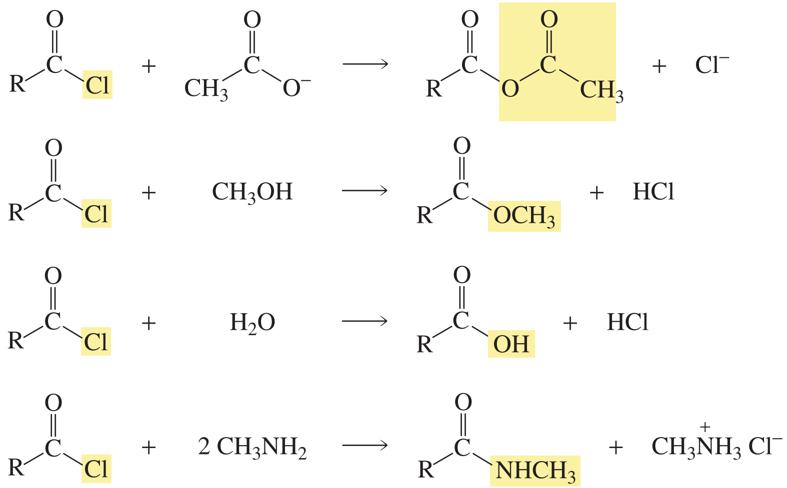
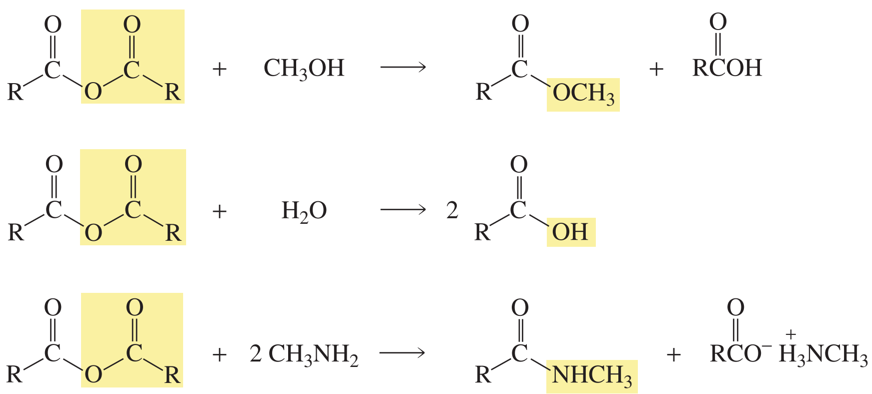
Summary of Reactions

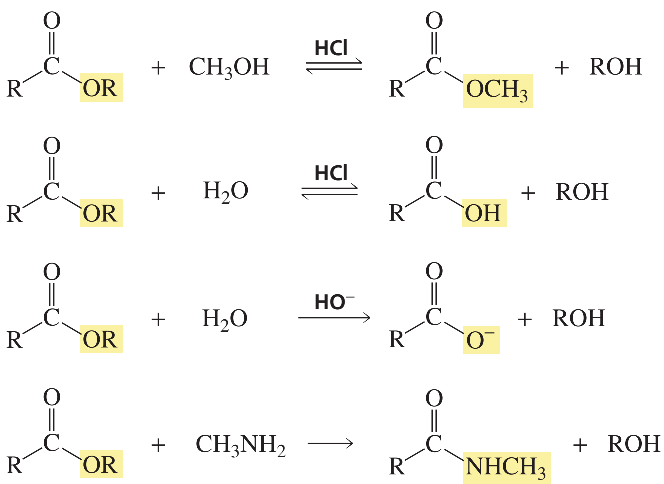
1. Reactions of acyl halides (Section 17.8)



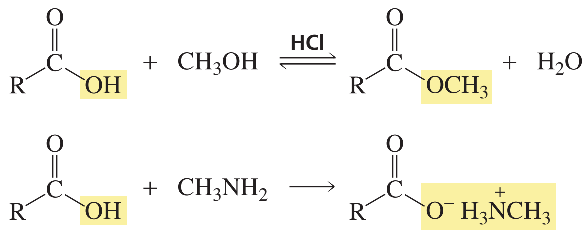
2. Reactions of acid anhydrides (Section 17.9)



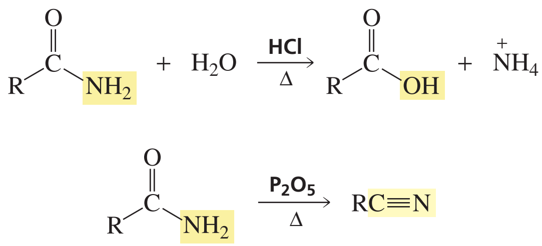
3. Reactions of esters (Sections 17.10–17.13)



4. Reactions of carboxylic acids (Section 17.14)



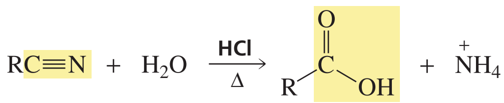
5. Reactions of amides (Sections 17.15 and 17.16)



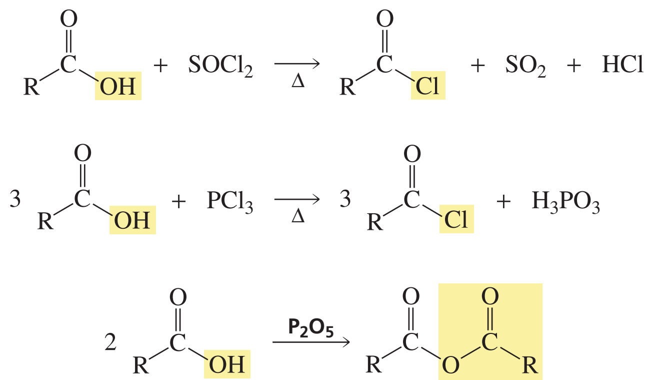
6. Gabriel synthesis of primary amines (Section 17.17)

$$RCH_2Br \xrightarrow[\text{2. HCl, } H_2O, \Delta \quad \text{3. } HO^-]{\text{1. phthalimide, } HO^-} RCH_2NH_2$$

