Chapter 16 Alcohols II. Reactions

16.1 Chemistry of the —OH group

The chemical properties of an alcohol, ROH, are determined by its functional group, —OH, the hydroxyl group. When we have learned the chemistry of the alcohols, we shall have learned much of the chemistry of the hydroxyl group in whatever compound it may occur; we shall know, in part at least, what to expect of hydroxyhalides, hydroxyacids, hydroxyaldehydes, etc.

Reactions of an alcohol can involve the breaking of either of two bonds: the C···OH bond, with removal of the —OH group; or the O···H bond, with removal of —H. Either kind of reaction can involve substitution, in which a group replaces the —OH or —H, or elimination, in which a double bond is formed.

Differences in the structure of R cause differences in reactivity, and in a few cases even profoundly alter the course of the reaction. We shall see what some of these effects of structure on reactivity are, and how they can be accounted for.

16.2 Reactions

Some of the more important reactions of alcohols are listed below, and are discussed in following sections.

REACTIONS OF ALCOHOLS

C···OH BOND CLEAVAGE

R+OH

1. Reaction with hydrogen halides. Discussed in Secs. 16.4–16.5.

$$R{-}OH + HX \longrightarrow RX + H_2O \qquad R \textit{ may rearrange}$$

Reactivity of HX: HI > HBr > HCl

Reactivity of ROH: allyl, benzyl > 3° > 2° > 1°

Examples:

$$CH_3CHCH_3 \xrightarrow[\text{or NaBr, } H_2SO_4,\ \text{reflux}]{\text{conc. HBr}} CH_3CHCH_3$$
(OH) — Isopropyl alcohol; (Br) — Isopropyl bromide

$$CH_3CH_2CH_2CH_2CH_2OH \xrightarrow[\text{heat}]{HCl,\ ZnCl_2} CH_3CH_2CH_2CH_2CH_2Cl$$
n-Pentyl alcohol — *n*-Pentyl chloride

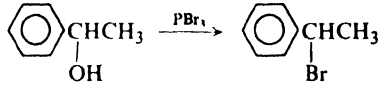
$$CH_3-\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3 \xrightarrow[\text{room temp.}]{\text{conc. HCl}} CH_3-\underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3$$
tert-Butyl alcohol — *tert*-Butyl chloride

2. Reaction with phosphorus trihalides. Discussed in Sec. 16.10.

$$R{-}OH + PX_3 \longrightarrow RX + H_3PO_3$$
$$(PX_3 = PBr_3,\ PI_3)$$

Examples:

$$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2OH \xrightarrow{PBr_3} CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Br$$
2-Methyl-1-butanol — 2-Methyl-1-bromobutane



1-Phenylethanol — 1-Bromo-1-phenylethane

$$CH_3CH_2OH \xrightarrow{P+I_2} CH_3CH_2I$$
Ethyl alcohol — Ethyl iodide

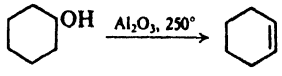
3. Dehydration. Discussed in Secs. 5.19–5.23, and 16.3.

$$-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}- \xrightarrow{\text{acid}} -C=C- + H_2O$$
(H, OH) — *Rearrangement may occur*

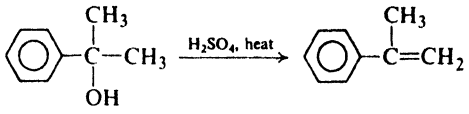
Reactivity of ROH: 3° > 2° > 1°

Examples:

$$CH_3CH_2CH_2CH_2OH \xrightarrow{H_2SO_4,\ \text{heat}} CH_3CH{=}CHCH_3 \text{ and } CH_3CH_2CH{=}CH_2$$
n-Butyl alcohol — 2-Butene (*Major product*) and 1-Butene



Cyclohexanol — Cyclohexene



2-Phenyl-2-propanol 2-Phenylpropene

O---H BOND CLEAVAGE

$$RO\dot{-}\dot{H}$$

4. Reaction as acids: reaction with active metals. Discussed in Sec. 16.6.

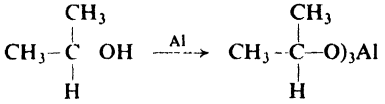
$$RO{-}H + M \longrightarrow RO^- M^+ + \tfrac{1}{2}H_2 \qquad M = Na, K, Mg, Al, \text{etc.}$$

Reactivity of ROH: $CH_3OH > 1^\circ > 2^\circ > 3^\circ$

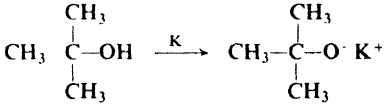
Examples:

$$CH_3CH_2OH \xrightarrow{Na} CH_3CH_2O^-Na^+ + \tfrac{1}{2}H_2$$

Sodium ethoxide



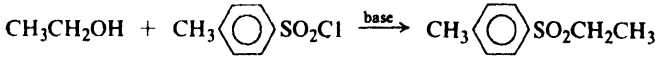
Aluminium isopropoxide



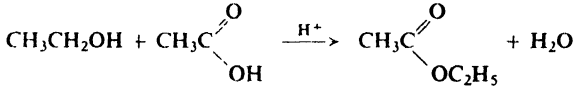
tert-Butyl alcohol Potassium *tert*-butoxide

5. Ester formation. Discussed in Secs. 16.7 and 18.16.

Examples:

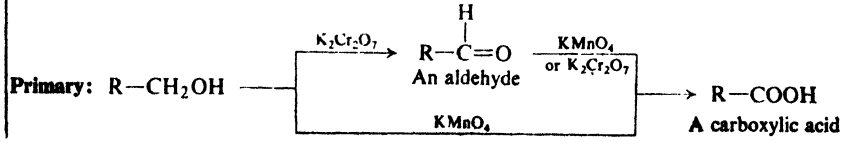


Tosyl chloride (*p*-Toluenesulfonyl chloride) Ethyl tosylate



Acetic acid Ethyl acetate

6. Oxidation. Discussed in Sec. 16.8.



Secondary: $R_2CHOH \xrightarrow{K_2Cr_2O_7 \text{ or } CrO_3} R_2C{=}O$ (A ketone)

Tertiary: $R_3COH \xrightarrow{\text{neut. } KMnO_4}$ no reaction

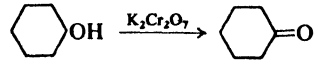
Examples:

$CH_3CH_2CH_2OH \xrightarrow{K_2Cr_2O_7} CH_3CH_2CH{=}O + H_2$

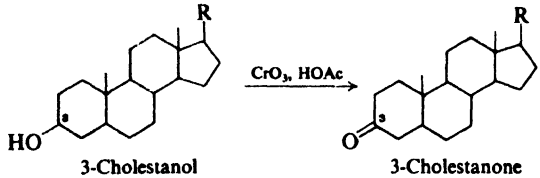
n-Propyl alcohol (1°) — Propionaldehyde

$CH_3CH_2CH(CH_3)CH_2OH \xrightarrow{KMnO_4} CH_3CH_2CH(CH_3)COOH$

2-Methyl-1-butanol (1°) — 2-Methylbutanoic acid



Cyclohexanol (2°) — Cyclohexanone



3-Cholestanol (2°) — 3-Cholestanone

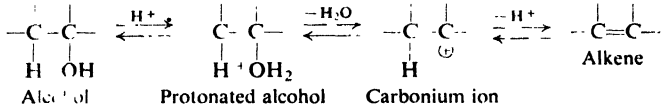
We can see that alcohols undergo many kinds of reactions, to yield many kinds of products. Because of the availability of alcohols, each of these reactions is one of the best ways to make the particular kind of product. After we have learned a little more about the reactions themselves, we shall look at some of the ways in which they can be applied to synthetic problems.

16.3 Dehydration

We discussed the dehydration of alcohols at some length earlier (Secs. 5.19–5.23). It might be well, however, to summarize what we know about this reaction at our present level of sophistication.

(a) Mechanism. According to the commonly accepted mechanism, we remember, dehydration involves (1) formation of the protonated alcohol, ROH_2^+, (2) its slow dissociation into a carbonium ion, and (3) fast expulsion of a hydrogen ion from the carbonium ion to form an alkene. Acid is required to convert the

alcohol into the protonated alcohol, which dissociates—by loss of the weakly basic water molecule—much more easily than the alcohol itself.

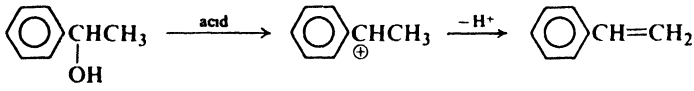


We recognize this mechanism as an example of E1 elimination with the protonated alcohol as substrate. We can account, in a general way, for the contrast between alcohols and alkyl halides, which mostly undergo elimination by the E2 mechanism. Since the alcohol must be protonated to provide a reasonably good leaving group, H_2O, dehydration requires an acidic medium. But for E2 elimination we need a fairly strong base to attack the substrate without waiting for it to dissociate into carbonium ions. A strong base and an acidic medium are, of course, incompatible: any base much stronger than the alcohol itself would become protonated at the expense of the alcohol.

(b) Reactivity. We know that the rate of elimination depends greatly upon the rate of formation of the carbonium ion, which in turn depends upon its stability.

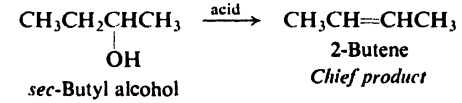
We know how to estimate the stability of a carbonium ion, on the basis of inductive effects and resonance. Because of the electron-releasing inductive effect of alkyl groups, stability and hence rate of formation of the simple alkyl cations follows the sequence $3^\circ > 2^\circ > 1^\circ$.

We know that because of resonance stabilization (Sec. 12.19) the benzyl cation should be an extremely stable ion, and so we are not surprised to find that an alcohol such as 1-phenylethanol (like a tertiary alcohol) undergoes dehydration extremely rapidly.



1-Phenylethanol A benzyl cation Styrene

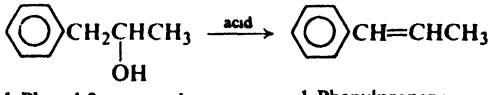
(c) Orientation. We know that expulsion of the hydrogen ion takes place in such a way as to favor the formation of the more stable alkene. We can estimate the relative stability of an alkene on the basis of the number of alkyl groups attached to the doubly-bonded carbons, and on the basis of conjugation with a benzene ring or with another carbon–carbon double bond. It is understandable, then, that *sec*-butyl alcohol yields chiefly 2-butene, and 1-phenyl-2-propanol yields only 1-phenylpropene.



sec-Butyl alcohol

2-Butene

Chief product



1-Phenyl-2-propanol

1-Phenylpropene

Only product

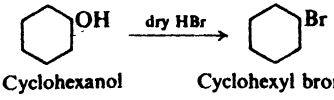
(d) Rearrangement. Finally, we know that a carbonium ion can rearrange, and that this rearrangement seems to occur whenever a 1,2-shift of hydrogen or alkyl group can form a more stable carbonium ion.

In all this we must not lose sight of the fact that the rates of formation of carbonium ions and of alkenes depend chiefly upon the stabilities of the transition states leading to their formation. A more stable carbonium ion is formed faster because the factors—inductive effects and resonance—that disperse the charge of a carbonium ion tend also to disperse the developing positive charge of an incipient carbonium ion in the transition state. In the same way, the factors that stabilize an alkene—conjugation of hyperconjugation, or perhaps change in hybridization—tend to stabilize the developing double bond in the transition state.

16.4 Reaction with hydrogen halides: facts

Alcohols react readily with hydrogen halides to yield alkyl halides and water. The reaction is carried out either by passing the dry hydrogen halide gas into the alcohol, or by heating the alcohol with the concentrated aqueous acid. Sometimes hydrogen bromide is generated in the presence of the alcohol by reaction between sulfuric acid and sodium bromide.

The least reactive of the hydrogen halides, HCl, requires the presence of zinc chloride for reaction with primary and secondary alcohols; on the other hand, the very reactive *tert*-butyl alcohol is converted to the chloride by simply being shaken with concentrated hydrochloric acid at room temperature. For example:



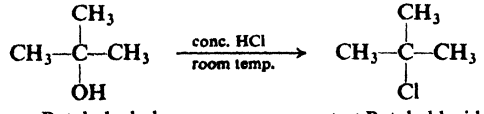
Cyclohexanol Cyclohexyl bromide

$$CH_3CH_2CH_2CH_2OH \xrightarrow[\text{reflux}]{NaBr,\ H_2SO_4} CH_3CH_2CH_2CH_2Br$$

n-Butyl alcohol *n*-Butyl bromide

$$CH_3CH_2CH_2OH \xrightarrow[\text{heat}]{HCl + ZnCl_2} CH_3CH_2CH_2Cl$$

n-Propyl alcohol *n*-Propyl chloride



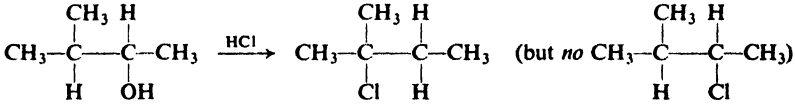
tert-Butyl alcohol *tert*-Butyl chloride

Let us list some of the facts that are known about the reaction between alcohols and hydrogen halides.

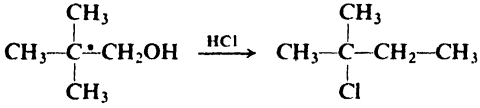
(a) The reaction is catalyzed by acids. Even though the aqueous hydrogen halides are themselves strong acids, the presence of additional sulfuric acid speeds up the formation of halides.

Problem 16.1 How do you account for the catalysis by $ZnCl_2$ of the HCl reaction? (*Hint:* $ZnCl_2$ is sometimes used as a (weak) Friedel-Crafts catalyst.)

(b) Rearrangement of the alkyl group occurs, except with most primary alcohols. The alkyl group in the halide does not always have the same structure as the alkyl group in the parent alcohol. For example:



3-Methyl-2-butanol — 2-Chloro-2-methylbutane (*tert*-Pentyl chloride)



Neopentyl alcohol — *tert*-Pentyl chloride

We see that the halogen does not always become attached to the carbon that originally held the hydroxyl (the first example); even the carbon skeleton may be different from that of the starting material (the second example).

On the other hand, as shown on p. 523 for *n*-propyl and *n*-butyl alcohols, most primary alcohols give high yields of primary halides *without* rearrangement.

(c) The order of reactivity of alcohols toward HX is allyl, benzyl > 3° > 2° > 1° < CH_3. Reactivity decreases through most of the series (and this order is the basis of the *Lucas test*, Sec. 16.11), passes through a *minimum* at 1°, and rises again at CH_3.

16.5 Reaction with hydrogen halides: mechanism

What do the facts that we have just listed suggest to us about the mechanism of reaction between alcohols and hydrogen halides?

Catalysis by acid suggests that here, as in dehydration, the protonated alcohol ROH_2^+ is involved. The occurrence of *rearrangement* suggests that carbonium ions are intermediates—although *not* with primary alcohols. The idea of carbonium ions is strongly supported by the *order of reactivity* of alcohols, which parallels the stability of carbonium ions—*except* for methyl.

On the basis of this evidence, we formulate the following mechanism. The

(1)	$ROH + HX \rightleftharpoons ROH_2^+ + X^-$	**S_N1:**
(2)	$ROH_2^+ \rightleftharpoons R^+ + H_2O$	*all except methanol and most 1° alcohols*
(3)	$R^+ + X^- \longrightarrow RX$	

alcohol accepts (step 1) the hydrogen ion to form the protonated alcohol, which dissociates (step 2) into water and a carbonium ion; the carbonium ion then combines (step 3) with a halide ion (not necessarily the one from step 1) to form the alkyl halide.

Looking at the mechanism we have written, we recognize the reaction for what it is: *nucleophilic substitution*, with the protonated alcohol as substrate and

halide ion as the nucleophile. Once the reaction type is recognized, the other pieces of evidence fall into place.

The particular set of equations written above is, of course, the S_N1 mechanism for substitution. Primary alcohols do not undergo rearrangement simply because they do not react by this mechanism. Instead, they react by the alternative S_N2 mechanism:

$$X^- + ROH_2^+ \longrightarrow \left[X\cdots R\cdots OH_2\right]^{\delta-\ \ \delta+} \longrightarrow X{-}R + H_2O$$

S_N2: *most 1° alcohols and methanol*

What we see here is another example of that characteristic of nucleophilic substitution: a shift in the molecularity of reaction, in this particular case between 2° and 1°. This shift is confirmed by the fact that reactivity passes through a minimum at 1° and rises again at methyl. Because of poor accommodation of the positive charge, formation of primary carbonium ions is very slow; so slow in this instance that the unimolecular reaction is replaced by the relatively unhindered bimolecular attack. The bimolecular reaction is even faster for the still less hindered methanol.

Thus alcohols, like halides, undergo substitution by both S_N1 and S_N2 mechanisms; but alcohols lean more toward the unimolecular mechanism. We encountered the same situation in elimination (Sec. 16.3), and the explanation here is essentially the same: we cannot have a strong nucleophile—a strong *base*—present in the acidic medium required for protonation of the alcohol.

Neopentyl alcohol reacts with almost complete rearrangement, showing that, although primary, it follows the carbonium ion mechanism. This unusual behavior is easily explained. Although neopentyl is a primary group, it is a very bulky one and, as we have seen (Problem 14.2, p. 465), compounds containing this group undergo S_N2 reactions very slowly. Formation of the neopentyl cation from neopentyl alcohol is slow, but is nevertheless much faster than the alternative bimolecular reaction.

Problem 16.2 Because of the great tendency of the neopentyl cation to rearrange, neopentyl chloride cannot be prepared from the alcohol. How might neopentyl chloride be prepared?

Problem 16.3 Predict the relative rates at which the following alcohols will react with aqueous HBr:

(a) benzyl alcohol, *p*-methylbenzyl alcohol, *p*-nitrobenzyl alcohol;
(b) benzyl alcohol, α-phenylethyl alcohol, β-phenylethyl alcohol.

Problem 16.4 When allowed to react with aqueous HBr, 3-buten-2-ol ($CH_3CHOHCH{=}CH_2$) yields not only 3-bromo-1-butene ($CH_3CHBrCH{=}CH_2$) but also 1-bromo-2-butene ($CH_3CH{=}CHCH_2Br$). (a) How do you account for these results? (*Hint:* See Sec. 8.21.) (b) Predict the product of the reaction between HBr and 2-buten-1-ol ($CH_3CH{=}CHCH_2OH$). (c) How does this "rearrangement" differ from those described in the last section?

Problem 16.5 (a) Write the steps in the reaction of an alcohol with HCl by the S_N1 mechanism. (b) What is the rate-determining step? (c) The rate of reaction depends upon the concentration of what substance? (d) The concentration of this substance depends in turn upon the concentrations of what other compounds? (e) Will

the rate depend *only* on [ROH]? Does an S_N1 reaction always follow first-order kinetics?

16.6 Alcohols as acids

We have seen that an alcohol, acting as a base, can accept a hydrogen ion to form the protonated alcohol, ROH_2^+. Let us now turn to reactions in which an alcohol, acting as an acid, loses a hydrogen ion to form the alkoxide ion, RO^-.

Since an alcohol contains hydrogen bonded to the very electronegative element oxygen, we would expect it to show appreciable acidity. The polarity of the O—H bond should facilitate the separation of the relatively positive hydrogen as the ion; viewed differently, electronegative oxygen should readily accommodate the negative charge of the electrons left behind.

The acidity of alcohols is shown by their reaction with active metals to form hydrogen gas, and by their ability to displace the weakly acidic hydrocarbons from their salts (e.g., Grignard reagents):

$$ROH + Na \longrightarrow RO^-Na^+ + \tfrac{1}{2}H_2$$

$$\underset{\text{Stronger acid}}{ROH} + R'MgX \longrightarrow \underset{\text{Weaker acid}}{R'H} + Mg(OR)X$$

With the possible exception of methanol, they are weaker acids than water, but stronger acids than acetylene or ammonia:

$$\underset{\text{Stronger base}}{RO^-Na^+} + \underset{\text{Stronger acid}}{H—OH} \longrightarrow \underset{\text{Weaker base}}{Na^+OH^-} + \underset{\text{Weaker acid}}{RO—H}$$

$$\underset{\text{Stronger base}}{HC{\equiv}C^-Na^+} + \underset{\text{Stronger acid}}{RO—H} \longrightarrow \underset{\text{Weaker base}}{RO^-Na^+} + \underset{\text{Weaker acid}}{HC{\equiv}C—H}$$

As before, these relative acidities are determined by displacement (Sec. 8.10). We may expand our series of acidities and basicities, then, to the following:

Relative acidities: $H_2O > ROH > HC{\equiv}CH > NH_3 > RH$

Relative basicities: $OH^- < OR^- < HC{\equiv}C^- < NH_2^- < R^-$

Not only does the alkyl group make an alcohol less acidic than water, but the *bigger* the alkyl group, the less acidic the alcohol: methanol is the strongest acid and tertiary alcohols are the weakest.

This acid-weakening effect of alkyl groups is *not* an electronic effect, as was once believed, with electron release destabilizing the anion and making it a stronger base. In the gas phase, the relative acidities of various alcohols and of alcohols and water are reversed; evidently, the easily polarized alkyl groups are helping to accommodate the negative charge, just as they help to accommodate the positive charge in carbonium ions (Secs. 5.18 and 11.18). Alcohols *are* weaker acids than water *in solution*—which is where we are normally concerned with acidity—and this is a solvation effect; a bulky group interferes with the ion-dipole interactions that stabilize the anion.

Since an alcohol is a weaker acid than water, an alkoxide is not prepared from the reaction of the alcohol with sodium hydroxide, but is prepared instead by reaction of the alcohol with the active metal itself.

As we shall see, the alkoxides are extremely useful reagents; they are used as powerful bases (stronger than hydroxide) and to introduce the —OR group into a molecule.

Problem 16.6 Which would you expect to be the stronger acid: (a) β-chloroethyl alcohol or ethyl alcohol? (b) *p*-Nitrobenzyl alcohol or benzyl alcohol? (c) *n*-Propyl alcohol or glycerol, $HOCH_2CHOHCH_2OH$?

Problem 16.7 Sodium metal was added to *tert*-butyl alcohol and allowed to react. When the metal was consumed, ethyl bromide was added to the resulting mixture. Work-up of the reaction mixture yielded a compound of formula $C_6H_{14}O$.

In a similar experiment, sodium metal was allowed to react with ethanol. When *tert*-butyl bromide was added, a gas was evolved, and work-up of the remaining mixture gave ethanol as the only organic material.

(a) Write equations for all reactions. (b) What familiar reaction type is involved in each case? (c) Why did the reactions take different courses?

16.7 Formation of alkyl sulfonates

Sulfonyl chlorides (the acid chlorides of sulfonic acids) are prepared by the action of phosphorus pentachloride or thionyl chloride on sulfonic acids or their salts:

$$\underset{\text{(or } ArSO_3Na\text{)}}{ArSO_2OH} + PCl_5 \xrightarrow{\text{heat}} \underset{\text{A sulfonyl chloride}}{ArSO_2Cl} + POCl_3 + \underset{\text{(or NaCl)}}{HCl}$$

Alcohols react with these sulfonyl chlorides to form esters, *alkyl sulfonates*:

$$ArSO_2Cl + ROH \xrightarrow[\text{or pyridine}]{\text{aqueous } OH^-} \underset{\text{An alkyl sulfonate}}{ArSO_2OR} + Cl^- + H_2O$$

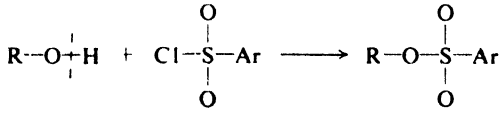
We have already seen (Sec. 14.6) that the weak basicity of the sulfonate anion, $ArSO_3^-$, makes it a good leaving group, and as a result alkyl sulfonates undergo nucleophilic substitution and elimination in much the same manner as alkyl halides.

Alkyl sulfonates offer a very real advantage over alkyl halides in reactions where stereochemistry is important; this advantage lies, not in the reactions of alkyl sulfonates, but in their *preparation*. Whether we use an alkyl halide or sulfonate, and whether we let it undergo substitution or elimination, our starting point for the study is almost certainly the alcohol. The sulfonate *must* be prepared from the alcohol; the halide nearly always *will* be. It is at the alcohol stage that any resolution will be carried out, or any diastereomers separated; the alcohol is then converted into the halide or sulfonate, the reaction we are studying is carried out, and the products are examined.

Now, any preparation of a halide from an alcohol must involve breaking of the carbon–oxygen bond, and hence is accompanied by the likelihood of stereo-

$$R\overset{|}{\underset{|}{\text{—}}}O\text{—}H \xrightarrow{HX \text{ or } PX_3} R\text{—}X$$

chemical inversion and the possibility of racemization. Preparation of a sulfonate, on the other hand, does not involve the breaking of the carbon–oxygen bond, and hence proceeds with complete retention; when we carry out a reaction with this sulfonate, we know exactly what we are starting with.



Problem 16.8 Outline all steps in the synthesis of *sec*-butyl tosylate, starting with benzene, toluene, and any necessary aliphatic and inorganic reagents.

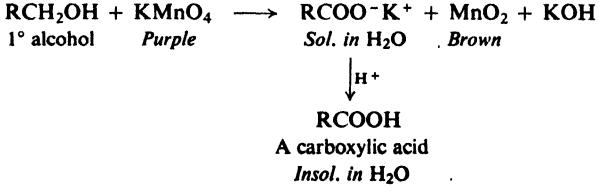
Problem 16.9 You prepare *sec*-butyl tosylate from alcohol of $[\alpha] +6.9°$. On hydrolysis with aqueous base, this ester gives *sec*-butyl alcohol of $[\alpha] -6.9°$. Without knowing the configuration or optical purity of the starting alcohol, what (if anything) can you say about the stereochemistry of the hydrolysis step?

16.8 Oxidation of alcohols

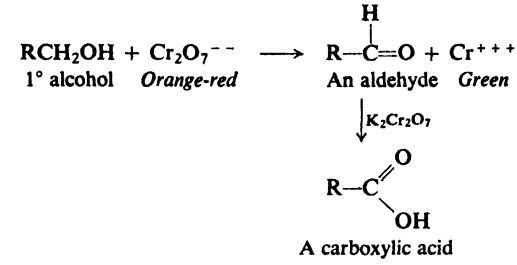
The compound that is formed by oxidation of an alcohol depends upon the number of hydrogens attached to the carbon bearing the —OH group, that is, upon whether the alcohol is primary, secondary, or tertiary. We have already encountered these products—aldehydes, ketones, and carboxylic acids—and should recognize them from their structures, even though we have not yet discussed much of their chemistry. They are important compounds, and their preparation by the oxidation of alcohols is of great value in organic synthesis (Secs. 16.9 and 16.10).

The number of oxidizing agents available to the organic chemist is growing at a tremendous rate. As with all synthetic methods, emphasis is on the development of highly *selective* reagents, which will operate on only one functional group in a complex molecule, and leave the other functional groups untouched. Of the many reagents that can be used to oxidize alcohols, we can consider only the most common ones, those containing Mn(VII) and Cr(VI).

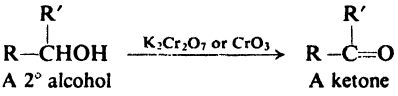
Primary alcohols can be oxidized to carboxylic acids, RCOOH, usually by heating with aqueous $KMnO_4$. When reaction is complete, the aqueous solution of the soluble potassium salt of the carboxylic acid is filtered from MnO_2, and the acid is liberated by the addition of a stronger mineral acid.



Primary alcohols can be oxidized to aldehydes, RCHO, by the use of $K_2Cr_2O_7$. Since, as we shall see (Sec. 19.9), aldehydes are themselves readily oxidized to acids, the aldehyde must be removed from the reaction mixture by special techniques before it is oxidized further.



Secondary alcohols are oxidized to ketones, R_2CO, by chromic acid in a form selected for the job at hand: aqueous $K_2Cr_2O_7$, CrO_3 in glacial acetic acid, CrO_3

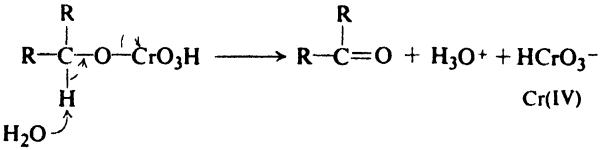


in pyridine, etc. Hot permanganate also oxidizes secondary alcohols; it is seldom used for the synthesis of ketones, however, since oxidation tends to go past the ketone stage, with breaking of carbon–carbon bonds.

With no hydrogen attached to the carbinol carbon, **tertiary alcohols are not oxidized at all under alkaline conditions.** If acid is present, they are rapidly dehydrated to alkenes, which are then oxidized.

Let us look briefly at the mechanism of just one oxidation reaction, to see the kind of thing that is involved here. Oxidation of secondary alcohols by Cr(VI) is believed to involve (1) formation of a chromate ester, which (2) loses a proton and an

(1) $$R_2CHOH + \underset{\text{Cr(VI)}}{HCrO_4^-} + H^+ \longrightarrow R_2CHOCrO_3H + H_2O$$

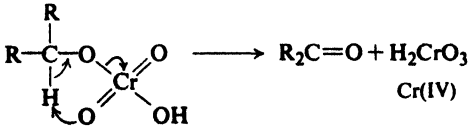
(2) 

(3) $$R_2CHOH + Cr(IV) \longrightarrow R_2COH + Cr(III)$$

(4) $$R_2COH + Cr(VI) \longrightarrow R_2C{=}O + Cr(V)$$

(5) $$R_2CHOH + Cr(V) \xrightarrow{\text{via an ester}} R_2C{=}O + Cr(III)$$

$HCrO_3^-$ ion to form the ketone. It is possible that the proton is lost to an oxygen of the ester group in a cyclic mechanism (2a). Additional alcohol is then oxidized, evidently by reactions (3)–(5), with chromium finally reaching the Cr(III) state.

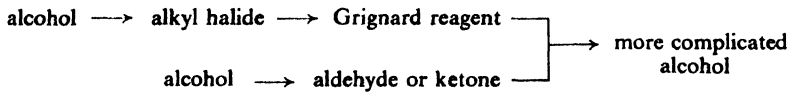
(2a) 

The difficult step in all this is breaking the carbon–hydrogen bond; this is made possible by the synchronous departure of $HCrO_3^-$, in what is really an E2 elimination—but here with the formation of a carbon–oxygen double bond.

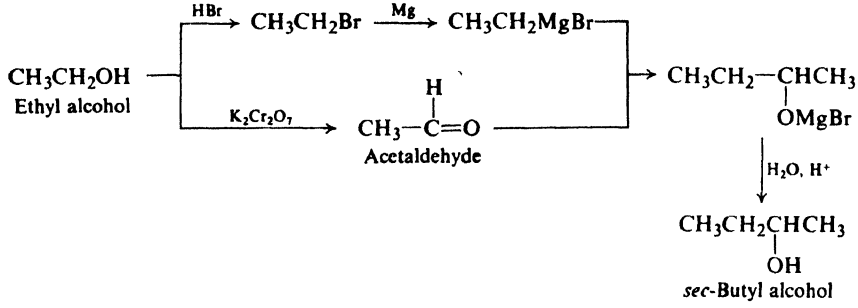
In connection with analysis, we shall encounter two reagents used to oxidize alcohols of special kinds: (a) *hypohalite* (Sec. 16.11), and (b) *periodic acid* (Sec. 16.12).

16.9 Synthesis of alcohols

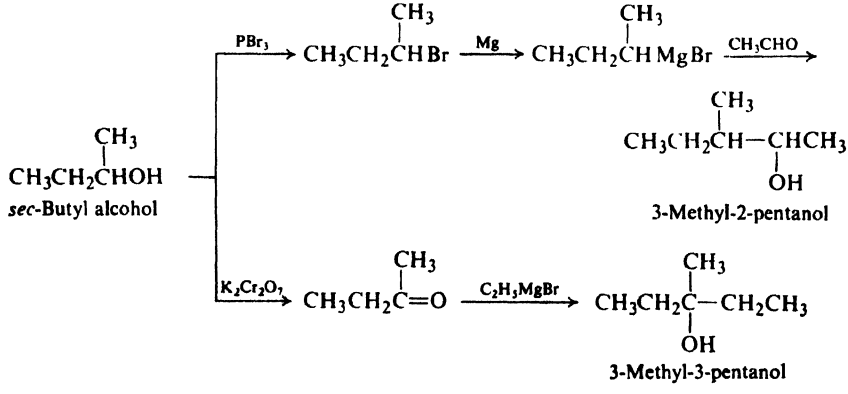
Let us try to get a broader picture of the synthesis of complicated alcohols. We learned (Sec. 15.12) that they are most often prepared by the reaction of Grignard reagents with aldehydes or ketones. In this chapter we have learned that aldehydes and ketones, as well as the alkyl halides from which the Grignard reagents are made, are themselves most often prepared from alcohols. Finally, we know that the simple alcohols are among our most readily available compounds. We have available to us, then, a synthetic route leading from simple alcohols to more complicated ones.



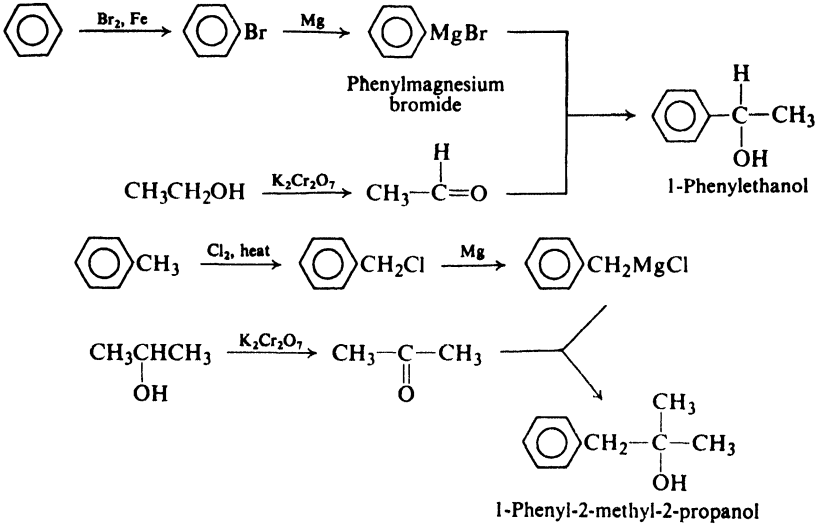
As a simple example, consider conversion of the two-carbon ethyl alcohol into the four-carbon *sec*-butyl alcohol:



Using the *sec*-butyl alcohol thus obtained, we could prepare even larger alcohols:

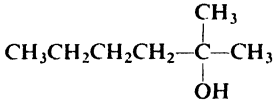


By combining our knowledge of alcohols with what we know about alkylbenzenes and aromatic substitution, we can extend our syntheses to include aromatic alcohols. For example:



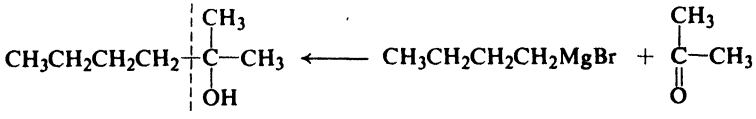
Granting that we know the chemistry of the individual steps, how do we go about planning a route to these more complicated alcohols? In almost every organic synthesis it is best to **work backward** from the compound we want. There are relatively few ways to make a complicated alcohol; there are relatively few ways to make the Grignard reagent or the aldehyde or ketone; and so on back to our ultimate starting materials. On the other hand, alcohols can undergo so many different reactions that, if we go at the problem the other way around, we find a bewildering number of paths, few of which take us where we want to go.

Let us suppose (and this is quite reasonable) that we have available all alcohols of four carbons or fewer, and that we want to make, say, 2-methyl-2-hexanol. Let us set down the structure and see what we need to make it.

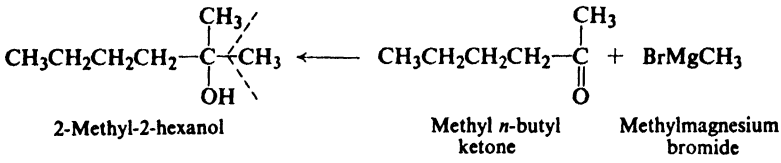


2-Methyl-2-hexanol

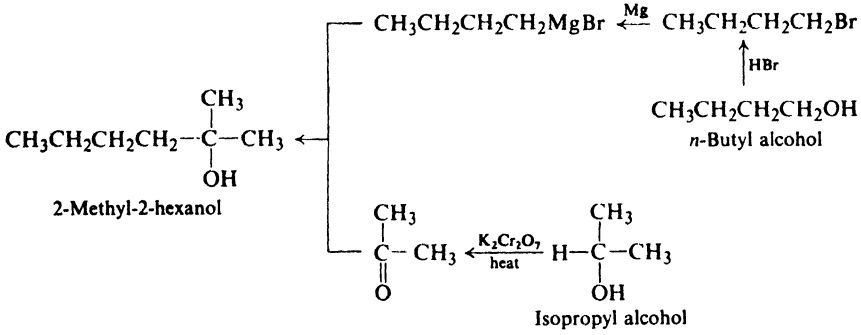
Since it is a tertiary alcohol, we must use a Grignard reagent and a ketone. But which Grignard reagent? And which ketone? Using the same approach as before (Sec. 15.14), we see that there are two possibilities:



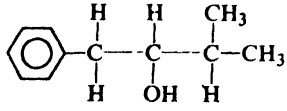
2-Methyl-2-hexanol | *n*-Butylmagnesium bromide | Acetone



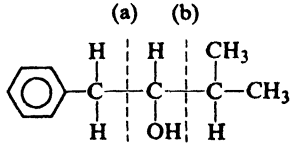
Of these two possibilities we would select the one involving the four-carbon Grignard reagent and the three-carbon ketone; now how are we to make *them*? The Grignard reagent can be made only from the corresponding alkyl halide, *n*-butyl bromide, and that in turn most likely from an alcohol, *n*-butyl alcohol. Acetone requires, of course, isopropyl alcohol. Putting together the entire synthesis, we have the following sequence:



Let us consider that in addition to our alcohols of four carbons or fewer we have available benzene and toluene, another reasonable assumption, and that we wish to make, say, 1-phenyl-3-methyl-2-butanol. Again we set down the structure of the desired alcohol and work backward to the starting materials. For a

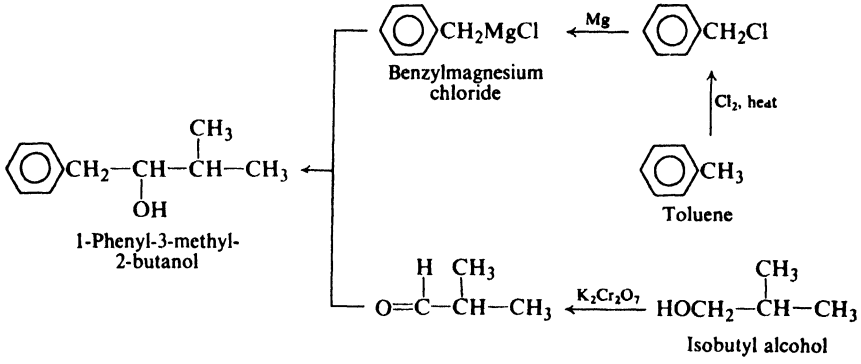


secondary alcohol, a Grignard reagent and an aldehyde are indicated, and again there are two choices: we may consider the molecule to be put together between (a) C–1 and C–2 or (b) C–2 and C–3. Of the two possibilities we select the first,



since this requires a compound with only one carbon attached to the benzene ring, which we have available in toluene. We need, then, a four-carbon aldehyde

and benzylmagnesium chloride. The aldehyde can readily be made from isobutyl alcohol, but how about benzylmagnesium chloride? This is, of course, made from benzyl chloride, which in turn is made from toluene by free-radical chlorination. Our synthesis is complete:



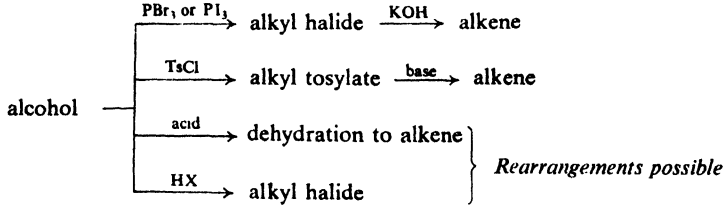
Now that we know how to make complicated alcohols from simple ones, what can we use them for?

16.10 Syntheses using alcohols

The alcohols that we have learned to make can be converted into other kinds of compounds having the same carbon skeleton; from complicated alcohols we can make complicated aldehydes, ketones, acids, halides, alkenes, alkynes, alkanes, etc.

Alkyl halides are prepared from alcohols by use of hydrogen halides or phosphorus halides. Phosphorus halides are often preferred because they tend less to bring about rearrangement (Sec. 16.4).

Alkenes are prepared from alcohols either by direct dehydration or by dehydrohalogenation of intermediate alkyl halides; to avoid rearrangement we often select dehydrohalogenation of halides even though this route involves an extra step. (Or, sometimes better, we use elimination from alkyl sulfonates.)



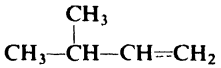
Alkanes, we learned (Sec. 3.15), are best prepared from the corresponding alkenes by hydrogenation, so that now we have a route from complicated alcohols to complicated alkanes.

Complicated aldehydes and ketones are made by oxidizing complicated alcohols. By reaction with Grignard reagents these aldehydes and ketones can be converted into even more complicated alcohols, and so on.

Given the time, necessary inorganic reagents, and the single alcohol ethanol, our chemical Crusoe of Sec. 15.5 could synthesize all the aliphatic compounds that have ever been made—and for that matter the aromatic ones, too.

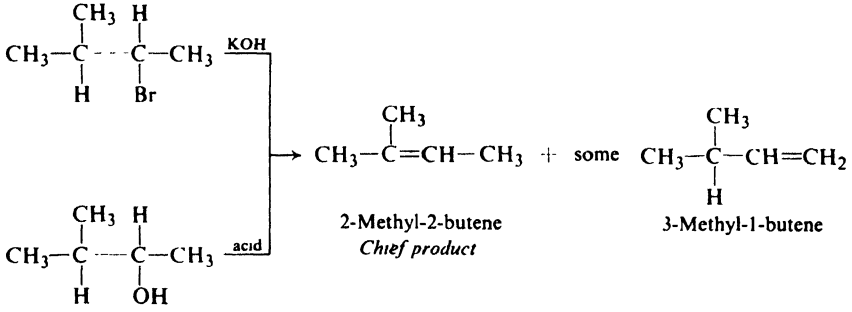
In planning the synthesis of these other kinds of compounds, we again follow our system of working backward. We try to limit the synthesis to as few steps as possible, but nevertheless do not sacrifice purity for time. For example, where rearrangement is likely to occur we prepare an alkene in two steps via the halide rather than by the single step of dehydration.

Assuming again that we have available alcohols of four carbons or fewer, benzene, and toluene, let us take as an example 3-methyl-1-butene. It could be



3-Methyl-1-butene

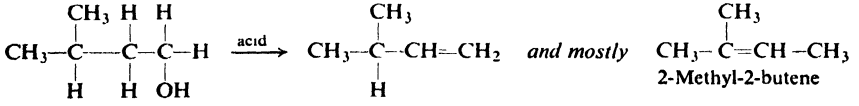
prepared by dehydrohalogenation of an alkyl halide of the same carbon skeleton, or by dehydration of an alcohol. If the halogen or hydroxyl group were attached to C–2, we would obtain some of the desired product, but much more of its isomer, 2-methyl-2-butene:



2-Methyl-2-butene
Chief product

3-Methyl-1-butene

We would select, then, the compound with the functional group attached to C–1. Even so, if we were to use the alcohol, there would be extensive rearrangement to yield, again, the more stable 2-methyl-2-butene:

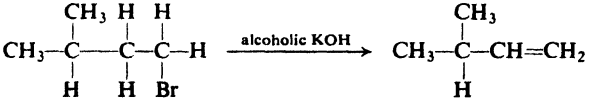


3-Methyl-1-butanol

3-Methyl-1-butene

2-Methyl-2-butene

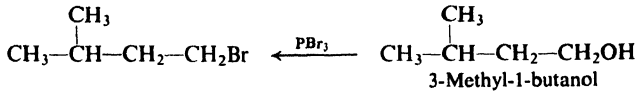
Only dehydrohalogenation of 1-bromo-3-methylbutane would yield the desired product in pure form:



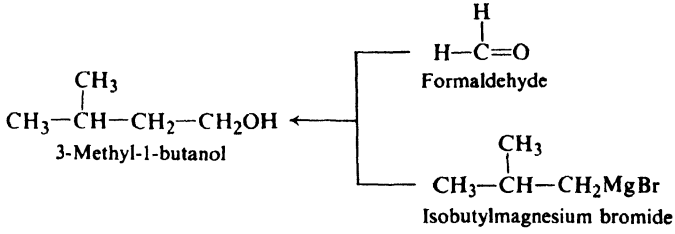
1-Bromo-3-methylbutane

3-Methyl-1-butene

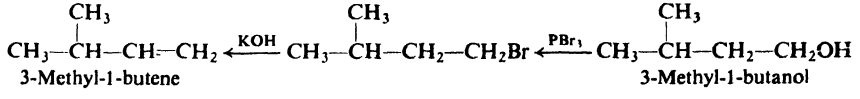
How do we prepare the necessary alkyl halide? Certainly not by bromination of an alkane, since even if we could make the proper alkane in some way, bromination would occur almost entirely at the tertiary position to give the wrong product. (Chlorination would give the proper chloride—but as a minor component of a grand mixture.) As usual, then, we would prepare the halide from the corresponding alcohol, in this case 3-methyl-1-butanol. Since this is a primary alcohol (without branching near the —OH group), and hence does not form the halide via the carbonium ion, rearrangement is not likely; we might use, then, either hydrogen bromide or PBr_3.

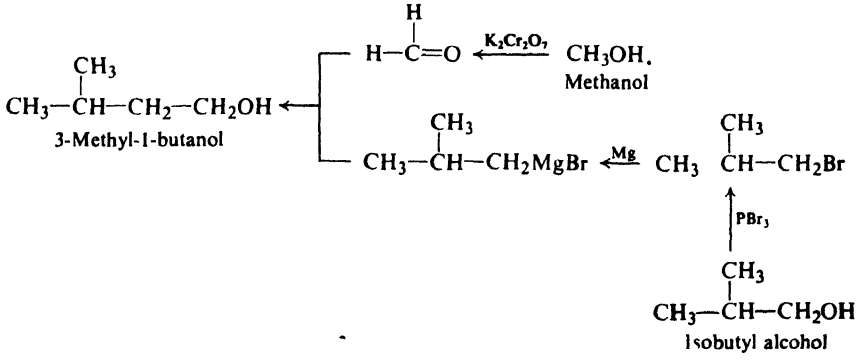


Now, how do we make 3-methyl-1-butanol? It is a primary alcohol and contains one carbon more than our largest available alcohol; therefore we would use the reaction of a Grignard reagent with formaldehyde. The necessary Grignard reagent is isobutylmagnesium bromide, which we could have prepared from



isobutyl bromide, and that in turn from isobutyl alcohol. The formaldehyde is made by oxidation of methanol. The entire sequence, from which we could expect to obtain quite pure 3-methyl-1-butene, is the following:





16.11 Analysis of alcohols. Characterization. Iodoform test

Alcohols dissolve in cold concentrated sulfuric acid. This property they share with alkenes, amines, practically all compounds containing oxygen, and easily sulfonated compounds. (Alcohols, like other oxygen-containing compounds, form oxonium salts, which dissolve in the highly polar sulfuric acid.)

Alcohols are not oxidized by cold, dilute, neutral permanganate (although primary and secondary alcohols are, of course, oxidized by permanganate under more vigorous conditions). However, as we have seen (Sec. 6.30), alcohols often contain impurities that *are* oxidized under these conditions, and so the permanganate test must be interpreted with caution.

Alcohols do not decolorize bromine in carbon tetrachloride. This property serves to distinguish them from alkenes and alkynes.

Alcohols are further distinguished from alkenes and alkynes—and, indeed, from nearly every other kind of compound—by their oxidation by chromic anhydride, CrO_3, in aqueous sulfuric acid: within *two seconds*, the clear orange solution turns blue-green and becomes opaque.

$$\underset{\substack{1^\circ \text{ or } 2^\circ \\ \textit{Clear,} \\ \textit{orange}}}{ROH} + HCrO_4^- \longrightarrow \textit{Opaque, blue-green}$$

Tertiary alcohols do not give this test. Aldehydes do, but are easily differentiated in other ways (Sec. 19.17).

Reaction of alcohols with sodium metal, with the evolution of hydrogen gas, is of some use in characterization; a *wet* compound of any kind, of course, will do the same thing, until the water is used up.

The presence of the —OH group in a molecule is often indicated by the formation of an ester upon treatment with an acid chloride or anhydride (Sec. 18.16). Some esters are sweet-smelling; others are solids with sharp melting points, and can be derivatives in identifications. (If the molecular formulas of starting material and product are determined, it is possible to calculate *how many* —OH groups are present.)

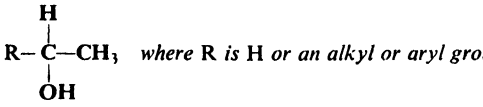
Problem 16.10 Make a table to show the response of each kind of compound we have studied so far toward the following reagents: (a) cold concentrated H_2SO_4; (b) cold, dilute, neutral $KMnO_4$; (c) Br_2 in CCl_4; (d) CrO_3 in H_2SO_4; (e) cold fuming sulfuric acid; (f) $CHCl_3$ and $AlCl_3$; (g) sodium metal.

Whether an alcohol is primary, secondary, or tertiary is shown by the **Lucas test**, which is based upon the difference in reactivity of the three classes toward hydrogen halides (Sec. 16.4). Alcohols (of not more than six carbons) are soluble in the *Lucas reagent*, a mixture of concentrated hydrochloric acid and zinc chloride. (Why are they more soluble in this than in water?) The corresponding alkyl chlorides are insoluble. Formation of a chloride from an alcohol is indicated by the cloudiness that appears when the chloride separates from the solution; hence, the time required for cloudiness to appear is a measure of the reactivity of the alcohol.

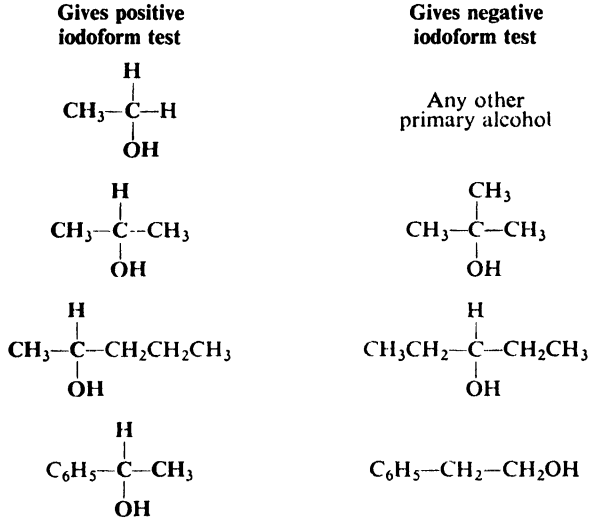
A tertiary alcohol reacts immediately with the Lucas reagent, and a secondary alcohol reacts within five minutes; a primary alcohol does not react appreciably

at room temperature. As we have seen, benzyl alcohol and allyl alcohol react as rapidly as tertiary alcohols with the Lucas reagent; allyl chloride, however, is soluble in the reagent. (Why?)

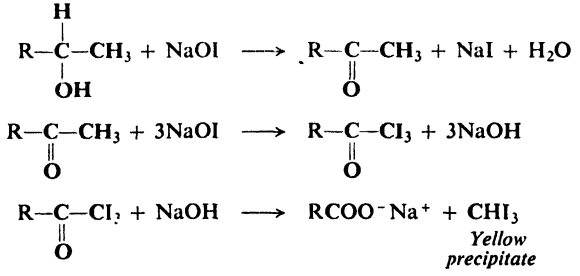
Whether or not an alcohol contains one particular structural unit is shown by the **iodoform test.** The alcohol is treated with iodine and sodium hydroxide (sodium hypoiodite, NaOI); an alcohol of the structure



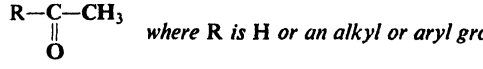
yields a yellow precipitate of iodoform (CHI_3, m.p. 119°). For example:



The reaction involves oxidation, halogenation, and cleavage.



As would be expected from the equations, a compound of structure

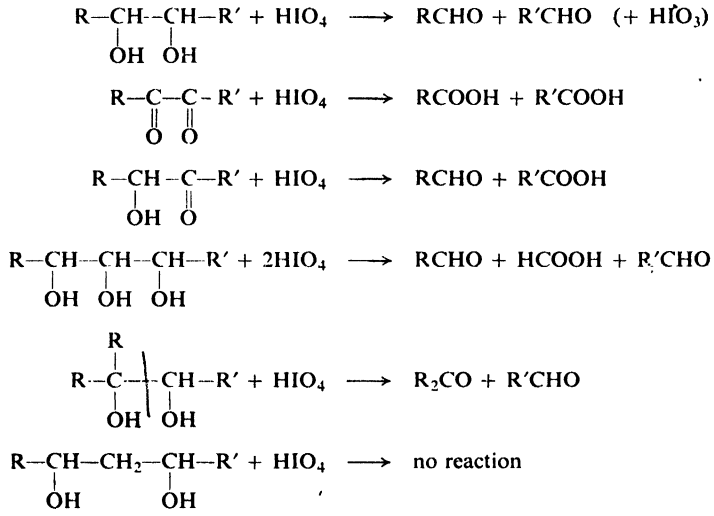


also gives a positive test (Sec. 19.17).

In certain special cases this reaction is used not as a test, but to synthesize the carboxylic acid, RCOOH. Here, hypobromite or the cheaper hypochlorite would probably be used.

16.12 Analysis of glycols. Periodic acid oxidation

Upon treatment with periodic acid, HIO_4, compounds containing two or more —OH or O groups attached to *adjacent* carbon atoms undergo oxidation with cleavage of carbon–carbon bonds. For example:



The oxidation is particularly useful in determination of structure. Qualitatively, oxidation by HIO_4 is indicated by formation of a white precipitate ($AgIO_3$) upon addition of silver nitrate. Since the reaction is usually quantitative, valuable information is given by the nature and amounts of the products, and by the quantity of periodic acid consumed.

Problem 16.11 When one mole of each of the following compounds is treated with HIO_4, what will the products be, and how many moles of HIO_4 will be consumed?

(a) $CH_3CHOHCH_2OH$
(b) $CH_3CHOHCHO$
(c) $CH_2OHCHOHCH_2OCH_3$
(d) $CH_2OHCH(OCH_3)CH_2OH$
(e) *cis*-1,2-cyclopentanediol
(f) $CH_2OH(CHOH)_3CHO$
(g) $CH_2OH(CHOH)_3CH_2OH$

Problem 16.12 Assign a structure to each of the following compounds:

A + one mole HIO_4 ⟶ $CH_3COCH_3 + HCHO$
B + one mole HIO_4 ⟶ $OHC(CH_2)_4CHO$
C + one mole HIO_4 ⟶ $HOOC(CH_2)_4CHO$
D + one mole HIO_4 ⟶ $2HOOC—CHO$
E + $3HIO_4$ ⟶ $2HCOOH + 2HCHO$
F + $3HIO_4$ ⟶ $2HCOOH + HCHO + CO_2$
G + $5HIO_4$ ⟶ $5HCOOH + HCHO$

16.13 Spectroscopic analysis of alcohols

Infrared. In the infrared spectrum of a hydrogen-bonded alcohol—and this is the kind that we commonly see—the most conspicuous feature is a strong, broad band in the 3200–3600 cm^{-1} region due to O—H stretching (see Fig. 16.1).

O—H stretching, ***strong, broad***

Alcohols, ROH (or phenols, ArOH) 3200–3600 cm^{-1}

(A monomeric alcohol, as discussed in Sec. 15.4, gives a sharp, variable band at 3610–3640 cm^{-1}.)

Another strong, broad band, due to C—O stretching, appears in the 1000–1200 cm^{-1} region, the exact frequency depending on the nature of the alcohol:

C—O stretching, ***strong, broad***

1° ROH	about 1050 cm^{-1}	3° ROH	about 1150 cm^{-1}
2° ROH	about 1100 cm^{-1}	ArOH	about 1230 cm^{-1}

(Compare the locations of this band in the spectra of Fig. 16.1.)

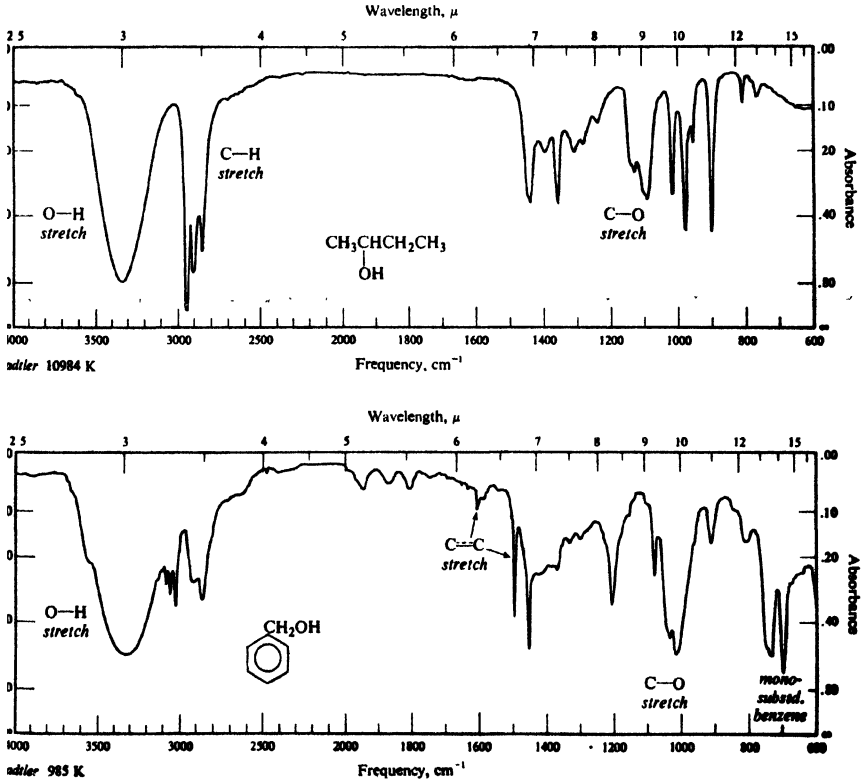


Figure 16.1. Infrared spectra of (a) *sec*-butyl alcohol and (b) benzyl alcohol.

Phenols (ArOH) also show both these bands, but the C—O stretching appears at somewhat higher frequencies. Ethers show C—O stretching, but the O—H band is absent. Carboxylic acids and esters show C—O stretching, but give absorption characteristic of the carbonyl group, C=O, as well. (For a comparison of certain oxygen compounds, see Table 20.3, p. 689.)

Nmr. Nmr absorption by a hydroxylic proton (O—H) is shifted downfield by hydrogen bonding. The chemical shift that is observed depends, therefore, on the degree of hydrogen bonding, which in turn depends on temperature, concentration, and the nature of the solvent (Sec. 15.4). As a result, the signal can appear anywhere in the range δ 1–5. It may be hidden among the peaks due to alkyl protons, although its presence there is often revealed through proton counting.

A hydroxyl proton ordinarily gives rise to a singlet in the nmr spectrum: its signal is not split by nearby protons, nor does it split their signals. Proton exchange between two (identical) molecules of alcohol

$$R^*\text{—O—H}^* + \text{R—O—H} \rightleftharpoons R^*\text{—O—H} + \text{R—O—H}^*$$

is so fast that the proton—now in one molecule and in the next instant in another—cannot see nearby protons in their various combinations of spin alignments, but in a single *average* alignment.

Presumably through its inductive effect, the oxygen of an alcohol causes a downfield shift for nearby protons: a shift of about the same size as other electronegative atoms (Table 13.4, p. 421).

Problem 16.13 Can you suggest a procedure that might move a hidden O—H peak into the open? (*Hint:* See Sec. 15.4.)

Problem 16.14 (a) Very dry, pure samples of alcohols show spin–spin splitting of the O—H signals. What splitting would you expect for a primary alcohol? a secondary alcohol? a tertiary alcohol? (b) This splitting disappears on the addition of a trace of acid or base. Write equations to show just how proton exchange would be speeded up by an acid (H:B); by a base (:B).

PROBLEMS

1. Refer to the isomeric pentyl alcohols of Problem 1(a), p. 515. (a) Indicate which (if any) will give a positive iodoform test. (b) Describe how each will respond to the Lucas reagent. (c) Describe how each will respond to chromic anhydride. (d) Outline all steps in a possible synthesis of each, starting from alcohols of four carbons or less, and using any necessary inorganic reagents.

2. Give structures and names of the chief products expected from the reaction (if any) of cyclohexanol with:

(a) cold conc. H_2SO_4
(b) H_2SO_4, heat
(c) cold dilute $KMnO_4$
(d) CrO_3, H_2SO_4
(e) Br_2/CCl_4
(f) conc. aqueous HBr
(g) $P + I_2$
(h) Na
(i) CH_3COOH, H^+
(j) H_2, Ni
(k) CH_3MgBr
(l) NaOH(aq)
(m) product (f) + Mg
(n) product (m) + product (d)
(o) product (b) + cold alk. $KMnO_4$
(p) product (b) + Br_2/CCl_4
(q) product (b) + C_6H_6, HF
(r) product (b) + H_2, Ni

(s) product (q) + HNO_3/H_2SO_4
(t) product (b) + N-bromosuccinimide
(u) product (b) + $CHCl_3$ + *t*-BuOK
(v) product (d) + C_6H_5MgBr
(w) tosyl chloride, OH^-
(x) product (w) + *t*-BuOK

3. Outline all steps in a possible laboratory synthesis of each of the following compounds from *n*-butyl alcohol, using any necessary inorganic reagents. Follow the general instructions on p. 224.

