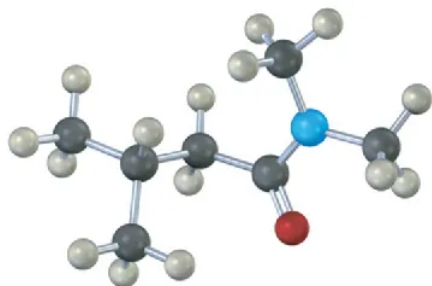


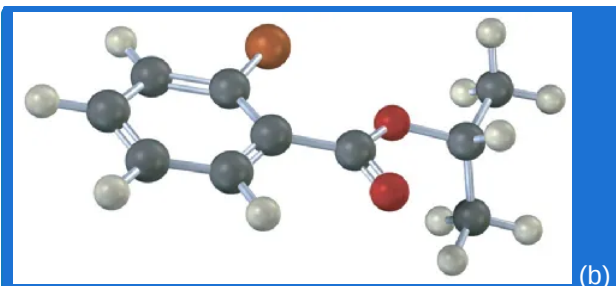
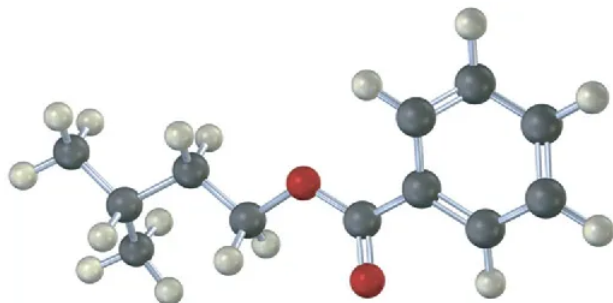
## 7.12: Additional Problems

### Visualizing Chemistry

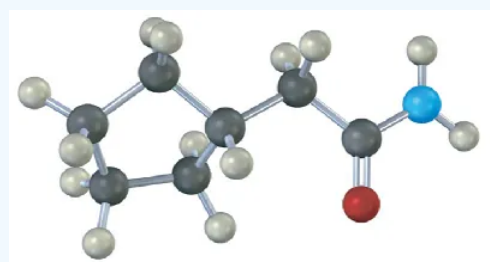
Name the following compounds: (a)



(b)

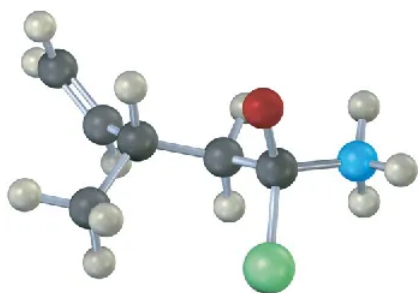


(b)

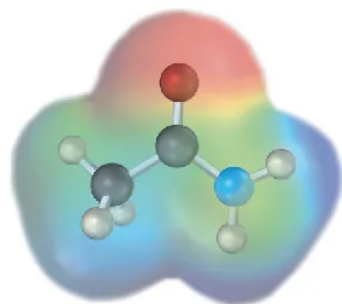


#### Problem 21-29

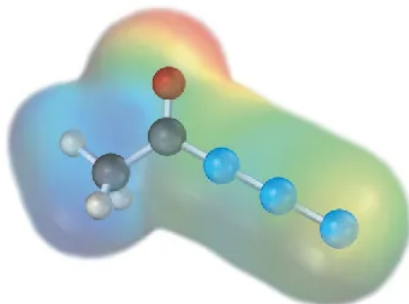
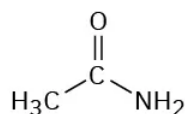
The following structure represents a tetrahedral alkoxide-ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product (green = Cl).



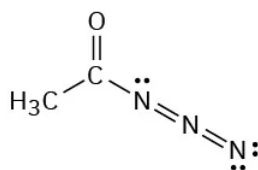
Electrostatic potential maps of a typical amide (acetamide) and an acyl azide (acetyl azide) are shown. Which of the two do you think is more reactive in nucleophilic acyl substitution reactions? Explain.



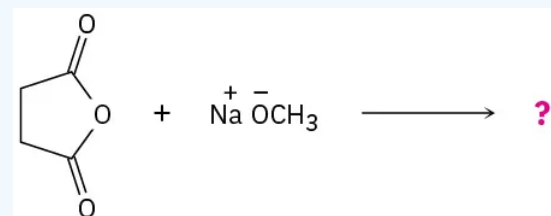
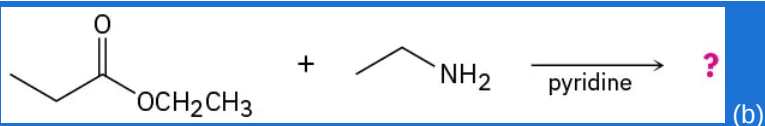
**Acetamide**



**Acetyl azide**

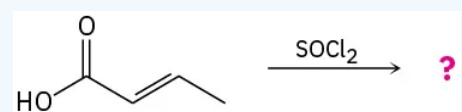
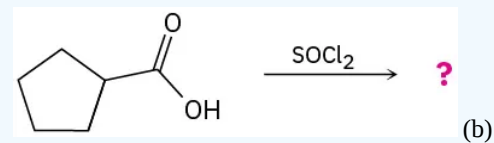


### Mechanism Problems



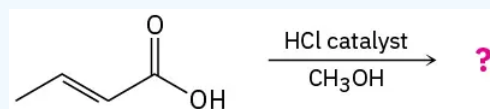
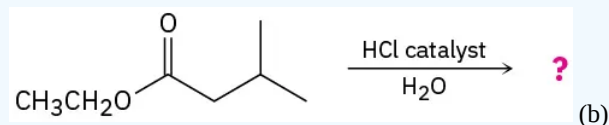
Problem 21-32

Predict the product(s) and write the mechanism for the following reactions: (a)



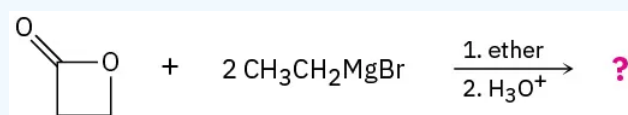
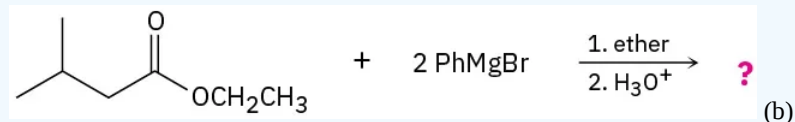
Problem 21-33

Predict the product(s) and write the mechanism for each of the following reactions: (a)



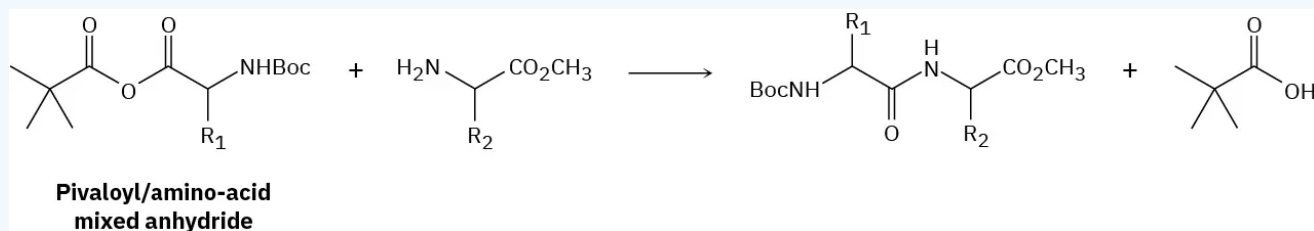
Problem 21-34

Predict the product(s) and write the mechanism for the following reactions: (a)



