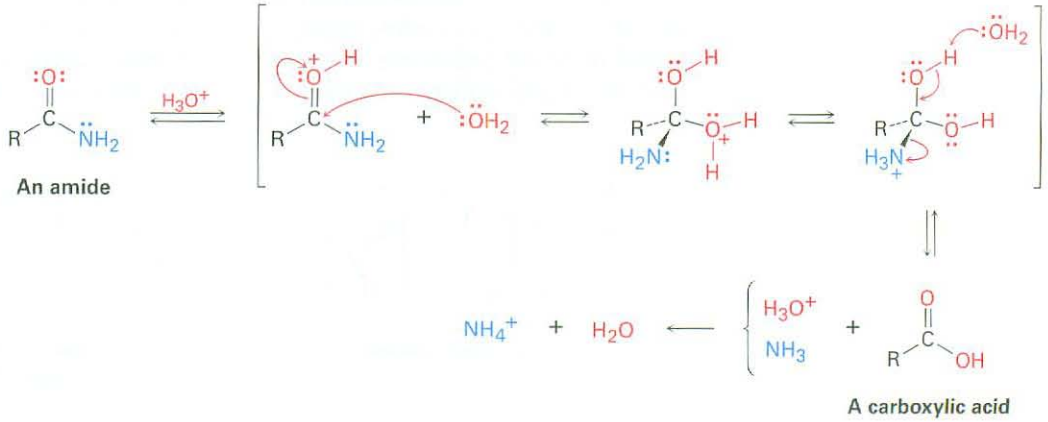
Preparation of Amides

Amides are usually prepared by reaction of an acid chloride with an amine (Section 21.4). Ammonia, monosubstituted amines, and disubstituted amines all undergo the reaction.



Reactions of Amides

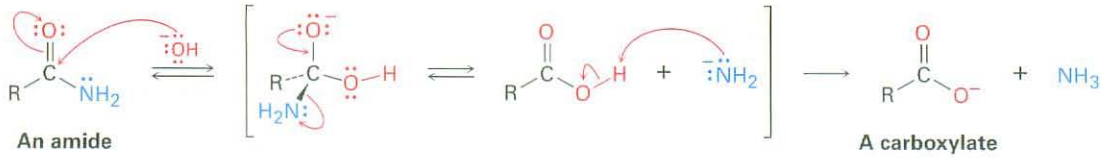
Conversion of Amides into Carboxylic Acids: Hydrolysis Amides undergo hydrolysis to yield carboxylic acids plus ammonia or an amine on heating in either aqueous acid or aqueous base. The conditions required for amide hydrolysis are more severe than those required for the hydrolysis of acid chlorides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



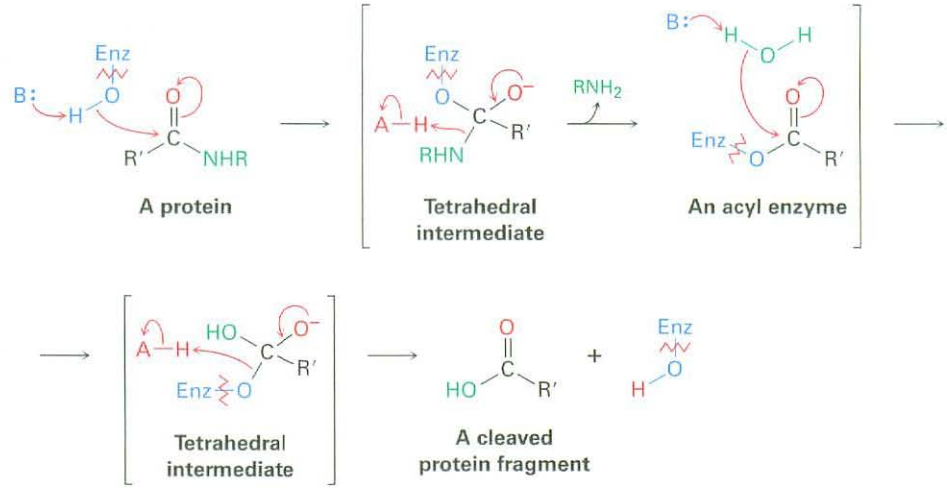
An amide

A carboxylic acid

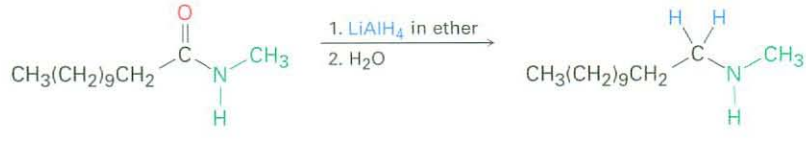
Basic hydrolysis occurs by nucleophilic addition of OH^- to the amide carbonyl group, followed by elimination of amide ion ($^-NH_2$) and subsequent deprotonation of the initially formed carboxylic acid by amide ion. The steps are reversible, with the equilibrium shifted toward product by the final deprotonation of the carboxylic acid. Basic hydrolysis is substantially more difficult than the analogous acid-catalyzed reaction because amide ion is a very poor leaving group, making the elimination step difficult.



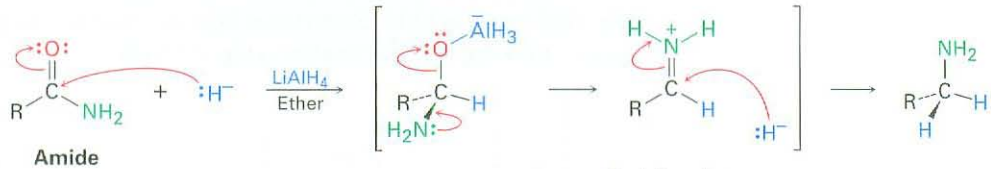
Amide hydrolysis is common in biological chemistry. Just as the hydrolysis of esters is the initial step in the digestion of dietary fats, the hydrolysis of amides is the initial step in the digestion of dietary proteins. The reaction is catalyzed by protease enzymes and occurs by a mechanism almost identical to that we just saw for fat hydrolysis. That is, an initial nucleophilic acyl substitution of an alcohol group in the enzyme on an amide linkage in the protein gives an acyl enzyme intermediate that then undergoes hydrolysis.



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



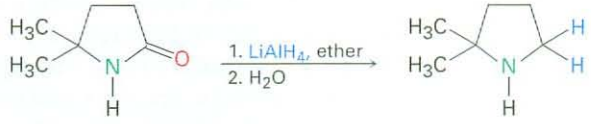
Amide reduction occurs by nucleophilic addition of hydride ion to the amide carbonyl group, followed by expulsion of the *oxygen* atom as an aluminate anion leaving group to give an iminium ion intermediate. The intermediate iminium ion is then further reduced by $LiAlH_4$ to yield the amine.



Amide **Iminium ion**

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products of a variety of reactions involving carboxylic acid derivatives.**

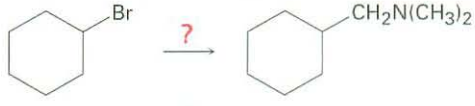
The reaction is effective with both acyclic and cyclic amides, or **lactams**, and is a good method for preparing cyclic amines.



A lactam **A cyclic amine (80%)**

Problem 21.20 How would you convert *N*-ethylbenzamide to each of the following products?
(a) Benzoic acid (b) Benzyl alcohol (c) $C_6H_5CH_2NHCH_2CH_3$

Problem 21.21 How would you use the reaction of an amide with $LiAlH_4$ as the key step in going from bromocyclohexane to (*N*,*N*-dimethylaminomethyl)cyclohexane? Write all the steps in the reaction sequence.



(*N*,*N*-Dimethylaminomethyl)cyclohexane

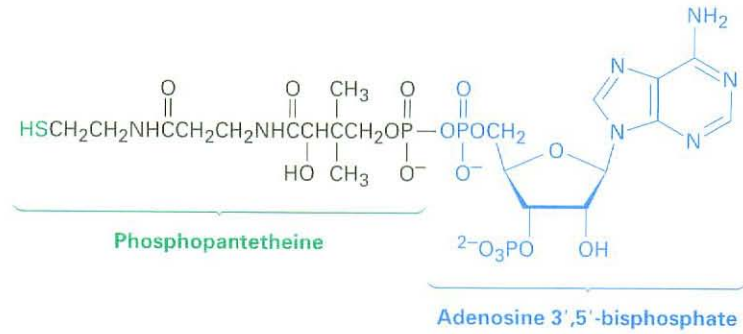
21.8 Chemistry of Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives

As mentioned in the chapter introduction, the substrate for nucleophilic acyl substitution reactions in living organisms is generally either a thioester (RCOSR′) or an acyl phosphate ($RCO_2PO_3^{2-}$ or $RCO_2PO_3R'^-$). Neither is as reactive as an acid chloride or acid anhydride, yet both are stable enough to exist in living organisms while still reactive enough to undergo acyl substitution.

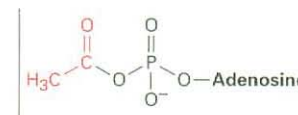
Acyl CoA's, such as acetyl CoA, are the most common thioesters in nature. Coenzyme A, abbreviated CoA, is a thiol formed by a phosphoric anhydride linkage (O=P−O−P=O) between phosphopantetheine and adenosine 3′,5′-bisphosphate. (The prefix "bis" means "two" and indicates that adenosine 3′,5′-bisphosphate has two phosphate groups, one on C3′ and one on C5′.) Reaction of coenzyme A with an acyl phosphate or acyl adenylate

gives the acyl CoA (Figure 21.9). As we saw in Section 21.3 (Figure 21.6), formation of the acyl adenylate occurs by reaction of a carboxylic acid with ATP and is itself a nucleophilic acyl substitution reaction that takes place on phosphorus.

