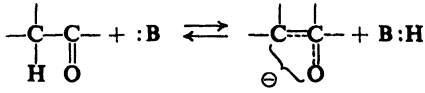
Chapter 21 Carbanions I

Aldol and Claisen Condensations

21.1 Acidity of α-hydrogens

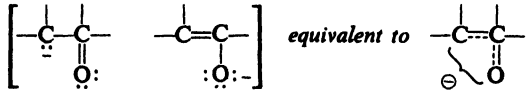
In our introduction to aldehydes and ketones, we learned that it is the carbonyl group that largely determines the chemistry of aldehydes and ketones. At that time, we saw in part how the carbonyl group does this: by providing a site at which nucleophilic addition can take place. Now we are ready to learn another part of the story: how the carbonyl group strengthens the acidity of the hydrogen atoms attached to the α-carbon and, by doing this, gives rise to a whole set of chemical reactions.

Ionization of an α-hydrogen,



I

yields a carbanion I that is a resonance hybrid of two structures II and III,



II III I

resonance that is possible only through participation by the carbonyl group. Resonance of this kind is *not* possible for carbanions formed by ionization of β-hydrogens, γ-hydrogens, etc., from saturated carbonyl compounds.

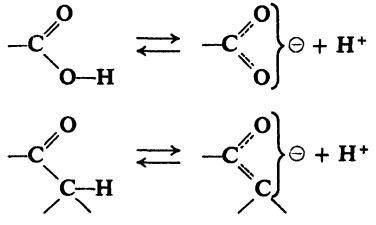
Problem 21.1 Which structure, II or III, would you expect to make the larger contribution to the carbanion I? Why?

Problem 21.2 Account for the fact that the diketone acetylacetone (2,4-pentanedione) is about as acidic as phenol, and much more acidic than, say, acetone. Which hydrogens are the most acidic?

Problem 21.3 How do you account for the following order of acidity?

$$(C_6H_5)_3CH > (C_6H_5)_2CH_2 > C_6H_5CH_3 > CH_4$$

The carbonyl group thus affects the acidity of α-hydrogens in just the way it affects the acidity of carboxylic acids: by helping to accommodate the negative charge of the anion.

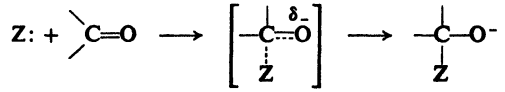


I

Resonance in I involves structures (II and III) of quite different stabilities, and hence is much less important than the resonance involving equivalent structures in a carboxylate ion. Compared with the hydrogen of a —COOH group, the α-hydrogen atoms of an aldehyde or ketone are very weakly acidic; the important thing is that they are considerably more acidic than hydrogen atoms anywhere else in the molecule, and that they are acidic enough for *significant*—even though very low—concentrations of carbanions to be generated.

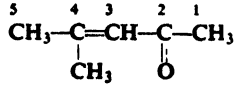
We shall use the term *carbanion* to describe ions like I since *part* of the charge is carried by carbon, even though the stability that gives these ions their importance is due to the very fact that most of the charge is *not* carried by carbon but by oxygen.

We saw before (Sec. 19.8) that the susceptibility of the carbonyl group to nucleophilic attack is due to the ability of oxygen to accommodate the negative charge that develops as a result of the attack,



precisely the same property of oxygen that underlies the acidity of α-hydrogens. We have started with two apparently unrelated chemical properties of carbonyl compounds and have traced them to a common origin—an indication of the simplicity underlying the seeming confusion of organic chemistry.

Problem 21.4 In the reaction of aqueous NaCN with an α,β-unsaturated ketone like



CN^- adds, not to C-2, but to C-4. (a) How do you account for this behavior?

(b) What product would you expect to isolate from the reaction mixture? (*Hint:* See Secs. 19.12 and 8.20.) (Check your answers in Sec. 27.5.)

21.2 Reactions involving carbanions

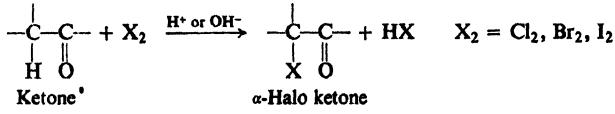
The carbonyl group occurs in compounds other than aldehydes and ketones—in esters, for example—and, wherever it is, it makes any α-hydrogens acidic and thus aids in formation of carbanions. Since these α-hydrogens are only weakly acidic, however, the carbanions are highly basic, exceedingly reactive particles. In their reactions they behave as we would expect: as *nucleophiles*. As nucleophiles, carbanions can attack carbon and, in doing so, form carbon–carbon bonds. *From the standpoint of synthesis, acid-strengthening by carbonyl groups is probably the most important structural effect in organic chemistry.*

We shall take up first the behavior of ketones toward the halogens, and see evidence that carbanions do indeed exist; at the same time, we shall see an elegant example of the application of kinetics, stereochemistry, and isotopic tracers to the understanding of reaction mechanisms. And while we are at it, we shall see something of the role that keto–enol tautomerism plays in the chemistry of carbonyl compounds.

Next, we shall turn to reactions in which the carbonyl group plays *both* its roles: the *aldol condensation*, in which a carbanion generated from one molecule of aldehyde or ketone adds, as a nucleophile, to the carbonyl group of a second molecule; and the *Claisen condensation*, in which a carbanion generated from one molecule of ester attacks the carbonyl group of a second molecule, with acyl substitution as the final result.

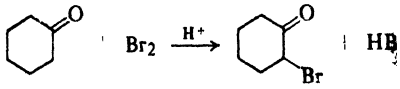
REACTIONS INVOLVING CARBANIONS

1. Halogenation of ketones. Discussed in Secs. 21.3–21.4.

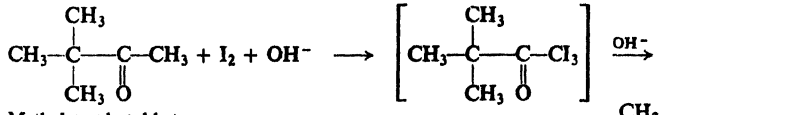


Ketone* α-Halo ketone

Examples:



Cyclohexanone 2-Bromocyclohexanone



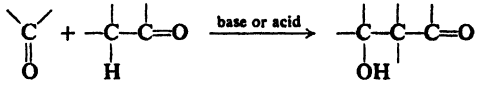
Methyl *tert*-butyl ketone (3,3-Dimethyl-2-butanone)

Iodoform

Trimethylacetate ion

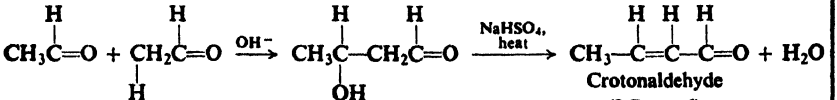
2. Nucleophilic addition to carbonyl compounds.

(a) Aldol condensation. Discussed in Secs. 21.5–21.8.

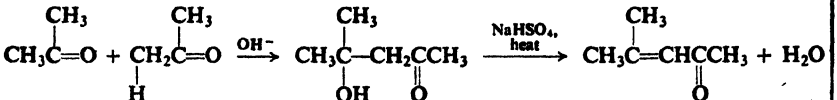


An aldol
(A β-hydroxy carbonyl compound)

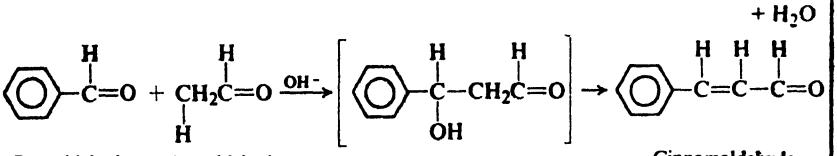
Examples:



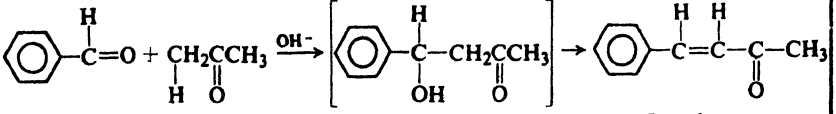
Acetaldehyde (*2 moles*) → Acetaldol (3-Hydroxybutanal) → Crotonaldehyde (2-Butenal)



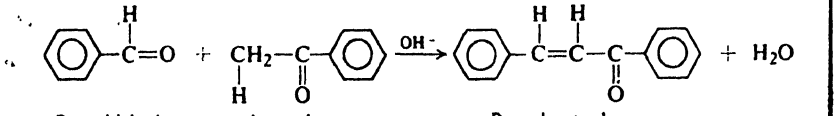
Acetone (*2 moles*) → Diacetone alcohol → Mesityl oxide (4-Methyl-3-penten-2-one)



Benzaldehyde + Acetaldehyde → Cinnamaldehyde (3-Phenyl-2-propenal)



Benzaldehyde + Acetone → Benzalacetone (*Benzal* is $C_6H_5CH=$) (4-Phenyl-3-buten-2-one)



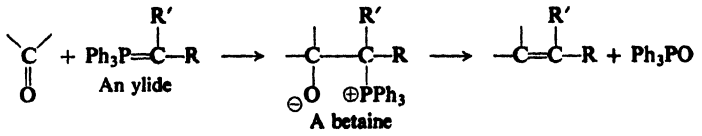
Benzaldehyde + Acetophenone → Benzalacetophenone (1,3-Diphenyl-2-propen-1-one)

(b) Reactions related to aldol condensation. Discussed in Sec. 21.9.

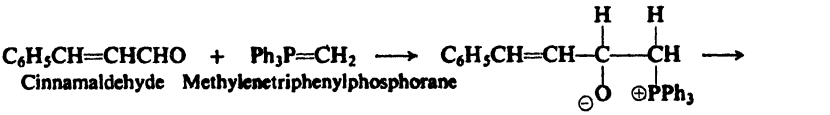
(c) Addition of Grignard reagents. Discussed in Sec. 19.11.

(d) Addition of organozinc compounds. Reformatsky reaction. Discussed in Sec. 21.13.

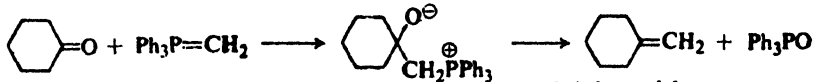
(e) **Wittig reaction.** Discussed in Sec. 21.10.



Examples:



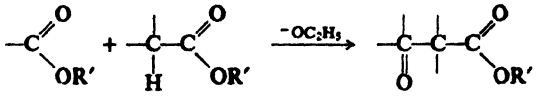
$C_6H_5CH{=}CH{-}CH{=}CH_2$
1-Phenyl-1,3-butadiene
(69%)



Cyclohexanone — Methylenecyclohexane (48%)

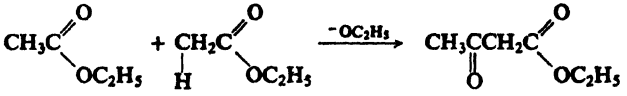
3. **Nucleophilic acyl substitution.**

(a) **Claisen condensation.** Discussed in Secs. 21.11–21.12.

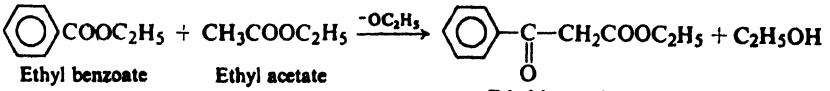


A β-keto ester

Examples:



Ethyl acetate (2 moles) — Ethyl acetoacetate



Ethyl benzoate — Ethyl acetate — Ethyl benzoylacetate

(b) **Acylation of organocadmium compounds.** Discussed in Sec. 19.7.

4. **Nucleophilic aliphatic substitution.**

(a) **Coupling of alkyl halides with organometallic compounds.** Discussed in Sec. 3.17.

(b) Synthesis of acetylides. Discussed in Sec. 8.12.

(c) Alkylation of malonic ester and acetoacetic ester. Discussed in Secs. 26.2–26.3.

5. Addition to α,β-unsaturated carbonyl compounds. Michael addition. Discussed in Sec. 27.7.

21.3 Base-promoted halogenation of ketones

Acetone reacts with bromine to form bromoacetone; the reaction is accelerated by bases (e.g., hydroxide ion, acetate ion, etc.). Study of the kinetics shows that

$$\underset{\text{Acetone}}{CH_3COCH_3} + Br_2 + :B \longrightarrow \underset{\text{Bromoacetone}}{CH_3COCH_2Br} + Br^- + H:B$$

the rate of reaction depends upon the concentration of acetone, [acetone], and of base, [:B], but is *independent of bromine concentration*:

$$\text{rate} = k\,[\text{acetone}][:B]$$

We have encountered this kind of situation before (Sec. 14.12) and know, in a general way, what it must mean: if the rate of reaction does not depend upon $[Br_2]$, it can only mean that the reaction *whose rate we are measuring* does not involve Br_2.

The kinetics is quite consistent with the following mechanism. The base

(1) $CH_3\overset{\overset{O}{\|}}{C}CH_3 + :B \rightleftharpoons H:B + CH_3C(=O)\overset{\ominus}{C}H_2$ (I) **Slow:** *rate-determining*

(2) $CH_3C(=O)\overset{\ominus}{C}H_2 + Br_2 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}CH_2Br + Br^-$ **Fast**

slowly abstracts a proton (step 1) from acetone to form carbanion. I, which then reacts rapidly with bromine (step 2) to yield bromoacetone. Step (1), generation of the carbanion. is the rate-determining step, since its rate determines the overall rate of the reaction sequence. As fast as carbanions are generated, they are snapped up by bromine molecules.

Strong support for this interpretation comes from the kinetics of iodination. Here. too, the rate of reaction depends upon [acetone] and [:B] but is independent of $[I_2]$. Furthermore, and most significant, at a given [acetone] and [:B], bromination and iodination *proceed at identical rates*. That is to say, in the rate expression

$$\text{rate} = k\,[\text{acetone}][:B]$$

the value of k is the same regardless of which halogen is involved. It *should* be, of course, according to the proposed mechanism, since in both cases it is the rate constant for the same reaction, abstraction of a proton from the ketone.

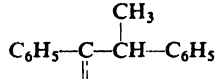
Study of the bromination of acetone, done by A. Lapworth (of the University of

Manchester) in 1904, showed for the first time how kinetics could be used to reveal the mechanism of an organic reaction. The carbanion mechanism has since been confirmed not only by the iodination work, but also by studies of stereochemistry and isotopic exchange.

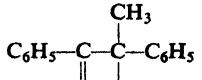
Problem 21.5 Show in detail exactly how each of the following facts provides evidence for the carbanion mechanism of base-promoted halogenation of ketones.

(a) In basic solution, (+)-phenyl *sec*-butyl ketone undergoes racemization; the rate constant for loss of optical activity is identical with the rate constant for bromination of this ketone.

(b) Ketone II undergoes racemization in basic solution, but ketone III does not.



II



III

(c) When (+)-phenyl *sec*-butyl ketone is allowed to stand in D_2O containing OD^-, it not only undergoes racemization, but also becomes labeled with deuterium at the α-position; the rate constants for racemization and hydrogen exchange are identical.

Problem 21.6 (a) Suggest a mechanism for the base-catalyzed racemization of the optically active ester, ethyl mandelate, $C_6H_5CHOHCOOC_2H_5$. (b) How do you account for the fact that optically active mandelic acid undergoes racemization in base *much more slowly* than the ester? (*Hint:* See Sec. 18.20.) (c) What would you predict about the rate of base-catalyzed racemization of α-methylmandelic acid, $C_6H_5C(CH_3)(OH)COOH$?

Problem 21.7 Suppose, as an alternative to the carbanion mechanism, that hydrogen exchange and racemization were both to arise by some kind of direct displacement of one hydrogen (H) by another (D) with inversion of configuration. What relationship would you then expect between the rates of racemization and exchange? (*Hint:* Take one molecule at a time, and see what happens when H is replaced by D with inversion.)

21.4 Acid-catalyzed halogenation of ketones. Enolization

Acids, like bases, speed up the halogenation of ketones. Acids are not, however, consumed, and hence we may properly speak of acid-*catalyzed* halogenation (as contrasted to base-*promoted* halogenation). Although the reaction is not,

$$\underset{\text{Acetone}}{CH_3COCH_3} + Br_2 \xrightarrow{\text{acid}} \underset{\text{Bromoacetone}}{CH_3COCH_2Br} + HBr$$

strictly speaking, a part of carbanion chemistry, this is perhaps the best place to take it up, since it shows a striking parallel in every aspect to the base-promoted reaction we have just left.

Here, too, the kinetics show the rate of halogenation to be independent of halogen concentration, but dependent upon ketone concentration and, this time, acid concentration. Here, too, we find the remarkable identity of rate constants for apparently different reactions: for bromination and iodination of acetone, and exchange of its hydrogens for deuterium; for iodination and racemization of phenyl *sec*-butyl ketone.

The interpretation, too, is essentially the same as the one we saw before: *preceding* the step that involves halogen, there is a rate-determining reaction that can lead not only to halogenation but also to racemization and to hydrogen exchange.

The rate-determining reaction here is the formation of the *enol*, which involves two steps: rapid, reversible protonation (step 1) of the carbonyl oxygen, followed by the slow loss of an α-hydrogen (step 2).

(1) $CH_3-\underset{\underset{O}{\|}}{C}-CH_3 + H{:}B \rightleftharpoons CH_3-\underset{\underset{+OH}{\|}}{C}-CH_3 + {:}B$ **Fast**

(2) $CH_3-\underset{\underset{+OH}{\|}}{C}-CH_3 + {:}B \longrightarrow CH_3-\underset{\underset{OH}{|}}{C}=CH_2 + H{:}B$ **Slow**

Enol

(3) $CH_3-\underset{\underset{OH}{|}}{C}=CH_2 + X_2 \longrightarrow CH_3-\underset{\underset{+OH}{\|}}{C}-CH_2X + X^-$ **Fast**

I

(4) $CH_3-\underset{\underset{+OH}{\|}}{C}-CH_2X + {:}B \rightleftharpoons CH_3-\underset{\underset{O}{\|}}{C}-CH_2X + H{:}B$ **Fast**

Once formed, the enol reacts rapidly with halogen (step 3). We might have expected the unsaturated enol to undergo addition and, indeed, the reaction starts out exactly as though this were going to happen: positive halogen attaches itself to form a cation. As usual (Sec. 6.11), attachment occurs in the way that yields the more stable cation.

The ion formed in this case, I, is an exceedingly stable one, owing its stability to the fact that it is hardly a "carbonium" ion at all, since oxygen can carry the charge and still have an octet of electrons. The ion is, actually, a protonated ketone; loss of the proton yields the product, bromoacetone.

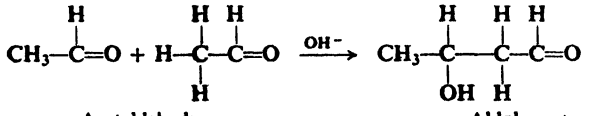
We may find it odd, considering that we call this reaction "acid-catalyzed," that the rate-determining step (2) is really the same as in the base-promoted reaction: abstraction of an α-hydrogen by a base—here, by the conjugate base of the catalyzing acid. Actually, what we see here must always hold true: a reaction that is truly *catalyzed* by acid or base is catalyzed by *both acid and base*. In our case, transfer of the proton from the acid H:B to carbonyl oxygen (step 1) makes the ketone more reactive and hence speeds up enolization. But, if this is truly catalysis, the acid must not be *consumed*. Regeneration of the acid H:B requires that the conjugate base :B get a proton from somewhere; it takes it from the α-carbon (step 2), and thus completes the enolization. Both acid and base speed up the rate-determining step (2): base directly, as one of the reactants, and acid indirectly, by increasing the concentration of the other reactant, the protonated ketone. Using a strong mineral acid in aqueous solution, we would not be aware of the role played by the base; the acid is H_3O^+ and the conjugate base, H_2O, is the solvent.

Problem 21.8 Show in detail how the enolization mechanism accounts for the following facts: (a) the rate constants for acid-catalyzed hydrogen–deuterium exchange and bromination of acetone are identical; (b) the rate constants for acid-catalyzed racemization and iodination of phenyl *sec*-butyl ketone are identical.

Problem 21.9 (a) In the acid-catalyzed dehydration of alcohols (Sec. 5.20), what is the base involved? (b) In the base-catalyzed racemization and hydrogen exchange of phenyl *sec*-butyl ketone (Problem 21.5, p. 707), what is the acid involved?