(a) *n*-butyl bromide
(b) 1-butene
(c) *n*-butyl hydrogen sulfate
(d) potassium *n*-butoxide
(e) *n*-butyraldehyde, $CH_3CH_2CH_2CHO$
(f) *n*-butyric acid, $CH_3CH_2CH_2COOH$
(g) *n*-butane
(h) 1,2-dibromobutane
(i) 1-chloro-2-butanol
(j) 1-butyne
(k) ethylcyclopropane
(l) 1,2-butanediol
(m) *n*-octane
(n) 3-octyne
(o) *cis*-3-octene
(p) *trans*-3-octene
(q) 4-octanol
(r) 4-octanone, $CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3$
(s) 5-(*n*-propyl)-5-nonanol
(t) *n*-butyl *n*-butyrate, $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}—OCH_2CH_2CH_2CH_3$

4. Give structures and (where possible) names of the principal organic products of the following:

(a) benzyl alcohol + Mg
(b) isobutyl alcohol + benzoic acid + H^+
(c) ethylene bromide + excess NaOH(aq)
(d) *n*-butyl alcohol + H_2, Pt
(e) crotyl alcohol ($CH_3CH{=}CHCH_2OH$) + Br_2/H_2O
(f) CH_3OH + C_2H_5MgBr
(g) *p*-bromobenzyl bromide + NaOH(aq)
(h) *tert*-butyl alcohol + C_6H_6 + H_2SO_4

5. In Great Britain during the past few years, thousands of motorists have been (politely) stopped by the police and asked to blow into a "breathalyser": a glass tube containing silica gel impregnated with certain chemicals, and leading into a plastic bag. If, for more than half the length of the tube, the original yellow color turns green, the motorist looks very unhappy and often turns red. What chemicals are impregnated on the silica gel, why does the tube turn green, and why does the motorist turn red?

6. Arrange the alcohols of each set in order of reactivity toward aqueous HBr:

(a) the isomeric pentyl alcohols of Problem 1(a), p. 515. (*Note:* It may be necessary to list these in groups of about the same reactivity.)
(b) 1-phenyl-1-propanol, 3-phenyl-1-propanol, 1-phenyl-2-propanol
(c) benzyl alcohol, *p*-cyanobenzyl alcohol, *p*-hydroxylbenzyl alcohol
(d) 2-buten-1-ol, 3-buten-1-ol
(e) cyclopentylcarbinol, 1-methylcyclopentanol, *trans*-2-methylcyclopentanol
(f) benzyl alcohol, diphenylcarbinol, methanol, triphenylcarbinol

7. Outline the sequence of steps that best accounts for the following facts.

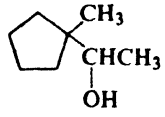
(a) 3-methyl-1-butene + HCl yields both 3-chloro-2-methylbutane and 2-chloro-2-methylbutane.

(b) Either 2-pentanol or 3-pentanol + HCl yields both 2-chloropentane and 3-chloropentane.

(c) 2,2,4-trimethyl-3-pentanol $\xrightarrow{Al_2O_3,\ heat}$ 2,4,4-trimethyl-2-pentene + 2,4,4-trimethyl-1-pentene + 2,3,4-trimethyl-2-pentene + 2,3,4-trimethyl-1-pentene + 3-methyl-2-isopropyl-1-butene + 3,3,4-trimethyl-1-pentene.

(d) 2,2-dimethylcyclohexanol $\xrightarrow{H^+}$ 1,2-dimethylcyclohexene + 1-isopropylcyclopentene. (*Hint:* Use models.)

(e) cyclobutyldiethylcarbinol $\xrightarrow{H^+}$ 1,2-diethylcyclopentene

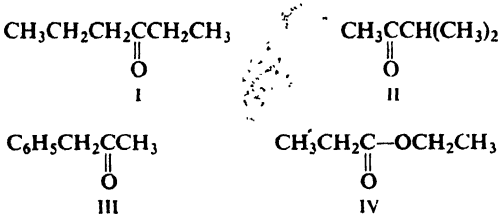
(f)  $\xrightarrow{H^+}$ 1,2-dimethylcyclohexene

8. Outline all steps in a possible laboratory synthesis of each of the following compounds from cyclohexanol and any necessary aliphatic, aromatic, or inorganic reagents.

(a) cyclohexanone ($C_6H_{10}O$)
(b) bromocyclohexane
(c) 1-methylcyclohexanol
(d) 1-methylcyclohexene
(e) *trans*-2-methylcyclohexanol
(f) cyclohexylmethylcarbinol
(g) *trans*-1,2-dibromocyclohexane
(h) cyclohexylcarbinol
(i) 1-bromo-1-phenylcyclohexane
(j) cyclohexanecarboxylic acid
(k) adipic acid, $HOOC(CH_2)_4COOH$
(l) norcarane (see p. 458)

9. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer.

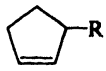
(a) 2,3-dimethyl-2-butanol
(b) 2-phenyl-2-propanol
(c) 2-phenylpropene
(d) 2-methyl-1-butene
(e) isopentane
(f) 1,2-dibromo-2-methylbutane
(g) 3-hexanol
(h) 3-hexanone (I)
(i) 4-ethyl-4-heptanol
(j) 2-bromo-2-methylhexane
(k) methylacetylene
(l) *trans*-1,2-dimethylcyclopropane
(m) 1-chloro-1-phenylethane (α-phenylethyl chloride)
(n) *sec*-butylbenzene
(o) methyl isopropyl ketone (II)
(p) 2-methylhexane
(q) benzyl methyl ketone (III)
(r) 2,2-dimethylhexane
(s) 2-bromo-1-phenylpropane
(t) 3-heptyne
(u) ethyl propionate (IV)



10. Compounds "labeled" at various positions by isotopic atoms are useful in determining reaction mechanisms and in following the fate of compounds in biological systems. Outline a possible synthesis of each of the following labeled compounds using $^{14}CH_3OH$ as the source of ^{14}C, and D_2O as the source of deuterium.

(a) 2-methyl-1-propanol-1-^{14}C, $(CH_3)_2CH^{14}CH_2OH$
(b) 2-methyl-1-propanol-2-^{14}C, $(CH_3)_2{}^{14}CHCH_2OH$
(c) 2-methyl-1-propanol-3-^{14}C, $^{14}CH_3CH(CH_3)CH_2OH$
(d) propene-1-^{14}C, $CH_3CH{=}{}^{14}CH_2$
(e) propene-2-^{14}C, $CH_3{}^{14}CH{=}CH_2$
(f) propene-3-^{14}C, $^{14}CH_3CH{=}CH_2$
(g) C_6H_5D
(h) $C_6H_5CH_2D$
(i) p-$DC_6H_4CH_3$
(j) $CH_3CH_2CHD^{14}CH_3$

11. When *trans*-2-methylcyclopentanol is treated with tosyl chloride and the product with potassium *tert*-butoxide, the only alkene obtained is 3-methylcyclopentene. (a) What is the stereochemistry of this reaction? (b) This is the final step of a general synthetic route to 3-alkylcyclopentenes, starting from cyclopentanone. Outline all steps in this

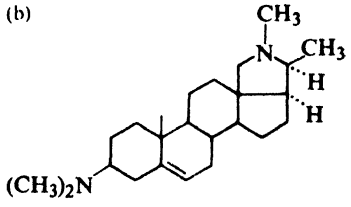


route, carefully choosing your reagents in each step. (c) What advantage does this sequence have over an analogous one involving an intermediate halide instead of a tosylate?

12. Making use of any necessary organic or inorganic reagents, outline all steps in the conversion of:

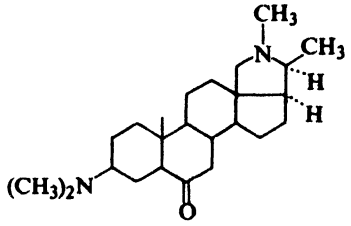
(a) androst-9(11)-ene (p. 516) into the saturated 11-keto derivative.

(b)



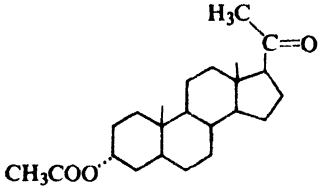
Conessine
(3β-dimethylaminocon-5-enine)
An alkaloid

into



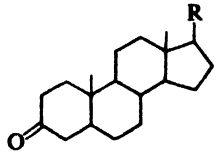
3β-Dimethylaminoconanin-6-one

(c)



5α-Pregnane-3α-ol-20-one
(acetate ester)

into



3-Cholestanone

where R = $-CH(CH_3)CH_2CH_2CH(CH_3)_2$

(*Hint:* $CH_3COOCH_3 + H_2O \xrightarrow{OH^-,\ heat} CH_3COO^- + CH_3OH$.)

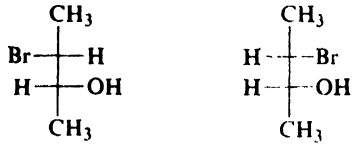
13. Assign structures to the compounds A through HH.

(a) ethylene + Cl_2(aq) ⟶ A (C_2H_5OCl)
A + $NaHCO_3$(aq) ⟶ B ($C_2H_6O_2$)
(b) ethylene + Cl_2(aq) ⟶ A (C_2H_5OCl)
A + HNO_3 ⟶ C ($C_2H_3O_2Cl$)
C + H_2O ⟶ D ($C_2H_4O_3$)
(c) E + $6HIO_4$ ⟶ 6HCOOH
(d) F ($C_{18}H_{34}O_2$) + HCO_2OH ⟶ G ($C_{18}H_{36}O_4$)
G + HIO_4 ⟶ $CH_3(CH_2)_7CHO + OHC(CH_2)_7COOH$
(e) allyl alcohol + Br_2/CCl_4 ⟶ H ($C_3H_6OBr_2$)
H + HNO_3 ⟶ I ($C_3H_4O_2Br_2$)
I + Zn ⟶ J ($C_3H_4O_2$)

(f) 1,2,3-tribromopropane + KOH(alc) $\longrightarrow$ K ($C_3H_4Br_2$)
K + NaOH(aq) $\longrightarrow$ L (C_3H_5OBr)
L + KOH(alc) $\longrightarrow$ M (C_3H_4O)
(g) 2,2-dichloropropane + NaOH(aq) $\longrightarrow$ [N ($C_3H_8O_2$)] $\longrightarrow$ O (C_3H_6O)
(h) propyne + Cl_2(aq) $\longrightarrow$ [P ($C_3H_6O_2Cl_2$)] $\longrightarrow$ Q ($C_3H_4OCl_2$)
Q + Cl_2(aq) $\longrightarrow$ R ($C_3H_3OCl_3$)
R + NaOH(aq) $\longrightarrow$ $CHCl_3$ + S ($C_2H_3O_2Na$)
(i) cyclohexene + $KMnO_4$ $\longrightarrow$ T ($C_6H_{12}O_2$)
T + CH_3COOH, H^+ $\longrightarrow$ U ($C_{10}H_{16}O_4$)
(j) V ($C_3H_8O_3$) + CH_3COOH, H^+ $\longrightarrow$ W ($C_9H_{14}O_6$)
(k) cyclohexanol + $K_2Cr_2O_7$, H^+ $\longrightarrow$ X ($C_6H_{10}O$)
X + *m*-$CH_3C_6H_4MgBr$, followed by H_2O $\longrightarrow$ Y ($C_{13}H_{18}O$)
Y + heat $\longrightarrow$ Z ($C_{13}H_{16}$)
Z + Ni (300°) $\longrightarrow$ AA ($C_{13}H_{12}$)
(l) (R)-(+)-1-bromo-2,4-dimethylpentane + Mg $\longrightarrow$ BB
BB + $(CH_3)_2CHCH_2CHO$, then H_2O $\longrightarrow$ CC ($C_{12}H_{26}O$), *a mixture*
CC + CrO_3 $\longrightarrow$ DD ($C_{12}H_{24}O$)
DD + CH_3MgBr, then H_2O $\longrightarrow$ EE ($C_{13}H_{28}O$), *a mixture*
EE + I_2, heat $\longrightarrow$ FF ($C_{13}H_{26}$), *a mixture*
FF + H_2, Ni $\longrightarrow$ GG ($C_{13}H_{28}$) + HH ($C_{13}H_{28}$)

	Optically active	*Optically inactive*

14. (a) On treatment with HBr, *threo*-3-bromo-2-butanol is converted into racemic 2,3-dibromobutane, and *erythro*-3-bromo-2-butanol is converted into *meso*-2,3-dibromobutane. What appears to be the stereochemistry of the reaction? Does it proceed with inversion or retention of configuration?



and enantiomer *Threo* and enantiomer *Erythro*

3-Bromo-2-butanol

(b) When optically active *threo*-3-bromo-2-butanol is treated with HBr, *racemic* 2,3-dibromobutane is obtained. Now what is the stereochemistry of the reaction? Can you think of a mechanism that accounts for this stereochemistry?

(c) These observations, reported in 1939 by Saul Winstein (p. 474) and Howard J. Lucas (of The California Institute of Technology), are the first of many described as "neighboring group effects." Does this term help you find an answer to (b)?

(d) On treatment with aqueous HBr, both *cis*- and *trans*-2-bromocyclohexanol are converted into the same product. In light of (b), what would you expect this product to be?

15. Interpret the following observations. (a) When dissolved in HSO_3F-SbF_5-SO_2 at $-60°$, methanol gave the following nmr spectrum: *a*, triplet, δ 4.7, 3H; *b*, quartet, δ 9.4, 2H. Under the same conditions, isobutyl alcohol gave: *a*, doublet, δ 1.1, 6H; *b* multiplet, δ 2.3, 1H; *c*, two overlapping triplets, δ 4.7, 2H; *d*, triplet, δ 9.4, 2H.

(b) Warming to $+50°$ had no effect on the methanol solution. At $-30°$, however, the isobutyl alcohol spectrum slowly disappeared, to be replaced by a single peak at δ 4.35. (c) Even at $-60°$, *tert*-butyl alcohol dissolved in HSO_3F-SbF_5-SO_2 to give immediately a single peak at δ 4.35.

16. Tricyclopropylcarbinol (R_3COH, R = cyclopropyl) gives a complex nmr spectrum in the region δ 0.2–1.1, and is transparent in the near ultraviolet. A solution of the alcohol in concentrated H_2SO_4 has the following properties:

(i) A freezing-point lowering corresponding to four particles for each molecule dissolved;
(ii) intense ultraviolet absorption (λ_{max} 270 mμ, ϵ_{max} 22,000);
(iii) an nmr spectrum with one peak, a singlet, δ 2.26.

When the solution is diluted and neutralized, the original alcohol is recovered.

(a) What substance is formed in sulfuric acid solution? Show how its formation accounts for each of the facts (i)–(iii). How do you account for the evident stability of this substance? (*Hint:* See Secs. 9.9 and 12.18.)
(b) A solution of 2-cyclopropyl-2-propanol in strong acid gives the following nmr spectrum:

a singlet, δ 2.60, 3H
b singlet, δ 3.14, 3H
c multiplet, δ 3.5–4, 5H

A similar solution of 2-cyclopropyl-1,1,1-trideuterio-2-propanol gives a similar spectrum except that *a* and *b* are each reduced to one-half their former area.

What general conclusion about the relative locations of the two methyl groups must you make? Can you suggest a specific geometry for the molecule that is consistent not only with this spectrum but also with your answer to part (a)? (*Hint:* Use models.)

17. By use of Table 16.1 tell which alcohol or alcohols each of the following is likely to be. Tell what further steps you would take to identify it or to confirm your identification. (Below, Ar = α-naphthyl, Sec. 30.2.)

$$\underset{\text{An isocyanate}}{ArNCO} + ROH \longrightarrow \underset{\text{A urethane}}{ArNHCOOR}$$

II: b.p. 115–7°; Lucas test, secondary; 3,5-dinitrobenzoate, m.p. 95–6°
JJ: b.p. 128–30°; negative halogen test; Lucas test, primary
KK: b.p. 128–31°; positive iodoform test
LL: b.p. 115–8°; 3,5-dinitrobenzoate, m.p. 60–1°
MM: b.p. 117–9°; α-naphthylurethane, m.p. 69–71°

Table 16.1 DERIVATIVES OF SOME ALCOHOLS

Alcohol	B.p., °C	α-Naphthylurethane M.p., °C	3,5-Dinitrobenzoate M.p., °C
3-Methyl-2-butanol	114	112	76
3-Pentanol	116	71	97
n-Butyl alcohol	118	71	64
2-Pentanol	119	76	61
1-Chloro-2-propanol	127	—	83
2-Methyl-1-butanol	128	97	62
Ethylene chlorohydrin	129	101	92
4-Methyl-2-pentanol	131	88	65
3-Methyl-1-butanol	132	67	62
2-Chloro-1-propanol	132	—	76

18. Describe simple chemical tests that would serve to distinguish between:

(a) *n*-butyl alcohol and *n*-octane
(b) *n*-butyl alcohol and 1-octene
(c) *n*-butyl alcohol and *n*-pentyl bromide
(d) *n*-butyl alcohol and 3-buten-1-ol
(e) 3-buten-1-ol and 2-buten-1-ol

(f) 3-pentanol and 1-pentanol
(g) 3-pentanol and 2-pentanol
(h) 3-phenyl-1-propanol and cinnamyl alcohol (3-phenyl-2-propen-1-ol)
(i) 1,2-propanediol and 1,3-propanediol
(j) *n*-butyl alcohol and *tert*-pentyl alcohol
(k) *p*-bromobenzyl alcohol and *p*-ethylbenzyl alcohol
(l) α-phenylethyl alcohol and β-phenylethyl alcohol

Tell exactly what you would *do* and *see*.

19. Although it is a secondary alcohol, 1-chloro-2-propanol behaves like a primary alcohol in the Lucas test. Can you suggest a reason for this behavior?

20. (a) Compound NN of formula $C_9H_{12}O$ responded to a series of tests as follows:

(1) Na ⟶ slow formation of gas bubbles
(2) acetic anhydride ⟶ pleasant smelling product
(3) CrO_3/H_2SO_4 ⟶ opaque blue-green *immediately*
(4) hot $KMnO_4$ ⟶ benzoic acid
(5) Br_2/CCl_4 ⟶ no decolorization
(6) I_2 + NaOH ⟶ yellow solid
(7) rotated plane-polarized light

What was NN? Write equations for all the above reactions.

(b) Compound OO, an isomer of NN, also was found to be optically active. It showed the same behavior as NN except for test (6). From the careful oxidation of OO by $KMnO_4$ there was isolated an acid of formula $C_9H_{10}O_2$. What was OO?

21. Identify each of the following isomers of formula $C_{20}H_{18}O$:

Isomer PP (m.p. 88°)	*a* singlet, δ 2.23, 1H
	b doublet, δ 3.92, 1H, J = 7 Hz
	c doublet, δ 4.98, 1H, J = 7 Hz
	d singlet, δ 6.81, 10 H
	e singlet, δ 6.99, 5H
Isomer QQ (m.p. 88°)	*a* singlet, δ 2.14, 1H
	b singlet, δ 3.55, 2H
	c broad peak, δ 7.25, 15H

What single simple chemical test would distinguish between these two isomers?

22. Give a structure or structures consistent with each of the nmr spectra in Fig. 16.2, p. 548.

23. Give a structure or structures consistent with each of the nmr spectra in Fig. 16.3, p. 549.

24. Upon hydrogenation, compound RR (C_4H_8O) is converted into SS ($C_4H_{10}O$). On the basis of their infrared spectra (Fig. 16.4, p. 550) give the structural formulas of RR and SS.

25. Give a structure or structures for the compound TT, whose infrared and nmr spectra are shown in Fig. 16.5, p. 550, and Fig. 16.6, p. 551.

26. *Geraniol*, $C_{10}H_{18}O$, a terpene found in rose oil, gives the infrared and nmr spectra shown in Fig. 16.7 (p. 551). In the next problem, chemical evidence is given from which its structure can be deduced; before working that problem, however, let us see how much information we can get from the spectra alone.

(a) Examine the infrared spectrum. Is geraniol aliphatic or aromatic? What functional group is clearly present? From the molecular formula, what other groupings must also be present in the molecule? Is their presence confirmed by the infrared spectrum?

(b) In the nmr spectrum, assign the number of protons to each signal on the basis of the integration curve. From the chemical shift values, and keeping in mind the infrared information, what kind of proton probably gives rise to each signal?

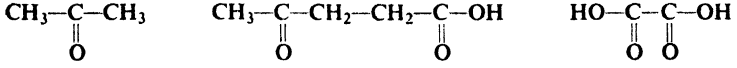
(c) When geraniol is shaken with D_2O, the peak at δ 3.32 disappears. Why?

(d) Write down likely groupings in the molecule. How many (if any) methyl groups are there? Methylene groups? Vinylic or allylic protons?

(e) What relationships among these groupings are suggested by chemical shift values, splittings, etc.?

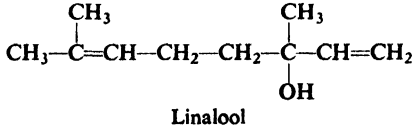
(f) Draw a structure or structures consistent with the spectra. Taking into account the source of geraniol, are any of these more likely than others?

27. *Geraniol*, $C_{10}H_{18}O$, a terpene found in rose oil, adds two moles of bromine to form a tetrabromide, $C_{10}H_{18}OBr_4$. It can be oxidized to a ten-carbon aldehyde or to a ten-carbon carboxylic acid. Upon vigorous oxidation, geraniol yields:



(a) Keeping in mind the isoprene rule (Sec. 8.26), what is the most likely structure for geraniol? (b) Nerol (Problem 19, p. 317) can be converted into the same saturated alcohol as geraniol, and yields the same oxidation products as geraniol, yet has different physical properties. What is the most probable structural relationship between geraniol and nerol? (c) Like nerol, geraniol is converted by sulfuric acid into α-terpineol (Problem 19, p. 317), but much more slowly than nerol. On this basis, what structures might you assign to nerol and geraniol? (*Hint:* Use models.)

28. Upon treatment with HBr, both geraniol (preceding problem) and *linalool* (from oil of lavender, bergamot, coriander) yield the same bromide, of formula $C_{10}H_{17}Br$. How do you account for this fact?



Linalool

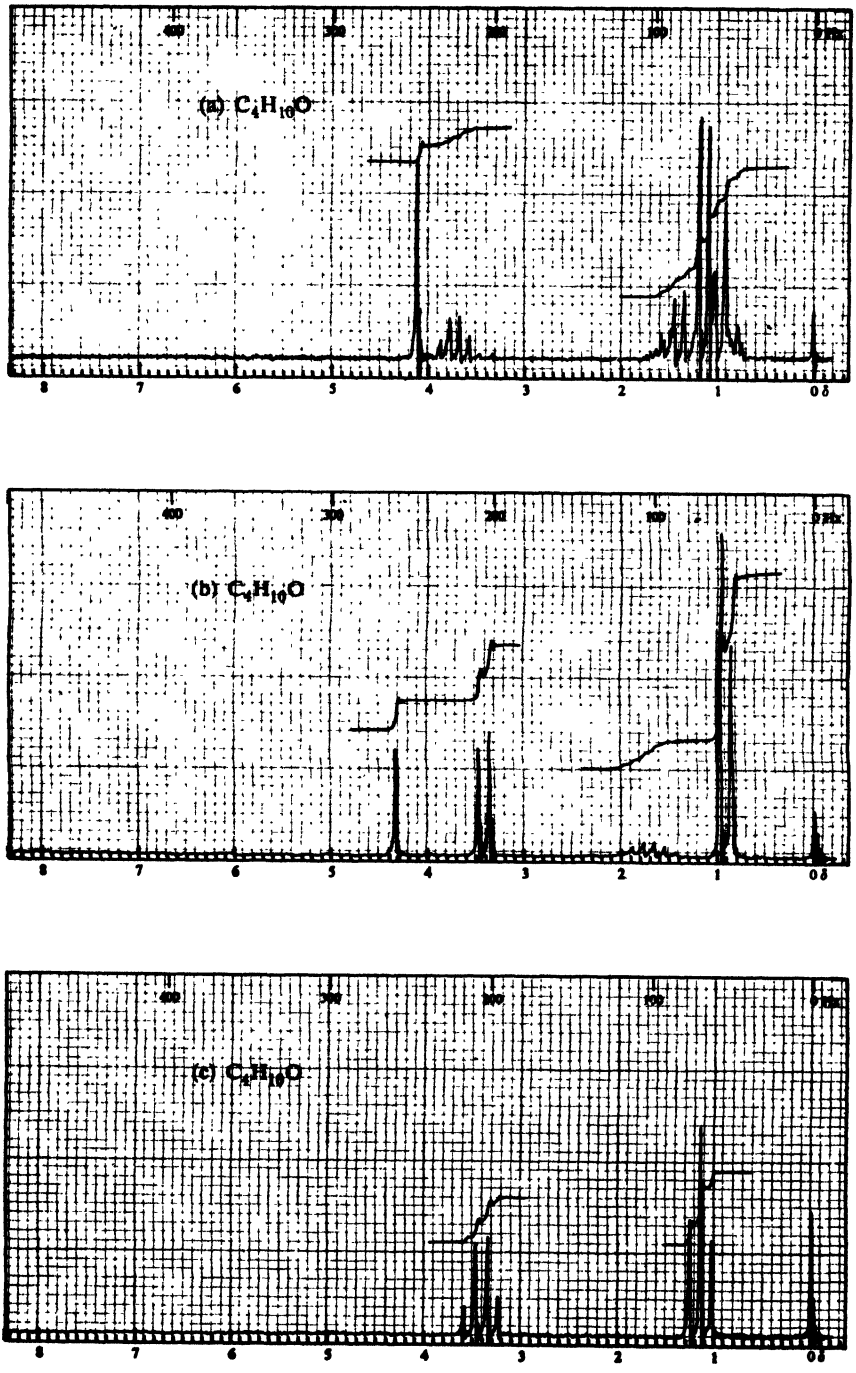


Figure 16.2. Nmr spectra for Problem 22, p. 546.

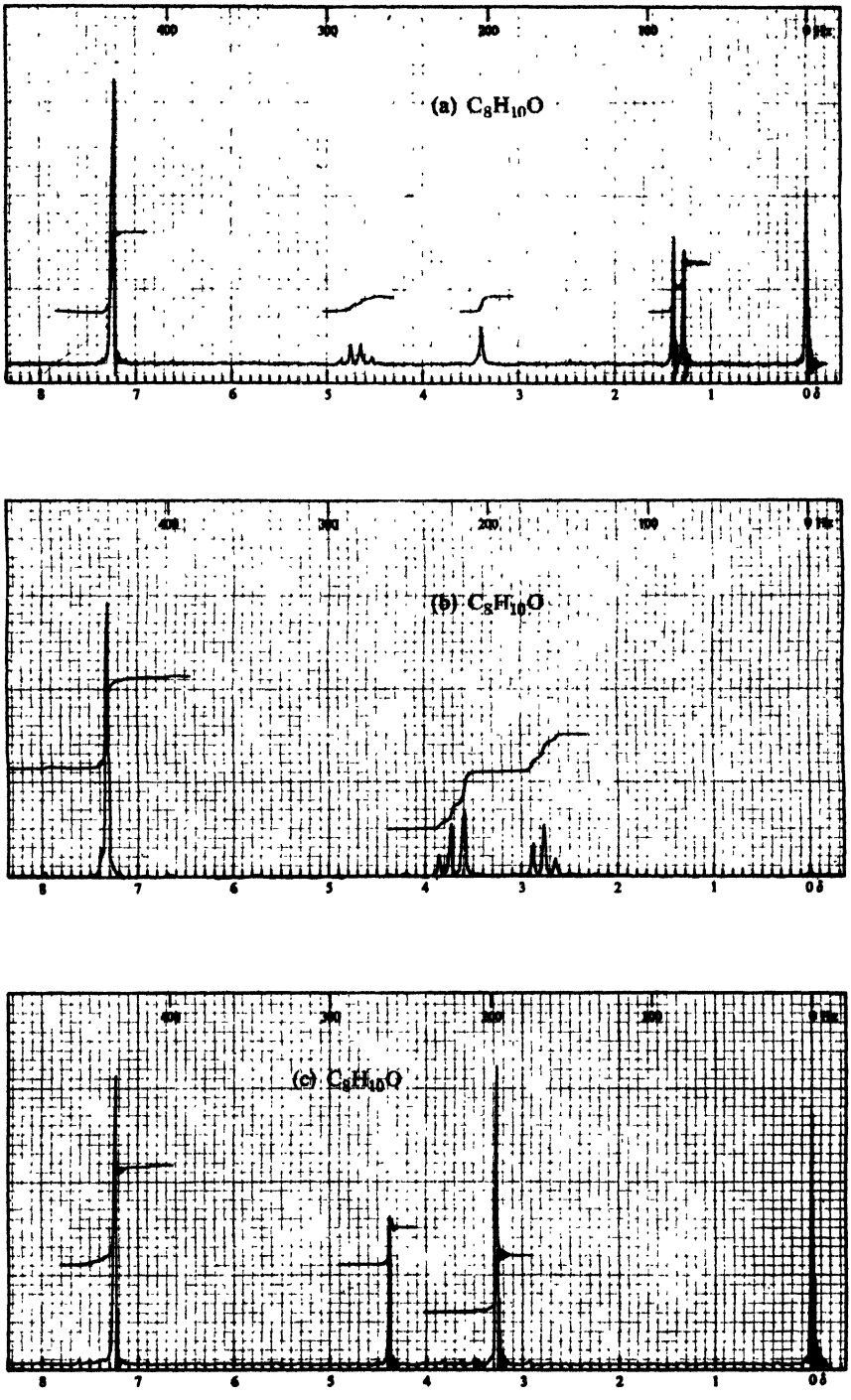
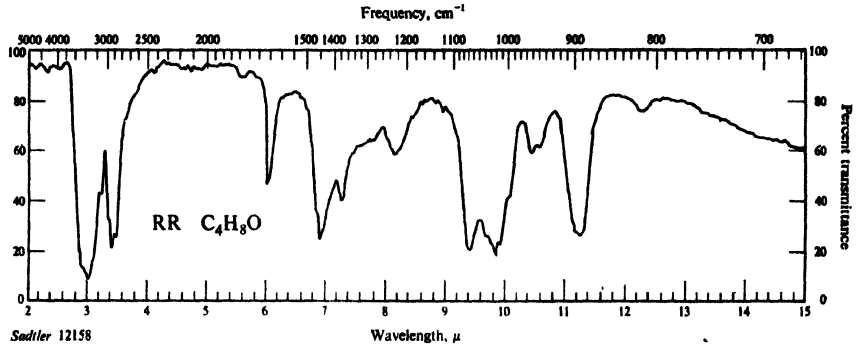


Figure 16.3. Nmr spectra for Problem 23, p. 546



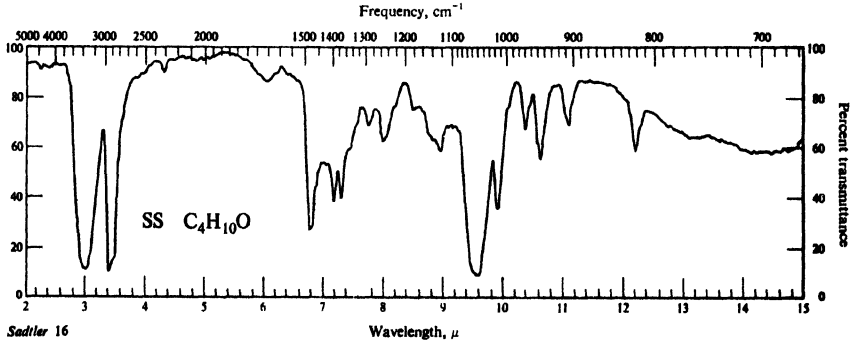


Figure 16.4. Infrared spectra for Problem 24, p. 546.

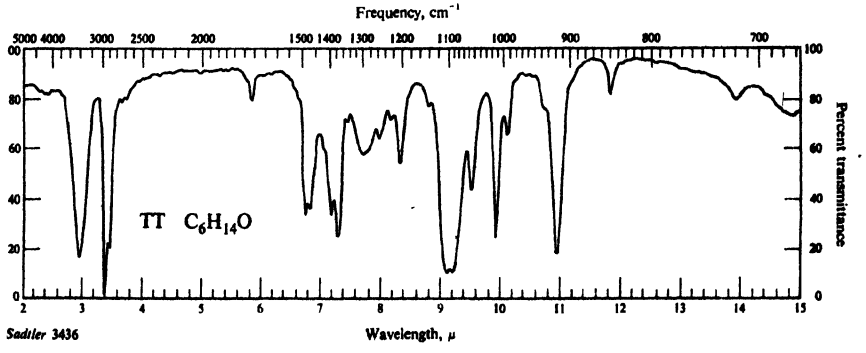


Figure 16.5. Infrared spectrum for Problem 25, p. 546.

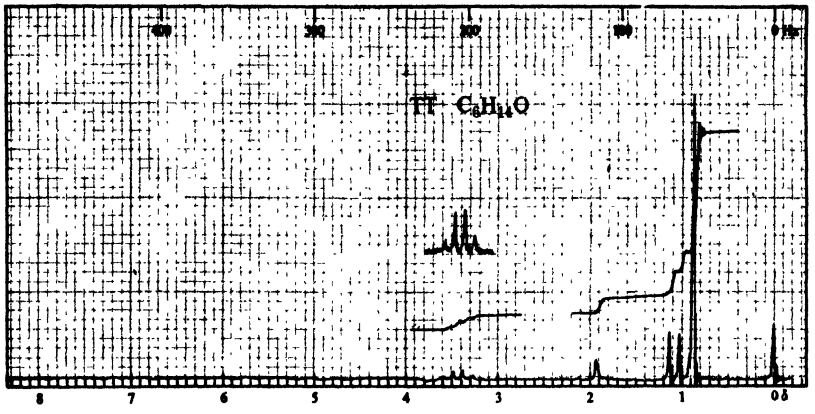
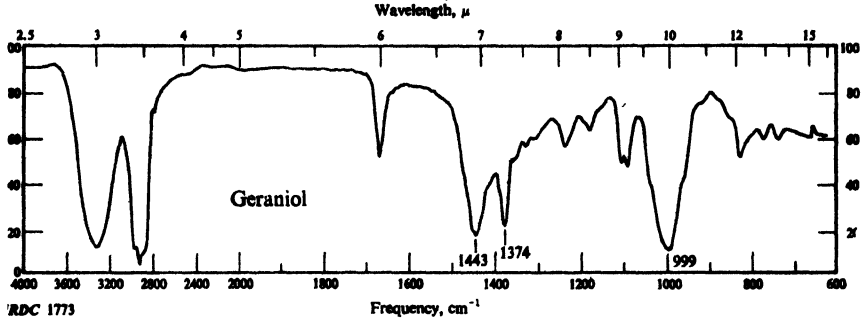


Figure 16.6. Nmr spectrum for Problem 25, p. 546.



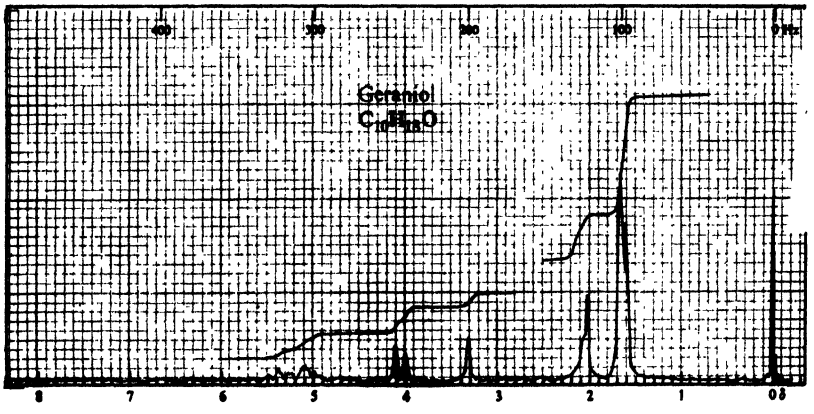


Figure 16.7. Infrared and nmr spectra for Problem 26, p. 546.

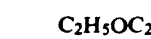
Chapter 17 Ethers and Epoxides

ETHERS

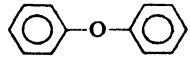
17.1 Structure and nomenclature of ethers

Ethers are compounds of the general formula R—O—R, Ar—O—R, or Ar—O—Ar.

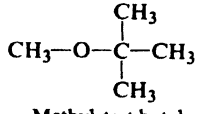
To name ethers we usually name the two groups that are attached to oxygen, and follow these names by the word *ether*:



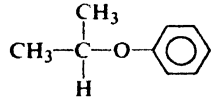
Ethyl ether



Phenyl ether

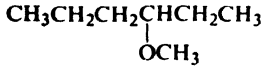


Methyl *tert*-butyl ether

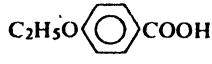


Isopropyl phenyl ether

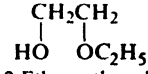
If one group has no simple name, the compound may be named as an *alkoxy* derivative:



3-Methoxyhexane

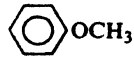


p-Ethoxybenzoic acid



2-Ethoxyethanol

The simplest aryl alkyl ether has the special name of *anisole*.

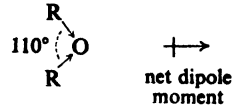


Anisole

If the two groups are identical, the ether is said to be *symmetrical* (e.g., *ethyl ether, phenyl ether*), if different, *unsymmetrical* (e.g., *methyl tert-butyl ether, anisole*).

17.2 Physical properties of ethers

Since the C—O—C bond angle is not 180°, the dipole moments of the two C—O bonds do not cancel each other; consequently, ethers possess a small net dipole moment (e.g., 1.18 D for ethyl ether).



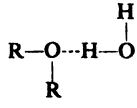
This weak polarity does not appreciably affect the boiling points of ethers, which are about the same as those of alkanes having comparable molecular weights, and much lower than those of isomeric alcohols. Compare, for example, the boiling points of *n*-heptane (98°), methyl *n*-pentyl ether (100°), and *n*-hexyl alcohol (157°). The hydrogen bonding that holds alcohol molecules strongly together is not possible for ethers, since they contain hydrogen bonded only to carbon (Sec. 15.4).

On the other hand, ethers show a solubility in water comparable to that of the alcohols, both ethyl ether and *n*-butyl alcohol, for example, being soluble to the extent of about 8 g per 100 g of water. We attributed the water solubility of the

Table 17.1 ETHERS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Methyl ether	−140	− 24	Anisole	− 37	154
Ethyl ether	−116	34.6	Phenetole (Ethyl phenyl ether)	− 33	172
n-Propyl ether	−122	91			
Isopropyl ether	− 60	69	Phenyl ether	27	259
n-Butyl ether	− 95	142	1,4-Dioxane	11	101
Vinyl ether		35	Tetrahydrofuran	−108	66
Allyl ether		94			

lower alcohols to hydrogen bonding between water molecules and alcohol molecules; presumably the water solubility of ether arises in the same way.



17.3 Industrial sources of ethers. Dehydration of alcohols

A number of symmetrical ethers containing the lower alkyl groups are prepared on a large scale. chiefly for use as solvents. The most important of these is

ethyl ether, the familiar anesthetic and the solvent we use in extractions and in the preparation of Grignard reagents; others include isopropyl ether and *n*-butyl ether.

These ethers are prepared by reactions of the corresponding alcohols with sulfuric acid. Since a molecule of water is lost for every pair of alcohol molecules, the reaction is a kind of *dehydration*. Dehydration to ethers rather than to alkenes

$$2R{-}O{-}H \xrightarrow{H_2SO_4,\ heat} R{-}O{-}R + H_2O$$

is controlled by the choice of reaction conditions. For example, ethylene is prepared by heating ethyl alcohol with concentrated sulfuric acid to 180°; ethyl ether is prepared by heating a mixture of ethyl alcohol and concentrated sulfuric acid to 140°, alcohol being continuously added to keep it in excess.

Dehydration is generally limited to the preparation of symmetrical ethers, because, as we might expect, a combination of two alcohols usually yields a mixture of three ethers.

Ether formation by dehydration is an example of nucleophilic substitution, with the protonated alcohol as substrate and a second molecule of alcohol as nucleophile.

Problem 17.1 (a) Give all steps of a likely mechanism for the dehydration of an alcohol to an ether. (b) Is this the only possibility? Give all steps of an alternative mechanism. (*Hint:* See Sec. 14.16.) (c) Dehydration of *n*-butyl alcohol gives *n*-butyl ether. Which of your alternatives appears to be operating here?

Problem 17.2 In ether formation by dehydration, as in other cases of substitution, there is a competing elimination reaction. What is this reaction, and what products does it yield? For what alcohols would elimination be most important?

Problem 17.3 (a) Upon treatment with sulfuric acid, a mixture of ethyl and *n*-propyl alcohols yields a mixture of three ethers. What are they? (b) On the other hand, a mixture of *tert*-butyl alcohol and ethyl alcohol gives a good yield of a single ether. What ether is this likely to be? How do you account for the good yield?

On standing in contact with air, most aliphatic ethers are converted slowly into unstable peroxides. Although present in only low concentrations, these peroxides are very dangerous, since they can cause violent explosions during the distillations that normally follow extractions with ether.

The presence of peroxides is indicated by formation of a red color when the ether is shaken with an aqueous solution of ferrous ammonium sulfate and potassium thiocyanate; the peroxide oxidizes ferrous ion to ferric ion, which reacts with thiocyanate ion to give the characteristic blood-red color of the complex.

$$\text{peroxide} + Fe^{++} \longrightarrow Fe^{+++} \xrightarrow{SCN^-} \underset{Red}{Fe(SCN)_n^{-(3-n)}} \qquad (n = 1 \text{ to } 6)$$

Peroxides can be removed from ethers in a number of ways, including washing with solutions of ferrous ion (which reduces peroxides), or distillation from concentrated H_2SO_4 (which oxidizes peroxides).

For use in the preparation of Grignard reagents, the ether (usually ethyl) must be free of traces of water and alcohol. This so-called **absolute ether** can be prepared by distillation of ordinary ether from concentrated H_2SO_4 (which

removes not only water and alcohol but also peroxides), and subsequent storing over metallic sodium. There is available today commercial anhydrous ether of such high quality that only the treatment with sodium is needed to make it ready for the Grignard reaction.

It is hard to overemphasize the hazards met in using ethyl ether, even when it is free of peroxides: it is highly volatile, and the flammability of its vapors makes explosions and fires ever-present dangers unless proper precautions are observed.

17.4 Preparation of ethers

The following methods are generally used for the laboratory preparation of ethers. (The Williamson synthesis is used for the preparation of aryl alkyl ethers industrially, as well.)

PREPARATION OF ETHERS

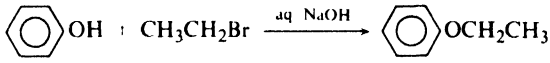
1. Williamson synthesis. Discussed in Sec. 17.5.

$$RX + \begin{matrix} R'O^-Na^+ \\ \text{or} \\ ArO^-Na^+ \end{matrix} \longrightarrow \begin{matrix} ROR' \\ \text{or} \\ ROAr \end{matrix} \qquad \textit{Yield from RX:}\ CH_3 > 1^\circ > 2^\circ\ (>3^\circ)$$

Examples:

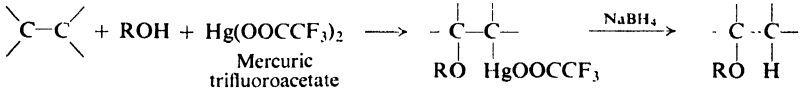
$$\left[(CH_3)_2CHOH \xrightarrow{Na}\right] (CH_3)_2CHO^-Na^+ + CH_3CH_2CH_2Br \longrightarrow CH_3CH_2CH_2OCH(CH_3)_2$$

Sodium isopropoxide; *n*-Propyl bromide; *n*-Propyl isopropyl ether



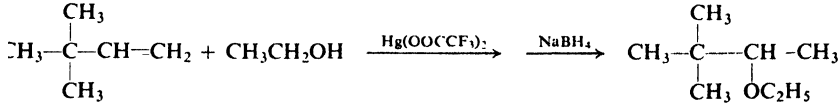
Phenol Ethyl bromide Phenyl ethyl ether

2. Alkoxymercuration-demercuration. Discussed in Sec. 17.6.



Markovnikov orientation

Example:



3,3-Dimethyl-1-butene 3-Ethoxy-2,2-dimethylbutane

No rearrangement

17.5 Preparation of ethers. Williamson synthesis

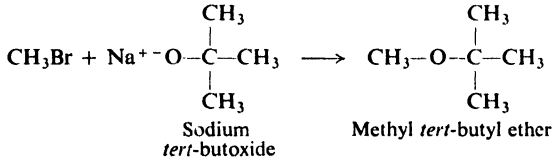
In the laboratory, the Williamson synthesis of ethers is important because of its versatility: it can be used to make unsymmetrical ethers as well as symmetrical ethers, and aryl alkyl ethers as well as dialkyl ethers.

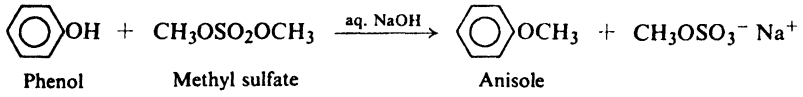
In the Williamson synthesis an alkyl halide (or substituted alkyl halide) is allowed to react with a sodium alkoxide or a sodium phenoxide:

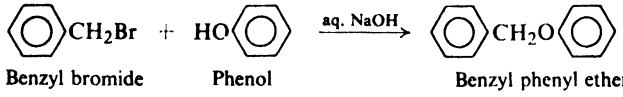
$$R{-}X + Na^+ {}^-O{-}R' \longrightarrow R{-}O{-}R' + Na^+X^-$$

$$R{-}X + Na^+ {}^-O{-}Ar \longrightarrow R{-}O{-}Ar + Na^+X^-$$

For the preparation of methyl aryl ethers, *methyl sulfate*, $(CH_3)_2SO_4$, is frequently used instead of the more expensive methyl halides.







The Williamson synthesis involves nucleophilic substitution of alkoxide ion or phenoxide ion for halide ion; it is strictly analogous to the preparation of alcohols by treatment of alkyl halides with aqueous hydroxide (Sec. 15.7). *Aryl halides cannot in general be used, because of their low reactivity toward nucleophilic substitution.*

Problem 17.4 (a) On what basis could you have predicted that methyl sulfate would be a good methylating agent in reactions like those presented above? (*Hint:* What is the *leaving group*? See Sec. 14.6.) (b) Can you suggest another class of compounds that might serve in place of alkyl halides in the Williamson synthesis?

Sodium alkoxides are made by direct action of sodium metal on dry alcohols:

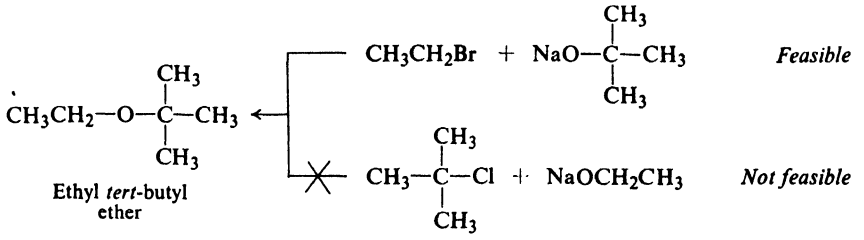
$$ROH + Na \longrightarrow \underset{\text{An alkoxide}}{RO^-Na^+} + \tfrac{1}{2}H_2$$

Sodium phenoxides, on the other hand, because of the appreciable acidity of phenols (Sec. 24.7), are made by the action of aqueous sodium hydroxide on phenols:

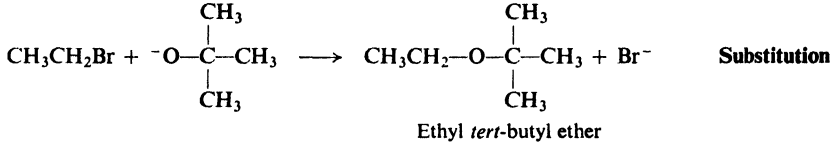
$$\underset{\text{Stronger acid}}{ArOH} + Na^+ {}^-OH \longrightarrow \underset{\text{A phenoxide}}{ArO^-Na^+} + \underset{\text{Weaker acid}}{H_2O}$$

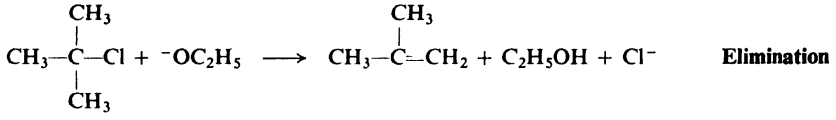
If we wish to make an unsymmetrical dialkyl ether, we have a choice of two combinations of reagents; one of these is nearly always better than the other.

In the preparation of ethyl *tert*-butyl ether, for example, the following combinations are conceivable:



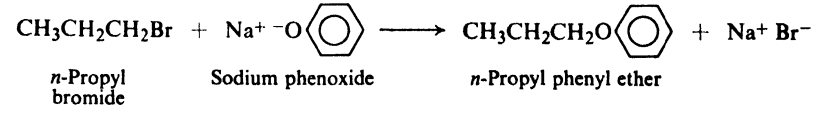
Which do we choose? As always, we must consider the danger of elimination competing with the desired substitution; elimination should be particularly serious here because of the strong basicity of the alkoxide reagent. We therefore reject the use of the tertiary halide, which we expect to yield mostly—or all—elimination product; we must use the other combination. The disadvantage of the slow

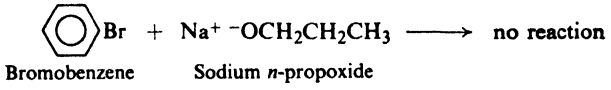




reaction between sodium and *tert*-butyl alcohol (Sec. 16.6) in the preparation of the alkoxide is more than offset by the tendency of the primary halide to undergo substitution rather than elimination. In planning a Williamson synthesis of a dialkyl ether, we must always keep in mind that the tendency for alkyl halides to undergo dehydrohalogenation is 3° > 2° > 1°.

For the preparation of an aryl alkyl ether there are again two combinations to be considered; here, one combination can usually be rejected out of hand. *n*-Propyl phenyl ether, for example, can be prepared only from the alkyl halide and the phenoxide, since the aryl halide is quite unreactive toward alkoxides.





Since alkoxides and phenoxides are prepared from the corresponding alcohols and phenols, and since alkyl halides are commonly prepared from the alcohols,

the Williamson method ultimately involves the synthesis of an ether from two hydroxy compounds.

Problem 17.5 Outline the synthesis, from alcohols and/or phenols, of:

(a) ethyl *tert*-butyl ether
(b) *n*-propyl phenyl ether
(c) isobutyl *sec*-butyl ether
(d) cyclohexyl methyl ether

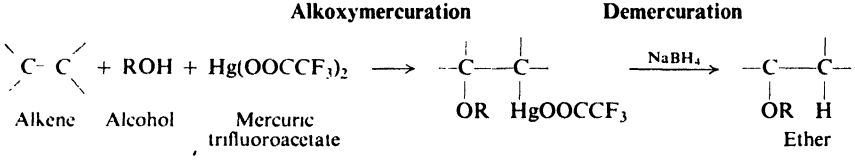
Problem 17.6 Outline the synthesis of phenyl *p*-nitrobenzyl ether from any of these starting materials: toluene, bromobenzene, phenol. (*Caution:* Double-check the nitration stage.)

Problem 17.7 When optically active 2-octanol of specific rotation $-8.24°$ is converted into its sodium salt, and the salt is then treated with ethyl bromide, there is obtained the optically active ether, 2-ethoxyoctane, with specific rotation $-14.6°$. Making use of the configuration and maximum rotation of 2-octanol given on p. 462, what, if anything, can you say about: (a) the configuration of (−)-2-ethoxyoctane? (b) the maximum rotation of 2-ethoxyoctane?

Problem 17.8 (*Work this after Problem 17.7.*) When (−)-2-bromooctane of specific rotation $-30.3°$ is treated with ethoxide ion in ethyl alcohol, there is obtained 2-ethoxyoctane of specific rotation $+15.3°$. Using the configuration and maximum rotation of the bromide given on p. 462, answer the following questions. (a) Does this reaction involve complete retention of configuration, complete inversion, or inversion plus racemization? (b) By what mechanism does this reaction appear to proceed? (c) In view of the reagent and solvent, is this the mechanism you would have expected to operate? (d) What mechanism do you suppose is involved in the alternative synthesis (Problem 17.7) of 2-ethoxyoctane from the salt of 2-octanol and ethyl bromide? (e) Why, then, do the products of the two syntheses have *opposite* rotations?

17.6 Preparation of ethers. Alkoxymercuration-demercuration

Alkenes react with mercuric trifluoroacetate in the presence of an alcohol to give alkoxymercurial compounds which on reduction yield ethers.

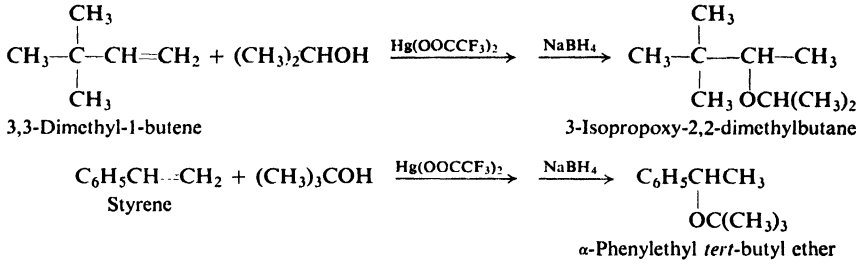


We recognize this two-stage process as the exact analog of the oxymercuration–demercuration synthesis of alcohols (Sec. 15.8). In place of water we use an alcohol which, not surprisingly, can play exactly the same role. Instead of introducing the hydroxy group to make an alcohol, we introduce an *alkoxy* group to make an ether. This example of *solvomercuration-demercuration* amounts to Markovnikov addition of an alcohol to a carbon–carbon double bond.

Problem 17.9 Write all steps of a likely mechanism for alkoxymercuration.

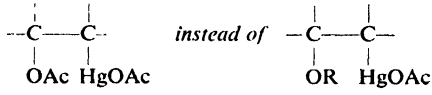
Alkoxymercuration-demercuration has all the advantages we saw for its counterpart: speed, convenience, high yield, and the virtual absence of rearrangement. Compared with the Williamson synthesis, it has one tremendous advantage: there is no competing elimination reaction. As a result, it can be used for the

synthesis of nearly every kind of alkyl ether except—evidently for steric reasons—di-*tert*-alkyl ethers. For example:



We notice that, instead of the mercuric acetate which was used in the preparation of alcohols, here mercuric *trifluoro*acetate is used. With a bulky alcohol—secondary or tertiary—as solvent, the trifluoroacetate is required for a good yield of ether.

Problem 17.10 In the presence of a secondary or tertiary alcohol, mercuric acetate adds to alkenes to give much—or even chiefly—organic acetate instead of ether



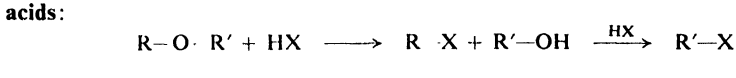
as the product. How do you account for the advantage of using mercuric trifluoroacetate? (*Hint:* Trifluoroacetic acid is a much stronger acid than acetic.)

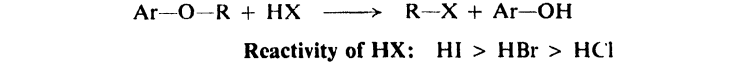
Problem 17.11 Starting with any alcohols, outline all steps in the synthesis of each of the following ethers, using the Williamson synthesis or alkoxymercuration-demercuration, whichever you think is best suited for the particular job.

(a) *n*-hexyl isopropyl ether
(b) 2-hexyl isopropyl ether
(c) cyclohexyl *tert*-butyl ether
(d) cyclohexyl ether

17.7 Reactions of ethers. Cleavage by acids

Ethers are comparatively unreactive compounds. The ether linkage is quite stable toward bases, oxidizing agents, and reducing agents. In so far as the ether linkage itself is concerned, ethers undergo just one kind of reaction, **cleavage by acids**:



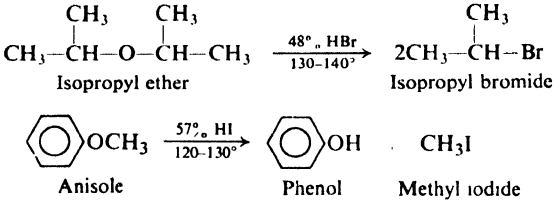


Reactivity of HX: HI > HBr > HCl

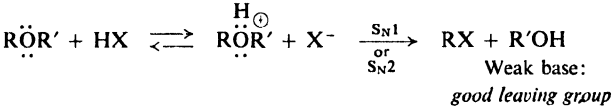
Cleavage takes place only under quite vigorous conditions: concentrated acids (usually HI or HBr) and high temperatures.

An alkyl ether yields initially an alkyl halide and an alcohol; the alcohol may react further to form a second mole of alkyl halide. Because of the low reactivity at the bond between oxygen and an aromatic ring, an aryl alkyl ether

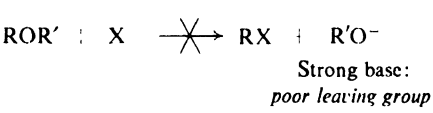
undergoes cleavage of the alkyl–oxygen bond and yields a phenol and an alkyl halide. For example:



Cleavage involves nucleophilic attack by halide ion on the protonated ether, with displacement of the weakly basic alcohol molecule:



Such a reaction occurs much more readily than displacement of the strongly basic alkoxide ion from the neutral ether.



Reaction of a protonated ether with halide ion, like the corresponding reaction of a protonated alcohol, can proceed by either an S_N1 or S_N2 mechanism, depending upon conditions and the structure of the ether. As we might expect, a primary

S_N1

(1) $$ROR'^{+}_{|H} \xrightarrow{\text{slow}} R^+ + HOR'$$

(2) $$R^+ + X^- \xrightarrow{\text{fast}} R{-}X$$

S_N2

$$ROR'^{+}_{|H} + X^- \longrightarrow \left[X^{\delta-} \cdots R \cdots O^{\delta+}_{|H} R' \right] \longrightarrow RX + HOR'$$

alkyl group tends to undergo S_N2 displacement, whereas a tertiary alkyl group tends to undergo S_N1 displacement.

Problem 17.12 Cleavage of optically active methyl *sec*-butyl ether by anhydrous HBr yields chiefly methyl bromide and *sec*-butyl alcohol; the *sec*-butyl alcohol has the same configuration and optical purity as the starting material. How do you interpret these results?

17.8 Electrophilic substitution in aromatic ethers

The alkoxy group, —OR, was listed (Sec. 11.5) as *ortho,para*-directing toward electrophilic aromatic substitution, and moderately activating. It is a much stronger activator than —R, but much weaker than —OH.

The carbonium ions resulting from *ortho* and *para* attack were considered (Sec. 11.20) to be stabilized by contribution from structures I and II. These structures

I II

are especially stable ones, since in them every atom (except hydrogen, of course) has a complete octet of electrons.

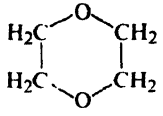
The ability of the oxygen to share more than a pair of electrons with the ring and to accommodate a positive charge is consistent with the basic character of ethers.

Problem 17.13 Predict the principal products of: (a) bromination of *p*-methylanisole; (b) nitration of *m*-nitroanisole; (c) nitration of benzyl phenyl ether.

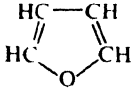
17.9 Cyclic ethers

In their preparation and properties, most cyclic ethers are just like the ethers we have already studied: the chemistry of the ether linkage is essentially the same whether it forms part of an open chain or part of an aliphatic ring.

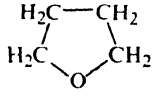
Problem 17.14 *1,4-Dioxane* is prepared industrially (for use as a water-soluble solvent) by dehydration of an alcohol. What alcohol is used?



1,4-Dioxane



Furan



Tetrahydrofuran

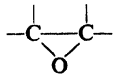
Problem 17.15 The unsaturated cyclic ether *furan* can readily be made from substances isolated from oat hulls and corncobs; one of its important uses involves its conversion into (a) *tetrahydrofuran*, and (b) 1,4-dichlorobutane. Using your knowledge of alkene chemistry and ether chemistry, show how these conversions can be carried out.

Cyclic ethers of one class deserve special attention because of their unusual reactivity; these compounds are the *epoxides*.

EPOXIDES

17.10 Preparation of epoxides

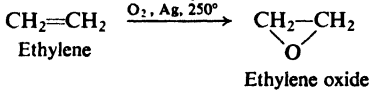
Epoxides are compounds containing the three-membered ring:



Epoxide ring
(Oxirane ring)

They are ethers, but the three-membered ring gives them unusual properties.

By far the most important epoxide is the simplest one, ethylene oxide. It is prepared on an industrial scale by catalytic oxidation of ethylene by air.



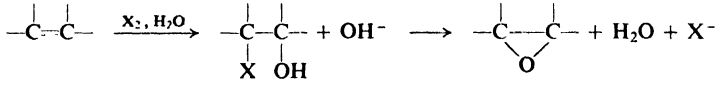
Ethylene

Ethylene oxide

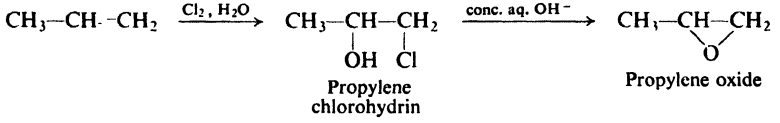
Other epoxides are prepared by the following methods.

