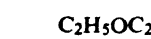
Chapter 17 Ethers and Epoxides

ETHERS

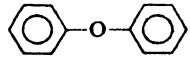
17.1 Structure and nomenclature of ethers

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

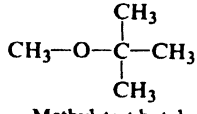
To name ethers we usually name the two groups that are attached to oxygen, and follow these names by the word *ether*:



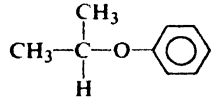
Ethyl ether



Phenyl ether

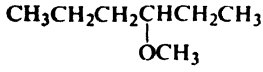


Methyl *tert*-butyl ether

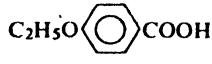


Isopropyl phenyl ether

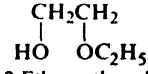
If one group has no simple name, the compound may be named as an *alkoxy* derivative:



3-Methoxyhexane

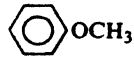


p-Ethoxybenzoic acid



2-Ethoxyethanol

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

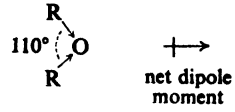


Anisole

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).



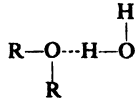
This weak polarity does not appreciably affect the boiling points of ethers, which are about the same as those of alkanes having comparable molecular weights, and much lower than those of isomeric alcohols. Compare, for example, the boiling points of *n*-heptane (98°), methyl *n*-pentyl ether (100°), 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

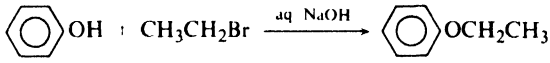
1. Williamson synthesis. Discussed in Sec. 17.5.

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

Examples:

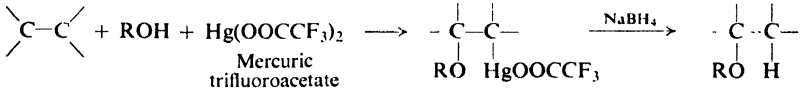
$$\left[(CH_3)_2CHOH \xrightarrow{Na}\right] (CH_3)_2CHO^-Na^+ + CH_3CH_2CH_2Br \longrightarrow CH_3CH_2CH_2OCH(CH_3)_2$$

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



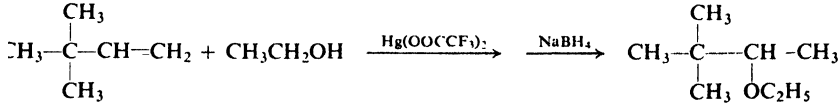
Phenol Ethyl bromide Phenyl ethyl ether

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

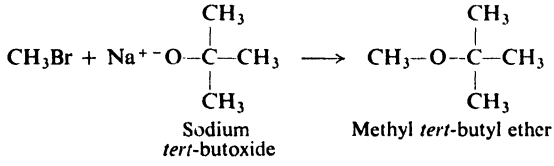
In the laboratory, the Williamson synthesis of ethers is important because of its versatility: it can be used to make unsymmetrical ethers as well as symmetrical ethers, and aryl alkyl ethers as well as dialkyl ethers.

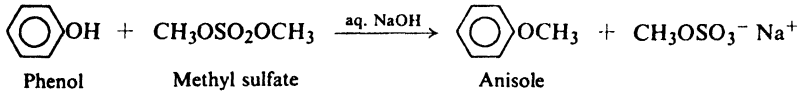
In the Williamson synthesis an alkyl halide (or substituted alkyl halide) is allowed to react with a sodium alkoxide or a sodium phenoxide:

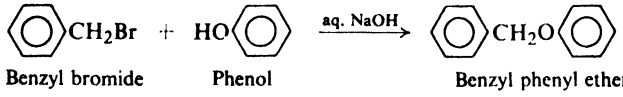
$$R{-}X + Na^+ {}^-O{-}R' \longrightarrow R{-}O{-}R' + Na^+X^-$$

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

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:

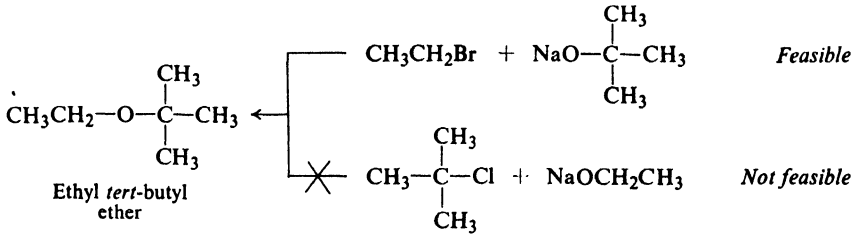
$$ROH + Na \longrightarrow \underset{\text{An alkoxide}}{RO^-Na^+} + \tfrac{1}{2}H_2$$

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:

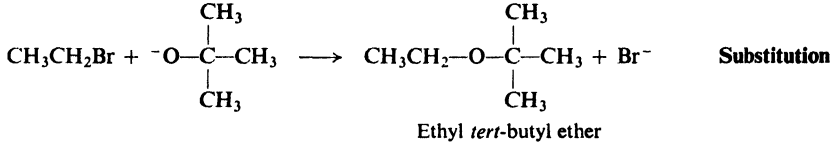
$$\underset{\text{Stronger acid}}{ArOH} + Na^+ {}^-OH \longrightarrow \underset{\text{A phenoxide}}{ArO^-Na^+} + \underset{\text{Weaker acid}}{H_2O}$$

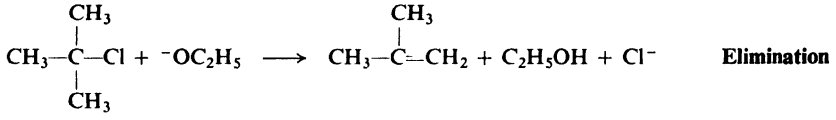
If we wish to make an unsymmetrical dialkyl ether, we have a choice of two combinations of reagents; one of these is nearly always better than the other.

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



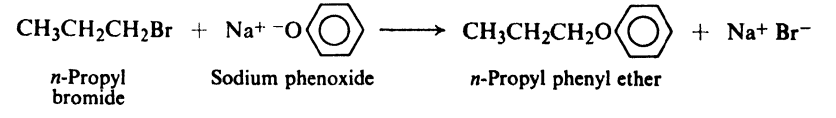
Which do we choose? As always, we must consider the danger of elimination competing with the desired substitution; elimination should be particularly serious here because of the strong basicity of the alkoxide reagent. We therefore reject the use of the tertiary halide, which we expect to yield mostly—or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

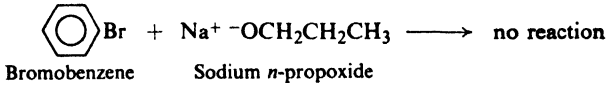




reaction between sodium and *tert*-butyl alcohol (Sec. 16.6) in the preparation of the alkoxide is more than offset by the tendency of the primary halide to undergo substitution rather than elimination. In planning a Williamson synthesis of a dialkyl ether, we must always keep in mind that the tendency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

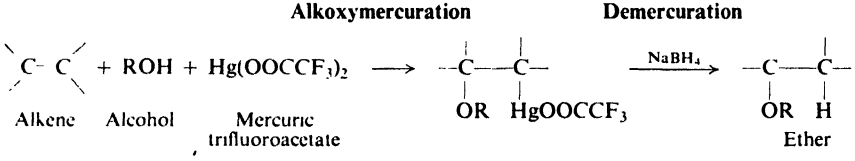
Problem 17.6 Outline the synthesis of phenyl *p*-nitrobenzyl ether from any of these starting materials: toluene, bromobenzene, phenol. (*Caution:* Double-check the nitration stage.)

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.

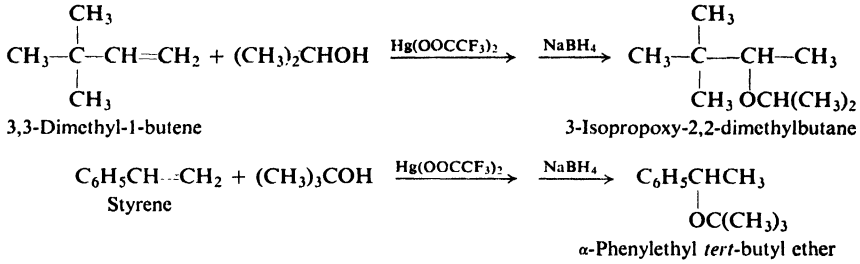


We recognize this two-stage process as the exact analog of the oxymercuration–demercuration synthesis of alcohols (Sec. 15.8). In place of water we use an alcohol which, not surprisingly, can play exactly the same role. Instead of introducing the hydroxy group to make an alcohol, we introduce an *alkoxy*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

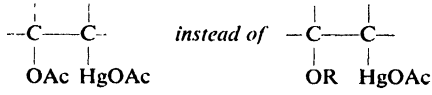
Alkoxymercuration-demercuration has all the advantages we saw for its counterpart: speed, convenience, high yield, and the virtual absence of rearrangement. Compared with the Williamson synthesis, it has one tremendous advantage: there is no competing elimination reaction. As a result, it can be used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



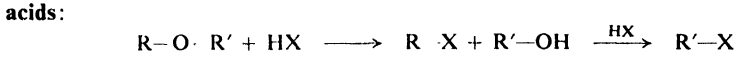
as the product. How do you account for the advantage of using mercuric trifluoroacetate? (*Hint:* Trifluoroacetic acid is a much stronger acid than acetic.)

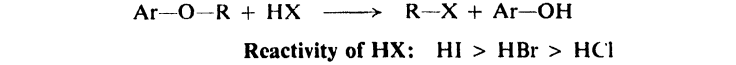
Problem 17.11 Starting with any alcohols, outline all steps in the synthesis of each of the following ethers, using the Williamson synthesis or alkoxymercuration-demercuration, whichever you think is best suited for the particular job.

(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**:



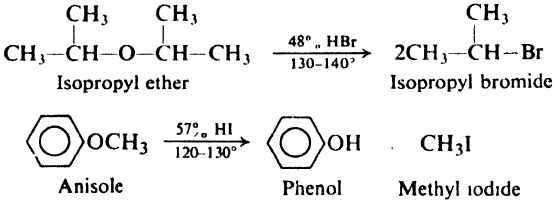


Reactivity of HX: HI > HBr > HCl

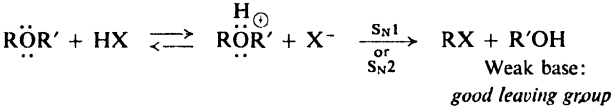
Cleavage takes place only under quite vigorous conditions: concentrated acids (usually HI or HBr) and high temperatures.

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

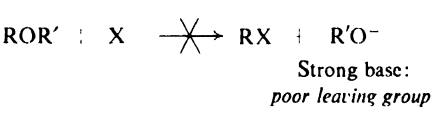
undergoes cleavage of the alkyl–oxygen bond and yields a phenol and an alkyl halide. For example:



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.

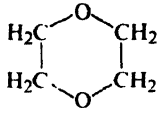
The ability of the oxygen to share more than a pair of electrons with the ring and to accommodate a positive charge is consistent with the basic character of ethers.

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

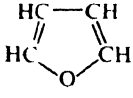
17.9 Cyclic ethers

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.

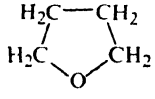
Problem 17.14 *1,4-Dioxane* is prepared industrially (for use as a water-soluble solvent) by dehydration of an alcohol. What alcohol is used?



1,4-Dioxane



Furan



Tetrahydrofuran

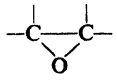
Problem 17.15 The unsaturated cyclic ether *furan* can readily be made from substances isolated from oat hulls and corncobs; one of its important uses involves its conversion into (a) *tetrahydrofuran*, and (b) 1,4-dichlorobutane. Using your knowledge of alkene chemistry and ether chemistry, show how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

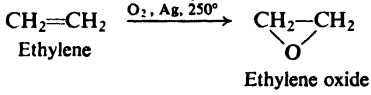
Epoxides are compounds containing the three-membered ring:



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.



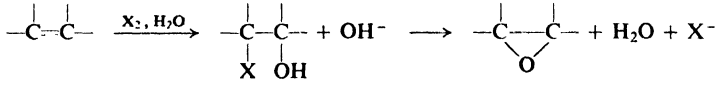
Ethylene

Ethylene oxide

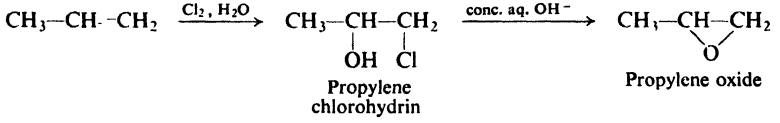
Other epoxides are prepared by the following methods.

PREPARATION OF EPOXIDES

1. From halohydrins. Discussed in Sec. 17.10.



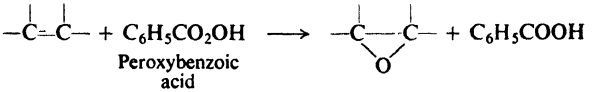
Example:



Propylene chlorohydrin

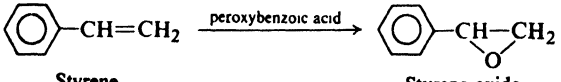
Propylene oxide

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



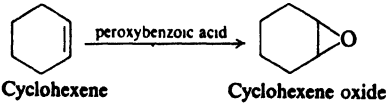
Peroxybenzoic acid

Examples:



Styrene

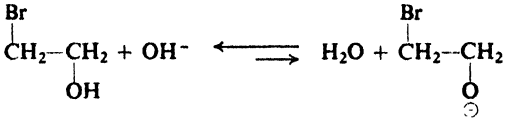
Styrene oxide

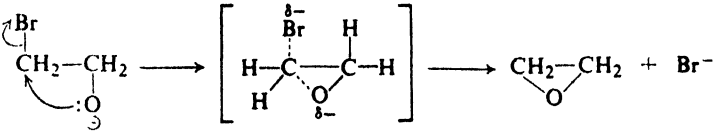


Cyclohexene

Cyclohexene oxide

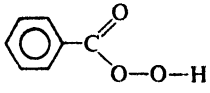
The conversion of halohydrins into epoxides by the action of base is simply an adaptation of the Williamson synthesis (Sec. 17.5); a cyclic compound is obtained because both alcohol and halide happen to be part of the same molecule. In the presence of hydroxide ion a small proportion of the alcohol exists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

(1) 

(2) 

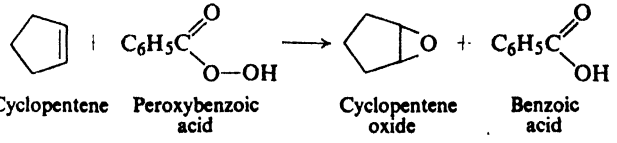
Since halohydrins are nearly always prepared from alkenes by addition of halogen and water to the carbon–carbon double bond (Sec. 6.14), this method amounts to the conversion of an alkene into an epoxide.

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

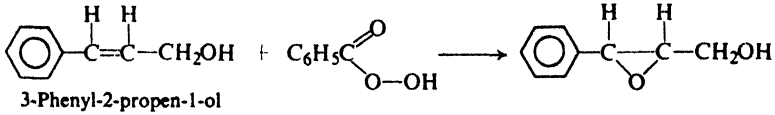


Peroxybenzoic acid

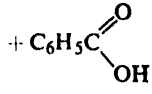
When allowed to stand in ether or chloroform solution, the peroxy acid and the unsaturated compound—which need not be a simple alkene—react to yield benzoic acid and the epoxide. For example:



Cyclopentene | Peroxybenzoic acid | Cyclopentene oxide | Benzoic acid



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



17.11 Reactions of epoxides

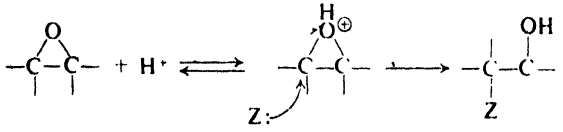
Epoxides owe their importance to their high reactivity, which is due to the ease of opening of the highly strained three-membered ring. The bond angles of the

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.

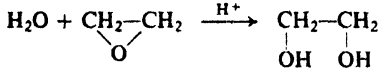
Epoxides undergo acid-catalyzed reactions with extreme ease, and—unlike ordinary ethers—can even be cleaved by bases. Some of the important reactions are outlined below.

REACTIONS OF EPOXIDES

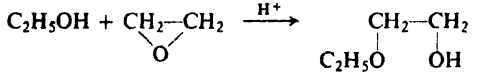
1. Acid-catalyzed cleavage. Discussed in Sec. 17.12.



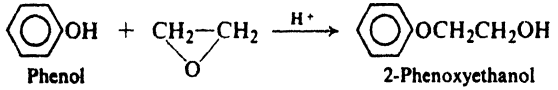
Examples:



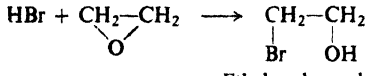
Ethylene glycol
(1,2-Ethanediol)



2-Ethoxyethanol

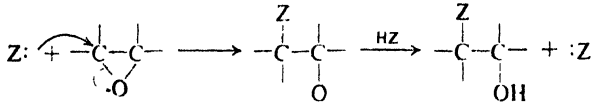


Phenol 2-Phenoxyethanol

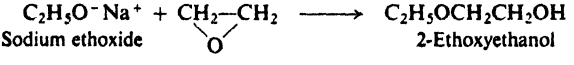


Ethylene bromohydrin
(2-Bromoethanol)

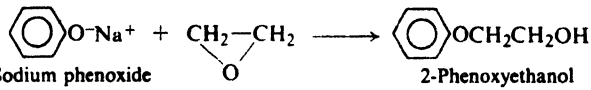
2. Base-catalyzed cleavage. Discussed in Sec. 17.13.



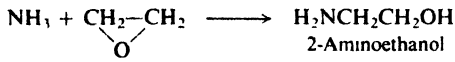
Examples:



Sodium ethoxide 2-Ethoxyethanol

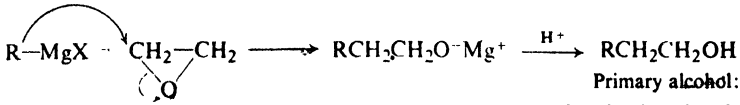


Sodium phenoxide — 2-Phenoxyethanol



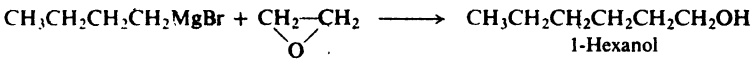
2-Aminoethanol
(Ethanolamine)

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

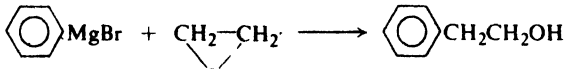


Primary alcohol:
chain has been lengthened by two carbons

Examples:



1-Hexanol

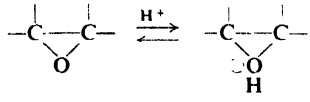


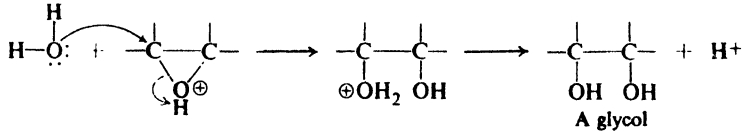
2-Phenylethanol
(β-Phenylethyl alcohol)

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

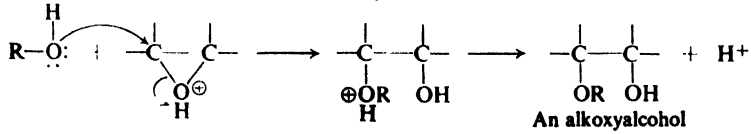
Like other ethers, an epoxide is converted by acid into the protonated epoxide, which can then undergo attack by any of a number of nucleophilic reagents.

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)

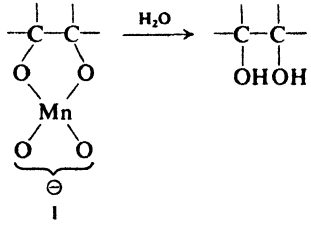
Problem 17.16 The following compounds are commercially available for use as water-soluble solvents. How could each be made?

(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.

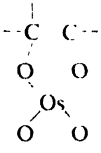
The two-stage process of epoxidation followed by hydrolysis is stereospecific, and gives glycols corresponding to *anti* addition to the carbon–carbon double bond. Exactly the same stereochemistry was observed (Problem 7.11, p. 242) for hydroxylation of alkenes by peroxyformic acid—and for good reason: 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

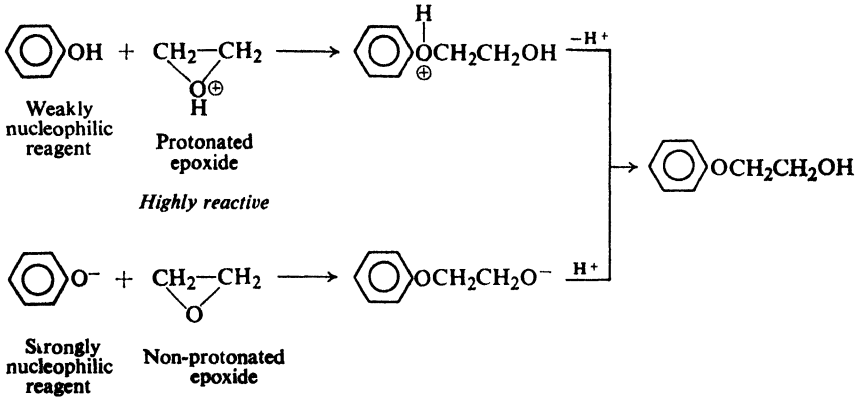
Thus, the two methods of hydroxylation—by peroxy acids and by permanganate—differ in stereochemistry because they differ in mechanism.

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.

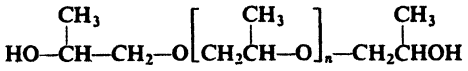
Let us look, for example, at the reaction of ethylene oxide with phenol. Acid catalyzes reaction by converting the epoxide into the highly reactive protonated epoxide. Base catalyzes reaction by converting the phenol into the more strongly nucleophilic phenoxide ion.



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,

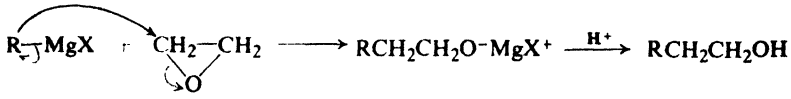


which are used in the manufacture of polyurethane foam rubber, are formed by the action of base (e.g., hydroxide ion) on propylene oxide in the presence of propylene glycol as an initiator. Write all steps in a likely mechanism for their formation.

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

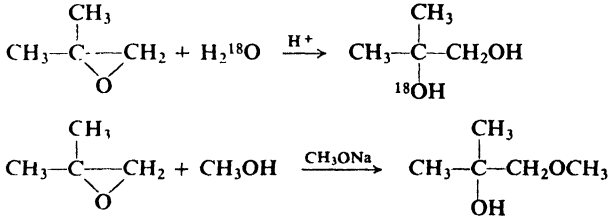
Grignard reagent attach itself to the relatively positive carbon and the electrophilic (acidic) magnesium attach itself to the relatively negative oxygen. Use of higher epoxides is complicated by rearrangements and formation of mixtures.



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.

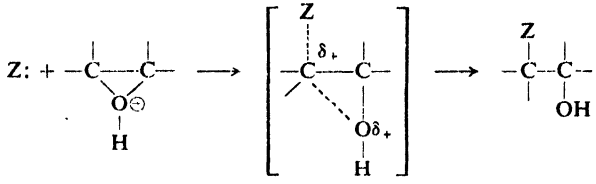
Our first thought is that two different mechanisms are involved here, S_N1 and S_N2. But the evidence indicates pretty clearly that both are of the S_N2 type: cleavage of the carbon-oxygen bond and attack by the nucleophile occur in a single step. (There is not only stereochemical evidence—complete inversion—but 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.*

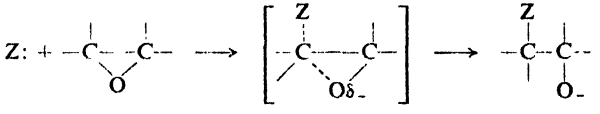
Acid-catalyzed S_N2 cleavage



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.)

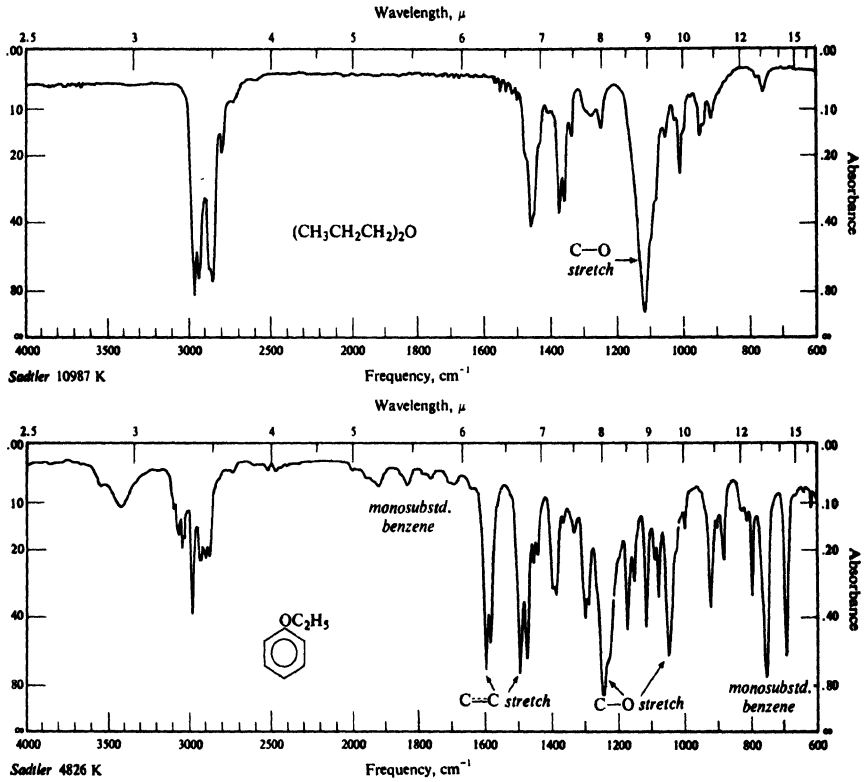


Figure 17.1. Infrared spectra of (*a*) *n*-propyl ether and (*b*) phenetole.

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.

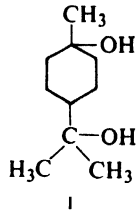
11. Give the structures and names of the products you would expect from the reaction of ethylene oxide with:

(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).

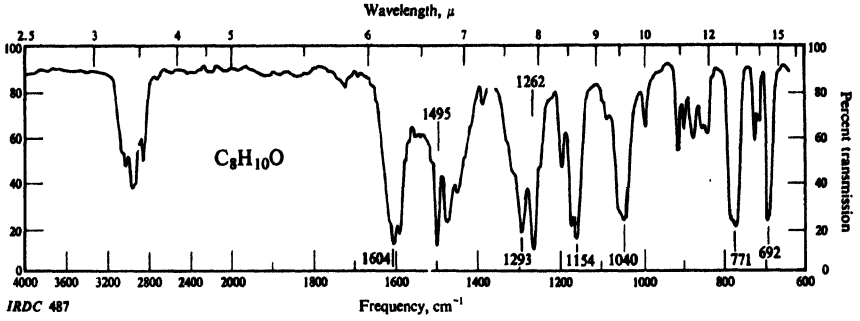
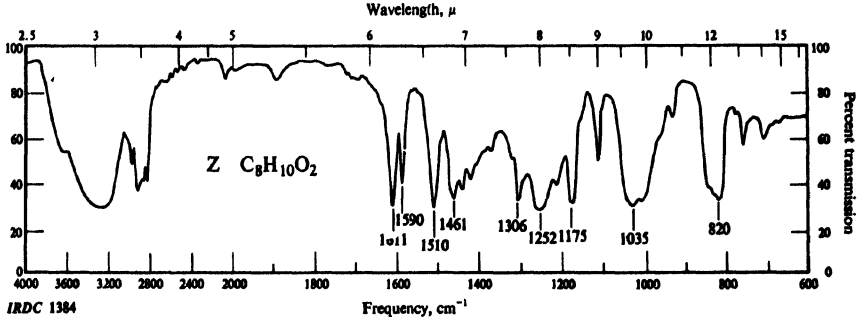


Figure 17.2. Infrared spectrum for Problem 16, p. 574.



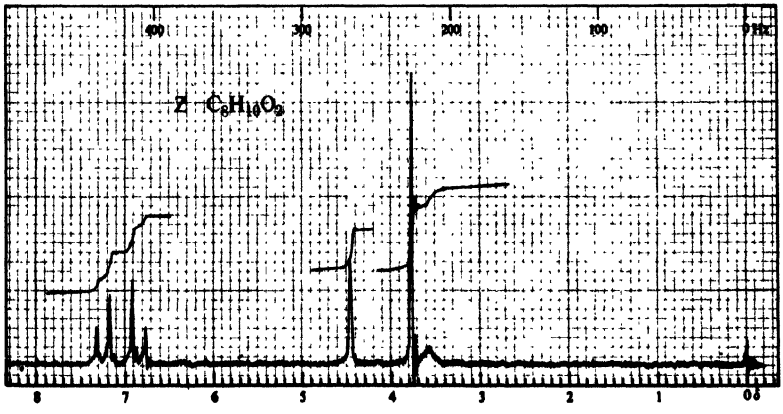


Figure 17.3. Infrared and nmr spectra for Problem 17, p. 574.

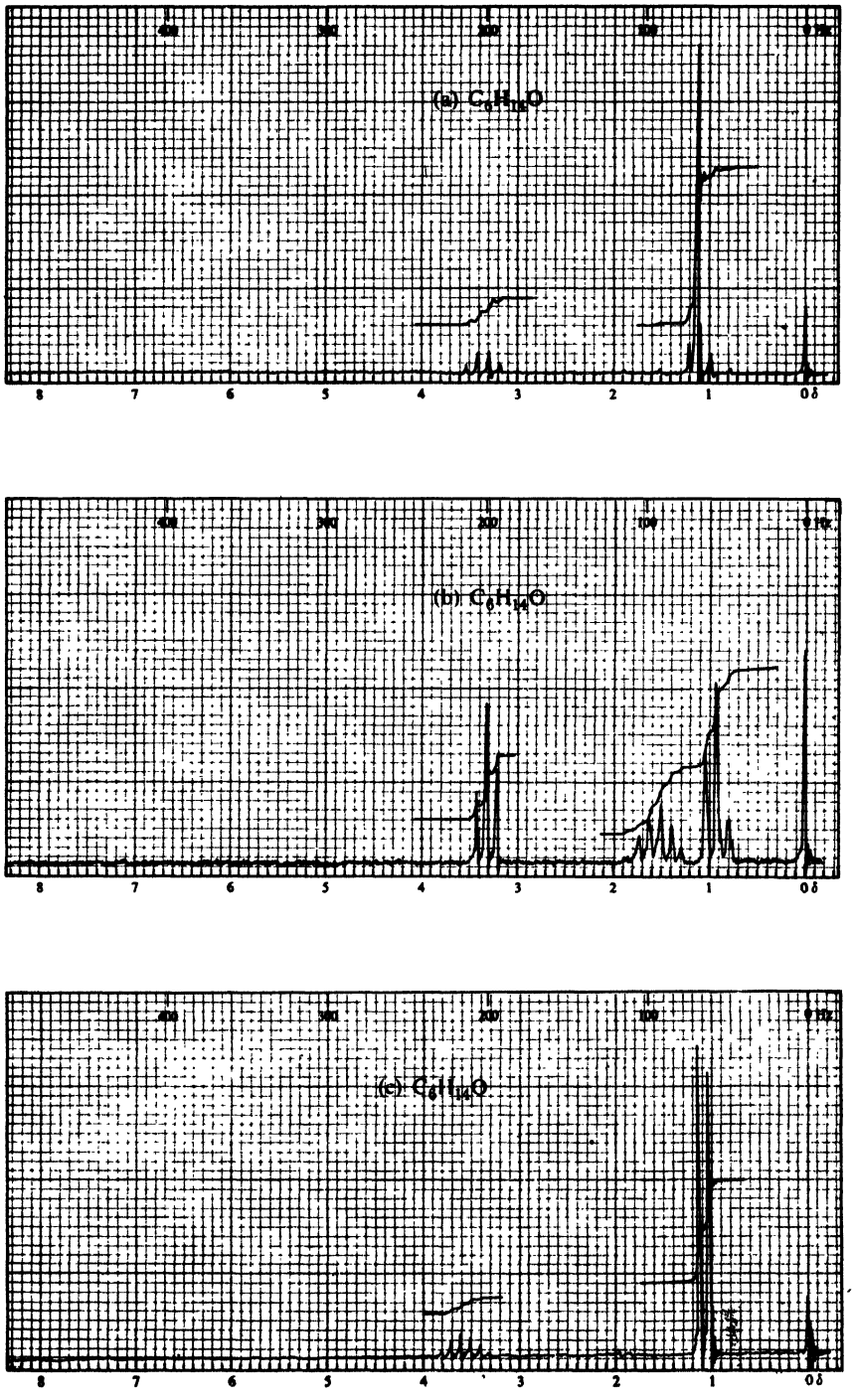
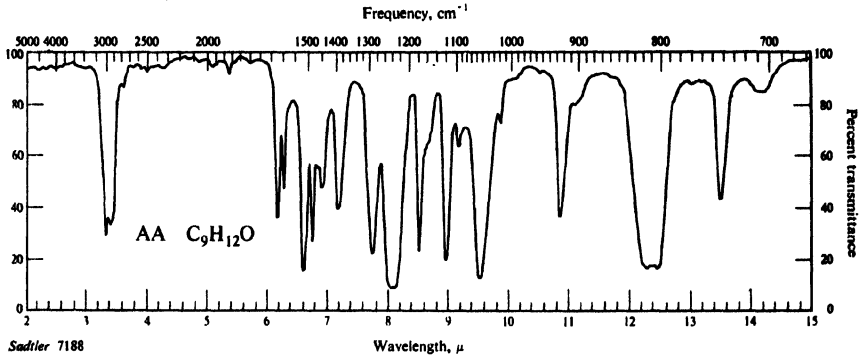
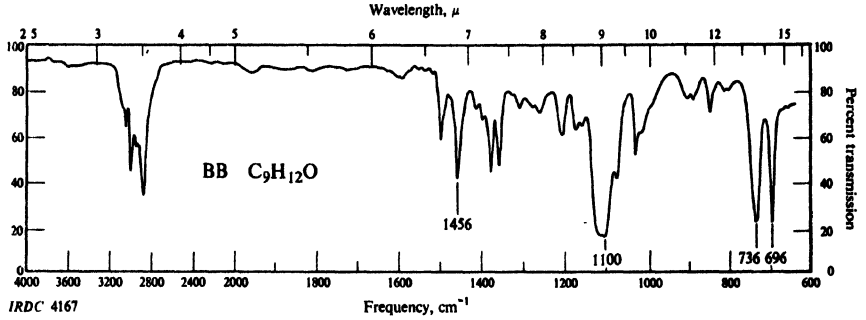


Figure 17.4. Nmr spectra for Problem 18, p. 574.





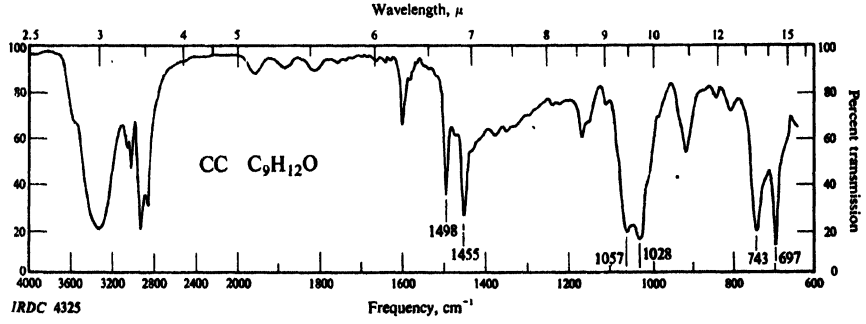


Figure 17.5. Infrared spectra for Problem 19, p. 574.

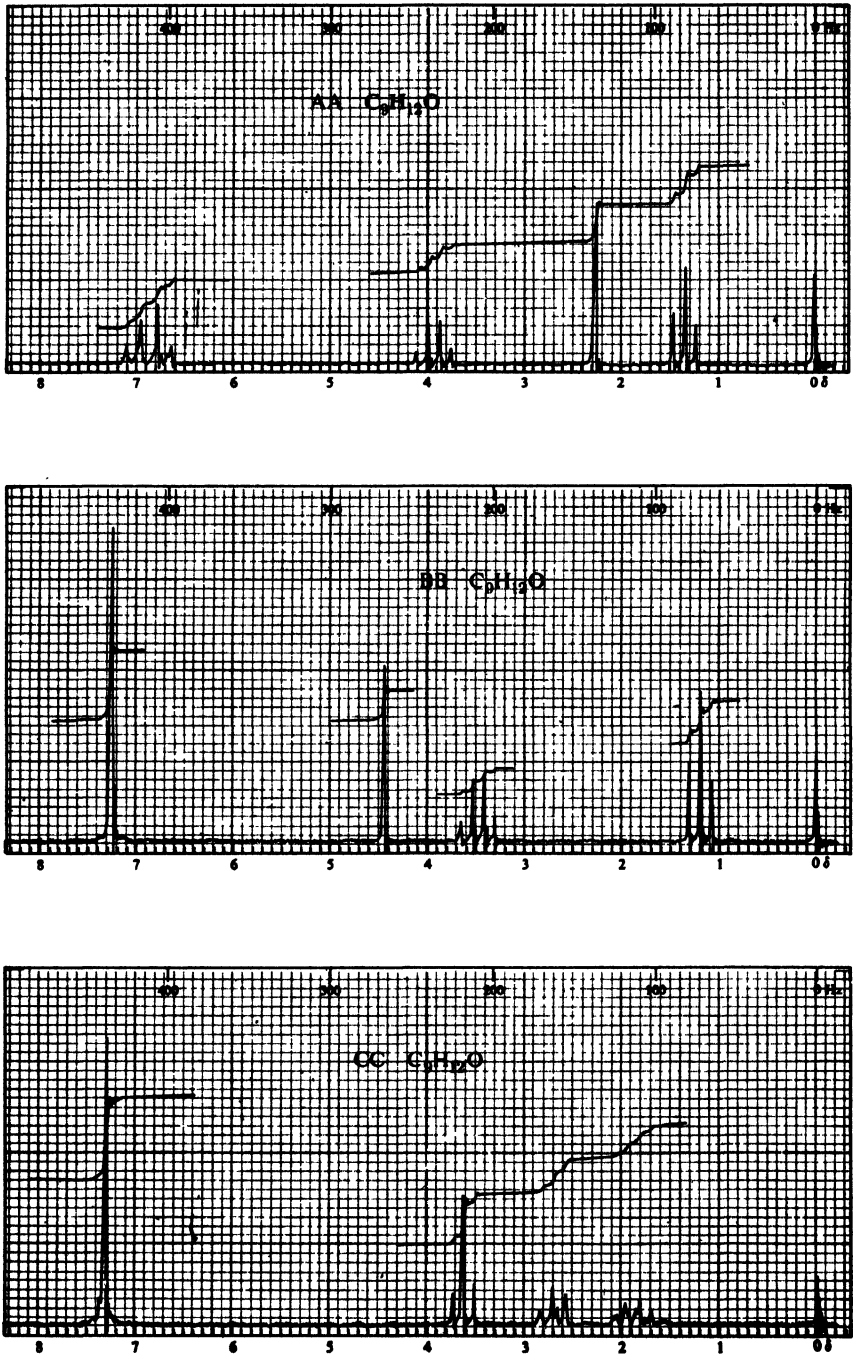


Figure 17.6. Nmr spectra for Problem 19, p. 574.