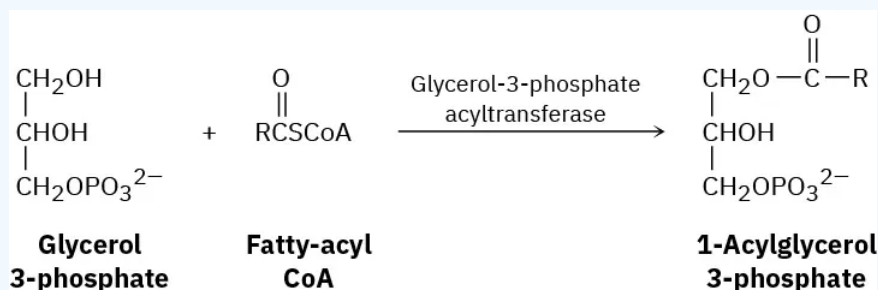
Problem 21-35

Pivalic mixed anhydrides are often used to form amide bonds between amino acids. Unlike with a symmetrical anhydride, this reaction is highly regioselective, with the nucleophile adding only to the amino-acid carbonyl. Provide the complete mechanism for the following reaction and explain the regioselectivity.

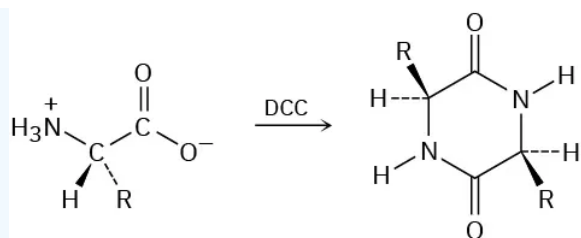


When 4-dimethylaminopyridine (DMAP) is added in catalytic amounts to acetic anhydride and an alcohol, it significantly increases the rate of ester formation. The process begins with a reaction between acetic anhydride and DMAP to form a highly reactive acetylpyridinium intermediate that is more reactive than acetic anhydride itself. Propose a mechanism for this process that includes the formation and reaction of the acetylpyridinium intermediate.

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.



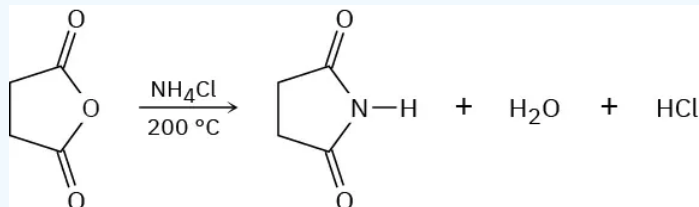
Treatment of an  $\alpha$ -amino acid with DCC yields a 2,5-diketopiperazine. Propose a mechanism.



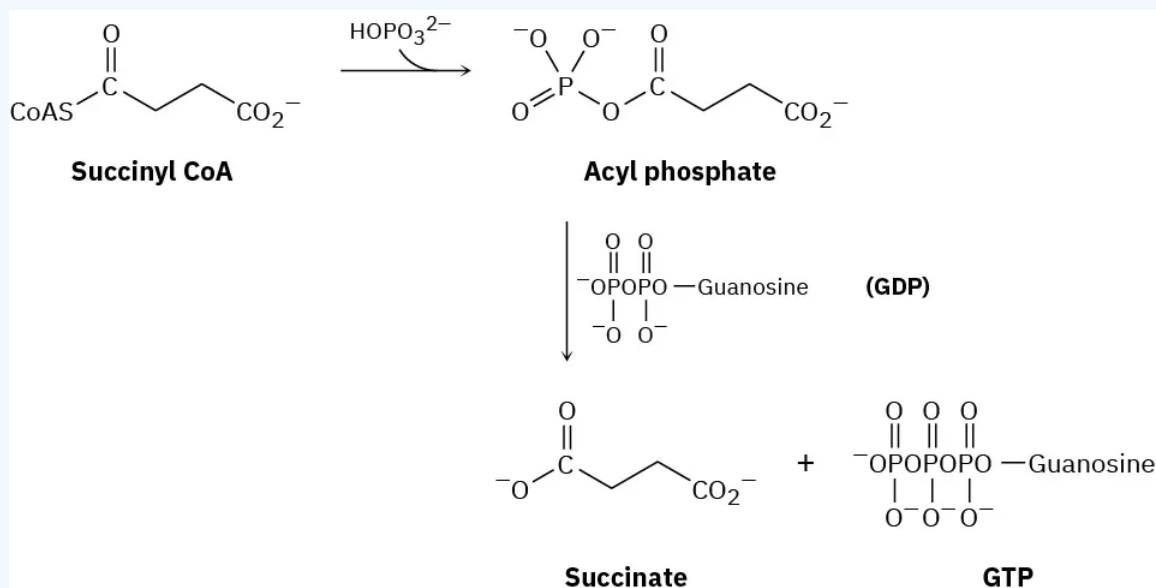
An  $\alpha$ -amino acid

A 2,5-diketopiperazine

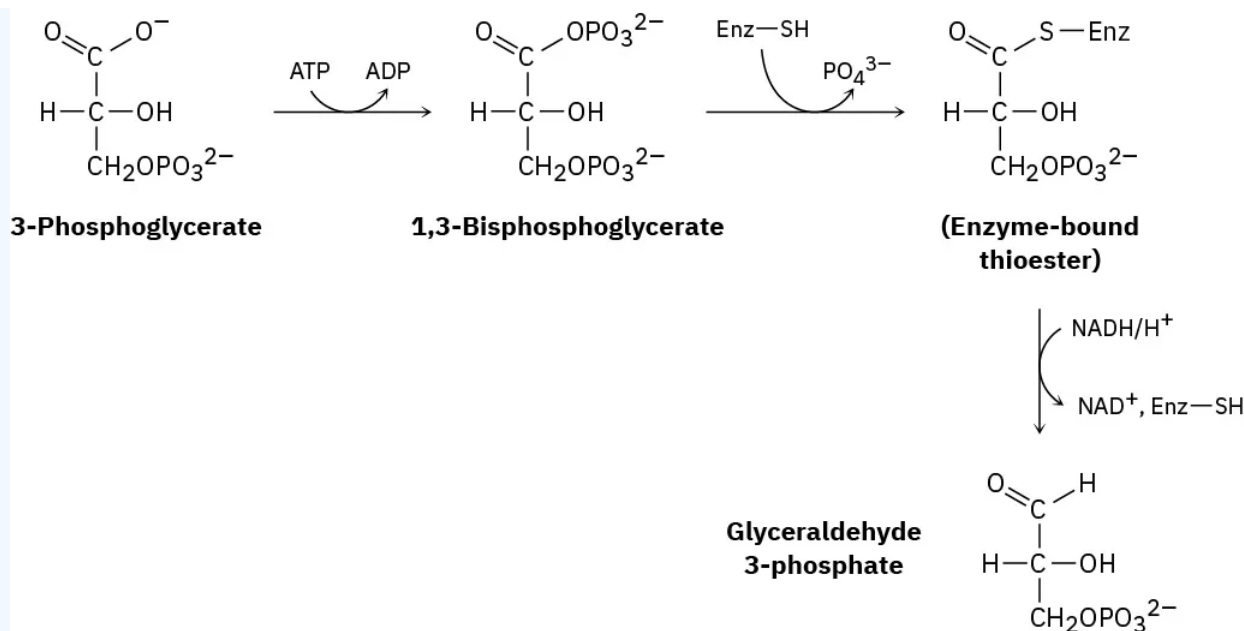
Succinic anhydride yields the cyclic imide succinimide when heated with ammonium chloride at 200 °C. Propose a mechanism for this reaction. Why do you suppose such a high reaction temperature is required?