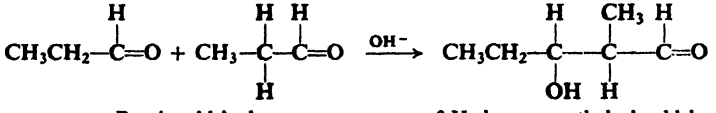
21.5 Aldol condensation

Under the influence of dilute base or dilute acid, two molecules of an aldehyde or a ketone may combine to form a β-hydroxyaldehyde or β-hydroxyketone. This reaction is called the **aldol condensation**. In every case the product results from addition of one molecule of aldehyde (or ketone) to a second molecule in such a way that the α-carbon of the first becomes attached to the carbonyl carbon of the second. For example:



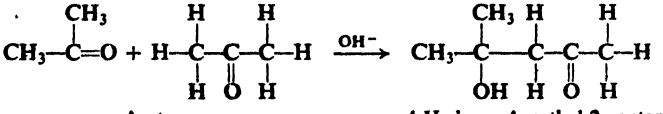
Acetaldehyde
2 moles

Aldol
(β-Hydroxybutyraldehyde)
(3-Hydroxybutanal)



Propionaldehyde
2 moles

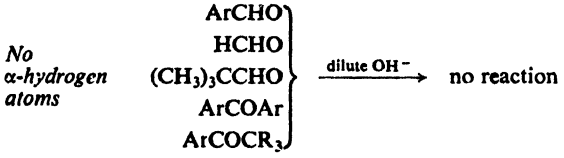
β-Hydroxy-α-methylvaleraldehyde
(3-Hydroxy-2-methylpentanal)



Acetone
2 moles

4-Hydroxy-4-methyl-2-pentanone
(Diacetone alcohol)

If the aldehyde or ketone does not contain an α-hydrogen, a simple aldol condensation cannot take place. For example:



(In concentrated base, however, these may undergo the Cannizzaro reaction, Sec. 19.16.)

The generally accepted mechanism for the base-catalyzed condensation involves the following steps, acetaldehyde being used as an example. Hydroxide ion

(1) $CH_3CHO + OH^- \rightleftharpoons H_2O + [CH_2CHO]^-$
Basic catalyst — I

(2) $CH_3-\overset{H}{\underset{|}{C}}=O + [CH_2CHO]^- \rightleftharpoons CH_3-\overset{H}{\underset{|}{C}}-CH_2CHO$

I (*Nucleophilic reagent*)

$\overset{|}{O^-}$

II

(3) $CH_3-\overset{H}{\underset{|}{C}}-CH_2CHO + H_2O \rightleftharpoons CH_3-\overset{H}{\underset{|}{C}}-CH_2CHO + OH^-$

$\overset{|}{O^-}$ $\overset{|}{OH}$

II III

abstracts (step 1) a hydrogen ion from the α-carbon of the aldehyde to form carbanion I, which attacks (step 2) carbonyl carbon to form ion II. II (an alkoxide) abstracts (step 3) a hydrogen ion from water to form the β-hydroxyaldehyde III, regenerating hydroxide ion. The purpose of hydroxide ion is thus to produce the carbanion I, which is the actual nucleophilic reagent.

Problem 21.10 Illustrate these steps for:

(a) propionaldehyde
(b) acetone
(c) acetophenone
(d) cyclohexanone
(e) phenylacetaldehyde

Problem 21.11 The aldol condensation of unsymmetrical ketones (methyl ethyl ketone, for example) is usually of little value in synthesis. Why do you think this is so?

The carbonyl group plays two roles in the aldol condensation. It not only provides the unsaturated linkage at which addition (step 2) occurs, but also makes the α-hydrogens acidic enough for carbanion formation (step 1) to take place.

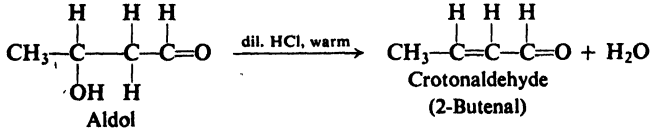
Problem 21.12 In *acid-catalyzed aldol condensations*, acid is believed to perform two functions: to catalyze conversion of carbonyl compound into the enol form, and to provide protonated carbonyl compound with which the enol can react. The reaction that then takes place can, depending upon one's point of view, be regarded either as acid-catalyzed nucleophilic addition to a carbonyl group, or as electrophilic addition to an alkene. On this basis, write all steps in the mechanism of acid-catalyzed aldol condensation of acetaldehyde. In the actual *condensation* step, identify the nucleophile and the electrophile.

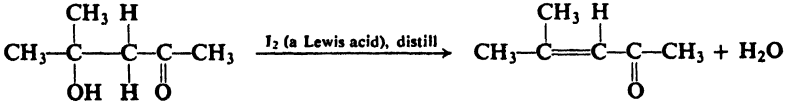
Problem 21.13 (a) When acetaldehyde at fairly high concentration was allowed to undergo base-catalyzed aldol condensation in heavy water (D_2O), the product was found to contain almost no deuterium bound to carbon. This finding has been taken as one piece of evidence that the slow step in this aldol condensation is formation of the carbanion. How would you justify this conclusion? (b) The kinetics also supports this conclusion. What kinetics would you expect if this were the case? (*Remember:* Two molecules of acetaldehyde are involved in aldol condensation.) (c) When the experiment in part (a) was carried out at low acetaldehyde concentration, the product was found to contain considerable deuterium bound to carbon. How do you account for this? (*Hint:* See Sec. 14.20.) (d) In contrast to acetaldehyde, acetone was found to undergo base-catalyzed hydrogen–deuterium exchange much faster than aldol condensation. What is one important factor contributing to this difference in behavior?

Problem 21.14 In alkaline solution, 4-methyl-4-hydroxy-2-pentanone is partly converted into acetone. What does this reaction amount to? Show all steps in the most likely mechanism. (*Hint:* See Problem 5.8, p. 170.)

21.6 Dehydration of aldol products

The β-hydroxyaldehydes and β-hydroxyketones obtained from aldol condensations are very easily dehydrated; the major products have the carbon–carbon double bond between the α- and β-carbon atoms. For example:

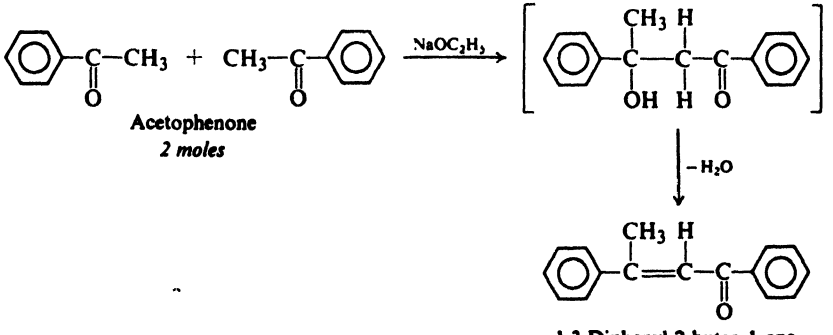




Both the ease and the orientation of elimination are related to the fact that the alkene obtained is a particularly stable one, since the carbon–carbon double bond is conjugated with the carbon–oxygen double bond of the carbonyl group (compare Sec. 8.16).

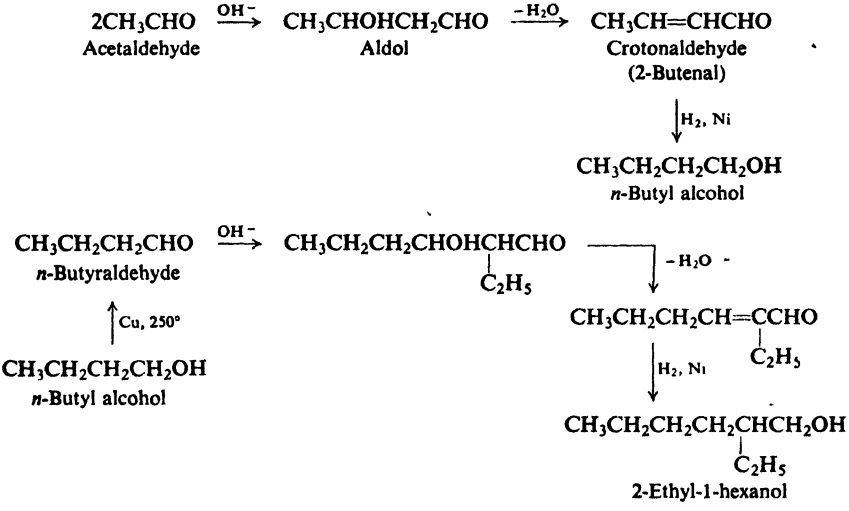
Problem 21.15 Draw resonance structures to account for the unusual stability of an α,β-unsaturated aldehyde or ketone. What is the significance of these structures in terms of orbitals? (See Sec. 8.17.)

As we know, an alkene in which the carbon–carbon double bond is conjugated with an aromatic ring is particularly stable (Sec. 12.17); in those cases where elimination of water from the aldol product can form such a conjugated alkene, the unsaturated aldehyde or ketone is the product actually isolated from the reaction. For example:

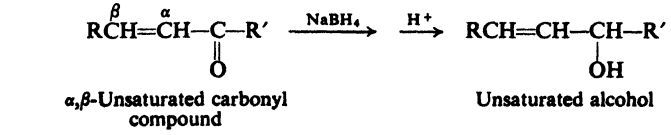


21.7 Use of aldol condensation in synthesis

Catalytic hydrogenation of α,β-unsaturated aldehydes and ketones yields saturated alcohols, addition of hydrogen occurring both at carbon–carbon and at carbon–oxygen double bonds. It is for the purpose of ultimately preparing saturated alcohols that the aldol condensation is often carried out. For example, *n*-butyl alcohol and 2-ethyl-1-hexanol are both prepared on an industrial scale in this way:



Unsaturated alcohols can be prepared if a reagent is selected that reduces only the carbonyl group and leaves the carbon–carbon double bond untouched; one such reagent is sodium borohydride, $NaBH_4$.



Problem 21.16 Outline the synthesis of the following alcohols starting from alcohols of smaller carbon number:

(a) 2-methyl-1-pentanol
(b) 4-methyl-2-pentanol
(c) 2-cyclohexylcyclohexanol
(d) 2,4-diphenyl-1-butanol
(e) 1,3-diphenyl-2-buten-1-ol

Problem 21.17 The insect repellent "6-12" (2-ethyl-1,3-hexanediol) is produced by the same chemical company that produces *n*-butyl alcohol and 2-ethyl-1-hexanol; suggest a method for its synthesis. How could you synthesize 2-methyl-2,4-pentanediol?

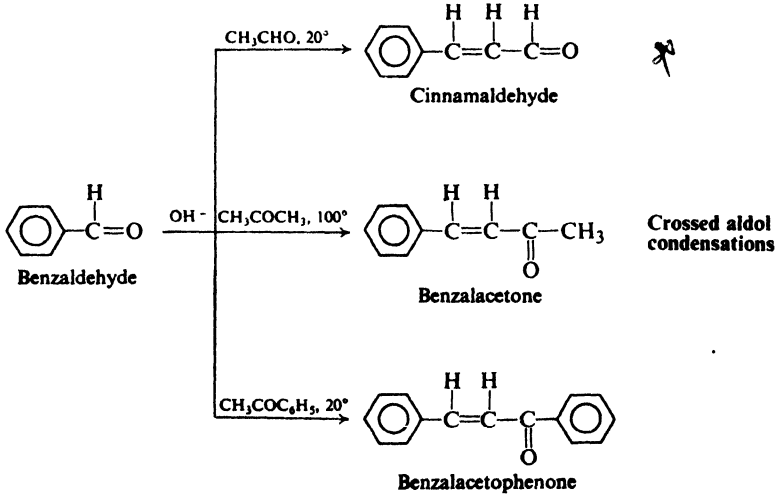
21.8 Crossed aldol condensation

An aldol condensation between two different carbonyl compounds—a so-called **crossed aldol condensation**—is not always feasible in the laboratory, since a

mixture of the four possible products may be obtained. On a commercial scale, however, such a synthesis may be worthwhile if the mixture can be separated and the components marketed.

Problem 21.18 *n*-Butyl alcohol, *n*-hexyl alcohol, 2-ethyl-1-hexanol, and 2-ethyl-1-butanol are marketed by the same chemical concern; how might they be prepared from cheap, readily available compounds?

Under certain conditions, a good yield of a single product can be obtained from a crossed aldol condensation: (a) one reactant contains no α-hydrogens and therefore is incapable of condensing with itself (e.g., aromatic aldehydes or formaldehyde); (b) this reactant is mixed with the catalyst; and then (c) a carbonyl

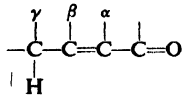


compound that contains α-hydrogens is added slowly to this mixture. There is thus present at any time only a very low concentration of the ionizable carbonyl compound, and the carbanion it forms reacts almost exclusively with the other carbonyl compound, which is present in large excess.

Problem 21.19 Outline the synthesis of each of the following from benzene or toluene and any readily available alcohols:

(a) 4-phenyl-2-butanol
(b) 1,3-diphenyl-1-propanol
(c) 1,3-diphenylpropane
(d) 2,3-diphenyl-1-propanol
(e) 1,5-diphenyl-1,4-pentadien-3-one (dibenzalacetone)

Problem 21.20 (a) What prediction can you make about the acidity of the γ-hydrogens of α,β-unsaturated carbonyl compounds,



as, for example, in crotonaldehyde? (b) In view of your answer to (a), suggest a way to synthesize 5-phenyl-2,4-pentadienal, $C_6H_5CH{=}CH{-}CH{=}CH{-}CHO$.

21.9 Reactions related to the aldol condensation

There are a large number of condensations that are closely related to the aldol condensation. Each of these reactions has its own name—*Perkin*, *Knoevenagel*, *Doebner*, *Claisen*, *Dieckmann*, for example—and at first glance each may seem quite different from the others. Closer examination shows, however, that like the aldol condensation each of these involves attack by a carbanion on a carbonyl group. In each case the carbanion is generated in very much the same way: the abstraction by base of a hydrogen ion *alpha* to a carbonyl group. Different bases may be used—sodium hydroxide, sodium ethoxide, sodium acetate, amines—and the carbonyl group to which the hydrogen is *alpha* may vary—aldehyde, ketone, anhydride, ester—but the chemistry is essentially the same as that of the aldol condensation. We shall take up a few of these condensations in the following problems and in following sections; in doing this, we must not lose sight of the fundamental resemblance of each of them to the aldol condensation.

Problem 21.21 Esters can be condensed with aromatic aldehydes in the presence of alkoxides; thus benzaldehyde and ethyl acetate, in the presence of sodium ethoxide, give ethyl cinnamate, $C_6H_5CH{=}CHCOOC_2H_5$. Show all steps in the most likely mechanism for this condensation.

Problem 21.22 Account for the following reactions:

(a) $C_6H_5CHO + CH_3NO_2 \xrightarrow{KOH} C_6H_5CH{=}CHNO_2 + H_2O$

(b) $C_6H_5CHO + C_6H_5CH_2CN \xrightarrow{NaOC_2H_5} C_6H_5CH{=}\underset{\displaystyle C_6H_5}{\underset{|}{C}}{-}CN + H_2O$

(c) $C_6H_5CHO + CH_3(C_6H_3(NO_2)NO_2) \xrightarrow{2^\circ\ \text{amine}} C_6H_5CH{=}CH(C_6H_3(NO_2)NO_2) + H_2O$

(d) $CH_3CHO + NaC{\equiv}CH \xrightarrow{NH_3(l)} CH_3\underset{\displaystyle ONa}{\underset{|}{C}}HC{\equiv}CH \xrightarrow{NH_4Cl} CH_3\underset{\displaystyle OH}{\underset{|}{C}}HC{\equiv}CH$

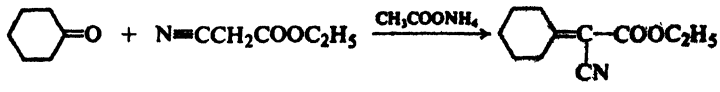
(e) **A Perkin condensation:**

$$\underset{\text{Acetic anhydride}}{C_6H_5CHO + (CH_3CO)_2O} \xrightarrow{CH_3COONa} \underset{\text{Cinnamic acid}}{C_6H_5CH{=}CHCOOH}$$

(f) **A Knoevenagel reaction:**

$$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow{2^\circ\ \text{amine}} C_6H_5CH{=}C(COOC_2H_5)_2$$

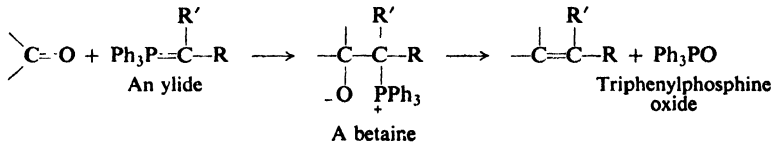
(g) **A Cope reaction:**



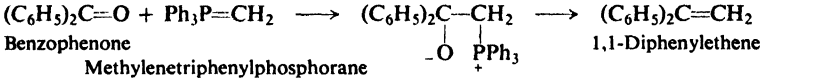
21.10 The Wittig reaction

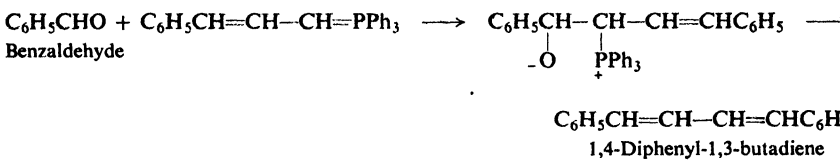
In 1954, Georg Wittig (then at the University of Tübingen) reported a method of synthesizing alkenes from carbonyl compounds, which amounts to the replace-

ment of carbonyl oxygen, =O, by the group =CRR′. The heart of the synthesis



is the nucleophilic attack on carbonyl carbon by an *ylide* to form a *betaine* which—often spontaneously—undergoes elimination to yield the product. For example:



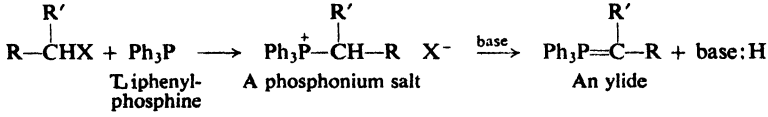


The reaction is carried out under mild conditions, and the position of the carbon–carbon double bond is not in doubt. Carbonyl compounds may contain a wide variety of substituents, and so may the ylide. (Indeed, in its broadest form, the Wittig reaction involves reactants other than carbonyl compounds, and may lead to products other than substituted alkenes.)

The phosphorus ylides have hybrid structures, and it is the negative charge on

carbon—the carbanion character of ylides—that is responsible for their characteristic reactions: in this case, nucleophilic attack on carbonyl carbon.

The preparation of ylides is a two-stage process, each stage of which belongs to a familiar reaction type: nucleophilic attack on an alkyl halide, and abstraction of a proton by a base.

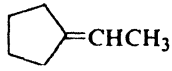


Many different bases have been used—chiefly alkoxides and organometallics—and in a variety of solvents. For example:

$$CH_2{=}CHCH_2Cl + Ph_3P \longrightarrow Ph_3\overset{+}{P}{-}CH_2CH{=}CH_2\ Cl^- \xrightarrow[DMF]{NaOEt} Ph_3P{=}CHCH{=}CH_2$$

Problem 21.23 What side reactions would you expect to encounter in the preparation of an ylide like $Ph_3P{=}C(CH_3)CH_2CH_3$?

Problem 21.24 Give the structure of an ylide and a carbonyl compound from which each of the following could be made.

(a) $CH_3CH_2CH_2CH{=}C(CH_3)CH_2CH_3$
(b) $C_6H_5C(CH_3){=}CHCH_2C_6H_5$
(c) $C_6H_5CH{=}CHC_6H_5$
(d) 
(e) 1,4-diphenyl-1,3-butadiene (an alternative to the set of reagents used on p. 715)
(f) $CH_2{=}CHCH{=}C(CH_3)COOCH_3$

Problem 21.25 Outline all steps in a possible laboratory synthesis of each ylide and each carbonyl compound in the preceding problem, starting from benzene, toluene, alcohols of four carbons or fewer, acetic anhydride, triphenylphosphine, and cyclopentanol, and using any needed inorganic reagents.

Problem 21.26 Give the structures of compounds A–C.

$C_6H_5OCH_2Cl + Ph_3P$, then t-BuOK $\longrightarrow$ A ($C_{25}H_{21}OP$)
A + methyl ethyl ketone $\longrightarrow$ Ph_3PO + B ($C_{11}H_{14}O$)
B + dilute aqueous acid $\longrightarrow$ C ($C_5H_{10}O$)

The above sequence offers a general route to what class of compounds?

Problem 21.27 Give the structures of compounds D–F.