PREPARATION OF EPOXIDES

1. From halohydrins. Discussed in Sec. 17.10.



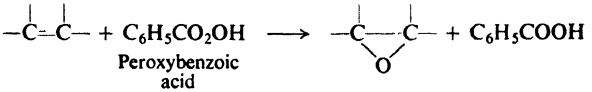
Example:



Propylene chlorohydrin

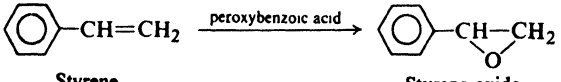
Propylene oxide

2. Peroxidation of carbon–carbon double bonds. Discussed in Sec. 17.10.



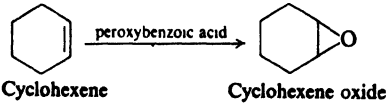
Peroxybenzoic acid

Examples:



Styrene

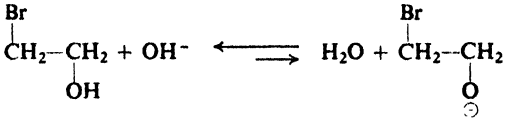
Styrene oxide

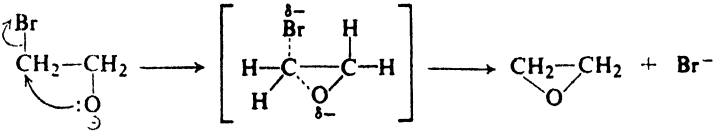


Cyclohexene

Cyclohexene oxide

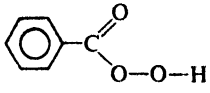
The conversion of halohydrins into epoxides by the action of base is simply an adaptation of the Williamson synthesis (Sec. 17.5); a cyclic compound is obtained because both alcohol and halide happen to be part of the same molecule. In the presence of hydroxide ion a small proportion of the alcohol exists as alkoxide; this alkoxide displaces halide ion from another portion of the same molecule to yield the cyclic ether.

(1) 

(2) 

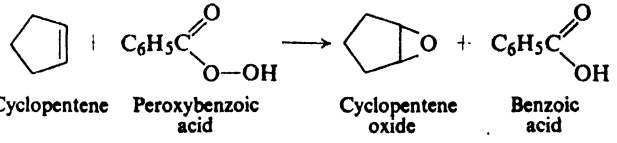
Since halohydrins are nearly always prepared from alkenes by addition of halogen and water to the carbon–carbon double bond (Sec. 6.14), this method amounts to the conversion of an alkene into an epoxide.

Alternatively, the carbon–carbon double bond may be oxidized directly to the epoxide group by peroxybenzoic acid:

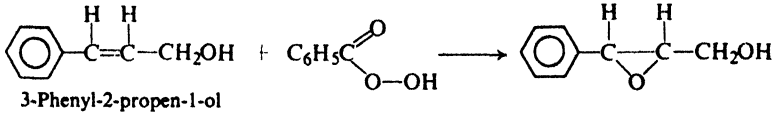


Peroxybenzoic acid

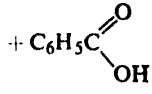
When allowed to stand in ether or chloroform solution, the peroxy acid and the unsaturated compound—which need not be a simple alkene—react to yield benzoic acid and the epoxide. For example:



Cyclopentene | Peroxybenzoic acid | Cyclopentene oxide | Benzoic acid



3-Phenyl-2-propen-1-ol
Cinnamyl alcohol



17.11 Reactions of epoxides

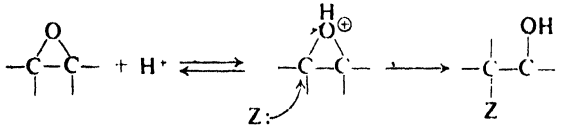
Epoxides owe their importance to their high reactivity, which is due to the ease of opening of the highly strained three-membered ring. The bond angles of the

ring, which average 60°, are considerably less than the normal tetrahedral carbon angle of 109.5°, or the divalent oxygen angle of 110° for open-chain ethers (Sec. 17.2). Since the atoms cannot be located to permit maximum overlap of orbitals (Sec. 9.9), the bonds are weaker than in an ordinary ether, and the molecule is less stable.

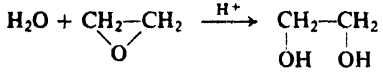
Epoxides undergo acid-catalyzed reactions with extreme ease, and—unlike ordinary ethers—can even be cleaved by bases. Some of the important reactions are outlined below.

REACTIONS OF EPOXIDES

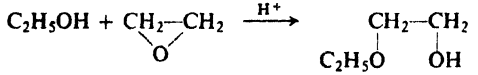
1. Acid-catalyzed cleavage. Discussed in Sec. 17.12.



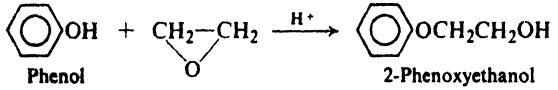
Examples:



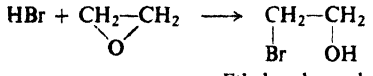
Ethylene glycol
(1,2-Ethanediol)



2-Ethoxyethanol

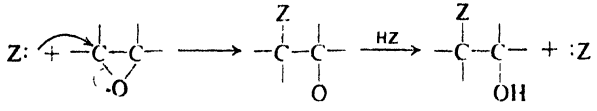


Phenol 2-Phenoxyethanol

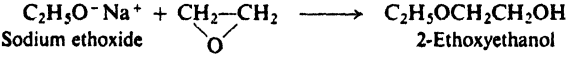


Ethylene bromohydrin
(2-Bromoethanol)

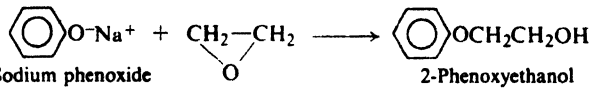
2. Base-catalyzed cleavage. Discussed in Sec. 17.13.



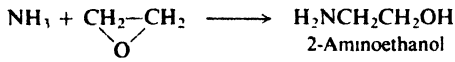
Examples:



Sodium ethoxide 2-Ethoxyethanol

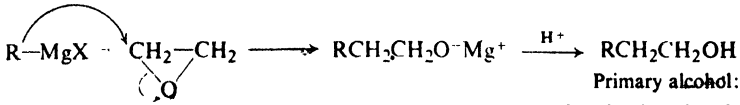


Sodium phenoxide — 2-Phenoxyethanol



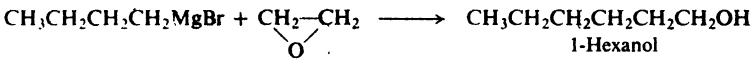
2-Aminoethanol
(Ethanolamine)

3. **Reaction with Grignard reagents.** Discussed in Sec. 17.14.

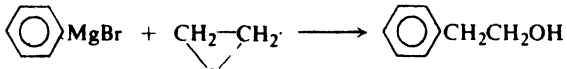


Primary alcohol:
chain has been lengthened by two carbons

Examples:



1-Hexanol

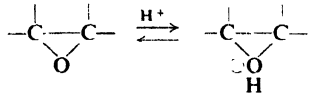


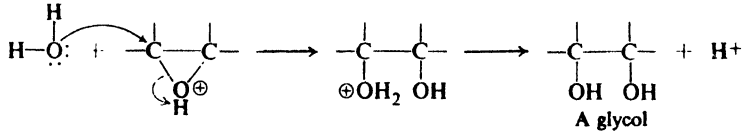
2-Phenylethanol
(β-Phenylethyl alcohol)

17.12 Acid-catalyzed cleavage of epoxides. *anti*-Hydroxylation

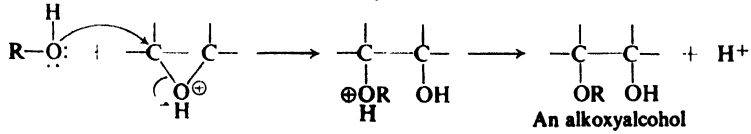
Like other ethers, an epoxide is converted by acid into the protonated epoxide, which can then undergo attack by any of a number of nucleophilic reagents.

An important feature of the reactions of epoxides is the formation of compounds that contain *two* functional groups. Thus, reaction with water yields a glycol; reaction with an alcohol yields a compound that is both ether and alcohol.





A glycol



An alkoxyalcohol
(A hydroxyether)

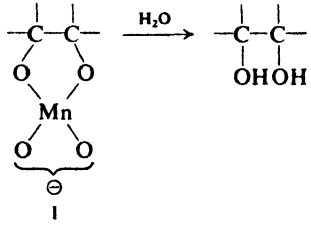
Problem 17.16 The following compounds are commercially available for use as water-soluble solvents. How could each be made?

(a) $CH_3CH_2—O—CH_2CH_2—O—CH_2CH_2—OH$	Carbitol
(b) $C_6H_5—O—CH_2CH_2—O—CH_2CH_2—OH$	Phenyl carbitol
(c) $HO—CH_2CH_2—O—CH_2CH_2—OH$	Diethylene glycol
(d) $HO—CH_2CH_2—O—CH_2CH_2—O—CH_2CH_2—OH$	Triethylene glycol

Problem 17.17 Show in detail (including structures and transition states) the steps in the acid-catalyzed hydrolysis of ethylene oxide by an S_N1 mechanism; by an S_N2 mechanism.

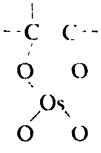
The two-stage process of epoxidation followed by hydrolysis is stereospecific, and gives glycols corresponding to *anti* addition to the carbon–carbon double bond. Exactly the same stereochemistry was observed (Problem 7.11, p. 242) for hydroxylation of alkenes by peroxyformic acid—and for good reason: an epoxide is formed there, too, but is rapidly cleaved in the acidic medium, formic acid. The interpretation is exactly the same as that given to account for *anti* addition of halogens (Sec. 7.12); indeed, epoxides and their hydrolysis served as a model on which the halonium ion mechanism was patterned.

Hydroxylation with permanganate gives *syn*-addition (Problem 7.11, p. 242). To account for this stereochemistry it has been suggested that an intermediate like I is involved:



I

Hydrolysis of such an intermediate would yield the *cis*-glycol. This mechanism is supported by the fact that osmium tetroxide, OsO_4, which also yields the *cis*-glycol, actually forms stable intermediates of structure II.



II

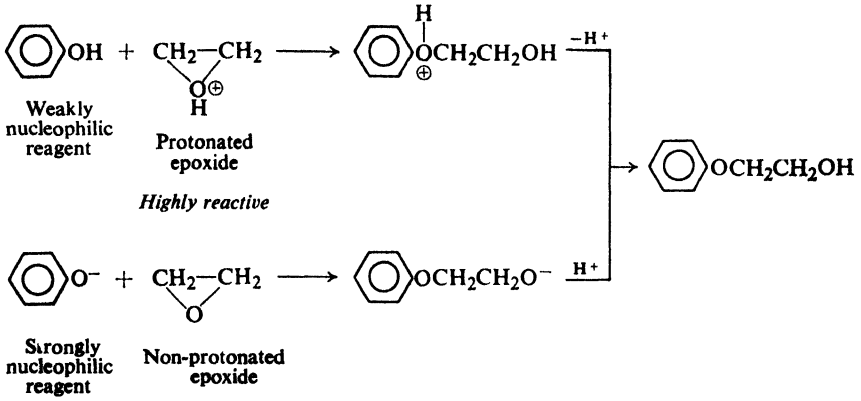
Thus, the two methods of hydroxylation—by peroxy acids and by permanganate—differ in stereochemistry because they differ in mechanism.

Problem 17.18 Using both models and drawings of the kind in Sec. 7.12, show all steps in the formation and hydrolysis of the epoxide of: (a) cyclopentene; (b) *cis*-2-butene; (c) *trans*-2-butene; (d) *cis*-2-pentene; (e) *trans*-2-pentene. (f) Which (if any) of the above products, as obtained, would be optically active?

17.13 Base-catalyzed cleavage of epoxides

Unlike ordinary ethers, epoxides can be cleaved under alkaline conditions. Here it is the epoxide itself, not the protonated epoxide, that undergoes nucleophilic attack. The lower reactivity of the non-protonated epoxide is compensated for by the more basic, more strongly nucleophilic reagent: alkoxide, phenoxide, ammonia, etc.

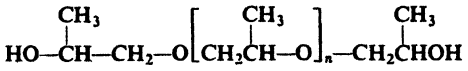
Let us look, for example, at the reaction of ethylene oxide with phenol. Acid catalyzes reaction by converting the epoxide into the highly reactive protonated epoxide. Base catalyzes reaction by converting the phenol into the more strongly nucleophilic phenoxide ion.



Problem 17.19 Write equations for the reaction of ethylene oxide with (a) methanol in the presence of a little H_2SO_4; (b) methanol in the presence of a little $CH_3O^-Na^+$; (c) aniline.

Problem 17.20 Using the reaction between phenol and ethylene oxide as an example, show why it is not feasible to bring about reaction between the protonated epoxide and the highly nucleophilic reagent phenoxide ion. (*Hint:* Consider what would happen if one started with a solution of sodium phenoxide and ethylene oxide and added acid to it.)

Problem 17.21 Poly(oxypropylene)glycols,

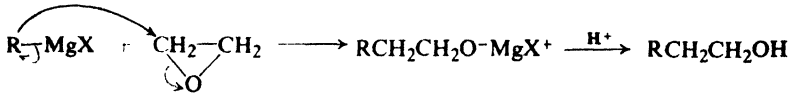


which are used in the manufacture of polyurethane foam rubber, are formed by the action of base (e.g., hydroxide ion) on propylene oxide in the presence of propylene glycol as an initiator. Write all steps in a likely mechanism for their formation.

17.14 Reaction of ethylene oxide with Grignard reagents

Reaction of Grignard reagents with ethylene oxide is an important method of preparing primary alcohols since the product contains two carbons more than the alkyl or aryl group of the Grignard reagent. As in reaction with the carbonyl group (Sec. 15.12), we see the nucleophilic (basic) alkyl or aryl group of the

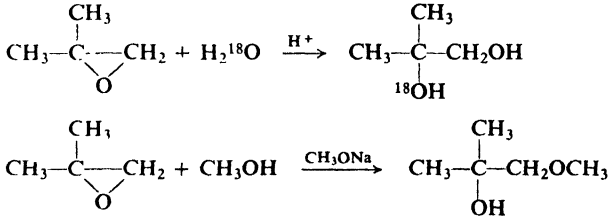
Grignard reagent attach itself to the relatively positive carbon and the electrophilic (acidic) magnesium attach itself to the relatively negative oxygen. Use of higher epoxides is complicated by rearrangements and formation of mixtures.



17.15 Orientation of cleavage of epoxides

There are two carbon atoms in an epoxide ring and, in principle, either one can suffer nucleophilic attack. In a symmetrical epoxide like ethylene oxide, the two carbons are equivalent, and attack occurs randomly at both. But in an unsymmetrical epoxide, the carbons are *not* equivalent, and the product we obtain depends upon which one is preferentially attacked. Just what is the orientation of cleavage of epoxides, and how does one account for it?

The preferred point of attack, it turns out, depends chiefly on whether the reaction is acid-catalyzed or base-catalyzed. Consider, for example, two reactions of isobutylene oxide:



Here, as in general, the nucleophile attacks the more substituted carbon in acid-catalyzed cleavage, and the less substituted carbon in base-catalyzed cleavage.

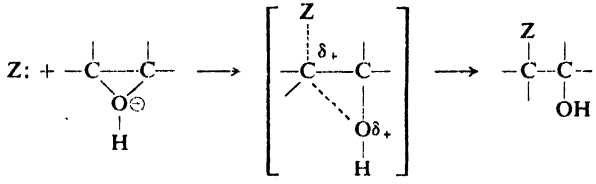
Our first thought is that two different mechanisms are involved here, S_N1 and S_N2. But the evidence indicates pretty clearly that both are of the S_N2 type: cleavage of the carbon-oxygen bond and attack by the nucleophile occur in a single step. (There is not only stereochemical evidence—complete inversion—but also evidence of several kinds that we cannot go into here.) How, then, are we to account for the difference in orientation—in particular, for S_N2 attack at the *more hindered* position in acid-catalyzed cleavage?

In an S_N2 reaction, we said earlier (Sec. 14.11), carbon loses electrons to the leaving group and gains electrons from the nucleophile, and as a result does not become appreciably positive or negative in the transition state; electronic factors are unimportant, and steric factors control reactivity. But in acid-catalyzed cleavage of an epoxide, the carbon–oxygen bond, already weak because of the angle strain of the three-membered ring, is further weakened by protonation: the leaving group is a very good one, a weakly basic alcohol hydroxyl. The nucleophile, on the other hand, is a poor one (water, alcohol, phenol). Although there are both bond-breaking and bond-making in the transition state, bond-breaking has

proceeded further than bond-making; the leaving group has taken electrons away to a much greater extent than the nucleophile has brought them up, and the carbon has acquired a considerable positive charge.

Crowding, on the other hand, is relatively unimportant, because both leaving group and nucleophile are far away. Stability of the transition state is determined chiefly by electronic factors, not steric factors. We speak of such a reaction as having considerable S_N1 *character*. Attack occurs not at the less hindered carbon, but at *the carbon that can best accommodate the positive charge.*

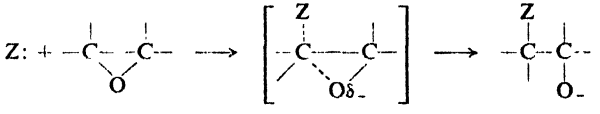
Acid-catalyzed S_N2 cleavage



Bond-breaking exceeds bond-making:
positive charge on carbon

In base-catalyzed cleavage, the leaving group is a poorer one—a strongly basic alkoxide oxygen—and the nucleophile is a good one (hydroxide, alkoxide, phenoxide). Bond-breaking and bond-making are more nearly balanced, and reactivity is controlled in the more usual way, by steric factors. *Attack occurs at the less hindered carbon.*

Base-catalyzed S_N2 cleavage



Bond-making balances bond-breaking.
no particular charge on carbon

Problem 17.22 Predict the chief product of each of the following reactions:

(a) styrene oxide + dry HCl
(b) styrene oxide + CH_3OH + a little CH_3ONa
(c) propylene oxide + aniline
(d) trimethylethylene oxide + HCl

One further point. We have encountered the two-step addition of unsymmetrical reagents in which the first step is attack by positive halogen; formation of halohydrins (Sec. 6.14), and ionic addition of IN_3 and BrN_3 (Problem 7, p. 247). The orientation is what would be expected if a carbonium ion were the intermediate. Propylene chlorohydrin, for example, is $CH_3CHOHCH_2Cl$; IN_3 adds to terminal alkenes to yield $RCH(N_3)CH_2I$. Yet the exclusively *anti* stereochemistry

(Problems 5 and 7, p. 247) indicates that the intermediate is not an open cation but a *halonium ion*; cleavage of this ring must involve attack by the nucleophile (H_2O or N_3^-) at the more hindered carbon. This is not really surprising, in view of what we have just said about epoxides. The halonium ion ring is even less stable than that of a protonated epoxide; cleavage has much S_N1 character, and takes place at the carbon atom that can best accommodate the positive charge. (Consider, too, the orientation of solvomercuration, in which the intermediate is a cyclic *mercurinium ion*.)

17.16 Analysis of ethers

Because of the low reactivity of the functional group, the chemical behavior of ethers—both aliphatic and aromatic—resembles that of the hydrocarbons to which they are related. They are distinguished from hydrocarbons, however, by their solubility in cold concentrated sulfuric acid through formation of oxonium salts.

Problem 17.23 Because of their highly reactive benzene rings, aryl ethers may decolorize bromine in carbon tetrachloride. How could this behavior be distinguished from the usual unsaturation test? (*Hint:* See Sec. 6.30.)

Problem 17.24 Expand the table you made in Problem 16.10, p. 536, to include ethers.

Problem 17.25 Describe simple chemical tests (if any) that would distinguish between an aliphatic ether and (a) an alkane; (b) an alkene; (c) an alkyne; (d) an alkyl halide; (e) a primary or secondary alcohol; (f) a tertiary alcohol; (g) an alkyl aryl ether

Identification as a previously reported ether is accomplished through the usual comparison of physical properties. This can be confirmed by cleavage with hot concentrated hydriodic acid (Sec. 17.7) and identification of one or both products. Aromatic ethers can be converted into solid bromination or nitration products whose melting points can then be compared with those of previously reported derivatives.

Proof of structure of a new ether would involve cleavage by hydriodic acid and identification of the products formed. Cleavage is used quantitatively in the **Zeisel method** to show the number of alkoxyl groups in an alkyl aryl ether.

Problem 17.26 How many methoxyl groups per molecule of papaverine would be indicated by the following results of a Zeisel analysis?

Treatment of *papaverine* ($C_{20}H_{21}O_4N$, one of the opium alkaloids) with hot concentrated hydriodic acid yields CH_3I, indicating the presence of the methoxyl group $-OCH_3$. When 4.24 mg of papaverine is treated with hydriodic acid and the CH_3I thus formed is passed into alcoholic silver nitrate, 11.62 mg of silver iodide is obtained.

17.17 Spectroscopic analysis of ethers

Infrared. The infrared spectrum of an ether does not, of course, show the O—H band characteristic of alcohols; but the strong band due to C—O stretching

is still present, in the 1060–1300 cm^{-1} range, and is the striking feature of the spectrum. (See Fig. 17.1).

C—O stretching, ***strong, broad***

Alkyl ethers 1060–1150 cm^{-1}

Aryl and vinyl ethers 1200–1275 cm^{-1} (and, weaker, at 1020–1075 cm^{-1})

Carboxylic acids and esters show C—O stretching, but show carbonyl absorption as well. (For a comparison of certain oxygen compounds, see Table 20.3, p. 689.)

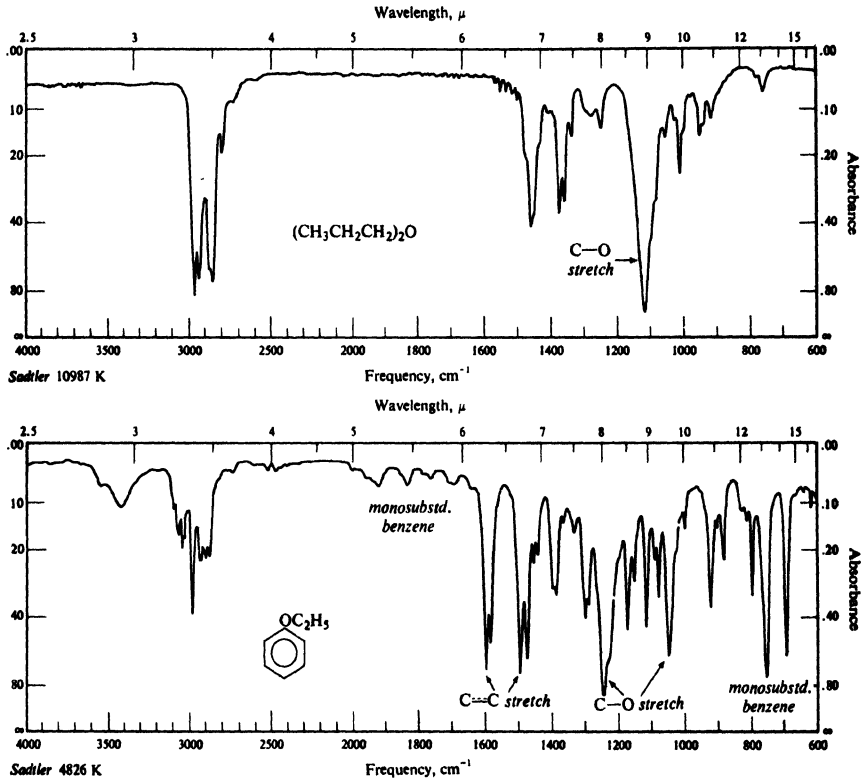


Figure 17.1. Infrared spectra of (*a*) *n*-propyl ether and (*b*) phenetole.

PROBLEMS

1. Write structural formulas for:

(a) methyl ether
(b) isopropyl ether
(c) methyl *n*-butyl ether
(d) isobutyl *tert*-butyl ether
(e) 3-methoxyhexane
(f) vinyl ether
(g) allyl ether
(h) β-chloroethyl ether
(i) anisole
(j) phenetole
(k) phenyl ether
(l) cyclohexene oxide
(m) *p*-nitrobenzyl *n*-propyl ether
(n) 1,2-epoxypentane

2. Name the following structures:

(a) $(CH_3)_2CHCH_2—O—CH_2CH(CH_3)_2$
(b) $CH_3—O—CH(CH_3)_2$
(c) $(CH_3)_3C—O—CH_2CH_3$
(d) $CH_3CH_2CH_2CH(OCH_3)CH_2CH_2CH_3$
(e) p-$BrC_6H_4OC_2H_5$
(f) o-$O_2NC_6H_4CH_2OC_6H_5$
(g) 2,4-$Br_2C_6H_3OCH_3$

3. Outline a possible laboratory synthesis of each of the following compounds from alcohols and phenols:

(a) methyl *tert*-butyl ether
(b) phenetole ($C_6H_5OC_2H_5$)
(c) *n*-butyl cyclohexyl ether
(d) *p*-tolyl benzyl ether
(e) isopropyl isobutyl ether
(f) isopropyl *tert*-butyl ether
(g) resorcinol dimethyl ether (1,3-dimethoxybenzene)

4. Arrange the compounds of each set in order of reactivity toward bromine:

(a) anisole, benzene, chlorobenzene, nitrobenzene, phenol
(b) anisole, *m*-hydroxyanisole, *o*-methylanisole, *m*-methylanisole
(c) p-$C_6H_4(OH)_2$, p-$CH_3OC_6H_4OH$, p-$C_6H_4(OCH_3)_2$

5. Write a balanced equation for each of the following. (If no reaction occurs, indicate "no reaction.")

(a) potassium *tert*-butoxide + ethyl iodide
(b) *tert*-butyl iodide + potassium ethoxide
(c) ethyl alcohol + H_2SO_4 (140°)
(d) *n*-butyl ether + boiling aqueous NaOH
(e) methyl ethyl ether + excess HI (hot)
(f) methyl ether + Na
(g) ethyl ether + cold conc. H_2SO_4
(h) ethyl ether + hot conc. H_2SO_4
(i) $C_6H_5OC_2H_5$ + hot conc. HBr
(j) $C_6H_5OC_2H_5$ + HNO_3, H_2SO_4
(k) p-$CH_3C_6H_4OCH_3$ + $KMnO_4$ + KOH + heat
(l) $C_6H_5OCH_2C_6H_5$ + Br_2, Fe

6. Like other oxygen-containing compounds, *n*-butyl *tert*-butyl ether dissolves in cold concentrated H_2SO_4. On standing, however, an acid-insoluble layer, made up of high-boiling hydrocarbon material, slowly separates from the solution. What is this material likely to be, and how is it formed?

7. Describe simple chemical tests that would distinguish between:

(a) *n*-butyl ether and *n*-pentyl alcohol
(b) ethyl ether and methyl iodide
(c) methyl *n*-propyl ether and 1-pentene
(d) isopropyl ether and allyl ether
(e) anisole and toluene
(f) vinyl ether and ethyl ether
(g) *n*-butyl *tert*-butyl ether and *n*-octane

Tell exactly what you would *do* and *see*.

8. An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, etc. Make use of any needed tables of physical constants.

(a) *n*-propyl ether (b.p. 91°) and 2-methylhexane (b.p. 91°)
(b) benzyl ethyl ether (b.p. 188°) and allyl phenyl ether (b.p. 192°)
(c) methyl *p*-tolyl ether (b.p. 176°) and methyl *m*-tolyl ether (b.p. 177°)

(d) ethyl *n*-propyl ether (b.p. 64°), 1-hexene (b.p. 64°), and methanol (b.p. 65°)
(e) anisole (b.p. 154°), bromobenzene (b.p. 156°), *o*-chlorotoluene (b.p. 159°), *n*-propylbenzene (b.p. 159°), and cyclohexanol (b.p. 162°)
(f) ethyl ether (b.p. 35°), *n*-pentane (b.p. 36°), and isoprene (b.p. 34°)
(g) methyl *o*-tolyl ether (b.p. 171°), phenetole (b.p. 172°), and isopentyl ether (b.p. 173°)

9. Three compounds, A, B, and C, have the formula C_8H_9OBr. They are insoluble in water, but are soluble in cold concentrated H_2SO_4. B is the only one of the three that gives a precipitate when treated with $AgNO_3$. The three compounds are unaffected by dilute $KMnO_4$ and Br_2/CCl_4. Further investigation of their chemical properties leads to the following results:

oxidation by hot alkaline $KMnO_4$:

A $\longrightarrow$ D ($C_8H_7O_3Br$), an acid
B $\longrightarrow$ E ($C_8H_8O_3$), an acid
C $\longrightarrow$ unaffected

treatment with hot conc. HBr:

A $\longrightarrow$ F (C_7H_7OBr)
B $\longrightarrow$ G (C_7H_7OBr)
C $\longrightarrow$ H (C_6H_5OBr), identified as *o*-bromophenol
E $\longrightarrow$ I ($C_7H_6O_3$), identified as salicylic acid, *o*-HOC_6H_4COOH

p-hydroxybenzoic acid $\xrightarrow{(CH_3)_2SO_4,\ NaOH}$ $\xrightarrow{HCl}$ J ($C_8H_8O_3$)

J + Br_2 + Fe $\longrightarrow$ D

What are the probable structures of A, B, and C? Of compounds D through J? Write equations for all reactions involved.

10. Before doing the chemical work described in the preceding problem, we could quickly have learned a good deal about the structure of A, B, and C from examination of their nmr spectra. What would you expect to see in the nmr spectrum of each compound? Give approximate chemical shift values, splittings, and relative peak areas.

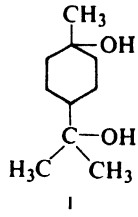
11. Give the structures and names of the products you would expect from the reaction of ethylene oxide with:

(a) H_2O, H^+
(b) H_2O, OH^-
(c) C_2H_5OH, H^+
(d) product of (c), H^+
(e) $HOCH_2CH_2OH$, H^+
(f) product of (e), H^+
(g) anhydrous HBr
(h) HCN
(i) HCOOH
(j) C_6H_5MgBr
(k) NH_3
(l) diethylamine ($C_2H_5NHC_2H_5$)
(m) phenol, H^+
(n) phenol, OH^-
(o) $HC{\equiv}C^-Na^+$

12. Propylene oxide can be converted into propylene glycol by the action of either dilute acid or dilute base. When optically active propylene oxide is used, the glycol obtained from acidic hydrolysis has a rotation opposite to that obtained from alkaline hydrolysis. What is the most likely interpretation of these facts?

13. In Sec. 17.10 a mechanism is proposed for the conversion of ethylene bromohydrin into ethylene oxide in the presence of base. (a) To what general class does this reaction belong? (b) Using models, show the likely steric course of this reaction. (c) Can you suggest a reason why sodium hydroxide readily converts *trans*-2-chlorocyclohexanol into cyclohexene oxide, but converts the *cis*-isomer into entirely different products? (d) Account for the fact that addition of chlorine and water to oleic acid (*cis*-9-octadecenoic acid) followed by treatment with base gives the same epoxide (same stereoisomer) as does treatment of oleic acid with a peroxy acid.

14. (a) Draw formulas for all the stereoisomers of I.



I

(b) Indicate which isomers, when separated from all others, will be optically active, and which will be optically inactive. (c) One of these stereoisomers is very readily converted into an ether, $C_{10}H_{18}O$. Which isomer is this, and what is the structure of the ether?

15. Give the structures (including configurations where pertinent) of compounds K through Y:

(a) $CH_2{=}CH_2 + Cl_2/H_2O \longrightarrow K\ (C_2H_5OCl)$
$K + H_2SO_4 + \text{heat} \longrightarrow L\ (C_4H_8OCl_2)$
$L + \text{alc. KOH} \longrightarrow M\ (C_4H_6O)$

(b) $ClCH_2CH\text{—}CH_2 + CH_3OH + H_2SO_4 \longrightarrow N\ (C_4H_9O_2Cl)$
(O)

$N + NaOCl \longrightarrow CHCl_3 + O\ (C_3H_6O_3)$
$N + NaOH(aq) \longrightarrow P\ (C_4H_8O_2)$

(c) $ClCH_2CH_2CH_2OH + KOH \longrightarrow Q\ (C_3H_6O)$
(d) $\text{benzene} + \text{ethylene oxide} + BF_3 \longrightarrow R\ (C_8H_{10}O)$
(e) $CH_2{=}CHCH_2CH_2CH_2OH + Hg(OAc)_2 + H_2O$, then $NaBH_4 \longrightarrow S\ (C_5H_{10}O)$
(f) $\text{methyl vinyl ether} + \text{dil. } H_2SO_4 \longrightarrow T\ (C_2H_4O)$
(g) $\text{cyclohexene oxide} + \text{anhydrous HCl} \longrightarrow U\ (C_6H_{11}OCl)$
(h) $\text{1-methylcyclohexene} + HCO_2OH \longrightarrow V\ (C_7H_{14}O_2)$
(i) racemic 3,4-epoxy-1-butene + cold alkaline $KMnO_4$, then dilute acid $\longrightarrow W\ (C_4H_{10}O_4)$
(j) *cis*-2-butene + Cl_2/H_2O, then OH^-, then dilute acid $\longrightarrow X\ (C_4H_{10}O_2)$
(k) *trans*-2-butene treated as in (j) $\longrightarrow Y\ (C_4H_{10}O_2)$

16. Give a structure or structures for the compound whose infrared spectrum is shown in Fig. 17.2 (p. 575). If you find more than one structure consistent with the spectrum, could you decide among the possibilities on the basis of the nmr spectrum? Tell what you would expect to see in each case.

17. Give a structure or structures for the compound Z, whose infrared and nmr spectra are shown in Fig. 17.3 (p. 575).

18. Give a structure or structures consistent with each nmr spectrum shown in Fig. 17.4 (p. 576).

19. Give the structures of compounds AA, BB, and CC on the basis of their infrared spectra (Fig. 17.5, p. 577) and their nmr spectra (Fig. 17.6, p. 578).

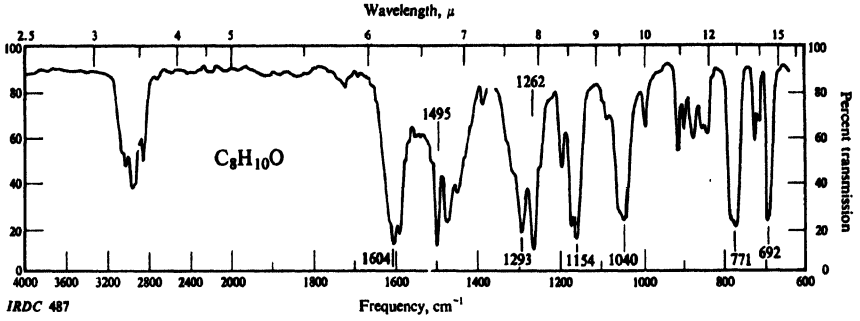
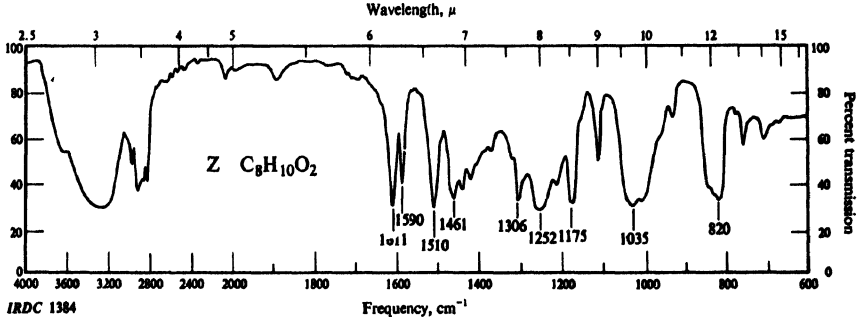


Figure 17.2. Infrared spectrum for Problem 16, p. 574.



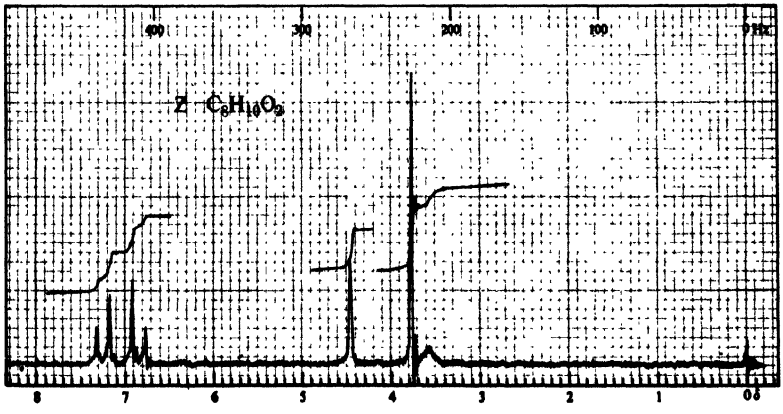


Figure 17.3. Infrared and nmr spectra for Problem 17, p. 574.

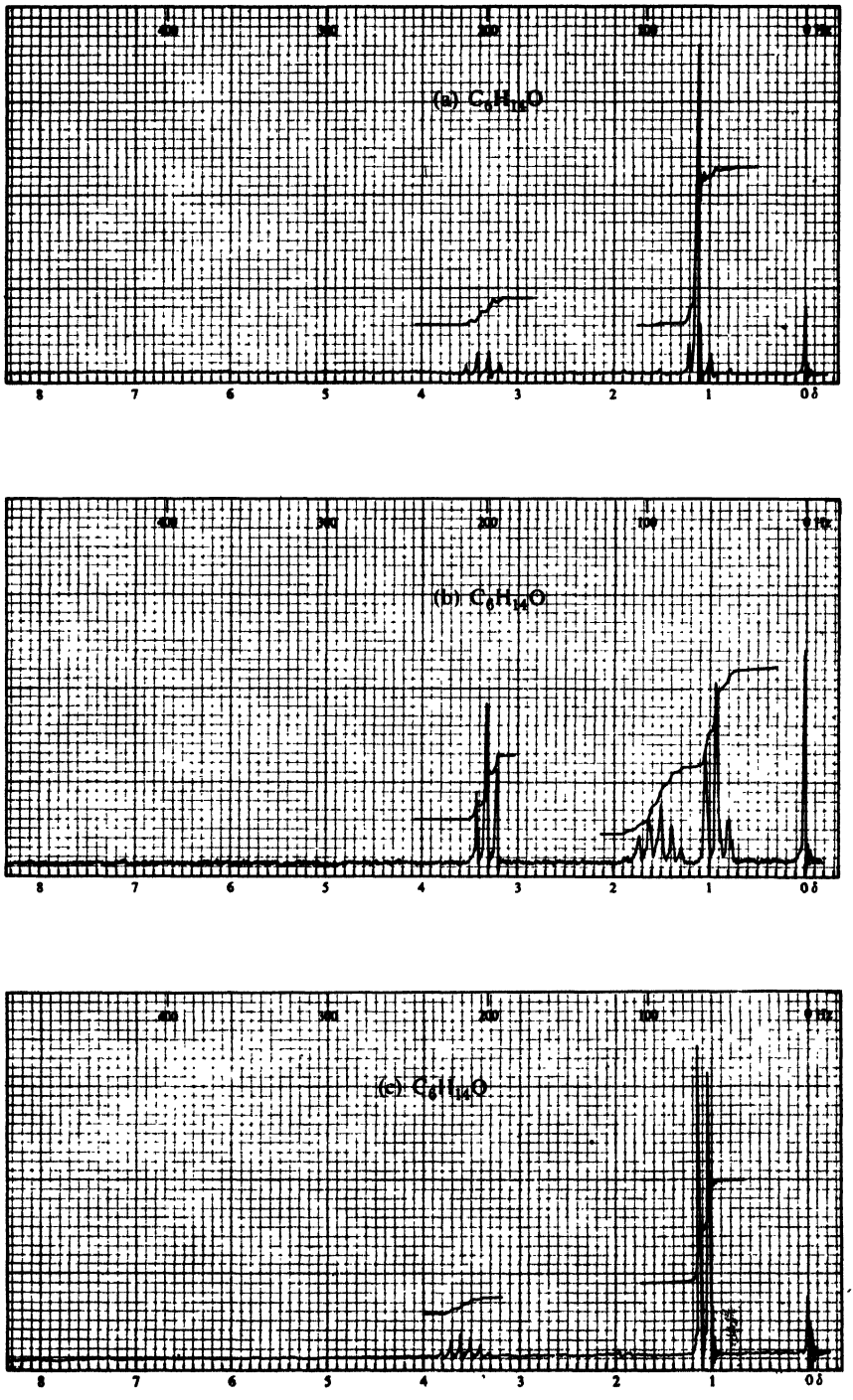
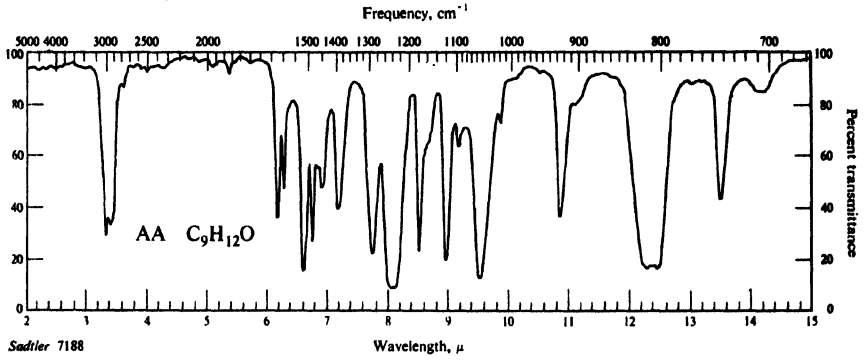
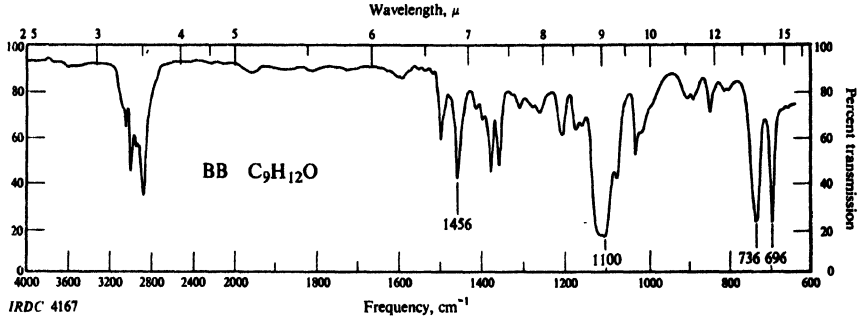


Figure 17.4. Nmr spectra for Problem 18, p. 574.





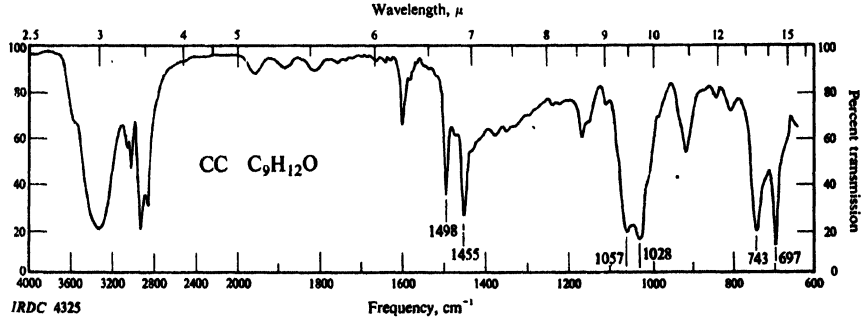


Figure 17.5. Infrared spectra for Problem 19, p. 574.

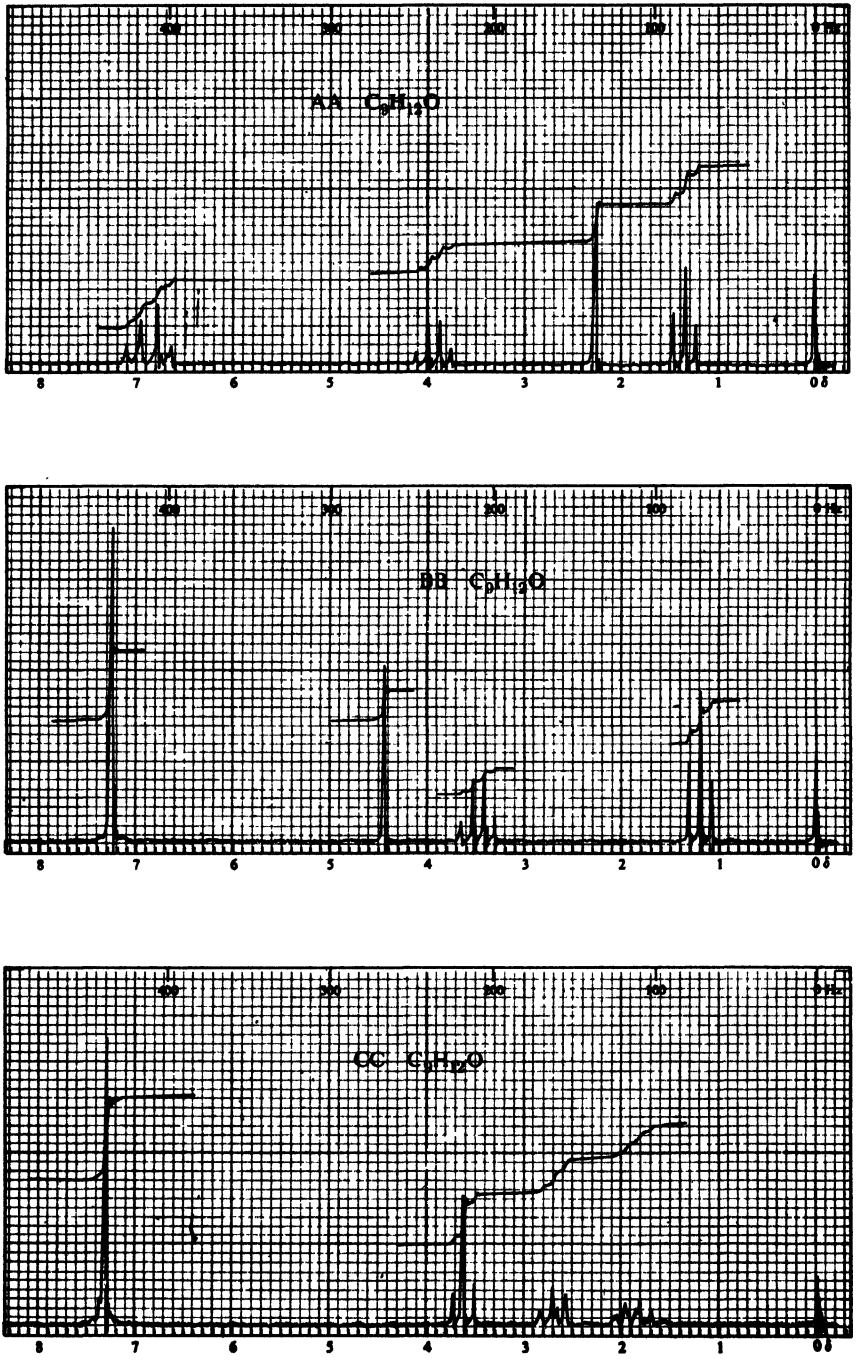


Figure 17.6. Nmr spectra for Problem 19, p. 574.

Chapter 18 Carboxylic Acids

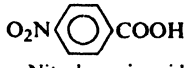
18.1 Structure

Of the organic compounds that show appreciable acidity, by far the most important are the carboxylic acids. These compounds contain the **carboxyl group**

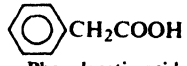
attached to either an alkyl group (RCOOH) or an aryl group (ArCOOH). For example:

HCOOH	CH_3COOH	$CH_3(CH_2)_{10}COOH$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
Formic acid	Acetic acid	Lauric acid	Oleic acid
Methanoic acid	Ethanoic acid	Dodecanoic acid	*cis*-9-Octadecenoic acid

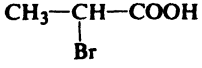
Benzoic acid



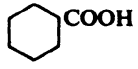
p-Nitrobenzoic acid



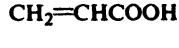
Phenylacetic acid



α-Bromopropionic acid
2-Bromopropanoic acid



Cyclohexanecarboxylic acid



Acrylic acid
Propenoic acid

Whether the group is aliphatic or aromatic, saturated or unsaturated, substituted or unsubstituted, the properties of the carboxyl group are essentially the same.

18.2 Nomenclature

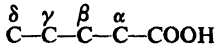
The aliphatic carboxylic acids have been known for a long time, and as a result have common names that refer to their sources rather than to their chemical structures. The **common names** of the more important acids are shown in Table 18.1. *Formic acid*, for example, adds the sting to the bite of an ant (Latin: *formica*, ant); *butyric acid* gives rancid butter its typical smell (Latin: *butyrum*, butter);

Table 18.1 CARBOXYLIC ACIDS

Name	Formula	M.p., °C	B.p., °C	Solub., g/100 g H_2O
Formic	HCOOH	8	100.5	∞
Acetic	CH_3COOH	16.6	118	∞
Propionic	CH_3CH_2COOH	−22	141	∞
Butyric	$CH_3(CH_2)_2COOH$	− 6	164	∞
Valeric	$CH_3(CH_2)_3COOH$	−34	187	3.7
Caproic	$CH_3(CH_2)_4COOH$	− 3	205	1.0
Caprylic	$CH_3(CH_2)_6COOH$	16	239	0.7
Capric	$CH_3(CH_2)_8COOH$	31	269	0.2
Lauric	$CH_3(CH_2)_{10}COOH$	44	225^{100}	i.
Myristic	$CH_3(CH_2)_{12}COOH$	54	251^{100}	i.
Palmitic	$CH_3(CH_2)_{14}COOH$	63	269^{100}	i.
Stearic	$CH_3(CH_2)_{16}COOH$	70	287^{100}	i.
Oleic	*cis*-9-Octadecenoic	16	223^{10}	i.
Linoleic	*cis,cis*-9,12-Octadecadienoic	− 5	230^{16}	i.
Linolenic	*cis,cis,cis*-9,12,15-Octadecatrienoic	−11	232^{17}	i.
Cyclohexanecarboxylic	*cyclo*-$C_6H_{11}COOH$	31	233	0.20
Phenylacetic	$C_6H_5CH_2COOH$	77	266	1.66
Benzoic	C_6H_5COOH	122	250	0.34
o-Toluic	*o*-$CH_3C_6H_4COOH$	106	259	0.12
m-Toluic	*m*-$CH_3C_6H_4COOH$	112	263	0.10
p-Toluic	*p*-$CH_3C_6H_4COOH$	180	275	0.03
o-Chlorobenzoic	*o*-ClC_6H_4COOH	141		0.22
m-Chlorobenzoic	*m*-ClC_6H_4COOH	154		0.04
p-Chlorobenzoic	*p*-ClC_6H_4COOH	242		0.009
o-Bromobenzoic	*o*-BrC_6H_4COOH	148		0.18
m-Bromobenzoic	*m*-BrC_6H_4COOH	156		0.04
p-Bromobenzoic	*p*-BrC_6H_4COOH	254		0.006
o-Nitrobenzoic	*o*-$O_2NC_6H_4COOH$	147		0.75
m-Nitrobenzoic	*m*-$O_2NC_6H_4COOH$	141		0.34
p-Nitrobenzoic	*p*-$O_2NC_6H_4COOH$	242		0.03
Phthalic	*o*-$C_6H_4(COOH)_2$	231		0.70
Isophthalic	*m*-$C_6H_4(COOH)_2$	348		0.01
Terephthalic	*p*-$C_6H_4(COOH)_2$	300 *subl.*		0.002
Salicylic	*o*-HOC_6H_4COOH	159		0.22
p-Hydroxybenzoic	*p*-HOC_6H_4COOH	213		0.65
Anthranilic	*o*-$H_2NC_6H_4COOH$	146		0.52
m-Aminobenzoic	*m*-$H_2NC_6H_4COOH$	179		0.77
p-Aminobenzoic	*p*-$H_2NC_6H_4COOH$	187		0.3
o-Methoxybenzoic	*o*-$CH_3OC_6H_4COOH$	101		0.5
m-Methoxybenzoic	*m*-$CH_3OC_6H_4COOH$	110		
p-Methoxybenzoic (Anisic)	*p*-$CH_3OC_6H_4COOH$	184		0.04

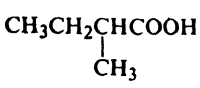
and *caproic, caprylic,* and *capric acids* are all found in goat fat (Latin: *caper,* goat).

Branched-chain acids and substituted acids are named as derivatives of the straight-chain acids. To indicate the position of attachment, the Greek letters, α-, β-, γ-, δ-, etc., are used; the α-carbon is the one bearing the carboxyl group.

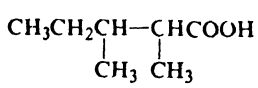


Used in common names

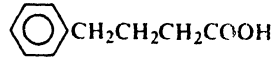
For example:



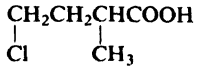
α-Methylbutyric acid



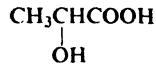
α,β-Dimethylvaleric acid



γ-Phenylbutyric acid



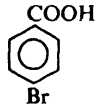
γ-Chloro-α-methylbutyric acid



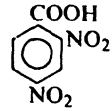
α-Hydroxypropionic acid
Lactic acid

Generally the parent acid is taken as the one of longest carbon chain, although some compounds are named as derivatives of acetic acid.

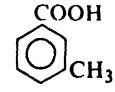
Aromatic acids, ArCOOH, are usually named as derivatives of the parent acid, **benzoic acid**, C_6H_5COOH. The methylbenzoic acids are given the special name of *toluic acids.*



p-Bromobenzoic acid

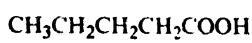


2,4-Dinitrobenzoic acid

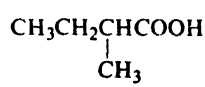


m-Toluic acid

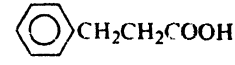
The **IUPAC names** follow the usual pattern. The longest chain carrying the carboxyl group is considered the parent structure, and is named by replacing the *-e* of the corresponding alkane with **-oic acid.** For example:



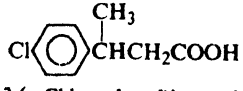
Pentanoic acid



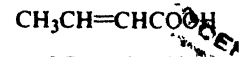
2-Methylbutanoic acid



3-Phenylpropanoic acid



3-(*p*-Chlorophenyl)butanoic acid



2-Butenoic acid

The position of a substituent is indicated as usual by a number. We should notice

$$\overset{5}{C}-\overset{4}{C}-\overset{3}{C}-\overset{2}{C}-\overset{1}{C}OOH \qquad \textit{Used in IUPAC names}$$

that the carboxyl carbon is always considered as C–1, and hence C–2 corresponds to α of the common names, C–3 to β, and so on. (*Caution:* Do not mix Greek letters with IUPAC names, or Arabic numerals with common names.)

The name of a **salt** of a carboxylic acid consists of the name of the cation (*sodium*, *potassium*, *ammonium*, etc.) followed by the name of the acid with the ending *-ic acid* changed to **-ate**. For example:

Sodium benzoate

$(CH_3COO)_2Ca$

Calcium acetate

$HCOONH_4$

Ammonium formate

$$CH_2(Br)-CH(Br)-COOK$$

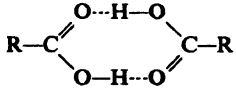
Potassium α,β-dibromopropionate
(Potassium 2,3-dibromopropanoate)

18.3 Physical properties

As we would expect from their structure, carboxylic acid molecules are polar, and like alcohol molecules can form hydrogen bonds with each other and with other kinds of molecules. The aliphatic acids therefore show very much the same solubility behavior as the alcohols: the first four are miscible with water, the five-carbon acid is partly soluble, and the higher acids are virtually insoluble. Water solubility undoubtedly arises from hydrogen bonding between the carboxylic acid and water. The simplest aromatic acid, benzoic acid, contains too many carbon atoms to show appreciable solubility in water.

Carboxylic acids are soluble in less polar solvents like ether, alcohol, benzene, etc.

We can see from Table 18.1 that as a class the carboxylic acids are even higher boiling than alcohols. For example, propionic acid (b.p. 141°) boils more than twenty degrees higher than the alcohol of comparable molecular weight, *n*-butyl alcohol (b.p. 118°). These very high boiling points are due to the fact that a pair of carboxylic acid molecules are held together not by one but by two hydrogen bonds:



Problem 18.1 At 110° and 454 mm pressure, 0.11 g acetic acid vapor occupies 63.7 cc; at 156° and 458 mm, 0.081 g occupies 66.4 cc. Calculate the molecular weight of acetic acid in the vapor phase at each temperature. How do you interpret these results?

The odors of the lower aliphatic acids progress from the sharp, irritating odors of formic and acetic acids to the distinctly unpleasant odors of butyric,

valeric, and caproic acids; the higher acids have little odor because of their low volatility.

18.4 Salts of carboxylic acids

Although much weaker than the strong mineral acids (sulfuric, hydrochloric, nitric), the carboxylic acids are tremendously more acidic than the very weak organic acids (alcohols, acetylene) we have so far studied; they are much stronger acids than water. Aqueous hydroxides therefore readily convert carboxylic acids into their salts; aqueous mineral acids readily convert the salts back into the carboxylic acids. Since we can do little with carboxylic acids without encountering

$$\underset{\text{Acid}}{\text{RCOOH}} \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} \underset{\text{Salt}}{\text{RCOO}^-}$$

this conversion to and from their salts, it is worthwhile for us to examine the properties of these salts.

Salts of carboxylic acid—like all salts—are crystalline non-volatile solids made up of positive and negative ions; their properties are what we would expect of such structures. The strong electrostatic forces holding the ions in the crystal lattice can be overcome only by heating to a high temperature, or by a very polar solvent. The temperature required for melting is so high that before it can be reached carbon–carbon bonds break and the molecule decomposes, generally in the neighborhood of 300–400°. A decomposition point is seldom useful for the identification of a compound, since it usually reflects the rate of heating rather than the identity of the compound.

The alkali metal salts of carboxylic acids (sodium, potassium, ammonium) are soluble in water but insoluble in non-polar solvents; most of the heavy metal salts (iron, silver, copper, etc.) are insoluble in water.

Thus we see that, except for the acids of four carbons or less, which are soluble both in water and in organic solvents, *carboxylic acids and their alkali metal salts show exactly opposite solubility behavior.* Because of the ready interconversion of acids and their salts, this difference in solubility behavior may be used in two important ways: for *identification* and for *separation.*

A water-insoluble organic compound that dissolves in cold dilute aqueous sodium hydroxide must be either a carboxylic acid or one of the few other kinds of organic compounds more acidic than water; that it is indeed a carboxylic acid can then be shown in other ways.

$$\underset{\substack{\text{Stronger acid}\\ \textit{Insoluble in } H_2O}}{\text{RCOOH}} + \text{NaOH} \longrightarrow \underset{\substack{\textit{Soluble in } H_2O\\ \text{Weaker acid}}}{\text{RCOONa}} + H_2O$$

Instead of sodium hydroxide, we can use aqueous sodium bicarbonate; even if the unknown is water-soluble, its acidity is shown by the evolution of bubbles of CO_2.

$$\underset{\textit{Insoluble in } H_2O}{\text{RCOOH}} + \text{NaHCO}_3 \longrightarrow \underset{\textit{Soluble in } H_2O}{\text{RCOONa}} + H_2O + CO_2\uparrow$$

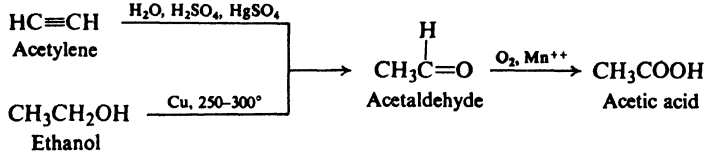
We can separate a carboxylic acid from non-acidic compounds by taking advantage of its solubility and their insolubility in aqueous base; once the separation has been accomplished, we can regenerate the acid by acidification of the aqueous solution. If we are dealing with solids, we simply stir the mixture with aqueous base and then filter the solution from insoluble, non-acidic materials; addition of mineral acid to the filtrate precipitates the carboxylic acid, which can be collected on a filter. If we are dealing with liquids, we shake the mixture with aqueous base in a separatory funnel and separate the aqueous layer from the insoluble organic layer; addition of acid to the aqueous layer again liberates the carboxylic acid, which can then be separated from the water. For completeness of separation and ease of handling, we often add a water-insoluble solvent like ether to the acidified mixture. The carboxylic acid is extracted from the water by the ether, in which it is more soluble; the volatile ether is readily removed by distillation from the comparatively high-boiling acid.

For example, an aldehyde prepared by the oxidation of a primary alcohol (Sec. 16.8) may very well be contaminated with the carboxylic acid; this acid can be simply washed out with dilute aqueous base. The carboxylic acid prepared by oxidation of an alkylbenzene (Sec. 12.10) may very well be contaminated with unreacted starting material; the carboxylic acid can be taken into solution by aqueous base, separated from the insoluble hydrocarbon, and regenerated by addition of mineral acid.

Since separations of this kind are more clear-cut and less wasteful of material, they are preferred wherever possible over recrystallization or distillation.

18.5 Industrial source

Acetic acid, by far the most important of all carboxylic acids, is prepared by air oxidation of acetaldehyde, which is readily available from the hydration of acetylene (Sec. 8.13), or the dehydrogenation of ethanol.