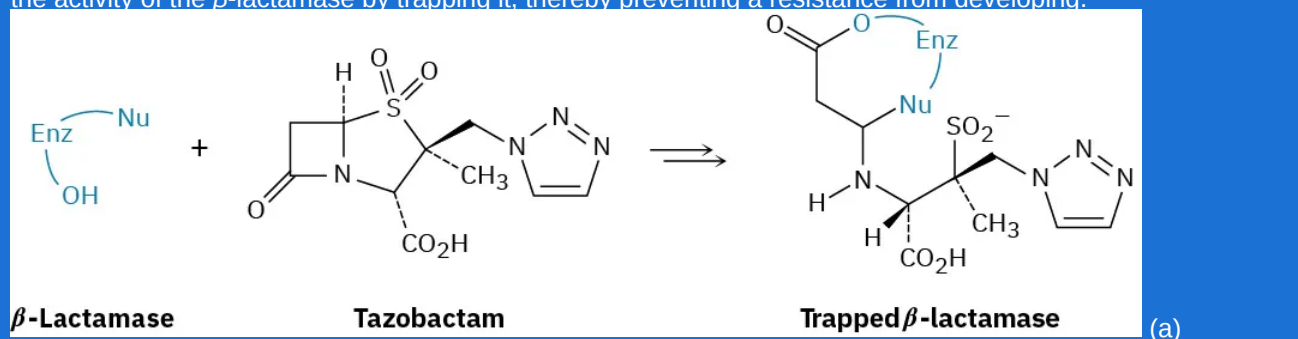
The hydrolysis of a biological thioester to the corresponding carboxylate is often more complex than the overall result might suggest. The conversion of succinyl CoA to succinate in the citric acid cycle, for instance, occurs by initial formation of an acyl phosphate, followed by reaction with guanosine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



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.



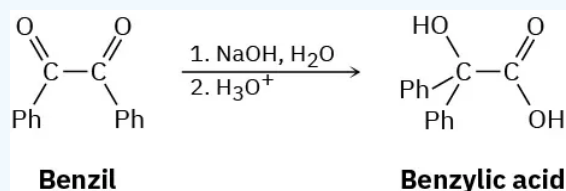
Bacteria typically develop a resistance to penicillins and other  $\beta$ -lactam antibiotics (see *Chemistry Matters* at the end of this chapter) due to bacterial synthesis of  $\beta$ -lactamase enzymes. Tazobactam, however, is able to inhibit the activity of the  $\beta$ -lactamase by trapping it, thereby preventing a resistance from developing.



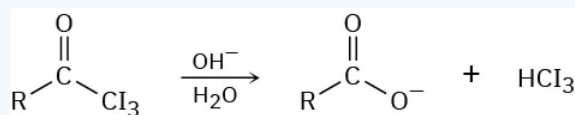
The first step in trapping is reaction of a hydroxyl group on the  $\beta$ -lactamase to open the  $\beta$ -lactam ring of tazobactam. Show the mechanism.

(b) The second step is opening the sulfur-containing ring in tazobactam to give an acyclic imine intermediate. Show the mechanism. (c) Cyclization of the imine intermediate gives the trapped  $\beta$ -lactamase product. Show the mechanism.

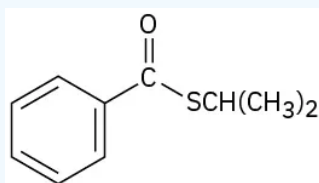
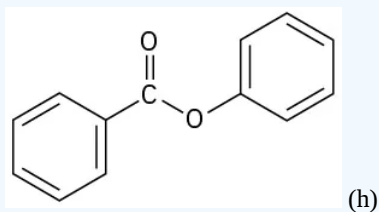
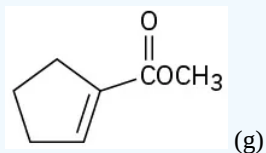
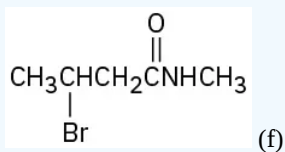
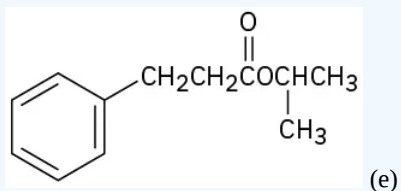
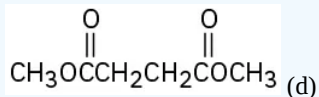
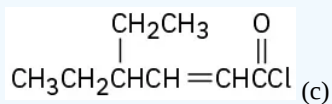
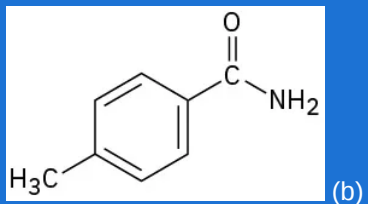
The following reaction, called the *benzilic acid rearrangement*, takes place by typical carbonyl-group reactions. Propose a mechanism (Ph = phenyl).



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.



## Naming Carboxylic Acid Derivatives



*p*-Bromophenylacetamide

(b) *m*-Benzoylbenzamide

(c) 2,2-Dimethylhexanamide (d) Cyclohexyl cyclohexanecarboxylate (e) Ethyl 2-cyclobutenecarboxylate (f) Succinic anhydride

Three acid chlorides having the formula  $C_6H_9ClO$

(b) Three amides having the formula  $C_7H_{11}NO$

## Nucleophilic Acyl Substitution Reactions

**Li(Ph)<sub>2</sub>Cu in ether**

(b) LiAlH<sub>4</sub>, then H<sub>3</sub>O<sup>+</sup> (c) CH<sub>3</sub>MgBr, then H<sub>3</sub>O<sup>+</sup> (d) H<sub>3</sub>O<sup>+</sup> (e) Cyclohexanol (f) Aniline (g) CH<sub>3</sub>CO<sub>2</sub><sup>-</sup> Na<sup>+</sup>

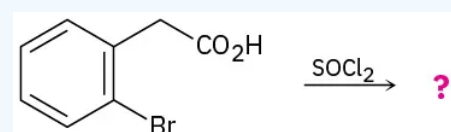
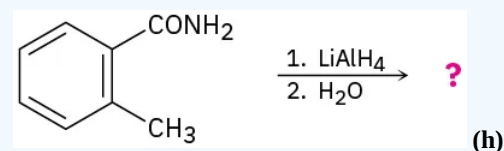
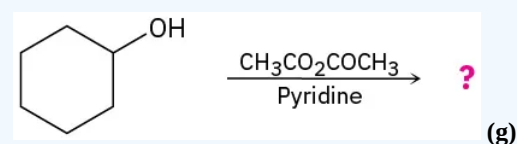
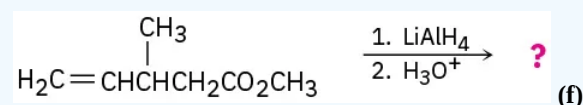
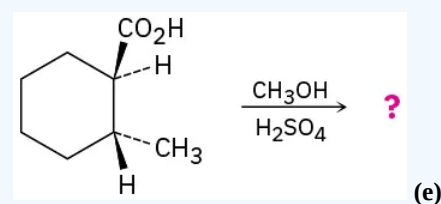
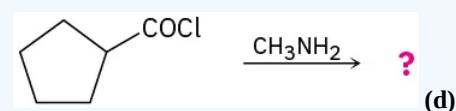
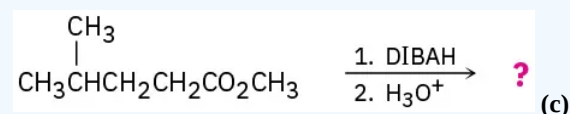
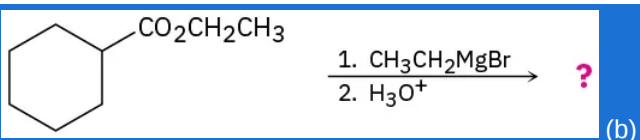
**Answer Problem 21-48 for reaction of the listed reagents with methyl propanoate.**

**Answer Problem 21-48 for reaction of the listed reagents with propanamide.**

**What product would you expect to obtain from Grignard reaction of an excess of phenylmagnesium bromide with dimethyl carbonate, CH<sub>3</sub>OCO<sub>2</sub>CH<sub>3</sub>?**

**1-Butanol**

(b) Butanal (c) 1-Bromobutane (d) Pentanenitrile (e) 1-Butene (f) *N*-Methylpentanamide (g) 2-Hexanone (h) Butylbenzene (i) Butanenitrile



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



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?