(a) $C_6H_5COCH_2CH{=}CH_2CH_2Br + Ph_3P$, then NaOEt $\longrightarrow$ D ($C_{11}H_{12}$)
(b) $BrCH_2CH_2CH_2Br + Ph_3P$, then base $\longrightarrow$ E ($C_{39}H_{34}P_2$)
E + o-$C_6H_4(CHO)_2$ $\longrightarrow$ F ($C_{11}H_{10}$)

Problem 21.28 Give the structures of compounds G and H, and account for the stereochemistry of each step.

trans-2-octene + $C_6H_5CO_2OH$ $\longrightarrow$ G ($C_8H_{16}O$)
G + Ph_2PLi, then CH_3I $\longrightarrow$ H ($C_{21}H_{29}OP$)
H $\longrightarrow$ *cis*-2-octene

21.11 Claisen condensation. Formation of β-keto esters

An α-hydrogen in an ester, like an α-hydrogen in an aldehyde or ketone, is weakly acidic, and for the same reason: through resonance, the carbonyl group helps accommodate the negative charge of the carbanion. Let us look at an exceedingly important reaction of esters that depends upon the acidity of α-hydrogens. It is—for esters—the exact counterpart of the aldol condensation; reaction takes a different turn at the end, but a turn that is typical of the chemistry of acyl compounds.

When ethyl acetate is treated with sodium ethoxide, and the resulting mixture

is acidified, there is obtained ethyl β-ketobutyrate (ethyl 3-oxobutanoate), generally known as **ethyl acetoacetate** or **acetoacetic ester**:

$$\underset{\substack{\text{Ethyl acetate}\\ \textit{2 moles}}}{2CH_3COOC_2H_5} + \underset{\substack{\text{Sodium}\\ \text{ethoxide}}}{Na^+ {}^-OC_2H_5} \xrightarrow{C_2H_5OH} \underset{\text{Sodioacetoacetic ester}}{CH_3COCHCOOC_2H_5{}^-Na^+} + 2C_2H_5OH$$

$$\downarrow H^+$$

$$\underset{\substack{\text{Ethyl acetoacetate}\\ \text{Acetoacetic ester}\\ \textit{A β-keto ester}}}{CH_3\overset{\beta}{C}OCH_2COOC_2H_5}$$

Ethyl acetoacetate is the ester of a *β-keto acid*; its preparation illustrates the reaction known as the **Claisen condensation**.

The generally accepted mechanism for the Claisen condensation (shown here for ethyl acetate) is:

(1) $$CH_3COOC_2H_5 + {}^-OC_2H_5 \rightleftharpoons C_2H_5OH + \underset{\text{I}}{{}^-CH_2COOC_2H_5}$$

(2) $$CH_3\overset{\displaystyle O}{\overset{\|}{C}}OC_2H_5 + \underset{\text{I}}{{}^-CH_2COOC_2H_5} \rightleftharpoons CH_3\overset{\displaystyle O^-}{\overset{|}{C}}(OC_2H_5)CH_2COOC_2H_5$$

$$\downarrow\uparrow$$

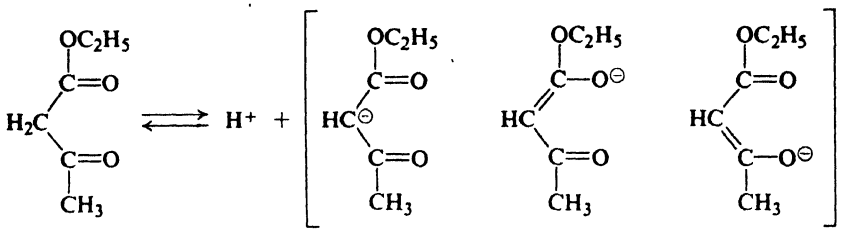
$$CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2COOC_2H_5 + {}^-OC_2H_5$$

(3) $$\underset{\text{Stronger acid}}{CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2COOC_2H_5} + {}^-OC_2H_5 \rightleftharpoons \underset{\text{Weaker acid}}{CH_3COCHCOOC_2H_5{}^-} + C_2H_5OH$$

Ethoxide ion abstracts (step 1) a hydrogen ion from the α-carbon of the ester to form carbanion I. The powerfully nucleophilic carbanion I attacks (step 2) the carbonyl carbon of a second molecule of ester to displace ethoxide ion and yield the keto ester.

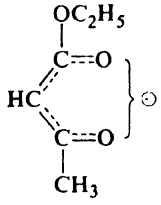
Like the aldol condensation and related reactions, the Claisen condensation involves nucleophilic attack by a carbanion on an electron-deficient carbonyl carbon. *In the aldol condensation, nucleophilic attack leads to addition, the typical reaction of aldehydes and ketones; in the Claisen condensation, nucleophilic attack leads to substitution, the typical reaction of acyl compounds* (Sec. 20.4).

When reaction is complete there is present, not acetoacetic ester, but its sodium salt, *sodioacetcacetic ester*. The α-hydrogens of acetoacetic ester are located *alpha* to *two* carbonyl groups, and hence ionization yields a particularly stable carbanion in which two carbonyl groups help accommodate the charge. As a result acetoacetic ester is a much stronger acid than ordinary esters or other compounds containing a single carbonyl group. It is considerably stronger than ethyl alcohol, and hence it reacts (step 3) with ethoxide ion to form ethyl alcohol and the anion



Acetoacetic ester

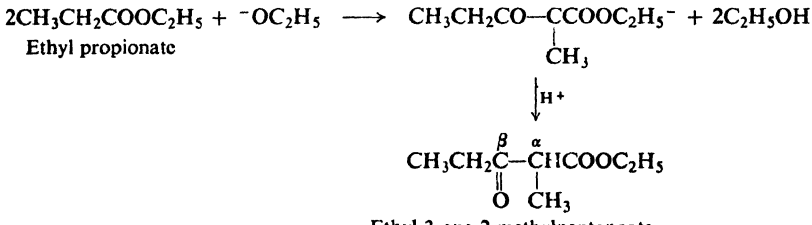
equivalent to



of sodioacetoacetic ester. Formation of the salt of acetoacetic ester is essential to the success of the reaction; of the various equilibria involved in the reaction, only (3) is favorable to the product we want.

Problem 21.29 Better yields are obtained if the Claisen condensation is carried out in ether with alcohol-free sodium ethoxide as catalyst instead of in ethyl alcohol solution. How do you account for this?

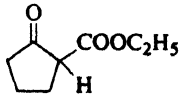
As we might expect, the Claisen condensation of more complicated esters yields the products resulting from ionization of an α-hydrogen of the ester; as a result, it is always the α-carbon of one molecule that becomes attached to the carbonyl carbon of another. For example:



Ethyl propionate

Ethyl 3-oxo-2-methylpentanoate
Ethyl α-methyl-β-ketovalerate
A β-keto ester

Problem 21.30 Sodium ethoxide converts ethyl adipate into 2-carbethoxycyclopentanone (II). This is an example of the **Dieckmann condensation.**

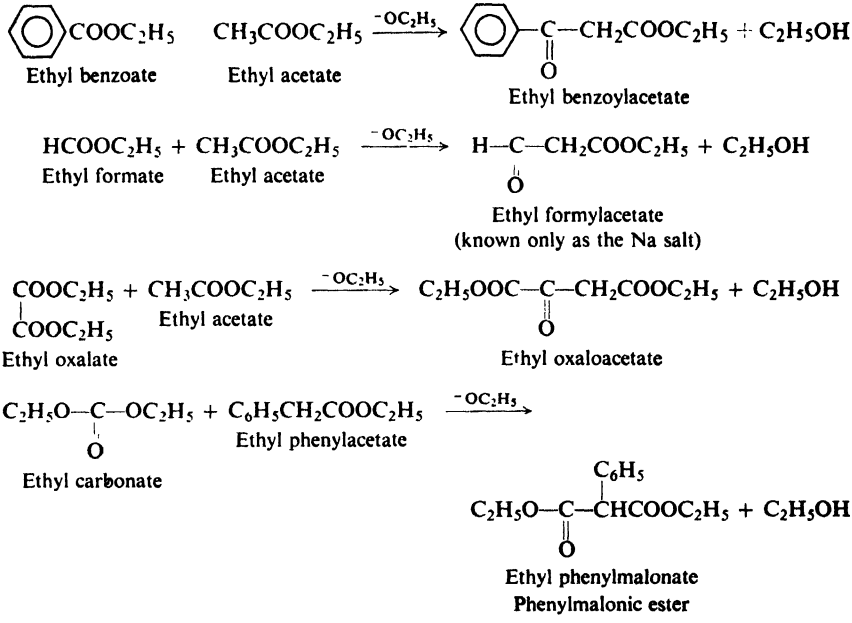


II

(a) How do you account for formation of II? (b) What product would you expect from the action of sodium ethoxide on ethyl pimelate (ethyl heptanedioate)? (c) Would you expect similar behavior from ethyl glutarate or ethyl succinate? Actually, ethyl succinate reacts with sodium ethoxide to yield a compound of formula $C_{12}H_{16}O_6$ containing a six-membered ring. What is the likely structure for this last product?

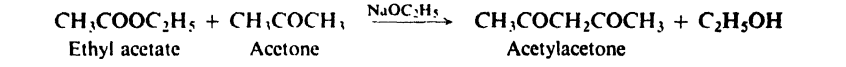
21.12 Crossed Claisen condensation

Like a crossed aldol condensation (Sec. 21.8), a **crossed Claisen condensation** is generally feasible only when one of the reactants has no α-hydrogens and thus is incapable of undergoing self-condensation. For example:



Problem 21.31 In what order should the reactants be mixed in each of the above crossed Claisen condensations? (*Hint:* See Sec. 21.8.)

Problem 21.32 Ketones (but not aldehydes) undergo a crossed Claisen condensation with esters. For example:



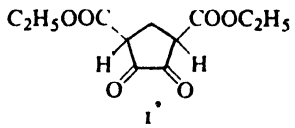
(a) Outline all steps in the most likely mechanism for this reaction. (b) Predict the principal products expected from the reaction in the presence of sodium ethoxide of ethyl propionate and acetone; (c) of ethyl benzoate and acetophenone; (d) of ethyl oxalate and cyclohexanone.

Problem 21.33 Outline the synthesis from simple esters of:

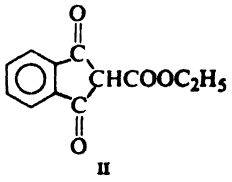
(a) ethyl α-phenylbenzoylacetate, $C_6H_5COCH(C_6H_5)COOC_2H_5$

(b) ethyl 2,3-dioxo-1,4-cyclopentanedicarboxylate (I). (*Hint:* Use ethyl oxalate as one ester.)

(c) ethyl 1,3-dioxo-2-indanecarboxylate (II)



I

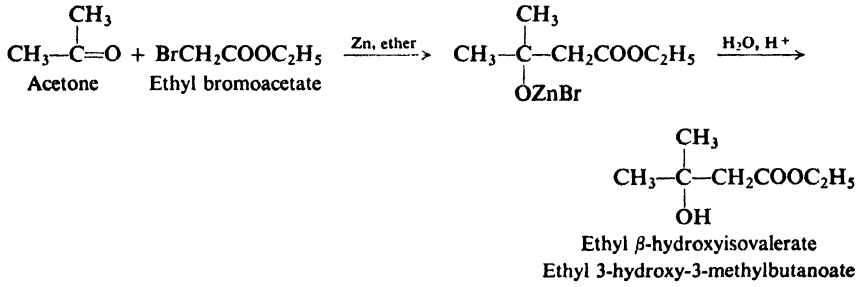


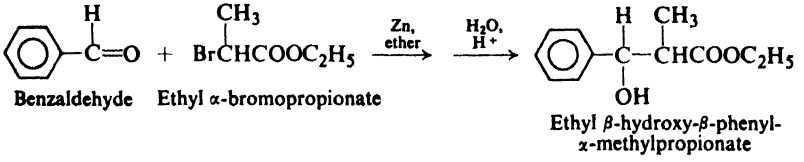
II

21.13 Reformatsky reaction. Preparation of β-hydroxy esters

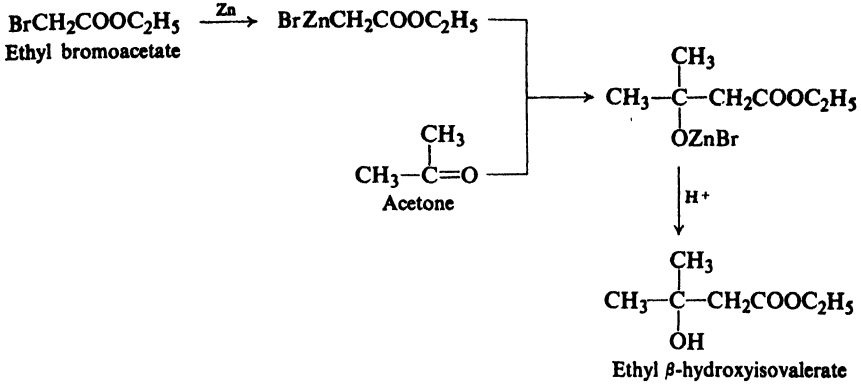
In the Claisen condensation, we have just seen, carbanions are generated from esters through abstraction of an α-hydrogen by base. But we are familiar with another way of generating carbanions—or rather, groups with considerable carbanion character: through formation of organometallic compounds. This approach, too, plays a part in the chemistry of esters.

If an α-bromo ester is treated with metallic zinc in the presence of an aldehyde or ketone, there is obtained a β-hydroxy ester. This reaction, known as the **Reformatsky reaction**, is the most important method of preparing β-hydroxy acids and their derivatives. For example:

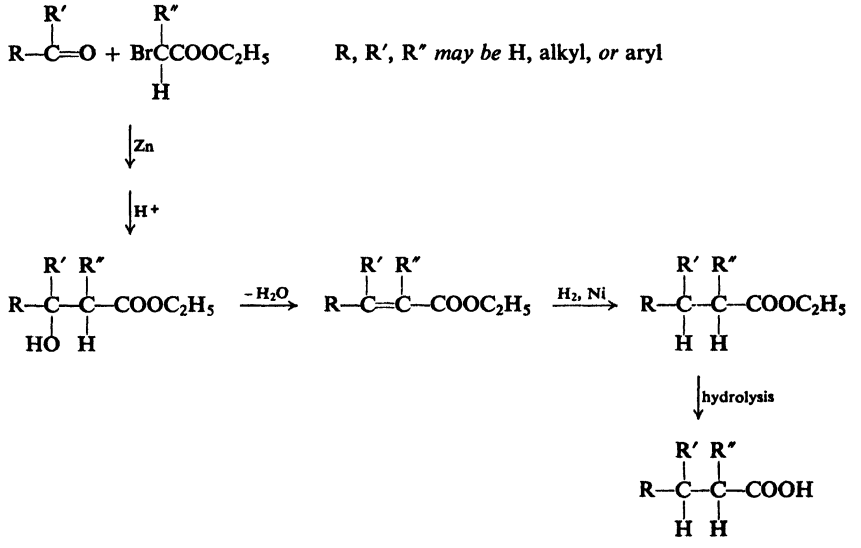




The α-bromo ester and zinc react in absolute ether to yield an intermediate organozinc compound, which then adds to the carbonyl group of the aldehyde or ketone. The formation and subsequent reaction of the organozinc compound is similar to the formation and reaction of a Grignard reagent. Zinc is used in place of magnesium simply because the organozinc compounds are less reactive than Grignard reagents; they do not react with the ester function but only with the aldehyde or ketone.



The Reformatsky reaction takes place only with esters containing bromine in the *alpha* position, and hence necessarily yields *beta*-hydroxy esters. By the proper

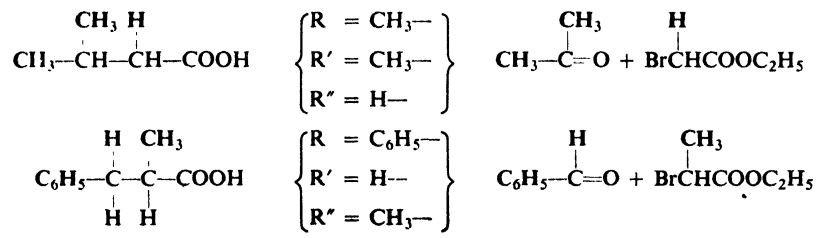


selection of ester and carbonyl compound, a wide variety of rather complicated β-hydroxy carboxylic acids can be prepared.

Like β-hydroxyaldehydes and -ketones, β-hydroxyesters and -acids are readily dehydrated. The unsaturated compounds thus obtained (chiefly α,β-unsaturated) can be hydrogenated to saturated carboxylic acids. Extended in this way, the Reformatsky reaction is a useful general method for preparing carboxylic acids, paralleling the aldol route to alcohols.

In planning the synthesis of a carboxylic acid by the Reformatsky reaction,

our problem is to select the proper starting materials; to do this, we have only to look at the structure of the product we want. For example:



Problem 21.34 Outline the synthesis of the following acids via the Reformatsky reaction:

(a) *n*-valeric acid; (b) α,γ-dimethylvaleric acid; (c) cinnamic acid; (d) α-methyl-β-phenylpropionic acid.

Problem 21.35 Outline the synthesis of the following, starting from benzaldehyde and ethyl bromoacetate:

(a) $C_6H_5CH_2CH_2COOH$
(b) $C_6H_5CH_2CH_2CHO$
(c) $C_6H_5CH_2CH_2CH_2CH_2COOH$

Problem 21.36 Give structures of compounds A, B, and C:

ethyl oxalate + ethyl acetate + sodium ethoxide $\longrightarrow$ A ($C_8H_{12}O_5$)
A + ethyl bromoacetate + Zn, then H_2O $\longrightarrow$ B ($C_{12}H_{20}O_7$)
B + OH^- + heat, then H^+ $\longrightarrow$ C ($C_6H_8O_7$), *citric acid*

PROBLEMS

1. Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetaldehyde with:

(a) dilute NaOH
(b) dilute HCl
(c) aqueous Na_2CO_3
(d) Br_2/CCl_4
(e) $Ph_3P{=}CH_2$

2. Answer Problem 1 for cyclohexanone.

3. Write balanced equations, naming all organic products, for the reaction (if any) of benzaldehyde with:

(a) dilute NaOH
(b) conc. NaOH
(c) acetaldehyde, dilute NaOH
(d) propionaldehyde, dilute NaOH
(e) acetone, dilute NaOH
(f) product (e), dilute NaOH
(g) acetophenone, NaOH
(h) acetic anhydride, sodium acetate, heat
(i) ethyl acetate, sodium ethoxide
(j) ethyl phenylacetate, sodium ethoxide
(k) formaldehyde, conc. NaOH
(l) crotonaldehyde, NaOH
(m) $Ph_3P{=}CHCH{=}CH_2$
(n) $Ph_3P{=}CH(OC_6H_5)$
(o) product (n), dilute acid

4. Write equations for all steps in the synthesis of the following from propionaldehyde, using any other needed reagents:

(a) α-methyl-β-hydroxyvaleraldehyde
(b) 2-methyl-1-pentanol
(c) 2-methyl-2-pentenal
(d) 2-methyl-2-penten-1-ol
(e) 2-methyl-1,3-pentanediol
(f) α-methylvaleric acid
(g) 2-methyl-3-phenylpropenal
(h) CH_3CD_2CHO
(i) $CH_3CH_2CH^{18}O$
(j) 2-methyl-3-hexene

5. Write equations for all steps in the synthesis of the following from acetophenone, using any other needed reagents:

(a) benzoic acid
(b) 1,3-diphenyl-2-buten-1-one
(c) 1,3-diphenyl-1-butanol
(d) 1,3-diphenyl-2-buten-1-ol
(e) 1,3-diphenyl-2-propen-1-one
(f) α-phenylpropionaldehyde (*Hint:* See Problem 21.26.)

6. Give the structures of the principal products expected from the reaction in the presence of sodium ethoxide of:

(a) ethyl *n*-butyrate
(b) ethyl phenylacetate
(c) ethyl isovalerate
(d) ethyl formate and ethyl propionate
(e) ethyl oxalate and ethyl succinate
(f) ethyl benzoate and ethyl phenylacetate
(g) ethyl propionate and cyclohexanone
(h) ethyl phenylacetate and acetophenone
(i) ethyl carbonate and acetophenone

7. Sodium ethoxide is added to a mixture of ethyl acetate and ethyl propionate (a) Give the structures of the products expected. (b) Would this reaction be a good method of synthesizing any one of these?

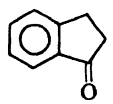
8. Outline all steps in a possible synthesis of each of the following via the Claisen condensation, using any needed reagents:

(a) $C_6H_5COCH(CH_3)COOC_2H_5$
(b) $C_6H_5CH_2COCH(C_6H_5)COOC_2H_5$
(c) $C_2H_5OOCCOCH(CH_3)COOC_2H_5$
(d) $C_6H_5CH(CHO)COOC_2H_5$
(e) $(CH_3)_2CHCOCH_2COCH_3$
(f) $C_6H_5COCH_2COCH_3$
(g) 2-benzoylcyclohexanone
(h) $C_2H_5OOCCH(CHO)CH_2COOC_2H_5$

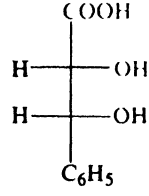
9. The cinnamic acid obtained by the Perkin condensation is the more stable *trans*-isomer. Suggest a method of preparing *cis*-cinnamic acid. (*Hint:* See Sec. 8.9.)