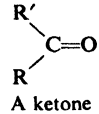
Chapter 19 Aldehydes and Ketones

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

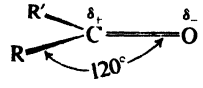


A ketone

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.

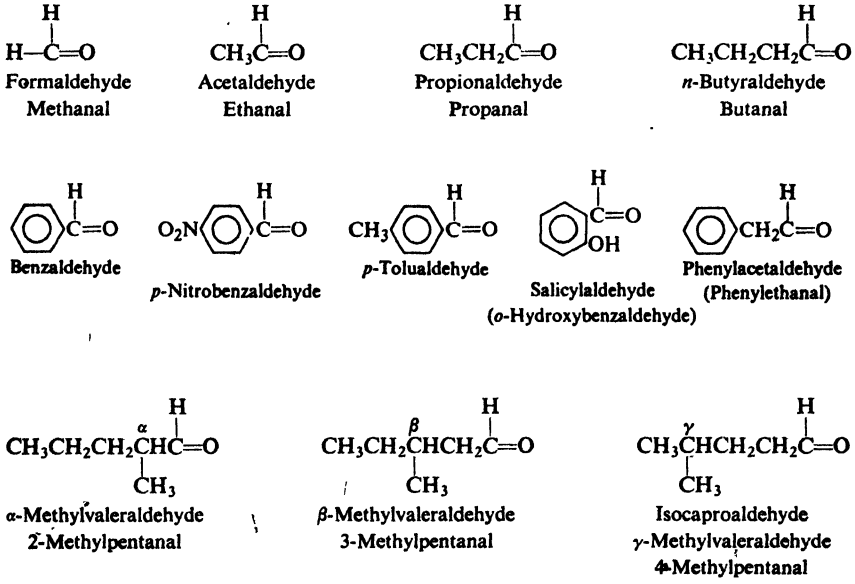
The electrons of the carbonyl double bond hold together atoms of quite different electronegativity, and hence the electrons are not equally shared; in particular, the mobile π cloud is pulled strongly toward the more electronegative atom, oxygen.

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

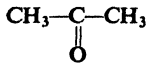
The common names of aldehydes are derived from the names of the corresponding carboxylic acids by replacing *-ic acid* by *-aldehyde*.

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.

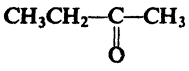


The simplest aliphatic ketone has the common name of *acetone*. For most other aliphatic ketones we name the two groups that are attached to carbonyl carbon, and follow these names by the word *ketone*. A ketone in which the carbonyl group is attached to a benzene ring is named as a *-phenone*, as illustrated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

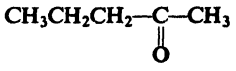
According to the IUPAC system, the longest chain carrying the carbonyl group is considered the parent structure, and is named by replacing the *-e* of the corresponding alkane with *-one*. The positions of various groups are indicated by numbers, the carbonyl carbon being given the lowest possible number.



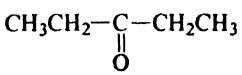
Acetone
Propanone



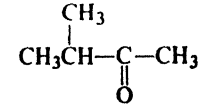
Methyl ethyl ketone
Butanone



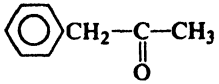
Methyl *n*-propyl ketone
2-Pentanone



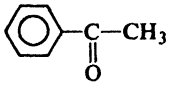
Ethyl ketone
3-Pentanone



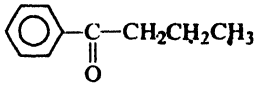
Methyl isopropyl ketone
3-Methyl-2-butanone



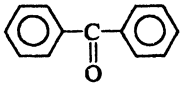
Benzyl methyl ketone
1-Phenyl-2-propanone



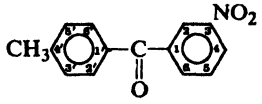
Acetophenone



n-Butyrophenone



Benzophenone



3-Nitro-4′-methylbenzophenone

19.3 Physical properties

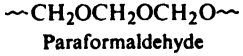
The polar carbonyl group makes aldehydes and ketones polar compounds, and hence they have higher boiling points than non-polar compounds of comparable molecular weight. By themselves, they are not capable of intermolecular hydrogen bonding since they contain hydrogen bonded only to carbon; as a result 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.

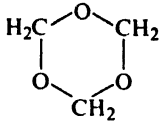
Table 19.1 ALDEHYDES AND KETONES

	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.

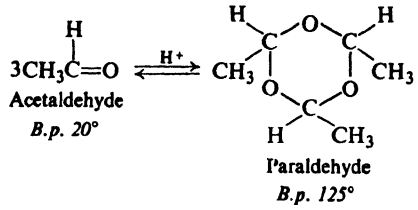


Paraformaldehyde



Trioxane

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



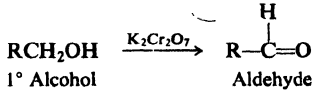
19.4 Preparation

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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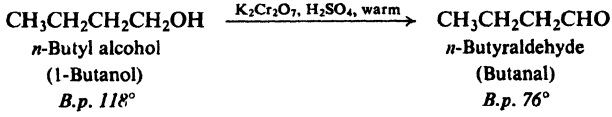
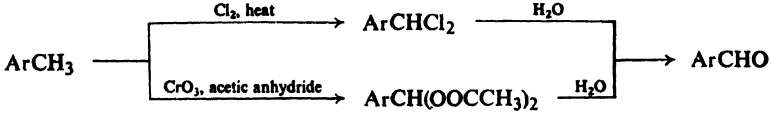
Example:



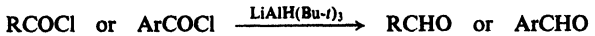
2. Oxidation of methylbenzenes. Discussed in Sec. 19.5.



Examples:

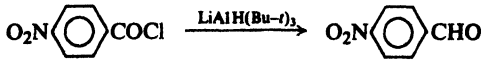
p-Nitrotoluene — *p*-Nitrobenzaldehyde

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



Acid chloride — Aldehyde

Examples:

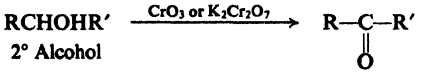


p-Nitrobenzoyl chloride — *p*-Nitrobenzaldehyde

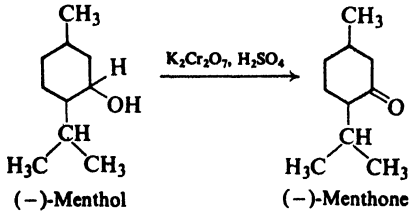
4. Reimer-Tiemann reaction. Phenolic aldehydes. Discussed in Sec. 24.12.

PREPARATION OF KETONES

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

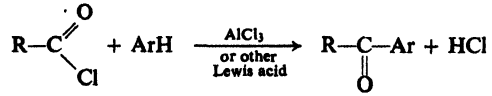


Example:



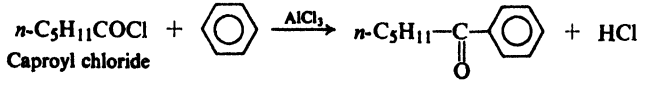
(−)-Menthol — (−)-Menthone

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



Acid chloride — Ketone

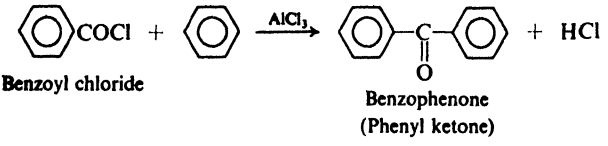
Examples:

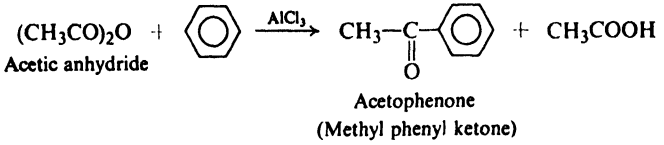


Caproyl chloride

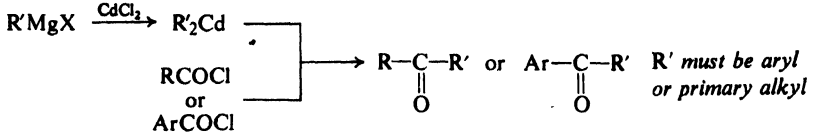
n-Pentyl phenyl ketone

No rearrangement of n-pentyl group

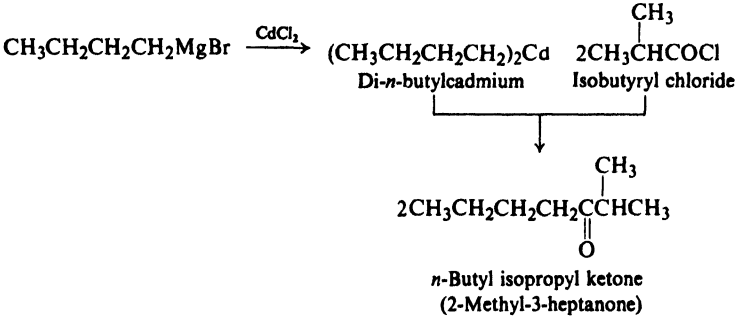


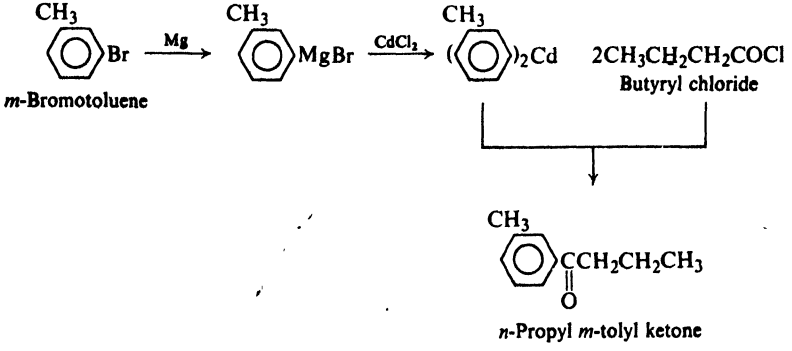


3. **Reaction of acid chlorides with organocadmium compounds.** Discussed in Sec. 19.7.



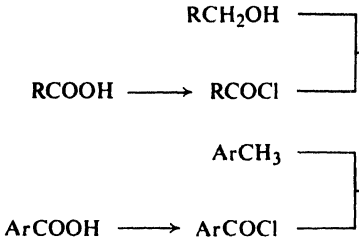
Examples:





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.

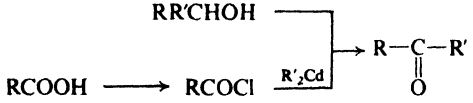


Preparation of aliphatic aldehydes

Preparation of aromatic aldehydes

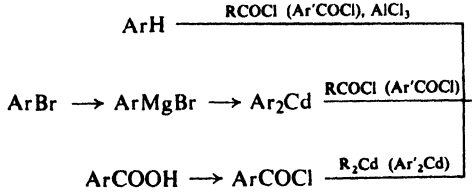
There are, in addition, a number of methods by which the aldehyde group is introduced into an aromatic ring: for example, the Reimer-Tiemann synthesis of phenolic aldehydes (Sec. 24.12).

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:

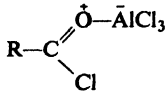
(1) $$RCOCl + AlCl_3 \longrightarrow RC{\equiv}\overset{\oplus}{O} + AlCl_4^-$$

(2) $$ArH + RC{\equiv}\overset{\oplus}{O} \longrightarrow \overset{\oplus}{Ar}(H)(COR)$$

(3) $$\overset{\oplus}{Ar}(H)(COR) + AlCl_4^- \longrightarrow Ar{-}C(=O){-}R + HCl + AlCl_3$$

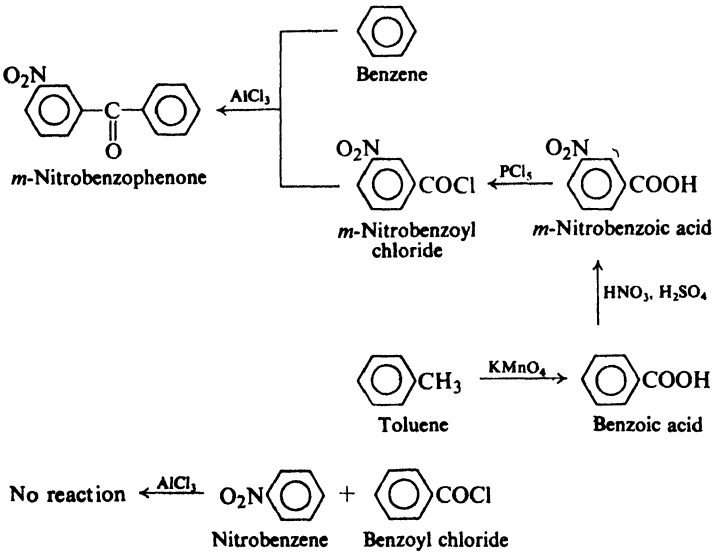
This fits the pattern of electrophilic aromatic substitution, the attacking reagent this time being the **acylium ion**, $R-C\equiv\overset{\oplus}{O}$. The acylium ion is considerably more stable than ordinary carbonium ions since in it every atom has an octet of electrons.

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.

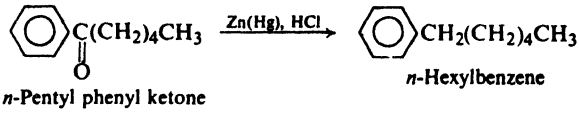
In planning the synthesis of diaryl ketones, ArCOAr', it is particularly important to select the right combination of ArCOCl and Ar'H. In the preparation of *m*-nitrobenzophenone, for example, the nitro group can be present in the acid chloride but not in the ring undergoing substitution, since as a strongly deactivating group it prevents the Friedel-Crafts reaction (Sec. 12.8).



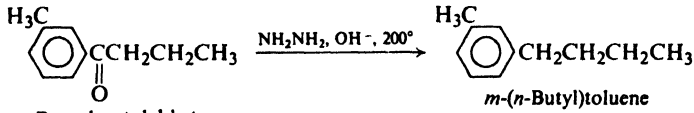
Friedel-Crafts acylation is one of the most important methods of preparing ketones in which the carbonyl group is attached to an aromatic ring. Once formed, these ketones may be converted into secondary alcohols by reduction, into tertiary alcohols by reaction with Grignard reagents, and into many other 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

$$R'_2Cd + 2RCOCl \longrightarrow 2R{-}\underset{\underset{O}{\|}}{C}{-}R' + CdCl_2$$

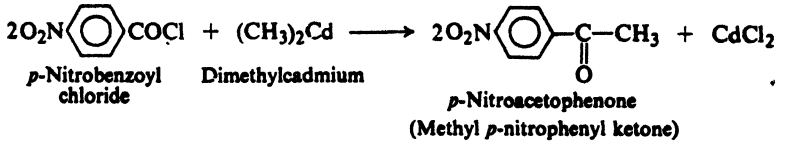
A ketone

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.

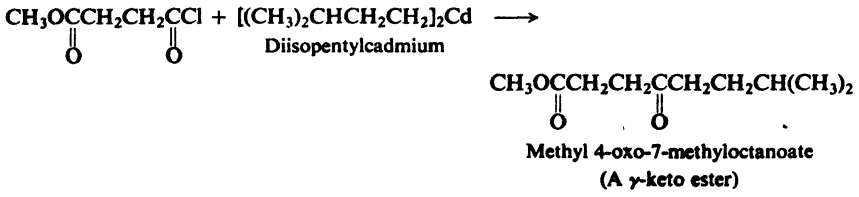
Only organocadmium compounds containing aryl or primary alkyl groups are stable enough for use. In spite of this limitation, the method is one of the most valuable for the synthesis of ketones.

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

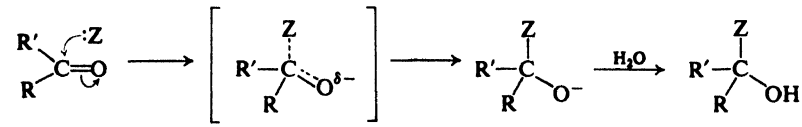
The carbonyl group, C=O, governs the chemistry of aldehydes and ketones. It does this in two ways: (a) by providing a site for nucleophilic addition, and (b) by increasing the acidity of the hydrogen atoms attached to the *alpha* carbon. Both these effects are quite consistent with the structure of the 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



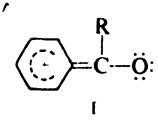
Reactant	Transition state	Product
Trigonal	*Becoming tetrahedral*	*Tetrahedral*
	Partial negative charge on oxygen	*Negative charge on oxygen*

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.

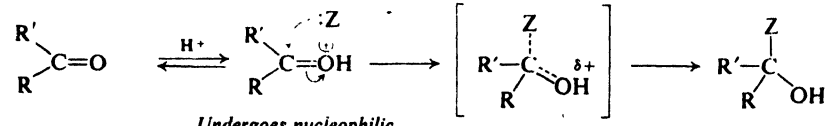
We might have expected an aryl group, with its electron-withdrawing inductive effect (Problem 18.7, p. 600), to stabilize the transition state and thus speed up reaction; however, it seems to stabilize the *reactant* even more, by resonance (contribution by I), and thus causes net deactivation.



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)

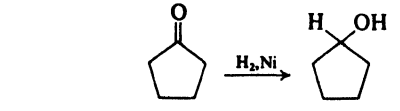
3-Methyl-2-butenoic acid

2. Reduction

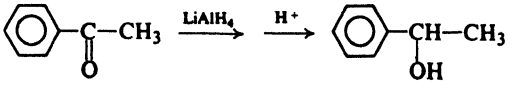
(a) Reduction to alcohols. Discussed in Sec. 19.10.

$$\text{>C=O} \xrightarrow[LiAlH_4 \text{ or } NaBH_4; \text{ then } H^+]{H_2 + Ni, Pt, \text{ or } Pd} \text{>CH(OH)}$$

Examples:

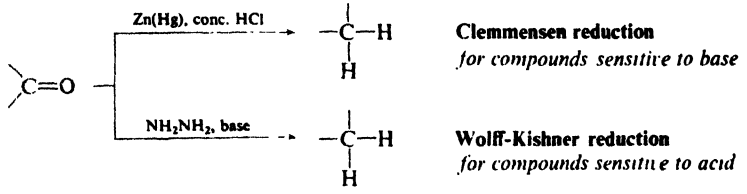


Cyclopentanone — Cyclopentanol

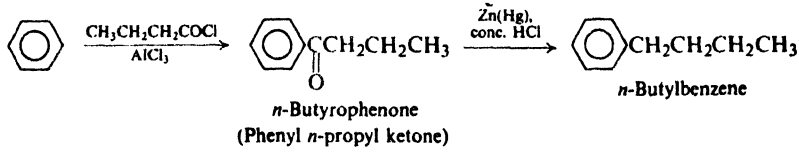


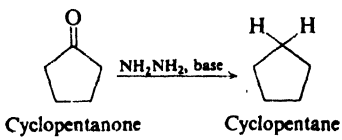
Acetophenone — α-Phenylethyl alcohol

(b) Reduction to hydrocarbons. Discussed in Sec. 19.10.



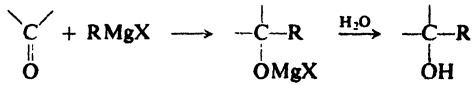
Examples



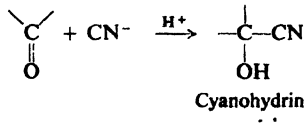


(c) Reductive amination. Discussed in Sec. 22.11.

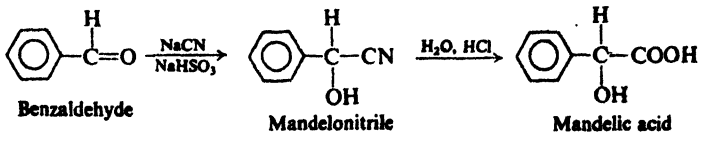
3. Addition of Grignard reagents. Discussed in Secs. 15.12–15.15 and 19.11.

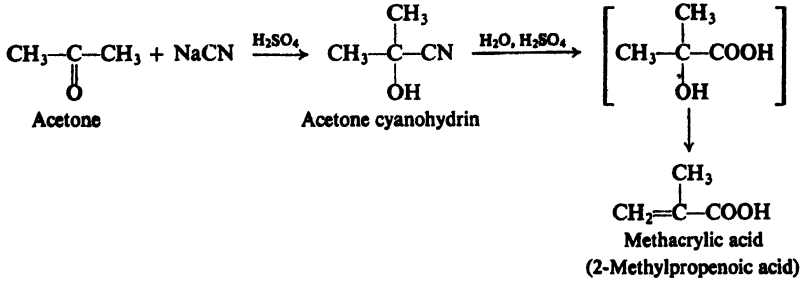


4. Addition of cyanide. Cyanohydrin formation. Discussed in Sec. 19.12.

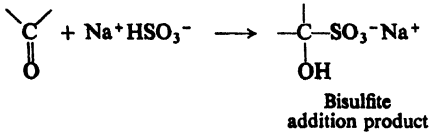


Examples:



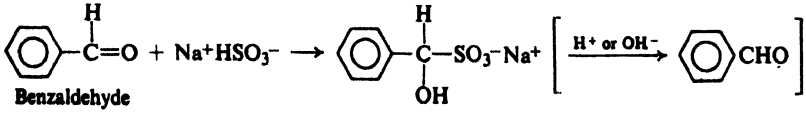


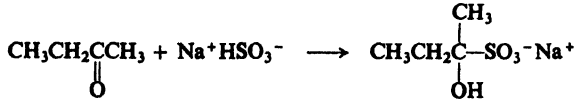
5. Addition of bisulfite. Discussed in Sec. 19.13.

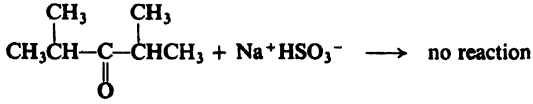


Used in purification
Not for hindered ketones

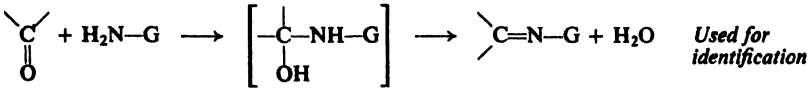
Examples:







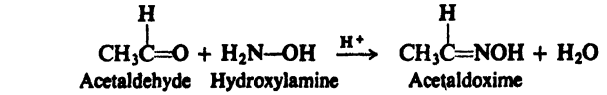
6. Addition of derivatives of ammonia. Discussed in Sec. 19.14.

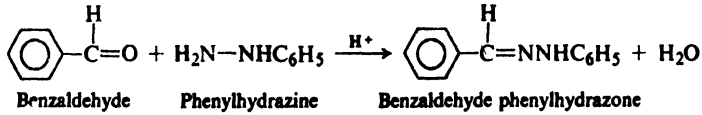


Used for identification

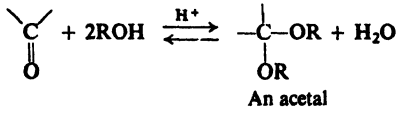
H_2N—G		Product	
H_2N—OH	Hydroxylamine	C=NOH	Oxime
H_2N—NH_2	Hydrazine	C=NNH_2	Hydrazone
H_2N—NHC_6H_5	Phenylhydrazine	C=$NNHC_6H_5$	Phenylhydrazone
H_2N—$NHCONH_2$	Semicarbazide	C=$NNHCONH_2$	Semicarbazone

Examples:

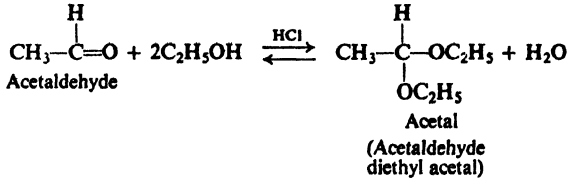




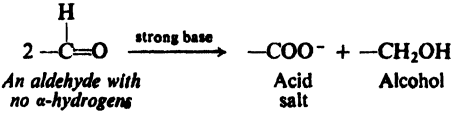
7. Addition of alcohols. Acetal formation. Discussed in Sec. 19.15.



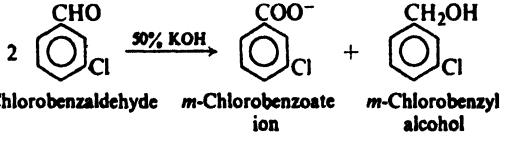
Example:

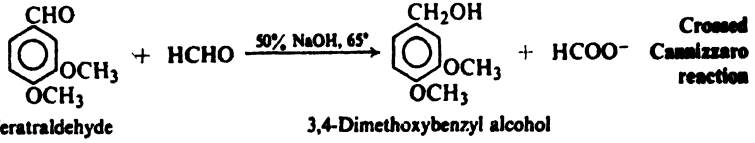


8. Cannizzaro reaction. Discussed in Sec. 19.16.

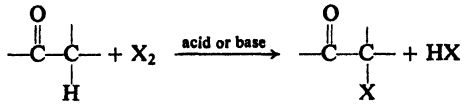


Examples:





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.

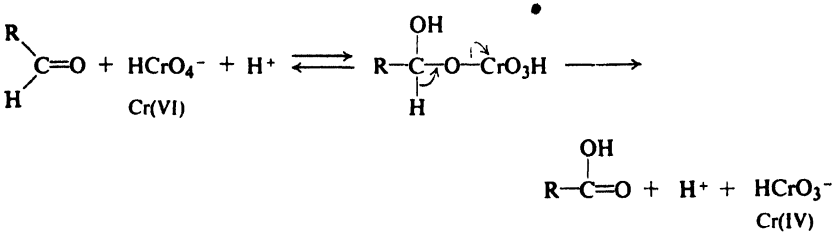
(c) Wittig reaction. Discussed in Sec. 21.10.

(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.

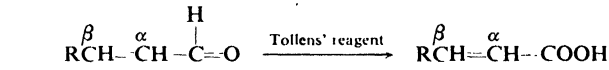
Aldehydes are oxidized not only by the same reagents that oxidize primary and secondary alcohols—permanganate and dichromate—but also by the very mild oxidizing agent silver ion. Oxidation by silver ion requires an alkaline medium; to prevent precipitation of the insoluble silver oxide, a complexing 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).

$$\underset{\text{Colorless solution}}{RCHO + Ag(NH_3)_2^+} \longrightarrow \underset{\text{Silver mirror}}{RCOO^- + Ag}$$

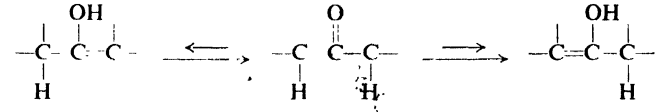
(Oxidation by complexed cupric ion is a characteristic of certain substituted carbonyl compounds, and will be taken up with *carbohydrates* in Sec. 34.6.)

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

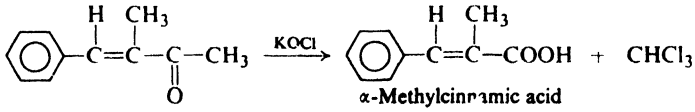


Enol — Ketone — Enol

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.

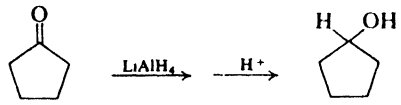
Methyl ketones are oxidized smoothly by means of hypohalite in the haloform reaction (Sec. 16.11). Besides being commonly used to detect these ketones (Sec. 19.17), this reaction is often useful in synthesis, hypohalite having the special advantage of not attacking carbon–carbon double bonds. For example:



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:

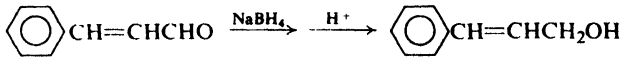


Cyclopentanone Cyclopentanol

$$CH_3CH{=}CHCHO \xrightarrow{H_2,\,Ni} CH_3CH_2CH_2CH_2OH$$

Crotonaldehyde — *n*-Butyl alcohol

From aldol condensation of acetaldehyde

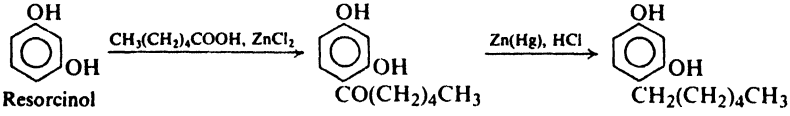


Cinnamaldehyde Cinnamyl alcohol

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

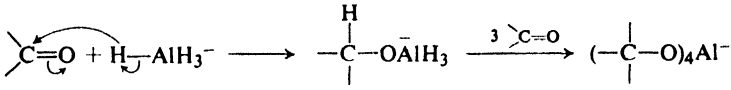
Used as an antiseptic

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

$$4R_2C{=}O + LiAlH_4 \longrightarrow (R_2CHO)_4AlLi \xrightarrow{H_2O} 4R_2CHOH + LiOH + Al(OH)_3$$

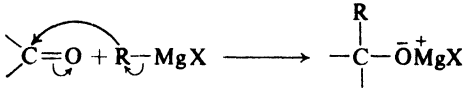
nucleophilic addition: this time the nucleophile is hydrogen transferred with a pair of electrons—as a hydride ion, $H{:}^-$—from the metal to carbonyl carbon:



19.11 Addition of Grignard reagents

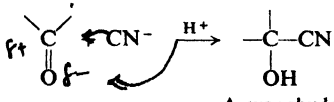
The addition of Grignard reagents to aldehydes and ketones has already been discussed as one of the most important methods of preparing complicated alcohols (Secs. 15.12–15.15).

The organic group, transferred *with a pair of electrons* from magnesium to carbonyl carbon, is a powerful nucleophile.



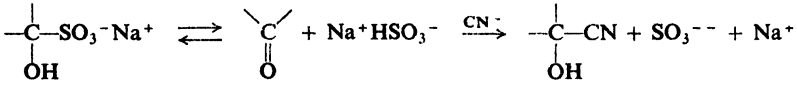
19.12 Addition of cyanide

The elements of HCN add to the carbonyl group of aldehydes and ketones to yield compounds known as **cyanohydrins**:

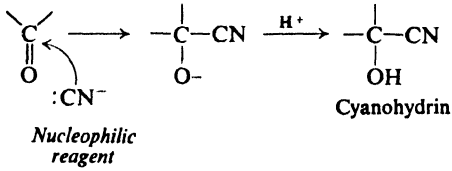


A cyanohydrin

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:

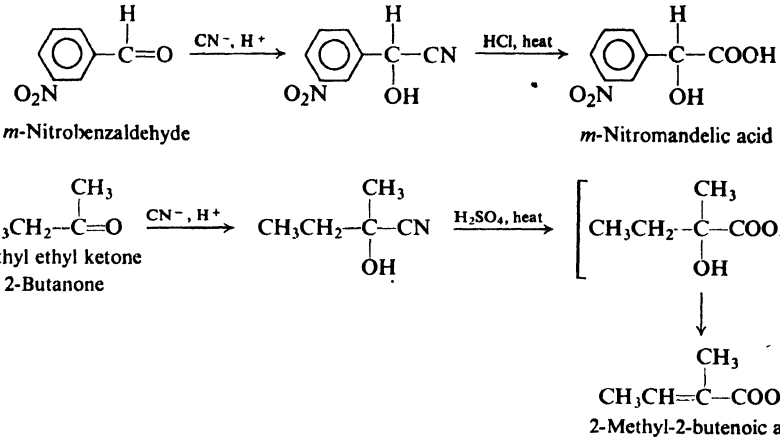


Addition appears to involve nucleophilic attack on carbonyl carbon by the strongly basic cyanide ion; subsequently (or possibly simultaneously) oxygen accepts a hydrogen ion to form the cyanohydrin product:



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:

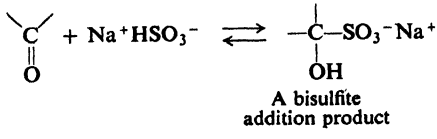


Problem 19.5 Each of the following is converted into the cyanohydrin, and the products are separated by careful fractional distillation or crystallization. For each reaction tell how many fractions will be collected, and whether each fraction, as collected, will be optically active or inactive, resolvable 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?

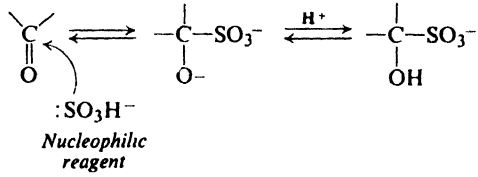
19.13 Addition of bisulfite

Sodium bisulfite adds to most aldehydes and to many ketones (especially methyl ketones) to form bisulfite addition products:

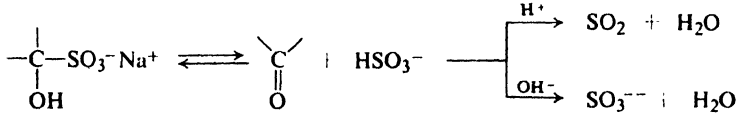


The reaction is carried out by mixing the aldehyde or ketone with a concentrated aqueous solution of sodium bisulfite; the product separates as a crystalline solid. Ketones containing bulky groups usually fail to react with bisulfite, presumably for steric reasons.

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.

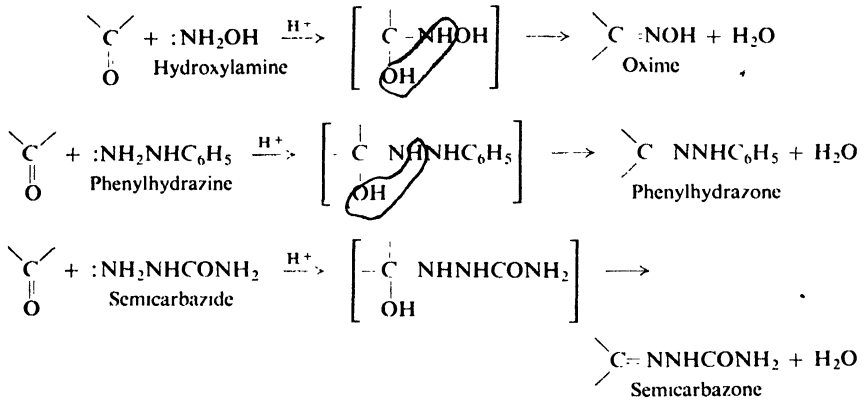


Bisulfite addition products are generally prepared for the purpose of separating a carbonyl compound from non-carbonyl compounds. The carbonyl compound can be purified by conversion into its bisulfite addition product, separation of the crystalline addition product from the non-carbonyl impurities, and 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

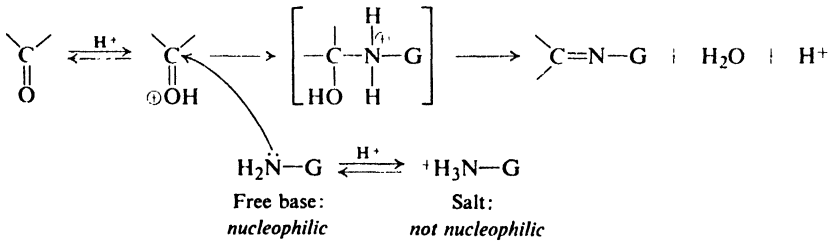
Certain compounds related to ammonia add to the carbonyl group to form derivatives that are important chiefly for the characterization and identification of aldehydes and ketones (Sec. 19.17). The products contain a carbon–nitrogen double bond resulting from elimination of a molecule of water from the 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



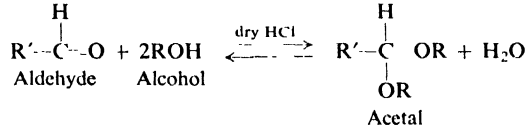
addition proceeds most rapidly are thus the result of a compromise: the solution must be acidic enough for an appreciable fraction of the carbonyl compound to be

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.

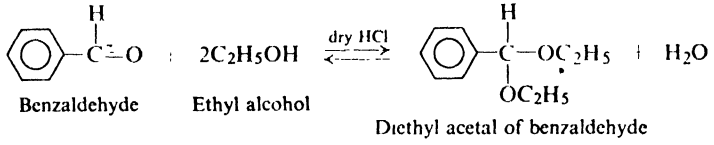
Problem 19.7 Semicarbazide (1 mole) is added to a mixture of cyclohexanone (1 mole) and benzaldehyde (1 mole). If the product is isolated immediately, it consists almost entirely of the semicarbazone of cyclohexanone; if the product is isolated after several hours, it consists almost entirely of the semicarbazone of benzaldehyde. How do you account for these observations? (*Hint:* See Sec. 8.22.)