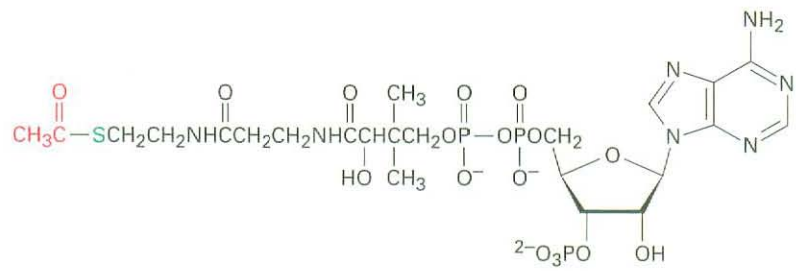
Figure 21.9 Formation of the thioester acetyl CoA by nucleophilic acyl substitution reaction of coenzyme A (CoA) with acetyl adenylate.



Coenzyme A (CoA)

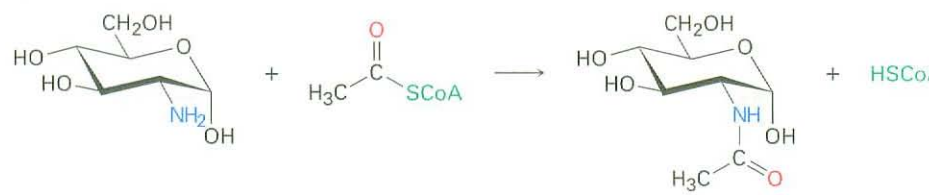


Acetyl adenylate



Acetyl CoA

Once formed, an acyl CoA is a substrate for further nucleophilic acyl substitution reactions. For example, *N*-acetylglucosamine, a component of cartilage and other connective tissues, is synthesized by an aminolysis reaction between glucosamine and acetyl CoA.

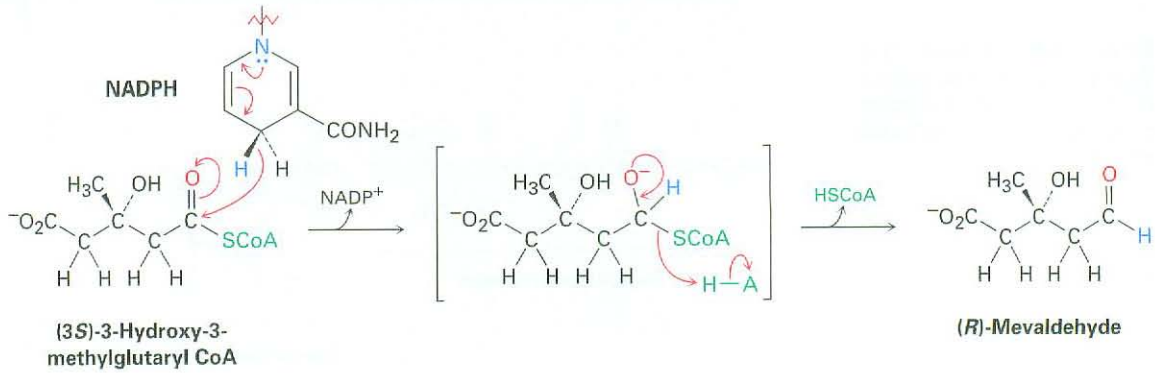


Glucosamine (an amine)

***N*-Acetylglucosamine (an amide)**

Another example of a nucleophilic acyl substitution reaction, this one a substitution by hydride ion to effect partial reduction of a thioester to an aldehyde, occurs in the biosynthesis of mevaldehyde, an intermediate in terpenoid

synthesis (Chapter 6 *Focus On*). In this reaction, (3*R*)-3-hydroxy-3-methylglutaryl CoA is reduced by hydride donation from NADPH.



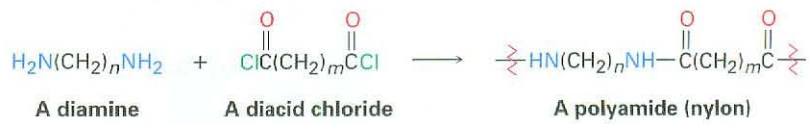
(3*S*)-3-Hydroxy-3-methylglutaryl CoA

(*R*)-Mevaldehyde

Problem 21.22 Write the mechanism of the reaction shown in Figure 21.9 between coenzyme A and acetyl adenylate to give acetyl CoA.

21.9 Polyamides and Polyesters: Step-Growth Polymers

When an amine reacts with an acid chloride, an amide is formed. What would happen, though, if a *diamine* and a *diacid chloride* were allowed to react? Each partner could form *two* amide bonds, linking more and more molecules together until a giant polyamide resulted. In the same way, reaction of a diol with a diacid would lead to a polyester.

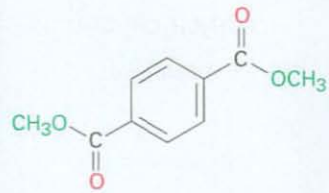
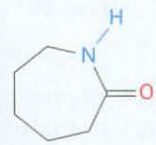
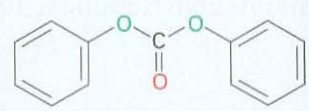
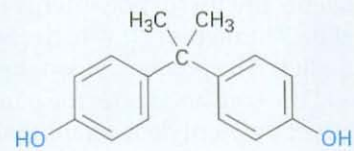
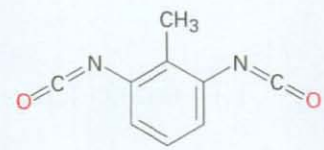


A diamine — A diacid chloride — A polyamide (nylon)

A diol — A diacid — A polyester

The alkene and diene polymers discussed in Sections 7.10 and 14.6 are called *chain-growth polymers* because they are produced by chain reactions. An initiator adds to a C=C bond to give a reactive intermediate, which adds to a second alkene molecule to produce a new intermediate, which adds to a third molecule, and so on. By contrast, polyamides and polyesters are called **step-growth polymers** because each bond in the polymer is formed independently of the others. A large number of different step-growth polymers have been made; some of the more important ones are shown in Table 21.2.

Table 21.2 Some Common Step-Growth Polymers and Their Uses

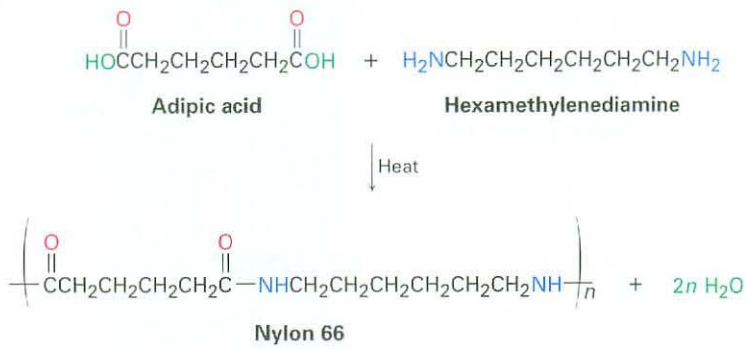
Monomers	Structure	Polymer	Uses
Adipic acid + Hexamethylenediamine	$HOCCH_2CH_2CH_2CH_2COH$ (O, O) + $H_2NCH_2CH_2CH_2CH_2CH_2CH_2NH_2$	Nylon 66	Fibers, clothing, tire cord
Dimethyl terephthalate + Ethylene glycol	 + $HOCH_2CH_2OH$	Dacron, Mylar, Terylene	Fibers, clothing, films, tire cord
Caprolactam		Nylon 6, Perlon	Fibers, castings
Diphenyl carbonate + Bisphenol A	 + 	Lexan, polycarbonate	Equipment housing, molded articles
Toluene-2,6-diisocyanate + Poly(2-butene-1,4-diol)	 + $HO\left(CH_2CH{=}CHCH_2\right)_nOH$	Polyurethane, Spandex	Fibers, coatings, foams

Wallace Hume Carothers

Wallace Hume Carothers (1896–1937) was born in Burlington, Iowa, and received his Ph.D. at the University of Illinois in 1924 with Roger Adams. He began his career with brief teaching positions at the University of South Dakota, the University of Illinois, and Harvard University, but moved to the DuPont Company in 1928 to head their new chemistry research program in polymers. A prolonged struggle with depression led to his suicide after only 9 years at DuPont.