10. Outline all steps in a possible laboratory synthesis of each of the following from benzene, toluene, acetic anhydride, triphenylphosphine, and alcohols of four carbons or fewer, using any needed inorganic reagents:

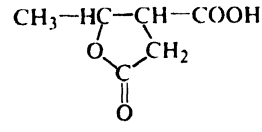
(a) 4-methyl-4-hydroxy-2-pentanone
(b) 4-methyl-2-pentanol
(c) crotonaldehyde, $CH_3CH{=}CHCHO$
(d) cinnamyl alcohol, $C_6H_5CH{=}CHCH_2OH$
(e) *p*-nitrocinnamaldehyde
(f) 1,3-butanediol
(g) 3-methyl-2-butenoic acid (via aldol condensation)
(h) 3-methyl-2-butenoic acid (a second way)
(i) 3-methyl-1-pentyn-3-ol (*Oblivon*, a hypnotic)
(j) 1-phenyl-1,3,5-hexatriene
(k) 1,6-diphenyl-1,3,5-hexatriene
(l) 2,3-dimethyl-2-pentenoic acid
(m) 3-hydroxy-4-phenylbutanoic acid
(n) α,α-dimethylcaproic acid
(o) indanone (I)
(p) racemic *erythro*-2,3-dihydroxy-3-phenylpropanoic acid (II and its enantiomer)



I



II



γ-Methylparaconic acid

11. How do you account for the formation of γ-methylparaconic acid (previous page) from the reaction of acetaldehyde with succinic acid?

12. Considerable quantities of acetone are consumed in the manufacture of methyl isobutyl ketone (MIBK). How do you think the synthesis of MIBK is accomplished?

13. Methyl ethyl ketone can be made to undergo the Claisen condensation with a given ester to yield either of two products, depending upon experimental conditions. (a) What are these two products? (b) How could you tell quickly and simply which product you had obtained? (*Note:* Use ethyl benzoate as the ester.)

14. The acetylenic ester $CH_3{-}C^{-}\ C\ {-}COOC_2H_5$ can be converted into ethyl acetoacetate. (a) How? (b) Outline a synthesis of the acetylenic ester from acetylene and any needed reagents.

15. The compound *pentaerythritol*, $C(CH_2OH)_4$, used in making explosives, is obtained from the reaction of acetaldehyde and formaldehyde in the presence of calcium hydroxide. Outline the probable steps in this synthesis.

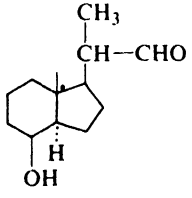
16. The labeled alkene, 1,3,3-trideuteriocyclohexene, needed for a particular stereochemical study, was prepared from cyclohexanone. Outline all steps in such a synthesis.

17. (a) The haloform test (Sec. 16.11) depends upon the fact that three hydrogens on the same carbon atom are successively replaced by halogen. Using acetone as an example, show why the carbon that suffers the initial substitution should be the preferred site of further substitution. (*Hint:* See Sec. 18.14.)

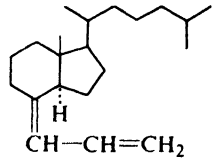
(b) The haloform test also depends upon the ease with which the trihalomethyl ketone produced in (a) is cleaved by base. What is the most likely mechanism for this cleavage? What factor makes such a reaction possible in this particular case?

18. Upon treatment with dilute NaOH, β-methylcrotonaldehyde, $(CH_3)_2C{=}CHCHO$, yields a product of formula $C_{10}H_{14}O$, called *dehydrocitral*. What is a likely structure for this product, and how is it formed? (*Hint:* See *citral*, Problem 26, p. 652.)

19. As part of the total synthesis of vitamin D_3, compound III was converted into IV by a number of stages, two of which involved use of the Wittig reaction. Show how this conversion might have been carried out.



III



IV

20. Meanwhile, back at the laboratory, our naïve graduate student (Problem 18, p. 650) had need of the hydroxy ester $(CH_3)_2C(OH)CH_2COOC_2H_5$. Turning once again to the Grignard reaction, he prepared methylmagnesium iodide and to it he added acetoacetic ester. Everything went well; indeed, even without the application of heat, the reaction mixture bubbled merrily. Working carefully and with great skill, he isolated an excellent yield of the starting material, acetoacetic ester. He poured this down the sink and fled, sobbing, to his research director's office, where he begged for a new research problem.

What reaction had taken place? What was the bubbbling due to? (In Problem 12, p. 881, we shall see how he made out with his new research problem.)

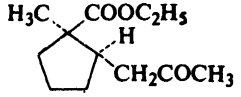
21. In contrast to simple carbonyl compounds, 1,3-dicarbonyl compounds—like acetoacetic ester or 2,4-pentanedione (acetylacetone)—exist to an appreciable extent in the enol form.

(a) Pure samples of keto and enol forms of acetoacetic ester have been isolated. Each retained its identity for weeks if acids and bases were carefully excluded. Write equations to show exactly how keto–enol interconversion is speeded up by a base. By an acid.

(b) Draw the structure of the enol form of, say, 2,4-pentanedione. Can you suggest one factor that would tend to stabilize the enol form of such a compound?

(c) Although the enol form of acetoacetic ester is an alcohol, it does *not* have a higher boiling point than the keto form. (Actually, it boils somewhat *lower*.) Can you suggest a second factor that would tend to stabilize the enol form of a 1,3-dicarbonyl compound?

22. Draw the structures (stereochemical where pertinent) of products A and B.

(a)  + NaOEt, then H_2O $\longrightarrow$ A ($C_{10}H_{14}O_2$), *highly enolic*

(b) methyl ethyl ketone + ethyl oxalate + NaOEt $\longrightarrow$ B ($C_6H_6O_3$)

23. (a) Fig. 21.1(*a*) (below) shows the nmr spectrum of a solution of acetylacetone, $CH_3COCH_2COCH_3$, in chloroform. Besides the peaks shown, there is a small hump, *e*, near δ 15 of about the same area as the peak *d* at δ 5.5. How do you interpret this spectrum? What *quantitative* conclusion can you draw?

(b) Fig. 21.1(*b*) (p. 726) shows the nmr spectrum of benzoylacetone, $C_6H_5COCH_2COCH_3$. There is an additional peak, *d*, near δ 16 of about the same area as the peak *b* at δ 6.1. How do you interpret this spectrum? How do you account for the difference between it and the spectrum in (*a*)?

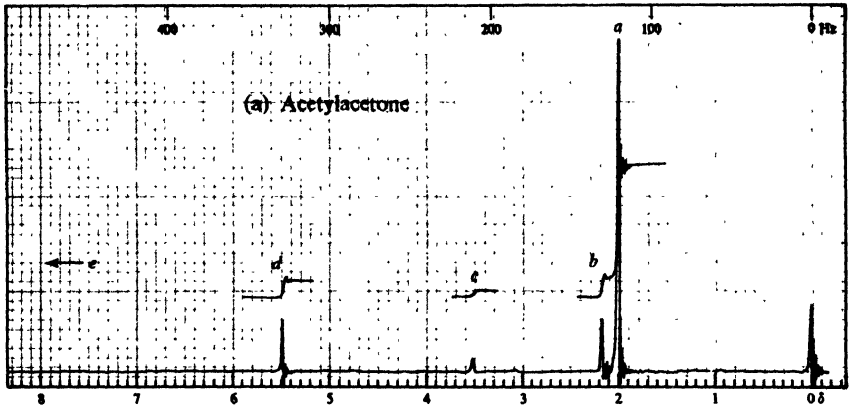


Figure 21.1(*a*). Nmr spectrum of acetylacetone.

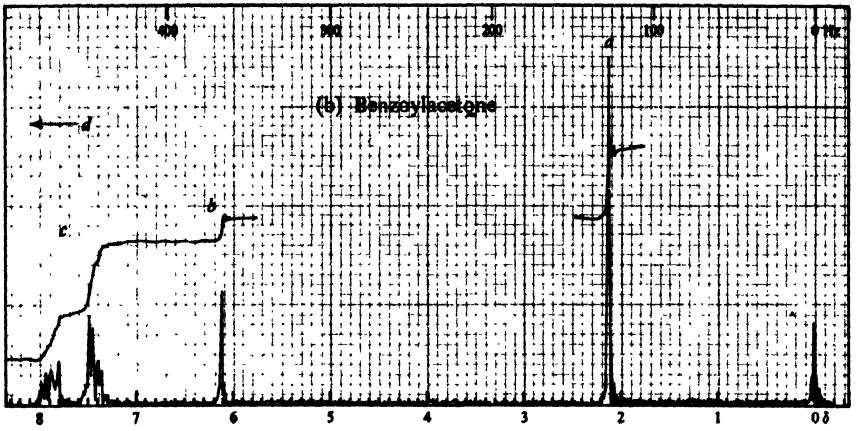


Figure 21.1(*b*). Nmr spectrum of benzoylacetone.

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°)

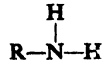
Aniline
(1°)

N-Methylaniline
(2°)

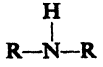
N,N-Dimethylaniline
(3°)

22.2 Classification

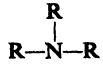
Amines are classified as **primary**, **secondary**, or **tertiary**, according to the number of groups attached to the nitrogen atom.



Primary
1°



Secondary
2°

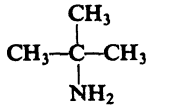


Tertiary
3°

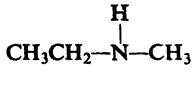
In their fundamental properties—*basicity* and the accompanying *nucleophilicity*—amines of different classes are very much the same. In many of their reactions, however, the final products depend upon the number of hydrogen atoms attached to the nitrogen atom, and hence are different for amines of different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

22.3 Nomenclature

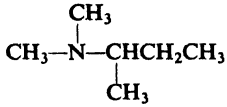
Aliphatic amines are named by naming the alkyl group or groups attached to nitrogen, and following these by the word *-amine*. More complicated ones are often named by prefixing *amino-* (or *N-methylamino-*, *N,N-diethylamino-*, etc.) to the name of the parent chain. For example:



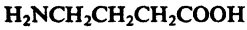
tert-Butylamine
(1°)



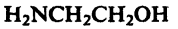
Methylethylamine
(2°)



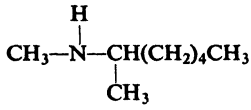
Dimethyl-*sec*-butylamine
(3°)



γ-Aminobutyric acid
(1°)

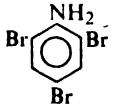


2-Aminoethanol
(Ethanolamine)
(1°)

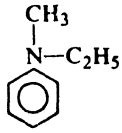


2-(N-Methylamino)heptane
(2°)

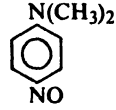
Aromatic amines—those in which nitrogen is attached directly to an aromatic ring—are generally named as derivatives of the simplest aromatic amine, **aniline**. An aminotoluene is given the special name of *toluidine*. For example:



2,4,6-Tribromoaniline
(1°)

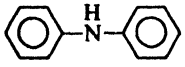


N-Methyl-N-ethylaniline
(3°)

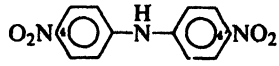


p-Nitroso-N,N-dimethylaniline
(3°)

p-Toluidine
(1°)



Diphenylamine
(2°)



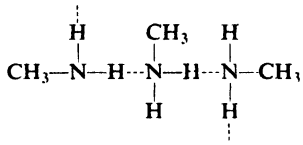
4,4'-Dinitrodiphenylamine
(2°)

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

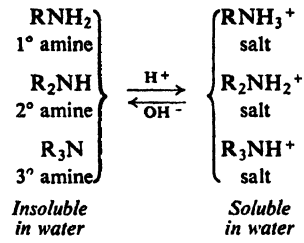
being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly "fishy" odors.

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.

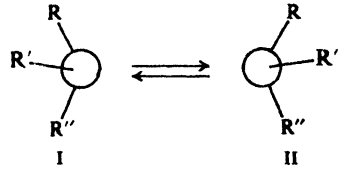
22.6 Stereochemistry of nitrogen

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—



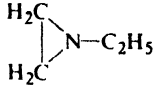
I II

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

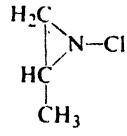
But such enantiomers have not yet been isolated—for simple amines—and spectroscopic studies have shown why: the energy barrier between the two pyramidal arrangements about nitrogen is ordinarily so low that they are rapidly interconverted. Just as rapid rotation about carbon–carbon single bonds prevents 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°.

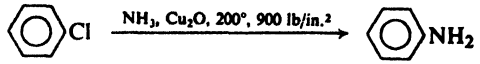
Problem 22.4 Racemization in certain free-radical and carbonium ion reactions has been attributed (Secs. 7.10 and 14.13) to loss of configuration in a flat intermediate. Account for the fact that the formation of alkyl carbanions, R: —which are believed to be *pyramidal*—can also lead to racemization.

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

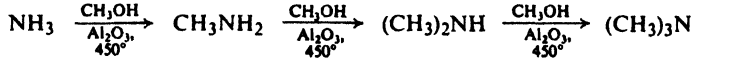
Nitrobenzene Anilinium chloride Aniline



Chlorobenzene Aniline

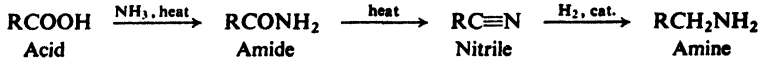
ammonia at high temperatures and high pressures in the presence of a catalyst. Process (b), we shall see (Chap. 25), involves nucleophilic aromatic substitution.

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

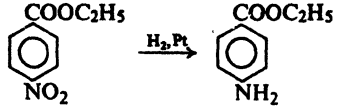
1. Reduction of nitro compounds. Discussed in Sec. 22.9.

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

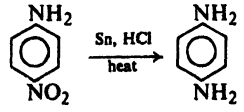
Nitro compound → 1° amine

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*

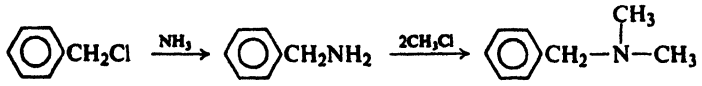
Examples:

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

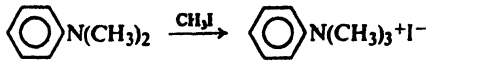
Acetic acid → Chloroacetic acid → Aminoacetic acid (Glycine; an amino acid) (1°)

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

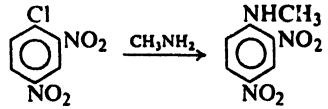
Ethyl chloride → Ethylamine (1°) → Methylethylamine (2°)



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

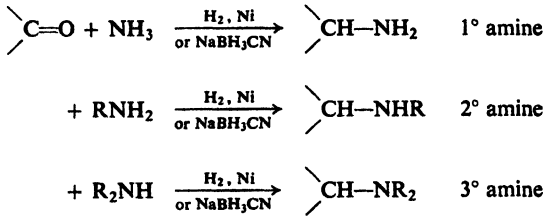


N,N-Dimethylaniline (3°) — Phenyltrimethylammonium iodide (4°)

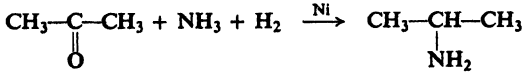


2,4-Dinitrochlorobenzene — N-Methyl-2,4-dinitroaniline (2°)

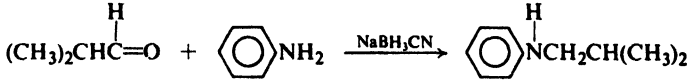
3. Reductive amination. Discussed in Sec. 22.11.



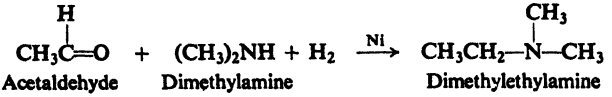
Examples:



Acetone — Isopropylamine (1°)

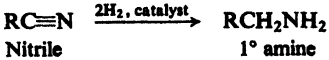


Isobutyraldehyde — Aniline (1°) — N-Isobutylaniline (2°)



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°)

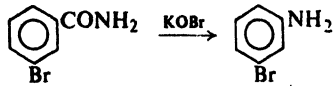
$$\underset{\text{1,4-Dichlorobutane}}{ClCH_2CH_2CH_2CH_2Cl} \xrightarrow{NaCN} \underset{\text{Adiponitrile}}{NC(CH_2)_4CN} \xrightarrow{H_2,\,Ni} \underset{\text{Hexamethylenediamine (1,6-Diaminohexane) (1°)}}{H_2NCH_2(CH_2)_4CH_2NH_2}$$

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

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

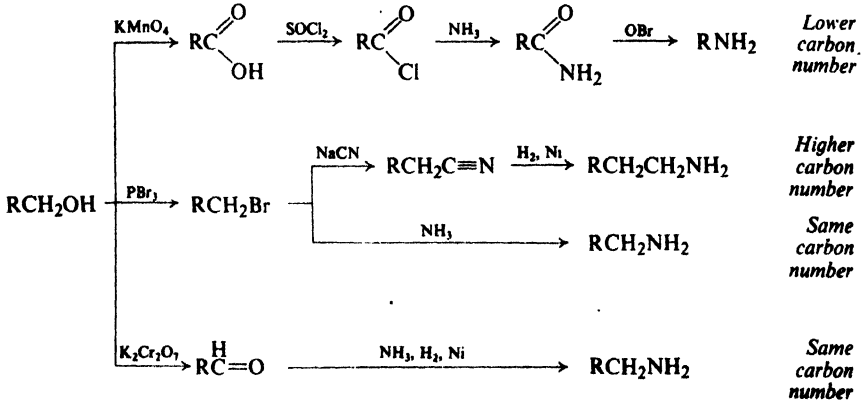
provides the best possible route to dozens of kinds of aromatic compounds.

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.

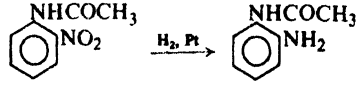


Problem 22.5 Show how *n*-pentylamine can be synthesized from available materials by the four routes just outlined.

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.

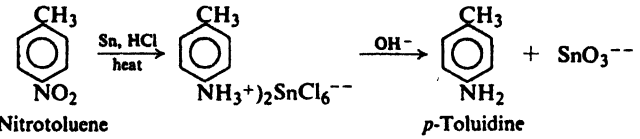
Hydrogenation of a nitro compound to an amine takes place smoothly when a solution of the nitro compound in alcohol is shaken with finely divided nickel or platinum under hydrogen gas. For example:



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.

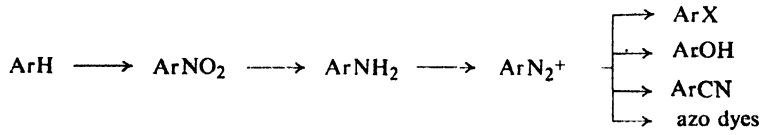
Chemical reduction in the laboratory is most often carried out by adding hydrochloric acid to a mixture of the nitro compound and a metal, usually granulated tin. In the acidic solution, the amine is obtained as its salt; the free amine is liberated by the addition of base, and is steam-distilled from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

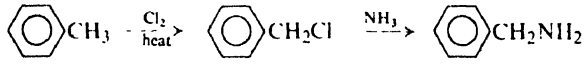
hydrogen to form alkene as well as attack carbon to form amine. Ammonolysis thus gives the highest yields with primary halides (where substitution predominates) and is virtually worthless with tertiary halides (where elimination predominates).

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

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

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:

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

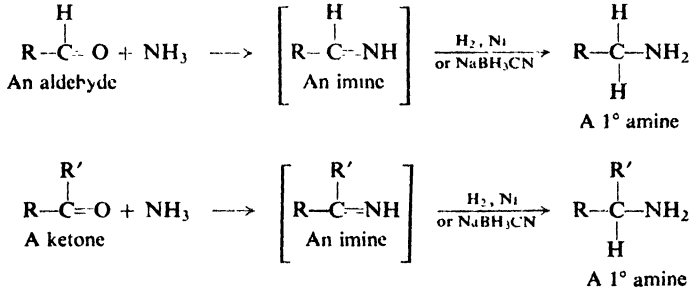
Finally, the tertiary amine can attack the alkyl halide to form a compound of the formula $R_4N^+X^-$, called a *quaternary ammonium salt* (discussed in Sec. 23.5):

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

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.