**Benzene**

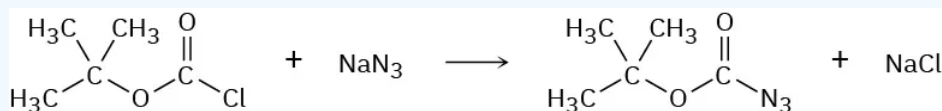
(b)

Bromobenzene (c) Methyl benzoate (d) Benzonitrile (e) Styrene

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

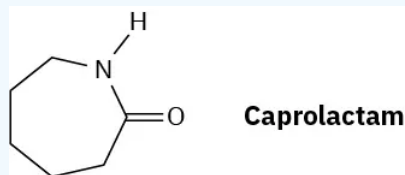
When *ethyl* benzoate is heated in methanol containing a small amount of HCl, *methyl* benzoate is formed. Propose a mechanism for the reaction.

*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.

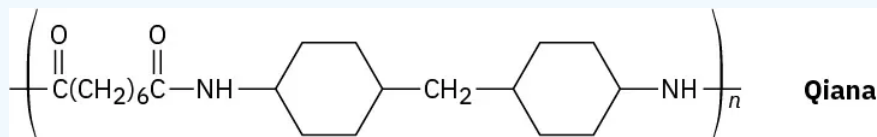


### Step-Growth Polymers

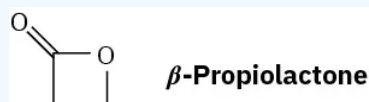
The step-growth polymer nylon 6 is prepared from caprolactam. The reaction involves initial reaction of caprolactam with water to give an intermediate open-chain amino acid, followed by heating to form the polymer. Propose mechanisms for both steps, and show the structure of nylon 6.



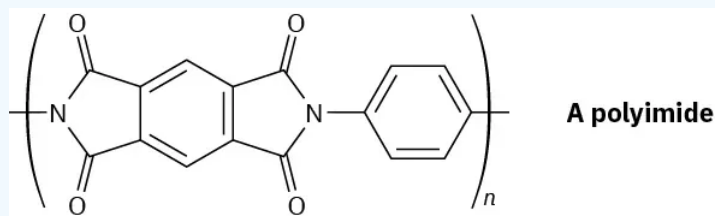
Qiana, a polyamide fiber with a silky texture, has the following structure. What are the monomer units used in the synthesis of Qiana?



What is the structure of the polymer produced by treatment of  $\beta$ -propiolactone with a small amount of hydroxide ion?



Polyimides with the structure shown are used as coatings on glass and plastics to improve scratch resistance. How would you synthesize a polyimide? (See Problem 21-39.)