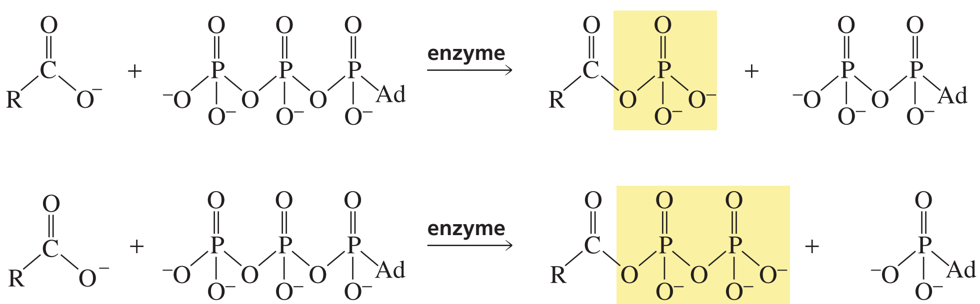
7. Hydrolysis of nitriles (Section 17.18)

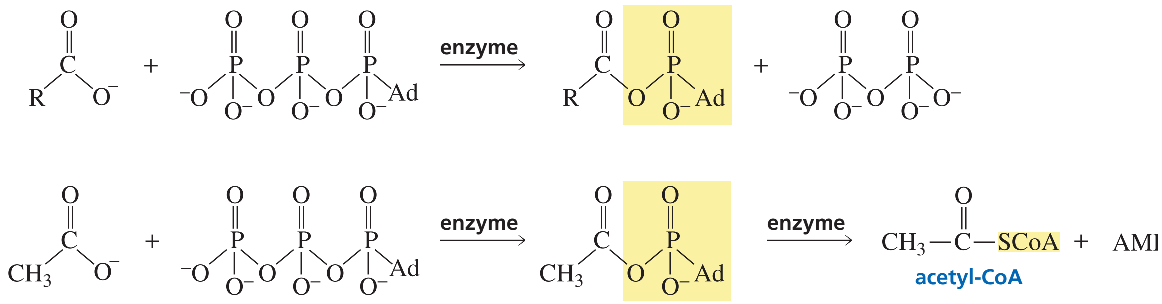


8. Activation of carboxylic acids by chemists (Section 17.20)

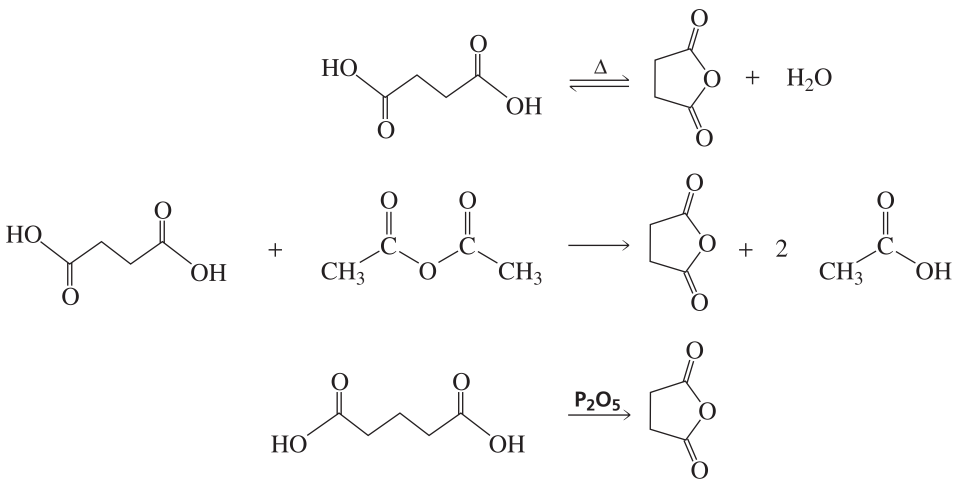


9. Activation of carboxylic acids by cells (Section 17.20)





10. Dehydration of dicarboxylic acids (Section 17.21)



Key Terms

acid anhydride (p. 673)
acyl adenylate (p. 713)
acyl group (p. 670)
acyl halide (p. 673)
acyl phosphate (p. 713)
acyl pyrophosphate (p. 713)
acyl transfer reaction (p. 682)
alcoholysis (p. 690)
α-carbon (p. 672)
amide (p. 675)
amino acid (p. 679)
aminolysis (p. 690)
biosynthesis (p. 713)
carbonyl carbon (p. 676)
carbonyl compound (p. 670)
carbonyl group (p. 670)
carbonyl oxygen (p. 676)
carboxyl group (p. 673)
carboxylic acid (p. 671)
carboxylic acid derivative (p. 670)
carboxyl oxygen (p. 674)
catalyst (p. 694)
detergent (p. 701)
ester (p. 674)
fatty acid (p. 700)
fats (p. 700)
Fischer esterification (p. 702)
Gabriel synthesis (p. 708)
hydrolysis (p. 690)
hydrophobic interactions (p. 700)
imide (p. 708)
lactam (p. 675)
lactone (p. 674)
micelle (p. 700)
mixed anhydride (p. 673)
neurotransmitter (p. 715)
nitriles (p. 675)
nucleophilic acyl substitution reaction (p. 682)
oils (p. 700)
phoshoanhydride bond (p. 714)
ritter reaction (p. 728)
saponification (p. 700)
soap (p. 700)
symmetrical anhydride (p. 673)
tetrahedral intermediate (p. 681)
thioester (p. 714)
transesterification reaction (p. 690)