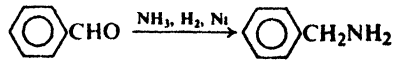
22.11 Reductive amination

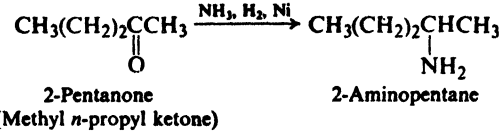
Many aldehydes (RCHO) and ketones (R_2CO) are converted into amines by **reductive amination**: reduction in the presence of ammonia. Reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $NaBH_3CN$. Reaction involves reduction of an intermediate compound (an *imine*, RCH=NH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

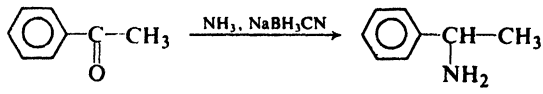
$$\underset{\substack{\text{Heptaldehyde}\\(\text{Heptanal})}}{CH_3(CH_2)_5CHO} \xrightarrow{NH_3,\ H_2,\ Ni} \underset{\substack{\textit{n}\text{-Heptylamine}\\(1\text{-Aminoheptane})}}{CH_3(CH_2)_5CH_2NH_2}$$





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

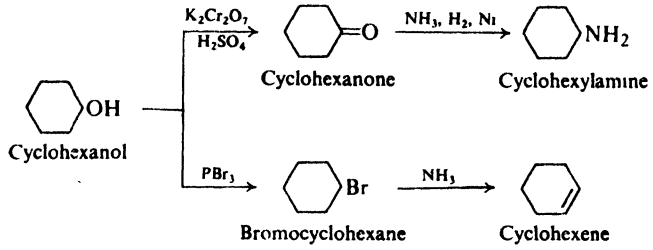
2-Aminopentane



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

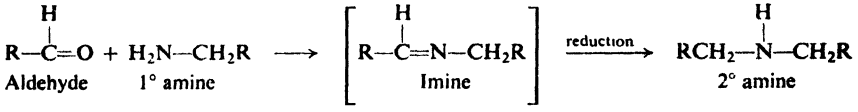
Cyclohexanone

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

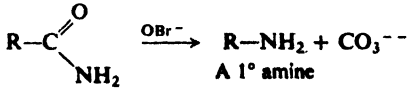
Imine

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

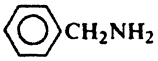


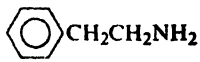
An amide

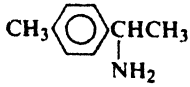
A 1° amine

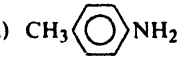
carbon to the adjacent nitrogen atom, and thus is an example of a *molecular rearrangement*. We shall return to the Hofmann degradation (Secs. 28.2–28.5) and discuss its mechanism in detail.

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) 

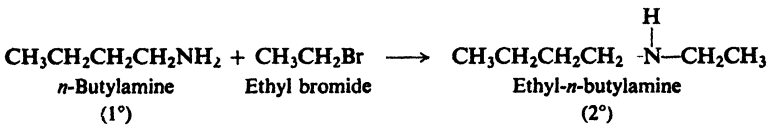
(b) 

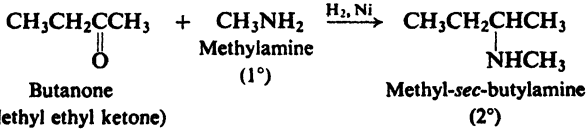
(d) 

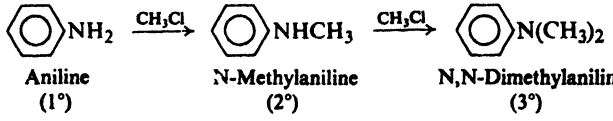
(e) 

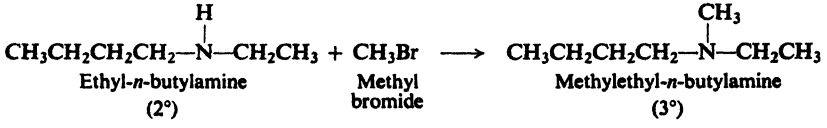
22.13 Synthesis of secondary and tertiary amines

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 ($C_4H_{12}N_2$)

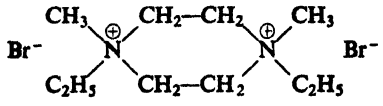
(b) $Br(CH_2)_5Br$ $\xrightarrow{NH_3}$ cadaverine ($C_5H_{14}N_2$)

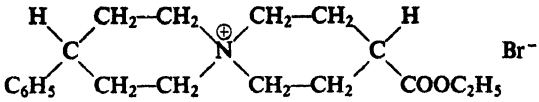
7. One of the raw materials for the manufacture of Nylon 66 is *hexamethylenediamine*, $NH_2(CH_2)_6NH_2$. Much of this amine is made by a process that begins with the 1,4-addition of chlorine to 1,3-butadiene. What do you think might be the subsequent steps in this process?

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

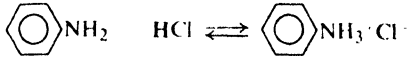
1. Basicity. Salt formation. Discussed in Secs. 22.5 and 23.2–23.4.

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

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

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

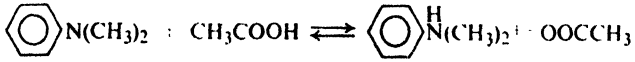
Examples:



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

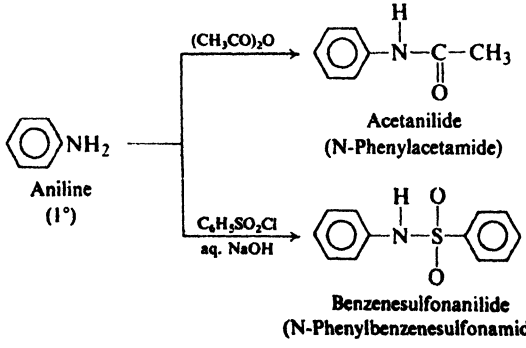
Secondary: R_2NH

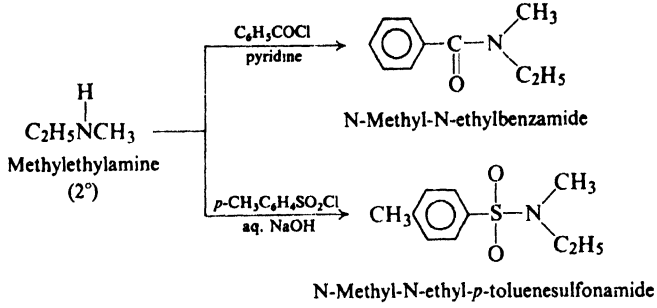
- $\xrightarrow{R'COCl}$ $R'CONR_2$ An N,N-disubstituted amide
- $\xrightarrow{ArSO_2Cl}$ $ArSO_2NR_2$ An N,N-disubstituted sulfonamide

Tertiary: R_3N

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

Examples:



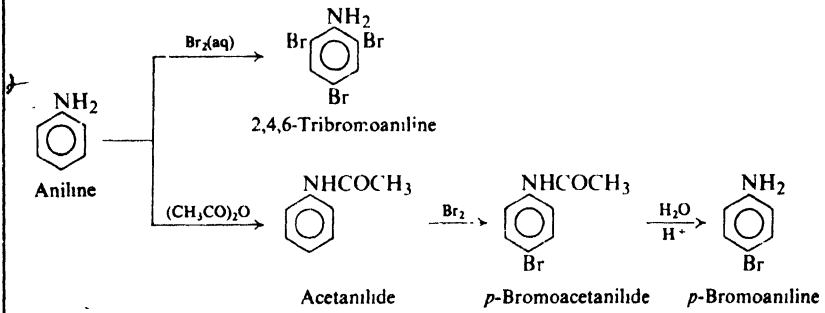


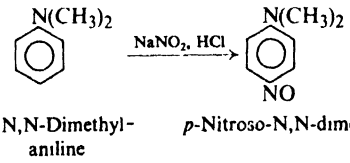
♥ **4. Ring substitution in aromatic amines.** Discussed in Secs. 23.7, 23.10, and 23.17.

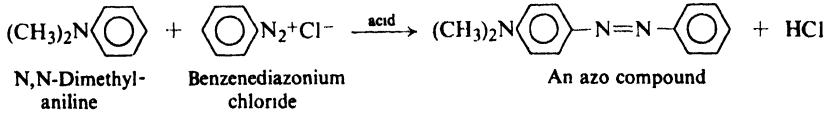
—NH_2, —NHR, —NR_2: Activate powerfully, and direct *ortho, para* in electrophilic aromatic substitution

—NHCOR: Less powerful activator than —NH_2

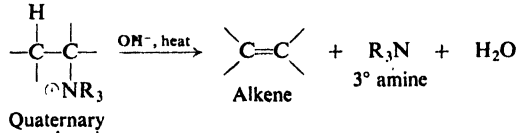
Examples:







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

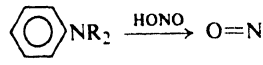


6. Reactions with nitrous acid. Discussed in Secs. 23.10–23.11.

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}

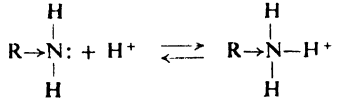
	K_b		K_b		K_b
p-NH_2	140×10^{-10}	*m*-NH_2	10×10^{-10}	*o*-NH_2	3×10^{-10}
p-OCH_3	20	*m*-OCH_3	2	*o*-OCH_3	3
p-CH_3	12	*m*-CH_3	5	*o*-CH_3	2.6
p-Cl	1	*m*-Cl	.3	*o*-Cl	.05
p-NO_2	.001	*m*-NO_2	.029	*o*-NO_2	.00006

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.

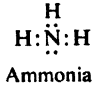
An aliphatic amine is more basic than ammonia because the electron-releasing alkyl groups tend to disperse the positive charge of the substituted ammonium ion, and therefore stabilize it in a way that is not possible for the unsubstituted ammonium ion. Thus an *ammonium* ion is stabilized by electron 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.)



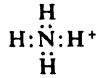
R *releases electrons:* *makes unshared pair more available*

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:

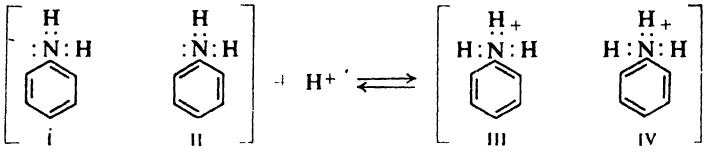


Ammonia



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

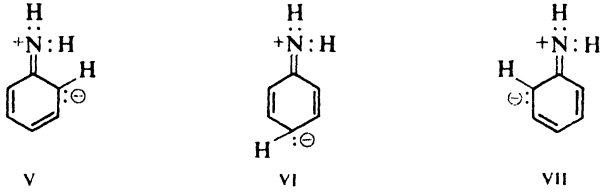


Aniline Anilinium ion

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.

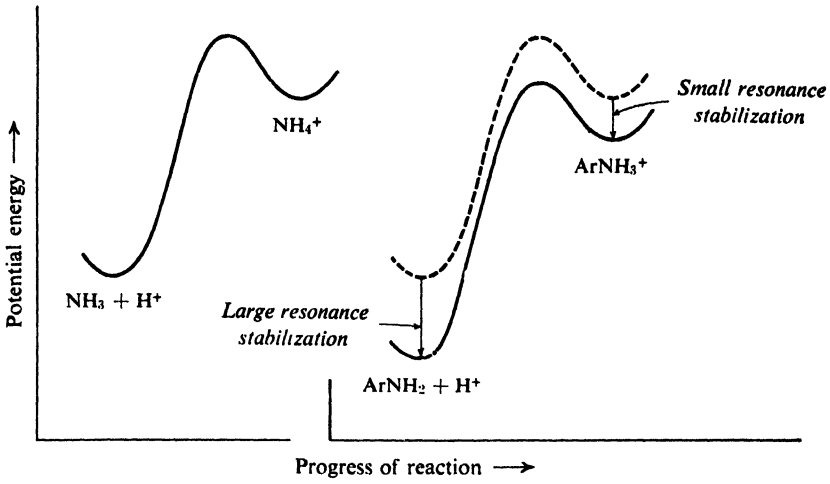


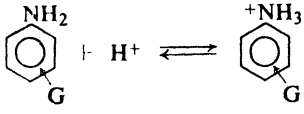
Figure 23.1. Molecular structure and position of equilibrium. Resonance-stabilized aromatic amine is weaker base than ammonia. (Plots aligned with each other for easy comparison.)

23.4 Effect of substituents on basicity of aromatic amines

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

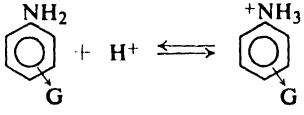
In Table 23.1 (p. 749) we see that an electron-releasing substituent like $-CH_3$ increases the basicity of aniline, and an electron-withdrawing substituent like $-X$ or $-NO_2$ decreases the basicity. These effects are understandable. Electron release tends to disperse the positive charge of the anilinium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

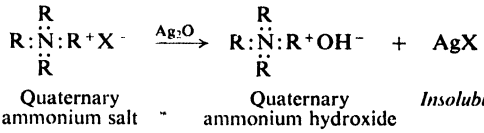
$$\underset{1^\circ}{RNH_2} \xrightarrow{RX} \underset{2^\circ}{R_2NH} \xrightarrow{RX} \underset{3^\circ}{R_3N} \xrightarrow{RX} \underset{4^\circ}{R_4N^+X^-}$$

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.

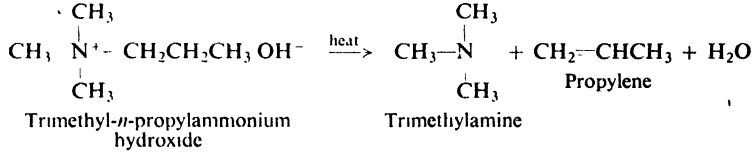
Quaternary ammonium salts are the products of the final stage of alkylation of nitrogen. They have the formula $R_4N^+X^-$. Four organic groups are covalently bonded to nitrogen, and the positive charge of this ion is balanced by some nega-

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.

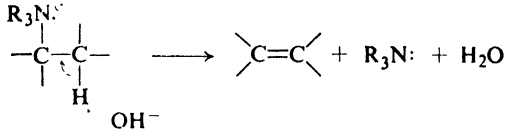


When a solution of a quaternary ammonium halide is treated with silver oxide, silver halide precipitates. When the mixture is filtered and the filtrate is evaporated to dryness, there is obtained a solid which is free of halogen. An aqueous solution of this substance is strongly alkaline, and is comparable 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.

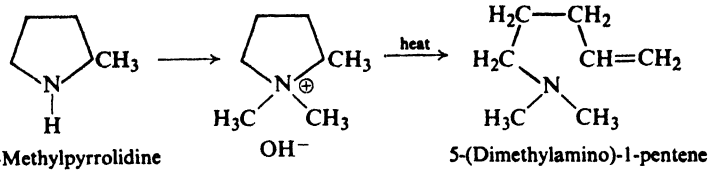
Problem 23.3 Predict the major products of E2 elimination from: (a) 2-methyl-3-pentyltrimethylammonium ion; (b) diethyldi-*n*-propylammonium ion; (c) dimethylethyl(2-chloroethyl)ammonium ion; (d) dimethylethyl-*n*-propylammonium ion.

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?

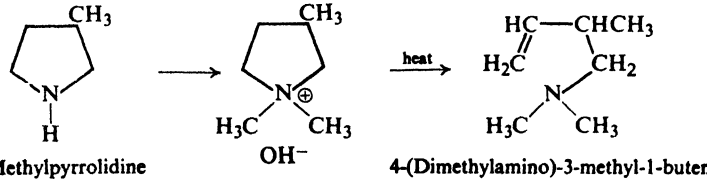
The formation of quaternary ammonium salts, followed by an elimination of the kind just described, is very useful in the determination of the structures of certain complicated nitrogen-containing compounds. The compound, which may be a primary, secondary, or tertiary amine, is converted into the quaternary 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

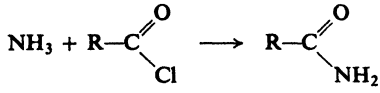
II

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?

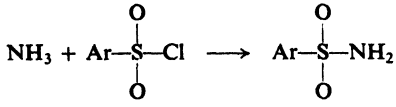
Problem 23.6 What products would be expected if I and II were subjected to exhaustive methylation and elimination?

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



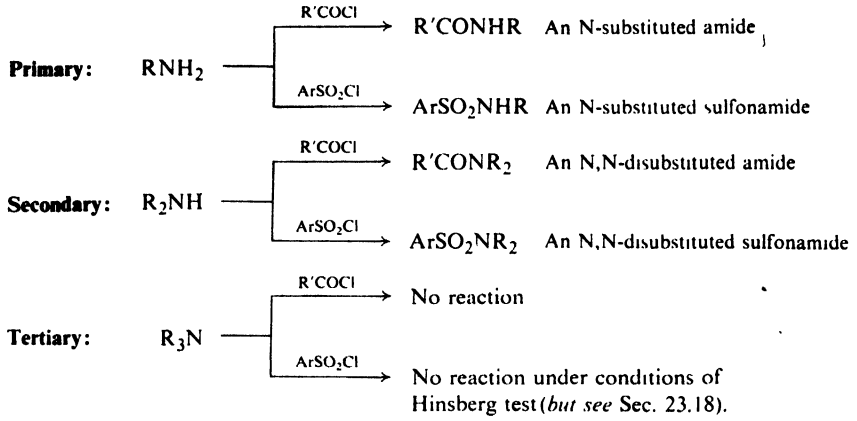
the $-NH_2$ group. Not surprisingly, acid chlorides of sulfonic acids react similarly.



A sulfonyl chloride A sulfonamide

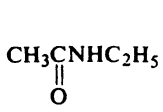
In these reactions ammonia serves as a nucleophilic reagent, attacking the carbonyl carbon or sulfur and displacing chloride ion. In the process nitrogen loses a proton to a second molecule of ammonia or another base.

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:

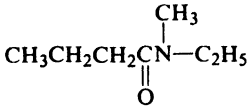


Tertiary amines, although basic, fail to yield amides, presumably because they cannot lose a proton (to stabilize the product) after attaching themselves to carbon or to sulfur. Here is a reaction which requires not only that amines be basic, but also that they possess a hydrogen atom attached to nitrogen.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

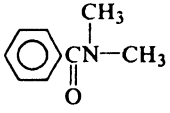
Substituted amides are generally named as derivatives of the unsubstituted amides. For example:



N-Ethylacetamide

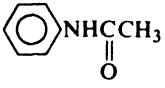


N-Methyl-N-ethylbutyramide

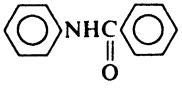


N,N-Dimethylbenzamide

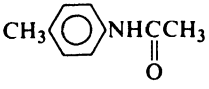
In many cases, and particularly where aromatic amines are involved, we are more interested in the amine from which the amide is derived than in the acyl group. In these cases the substituted amide is named as an acyl derivative of the amine. For example:



Acetanilide

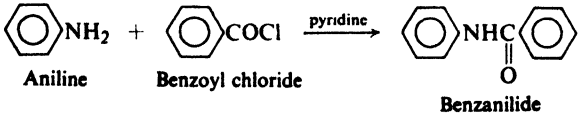


Benzanilide

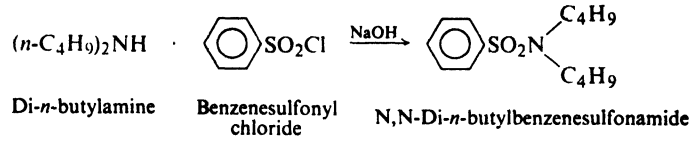


Aceto-*p*-toluidide

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:

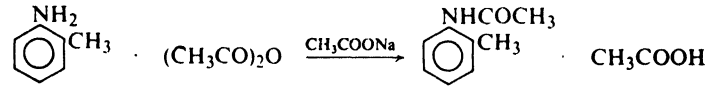


Aniline + Benzoyl chloride → Benzanilide



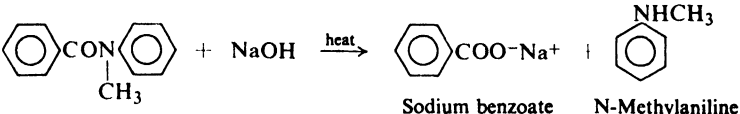
Di-*n*-butylamine | Benzenesulfonyl chloride | N,N-Di-*n*-butylbenzenesulfonamide

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

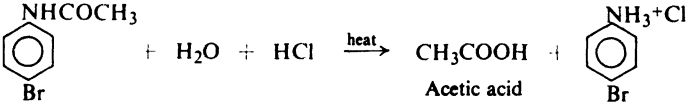


o-Toluidine | Acetic anhydride | Aceto-*o*-toluidide

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.