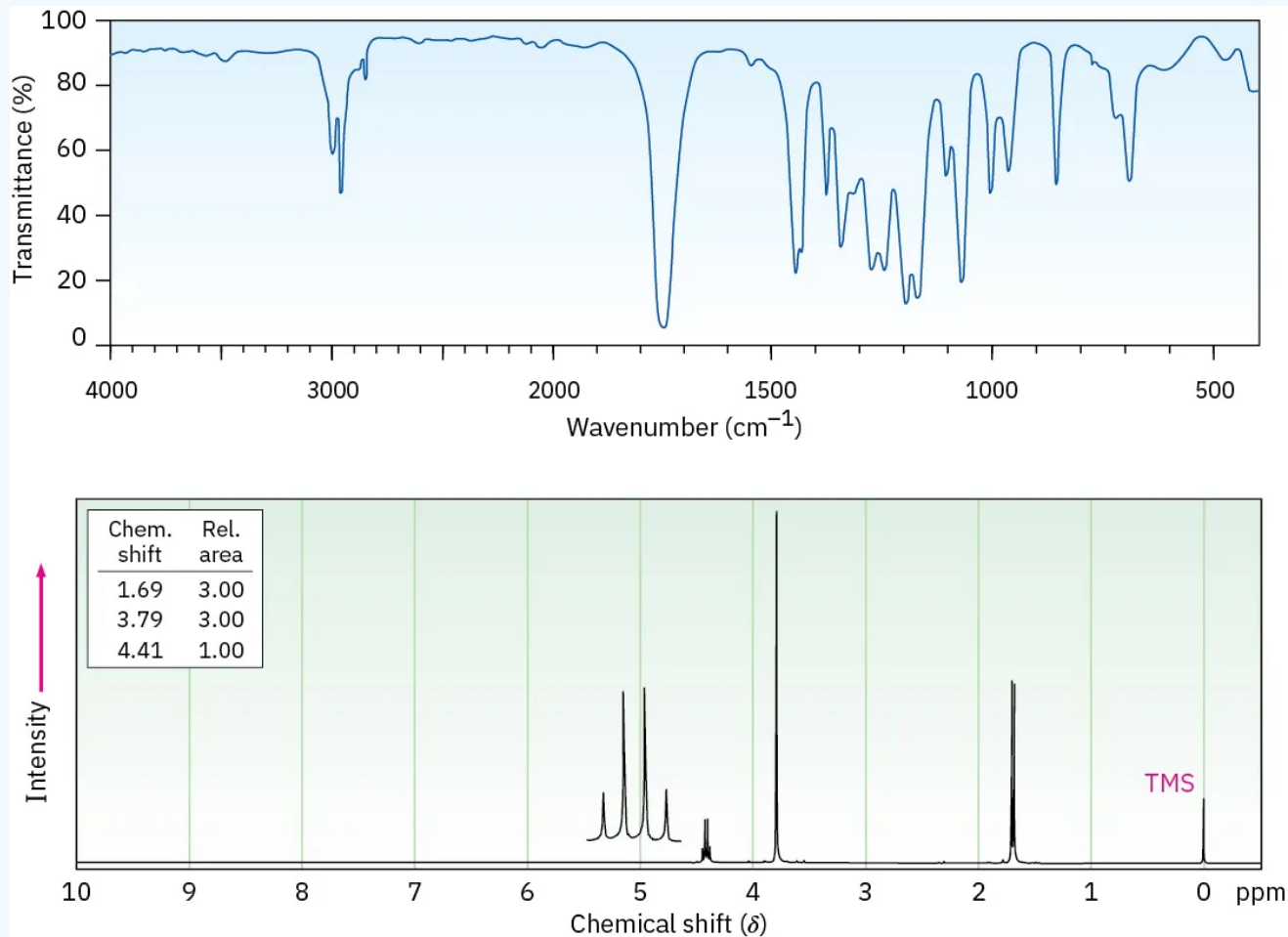


## Spectroscopy

*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

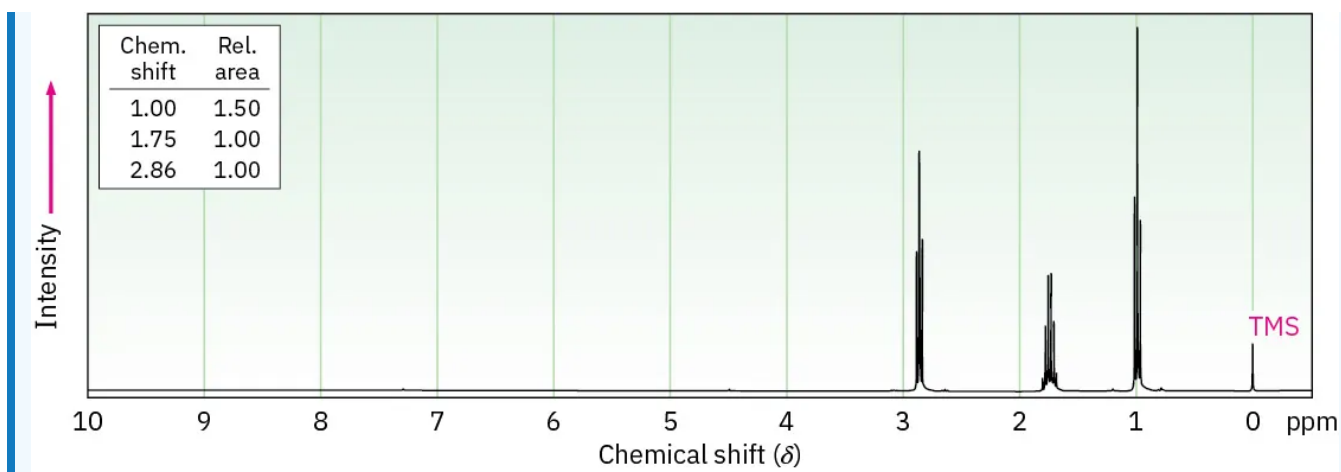
Propose a structure for a compound,  $C_4H_7ClO_2$ , that has the following IR and  $^1H$  NMR spectra:



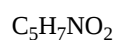
$^1H$  NMR spectra: (a)

$C_4H_7ClO_2$

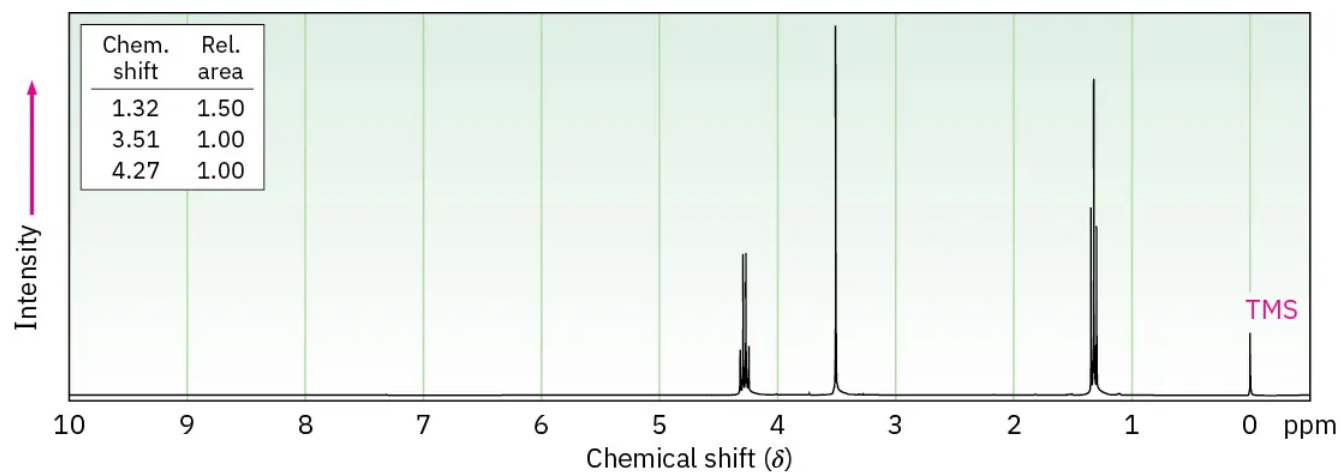
IR: 1810  $cm^{-1}$



(b)

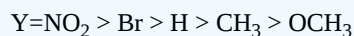


IR: 2250, 1735  $cm^{-1}$

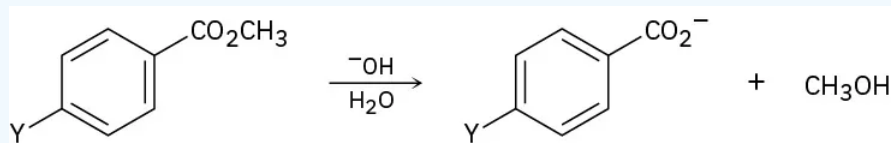


### General Problems

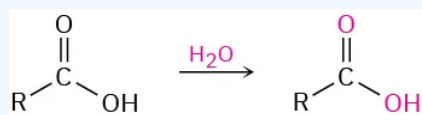
The following reactivity order has been found for the basic hydrolysis of *p*-substituted methyl benzoates:



How can you explain this reactivity order? Where would you expect  $Y=C$  Unexpected text node: ' N, Y=CHO, and Y=NH' <sub>2</sub> to be in the reactivity list?

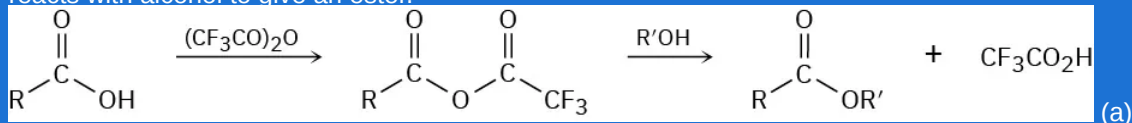


When a carboxylic acid is dissolved in isotopically labeled water, the label rapidly becomes incorporated into both oxygen atoms of the carboxylic acid. Explain.



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

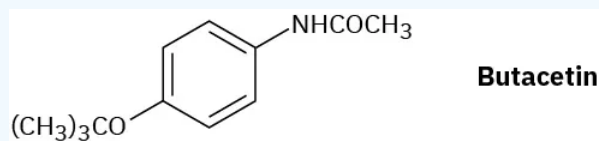
Treatment of a carboxylic acid with trifluoroacetic anhydride leads to an unsymmetrical anhydride that rapidly reacts with alcohol to give an ester.



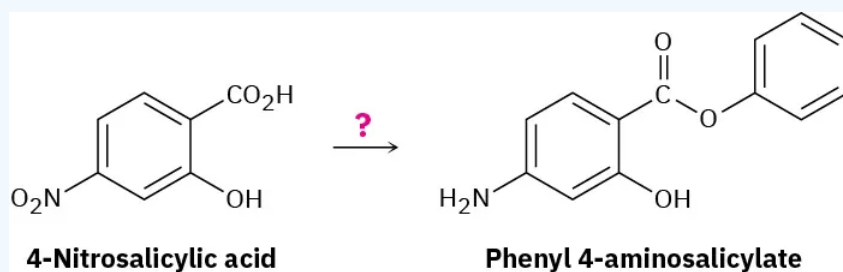
Propose a mechanism for formation of the unsymmetrical anhydride.

(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?

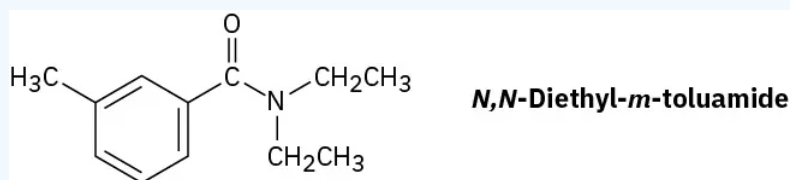
Butacetin is an analgesic (pain-killing) agent that is synthesized commercially from *p*-fluoronitrobenzene. Propose a synthesis.