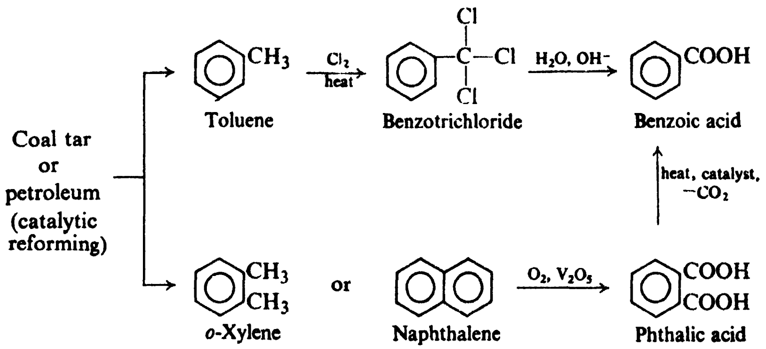


Large amounts of acetic acid are also produced as the dilute aqueous solution known as *vinegar*. Here, too, the acetic acid is prepared by air oxidation; the compound that is oxidized is ethyl alcohol, and the catalysts are bacterial (*Acetobacter*) enzymes.

The most important sources of aliphatic carboxylic acids are the animal and vegetable **fats** (Secs. 33.2–33.4). From fats there can be obtained, in purity of over 90%, straight-chain carboxylic acids of even carbon number ranging from six to eighteen carbon atoms. These acids can be converted into the corresponding alcohols (Sec. 18.18), which can then be used, in the ways we have already studied (Sec. 16.10), to make a great number of other compounds containing long, straight-chain units.

The most important of the aromatic carboxylic acids, **benzoic acid** and the

phthalic acids, are prepared on an industrial scale by a reaction we have already encountered: oxidation of alkylbenzenes (Sec. 12.10). The toluene and xylenes required are readily available from coal tar and, by catalytic reforming of aliphatic hydrocarbons (Sec. 12.4), from petroleum; another precursor of phthalic acid (the *ortho* isomer) is the aromatic hydrocarbon *naphthalene*, also found in coal tar. Cheap oxidizing agents like chlorine or even air (in the presence of catalysts) are used.



Problem 18.2 In the presence of peroxides, carboxylic acids (or esters) react with 1-alkenes to yield more complicated acids. For example:

$$\underset{\text{1-Hexene}}{n\text{-}C_4H_9CH{=}CH_2} + \underset{n\text{-Butyric acid}}{CH_3CH_2CH_2COOH} \xrightarrow{\text{peroxides}} \underset{\substack{\text{2-Ethyloctanoic acid} \\ (70\%\ yield)}}{n\text{-}C_4H_9CH_2CH_2\underset{C_2H_5}{\underset{|}{C}}HCOOH}$$

(a) Outline all steps in a likely mechanism for this reaction. (*Hint:* See Sec. 6.18.) Predict the products of similar reactions between: (b) 1-octene and propionic acid; (c) 1-decene and isobutyric acid; and (d) 1-octene and ethyl malonate, $CH_2(COOC_2H_5)_2$.

Problem 18.3 (a) Carbon monoxide converts a sulfuric acid solution of each of the following into 2,2-dimethylbutanoic acid: 2-methyl-2-butene, *tert*-pentyl alcohol, neopentyl alcohol. Suggest a likely mechanism for this method of synthesizing carboxylic acids. (b) *n*-Butyl alcohol and *sec*-butyl alcohol give the same product. What would you expect it to be?

18.6 Preparation

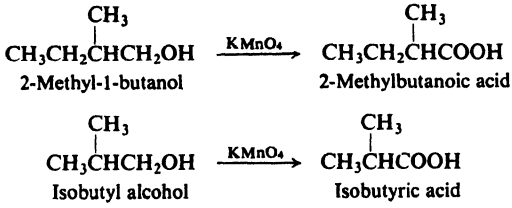
The straight-chain aliphatic acids up to C_6, and those of even carbon number up to C_{18}, are commercially available, as are the simple aromatic acids. Other carboxylic acids can be prepared by the methods outlined below.

PREPARATION OF CARBOXYLIC ACIDS

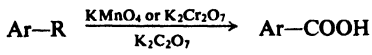
1. **Oxidation of primary alcohols.** Discussed in Sec. 16.8.

$$RCH_2OH \xrightarrow{KMnO_4} RCOOH$$

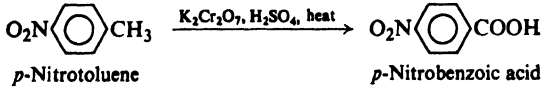
Examples:

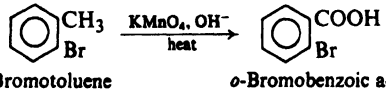


2. Oxidation of alkylbenzenes. Discussed in Sec. 12.10.

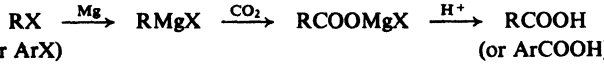


Examples:

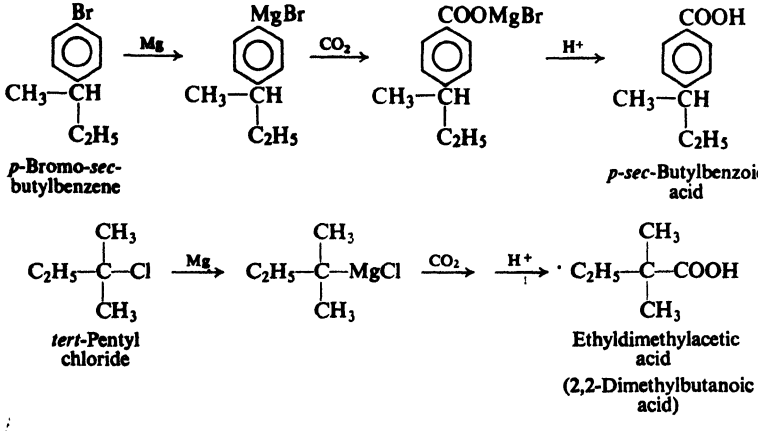




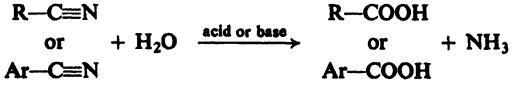
3. Carbonation of Grignard reagents. Discussed in Sec. 18.7.



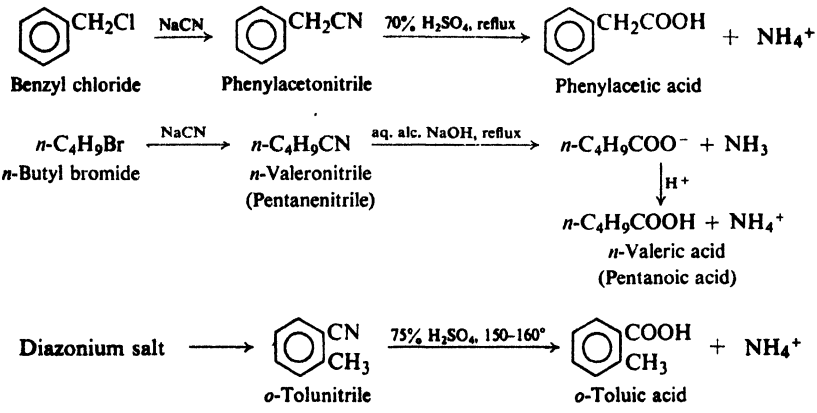
Examples:



4. Hydrolysis of nitriles. Discussed in Sec. 18.8.



Examples:



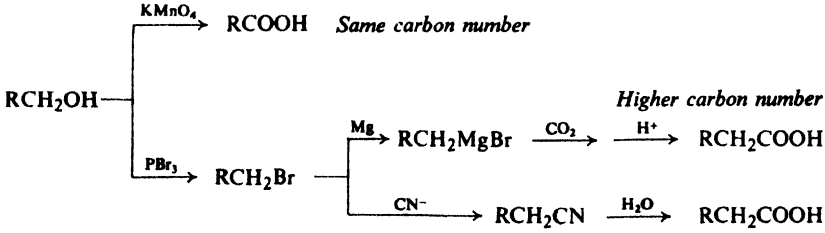
5. **Malonic ester synthesis.** Discussed in Sec. 26.2.

6. **Special methods for phenolic acids.** Discussed in Sec. 24.11.

All the methods listed are important; our choice is governed by the availability of starting materials.

Oxidation is the most direct and is generally used when possible, some lower aliphatic acids being made from the available alcohols, and substituted aromatic acids from substituted toluenes.

The **Grignard synthesis** and the **nitrile synthesis** have the special advantage of increasing the length of a carbon chain, and thus extending the range of available materials. In the aliphatic series both Grignard reagents and nitriles are prepared from halides, which in turn are usually prepared from alcohols. The syntheses thus amount to the preparation of acids from alcohols containing one less carbon atom.



Problem 18.4 What carboxylic acid can be prepared from *p*-bromotoluene: (a) by direct oxidation? (b) by free-radical chlorination followed by the nitrile synthesis?

Aromatic nitriles generally cannot be prepared from the unreactive aryl halides (Sec. 25.5). Instead they are made from diazonium salts by a reaction we shall discuss later (Sec. 23.13). Diazonium salts are prepared from aromatic

amines, which in turn are prepared from nitro compounds. Thus the carboxyl group eventually occupies the position on the ring where a nitro group was originally introduced by direct nitration (Sec. 11.8).

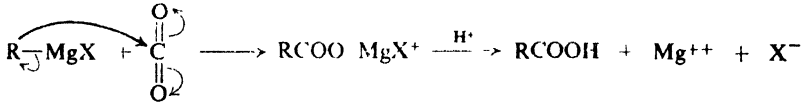
$$\underset{}{ArH} \longrightarrow \underset{\text{Nitro compound}}{ArNO_2} \longrightarrow \underset{\text{Amine}}{ArNH_2} \longrightarrow \underset{\text{Diazonium ion}}{ArN_2^+} \longrightarrow \underset{\text{Nitrile}}{ArC{\equiv}N} \longrightarrow \underset{\text{Acid}}{ArCOOH}$$

For the preparation of quite complicated acids, the most versatile method of all is used, the *malonic ester synthesis* (Sec. 26.2).

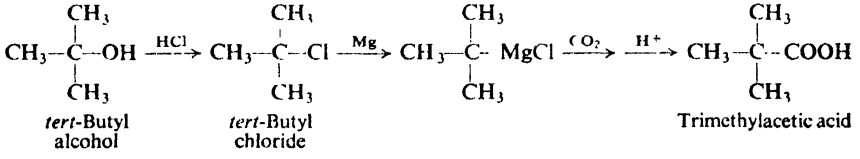
18.7 Grignard synthesis

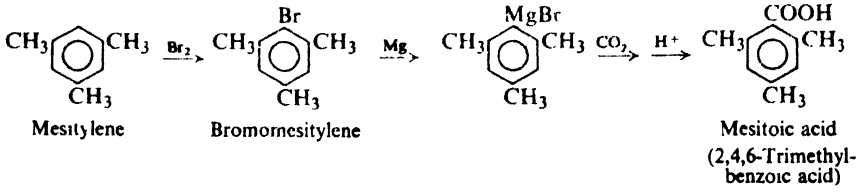
The Grignard synthesis of a carboxylic acid is carried out by bubbling gaseous CO_2 into the ether solution of the Grignard reagent, or by pouring the Grignard reagent on crushed Dry Ice (solid CO_2); in the latter method Dry Ice serves not only as reagent but also as cooling agent.

The Grignard reagent adds to the carbon–oxygen double bond just as in the reaction with aldehydes and ketones (Sec. 15.12). The product is the magnesium salt of the carboxylic acid, from which the free acid is liberated by treatment with mineral acid.



The Grignard reagent can be prepared from primary, secondary, tertiary, or aromatic halides; the method is limited only by the presence of other reactive groups in the molecule (Sec. 15.15). The following syntheses illustrate the application of this method:





18.8 Nitrile synthesis

Aliphatic nitriles are prepared by treatment of alkyl halides with sodium cyanide in a solvent that will dissolve both reactants; in dimethyl sulfoxide,

reaction occurs rapidly and exothermically at room temperature. The resulting nitrile is then hydrolyzed to the acid by boiling aqueous alkali or acid.

$$RX + CN^- \longrightarrow RC{\equiv}N + X^-$$

$$RC{\equiv}N \xrightarrow{H_2O} \begin{cases} \xrightarrow{H^+} RCOOH + NH_4^+ \\ \xrightarrow{OH^-} RCOO^- + NH_3 \end{cases}$$

The reaction of an alkyl halide with cyanide ion involves nucleophilic substitution (Sec. 14.5). The fact that HCN is a very weak acid tells us that cyanide ion is a strong base; as we might expect, this strongly basic ion can abstract hydrogen ion and thus cause elimination as well as substitution. Indeed, with

$CH_3CH_2CH_2CH_2Br + CN^- \dashrightarrow CH_3CH_2CH_2CH_2CN$ — 1° halide: *substitution*

n-Butyl bromide — Valeronitrile

$$CH_3{-}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}{-}Br + CN^- \longrightarrow CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH_2 + HCN$$

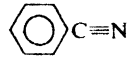
3° halide: *elimination*

tert-Butyl bromide — Isobutylene

tertiary halides elimination is the principal reaction; even with secondary halides the yield of substitution product is poor. Here again we find a nucleophilic substitution reaction that is of synthetic importance *only when primary halides are used.*

As already mentioned, aromatic nitriles are made, not from the unreactive aryl halides, but from diazonium salts (Sec. 23.13).

Although nitriles are sometimes named as *cyanides* or as *cyano* compounds, they generally take their names from the acids they yield upon hydrolysis. They are named by dropping *-ic acid* from the common name of the acid and adding **-nitrile**; usually for euphony an "o" is inserted between the root and the ending (e.g., *acetonitrile*). In the IUPAC system they are named by adding *-nitrile* to the name of the parent hydrocarbon (e.g., *ethanenitrile*). For example:

$CH_3C{\equiv}N$	$CH_3(CH_2)_3C{\equiv}N$		
Acetonitrile (Ethanenitrile)	*n*-Valeronitrile (Pentanenitrile)	Benzonitrile	*p*-Tolunitrile

18.9 Reactions

The characteristic chemical behavior of carboxylic acids is, of course, determined by their functional group, **carboxyl**, —COOH. This group is made up of a carbonyl group (C=O) and a hydroxyl group (—OH). As we shall see, it is the —OH that actually undergoes nearly every reaction—loss of H^+, or replacement by another group—but *it does so in a way that is possible only because of the effect of the* C=O.

The rest of the molecule undergoes reactions characteristic of its structure; it may be aliphatic or aromatic, saturated or unsaturated, and may contain a variety of other functional groups.

REACTIONS OF CARBOXYLIC ACIDS

1. Acidity. Salt formation. Discussed in Secs. 18.4, 18.10–18.14.

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

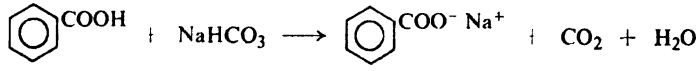
Examples:

$$2CH_3COOH + Zn \longrightarrow (CH_3COO^-)_2Zn^{++} + H_2$$

Acetic acid — Zinc acetate

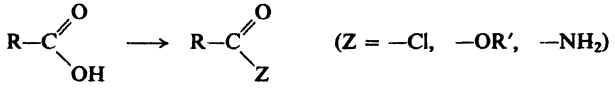
$$CH_3(CH_2)_{10}COOH + NaOH \longrightarrow CH_3(CH_2)_{10}COO^-Na^+ + H_2O$$

Lauric acid — Sodium laurate

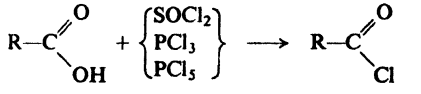


Benzoic acid — Sodium benzoate

2. Conversion into functional derivatives

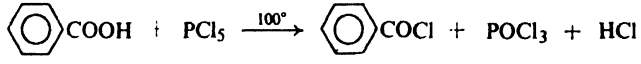


(a) Conversion into acid chlorides. Discussed in Sec. 18.15.



Acid chloride

Examples:



Benzoic acid — Benzoyl chloride

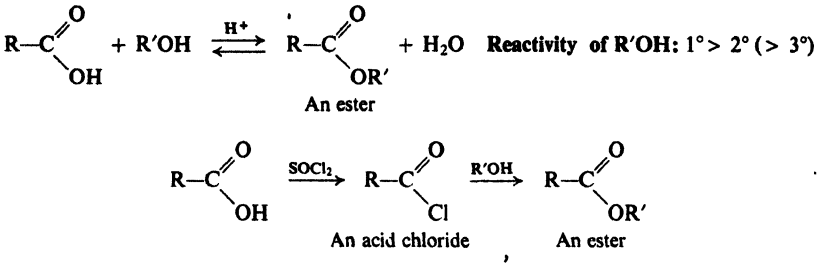
$$n\text{-}C_{17}H_{35}COOH + SOCl_2 \xrightarrow{\text{reflux}} n\text{-}C_{17}H_{35}COCl + SO_2 + HCl$$

Stearic acid — Thionyl chloride — Stearoyl chloride

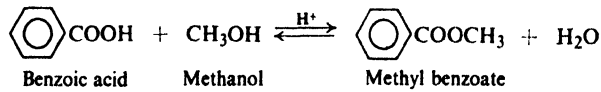
$$3CH_3COOH + PCl_3 \xrightarrow{50^\circ} 3CH_3COCl + H_3PO_3$$

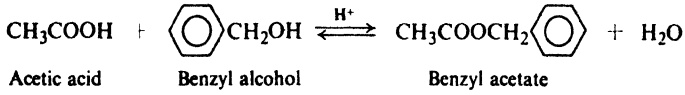
Acetic acid — Acetyl chloride

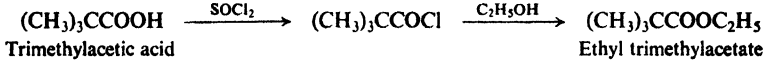
(b) Conversion into esters. Discussed in Secs. 18.16 and 20.15.



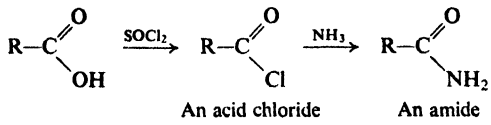
Examples:



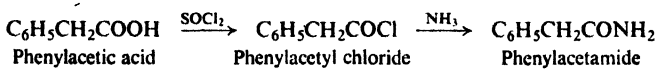




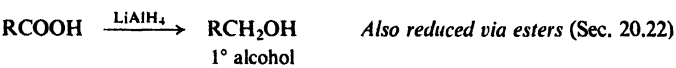
(c) Conversion into amides. Discussed in Sec. 18.17.



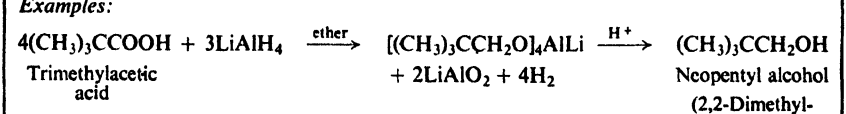
Example:

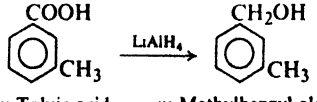


3. Reduction. Discussed in Sec. 18.18.



Examples:





4. Substitution in alkyl or aryl group

(a) Alpha-halogenation of aliphatic acids. Hell-Volhard-Zelinsky reaction. Discussed in Sec. 18.19.

$$RCH_2COOH + X_2 \xrightarrow{P} \underset{\displaystyle X}{RCHCOOH} + HX \qquad X_2 = Cl_2, Br_2$$

An α-haloacid

Examples:

$$\underset{\text{Acetic acid}}{CH_3COOH} \xrightarrow{Cl_2, P} \underset{\text{Chloroacetic acid}}{ClCH_2COOH} \xrightarrow{Cl_2, P} \underset{\text{Dichloroacetic acid}}{Cl_2CHCOOH} \xrightarrow{Cl_2, P} \underset{\text{Trichloroacetic acid}}{Cl_3CCOOH}$$

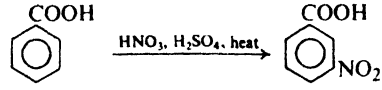
$$\underset{\text{Isovaleric acid}}{\begin{matrix}CH_3\\ |\\ CH_3CHCH_2COOH\end{matrix}} \xrightarrow{Br_2, P} \underset{\displaystyle Br}{\begin{matrix}CH_3\\ |\\ CH_3CHCHCOOH\\ |\end{matrix}}$$

α-Bromoisovaleric acid

(b) Ring substitution in aromatic acids. Discussed in Secs. 11.5 and 11.17.

—COOH: deactivates, and directs *meta* in electrophilic substitution.

Example:



Benzoic acid *m*-Nitrobenzoic acid

The most characteristic property of the carboxylic acids is the one that gives them their name: **acidity**. Their tendency to give up a hydrogen ion is such that in aqueous solution a measurable equilibrium exists between acid and ions; they are thus much more acidic than any other class of organic compounds we have studied so far.

$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+$$

The OH of an acid can be replaced by a number of groups—Cl, OR', NH_2—to yield compounds known as *acid chlorides*, *esters*, and *amides*. These compounds are called **functional derivatives** of acids; they all contain the **acyl group**:

The functional derivatives are all readily reconverted into the acid by simple hydrolysis, and are often converted one into another.

One of the few reducing agents capable of reducing an acid directly to an alcohol is *lithium aluminum hydride*, $LiAlH_4$.

The hydrocarbon portion of an aliphatic acid can undergo the free-radical halogenation characteristic of alkanes, but because of the random nature of the substitution it is seldom used. The presence of a small amount of phosphorus, however, causes halogenation (by an ionic mechanism) to take place *exclusively at the alpha position*. This reaction is known as the **Hell-Volhard-Zelinsky reaction**, and it is of great value in synthesis.

An aromatic ring bearing a carboxyl group undergoes the aromatic electrophilic substitution reactions expected of a ring carrying a deactivating, *meta*-directing group. Deactivation is so strong that the Friedel-Crafts reaction does not take place. We have already accounted for this effect of the —COOH group on the basis of its strong electron-withdrawing tendencies (Sec. 11.18).

—COOH withdraws electrons deactivates, directs meta in electrophilic substitution

Decarboxylation—elimination of the —COOH group as CO_2—is of limited importance for aromatic acids, and highly important for certain substituted aliphatic acids: malonic acids (Sec. 26.2) and β-keto acids (Sec. 26.3). It is worthless for most simple aliphatic acids, yielding a complicated mixture of hydrocarbons.

18.10 Ionization of carboxylic acids. Acidity constant

In aqueous solution a carboxylic acid exists in equilibrium with the carboxylate anion and the hydrogen ion (actually, of course, the hydronium ion, H_3O^+).

$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+$$

As for any equilibrium, the concentrations of the components are related by the expression

$$K_a = \frac{[RCOO^-][H_3O^+]}{[RCOOH]}$$

(Since the concentration of water, the solvent, remains essentially constant, this term is usually omitted.) The equilibrium constant is called here the **acidity constant**, K_a (*a for acidity*).

Every carboxylic acid has its characteristic K_a, which indicates how strong an acid it is. Since the acidity constant is the ratio of ionized to unionized material, the larger the K_a the greater the extent of the ionization (under a given set of conditions) and the stronger the acid. We use the K_a's, then, to compare in an exact way the strengths of different acids.

We see in Table 18.2 (p. 600) that unsubstituted aliphatic and aromatic acids have K_a's of about 10^{-4} to 10^{-5} (0.0001 to 0.00001). This means that they are weakly acidic, with only a slight tendency to release protons.

By the same token, carboxylate anions are moderately basic, with an appreciable tendency to combine with protons. They react with water to increase the

concentration of hydroxide ions, a reaction often referred to as *hydrolysis*. As

$$RCOO^- + H_2O \rightleftharpoons RCOOH + OH^-$$

a result aqueous solutions of carboxylate salts are slightly alkaline. (The basicity of an aqueous solution of a carboxylate salt is due chiefly, of course, to the carboxylate anions, not to the comparatively few hydroxide ions they happen to generate.)

We may now expand the series of relative acidities and basicities:

Relative acidities: $RCOOH > HOH > ROH > HC{\equiv}CH > NH_3 > RH$

Relative basicities: $RCOO^- < HO^- < RO^- < HC{\equiv}C^- < NH_2^- < R^-$

Certain substituted acids are much stronger or weaker than a typical acid like CH_3COOH. We shall see that the acid-strengthening or acid-weakening effect of a substituent can be accounted for in a reasonable way; however, we must first learn a little more about equilibrium in general.

18.11 Equilibrium

So far we have dealt very little with the problem of equilibrium. Under the conditions employed, most of our reactions have been essentially irreversible; that is, they have been one-way reactions. With a few exceptions—1,4-addition, for example (Sec. 8.22)—the products obtained, and their relative yields, have been determined by how fast reactions go and not by how nearly to completion they proceed before equilibrium is reached. Consequently, we have been concerned with the relationship between structure and rate; now we shall turn to the relationship between structure and equilibrium.

Let us consider the reversible reaction between A and B to form C and D. The

$$A + B \rightleftharpoons C + D$$

yield of C and D does not depend upon how fast A and B react, but rather upon how completely they have reacted when equilibrium is reached.

The concentrations of the various components are related by the familiar expression,

$$K_{eq} = \frac{[C][D]}{[A][B]}$$

in which K_{eq} is the equilibrium constant. The more nearly a reaction has proceeded to completion when it reaches equilibrium, the larger is [C][D] compared with [A][B], and hence the larger the K_{eq}. The value of K_{eq} is therefore a measure of the tendency of the reaction to go to completion.

The value of K_{eq} is determined by the change in *free energy*, G, on proceeding from reactants to products (Fig. 18.1). The exact relationship is given by the expression,

$$\Delta G^\circ = -2.303RT \log K_{eq}$$

where ΔG° is the *standard free energy change*.

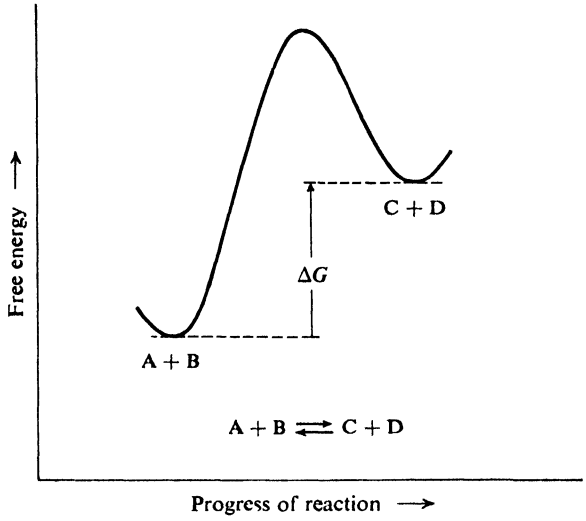


Figure 18.1. Free energy curve for a reversible reaction.

Free energy change is related to our familiar quantity ΔH (precisely $\Delta H°$, which is only slightly different) by the expression,

$$\Delta G° = \Delta H - T\Delta S°$$

where $\Delta S°$ is the *standard entropy change*. Entropy corresponds roughly, to the *randomness* of the system. To the extent that $T\Delta S°$ contributes to $\Delta G°$, equilibrium tends to shift toward the side in which fewer restrictions are placed on the positions of atoms and molecules. ("Die Energie der Welt ist constant. Die Entropie der Welt strebt einem Maximum zu." *Clausius, 1865.*)

Under the same experimental conditions two reversible reactions have K_{eq}'s of different sizes because of a difference in $\Delta G°$. In attempting to understand the effect of structure on position of equilibrium, we shall estimate differences in relative stabilities of reactants and products. Now, what we estimate in this way are not differences in free energy change but differences in potential energy change. It turns out that very often these differences are *proportional to* differences in $\Delta G°$. So long as we compare closely related compounds, the predictions we make by this approach are generally good ones.

These predictions are good ones despite the fact that the free energy changes on which they depend are made up to varying degrees of ΔH and $\Delta S°$. For example, *p*-nitrobenzoic acid is a stronger acid than benzoic acid. We attribute this (Sec. 18.14) to stabilization of the *p*-nitrobenzoate anion (relative to the benzoate anion) through dispersal of charge by the electron-withdrawing nitro group. Yet, in this case, the greater acidity is due about as much to a more favorable $\Delta S°$ as to a more favorable ΔH. How can our simple "stabilization by dispersal of charge" account for an effect that involves the randomness of a system?

Stabilization *is* involved, but it appears partly in the $\Delta S°$ for this reason.

Ionization of an acid is possible only because of solvation of the ions produced: the many ion–dipole bonds provide the energy needed for dissociation. But solvation requires that molecules of solvent leave their relatively unordered arrangement to cluster in some ordered fashion about the ions. This is good for the ΔH but bad for the $\Delta S°$. Now, because of its greater intrinsic stability, the *p*-nitrobenzoate anion does not *need* as many solvent molecules to help stabilize it as the benzoate anion does. The $\Delta S°$ is thus more favorable. We can visualize the *p*-nitrobenzoate ion accepting only as many solvent molecules as it has to, and stopping when the gain in stability (decrease in enthalpy) is no longer worth the cost in entropy.

(In the same way, it has been found that very often a more polar solvent speeds up a reaction—as, for example, an S_N1 reaction of alkyl halides (Sec. 14.16)—not so much by lowering E_{act} as by bringing about a more favorable entropy of activation. A more polar solvent is already rather ordered, and its clustering about the ionizing molecule amounts to very little loss of randomness—indeed, it may even amount to an *increase* in randomness.)

By the organic chemist's approach we can make *very* good predictions indeed. We can not only account for, say, the relative acidities of a set of acids, but we can correlate these acidities *quantitatively* with the relative acidities of another set of acids, or even with the relative rates of a set of reactions. These relationships are summarized in the Hammett equation (named for Louis P. Hammett of Columbia University),

$$\log \frac{K}{K_0} = \rho\sigma \qquad \text{or} \qquad \log \frac{k}{k_0} = \rho\sigma$$

where K or k refers to the reaction of a *m*- or *p*-substituted phenyl compound (say, ionization of a substituted benzoic acid) and K_0 or k_0 refers to the same reaction of the unsubstituted compound (say, ionization of benzoic acid).

The *substituent constant* (σ, *sigma*) is a number (+ or −) indicating the relative electron-withdrawing or electron-releasing effect of a particular substituent. The *reaction constant* (ρ, *rho*) is a number (+ or −) indicating the relative *need* of a particular reaction for electron withdrawal or electron release.

A vast amount of research has shown that the Hammett relationship holds for *hundreds of sets of reactions*. (Ionization of 40-odd *p*-substituted benzoic acids, for example, is *one* set.) By use of just two tables—one of σ constants and one of ρ constants—we can calculate the relative K_{eq}'s or relative rates for thousands of individual reactions. For example, from the σ value for *m*-NO_2 (+0.710) and the ρ value for ionization of benzoic acids in water at 25° (+1.000), we can calculate that K_a for *m*-nitrobenzoic acid is 5.13 times as big as the K_a for benzoic acid. Using the same σ value, and the ρ value for acid-catalyzed hydrolysis of benzamides in 60% ethanol at 80° (−0.298), we can calculate that *m*-nitrobenzamide will be hydrolyzed only 0.615 as fast as benzamide.

The Hammett relationship is called a *linear free energy relationship* since it is based on—and reveals—the fact that a linear relationship exists between free energy change and the effect exerted by a substituent. Other linear free energy relationships are known, which take into account steric as well as electronic effects, and which apply to *ortho* substituted phenyl compounds as well as *meta* and *para*, and to aliphatic as well as aromatic compounds. Together they make up what is perhaps the greatest accomplishment of physical-organic chemistry.

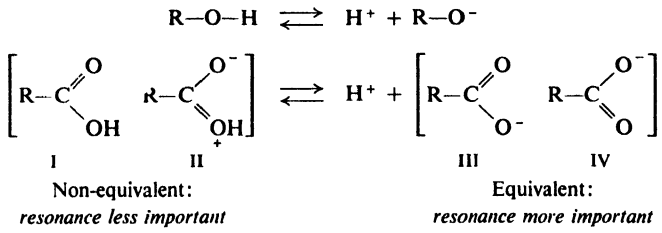
In dealing with rates, we compare the stability of the reactants with the stability of the transition state. In dealing with equilibria, we shall compare the stability of the reactants with the stability of the products. For closely related reactions, we are justified in assuming that the more stable the products relative to the reactants, the further reaction proceeds toward completion.

18.12 Acidity of carboxylic acids

Let us see how the acidity of carboxylic acids is related to structure. In doing this we shall assume that acidity is determined chiefly by the difference in stability between the acid and its anion.

First, and most important, there is the fact that carboxylic acids are acids at all. How can we account for the fact that the —OH of a carboxylic acid tends to release a hydrogen ion so much more readily than the —OH of, say, an alcohol? Let us examine the structures of the reactants and products in these two cases.

We see that the alcohol and alkoxide ion are each represented satisfactorily by a single structure. However, we can draw two reasonable structures (I and II) for the carboxylic acid and two reasonable structures (III and IV) for the carboxylate anion. Both acid and anion are resonance hybrids. But is resonance equally



important in the two cases? By the principles of Sec. 6.27 we know that resonance is much more important between the exactly equivalent structures III and IV than between the non-equivalent structures I and II. As a result, although both acid and anion are stabilized by resonance, stabilization is far greater for the anion than for the acid (see Fig. 18.2). Equilibrium is shifted in the direction of increased ionization, and K_a is increased.

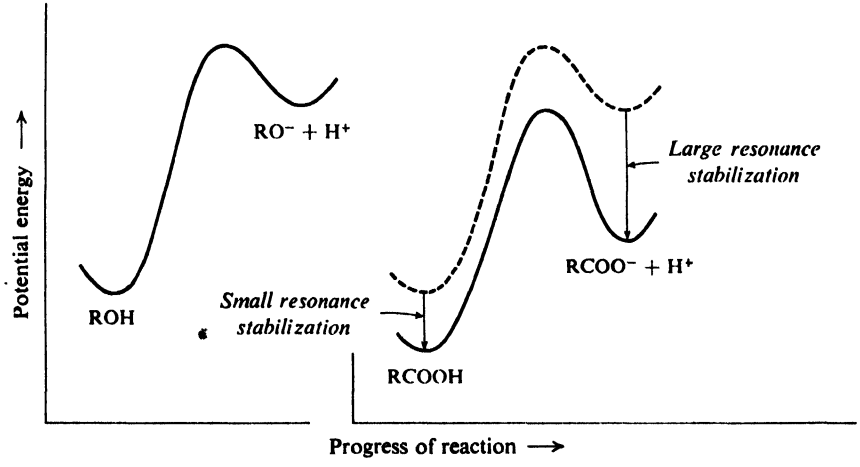


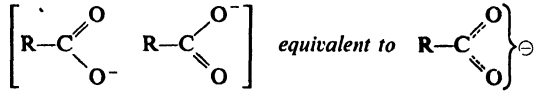
Figure 18.2. Molecular structure and position of equilibrium. Carboxylic acid yields resonance-stabilized anion; is stronger acid than alcohol. (Plots aligned with each other for easy comparison.)

Strictly speaking, resonance is less important for the acid because the contributing structures are of *different stability*, whereas the equivalent structures for the ion must necessarily be of *equal stability*. In structure II two atoms of similar electronegativity carry opposite charges; since energy must be supplied to separate opposite charges, II should contain more energy and hence be less stable than I. Consideration of *separation of charge* is one of the rules of thumb (Sec. 6.27) that can be used to estimate relative stability and hence relative importance of a contributing structure.

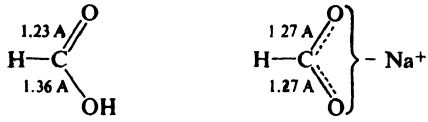
The acidity of a carboxylic acid is thus due to the powerful resonance stabilization of its anion. *This stabilization and the resulting acidity are possible only because of the presence of the carbonyl group.*

18.13 Structure of carboxylate ions

According to the resonance theory, then, a carboxylate ion is a hybrid of two structures which, being of equal stability, contribute equally. Carbon is joined to each oxygen by a "one-and-one-half" bond. The negative charge is evenly distributed over both oxygen atoms.



That the anion is indeed a resonance hybrid is supported by the evidence of bond length. Formic acid, for example, contains a carbon–oxygen double bond and a carbon–oxygen single bond; we would expect these bonds to have different lengths. Sodium formate, on the other hand, if it is a resonance hybrid, ought to contain two equivalent carbon–oxygen bonds; we would expect these to have the same length, intermediate between double and single bonds. X-ray and electron diffraction show that these expectations are correct. Formic acid contains one carbon–oxygen bond of 1.36 A (single bond) and another of 1.23 A (double bond); sodium formate contains two equal carbon–oxygen bonds, each 1.27 A long.



Formic acid Sodium formate

Problem 18.5. How do you account for the fact that the three carbon–oxygen bonds in $CaCO_3$ have the same length, and that this length (1.31 A) is greater than that found in sodium formate?

What does this resonance mean in terms of orbitals? Carboxyl carbon is joined to the three other atoms by σ bonds (Fig. 18.3); since these bonds utilize sp^2 orbitals (Sec. 5.2), they lie in a plane and are 120° apart. The remaining p orbital of the carbon overlaps equally well p orbitals from *both* of the oxygens, to form hybrid bonds (compare benzene, Sec. 10.8). In this way the electrons

are bound not just to one or two nuclei but to *three* nuclei (one carbon and two oxygens); they are therefore held more tightly, the bonds are stronger, and the anion is more stable. This participation of electrons in more than one bond, this smearing-out or delocalization of the electron cloud, is what is meant by representing the anion as a resonance hybrid of two structures.

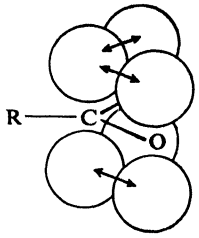


Figure 18.3. Carboxylate ion. Overlap of *p* orbitals in both directions: delocalization of π electrons, and dispersal of charge.

Problem 18.6 How do you account for the fact that the α-hydrogens of an aldehyde (say, *n*-butyraldehyde) are much more acidic than any other hydrogens in the molecule? (Check your answer in Sec. 21.1.)

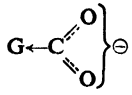
$$\overset{\gamma}{C}H_3\overset{\beta}{C}H_2\overset{\alpha}{C}H_2\overset{H}{C}{=}O$$

n-Butyraldehyde

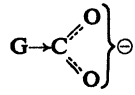
18.14 Effect of substituents on acidity

Next, let us see how changes in the structure of the group bearing the —COOH affect the acidity. Any factor that stabilizes the anion more than it stabilizes the acid should increase the acidity; any factor that makes the anion less stable should decrease acidity. From what we have learned about carbonium ions, we know what we might reasonably expect. Electron-withdrawing substituents should disperse the negative charge, stabilize the anion, and thus increase acidity. Electron-releasing substituents should intensify the negative charge, destabilize the anion, and thus decrease acidity.

Acid Strength



G withdraws electrons: *stabilizes anion, strengthens acid*



G releases electrons: *destabilizes anion, weakens acid*

The K_a's listed in Table 18.2 are in agreement with this prediction.

Looking first at the aliphatic acids, we see that the electron-withdrawing halogens strengthen acids: chloroacetic acid is 100 times as strong as acetic acid, dichloroacetic acid is still stronger, and trichloroacetic acid is more than 10,000 times as strong as the unsubstituted acid. The other halogens exert similar effects.

Table 18.2 ACIDITY CONSTANTS OF CARBOXYLIC ACIDS

	K_a		K_a
HCOOH	17.7×10^{-5}	$CH_3CHClCH_2COOH$	8.9×10^{-5}
CH_3COOH	1.75 „	$ClCH_2CH_2CH_2COOH$	2.96 „
$ClCH_2COOH$	136 „	FCH_2COOH	260 „
$Cl_2CHCOOH$	5530 „	$BrCH_2COOH$	125 „
Cl_3CCOOH	23200 „	ICH_2COOH	67 „
$CH_3CH_2CH_2COOH$	1.52 „	$C_6H_5CH_2COOH$	4.9 „
$CH_3CH_2CHClCOOH$	139 „	p-$O_2NC_6H_4CH_2COOH$	14.1 „

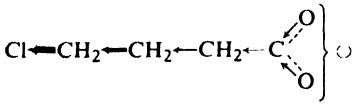
ACIDITY CONSTANTS OF SUBSTITUTED BENZOIC ACIDS

K_a of benzoic acid $= 6.3 \times 10^{-5}$

	K_a		K_a		K_a
p-NO_2	36×10^{-5}	m-NO_2	32×10^{-5}	o-NO_2	670×10^{-5}
p-Cl	10.3 „	m-Cl	15.1 „	o-Cl	120 „
p-CH_3	4.2 „	m-CH_3	5.4 „	o-CH_3	12.4 „
p-OCH_3	3.3 „	m-OCH_3	8.2 „	o-OCH_3	8.2 „
p-OH	2.6 „	m-OH	8.3 „	o-OH	105 „
p-NH_2	1.4 „	m-NH_2	1.9 „	o-NH_2	1.6 „

Problem 18.7 (a) What do the K_a's of the monohaloacetic acids tell us about the relative strengths of the inductive effects of the different halogens? (b) On the basis of Table 18.2, what kind of inductive effect does the phenyl group, $-C_6H_5$, appear to have?

α-Chlorobutyric acid is about as strong as chloroacetic acid. As the chlorine is moved away from the —COOH, however, its effect rapidly dwindles: β-chlorobutyric acid is only six times as strong as butyric acid, and γ-chlorobutyric acid is only twice as strong. It is typical of inductive effects that they decrease rapidly with distance, and are seldom important when acting through more than four atoms.



Inductive effect: *decreases with distance*

The aromatic acids are similarly affected by substituents: $-CH_3$, —OH, and $-NH_2$ make benzoic acid weaker, and —Cl and $-NO_2$ make benzoic acid stronger. We recognize the acid-weakening groups as the ones that activate the ring toward electrophilic substitution (and deactivate toward nucleophilic substitution). The acid-strengthening groups are the ones that deactivate toward electrophilic substitution (and activate toward nucleophilic substitution). Furthermore, the groups that have the largest effects on reactivity—whether activating or deactivating—have the largest effects on acidity.

The —OH and $-OCH_3$ groups display both kinds of effect we have attributed to them (Sec. 11.20): from the *meta* position, an electron-withdrawing acid-strengthening inductive

effect; and from the *para* position, an electron-releasing acid-weakening resonance effect (which at this position outweighs the inductive effect). Compare the two effects exerted by halogen (Sec. 11.21).

ortho-Substituted aromatic acids do not fit into the pattern set by their *meta* and *para* isomers, and by aliphatic acids. Nearly all *ortho* substituents exert an effect of the same kind—acid-strengthening—whether they are electron-withdrawing or electron-releasing, and the effect is unusually large. (Compare, for example, the effects of *o*-NO_2 and *o*-CH_3, of *o*-NO_2 and *m*- or *p*-NO_2.) This *ortho* effect undoubtedly has to do with the *nearness* of the groups involved, but is more than just steric hindrance arising from their bulk.

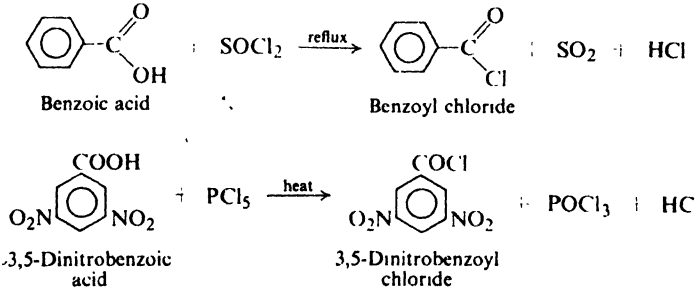
Thus we see that the same concepts—inductive effect and resonance—that we found so useful in dealing with rates of reaction are also useful in dealing with equilibria. By using these concepts to estimate the stabilities of anions, we are able to predict the relative strengths of acids; in this way we can account not only for the effect of substituents on the acid strength of carboxylic acids but also for the very fact that the compounds are acids.

Problem 18.8 There is evidence that certain groups like *p*-methoxy weaken the acidity of benzoic acids not so much by destabilizing the anion as by stabilizing the acid. Draw structures to show the kind of resonance that might be involved. Why would you expect such resonance to be more important for the acid than for the anion?

18.15 Conversion into acid chlorides

A carboxylic acid is perhaps more often converted into the acid chloride than into any other of its functional derivatives. From the highly reactive acid chloride there can then be obtained many other kinds of compounds, including esters and amides (Sec. 20.8).

An acid chloride is prepared by substitution of —Cl for the —OH of a carboxylic acid. Three reagents are commonly used for this purpose: *thionyl chloride*, $SOCl_2$; *phosphorus trichloride*, PCl_3; and *phosphorus pentachloride*, PCl_5. (Of what inorganic acids might we consider these reagents to be the acid chlorides?) For example:



Thionyl chloride is particularly convenient, since the products formed besides the acid chloride are gases and thus easily separated from the acid chloride; any excess of the low-boiling thionyl chloride (79) is easily removed by distillation.

18.16 Conversion into esters

Acids are frequently converted into their esters via the acid chlorides:

$$\underset{\text{Acid}}{RCOOH} \xrightarrow{SOCl_2,\ \text{etc.}} \underset{\text{Acid chloride}}{RCOCl} \xrightarrow{R'OH} \underset{\text{Ester}}{RCOOR'}$$

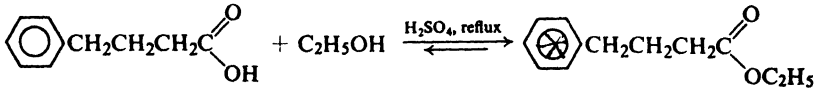
A carboxylic acid is converted directly into an ester when heated with an alcohol in the presence of a little mineral acid, usually concentrated sulfuric acid or dry hydrogen chloride. This reaction is reversible, and generally reaches equilibrium when there are appreciable quantities of both reactants and products present.

$$\underset{\text{Acid}}{RCOOH} + \underset{\text{Alcohol}}{R'OH} \overset{H^+}{\rightleftharpoons} \underset{\text{Ester}}{RCOOR'} + H_2O$$

For example, when we allow one mole of acetic acid and one mole of ethyl alcohol to react in the presence of a little sulfuric acid until equilibrium is reached (after several hours), we obtain a mixture of about two-thirds mole each of ester and water. and one-third mole each of acid and alcohol. We obtain this same equilibrium mixture, of course, if we start with one mole of ester and one mole of water, again in the presence of sulfuric acid. *The same catalyst, hydrogen ion, that catalyzes the forward reaction, esterification, necessarily catalyzes the reverse reaction, hydrolysis.*

This reversibility is a disadvantage in the preparation of an ester directly from an acid; the preference for the acid chloride route is due to the fact that both steps—preparation of acid chloride from acid, and preparation of ester from acid chloride—are essentially irreversible and go to completion.

Direct esterification, however, has the advantage of being a single-step synthesis; it can often be made useful by application of our knowledge of equilibria. If either the acid or the alcohol is cheap and readily available, it can be used in large excess to shift the equilibrium toward the products and thus to increase the yield of ester. For example, it is worthwhile to use eight moles of cheap ethyl alcohol to convert one mole of valuable γ-phenylbutyric acid more completely into the ester:



γ-Phenylbutyric acid, *1 mole*; Ethyl alcohol, *8 moles*; Ethyl γ-phenylbutyrate, *85–88% yield*

Sometimes the equilibrium is shifted by removing one of the products. An elegant way of doing this is illustrated by the preparation of ethyl adipate. The dicarboxylic acid adipic acid, an excess of ethyl alcohol, and toluene are heated with a little sulfuric acid under a distillation column. The lowest boiling component (b.p. 75°) of the reaction mixture is an azeotrope of water, ethyl alcohol, and toluene (compare Sec. 15.6); consequently, as fast as water is formed it is

removed as the azeotrope by distillation. In this way a 95–97% yield of ester is obtained:

$$\underset{\substack{\text{Adipic acid}\\ \textit{Non-volatile}}}{HOOC(CH_2)_4COOH} + \underset{\substack{\text{Ethyl alcohol}\\ \textit{B.p. 78°}}}{2C_2H_5OH} \xrightarrow[\text{toluene (b.p. 111°),}]{H_2SO_4} \underset{\substack{\text{Ethyl adipate}\\ \textit{B.p. 245°}}}{C_2H_5OOC(CH_2)_4COOC_2H_5} + \underset{\substack{\textit{Removed as}\\ \textit{azeotrope, b.p. 75°}}}{2H_2O}$$

The equilibrium is particularly unfavorable when phenols (ArOH) are used instead of alcohols; yet, if water is removed during the reaction, phenolic esters (RCOOAr) are obtained in high yield.

The presence of bulky groups near the site of reaction, whether in the alcohol or in the acid, slows down esterification (as well as its reverse, hydrolysis). This

Reactivity in esterification

$$CH_3OH > 1° > 2° (> 3°)$$

$$HCOOH > CH_3COOH > RCH_2COOH > R_2CHCOOH > R_3CCOOH$$

steric hindrance can be so marked that special methods are required to prepare esters of tertiary alcohols or esters of acids like 2,4,6-trimethylbenzoic acid (mesitoic acid).

The mechanism of esterification is necessarily the exact reverse of the mechanism of hydrolysis of esters. We shall discuss both mechanisms when we take up the chemistry of esters (Sec. 20.18) after we have learned a little more about the carbonyl group.

Problem 18.9 (a) In the formation of an acid chloride, which bond of a carboxylic acid is broken, C—OH or CO—H? (b) When labeled methanol, $CH_3{}^{18}OH$, was allowed to react with ordinary benzoic acid, the methyl benzoate produced was found to be enriched in ^{18}O, whereas the water formed contained only ordinary oxygen. In this esterification, which bond of the carboxylic acid is broken, C—OH or CO—H? Which bond of the alcohol?

18.17 Conversion into amides

Amides are compounds in which the —OH of the carboxylic acid has been

$$\underset{\text{Acid}}{RCOOH} \longrightarrow \underset{\text{Acid chloride}}{RCOCl} \xrightarrow{NH_3} \underset{\text{Amide}}{R-C(=O)-NH_2}$$

replaced by $-NH_2$. These are generally prepared by reaction of ammonia with acid chlorides.

18.18 Reduction of acids to alcohols

Conversion of alcohols into acids (Sec. 18.6) is important because, in general, alcohols are more available than acids. This is not always true, however; long

straight-chain acids from fats are more available than are the corresponding alcohols, and here the reverse process becomes important: reduction of acids to alcohols.

Lithium aluminum hydride, $LiAlH_4$, is one of the few reagents that can reduce an acid to an alcohol; the initial product is an alkoxide from which the alcohol is liberated by hydrolysis:

$$4RCOOH + 3LiAlH_4 \longrightarrow 4H_2 + 2LiAlO_2 + (RCH_2O)_4AlLi \xrightarrow{H_2O} \underset{\text{1° alcohol}}{4RCH_2OH}$$

Because of the excellent yields it gives, $LiAlH_4$ is widely used in the laboratory for the reduction of not only acids but many other classes of compounds. Since it is somewhat expensive, it can be used in industry only for the reduction of small amounts of valuable raw materials, as in the synthesis of certain drugs and hormones.

As an alternative to direct reduction, acids are often converted into alcohols by a two-step process: esterification, and reduction of the ester. Esters can be reduced in a number of ways (Sec. 20.22) that are adaptable to both laboratory and industry.

We have seen (Sec. 18.5) that in the carboxylic acids obtained from fats we have available long straight-chain units for use in organic synthesis. Reduction of these acids to alcohols (either directly or as esters) is a fundamental step in the utilization of these raw materials, since from the alcohols, as we know, a host of other compounds can be prepared (Sec. 16.10). Although only acids of even carbon number are available, it is possible, of course, to increase the chain length and thus prepare compounds of odd carbon number. (For an alternative source of alcohols both of even and odd carbon number, see Sec. 32.6.)

Problem 18.10 Outline the synthesis from lauric acid (n-$C_{11}H_{23}COOH$, dodecanoic acid) of the following compounds: (a) 1-bromododecane; (b) tridecanoic acid (C_{13} acid); (c) 1-tetradecanol; (d) 1-dodecene; (e) dodecane; (f) 1-dodecyne; (g) methyl n-decyl ketone; (h) 2-dodecanol; (i) undecanoic acid; (j) 2-tetradecanol; (k) 2-methyl-2-tetradecanol.

18.19 Halogenation of aliphatic acids. Substituted acids

In the presence of a small amount of phosphorus, aliphatic carboxylic acids react smoothly with chlorine or bromine to yield a compound in which α-hydrogen has been replaced by halogen. This is the **Hell-Volhard-Zelinsky reaction**. Because of its specificity—*only alpha halogenation*—and the readiness with which it takes place, it is of considerable importance in synthesis.

$$CH_3COOH \xrightarrow{Cl_2,\,P} ClCH_2COOH \xrightarrow{Cl_2,\,P} Cl_2CHCOOH \xrightarrow{Cl_2,\,P} Cl_3CCOOH$$

$$CH_3CH_2COOH \xrightarrow{Br_2,\,P} CH_3CHBrCOOH \xrightarrow{Br_2,\,P} CH_3CBr_2COOH \xrightarrow{Br_2,\,P} \text{no further substitution}$$

The function of the phosphorus is ultimately to convert a little of the acid into acid halide. In this form (for reasons we cannot go into here) each molecule of acid sooner or later undergoes α-halogenation.

$$P + X_2 \longrightarrow PX_3$$

$$RCH_2COOH + PX_3 \longrightarrow RCH_2COX$$

$$RCH_2COX + X_2 \longrightarrow \underset{\displaystyle X}{\overset{\displaystyle |}{RCHCOX}} + HX$$

$$\underset{\displaystyle X}{\overset{\displaystyle |}{RCHCOX}} + RCH_2COOH \rightleftharpoons \underset{\displaystyle X}{\overset{\displaystyle |}{RCHCOOH}} + RCH_2COX$$

α-Haloacid

The halogen of these halogenated acids undergoes *nucleophilic displacement* and *elimination* much as it does in the simpler alkyl halides (Secs. 14.5 and 5.12). Halogenation is therefore the first step in the conversion of a carboxylic acid into many important substituted carboxylic acids:

$$\underset{\displaystyle Br}{\overset{\displaystyle |}{RCHCOOH}} + \text{large excess of } NH_3 \longrightarrow \underset{\displaystyle NH_2}{\overset{\displaystyle |}{RCHCOOH}}$$

An α-halogenated acid — An α-amino acid

$$\underset{\displaystyle Br}{\overset{\displaystyle |}{RCHCOOH}} + NaOH \longrightarrow \underset{\displaystyle OH}{\overset{\displaystyle |}{RCHCOONa}} \xrightarrow{H^+} \underset{\displaystyle OH}{\overset{\displaystyle |}{RCHCOOH}}$$

An α-hydroxy acid

$$\underset{\displaystyle Br}{\overset{\displaystyle |}{RCH_2CHCOOH}} + KOH\ (alc) \longrightarrow RCH{=}CHCOO^- \xrightarrow{H^+} RCH{=}CHCOOH$$

An α,β-unsaturated acid

These new substituents can, in turn, undergo *their* characteristic reactions.

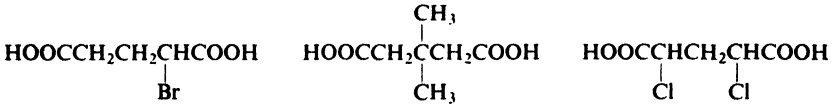
Problem 18.11 Predict the product of each of the following reactions:

(a) $CH_2{=}CHCOOH + H_2/Ni$
(b) *trans*-$CH_3CH{=}CHCOOH + Br_2/CCl_4$
(c) $C_6H_5CH(OH)CH_2COOH + H^+$, heat $\longrightarrow C_9H_8O_2$
(d) *o*-$HOOCC_6H_4CH_2OH + H^+$, heat $\longrightarrow C_8H_6O_2$

18.20 Dicarboxylic acids

If the substituent is a second carboxyl group, we have a *dicarboxylic acid.* For example:

$HOOCCH_2COOH$	$HOOCCH_2CH_2COOH$	$HOOCCH_2CH_2CH_2CH_2COOH$
Malonic acid	Succinic acid	Adipic acid
Propanedioic acid	Butanedioic acid	Hexanedioic acid



α-Bromoglutaric acid
2-Bromopentanedioic acid

β,β-Dimethylglutaric acid
3,3-Dimethylpentanedioic acid

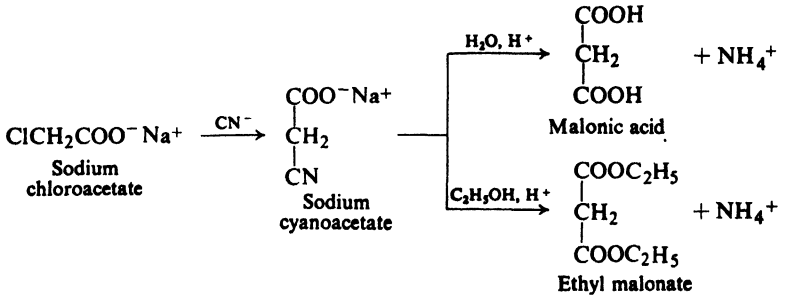
α,α′-Dichloroglutaric acid
2,4-Dichloropentanedioic acid

We have already encountered the benzenedicarboxylic acids, the *phthalic acids* (Sec. 12.10).

Table 18.3 DICARBOXYLIC ACIDS

Name	Formula	M.p., °C	Solub., g/100 g H_2O at 20°	K_1	K_2
Oxalic	HOOC—COOH	189	9	5400×10^{-5}	5.2×10^{-5}
Malonic	$HOOCCH_2COOH$	136	74	140	0.20
Succinic	$HOOC(CH_2)_2COOH$	185	6	6.4	0.23
Glutaric	$HOOC(CH_2)_3COOH$	98	64	4.5	0.38
Adipic	$HOOC(CH_2)_4COOH$	151	2	3.7	0.39
Maleic	*cis*-HOOCCH=CHCOOH	130.5	79	1000	0.055
Fumaric	*trans*-HOOCCH=CHCOOH	302	0.7	96	4.1
Phthalic	$1,2\text{-}C_6H_4(COOH)_2$	231	0.7	110	0.4
Isophthalic	$1,3\text{-}C_6H_4(COOH)_2$	348.5	0.01	24	2.5
Terephthalic	$1,4\text{-}C_6H_4(COOH)_2$	300 *subl*	0.002	29	3.5

Most dicarboxylic acids are prepared by adaptation of methods used to prepare monocarboxylic acids. Where hydrolysis of a nitrile yields a monocarboxylic acid, hydrolysis of a dinitrile or a cyanocarboxylic acid yields a dicarboxylic acid; where oxidation of a methylbenzene yields a benzoic acid, oxidation of a dimethylbenzene yields a phthalic acid. For example:



Problem 18.12 Why is chloroacetic acid converted into its salt before treatment with cyanide in the above preparation?

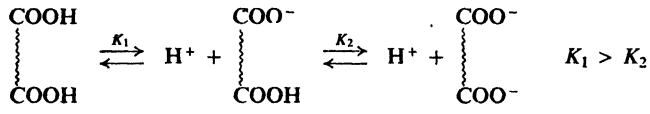
Problem 18.13 Outline a synthesis of: (a) pentanedioic acid from 1,3-propanediol (available from a fermentation of glycerol); (b) nonanedioic acid from *cis*-9-octadecenoic acid (oleic acid, obtained from fats); (c) succinic acid from 1,4-butynediol (available from acetylene and formaldehyde).

In general, dicarboxylic acids show the same chemical behavior as monocarboxylic acids. It is possible to prepare compounds in which only one of the carboxyl groups has been converted into a derivative; it is possible to prepare compounds in which the two carboxyl groups have been converted into different derivatives.

Problem 18.14 Predict the products of the following reactions:

(a) adipic acid (146 g) + 95% ethanol (146 g) + benzene + conc. H_2SO_4, 100°
(b) adipic acid (146 g) + 95% ethanol (50 g) + benzene + conc. H_2SO_4, 100°
(c) succinic acid + $LiAlH_4$
(d) pentanedioic acid + 1 mole Br_2, P
(e) terephthalic acid + excess $SOCl_2$
(f) maleic acid (*cis*-butenedioic acid) + Br_2/CCl_4

As with other acids containing more than one ionizable hydrogen (H_2SO_4, H_2CO_3, H_3PO_4, etc.), ionization of the second carboxyl group occurs less readily than ionization of the first (compare K_1's with K_2's in Table 18.3). More energy



is required to separate a positive hydrogen ion from the doubly charged anion than from the singly charged anion.

Problem 18.15 Compare the acidity (first ionization) of oxalic acid with that of formic acid; of malonic acid with that of acetic acid. How do you account for these differences?

Problem 18.16 Arrange oxalic, malonic, succinic, and glutaric acids in order of acidity (first ionization). How do you account for this order?

In addition to the reactions typical of any carboxylic acid, we shall find, some of these dicarboxylic acids undergo reactions that are possible only because there are two carboxyl groups in each molecule, and because these carboxyl groups are located in a particular way with respect to each other.

Problem 18.17 Give a likely structure for the product of each of the following reactions:

(a) oxalic acid + ethylene glycol $\longrightarrow$ $C_4H_4O_4$
(b) succinic acid + heat $\longrightarrow$ $C_4H_4O_3$
(c) terephthalic acid + ethylene glycol $\longrightarrow$ $(C_{10}H_8O_4)_n$, the polymer Dacron

18.21 Analysis of carboxylic acids. Neutralization equivalent

Carboxylic acids are recognized through their acidity. They dissolve in aqueous sodium hydroxide and in aqueous sodium bicarbonate. The reaction with bicarbonate releases bubbles of carbon dioxide (see Sec. 18.4).