Problems

38. Write a structure for each of the following compounds:
   a. *N,N*-dimethylhexanamide
   b. 3,3-dimethylhexanamide
   c. cyclohexanecarbonyl chloride
   d. propanenitrile
   e. propionyl bromide
   f. sodium acetate
   g. benzoic anhydride
   h. *β*-valerolactone
   i. 3-methylbutanenitrile
   j. cycloheptanecarboxylic acid

39. Name the following compounds:

a. $CH_3CH_2\overset{CH_2CH_3}{\overset{|}{C}}HCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$

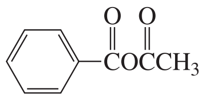
b. $CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_3$

c. $CH_3CH_2CH_2CH_2C{\equiv}N$

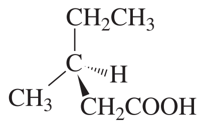
d. $CH_3CH_2\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_2CH_3$

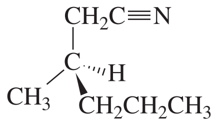
e. $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}N(CH_3)_2$

f. $CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}Cl$

g. 

h. $CH_2{=}CHCH_2\overset{O}{\overset{\|}{C}}NHCH_3$

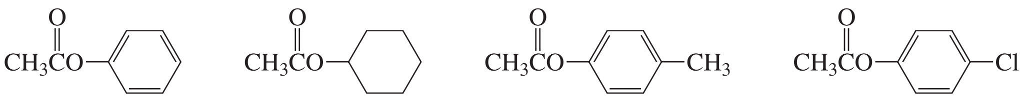
i. 

j. 

40. What products would be formed from the reaction of benzoyl chloride with the following reagents?

a. sodium acetate
b. water
c. dimethylamine
d. aqueous HCl
e. aqueous NaOH
f. cyclohexanol
g. benzylamine
h. 4-chlorophenol
i. isopropyl alcohol
j. aniline

41. a. List the following esters in order of decreasing reactivity in the first step of a nucleophilic acyl substitution reaction (formation of the tetrahedral intermediate):



A B C D

b. List the same esters in order of decreasing reactivity in the second step of a nucleophilic acyl substitution reaction (collapse of the tetrahedral intermediate).

42. a. Which compound would you expect to have a higher dipole moment, methyl acetate or butanone?

$CH_3\overset{O}{\overset{\|}{C}}OCH_3$ **methyl acetate**

$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3$ **butanone**

b. Which would you expect to have a higher boiling point?

43. How could you use ^1H NMR spectroscopy to distinguish among the following esters?

A: $CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3$

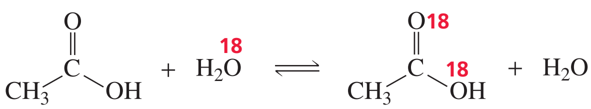
B: $H\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_3$

C: $CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_3$

D: $H\overset{O}{\overset{\|}{C}}O\overset{CH_3}{\overset{|}{C}}HCH_3$

44. If propionyl chloride is added to one equivalent of methylamine, only a 50% yield of *N*-methylpropanamide is obtained. If, however, the acyl chloride is added to two equivalents of methylamine, the yield of *N*-methylpropanamide is almost 100%. Explain these observations.

45. a. When a carboxylic acid is dissolved in isotopically labeled water (H_2O^{18}), the label is incorporated into both oxygens of the acid. Propose a mechanism to account for this.