19.15 Addition of alcohols. Acetal formation

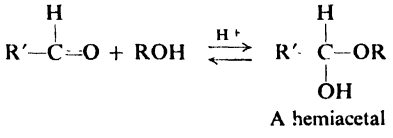
Alcohols add to the carbonyl group of aldehydes in the presence of anhydrous acids to yield **acetals**:



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.)

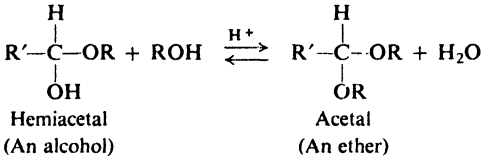


There is good evidence that in alcoholic solution an aldehyde exists in equilibrium with a compound called a **hemiacetal**:

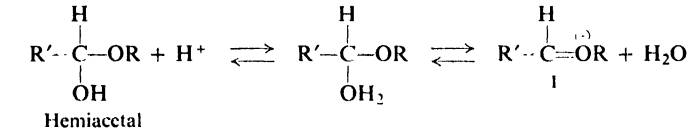


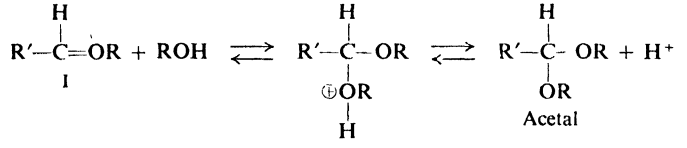
A hemiacetal is formed by the addition of the nucleophilic alcohol molecule to the carbonyl group; it is both an ether and an alcohol. With a few exceptions, hemiacetals are too unstable to be isolated.

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,

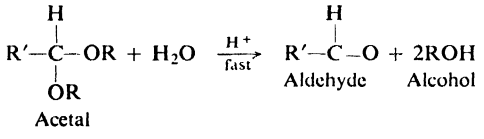




this mechanism is strictly analogous to the S_N1 route we have previously encountered (Sec. 17.3) for the formation of ethers.

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,

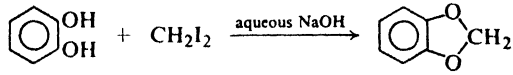
which is a hybrid of structures Ia and Ib. Contribution from Ib, in which every atom has an octet of electrons, makes this ion considerably more stable than ordinary carbonium ions. (Indeed, Ib *alone* may pretty well represent the ion, in which case it is not a carbonium ion at all but an *oxonium* 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

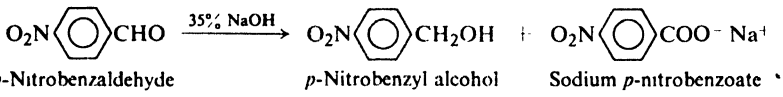
Problem 19.13 The simplest way to prepare an aldehyde, $RCH^{18}O$, labeled at the carbonyl oxygen, is to allow an ordinary aldehyde to stand in $H_2{}^{18}O$ in the presence of a little acid. Suggest a detailed mechanism for this oxygen exchange.

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.)

$$\underset{\text{Formaldehyde}}{2HCHO} \xrightarrow{50\%\ NaOH} \underset{\text{Methanol}}{CH_3OH} + \underset{\text{Sodium formate}}{HCOO^-Na^+}$$

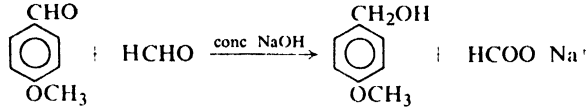


p-Nitrobenzaldehyde — *p*-Nitrobenzyl alcohol — Sodium *p*-nitrobenzoate

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:

$$ArCHO + HCHO \xrightarrow{\text{conc. NaOH}} ArCH_2OH + HCOO^-Na^+$$

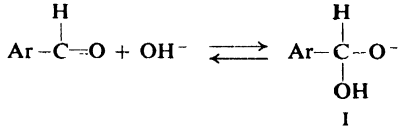
The high tendency for formaldehyde to undergo oxidation makes this **crossed Cannizzaro reaction** a useful synthetic tool. For example:



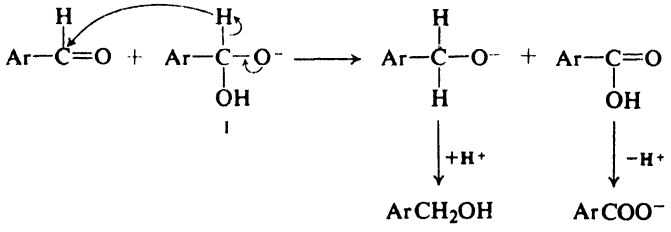
Anisaldehyde (*p*-Methoxybenzaldehyde) — *p*-Methoxybenzyl alcohol

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)

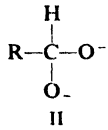


(2)



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

Chapter 18 Carboxylic Acids

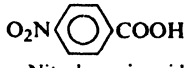
18.1 Structure

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

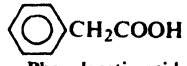
attached to either an alkyl group (RCOOH) or an aryl group (ArCOOH). For example:

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

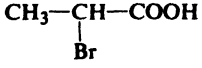
Benzoic acid



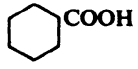
p-Nitrobenzoic acid



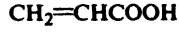
Phenylacetic acid



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

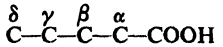
The aliphatic carboxylic acids have been known for a long time, and as a result have common names that refer to their sources rather than to their chemical structures. The **common names** of the more important acids are shown in Table 18.1. *Formic acid*, for example, adds the sting to the bite of an 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

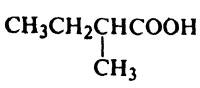
and *caproic, caprylic,* and *capric acids* are all found in goat fat (Latin: *caper,* goat).

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.

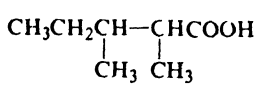


Used in common names

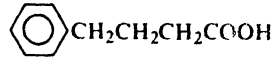
For example:



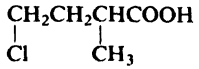
α-Methylbutyric acid



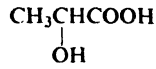
α,β-Dimethylvaleric acid



γ-Phenylbutyric acid



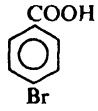
γ-Chloro-α-methylbutyric acid



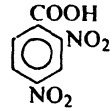
α-Hydroxypropionic acid
Lactic acid

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

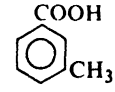
Aromatic acids, ArCOOH, are usually named as derivatives of the parent acid, **benzoic acid**, C_6H_5COOH. The methylbenzoic acids are given the special name of *toluic acids.*



p-Bromobenzoic acid

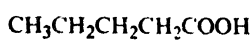


2,4-Dinitrobenzoic acid

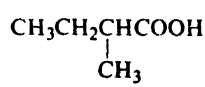


m-Toluic acid

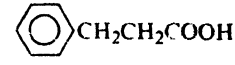
The **IUPAC names** follow the usual pattern. The longest chain carrying the carboxyl group is considered the parent structure, and is named by replacing the *-e* of the corresponding alkane with **-oic acid.** For example:



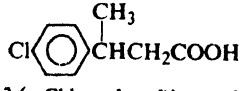
Pentanoic acid



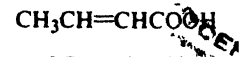
2-Methylbutanoic acid



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

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

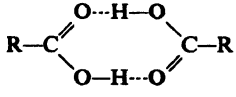
Potassium α,β-dibromopropionate
(Potassium 2,3-dibromopropanoate)

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.

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

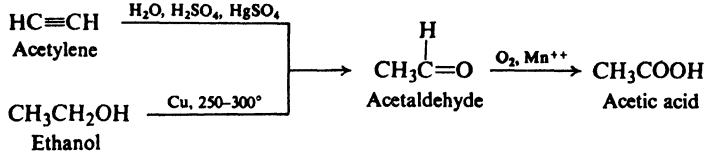
We can separate a carboxylic acid from non-acidic compounds by taking advantage of its solubility and their insolubility in aqueous base; once the separation has been accomplished, we can regenerate the acid by acidification of the aqueous solution. If we are dealing with solids, we simply stir the mixture 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.

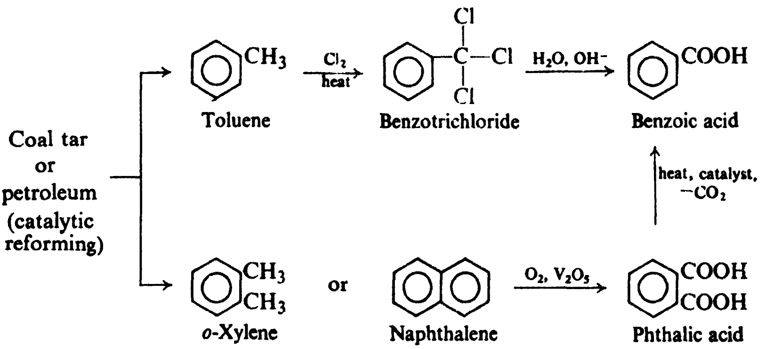


Large amounts of acetic acid are also produced as the dilute aqueous solution known as *vinegar*. Here, too, the acetic acid is prepared by air oxidation; the compound that is oxidized is ethyl alcohol, and the catalysts are bacterial (*Acetobacter*) enzymes.

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:

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

(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

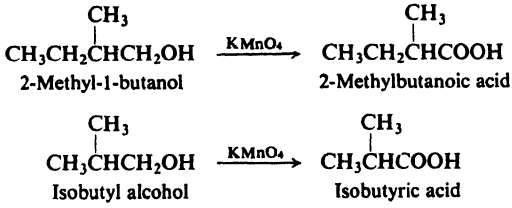
The straight-chain aliphatic acids up to C_6, and those of even carbon number up to C_{18}, are commercially available, as are the simple aromatic acids. Other carboxylic acids can be prepared by the methods outlined below.

PREPARATION OF CARBOXYLIC ACIDS

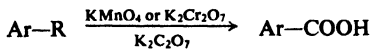
1. **Oxidation of primary alcohols.** Discussed in Sec. 16.8.

$$RCH_2OH \xrightarrow{KMnO_4} RCOOH$$

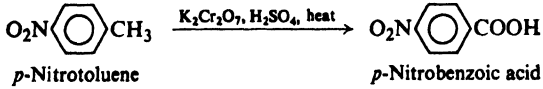
Examples:

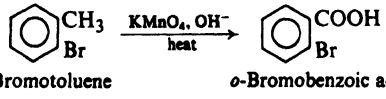


2. Oxidation of alkylbenzenes. Discussed in Sec. 12.10.

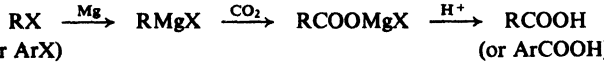


Examples:

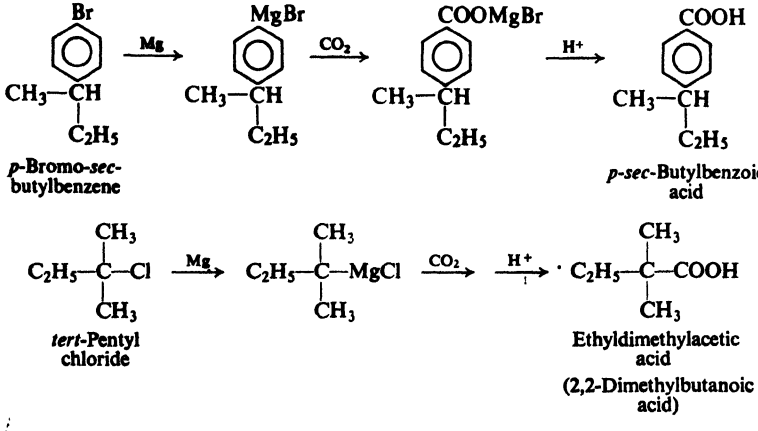




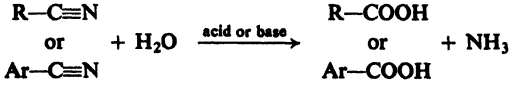
3. Carbonation of Grignard reagents. Discussed in Sec. 18.7.



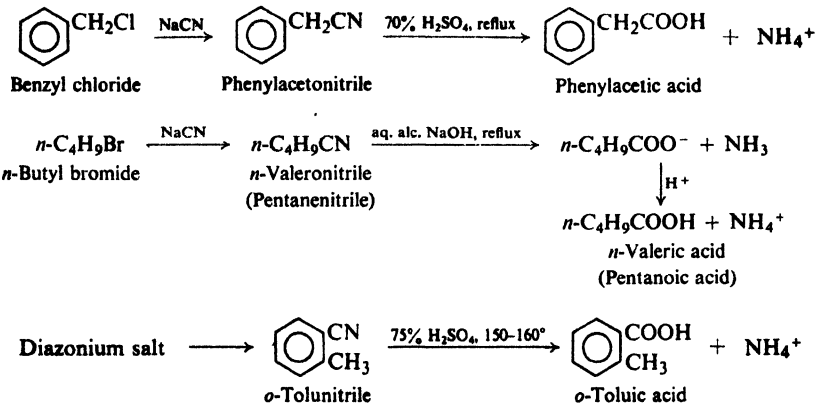
Examples:



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



Examples:



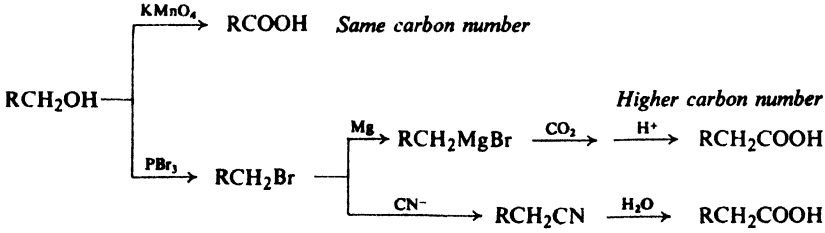
5. **Malonic ester synthesis.** Discussed in Sec. 26.2.

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).

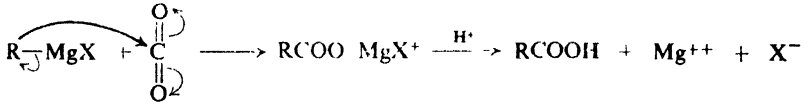
$$\underset{}{ArH} \longrightarrow \underset{\text{Nitro compound}}{ArNO_2} \longrightarrow \underset{\text{Amine}}{ArNH_2} \longrightarrow \underset{\text{Diazonium ion}}{ArN_2^+} \longrightarrow \underset{\text{Nitrile}}{ArC{\equiv}N} \longrightarrow \underset{\text{Acid}}{ArCOOH}$$

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

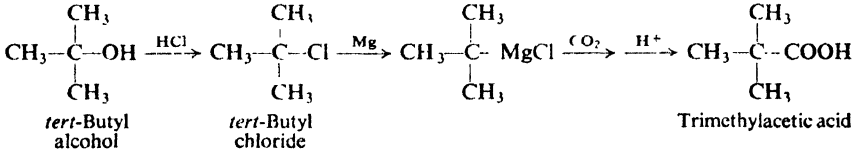
18.7 Grignard synthesis

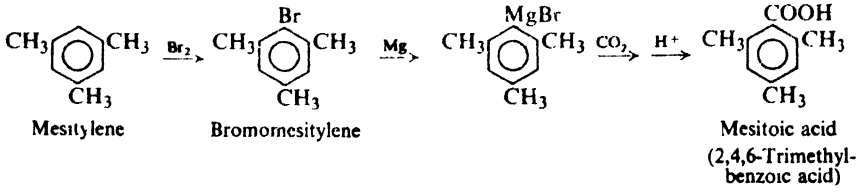
The Grignard synthesis of a carboxylic acid is carried out by bubbling gaseous CO_2 into the ether solution of the Grignard reagent, or by pouring the Grignard reagent on crushed Dry Ice (solid CO_2); in the latter method Dry Ice serves not only as reagent but also as cooling agent.

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

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

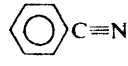
3° halide: *elimination*

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.

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

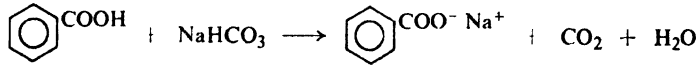
Examples:

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

Acetic acid — Zinc acetate

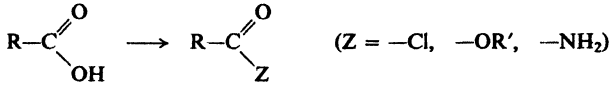
$$CH_3(CH_2)_{10}COOH + NaOH \longrightarrow CH_3(CH_2)_{10}COO^-Na^+ + H_2O$$

Lauric acid — Sodium laurate

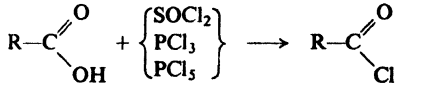


Benzoic acid — Sodium benzoate

2. Conversion into functional derivatives

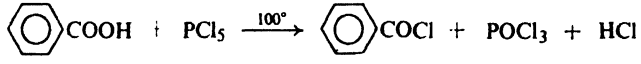


(a) Conversion into acid chlorides. Discussed in Sec. 18.15.



Acid chloride

Examples:



Benzoic acid — Benzoyl chloride

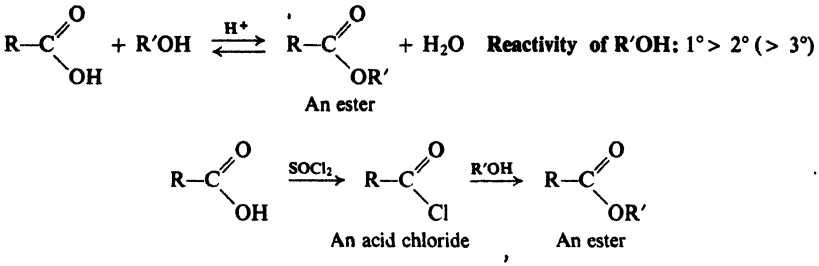
$$n\text{-}C_{17}H_{35}COOH + SOCl_2 \xrightarrow{\text{reflux}} n\text{-}C_{17}H_{35}COCl + SO_2 + HCl$$

Stearic acid — Thionyl chloride — Stearoyl chloride

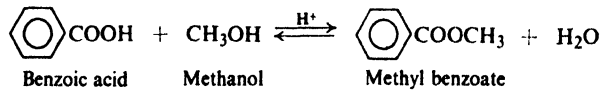
$$3CH_3COOH + PCl_3 \xrightarrow{50^\circ} 3CH_3COCl + H_3PO_3$$

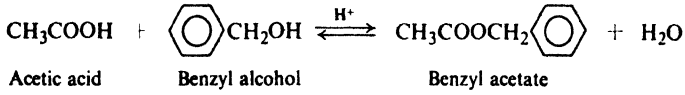
Acetic acid — Acetyl chloride

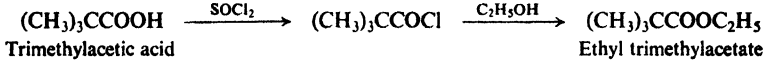
(b) Conversion into esters. Discussed in Secs. 18.16 and 20.15.



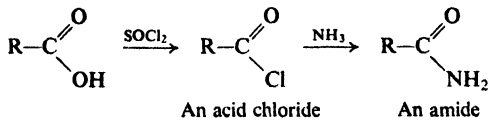
Examples:



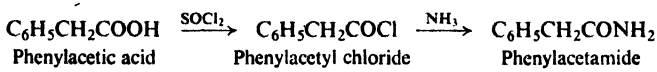




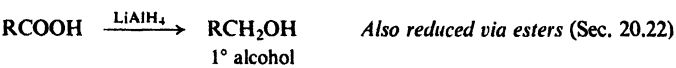
(c) Conversion into amides. Discussed in Sec. 18.17.



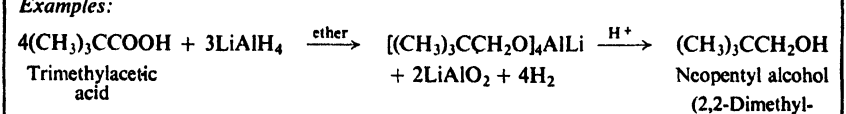
Example:

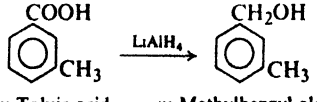


3. Reduction. Discussed in Sec. 18.18.



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:

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

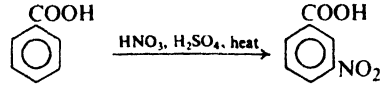
$$\underset{\text{Isovaleric acid}}{\begin{matrix}CH_3\\ |\\ CH_3CHCH_2COOH\end{matrix}} \xrightarrow{Br_2, P} \underset{\displaystyle Br}{\begin{matrix}CH_3\\ |\\ CH_3CHCHCOOH\\ |\end{matrix}}$$

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*.

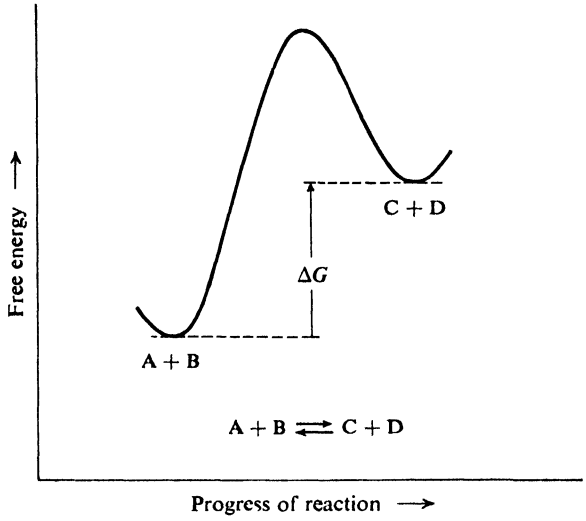


Figure 18.1. Free energy curve for a reversible reaction.

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.

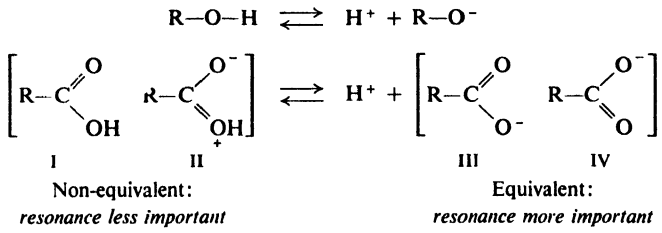
In dealing with rates, we compare the stability of the reactants with the stability of the transition state. In dealing with equilibria, we shall compare the stability of the reactants with the stability of the products. For closely related reactions, we are justified in assuming that the more stable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

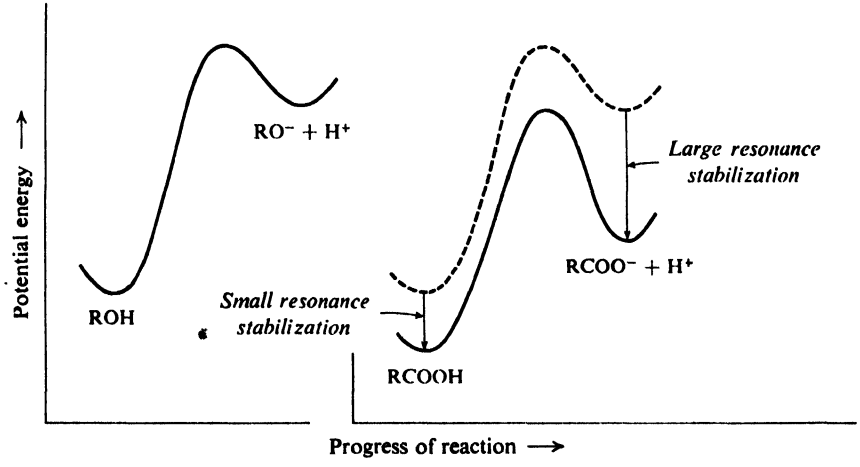


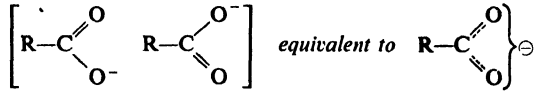
Figure 18.2. Molecular structure and position of equilibrium. Carboxylic acid yields resonance-stabilized anion; is stronger acid than alcohol. (Plots aligned with each other for easy comparison.)

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.

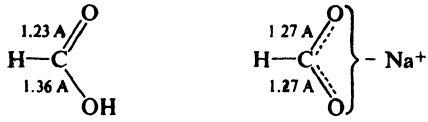
The acidity of a carboxylic acid is thus due to the powerful resonance stabilization of its anion. *This stabilization and the resulting acidity are possible only because of the presence of the carbonyl group.*

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.

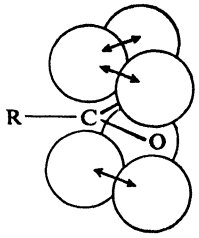


Figure 18.3. Carboxylate ion. Overlap of *p* orbitals in both directions: delocalization of π electrons, and dispersal of charge.

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.)

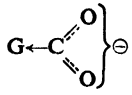
$$\overset{\gamma}{C}H_3\overset{\beta}{C}H_2\overset{\alpha}{C}H_2\overset{H}{C}{=}O$$

n-Butyraldehyde

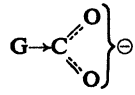
18.14 Effect of substituents on acidity

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 „

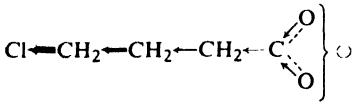
ACIDITY CONSTANTS OF SUBSTITUTED BENZOIC ACIDS

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.

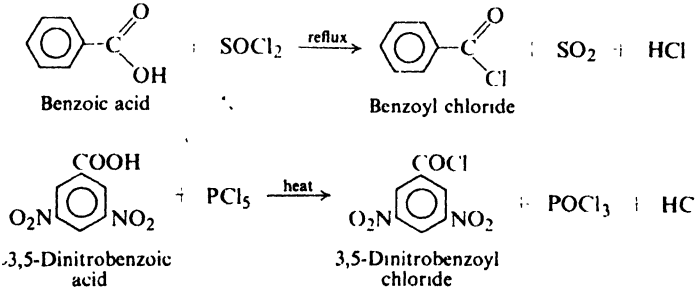
Thus we see that the same concepts—inductive effect and resonance—that we found so useful in dealing with rates of reaction are also useful in dealing with equilibria. By using these concepts to estimate the stabilities of anions, we are able to predict the relative strengths of acids; in this way we 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:

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

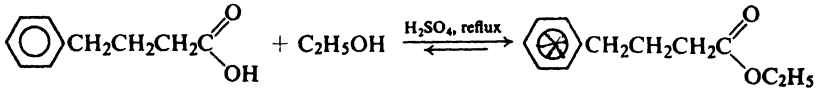
A carboxylic acid is converted directly into an ester when heated with an alcohol in the presence of a little mineral acid, usually concentrated sulfuric acid or dry hydrogen chloride. This reaction is reversible, and generally reaches equilibrium when there are appreciable quantities of both reactants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

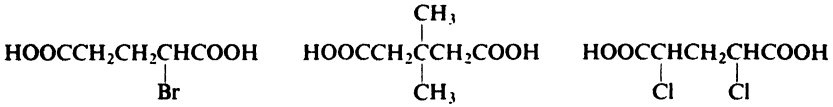
Problem 18.11 Predict the product of each of the following reactions:

(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

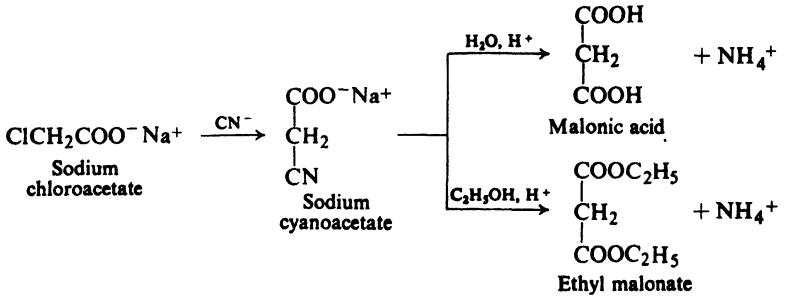
α,α′-Dichloroglutaric acid
2,4-Dichloropentanedioic acid

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?

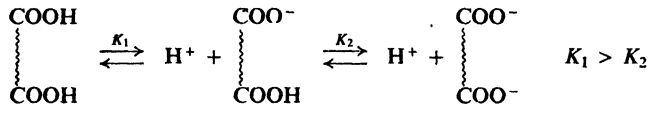
Problem 18.13 Outline a synthesis of: (a) pentanedioic acid from 1,3-propanediol (available from a fermentation of glycerol); (b) nonanedioic acid from *cis*-9-octadecenoic acid (oleic acid, obtained from fats); (c) succinic acid from 1,4-butynediol (available from acetylene and formaldehyde).

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

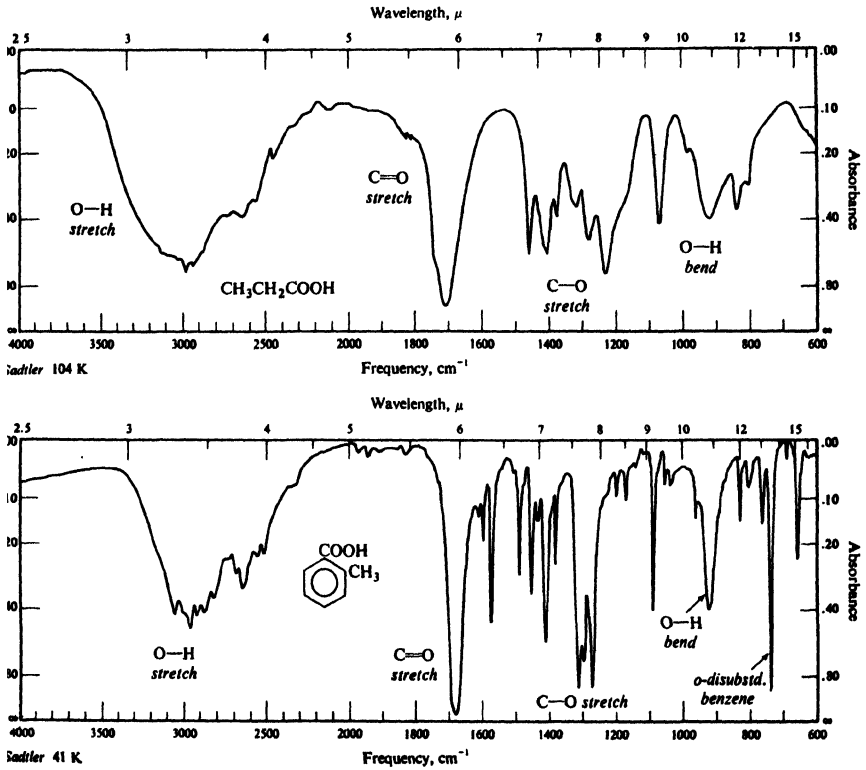


Figure 18.4. Infrared spectra of (*a*) propionic acid and (*b*) *o*-toluic acid.

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.

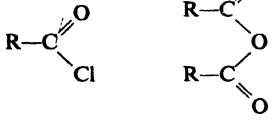
Chapter 20

Functional Derivatives of Carboxylic Acids

Nucleophilic Acyl Substitution

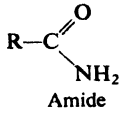
20.1 Structure

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′.

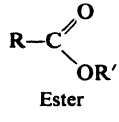


Acid chloride

Anhydride



Amide



Ester

R *may be alkyl or aryl*

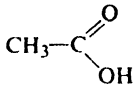
They all contain the **acyl group**:

Acyl group

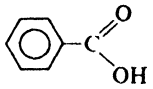
Like the acid to which it is related, an acid derivative may be aliphatic or aromatic, substituted or unsubstituted; whatever the structure of the rest of the molecule, the properties of the functional group remain essentially the same.

20.2 Nomenclature

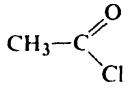
The names of acid derivatives are taken in simple ways from either the common name or the IUPAC name of the corresponding carboxylic acid. For example:



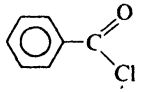
Acetic acid
Ethanoic acid



Benzoic acid

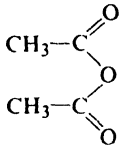


Acetyl chloride
Ethanoyl chloride

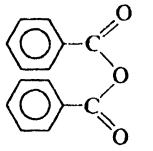


Benzoyl chloride

Change:
-ic acid to *-yl chloride*

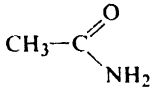


Acetic anhydride
Ethanoic anhydride

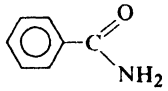


Benzoic anhydride

acid to ***anhydride***

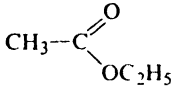


Acetamide
Ethanamide

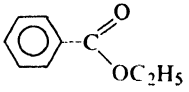


Benzamide

-ic acid of common name
(or *-oic acid* of IUPAC name)
to *-amide*



Ethyl acetate
Ethyl ethanoate

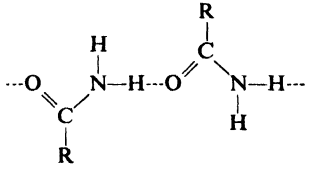


Ethyl benzoate

-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.

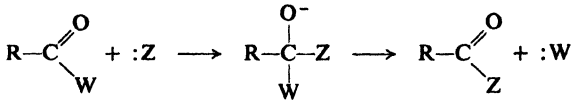
Each derivative is nearly always prepared—directly or indirectly—from the corresponding carboxylic acid, and can be readily converted back into the carboxylic acid by simple hydrolysis. Much of the chemistry of acid derivatives involves their conversion one into another, and into the parent acid. In 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.)

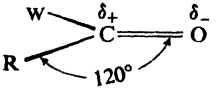
Acyl compounds—carboxylic acids and their derivatives—typically undergo **nucleophilic substitution** in which —OH, —Cl, —OOCR, $—NH_2$, or —OR′ is replaced by some other basic group. Substitution takes place much more readily than at a saturated carbon atom; indeed, many of these substitutions do not 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′

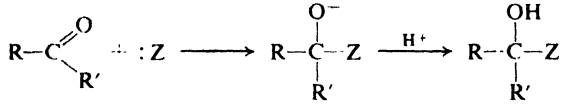
To account for the properties of acyl compounds, let us turn to the carbonyl group. We have encountered this group in our study of aldehydes and ketones (Secs. 19.1 and 19.8), and we know what it is like and what in general to expect of it.

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:

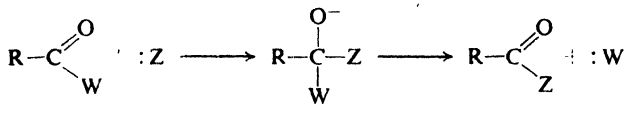


We saw before that both electronic and steric factors make the carbonyl group particularly susceptible to nucleophilic attack at the carbonyl carbon: (a) the tendency of oxygen to acquire electrons even at the expense of gaining a negative charge; and (b) the relatively unhindered transition state leading 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

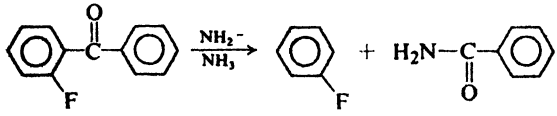
($:R^-$) which, as we know, are the strongest bases of all. (Witness the low acidity of H_2 and RH.) And so with aldehydes and ketones addition almost always takes place instead.

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),

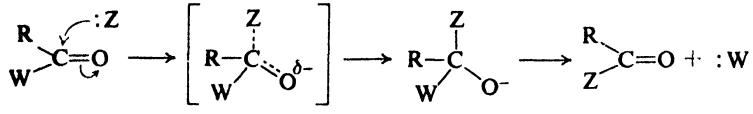
$$OH^- + R{-}\underset{\underset{O}{\|}}{C}{-}CX_3 \xrightarrow{H_2O} RCOO^- + CHX_3$$

(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

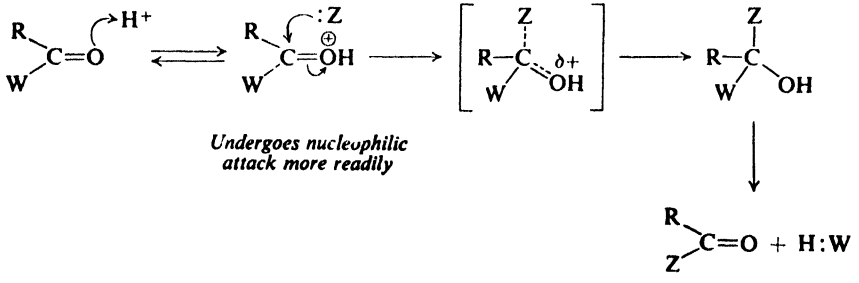


Reactant	Transition state	Intermediate	Product	Leaving group
Trigonal	*Becoming tetrahedral*	*Tetrahedral*	*Trigonal*	*Weaker base leaves more readily*
	Partial negative charge on oxygen	*Negative charge on oxygen*		

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

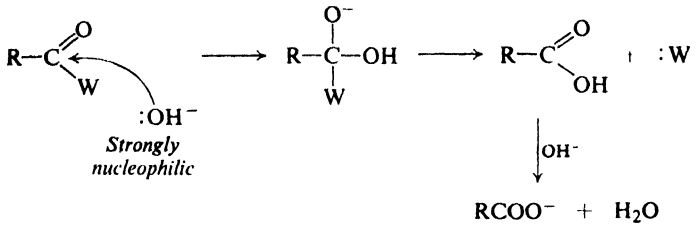


Undergoes nucleophilic attack more readily

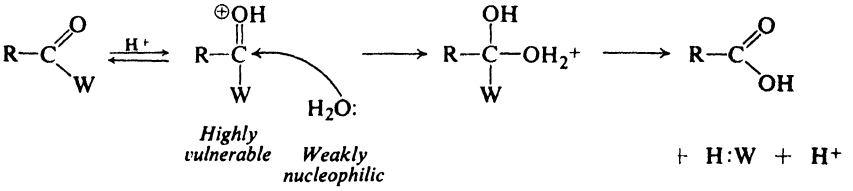
carbonyl group even more susceptible to the nucleophilic attack; oxygen can now acquire the π electrons without having to accept a negative charge.