Polyamides (Nylons)

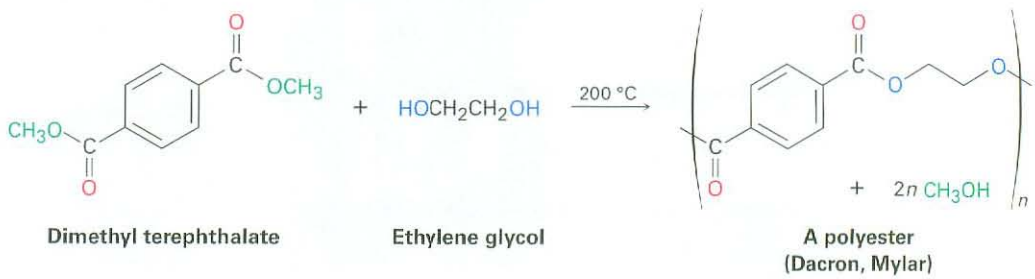
The best known step-growth polymers are the polyamides, or *nylons*, first prepared by Wallace Carothers at the DuPont Company by heating a diamine with a diacid. For example, nylon 66 is prepared by reaction of adipic acid (hexanedioic acid) with hexamethylenediamine (1,6-hexanediamine) at 280 °C. The designation "66" tells the number of carbon atoms in the diamine (the first 6) and the diacid (the second 6).



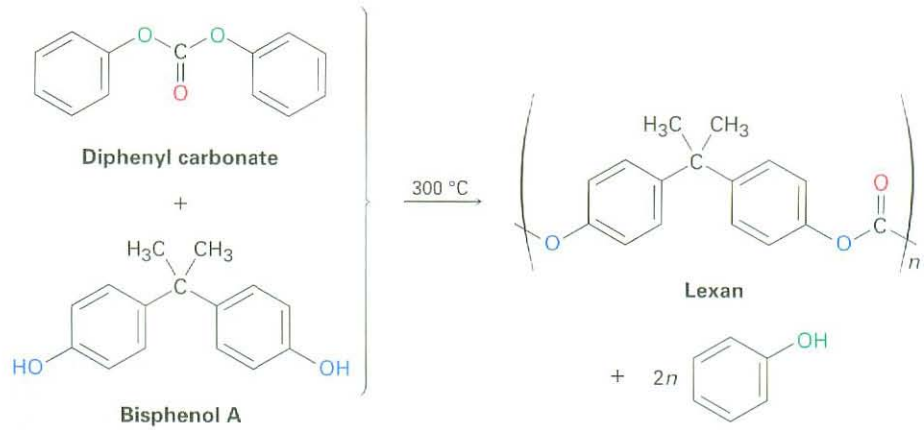
Nylons are used both in engineering applications and in making fibers. A combination of high impact strength and abrasion resistance makes nylon an excellent metal substitute for bearings and gears. As fiber, nylon is used in a variety of applications, from clothing to tire cord to ropes.

Polyesters

The most generally useful polyester is that made by reaction between dimethyl terephthalate (dimethyl 1,4-benzenedicarboxylate) and ethylene glycol (1,2-ethanediol). The product is used under the trade name Dacron to make clothing fiber and tire cord and under the name Mylar to make recording tape. The tensile strength of poly(ethylene terephthalate) film is nearly equal to that of steel.

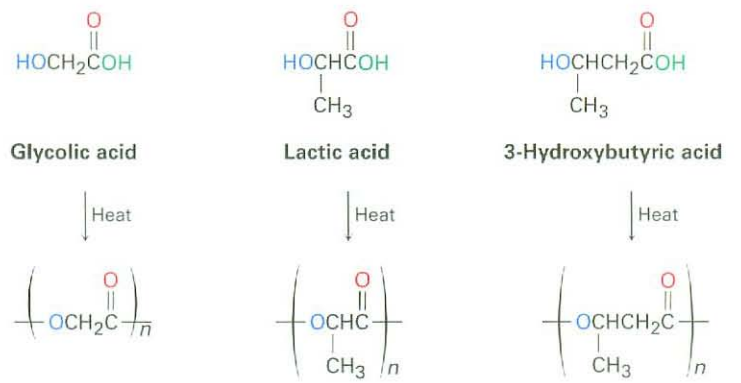


Lexan, a polycarbonate prepared from diphenyl carbonate and bisphenol A, is another commercially valuable polyester. Lexan has an unusually high impact strength, making it valuable for use in telephones, bicycle safety helmets, and laptop computer cases.



Sutures and Biodegradable Polymers

Because plastics are too often thrown away rather than recycled, much work has been carried out on developing *biodegradable* polymers, which can be broken down rapidly in landfills by soil microorganisms. Among the most common biodegradable polymers are poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and polyhydroxybutyrate (PHB). All are polyesters and are therefore susceptible to hydrolysis of their ester links. Copolymers of PGA with PLA have found a particularly wide range of uses. A 90/10 copolymer of poly(glycolic acid) with poly(lactic acid) is used to make absorbable sutures, for instance. The sutures are entirely hydrolyzed and absorbed by the body within 90 days after surgery.



In Europe, interest has centered particularly on polyhydroxybutyrate, which can be made into films for packaging as well as into molded items. The polymer degrades within 4 weeks in landfills, both by ester hydrolysis and by an E1cB elimination reaction of the oxygen atom β to the carbonyl group. The use of polyhydroxybutyrate is limited at present by its cost—about four times that of polypropylene.

Problem 21.23 Draw structures of the step-growth polymers you would expect to obtain from the following reactions:

(a) $BrCH_2CH_2CH_2Br + HOCH_2CH_2CH_2OH \xrightarrow{\text{Base}} ?$

(b) $HOCH_2CH_2OH + HO_2C(CH_2)_6CO_2H \xrightarrow{H_2SO_4 \text{ catalyst}} ?$

(c)

Problem 21.24 Kevlar, a nylon polymer prepared by reaction of 1,4-benzenedicarboxylic acid (terephthalic acid) with 1,4-benzenediamine (*p*-phenylenediamine), is so strong that it's used to make bulletproof vests. Draw the structure of a segment of Kevlar.

Problem 21.25 Draw the structure of the polymer you would expect to obtain from reaction of dimethyl terephthalate with a triol such as glycerol. What structural feature would this new polymer have that was not present in Dacron? How do you think this new feature might affect the properties of the polymer?

21.10 Spectroscopy of Carboxylic Acid Derivatives

Infrared Spectroscopy

All carbonyl-containing compounds have intense IR absorptions in the range 1650 to 1850 cm^{-1}. As shown in Table 21.3, the exact position of the absorption provides information about the specific kind of carbonyl group. For comparison, the IR absorptions of aldehydes, ketones, and carboxylic acids are included in the table, along with values for carboxylic acid derivatives.

Table 21.3 Infrared Absorptions of Some Carbonyl Compounds

Carbonyl type	Example	Absorption (cm^{-1})
Saturated acid chloride	Acetyl chloride	1810
Aromatic acid chloride	Benzoyl chloride	1770
Saturated acid anhydride	Acetic anhydride	1820, 1760
Saturated ester	Ethyl acetate	1735
Aromatic ester	Ethyl benzoate	1720
Saturated amide	Acetamide	1690
Aromatic amide	Benzamide	1675
N-Substituted amide	*N*-Methylacetamide	1680
N,N-Disubstituted amide	*N,N*-Dimethylacetamide	1650
(Saturated aldehyde	Acetaldehyde	1730)
(Saturated ketone	Acetone	1715)
(Saturated carboxylic acid	Acetic acid	1710)

Acid chlorides are easily detected by their characteristic absorption near 1800 cm^{-1}. Acid anhydrides can be identified by the fact that they show two absorptions in the carbonyl region, one at 1820 cm^{-1} and another at 1760 cm^{-1}. Esters are detected by their absorption at 1735 cm^{-1}, a position somewhat higher than that for either aldehydes or ketones. Amides, by contrast, absorb near the low wavenumber end of the carbonyl region, with the degree of substitution on nitrogen affecting the exact position of the IR band.

Problem 21.26 What kinds of functional groups might compounds have if they show the following IR absorptions?

(a) Absorption at 1735 cm^{-1}
(b) Absorption at 1810 cm^{-1}
(c) Absorptions at 2500–3300 cm^{-1} and 1710 cm^{-1}
(d) Absorption at 1715 cm^{-1}

Problem 21.27 Propose structures for compounds that have the following formulas and IR absorptions:

(a) $C_6H_{12}O_2$, 1735 cm^{-1}
(b) C_4H_9NO, 1650 cm^{-1}
(c) C_4H_5ClO, 1780 cm^{-1}

Nuclear Magnetic Resonance Spectroscopy

Hydrogens on the carbon next to a carbonyl group are slightly deshielded and absorb near 2 δ in the ^1H NMR spectrum. The exact nature of the carbonyl group can't be determined by ^1H NMR, however, because the α hydrogens of all acid derivatives absorb in the same range. Figure 21.10 shows the ^1H NMR spectrum of ethyl acetate.

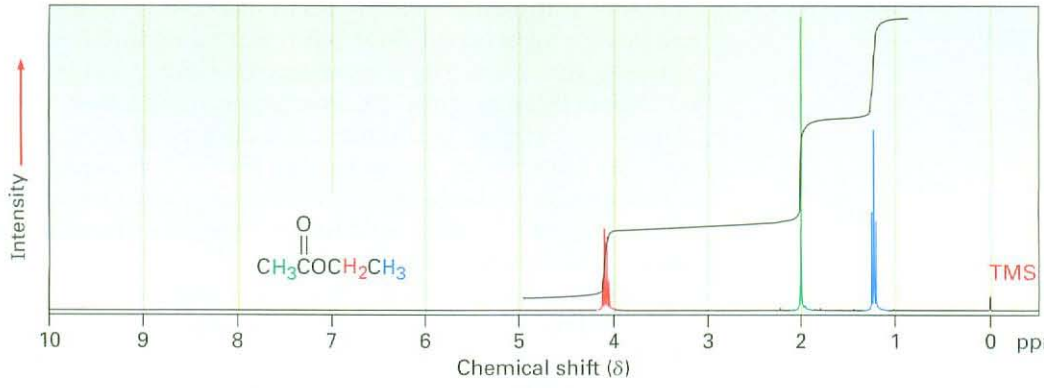


Figure 21.10 Proton NMR spectrum of ethyl acetate.