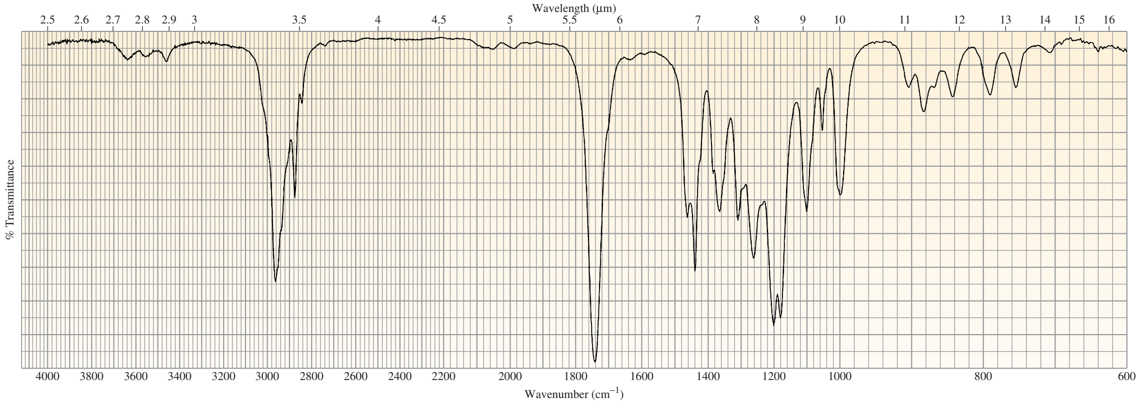


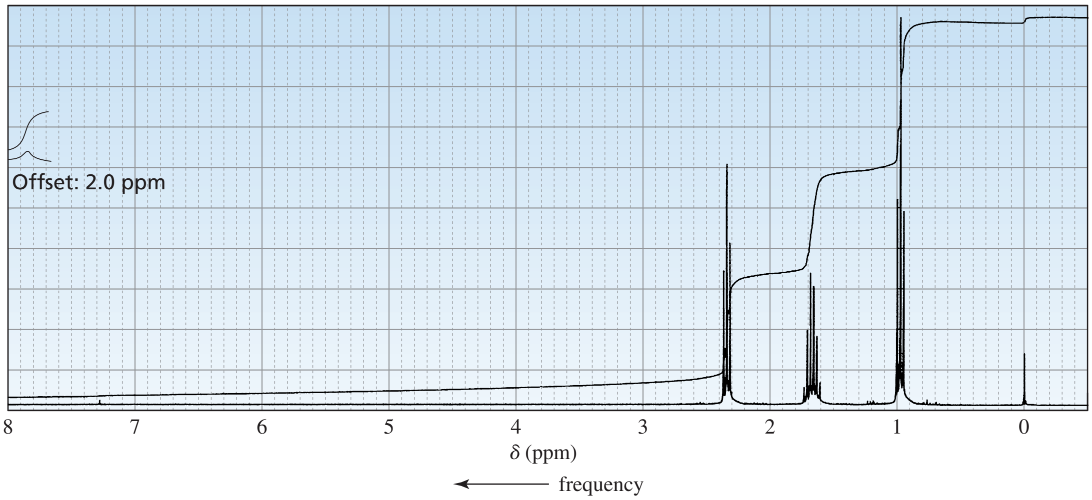
b. If a carboxylic acid is dissolved in isotopically labeled methanol ($CH_3{}^{18}OH$) and an acid catalyst is added, where will the label reside in the product?

46. What reagents would you use to convert methyl propanoate into the following compounds?

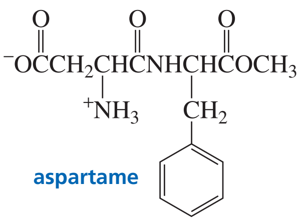
a. isopropyl propanoate
b. sodium propanoate
c. *N*-ethylpropanamide
d. propanoic acid

47. A compound with molecular formula $C_5H_{10}O_2$ gives the following IR spectrum. When it undergoes acid-catalyzed hydrolysis, the compound with the following ^1H NMR spectrum is formed. Identify the compounds.





48. Aspartame, the sweetener used in the commercial products NutraSweet® and Equal®, is 160 times sweeter than sucrose. What products would be obtained if aspartame were hydrolyzed completely in an aqueous solution of HCl?



49. a. Which of the following reactions will not give the carbonyl product shown?

1. $CH_3\overset{O}{\overset{\parallel}{C}}OH + CH_3\overset{O}{\overset{\parallel}{C}}O^- \longrightarrow CH_3\overset{O}{\overset{\parallel}{C}}O\overset{O}{\overset{\parallel}{C}}CH_3$

2. $CH_3\overset{O}{\overset{\parallel}{C}}Cl + CH_3\overset{O}{\overset{\parallel}{C}}O^- \longrightarrow CH_3\overset{O}{\overset{\parallel}{C}}O\overset{O}{\overset{\parallel}{C}}CH_3$

3. $CH_3\overset{O}{\overset{\parallel}{C}}NH_2 + Cl^- \longrightarrow CH_3\overset{O}{\overset{\parallel}{C}}Cl$

4. $CH_3\overset{O}{\overset{\parallel}{C}}OH + CH_3NH_2 \longrightarrow CH_3\overset{O}{\overset{\parallel}{C}}NHCH_3$

5. $CH_3\overset{O}{\overset{\parallel}{C}}OCH_3 + CH_3NH_2 \longrightarrow CH_3\overset{O}{\overset{\parallel}{C}}NHCH_3$

6. $CH_3\overset{O}{\overset{\parallel}{C}}OCH_3 + Cl^- \longrightarrow CH_3\overset{O}{\overset{\parallel}{C}}Cl$

7. $CH_3\overset{O}{\overset{\|}{C}}NHCH_3 + CH_3\overset{O}{\overset{\|}{C}}O^- \longrightarrow CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3$

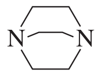
8. $CH_3\overset{O}{\overset{\|}{C}}Cl + H_2O \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OH$

9. $CH_3\overset{O}{\overset{\|}{C}}NHCH_3 + H_2O \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OH$

10. $CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}H_3 + CH_3OH \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OCH_3$

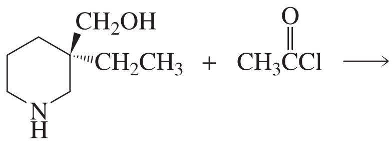
b. Which of the reactions that do not occur can be made to occur if an acid catalyst is added to the reaction mixture?

50. 1,4-Diazabicyclo[2.2.2]octane (abbreviated DABCO) is a tertiary amine that catalyzes transesterification reactions. Propose a mechanism to show how it does this.