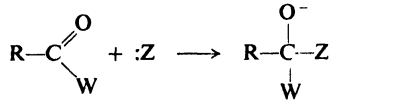


N-Methylbenzanilide | Sodium benzoate | N-Methylaniline



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

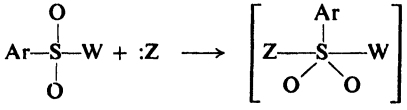
Sulfonamides are hydrolyzed more slowly than amides of carboxylic acids; examination of the structures involved shows us what probably underlies this difference. Nucleophilic attack on a trigonal acyl carbon (Sec. 20.4) is relatively unhindered; it involves the temporary attachment of a fourth group,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



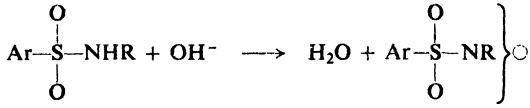
Tetrahedral S | Pentavalent S

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?

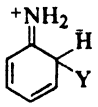
Problem 23.8 In contrast to carboxylic esters, we know, alkyl sulfonates undergo nucleophilic attack at alkyl carbon. What *two* factors are responsible for this difference

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

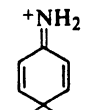
The conversion of an amine into a sulfonamide is used in determining the class of the amine; this is discussed in the section on analysis (Sec. 23.18).

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.

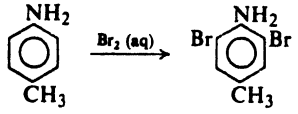
In such structures nitrogen shares more than one pair of electrons with the ring, and hence carries the charge of the "carbonium ion." Thus the basicity of nitrogen accounts for one more characteristic of aromatic amines.

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.)

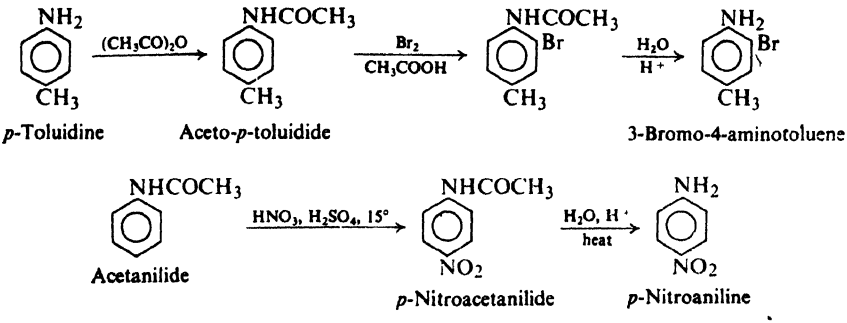
In electrophilic substitution, the chief problem encountered with aromatic amines is that they are *too* reactive. In halogenation, substitution tends to occur at every available *ortho* or *para* position. For example:



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.

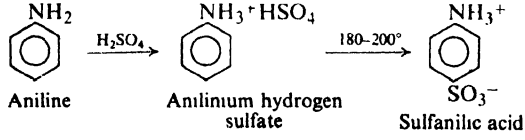
There is, fortunately, a simple way out of these difficulties: We *protect* the amino group: we acetylate the amine, then carry out the substitution, and finally hydrolyze the amide to the desired substituted amine. For example:



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

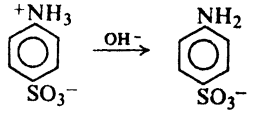


known to be reversible, and the *p*-isomer is known to be the most stable isomer; it may well be that the product obtained, the *p*-isomer, is determined by the position of an equilibrium and not by relative rates of formation (see Sec. 8.22 and Sec. 12.11). It also seems likely that, in some cases at 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^+.

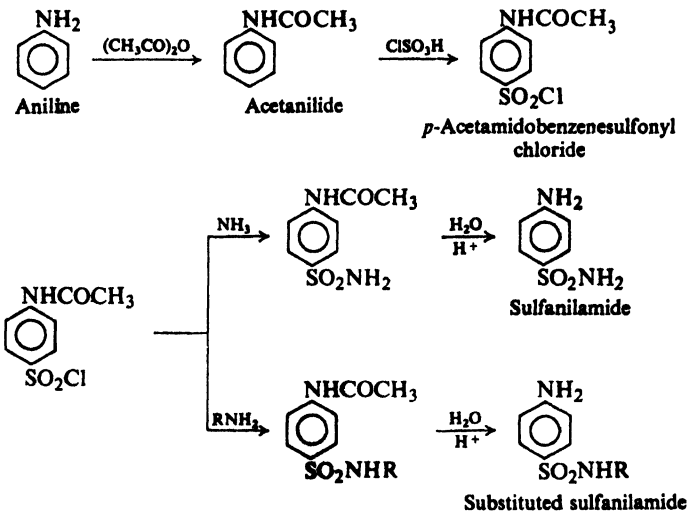
We can expect to encounter dipolar ions whenever we have a molecule containing both an amino group and an acid group, providing the amine is more basic than the anion of the acid.

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?

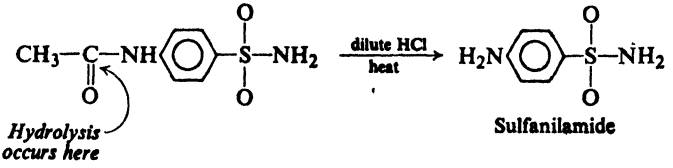
23.9 Sulfanilamide. The sulfa drugs

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:



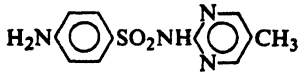
The selective removal of the acetyl group in the final step is consistent with the general observation that amides of carboxylic acids are more easily hydrolyzed than amides of sulfonic acids.



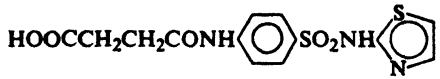
The antibacterial activity—and toxicity—of a sulfanilamide stems from a rather simple fact: enzymes in the bacteria (and in the patients) confuse it for *p*-aminobenzoic acid, which is an essential metabolite. In what is known as *metabolite antagonism*, the sulfanilamide competes with *p*-aminobenzoic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

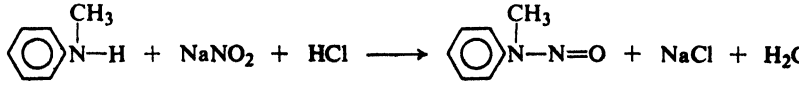
$$\underset{\substack{1^\circ \text{ aliphatic}\\ \text{amine}}}{RNH_2} + NaNO_2 + HX \longrightarrow \underset{\textit{Unstable}}{[RN_2^+X^-]} \xrightarrow{H_2O} N_2 + \text{mixture of alcohols and alkenes}$$

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.

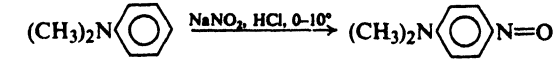
Secondary amines, both aliphatic and aromatic, react with nitrous acid to yield N-nitrosoamines.



N-Methylaniline

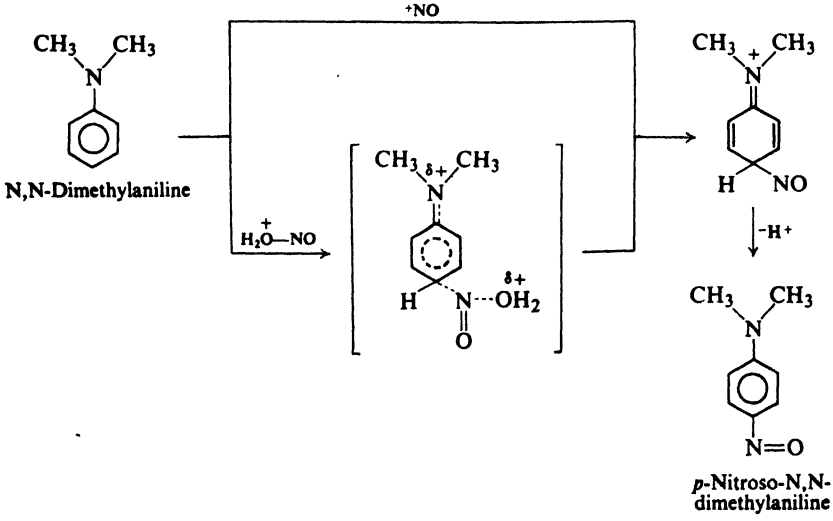
N-Nitroso-N-methylaniline

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

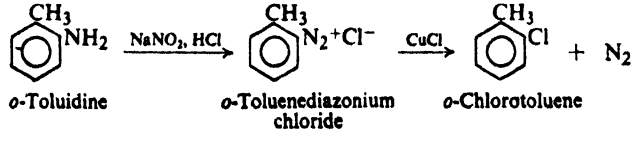
1. Replacement of nitrogen

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

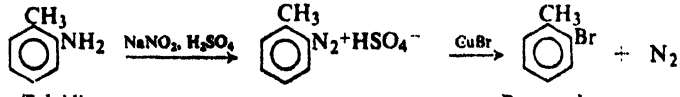
(a) **Replacement by —Cl, —Br, and —CN. Sandmeyer reaction.** Discussed in Secs. 23.12–23.13.

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

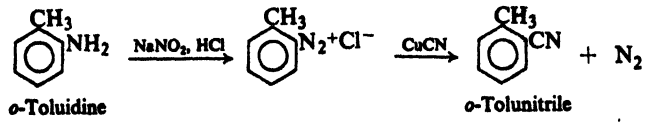
Examples:



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



o-Toluidine — *o*-Bromotoluene

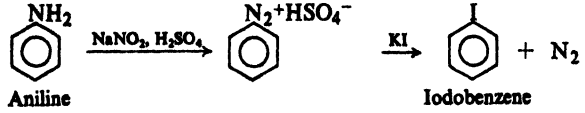


o-Toluidine *o*-Tolunitrile

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

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

Example:

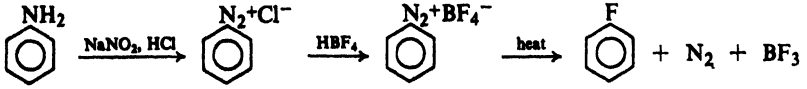


Aniline Iodobenzene

(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

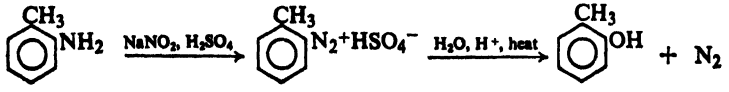
Isolated as crystalline salt

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

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

A phenol

Example:

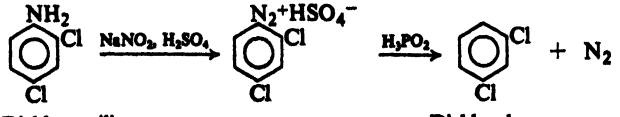


o-Toluidine *o*-Cresol

(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.

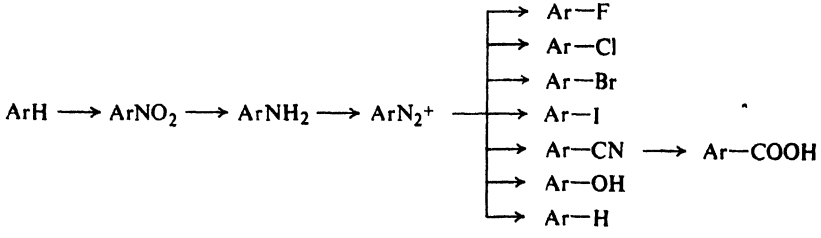
An azo compound

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, $ArN_2^+PF_6^-$.

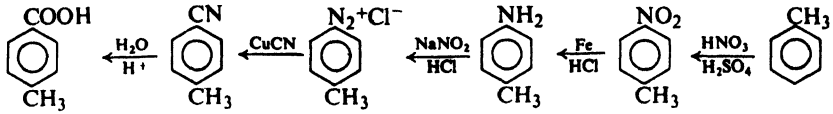
The advantages of the synthesis of aryl halides from diazonium salts will be discussed in detail in Sec. 25.3. Aryl fluorides and iodides cannot generally be prepared by direct halogenation. Aryl chlorides and bromides can be prepared by direct halogenation, but, when a mixture of *o*- and *p*-isomers 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:

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

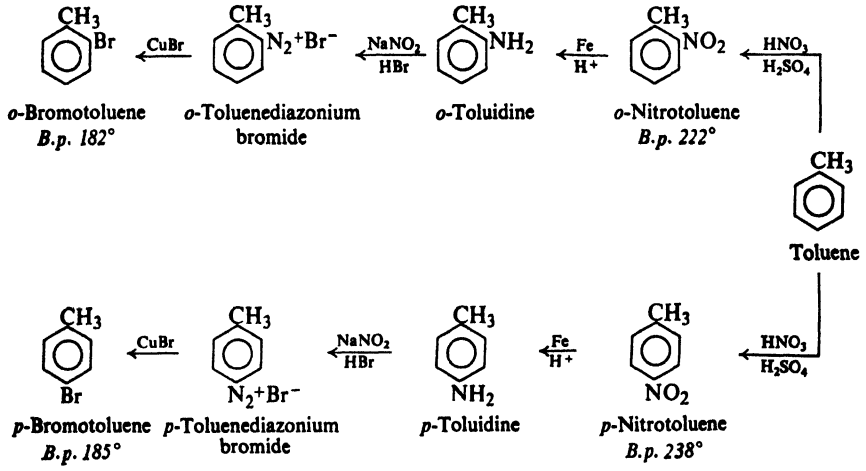
An especially elegant way of carrying out this replacement is to use hypophosphorous acid as the diazotizing acid. The amine is dissolved in hypophosphorous acid, and sodium nitrite is added; the diazonium salt is reduced as fast as it is formed.

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

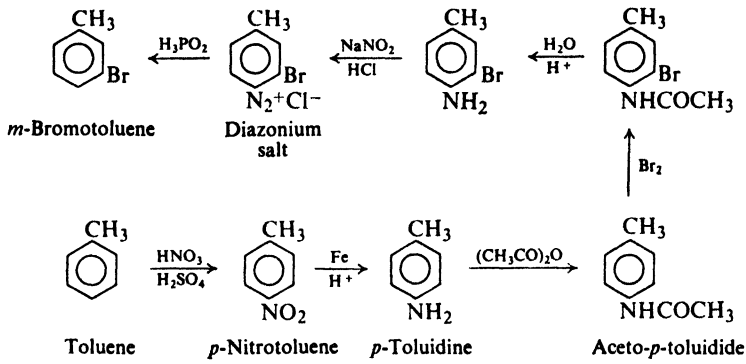
Let us look at a few examples of how diazonium salts can be used in organic synthesis.

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.

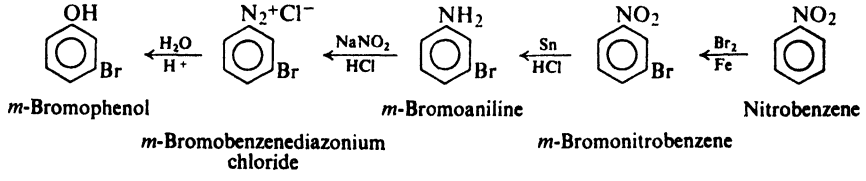
Synthesis of *m*-bromotoluene is a more complicated matter. The problem here is one of preparing a compound in which two *ortho,para*-directing groups are situated *meta* to each other. Bromination of toluene or methylation of bromobenzene would not yield the correct isomer. *m*-Bromotoluene is obtained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

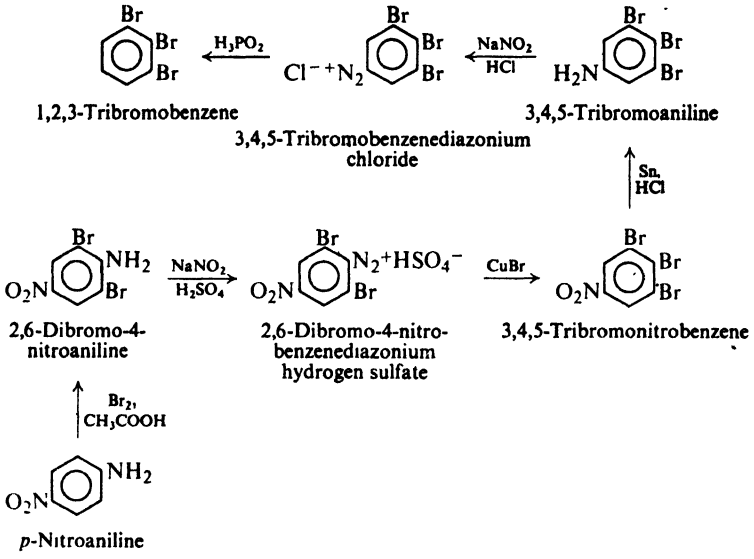
In the synthesis of *m*-bromotoluene, advantage was taken of the fact that the diazonium group is prepared from a group that is strongly *ortho,para*-directing. Ultimately, however, the diazonium group is prepared from the $-NO_2$ group, which is a strongly *meta*-directing group. Advantage can be taken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

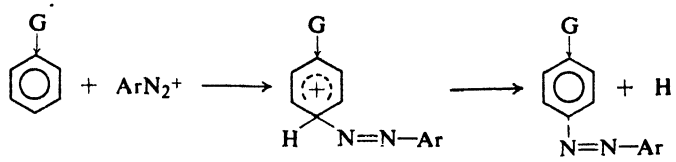
23.17 Coupling of diazonium salts. Synthesis of azo compounds

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.

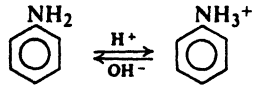
The electrophilic reagent is the diazonium ion, ArN_2^+. In the presence of hydroxide ion, the diazonium ion exists in equilibrium with an un-ionized compound, Ar—N=N—OH, and salts (Ar—N=N—O^-Na^+) derived from it:

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

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.

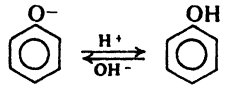
But what is the effect of high acidity on the amine or phenol with which the diazonium salt is reacting? Acid converts an amine into its ion, which, because of the positive charge, is relatively unreactive toward electrophilic aromatic substitution: much too unreactive to be attacked by the weakly electrophilic

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.

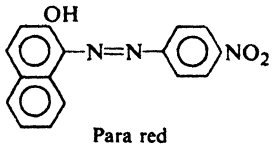
The conditions under which coupling proceeds most rapidly are the result of a compromise. The solution must not be so alkaline that the concentration of diazonium ion is too low; it must not be so acidic that the concentration of free amine or phenoxide ion is too low. It turns out that amines couple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

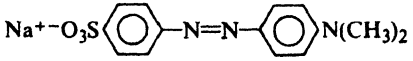
Problem 23.20 (a) Coupling of diazonium salts with primary or secondary aromatic amines (but not with tertiary aromatic amines) is complicated by a side reaction that yields an isomer of the azo compound. Judging from the reaction of secondary aromatic amines with nitrous acid (Sec. 23.10), suggest a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

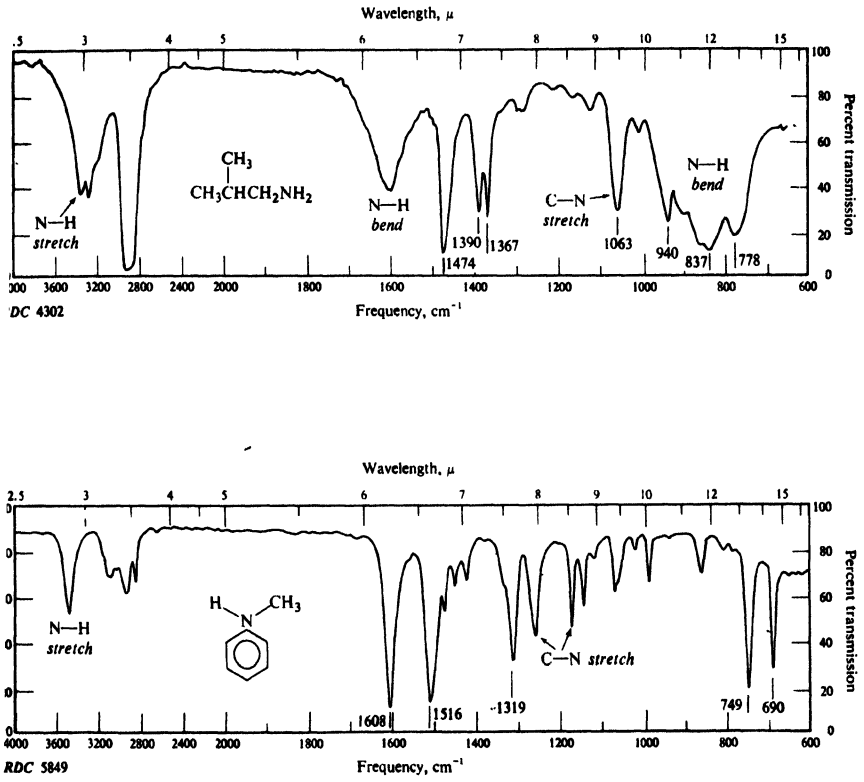


Figure 23.2. Infrared spectra of (*a*) isobutylamine and (*b*) N-methylaniline.