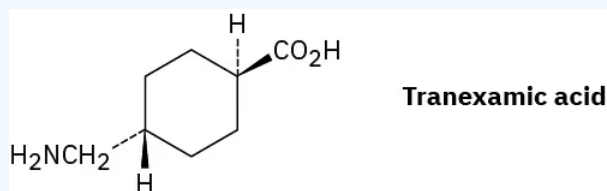
Phenyl 4-aminosalicylate is a drug used in the treatment of tuberculosis. Propose a synthesis of this compound starting from 4-nitrosalicylic acid.



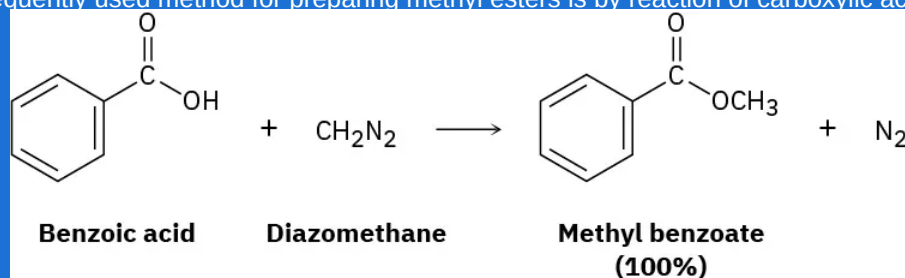
*N,N*-Diethyl-*m*-toluamide (DEET) is the active ingredient in many insect-repellent preparations. How might you synthesize this substance from *m*-bromotoluene?



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.)



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



$\text{CH}_2\text{N}_2$ .

The reaction occurs in two steps: (1) protonation of diazomethane by the carboxylic acid to yield methyldiazonium ion,  $\text{CH}_3\text{N}_2^+$ , plus a carboxylate ion; and (2) reaction of the carboxylate ion with  $\text{CH}_3\text{N}_2^+$ .

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

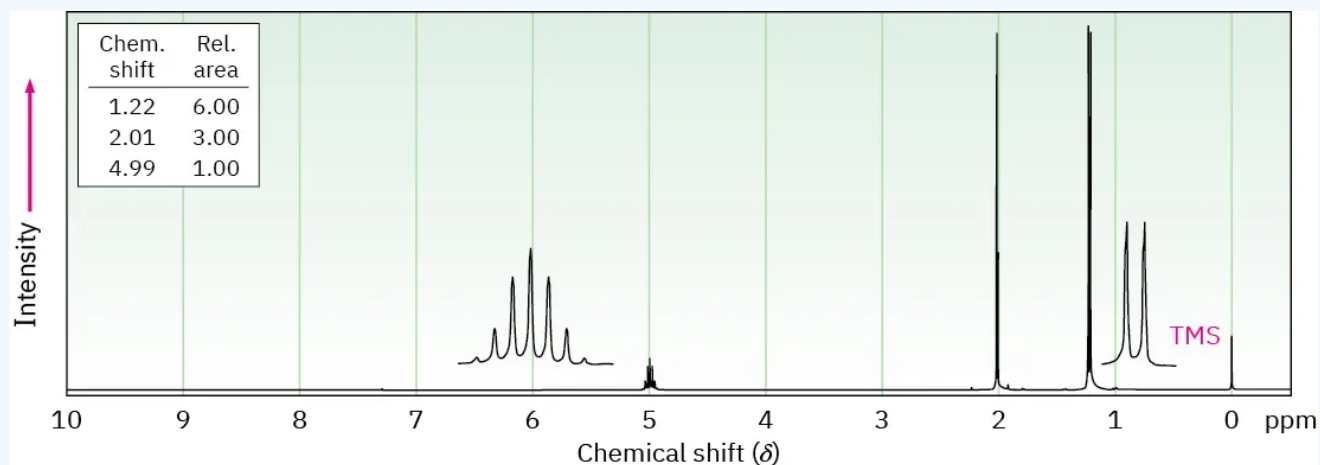
(b) What kind of reaction occurs in step 2?

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 (Table 21.2)? How do you think this new feature might affect the properties of the polymer?

### **1H NMR spectra: (a)**

$\text{C}_5\text{H}_{10}\text{O}_2$

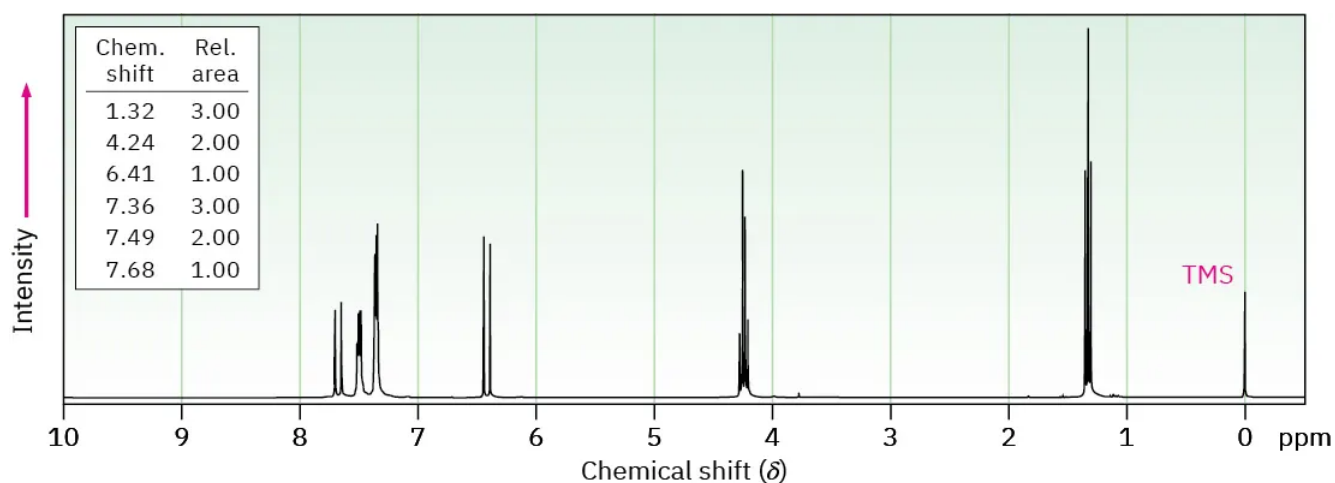
IR:  $1735\text{ cm}^{-1}$



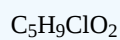
(b)