(Phenols, Sec. 24.7, are more acidic than water, but—with certain exceptions—are considerably weaker than carboxylic acids; they dissolve in aqueous sodium hydroxide, but *not* in aqueous sodium bicarbonate. Sulfonic acids are even more acidic than carboxylic acids, but they contain sulfur, which can be detected by elemental analysis.)

Once characterized as a carboxylic acid, an unknown is identified as a particular acid on the usual basis of its physical properties and the physical properties of derivatives. The derivatives commonly used are *amides* (Secs. 20.11 and 23.6) and *esters* (Sec. 20.15).

Problem 18.18 Expand the table you made in Problem 17.24, p. 570, to include the kinds of compounds and tests we have taken up since then.

Particularly useful both in identification of previously studied acids and in proof of structure of new ones is the **neutralization equivalent**: *the equivalent weight of the acid as determined by titration with standard base.* A weighed sample of the acid is dissolved in water or aqueous alcohol, and the volume of standard base needed to neutralize the solution is measured. For example, a 0.224-g sample of an unknown acid (m.p. 139–140°) required 13.6 ml of 0.104 N sodium hydroxide solution for neutralization (to a phenolphthalein end point). Since each 1000 ml of the base contains 0.104 equivalents, and since the number of equivalents of base required equals the number of equivalents of acid present,

$$\frac{13.6}{1000} \times 0.104 \text{ equivalents of acid} = 0.224 \text{ g}$$

and

$$1 \text{ equivalent of acid} = 0.224 \times \frac{1000}{13.6} \times \frac{1}{0.104} = 158 \text{ g}$$

Problem 18.19 Which of the following compounds might the above acid be: (a) *o*-chlorobenzoic acid (m.p. 141°) or (b) 2,6-dichlorobenzoic acid (m.p. 139°)?

Problem 18.20 A 0.187-g sample of an acid (b.p. 203–205°) required 18.7 ml of 0.0972 N NaOH for neutralization. (a) What is the neutralization equivalent? (b) Which of the following acids might it be: *n*-caproic acid (b.p. 205°), methoxyacetic acid (b.p. 203°), or ethoxyacetic acid (b.p. 206°)?

Problem 18.21 (a) How many equivalents of base would be neutralized by one mole of phthalic acid? What is the neutralization equivalent of phthalic acid? (b) What is the relation between neutralization equivalent and the number of acidic hydrogens per molecule of acid? (c) What is the neutralization equivalent of 1,3,5-benzenetricarboxylic acid? Of mellitic acid, $C_6(COOH)_6$?

A metal salt of a carboxylic acid is recognized through these facts: (a) it leaves a residue when strongly heated (*ignition test*); (b) it decomposes at a fairly high temperature, instead of melting; and (c) it is converted into a carboxylic acid upon treatment with dilute mineral acid.

Problem 18.22 The residue left upon ignition of a sodium salt of a carboxylic acid was white, soluble in water, turned moist litmus blue, and reacted with dilute hydrochloric acid with the formation of bubbles. What was its probable chemical composition?

18.22 Spectroscopic analysis of carboxylic acids

Infrared. The carboxyl group is made up of a carbonyl group (C=O) and a hydroxyl group (OH), and the infrared spectrum of carboxylic acids reflects both these structural units. For hydrogen-bonded (dimeric) acids, O—H stretching gives a strong, broad band in the 2500–3000 cm^{-1} range (see Fig. 18.4, below).

O—H stretching, *strong, broad*

—COOH and enols	2500–3000 cm^{-1}
ROH and ArOH	3200–3600 cm^{-1}

With acids we encounter, for the first time, absorption due to stretching of the carbonyl group. This strong band appears in a region that is usually free of other

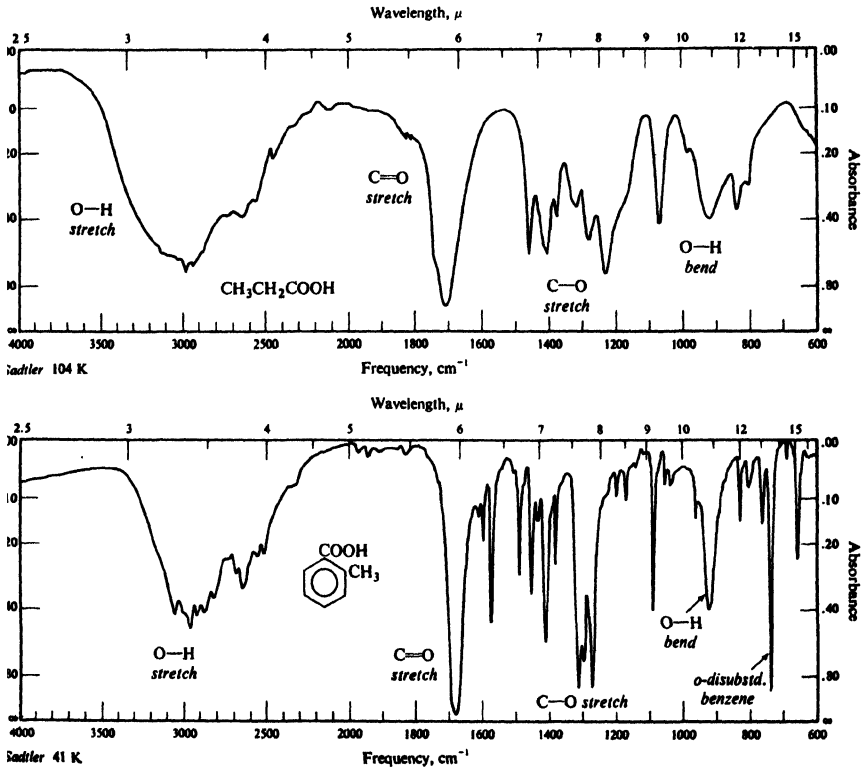


Figure 18.4. Infrared spectra of (*a*) propionic acid and (*b*) *o*-toluic acid.

strong absorption, and by its exact frequency gives much information about structure. For (hydrogen-bonded) acids, the C—O band is at about 1700 cm^{-1}.

C=O stretching, *strong*

R—C(=O)—OH	1700–1725 cm^{-1}	—C=C—C(=O)—OH	1680–1700 cm^{-1}
Ar—C(=O)—OH	1680–1700 cm^{-1}	—C=CH—C(=O)— (OH·····O) (enols)	1540–1640 cm^{-1}

Acids also show a C—O stretching band at about 1250 cm^{-1} (compare alcohols, Sec. 16.13, and ethers, Sec. 17.17), and bands for O—H bending near 1400 cm^{-1} and 920 cm^{-1} (*broad*).

Enols, too, show both O—H and C=O absorption; these can be distinguished by the particular frequency of the C=O band. Aldehydes, ketones, and esters show carbonyl absorption, but the O—H band is missing. (For a comparison of certain oxygen compounds, see Table 20.3, p. 689.)

Nmr. The outstanding feature of the nmr spectrum of a carboxylic acid is the absorption far downfield (δ 10.5–12) by the proton of —COOH. (Compare the absorption by the acidic proton of phenols, ArOH, in Sec. 24.14.)

PROBLEMS

1. Give the common names and IUPAC names for the straight-chain saturated carboxylic acids containing the following numbers of carbon atoms: 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18.

2. Give the structural formula and, where possible, a second name (by a different system) for each of the following:

(a) isovaleric acid
(b) trimethylacetic acid
(c) α,β-dimethylcaproic acid
(d) 2-methyl-4-ethyloctanoic acid
(e) phenylacetic acid
(f) γ-phenylbutyric acid
(g) adipic acid
(h) *p*-toluic acid
(i) phthalic acid
(j) isophthalic acid
(k) terephthalic acid
(l) *p*-hydroxybenzoic acid
(m) potassium α-methylbutyrate
(n) magnesium 2-chloropropanoate
(o) maleic acid
(p) α,α'-dibromosuccinic acid
(q) isobutyronitrile
(r) 2,4-dinitrobenzonitrile

3. Write equations to show how each of the following compounds could be converted into benzoic acid:

(a) toluene
(b) bromobenzene
(c) benzonitrile
(d) benzyl alcohol
(e) benzotrichloride
(f) acetophenone, $C_6H_5COCH_3$ (*Hint:* See Sec. 16.11.)

4. Write equations to show how each of the following compounds could be converted into *n*-butyric acid:

(a) *n*-butyl alcohol
(b) *n*-propyl alcohol
(c) *n*-propyl alcohol (a second way)
(d) methyl *n*-propyl ketone

Which of the above methods could be used to prepare trimethylacetic acid?

5. Write equations to show how tetrahydrofuran could be converted into: (a) succinic acid; (b) glutaric acid; (c) adipic acid.

6. Write equations to show the reaction (if any) of benzoic acid with:

(a) KOH
(b) Al
(c) CaO
(d) Na_2CO_3
(e) NH_3(aq)
(f) H_2, Ni, 20°, 1 atm.
(g) $LiAlH_4$
(h) hot $KMnO_4$
(i) PCl_5
(j) PCl_3
(k) $SOCl_2$
(l) Br_2/Fe
(m) Br_2 + P
(n) HNO_3/H_2SO_4
(o) fuming sulfuric acid
(p) CH_3Cl, $AlCl_3$
(q) $Tl(OOCCF_3)_3$
(r) *n*-propyl alcohol, H^+

7. Answer Problem 6 for *n*-valeric acid.

8. Write equations to show how isobutyric acid could be converted into each of the following, using any needed reagents.

(a) ethyl isobutyrate
(b) isobutyryl chloride
(c) isobutyramide
(d) magnesium isobutyrate
(e) isobutyl alcohol

9. Write equations to show all steps in the conversion of benzoic acid into:

(a) sodium benzoate
(b) benzoyl chloride
(c) benzamide
(d) benzene
(e) *n*-propyl benzoate
(f) *p*-tolyl benzoate
(g) *m*-bromophenyl benzoate
(h) benzyl alcohol

10. Write equations to show how phenylacetic acid could be converted into each of the following, using any needed reagents.

(a) sodium phenylacetate
(b) ethyl phenylacetate
(c) phenylacetyl chloride
(d) phenylacetamide
(e) *p*-bromophenylacetic acid
(f) *p*-nitrophenylacetic acid
(g) β-phenylethyl alcohol
(h) α-bromophenylacetic acid
(i) α-aminophenylacetic acid
(j) α-hydroxyphenylacetic acid
(k) phenylmalonic acid, $C_6H_5CH(COOH)_2$

11. Complete the following, giving the structures and names of the principal organic products.

(a) $C_6H_5CH{=}CHCOOH + KMnO_4 + OH^- +$ heat
(b) $p\text{-}CH_3C_6H_4COOH + HNO_3 + H_2SO_4$
(c) succinic acid + $LiAlH_4$, followed by H^+
(d) $C_6H_5COOH + C_6H_5CH_2OH + H^+$
(e) product (d) + $HNO_3 + H_2SO_4$
(f) $C_6H_5CH_2COOH + Tl(OOCCF_3)_3$
(g) cyclo-$C_6H_{11}MgBr + CO_2$, followed by H_2SO_4
(h) product (g) + $C_2H_5OH + H^+$
(i) product (g) + $SOCl_2$ + heat
(j) $m\text{-}CH_3C_6H_4OCH_3 + KMnO_4 + OH^-$
(k) mesitylene + $K_2Cr_2O_7 + H_2SO_4$
(l) isobutyric acid + isobutyl alcohol + H^+
(m) salicylic acid ($o\text{-}HOC_6H_4COOH$) + Br_2, Fe
(n) sodium acetate + *p*-nitrobenzyl bromide (What would you predict?)
(o) linolenic acid + excess H_2, Ni
(p) oleic acid + $KMnO_4$, heat
(q) linoleic acid + O_3, then H_2O, Zn
(r) benzoic acid ($C_7H_6O_2$) + H_2, Ni, heat, pressure $\longrightarrow$ $C_7H_{12}O_2$
(s) benzoic acid + ethylene glycol + $H^+ \longrightarrow C_{16}H_{14}O_4$
(t) phthalic acid + ethyl alcohol + $H^+ \longrightarrow C_{12}H_{14}O_4$
(u) oleic acid + Br_2/CCl_4
(v) product (u) + KOH (alcoholic)
(w) oleic acid + HCO_2OH

12. Outline a possible laboratory synthesis of the following labeled compounds, using $Ba^{14}CO_3$ or $^{14}CH_3OH$ as the source of ^{14}C.

(a) $CH_3CH_2CH_2{}^{14}COOH$
(b) $CH_3CH_2{}^{14}CH_2COOH$
(c) $CH_3{}^{14}CH_2CH_2COOH$
(d) $^{14}CH_3CH_2CH_2COOH$

13. Outline all steps in a possible laboratory synthesis of each of the following compounds from toluene and any needed aliphatic and inorganic reagents.

(a) benzoic acid
(b) phenylacetic acid
(c) *p*-toluic acid
(d) *m*-chlorobenzoic acid
(e) *p*-chlorobenzoic acid
(f) *p*-bromophenylacetic acid
(g) α-chlorophenylacetic acid

14. Outline a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer, using any needed inorganic reagents.

(a) ethyl α-methylbutyrate
(b) 3,5-dinitrobenzoyl chloride
(c) α-amino-*p*-bromophenylacetic acid
(d) α-hydroxypropionic acid
(e) p-$HO_3SC_6H_4COOH$
(f) 2-pentenoic acid
(g) *p*-toluamide
(h) *n*-hexyl benzoate
(i) 3-bromo-4-methylbenzoic acid
(j) α-methylphenylacetic acid
(k) 2-bromo-4-nitrobenzoic acid
(l) 1,2,4-benzenetricarboxylic acid

15. Without referring to tables, arrange the compounds of each set in order of acidity:

(a) butanoic acid, 2-bromobutanoic acid, 3-bromobutanoic acid, 4-bromobutanoic acid
(b) benzoic acid, *p*-chlorobenzoic acid, 2,4-dichlorobenzoic acid, 2,4,6-trichlorobenzoic acid
(c) benzoic acid, *p*-nitrobenzoic acid, *p*-toluic acid
(d) α-chlorophenylacetic acid, *p*-chlorophenylacetic acid, phenylacetic acid, α-phenylpropionic acid
(e) *p*-nitrobenzoic acid, *p*-nitrophenylacetic acid, β-(*p*-nitrophenyl)propionic acid
(f) acetic acid, acetylene, ammonia, ethane, ethanol, sulfuric acid, water
(g) acetic acid, malonic acid, succinic acid

16. Arrange the monosodium salts of the acids in Problem 15(f) in order of basicity.

17. The two water-insoluble solids, benzoic acid and *o*-chlorobenzoic acid, can be separated by treatment with an aqueous solution of sodium formate. What reaction takes place? (*Hint:* Look at the K_a's in Table 18.2.)

18. Arrange the compounds of each set in order of reactivity in the indicated reaction:

(a) esterification by benzoic acid: *sec*-butyl alcohol, methanol, *tert*-pentyl alcohol, *n*-propyl alcohol
(b) esterification by ethyl alcohol: benzoic acid, 2,6-dimethylbenzoic acid, *o*-toluic acid
(c) esterification by methanol: acetic acid, formic acid, isobutyric acid, propionic acid, trimethylacetic acid

19. Give stereochemical formulas of compounds A–F:

(a) racemic β-bromobutyric acid + one mole Br_2, P $\longrightarrow$ A + B
(b) fumaric acid + HCO_2OH $\longrightarrow$ C ($C_4H_6O_6$)
(c) 1,4-cyclohexadiene + $CHBr_3$/*t*-BuOK $\longrightarrow$ D ($C_7H_8Br_2$)
D + $KMnO_4$ $\longrightarrow$ E ($C_7H_8Br_2O_4$)
E + H_2, Ni(base) $\longrightarrow$ F ($C_7H_{10}O_4$)

20. Give structures of compounds G through J:

$$\text{acetylene} + CH_3MgBr \longrightarrow G + CH_4$$
$$G + CO_2 \longrightarrow H \xrightarrow{H^+} I\ (C_3H_2O_2)$$
$$I \xrightarrow{H_2O,\ H_2SO_4,\ HgSO_4} J\ (C_3H_4O_3)$$
$$J + KMnO_4 \longrightarrow CH_2(COOH)_2$$

21. Describe simple chemical tests (other than color change of an indicator) that would serve to distinguish between:

(a) propionic acid and *n*-pentyl alcohol
(b) isovaleric acid and *n*-octane
(c) ethyl *n*-butyrate and isobutyric acid
(d) propionyl chloride and propionic acid
(e) *p*-aminobenzoic acid and benzamide
(f) $C_6H_5CH{=}CHCOOH$ and $C_6H_5CH{=}CHCH_3$

Tell exactly what you would *do* and *see*.

22. Compare benzoic acid and sodium benzoate with respect to:

(a) volatility
(b) melting point
(c) solubility in water and (d) in ether
(e) degree of ionization of solid
(f) degree of ionization in water
(g) acidity and basicity

Does this comparison hold generally for acids and their salts?

23. Tell how you would separate by chemical means the following mixtures, recovering each component in reasonably pure form:

(a) caproic acid and ethyl caproate
(b) *n*-butyl ether and *n*-butyric acid
(c) isobutyric acid and 1-hexanol
(d) sodium benzoate and triphenylcarbinol

Tell exactly what you would *do* and *see*.

24. An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, neutralization equivalent, etc. Make use of any needed tables of physical constants.

(a) acrylic acid ($CH_2{=}CHCOOH$, b.p. 142°) and propionic acid (b.p. 141°)
(b) mandelic acid ($C_6H_5CHOHCOOH$, m.p. 120°) and benzoic acid (m.p. 122°)
(c) *o*-chlorobenzoic acid (m.p. 141°), mesotartaric acid (m.p. 140°), *m*-nitrobenzoic acid (m.p. 141°), and suberic acid ($HOOC(CH_2)_6COOH$, m.p. 144°)
(d) chloroacetic acid (b.p. 189°), α-chloropropionic acid (b.p. 186°), dichloroacetic acid (b.p. 194°), and *n*-valeric acid (b.p. 187°)
(e) 3-nitrophthalic acid (m.p. 220°) and 2,4,6-trinitrobenzoic acid (m.p. 220°)
(f) *p*-chlorobenzoic acid (m.p. 242°), *p*-nitrobenzoic acid (m.p. 242°), *o*-nitrocinnamic acid ($o\text{-}O_2NC_6H_4CH{=}CHCOOH$, m.p. 240°)
(g) The following compounds, all of which boil within a few degrees of each other:

o-chloroanisole
β-chlorostyrene
p-cresyl ethyl ether
cis-decalin (see Problem 8, p. 315)
2,4-dichlorotoluene
isodurene
linalool (see Problem 28, p. 547)
4-methylpentanoic acid
α-phenylethyl chloride
o-toluidine ($o\text{-}CH_3C_6H_4NH_2$)

25. By use of Table 18.4 tell which acid or acids each of the following is likely to be. Tell what further steps you would take to identify it or to confirm your identification.

K: m.p. 155–7°; positive halogen test; *p*-nitrobenzyl ester, m.p. 104–6°; neutralization equivalent, 158 ± 2
L: m.p. 152–4°; negative tests for halogen and nitrogen
M: m.p. 153–5°; positive chlorine test; neutralization equivalent, 188 ± 4
N: m.p. 72–3°; anilide, m.p. 117–8°; amide, m.p. 155–7°
O: m.p. 79–80°; amide, m.p. 97–9°
P: m.p. 78–80°; negative tests for halogen and nitrogen; positive test with CrO_3/H_2SO_4

Table 18.4 DERIVATIVES OF SOME CARBOXYLIC ACIDS

	Acid M.p., °C	Amide M.p., °C	Anilide M.p., °C	*p*-Nitrobenzyl ester M.p., °C
trans-Crotonic ($CH_3CH{=}CHCOOH$)	72	161	118	67
Phenylacetic	77	156	118	65
Arachidic (n-$C_{19}H_{39}COOH$)	77	108	92	—
α-Hydroxyisobutyric	79	98	136	80
Glycolic ($HOCH_2COOH$)	80	120	97	107
β-Iodopropionic	82	101	—	—
Iodoacetic	83	95	143	—
Adipic ($HOOC(CH_2)_4COOH$)	151	220	241	106
p-Nitrophenylacetic	153	198	198	—
2,5-Dichlorobenzoic	153	155	—	—
m-Chlorobenzoic	154	134	122	107
2,4,6-Trimethylbenzoic	155	—	—	188
m-Bromobenzoic	156	155	136	105
p-Chlorophenoxyacetic	158	133	125	—
Salicylic (o-HOC_6H_4COOH)	159	142	136	98

26. An unknown acid was believed to be either *o*-nitrobenzoic acid (m.p. 147°) or anthranilic acid (m.p. 146°). A 0.201-g sample neutralized 12.4 ml of 0.098 N NaOH. Which acid was it?

27. Carboxylic acid Q contained only carbon, hydrogen, and oxygen, and had a neutralization equivalent of 149 ± 3. Vigorous oxidation by $KMnO_4$ converted Q into R, m.p. 345–50°, neutralization equivalent 84 ± 2.

When Q was heated strongly with soda lime a liquid S of b.p. 135–7° distilled. Vigorous oxidation by $KMnO_4$ converted S into T, m.p. 121–2°, neutralization equivalent 123 ± 2.

U, an isomer of Q, gave upon oxidation V, m.p. 375–80°, neutralization equivalent 70 ± 2.

What were compounds Q through V? (Make use of any needed tables of physical constants.)

28. *Tropic acid* (obtained from the alkaloid atropine, found in deadly nightshade, *Atropa belladona*), $C_9H_{10}O_3$, gives a positive CrO_3/H_2SO_4 test and is oxidized by hot $KMnO_4$ to benzoic acid. Tropic acid is converted by the following sequence of reactions into *hydratropic acid*:

$$\text{tropic acid} \xrightarrow{HBr} C_9H_9O_2Br \xrightarrow{OH^-} C_9H_8O_2 \text{ (atropic acid)}$$

$$\text{atropic acid} \xrightarrow{H_2,Ni} \text{hydratropic acid } (C_9H_{10}O_2)$$

(a) What structure or structures are possible at this point for hydratropic acid? For tropic acid?

(b) When α-phenylethyl chloride is treated with magnesium in ether, the resulting solution poured over dry ice, and the mixture then acidified, there is obtained an acid whose amide has the same melting point as the amide of hydratropic acid. A mixed melting point determination shows no depression. Now what is the structure of hydratropic acid? Of tropic acid?

29. Give a structure or structures consistent with each of the following sets of nmr data:

(a) $C_3H_5ClO_2$
a doublet, δ 1.73, 3H
b quartet, δ 4.47, 1H
c singlet, δ 11.22, 1H

(b) $C_3H_5ClO_2$
a singlet, δ 3.81, 3H
b singlet, δ 4.08, 2H

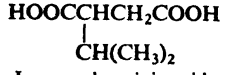
(c) $C_4H_7BrO_2$
a triplet, δ 1.30, 3H
b singlet, δ 3.77, 2H
c quartet, δ 4.23, 2H

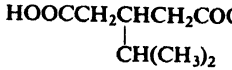
(d) $C_4H_7BrO_2$
a triplet, δ 1.08, 3H
b quintet, δ 2.07, 2H
c triplet, δ 4.23, 1H
d singlet, δ 10.97, 1H

(e) $C_4H_8O_3$
a triplet, δ 1.27, 3H
b quartet, δ 3.66, 2H
c singlet, δ 4.13, 2H
d singlet, δ 10.95, 1H

30. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 18.5 (p. 616)?

n-butyric acid
crotonic acid ($CH_3CH{=}CHCOOH$)
malic acid ($HOOCCHOHCH_2COOH$)
benzoic acid
p-nitrobenzoic acid
mandelic acid ($C_6H_5CHOHCOOH$)
p-nitrobenzyl alcohol


Isopropylsuccinic acid


β-Isopropylglutaric acid

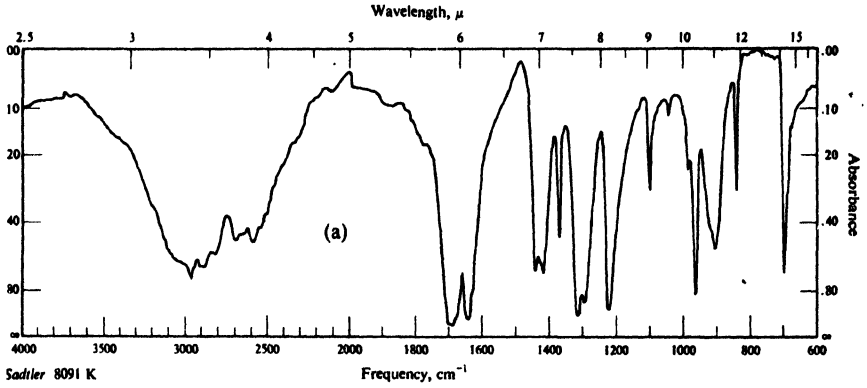
What single structure for carvotanacetone is consistent with all these facts?

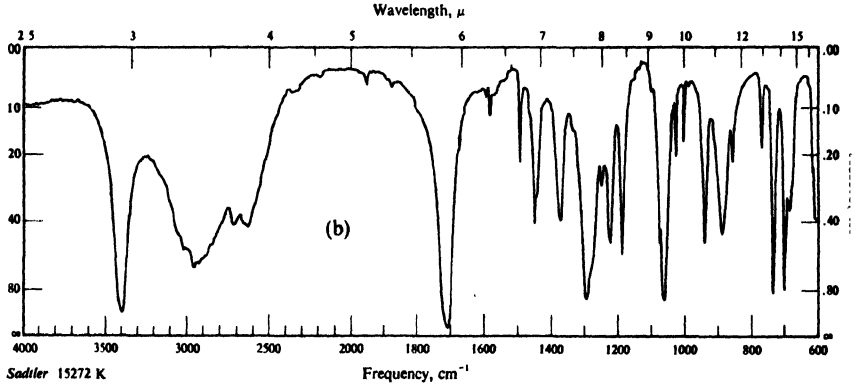
28. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 19.2 (p. 654)?

isobutyraldehyde
2-butanone
tetrahydrofuran
ethyl vinyl ether
cyclopropylcarbinol
3-buten-2-ol

29. Give a structure or structures consistent with each of the nmr spectra in Fig. 19.3 (p. 655).

30. Give the structures of compounds P, Q, and R on the basis of their infrared spectra (Fig. 19.4, p. 656) and their nmr spectra (Fig. 19.5, p. 657).





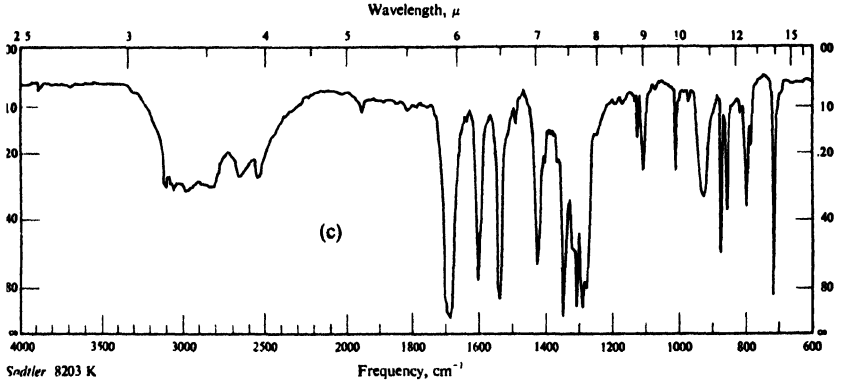


Figure 18.5. Infrared spectra for Problem 30, p. 615.

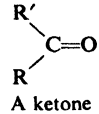
Chapter 19 Aldehydes and Ketones

Nucleophilic Addition

19.1 Structure

Aldehydes are compounds of the general formula RCHO; ketones are compounds of the general formula RR'CO. The groups R and R' may be aliphatic or aromatic.

An aldehyde

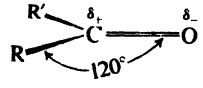


A ketone

Both aldehydes and ketones contain the carbonyl group, C O, and are often referred to collectively as **carbonyl compounds.** *It is the carbonyl group that largely determines the chemistry of aldehydes and ketones.*

It is not surprising to find that aldehydes and ketones resemble each other closely in most of their properties. However, there is a hydrogen atom attached to the carbonyl group of aldehydes, and there are two organic groups attached to the carbonyl group of ketones. This difference in structure affects their properties in two ways: (a) aldehydes are quite easily oxidized, whereas ketones are oxidized only with difficulty; (b) aldehydes are usually more reactive than ketones toward nucleophilic addition, the characteristic reaction of carbonyl compounds.

Let us examine the structure of the carbonyl group. Carbonyl carbon is joined to three other atoms by σ bonds; since these bonds utilize sp^2 orbitals (Sec. 1.10), they lie in a plane, and are 120° apart. The remaining p orbital of the carbon overlaps a p orbital of oxygen to form a π bond; carbon and oxygen are thus



joined by a double bond. The part of the molecule immediately surrounding carbonyl carbon is *flat*; oxygen, carbonyl carbon, and the two atoms directly attached to carbonyl carbon lie in a plane.

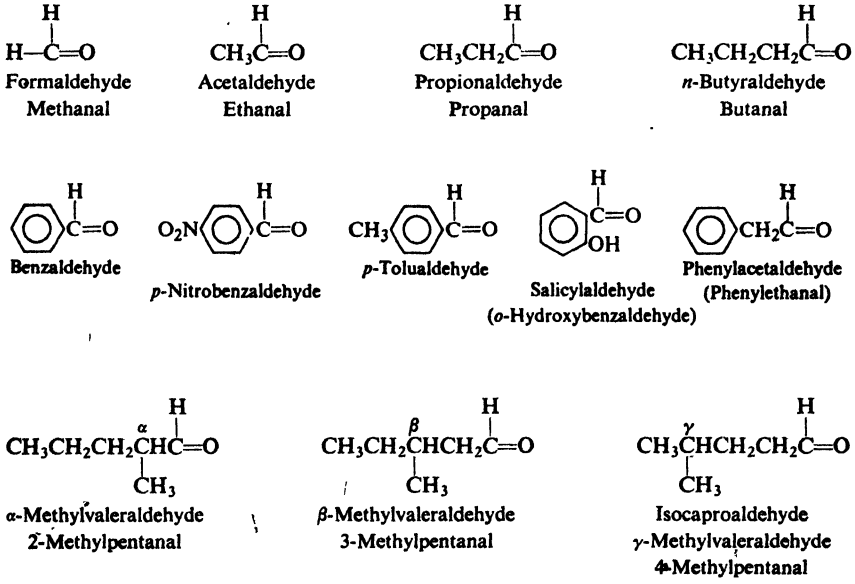
The electrons of the carbonyl double bond hold together atoms of quite different electronegativity, and hence the electrons are not equally shared; in particular, the mobile π cloud is pulled strongly toward the more electronegative atom, oxygen.

The facts are consistent with the orbital picture of the carbonyl group. Electron diffraction and spectroscopic studies of aldehydes and ketones show that carbon, oxygen, and the two other atoms attached to carbonyl carbon lie in a plane; the three bond angles of carbon are very close to 120°. The large dipole moments (2.3–2.8 D) of aldehydes and ketones indicate that the electrons of the carbonyl group are quite unequally shared. We shall see how the physical and chemical properties of aldehydes and ketones are determined by the structure of the carbonyl group.

19.2 Nomenclature

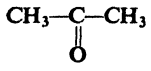
The common names of aldehydes are derived from the names of the corresponding carboxylic acids by replacing *-ic acid* by *-aldehyde*.

The IUPAC names of aldehydes follow the usual pattern. The longest chain carrying the —CHO group is considered the parent structure and is named by replacing the *-e* of the corresponding alkane by *-al*. The position of a substituent is indicated by a number, the carbonyl carbon always being considered as C–1. Here, as with the carboxylic acids, we notice that C–2 of the IUPAC name corresponds to *alpha* of the common name.

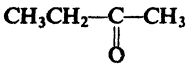


The simplest aliphatic ketone has the common name of *acetone*. For most other aliphatic ketones we name the two groups that are attached to carbonyl carbon, and follow these names by the word *ketone*. A ketone in which the carbonyl group is attached to a benzene ring is named as a *-phenone*, as illustrated below.

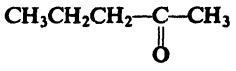
According to the IUPAC system, the longest chain carrying the carbonyl group is considered the parent structure, and is named by replacing the *-e* of the corresponding alkane with *-one*. The positions of various groups are indicated by numbers, the carbonyl carbon being given the lowest possible number.



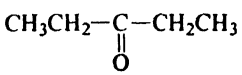
Acetone
Propanone



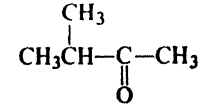
Methyl ethyl ketone
Butanone



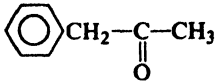
Methyl *n*-propyl ketone
2-Pentanone



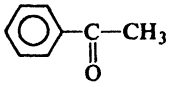
Ethyl ketone
3-Pentanone



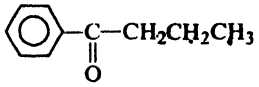
Methyl isopropyl ketone
3-Methyl-2-butanone



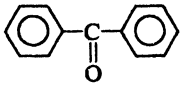
Benzyl methyl ketone
1-Phenyl-2-propanone



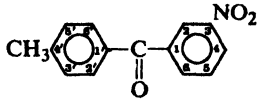
Acetophenone



n-Butyrophenone



Benzophenone



3-Nitro-4′-methylbenzophenone

19.3 Physical properties

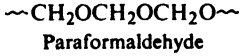
The polar carbonyl group makes aldehydes and ketones polar compounds, and hence they have higher boiling points than non-polar compounds of comparable molecular weight. By themselves, they are not capable of intermolecular hydrogen bonding since they contain hydrogen bonded only to carbon; as a result they have lower boiling points than comparable alcohols or carboxylic acids. For example, compare *n*-butyraldehyde (b.p. 76°) and methyl ethyl ketone (b.p. 80°) with *n*-pentane (b.p. 36°) and ethyl ether (b.p. 35°) on the one hand, and with *n*-butyl alcohol (b.p. 118°) and propionic acid (b.p. 141°) on the other.

The lower aldehydes and ketones are appreciably soluble in water, presumably because of hydrogen bonding between solute and solvent molecules; borderline solubility is reached at about five carbons. Aldehydes and ketones are soluble in the usual organic solvents.

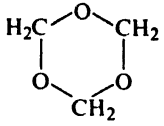
Table 19.1 ALDEHYDES AND KETONES

	M.p., °C	B.p., °C	Solub., g/100 g H_2O
Formaldehyde	− 92	− 21	v.sol.
Acetaldehyde	−121	20	∞
Propionaldehyde	− 81	49	16
n-Butyraldehyde	− 99	76	7
n-Valeraldehyde	− 91	103	sl.s
Caproaldehyde		131	sl.s
Heptaldehyde	− 42	155	0.1
Phenylacetaldehyde		194	sl.s
Benzaldehyde	− 26	178	0.3
o-Tolualdehyde		196	
m-Tolualdehyde		199	
p-Tolualdehyde		205	
Salicyaldehyde (*o*-Hydroxybenzaldehyde)	2	197	1.7
p-Hydroxybenzaldehyde	116		1.4
Anisaldehyde	3	248	0.2
Vanillin	82	285	1
Piperonal	37	263	0.2
Acetone	− 94	56	∞
Methyl ethyl ketone	− 86	80	26
2-Pentanone	− 78	102	6.3
3-Pentanone	− 41	101	5
2-Hexanone	− 35	150	2.0
3-Hexanone		124	sl.s
Methyl isobutyl ketone	− 85	119	1.9
Acetophenone	21	202	
Propiophenone	21	218	
n-Butyrophenone	11	232	
Benzophenone	48	306	

Formaldehyde is a gas (b.p. −21°), and is handled either as an aqueous solution (*Formalin*), or as one of its solid polymers: *paraformaldehyde* $(CH_2O)_n$, or *trioxane*, $(CH_2O)_3$. When dry formaldehyde is desired, as, for example, for reaction with a Grignard reagent, it is obtained by heating paraformaldehyde or trioxane.

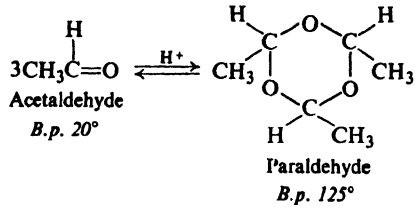


Paraformaldehyde



Trioxane

Acetaldehyde (b.p. 20°) is often generated from its higher-boiling trimer by heating the trimer with acid:



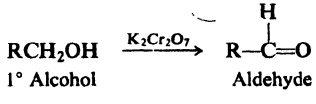
19.4 Preparation

A few of the many laboratory methods of preparing aldehydes and ketones are outlined below; most of these are already familiar to us. Some of the methods involve oxidation or reduction in which an alcohol, hydrocarbon, or acid chloride is converted into an aldehyde or ketone of the same carbon number. Other methods involve the formation of new carbon–carbon bonds, and yield aldehydes or ketones of higher carbon number than the starting materials.

Industrial preparation is generally patterned after these laboratory methods, but with use of cheaper reagents: alcohols are oxidized catalytically with air, or by dehydrogenation over hot copper.

PREPARATION OF ALDEHYDES

1. Oxidation of primary alcohols. Discussed in Secs. 16.8 and 19.5.



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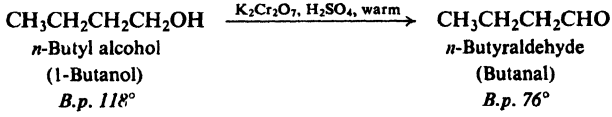
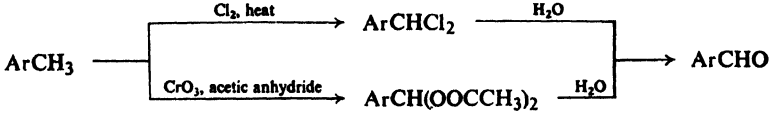
Example:



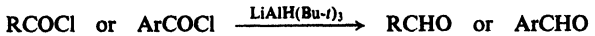
2. Oxidation of methylbenzenes. Discussed in Sec. 19.5.



Examples:

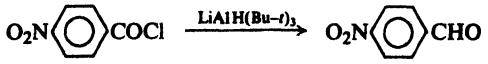
p-Nitrotoluene — *p*-Nitrobenzaldehyde

3. Reduction of acid chlorides. Discussed in Sec. 19.4.



Acid chloride — Aldehyde

Examples:

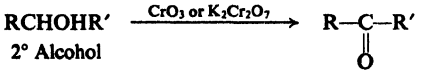


p-Nitrobenzoyl chloride — *p*-Nitrobenzaldehyde

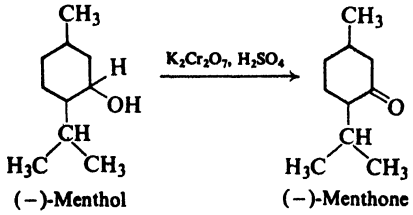
4. Reimer-Tiemann reaction. Phenolic aldehydes. Discussed in Sec. 24.12.

PREPARATION OF KETONES

1. Oxidation of secondary alcohols. Discussed in Sec. 16.8.

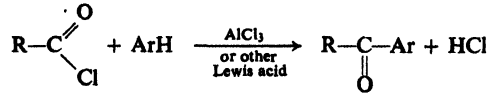


Example:



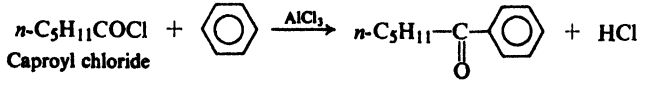
(−)-Menthol — (−)-Menthone

2. Friedel-Crafts acylation. Discussed in Sec. 19.6.



Acid chloride — Ketone

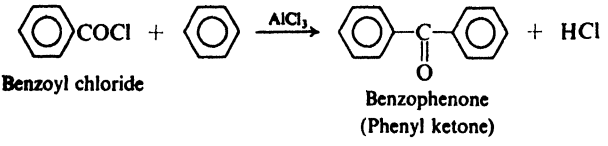
Examples:

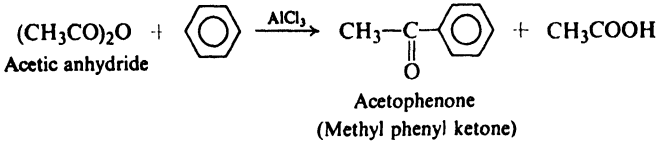


Caproyl chloride

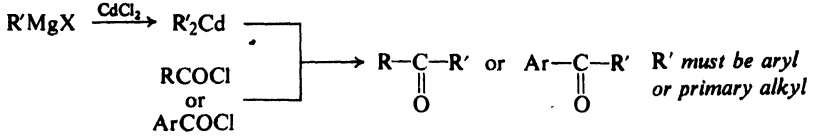
n-Pentyl phenyl ketone

No rearrangement of n-pentyl group

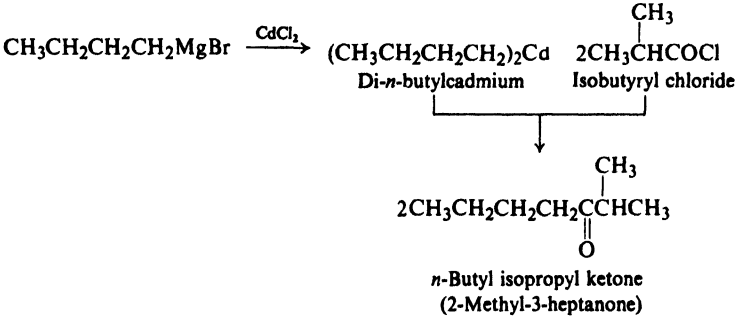


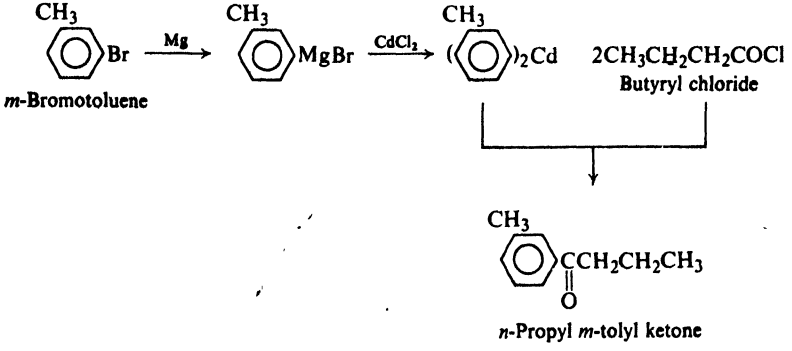


3. **Reaction of acid chlorides with organocadmium compounds.** Discussed in Sec. 19.7.



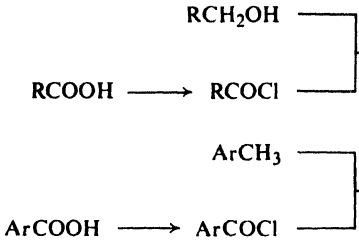
Examples:





4. **Acetoacetic ester synthesis.** Discussed in Sec. 26.3.

Depending upon the availability of starting materials, **aliphatic aldehydes** can be prepared from alcohols or acid chlorides of the same carbon skeleton, and **aromatic aldehydes** can be prepared from methylbenzenes or aromatic acid chlorides.

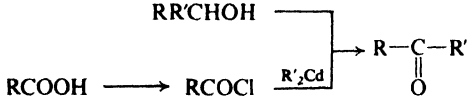


Preparation of aliphatic aldehydes

Preparation of aromatic aldehydes

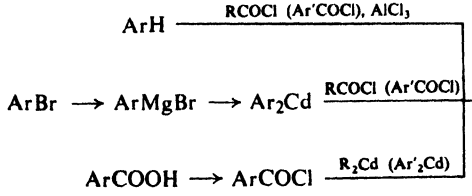
There are, in addition, a number of methods by which the aldehyde group is introduced into an aromatic ring: for example, the Reimer-Tiemann synthesis of phenolic aldehydes (Sec. 24.12).

Aliphatic ketones are readily prepared from the corresponding secondary alcohols, if these are available. More complicated aliphatic ketones can be prepared by the reaction of acid chlorides with organocadmium compounds. A



Preparation of aliphatic ketones

particularly useful method for making complicated aliphatic ketones, the acetoacetic ester synthesis, will be discussed later (Sec. 26.3). **Aromatic ketones** containing a carbonyl group attached directly to an aromatic ring are conveniently prepared by Friedel-Crafts acylation (Sec. 19.6).



Preparation of aromatic ketones

19.5 Preparation of aldehydes by oxidation methods

Aldehydes are easily oxidized to carboxylic acids by the same reagent, acidic dichromate, that is used in their synthesis. How is it possible, then, to stop the oxidation of a primary alcohol or a methylbenzene (Sec. 19.4) at the aldehyde stage? The answer is to remove the aldehyde as fast as it is formed, before it can undergo further oxidation. This "removal" can be accomplished either physically or chemically.

An aldehyde always has a lower boiling point than the alcohol from which it is formed. (Why?) Acetaldehyde, for example, has a boiling point of 20°; ethyl alcohol has a boiling point of 78°. When a solution of dichromate and sulfuric

acid is dripped into boiling ethyl alcohol, acetaldehyde is formed in a medium whose temperature is some 60 degrees above its boiling point; before it can undergo appreciable oxidation, it escapes from the reaction medium. Reaction is carried out under a fractionating column that allows aldehyde to pass but returns alcohol to the reaction vessel.

In the case of methylbenzenes, oxidation of the side chain can be interrupted by trapping the aldehyde in the form of a non-oxidizable derivative, the *gem*-diacetate (Latin: *Gemini*, twins), which is isolated and then hydrolyzed.

$$ArCH_3 \xrightarrow{\text{acetic anhydride}} ArCH(OCCH_3)_2 \xrightarrow{\text{hydrolysis}} ArCHO$$

A *gem*-diacetate
Not oxidized

Problem 19.1 A *gem*-diacetate is the ester of what "alcohol"?

Problem 19.2 Optically active alcohols in which the chiral center carries the —OH undergo racemization in acidic solutions. (Why?) Give a detailed experimental procedure (including apparatus) for studying the stereochemistry of acidic hydrolysis of *sec*-butyl benzoate that would prevent racemization of the alcohol subsequent to hydrolysis. *sec*-Butyl benzoate has a boiling point of 234°; an azeotrope of 68% *sec*-butyl alcohol and 32% water has a boiling point of 88.5°.

19.6 Preparation of ketones by Friedel-Crafts acylation

One of the most important modifications of the Friedel-Crafts reaction involves the use of acid chlorides rather than alkyl halides. An acyl group, RCO—, becomes attached to the aromatic ring, thus forming a ketone; the process is called **acylation.** As usual for the Friedel-Crafts reaction (Sec. 12.8), the aromatic ring undergoing substitution must be at least as reactive as that of a halobenzene; catalysis by aluminum chloride or another Lewis acid is required.

$$ArH + R{-}C(=O){-}Cl \xrightarrow{AlCl_3} Ar{-}C(=O){-}R + HCl$$

A ketone

The most likely mechanism for Friedel-Crafts acylation is analogous to the carbonium ion mechanism for Friedel-Crafts alkylation (Sec. 11.10), and involves the following steps:

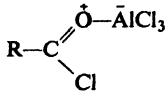
(1) $$RCOCl + AlCl_3 \longrightarrow RC{\equiv}\overset{\oplus}{O} + AlCl_4^-$$

(2) $$ArH + RC{\equiv}\overset{\oplus}{O} \longrightarrow \overset{\oplus}{Ar}(H)(COR)$$

(3) $$\overset{\oplus}{Ar}(H)(COR) + AlCl_4^- \longrightarrow Ar{-}C(=O){-}R + HCl + AlCl_3$$

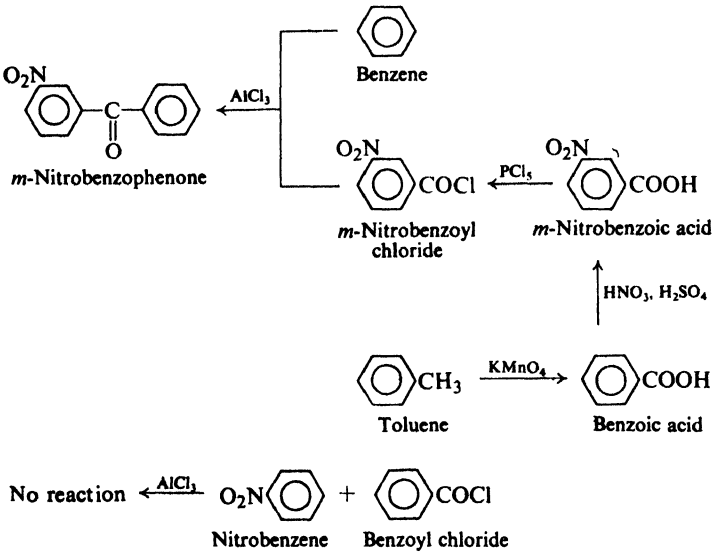
This fits the pattern of electrophilic aromatic substitution, the attacking reagent this time being the **acylium ion**, $R-C\equiv\overset{\oplus}{O}$. The acylium ion is considerably more stable than ordinary carbonium ions since in it every atom has an octet of electrons.

Alternatively, it may be that the electrophile is a complex between acid chloride and Lewis acid:



In this case, from the standpoint of the acid chloride, reaction is acid-catalyzed nucleophilic acyl substitution, of the kind discussed in Sec. 20.4, with the aromatic ring acting as the nucleophile.

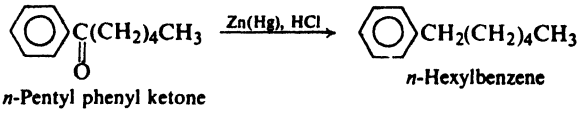
In planning the synthesis of diaryl ketones, ArCOAr', it is particularly important to select the right combination of ArCOCl and Ar'H. In the preparation of *m*-nitrobenzophenone, for example, the nitro group can be present in the acid chloride but not in the ring undergoing substitution, since as a strongly deactivating group it prevents the Friedel-Crafts reaction (Sec. 12.8).



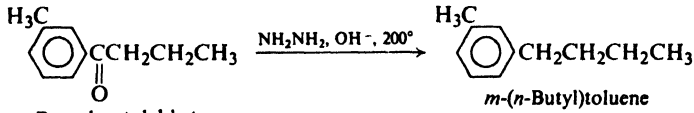
Friedel-Crafts acylation is one of the most important methods of preparing ketones in which the carbonyl group is attached to an aromatic ring. Once formed, these ketones may be converted into secondary alcohols by reduction, into tertiary alcohols by reaction with Grignard reagents, and into many other important classes of compounds, as we shall see.

Of particular importance is the conversion of the acyl group into an alkyl group. This can be accomplished by the **Clemmensen reduction** (amalgamated

zinc and concentrated hydrochloric acid), or the **Wolff-Kishner reduction** (hydrazine and base). For example:



n-Pentyl phenyl ketone — *n*-Hexylbenzene



n-Propyl *m*-tolyl ketone — *m*-(*n*-Butyl)toluene

A straight-chain alkyl group longer than ethyl generally cannot be attached in good yield to an aromatic ring by Friedel-Crafts alkylation because of rearrangement (Sec. 12.7). Such a group is readily introduced, however, in two steps: (1) formation of a ketone by Friedel-Crafts acylation (or by the reaction of an organocadmium compound with an acyl chloride, described in the following section); (2) Clemmensen or Wolff-Kishner reduction of the ketone.

19.7 Preparation of ketones by use of organocadmium compounds

Grignard reagents react with dry cadmium chloride to yield the corresponding organocadmium compounds, which react with acid chlorides to yield ketones:

$$2R'MgX + CdCl_2 \longrightarrow R'_2Cd + 2MgXCl$$

R′ must be aryl or primary alkyl

$$R'_2Cd + 2RCOCl \longrightarrow 2R{-}\underset{\underset{O}{\|}}{C}{-}R' + CdCl_2$$

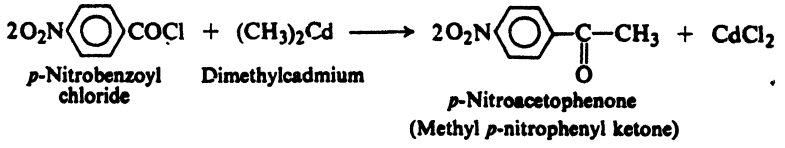
A ketone

Here, as in its other reactions (Sec. 20.7), the acid chloride is undergoing nucleophilic substitution, the nucleophile being the basic alkyl or aryl group of the organometallic compound.

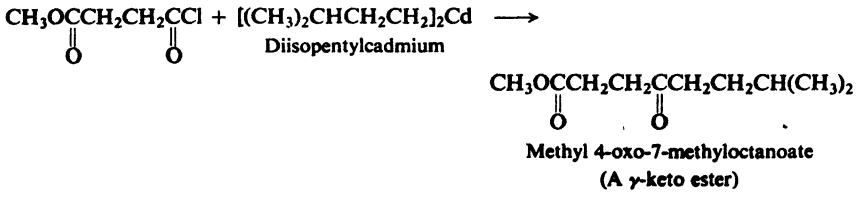
Only organocadmium compounds containing aryl or primary alkyl groups are stable enough for use. In spite of this limitation, the method is one of the most valuable for the synthesis of ketones.

Grignard reagents themselves react readily with acid chlorides, but the products are usually tertiary alcohols; these presumably result from reaction of initially formed ketones with more Grignard reagent. (If tertiary alcohols are desired, they are better prepared from esters than from acid chlorides, Sec. 20.21.) Organocadmium compounds, being less reactive, do not react with ketones.

The comparatively low reactivity of organocadmium compounds not only makes the synthesis of ketones possible, but in addition widens the applicability of the method. Organocadmium compounds do not react with many of the functional groups with which the Grignard reagent does react: $-NO_2$, $-CN$, $-CO-$, $-COOR$, for example. Consequently, the presence of one of these groups in the acid chloride molecule does not interfere with the synthesis of a ketone (compare with Sec. 15.15). For example:



p-Nitrobenzoyl chloride — Dimethylcadmium — *p*-Nitroacetophenone (Methyl *p*-nitrophenyl ketone)



Methyl 4-oxo-7-methyloctanoate (A γ-keto ester)

Problem 19.3 Would it be feasible to make *p*-nitroacetophenone via the reaction between di(*p*-nitrophenyl)cadmium, $(p\text{-}O_2NC_6H_4)_2Cd$, and acetyl chloride?

19.8 Reactions. Nucleophilic addition

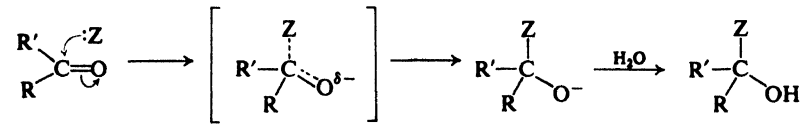
The carbonyl group, C=O, governs the chemistry of aldehydes and ketones. It does this in two ways: (a) by providing a site for nucleophilic addition, and (b) by increasing the acidity of the hydrogen atoms attached to the *alpha* carbon. Both these effects are quite consistent with the structure of the carbonyl group and, in fact, are due to the same thing: the ability of oxygen to accommodate a negative charge.

In this section, we shall examine the carbonyl group as a site for nucleophilic addition; in Sec. 21.1, we shall see how the acid-strengthening effect arises.

The carbonyl group contains a carbon–oxygen double bond; since the mobile π electrons are pulled strongly toward oxygen, carbonyl carbon is electron-deficient and carbonyl oxygen is electron-rich. Because it is flat, this part of the molecule is open to relatively unhindered attack from above or below, in a direction perpendicular to the plane of the group. It is not surprising that this accessible, polarized group is highly reactive.

What kind of reagents will attack such a group? Since the important step in these reactions is the formation of a bond to the electron-deficient (acidic) carbonyl carbon, the carbonyl group is most susceptible to attack by electron-rich, nucleophilic reagents, that is, by bases. **The typical reaction of aldehydes and ketones is nucleophilic addition.**

Nucleophilic addition



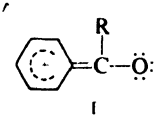
Reactant	Transition state	Product
Trigonal	*Becoming tetrahedral*	*Tetrahedral*
	Partial negative charge on oxygen	*Negative charge on oxygen*

As might be expected, we can get a much truer picture of the reactivity of the carbonyl group by looking at the transition state for attack by a nucleophile. In the reactant, carbon is trigonal. In the transition state, carbon has begun to acquire the tetrahedral configuration it will have in the product; the attached groups are thus being brought closer together. We might expect moderate steric hindrance in this reaction; that is, larger groups (R and R') will tend to resist crowding more than smaller groups. But the transition state is a relatively roomy one compared, say, with the transition state for an S_N2 reaction, with its pentavalent carbon; it is this comparative uncrowdedness that we are really referring to when we say that the carbonyl group is "accessible" to attack.

In the transition state, oxygen has started to acquire the electrons—and the negative charge—that it will have in the product. *It is the tendency of oxygen to acquire electrons—its ability to carry a negative charge—that is the real cause of the reactivity of the carbonyl group toward nucleophiles.* (The polarity of the carbonyl group is not the *cause* of the reactivity; it is simply another *manifestation* of the electronegativity of oxygen.)

Aldehydes generally undergo nucleophilic addition more readily than ketones. This difference in reactivity is consistent with the transition states involved, and seems to be due to a combination of electronic and steric factors. A ketone contains a second alkyl or aryl group where an aldehyde contains a hydrogen atom. A second alkyl or aryl group of a ketone is larger than the hydrogen of an aldehyde, and resists more strongly the crowding together in the transition state. An alkyl group releases electrons, and thus destabilizes the transition state by intensifying the negative charge developing on oxygen.

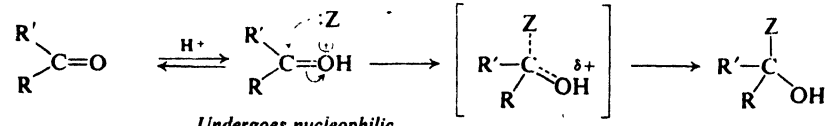
We might have expected an aryl group, with its electron-withdrawing inductive effect (Problem 18.7, p. 600), to stabilize the transition state and thus speed up reaction; however, it seems to stabilize the *reactant* even more, by resonance (contribution by I), and thus causes net deactivation.



I

If acid is present, hydrogen ion becomes attached to carbonyl oxygen. This prior protonation lowers the E_{act} for nucleophilic attack, since it permits oxygen to

Acid-catalyzed nucleophilic addition



Undergoes nucleophilic attack more readily

acquire the π electrons without having to accept a negative charge. Thus nucleophilic addition to aldehydes and ketones can be catalyzed by acids (sometimes, by *Lewis* acids).

REACTIONS OF ALDEHYDES AND KETONES

1. Oxidation. Discussed in Sec. 19.9.

(a) Aldehydes

$$RCHO \text{ or } ArCHO \xrightarrow[KMnO_4 \text{ or } K_2Cr_2O_7]{Ag(NH_3)_2^+} RCOOH \text{ or } ArCOOH$$

Used chiefly for detection of aldehydes

Examples:

$$CH_3CHO + 2Ag(NH_3)_2^+ + 3OH^- \longrightarrow 2Ag + CH_3COO^- + 4NH_3 + 2H_2O$$

Colorless solution — *Silver mirror* — *Tollens' test*

(b) Methyl ketones

$$R{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \text{ or } Ar{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \xrightarrow{OX^-} RCOO^- \text{ or } ArCOO^- + CHX_3$$

Haloform reaction

Examples:

$$C_2H_5{-}\underset{\underset{O}{\|}}{C}{-}CH_3 + 3OI^- \longrightarrow C_2H_5COO^- + CHI_3 + 2OH^-$$

Iodoform
Yellow; m.p. 119°

$$CH_3CH{=}\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow[60°]{KOCl} CHCl_3 + CH_3C{=}CHCOOK \xrightarrow{H_2SO_4} CH_3C{=}CHCOOH$$

Mesityl oxide
(4-Methyl-3-penten-2-one)

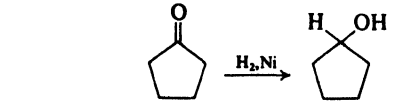
3-Methyl-2-butenoic acid

2. Reduction

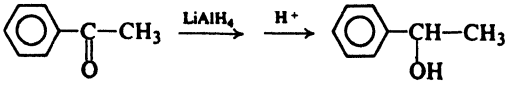
(a) Reduction to alcohols. Discussed in Sec. 19.10.

$$\text{>C=O} \xrightarrow[LiAlH_4 \text{ or } NaBH_4; \text{ then } H^+]{H_2 + Ni, Pt, \text{ or } Pd} \text{>CH(OH)}$$

Examples:

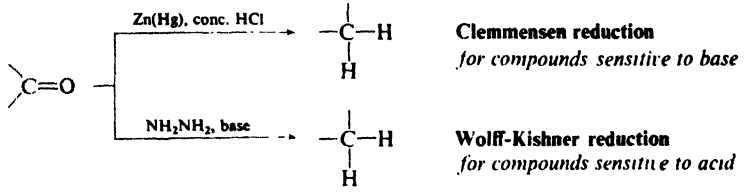


Cyclopentanone — Cyclopentanol

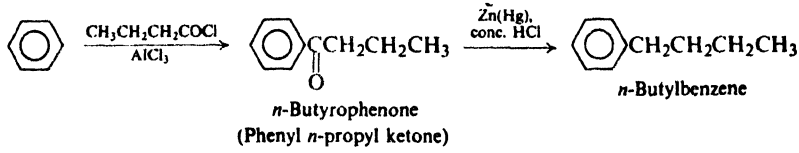


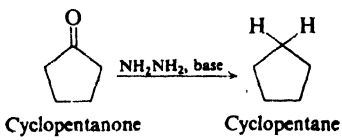
Acetophenone — α-Phenylethyl alcohol

(b) Reduction to hydrocarbons. Discussed in Sec. 19.10.