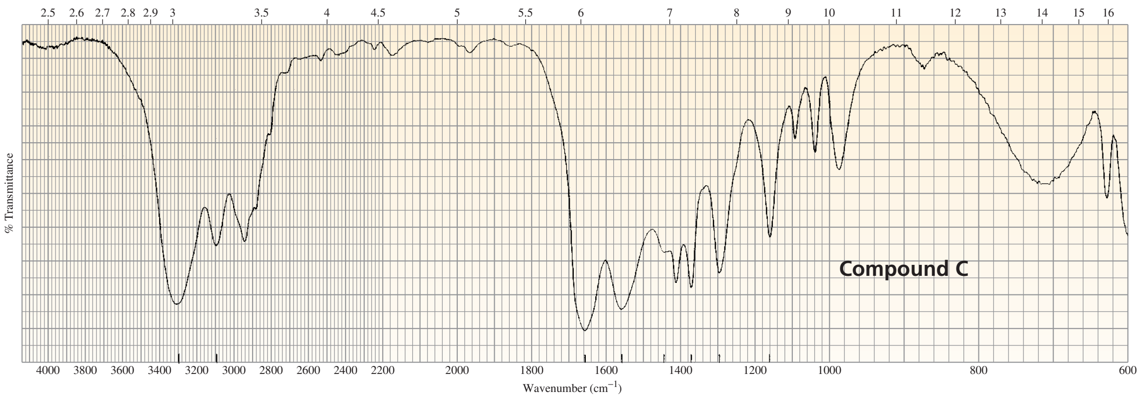


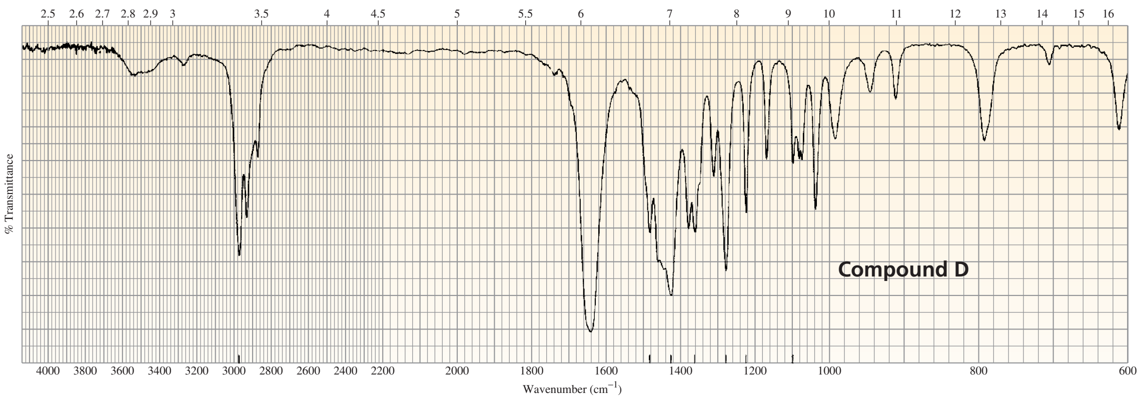
1,4-diazabicyclo[2.2.2]octane
DABCO

51. Identify the major and minor products of the following reaction:



52. Two products, A and B, are obtained from the reaction of 1-bromobutane with NH_3. Compound A reacts with acetyl chloride to form C, and B reacts with acetyl chloride to form D. The IR spectra of C and D are shown. Identify A, B, C, and D.





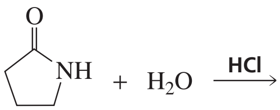
53. Phosgene ($COCl_2$) was used as a poison gas in World War I. Give the product that would be formed from the reaction of phosgene with each of the following reagents:

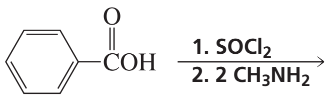
1. one equivalent of methanol
2. excess methanol
3. excess propylamine
4. one equivalent of ethanol followed by one equivalent of methylamine

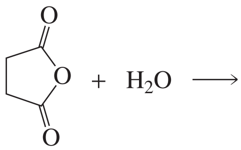
54. When Ethyl Ester treated butanedioic acid with thionyl chloride, she was surprised to find that the product she obtained was an anhydride rather than an acyl chloride. Propose a mechanism to explain why she obtained an anhydride.

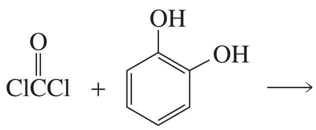
55. Give the products of the following reactions:

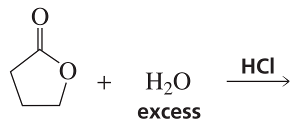
a. $CH_3\overset{\overset{\displaystyle O}{\|}}{C}Cl$ + KF ⟶

b. 

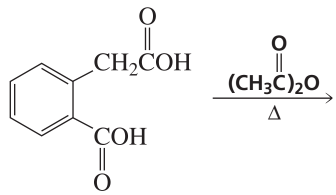
c. 

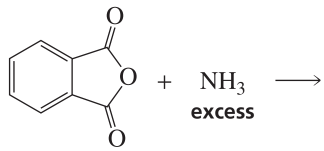
d. 

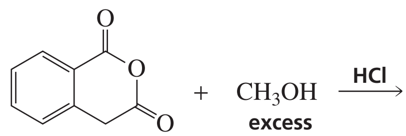
e. 

f. 

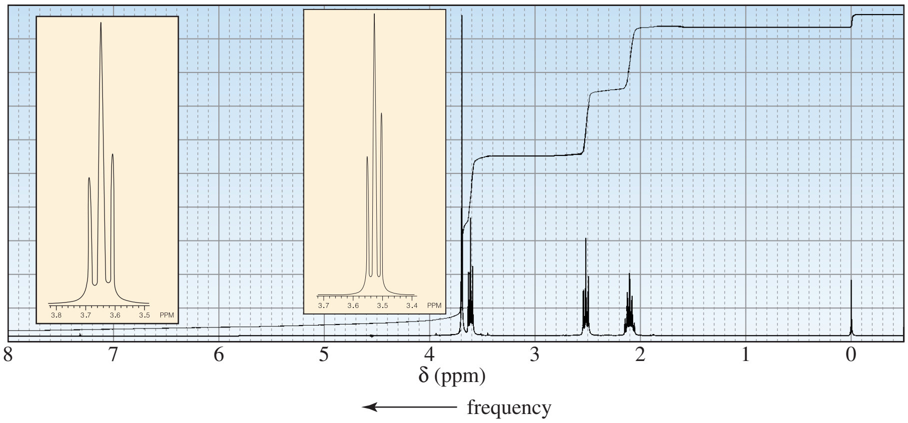
g. $CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2O\overset{\overset{\displaystyle O}{\|}}{C}CH_3$ + CH_3OH (excess) $\xrightarrow{CH_3O^-}$

h. 

i. 

j. 

56. When treated with an equivalent of methanol, compound A, with molecular formula $C_4H_6Cl_2O$, forms the compound whose ^1H NMR spectrum is shown below. Identify compound A.



57. a. Identify the two products obtained from the following reaction:

$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}O\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \ (\text{excess}) + CH_3\overset{\overset{\displaystyle NH_2}{|}}{C}HCH_2CH_2OH \longrightarrow$$

b. Eddie Amine carried out the preceding reaction, but stopped it before it was half over, whereupon he isolated the major product. He was surprised to find that the product he isolated was neither of the products obtained when the reaction was allowed to go to completion. What product did he isolate?