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

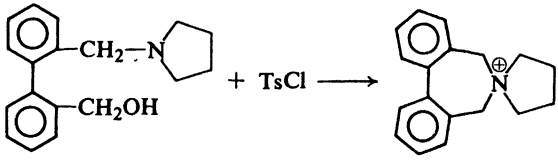
Review the instructions on page 224. Assume that an *ortho,para* mixture of isomeric nitro compounds can be separated by distillation (see Sec. 11.7).

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.

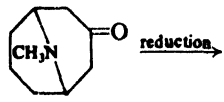
22. A solid compound D, of formula $C_{15}H_{15}ON$, was insoluble in water, dilute HCl, or dilute NaOH. After prolonged heating of D with aqueous NaOH, a liquid, E, was observed floating on the surface of the alkaline mixture. E did not solidify upon cooling to room temperature; it was steam-distilled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

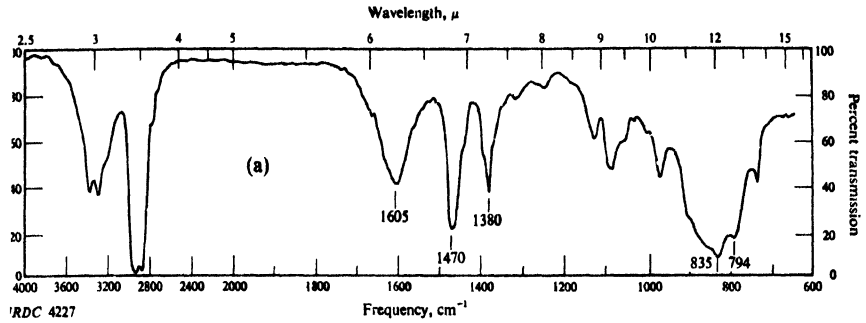
What was W? Write equations for all reactions.

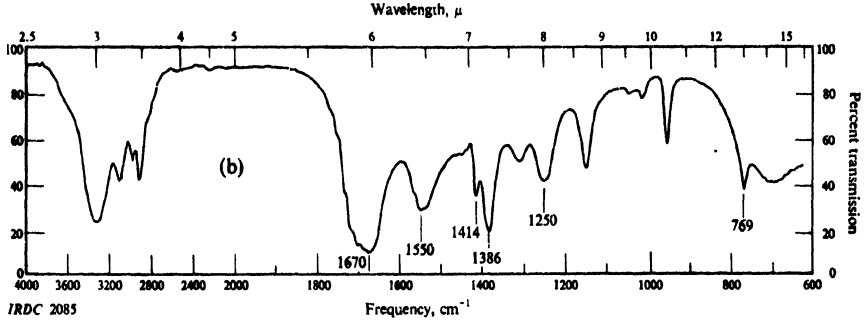
26. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 23.3 (p. 783)?

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).





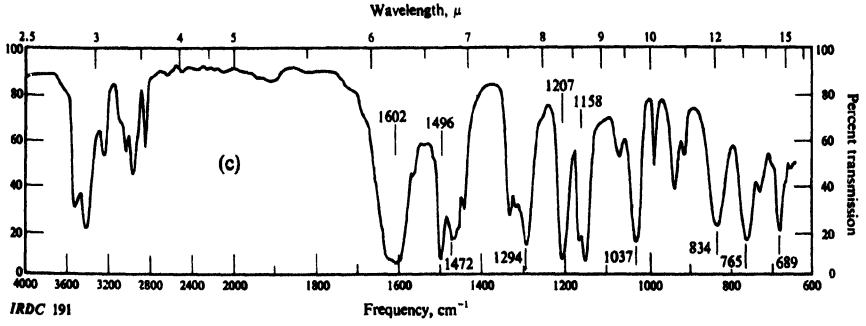


Figure 23.3. Infrared spectra for Problem 26, p. 782.

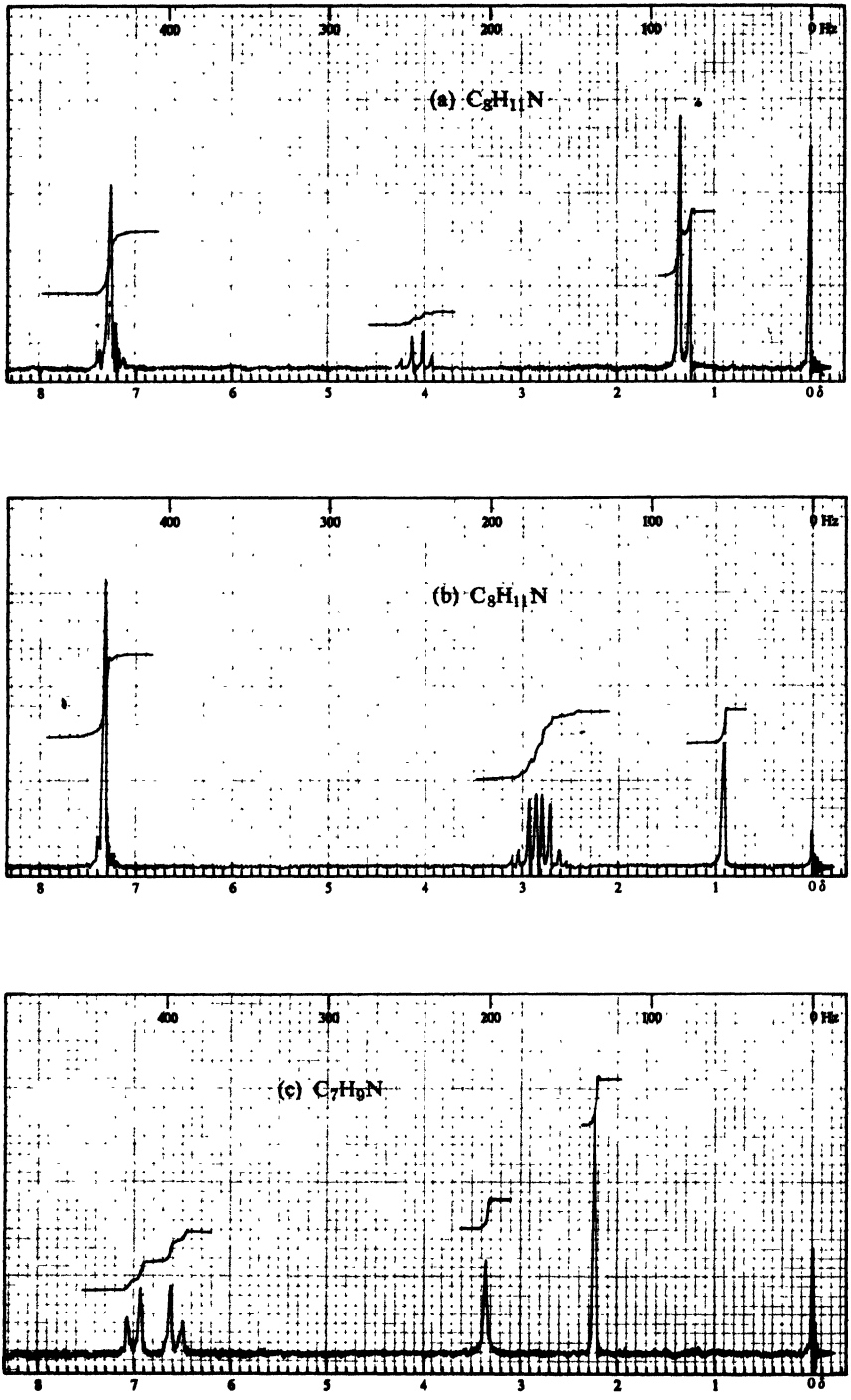
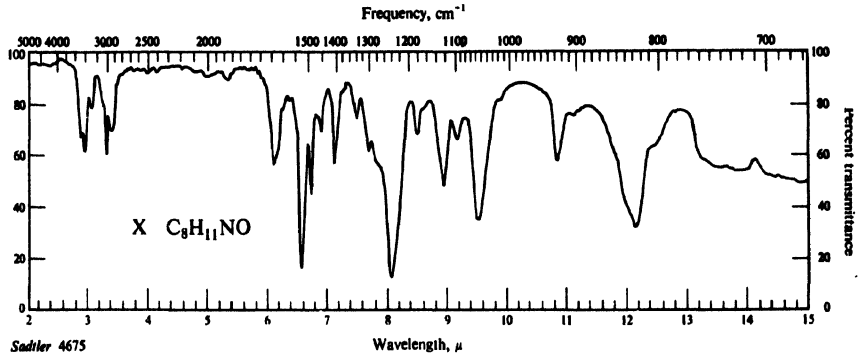
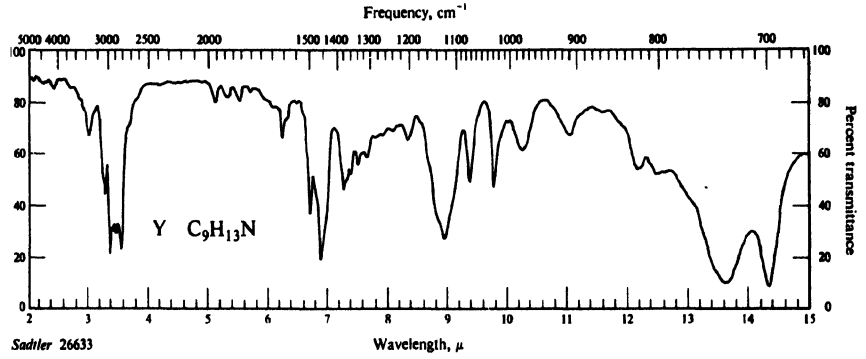


Figure 23.4. Nmr spectra for Problem 27, p. 782.





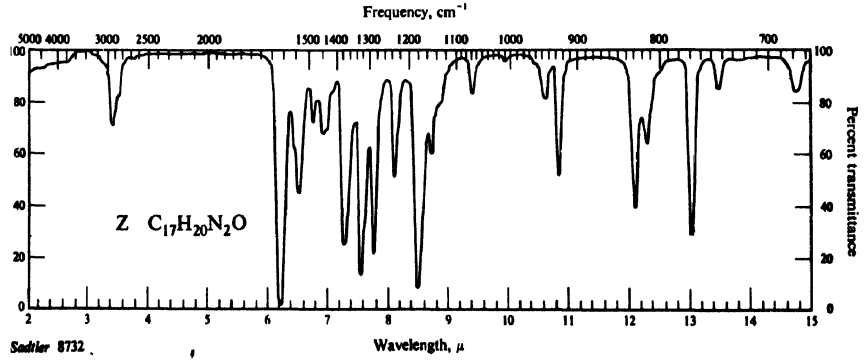


Figure 23.5. Infrared spectra for Problem 28, p. 782.

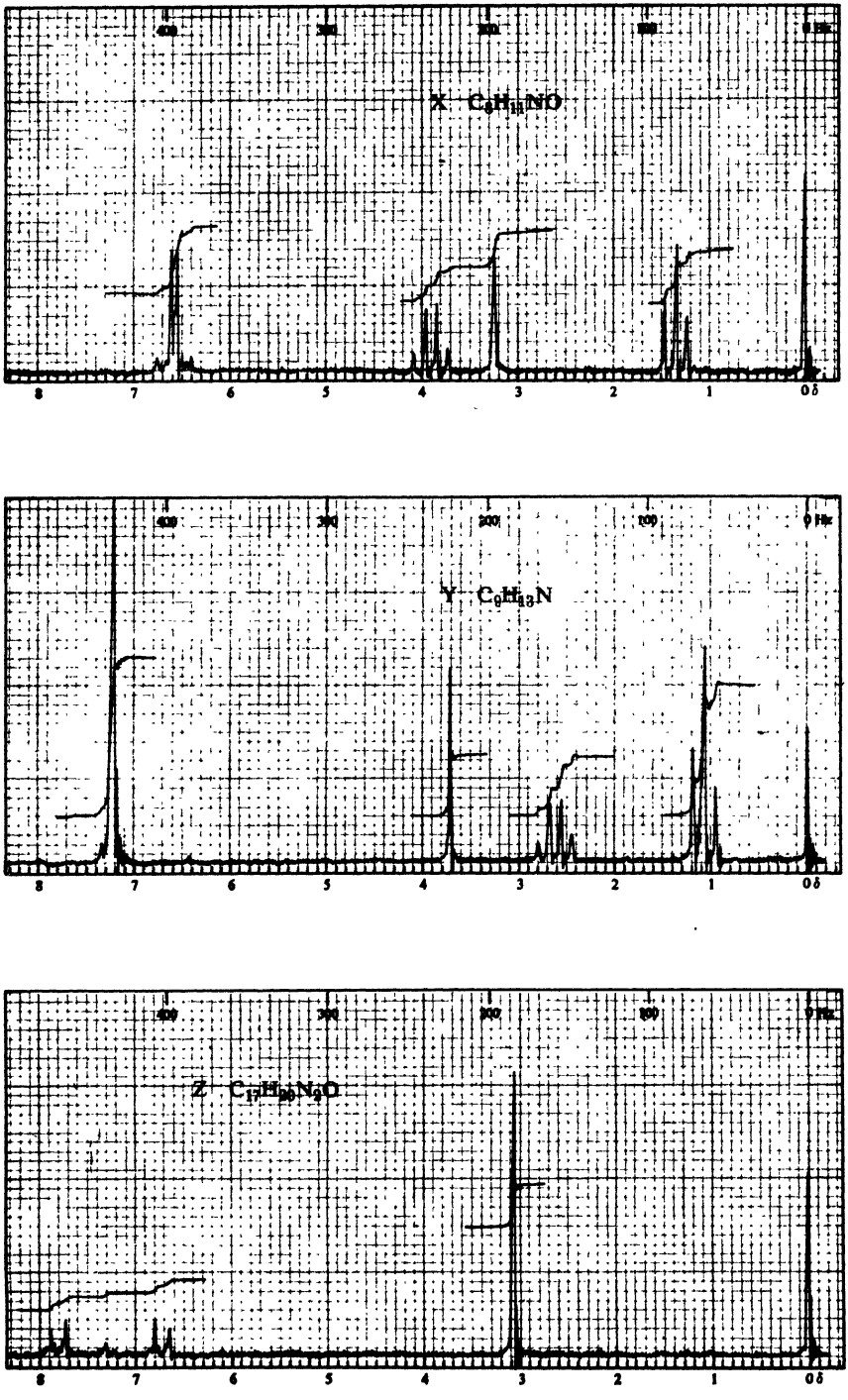


Figure 23.6. Nmr spectra for Problem 28, p. 782.

Chapter 24 Phenols

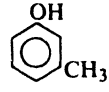
24.1 Structure and nomenclature

Phenols are compounds of the general formula ArOH, where Ar is **phenyl**, substituted phenyl, or one of the other aryl groups we shall study later (e.g., naphthyl, Chap. 30). *Phenols differ from alcohols in having the* —OH *group attached directly to an aromatic ring.*

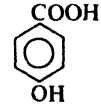
Phenols are generally named as derivatives of the simplest member of the family, **phenol**. The methylphenols are given the special name of *cresols*. Occasionally phenols are named as *hydroxy*– compounds.

Phenol

o-Chlorophenol



m-Cresol



p-Hydroxybenzoic acid

Catechol

Resorcinol

Hydroquinone

Salicylic acid

Both phenols and alcohols contain the —OH group, and as a result the two families resemble each other to a limited extent. We have already seen, for example, that both alcohols and phenols can be converted into ethers and esters. In most of their properties, however, and in their preparations, the two kinds of compound differ so greatly that they well deserve to be classified as different families.

24.2 Physical properties

The simplest phenols are liquids or low-melting solids; because of hydrogen bonding, they have quite high boiling points. Phenol itself is somewhat soluble

in water (9 g per 100 g of water), presumably because of hydrogen bonding with the water; most other phenols are essentially insoluble in water. Unless some group capable of producing color is present, phenols themselves are colorless. However, like aromatic amines, they are easily oxidized; unless carefully purified, many phenols are colored by oxidation products.

Table 24.1 PHENOLS

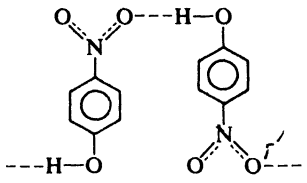
Name	M.p., °C	B.p., °C	Solub., g/100 g H_2O at 25°	K_a
Phenol	41	182	9.3	1.1×10^{-10}
o-Cresol	31	191	2.5	0.63
m-Cresol	11	201	2.6	0.98
p-Cresol	35	202	2.3	0.67
o-Fluorophenol	16	152		15
m-Fluorophenol	14	178		5.2
p-Fluorophenol	48	185		1.1
o-Chlorophenol	9	173	2.8	77
m-Chlorophenol	33	214	2.6	16
p-Chlorophenol	43	220	2.7	6.3
o-Bromophenol	5	194		41
m-Bromophenol	33	236		14
p-Bromophenol	64	236	1.4	5.6
o-Iodophenol	43			34
m-Iodophenol	40			13
p-Iodophenol	94			6.3
o-Aminophenol	174		1.7[0]	2.0
m-Aminophenol	123		2.6	69
p-Aminophenol	186		1.1[0]	
o-Nitrophenol	45	217	0.2	600
m-Nitrophenol	96		1.4	50
p-Nitrophenol	114		1.7	690
2,4-Dinitrophenol	113		0.6	1000000
2,4,6-Trinitrophenol (picric acid)	122		1.4	very large
Catechol	104	246	45	1
Resorcinol	110	281	123	3
Hydroquinone	173	286	8	2

An important point emerges from a comparison of the physical properties of the isomeric nitrophenols (Table 24.2). We notice that *o*-nitrophenol has a much lower boiling point and much lower solubility in water than its isomers; it is the only one of the three that is readily steam-distillable. How can these differences be accounted for?

Table 24.2 PROPERTIES OF THE NITROPHENOLS

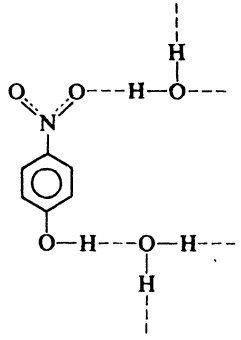
	B.p., °C at 70 mm	Solub., g/100 g H_2O	
o-Nitrophenol	100	0.2	Volatile in steam
m-Nitrophenol	194	1.35	Non-volatile in steam
p-Nitrophenol	*dec.*	1.69	Non-volatile in steam

Let us consider first the *m*- and *p*-isomers. They have very high boiling points because of intermolecular hydrogen bonding:



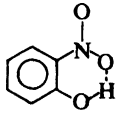
Intermolecular hydrogen bonding

Their solubility in water is due to hydrogen bonding with water molecules:



Steam distillation depends upon a substance having an appreciable vapor pressure at the boiling point of water; by lowering the vapor pressure, intermolecular hydrogen bonding inhibits steam distillation of the *m*- and *p*-isomers.

What is the situation for the *o*-isomer? Examination of models shows that the $-NO_2$ and $-OH$ groups are located exactly right for the formation of a



o-Nitrophenol

Intramolecular hydrogen bonding: chelation

hydrogen bond *within a single molecule*. This **intramolecular hydrogen bonding** takes the place of *inter*molecular hydrogen bonding with other phenol molecules and with water molecules; therefore *o*-nitrophenol does not have the low volatility of an associated liquid, nor does it have the solubility characteristic of a compound that forms hydrogen bonds with water.

The holding of a hydrogen or metal atom between two atoms of a single molecule is called **chelation** (Greek: *chele*, claw). See, for example, *chlorophyll* (p. 1004) and *hemin* (p. 1152).

Intramolecular hydrogen bonding seems to occur whenever the structure of a compound permits; we shall encounter other examples of its effect on physical properties.

Problem 24.1 Interpret the following observations. The O—H bands (Sec. 15.4) for the isomeric nitrophenols in solid form (KBr pellets) and in $CHCl_3$ solution are:

	KBr	$CHCl_3$
o-	3200 cm^{-1}	3200 cm^{-1}
m-	3330	3520
p-	3325	3530

Problem 24.2 In which of the following compounds would you expect intramolecular hydrogen bonding to occur: *o*-nitroaniline, *o*-cresol, *o*-hydroxybenzoic acid (salicylic acid), *o*-hydroxybenzaldehyde (salicylaldehyde), *o*-fluorophenol, *o*-hydroxybenzonitrile.