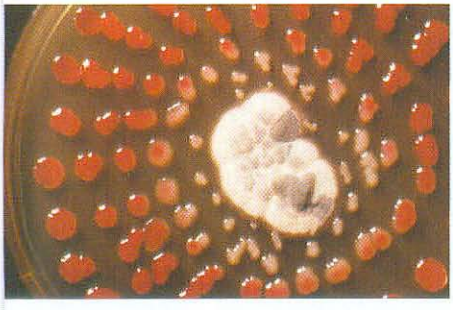
Although ^{13}C NMR is useful for determining the presence or absence of a carbonyl group in a molecule, the identity of the carbonyl group is difficult to determine. Aldehydes and ketones absorb near 200 δ, while the carbonyl carbon atoms of various acid derivatives absorb in the range 160 to 180 δ (Table 21.4).

Table 21.4 ^{13}C NMR Absorptions in Some Carbonyl Compounds

Compound	Absorption (δ)	Compound	Absorption (δ)
Acetic acid	177.3	Acetic anhydride	166.9
Ethyl acetate	170.7	Acetone	205.6
Acetyl chloride	170.3	Acetaldehyde	201.0
Acetamide	172.6		

Focus On . . .

β-Lactam Antibiotics



Penicillium mold growing in a petri dish.

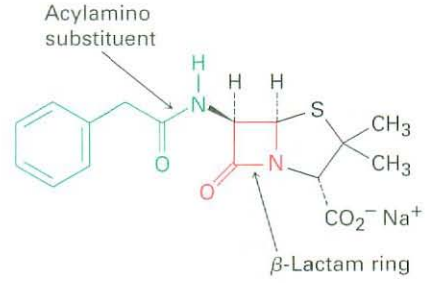
The value of hard work and logical thinking shouldn't be underestimated, but pure luck also plays a role in most real scientific breakthroughs. What has been called "the supreme example [of luck] in all scientific history" occurred in the late summer of 1928, when the Scottish bacteriologist Alexander Fleming went on vacation, leaving in his lab a culture plate recently inoculated with the bacterium *Staphylococcus aureus*.

While Fleming was away, an extraordinary chain of events occurred. First, a 9-day cold spell lowered the laboratory temperature to a point where the *Staphylococcus* on the plate could not grow. During this time, spores from a colony of the mold *Penicillium notatum* being grown on the floor below wafted up into Fleming's lab and landed in the culture plate. The temperature then rose, and both *Staphylococcus* and *Penicillium* began to grow. On returning from vacation, Fleming discarded the plate into a tray of antiseptic, intending to sterilize it. Evidently, though, the plate did not sink deeply enough into the antiseptic, because when Fleming happened to glance at it a few days later, what he saw changed the course of human history. He noticed that the growing *Penicillium* mold appeared to dissolve the colonies of staphylococci.

Fleming realized that the *Penicillium* mold must be producing a chemical that killed the *Staphylococcus* bacteria, and he spent several years trying to isolate the substance. Finally, in 1939, the Australian pathologist Howard Florey and the German refugee Ernst Chain managed to isolate the active substance, called *penicillin*. The dramatic ability of penicillin to cure infections in mice was soon demonstrated, and successful tests in humans followed shortly thereafter. By 1943, penicillin was being produced on a large scale for military use in World War II, and by 1944 it was being used on civilians. Fleming, Florey, and Chain shared the 1945 Nobel Prize in medicine.

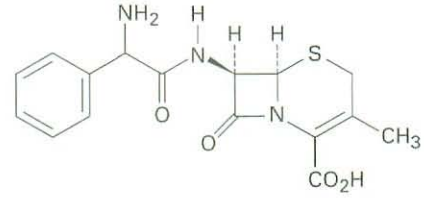
(continued)

Now called benzylpenicillin, or penicillin G, the substance first discovered by Fleming is but one member of a large class of so-called β-lactam antibiotics, compounds with a four-membered lactam (cyclic amide) ring. The four-membered lactam ring is fused to a five-membered, sulfur-containing ring, and the carbon atom next to the lactam carbonyl group is bonded to an acylamino substituent, RCONH−. This acylamino side chain can be varied in the laboratory to provide many hundreds of penicillin analogs with different biological activity profiles. Ampicillin, for instance, has an α-aminophenylacetamido substituent [$PhCH(NH_2)CONH-$].



Benzylpenicillin (penicillin G)

Closely related to the penicillins are the *cephalosporins*, a group of β-lactam antibiotics that contain an unsaturated six-membered, sulfur-containing ring. Cephalexin, marketed under the trade name Keflex, is an example. Cephalosporins generally have much greater antibacterial activity than penicillins, particularly against resistant strains of bacteria.



Cephalexin (a cephalosporin)

The biological activity of penicillins and cephalosporins is due to the presence of the strained β-lactam ring, which reacts with and deactivates the transpeptidase enzyme needed to synthesize and repair bacterial cell walls. With the wall either incomplete or weakened, the bacterial cell ruptures and dies.

SUMMARY AND KEY WORDS

acid anhydride (RCO_2COR'), 785

acid halide (RCOX), 785

acyl phosphate ($RCOPO_3^{2-}$), 785

amide (*$RCONH_2$*), 785

Carboxylic acids can be transformed into a variety of **carboxylic acid derivatives** in which the carboxyl −OH group has been replaced by another substituent. **Acid halides**, **acid anhydrides**, **esters**, and **amides** are the most common such derivatives in the laboratory; **thioesters** and **acyl phosphates** are common in biological molecules.

The chemistry of carboxylic acid derivatives is dominated by the **nucleophilic acyl substitution reaction**. Mechanistically, these substitutions take place by

carboxylic acid derivative, 785
ester (RCO_2R'), 785
Fischer esterification reaction, 795
lactam, 816
lactone, 809
nucleophilic acyl substitution reaction, 789
saponification, 809
step-growth polymer, 818
thioester (RCOSR'), 785

addition of a nucleophile to the polar carbonyl group of the acid derivative to give a tetrahedral intermediate, followed by expulsion of a leaving group.

The reactivity of an acid derivative toward substitution depends both on the steric environment near the carbonyl group and on the electronic nature of the substituent, Y. The reactivity order is acid halide > acid anhydride > thioester > ester > amide.

The most common reactions of carboxylic acid derivatives are substitution by water *(hydrolysis)* to yield an acid, by an alcohol *(alcoholysis)* to yield an ester, by an amine *(aminolysis)* to yield an amide, by hydride ion to yield an alcohol *(reduction)*, and by an organometallic reagent to yield an alcohol *(Grignard reaction)*.

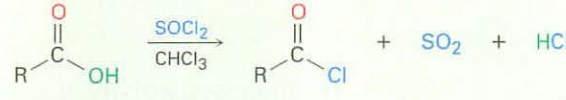
Step-growth polymers, such as polyamides and polyesters, are prepared by reactions between difunctional molecules. Polyamides (nylons) are formed by reaction between a diacid and a diamine; polyesters are formed from a diacid and a diol.

IR spectroscopy is a valuable tool for the structural analysis of acid derivatives. Acid chlorides, anhydrides, esters, and amides all show characteristic IR absorptions that can be used to identify these functional groups.

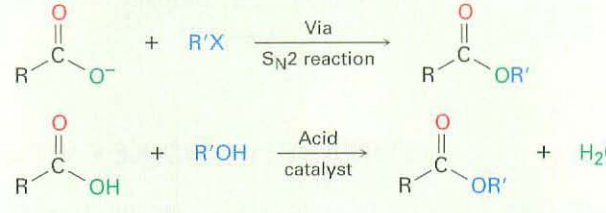
SUMMARY OF REACTIONS

1. Reactions of carboxylic acids (Section 21.3)

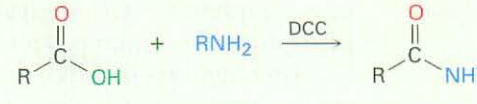
(a) Conversion into acid chlorides



(b) Conversion into esters



(c) Conversion into amides



(d) Reduction to yield primary alcohols

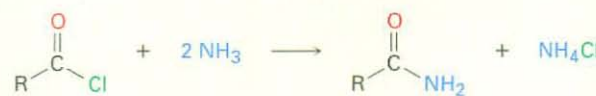
2. Reactions of acid chlorides (Section 21.4)

(a) Hydrolysis to yield acids

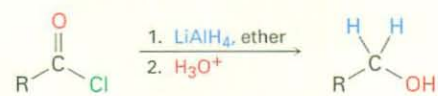
(b) Reaction with carboxylates to yield anhydrides