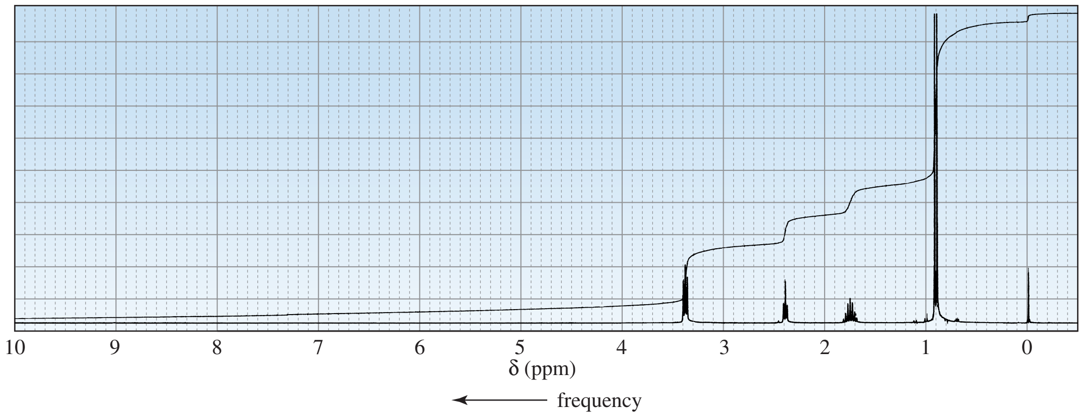
58. An aqueous solution of a primary or secondary amine reacts with an acyl chloride to form an amide as the major product. However, if the amine is tertiary, an amide is not formed. What product *is* formed? Explain.

59. a. Ann Hydride did not obtain any ester when she added 2,4,6-trimethylbenzoic acid to an acidic solution of methanol. Why? (*Hint:* Build models.)

b. Would Ann have encountered the same problem if she had tried to synthesize the methyl ester of *p*-methylbenzoic acid in the same way?

c. How could she prepare the methyl ester of 2,4,6-trimethylbenzoic acid? (*Hint:* See Section 16.12.)

60. When a compound with molecular formula $C_{11}H_{14}O_2$ undergoes acid-catalyzed hydrolysis, one of the products that is isolated gives the following ^1H NMR spectrum. Identify the compound.



61. List the following compounds in order of decreasing frequency of the carbon–oxygen double-bond stretch:

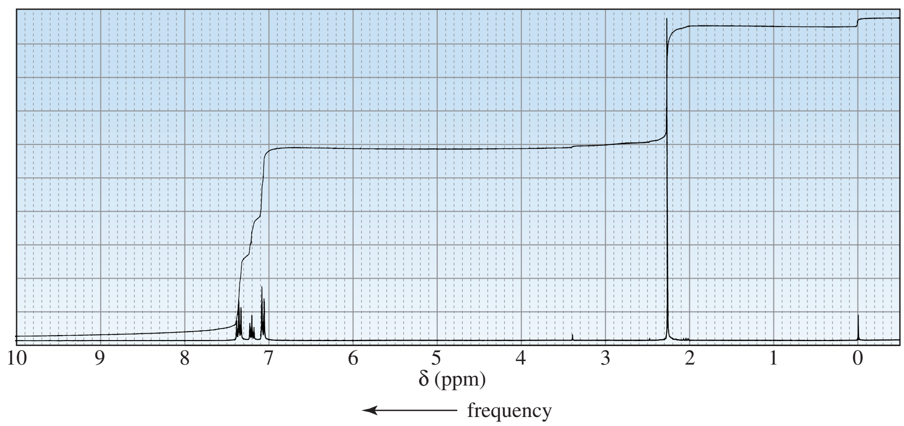
$CH_3C(=O)OCH_3$ $\quad$ $CH_3C(=O)Cl$ $\quad$ $CH_3C(=O)H$ $\quad$ $CH_3C(=O)NH_2$

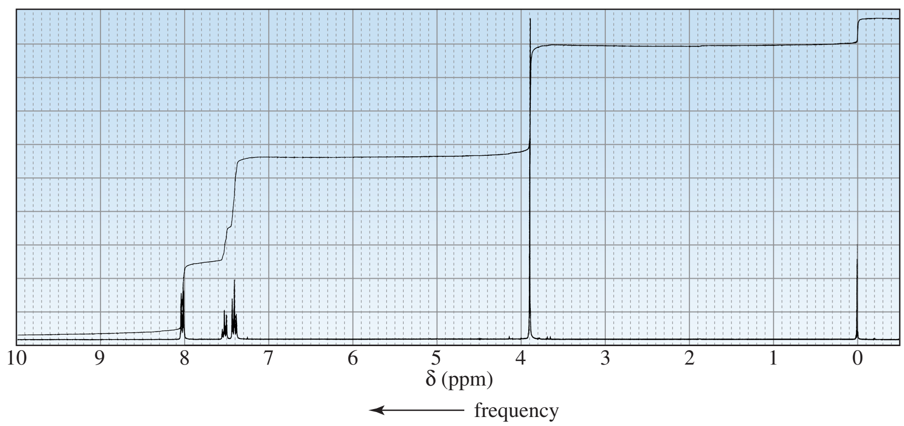
62. a. If the equilibrium constant for the reaction of acetic acid and ethanol to form ethyl acetate is 4.02, what will be the concentration of ethyl acetate at equilibrium if the reaction is carried out with equal amounts of acetic acid and ethanol?
b. What will be the concentration of ethyl acetate at equilibrium if the reaction is carried out with 10 times more ethanol than acetic acid? *Hint:* Recall the quadratic equation: For $ax^2 + bx + c = 0$,