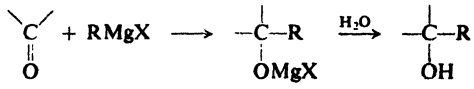
Examples



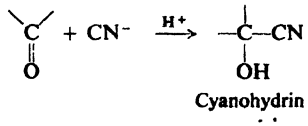


(c) Reductive amination. Discussed in Sec. 22.11.

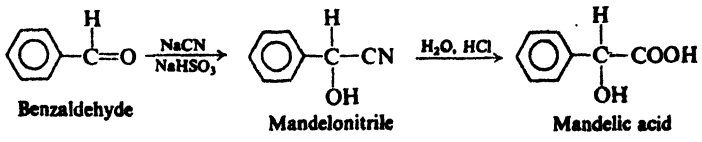
3. Addition of Grignard reagents. Discussed in Secs. 15.12–15.15 and 19.11.

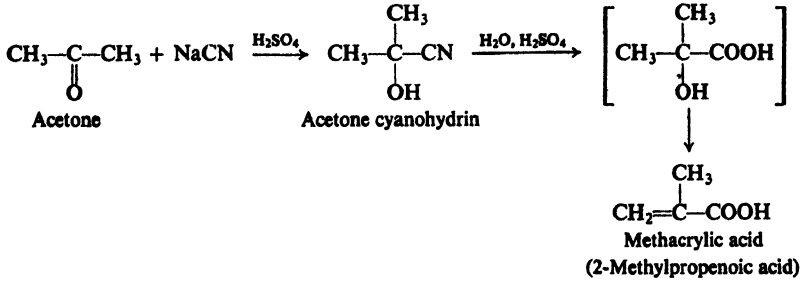


4. Addition of cyanide. Cyanohydrin formation. Discussed in Sec. 19.12.

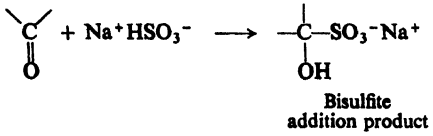


Examples:



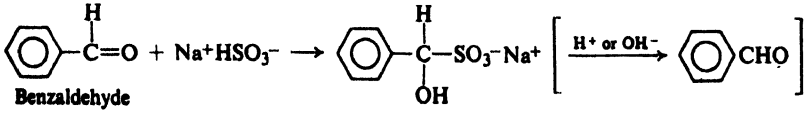


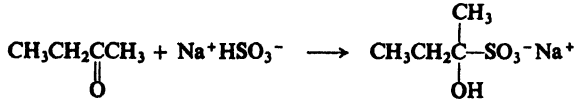
5. Addition of bisulfite. Discussed in Sec. 19.13.

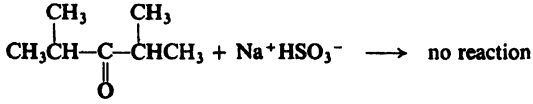


Used in purification
Not for hindered ketones

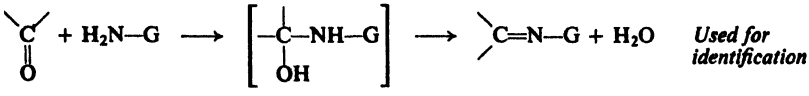
Examples:







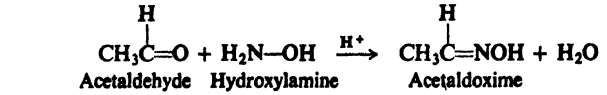
6. Addition of derivatives of ammonia. Discussed in Sec. 19.14.

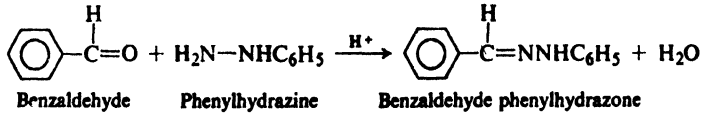


Used for identification

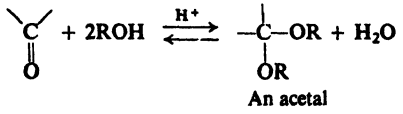
H_2N—G		Product	
H_2N—OH	Hydroxylamine	C=NOH	Oxime
H_2N—NH_2	Hydrazine	C=NNH_2	Hydrazone
H_2N—NHC_6H_5	Phenylhydrazine	C=$NNHC_6H_5$	Phenylhydrazone
H_2N—$NHCONH_2$	Semicarbazide	C=$NNHCONH_2$	Semicarbazone

Examples:

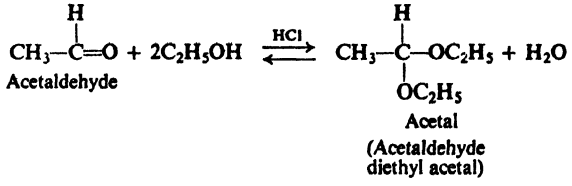




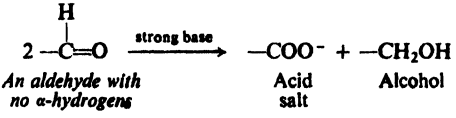
7. Addition of alcohols. Acetal formation. Discussed in Sec. 19.15.



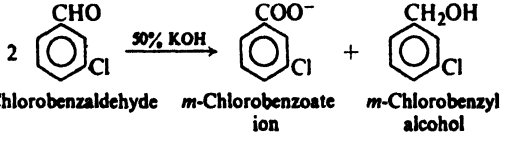
Example:

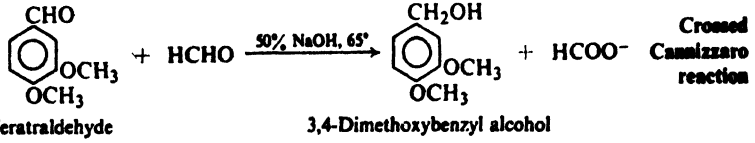


8. Cannizzaro reaction. Discussed in Sec. 19.16.

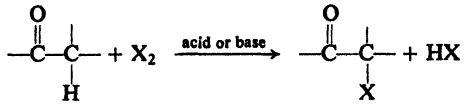


Examples:





9. Halogenation of ketones. Discussed in Secs. 21.3–21.4.



α-Halogenation

$X_2 = Cl_2, Br_2, I_2$

10. Addition of carbanions.

(a) Aldol condensation. Discussed in Secs. 21.5–21.8.

(b) Reactions related to aldol condensation. Discussed in Sec. 21.9.

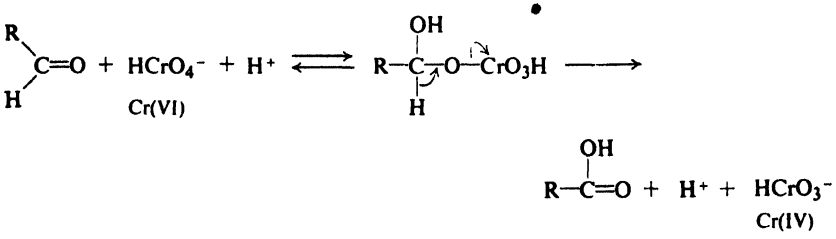
(c) Wittig reaction. Discussed in Sec. 21.10.

(d) Reformatsky reaction. Discussed in Sec. 21.13.

19.9 Oxidation

Aldehydes are easily oxidized to carboxylic acids; ketones are not. Oxidation is the reaction in which aldehydes differ most from ketones, and this difference stems directly from their difference in structure: by definition, an aldehyde has a hydrogen atom attached to the carbonyl carbon, and a ketone has not. Regardless of exact mechanism, this hydrogen is abstracted in oxidation, either as a proton or an atom, and the analogous reaction for a ketone—abstraction of an alkyl or aryl group—does not take place.

Oxidation by chromic acid, for example, seems to involve a rate-determining step analogous to that for oxidation of secondary alcohols (Sec. 16.8): elimination (again possibly by a cyclic mechanism) from an intermediate chromate ester.



The intermediate is the chromate ester of the aldehyde *hydrate*, $RCH(OH)_2$; it seems likely that the ester is formed *from* the hydrate, which exists in equilibrium with the aldehyde. In that case, what we are dealing with is essentially oxidation of a special kind of alcohol—a *gem*-diol.

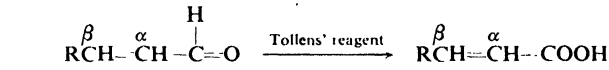
Aldehydes are oxidized not only by the same reagents that oxidize primary and secondary alcohols—permanganate and dichromate—but also by the very mild oxidizing agent silver ion. Oxidation by silver ion requires an alkaline medium; to prevent precipitation of the insoluble silver oxide, a complexing agent is added: ammonia

Tollens' reagent contains the silver ammonia ion, $Ag(NH_3)_2^+$. Oxidation of the aldehyde is accompanied by reduction of silver ion to free silver (in the form of a *mirror* under the proper conditions).

$$\underset{\text{Colorless solution}}{RCHO + Ag(NH_3)_2^+} \longrightarrow \underset{\text{Silver mirror}}{RCOO^- + Ag}$$

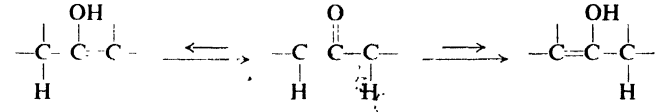
(Oxidation by complexed cupric ion is a characteristic of certain substituted carbonyl compounds, and will be taken up with *carbohydrates* in Sec. 34.6.)

Oxidation by Tollens' reagent is useful chiefly for detecting aldehydes, and in particular for differentiating them from ketones (see Sec. 19.17). The reaction is of value in synthesis in those cases where aldehydes are more readily available than the corresponding acids: in particular, for the synthesis of unsaturated acids from the unsaturated aldehydes obtained from the aldol condensation (Sec. 21.6), where advantage is taken of the fact that Tollens' reagent does not attack carbon–carbon double bonds.



α,β-Unsaturated aldehyde — α,β-Unsaturated acid

Oxidation of ketones requires breaking of carbon–carbon bonds, and (except for the haloform reaction) takes place only under vigorous conditions. Cleavage involves the double bond of the *enol* form (Sec. 8.13) and, where the structure

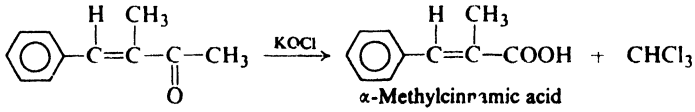


Enol — Ketone — Enol

permits, occurs on either side of the carbonyl group; in general, then, mixtures of carboxylic acids are obtained (see Sec. 6.29).

Problem 19.4 Predict the product(s) of vigorous oxidation of: (a) 3-hexanone; (b) cyclohexanone.

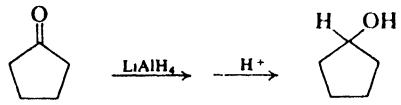
Methyl ketones are oxidized smoothly by means of hypohalite in the haloform reaction (Sec. 16.11). Besides being commonly used to detect these ketones (Sec. 19.17), this reaction is often useful in synthesis, hypohalite having the special advantage of not attacking carbon–carbon double bonds. For example:



Available by aldol condensation (Sec. 21.8) — α-Methylcinnamic acid

19.10 Reduction

Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, either by catalytic hydrogenation or by use of chemical reducing agents like lithium aluminum hydride, $LiAlH_4$. Such reduction is useful for the preparation of certain alcohols that are less available than the corresponding carbonyl compounds, in particular carbonyl compounds that can be obtained by the aldol condensation (Sec. 21.7). For example:

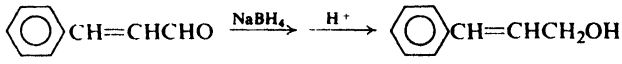


Cyclopentanone Cyclopentanol

$$CH_3CH{=}CHCHO \xrightarrow{H_2,\,Ni} CH_3CH_2CH_2CH_2OH$$

Crotonaldehyde — *n*-Butyl alcohol

From aldol condensation of acetaldehyde

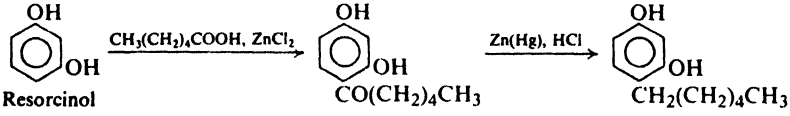


Cinnamaldehyde Cinnamyl alcohol

From aldol condensation of benzaldehyde and acetaldehyde (Sec. 21.8)

Sodium borohydride, $NaBH_4$, does not reduce carbon–carbon double bonds, not even those conjugated with carbonyl groups, and is thus useful for the reduction of such unsaturated carbonyl compounds to unsaturated alcohols.

Aldehydes and ketones can be reduced to hydrocarbons by the action (a) of amalgamated zinc and concentrated hydrochloric acid, the **Clemmensen reduction**; or (b) of hydrazine, NH_2NH_2, and a strong base like KOH or potassium *tert*-butoxide, the **Wolff-Kishner reduction**. These are particularly important when applied to the alkyl aryl ketones obtained from Friedel-Crafts acylation, since this reaction sequence permits, indirectly, the attachment of straight alkyl chains to the benzene ring. For example:



Resorcinol

4-*n*-Hexylresorcinol

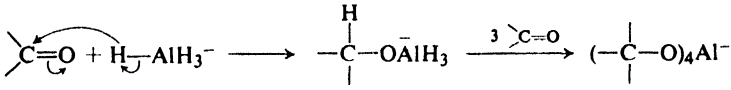
Used as an antiseptic

A special sort of oxidation and reduction, the *Cannizzaro reaction*, will be discussed in Sec. 19.16.

Let us look a little more closely at reduction by metal hydrides. Alcohols are formed from carbonyl compounds, smoothly and in high yield, by the action of such compounds as lithium aluminum hydride, $LiAlH_4$. Here again, we see

$$4R_2C{=}O + LiAlH_4 \longrightarrow (R_2CHO)_4AlLi \xrightarrow{H_2O} 4R_2CHOH + LiOH + Al(OH)_3$$

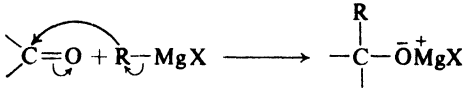
nucleophilic addition: this time the nucleophile is hydrogen transferred with a pair of electrons—as a hydride ion, $H{:}^-$—from the metal to carbonyl carbon:



19.11 Addition of Grignard reagents

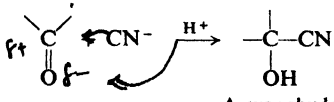
The addition of Grignard reagents to aldehydes and ketones has already been discussed as one of the most important methods of preparing complicated alcohols (Secs. 15.12–15.15).

The organic group, transferred *with a pair of electrons* from magnesium to carbonyl carbon, is a powerful nucleophile.



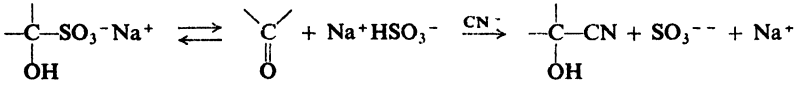
19.12 Addition of cyanide

The elements of HCN add to the carbonyl group of aldehydes and ketones to yield compounds known as **cyanohydrins**:

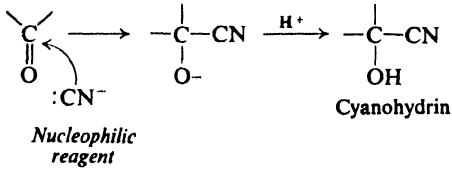


A cyanohydrin

The reaction is often carried out by adding mineral acid to a mixture of the carbonyl compound and aqueous sodium cyanide. In a useful modification, cyanide is added to the bisulfite addition product (Sec. 19.13) of the carbonyl compound, the bisulfite ion serving as the necessary acid:

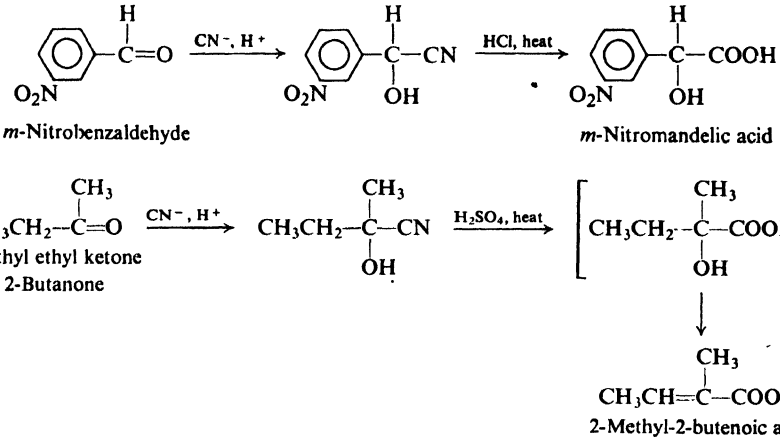


Addition appears to involve nucleophilic attack on carbonyl carbon by the strongly basic cyanide ion; subsequently (or possibly simultaneously) oxygen accepts a hydrogen ion to form the cyanohydrin product:



Although it is the elements of HCN that become attached to the carbonyl group, a highly acidic medium—in which the concentration of un-ionized HCN is highest—actually retards reaction. This is to be expected, since the very weak acid HCN is a poor source of cyanide ion.

Cyanohydrins are nitriles, and their principal use is based on the fact that, like other nitriles, they undergo hydrolysis; in this case the products are α-hydroxy-acids or unsaturated acids. For example:

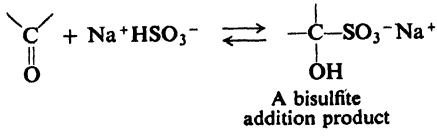


Problem 19.5 Each of the following is converted into the cyanohydrin, and the products are separated by careful fractional distillation or crystallization. For each reaction tell how many fractions will be collected, and whether each fraction, as collected, will be optically active or inactive, resolvable or non-resolvable.

(a) Acetaldehyde; (b) benzaldehyde; (c) acetone;
(d) R-(+)-glyceraldehyde, $CH_2OHCHOHCHO$; (e) (±)-glyceraldehyde.
(f) How would your answer to each of the above be changed if each mixture were subjected to hydrolysis to hydroxy acids before fractionation?

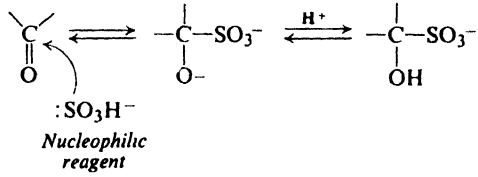
19.13 Addition of bisulfite

Sodium bisulfite adds to most aldehydes and to many ketones (especially methyl ketones) to form bisulfite addition products:

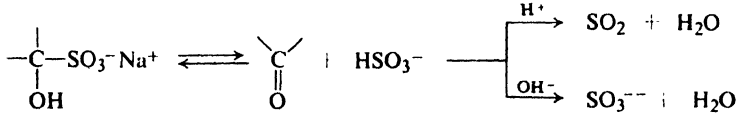


The reaction is carried out by mixing the aldehyde or ketone with a concentrated aqueous solution of sodium bisulfite; the product separates as a crystalline solid. Ketones containing bulky groups usually fail to react with bisulfite, presumably for steric reasons.

Addition involves nucleophilic attack by bisulfite ion on carbonyl carbon, followed by attachment of a hydrogen ion to carbonyl oxygen:



Like other carbonyl addition reactions, this one is reversible. Addition of acid or base destroys the bisulfite ion in equilibrium with the addition product, and regenerates the carbonyl compound.

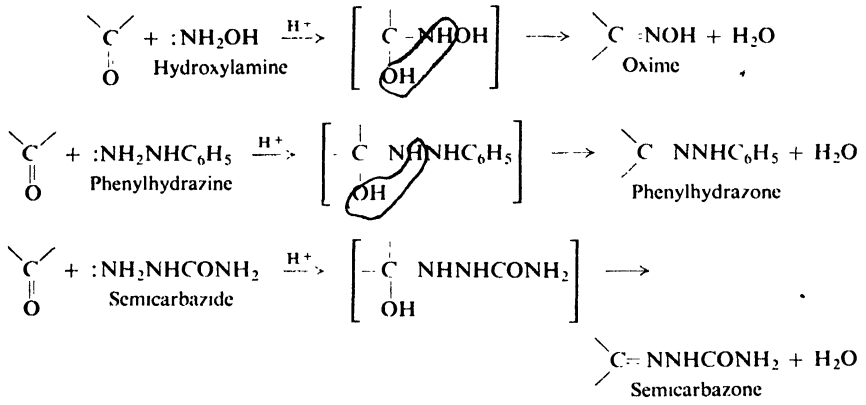


Bisulfite addition products are generally prepared for the purpose of separating a carbonyl compound from non-carbonyl compounds. The carbonyl compound can be purified by conversion into its bisulfite addition product, separation of the crystalline addition product from the non-carbonyl impurities, and subsequent regeneration of the carbonyl compound. A non-carbonyl compound can be freed of carbonyl impurities by washing it with aqueous sodium bisulfite; any contaminating aldehyde or ketone is converted into its bisulfite addition product which, being somewhat soluble in water, dissolves in the aqueous layer.

Problem 19.6 Suggest a practical situation that might arise in the laboratory in which you would need to (a) separate an aldehyde from undesired non-carbonyl materials; (b) remove an aldehyde that is contaminating a non-carbonyl compound. Describe how you could carry out the separations, telling exactly what you would do and see.

19.14 Addition of derivatives of ammonia

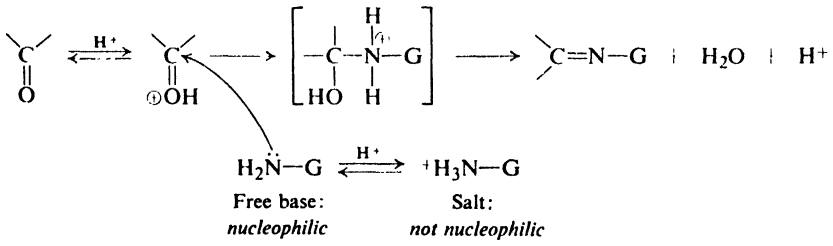
Certain compounds related to ammonia add to the carbonyl group to form derivatives that are important chiefly for the characterization and identification of aldehydes and ketones (Sec. 19.17). The products contain a carbon–nitrogen double bond resulting from elimination of a molecule of water from the initial addition products. Some of these reagents and their products are:



Like ammonia, these derivatives of ammonia are basic, and therefore react with acids to form salts: hydroxylamine hydrochloride, $HONH_3^+Cl^-$; phenylhydrazine hydrochloride, $C_6H_5NHNH_3^+Cl^-$; and semicarbazide hydrochloride, $NH_2CONHNH_3^+Cl^-$. The salts are less easily oxidized by air than the free bases, and it is in this form that the reagents are best preserved and handled. When needed, the basic reagents are liberated from their salts in the presence of the carbonyl compound by addition of a base, usually sodium acetate.

$$\underset{\substack{\text{Phenylhydrazine}\\\text{hydrochloride}\\\textit{Stronger acid}}}{C_6H_5NHNH_3^+Cl^-} + \underset{\substack{\text{Sodium}\\\text{acetate}\\\textit{Stronger base}}}{CH_3COO\ Na^+} \rightleftharpoons \underset{\substack{\text{Phenylhydrazine}\\\textit{Weaker base}}}{C_6H_5NHNH_2} + \underset{\substack{\text{Acetic acid}\\\textit{Weaker acid}}}{CH_3COOH} + Na^+Cl^-$$

It is often necessary to adjust the reaction medium to just the right acidity. Addition involves nucleophilic attack by the basic nitrogen compound on carbonyl carbon. Protonation of carbonyl oxygen makes carbonyl carbon more susceptible to nucleophilic attack; in so far as the carbonyl compound is concerned, then, addition will be favored by high acidity. But the ammonia derivative, $H_2N—G$, can also undergo protonation to form the ion, $^+H_3N—G$, which lacks unshared electrons and is no longer nucleophilic; in so far as the nitrogen compound is concerned, then, addition is favored by low acidity. The conditions under which



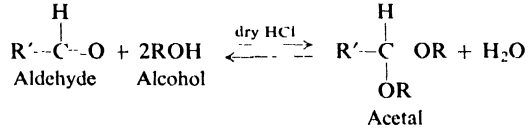
addition proceeds most rapidly are thus the result of a compromise: the solution must be acidic enough for an appreciable fraction of the carbonyl compound to be

protonated, but not so acidic that the concentration of the free nitrogen compound is too low. The exact conditions used depend upon the basicity of the reagent, and upon the reactivity of the carbonyl compound.

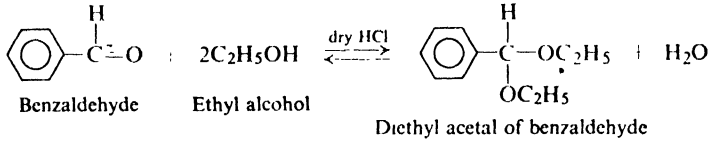
Problem 19.7 Semicarbazide (1 mole) is added to a mixture of cyclohexanone (1 mole) and benzaldehyde (1 mole). If the product is isolated immediately, it consists almost entirely of the semicarbazone of cyclohexanone; if the product is isolated after several hours, it consists almost entirely of the semicarbazone of benzaldehyde. How do you account for these observations? (*Hint:* See Sec. 8.22.)

19.15 Addition of alcohols. Acetal formation

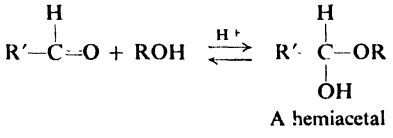
Alcohols add to the carbonyl group of aldehydes in the presence of anhydrous acids to yield **acetals**:



The reaction is carried out by allowing the aldehyde to stand with an excess of the anhydrous alcohol and a little anhydrous acid, usually hydrogen chloride. In the preparation of ethyl acetals the water is often removed as it is formed by means of the azeotrope of water, benzene, and ethyl alcohol (b.p. 64.9°, Sec. 15.6). (Simple *ketals* are usually difficult to prepare by reaction of ketones with alcohols, and are made in other ways.)

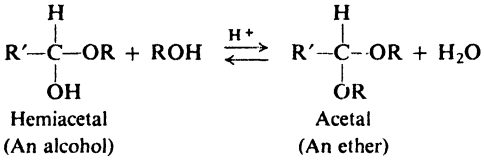


There is good evidence that in alcoholic solution an aldehyde exists in equilibrium with a compound called a **hemiacetal**:

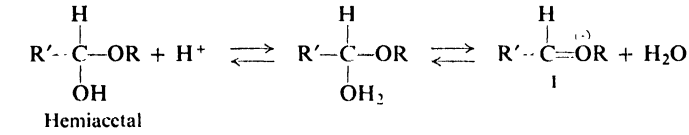


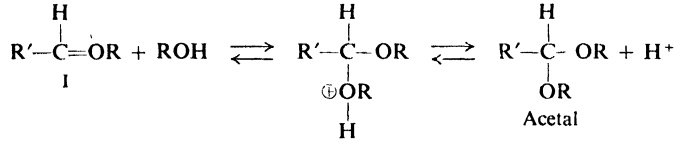
A hemiacetal is formed by the addition of the nucleophilic alcohol molecule to the carbonyl group; it is both an ether and an alcohol. With a few exceptions, hemiacetals are too unstable to be isolated.

In the presence of acid the hemiacetal, acting as an alcohol, reacts with more of the solvent alcohol to form the acetal, an ether:



The reaction involves the formation (step 1) of the ion I, which then combines (step 2) with a molecule of alcohol to yield the protonated acetal. As we can see,

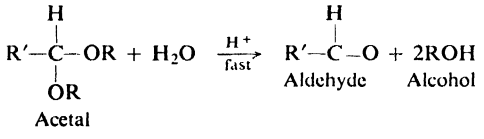




this mechanism is strictly analogous to the S_N1 route we have previously encountered (Sec. 17.3) for the formation of ethers.

Acetal formation thus involves (a) nucleophilic addition to a carbonyl group, and (b) ether formation via a carbonium ion.

Acetals have the structure of ethers and, like ethers, are cleaved by acids and are stable toward bases. Acetals differ from ethers, however, in the extreme *ease* with which they undergo acidic cleavage; they are rapidly converted even at room



temperature into the aldehyde and alcohol by dilute mineral acids. The mechanism of hydrolysis is exactly the reverse of that by which acetals are formed.

Problem 19.8 Account for the fact that anhydrous acids bring about formation of acetals whereas aqueous acids bring about hydrolysis of acetals.

The heart of the chemistry of acetals is the "carbonium" ion,

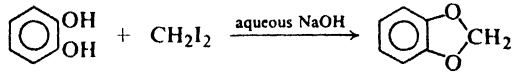
which is a hybrid of structures Ia and Ib. Contribution from Ib, in which every atom has an octet of electrons, makes this ion considerably more stable than ordinary carbonium ions. (Indeed, Ib *alone* may pretty well represent the ion, in which case it is not a carbonium ion at all but an *oxonium* ion.)

Now, generation of this ion is the rate-determining step both in formation of acetals (reading to the right in equation 1) and in their hydrolysis (reading to the left in equation 2). The same factor—the providing of electrons by oxygen—that stabilizes the ion also stabilizes the transition state leading to its formation. Generation of the ion is speeded up, and along with it the entire process: formation or hydrolysis of the acetal.

(Oddly enough, oxygen causes activation in *nucleophilic* substitution here in precisely the same way it activates aromatic ethers toward *electrophilic* substitution (Sec. 17.8); the common feature is, of course, development of a positive charge in the transition state of the rate-determining step.)

We shall find the chemistry of hemiacetals and acetals to be fundamental to the study of carbohydrates (Chaps. 34 and 35).

Problem 19.9 (a) The following reaction is an example of what familiar synthesis?



II

(b) To what family of compounds does II belong? (c) What will II yield upon treatment with acid? With base?

Problem 19.10 Suggest a convenient chemical method for separating unreacted benzaldehyde from benzaldehyde diethyl acetal. (Compare Problem 19.6, p. 639.)

Problem 19.11 *Glyceraldehyde*, $CH_2OHCHOHCHO$, is commonly made from the acetal of acrolein, $CH_2{=}CH{-}CHO$. Show how this could be done. Why is acrolein itself not used?

Problem 19.12 How do you account for the following differences in ease of hydrolysis?

(a) $RC(OR')_3$ ≫ $RCH(OR')_2$ ≫ RCH_2OR'
An ortho ester — An acetal — An ether

(b) $R_2C(OR')_2$ > $RCH(OR')_2$ > $H_2C(OR')_2$
A ketal — An acetal — A formal

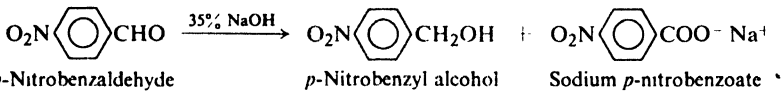
Problem 19.13 The simplest way to prepare an aldehyde, $RCH^{18}O$, labeled at the carbonyl oxygen, is to allow an ordinary aldehyde to stand in $H_2{}^{18}O$ in the presence of a little acid. Suggest a detailed mechanism for this oxygen exchange.

19.16 Cannizzaro reaction

In the presence of concentrated alkali, aldehydes containing no α-hydrogens undergo self-oxidation-and-reduction to yield a mixture of an alcohol and a salt

of a carboxylic acid. This reaction, known as the **Cannizzaro reaction**, is generally brought about by allowing the aldehyde to stand at room temperature with concentrated aqueous or alcoholic hydroxide. (Under these conditions an aldehyde containing α-hydrogens would undergo aldol condensation faster, Sec. 21.5.)

$$\underset{\text{Formaldehyde}}{2HCHO} \xrightarrow{50\%\ NaOH} \underset{\text{Methanol}}{CH_3OH} + \underset{\text{Sodium formate}}{HCOO^-Na^+}$$

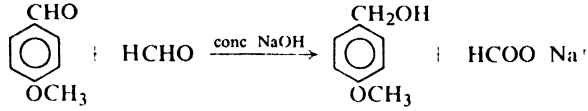


p-Nitrobenzaldehyde — *p*-Nitrobenzyl alcohol — Sodium *p*-nitrobenzoate

In general, a mixture of two aldehydes undergoes a Cannizzaro reaction to yield all possible products. If one of the aldehydes is formaldehyde, however, reaction yields almost exclusively sodium formate and the alcohol corresponding to the other aldehyde:

$$ArCHO + HCHO \xrightarrow{\text{conc. NaOH}} ArCH_2OH + HCOO^-Na^+$$

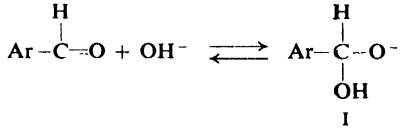
The high tendency for formaldehyde to undergo oxidation makes this **crossed Cannizzaro reaction** a useful synthetic tool. For example:



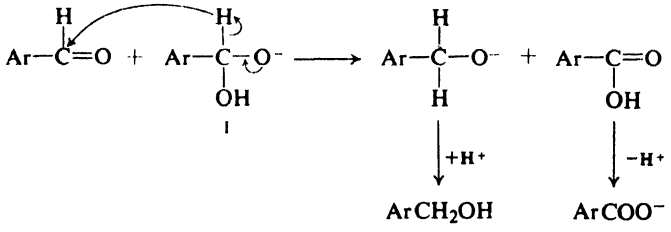
Anisaldehyde (*p*-Methoxybenzaldehyde) — *p*-Methoxybenzyl alcohol

Evidence, chiefly from kinetics and experiments with isotopically labeled compounds, indicates that even this seemingly different reaction follows the familiar pattern for carbonyl compounds: nucleophilic addition. Two successive additions

(1)

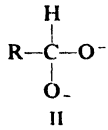


(2)



are involved: addition of hydroxide ion (step 1) to give intermediate I; and addition of a hydride ion from I (step 2) to a second molecule of aldehyde. The presence of the negative charge on I aids in the loss of hydride ion.

Problem 19.14 In the case of some aldehydes there is evidence that intermediate II is the hydride donor in the Cannizzaro reactions. (a) How would II be formed from I?



II

(b) Why would you expect II to be a better hydride donor than I? (*Hint:* What is one product of the hydride transfer from II?)

Problem 19.15 Suggest an experiment to prove that a hydride transfer of the kind shown in step (2) is actually involved, that is, that hydrogen is transferred from I and not from the solvent.

Problem 19.16 From examination of the mechanism, can you suggest one factor that would tend to make a crossed Cannizzaro reaction involving formaldehyde take place in the particular way it does?

Problem 19.17 Phenylglyoxal, C_6H_5COCHO, is converted by aqueous sodium hydroxide into sodium mandelate, $C_6H_5CHOHCOONa$. Suggest a likely mechanism for this conversion.

Problem 19.18 In the **benzilic acid rearrangement**, the diketone *benzil* is converted by sodium hydroxide into the salt of *benzilic acid.*

$$\underset{\text{Benzil}}{C_6H_5COCOC_6H_5} \xrightarrow{OH^-} (C_6H_5)_2C(OH)COO^- \xrightarrow{H^+} \underset{\text{Benzilic acid}}{(C_6H_5)_2C(OH)COOH}$$

If sodium methoxide is used instead of sodium hydroxide, the ester $(C_6H_5)_2C(OH)COOCH_3$ is obtained. Suggest a possible mechanism for this rearrangement.

19.17 Analysis of aldehydes and ketones

Aldehydes and ketones are characterized through the addition to the carbonyl group of nucleophilic reagents, especially derivatives of ammonia (Sec. 19.14). An aldehyde or ketone will, for example, react with 2,4-dinitrophenylhydrazine to form an insoluble yellow or red solid.

Aldehydes are characterized, and in particular are differentiated from ketones, through their ease of oxidation: aldehydes give a positive test with Tollens' reagent (Sec. 19.9); ketones do not. A positive Tollens' test is also given by a few other kinds of easily oxidized compounds, e.g., certain phenols and amines; these compounds do not, however, give positive tests with 2,4-dinitrophenylhydrazine.

Aldehydes are also, of course, oxidized by many other oxidizing agents: by cold, dilute, neutral $KMnO_4$ and by CrO_3 in H_2SO_4 (Sec. 6.30).

A highly sensitive test for aldehydes is the *Schiff test.* An aldehyde reacts with the fuchsin-aldehyde reagent to form a characteristic magenta color.

Aliphatic aldehydes and ketones having α-hydrogen react with Br_2 in CCl_4. This reaction is generally too slow to be confused with a test for unsaturation, and moreover it liberates HBr.

Aldehydes and ketones are generally identified through the melting points of

derivatives like 2,4-dinitrophenylhydrazones, oximes, and semicarbazones (Sec. 19.14).

Methyl ketones are characterized through the iodoform test (see Sec. 16.11).

Problem 19.19 Make a table to summarize the behavior of each class of compound we have studied toward each of the oxidizing agents we have studied.

Problem 19.20 A convenient test for aldehydes and most ketones depends upon the fact that a carbonyl compound generally causes a change in color when it is added to a solution of hydroxylamine hydrochloride and an acid-base indicator. What is the basis of this test?

Problem 19.21 Expand the table you made in Problem 18.18, p. 608, to include aldehydes and ketones, and, in particular, emphasize oxidizing agents.

19.18 Spectroscopic analysis of aldehydes and ketones

Infrared. Infrared spectroscopy is by far the best way to detect the presence of a carbonyl group in a molecule. The strong band due to C=O stretching appears at about 1700 cm^{-1}, where it is seldom obscured by other strong absorptions; it is one of the most useful bands in the infrared spectrum, and is often the first one looked for (see Fig. 19.1).

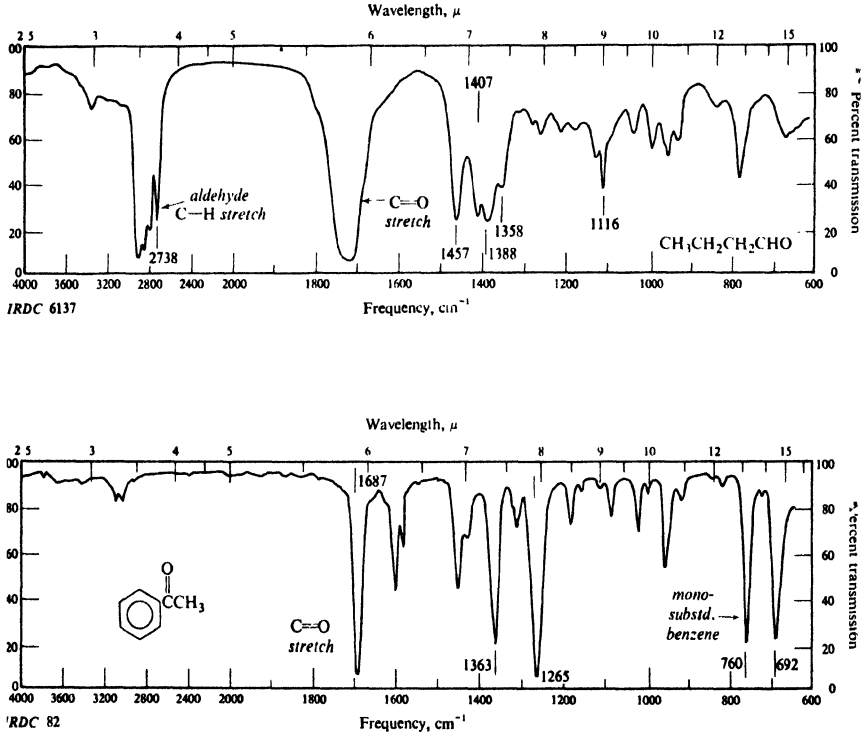
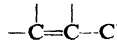
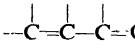
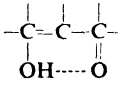


Figure 19.1. Infrared spectra of (*a*) *n*-butyraldehyde and (*b*) acetophenone.

The carbonyl band is given not only by aldehydes and ketones, but also by carboxylic acids and their derivatives. Once identified as arising from an aldehyde or ketone (see below), its exact frequency can give a great deal of information about the structure of the molecule.

C=O stretching, *strong*

RCHO 1725 cm^{-1}	R_2CO 1710 cm^{-1}	Cyclobutanones 1780 cm^{-1}
ArCHO 1700 cm^{-1}	ArCOR 1690 cm^{-1}	Cyclopentanones 1740 cm^{-1}
 1685 cm^{-1}	 1675 cm^{-1}	 1540–1640 cm^{-1} (enols)

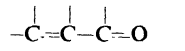
The —CHO group of an aldehyde has a characteristic C—H stretching band near 2720 cm^{-1}; this, in conjunction with the carbonyl band, is fairly certain evidence for an aldehyde (see Fig. 19.1).

Carboxylic acids (Sec. 18.22) and esters (Sec. 20.25) also show carbonyl absorption, and in the same general region as aldehydes and ketones. Acids, however, also show the broad O—H band. Esters usually show the carbonyl band at somewhat higher frequencies than ketones of the same general structure; furthermore, esters show characteristic C—O stretching bands. (For a comparison of certain oxygen compounds, see Table 20.3, p. 689.)

Nmr. The proton of an aldehyde group, —CHO, absorbs far downfield, at δ 9–10. Coupling of this proton with adjacent protons has a small constant (J 1–3 Hz), and the fine splitting is often seen superimposed on other splittings.

Ultraviolet. The ultraviolet spectrum can tell a good deal about the structure of carbonyl compounds: particularly, as we might expect from our earlier discussion (Sec. 13.5), about conjugation of the carbonyl group with a carbon–carbon double bond.

Saturated aldehydes and ketones absorb weakly in the near ultraviolet. Conjugation moves this weak band (the R band) to longer wavelengths (why?) and, more important, moves a very intense band (the K band) from the far ultraviolet to the near ultraviolet.

		
λ_{max} 270–300 mμ	λ_{max} 300–350 mμ	λ_{max} 215–250 mμ
ϵ_{max} 10–20	ϵ_{max} 10–20	ϵ_{max} 10,000–20,000

The exact position of this K band gives information about the number and location of substituents in the conjugated system.

PROBLEMS

1. Neglecting enantiomerism, give structural formulas, common names, and IUPAC names for:

(a) the seven carbonyl compounds of formula $C_5H_{10}O$
(b) the five carbonyl compounds of formula C_8H_8O that contain a benzene ring

2. Give the structural formula of:

(a) acetone
(b) benzaldehyde
(c) methyl isobutyl ketone
(d) trimethylacetaldehyde
(e) acetophenone
(f) cinnamaldehyde
(g) 4-methylpentanal
(h) phenylacetaldehyde
(i) benzophenone
(j) α,γ-dimethylcaproaldehyde
(k) 3-methyl-2-pentanone
(l) 2-butenal
(m) 4-methyl-3-penten-2-one (mesityl oxide)
(n) 1,3-diphenyl-2-propen-1-one (benzalacetophenone)
(o) 3-hydroxypentanal
(p) benzyl phenyl ketone
(q) salicyaldehyde
(r) *p,p'*-dihydroxybenzophenone
(s) *m*-tolualdehyde

3. Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetaldehyde with:

(a) Tollens' reagent
(b) CrO_3/H_2SO_4
(c) cold dilute $KMnO_4$
(d) $KMnO_4$, H^+, heat
(e) H_2, Ni, 20 lb/in^2, 30°
(f) $LiAlH_4$
(g) $NaBH_4$
(h) C_6H_5MgBr, then H_2O
(i) isopropylmagnesium chloride, then H_2O
(j) $NaHSO_3$
(k) CN^-, H^+
(l) hydroxylamine
(m) phenylhydrazine
(n) 2,4-dinitrophenylhydrazine
(o) semicarbazide
(p) ethyl alcohol, dry HCl(g)

4. Answer Problem 3 for cyclohexanone.

5. Write balanced equations, naming all organic products, for the reaction (if any) of benzaldehyde with:

(a) conc. NaOH
(b) formaldehyde, conc. NaOH
(c) CN^-, H^+
(d) product (c) + H_2O, H^+, heat
(e) CH_3MgI, then H_2O
(f) product (e) + H^+, heat
(g) $(CH_3)_2{}^{14}CHMgBr$, then H_2O
(h) $H_2{}^{18}O$, H^+

6. Write equations for all steps in the synthesis of the following from propionaldehyde, using any other needed reagents:

(a) *n*-propyl alcohol
(b) propionic acid
(c) α-hydroxybutyric acid
(d) *sec*-butyl alcohol
(e) 1-phenyl-1-propanol
(f) methyl ethyl ketone
(g) *n*-propyl propionate
(h) 2-methyl-3-pentanol

7. Write equations for all steps in the synthesis of the following from acetophenone, using any other needed reagents:

(a) ethylbenzene
(b) benzoic acid
(c) α-phenylethyl alcohol
(d) 2-phenyl-2-butanol
(e) diphenylmethylcarbinol
(f) α-hydroxy-α-phenylpropionic acid

8. Outline all steps in a possible laboratory synthesis of each of the following from benzene, toluene, and alcohols of four carbons or fewer, using any needed inorganic reagents:

(a) isobutyraldehyde
(b) phenylacetaldehyde
(c) *p*-bromobenzaldehyde
(d) methyl ethyl ketone
(e) 2,4-dinitrobenzaldehyde
(f) *p*-nitrobenzophenone
(g) 2-methyl-3-pentanone
(h) benzyl methyl ketone
(i) *m*-nitrobenzophenone
(j) *n*-propyl *p*-tolyl ketone
(k) α-methylbutyraldehyde
(l) *n*-butyl isobutyl ketone
(m) *p*-nitroacetophenone
(n) 3-nitro-4'-methylbenzophenone
(o) *p*-nitropropiophenone

9. Outline all steps in a possible laboratory synthesis of each of the following from benzene, toluene, and alcohols of four carbons or fewer, using any needed inorganic reagents:

(a) *n*-butylbenzene
(b) α-hydroxy-*n*-valeric acid
(c) 2-methylheptane
(d) 2,3,5-trimethyl-3-hexanol
(e) *p*-nitro-α-hydroxyphenylacetic acid
(f) 1,2-diphenyl-2-propanol
(g) ethylphenyl-*p*-bromophenylcarbinol
(h) 3-methyl-2-butenoic acid

10. (a) What are A, B, and C?

$$C_6H_5C(CH_3)_2CH_2COOH + PCl_3 \longrightarrow A\ (C_{11}H_{13}OCl)$$
$$A + AlCl_3/CS_2 \longrightarrow B\ (C_{11}H_{12}O)$$
$$B + N_2H_4, OH^-, \text{heat, high-boiling solvent} \longrightarrow C\ (C_{11}H_{14})$$

C gave the following nmr spectrum:

a singlet, δ 1.22, 6H
b triplet, δ 1.85, 2H, $J = 7$ Hz
c triplet, δ 2.83, 2H, $J = 7$ Hz
d singlet, δ 7.02, 4H

(b) C was also formed by treatment of the alcohol D ($C_{11}H_{16}O$) with concentrated sulfuric acid. What is the structure of D?

11. In the oxidation of an alcohol RCH_2OH to an aldehyde by chromic acid, the chief side-reaction is formation, not of the carboxylic acid, but of the ester $RCOOCH_2R$. Experiment has shown that a mixture of isobutyl alcohol and isobutyraldehyde is oxidized much faster than either compound alone. Suggest a possible explanation for these facts. (*Hint:* See Sec. 19.9.)

12. Give stereochemical formulas for compounds E–J.

R-(+)-*glyceraldehyde* ($CH_2OHCHOHCHO$) + CN^-, H^+ $\longrightarrow$ E + F
(both E and F have the formula $C_4H_7O_3N$)
E + F + OH^-, H_2O, heat; then H^+ $\longrightarrow$ G + H (both $C_4H_8O_5$)
G + HNO_3 $\longrightarrow$ I ($C_4H_6O_4$), *optically active*
H + HNO_3 $\longrightarrow$ J ($C_4H_6O_4$), *optically inactive*

13. (a) *cis*-1,2-Cyclopentanediol reacts with acetone in the presence of dry HCl to yield compound K, $C_8H_{14}O_2$, which is resistant to boiling alkali, but which is readily converted into the starting materials by aqueous acids. What is the most likely structure of K? To what class of compounds does it belong?

(b) *trans*-1,2-Cyclopentanediol does not form an analogous compound. How do you account for this fact?

14. The oxygen exchange described in Problem 19.13 (p. 643) can be carried out by use of hydroxide ion instead of hydrogen ion as catalyst. Suggest a detailed mechanism for exchange under these conditions. (*Hint:* See Sec. 19.16.)

15. Vinyl alkyl ethers, $RCH{-}CHOR'$, are very rapidly hydrolyzed by dilute aqueous acid to form the alcohol R'OH and the aldehyde RCH_2CHO. Hydrolysis in $H_2{}^{18}O$ gives alcohol R'OH containing only ordinary oxygen. Outline all steps in the most likely mechanism for the hydrolysis. Show how this mechanism accounts not only for the results of the tracer experiment, but also for the extreme ease with which hydrolysis takes place.

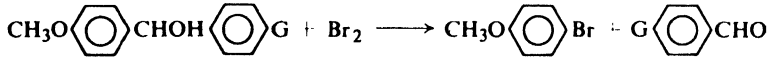
16. (a) Optically active 2-octyl brosylate was found to react with pure water to yield 2-octanol with complete inversion of configuration. With mixtures of water and the "inert" solvent dioxane (p. 561), however, inversion was accompanied by racemization, the extent of racemization increasing with the concentration of dioxane. From this and other evidence, R. A. Sneen (of Purdue University) has proposed that inverted alcohol is formed through (S_N2) attack by water, and that retained alcohol is formed via an initial attack by dioxane.

Show in detail how nucleophilic attack by dioxane could ultimately lead to the formation of alcohol with retention of configuration.

(b) In the mixed solvent methanol and acetone (*no* water present), 2-octyl brosylate was found to yield not only the 2-octyl methyl ether, but also some *2-octanol*. When the same reaction was carried out in the presence of the base pyridine (to neutralize the sulfonic acid formed), no 2-octanol was obtained; there was obtained instead, in impure form, a substance whose infrared spectrum showed no absorption in the carbonyl region, but which reacted with an acidic solution of 2,4-dinitrophenylhydrazine to yield the 2,4-dinitrophenylhydrazone of acetone. Sneen has proposed that the 2-octanol was formed by a series of reactions initiated by nucleophilic attack on 2-octyl brosylate by acetone.

Outline all steps in mechanism for the formation of 2-octanol under these conditions. What compound is probably responsible for the formation of the 2,4-dinitrophenylhydrazone? How do you account for the effect of added base?

17. On treatment with bromine, certain diarylcarbinols (I) are converted into a 50:50 mixture of aryl bromide (II) and aldehyde (III).



I II III

Whether G is $-NO_2$, $-H$, $-Br$, or $-CH_3$, bromine appears *only* in the ring containing the $-OCH_3$ group. The rate of reaction is affected moderately by the nature of G, decreasing along the series: G = $-CH_3$ > $-H$ > $-Br$ > $-NO_2$. The rate of reaction is slowed down by the presence of added bromide ion.

Outline all steps in the most likely mechanism for this reaction. Show how your mechanism accounts for each of the above facts.

18. A naïve graduate student needed a quantity of benzhydrol, $(C_6H_5)_2CHOH$, and decided to prepare it by the reaction between phenymagnesium bromide and benzaldehyde. He prepared a mole of the Grignard reagent. To insure a good yield, he then added, not one, but *two* moles of the aldehyde. On working up the reaction mixture, he was at first gratified to find he had obtained a good yield of a crystalline product, but his hopes were dashed when closer examination revealed that he had made, not benzhydrol, but the ketone benzophenone. Bewildered, the student made the first of many trips to his research director's office.

He returned shortly, red-faced, to the laboratory, carried out the reaction again using equimolar amounts of the reactants, and obtained a good yield of the compound he wanted.

What had gone wrong in his first attempt? How had his generosity with benzaldehyde betrayed him? (*Hint*: See Sec. 19.16. Examine the structure of the initial addition product.) (In Problem 20, p. 724, we shall follow his further adventures.)

19. (a) Give structural formulas of compounds L and M, and of *isoeugenol* and *vanillin*.

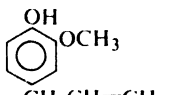
eugenol (below) + KOH, 225° ⟶ isoeugenol ($C_{10}H_{12}O_2$)

isoeugenol + $(CH_3COO)_2$ ⟶ L ($C_{12}H_{14}O_3$) (See Sec. 20.10)

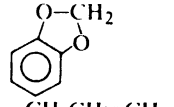
L + $K_2Cr_2O_7$, H_2SO_4, 75 ⟶ M ($C_{10}H_{10}O_4$)

M + HSO_3^-, H_2O, boil ⟶ vanillin ($C_8H_8O_3$)

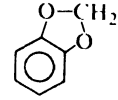
(b) Account for the conversion of eugenol into isoeugenol.



Eugenol



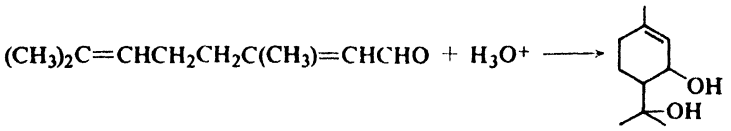
Safrole



Piperonal

(c) Suggest a way to convert *safrole* into *piperonal* (above).

20. Suggest a mechanism for the following reaction.



3,8-Carvomenthenediol

The ring-closing step can be considered as either nucleophilic addition or electrophilic addition depending on one's point of view. Show how this is so, identifying both the electrophile and the nucleophile.

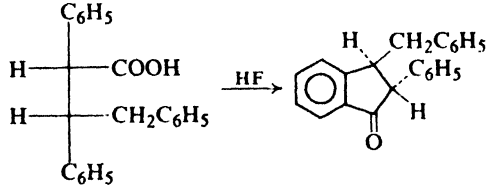
21. The trimer of trichloroacetaldehyde (compare *paraldehyde*, p. 621) exists in two forms, N and O, which give the following nmr data.

N: singlet, δ 4.28

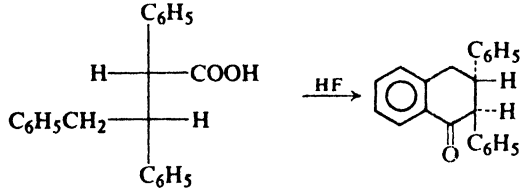
O: two singlets, δ 4.63 and δ 5.50, peak area ratio 2:1

Show in as much detail as you can the structure of each of these.

22. How do you account for the difference in behavior between diastereomers IV and V? (*Hint:* Draw Newman projections. What are the bulkiest groups?)

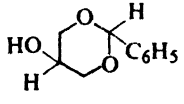


IV



V

23. The acetal (VI) of glycerol and benzaldehyde has been found to exist in two configurations. (a) Draw them. (b) One of these exists preferentially in a conformation



VI

in which the phenyl group occupies an axial position. Which configuration is this, and what counterbalances the unfavorable steric factor?

24. Describe a simple chemical test that would serve to distinguish between:

(a) *n*-valeraldehyde and ethyl ketone
(b) phenylacetaldehyde and benzyl alcohol
(c) cyclohexanone and methyl *n*-caproate
(d) 2-pentanone and 3-pentanone
(e) propionaldehyde and ethyl ether
(f) diethyl acetal and *n*-valeraldehyde
(g) diethyl acetal and *n*-propyl ether
(h) methyl *m*-tolyl ketone and propiophenone
(i) 2-pentanone and 2-pentanol
(j) paraldehyde and isobutyl ether
(k) dioxane and trioxane

Tell exactly what you would *do* and *see*.

25. An unknown compound is believed to be one of the following, all of which boil within a few degrees of each other. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible use simple chemical tests; where necessary use more elaborate chemical methods such as quantitative hydrogenation, cleavage, neutralization equivalent, saponification equivalent, etc. Make use of any needed tables of physical constants.

(a) phenylacetaldehyde
m-tolualdehyde
o-tolualdehyde
acetophenone
p-tolualdehyde
(b) methyl β-phenylethyl ketone
cyclohexylbenzene
benzyl *n*-butyrate
γ-phenylpropyl alcohol
n-caprylic acid
(c) isophorone (3,5,5-trimethyl-2-cyclohexen-1-one)
n-dodecane
benzyl *n*-butyl ether
ethyl benzoate
m-cresyl acetate
n-nonyl alcohol
(d) *p*-chloroacetophenone
methyl *o*-chlorobenzoate
p-chlorobenzyl chloride
m-chloronitrobenzene

26. *Citral*, $C_{10}H_{16}O$, is a terpene that is the major constituent of lemongrass oil. It reacts with hydroxylamine to yield a compound of formula $C_{10}H_{17}ON$, and with Tollens' reagent to give a silver mirror and a compound of formula $C_{10}H_{16}O_2$. Upon vigorous oxidation citral yields acetone, oxalic acid (HOOC—COOH), and levulinic acid ($CH_3COCH_2CH_2COOH$).

(a) Propose a structure for citral that is consistent with these facts and with the isoprene rule (Sec. 8.26.)

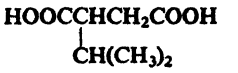
(b) Actually citral seems to consist of two isomers, citral *a* (*geranial*) and citral *b* (*neral*), which yield the same oxidation products. What is the most likely structural difference between these two isomers?

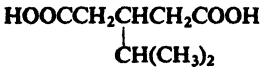
(c) Citral *a* is obtained by mild oxidation of geraniol (Problem 27, p. 547); citral *b* is obtained in a similar way from nerol. On this basis assign structures to citral *a* and citral *b*.

27. (+)-*Carvotanacetone*, $C_{10}H_{16}O$, is a terpene found in thuja oil. It reacts with hydroxylamide and semicarbazide to form crystalline derivatives. It gives negative tests with Tollens' reagent, but rapidly decolorizes cold dilute $KMnO_4$.

Carvotanacetone can be reduced successively to *carvomenthone*, $C_{10}H_{18}O$, and *carvomenthol*, $C_{10}H_{20}O$. Carvomenthone reacts with hydroxylamine but not with cold dilute $KMnO_4$. Carvomenthol does not react with hydroxylamine or cold dilute $KMnO_4$, but gives a positive test with CrO_3/H_2SO_4.

One set of investigators found that oxidation of carvotanacetone gave isopropylsuccinic acid and pyruvic acid, $CH_3COCOOH$; another set of investigators isolated acetic acid and β-isopropylglutaric acid.


Isopropylsuccinic acid


β-Isopropylglutaric acid

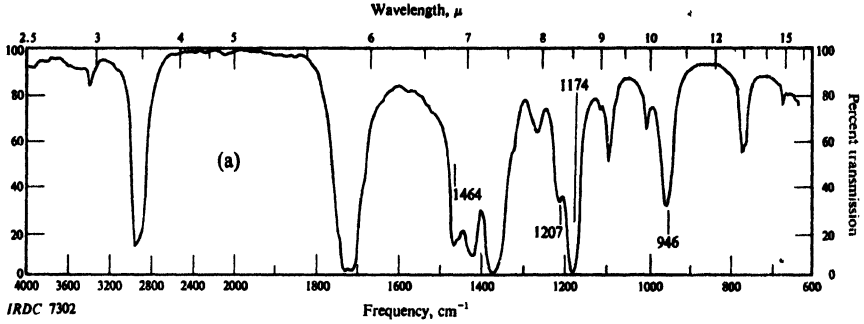
What single structure for carvotanacetone is consistent with all these facts?

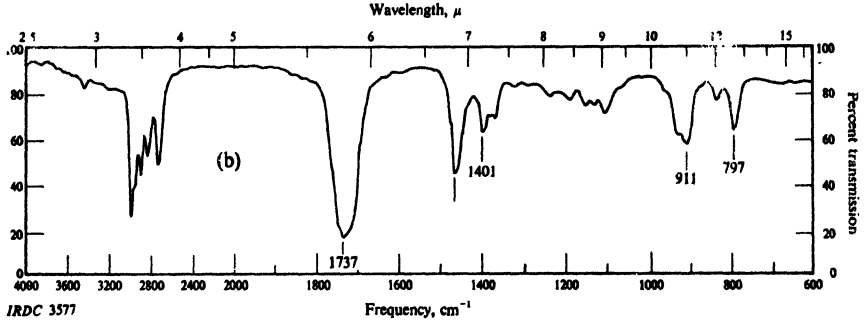
28. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 19.2 (p. 654)?

isobutyraldehyde	ethyl vinyl ether
2-butanone	cyclopropylcarbinol
tetrahydrofuran	3-buten-2-ol

29. Give a structure or structures consistent with each of the nmr spectra in Fig. 19.3 (p. 655).

30. Give the structures of compounds P, Q, and R on the basis of their infrared spectra (Fig. 19.4, p. 656) and their nmr spectra (Fig. 19.5, p. 657).





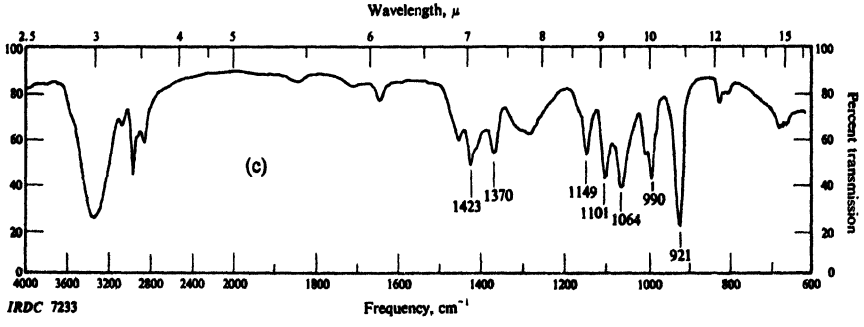


Figure 19.2. Infrared spectra for Problem 28, p. 653.