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

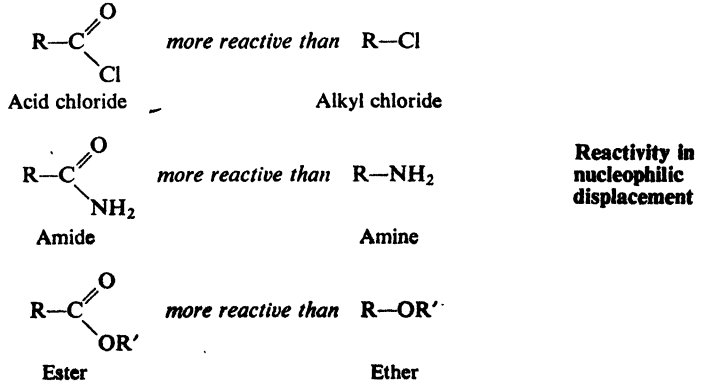


Acidic hydrolysis



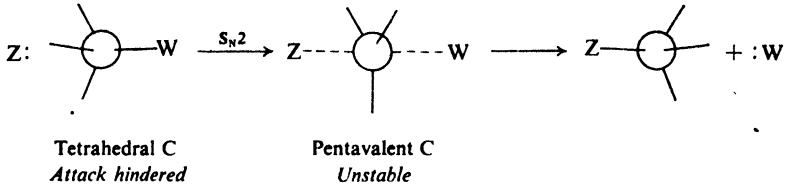
20.5 Nucleophilic substitution: alkyl *vs.* acyl

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

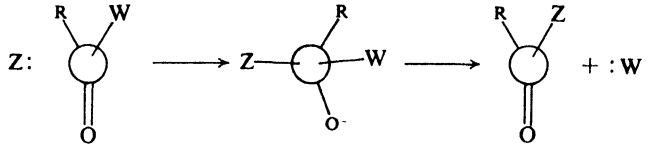


Tetrahedral C
Attack hindered

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

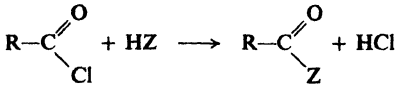
Acid chlorides are prepared from the corresponding acids by reaction with thionyl chloride, phosphorus trichloride, or phosphorus pentachloride, as discussed in Sec. 18.15.

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

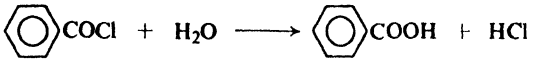
1. Conversion into acids and derivatives. Discussed in Sec. 20.8.



(a) Conversion into acids. Hydrolysis.

$$RCOCl + H_2O \longrightarrow RCOOH + HCl$$
An acid

Example:

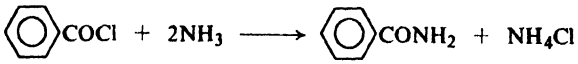


Benzoyl chloride — Benzoic acid

(b) Conversion into amides. Ammonolysis

$$RCOCl + 2NH_3 \longrightarrow RCONH_2 + NH_4Cl$$
An amide

Example:

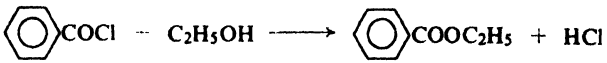


Benzoyl chloride — Benzamide

(c) Conversion into esters. Alcoholysis

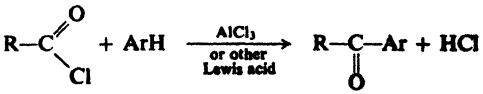
$$RCOCl + R'OH \longrightarrow RCOOR' + HCl$$
An ester

Example:



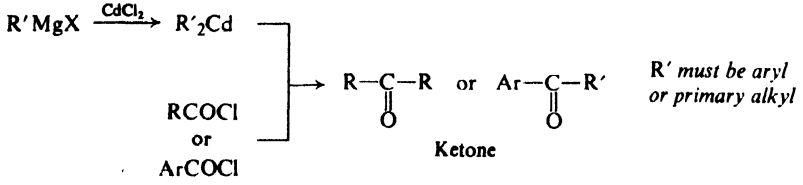
Benzoyl chloride — Ethyl alcohol — Ethyl benzoate

2. Formation of ketones. Friedel-Crafts acylation. Discussed in Sec. 19.6.

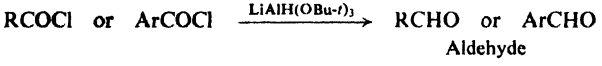


A ketone

3. Formation of ketones. Reaction with organocadmium compounds. Discussed in Sec. 19.7.

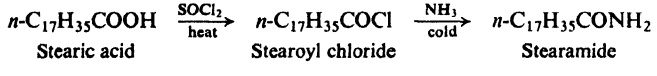


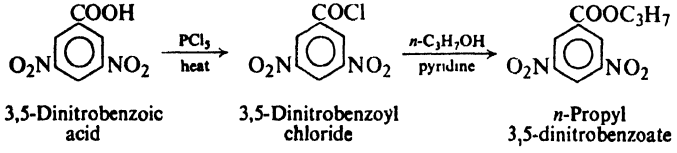
4. Formation of aldehydes by reduction. Discussed in Sec. 19.4.

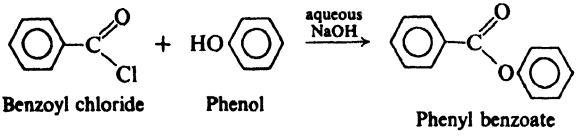


20.8 Conversion of acid chlorides into acid derivatives

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.

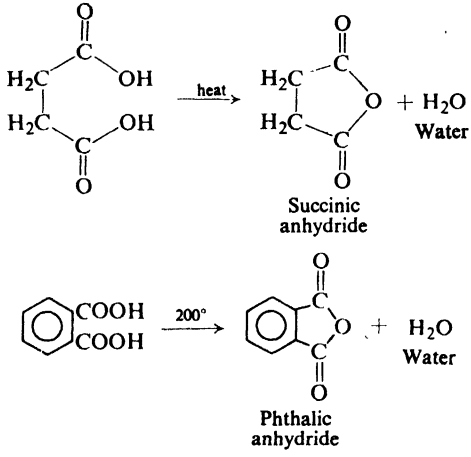
$$CH_3COOH \xrightarrow[700^\circ]{AlPO_4} H_2O + \underset{\text{Ketene}}{CH_2{=}C{=}O} \xrightarrow{CH_3COOH} \underset{\text{Acetic anhydride}}{(CH_3CO)_2O}$$

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

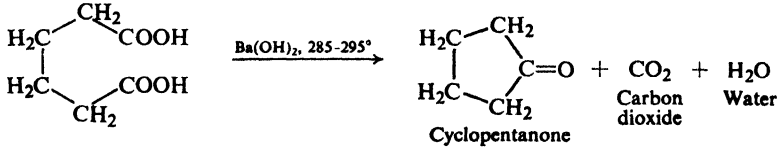
$$CH_3COCH_3 \xrightarrow{700\text{–}750^\circ} CH_4 + \underset{\text{Ketene}}{CH_2{=}C{=}O}$$

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

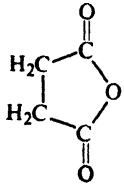
Example:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + H_2O \longrightarrow \underset{\text{Acetic acid}}{2CH_3COOH}$$

(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

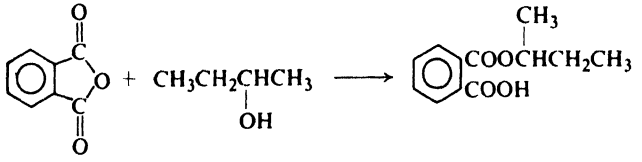
$$+ 2NH_3 \longrightarrow \underset{\text{Ammonium succinamate}}{\begin{matrix}CH_2CONH_2\\ |\\ CH_2COONH_4\end{matrix}} \xrightarrow{H^+} \underset{\text{Succinamic acid}}{\begin{matrix}CH_2CONH_2\\ |\\ CH_2COOH\end{matrix}}$$

(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



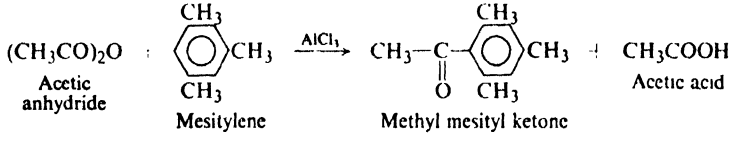
Phthalic anhydride *sec*-Butyl alcohol *sec*-Butyl hydrogen phthalate

2. Formation of ketones. Friedel-Crafts acylation. Discussed in Sec. 19.6.

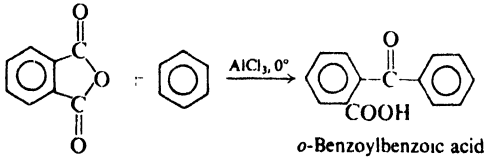
$$(RCO)_2O + ArH \xrightarrow[\text{or other Lewis acid}]{AlCl_3} R{-}\underset{\underset{O}{\|}}{C}{-}Ar + RCOOH$$

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).

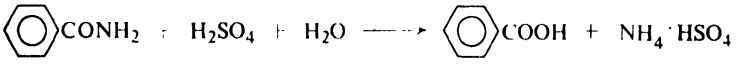
REACTIONS OF AMIDES

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.

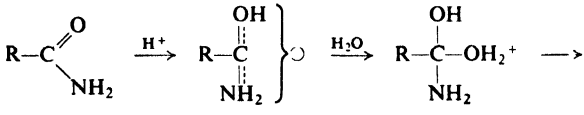
3. Hofmann degradation of amides. Discussed in Secs. 22.12 and 28.2–28.5.

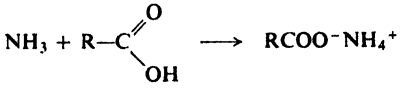
$$RCONH_2 \text{ or } ArCONH_2 \xrightarrow{OBr^-} RNH_2 \text{ or } ArNH_2 + CO_3^{--}$$

Amide — 1° amine

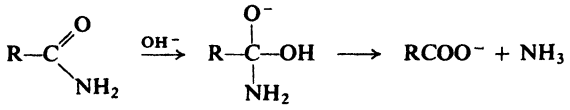
20.13 Hydrolysis of amides

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:



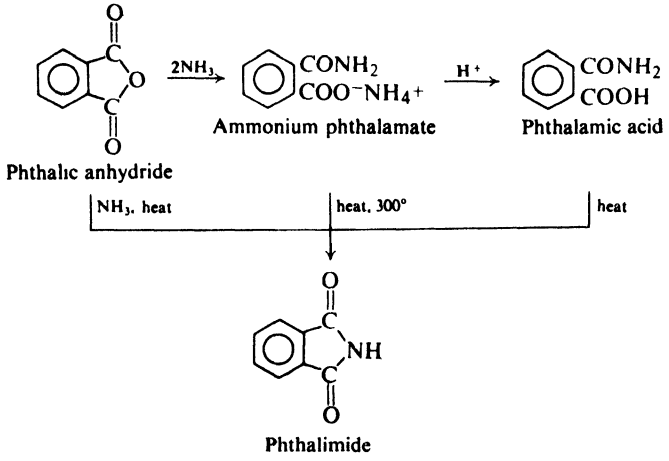


Under alkaline conditions hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the amide itself:



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

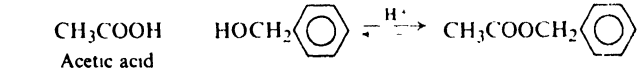
1. From acids. Discussed in Secs. 18.16 and 20.18.

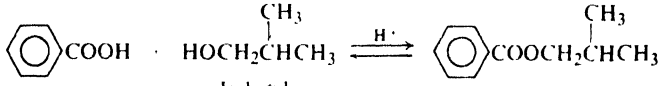
$$\underset{\text{Carboxylic acid}}{RCOOH} + \underset{\text{Alcohol}}{R'OH} \underset{}{\overset{H^+}{\rightleftharpoons}} \underset{\text{Ester}}{RCOOR'} + H_2O$$

R *may be alkyl or aryl*; R′ is *usually alkyl*

Reactivity of R′OH: 1° > 2° (> 3°)

Examples:



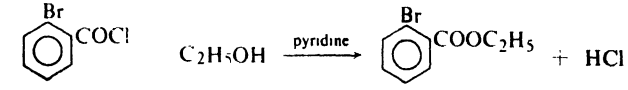


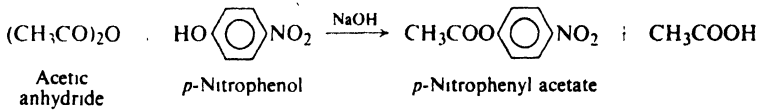
2. From acid chlorides or anhydrides. Discussed in Secs. 20.8 and 20.10.

$$RCOCl + R'OH \text{ (or ArOH)} \longrightarrow RCOOR' \text{ (or RCOOAr)} + HCl$$

$$(RCO)_2O + R'OH \text{ (or ArOH)} \longrightarrow RCOOR' \text{ (or RCOOAr)} + RCOOH$$

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).

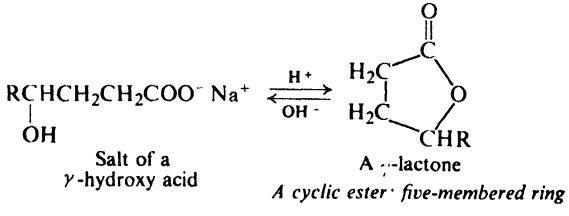
Table 20.2 ESTERS OF CARBOXYLIC ACIDS

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.

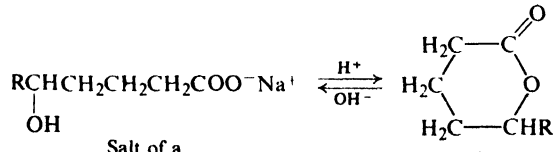
A hydroxy acid is both alcohol and acid. In those cases where a five- or six-membered ring can be formed, *intramolecular* esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield a cyclic ester known as a **lactone**. Treatment with base (actually hydrolysis of an ester) 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

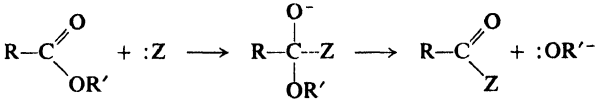
A cyclic ester: six-membered ring

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).

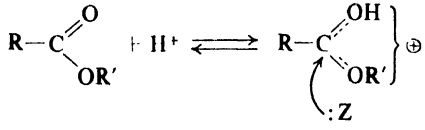
20.16 Reactions of esters

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.

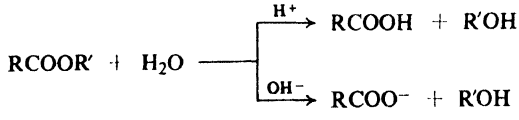


Acid catalysis:
makes carbon more susceptible to nucleophilic attack

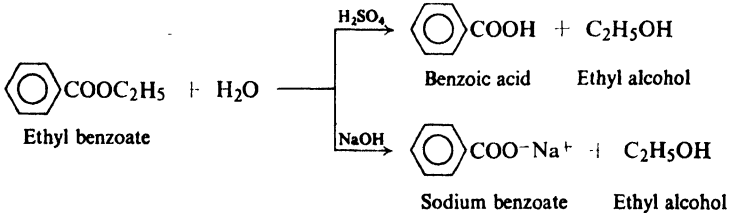
REACTIONS OF ESTERS

1. Conversion into acids and acid derivatives.

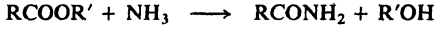
(a) Conversion into acids. Hydrolysis. Discussed in Secs. 20.17 and 20.18.



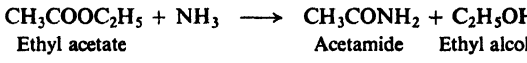
Example:



(b) Conversion into amides. Ammonolysis. Discussed in Sec. 20.19.



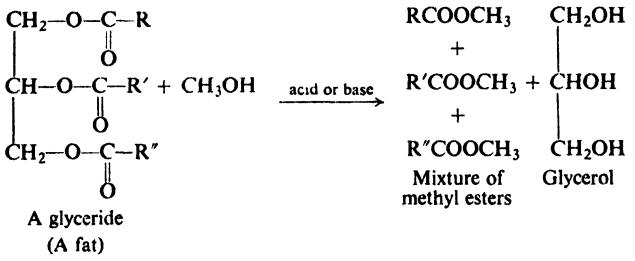
Example:



(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:

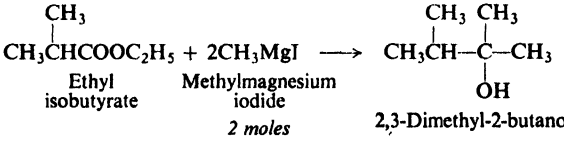


2. **Reaction with Grignard reagents.** Discussed in Sec. 20.21.

$$RCOOR' + 2R''MgX \longrightarrow R{-}\underset{\displaystyle OH}{\overset{\displaystyle R''}{\overset{|}{\underset{|}{C}}}}{-}R''$$

Tertiary alcohol

Example:



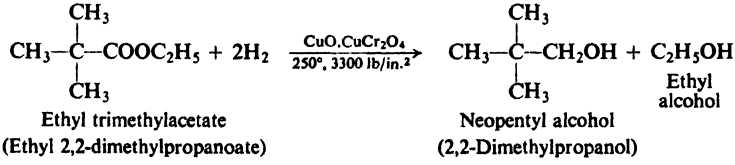
3. **Reduction to alcohols.** Discussed in Sec. 20.22.

(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**

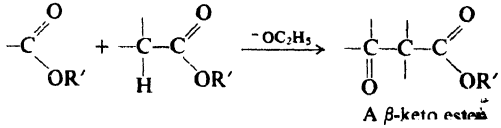
$$4RCOOR' + 2LiAlH_4 \xrightarrow[\text{ether}]{\text{anhyd.}} \left\{\begin{matrix} LiAl(OCH_2R)_4 \\ + \\ LiAl(OR')_4 \end{matrix}\right\} \xrightarrow{H^+} \left\{\begin{matrix} RCH_2OH \\ + \\ R'OH \end{matrix}\right\}$$

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.

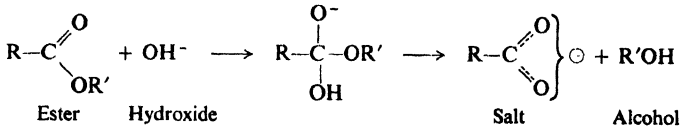


A β-keto ester

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



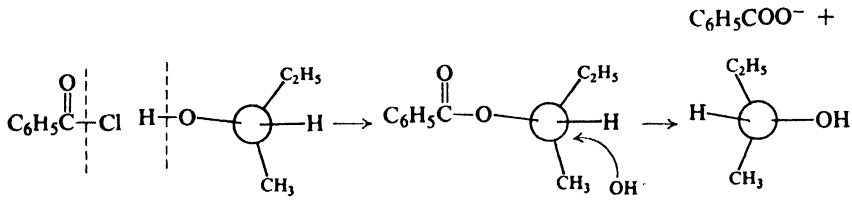
carboxylate anion (Sec. 18.13) shows little tendency to react with an alcohol.

Let us look at the various aspects of the mechanism we have written, and see what evidence there is for each of them.

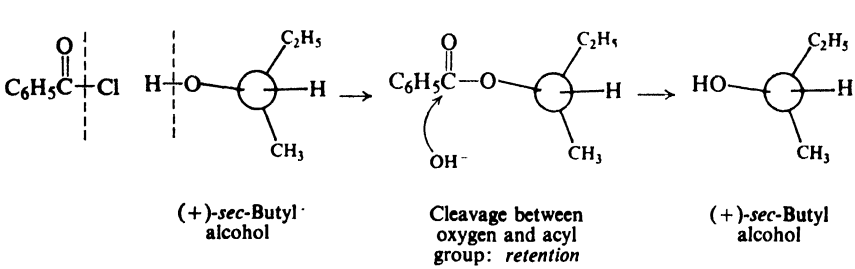
First, reaction involves attack on the ester by hydroxide ion. This is consistent with the **kinetics**, which is second-order, with the rate depending on both ester concentration and hydroxide concentration.

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):

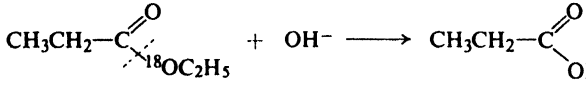


If, on the other hand, the bond between oxygen and the *sec*-butyl group remains intact during hydrolysis, then we would expect to obtain *sec*-butyl alcohol of the same configuration as the starting material:



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.

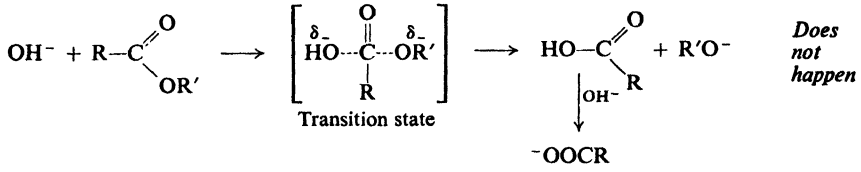
Tracer studies have confirmed the kind of bond cleavage indicated by the stereochemical evidence. When ethyl propionate labeled with ^{18}O was hydrolyzed by base in ordinary water, the ethanol produced was found to be enriched in ^{18}O; the propionic acid contained only the ordinary amount of ^{18}O:



The alcohol group retained the oxygen that it held in the ester; cleavage occurred between oxygen and the acyl group.

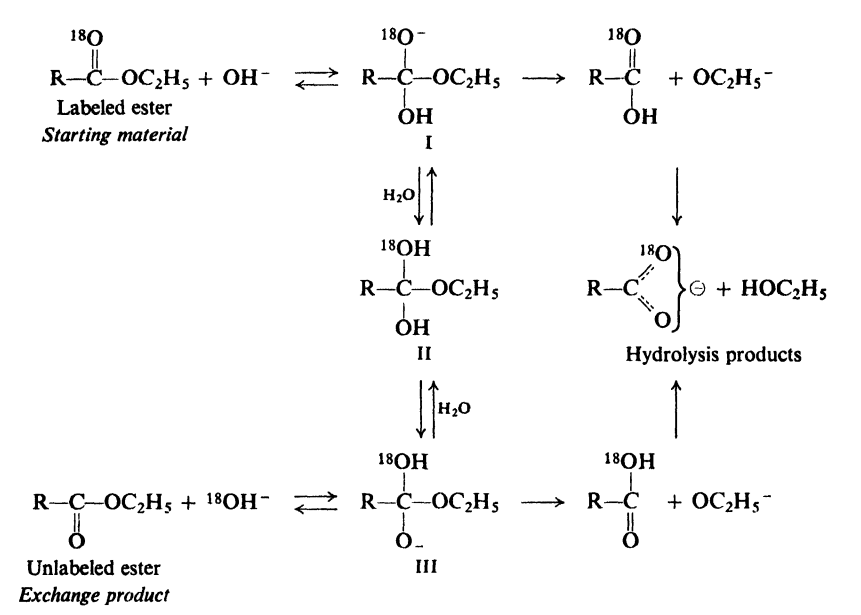
The study of a number of other hydrolyses by both tracer and stereochemical methods has shown that cleavage between oxygen and the acyl group is the usual one in ester hydrolysis. This behavior indicates that the preferred point of nucleophilic attack is the carbonyl carbon rather than the alkyl carbon; 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

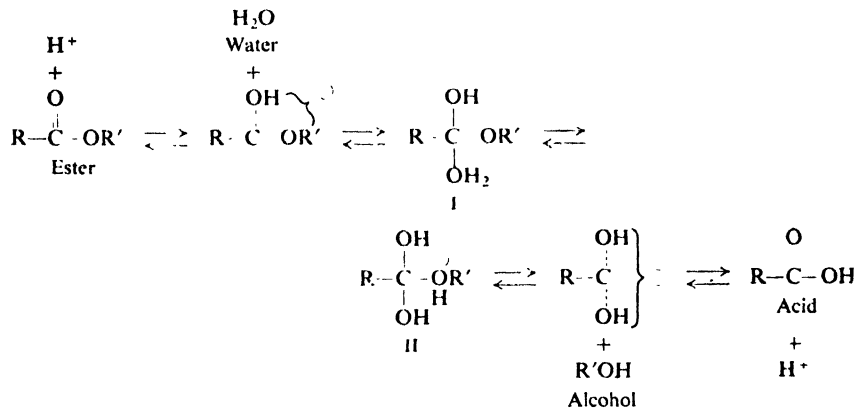
Hydrolysis of esters is promoted not only by base but also by acid. Acidic hydrolysis, as we have seen (Sec. 18.16), is reversible,

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

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?

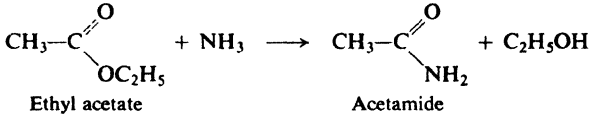
Problem 20.18 Account for the fact (Sec. 18.16) that the presence of bulky substituents in either the alcohol group or the acid group slows down both esterification and hydrolysis.

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:



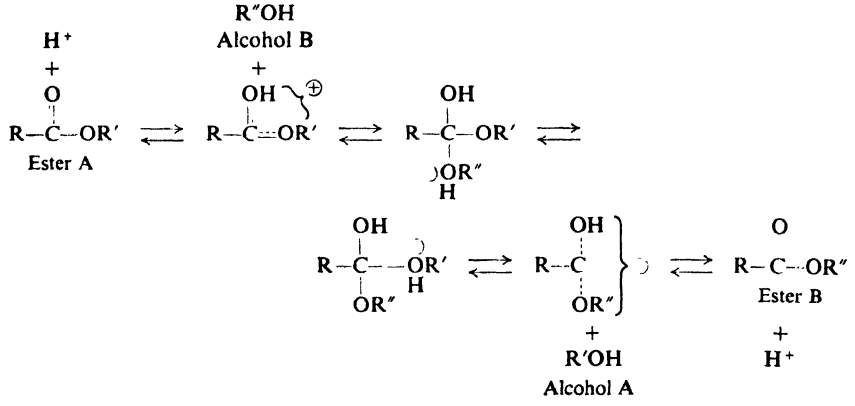
Ethyl acetate Acetamide

20.20 Transesterification

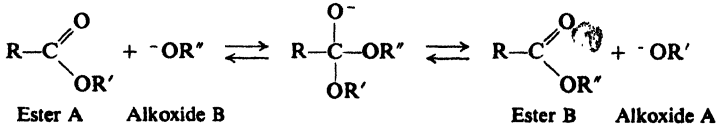
In the esterification of an acid, an alcohol acts as a nucleophilic reagent; in hydrolysis of an ester, an alcohol is displaced by a nucleophilic reagent. Knowing this, we are not surprised to find that one alcohol is capable of displacing another alcohol from an ester. This *alcoholysis* (cleavage by 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:

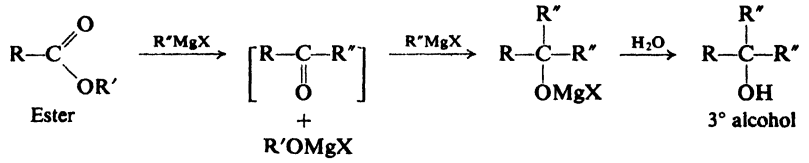


Ester A Alkoxide B Ester B Alkoxide A

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:

$$\underset{\substack{\text{Methyl laurate}\\\text{(Methyl dodecanoate)}}}{CH_3(CH_2)_{10}COOCH_3} \xrightarrow[150°,\ 5000\ lb/in.^2]{H_2,\ CuO.CuCr_2O_4} \underset{\substack{\text{Lauryl alcohol}\\\text{(1-Dodecanol)}}}{CH_3(CH_2)_{10}CH_2OH} + CH_3OH$$

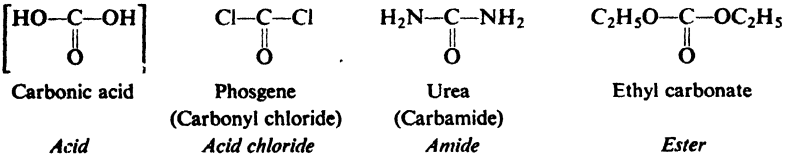
Chemical reduction is carried out by use of sodium metal and alcohol, or more usually by use of lithium aluminium hydride. For example:

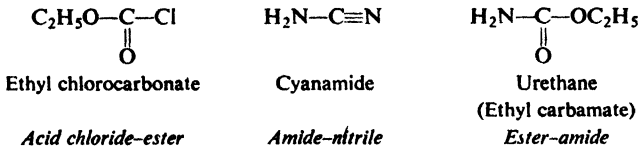
$$\underset{\substack{\text{Ethyl palmitate}\\\text{(Ethyl hexadecanoate)}}}{CH_3(CH_2)_{14}COOC_2H_5} \xrightarrow{LiAlH_4} \underset{\text{1-Hexadecanol}}{CH_3(CH_2)_{14}CH_2OH}$$

Problem 20.22 Predict the products of the hydrogenolysis of *n*-butyl oleate over copper chromite.

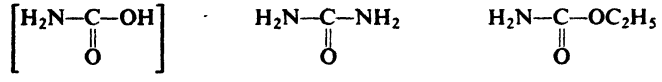
20.23 Functional derivatives of carbonic acid

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:

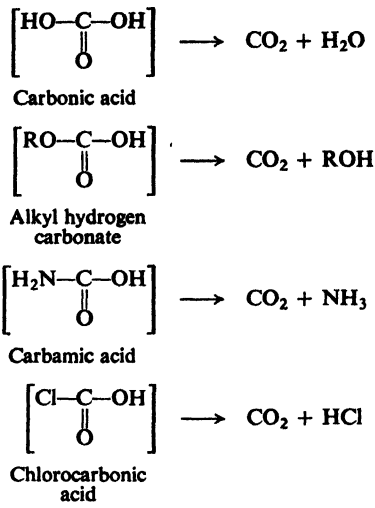




We use these functional relationships to carbonic acid simply for convenience. Many of these compounds could just as well be considered as derivatives of other acids, and, indeed, are often so named. For example:

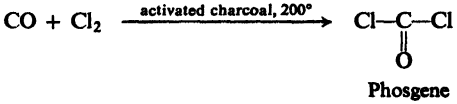


In general, a derivative of carbonic acid containing an —OH group is unstable, and decomposes to carbon dioxide. For example:

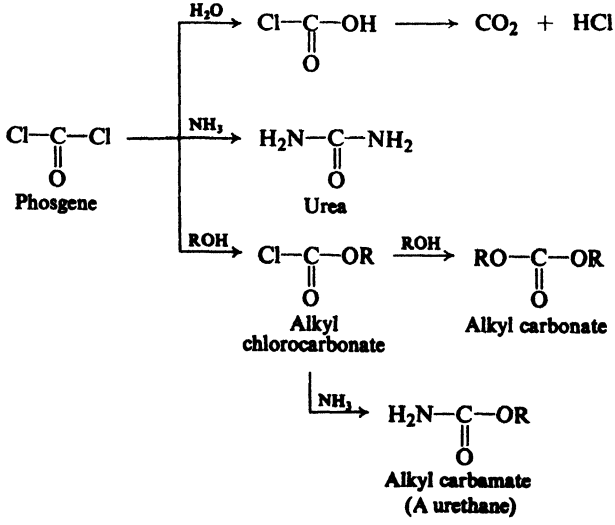


Most derivatives of carbonic acid are made from one of three industrially available compounds: phosgene, urea, or cyanamide.

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*).

$$\underset{\text{Urea}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2} \xrightarrow{H_2O} \begin{cases} \xrightarrow{H^+} NH_4^+ + CO_2 \\ \xrightarrow{OH^-} NH_3 + CO_3^{--} \\ \xrightarrow{\text{urease}} NH_3 + CO_2 \end{cases}$$

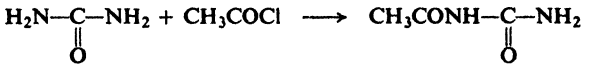
Urea reacts with nitrous acid to yield carbon dioxide and nitrogen; this is a useful way to destroy excess nitrous acid in diazotizations.

$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 \xrightarrow{HONO} CO_2 + N_2$$

Urea is converted by hypohalites into nitrogen and carbonate.

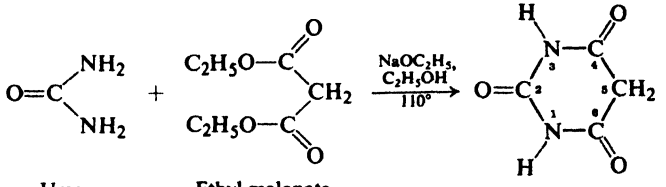
$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 \xrightarrow{Br_2\ OH^-} N_2 + CO_3^{--} + Br^-$$

Treatment of urea with acid chlorides or anhydrides yields **ureides.** Of special



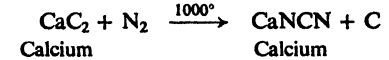
Acetylurea
A ureide

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.

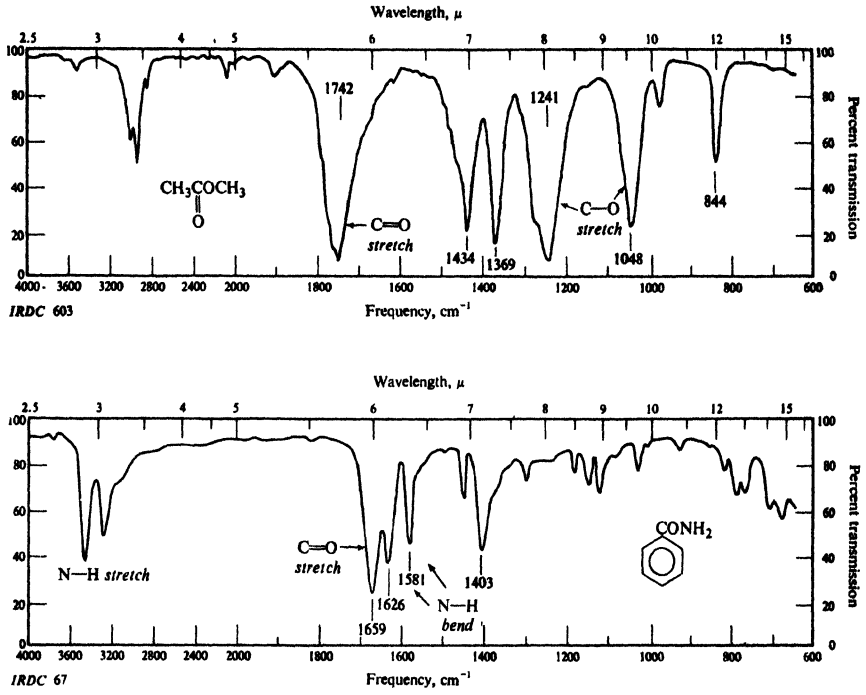


Figure 20.1. Infrared spectra of (*a*) methyl acetate and (*b*) benzamide.

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

Chapter 22 Amines I. Preparation and Physical Properties

22.1 Structure

Nearly all the organic compounds that we have studied so far are bases, although very weak ones. Much of the chemistry of alcohols, ethers, esters, and even of alkenes and aromatic hydrocarbons is understandable in terms of the basicity of these compounds.

Of the organic compounds that show appreciable basicity (for example, those strong enough to turn litmus blue), by far the most important are the **amines**. An amine has the general formula RNH_2, R_2NH, or R_3N, where R is any alkyl or aryl group. For example:

CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3N$	$H_2NCH_2CH_2NH_2$
Methylamine	Dimethylamine	Trimethylamine	Ethylenediamine
(1°)	(2°)	(3°)	(1°)

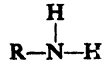
Aniline
(1°)

N-Methylaniline
(2°)

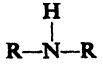
N,N-Dimethylaniline
(3°)

22.2 Classification

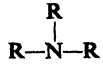
Amines are classified as **primary**, **secondary**, or **tertiary**, according to the number of groups attached to the nitrogen atom.



Primary
1°



Secondary
2°

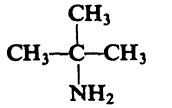


Tertiary
3°

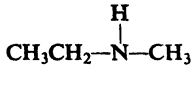
In their fundamental properties—*basicity* and the accompanying *nucleophilicity*—amines of different classes are very much the same. In many of their reactions, however, the final products depend upon the number of hydrogen atoms attached to the nitrogen atom, and hence are different for amines of different classes.

22.3 Nomenclature

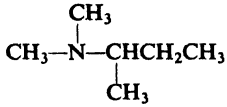
Aliphatic amines are named by naming the alkyl group or groups attached to nitrogen, and following these by the word *-amine*. More complicated ones are often named by prefixing *amino-* (or *N-methylamino-*, *N,N-diethylamino-*, etc.) to the name of the parent chain. For example:



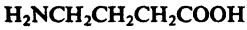
tert-Butylamine
(1°)



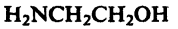
Methylethylamine
(2°)



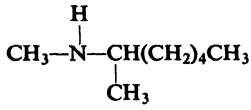
Dimethyl-*sec*-butylamine
(3°)



γ-Aminobutyric acid
(1°)

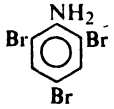


2-Aminoethanol
(Ethanolamine)
(1°)

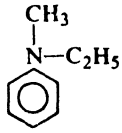


2-(N-Methylamino)heptane
(2°)

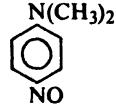
Aromatic amines—those in which nitrogen is attached directly to an aromatic ring—are generally named as derivatives of the simplest aromatic amine, **aniline**. An aminotoluene is given the special name of *toluidine*. For example:



2,4,6-Tribromoaniline
(1°)

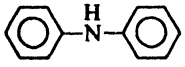


N-Methyl-N-ethylaniline
(3°)

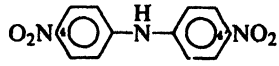


p-Nitroso-N,N-dimethylaniline
(3°)

p-Toluidine
(1°)



Diphenylamine
(2°)



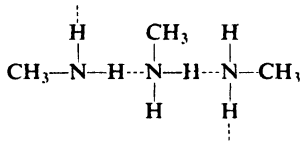
4,4'-Dinitrodiphenylamine
(2°)

Salts of amines are generally named by replacing *-amine* by *-ammonium* (or *-aniline* by *-anilinium*), and adding the name of the anion (*chloride*, *nitrate*, *sulfate*, etc.). For example:

$(C_2H_5NH_3^+)_2SO_4^{--}$	$(CH_3)_3NH^+NO_3^-$	$C_6H_5NH_3^+Cl^-$
Ethylammonium sulfate	Trimethylammonium nitrate	Anilinium chloride

22.4 Physical properties of amines

Like ammonia, amines are polar compounds and, except for tertiary amines, can form intermolecular hydrogen bonds. Amines have higher boiling points



than non-polar compounds of the same molecular weight, but lower boiling points than alcohols or carboxylic acids.