$\text{C}_{11}\text{H}_{12}\text{O}_2$

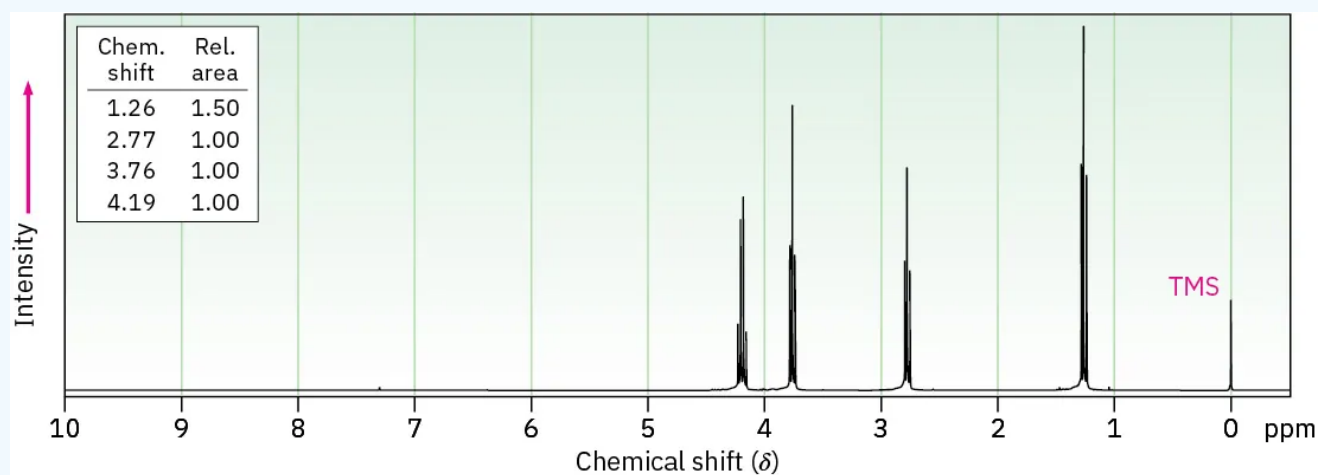
IR:  $1710\text{ cm}^{-1}$



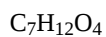
1H NMR spectra: (a)



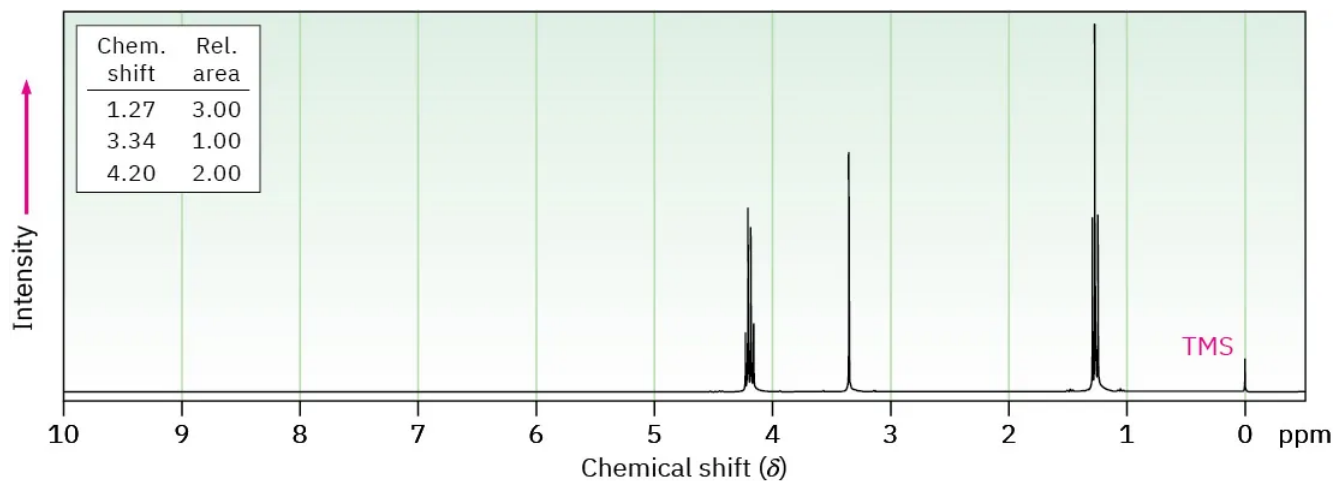
IR:  $1735\text{ cm}^{-1}$



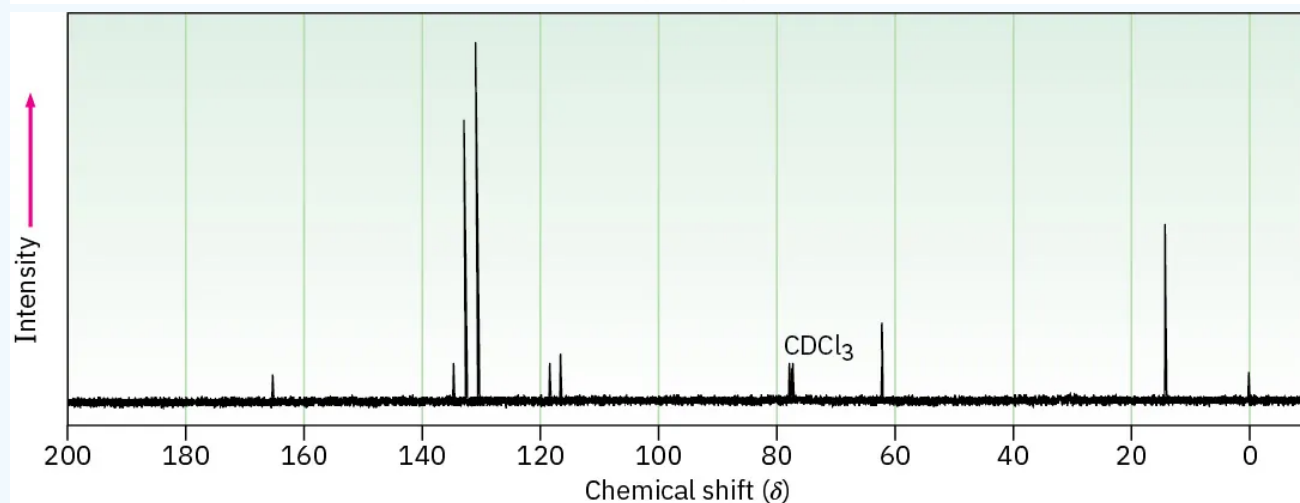
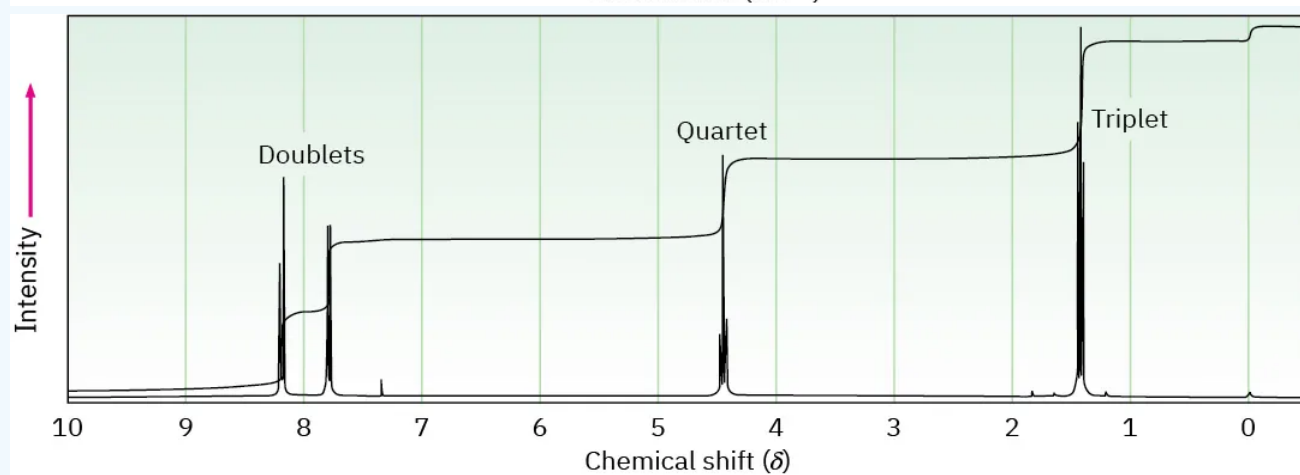
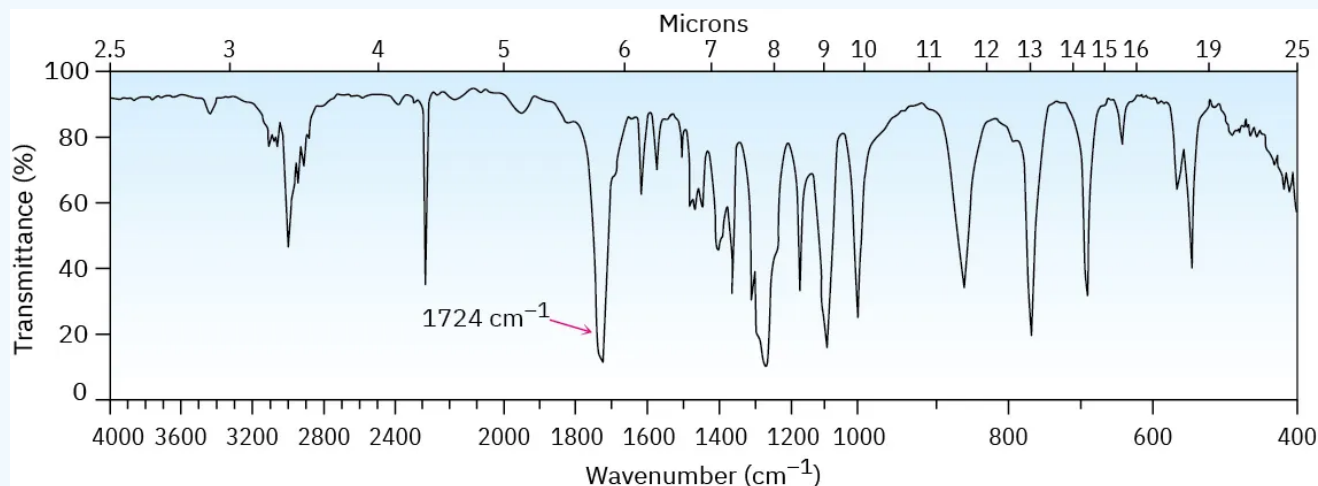
(b)