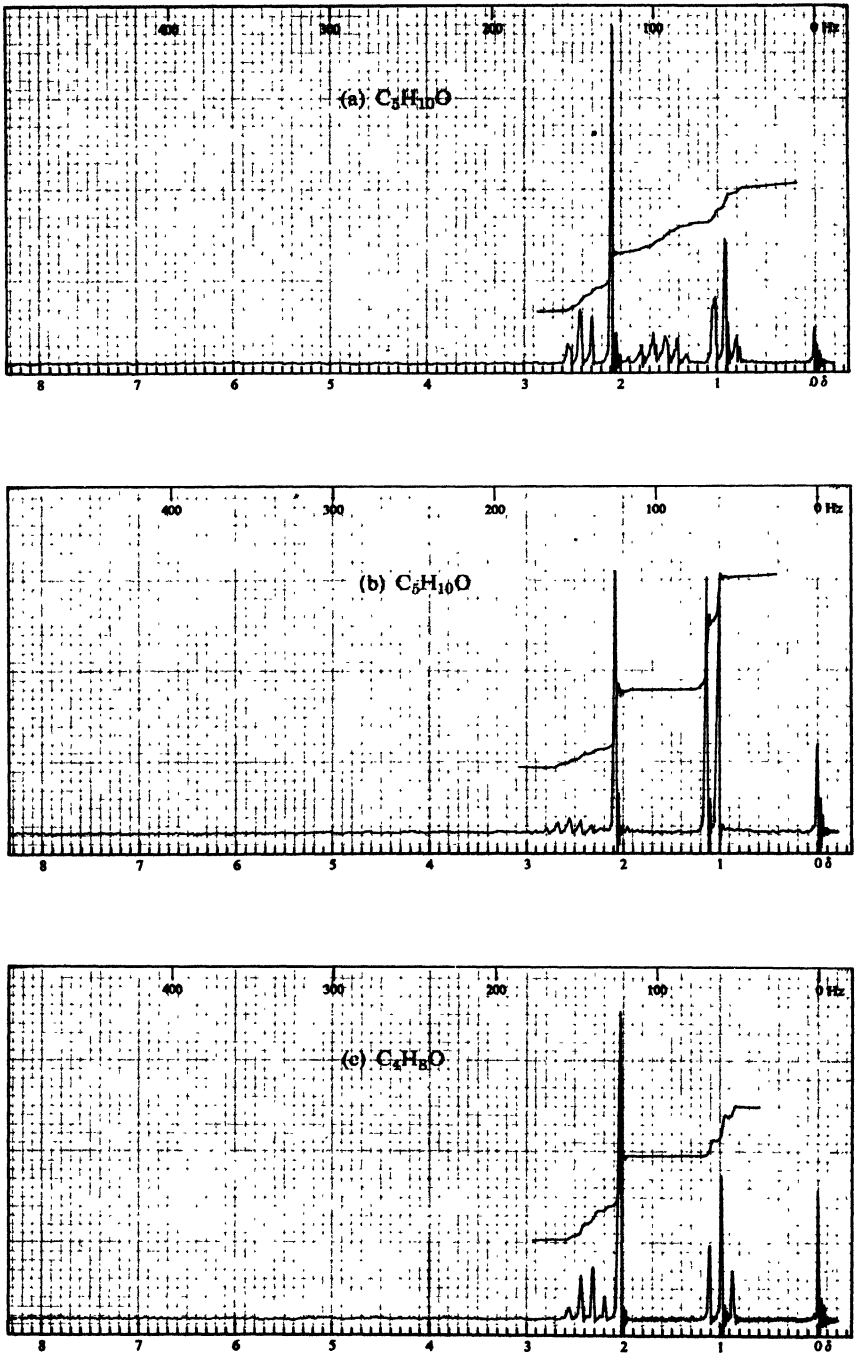
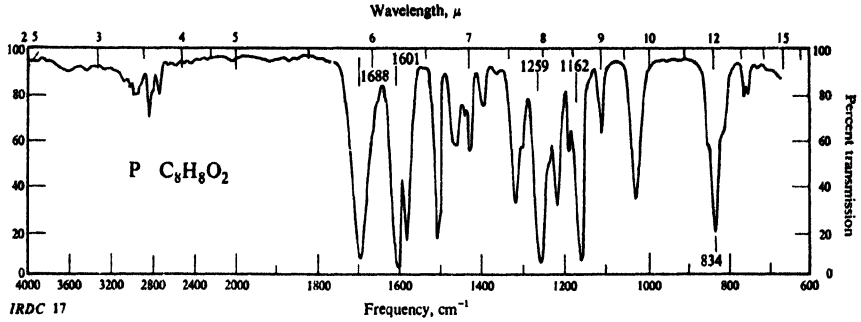
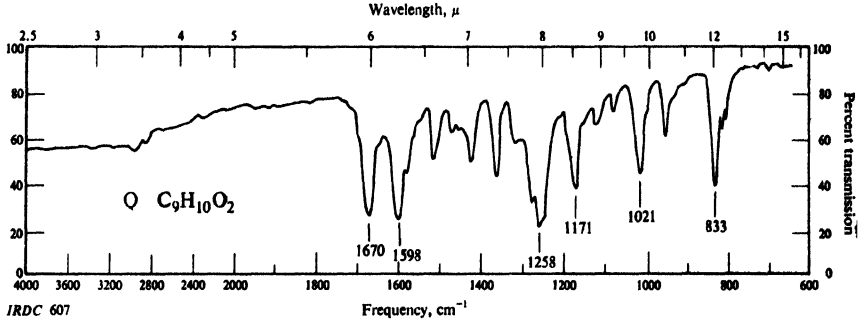


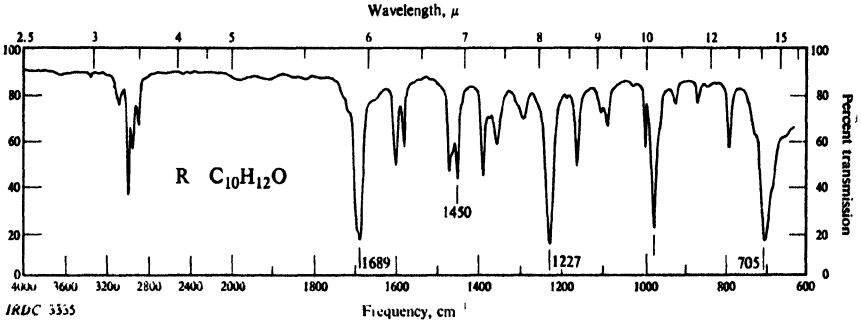
Figure 19.3. Nmr spectra for Problem 29, p. 653.



IRDC 17



IRDC 607



IRDC 5355

...a for Problem 30, p. 653.

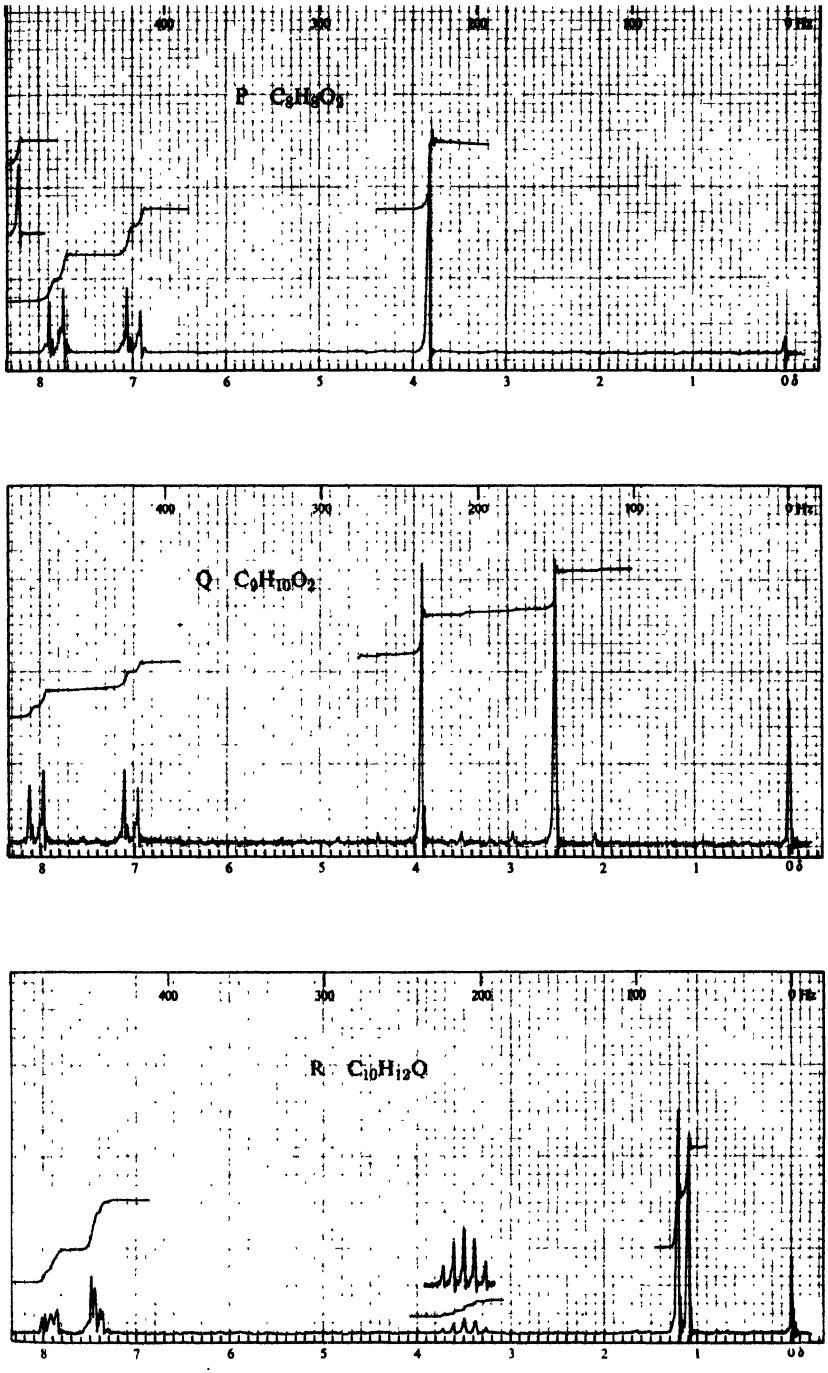


Figure 19.5. Nmr spectra for Problem 30, p. 655.

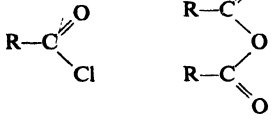
Chapter 20

Functional Derivatives of Carboxylic Acids

Nucleophilic Acyl Substitution

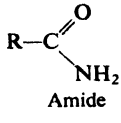
20.1 Structure

Closely related to the carboxylic acids and to each other are a number of chemical families known as **functional derivatives of carboxylic acids**: *acid chlorides*, *anhydrides*, *amides*, and *esters*. These derivatives are compounds in which the —OH of a carboxyl group has been replaced by —Cl, —OOCR, —NH_2, or —OR′.

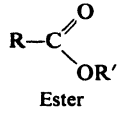


Acid chloride

Anhydride



Amide



Ester

R *may be alkyl or aryl*

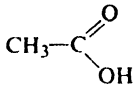
They all contain the **acyl group**:

Acyl group

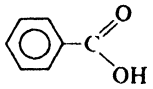
Like the acid to which it is related, an acid derivative may be aliphatic or aromatic, substituted or unsubstituted; whatever the structure of the rest of the molecule, the properties of the functional group remain essentially the same.

20.2 Nomenclature

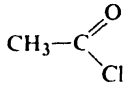
The names of acid derivatives are taken in simple ways from either the common name or the IUPAC name of the corresponding carboxylic acid. For example:



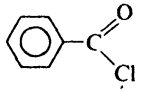
Acetic acid
Ethanoic acid



Benzoic acid

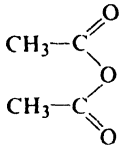


Acetyl chloride
Ethanoyl chloride

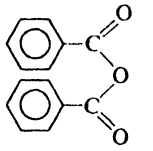


Benzoyl chloride

Change:
-ic acid to *-yl chloride*

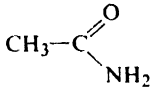


Acetic anhydride
Ethanoic anhydride

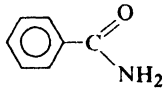


Benzoic anhydride

acid to ***anhydride***

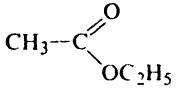


Acetamide
Ethanamide

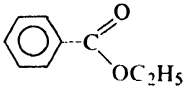


Benzamide

-ic acid of common name
(or *-oic acid* of IUPAC name)
to *-amide*



Ethyl acetate
Ethyl ethanoate

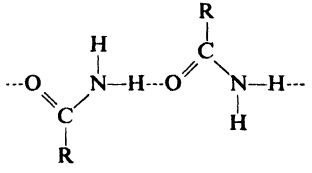


Ethyl benzoate

-ic acid to *-ate*,
preceded by name of
alcohol or phenol group

20.3 Physical properties

The presence of the C O group makes the acid derivatives polar compounds. Acid chlorides and anhydrides (Table 20.1) and esters (Table 20.2, p. 674) have boiling points that are about the same as those of aldehydes or ketones of comparable molecular weight (see Sec. 15.4). Amides (Table 20.1) have quite high boiling points because they are capable of strong intermolecular hydrogen bonding.



The border line for solubility in water ranges from three to five carbons for the esters to five or six carbons for the amides. The acid derivatives are soluble in the usual organic solvents.

Volatile esters have pleasant, rather characteristic odors; they are often used in the preparation of perfumes and artificial flavorings. Acid chlorides have sharp, irritating odors, at least partly due to their ready hydrolysis to HCl and carboxylic acids.

Table 20.1 ACID CHLORIDES, ANHYDRIDES, AND AMIDES

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Acetyl chloride	−112	51	Succinic anhydride	120	
Propionyl chloride	− 94	80	Maleic anhydride	60	
n-Butyryl chloride	− 89	102			
n-Valeryl chloride	−110	128	Formamide	3	200*d*
Stearoyl chloride	23	215^{15}	Acetamide	82	221
Benzoyl chloride	− 1	197	Propionamide	79	213
p-Nitrobenzoyl chloride	72	154^{15}	*n*-Butyramide	116	216
			n-Valeramide	106	232
3,5-Dinitrobenzoyl chloride	74	196^{12}	Stearamide	109	251^{12}
			Benzamide	130	290
Acetic anhydride	− 73	140	Succinimide	126	
Phthalic anhydride	131	284	Phthalimide	238	

20.4 Nucleophilic acyl substitution. Role of the carbonyl group

Before we take up each kind of acid derivative separately, it will be helpful to outline certain general patterns into which we can then fit the rather numerous individual facts.

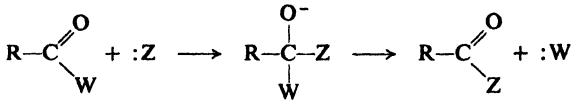
Each derivative is nearly always prepared—directly or indirectly—from the corresponding carboxylic acid, and can be readily converted back into the carboxylic acid by simple hydrolysis. Much of the chemistry of acid derivatives involves their conversion one into another, and into the parent acid. In addition, each derivative has certain characteristic reactions of its own.

The derivatives of carboxylic acids, like the acids themselves, contain the carbonyl group, C=O. This group is retained in the products of most reactions undergone by these compounds, and does not suffer any permanent changes itself. But by its presence in the molecule it determines the characteristic reactivity of these compounds, and is the kev to the understanding of their chemistry.

Here, too, as in aldehydes and ketones, the carbonyl group performs two functions: (a) it provides a site for nucleophilic attack, and (b) it increases the acidity of hydrogens attached to the *alpha* carbon.

(We shall discuss reactions resulting from the acidity of α-hydrogens in Secs. 21.11–21.12 and 26.1–26.3.)

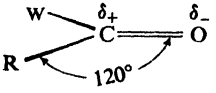
Acyl compounds—carboxylic acids and their derivatives—typically undergo **nucleophilic substitution** in which —OH, —Cl, —OOCR, $—NH_2$, or —OR′ is replaced by some other basic group. Substitution takes place much more readily than at a saturated carbon atom; indeed, many of these substitutions do not usually take place at all in the absence of the carbonyl group, as, for example, replacement of $—NH_2$ by —OH.



—W = —OH, —Cl, —OOCR, —NH_2, —OR′

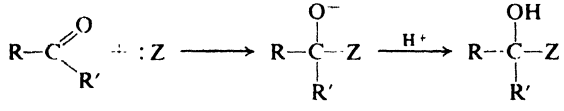
To account for the properties of acyl compounds, let us turn to the carbonyl group. We have encountered this group in our study of aldehydes and ketones (Secs. 19.1 and 19.8), and we know what it is like and what in general to expect of it.

Carbonyl carbon is joined to three other atoms by σ bonds; since these bonds utilize sp^2 orbitals (Sec. 1.10), they lie in a plane and are 120° apart. The remaining p orbital of the carbon overlaps a p orbital of oxygen to form a π bond; carbon and oxygen are thus joined by a double bond. The part of the molecule immediately surrounding carbonyl carbon is *flat*; oxygen, carbonyl carbon, and the two atoms directly attached to carbonyl carbon lie in a plane:

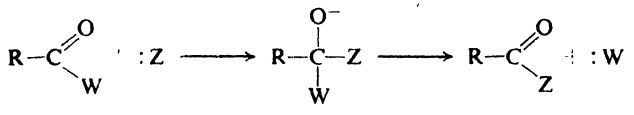


We saw before that both electronic and steric factors make the carbonyl group particularly susceptible to nucleophilic attack at the carbonyl carbon: (a) the tendency of oxygen to acquire electrons even at the expense of gaining a negative charge; and (b) the relatively unhindered transition state leading from the trigonal reactant to the tetrahedral intermediate. These factors make acyl compounds, too, susceptible to nucleophilic attack.

It is in the second step of the reaction that acyl compounds differ from aldehydes and ketones. The tetrahedral intermediate from an aldehyde or ketone gains a proton, and the result is *addition*. The tetrahedral intermediate from an acyl



Aldehyde or ketone
Addition



Acyl compound
Substitution

compound ejects the :W group, returning to a trigonal compound, and thus the result is *substitution*.

We can see why the two classes of compounds differ as they do. The ease with which :W is lost depends upon its basicity: the weaker the base, the better the leaving group. For acid chlorides, acid anhydrides, esters, and amides, :W is, respectively: the very weak base Cl^-; the moderately weak base $RCOO^-$; and the strong bases $R'O^-$ and NH_2^-. But for an aldehyde or ketone to undergo substitution, the leaving group would have to be hydride ion ($:H^-$) or alkide ion

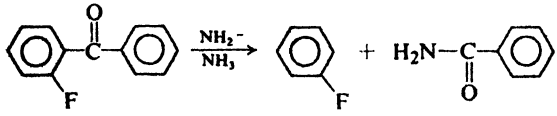
($:R^-$) which, as we know, are the strongest bases of all. (Witness the low acidity of H_2 and RH.) And so with aldehydes and ketones addition almost always takes place instead.

Problem 20.1 Suggest a likely mechanism for each of the following reactions, and account for the behavior shown:

(a) The last step in the haloform reaction (Sec. 16.11),

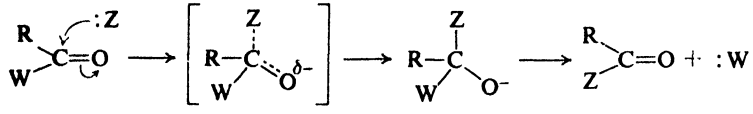
$$OH^- + R{-}\underset{\underset{O}{\|}}{C}{-}CX_3 \xrightarrow{H_2O} RCOO^- + CHX_3$$

(b) The reaction of *o*-fluorobenzophenone with amide ion,



Thus, nucleophilic acyl substitution proceeds by two steps, with the intermediate formation of a tetrahedral compound. Generally, the overall rate is affected by the rate of both steps, but the *first* step is the more important. The first step, formation of the tetrahedral intermediate, is affected by the same factors

Nucleophilic acyl substitution

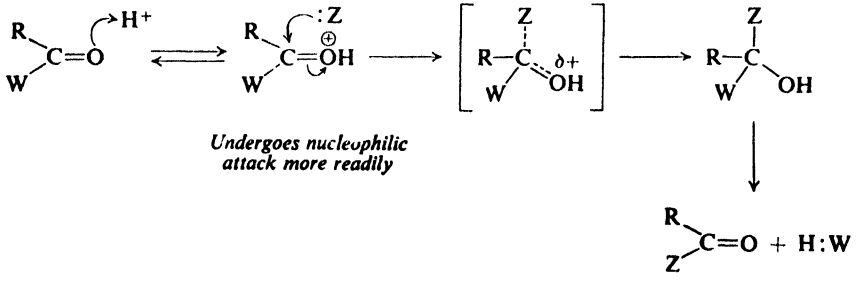


Reactant	Transition state	Intermediate	Product	Leaving group
Trigonal	*Becoming tetrahedral*	*Tetrahedral*	*Trigonal*	*Weaker base leaves more readily*
	Partial negative charge on oxygen	*Negative charge on oxygen*		

as in addition to aldehydes and ketones (Sec. 19.8): it is favored by electron withdrawal, which stabilizes the developing negative charge; and it is hindered by the presence of bulky groups, which become crowded together in the transition state. The second step depends, as we have seen, on the basicity of the leaving group, :W.

If acid is present, H^+ becomes attached to carbonyl oxygen, thus making the

Acid-catalyzed nucleophilic acyl substitution

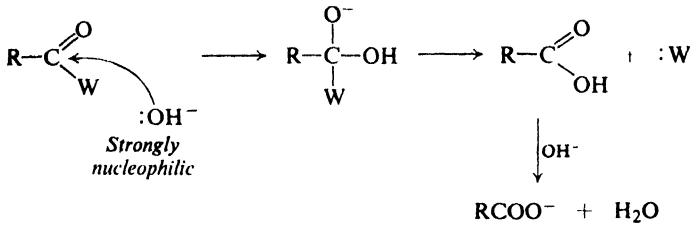


Undergoes nucleophilic attack more readily

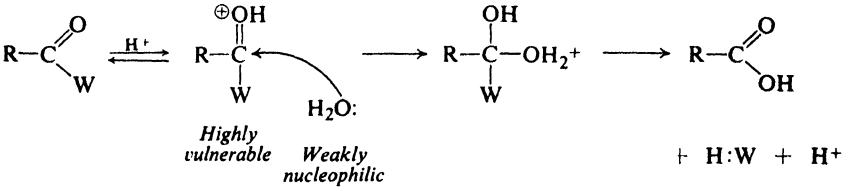
carbonyl group even more susceptible to the nucleophilic attack; oxygen can now acquire the π electrons without having to accept a negative charge.

It is understandable that acid derivatives are hydrolyzed more readily in either alkaline or acidic solution than in neutral solution: alkaline solutions provide hydroxide ion, which acts as a strongly nucleophilic reagent; acid solutions provide hydrogen ion, which attaches itself to carbonyl oxygen and thus renders the molecule vulnerable to attack by the weakly nucleophilic reagent, water.

Alkaline hydrolysis

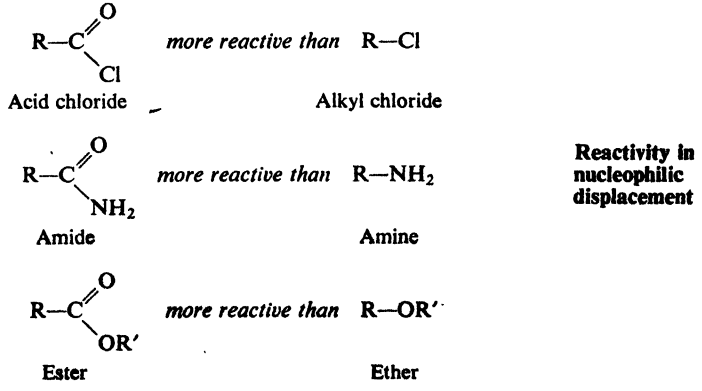


Acidic hydrolysis



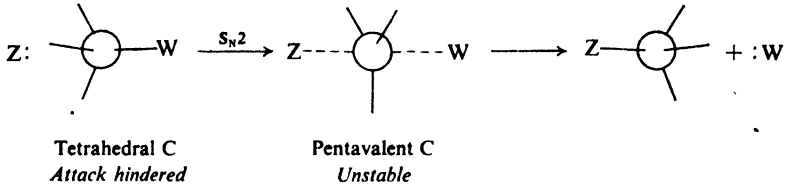
20.5 Nucleophilic substitution: alkyl *vs.* acyl

As we have said, nucleophilic substitution takes place much more readily at an acyl carbon than at saturated carbon. Thus, toward nucleophilic attack acid chlorides are more reactive than alkyl chlorides, amides are more reactive than amines (RNH_2), and esters are more reactive than ethers.



It is, of course, the carbonyl group that makes acyl compounds more reactive than alkyl compounds. Nucleophilic attack (S_N2) on a tetrahedral alkyl carbon involves a badly crowded transition state containing pentavalent carbon; a bond must be partly broken to permit the attachment of the nucleophile:

Alkyl nucleophilic substitution

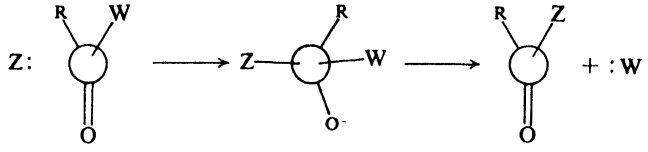


Tetrahedral C
Attack hindered

Pentavalent C
Unstable

Nucleophilic attack on a flat acyl compound involves a relatively unhindered transition state leading to a tetrahedral intermediate that is actually a compound; since the carbonyl group is unsaturated, attachment of the nucleophile requires

Acyl nucleophilic substitution



Trigonal C
Attack relatively unhindered

Tetrahedral C
Stable

breaking only of the weak π bond, and places a negative charge on an atom quite willing to accept it; oxygen.

ACID CHLORIDES

20.6 Preparation of acid chlorides

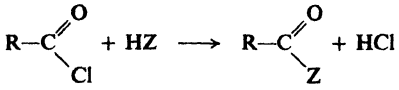
Acid chlorides are prepared from the corresponding acids by reaction with thionyl chloride, phosphorus trichloride, or phosphorus pentachloride, as discussed in Sec. 18.15.

20.7 Reactions of acid chlorides

Like other acid derivatives, acid chlorides typically undergo nucleophilic substitution. Chlorine is expelled as chloride ion or hydrogen chloride, and its place is taken by some other basic group. Because of the carbonyl group these reactions take place much more rapidly than the corresponding nucleophilic substitution reactions of the alkyl halides. Acid chlorides are the most reactive of the derivatives of carboxylic acids.

REACTIONS OF ACID CHLORIDES

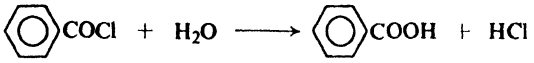
1. Conversion into acids and derivatives. Discussed in Sec. 20.8.



(a) Conversion into acids. Hydrolysis.

$$RCOCl + H_2O \longrightarrow RCOOH + HCl$$
An acid

Example:

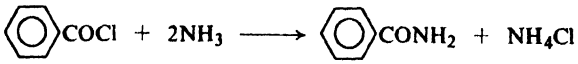


Benzoyl chloride — Benzoic acid

(b) Conversion into amides. Ammonolysis

$$RCOCl + 2NH_3 \longrightarrow RCONH_2 + NH_4Cl$$
An amide

Example:

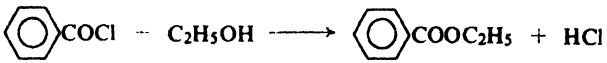


Benzoyl chloride — Benzamide

(c) Conversion into esters. Alcoholysis

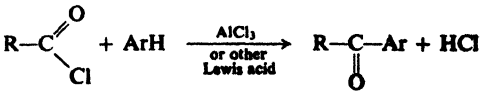
$$RCOCl + R'OH \longrightarrow RCOOR' + HCl$$
An ester

Example:



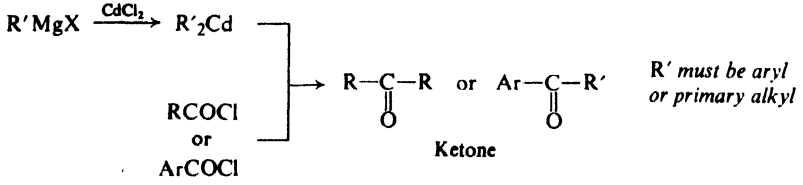
Benzoyl chloride — Ethyl alcohol — Ethyl benzoate

2. Formation of ketones. Friedel-Crafts acylation. Discussed in Sec. 19.6.

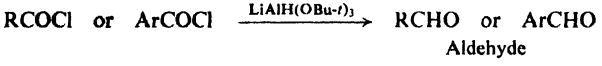


A ketone

3. Formation of ketones. Reaction with organocadmium compounds. Discussed in Sec. 19.7.

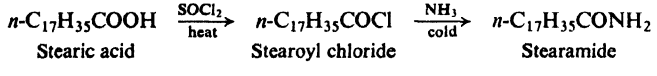


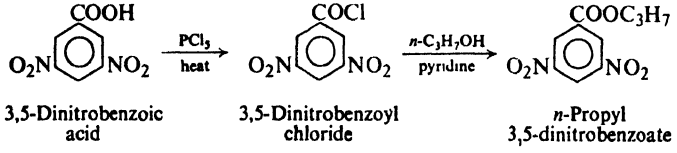
4. Formation of aldehydes by reduction. Discussed in Sec. 19.4.

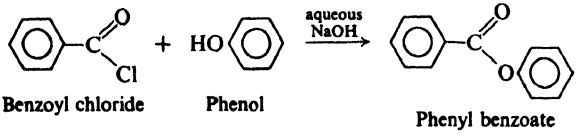


20.8 Conversion of acid chlorides into acid derivatives

In the laboratory, amides and esters are usually prepared from the acid chloride rather than from the acid itself. Both the preparation of the acid chloride and its reactions with ammonia or an alcohol are rapid, essentially irreversible reactions. It is more convenient to carry out these two steps than the single slow, reversible reaction with the acid. For example:







Aromatic acid chlorides (ArCOCl) are considerably less reactive than the aliphatic acid chlorides. With cold water, for example, acetyl chloride reacts almost explosively, whereas benzoyl chloride reacts only very slowly. The reaction of aromatic acid chlorides with an alcohol or a phenol is often carried out using the **Schotten-Baumann** technique: the acid chloride is added in portions (followed by vigorous shaking) to a mixture of the hydroxy compound and a base, usually aqueous sodium hydroxide or pyridine (an organic base, Sec. 31.11). Although the function of the base is not clear, it seems not only to neutralize the hydrogen chloride that would otherwise be liberated, but also to catalyze the reaction.

ACID ANHYDRIDES

20.9 Preparation of acid anhydrides

Only one monocarboxylic acid anhydride is encountered very often; however, this one, **acetic anhydride**, is immensely important. It is prepared by the reaction of acetic acid with **ketene**, $CH_2{=}C{=}O$, which itself is prepared by high-temperature dehydration of acetic acid.

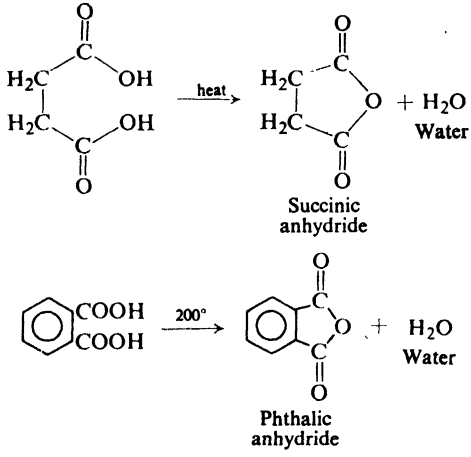
$$CH_3COOH \xrightarrow[700^\circ]{AlPO_4} H_2O + \underset{\text{Ketene}}{CH_2{=}C{=}O} \xrightarrow{CH_3COOH} \underset{\text{Acetic anhydride}}{(CH_3CO)_2O}$$

Ketene is an extremely reactive, interesting compound, which we have already encountered as a source of *methylene* (Sec. 9.15). It is made in the laboratory

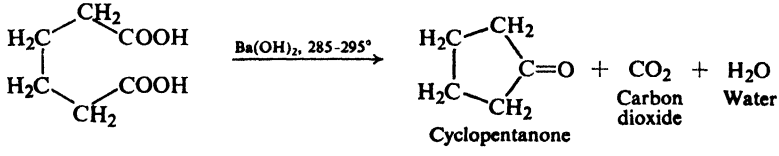
$$CH_3COCH_3 \xrightarrow{700\text{–}750^\circ} CH_4 + \underset{\text{Ketene}}{CH_2{=}C{=}O}$$

by pyrolysis of acetone, and ordinarily used as soon as it is made.

In contrast to monocarboxylic acids, certain *di*carboxylic acids yield anhydrides on simple heating: in those cases where a five- or six-membered ring is produced. For example:



Ring size is crucial: with adipic acid, for example, anhydride formation would produce a seven-membered ring, and does not take place. Instead, carbon dioxide is lost and cyclopentanone, a ketone with a five-membered ring, is formed.



Problem 20.2 Cyclic anhydrides can be formed from only the *cis*-1,2-cyclopentanedicarboxylic acid, but from both the *cis*- and *trans*-1,2-cyclohexanedicarboxylic acids. How do you account for this?

Problem 20.3 *Maleic acid* ($C_4H_4O_4$, m.p. 130°, highly soluble in water, heat of combustion 327 kcal) and *fumaric acid* ($C_4H_4O_4$, m.p. 302°, insoluble in water, heat of combustion 320 kcal) are both dicarboxylic acids; they both decolorize Br_2 in CCl_4 and aqueous $KMnO_4$; on hydrogenation both yield succinic acid. When heated (maleic acid at 100°, fumaric acid at 250–300°), both acids yield the same anhydride, which is converted by cold water into maleic acid. Interpret these facts.

20.10 Reactions of acid anhydrides

Acid anhydrides undergo the same reactions as acid chlorides, but a little more slowly; where acid chlorides yield a molecule of HCl, anhydrides yield a molecule of carboxylic acid.

Compounds containing the acetyl group are often prepared from acetic anhydride; it is cheap, readily available, less volatile and more easily handled than acetyl chloride, and it does not form corrosive hydrogen chloride. It is widely used industrially for the esterification of the polyhydroxy compounds known as *carbohydrates*, especially cellulose (Chap. 35).

REACTIONS OF ACID ANHYDRIDES

1. Conversion into acids and acid derivatives. Discussed in Sec. 20.10.

$$(RCO)_2O + HZ \longrightarrow RCOZ + RCOOH$$

(a) Conversion into acids. Hydrolysis

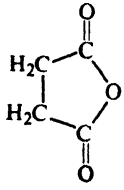
Example:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + H_2O \longrightarrow \underset{\text{Acetic acid}}{2CH_3COOH}$$

(b) Conversion into amides. Ammonolysis

Examples:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + 2NH_3 \longrightarrow \underset{\text{Acetamide}}{CH_3CONH_2} + \underset{\text{Ammonium acetate}}{CH_3COO^-NH_4^+}$$



Succinic anhydride

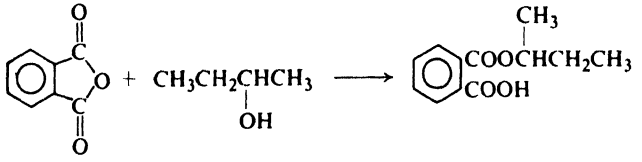
$$+ 2NH_3 \longrightarrow \underset{\text{Ammonium succinamate}}{\begin{matrix}CH_2CONH_2\\ |\\ CH_2COONH_4\end{matrix}} \xrightarrow{H^+} \underset{\text{Succinamic acid}}{\begin{matrix}CH_2CONH_2\\ |\\ CH_2COOH\end{matrix}}$$

(c) Conversion into esters. Alcoholysis

Examples:

$$(CH_3CO)_2O + CH_3OH \longrightarrow \underset{\text{Methyl acetate (An ester)}}{CH_3COOCH_3} + CH_3COOH$$

Acetic anhydride — Acetic acid



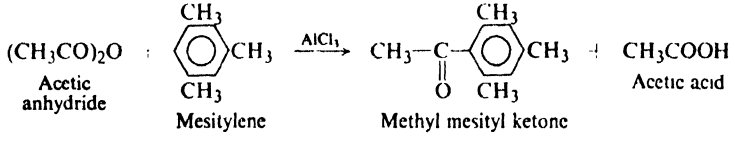
Phthalic anhydride *sec*-Butyl alcohol *sec*-Butyl hydrogen phthalate

2. Formation of ketones. Friedel-Crafts acylation. Discussed in Sec. 19.6.

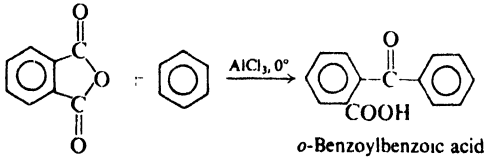
$$(RCO)_2O + ArH \xrightarrow[\text{or other Lewis acid}]{AlCl_3} R{-}\underset{\underset{O}{\|}}{C}{-}Ar + RCOOH$$

A ketone

Examples:



Acetic anhydride — Mesitylene — Methyl mesityl ketone — Acetic acid



Phthalic anhydride — *o*-Benzoylbenzoic acid

Only "half" of the anhydride appears in the acyl product; the other "half" forms a carboxylic acid. A cyclic anhydride, we see, undergoes exactly the same reactions as any other anhydride. However, since both "halves" of the anhydride are attached to each other by carbon–carbon bonds, the acyl compound and the carboxylic acid formed will have to be part of the same molecule. Cyclic anhydrides

can thus be used to make compounds containing both the acyl group and the carboxyl group: compounds that are, for example, both acids and amides, both acids and esters, etc. These difunctional compounds are of great value in further synthesis.

Problem 20.4 Give structural formulas for compounds A through G.

$$\text{Benzene} + \text{succinic anhydride} \xrightarrow{AlCl_3} A\ (C_{10}H_{10}O_3)$$

$$A + Zn(Hg) \xrightarrow{HCl} B\ (C_{10}H_{12}O_2)$$

$$B + SOCl_2 \longrightarrow C\ (C_{10}H_{11}OCl)$$

$$C \xrightarrow{AlCl_3} D\ (C_{10}H_{10}O)$$

$$D + H_2 \xrightarrow{Pt} E\ (C_{10}H_{12}O)$$

$$E + H_2SO_4 \xrightarrow{heat} F\ (C_{10}H_{10})$$

$$F \xrightarrow{Pt,\ heat} G\ (C_{10}H_8) + H_2$$

Problem 20.5 (a) What product will be obtained if D of the preceding problem is treated with C_6H_5MgBr and then water? (b) What will you finally get if the product from (a) replaces E in the preceding problem?

Problem 20.6 When heated with acid (e.g., concentrated H_2SO_4), *o*-benzoylbenzoic acid yields a product of formula $C_{14}H_8O_2$. What is the structure of this product? What general type of reaction has taken place?

Problem 20.7 Predict the products of the following reactions:

(a) toluene + phthalic anhydride + $AlCl_3$
(b) the product from (a) + conc. H_2SO_4 + heat

Problem 20.8 (a) The two 1,3-cyclobutanedicarboxylic acids (p. 302) have been assigned configurations on the basis of the fact that one can be converted into an anhydride and the other cannot. Which configuration would you assign to the one that can form the anhydride, and why? (b) The method of (a) cannot be used to assign configurations to the 1,2-cyclohexanedicarboxylic acids, since *both* give anhydrides. Why is this? (c) Could the method of (a) be used to assign configurations to the 1,3-cyclohexanedicarboxylic acids?

Problem 20.9 Alcohols are the class of compounds most commonly resolved (Sec. 7.9), despite the fact that they are not acidic enough or basic enough to form (stable) salts. Outline all steps in a procedure for the resolution of *sec*-butyl alcohol, using as resolving agent the base (−)-B.

AMIDES

20.11 Preparation of amides

In the laboratory amides are prepared by the reaction of ammonia with acid chlorides or, when available, acid anhydrides (Secs. 20.8 and 20.10). In industry they are often made by heating the ammonium salts of carboxylic acids.

20.12 Reactions of amides

An amide is hydrolyzed when heated with aqueous acids or aqueous bases. The products are ammonia and the carboxylic acid, although one product or the other is obtained in the form of a salt, depending upon the acidity or basicity of the medium.

Another reaction of importance, the Hoffmann degradation of amides, will be discussed later (Sec. 22.12).

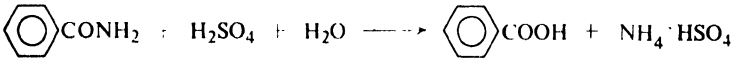
REACTIONS OF AMIDES

1. Hydrolysis. Discussed in Sec. 20.13.

$$RCONH_2 + H_2O \xrightarrow{H^+} RCOOH + NH_4^+$$

$$RCONH_2 + H_2O \xrightarrow{OH^-} RCOO^- + NH_3$$

Examples:



Benzamide — Benzoic acid

$$CH_3CH_2CH_2CONH_2 + NaOH + H_2O \longrightarrow CH_3CH_2CH_2COO^-Na^+ + NH_3$$

Butyramide — Sodium butyrate

2. Conversion into imides. Discussed in Sec. 20.14.

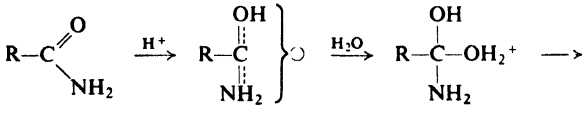
3. Hofmann degradation of amides. Discussed in Secs. 22.12 and 28.2–28.5.

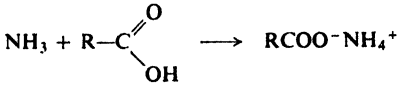
$$RCONH_2 \text{ or } ArCONH_2 \xrightarrow{OBr^-} RNH_2 \text{ or } ArNH_2 + CO_3^{--}$$

Amide — 1° amine

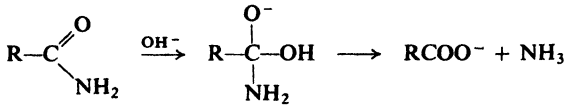
20.13 Hydrolysis of amides

Hydrolysis of amides is typical of the reactions of carboxylic acid derivatives. It involves nucleophilic substitution, in which the $-NH_2$ group is replaced by $-OH$. Under acidic conditions hydrolysis involves attack by water on the protonated amide:



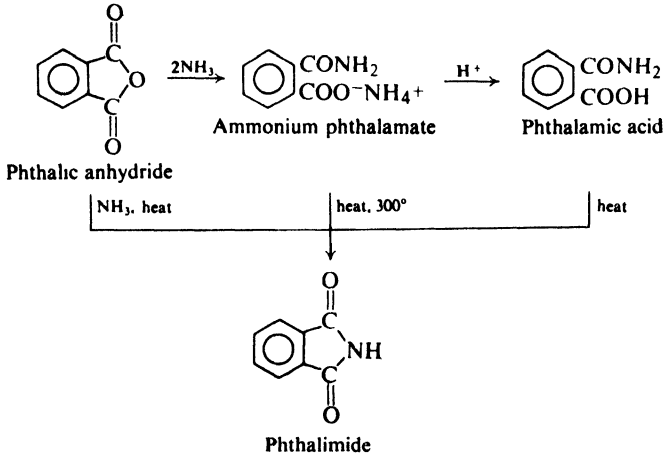


Under alkaline conditions hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the amide itself:



20.14 Imides

Like other anhydrides, cyclic anhydrides react with ammonia to yield amides; in this case the product contains both $-CONH_2$ and $-COOH$ groups. If this acid-amide is heated, a molecule of water is lost, a ring forms, and a product is obtained in which two acyl groups have become attached to nitrogen; compounds of this sort are called **imides**. Phthalic anhydride gives *phthalamic acid* and *phthalimide*:



Problem 20.10 Outline all steps in the synthesis of *succinimide* from succinic acid.

Problem 20.11 Account for the following sequence of acidities. (*Hint:* See Sec. 18.12.)

	K_a
Ammonia	10^{-33}
Benzamide	10^{-14} to 10^{-15}
Phthalimide	5×10^{-9}

ESTERS

20.15 Preparation of esters

Esters are usually prepared by the reaction of alcohols or phenols with acids or acid derivatives. The most common methods are outlined below.

PREPARATION OF ESTERS

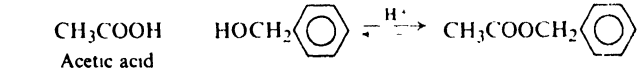
1. From acids. Discussed in Secs. 18.16 and 20.18.

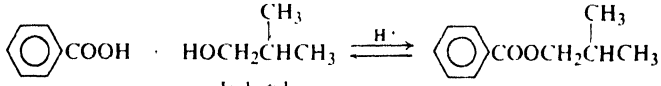
$$\underset{\text{Carboxylic acid}}{RCOOH} + \underset{\text{Alcohol}}{R'OH} \underset{}{\overset{H^+}{\rightleftharpoons}} \underset{\text{Ester}}{RCOOR'} + H_2O$$

R *may be alkyl or aryl*; R′ is *usually alkyl*

Reactivity of R′OH: 1° > 2° (> 3°)

Examples:



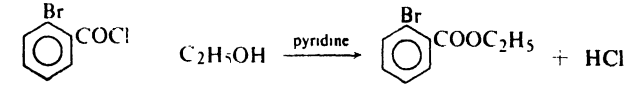


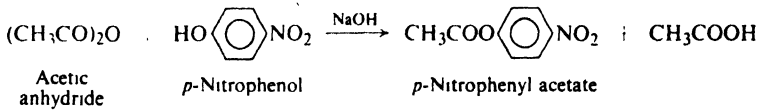
2. From acid chlorides or anhydrides. Discussed in Secs. 20.8 and 20.10.

$$RCOCl + R'OH \text{ (or ArOH)} \longrightarrow RCOOR' \text{ (or RCOOAr)} + HCl$$

$$(RCO)_2O + R'OH \text{ (or ArOH)} \longrightarrow RCOOR' \text{ (or RCOOAr)} + RCOOH$$

Examples:





3. From esters. Transesterification. Discussed in Sec. 20.20.

The direct reaction of alcohols or phenols with acids involves an equilibrium and—especially in the case of phenols—requires effort to drive to completion (see Sec. 18.16). In the laboratory, reaction with an acid chloride or anhydride is more commonly used.

The effect of the structure of the alcohol and of the acid on ease of esterification has already been discussed (Sec. 18.16).

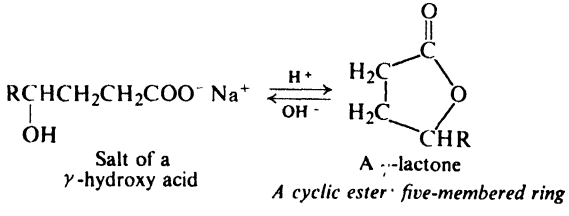
Table 20.2 ESTERS OF CARBOXYLIC ACIDS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Methyl acetate	−98	57.5	Ethyl formate	−80	54
Ethyl acetate	−84	77	Ethyl acetate	−84	77
n-Propyl acetate	−92	102	Ethyl propionate	−74	99
n-Butyl acetate	−77	126	Ethyl *n*-butyrate	−93	121
n-Pentyl acetate		148	Ethyl *n*-valerate	−91	146
Isopentyl acetate	−78	142	Ethyl stearate	34	215[15]
Benzyl acetate	−51	214	Ethyl phenylacetate		226
Phenyl acetate		196	Ethyl benzoate	−35	213

As was mentioned earlier, esterification using aromatic acid chlorides, ArCOCl, is often carried out in the presence of base (the Schotten-Baumann technique, Sec. 20.8).

Problem 20.12 When benzoic acid is esterified by methanol in the presence of a little sulfuric acid, the final reaction mixture contains five substances: benzoic acid, methanol, water, methyl benzoate, sulfuric acid. Outline a procedure for the separation of the pure ester.

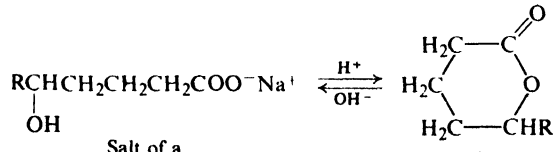
A hydroxy acid is both alcohol and acid. In those cases where a five- or six-membered ring can be formed, *intramolecular* esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield a cyclic ester known as a **lactone**. Treatment with base (actually hydrolysis of an ester) rapidly opens the



Salt of a γ-hydroxy acid

A γ-lactone

A cyclic ester: five-membered ring



Salt of a δ-hydroxy acid

A δ-lactone

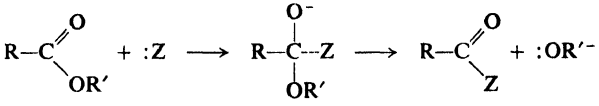
A cyclic ester: six-membered ring

lactone ring to give the open-chain salt. We shall encounter lactones again in our study of carbohydrates (Sec. 34.8).

Problem 20.13 Suggest a likely structure for the product formed by heating each of these acids. (a) *Lactic acid*, $CH_3CHOHCOOH$, gives *lactide*, $C_6H_8O_4$. (b) 10-Hydroxydecanoic acid gives a material of high molecular weight (1000–9000).

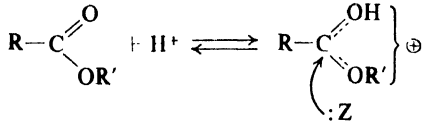
20.16 Reactions of esters

Esters undergo the nucleophilic substitution that is typical of carboxylic acid derivatives. Attack occurs at the electron-deficient carbonyl carbon, and results in the replacement of the —OR′ group by —OH, —OR″, or —NH_2:



$$:Z = :OH^-,\ :OR''^-,\ :NH_3$$

These reactions are sometimes carried out in the presence of acid. In these acid-catalyzed reactions, H^+ attaches itself to the oxygen of the carbonyl group, and thus renders carbonyl carbon even more susceptible to nucleophilic attack.

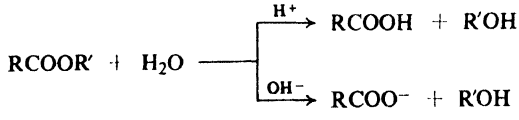


Acid catalysis:
makes carbon more susceptible to nucleophilic attack

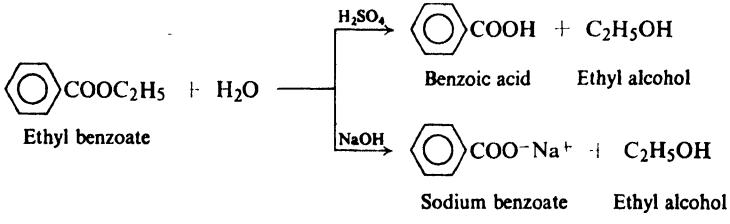
REACTIONS OF ESTERS

1. Conversion into acids and acid derivatives.

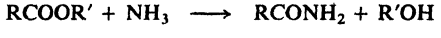
(a) Conversion into acids. Hydrolysis. Discussed in Secs. 20.17 and 20.18.



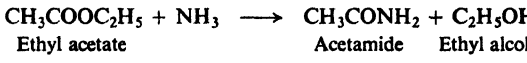
Example:



(b) Conversion into amides. Ammonolysis. Discussed in Sec. 20.19.



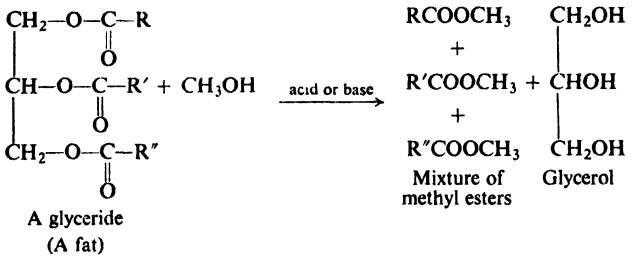
Example:



(c) **Conversion into esters. Transesterification. Alcoholysis.** Discussed in Sec. 20.20.

$$RCOOR' + R''OH \underset{}{\overset{\text{acid or base}}{\rightleftharpoons}} RCOOR'' + R'OH$$

Example:

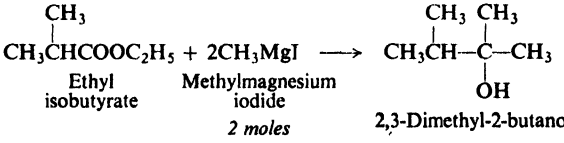


2. **Reaction with Grignard reagents.** Discussed in Sec. 20.21.

$$RCOOR' + 2R''MgX \longrightarrow R{-}\underset{\displaystyle OH}{\overset{\displaystyle R''}{\overset{|}{\underset{|}{C}}}}{-}R''$$

Tertiary alcohol

Example:



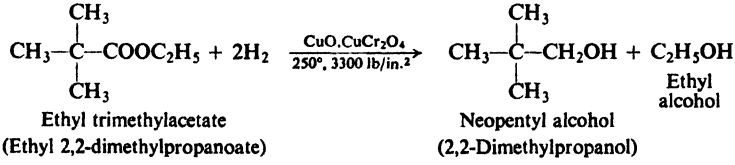
3. **Reduction to alcohols.** Discussed in Sec. 20.22.

(a) **Catalytic hydrogenation. Hydrogenolysis**

$$RCOOR' + 2H_2 \xrightarrow[\substack{250^\circ \\ 3000\text{–}6000\ \text{lb/in.}^2}]{CuO.CuCr_2O_4} RCH_2OH + R'OH$$

1° alcohol

Example:



(b) **Chemical reduction**

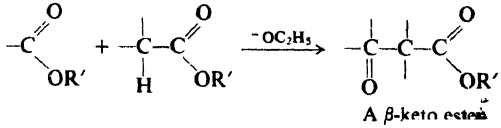
$$4RCOOR' + 2LiAlH_4 \xrightarrow[\text{ether}]{\text{anhyd.}} \left\{\begin{matrix} LiAl(OCH_2R)_4 \\ + \\ LiAl(OR')_4 \end{matrix}\right\} \xrightarrow{H^+} \left\{\begin{matrix} RCH_2OH \\ + \\ R'OH \end{matrix}\right\}$$

Example:

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_3 \xrightarrow{LiAlH_4} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

Methyl oleate (Methyl *cis*-9-octadecenoate) → Oleyl alcohol (*cis*-9-Octadecen-1-ol)

4. Reaction with carbanions. Claisen condensation. Discussed in Secs. 21.11 and 21.12.

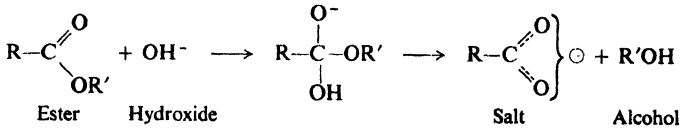


A β-keto ester

20.17 Alkaline hydrolysis of esters

A carboxylic ester is hydrolyzed to a carboxylic acid and an alcohol or phenol when heated with aqueous acid or aqueous base. Under alkaline conditions, of course, the carboxylic acid is obtained as its salt, from which it can be liberated by addition of mineral acid.

Base promotes hydrolysis of esters by providing the strongly nucleophilic reagent OH^-. This reaction is essentially irreversible, since a resonance-stabilized



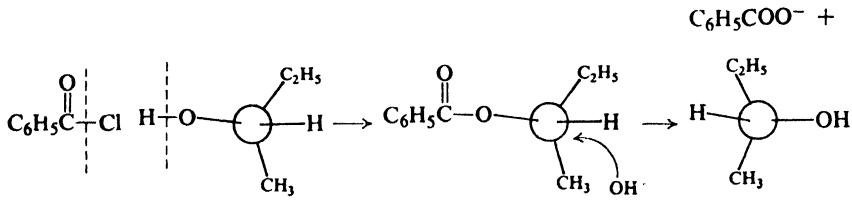
carboxylate anion (Sec. 18.13) shows little tendency to react with an alcohol.

Let us look at the various aspects of the mechanism we have written, and see what evidence there is for each of them.

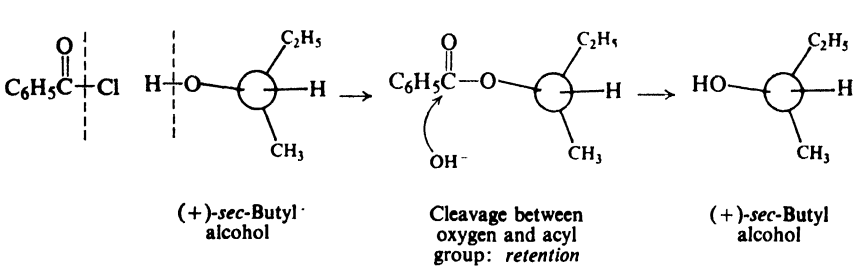
First, reaction involves attack on the ester by hydroxide ion. This is consistent with the **kinetics**, which is second-order, with the rate depending on both ester concentration and hydroxide concentration.

Next, hydroxide attacks at the carbonyl carbon and displaces alkoxide ion. That is to say, reaction involves cleavage of the bond between oxygen and the acyl group, $RCO\text{-}OR'$. For this there are two lines of evidence, the first being the **stereochemistry**.

Let us consider, for example, the formation and subsequent hydrolysis of an ester of optically active *sec*-butyl alcohol. Reaction of (+)-*sec*-butyl alcohol with benzoyl chloride must involve cleavage of the hydrogen–oxygen bond and hence cannot change the configuration about the chiral center (see Sec. 7.4). If hydrolysis of this ester involves cleavage of the bond between oxygen and the *sec*-butyl group, we would expect almost certainly inversion (or inversion plus racemization if the reaction goes by an S_N1 type of mechanism):

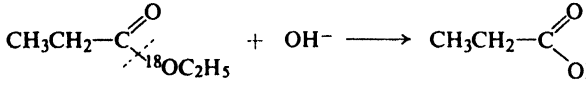


If, on the other hand, the bond between oxygen and the *sec*-butyl group remains intact during hydrolysis, then we would expect to obtain *sec*-butyl alcohol of the same configuration as the starting material:



When *sec*-butyl alcohol of rotation +13.8° was actually converted into the benzoate and the benzoate was hydrolyzed in alkali, there was obtained *sec*-butyl alcohol of rotation +13.8°. This complete retention of configuration strongly indicates that bond cleavage occurs between oxygen and the acyl group.

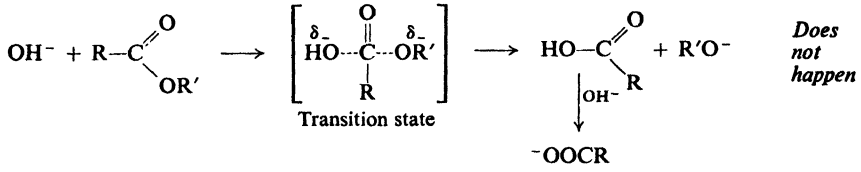
Tracer studies have confirmed the kind of bond cleavage indicated by the stereochemical evidence. When ethyl propionate labeled with ^{18}O was hydrolyzed by base in ordinary water, the ethanol produced was found to be enriched in ^{18}O; the propionic acid contained only the ordinary amount of ^{18}O:



The alcohol group retained the oxygen that it held in the ester; cleavage occurred between oxygen and the acyl group.

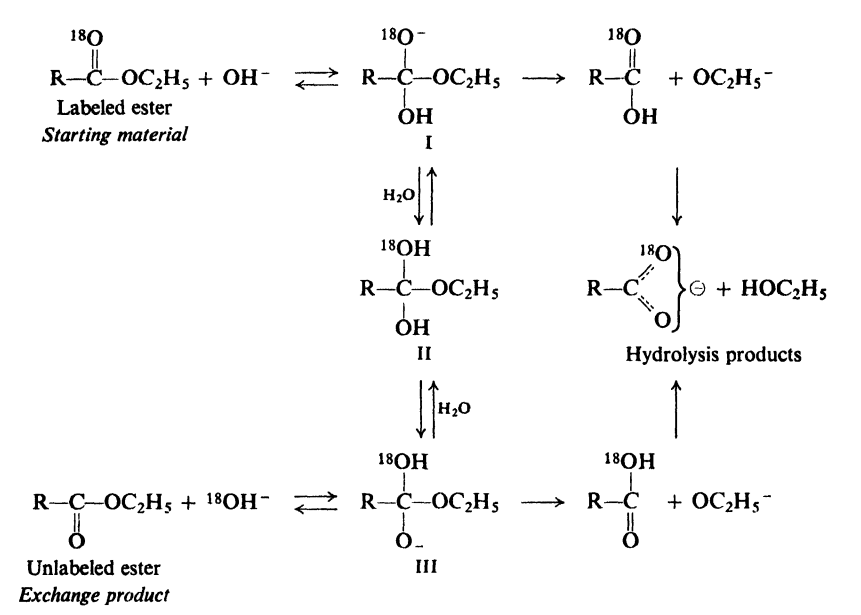
The study of a number of other hydrolyses by both tracer and stereochemical methods has shown that cleavage between oxygen and the acyl group is the usual one in ester hydrolysis. This behavior indicates that the preferred point of nucleophilic attack is the carbonyl carbon rather than the alkyl carbon; this is, of course, what we might have expected in view of the generally greater reactivity of carbonyl carbon (Sec. 20.5).

Finally, according to the mechanism, attack by hydroxide ion on carbonyl carbon does not displace alkoxide ion in one step,



but rather in *two steps* with the intermediate formation of a tetrahedral compound. These alternative mechanisms were considered more or less equally likely until 1950 when elegant work on **isotopic exchange** was reported by Myron Bender (now at Northwestern University).