Amines of all three classes are capable of forming hydrogen bonds with water. As a result, smaller amines are quite soluble in water, with borderline solubility

Table 22.1 AMINES

Name	M.p., °C	B.p., °C	Solub., g/100 g H_2O	K_b
Methylamine	− 92	− 7.5	v.sol.	4.5×10^{-4}
Dimethylamine	− 96	7.5	v.sol.	5.4
Trimethylamine	−117	3	91	0.6
Ethylamine	− 80	17	∞	5.1
Diethylamine	− 39	55	v sol.	10.0
Triethylamine	−115	89	14	5.6
n-Propylamine	− 83	49	∞	4.1
Di-*n*-propylamine	− 63	110	s.sol.	10
Tri-*n*-propylamine	− 93	157	s.sol.	4.5
Isopropylamine	−101	34	∞	4
n-Butylamine	− 50	78	v.sol.	4.8
Isobutylamine	− 85	68	∞	3
sec-Butylamine	−104	63	∞	4
tert-Butylamine	− 67	46	∞	5
Cyclohexylamine		134	s.sol.	5
Benzylamine		185	∞	0.2
α-Phenylethylamine		187	4.2	
β-Phenylethylamine		195	s.	
Ethylenediamine	8	117	s.	
Tetramethylenediamine $[H_2N(CH_2)_4NH_2]$	27	158	v.sol.	0.85
Hexamethylenediamine	39	196	v.sol.	5
Tetramethylammonium hydroxide	63	135*d*	220	strong base

Table 22.1 AMINES (*continued*)

Name	M.p., °C	B.p.,, °C	Solub., g/100 g H_2O	K_b
Aniline	− 6	184	3.7	4.2×10^{-10}
Methylaniline	− 57	196	v.sl.sol.	7.1
Dimethylaniline	3	194	1.4	11.7
Diphenylamine	53	302	i.	0.0006
Triphenylamine	127	365	i.	
o-Toluidine	− 28	200	1.7	2.6
m-Toluidine	− 30	203	s.sol.	5
p-Toluidine	44	200	0.7	12
o-Anisidine (*o*-$CH_3OC_6H_4NH_2$)	5	225	s.sol.	3
m-Anisidine		251	s.sol.	2
p-Anisidine	57	244	v.sl.sol.	20
o-Chloroaniline	− 2	209	i.	0.05
m-Chloroaniline	− 10	236		0.3
p-Chloroaniline	70	232		1
o-Bromoaniline	32	229	s.sol.	0.03
m-Bromoaniline	19	251	v.sl.sol.	0.4
p-Bromoaniline	66	*d*	i.	0.7
o-Nitroaniline	71	284	0.1	0.00006
m-Nitroaniline	114	307*d*	0.1	0.029
p-Nitroaniline	148	332	0.05	0.001
2,4-Dinitroaniline	187		s.sol.	
2,4,6-Trinitroaniline (picramide)	188		0.1	
o-Phenylenediamine [*o*-$C_6H_4(NH_2)_2$]	104	252	3	3
m-Phenylenediamine	63	287	25	10
p-Phenylenediamine	142	267	3.8	140
Benzidine	127	401	0.05	9
p-Aminobenzoic acid	187		0.3	0.023
Sulfanilic acid	288*d*		1	0.17
Sulfanilamide	163		0.4	

Name	Formula	M.p., °C
Acetanilide	$C_6H_5NHCOCH_3$	114
Benzanilide	$C_6H_5NHCOC_6H_5$	163
Aceto-*o*-toluidide	*o*-$CH_3C_6H_4NHCOCH_3$	110
Aceto-*m*-toluidide	*m*-$CH_3C_6H_4NHCOCH_3$	66
Aceto-*p*-toluidide	*p*-$CH_3C_6H_4NHCOCH_3$	147
o-Nitroacetanilide	*o*-$O_2NC_6H_4NHCOCH_3$	93
m-Nitroacetanilide	*m*-$O_2NC_6H_4NHCOCH_3$	154
p-Nitroacetanilide	*p*-$O_2NC_6H_4NHCOCH_3$	216

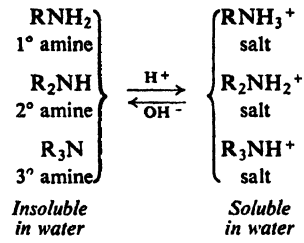
being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly "fishy" odors.

Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results.

Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

22.5 Salts of amines

Aliphatic amines are about as basic as ammonia; aromatic amines are considerably less basic. Although amines are much weaker bases than hydroxide ion or ethoxide ion, they are much stronger bases than alcohols, ethers, esters, etc.; they are much stronger bases than water. Aqueous mineral acids or carboxylic acids readily convert amines into their salts; aqueous hydroxide ion readily converts the salts back into the free amines. As with the carboxylic acids, we can



do little with amines without encountering this conversion into and from their salts; it is therefore worthwhile to look at the properties of these salts.

In Sec. 18.4 we contrasted physical properties of carboxylic acids with those of their salts; amines and their salts show the same contrast. Amine salts are typical ionic compounds. They are non-volatile solids, and when heated generally decompose before the high temperature required for melting is reached. The halides, nitrates, and sulfates are soluble in water but are insoluble in non-polar solvents.

The difference in solubility behavior between amines and their salts can be used both to detect amines and to separate them from non-basic compounds. A water-insoluble organic compound that dissolves in cold, dilute aqueous hydrochloric acid must be appreciably basic, which means almost certainly that it is an amine. An amine can be separated from non-basic compounds by its solubility in acid; once separated, the amine can be regenerated by making the aqueous solution alkaline. (See Sec. 18.4 for a comparable situation for carboxylic acids.)

Problem 22.1 Describe exactly how you would go about separating a mixture of the three water-insoluble liquids, aniline (b.p. 184°), *n*-butylbenzene (b.p. 183°), and *n*-valeric acid (b.p. 187°), recovering each compound pure and in essentially quantitative yield. Do the same for a mixture of the three water-insoluble solids, *p*-toluidine, *o*-bromobenzoic acid, and *p*-nitroanisole.

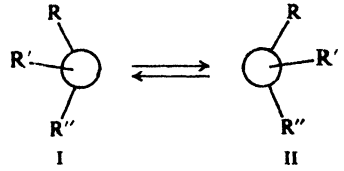
22.6 Stereochemistry of nitrogen

So far in our study of organic chemistry, we have devoted considerable time to the spatial arrangement of atoms and groups attached to carbon atoms, that is, to the stereochemistry of carbon. Now let us look briefly at the stereochemistry of nitrogen.

Amines are simply ammonia in which one or more hydrogen atoms have been replaced by organic groups. Nitrogen uses sp^3 orbitals, which are directed

to the corners of a tetrahedron. Three of these orbitals overlap *s* orbitals of hydrogen or carbon; the fourth contains an unshared pair of electrons (see Fig. 1.11, p. 18). Amines, then, are like ammonia, pyramidal, and with very nearly the same bond angles (108° in trimethylamine, for example).

From an examination of models, we can see that a molecule in which nitrogen carries three different groups is not superimposable on its mirror image; it is chiral and should exist in two enantiomeric forms (I and II) each of which—



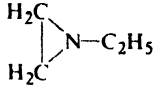
I II

separated from the other—might be expected to show optical activity.

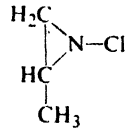
But such enantiomers have not yet been isolated—for simple amines—and spectroscopic studies have shown why: the energy barrier between the two pyramidal arrangements about nitrogen is ordinarily so low that they are rapidly interconverted. Just as rapid rotation about carbon–carbon single bonds prevents isolation of conformational enantiomers (Sec. 4.20), so rapid *inversion* about nitrogen prevents isolation of enantiomers like I and II. Evidently, an unshared pair of electrons of nitrogen cannot ordinarily serve as a fourth group to maintain configuration.

Next, let us consider the quaternary ammonium salts, compounds in which four alkyl groups are attached to nitrogen. Here all four sp^3 orbitals are used to form bonds, and quaternary nitrogen is tetrahedral. Quaternary ammonium salts in which nitrogen holds four different groups have been found to exist as *configurational* enantiomers, capable of showing optical activity: methylallylphenylbenzylammonium iodide, for example.

Problem 22.2 At room temperature, the nmr spectrum of 1-ethylaziridine (III) shows the triplet-quartet of an ethyl group, and two other signals of equal peak area. When the temperature is raised to 120°, the latter two signals merge into a single signal. How do you interpret these observations?



III



IV

Problem 22.3 Account for the following, drawing all pertinent stereochemical formulas. (a) 1-Chloro-2-methylaziridine (IV, above) was prepared in two isomeric forms separable at 25° by ordinary gas chromatography. (b) The reaction of $(C_6H_5)_2C{=}NCH_3$ with R-(+)-2-phenylperoxypropionic acid gave a product, $C_{14}H_{13}ON$, with $[\alpha]$ +12.5°, which showed no loss of optical activity up to (at least) 90°.

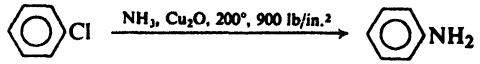
Problem 22.4 Racemization in certain free-radical and carbonium ion reactions has been attributed (Secs. 7.10 and 14.13) to loss of configuration in a flat intermediate. Account for the fact that the formation of alkyl carbanions, R: —which are believed to be *pyramidal*—can also lead to racemization.

22.7 Industrial source

Some of the simplest and most important amines are prepared on an industrial scale by processes that are not practicable as laboratory methods.

The most important of all amines, **aniline**, is prepared in several ways: (a) reduction of nitrobenzene by the cheap reagents, iron and dilute hydrochloric acid (or by catalytic hydrogenation, Sec. 22.9); (b) treatment of chlorobenzene with

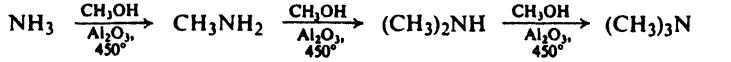
Nitrobenzene Anilinium chloride Aniline



Chlorobenzene Aniline

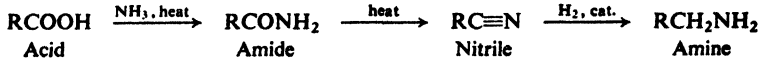
ammonia at high temperatures and high pressures in the presence of a catalyst. Process (b), we shall see (Chap. 25), involves nucleophilic aromatic substitution.

Methylamine, dimethylamine, and trimethylamine are synthesized on an industrial scale from methanol and ammonia:



Ammonia Methylamine Dimethylamine Trimethylamine

Alkyl halides are used to make some higher alkylamines, just as in the laboratory (Sec. 22.10). The acids obtained from fats (Sec. 33.4) can be converted into long-chain 1-aminoalkanes of even carbon number via reduction of nitriles (Sec. 22.8).



Acid Amide Nitrile Amine

22.8 Preparation

Some of the many methods that are used to prepare amines in the laboratory are outlined on the following pages.

PREPARATION OF AMINES

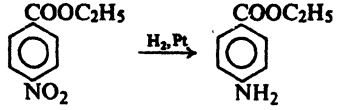
1. Reduction of nitro compounds. Discussed in Sec. 22.9.

$$\underset{\text{or } RNO_2}{ArNO_2} \xrightarrow{\text{metal, } H^+ \text{; or } H_2\text{, catalyst}} \underset{\text{or } RNH_2}{ArNH_2}$$

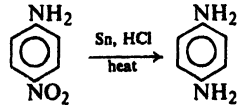
Nitro compound → 1° amine

Chiefly for aromatic amines

Examples:



Ethyl *p*-nitrobenzoate → Ethyl *p*-aminobenzoate



p-Nitroaniline → *p*-Phenylenediamine

$$CH_3CH_2CH_2NO_2 \xrightarrow{Fe,\ HCl} CH_3CH_2CH_2NH_2$$

1-Nitropropane → *n*-Propylamine

2. Reaction of halides with ammonia or amines. Discussed in Secs. 22.10 and 22.13.

$$NH_3 \xrightarrow{RX} \underset{\text{1° amine}}{RNH_2} \xrightarrow{RX} \underset{\text{2° amine}}{R_2NH} \xrightarrow{RX} \underset{\text{3° amine}}{R_3N} \xrightarrow{RX} \underset{\text{Quaternary ammonium salt (4°)}}{R_4N^+X^-}$$

RX *must be alkyl, or aryl with electron-withdrawing substituents*

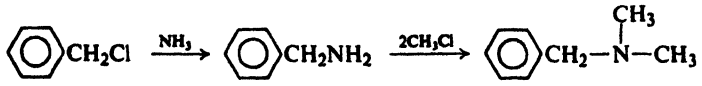
Examples:

$$CH_3COOH \xrightarrow[P]{Cl_2} \underset{\text{Cl}}{CH_2COOH} \xrightarrow{NH_3} \underset{\text{NH}_2}{CH_2COO^-NH_4^+} \xrightarrow{H^+} \underset{\text{NH}_2}{CH_2COOH} \text{ (or } \underset{^+\text{NH}_3}{CH_2COO^-}\text{)}$$

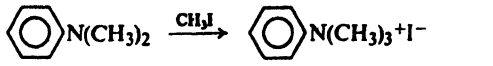
Acetic acid → Chloroacetic acid → Aminoacetic acid (Glycine; an amino acid) (1°)

$$C_2H_5Cl \xrightarrow{NH_3} \underset{\text{(1°)}}{C_2H_5NH_2} \xrightarrow{CH_3Cl} \underset{\text{(2°)}}{C_2H_5{-}\overset{\overset{H}{|}}{N}{-}CH_3}$$

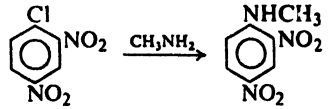
Ethyl chloride → Ethylamine (1°) → Methylethylamine (2°)



Benzyl chloride → Benzylamine (1°) → Benzyldimethylamine (3°)

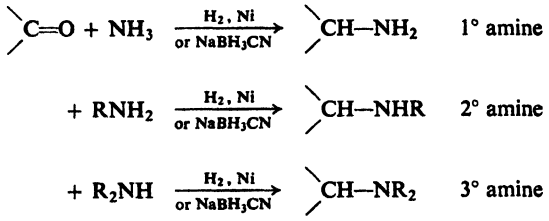


N,N-Dimethylaniline (3°) — Phenyltrimethylammonium iodide (4°)

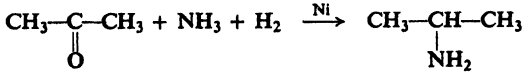


2,4-Dinitrochlorobenzene — N-Methyl-2,4-dinitroaniline (2°)

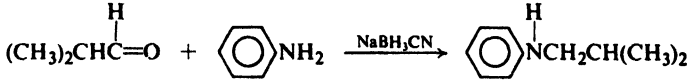
3. Reductive amination. Discussed in Sec. 22.11.



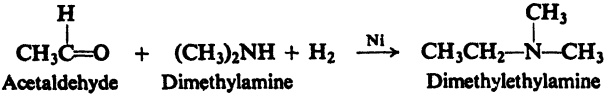
Examples:



Acetone — Isopropylamine (1°)

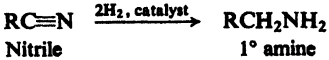


Isobutyraldehyde — Aniline (1°) — N-Isobutylaniline (2°)



Acetaldehyde — Dimethylamine (2°) — Dimethylethylamine (3°)

4. Reduction of nitriles. Discussed in Sec. 22.8.



Nitrile — 1° amine

Examples:

Benzyl chloride — Phenylacetonitrile (Benzyl cyanide) — β-Phenylethylamine (1°)

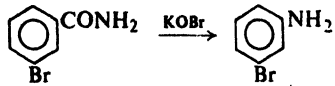
$$\underset{\text{1,4-Dichlorobutane}}{ClCH_2CH_2CH_2CH_2Cl} \xrightarrow{NaCN} \underset{\text{Adiponitrile}}{NC(CH_2)_4CN} \xrightarrow{H_2,\,Ni} \underset{\text{Hexamethylenediamine (1,6-Diaminohexane) (1°)}}{H_2NCH_2(CH_2)_4CH_2NH_2}$$

5. Hofmann degradation of amides. Discussed in Secs. 22.13 and 28.2–28.5.

$$\underset{\text{Amide}}{RCONH_2 \text{ or } ArCONH_2} \xrightarrow{OBr^-} \underset{\text{1° amine}}{RNH_2 \text{ or } ArNH_2} + CO_3^{--}$$

Examples:

$$\underset{\text{Caproamide (Hexanamide)}}{CH_3(CH_2)_4CONH_2} \xrightarrow{KOBr} \underset{\textit{n}\text{-Pentylamine}}{CH_3(CH_2)_4NH_2}$$



m-Bromobenzamide *m*-Bromoaniline

Reduction of aromatic nitro compounds is by far the most useful method of preparing amines, since it uses readily available starting materials, and yields the most important kind of amines, *primary aromatic amines.* These amines can be converted into aromatic diazonium salts, which are among the most versatile class of organic compounds known (see Secs. 23.11–23.17). The sequence

$$\text{nitro compound} \longrightarrow \text{amine} \longrightarrow \text{diazonium salt}$$

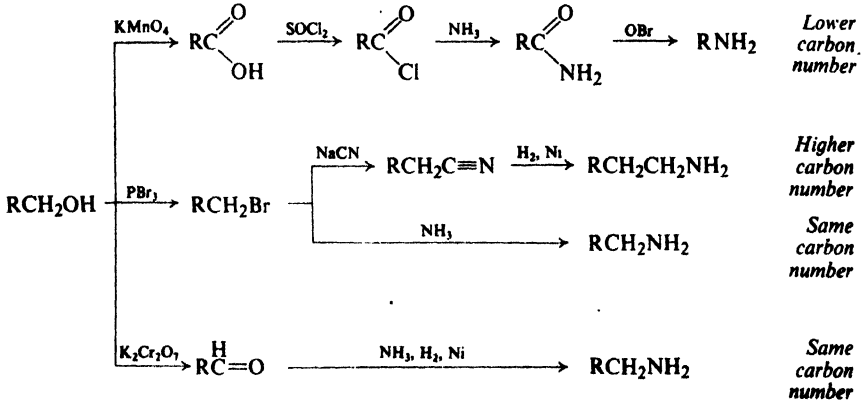
provides the best possible route to dozens of kinds of aromatic compounds.

Reduction of aliphatic nitro compounds is limited by the availability of the starting materials.

Ammonolysis of halides is usually limited to the aliphatic series, because of the generally low reactivity of aryl halides toward nucleophilic substitution. (However, see Chap. 25.) Ammonolysis has the disadvantage of yielding a mixture of different classes of amines. It is important to us as one of the most general methods of introducing the amino ($-NH_2$) group into molecules of all kinds; it can be used, for example, to convert bromoacids into amino acids. The exactly analogous reaction of halides with amines permits the preparation of every class of amine (as well as quaternary ammonium salts, $R_4N^+X^-$).

Reductive amination, the catalytic or chemical reduction of aldehydes (RCHO) and ketones (R_2CO) in the presence of ammonia or an amine, accomplishes much the same purpose as the reaction of halides. It too can be used to prepare any class of amine, and has certain advantages over the halide reaction. The formation of mixtures is more readily controlled in reductive amination than in ammonolysis of halides. Reductive amination of ketones yields amines containing a *sec*-alkyl group; these amines are difficult to prepare by ammonolysis because of the tendency of *sec*-alkyl halides to undergo elimination rather than substitution.

Synthesis via **reduction of nitriles** has the special feature of *increasing the length of a carbon chain*, producing a primary amine that has one more carbon atom than the alkyl halide from which the nitrile was made. The **Hofmann degradation of amides** has the feature of *decreasing the length of a carbon chain* by one carbon atom; it is also of interest as an example of an important class of reactions involving rearrangement.

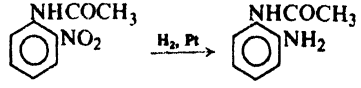


Problem 22.5 Show how *n*-pentylamine can be synthesized from available materials by the four routes just outlined.

22.9 Reduction of nitro compounds

Like many organic compounds, nitro compounds can be reduced in two general ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction, usually by a metal and acid.

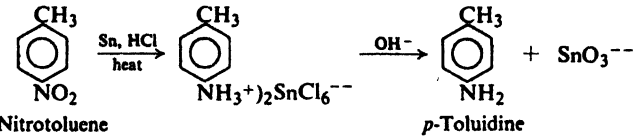
Hydrogenation of a nitro compound to an amine takes place smoothly when a solution of the nitro compound in alcohol is shaken with finely divided nickel or platinum under hydrogen gas. For example:



o-Nitroacetanilide *o*-Aminoacetanilide

This method cannot be used when the molecule also contains some other easily hydrogenated group, such as a carbon–carbon double bond.

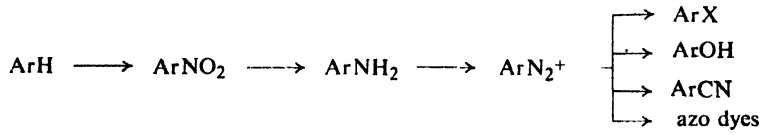
Chemical reduction in the laboratory is most often carried out by adding hydrochloric acid to a mixture of the nitro compound and a metal, usually granulated tin. In the acidic solution, the amine is obtained as its salt; the free amine is liberated by the addition of base, and is steam-distilled from the reaction



p-Nitrotoluene *p*-Toluidine

mixture. The crude amine is generally contaminated with some unreduced nitro compound, from which it can be separated by taking advantage of the basic properties of the amine; the amine is soluble in aqueous mineral acid, and the nitro compound is not.

Reduction of nitro compounds to amines is an essential step in what is probably the most important synthetic route in aromatic chemistry. Nitro compounds are readily prepared by direct nitration; when a mixture of *o*- and *p*-isomers is obtained, it can generally be separated to yield the pure isomers. The primary aromatic amines obtained by the reduction of these nitro compounds are readily converted into diazonium salts; the diazonium group, in turn, can be replaced by a large number of other groups (Sec. 23.11). In most cases this sequence is the best method of introducing these other groups into the aromatic ring. In addition, diazonium salts can be used to prepare the extremely important class of compounds. the *azo dyes.*



22.10 Ammonolysis of halides

Many organic halogen compounds are converted into amines by treatment with aqueous or alcoholic solutions of ammonia. The reaction is generally carried out either by allowing the reactants to stand together at room temperature or by heating them under pressure. Displacement of halogen by NH_3 yields the amine salt, from which the free amine can be liberated by treatment with hydroxide ion.

$$RX + NH_3 \longrightarrow RNH_3^+X^-$$

$$RNH_3^+X^- + OH^- \longrightarrow RNH_2 + H_2O + X^-$$

Ammonolysis of halides belongs to the class of reactions that we have called nucleophilic substitution. The organic halide is attacked by the nucleophilic ammonia molecule in the same way that it is attacked by hydroxide ion, alkoxide ion, cyanide ion, acetylide ion, and water:

$$H_3N: + R{-}X \longrightarrow \left[H_3N^{\delta+}\cdots R\cdots X^{\delta-}\right] \longrightarrow H_3\overset{+}{N}{-}R + X^-$$

Like these other nucleophilic substitution reactions, ammonolysis is limited chiefly to alkyl halides or substituted alkyl halides. As with other reactions of this kind, elimination tends to compete (Sec. 14.23) with substitution: ammonia can attack

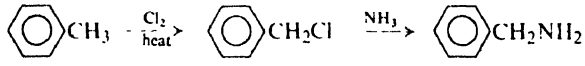
hydrogen to form alkene as well as attack carbon to form amine. Ammonolysis thus gives the highest yields with primary halides (where substitution predominates) and is virtually worthless with tertiary halides (where elimination predominates).

$$CH_3CH_2CH_2CH_2Br \xrightarrow{NH_3} CH_3CH_2CH_2CH_2NH_3^+Br^- \quad \textit{Substitution}$$

$$CH_3-\underset{\displaystyle Br}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_3 \xrightarrow{NH_3} CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}}=CH_2 + NH_4Br \quad \textit{Elimination}$$

Because of their generally low reactivity, aryl halides are converted into amines only (a) if the ring carries $-NO_2$ groups, or other strongly electron-withdrawing groups, at positions *ortho* and *para* to the halogen, or (b) if a high temperature or a strongly basic reagent is used (Chap. 25).

Some examples of the application of ammonolysis to synthesis are:



Toluene — Benzyl chloride — Benzylamine

$$CH_3CH_2COOH \xrightarrow[P]{Br_2} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCOOH \xrightarrow{NH_3} CH_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

Propionic acid — α-Bromopropionic acid — Alanine (α-Aminopropionic acid)

$$CH_2=CH_2 \xrightarrow{Cl_2} ClCH_2CH_2Cl \xrightarrow{2NH_3} H_2NCH_2CH_2NH_2$$

Ethylene — Ethylene chloride — Ethylenediamine

A serious disadvantage to the synthesis of amines by ammonolysis is the formation of more than one class of amine. The primary amine salt, formed by

$$RX + NH_3 \longrightarrow \underset{1^\circ \text{ amine salt}}{RNH_3^+X^-}$$

the initial substitution, reacts with the reagent ammonia to yield the ammonium salt and the free primary amine; the following equilibrium thus exists:

$$RNH_3^+ + NH_3 \rightleftharpoons \underset{1^\circ \text{ amine}}{RNH_2} + NH_4^+$$

The free primary amine, like the ammonia from which it was made, is a nucleophilic reagent; it too can attack the alkyl halide, to yield the salt of a secondary amine:

$$\underset{1^\circ \text{ amine}}{RNH_2} + RX \longrightarrow R_2NH_2^+X^- \xrightleftharpoons{NH_3} \underset{2^\circ \text{ amine}}{R_2NH}$$

The secondary amine, which is in equilibrium with its salt, can in turn attack the alkyl halide to form the salt of a tertiary amine:

$$\underset{\text{2° amine}}{R_2NH} + RX \longrightarrow R_3NH^+X^- \xrightleftharpoons{NH_3} \underset{\text{3° amine}}{R_3N}$$

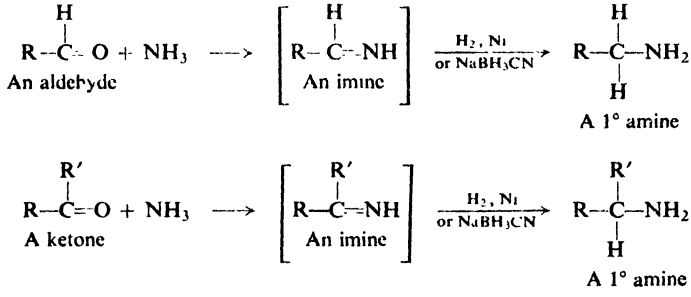
Finally, the tertiary amine can attack the alkyl halide to form a compound of the formula $R_4N^+X^-$, called a *quaternary ammonium salt* (discussed in Sec. 23.5):

$$\underset{\text{3° amine}}{R_3N} + RX \longrightarrow \underset{\substack{\text{Quaternary ammonium salt}\\(4°)}}{R_4N^+X^-}$$

The presence of a large excess of ammonia lessens the importance of these last reactions and increases the yield of primary amine; under these conditions, a molecule of alkyl halide is more likely to encounter, and be attacked by, one of the numerous ammonia molecules rather than one of the relatively few amine molecules. At best, the yield of primary amine is always cut down by the formation of the higher classes of amines. Except in the special case of methylamine, the primary amine can be separated from these by-products by distillation.

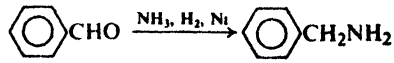
22.11 Reductive amination

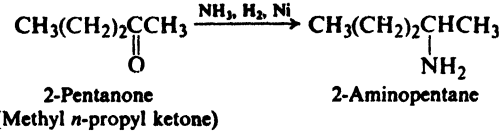
Many aldehydes (RCHO) and ketones (R_2CO) are converted into amines by **reductive amination**: reduction in the presence of ammonia. Reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $NaBH_3CN$. Reaction involves reduction of an intermediate compound (an *imine*, RCH=NH or R_2C=NH) that contains a carbon–nitrogen double bond.



Reductive amination has been used successfully with a wide variety of aldehydes and ketones, both aliphatic and aromatic. For example:

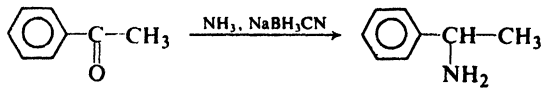
$$\underset{\substack{\text{Heptaldehyde}\\(\text{Heptanal})}}{CH_3(CH_2)_5CHO} \xrightarrow{NH_3,\ H_2,\ Ni} \underset{\substack{\textit{n}\text{-Heptylamine}\\(1\text{-Aminoheptane})}}{CH_3(CH_2)_5CH_2NH_2}$$





2-Pentanone
(Methyl *n*-propyl ketone)

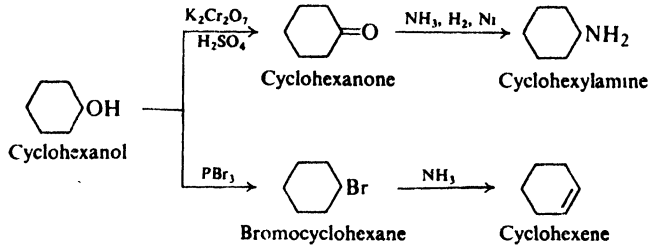
2-Aminopentane



Acetophenone
(Methyl phenyl ketone)

α-Phenylethylamine

Reductive amination of ketones yields amines containing a *sec*-alkyl group; such amines are difficult to obtain by ammonolysis because of the tendency for *sec*-alkyl halides to undergo elimination. For example, cyclohexanone is converted into cyclohexylamine in good yield, whereas ammonolysis of bromocyclohexane yields only cyclohexene.



Cyclohexanol

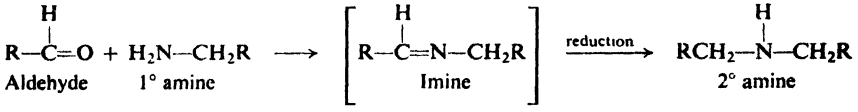
Cyclohexanone

Cyclohexylamine

Bromocyclohexane

Cyclohexene

During reductive amination the aldehyde or ketone can react not only with ammonia but also with the primary amine that has already been formed, and thus yield a certain amount of secondary amine. The tendency for the reaction to go



Aldehyde 1° amine

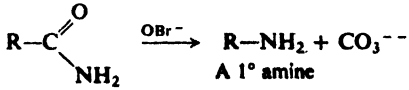
Imine

2° amine

beyond the desired stage can be fairly well limited by the proportions of reactants employed and is seldom a serious handicap.

22.12 Hofmann degradation of amides

As a method of synthesis of amines, the Hofmann degradation of amides has the special feature of yielding a product containing one less carbon than the starting material. As we can see, reaction involves migration of a group from carbonyl

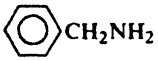


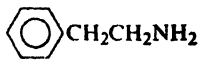
An amide

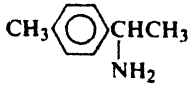
A 1° amine

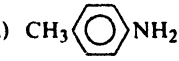
carbon to the adjacent nitrogen atom, and thus is an example of a *molecular rearrangement*. We shall return to the Hofmann degradation (Secs. 28.2–28.5) and discuss its mechanism in detail.

Problem 22.6 Using a different method in each case, show how the following amines could be prepared from *toluene* and any aliphatic reagents:

(a) 

(c) 

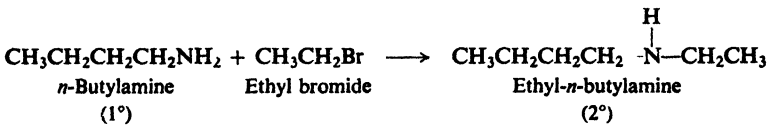
(b) 

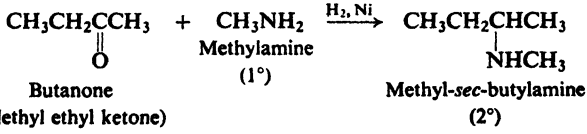
(d) 

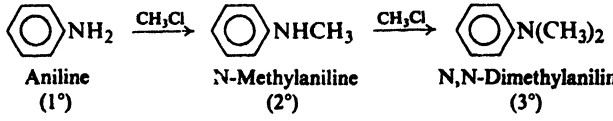
(e) 

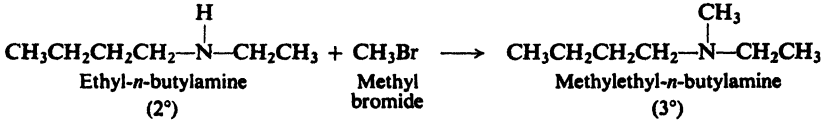
22.13 Synthesis of secondary and tertiary amines

So far we have been chiefly concerned with the synthesis of primary amines. Secondary and tertiary amines are prepared by adaptations of one of the processes already described: ammonolysis of halides or reductive amination. For example:









Where ammonia has been used to produce a primary amine, a primary amine can be used to produce a secondary amine, or a secondary amine can be used to produce a tertiary amine. In each of these syntheses there is a tendency for reaction to proceed beyond the first stage and to yield an amine of a higher class than the one that is wanted.

PROBLEMS

1. Draw structures, give names, and classify as primary, secondary, or tertiary:

(a) the eight isomeric amines of formula $C_4H_{11}N$
(b) the five isomeric amines of formula C_7H_9N that contain a benzene ring

2. Give the structural formulas of the following compounds:

(a) *sec*-butylamine
(b) *o*-toluidine
(c) anilinium chloride
(d) diethylamine
(e) *p*-aminobenzoic acid
(f) benzylamine
(g) isopropylammonium benzoate
(h) *o*-phenylenediamine
(i) N,N-dimethylaniline
(j) ethanolamine (2-aminoethanol)
(k) β-phenylethylamine
(l) N,N-dimethylaminocyclohexane
(m) diphenylamine
(n) 2,4-dimethylaniline
(o) tetra-*n*-butylammonium iodide
(p) *p*-anisidine

3. Show how *n*-propylamine could be prepared from each of the following:

(a) *n*-propyl bromide
(b) *n*-propyl alcohol
(c) propionaldehyde
(d) 1-nitropropane
(e) propionitrile
(f) *n*-butyramide
(g) *n*-butyl alcohol
(h) ethyl alcohol

Which of these methods can be applied to the preparation of aniline? Of benzylamine?

4. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or less, using any needed inorganic reagents.

(a) isopropylamine
(b) *n*-pentylamine
(c) *p*-toluidine
(d) ethylisopropylamine
(e) α-phenylethylamine
(f) β-phenylethylamine
(g) *m*-chloroaniline
(h) *p*-aminobenzoic acid
(i) 3-aminoheptane
(j) N-ethylaniline
(k) 2,4-dinitroaniline
(l) the drug *benzedrine* (2-amino-1-phenylpropane)
(m) *p*-nitrobenzylamine
(n) 2-amino-1-phenylethanol

5. Outline all steps in a possible laboratory synthesis from palmitic acid, $n\text{-}C_{15}H_{31}COOH$, of:

(a) $n\text{-}C_{16}H_{33}NH_2$
(b) $n\text{-}C_{17}H_{35}NH_2$
(c) $n\text{-}C_{15}H_{31}NH_2$
(d) $n\text{-}C_{15}H_{31}CH(NH_2)\text{-}n\text{-}C_{16}H_{33}$

6. On the basis of the following synthesis give the structures of *putrescine* and *cadaverine*, found in rotting flesh:

(a) ethylene bromide $\xrightarrow{KCN}$ $C_4H_4N_2$ $\xrightarrow{Na,\ C_2H_5OH}$ putrescine ($C_4H_{12}N_2$)

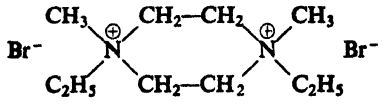
(b) $Br(CH_2)_5Br$ $\xrightarrow{NH_3}$ cadaverine ($C_5H_{14}N_2$)

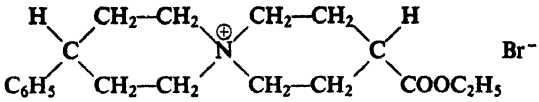
7. One of the raw materials for the manufacture of Nylon 66 is *hexamethylenediamine*, $NH_2(CH_2)_6NH_2$. Much of this amine is made by a process that begins with the 1,4-addition of chlorine to 1,3-butadiene. What do you think might be the subsequent steps in this process?

8. Outline all steps in a possible synthesis of β-alanine (β-aminopropionic acid) from succinic anhydride.

9. Using models and then drawing formulas, show the stereoisomeric forms in which each of the following compounds can exist. Tell which stereoisomers when separated from all others would be optically active and which would be optically inactive.

(a) α-phenylethylamine
methyl-N-ethylaniline
ethylethyl-*n*-propylphenylammonium bromide

(d) 

(e) 

(f) methylethylphenylamine oxide, $(CH_3)(C_2H_5)(C_6H_5)N{-}O$

10. Two geometric isomers of benzaldoxime, $C_6H_5CH{=}NOH$, are known. (a) Draw their structures, showing the geometry of the molecules. (b) Show how this geometry results from their electronic configurations. (c) Would you predict geometric isomerism for benzophenoneoxime, $(C_6H_5)_2C{=}NOH$? For acetophenoneoxime, $C_6H_5C(CH_3){=}NOH$? For azobenzene, $C_6H_5N{=}NC_6H_5$?

11. (a) Give structural formulas of compounds A through D.

$$\text{phthalimide (Sec. 20.14)} + \text{KOH (alc.)} \longrightarrow \text{A } (C_8H_4O_2NK)$$

$$\text{A} + CH_3CH_2CH_2Br, \text{ heat} \longrightarrow \text{B } (C_{11}H_{11}O_2N)$$

$$\text{B} + H_2O, OH^-, \text{ heat} \longrightarrow \text{C } (C_3H_9N) + \text{D}$$

(b) This sequence illustrates the **Gabriel synthesis.** What class of compounds does it produce? What particular advantage does it have over alternative methods for the production of these compounds? On what special property of phthalimide does the synthesis depend?