$$x = \frac{-b \pm (b^2 - 4ac)^{1/2}}{2a}$$

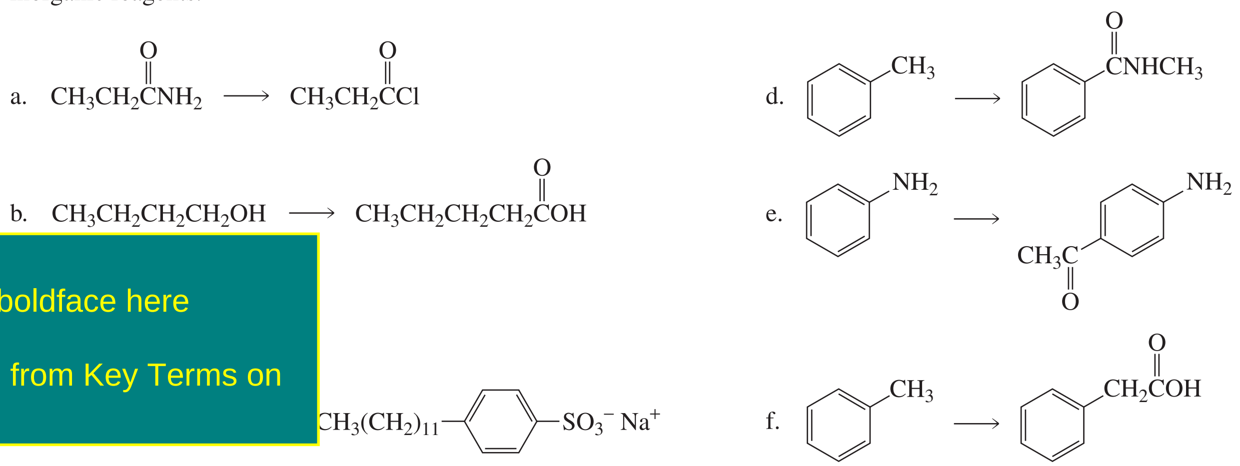
c. What will be the concentration of ethyl acetate at equilibrium if the reaction is carried out with 100 times more ethanol than acetic acid?

63. The ^1H NMR spectra for two esters with molecular formula $C_8H_8O_2$ are shown below. If each of the esters is added to an aqueous solution with a pH of 10, which of the esters will be hydrolyzed more completely when the hydrolysis reactions have reached equilibrium?





64. Show how the following compounds could be prepared from the given starting materials. You can use any necessary organic or inorganic reagents.

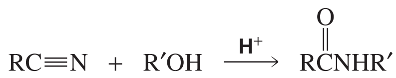


a detergent

Ray,
pls. check boldface here
s/b italics?
s/b deleted from Key Terms on p. 722?

65. Is the acid-catalyzed hydrolysis of acetamide a reversible or an irreversible reaction? Explain.

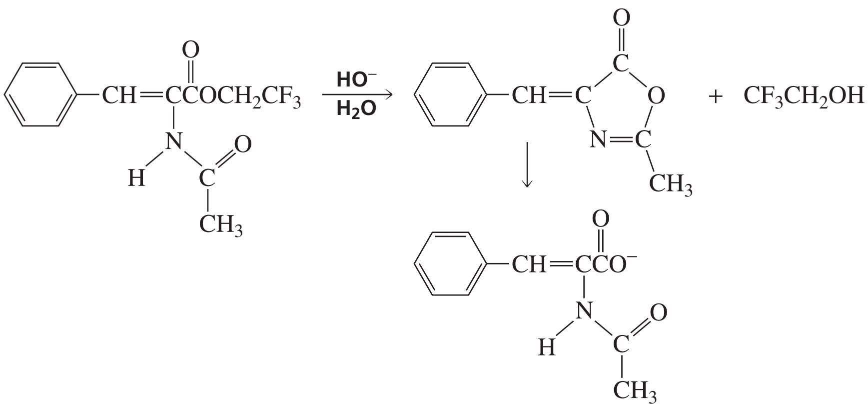
66. The reaction of a nitrile with an alcohol in the presence of a strong acid forms a secondary amide. This reaction is known as the **Ritter reaction**. The Ritter reaction does not work with primary alcohols.



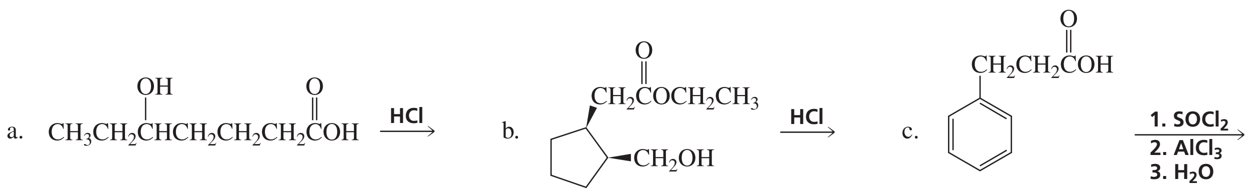
the Ritter reaction

a. Propose a mechanism for the Ritter reaction.
b. Why does the Ritter reaction not work with primary alcohols?
c. How does the Ritter reaction differ from the acid-catalyzed hydrolysis of a nitrile to form a primary amide?

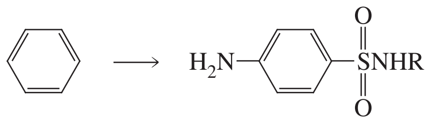
67. The intermediate shown here is formed during the hydroxide-ion-promoted hydrolysis of the ester group. Propose a mechanism for the reaction.



68. What product would you expect to obtain from each of the following reactions?

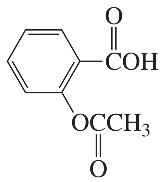


69. Sulfonamides, the first antibiotics, were introduced clinically in 1934 (Sections 25.8 and 30.4). Show how a sulfonamide can be prepared from benzene.