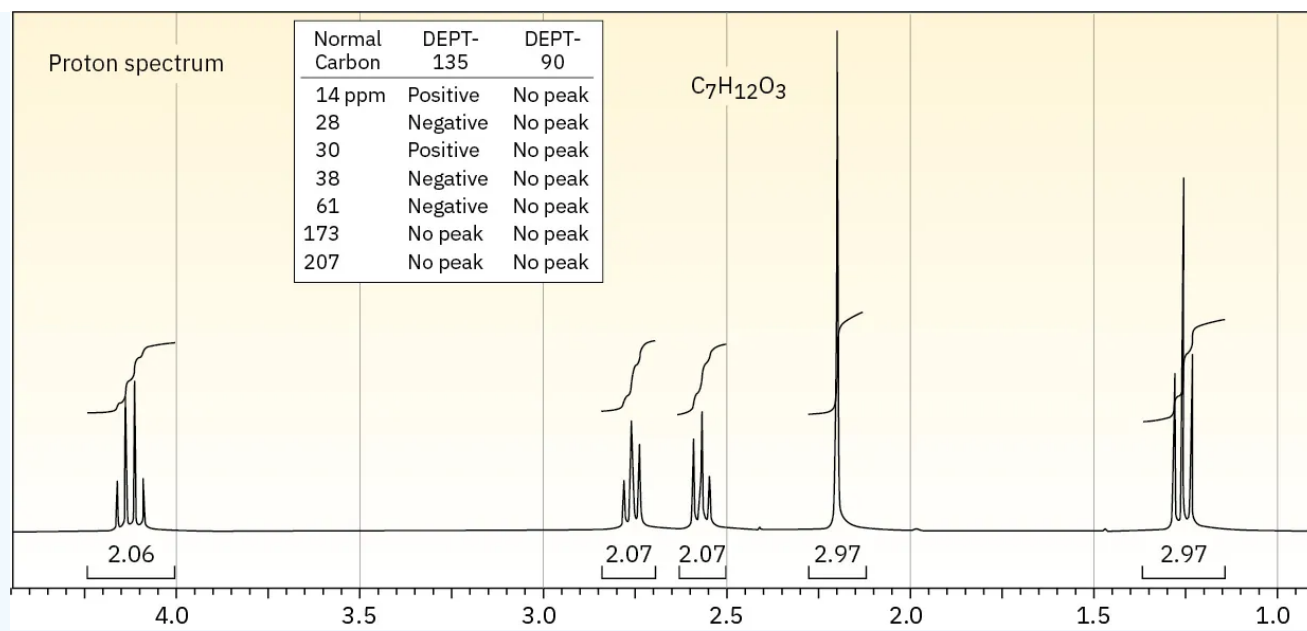
IR:  $1735\text{ cm}^{-1}$



Propose a structure for the compound with the formula  $C_{19}H_{19}NO_2$  and the following IR and NMR spectra

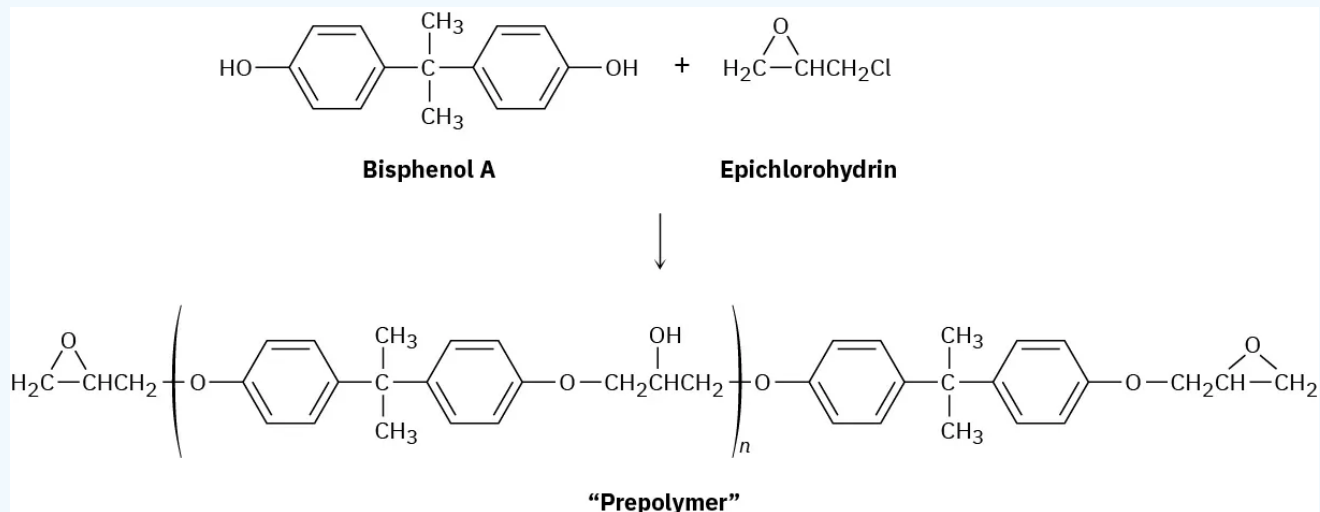


Draw the structure of the compound that produced the following spectra. The infrared spectrum has strong bands at 1720 and  $1738\text{ cm}^{-1}$ .



When an amide is formed from an acid chloride or an anhydride, two equivalents of base are required. However, when an ester is used as the starting material, only one equivalent of base is needed. Explain this reactivity in terms of basicity of the leaving groups.

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  $H_2NCH_2CH_2NHCH_2CH_2NH_2$ .



Draw structures to show how addition of the triamine results in a strengthening of the polymer.

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