Chapter 23

Amines II. Reactions

23.1 Reactions

Like ammonia, the three classes of amines contain nitrogen that bears an unshared pair of electrons; as a result, amines closely resemble ammonia in chemical properties. The tendency of nitrogen to share this pair of electrons underlies the entire chemical behavior of amines: their basicity, their action as nucleophiles, and the unusually high reactivity of aromatic rings bearing amino or substituted amino groups.

REACTIONS OF AMINES

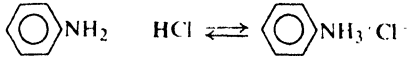
1. Basicity. Salt formation. Discussed in Secs. 22.5 and 23.2–23.4.

$$RNH_2 + H^+ \rightleftharpoons RNH_3^+$$

$$R_2NH + H^+ \rightleftharpoons R_2NH_2^+$$

$$R_3N + H^+ \rightleftharpoons R_3NH^+$$

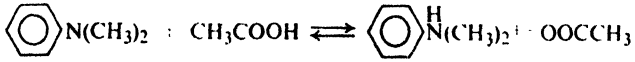
Examples:



Aniline — Anilinium chloride (Aniline hydrochloride)

$$(CH_3)_2NH + HNO_3 \rightleftharpoons (CH_3)_2NH_2^+NO_3^-$$

Dimethylamine — Dimethylammonium nitrate



N,N-Dimethylaniline — N,N-Dimethylanilinium acetate

2. Alkylation. Discussed in Secs. 22.13 and 23.5.

$$RNH_2 \xrightarrow{RX} R_2NH \xrightarrow{RX} R_3N \xrightarrow{RX} R_4N^+X^-$$

$$ArNH_2 \xrightarrow{RX} ArNHR \xrightarrow{RX} ArNR_2 \xrightarrow{RX} ArNR_3^+X^-$$

Examples:

$$(n\text{-}C_4H_9)_2NH + \bigcirc CH_2Cl \longrightarrow (n\text{-}C_4H_9)_2NCH_2\bigcirc$$

Di-*n*-butylamine (2°) | Benzyl chloride | Benzyldi(*n*-butyl)amine (3°)

$$n\text{-}C_3H_7NH_2 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{H}{\underset{|}{N}}CH_3 \xrightarrow{CH_3I} n\text{-}C_3H_7NCH_3 \xrightarrow{CH_3I} n\text{-}C_3H_7\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{N}}}}CH_3{}^+I^-$$

n-Propylamine (1°) | *n*-Propylmethylamine (2°) | *n*-Propyldimethylamine (3°) | *n*-Propyltrimethylammonium iodide (4°)

3. Conversion into amides. Discussed in Sec. 23.6.

Primary: RNH_2

- $\xrightarrow{R'COCl}$ $R'CONHR$ An N-substituted amide
- $\xrightarrow{ArSO_2Cl}$ $ArSO_2NHR$ An N-substituted sulfonamide

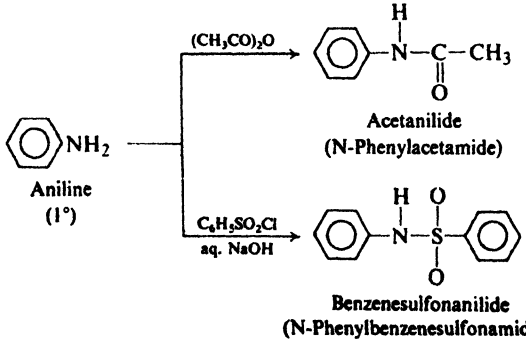
Secondary: R_2NH

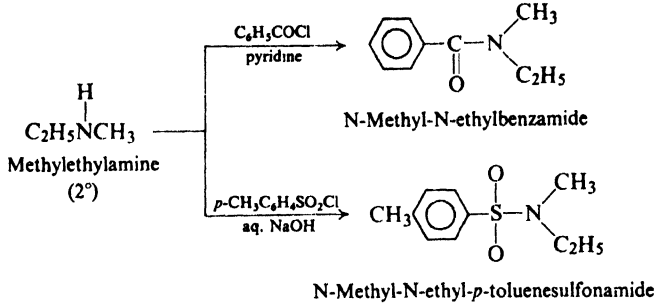
- $\xrightarrow{R'COCl}$ $R'CONR_2$ An N,N-disubstituted amide
- $\xrightarrow{ArSO_2Cl}$ $ArSO_2NR_2$ An N,N-disubstituted sulfonamide

Tertiary: R_3N

- $\xrightarrow{R'COCl}$ No reaction
- $\xrightarrow{ArSO_2Cl}$ No reaction under conditions of Hinsberg test (*but see* Sec. 23.18).

Examples:



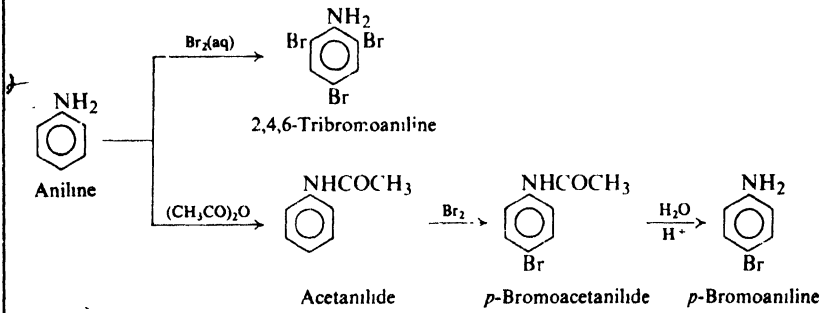


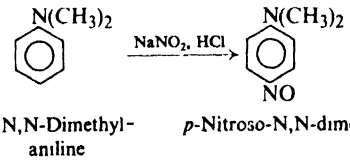
♥ **4. Ring substitution in aromatic amines.** Discussed in Secs. 23.7, 23.10, and 23.17.

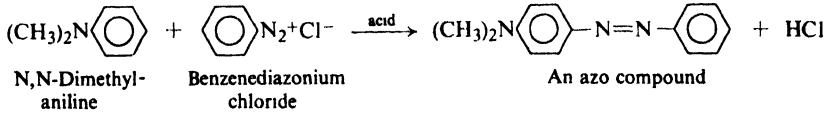
—NH_2, —NHR, —NR_2: Activate powerfully, and direct *ortho, para* in electrophilic aromatic substitution

—NHCOR: Less powerful activator than —NH_2

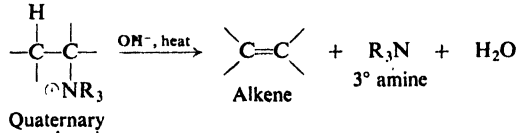
Examples:







5. Hofmann elimination from quaternary ammonium salts. Discussed in Sec. 23.5.

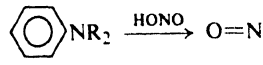


6. Reactions with nitrous acid. Discussed in Secs. 23.10–23.11.

Primary aromatic: $ArNH_2 \xrightarrow{HONO} Ar{-}N{\equiv}N^+$ Diazonium salt

Primary aliphatic: $RNH_2 \xrightarrow{HONO} [R{-}N{\equiv}N^+] \xrightarrow{H_2O} N_2 +$ mixture of alcohols and alkenes

Secondary aromatic or aliphatic: $ArNHR$ or $R_2NH \xrightarrow{HONO} Ar{-}\underset{\displaystyle R}{\underset{|}{N}}{-}N{=}O$ or $R_2N{-}N{=}O$ N-Nitrosoamine

Tertiary aromatic:  *p*-Nitroso compound

23.2 Basicity of amines. Basicity constant

Like ammonia, amines are converted into their salts by aqueous mineral acids and are liberated from their salts by aqueous hydroxides. Like ammonia, therefore, amines are more basic than water and less basic than hydroxide ion:

$$\underset{\text{Stronger base}}{RNH_2} + H_3O^+ \longrightarrow RNH_3^+ + \underset{\text{Weaker base}}{H_2O}$$

$$RNH_3^+ + \underset{\text{Stronger base}}{OH^-} \longrightarrow \underset{\text{Weaker base}}{RNH_2} + H_2O$$

We found it convenient to compare acidities of carboxylic acids by measuring the extent to which they give up hydrogen ion to water; the equilibrium constant for this reaction was called the acidity constant, K_a. In the same way, it is convenient to compare basicities of amines by measuring the extent to which they accept hydrogen ion from water; the equilibrium constant for this reaction is called a **basicity constant**, K_b.

$$RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$$

$$K_b = \frac{[RNH_3^+][OH^-]}{[RNH_2]}$$

(As in the analogous expression for an acidity constant, the concentration of the solvent, water, is omitted.) Each amine has its characteristic K_b; the larger the K_b, the stronger the base.

We must not lose sight of the fact that the principal base in an aqueous solution of an amine (or of ammonia, for that matter) is the *amine* itself, not hydroxide ion. Measurement of $[OH^-]$ is simply a convenient way to compare basicities.

We see in Table 22.1 (p. 729) that aliphatic amines of all three classes have K_b's of about 10^{-3} to 10^{-4} (0.001 to 0.0001); they are thus somewhat stronger bases than ammonia ($K_b = 1.8 \times 10^{-5}$). Aromatic amines, on the other hand, are considerably weaker bases than ammonia, having K_b's of 10^{-9} or less. Substituents

on the ring have a marked effect on the basicity of aromatic amines, *p*-nitroaniline, for example, being only 1/4000 as basic as aniline (Table 23.1).

Table 23.1 BASICITY CONSTANTS OF SUBSTITUTED ANILINES

K_b of aniline = 4.2×10^{-10}

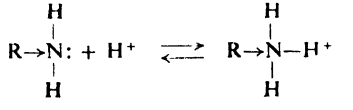
	K_b		K_b		K_b
p-NH_2	140×10^{-10}	*m*-NH_2	10×10^{-10}	*o*-NH_2	3×10^{-10}
p-OCH_3	20	*m*-OCH_3	2	*o*-OCH_3	3
p-CH_3	12	*m*-CH_3	5	*o*-CH_3	2.6
p-Cl	1	*m*-Cl	.3	*o*-Cl	.05
p-NO_2	.001	*m*-NO_2	.029	*o*-NO_2	.00006

23.3 Structure and basicity

Let us see how basicity of amines is related to structure. We shall handle basicity just as we handled acidity: we shall compare the stabilities of amines with the stabilities of their ions; the more stable the ion relative to the amine from which it is formed, the more basic the amine.

First of all, amines are more basic than alcohols, ethers, esters, etc., for the same reason that ammonia is more basic than water: nitrogen is less electronegative than oxygen, and can better accommodate the positive charge of the ion.

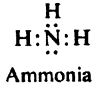
An aliphatic amine is more basic than ammonia because the electron-releasing alkyl groups tend to disperse the positive charge of the substituted ammonium ion, and therefore stabilize it in a way that is not possible for the unsubstituted ammonium ion. Thus an *ammonium* ion is stabilized by electron release in the same way as a *carbonium* ion (Sec. 5.17). From another point of view, we can consider that an alkyl group pushes electrons toward nitrogen, and thus makes the fourth pair more available for sharing with an acid. (The differences in basicity among primary, secondary, and tertiary aliphatic amines are due to a combination of solvation and electronic factors.)



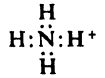
R *releases electrons:* *makes unshared pair more available*

R *releases electrons* *stabilizes ion, increases basicity*

How can we account for the fact that aromatic amines are weaker bases than ammonia? Let us compare the structures of aniline and the anilinium ion with the structures of ammonia and the ammonium ion. We see that ammonia and the ammonium ion are each represented satisfactorily by a single structure:

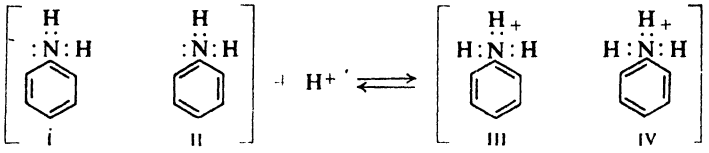


Ammonia



Ammonium ion

Aniline and anilinium ion contain the benzene ring and therefore are hybrids of the Kekulé structures I and II, and III and IV. This resonance presumably stabilizes

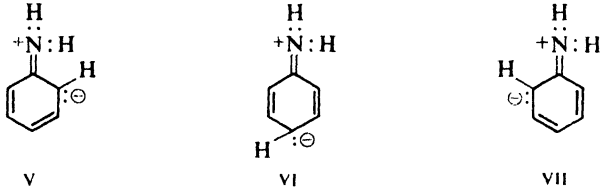


Aniline Anilinium ion

both amine and ion to the same extent. It lowers the energy content of each by the same number of kcal/mole, and hence does not affect the *difference* in their energy contents, that is, does not affect ΔG of ionization. If there were no other factors involved, then, we might expect the basicity of aniline to be about the same as the basicity of ammonia.

However, there are additional structures to be considered. To account for the powerful activating effect of the $-NH_2$ group on electrophilic aromatic substitution (Sec. 11.20), we considered that the intermediate carbonium ion is stabilized by structures in which there is a double bond between nitrogen and the ring; contribution from these structures is simply a way of indicating the tendency for nitrogen to share its fourth pair of electrons and to accept a positive charge. It is generally believed that the $-NH_2$ group tends to share electrons with the ring, not only in the carbonium ion which is the intermediate in electrophilic aromatic substitution, but also in the aniline molecule itself.

Thus aniline is a hybrid not only of structures I and II but also of structures V, VI, and VII. We cannot draw comparable structures for the anilinium ion.



Contribution from the three structures V, VI, and VII stabilizes the amine in a way that is not possible for the ammonium ion; resonance thus lowers the energy content of aniline more than it lowers the energy content of the anilinium ion. The net effect is to shift the equilibrium in the direction of less ionization, that is, to make K_b smaller (Fig. 23.1). (See, however, the discussion in Sec. 18.11.)

The low basicity of aromatic amines is thus due to the fact that the amine is stabilized by resonance to a greater extent than is the ion.

From another point of view, we can say that aniline is a weaker base than ammonia because the fourth pair of electrons is partly shared with the ring and is thus less available for sharing with a hydrogen ion. The tendency (through resonance) for the $-NH_2$ group to release electrons to the aromatic ring makes the ring more reactive toward electrophilic attack; at the same time this tendency necessarily makes the amine less basic. Similar considerations apply to other aromatic amines.

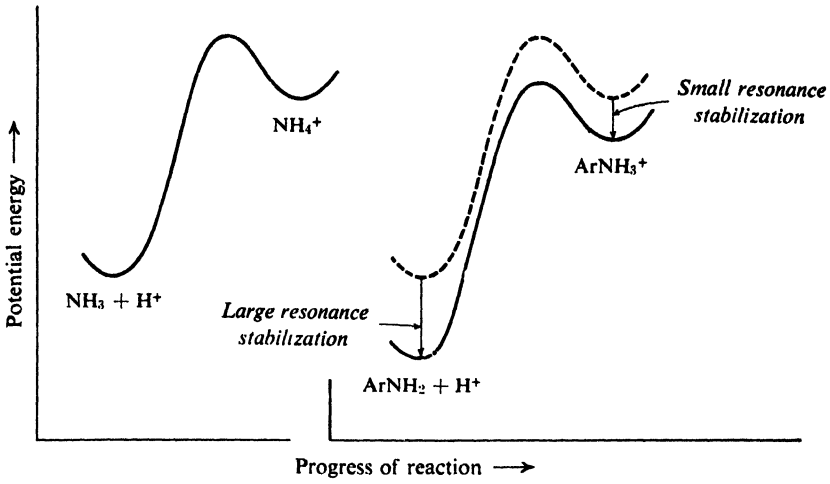


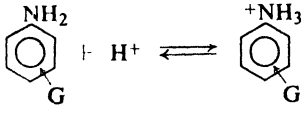
Figure 23.1. Molecular structure and position of equilibrium. Resonance-stabilized aromatic amine is weaker base than ammonia. (Plots aligned with each other for easy comparison.)

23.4 Effect of substituents on basicity of aromatic amines

How is the basicity of an aromatic amine affected by substituents on the ring?

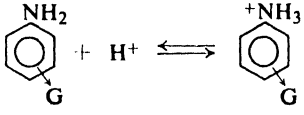
In Table 23.1 (p. 749) we see that an electron-releasing substituent like $-CH_3$ increases the basicity of aniline, and an electron-withdrawing substituent like $-X$ or $-NO_2$ decreases the basicity. These effects are understandable. Electron release tends to disperse the positive charge of the anilinium ion, and thus stabilizes the ion relative to the amine. Electron withdrawal tends to intensify the positive charge of the anilinium ion, and thus destabilizes the ion relative to the amine.

Basicity of Aromatic Amines



G releases electrons:
stabilizes cation,
increases basicity

G = $-NH_2$
$-OCH_3$
$-CH_3$



G withdraws electrons
destabilizes cation,
decreases basicity

G = $-NH_3^+$
$-NO_2$
$-SO_3^-$
$-COOH$
$-X$

We notice that the base-strengthening substituents are the ones that activate an aromatic ring toward electrophilic substitution; the base-weakening substituents are the ones that deactivate an aromatic ring toward electrophilic substitution (see Sec. 11.5). Basicity depends upon position of equilibrium, and hence

on relative stabilities of reactants and products. Reactivity in electrophilic aromatic substitution depends upon rate, and hence on relative stabilities of reactants and transition state. The effect of a particular substituent is the same in both cases, however, since the controlling factor is accommodation of a positive charge.

A given substituent affects the basicity of an amine and the acidity of a carboxylic acid in opposite ways (compare Sec. 18.14). This is to be expected, since basicity depends upon ability to accommodate a positive charge, and acidity depends upon ability to accommodate a negative charge.

Once again we see the operation of the **ortho effect** (Sec. 18.14). Even electron-releasing substituents weaken basicity when they are *ortho* to the amino group, and electron-withdrawing substituents do so to a much greater extent from the *ortho* position than from the *meta* or *para* position.

From another point of view, we can consider that an electron-releasing group pushes electrons toward nitrogen and makes the fourth pair more available for sharing with an acid, whereas an electron-withdrawing group helps pull electrons away from nitrogen and thus makes the fourth pair less available for sharing.

Problem 23.1 (a) Besides destabilizing the anilinium ion, how else might a nitro group affect basicity? (*Hint:* See structures V–VII on p. 750.) (b) Why does the nitro group exert a larger base-weakening effect from the *para* position than from the nearer *meta* position?

Problem 23.2 Draw the structural formula of the product expected (if any) from the reaction of trimethylamine and BF_3.

23.5 Quaternary ammonium salts. Exhaustive methylation. Hofmann elimination

Like ammonia, an amine can react with an alkyl halide; the product is an amine of the next higher class. The alkyl halide undergoes nucleophilic substitution, with the basic amine serving as the nucleophilic reagent. We see that one of

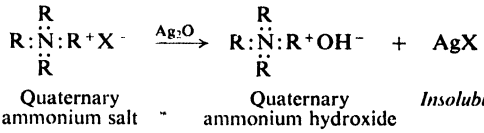
$$\underset{1^\circ}{RNH_2} \xrightarrow{RX} \underset{2^\circ}{R_2NH} \xrightarrow{RX} \underset{3^\circ}{R_3N} \xrightarrow{RX} \underset{4^\circ}{R_4N^+X^-}$$

the hydrogens attached to nitrogen has been replaced by an alkyl group; the reaction is therefore often referred to as *alkylation of amines.* The amine can be aliphatic or aromatic, primary, secondary, or tertiary; the halide is generally an alkyl halide.

We have already encountered alkylation of amines as a side reaction in the preparation of primary amines by the ammonolysis of halides (Sec. 22.10), and as a method of synthesis of secondary and tertiary amines (Sec. 22.13). Let us look at one further aspect of this reaction, the formation of quaternary ammonium salts.

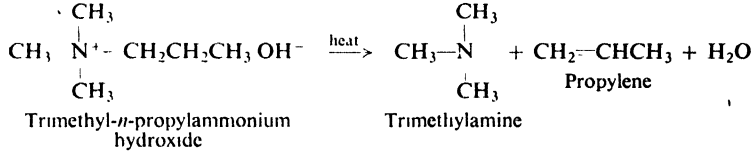
Quaternary ammonium salts are the products of the final stage of alkylation of nitrogen. They have the formula $R_4N^+X^-$. Four organic groups are covalently bonded to nitrogen, and the positive charge of this ion is balanced by some nega-

tive ion. When the salt of a primary, secondary, or tertiary amine is treated with hydroxide ion, nitrogen gives up a hydrogen ion and the free amine is liberated. The quaternary ammonium ion, having no proton to give up, is not affected by hydroxide ion.

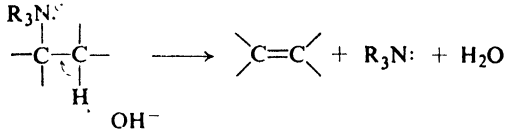


When a solution of a quaternary ammonium halide is treated with silver oxide, silver halide precipitates. When the mixture is filtered and the filtrate is evaporated to dryness, there is obtained a solid which is free of halogen. An aqueous solution of this substance is strongly alkaline, and is comparable to a solution of sodium hydroxide or potassium hydroxide. A compound of this sort is called a **quaternary ammonium hydroxide**. It has the structure $R_4N^+OH^-$. Its aqueous solution is basic for the same reason that solutions of sodium or potassium hydroxide are basic: the solution contains hydroxide ions.

When a quaternary ammonium hydroxide is heated strongly (to 125° or higher), it decomposes to yield water, a tertiary amine, and an alkene. Trimethyl-*n*-propylammonium hydroxide, for example, yields trimethylamine and propylene:



This reaction, called the **Hofmann elimination**, is quite analogous to the dehydrohalogenation of an alkyl halide (Sec. 14.18). Most commonly, reaction is E2: hydroxide ion abstracts a proton from carbon; a molecule of tertiary amine is expelled, and the double bond is generated. Bases other than hydroxide ion can be used.



E1 elimination from quaternary ammonium ions is also known. Competing with either E2 or E1 elimination there is, as usual, substitution: either S_N2 or S_N1. (*Problem:* What products would you expect from substitution?)

Orientation in the E2 reaction is typically strongly Hofmann (Sec. 14.21)—not surprisingly, since it was for this reaction that Hofmann formulated his rule. For example:

$$\underset{\substack{\text{2-Pentyltrimethyl-}\\\text{ammonium ion}}}{CH_3CH_2CH_2\overset{\displaystyle N(CH_3)_3}{\overset{|}{C}}HCH_3} \xrightarrow[C_2H_5OH]{C_2H_5ONa} \underset{\substack{\text{1-Pentene}\\96\%}}{CH_3CH_2CH_2CH{=}CH_2} + \underset{\substack{\text{2-Pentene}\\4\%}}{CH_3CH_2CH{=}CHCH_3}$$

The transition state has considerable carbanion character, at least partly because powerful electron withdrawal by the positively charged nitrogen favors development of negative charge. There is preferential abstraction of a proton from the carbon that can best accommodate the partial negative charge: in the example given, from the primary carbon rather than the secondary.

Sulfonium ions, R_3S^+, react similarly to quaternary ammonium ions.

The stereochemistry of Hofmann elimination is commonly *anti*, but less so than was formerly believed. *Syn* elimination is important for certain cyclic compounds, and can be made important even for open-chain compounds by the proper choice of base and solvent. Quaternary ammonium ions are more prone to *syn* elimination than alkyl halides and sulfonates. Electronically, *anti* formation of the double bond is favored in eliminations; but when the alkene character of the transition state is slight—as here—other factors come into play: conformational factors, it has been postulated.

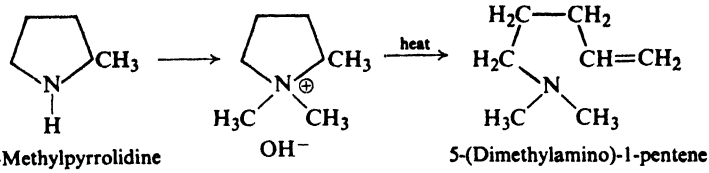
Problem 23.3 Predict the major products of E2 elimination from: (a) 2-methyl-3-pentyltrimethylammonium ion; (b) diethyldi-*n*-propylammonium ion; (c) dimethylethyl(2-chloroethyl)ammonium ion; (d) dimethylethyl-*n*-propylammonium ion.

Problem 23.4 When dimethyl-*tert*-pentylsulfonium ethoxide is heated in ethanol, the alkene obtained is chiefly (86%) 2-methyl-1-butene; when the corresponding sulfonium iodide is heated in ethanol, the alkene obtained is chiefly (86%) 2-methyl-2-butene.

(a) How do you account for the difference in products? (b) From the sulfonium iodide reaction there is also obtained considerable material identified as an ether. What ether would you expect it to be, and how is it formed? (c) What ether would you expect to obtain from the sulfonium ethoxide reaction?

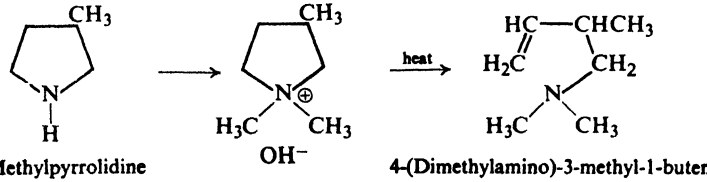
The formation of quaternary ammonium salts, followed by an elimination of the kind just described, is very useful in the determination of the structures of certain complicated nitrogen-containing compounds. The compound, which may be a primary, secondary, or tertiary amine, is converted into the quaternary ammonium hydroxide by treatment with excess methyl iodide and silver oxide. The number of methyl groups taken up by nitrogen depends upon the class of the amine; a primary amine will take up three methyl groups, a secondary amine will take up two, and a tertiary amine only one. This process is known as **exhaustive methylation of amines**.

When heated, a quaternary ammonium hydroxide undergoes elimination to an alkene and a tertiary amine. From the structures of these products it is often possible to deduce the structure of the original amine. As a simple example, contrast the products (I and II) obtained from the following isomeric cyclic amines:



2-Methylpyrrolidine 5-(Dimethylamino)-1-pentene

I



3-Methylpyrrolidine 4-(Dimethylamino)-3-methyl-1-butene

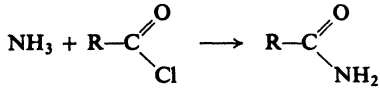
II

Problem 23.5 (a) What products would be expected from the hydrogenation of I and II? (b) How could you prepare an authentic sample of each of these expected hydrogenation products?

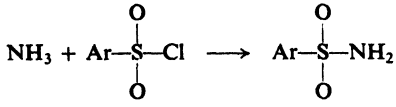
Problem 23.6 What products would be expected if I and II were subjected to exhaustive methylation and elimination?

23.6 Conversion of amines into substituted amides

We have learned (Sec. 20.11) that ammonia reacts with acid chlorides of carboxylic acids to yield amides, compounds in which —Cl has been replaced by



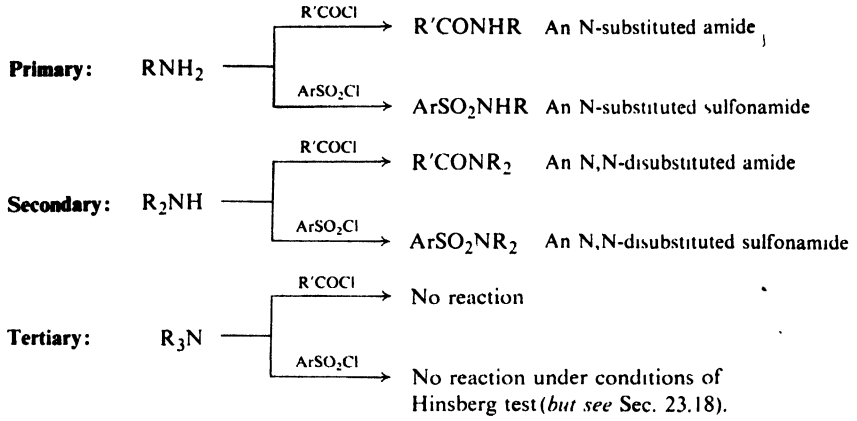
the $-NH_2$ group. Not surprisingly, acid chlorides of sulfonic acids react similarly.



A sulfonyl chloride A sulfonamide

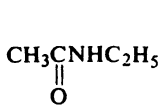
In these reactions ammonia serves as a nucleophilic reagent, attacking the carbonyl carbon or sulfur and displacing chloride ion. In the process nitrogen loses a proton to a second molecule of ammonia or another base.

In a similar way primary and secondary amines can react with acid chlorides to form **substituted amides**, compounds in which —Cl has been replaced by the —NHR or $-NR_2$ group:

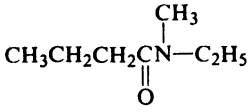


Tertiary amines, although basic, fail to yield amides, presumably because they cannot lose a proton (to stabilize the product) after attaching themselves to carbon or to sulfur. Here is a reaction which requires not only that amines be basic, but also that they possess a hydrogen atom attached to nitrogen. (However, see Sec. 23.19.)

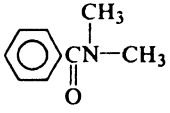
Substituted amides are generally named as derivatives of the unsubstituted amides. For example:



N-Ethylacetamide

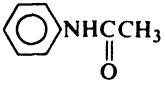


N-Methyl-N-ethylbutyramide

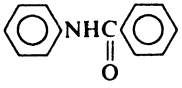


N,N-Dimethylbenzamide

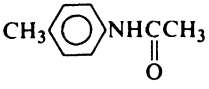
In many cases, and particularly where aromatic amines are involved, we are more interested in the amine from which the amide is derived than in the acyl group. In these cases the substituted amide is named as an acyl derivative of the amine. For example:



Acetanilide

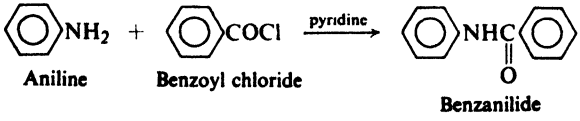


Benzanilide

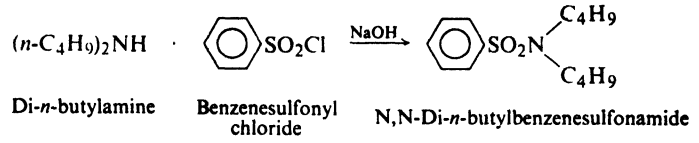


Aceto-*p*-toluidide

Substituted amides of aromatic carboxylic acids or of sulfonic acids are prepared by the Schotten-Baumann technique: the acid chloride is added to the amine in the presence of a base, either aqueous sodium hydroxide or pyridine. For example:

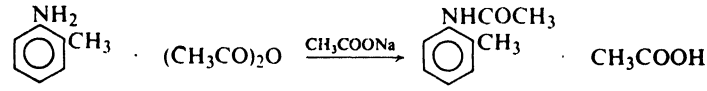


Aniline + Benzoyl chloride → Benzanilide



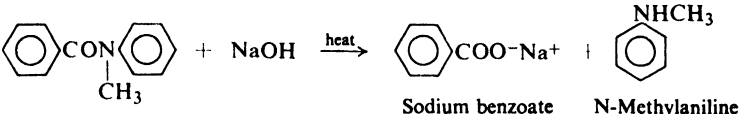
Di-*n*-butylamine | Benzenesulfonyl chloride | N,N-Di-*n*-butylbenzenesulfonamide

Acetylation is generally carried out using acetic anhydride rather than acetyl chloride. For example:

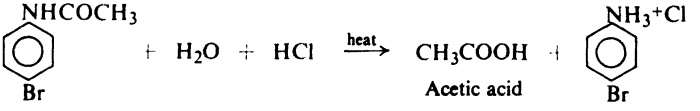


o-Toluidine | Acetic anhydride | Aceto-*o*-toluidide

Like simple amides, substituted amides undergo hydrolysis; the products are the acid and the amine, although one or the other is obtained as its salt, depending upon the acidity or alkalinity of the medium.

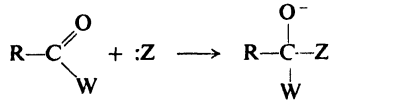


N-Methylbenzanilide | Sodium benzoate | N-Methylaniline



p-Bromoacetanilide | Acetic acid | *p*-Bromoanilinium chloride

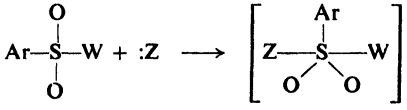
Sulfonamides are hydrolyzed more slowly than amides of carboxylic acids; examination of the structures involved shows us what probably underlies this difference. Nucleophilic attack on a trigonal acyl carbon (Sec. 20.4) is relatively unhindered; it involves the temporary attachment of a fourth group, the nucleophilic reagent. Nucleophilic attack on tetrahedral sulfonyl sulfur is relatively hindered; it involves the temporary attachment of a *fifth* group. The tetrahedral



Trigonal C | Tetrahedral C

Attack relatively unhindered | *Stable octet*

Acyl nucleophilic substitution



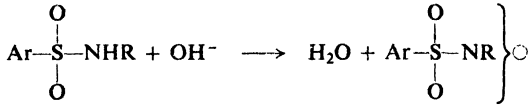
Tetrahedral S | Pentavalent S

Attack hindered | *Unstable decet*

Sulfonyl nucleophilic substitution

carbon of the acyl intermediate makes use of the permitted octet of electrons; although sulfur may be able to use more than eight electrons in covalent bonding, this is a less stable system than the octet. Thus both steric and electronic factors tend to make sulfonyl compounds less reactive than acyl compounds.

There is a further contrast between the amides of the two kinds of acids. The substituted amide from a primary amine still has a hydrogen attached to nitrogen, and as a result is *acidic*: in the case of a sulfonamide, this acidity is appreciable, and much greater than for the amide of a carboxylic acid. A monosubstituted sulfonamide is less acidic than a carboxylic acid, but about the same as a phenol (Sec. 24.7); it reacts with aqueous hydroxides to form salts.



This difference in acidity, too, is understandable. A sulfonic acid is more acidic than a carboxylic acid because the negative charge of the anion is dispersed over three oxygens instead of just two. In the same way, a sulfonamide is more acidic than the amide of a carboxylic acid because the negative charge is dispersed over two oxygens plus nitrogen instead of over just one oxygen plus nitrogen.

Problem 23.7 (a) Although amides of carboxylic acids are very weakly acidic ($K_a = 10^{-14}$ to 10^{-15}), they are still enormously more acidic than ammonia ($K_a = 10^{-33}$) or amines, RNH_2. Account in detail for this.

(b) Diacetamide, $(CH_3CO)_2NH$, is much more acidic ($K_a = 10^{-11}$) than acetamide ($K_a = 8.3 \times 10^{-16}$), and roughly comparable to benzenesulfonamide ($K_a = 10^{-10}$). How can you account for this?

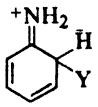
Problem 23.8 In contrast to carboxylic esters, we know, alkyl sulfonates undergo nucleophilic attack at alkyl carbon. What *two* factors are responsible for this difference

in behavior? (*Hint:* See Sec. 14.6.)

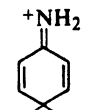
The conversion of an amine into a sulfonamide is used in determining the class of the amine; this is discussed in the section on analysis (Sec. 23.18).

23.7 Ring substitution in aromatic amines

We have already seen that the $-NH_2$, $-NHR$, and $-NR_2$ groups act as powerful activators and *ortho,para* directors in electrophilic aromatic substitution. These effects were accounted for by assuming that the intermediate carbonium ion is stabilized by structures like I and II in which nitrogen bears a positive charge



I



II

and is joined to the ring by a double bond. Such structures are especially stable since in them every atom (except hydrogen) has a complete octet of electrons; indeed, structure I or II *by itself* must pretty well represent the intermediate.

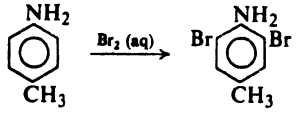
In such structures nitrogen shares more than one pair of electrons with the ring, and hence carries the charge of the "carbonium ion." Thus the basicity of nitrogen accounts for one more characteristic of aromatic amines.

The acetamido group, $-NHCOCH_3$, is also activating and *ortho,para*-directing, but less powerfully so than a free amino group. Electron withdrawal by oxygen of the carbonyl group makes the nitrogen of an amide a much poorer source of electrons than the nitrogen of an amine. Electrons are less available for sharing with a hydrogen ion, and therefore amides are much weaker bases than amines: amides of carboxylic acids do not dissolve in dilute aqueous acids. Electrons are less available for sharing with an aromatic ring, and therefore an acetamido group activates an aromatic ring less strongly than an amino group.

More precisely, electron withdrawal by carbonyl oxygen destabilizes a positive charge on nitrogen, whether this charge is acquired by *protonation* or by *electrophilic attack on the ring.*

(We have seen (Sec. 11.5) that the $-NR_3^+$ group is a powerful deactivator and *meta* director. In a quaternary ammonium salt, nitrogen no longer has electrons to share with the ring; on the contrary, the full-fledged positive charge on nitrogen makes the group strongly electron-attracting.)

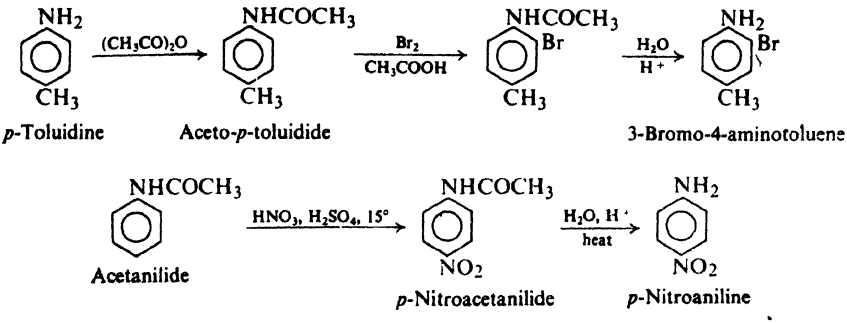
In electrophilic substitution, the chief problem encountered with aromatic amines is that they are *too* reactive. In halogenation, substitution tends to occur at every available *ortho* or *para* position. For example:



p-Toluidine 3,5-Dibromo-4-aminotoluene

Nitric acid not only nitrates, but oxidizes the highly reactive ring as well, with loss of much material as tar. Furthermore, in the strongly acidic nitration medium, the amine is converted into the anilinium ion; substitution is thus controlled not by the $-NH_2$ group but by the $-NH_3^+$ group which, because of its positive charge, directs much of the substitution to the *meta* position.