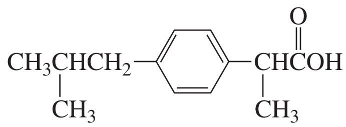


a sulfonamide

70. a. How could aspirin be synthesized, starting with benzene?
    b. Ibuprofen is the active ingredient in pain relievers such as Advil®, Motrin®, and Nuprin®. How could ibuprofen be synthesized, starting with benzene?

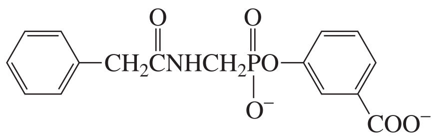


aspirin

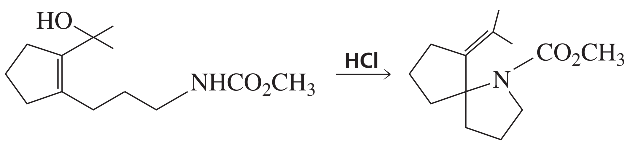


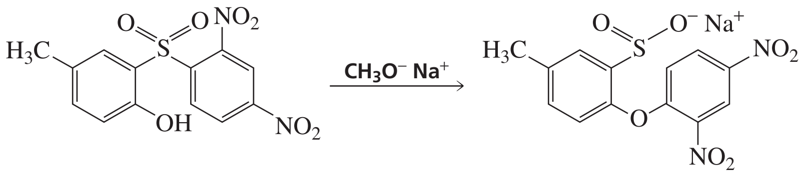
ibuprofen

71. The following compound has been found to be an inhibitor of penicillinase. The enzyme can be reactivated by hydroxylamine (NH_2OH). Propose a mechanism to account for the inhibition and for the reactivation.

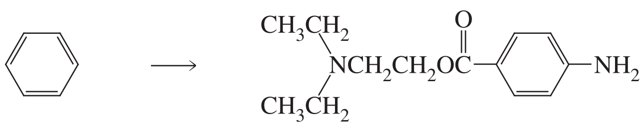


72. For each of the following reactions, propose a mechanism that will account for the formation of the product:

a. 

b. 

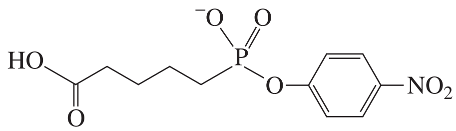
73. Show how Novocain®, a painkiller used frequently by dentists (Section 30.3), can be prepared from benzene.



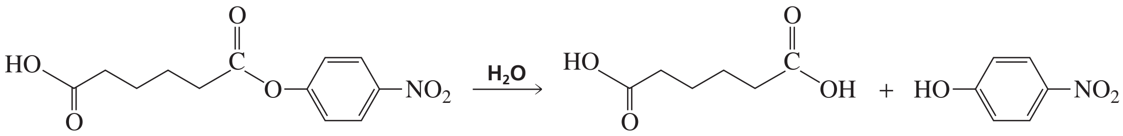
Novocain®

74. Catalytic antibodies catalyze a reaction by binding to the transition state, thereby stabilizing it. As a result, the energy of activation is lowered and the reaction goes faster. The synthesis of the antibody is carried out in the presence of a transition state analog—a

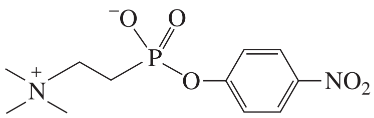
stable molecule that structurally resembles the transition state. This causes an antibody to be generated that will recognize and bind to the transition state. For example, the following transition state analog has been used to generate a catalytic antibody that catalyzes the hydrolysis of the structurally similar ester:



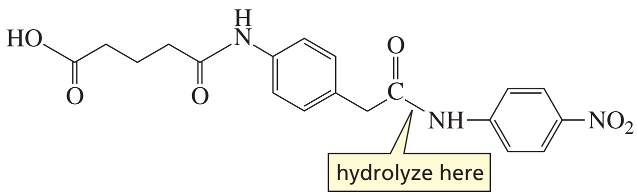
transition state analog



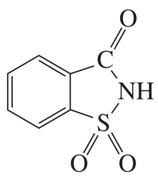
a. Draw the transition state for the hydrolysis reaction.
b. The following transition state analog is used to generate a catalytic antibody for the catalysis of ester hydrolysis. Give the structure of an ester whose rate of hydrolysis would be increased by this catalytic antibody.



c. Design a transition state analog that would catalyze amide hydrolysis at the amide group indicated.



75. Saccharin, an artificial sweetener, is about 300 times sweeter than sucrose. Describe how saccharin could be prepared, using benzene as the starting material.



saccharin

76. Information about the mechanism of reaction of a series of substituted benzenes can be obtained by plotting the logarithm of the observed rate constant obtained at a particular pH against the Hammett substituent constant (σ) for the particular substituent. The σ value for hydrogen is 0. Electron-donating substituents have negative σ values; electron-withdrawing substituents have positive σ values. The more strongly electron donating the substituent, the more negative its σ value will be; the more strongly electron withdrawing the substituent, the more positive value its σ value will be. The slope of a plot of the logarithm of the rate constant versus σ is called the ρ (rho) value. The ρ value for the hydroxide-ion-promoted hydrolysis of a series of meta- and para-substituted ethyl benzoates is $+2.46$; the ρ value for amide formation for the reaction of a series of meta- and para-substituted anilines with benzoyl chloride is -2.78.
a. Why does one set of experiments give a positive ρ value while the other set of experiments gives a negative ρ value?
b. Why do you think that ortho-substituted compounds were not included in the experiment?
c. What would you predict the sign of the ρ value to be for the ionization of a series of meta- and para-substituted benzoic acids?