(c) Alcoholysis to yield esters

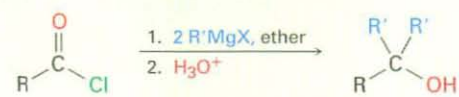
(d) Aminolysis to yield amides



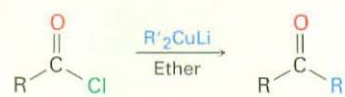
(e) Reduction to yield primary alcohols



(f) Grignard reaction to yield tertiary alcohols



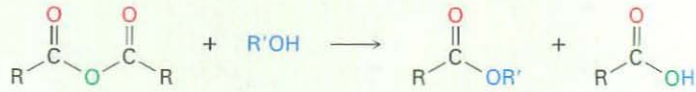
(e) Diorganocopper reaction to yield ketones



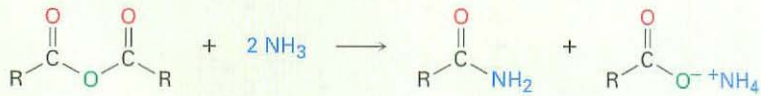
3. Reactions of acid anhydrides (Section 21.5)

(a) Hydrolysis to yield acids

(b) Alcoholysis to yield esters

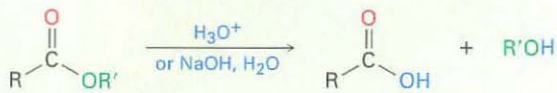


(c) Aminolysis to yield amides

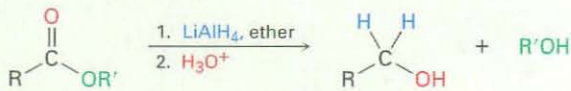


4. Reactions of esters and lactones (Section 21.6)

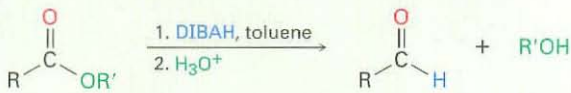
(a) Hydrolysis to yield acids



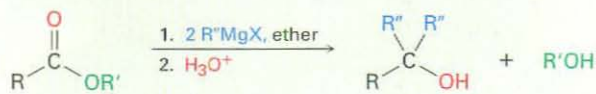
(b) Reduction to yield primary alcohols



(c) Partial reduction to yield aldehydes

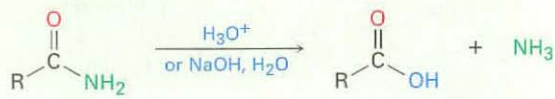


(d) Grignard reaction to yield tertiary alcohols

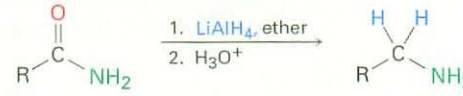


5. Reactions of amides (Section 21.7)

(a) Hydrolysis to yield acids



(b) Reduction to yield amines



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

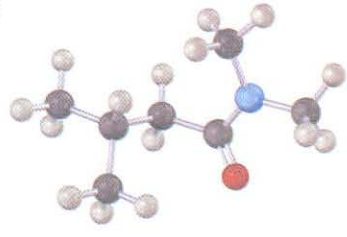
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

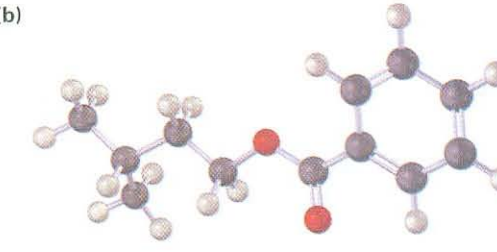
(Problems 21.1–21.27 appear within the chapter.)

21.28 ■ Name the following compounds:

(a)

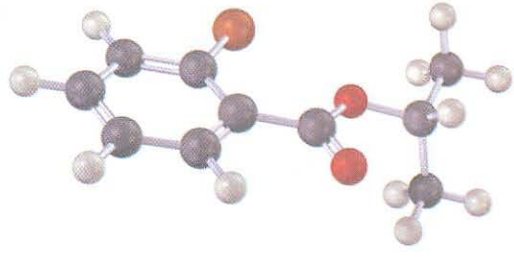


(b)

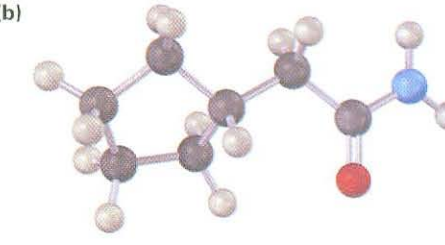


21.29 How would you prepare the following compounds starting with an appropriate carboxylic acid and any other reagents needed? (Reddish brown = Br.)

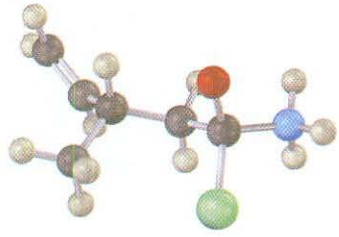
(a)



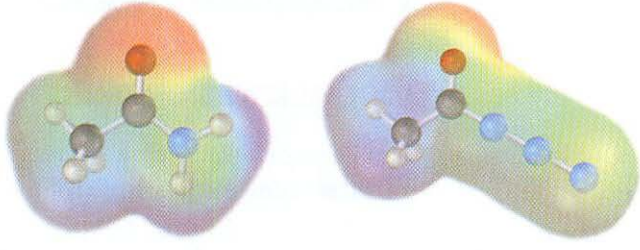
(b)



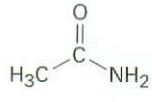
21.30 ■ The following structure represents a tetrahedral alkoxide-ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product (yellow-green = Cl):

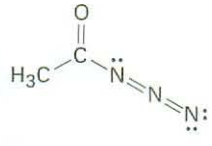


21.31 Electrostatic potential maps of a typical amide (acetamide) and an acyl azide (acetyl azide) are shown. Which of the two do you think is more reactive in nucleophilic acyl substitution reactions? Explain.



Acetamide



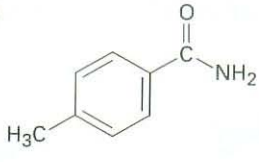


Acetyl azide

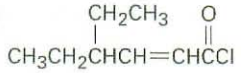
ADDITIONAL PROBLEMS

21.32 ■ Give IUPAC names for the following compounds:

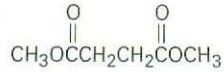
(a)



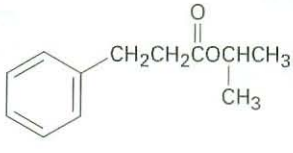
(b)



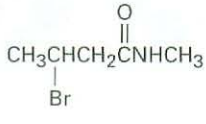
(c)



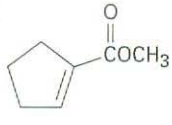
(d)



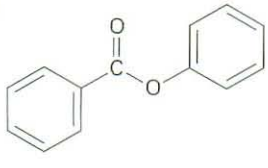
(e)



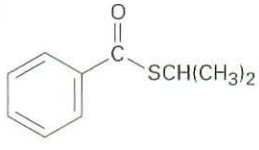
(f)



(g)



(h)



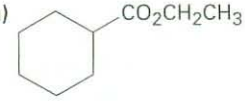
■ Assignable in OWL

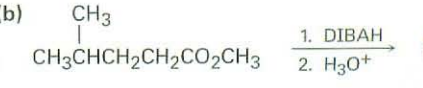
21.33 ■ Draw structures corresponding to the following names:
(a) *p*-Bromophenylacetamide
(b) *m*-Benzoylbenzamide
(c) 2,2-Dimethylhexanamide
(d) Cyclohexyl cyclohexanecarboxylate
(e) Ethyl 2-cyclobutenecarboxylate
(f) Succinic anhydride

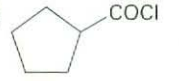
21.34 Draw and name compounds that meet the following descriptions:
(a) Three acid chlorides having the formula C_6H_9ClO
(b) Three amides having the formula $C_7H_{11}NO$

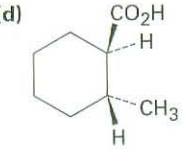
21.35 ■ How might you prepare the following compounds from butanoic acid?
(a) 1-Butanol (b) Butanal (c) 1-Bromobutane
(d) Pentanenitrile (e) 1-Butene (f) *N*-Methylpentanamide
(g) 2-Hexanone (h) Butylbenzene (i) Butanenitrile

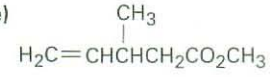
21.36 ■ Predict the product(s) of the following reactions:

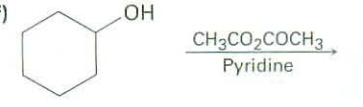
(a) 

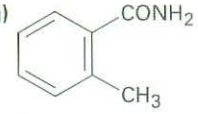
(b) 

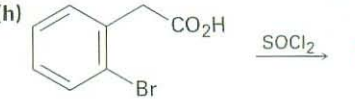
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

21.37 ■ Predict the product, if any, of reaction between propanoyl chloride and the following reagents:
(a) $Li(Ph)_2Cu$ in ether (b) $LiAlH_4$, then H_3O^+
(c) CH_3MgBr, then H_3O^+ (d) H_3O^+
(e) Cyclohexanol (f) Aniline
(g) $CH_3CO_2^-\ ^+Na$

21.38 ■ Answer Problem 21.37 for reaction of the listed reagents with methyl propanoate.

21.39 ■ Answer Problem 21.37 for reaction of the listed reagents with propanamide.

21.40 What product would you expect to obtain from Grignard reaction of an excess of phenylmagnesium bromide with dimethyl carbonate, $CH_3OCO_2CH_3$?