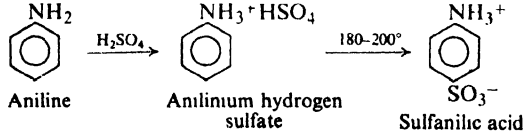
There is, fortunately, a simple way out of these difficulties: We *protect* the amino group: we acetylate the amine, then carry out the substitution, and finally hydrolyze the amide to the desired substituted amine. For example:



Problem 23.9 Nitration of un-acetylated aniline yields a mixture of about two-thirds *meta* and one-third *para* product. Since almost all the aniline is in the form of the anilinium ion, how do you account for the fact that even more *meta* product is not obtained?

23.8 Sulfonation of aromatic amines. Dipolar ions

Aniline is usually sulfonated by "baking" the salt, anilinium hydrogen sulfate, at 180–200°; the chief product is the *p*-isomer. In this case we cannot discuss orientation on our usual basis of which isomer is formed *faster*. Sulfonation is

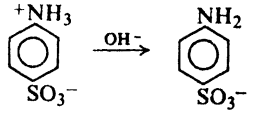


known to be reversible, and the *p*-isomer is known to be the most stable isomer; it may well be that the product obtained, the *p*-isomer, is determined by the position of an equilibrium and not by relative rates of formation (see Sec. 8.22 and Sec. 12.11). It also seems likely that, in some cases at least, sulfonation of amines proceeds by a mechanism that is entirely different from ordinary aromatic substitution.

Whatever the mechanism by which it is formed, the chief product of this reaction is *p*-aminobenzenesulfonic acid, known as **sulfanilic acid**; it is an important and interesting compound.

First of all, its properties are not those we would expect of a compound containing an amino group and a sulfonic acid group. Both aromatic amines and aromatic sulfonic acids have low melting points; benzenesulfonic acid, for example, melts at 66°, and aniline at −6°. Yet sulfanilic acid has such a high melting point that on being heated it decomposes (at 280–300°) before its melting point can be reached. Sulfonic acids are generally very soluble in water; indeed, we have seen that the sulfonic acid group is often introduced into a molecule to make it water-soluble. Yet sulfanilic acid is not only insoluble in organic solvents, but also nearly insoluble in water. Amines dissolve in aqueous mineral acids because of their conversion into water-soluble salts. Sulfanilic acid is soluble in aqueous bases but insoluble in aqueous acids.

These properties of sulfanilic acid are understandable when we realize that sulfanilic acid actually has the structure I which contains the $-NH_3^+$ and $-SO_3^-$ groups. Sulfanilic acid is a salt, but of a rather special kind, called a **dipolar ion**



I II

Insoluble in water *Soluble in water*

(sometimes called a *zwitterion*, from the German, *Zwitter*, hermaphrodite). It is the product of reaction between an acidic group and a basic group that are part of the same molecule. The hydrogen ion is attached to nitrogen rather than oxygen simply because the $-NH_2$ group is a stronger base than the $-SO_3^-$ group. A high melting point and insolubility in organic solvents are properties we would expect of a salt. Insolubility in water is not surprising, since many salts are insoluble in water. In alkaline solution, the strongly basic hydroxide ion pulls hydrogen ion away from the weakly basic $-NH_2$ group to yield the *p*-aminobenzenesulfonate ion (II), which, like most sodium salts, is soluble in water. In aqueous acid, however, the sulfanilic acid structure is not changed, and therefore the compound remains insoluble; sulfonic acids are strong acids and their anions (very weak bases) show little tendency to accept hydrogen ion from H_3O^+.

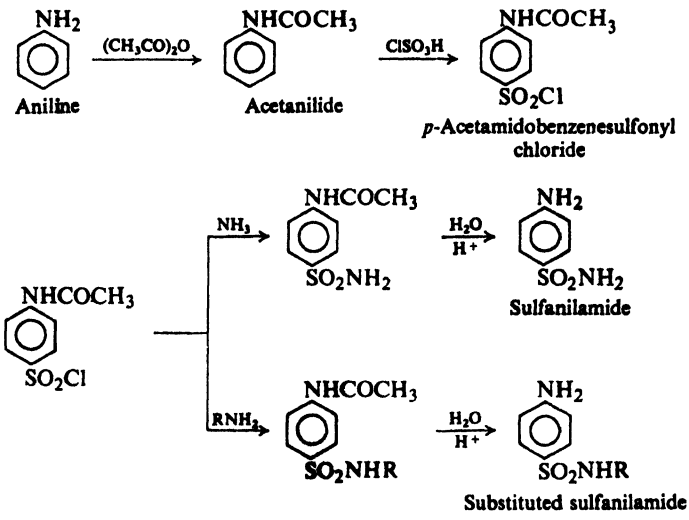
We can expect to encounter dipolar ions whenever we have a molecule containing both an amino group and an acid group, providing the amine is more basic than the anion of the acid.

Problem 23.10 *p*-Aminobenzoic acid is not a dipolar ion, whereas glycine (aminoacetic acid) is a dipolar ion. How can you account for this?

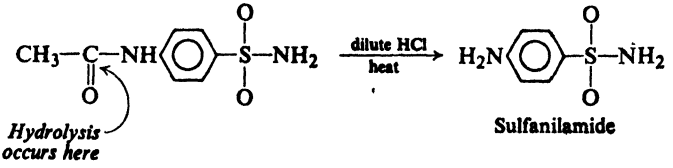
23.9 Sulfanilamide. The sulfa drugs

The amide of sulfanilic acid (*sulfanilamide*) and certain related substituted amides are of considerable medical importance as the *sulfa drugs*. Although they have been supplanted to a wide extent by the antibiotics (such as penicillin, terramycin, chloromycetin, and aureomycin), the sulfa drugs still have their medical uses, and make up a considerable portion of the output of the pharmaceutical industry.

Sulfonamides are prepared by the reaction of a sulfonyl chloride with ammonia or an amine. The presence in a sulfonic acid molecule of an amino group, however, poses a special problem: if sulfanilic acid were converted to the acid chloride, the sulfonyl group of one molecule could attack the amino group of another to form an amide linkage. This problem is solved by protecting the amino group through acetylation prior to the preparation of the sulfonyl chloride. Sulfanilamide and related compounds are generally prepared in the following way:



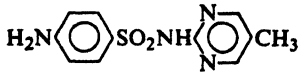
The selective removal of the acetyl group in the final step is consistent with the general observation that amides of carboxylic acids are more easily hydrolyzed than amides of sulfonic acids.



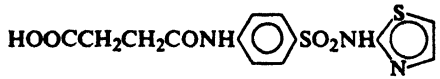
The antibacterial activity—and toxicity—of a sulfanilamide stems from a rather simple fact: enzymes in the bacteria (and in the patients) confuse it for *p*-aminobenzoic acid, which is an essential metabolite. In what is known as *metabolite antagonism*, the sulfanilamide competes with *p*-aminobenzoic acid for reactive

sites on the enzymes; deprived of the essential metabolite, the organism fails to reproduce, and dies.

Just how good a drug the sulfanilamide is depends upon the nature of the group R attached to amido nitrogen. This group must confer just the right degree of acidity to the amido hydrogen (Sec. 23.6), but acidity is clearly only one of the factors involved. Of the hundreds of such compounds that have been synthesized, only a half dozen or so have had the proper combination of high antibacterial activity and low toxicity to human beings that is necessary for an effective drug; in nearly all these effective compounds the group R contains a heterocyclic ring (Chap. 31).



Sulfamerazine



Succinoylsulfathiazole

23.10 Reactions of amines with nitrous acid

Each class of amine yields a different kind of product in its reaction with nitrous acid, HONO. This unstable reagent is generated in the presence of the amine by the action of mineral acid on sodium nitrite.

Primary aromatic amines react with nitrous acid to yield *diazonium salts*; this is one of the most important reactions in organic chemistry. Following sections are devoted to the preparation and properties of aromatic diazonium salts.

$$\underset{\substack{1^\circ \text{ aromatic}\\ \text{amine}}}{ArNH_2} + NaNO_2 + 2HX \xrightarrow{\text{cold}} \underset{\text{A diazonium salt}}{ArN_2^+X^-} + NaX + 2H_2O$$

Primary aliphatic amines also react with nitrous acid to yield diazonium salts; but since aliphatic diazonium salts are quite unstable and break down to yield a complicated mixture of organic products (see Problem 23.11, below), this reaction is of little synthetic value. The fact that nitrogen is evolved quantitatively is of some

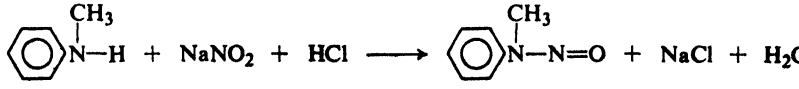
$$\underset{\substack{1^\circ \text{ aliphatic}\\ \text{amine}}}{RNH_2} + NaNO_2 + HX \longrightarrow \underset{\textit{Unstable}}{[RN_2^+X^-]} \xrightarrow{H_2O} N_2 + \text{mixture of alcohols and alkenes}$$

importance in analysis, however, particularly of amino acids and proteins.

Problem 23.11 The reaction of *n*-butylamine with sodium nitrite and hydrochloric acid yields nitrogen and the following mixture: *n*-butyl alcohol, 25%; *sec*-butyl alcohol, 13%; 1-butene and 2-butene, 37%; *n*-butyl chloride, 5%; *sec*-butyl chloride, 3%. (a) What is the most likely intermediate common to all of these products? (b) Outline reactions that account for the various products.

Problem 23.12 Predict the organic products of the reaction of: (a) isobutylamine with nitrous acid; (b) neopentylamine with nitrous acid.

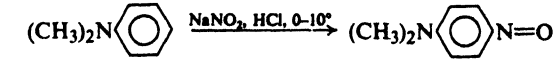
Secondary amines, both aliphatic and aromatic, react with nitrous acid to yield N-nitrosoamines.



N-Methylaniline

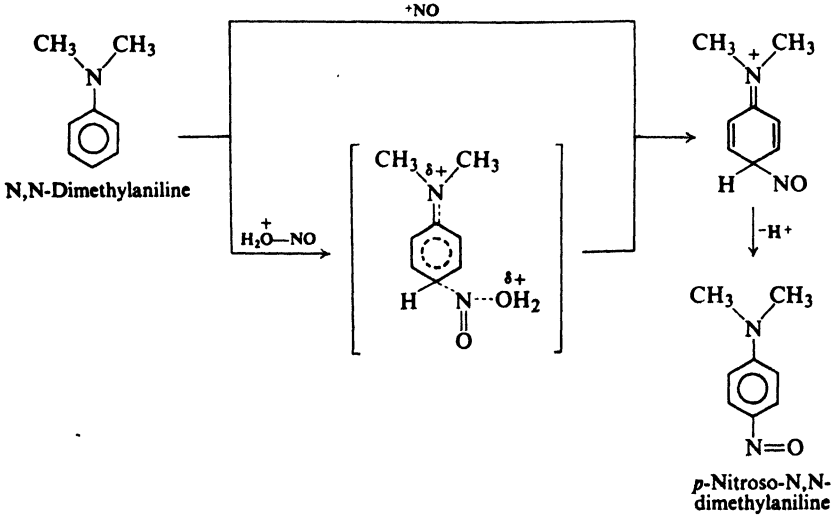
N-Nitroso-N-methylaniline

Tertiary aromatic amines undergo ring substitution, to yield compounds in which a nitroso group, —N=O, is joined to carbon; thus N,N-dimethylaniline yields chiefly *p*-nitroso-N,N-dimethylaniline.



N,N-Dimethylaniline *p*-Nitroso-N,N-dimethylaniline

Ring nitrosation is an electrophilic aromatic substitution reaction, in which the attacking reagent is either the *nitrosonium ion*, ^+NO, or some species (like $H_2\overset{+}{O}$—NO or NOCl) that can easily transfer ^+NO to the ring. The nitrosonium ion is very weakly electrophilic compared with the reagents involved in nitration, sulfonation, halogenation, and the Friedel-Crafts reaction; nitrosation ordinarily occurs only in rings bearing the powerfully activating dialkylamino (—NR_2) or hydroxy (—OH) group.



Despite the differences in final product, the reaction of nitrous acid with all these amines involves the same initial step: *electrophilic attack by* ^+NO *with displacement of* H^+. This attack occurs at the position of highest electron availability in primary and secondary amines: at nitrogen. Tertiary aromatic amines are attacked at the highly reactive ring.

Tertiary aliphatic amines (and, to an extent, tertiary aromatic amines, too, particularly if the *para* position is blocked) react with nitrous acid to yield an N-nitroso derivative of a *secondary* amine; the group that is lost from nitrogen appears as an aldehyde or ketone. Although this reaction is not really understood, it too seems to involve the initial attack by ^+NO on nitrogen.

Problem 23.13 (a) Write equations to show how the molecule $H_2\overset{+}{O}$—NO is formed in the nitrosating mixture. (b) Why can this transfer ^+NO to the ring more easily than HONO can? (c) Write equations to show how NOCl can be formed from $NaNO_2$ and aqueous hydrochloric acid. (d) Why is NOCl a better nitrosating agent than HONO?

Problem 23.14 (a) Which, if either, of the following seems likely? (i) The ring of N-methylaniline is much less reactive toward electrophilic attack than the ring of N,N-dimethylaniline. (ii) Nitrogen of N-methylaniline is much more reactive toward electrophilic attack than nitrogen of N,N-dimethylaniline.

(b) How do you account for the fact that the two amines give different products with nitrous acid?

23.11 Diazonium salts. Preparation and reactions

When a primary aromatic amine, dissolved or suspended in cold aqueous mineral acid, is treated with sodium nitrite, there is formed a diazonium salt.

$$\underset{\text{1° aromatic amine}}{ArNH_2} + NaNO_2 + 2HX \xrightarrow{\text{cold}} \underset{\text{A diazonium salt}}{ArN{\equiv}N{:}^{+}X^{-}} + NaX + 2H_2O$$

Since diazonium salts slowly decompose even at ice-bath temperatures, the solution is used immediately after preparation.

The large number of reactions undergone by diazonium salts may be divided into two classes: **replacement**, in which nitrogen is lost as N_2, and some other atom or group becomes attached to the ring in its place; and **coupling**, in which the nitrogen is retained in the product.

REACTIONS OF DIAZONIUM SALTS

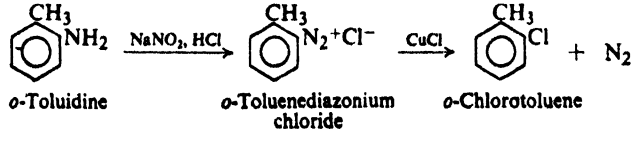
1. Replacement of nitrogen

$$ArN_2^+ + :Z \longrightarrow ArZ + N_2$$

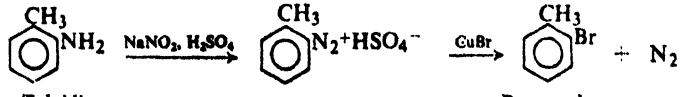
(a) **Replacement by —Cl, —Br, and —CN. Sandmeyer reaction.** Discussed in Secs. 23.12–23.13.

$$ArN_2^+ \xrightarrow{CuCl} ArCl + N_2$$
$$ArN_2^+ \xrightarrow{CuBr} ArBr + N_2$$
$$ArN_2^+ \xrightarrow{CuCN} ArCN + N_2$$

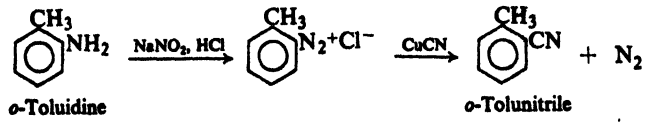
Examples:



o-Toluidine — *o*-Toluenediazonium chloride — *o*-Chlorotoluene



o-Toluidine — *o*-Bromotoluene

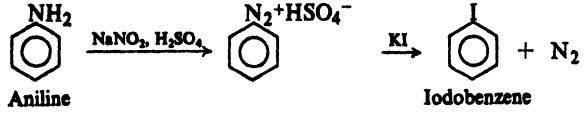


o-Toluidine *o*-Tolunitrile

(b) **Replacement by —I.** Discussed in Sec. 23.12.

$$ArN_2^+ + I^- \longrightarrow ArI + N_2$$

Example:

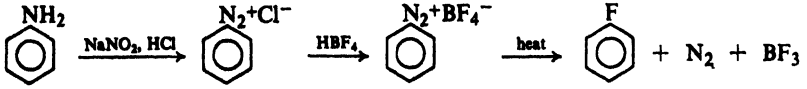


Aniline Iodobenzene

(c) **Replacement by —F.** Discussed in Sec. 23.12.

$$ArN_2^+BF_4^- \xrightarrow{\text{heat}} ArF + N_2 + BF_3$$

Example:



Aniline Benzenediazonium chloride Benzenediazonium fluoborate Fluorobenzene

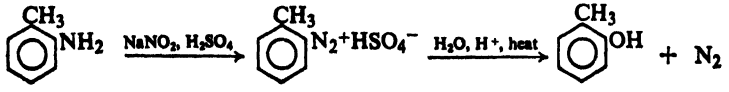
Isolated as crystalline salt

(d) **Replacement by —OH.** Discussed in Sec. 23.14.

$$ArN_2^+ + H_2O \xrightarrow{H^+} ArOH + N_2$$

A phenol

Example:

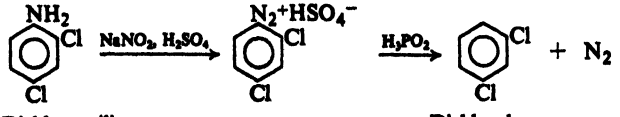


o-Toluidine *o*-Cresol

(e) **Replacement by —H.** Discussed in Sec. 23.15.

$$ArN_2^+ + H_3PO_2 \xrightarrow{H_2O} ArH + H_3PO_3 + N_2$$

Example:



2,4-Dichloroaniline *m*-Dichlorobenzene

2. Coupling. Discussed in Sec. 23.17.

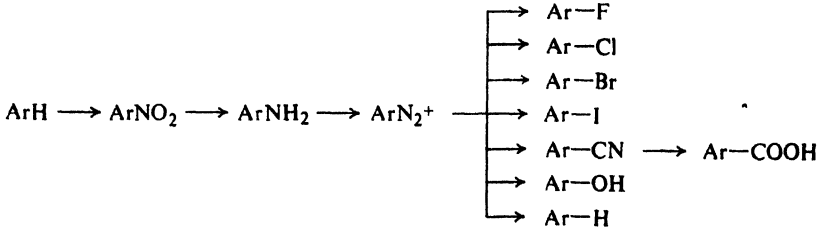
An azo compound

G must be a strongly electron-releasing group: OH, NR_2, NHR, NH_2

Example:

Benzenediazonium chloride — Phenol — *p*-Hydroxyazobenzene *p*-(Phenylazo)phenol

Replacement of the diazonium group is the best general way of introducing F, Cl, Br, I, CN, OH, and H into an aromatic ring. Diazonium salts are valuable in synthesis not only because they react to form so many classes of compounds, but also because they can be prepared from nearly all primary aromatic amines. There are few groups whose presence in the molecule interferes with diazotization; in this respect, diazonium salts are quite different from Grignard reagents (Sec. 15.15). The amines from which diazonium compounds are prepared are readily obtained from the corresponding nitro compounds, which are prepared by direct nitration. Diazonium salts are thus the most important link in the sequence:



In addition to the atoms and groups just listed, there are dozens of other groups that can be attached to an aromatic ring by replacement of the diazonium nitrogen, as, for example, —Ar, $—NO_2$, —OR, —SH, —SR, —NCS, —NCO, $—PO_3H_2$, $—AsO_3H_2$, $—SbO_3H_2$; the best way to introduce most of these groups is via diazotization.

The coupling of diazonium salts with aromatic phenols and amines yields *azo compounds*, which are of tremendous importance to the dye industry.

23.12 Diazonium salts. Replacement by halogen. Sandmeyer reaction

Replacement of the diazonium group by —Cl or —Br is carried out by mixing the solution of freshly prepared diazonium salt with cuprous chloride or cuprous

bromide. At room temperature, or occasionally at elevated temperatures, nitrogen is steadily evolved, and after several hours the aryl chloride or aryl bromide can be isolated from the reaction mixture. This procedure, using cuprous halides, is generally referred to as the **Sandmeyer reaction.**

$$ArN_2^+X^- \xrightarrow{CuX} ArX + N_2$$

Sometimes the synthesis is carried out by a modification known as the *Gattermann reaction,* in which copper powder and hydrogen halide are used in place of the cuprous halide.

Replacement of the diazonium group by —I does not require the use of a cuprous halide or copper; the diazonium salt and potassium iodide are simply mixed together and allowed to react.

$$ArN_2^+X^- + I^- \longrightarrow ArI + N_2 + X^-$$

Replacement of the diazonium group by —F is carried out in a somewhat different way. Addition of fluoboric acid, HBF_4, to the solution of diazonium salt causes the precipitation of the diazonium fluoborate, $ArN_2^+BF_4^-$, which can be collected on a filter, washed, and dried. The diazonium fluoborates are unusual among diazonium salts in being fairly stable compounds. On being heated, the dry diazonium fluoborate decomposes to yield the aryl fluoride, boron trifluoride,

$$ArN_2^+X^- \xrightarrow{HBF_4} ArN_2^+BF_4^- \xrightarrow{heat} ArF + BF_3 + N_2$$

and nitrogen. An analogous procedure involves the diazonium hexafluorophosphate, $ArN_2^+PF_6^-$.

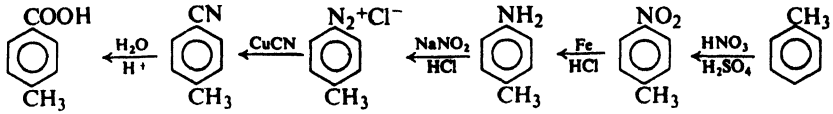
The advantages of the synthesis of aryl halides from diazonium salts will be discussed in detail in Sec. 25.3. Aryl fluorides and iodides cannot generally be prepared by direct halogenation. Aryl chlorides and bromides can be prepared by direct halogenation, but, when a mixture of *o*- and *p*-isomers is obtained, it is difficult to isolate the pure compounds because of their similarity in boiling point. Diazonium salts ultimately go back to nitro compounds, which are usually obtainable in pure form.

23.13 Diazonium salts. Replacement by —CN. Synthesis of carboxylic acids

Replacement of the diazonium group by —CN is carried out by allowing the diazonium salt to react with cuprous cyanide. To prevent loss of cyanide as HCN, the diazonium solution is neutralized with sodium carbonate before being mixed with the cuprous cyanide.

$$ArN_2^+X^- \xrightarrow{CuCN} ArCN + N_2$$

Hydrolysis of nitriles yields carboxylic acids. The synthesis of nitriles from diazonium salts thus provides us with an excellent route from nitro compounds to carboxylic acids. For example:



p-Toluic acid | *p*-Tolunitrile | *p*-Toluenediazonium chloride | *p*-Toluidine | *p*-Nitrotoluene | Toluene

This way of making aromatic carboxylic acids is more generally useful than either carbonation of a Grignard reagent or oxidation of side chains. We have just seen that pure bromo compounds, which are needed to prepare the Grignard reagent, are themselves most often prepared via diazonium salts; furthermore, there are many groups that interfere with the preparation and use of the Grignard reagent (Sec. 15.15). The nitro group can generally be introduced into a molecule more readily than an alkyl side chain; furthermore, conversion of a side chain into a carboxyl group cannot be carried out on molecules that contain other groups sensitive to oxidation.

23.14 Diazonium salts. Replacement by —OH. Synthesis of phenols

Diazonium salts react with water to yield phenols. This reaction takes place

$$ArN_2^+X^- + H_2O \longrightarrow ArOH + N_2 + H^+$$

slowly in the ice-cold solutions of diazonium salts, and is the reason diazonium salts are used immediately upon preparation; at elevated temperatures it can be made the chief reaction of diazonium salts.

As we shall see, phenols can couple with diazonium salts to form azo compounds (Sec. 23.17); the more acidic the solution, however, the more slowly this coupling occurs. To minimize coupling during the synthesis of a phenol, therefore —coupling, that is, between phenol that has been formed and diazonium ion that has not yet reacted—the diazonium solution is added slowly to a large volume of boiling dilute sulfuric acid.

This is the best general way to make the important class of compounds, the phenols.

23.15 Diazonium salts. Replacement by —H

Replacement of the diazonium group by —H can be brought about by a number of reducing agents; perhaps the most useful of these is *hypophosphorus acid*, H_3PO_2. The diazonium salt is simply allowed to stand in the presence of the hypophosphorous acid; nitrogen is lost, and hypophosphorous acid is oxidized to phosphorous acid:

$$ArN_2^+X^- + H_3PO_2 + H_2O \longrightarrow ArH + N_2 + H_3PO_3 + HX$$

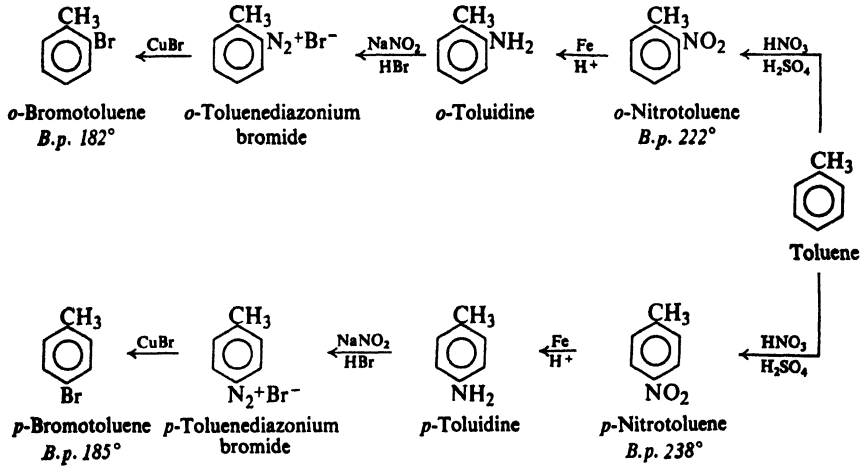
An especially elegant way of carrying out this replacement is to use hypophosphorous acid as the diazotizing acid. The amine is dissolved in hypophosphorous acid, and sodium nitrite is added; the diazonium salt is reduced as fast as it is formed.

This reaction of diazonium salts provides a method of removing an $-NH_2$ or $-NO_2$ group from an aromatic ring. This process can be extremely useful in synthesis, as is shown in some of the examples in the following section.

23.16 Syntheses using diazonium salts

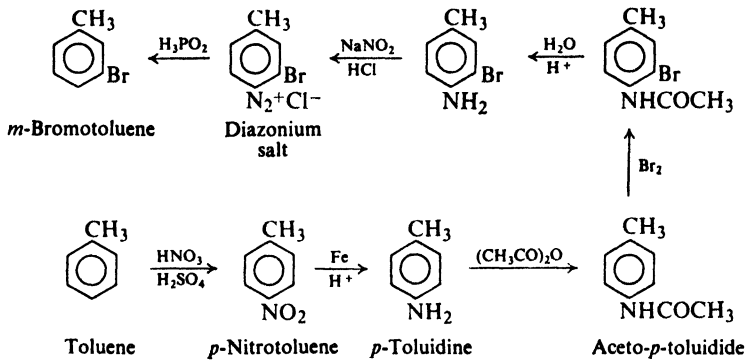
Let us look at a few examples of how diazonium salts can be used in organic synthesis.

To begin with, we might consider some rather simple compounds, the three isomeric bromotoluenes. The best synthesis of each employs diazotization, but not for the same purpose in the three cases. The *o*- and *p*-bromotoluenes are prepared from the corresponding *o*- and *p*-nitrotoluenes:



The advantage of these many-step syntheses over direct bromination is, as we have seen, that a pure product is obtained. Separation of the *o*- and *p*-bromotoluenes obtained by direct bromination is not feasible.

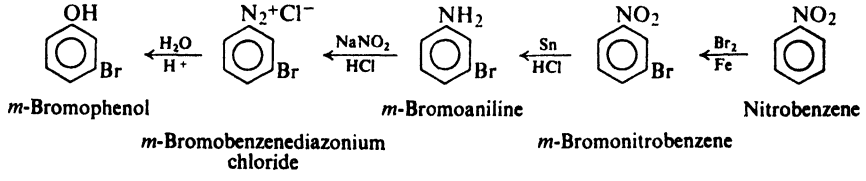
Synthesis of *m*-bromotoluene is a more complicated matter. The problem here is one of preparing a compound in which two *ortho,para*-directing groups are situated *meta* to each other. Bromination of toluene or methylation of bromobenzene would not yield the correct isomer. *m*-Bromotoluene is obtained by the following sequence of reactions:



The key to the synthesis is the introduction of a group that is a much stronger *ortho,para* director than $-CH_3$, and that can be easily removed after it has done its job of directing bromine to the correct position. Such a group is the $-NHCOCH_3$ group: it is introduced into the *para* position of toluene via nitration, reduction, and acetylation; it is readily removed by hydrolysis, diazotization, and reduction.

Problem 23.15 Outline the synthesis from benzene or toluene of the following compounds: *m*-nitrotoluene, *m*-iodotoluene, 3,5-dibromotoluene, 1,3,5-tribromobenzene, the three toluic acids ($CH_3C_6H_4COOH$). the three methylphenols (cresols).

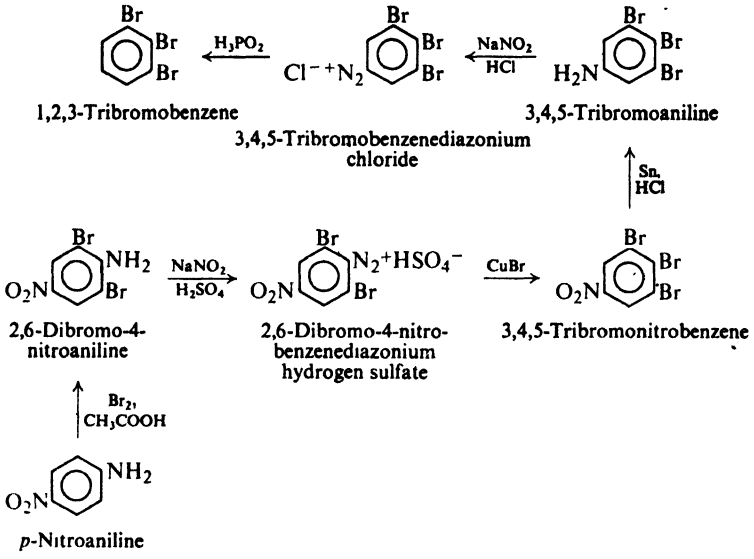
In the synthesis of *m*-bromotoluene, advantage was taken of the fact that the diazonium group is prepared from a group that is strongly *ortho,para*-directing. Ultimately, however, the diazonium group is prepared from the $-NO_2$ group, which is a strongly *meta*-directing group. Advantage can be taken of this fact, too, as in the preparation of *m*-bromophenol:



Here again there is the problem of preparing a compound with two *ortho,para* directors situated *meta* to each other. Bromination at the nitro stage gives the necessary *meta* orientation.

Problem 23.16 Outline the synthesis from benzene or toluene of the following compounds: *m*-dibromobenzene, *m*-bromoiodobenzene.

As a final example, let us consider the preparation of 1,2,3-tribromobenzene:



In this synthesis advantage is taken of the fact that the $-NO_2$ group is a *meta* director, that the $-NH_2$ group is an *ortho,para* director, and that each of them can be converted into a diazonium group. One diazonium group is replaced by —Br, the other by —H.

Problem 23.17 Outline the synthesis from benzene or toluene of the following compounds: 2,6-dibromotoluene, 3,5-dibromonitrobenzene.

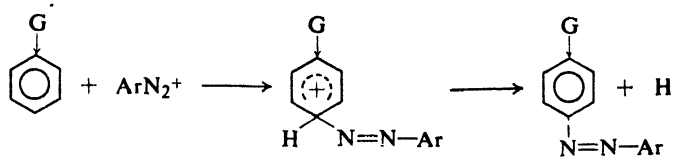
23.17 Coupling of diazonium salts. Synthesis of azo compounds

Under the proper conditions, diazonium salts react with certain aromatic compounds to yield products of the general formula Ar—N=N—Ar', called **azo compounds**. In this reaction, known as **coupling**, the nitrogen of the diazonium group is retained in the product, in contrast to the replacement reactions we have studied up to this point, in which nitrogen is lost.

$$ArN_2^+ + Ar'H \longrightarrow \underset{\text{An azo compound}}{Ar{-}N{=}N{-}Ar'} + H^+$$

The aromatic ring (Ar'H) undergoing attack by the diazonium ion must, in general, contain a powerfully electron-releasing group, generally —OH, $-NR_2$, —NHR, or $-NH_2$. Substitution usually occurs *para* to the activating group. Typically, coupling with phenols is carried out in mildly alkaline solution, and with amines in mildly acidic solution.

Activation by electron-releasing groups, as well as the evidence of kinetics studies, indicates that coupling is electrophilic aromatic substitution in which the diazonium ion is the attacking reagent:



It is significant that the aromatic compounds which undergo coupling are also the ones which undergo nitrosation. Like the nitrosonium ion, ^+NO, the diazonium ion, ArN_2^+, is evidently very weakly electrophilic, and is capable of attacking only very reactive rings.

Problem 23.18 Benzenediazonium chloride couples with phenol, but not with the less reactive anisole. 2,4-Dinitrobenzenediazonium chloride, however, couples with anisole; 2,4,6-trinitrobenzenediazonium chloride even couples with the hydrocarbon mesitylene (1,3,5-trimethylbenzene). (a) How can you account for these differences in behavior? (b) Would you expect *p*-toluenediazonium chloride to be more or less reactive as a coupling reagent than benzenediazonium chloride?

In the laboratory we find that coupling involves more than merely mixing together a diazonium salt and a phenol or amine. Competing with any other reaction of diazonium salts is the reaction with water to yield a phenol. If coupling proceeds slowly because of unfavorable conditions, phenol formation may very well become the major reaction. Furthermore, the phenol formed from the diazonium salt can itself undergo coupling; even a relatively small amount of this undesired coupling product could contaminate the desired material—usually a dye whose color should be as pure as possible—to such an extent that the product would be worthless. Conditions under which coupling proceeds as rapidly as possible must therefore be selected.

It is most important that the coupling medium be adjusted to the right degree of acidity or alkalinity. This is accomplished by addition of the proper amount of hydroxide or salts like sodium acetate or sodium carbonate. It will be well to examine this matter in some detail, since it illustrates a problem that is frequently encountered in organic chemical practice.

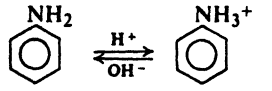
The electrophilic reagent is the diazonium ion, ArN_2^+. In the presence of hydroxide ion, the diazonium ion exists in equilibrium with an un-ionized compound, Ar—N=N—OH, and salts (Ar—N=N—O^-Na^+) derived from it:

$$\underset{\textit{Couples}}{Ar{-}N{\equiv}N^+OH^-} \underset{H^+}{\overset{NaOH}{\rightleftharpoons}} \underset{\textit{Does not couple}}{Ar{-}N{=}N{-}OH} \underset{H^+}{\overset{NaOH}{\rightleftharpoons}} \underset{\textit{Does not couple}}{Ar{-}N{=}N{-}O^-Na^+}$$

For our purpose we need only know that hydroxide tends to convert diazonium ion, which couples, into compounds which do not couple. In so far as the electrophilic reagent is concerned, then, coupling will be favored by a low concentration of hydroxide ion, that is, by high acidity.

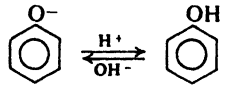
But what is the effect of high acidity on the amine or phenol with which the diazonium salt is reacting? Acid converts an amine into its ion, which, because of the positive charge, is relatively unreactive toward electrophilic aromatic substitution: much too unreactive to be attacked by the weakly electrophilic

diazonium ion. The higher the acidity, the higher the proportion of amine that exists as its ion, and the lower the rate of coupling.



Couples *Does not couple*

An analogous situation exists for a phenol. A phenol is appreciably acidic; in aqueous solutions it exists in equilibrium with phenoxide ion:



Couples rapidly *Couples slowly*

The fully developed negative charge makes $-O^-$ much more powerfully electron-releasing than —OH; the phenoxide ion is therefore much more reactive than the un-ionized phenol toward electrophilic aromatic substitution. The higher the acidity of the medium, the higher the proportion of phenol that is un-ionized, and the lower the rate of coupling. In so far as the amine or phenol is concerned, then, coupling is favored by low acidity.

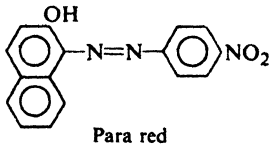
The conditions under which coupling proceeds most rapidly are the result of a compromise. The solution must not be so alkaline that the concentration of diazonium ion is too low; it must not be so acidic that the concentration of free amine or phenoxide ion is too low. It turns out that amines couple fastest in mildly acidic solutions, and phenols couple fastest in mildly alkaline solutions.

Problem 23.19 Suggest a reason for the use of *excess* mineral acid in the diazotization process.

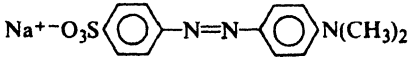
Problem 23.20 (a) Coupling of diazonium salts with primary or secondary aromatic amines (but not with tertiary aromatic amines) is complicated by a side reaction that yields an isomer of the azo compound. Judging from the reaction of secondary aromatic amines with nitrous acid (Sec. 23.10), suggest a possible structure for this by-product.

(b) Upon treatment with mineral acid, this by-product regenerates the original reactants which recombine to form the azo compound. What do you think is the function of the acid in this regeneration? (*Hint:* See Problem 5.8, p. 170.)