Bender carried out the alkaline hydrolysis of carbonyl-labeled ethyl benzoate, $C_6H_5C^{18}OOC_2H_5$, in ordinary water, and focused his attention, not on the product, but on the *reactant.* He interrupted the reaction after various periods of time, and isolated the unconsumed ester and analyzed it for ^{18}O content. He found that in the alkaline solution the ester was undergoing not only hydrolysis but also *exchange of its* ^{18}O *for ordinary oxygen from the solvent.*



Oxygen exchange is not consistent with the one-step mechanism, which provides no way for it to happen. Oxygen exchange is consistent with a two-step mechanism in which intermediate I is not only formed, but partly reverts into starting material and partly is converted (probably via the neutral species II) into III—an intermediate that is equivalent to I except for the position of the label. If all this is so, the "reversion" of intermediate III into "starting material" yields ester that has lost its ^{18}O.

Bender's work does not *prove* the mechanism we have outlined. Conceivably, oxygen exchange—and hence the tetrahedral intermediate—simply represent a blind-alley down which ester molecules venture but which does not lead to hydrolysis. Such coincidence is unlikely, however, particularly in light of certain kinetic relationships between oxygen exchange and hydrolysis.

Similar experiments have indicated the reversible formation of tetrahedral intermediates in hydrolysis of other esters, amides, anhydrides, and acid chlorides, and are the basis of the general mechanism we have shown for nucleophilic acyl substitution.

Exchange experiments are also the basis of our estimate of the relative importance of the two steps: differences in rate of hydrolysis of acyl derivatives depend chiefly on how fast intermediates are formed, and also on what fraction of the intermediate goes on to product. As we have said, the rate of formation of the intermediate is affected by both electronic and steric factors: in the transition state, a negative charge is developing and carbon is changing from trigonal toward tetrahedral.

Even in those cases where oxygen exchange cannot be detected, we cannot rule out the possibility of an intermediate; it may simply be that it goes on to hydrolysis products much faster than it does anything else.

Problem 20.14 The relative rates of alkaline hydrolysis of ethyl *p*-substituted benzoates, *p*-$GC_6H_4COOC_2H_5$, are:

G =	NO_2	Cl	H	CH_3	OCH_3
	110	4	1	0.5	0.2

(a) How do you account for this order of reactivity? (b) What kind of effect, activating or deactivating, would you expect from *p*-Br? from *p*-NH_2? from *p*-$C(CH_3)_3$? (c) Predict the order of reactivity toward alkaline hydrolysis of: *p*-aminophenyl acetate, *p*-methylphenyl acetate, *p*-nitrophenyl acetate, phenyl acetate.

Problem 20.15 The relative rates of alkaline hydrolysis of alkyl acetates, CH_3COOR, are:

R =	CH_3	C_2H_5	$(CH_3)_2CH$	$(CH_3)_3C$
	1	0.6	0.15	0.008

(a) What two factors might be at work here? (b) Predict the order of reactivity toward alkaline hydrolysis of: methyl acetate, methyl formate, methyl isobutyrate, methyl propionate, and methyl trimethylacetate.

Problem 20.16 Exchange experiments show that the fraction of the tetrahedral intermediate that goes on to products follows the sequence:

acid chloride > acid anhydride > ester > amide

What is one factor that is probably at work here?

20.18 Acidic hydrolysis of esters

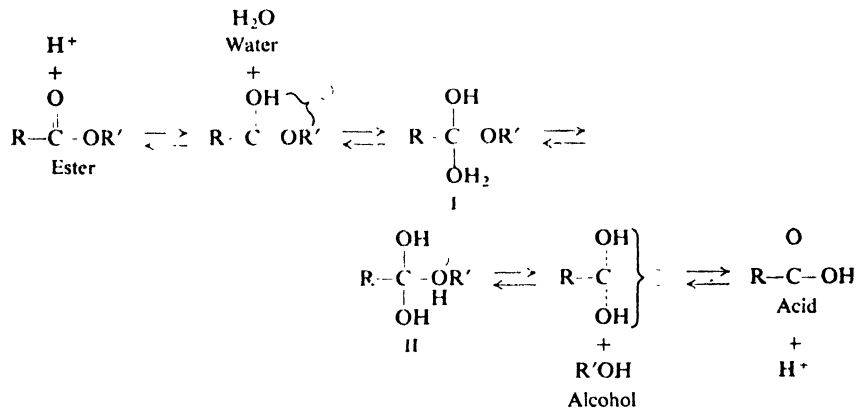
Hydrolysis of esters is promoted not only by base but also by acid. Acidic hydrolysis, as we have seen (Sec. 18.16), is reversible,

$$RCOOR' + H_2O \underset{H^+}{\overset{H^+}{\rightleftharpoons}} RCOOH + R'OH$$

and hence the mechanism for hydrolysis is also—taken in the opposite direction—

the mechanism for esterification. Any evidence about one reaction must apply to both.

The mechanism for acid-catalyzed hydrolysis and esterification is contained in the following equilibria:



Mineral acid speeds up both processes by protonating carbonyl oxygen and thus rendering carbonyl carbon more susceptible to nucleophilic attack (Sec. 20.4). In hydrolysis, the nucleophile is a water molecule and the leaving group is an alcohol; in esterification, the roles are exactly reversed.

As in alkaline hydrolysis, there is almost certainly a tetrahedral intermediate —or, rather, several of them. The existence of more than one intermediate is required by, among other things, the reversible nature of the reaction. Looking only at hydrolysis, intermediate II is *likely*, since it permits separation of the weakly basic alcohol molecule instead of the strongly basic alkoxide ion; but consideration of esterification shows that II almost certainly *must* be involved, since it is the product of attack by alcohol on the protonated acid.

The evidence for the mechanism is much the same as in alkaline hydrolysis. The position of cleavage, $RCO\overset{|}{\underset{|}{+}}OR'$ and $RCO\overset{|}{\underset{|}{+}}OH$, has been shown by ^{18}O studies of both hydrolysis and esterification. The existence of the tetrahedral intermediates was demonstrated, as in the alkaline reaction, by ^{18}O exchange between the carbonyl oxygen of the ester and the solvent.

Problem 20.17 Write the steps to account for exchange between $RC^{18}OOR'$ and H_2O in acidic solution. There is reason to believe that a key intermediate here is identical with one in alkaline hydrolysis. What might this intermediate be?

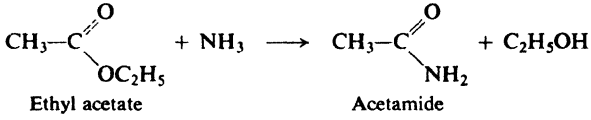
Problem 20.18 Account for the fact (Sec. 18.16) that the presence of bulky substituents in either the alcohol group or the acid group slows down both esterification and hydrolysis.

Problem 20.19 Acidic hydrolysis of *tert*-butyl acetate in water enriched in ^{18}O has been found to yield *tert*-butyl alcohol enriched in ^{18}O and acetic acid containing ordinary oxygen. Acidic hydrolysis of the acetate of optically active 3,7-dimethyl-3-octanol has been found to yield alcohol of much lower optical purity than the starting

alcohol, and having the opposite sign of rotation. (a) How do you interpret these two sets of results? (b) Is it surprising that these particular esters should show this kind of behavior?

20.19 Ammonolysis of esters

Treatment of an ester with ammonia, generally in ethyl alcohol solution, yields the amide. This reaction involves nucleophilic attack by a base, ammonia, on the electron-deficient carbon; the alkoxy group, —OR′, is replaced by —NH_2. For example:



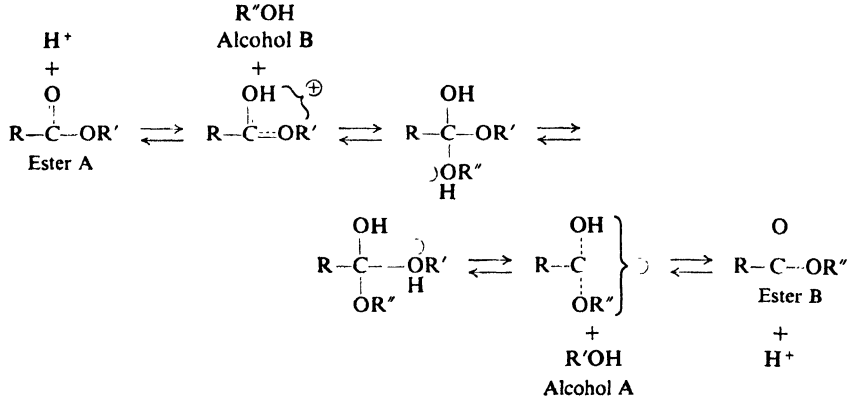
Ethyl acetate Acetamide

20.20 Transesterification

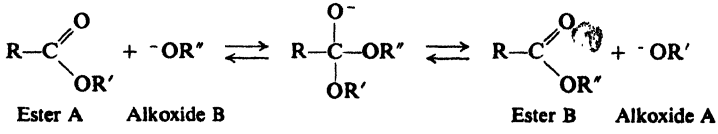
In the esterification of an acid, an alcohol acts as a nucleophilic reagent; in hydrolysis of an ester, an alcohol is displaced by a nucleophilic reagent. Knowing this, we are not surprised to find that one alcohol is capable of displacing another alcohol from an ester. This *alcoholysis* (cleavage by an alcohol) of an ester is called **transesterification.**

$$RCOOR' + R''OH \xrightleftharpoons{H^+ \text{ or } OR''^-} RCOOR'' + R'OH$$

Transesterification is catalyzed by acid (H_2SO_4 or dry HCl) or base (usually alkoxide ion). The mechanisms of these two reactions are exactly analogous to those we have already studied. For acid-catalyzed transesterification:



For base-catalyzed transesterification:

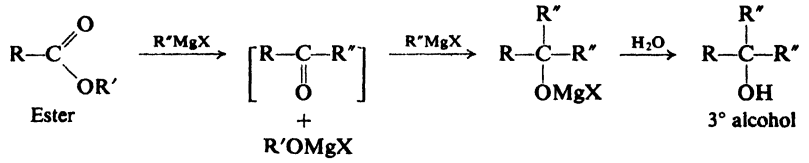


Ester A Alkoxide B Ester B Alkoxide A

Transesterification is an equilibrium reaction. To shift the equilibrium to the right, it is necessary to use a large excess of the alcohol whose ester we wish to make, or else to remove one of the products from the reaction mixture. The second approach is the better one when feasible, since in this way the reaction can be driven to completion.

20.21 Reaction of esters with Grignard reagents

The reaction of carboxylic esters with Grignard reagents is an excellent method for preparing tertiary alcohols. As in the reaction with aldehydes and ketones (Sec. 19.11), the nucleophilic (basic) alkyl or aryl group of the Grignard reagent attaches itself to the electron-deficient carbonyl carbon. Expulsion of the alkoxide group would yield a ketone, and in certain special cases ketones are indeed isolated from this reaction. However, as we know, ketones themselves readily react with Grignard reagents to yield tertiary alcohols (Sec. 15.13); in the present case the products obtained correspond to the addition of the Grignard reagent to such a ketone:



Two of the three groups attached to the carbon bearing the hydroxyl group in the alcohol come from the Grignard reagent and hence must be identical; this, of course, places limits upon the alcohols that can be prepared by this method. But, where applicable, reaction of a Grignard reagent with an ester is preferred to reaction with a ketone because esters are generally more accessible.

Problem 20.20 Starting from valeric acid, and using any needed reagents, outline the synthesis of 3-ethyl-3-heptanol via the reaction of a Grignard reagent with: (a) a ketone; (b) an ester.

Problem 20.21 (a) Esters of which acid would yield *secondary* alcohols on reaction with Grignard reagents? (b) Starting from alcohols of four carbons or fewer, outline all steps in the synthesis of 4-heptanol.

20.22 Reduction of esters

Like many organic compounds, esters can be reduced in two ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction. In either case, the ester is cleaved to yield (in addition to the alcohol or phenol from which it was derived) a primary alcohol corresponding to the acid portion of the ester.

$$\underset{\text{Ester}}{RCOOR'} \xrightarrow{\text{reduction}} \underset{1^\circ \text{ alcohol}}{RCH_2OH} + R'OH$$

Hydrogenolysis (cleavage by hydrogen) of an ester requires more severe conditions than simple hydrogenation of (addition of hydrogen to) a carbon–

carbon double bond. High pressures and elevated temperatures are required; the catalyst used most often is a mixture of oxides known as *copper chromite*, of approximately the composition $CuO.CuCr_2O_4$. For example:

$$\underset{\substack{\text{Methyl laurate}\\\text{(Methyl dodecanoate)}}}{CH_3(CH_2)_{10}COOCH_3} \xrightarrow[150°,\ 5000\ lb/in.^2]{H_2,\ CuO.CuCr_2O_4} \underset{\substack{\text{Lauryl alcohol}\\\text{(1-Dodecanol)}}}{CH_3(CH_2)_{10}CH_2OH} + CH_3OH$$

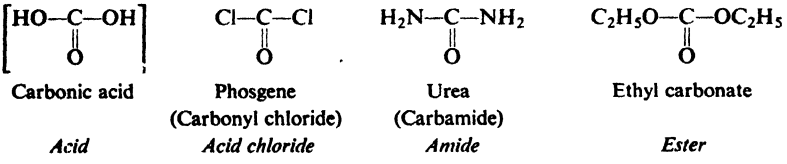
Chemical reduction is carried out by use of sodium metal and alcohol, or more usually by use of lithium aluminium hydride. For example:

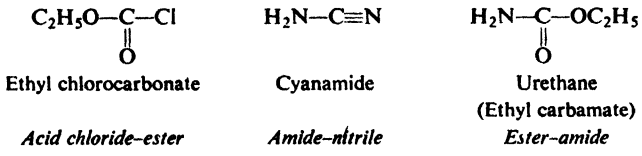
$$\underset{\substack{\text{Ethyl palmitate}\\\text{(Ethyl hexadecanoate)}}}{CH_3(CH_2)_{14}COOC_2H_5} \xrightarrow{LiAlH_4} \underset{\text{1-Hexadecanol}}{CH_3(CH_2)_{14}CH_2OH}$$

Problem 20.22 Predict the products of the hydrogenolysis of *n*-butyl oleate over copper chromite.

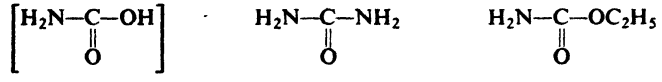
20.23 Functional derivatives of carbonic acid

Much of the chemistry of the functional derivatives of carbonic acid is already quite familiar to us through our study of carboxylic acids. The first step in dealing with one of these compounds is to recognize just how it is related to the parent acid. Since carbonic acid is bifunctional, each of its derivatives, too, contains two functional groups; these groups can be the same or different. For example:

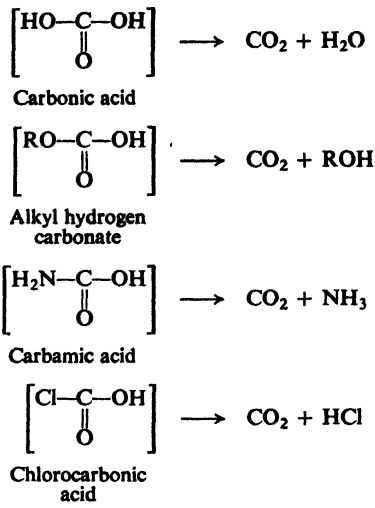




We use these functional relationships to carbonic acid simply for convenience. Many of these compounds could just as well be considered as derivatives of other acids, and, indeed, are often so named. For example:

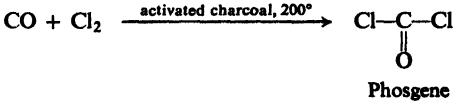


In general, a derivative of carbonic acid containing an —OH group is unstable, and decomposes to carbon dioxide. For example:

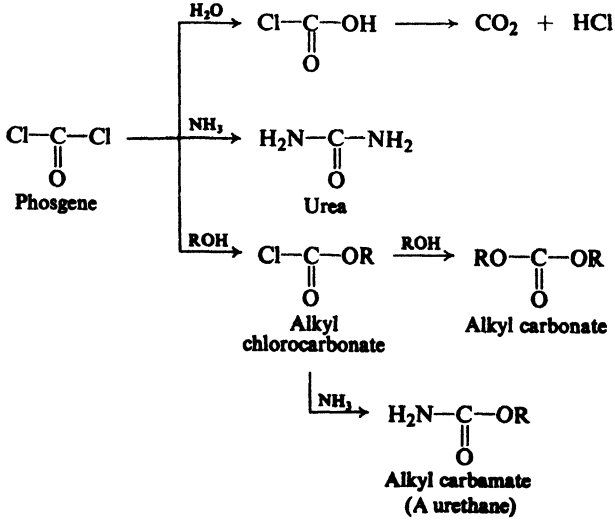


Most derivatives of carbonic acid are made from one of three industrially available compounds: phosgene, urea, or cyanamide.

Phosgene, $COCl_2$, a highly poisonous gas, is manufactured by the reaction between carbon monoxide and chlorine.



It undergoes the usual reactions of an acid chloride.



Problem 20.23 Suggest a possible synthesis of (a) 2-pentylurethane, $H_2NCOO\text{-}CH(CH_3)(n\text{-}C_3H_7)$, used as a hypnotic; (b) benzyl chlorocarbonate (*carbobenzoxy chloride*), $C_6H_5CH_2OCOCl$, used in the synthesis of peptides (Sec. 36.10).

Urea, H_2NCONH_2, is excreted in the urine as the chief nitrogen-containing end product of protein metabolism. It is synthesized on a large scale for use as a fertilizer and as a raw material in the manufacture of urea–formaldehyde plastics and of drugs.

$$CO_2 + 2NH_3 \rightleftharpoons \underset{\text{Ammonium carbamate}}{H_2NCOONH_4} \xrightleftharpoons{\text{heat, pressure}} \underset{\text{Urea}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2}$$

Urea is weakly basic, forming salts with strong acids. The fact that it is a stronger base than ordinary amides is attributed to resonance stabilization of the cation:

$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 + H^+ \rightleftharpoons \left[H_2N{-}\overset{\overset{\oplus OH}{\|}}{C}{-}NH_2 \quad H_2\overset{\oplus}{N}{=}\overset{\overset{OH}{|}}{C}{-}NH_2 \quad H_2N{-}\overset{\overset{OH}{|}}{C}{=}\overset{\oplus}{N}H_2 \right]$$

$$\textit{equivalent to} \quad \left\{ H_2N{=}\overset{\overset{OH}{\|}}{C}{=}NH_2 \right\}^{\oplus}$$

Problem 20.24 Account for the fact that *guanidine*, $(H_2N)_2C{=}NH$, is *strongly* basic.

Urea undergoes hydrolysis in the presence of acids, bases, or the enzyme *urease* (isolable from jack beans; generated by many bacteria, such as *Micrococcus ureae*).

$$\underset{\text{Urea}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2} \xrightarrow{H_2O} \begin{cases} \xrightarrow{H^+} NH_4^+ + CO_2 \\ \xrightarrow{OH^-} NH_3 + CO_3^{--} \\ \xrightarrow{\text{urease}} NH_3 + CO_2 \end{cases}$$

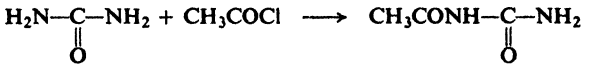
Urea reacts with nitrous acid to yield carbon dioxide and nitrogen; this is a useful way to destroy excess nitrous acid in diazotizations.

$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 \xrightarrow{HONO} CO_2 + N_2$$

Urea is converted by hypohalites into nitrogen and carbonate.

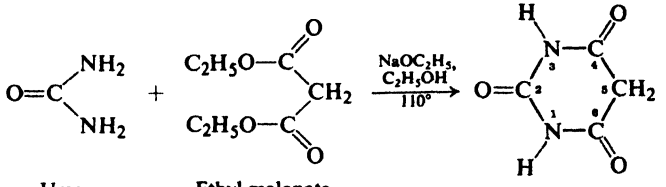
$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 \xrightarrow{Br_2\ OH^-} N_2 + CO_3^{--} + Br^-$$

Treatment of urea with acid chlorides or anhydrides yields **ureides.** Of special



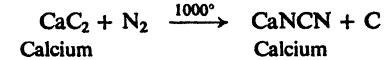
Acetylurea
A ureide

importance are the cyclic ureides formed by reaction with malonic esters; these are known as **barbiturates** and are important hypnotics (sleep-producers). For example:



Urea Ethyl malonate Barbituric acid (Malonylurea)

Cyanamide, $H_2N—C{\equiv}N$, is obtained in the form of its calcium salt by the high-temperature reaction between calcium carbide and nitrogen. This reaction is



Calcium carbide Calcium cyanamide

important as a method of nitrogen fixation; calcium cyanamide is used as a fertilizer, releasing ammonia by the action of water.

Problem 20.25 Give the electronic structure of the cyanamide anion, $(NCN)^{--}$. Discuss its molecular shape, bond lengths, and location of charge.

Problem 20.26 Give equations for the individual steps probably involved in the conversion of calcium cyanamide into ammonia in the presence of water. What other product or products will be formed in this process? Label each step with the name of the fundamental reaction type to which it belongs.

Problem 20.27 Cyanamide reacts with water in the presence of acid or base to yield urea; with methanol in the presence of acid to yield methylisourea, $H_2NC(=NH)OCH_3$; with hydrogen sulfide to yield *thiourea*, $H_2NC(=S)NH_2$; and with ammonia to yield *guanidine*, $H_2NC(=NH)NH_2$. (a) What functional group of cyanamide is involved in each of these reactions? (b) To what general class of reaction do these belong? (c) Show the most probable mechanisms for these reactions, pointing out the function of acid or base wherever involved.

20.24 Analysis of carboxylic acid derivatives. Saponification equivalent

Functional derivatives of carboxylic acids are recognized by their hydrolysis—under more or less vigorous conditions—to carboxylic acids. Just *which kind* of derivative it is is indicated by the other products of the hydrolysis.

Problem 20.28 Which kind (or kinds) of acid derivative: (a) rapidly forms a white precipitate (insoluble in HNO_3) upon treatment with alcoholic silver nitrate?

(b) reacts with boiling aqueous NaOH to liberate a gas that turns moist litmus paper blue? (c) reacts immediately with cold NaOH to liberate a gas that turns moist litmus blue? (d) yields *only* a carboxylic acid upon hydrolysis? (e) yields an alcohol when heated with acid or base?

Identification or proof of structure of an acid derivative involves the identification or proof of structure of the carboxylic acid formed upon hydrolysis (Sec. 18.21). In the case of an ester, the alcohol that is obtained is also identified (Sec. 16.11). (In the case of a substituted amide, Sec. 23.6, the amine obtained is identified, Sec. 23.19.)

If an ester is hydrolyzed in a known amount of base (taken in excess), the amount of base used up can be measured and used to give the **saponification equivalent**: the equivalent weight of the ester, which is similar to the neutralization equivalent of an acid (see Sec. 18.21).

$$\underset{\textit{one equivalent}}{RCOOR'} + \underset{\textit{one equivalent}}{OH^-} \longrightarrow RCOO^- + R'OH$$

Problem 20.29 (a) What is the saponification equivalent of *n*-propyl acetate? (b) There are eight other simple aliphatic esters that have the same saponification equivalent. What are they? (c) In contrast, how many simple aliphatic acids have this equivalent weight? (d) Is saponification equivalent as helpful in identification as neutralization equivalent?

Problem 20.30 (a) How many equivalents of base would be used up by one mole of methyl phthalate, *o*-$C_6H_4(COOCH_3)_2$? What is the saponification equivalent of methyl phthalate? (b) What is the relation between saponification equivalent and the number of ester groups per molecule? (c) What is the saponification equivalent of glyceryl stearate (tristearoylglyerol)?

20.25 Spectroscopic analysis of carboxylic acid derivatives

Infrared. The infrared spectrum of an acyl compound shows the strong band in the neighborhood of 1700 cm^{-1} that we have come to expect of C=O stretching (see Fig. 20.1).

The exact frequency depends on the family the compound belongs to (see Table 20.3, p. 689) and, for a member of a particular family, on its exact structure. For esters, for example:

C=O stretching, *strong*

RCOOR 1740 cm^{-1}	ArCOOR 1715–1730 cm^{-1}	RCOOAr 1770 cm^{-1}
	or	or
	$-\overset{|}{C}=\overset{|}{C}-COOR$	$RCOO\overset{|}{C}=\overset{|}{C}-$

Esters are distinguished from acids by the absence of the O—H band. They are distinguished from ketones by two strong C—O stretching bands in the 1050–1300 cm^{-1} region; the exact position of these bands, too, depends on the ester's structure.

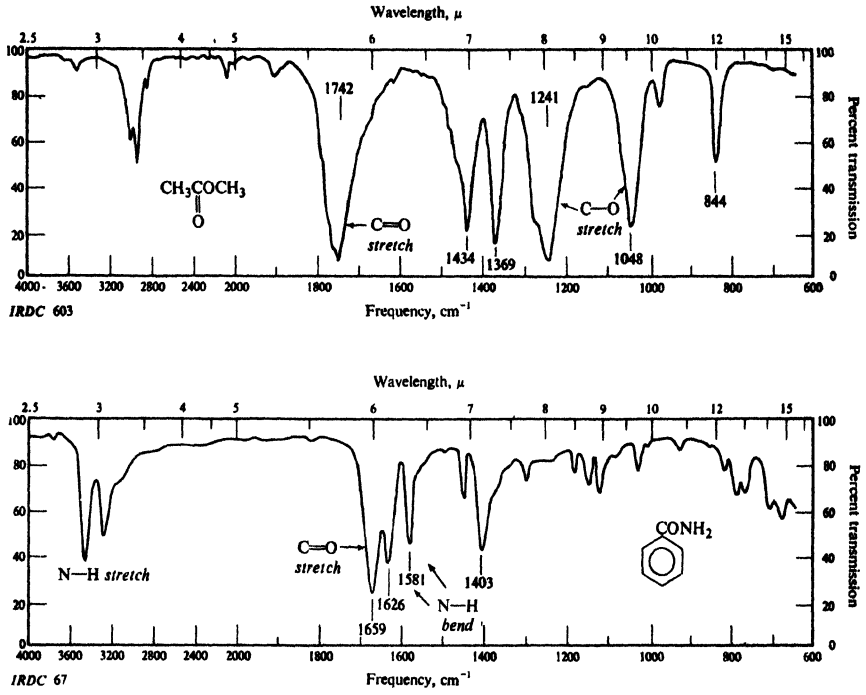


Figure 20.1. Infrared spectra of (*a*) methyl acetate and (*b*) benzamide.

Besides the carbonyl band, amides ($RCONH_2$) show absorption due to N—H stretching in the 3050–3550 cm^{-1} region (the number of bands and their location depending on the degree of hydrogen bonding), and absorption due to N—H bending in the 1600–1640 cm^{-1} region.

Table 20.3 INFRARED ABSORPTION BY SOME OXYGEN COMPOUNDS

Compound	O—H	C—O	C=O
Alcohols	3200–3600 cm^{-1}	1000–1200 cm^{-1}	—
Phenols	3200–3600	1140–1230	—
Ethers, aliphatic	—	1060–1150	—
Ethers, aromatic	—	1200–1275 1020–1075	—
Aldehydes, ketones	—	—	1675–1725 cm^{-1}
Carboxylic acids	2500–3000	1250	1680–1725
Esters	—	1050–1300 (*two bands*)	1715–1740
Acid chlorides	—	—	1750–1810
Amides ($RCONH_2$)	(N—H 3050–3550)	—	1650–1690

Nmr. As we can see in Table 13.4 (p. 421), the protons in the alkyl portion of an ester ($RCOOCH_2R'$) absorb farther downfield than the protons in the acyl portion (RCH_2COOR').

Absorption by the —CO—NH protons of an amide appears in the range δ 5–8, typically as a broad, low hump.

PROBLEMS

1. Draw structures and give names of:

(a) nine isomeric esters of formula $C_5H_{10}O_2$
(b) six isomeric esters of formula $C_8H_8O_2$
(c) three isomeric methyl esters of formula $C_7H_{12}O_4$

2. Write balanced equations, naming all organic products, for the reaction (if any) of *n*-butyryl chloride with:

(a) H_2O
(b) isopropyl alcohol
(c) *p*-nitrophenol
(d) ammonia
(e) toluene, $AlCl_3$
(f) nitrobenzene, $AlCl_3$
(g) $NaHCO_3$ (aq)
(h) alcoholic $AgNO_3$
(i) CH_3NH_2
(j) $(CH_3)_2NH$
(k) $(CH_3)_3N$
(l) $C_6H_5NH_2$
(m) $(C_6H_5)_2Cd$
(n) C_6H_5MgBr

(Check your answers to (i) through (l) in Sec. 23.6.)

3. Answer Problem 2, parts (a) through (l) for acetic anhydride.

4. Write equations to show the reaction (if any) of succinic anhydride with:

(a) hot aqueous NaOH
(b) aqueous ammonia
(c) aqueous ammonia, then cold dilute HCl
(d) aqueous ammonia, then strong heat
(e) benzyl alcohol
(f) toluene, $AlCl_3$, heat

5. Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetamide with:

(a) hot HCl (aq)
(b) hot NaOH (aq)

6. Answer Problem 5 for phenylacetonitrile.

7. Write balanced equations, naming all organic products, for the reaction (if any) of methyl *n*-butyrate with:

(a) hot H_2SO_4 (aq)
(b) hot KOH (aq)
(c) isopropyl alcohol + H_2SO_4
(d) benzyl alcohol + $C_6H_5CH_2ONa$
(e) ammonia
(f) phenylmagnesium bromide
(g) isobutylmagnesium bromide
(h) $LiAlH_4$, then acid

8. Outline the synthesis of each of the following labeled compounds, using $H_2{}^{18}O$ as the source of ^{18}O.

(a) $C_6H_5-\overset{\overset{O}{\|}}{C}-{}^{18}OCH_3$ (b) $C_6H_5-\overset{\overset{{}^{18}O}{\|}}{C}-OCH_3$ (c) $C_6H_5-\overset{\overset{{}^{18}O}{\|}}{C}-{}^{18}OCH_3$

Predict the product obtained from each upon alkaline hydrolysis in ordinary H_2O.

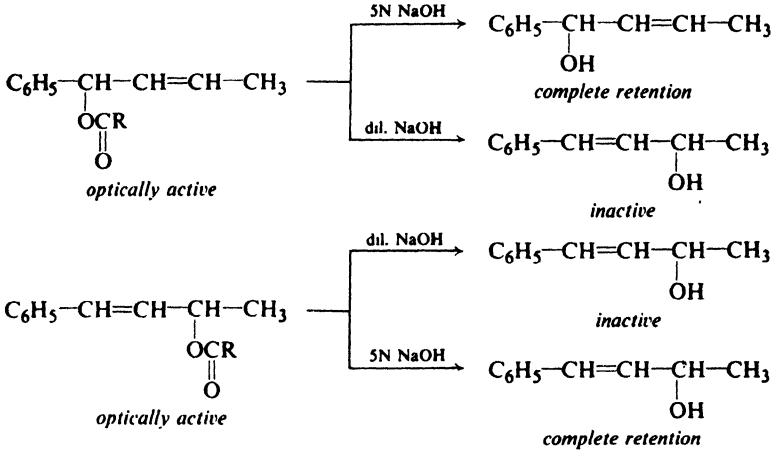
9. Outline the synthesis of each of the following labeled compounds, using $^{14}CO_2$ or $^{14}CH_3OH$ and $H_2{}^{18}O$ as the source of the "tagged" atoms.

(a) $CH_3CH_2{}^{14}COCH_3$
(b) $CH_3CH_2CO{}^{14}CH_3$
(c) $CH_3{}^{14}CH_2COCH_3$
(d) $^{14}CH_3CH_2COCH_3$
(e) $C_6H_5{}^{14}CH_2CH_3$
(f) $C_6H_5CH_2{}^{14}CH_3$
(g) $CH_3CH_2C{}^{18}OCH_3$

10. Predict the product of the reaction of γ-butyrolactone with (a) ammonia, (b) $LiAlH_4$, (c) $C_2H_5OH + H_2SO_4$.

11. When *sec*-butyl alcohol of rotation $+13.8°$ was treated with tosyl chloride, and the resulting tosylate was allowed to react with sodium benzoate, there was obtained *sec*-butyl benzoate. Alkaline hydrolysis of this ester gave *sec*-butyl alcohol of rotation $-13.4°$. In which step must inversion have taken place? How do you account for this?

12. Account for the following observations. (*Hint:* See Sec. 14.13, and Problem 14.9 on p. 473.)



13. An unknown compound is believed to be one of the following, all of which boil within a few degrees of each other. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible use simple chemical tests; where necessary use more elaborate chemical methods like quantitative hydrogenation, cleavage, neutralization equivalent, saponification equivalent, etc. Make use of any needed tables of physical constants.

benzyl acetate	methyl *o*-toluate
ethyl benzoate	methyl *m*-toluate
isopropyl benzoate	methyl *p*-toluate
methyl phenylacetate	

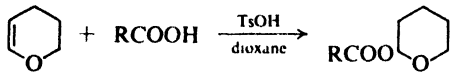
14. Describe simple chemical tests that would serve to distinguish between:

(a) propionic acid and methyl acetate
(b) *n*-butyryl chloride and *n*-butyl chloride
(c) *p*-nitrobenzamide and ethyl *p*-nitrobenzoate
(d) glyceryl tristearate and glyceryl trioleate
(e) benzonitrile and nitrobenzene
(f) acetic anhydride and *n*-butyl alcohol
(g) glyceryl monopalmitate and glyceryl tripalmitate
(h) ammonium benzoate and benzamide
(i) *p*-bromobenzoic acid and benzoyl bromide

Tell exactly what you would *do* and *see*.

15. Tell how you would separate by chemical means the following mixtures, recovering each component in reasonably pure form: (a) benzoic acid and ethyl benzoate; (b) *n*-valeronitrile and *n*-valeric acid; (c) ammonium benzoate and benzamide. Tell exactly what you would do and see.

16. Carboxyl groups are often masked by reaction with **dihydropyran**, which yields esters that are stable toward base but easily hydrolyzed by dilute aqueous acids. Account in detail both for the formation of these esters and for their ease of hydrolysis. (*Hint*: See Sec. 19.15.)



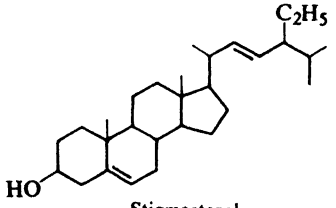
Dihydropyran (DHP) — Tetrahydropyranyl ester (RCOOTHP)

17. Treatment of 2,4-pentanedione with KCN and acetic acid, followed by hydrolysis, gives two products, A and B. Both A and B are dicarboxylic acids of formula $C_7H_{12}O_6$. A melts at 98°. When heated, B gives first a lactonic acid ($C_7H_{10}O_5$, m.p. 90°) and finally a dilactone ($C_7H_8O_4$, m.p. 105°). (a) What structure must B have that permits ready formation of both a monolactone and a dilactone? (b) What is the structure of A? (*Hint:* Use models.)

18. Give the structures (including configurations where pertinent) of compounds C through O.

(a) Urea (H_2NCONH_2) + hot dilute NaOH $\longrightarrow$ C + NH_3
(b) Phosgene ($COCl_2$) + 1 mole C_2H_5OH, then + NH_3 $\longrightarrow$ D ($C_3H_7O_2N$)
(c) bromobenzene + Mg, ether $\longrightarrow$ E (C_6H_5MgBr)
E + ethylene oxide, followed by H^+ $\longrightarrow$ F ($C_8H_{10}O$)
F + PBr_3 $\longrightarrow$ G (C_8H_9Br)
G + NaCN $\longrightarrow$ H (C_9H_9N)
H + H_2SO_4, H_2O, heat $\longrightarrow$ I ($C_9H_{10}O_2$)
I + $SOCl_2$ $\longrightarrow$ J (C_9H_9OCl)
J + anhydrous HF $\longrightarrow$ K (C_9H_8O)
K + H_2, catalyst $\longrightarrow$ L ($C_9H_{10}O$)
L + H_2SO_4, warm $\longrightarrow$ M (C_9H_8)
(d) *trans*-2-methylcyclohexanol + acetyl chloride $\longrightarrow$ N
N + NaOH (aq) + heat $\longrightarrow$ O + sodium acetate

19. *Progesterone* is a hormone, secreted by the corpus luteum, that is involved in the control of pregnancy. Its structure was established, in part, by the following synthesis from the steroid *stigmasterol*, obtained from soybean oil.



Stigmasterol

Stigmasterol ($C_{29}H_{48}O$) + $(CH_3CO)_2O$ $\longrightarrow$ P ($C_{31}H_{50}O_2$)
P + Br_2 $\longrightarrow$ Q ($C_{31}H_{50}O_2Br_2$)
Q + O_3, then Ag_2O $\longrightarrow$ R ($C_{24}H_{36}O_4Br_2$)
R + Zn/CH_3COOH $\longrightarrow$ S ($C_{24}H_{36}O_4$)
S + C_2H_5OH, H^+ $\longrightarrow$ T ($C_{26}H_{40}O_4$)
T + C_6H_5MgBr, then H_2O $\longrightarrow$ U ($C_{36}H_{46}O_3$)

U + acid, warm $\longrightarrow$ V ($C_{36}H_{44}O_2$)
V + Br_2; then CrO_3, H^+ $\longrightarrow$ W ($C_{23}H_{34}O_3Br_2$)
W + Zn/CH_3COOH $\longrightarrow$ X ($C_{23}H_{34}O_3$)
X + H_2O, H^+, heat $\longrightarrow$ Y ($C_{21}H_{32}O_2$), *pregnenolone*
Y + Br_2; then CrO_3, H^+ $\longrightarrow$ Z ($C_{21}H_{30}O_2Br_2$)
Z + Zn/CH_3COOH $\longrightarrow$ *progesterone* ($C_{21}H_{30}O_2$)

(a) Give structures for progesterone and the intermediates P–Z.

(b) Progesterone shows strong absorption in the near ultraviolet: λ_{max} 240 mμ, ϵ_{max} 17,600. On this basis, what is the structure for progesterone?

20. On the basis of the following evidence assign structures to: (a) Compounds AA to DD, isomers of formula $C_3H_8O_2$; (b) compounds EE to MM, isomers of formula $C_3H_6O_2$. (*Note:* α-Hydroxy ketones, —CHOH—CO—, give positive tests with Tollens' reagent and with Fehling's and Benedict's solutions (p. 1075), but negative Schiff's tests.

		$NaHCO_3$	*Acetic anhydride*	*Tollens'*	*Schiff's*	*HIO_4*
(a)	AA	—	$C_7H_{12}O_4$	−	−	−
	BB	−	$C_7H_{12}O_4$	−	−	+
	CC	−	$C_5H_{10}O_3$	−	−	−
	DD	−	−	−[1]	−[1]	−
(b)	EE	−	$C_5H_8O_3$	+	+	+
	FF	−	$C_5H_8O_3$	+	−	+
	GG	−	$C_5H_8O_3$	+	+	−
	HH	CO_2	−	−	−	−
	II	−[2]	−	+	−	−
	JJ	−	−	−	−	−
	KK	−	$C_7H_{10}O_4$	−	−	+
	LL	−	−	−[1]	−[1]	−[1]
	MM	−	$C_5H_8O_3$	−	−	−[1]

[1] After treatment with dilute acid, solution gives positive test.
[2] After treatment with NaOH, solution gives positive iodoform test.

21. 2,5-Dimethyl-1,1-cyclopentanedicarboxylic acid can be prepared as a mixture of two optically inactive substances of different physical properties, NN and OO. When each is heated and the reaction mixture worked up by fractional crystallization, NN yields a single product, PP, of formula $C_8H_{14}O_2$, and OO yields two products, QQ and RR, both of formula $C_8H_{14}O_2$.

(a) Give stereochemical formulas for NN, OO, PP, QQ, and RR. (b) Describe another method by which you could assign configurations to NN and OO.

22. (a) (−)-*Erythrose*, $C_4H_8O_4$, gives tests with Tollens' reagent and Benedict's solution (p. 1075), and is oxidized by bromine water to an optically active acid, $C_4H_8O_5$. Treatment with acetic anhydride yields $C_{10}H_{14}O_7$. Erythrose consumes three moles of HIO_4 and yields three moles of formic acid and one mole of formaldehyde. Oxidation of erythrose by nitric acid yields an *optically inactive* compound of formula $C_4H_6O_6$.

(−)-*Threose*, an isomer of erythrose, shows similar chemical behavior except that nitric acid oxidation yields an *optically active* compound of formula $C_4H_6O_6$.

On the basis of this evidence what structure or structures are possible for (−)-erythrose? For (−)-threose?

(b) When R-glyceraldehyde, $CH_2OHCHOHCHO$, is treated with cyanide and the resulting product is hydrolyzed, two monocarboxylic acids are formed (see Problem 12, p. 649). These acids are identical with the acids obtained by oxidation with bromine water of (−)-threose and (−)-erythrose.

Assign a single structure to (−)-erythrose and to (−)-threose.

23. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 20.2 (p. 695)?

ethyl acetate
ethyl acrylate (CH_2=$CHCOOC_2H_5$)
isobutyric acid
methacrylic acid [CH_2=$C(CH_3)COOH$]
methacrylamide [CH_2=$C(CH_3)CONH_2$]
phenylacetamide

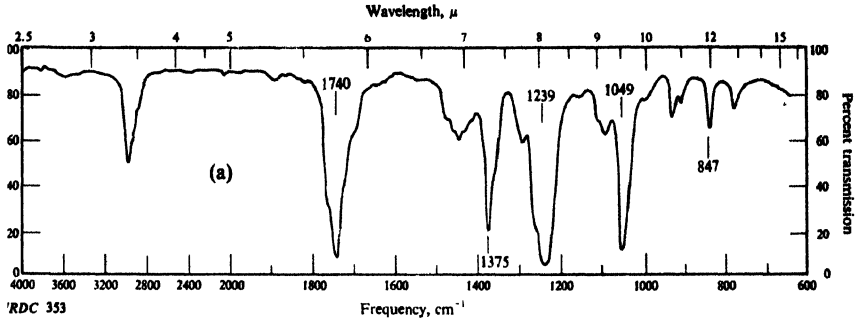
24. Give a structure or structures consistent with each of the nmr spectra shown in Fig. 20.3 (p. 696).

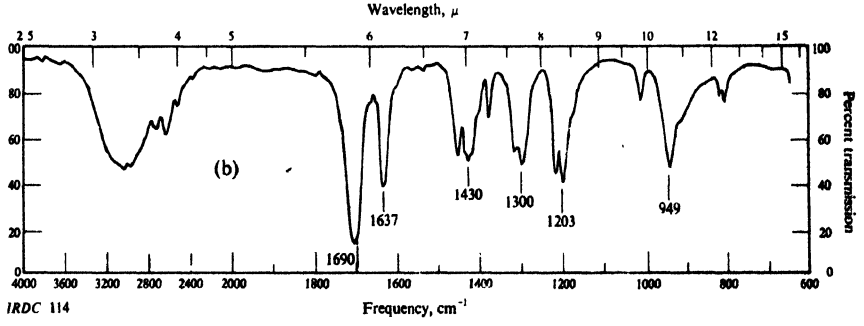
25. Give the structures of compounds SS, TT, and UU on the basis of their infrared spectra (Fig. 20.4, p. 697) and their nmr spectra (Fig. 20.5, p. 698).

26. Give a structure or structures consistent with the nmr spectrum shown in Fig. 20.6 (p. 699).

27. Give the structure of compound VV on the basis of its infrared and nmr spectra shown in Fig. 20.7 (p. 699).

28. Give a structure or structures consistent with each of the nmr spectra shown in Fig. 20.8 (p. 700).





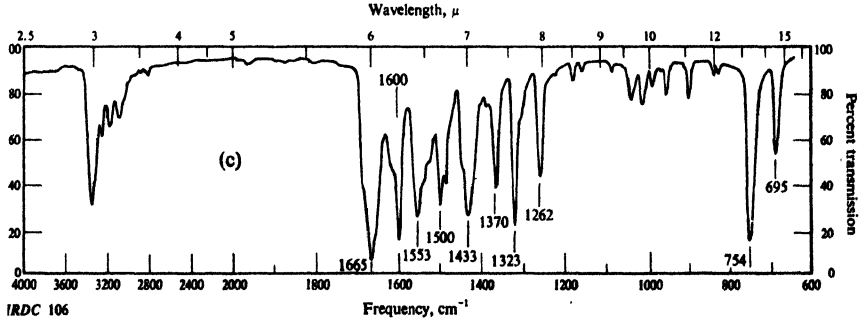


Figure 20.2. Infrared spectra for Problem 23, p. 694.

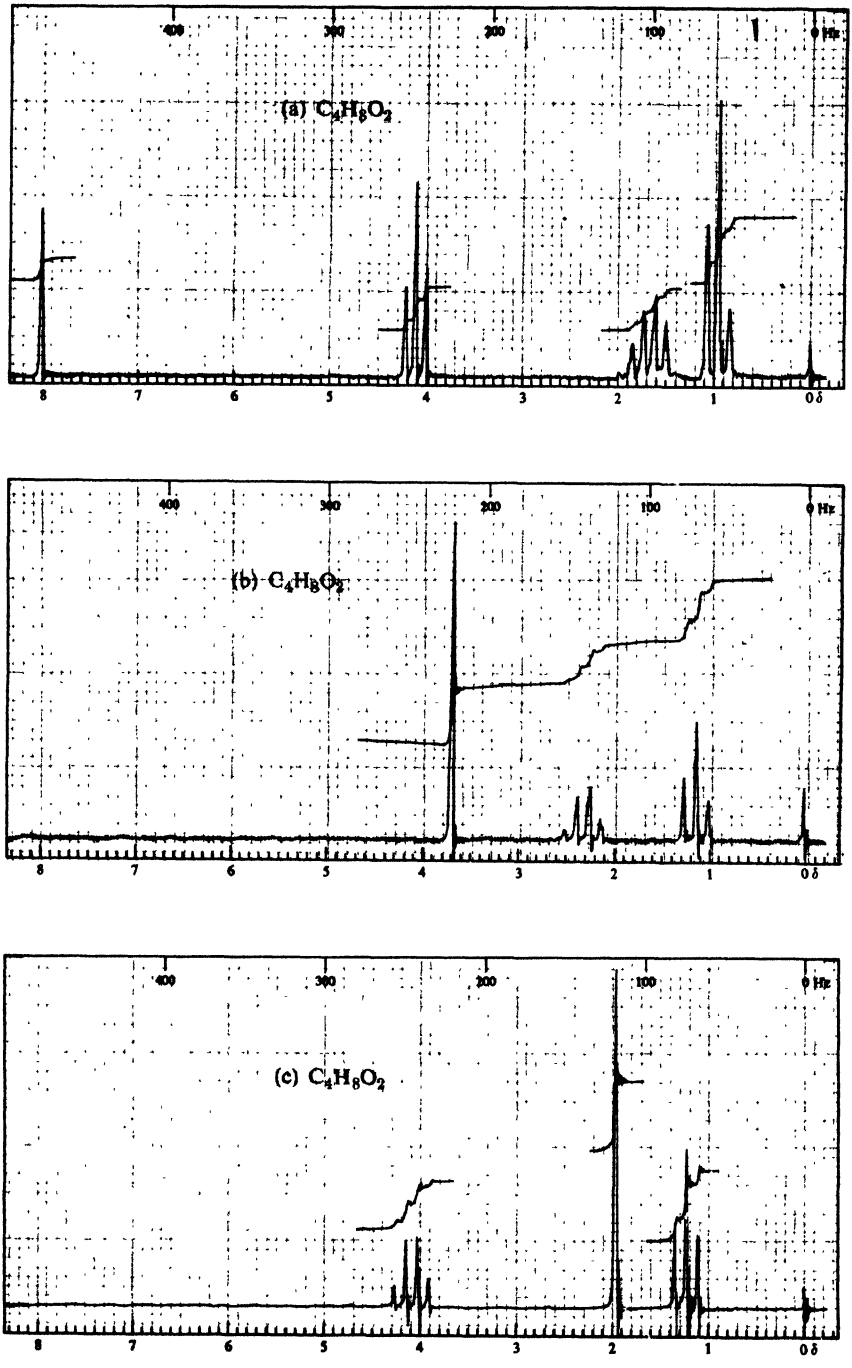
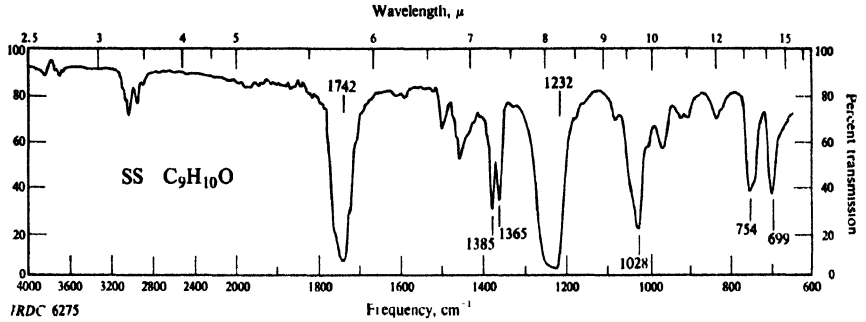
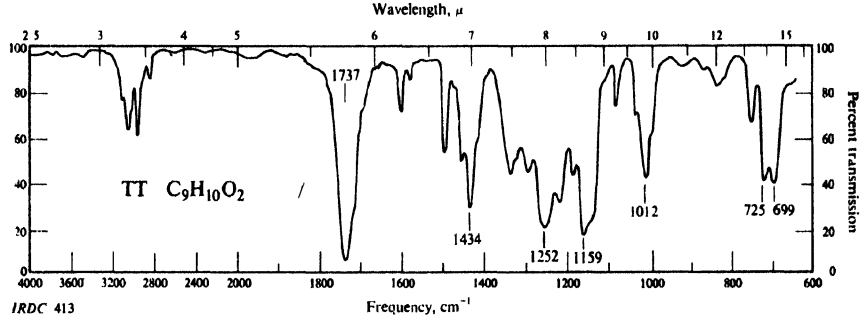


Figure 20.3. Nmr spectra for Problem 24, p. 694.





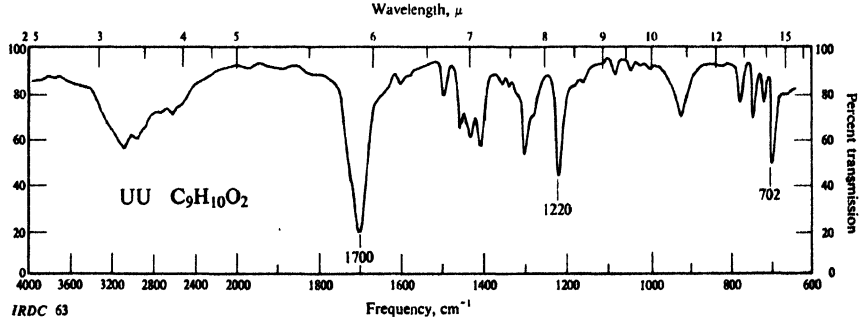


Figure 20.4. Infrared spectra for Problem 25, p. 694.

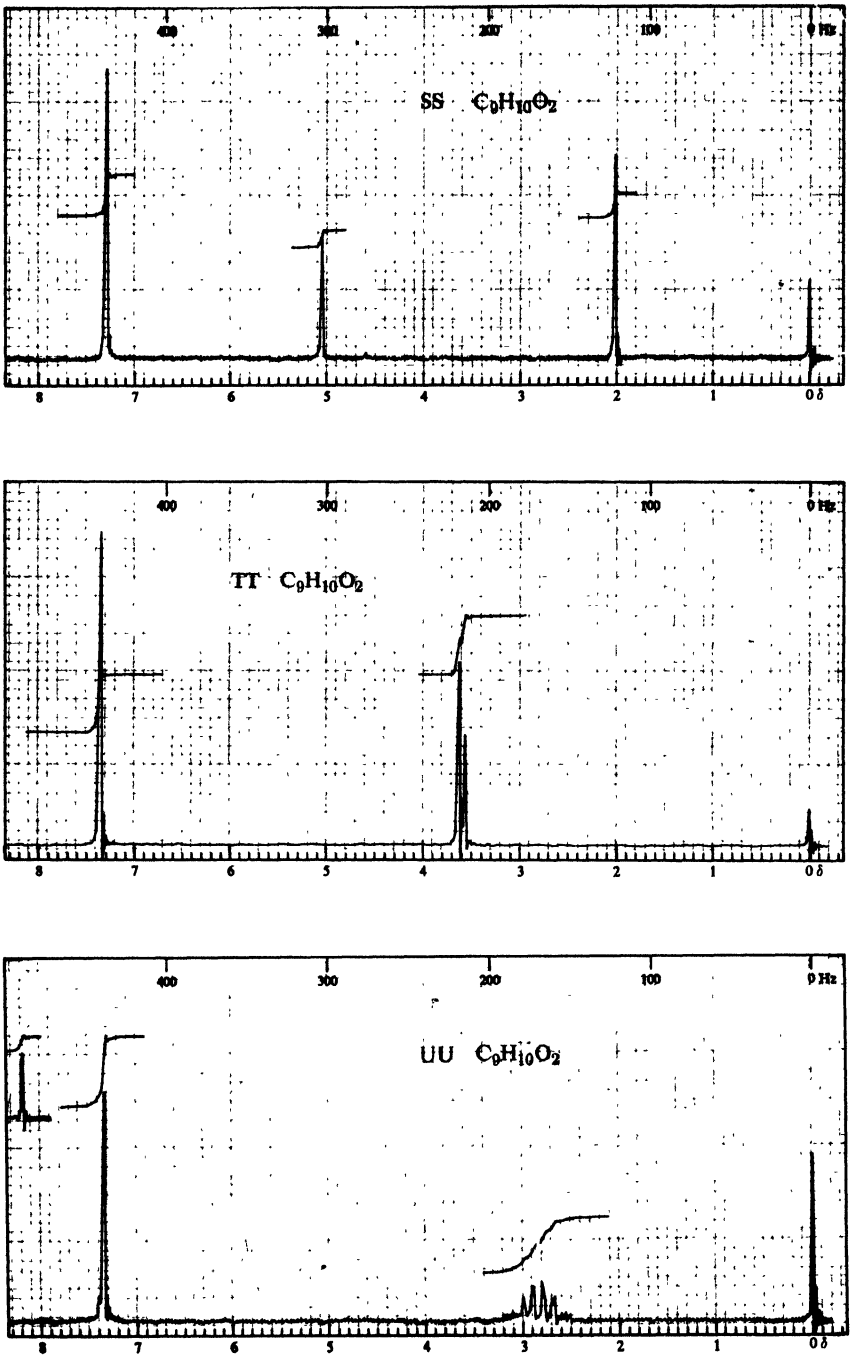


Figure 20.5. Nmr spectra for Problem 25, p. 694.

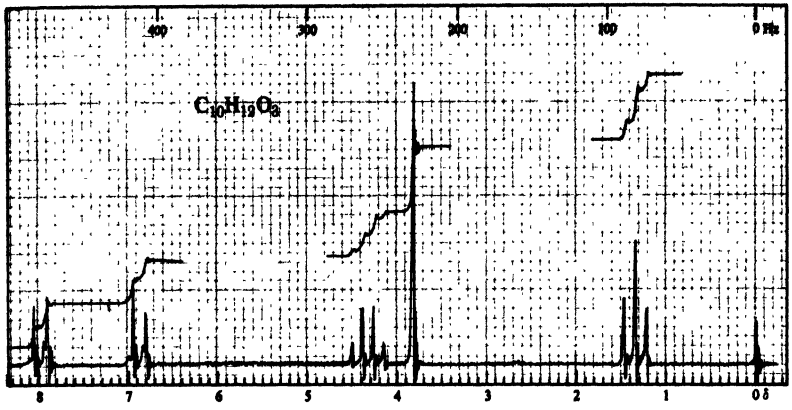
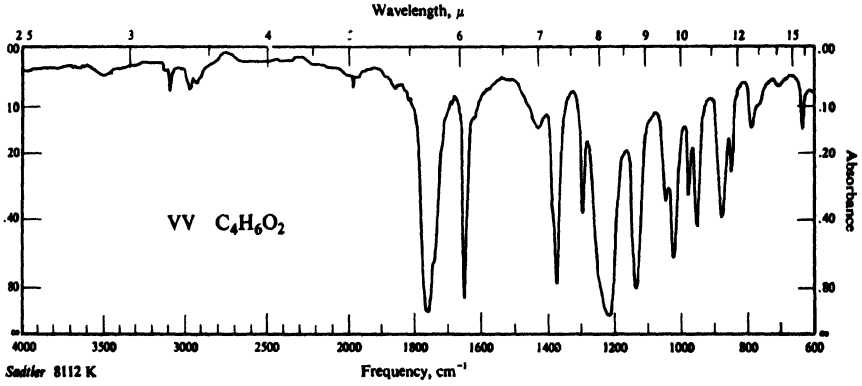


Figure 20.6. Nmr spectrum for Problem 26, p. 694.



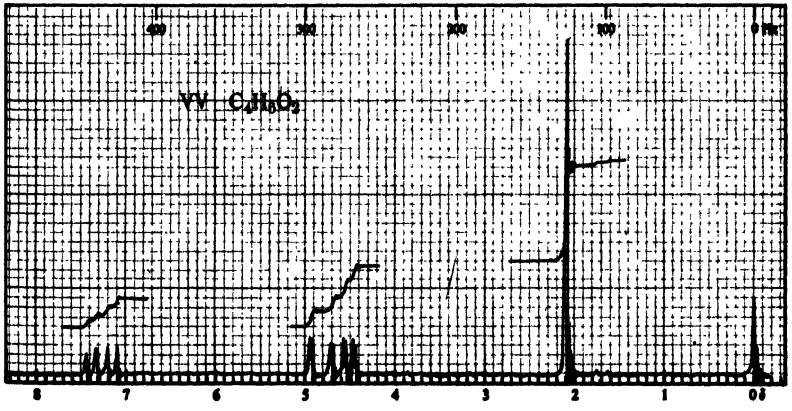


Figure 20.7. Infrared and nmr spectra for Problem 27, p. 594.

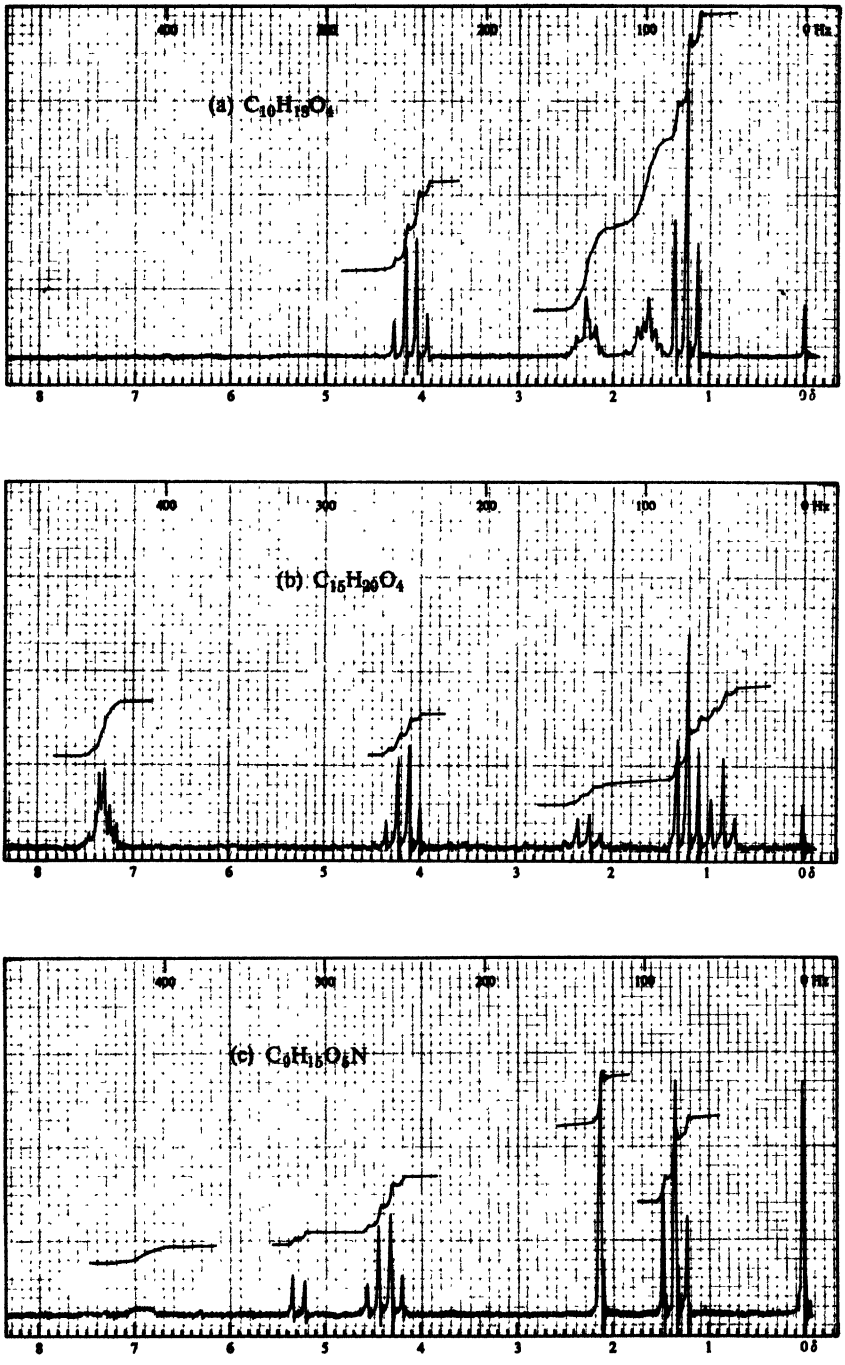


Figure 20.8. Nmr spectra for Problem 28, p. 694.