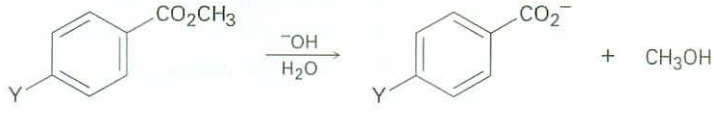
21.41 Treatment of 5-aminopentanoic acid with DCC (dicyclohexylcarbodiimide) yields a lactam. Show the structure of the product and the mechanism of the reaction.

21.42 ■ Outline methods for the preparation of acetophenone (phenyl methyl ketone) starting from the following:
(a) Benzene (b) Bromobenzene (c) Methyl benzoate
(d) Benzonitrile (e) Styrene

21.43 ■ The following reactivity order has been found for the basic hydrolysis of *p*-substituted methyl benzoates:

$$Y = NO_2 > Br > H > CH_3 > OCH_3$$

How can you explain this reactivity order? Where would you expect Y = C≡N, Y = CHO, and Y = NH_2 to be in the reactivity list?

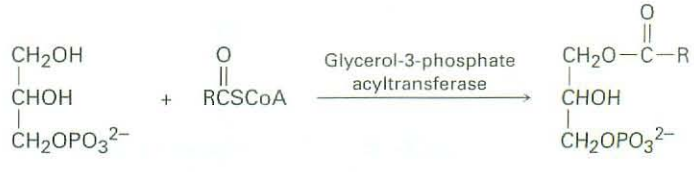


21.44 ■ The following reactivity order has been found for the saponification of alkyl acetates by aqueous NaOH. Explain.

$$CH_3CO_2CH_3 > CH_3CO_2CH_2CH_3 > CH_3CO_2CH(CH_3)_2 > CH_3CO_2C(CH_3)_3$$

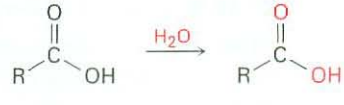
21.45 Explain the observation that attempted Fischer esterification of 2,4,6-trimethylbenzoic acid with methanol and HCl is unsuccessful. No ester is obtained, and the acid is recovered unchanged. What alternative method of esterification might be successful?

21.46 ■ Fats are biosynthesized from glycerol 3-phosphate and fatty-acyl CoA's by a reaction sequence that begins with the following step. Show the mechanism of the reaction.



Glycerol 3-phosphate **Fatty-acyl CoA** **1-Acylglycerol 3-phosphate**

21.47 When a carboxylic acid is dissolved in isotopically labeled water, the label rapidly becomes incorporated into *both* oxygen atoms of the carboxylic acid. Explain.

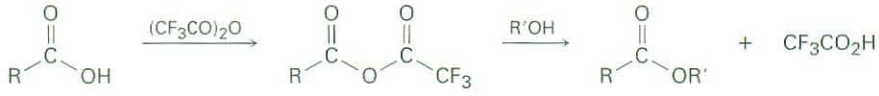


21.48 ■ When *ethyl* benzoate is heated in methanol containing a small amount of HCl, *methyl* benzoate is formed. Propose a mechanism for the reaction.

21.49 ■ *tert*-Butoxycarbonyl azide, a reagent used in protein synthesis, is prepared by treating *tert*-butoxycarbonyl chloride with sodium azide. Propose a mechanism for this reaction.

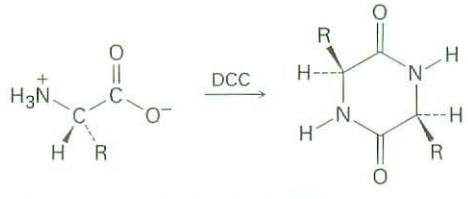
21.50 We said in Section 21.6 that mechanistic studies on ester hydrolysis have been carried out using ethyl propanoate labeled with ^{18}O in the ether-like oxygen. Assume that ^{18}O-labeled acetic acid is your only source of isotopic oxygen, and then propose a synthesis of the labeled ethyl propanoate.

21.51 ■ Treatment of a carboxylic acid with trifluoroacetic anhydride leads to an unsymmetrical anhydride that rapidly reacts with alcohol to give an ester.



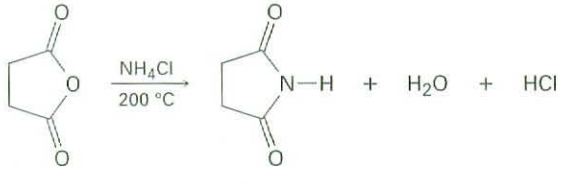
(a) Propose a mechanism for formation of the unsymmetrical anhydride.
(b) Why is the unsymmetrical anhydride unusually reactive?
(c) Why does the unsymmetrical anhydride react as indicated rather than giving a trifluoroacetate ester plus carboxylic acid?

21.52 Treatment of an α-amino acid with DCC yields a 2,5-diketopiperazine. Propose a mechanism.

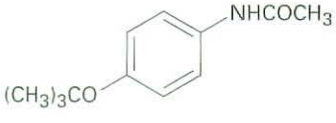


An α-amino acid **A 2,5-diketopiperazine**

21.53 ■ Succinic anhydride yields the cyclic imide succinimide when heated with ammonium chloride at 200 °C. Propose a mechanism for this reaction. Why do you suppose such a high reaction temperature is required?



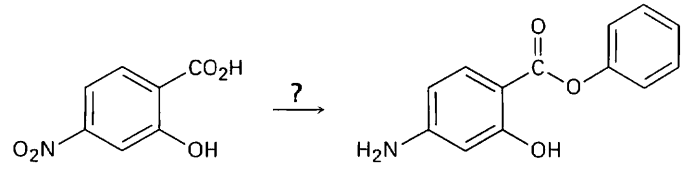
21.54 Butacetin is an analgesic (pain-killing) agent that is synthesized commercially from *p*-fluoronitrobenzene. Propose a synthesis.



Butacetin

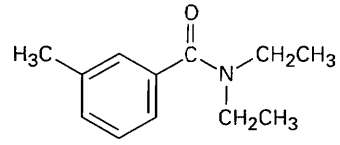
■ Assignable in OWL

21.55 Phenyl 4-aminosalicylate is a drug used in the treatment of tuberculosis. Propose a synthesis of this compound starting from 4-nitrosalicylic acid.



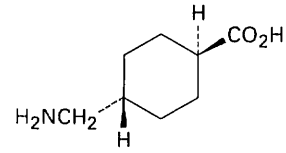
4-Nitrosalicylic acid **Phenyl 4-aminosalicylate**

21.56 *N,N*-Diethyl-*m*-toluamide (DEET) is the active ingredient in many insect-repellent preparations. How might you synthesize this substance from *m*-bromotoluene?



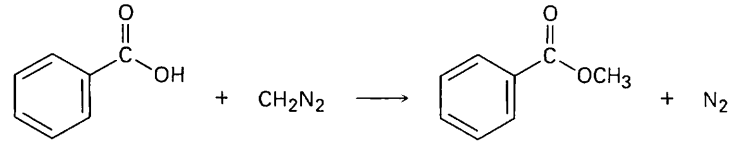
***N,N*-Diethyl-*m*-toluamide**

21.57 Tranexamic acid, a drug useful against blood clotting, is prepared commercially from *p*-methylbenzonitrile. Formulate the steps likely to be used in the synthesis. (Don't worry about cis–trans isomers; heating to 300 °C interconverts the isomers.)



Tranexamic acid

21.58 One frequently used method for preparing methyl esters is by reaction of carboxylic acids with diazomethane, CH_2N_2.



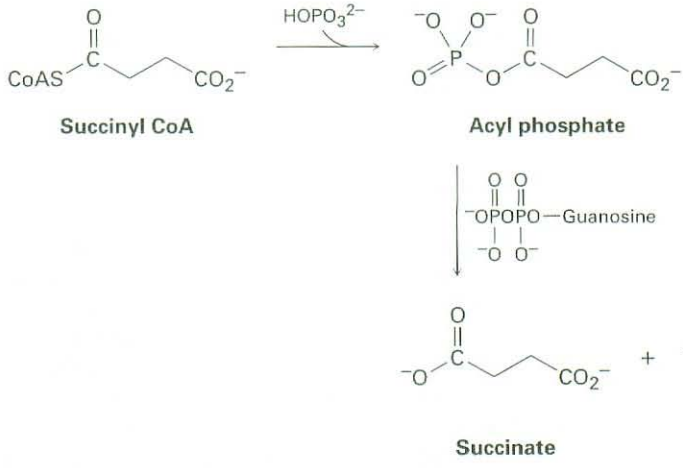
Benzoic acid **Diazomethane** **Methyl benzoate (100%)**

The reaction occurs in two steps: (1) protonation of diazomethane by the carboxylic acid to yield methyldiazonium ion, $CH_3N_2^+$, plus a carboxylate ion; and (2) reaction of the carboxylate ion with $CH_3N_2^+$.