Azo compounds are the first compounds we have encountered that as a class are strongly colored. They can be intensely yellow, orange, red, blue, or even green, depending upon the exact structure of the molecule. Because of their color, the azo compounds are of tremendous importance as dyes; about half of the dyes in industrial use today are azo dyes. Some of the acid–base indicators with which the student is already familiar are azo compounds.



Para red
A red dye



Methyl orange
An acid-base indicator:
red in acid, *yellow* in base

Problem 23.21 An azo compound is cleaved at the azo linkage by stannous chloride, $SnCl_2$, to form two amines. (a) What is the structure of the azo compound that is cleaved to 3-bromo-4-aminotoluene and 2-methyl-4-aminophenol? (b) Outline a synthesis of this azo compound, starting with benzene and toluene.

Problem 23.22 Show how *p*-amino-N,N-dimethylaniline can be made via an azo compound.

23.18 Analysis of amines. Hinsberg test

Amines are characterized chiefly through their basicity. A water-insoluble compound that dissolves in cold dilute hydrochloric acid—or a water-soluble compound (not a salt, Sec. 18.21) whose aqueous solution turns litmus blue—must almost certainly be an amine (Secs. 22.5 and 23.2). Elemental analysis shows the presence of nitrogen.

Whether an amine is primary, secondary, or tertiary is best shown by the **Hinsberg test**. The amine is shaken with benzenesulfonyl chloride in the presence of aqueous *potassium* hydroxide (Sec. 23.6). Primary and secondary amines form substituted sulfonamides; tertiary amines do not—*if* the test is carried out properly.

The monosubstituted sulfonamide from a primary amine has an acidic hydrogen attached to nitrogen. Reaction with potassium hydroxide converts this amide into a soluble salt which, *if the amine contained fewer than eight carbons*, is at least partly soluble. Acidification of this solution regenerates the insoluble amide.

The disubstituted sulfonamide from a secondary amine has no acidic hydrogen and remains insoluble in the alkaline reaction mixture.

What do we observe when we treat an amine with benzenesulfonyl chloride and excess potassium hydroxide? A *primary amine* yields a clear solution, from which, upon acidification, an insoluble material separates. A *secondary amine* yields an insoluble compound, which is unaffected by acid. A *tertiary amine* yields an insoluble compound (the unreacted amine itself) which dissolves upon acidification of the mixture.

$$\underset{\text{1° Amine}}{RNH_2} + C_6H_5SO_2Cl \xrightarrow{OH^-} [C_6H_5SO_2NHR] \xrightarrow{KOH} \underset{\textit{Clear solution}}{C_6H_5SO_2NR^-K^+} \xrightarrow{H^+} \underset{\textit{Insoluble}}{C_6H_5SO_2NHR}$$

$$R_2NH + C_6H_5SO_2Cl \xrightarrow{OH^-} C_6H_5SO_2NR_2 \xrightarrow{KOH \text{ or } H^+} \text{No reaction}$$

2° Amine — *Insoluble*

$$R_3N + C_6H_5SO_2Cl \xrightarrow{OH^-} R_3N \xrightarrow{HCl} R_3NH^+Cl^-$$

3° Amine — *Insoluble* — *Clear solution*

Like all experiments, the Hinsberg test must be done *carefully* and interpreted *thoughtfully*. Among other things, misleading side-reactions can occur if the proportions of reagents are incorrect, or if the temperature is too high or the time of reaction too long. Tertiary amines evidently *react*—after all, they are just as nucleophilic as other amines; but the initial product (I) has no acidic proton to

$$C_6H_5SO_2Cl + R_3N \longrightarrow \underset{\text{I}}{C_6H_5SO_2NR_3^+Cl^-} \xrightarrow{OH^-} C_6H_5SO_3^- + R_3N + Cl^-$$

ose, and ordinarily is hydrolyzed to regenerate the amine.

Problem 23.23 In non-aqueous medium, the product $C_6H_5SO_2N(CH_3)_3^+Cl^-$ can actually be isolated from the reaction of benzenesulfonyl chloride with one equivalent of trimethylamine. When *two* equivalents of the amine are used, there is formed, slowly, $C_6H_5SO_2N(CH_3)_2$ and $(CH_3)_4N^+Cl^-$. (a) Give all steps in a likely mechanism for this latter reaction. What fundamental type of reaction is probably involved?

(b) If, in carrying out the Hinsberg test, the reaction mixture is heated or allowed to stand, many primary amines give precipitates. What are these precipitates likely to be? What incorrect conclusion about the unknown amine are you likely to draw?

Problem 23.24 The sulfonamides of big primary amines are only partially soluble in aqueous KOH. (a) In the Hinsberg test, what incorrect conclusion might you draw about such an amine? (b) How might you modify the procedure to avoid this mistake?

Behavior toward nitrous acid (Sec. 23.10) is of some use in determining the class of an amine. In particular, the behavior of primary aromatic amines is quite characteristic: treatment with nitrous acid converts them into diazonium salts, which yield highly colored azo compounds upon treatment with β-naphthol (a phenol, see Sec. 23.17).

Among the numerous derivatives useful in identifying amines are: amides (e.g., acetamides, benzamides, or sulfonamides) for primary and secondary amines; quaternary ammonium salts (e.g., those from benzyl chloride or methyl iodide) for tertiary amines.

We have already discussed proof of structure by use of exhaustive methylation and elimination (Sec. 23.5).

23.19 Analysis of substituted amides

A substituted amide of a carboxylic acid is characterized by the presence of nitrogen, insolubility in dilute acid and dilute base, and hydrolysis to a carboxylic acid and an amine. It is generally identified through identification of its hydrolysis products (Secs. 18.21 and 23.18).

23.20 Spectroscopic analysis of amines and substituted amides

Infrared. The number and positions of absorption bands depend on the class to which the amine belongs (see Fig. 23.2).

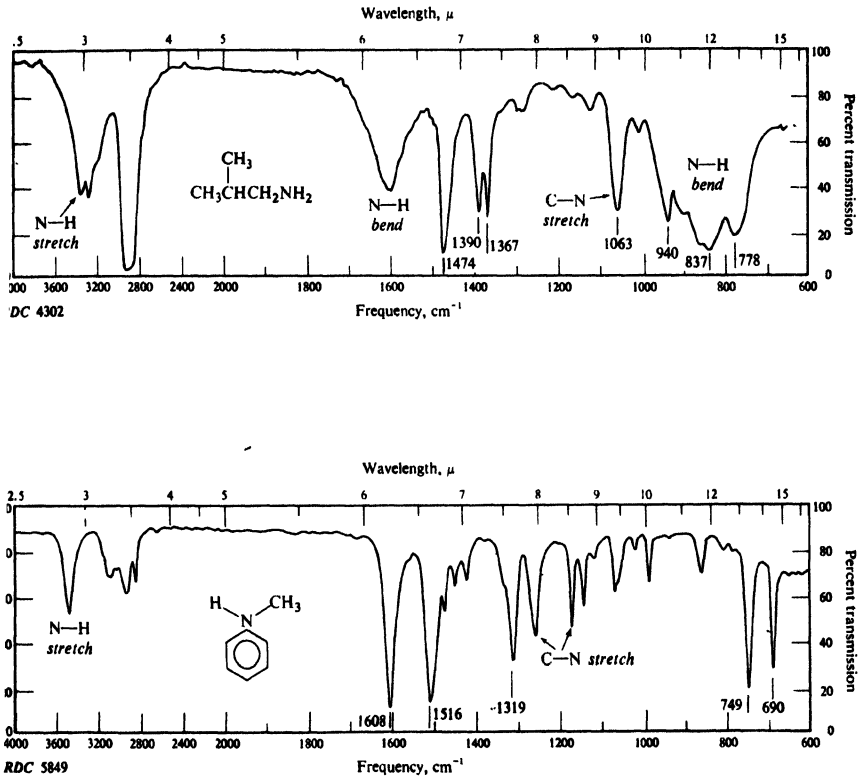


Figure 23.2. Infrared spectra of (*a*) isobutylamine and (*b*) N-methylaniline.

An amide, substituted or unsubstituted, shows the C O band in the 1640–1690 cm^{-1} region. In addition, if it contains a free N—H group, it will show N—H stretching at 3050–3550 cm^{-1}, and —NH bending at 1600–1640 cm^{-1} ($RCONH_2$) or 1530–1570 cm^{-1} (RCONHR′).

N—H stretching 3200–3500 cm^{-1}

1° Amines	2° Amines	3° Amines
Often two bands	*One band*	*No band*

N—H bending

1° Amines Strong bands 650–900 cm^{-1} (*broad*) and 1560–1650 cm^{-1}

C—N stretching

Aliphatic 1030–1230 cm^{-1} (*weak*) (3°: *usually a doublet*)

Aromatic 1180–1360 cm^{-1} (*strong*) *Two bands*

Nmr. Absorption by N—H protons of amines falls in the range δ 1–5, where it is often detected only by proton counting. Absorption by —CO—NH— protons of amides (Sec. 20.25) appears as a broad, low hump farther downfield (δ 5–8).

PROBLEMS

1. Write complete equations, naming all organic products, for the reaction (if any) of *n*-butylamine with:

(a) dilute HCl
(b) dilute H_2SO_4
(c) acetic acid
(d) dilute NaOH
(e) acetic anhydride
(f) isobutyryl chloride
(g) *p*-nitrobenzoyl chloride + pyridine
(h) benzenesulfonyl chloride + KOH (aq)
(i) ethyl bromide
(j) benzyl bromide
(k) bromobenzene
(l) excess methyl iodide, then Ag_2O
(m) product (l) + strong heat
(n) $CH_3COCH_3 + H_2 + Ni$
(o) HONO ($NaNO_2$ + HCl)
(p) phthalic anhydride
(q) sodium chloroacetate
(r) 2,4,6-trinitrochlorobenzene

2. Without referring to tables, arrange the compounds of each set in order of basicity:

(a) ammonia, aniline, cyclohexylamine
(b) ethylamine, 2-aminoethanol, 3-amino-1-propanol
(c) aniline, *p*-methoxyaniline, *p*-nitroaniline
(d) benzylamine, *m*-chlorobenzylamine, *m*-ethylbenzylamine
(e) *p*-chloro-N-methylaniline, 2,4-dichloro-N-methylaniline, 2,4,6-trichloro-N-methylaniline

3. Which is the more strongly basic, an aqueous solution of trimethylamine or an aqueous solution of tetramethylammonium hydroxide? Why? (*Hint:* What is the principal base in each solution?)

4. Compare the behavior of the three amines, aniline, N-methylaniline, and N,N-dimethylaniline, toward each of the following reagents:

(a) dilute HCl
(b) $NaNO_2$ + HCl (aq)
(c) methyl iodide
(d) benzenesulfonyl chloride + KOH (aq)
(e) acetic anhydride
(f) benzoyl chloride + pyridine
(g) bromine water

5. Answer Problem 4 for ethylamine, diethylamine, and triethylamine.

6. Give structures and names of the principal organic products expected from the action (if any) of sodium nitrite and hydrochloric acid on:

(a) *p*-toluidine
(b) N,N-diethylaniline
(c) *n*-propylamine
(d) sulfanilic acid
(e) N-methylaniline
(f) 2-amino-3-methylbutane
(g) benzidine (4,4′-diaminobiphenyl)
(h) benzylamine

7. Write equations for the reaction of *p*-nitrobenzenediazonium sulfate with:

(a) *m*-phenylenediamine
(b) hot dilute H_2SO_4
(c) HBr + Cu
(d) *p*-cresol
(e) KI
(f) CuCl
(g) CuCN
(h) HBF_4, then heat
(i) H_3PO_2

8. Give the reagents and any special conditions necessary to convert *p*-toluenediazonium chloride into:

(a) toluene
(b) *p*-cresol, p-$CH_3C_6H_4OH$
(c) *p*-chlorotoluene
(d) *p*-bromotoluene
(e) *p*-iodotoluene
(f) *p*-fluorotoluene
(g) *p*-tolunitrile, p-$CH_3C_6H_4CN$
(h) 4-methyl-4′-(N,N-dimethylamino)azobenzene
(i) 2,4-dihydroxy-4′-methylazobenzene

9. Write balanced equations, naming all organic products, for the following reactions:

(a) *n*-butyryl chloride + methylamine
(b) acetic anhydride + N-methylaniline
(c) tetra-*n*-propylammonium hydroxide + heat
(d) isovaleryl chloride + diethylamine
(e) tetramethylammonium hydroxide + heat
(f) trimethylamine + acetic acid
(g) N,N-dimethylacetamide + boiling dilute HCl
(h) benzanilide + boiling aqueous NaOH
(i) methyl formate + aniline
(j) excess methylamine + phosgene ($COCl_2$)
(k) m-$O_2NC_6H_4NHCH_3 + NaNO_2 + H_2SO_4$
(l) aniline + Br_2 (aq) in excess
(m) *m*-toluidine + Br_2 (aq) in excess
(n) *p*-toluidine + Br_2 (aq) in excess
(o) *p*-toluidine + $NaNO_2$ + HCl
(p) $C_6H_5NHCOCH_3 + HNO_3 + H_2SO_4$
(q) p-$CH_3C_6H_4NHCOCH_3 + HNO_3 + H_2SO_4$
(r) p-$C_2H_5C_6H_4NH_2$ + large excess of CH_3I
(s) benzanilide + Br_2 + Fe

10. Outline all steps in 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) 4-amino-2-bromotoluene
(b) 4-amino-3-bromotoluene
(c) *p*-aminobenzenesulfonanilide (p-$H_2NC_6H_4SO_2NHC_6H_5$)
(d) monoacetyl *p*-phenylenediamine (*p*-aminoacetanilide)
(e) *p*-nitroso-N,N-diethylaniline
(f) 4-amino-3-nitrobenzoic acid
(g) 2,6-dibromo-4-isopropylaniline
(h) *p*-aminobenzylamine
(i) N-nitroso-N-isopropylaniline
(j) N-ethyl-N-methyl-*n*-valeramide
(k) *n*-hexylamine
(l) 1-amino-1-phenylbutane
(m) aminoacetamide
(n) hippuric acid ($C_6H_5CONHCH_2COOH$)

11. Outline all steps in a possible laboratory synthesis from benzene, toluene, and any needed inorganic reagents of:

(a) the six isomeric dibromotoluenes, $CH_3C_6H_3Br_2$. (*Note:* One may be more difficult to make than any of the others.)
(b) the three isomeric chlorobenzoic acids, each one free of the others
(c) the three isomeric bromofluorobenzenes

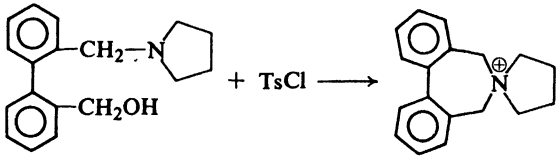
Review the instructions on page 224. Assume that an *ortho,para* mixture of isomeric nitro compounds can be separated by distillation (see Sec. 11.7).

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

(a) *p*-fluorotoluene
(b) *m*-fluorotoluene
(c) *p*-iodobenzoic acid
(d) *m*-bromoaniline
(e) 3-bromo-4-methylbenzoic acid
(f) 2-bromo-4-methylbenzoic acid
(g) *m*-ethylphenol
(h) 3,5-dibromoaniline
(i) 3-bromo-4-iodotoluene
(j) 2-amino-4-methylphenol
(k) 2,6-dibromoiodobenzene
(l) 4-iodo-3-nitrotoluene
(m) *p*-hydroxyphenylacetic acid
(n) 2-bromo-4-chlorotoluene

13. When adipic acid (hexanedioic acid) and hexamethylenediamine (1,6-diaminohexane) are mixed, a salt is obtained. On heating, this salt is converted into Nylon 66, a high-molecular-weight compound of formula $(C_{12}H_{22}O_2N_2)_n$. (a) Draw the structural formula for Nylon 66. To what class of compounds does it belong? (b) Write an equation for the chemistry involved when a drop of hydrochloric acid makes a hole in a Nylon 66 stocking.

14. Account for the following reactions, making clear the role played by tosyl chloride.



15. If halide ion is present during hydrolysis of benzenediazonium ion or *p*-nitrobenzenediazonium ion, there is obtained not only the phenol, but also the aryl halide: the higher the halide ion concentration, the greater the proportion of aryl halide obtained. The presence of halide ion has no effect on the rate of decomposition of benzenediazonium ion, but speeds up decomposition of the *p*-nitrobenzenediazonium ion.

(a) Suggest a mechanism or mechanisms to account for these facts. (b) What factor is responsible for the unusually high reactivity of diazonium ions in this reaction—and, indeed, in most of their reactions? (*Hint:* See Sec. 14.5.)

16. Describe simple chemical tests (other than color reactions with indicators) that would serve to distinguish between:

(a) N-methylaniline and *o*-toluidine
(b) aniline and cyclohexylamine
(c) n-$C_4H_9NH_2$ and $(n\text{-}C_4H_9)_2NH$
(d) $(n\text{-}C_4H_9)_2NH$ and $(n\text{-}C_4H_9)_3N$
(e) $(CH_3)_3NHCl$ and $(CH_3)_4NCl$
(f) $C_6H_5NH_3Cl$ and o-$ClC_6H_4NH_2$
(g) $(C_2H_5)_2NCH_2CH_2OH$ and $(C_2H_5)_4NOH$
(h) aniline and acetanilide
(i) $(C_6H_5NH_3)_2SO_4$ and p-$H_3\overset{+}{N}C_6H_4SO_3^-$
(j) $ClCH_2CH_2NH_2$ and $CH_3CH_2NH_3Cl$
(k) 2,4,6-trinitroaniline and aniline
(l) $C_6H_5NHSO_2C_6H_5$ and $C_6H_5NH_3HSO_4$

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

17. Describe simple chemical methods for the separation of the following mixtures, recovering each component in essentially pure form:

(a) triethylamine and *n*-heptane
(b) aniline and anisole
(c) stearamide and octadecylamine
(d) o-$O_2NC_6H_4NH_2$ and p-$H_3\overset{+}{N}C_6H_4SO_3^-$
(e) $C_6H_5NHCH_3$ and $C_6H_5N(CH_3)_2$
(f) *n*-caproic acid, tri-*n*-propylamine, and cyclohexane
(g) *o*-nitrotoluene and *o*-toluidine
(h) *p*-ethylaniline and propionanilide

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

18. The compounds in each of the following sets boil (or melt) within a few degrees of each other. Describe simple chemical tests that would serve to distinguish among the members of each set.

(a) aniline, benzylamine, and N,N-dimethylbenzylamine
(b) *o*-chloroacetanilide and 2,4-diaminochlorobenzene
(c) N-ethylbenzylamine, N-ethyl-N-methylaniline, β-phenylethylamine, and *o*-toluidine
(d) acetanilide and ethyl oxamate ($C_2H_5OOCCONH_2$)

(e) benzonitrile, N,N-dimethylaniline, and formamide
(f) N,N-dimethyl-*m*-toluidine, nitrobenzene, and *m*-tolunitrile
(g) N-(*sec*-butyl)benzenesulfonamide

p-chloroaniline	*o*-nitroaniline
N,N-dibenzylaniline	*p*-nitrobenzyl chloride
2,4-dinitroaniline	*p*-toluenesulfonyl chloride

N-ethyl-N-(*p*-tolyl)-*p*-toluenesulfonamide

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

19. An unknown amine is believed to be one of those in Table 23.2. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible use simple chemical tests.

Table 23.2 DERIVATIVES OF SOME AMINES

Amine	B.p., °C	Benzene-sulfonamide M.p., °C	Acetamide M.p., °C	Benzamide M.p., °C	*p*-Toluene-sulfonamide M.p., °C
m-Toluidine	203	95	66	125	114
N-Ethylaniline	205		54	60	87
N-Methyl-*m*-toluidine	206		66		
N,N-Diethyl-*o*-toluidine	206				
N-Methyl-*o*-toluidine	207		55	66	120
N-Methyl-*p*-toluidine	207	64	83	53	60
N,N-Dimethyl-*o*-chloroaniline	207				
o-Chloroaniline	209	129	87	99	105

20. *Choline*, a constituent of *phospholipids* (fat-like phosphate esters of great physiological importance), has the formula $C_5H_{15}O_2N$. It dissolves readily in water to form a strongly basic solution. It can be prepared by the reaction of ethylene oxide with trimethylamine in the presence of tarer.

(a) What is a likely structure for choline? (b) What is a likely structure for its acetyl derivative, *acetylcholine*, $C_7H_{17}O_3N$, important in nerve action?

21. *Novocaine*, a local anesthetic, is a compound of formula $C_{13}H_{20}O_2N_2$. It is insoluble in water and dilute NaOH, but soluble in dilute HCl. Upon treatment with $NaNO_2$ and HCl and then with β-naphthol, a highly colored solid is formed.

When Novocaine is boiled with aqueous NaOH, it slowly dissolves. The alkaline solution is shaken with ether and the layers are separated.

Acidification of the aqueous layer causes the precipitation of a white solid A; continued addition of acid causes A to redissolve. Upon isolation A is found to have a melting point of 185–6° and the formula $C_7H_7O_2N$.

Evaporation of the ether layer leaves a liquid B of formula $C_6H_{15}ON$. B dissolves in water to give a solution that turns litmus blue. Treatment of B with acetic anhydride gives C, $C_8H_{17}O_2N$, which is insoluble in water and dilute base, but soluble in dilute HCl.

B is found to be identical with the compound formed by the action of diethylamine on ethylene oxide.

(a) What is the structure of Novocaine? (b) Outline all steps in a complete synthesis of Novocaine from toluene and readily available aliphatic and inorganic reagents.

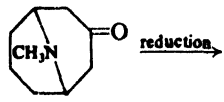
22. A solid compound D, of formula $C_{15}H_{15}ON$, was insoluble in water, dilute HCl, or dilute NaOH. After prolonged heating of D with aqueous NaOH, a liquid, E, was observed floating on the surface of the alkaline mixture. E did not solidify upon cooling to room temperature; it was steam-distilled and separated. Acidification of the alkaline mixture with hydrochloric acid caused precipitation of a white solid, F.

Compound E was soluble in dilute HCl, and reacted with benzenesulfonyl chloride and excess KOH to give a base-insoluble solid, G.

Compound F, m.p. 180°, was soluble in aqueous $NaHCO_3$, and contained no nitrogen.

What were compounds D, E, F, and G?

23. Give the structures of compounds H through Q:



H($C_9H_{17}ON$, an alcohol)

H + heat ⟶ I ($C_9H_{15}N$)
I + CH_3I, then Ag_2O ⟶ J ($C_{10}H_{19}ON$)
J + heat ⟶ K ($C_{10}H_{17}N$)
K + CH_3I, then Ag_2O ⟶ L ($C_{11}H_{21}ON$)
L + heat ⟶ M (C_8H_{10})
M + Br_2 ⟶ N ($C_8H_{10}Br_2$)
N + $(CH_3)_2NH$ ⟶ O ($C_{12}H_{26}N_2$)
O + CH_3I, then Ag_2O ⟶ P ($C_{14}H_{30}O_2N_2$)
P + heat ⟶ Q (C_8H_8)

24. *Pantothenic acid*, $C_9H_{17}O_5N$ occurs in Coenzyme A (p. 1173), essential to metabolism of carbohydrates and fats. It reacts with dilute NaOH to give $C_9H_{16}O_5NNa$, with ethyl alcohol to give $C_{11}H_{21}O_5N$, and with hot NaOH to give compound V (see below) and β-aminopropionic acid. Its nitrogen is non-basic. Pantothenic acid has been synthesized as follows:

isobutyraldehyde + formaldehyde + K_2CO_3 ⟶ R ($C_5H_{10}O_2$)
R + $NaHSO_3$, then KCN ⟶ S ($C_6H_{11}O_2N$)
S + H_2O, H^+, heat ⟶ [T ($C_6H_{12}O_4$)] ⟶ U ($C_6H_{10}O_3$)
U + NaOH(aq), warm ⟶ V ($C_6H_{11}O_4Na$)
U + sodium β-aminopropionate, then H^+ ⟶ pantothenic acid ($C_9H_{17}O_5N$)

What is the structure of pantothenic acid?

25. An unknown compound W contained chlorine and nitrogen. It dissolved readily in water to give a solution that turned litmus red. Titration of W with standard base gave a neutralization equivalent of 131 ± 2.

When a sample of W was treated with aqueous NaOH a liquid separated; it contained nitrogen but not chlorine. Treatment of the liquid with nitrous acid followed by β-naphthol gave a red precipitate.

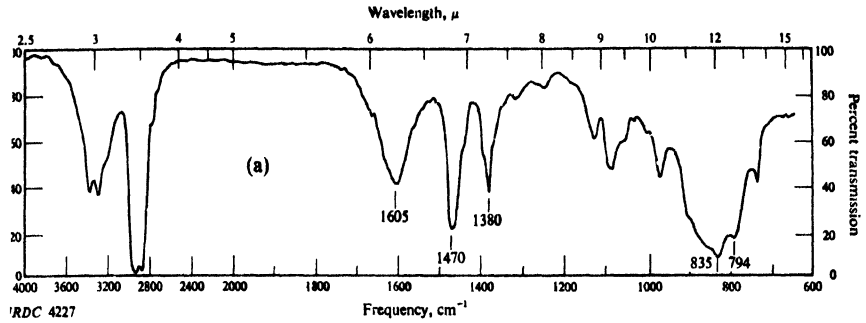
What was W? Write equations for all reactions.

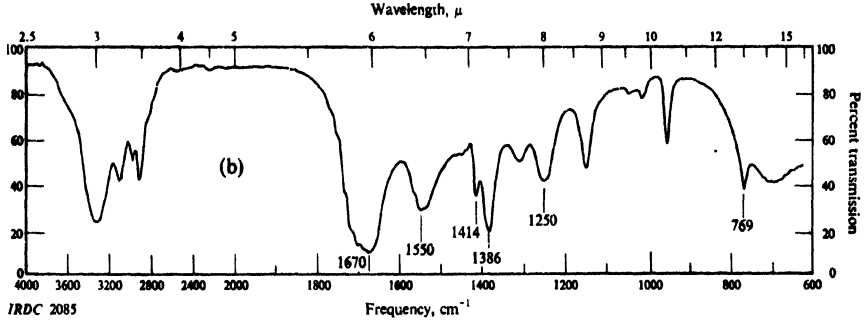
26. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 23.3 (p. 783)?

n-butylamine	*o*-anisidine
diethylamine	*m*-anisidine
N-methylformamide	aniline
N,N-dimethylformamide	N,N-dimethyl-*o*-toluidine
2-(dimethylamino)ethanol	acetanilide

27. Give a structure or structures consistent with each of the nmr spectra shown in Fig. 23.4 (p. 784).

28. Give the structures of compounds X, Y, and Z on the basis of their infrared spectra (Fig. 23.5, p. 785) and their nmr spectra (Fig. 23.6, p. 786).





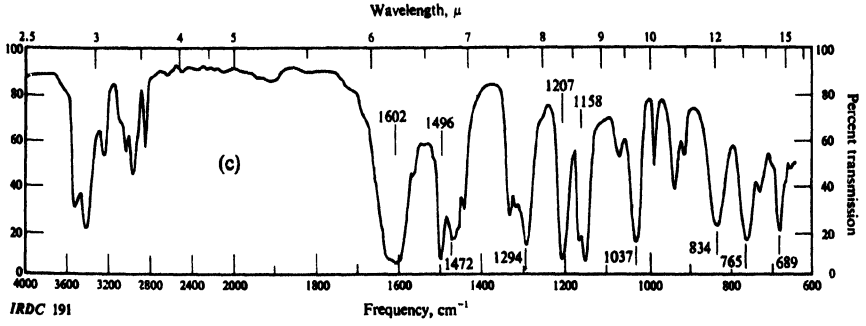


Figure 23.3. Infrared spectra for Problem 26, p. 782.

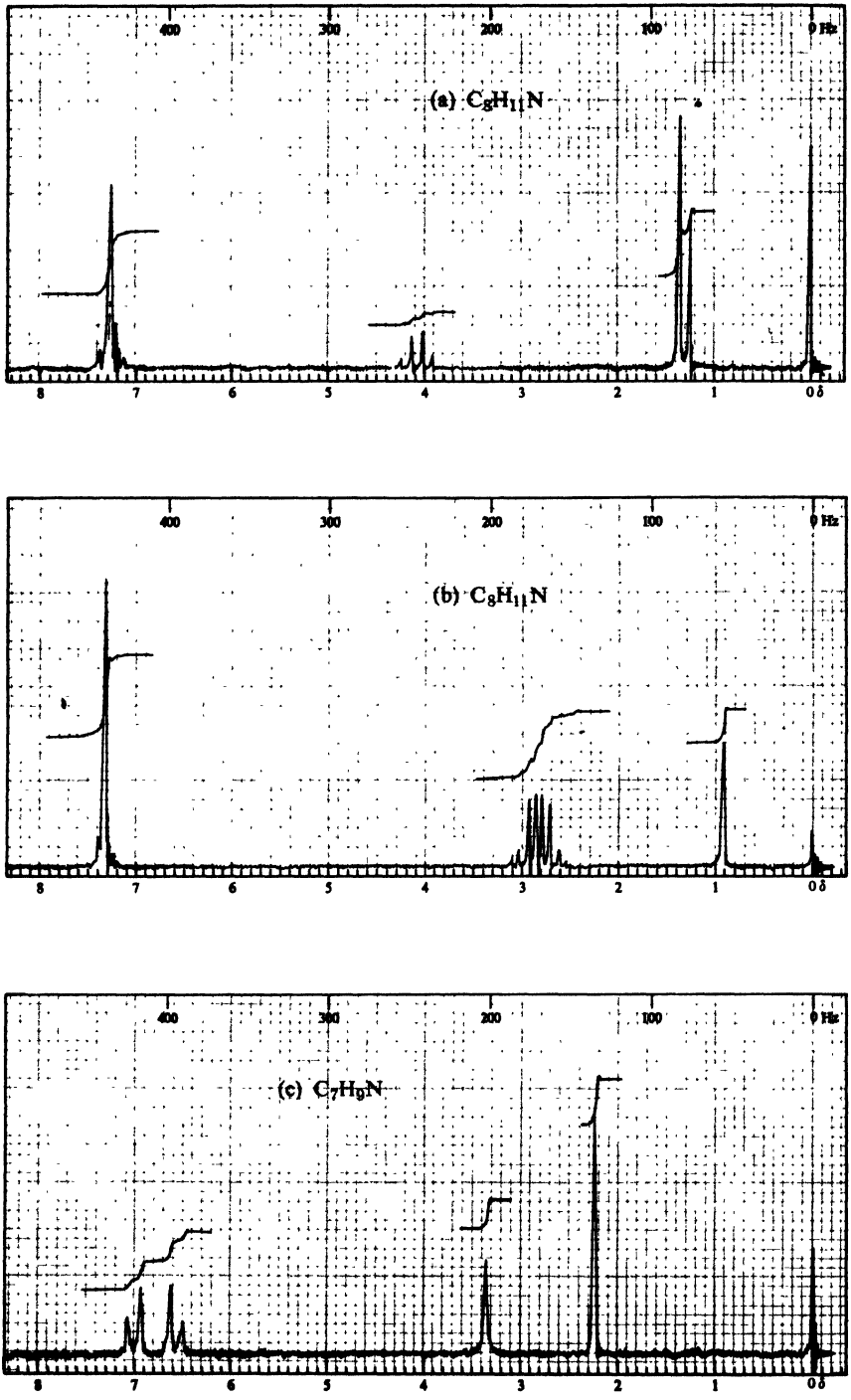
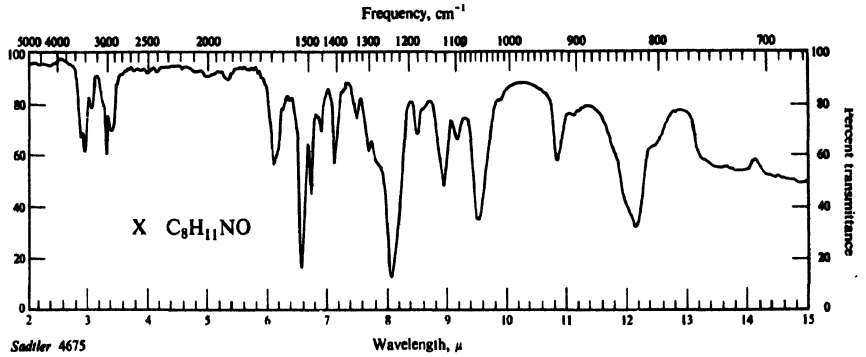
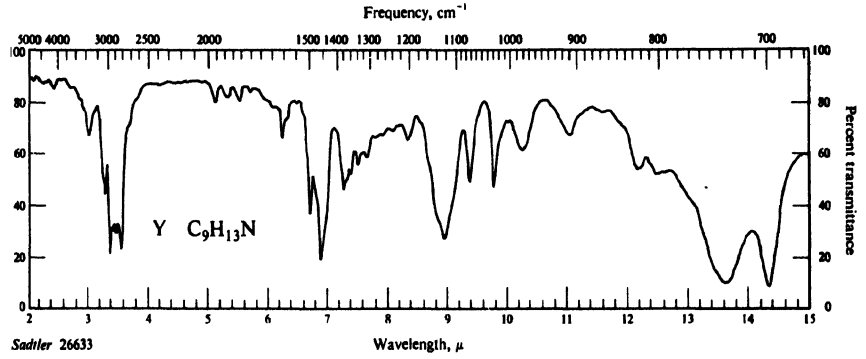


Figure 23.4. Nmr spectra for Problem 27, p. 782.





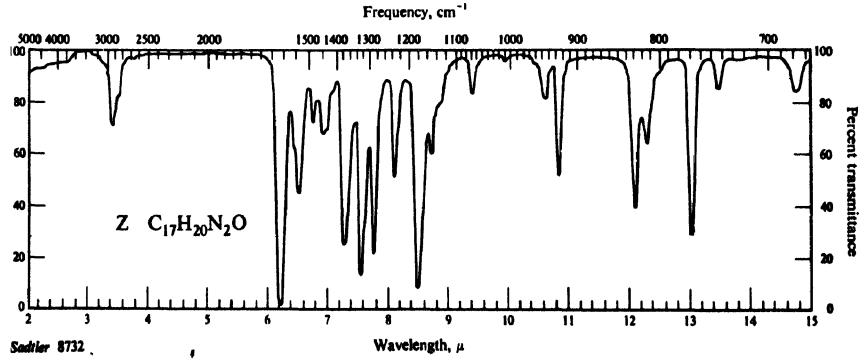


Figure 23.5. Infrared spectra for Problem 28, p. 782.

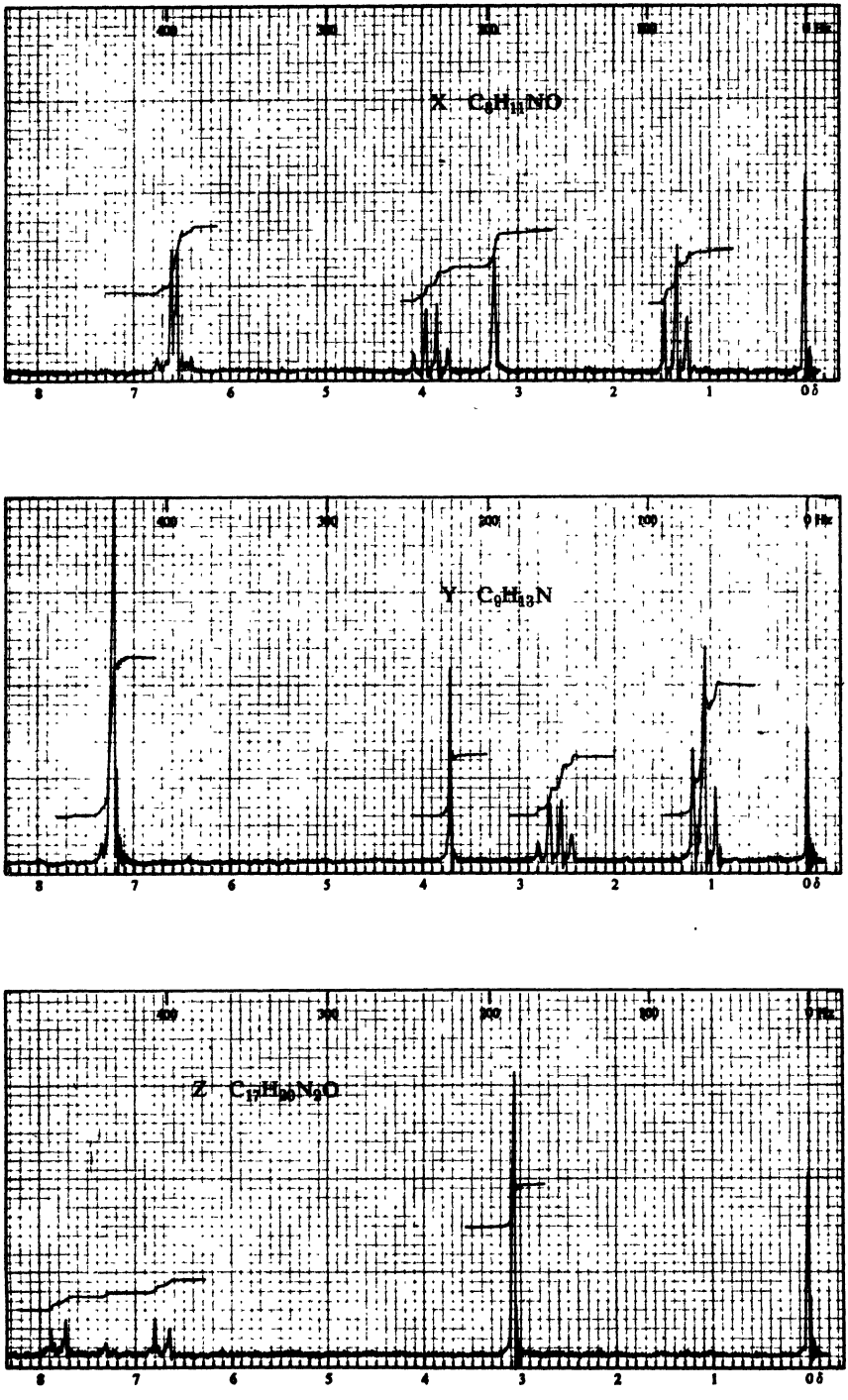


Figure 23.6. Nmr spectra for Problem 28, p. 782.