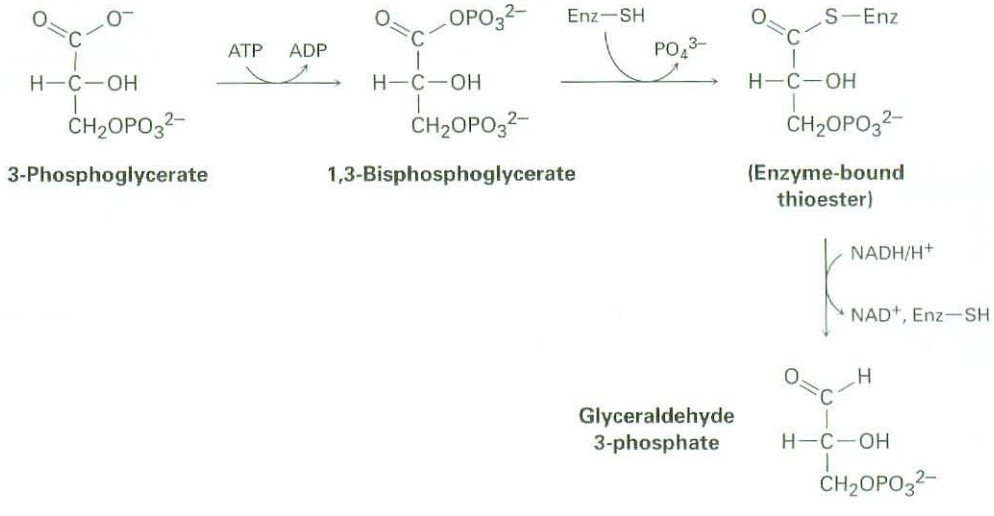
(a) Draw two resonance structures of diazomethane, and account for step 1.

(b) What kind of reaction occurs in step 2?

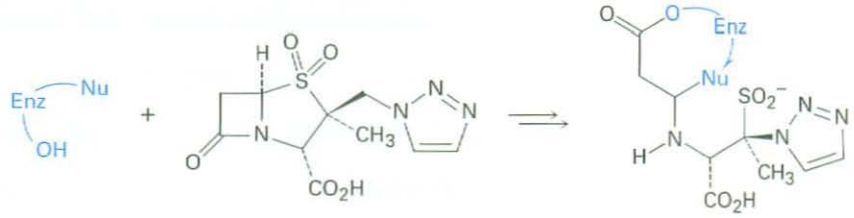
21.59 ■ The hydrolysis of a biological thioester to the corresponding carboxylate is often more complex than the overall result might suggest. The conversion of succinyl CoA to succinate in the citric acid cycle, for instance, occurs by initial formation of an acyl phosphate, followed by reaction with guanosine diphosphate (GDP, a relative of ADP) to give succinate and guanosine triphosphate (GTP, a relative of ATP). Suggest mechanisms for both steps.



21.60 One step in the *gluconeogenesis* pathway for the biosynthesis of glucose is the partial reduction of 3-phosphoglycerate to give glyceraldehyde 3-phosphate. The process occurs by phosphorylation with ATP to give 1,3-bisphosphoglycerate, reaction with a thiol group on the enzyme to give an enzyme-bound thioester, and reduction with NADH. Suggest mechanisms for all three reactions.



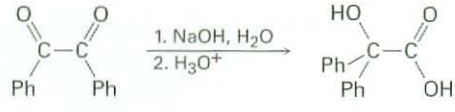
21.61 Penicillins and other β-lactam antibiotics (see the *Focus On* in this chapter) typically develop a resistance to bacteria due to bacterial synthesis of β-lactamase enzymes. Tazobactam, however, is able to inhibit the activity of the β-lactamase by trapping it, thereby preventing resistance from developing.



β-Lactamase **Tazobactam** **Trapped β-lactamase**

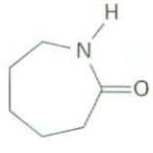
(a) The first step in trapping is reaction of a hydroxyl group on the β-lactamase to open the β-lactam ring of tazobactam. Show the mechanism.
(b) The second step is opening of the sulfur-containing ring in tazobactam to give an acyclic iminium ion intermediate. Show the mechanism.
(c) Cyclization of the iminium ion intermediate gives the trapped β-lactamase product. Show the mechanism.

21.62 ■ The following reaction, called the *benzilic acid rearrangement*, takes place by typical carbonyl-group reactions. Propose a mechanism (Ph = phenyl).



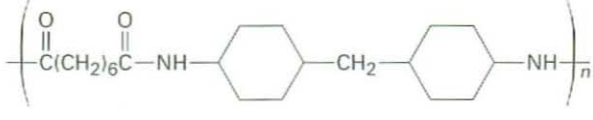
Benzil **Benzylic acid**

21.63 ■ The step-growth polymer nylon 6 is prepared from caprolactam. The reaction involves initial reaction of caprolactam with water to give an intermediate open-chain amino acid, followed by heating to form the polymer. Propose mechanisms for both steps, and show the structure of nylon 6.



Caprolactam

21.64 *Qiana*, a polyamide fiber with a silky texture, has the following structure. What are the monomer units used in the synthesis of Qiana?

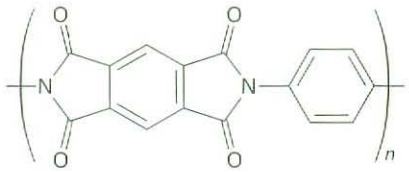


Qiana

21.65 What is the structure of the polymer produced by treatment of β-propiolactone with a small amount of hydroxide ion?

β-Propiolactone

21.66 Polyimides having the structure shown are used as coatings on glass and plastics to improve scratch resistance. How would you synthesize a polyimide? (See Problem 21.53.)

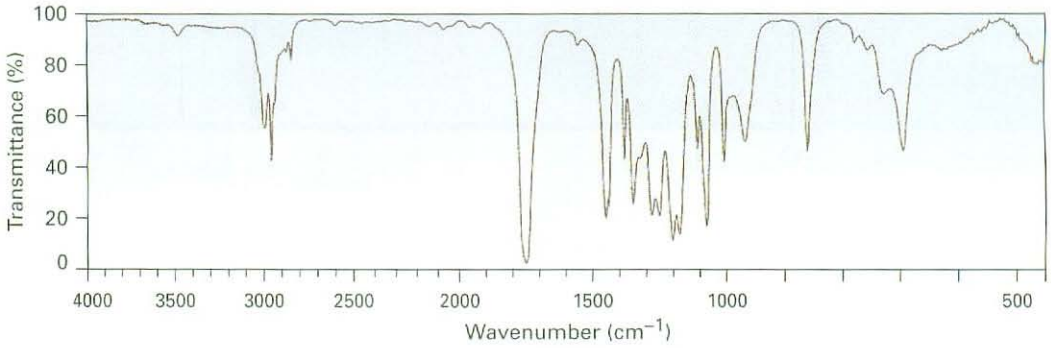


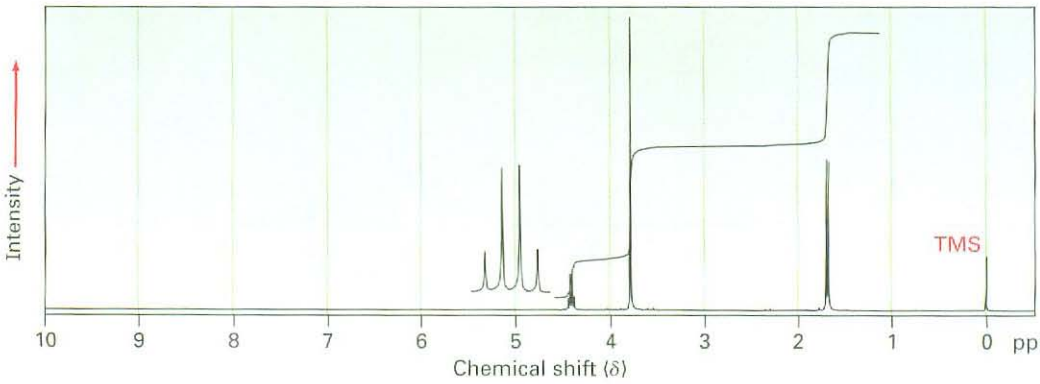
A polyimide

21.67 How would you distinguish spectroscopically between the following isomer pairs? Tell what differences you would expect to see.

(a) *N*-Methylpropanamide and *N*,*N*-dimethylacetamide
(b) 5-Hydroxypentanenitrile and cyclobutanecarboxamide
(c) 4-Chlorobutanoic acid and 3-methoxypropanoyl chloride
(d) Ethyl propanoate and propyl acetate

21.68 ■ Propose a structure for a compound, $C_4H_7ClO_2$, that has the following IR and ^1H NMR spectra:

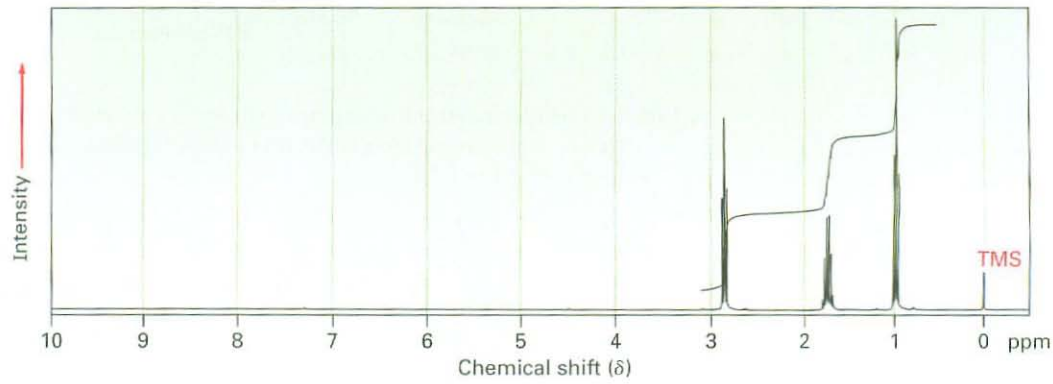




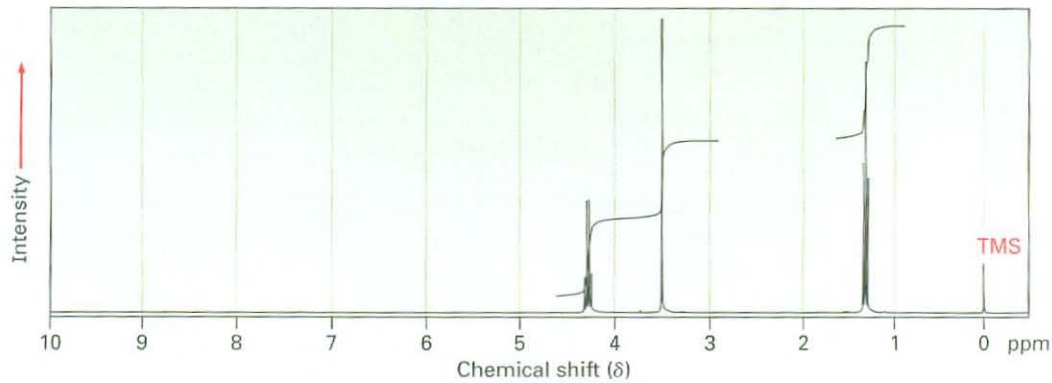
■ Assignable in OWL

21.69 ■ Assign structures to compounds with the following ^{1}H NMR spectra:

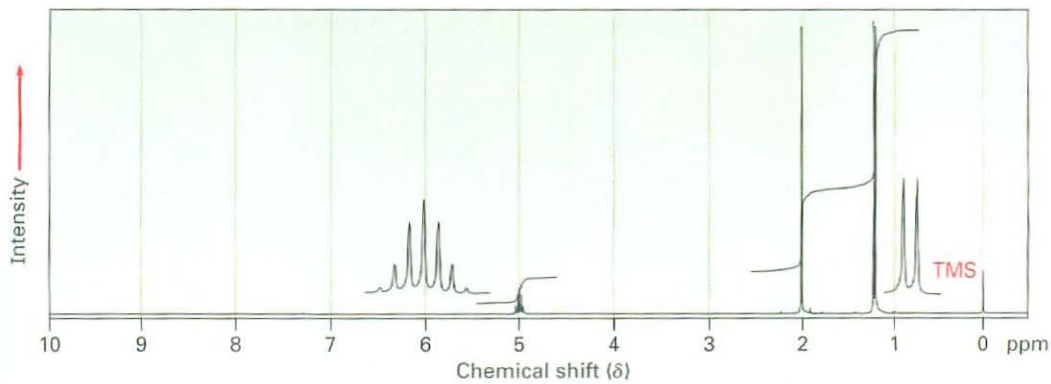
(a) C_4H_7ClO
IR: 1810 cm^{-1}



(b) $C_5H_7NO_2$
IR: 2250, 1735 cm^{-1}



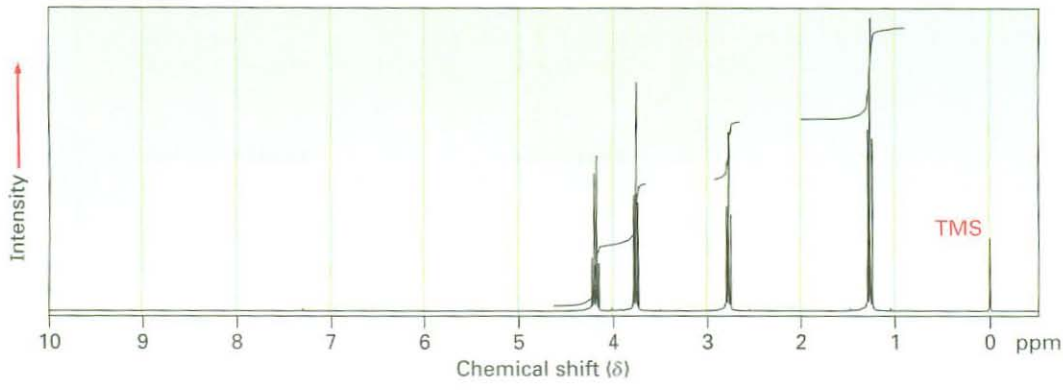
(c) $C_5H_{10}O_2$
IR: 1735 cm^{-1}



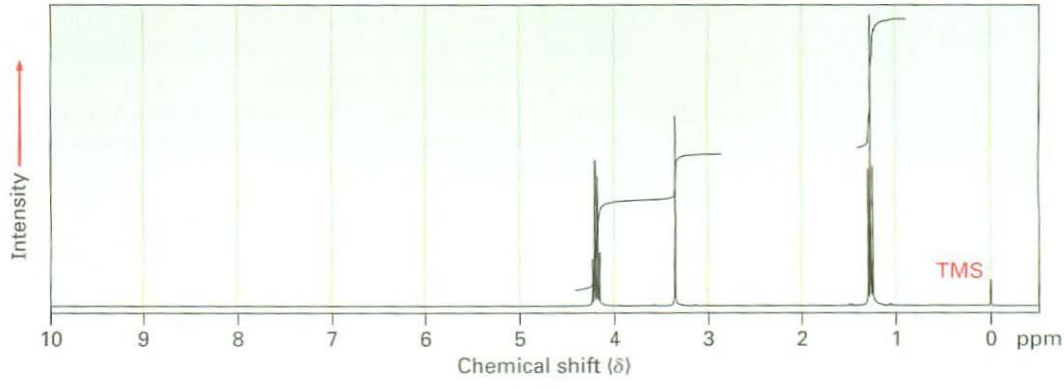
■ Assignable in OWL

21.70 ■ Propose structures for compounds with the following ^{1}H NMR spectra:

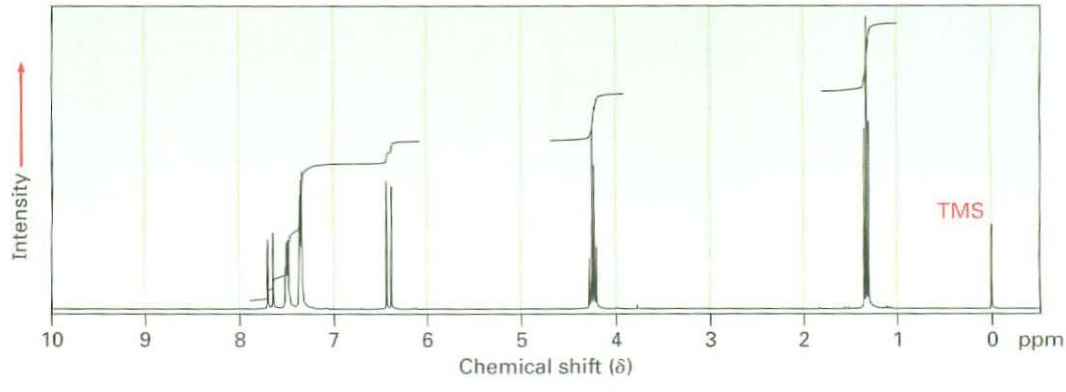
(a) $C_5H_9ClO_2$
IR: 1735 cm^{-1}



(b) $C_7H_{12}O_4$
IR: 1735 cm^{-1}

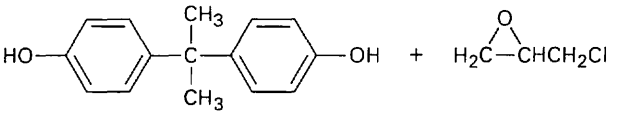


(c) $C_{11}H_{12}O_2$
IR: 1710 cm^{-1}

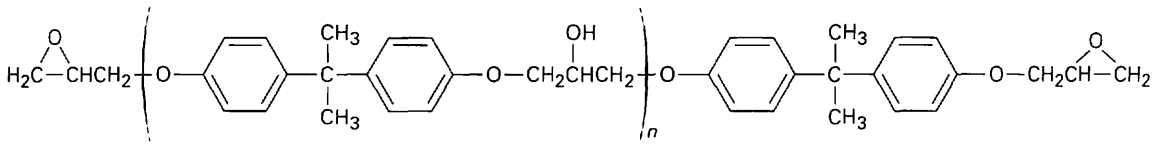


■ Assignable in OWL

21.71 Epoxy adhesives are prepared in two steps. S_N2 reaction of the disodium salt of bisphenol A with epichlorohydrin forms a "prepolymer," which is then "cured" by treatment with a triamine such as $H_2NCH_2CH_2NHCH_2CH_2NH_2$.



Bisphenol A **Epichlorohydrin**



"Prepolymer"

Draw structures to show how addition of the triamine results in strengthening the polymer. Amines are good nucleophiles and can open epoxide rings in the same way other bases can.

21.72 In the *iodoform reaction,* a triiodomethyl ketone reacts with aqueous NaOH to yield a carboxylate ion and iodoform (triiodomethane). Propose a mechanism for this reaction.