24.3 Salts of phenols

Phenols are fairly acidic compounds, and in this respect differ markedly from alcohols, which are even more weakly acidic than water. Aqueous hydroxides convert phenols into their salts; aqueous mineral acids convert the salts back into the free phenols. As we might expect, phenols and their salts have opposite solubility properties, the salts being soluble in water and insoluble in organic solvents.

$$\underset{\text{A phenol (acid)}}{\text{ArOH}} \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} \underset{\text{A phenoxide ion (salt)}}{\text{ArO}^-}$$

Insoluble in water — *Soluble in water*

Most phenols have K_a's in the neighborhood of 10^{-10}, and are thus considerably weaker acids than the carboxylic acids (K_a's about 10^{-5}). Most phenols are weaker than carbonic acid, and hence, unlike carboxylic acids, do not dissolve in aqueous bicarbonate solutions. Indeed, phenols are conveniently liberated from their salts by the action of carbonic acid.

$$\underset{}{CO_2 + H_2O} \rightleftharpoons \underset{\text{Stronger acid}}{H_2CO_3} + \underset{\textit{Soluble in water}}{ArO^-Na^+} \longrightarrow \underset{\text{Weaker acid}}{ArOH} + \underset{}{Na^+HCO_3^-}$$

Insoluble in water

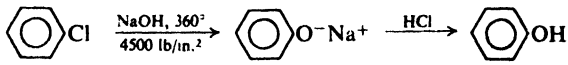
The acid strength of phenols and the solubility of their salts in water are useful both in analysis and in separations. A water-insoluble substance that dissolves in aqueous hydroxide but not in aqueous bicarbonate must be more acidic than water, but less acidic than a carboxylic acid; most compounds in this range of acidity are phenols. A phenol can be separated from non-acidic compounds by means of its solubility in base; it can be separated from carboxylic acids by means of its insolubility in bicarbonate.

Problem 24.3 Outline the separation by chemical methods of a mixture of *p*-cresol, *p*-toluic acid, *p*-toluidine, and *p*-nitrotoluene. Describe exactly what you would *do* and *see*.

24.4 · Industrial source

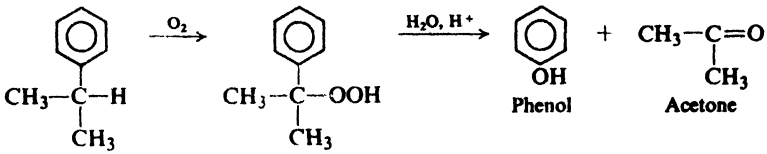
Most phenols are made industrially by the same methods that are used in the laboratory; these are described in Sec. 24.5. There are, however, special ways of obtaining certain of these compounds on a commercial scale, including the most important one, phenol. In quantity produced, phenol ranks near the top of the list of synthetic aromatic compounds. Its principal use is in the manufacture of the phenol–formaldehyde polymers (Sec. 32.7).

A certain amount of phenol, as well as the cresols, is obtained from coal tar (Sec. 12.4). Most of it (probably over 90%) is synthesized. One of the synthetic processes used is the fusion of sodium benzenesulfonate with alkali (Sec. 30.12); another is the Dow process, in which chlorobenzene is allowed to react with aqueous sodium hydroxide at a temperature of about 360°. Like the synthesis of aniline from chlorobenzene (Sec. 22.7), this second reaction involves nucleophilic substitution under conditions that are not generally employed in the laboratory (Sec. 25.4).



Chlorobenzene Sodium phenoxide Phenol

An increasingly important process for the synthesis of phenol starts with *cumene*, isopropylbenzene. Cumene is converted by air oxidation into cumene hydroperoxide, which is converted by aqueous acid into phenol and acetone.

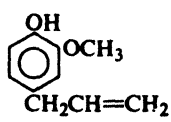


Cumene Cumene hydroperoxide Phenol Acetone

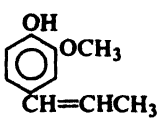
(The mechanism of this reaction is discussed in Sec. 28.6.)

Problem 24.4 Outline a synthesis of cumene from cheap, readily available hydrocarbons.

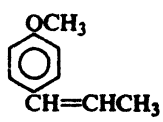
Certain phenols and their ethers are isolated from the *essential oils* of various plants (so called because they contain the *essence*—odor or flavor—of the plants). A few of these are:



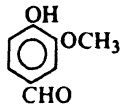
Eugenol
Oil of cloves



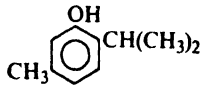
Isoeugenol
Oil of nutmeg



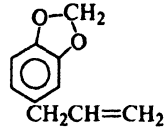
Anethole
Oil of aniseed



Vanillin
Oil of vanilla bean



Thymol
Oil of thyme and mint



Safrole
Oil of sassafras

24.5 Preparation

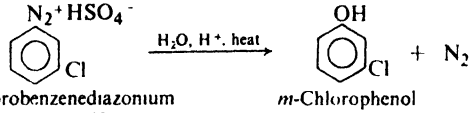
In the laboratory, phenols are generally prepared by one of the two methods outlined below.

PREPARATION OF PHENOLS

1. Hydrolysis of diazonium salts. Discussed in Sec. 23.14.

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

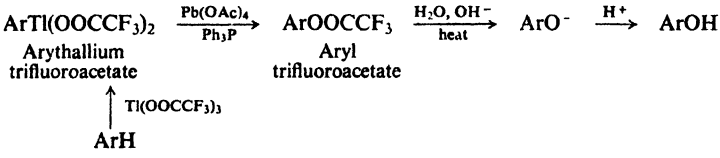
Example:



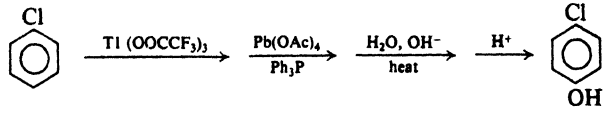
m-Chlorobenzenediazonium hydrogen sulfate

m-Chlorophenol

2. Oxidation of arylthallium compounds. Discussed in Sec. 24.5.



Example:



Chlorobenzene

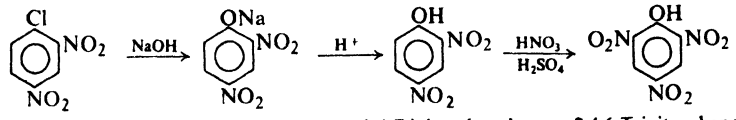
p-Chlorophenol
Only isomer

3. Alkali fusion of sulfonates. Discussed in Sec. 30.12.

Hydrolysis of diazonium salts is a highly versatile method of making phenols. It is the last step in a synthetic route that generally begins with nitration (Secs. 23.11 and 23.14).

Much simpler and more direct is a recently developed route via thallation. An arylthallium compound is oxidized by lead tetraacetate (in the presence of triphenylphosphine, Ph_3P) to the phenolic ester of trifluoroacetic acid, which on hydrolysis yields the phenol. The entire sequence, including thallation, can be carried out without isolation of intermediates. Although the full scope of the method has not yet been reported, it has two advantages over the diazonium route: (a) the speed and high yield made possible by the fewer steps; and (b) orientation control in the thallation step. (Review Secs. 11.7 and 11.13.)

Of limited use is the hydrolysis of aryl halides containing strongly electron-withdrawing groups *ortho* and *para* to the halogen (Sec. 25.9); 2,4-dinitrophenol and 2,4,6-trinitrophenol (*picric acid*) are produced in this way on a large scale:



2,4-Dinitrochlorobenzene — Sodium 2,4-dinitrophenoxide — 2,4-Dinitrophenol — 2,4,6-Trinitrophenol — Picric acid

Problem 24.5 Outline all steps in the synthesis *from toluene* of: (a) *p*-cresol via diazotization; (b) *p*-cresol via thallation; (c) and (d) *m*-cresol via each route. (*Hint:* See Secs. 23.16 and 11.13.)

24.6 Reactions

Aside from acidity, the most striking chemical property of a phenol is the extremely high reactivity of its ring toward electrophilic substitution. Even in ring substitution, acidity plays an important part; ionization of a phenol yields the $-O^-$ group, which, because of its full-fledged negative charge, is even more strongly electron-releasing than the —OH group.

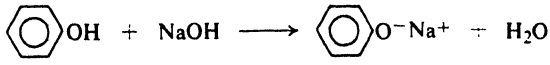
Phenols undergo not only those electrophilic substitution reactions that are typical of most aromatic compounds, but also many others that are possible only because of the unusual reactivity of the ring. We shall have time to take up only a few of these reactions.

REACTIONS OF PHENOLS

1. Acidity. Salt formation. Discussed in Secs. 24.3 and 24.7.

$$ArOH + H_2O \rightleftharpoons ArO^- + H_3O^+$$

Example:

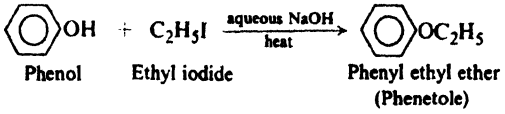


Phenol — Sodium phenoxide

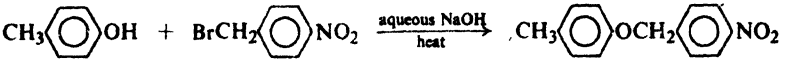
2. Ether formation. Williamson synthesis. Discussed in Secs. 17.5 and 24.8.

$$ArO^- + RX \longrightarrow ArOR + X^-$$

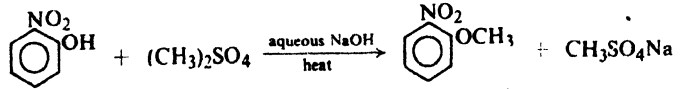
Examples:



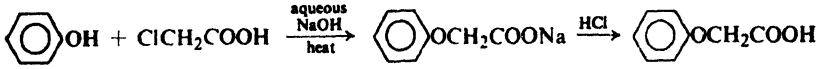
Phenol Ethyl iodide Phenyl ethyl ether (Phenetole)



p-Cresol *p*-Nitrobenzyl bromide *p*-Tolyl *p*-nitrobenzyl ether

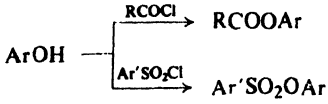


o-Nitrophenol Methyl sulfate *o*-Nitroanisole (*o*-Nitrophenyl methyl ether)

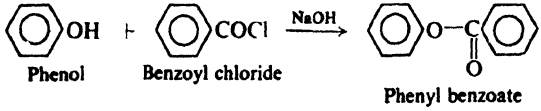


Phenol Chloroacetic acid Phenoxyacetic acid

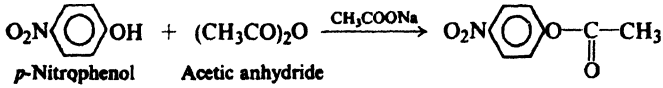
3. **Ester formation.** Discussed in Secs. 20.8, 20.15, and 24.9.



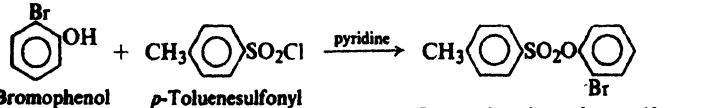
Examples:



Phenol Benzoyl chloride Phenyl benzoate



p-Nitrophenol Acetic anhydride *p*-Nitrophenyl acetate



o-Bromophenol *p*-Toluenesulfonyl chloride *o*-Bromophenyl *p*-toluenesulfonate

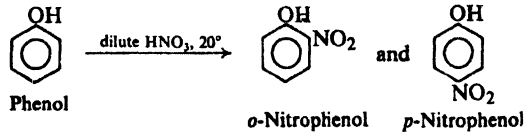
4. **Ring substitution.** Discussed in Sec. 24.10.

—OH, —O⁻ } Activate powerfully, and direct *ortho,para* in electrophilic aromatic substitution.

—OR: Less powerful activator than —OH.

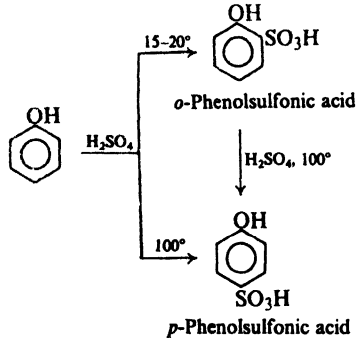
(a) **Nitration.** Discussed in Sec. 24.10.

Example:



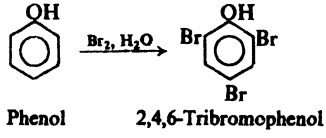
(b) **Sulfonation.** Discussed in Sec. 24.10.

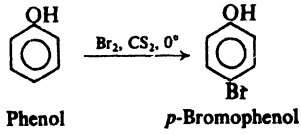
Example:



(c) **Halogenation.** Discussed in Sec. 24.10.

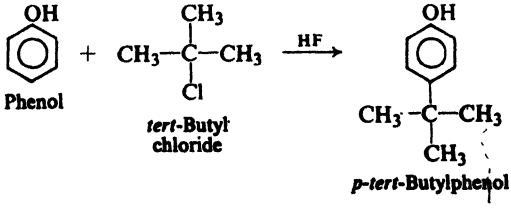
Examples:





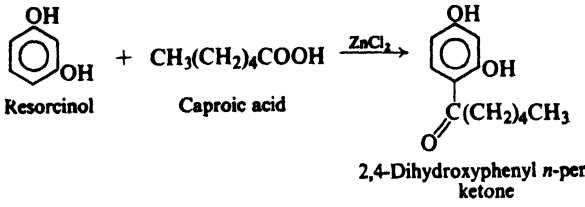
(d) **Friedel-Crafts alkylation.** Discussed in Sec. 24.10.

Example:

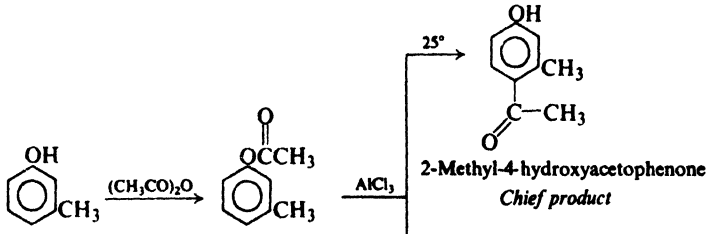


(e) Friedel-Crafts acylation. Fries rearrangement. Discussed in Secs. 24.9 and 24.10.

Examples:



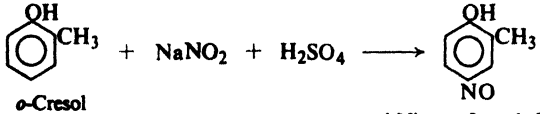
Resorcinol Caproic acid 2,4-Dihydroxyphenyl *n*-pentyl ketone



m-Cresol *m*-Cresyl acetate

(f) Nitrosation. Discussed in Sec. 24.10.

Example:

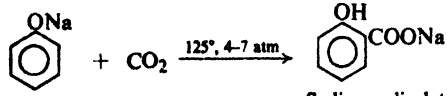


o-Cresol 4-Nitroso-2-methylphenol

(g) Coupling with diazonium salts. Discussed in Secs. 23.17 and 24.10.

(h) Carbonation. Kolbe reaction. Discussed in Sec. 24.11.

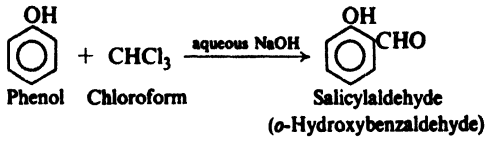
Example:



Sodium phenoxide Sodium salicylate (Sodium *o*-hydroxybenzoate)

(i) Aldehyde formation. Reimer-Tiemann reaction. Discussed in Sec. 24.12.

Example:



(j) Reaction with formaldehyde. Discussed in Sec. 32.7.

24.7 Acidity of phenols

Phenols are converted into their salts by aqueous hydroxides, but not by aqueous bicarbonates. The salts are converted into the free phenols by aqueous mineral acids, carboxylic acids, or carbonic acid.

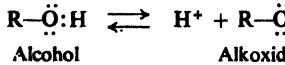
$$\underset{\text{Stronger acid}}{ArOH} + OH^- \longrightarrow \underset{\text{Weaker acid}}{ArO^-} + H_2O$$

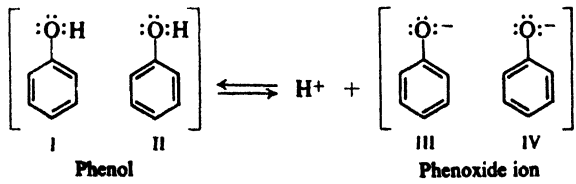
$$\underset{\text{Stronger acid}}{ArO^-} + H_2CO_3 \longrightarrow \underset{\text{Weaker acid}}{ArOH} + HCO_3^-$$

Phenols must therefore be considerably stronger acids than water, but considerably weaker acids than the carboxylic acids. Table 24.1 (p. 788) shows that this is indeed so: most phenols have K_a's of about 10^{-10}, whereas carboxylic acids have K_a's of about 10^{-5}.

Although weaker than carboxylic acids, phenols are tremendously more acidic than alcohols, which have K_a's in the neighborhood of 10^{-16} to 10^{-18} How does it happen that an —OH attached to an aromatic ring is so much more acidic than an —OH attached to an alkyl group? The answer is to be found in an examination of the structures involved. As usual we shall assume that differences in acidity are due to differences in stabilities of reactants and products (Sec. 18.12).

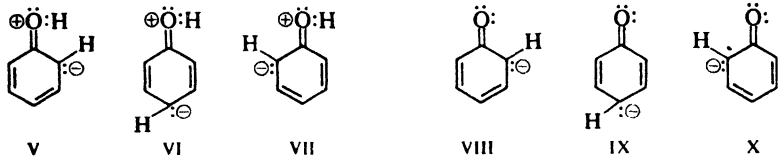
Let us examine the structures of reactants and products in the ionization of an alcohol and of phenol. We see that the alcohol and the alkoxide ion are each represented satisfactorily by a single structure. Phenol and the phenoxide ion





contain a benzene ring and therefore must be hybrids of the Kekulé structures I and II, and III and IV. This resonance presumably stabilizes both molecule 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. If there were no other factors involved, then, we might expect the acidity of a phenol to be about the same as the acidity of an alcohol.

However, there are additional structures to be considered. Being basic, oxygen can share more than a pair of electrons with the ring; this is indicated by contribution from structures V–VII for phenol, and VIII–X for the phenoxide ion.



V VI VII VIII IX X

Phenol Phenoxide ion

Now, are these two sets of structures equally important? Structures V-VII for phenol carry both positive and negative charges; structures VIII–X for phenoxide ion carry only a negative charge. Since energy must be supplied to separate opposite charges, the structures for the phenol should contain more energy and hence be less stable than the structures for phenoxide ion. (We have already encountered the effect of *separation of charge* on stability in Sec. 18.12.) The net effect of resonance is therefore to stabilize the phenoxide ion to a greater extent than the phenol, and thus to shift the equilibrium toward ionization and make K_a larger than for an alcohol (Fig. 24.1).

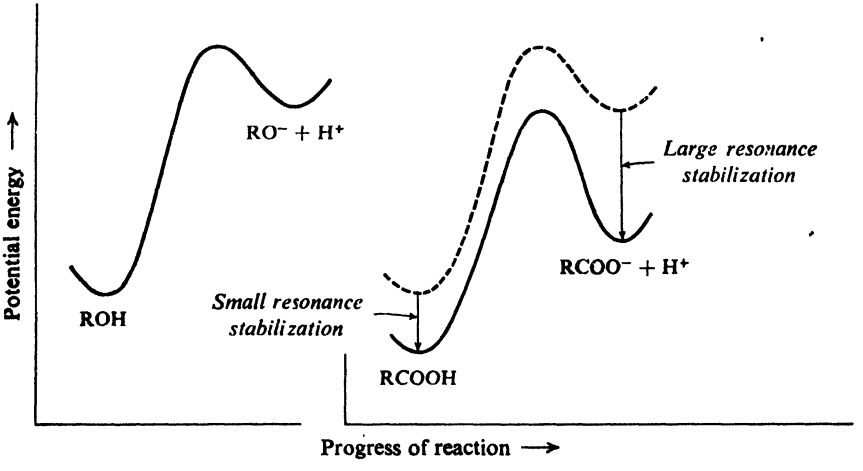


Figure 24.1. Molecular structure and position of equilibrium. Phenol yields resonance-stabilized anion; is stronger acid than alcohol. (Plots aligned with each other for easy comparison.)

We have seen (Sec. 23.3) that aromatic amines are weaker bases than aliphatic amines, since resonance stabilizes the free amine to a greater extent than it does the ion. Here we have exactly the opposite situation, phenols being stronger acids than their aliphatic counterparts, the alcohols, because resonance stabilizes the ion to a greater extent than it does the free phenol. (Actually, of course, resonance with the ring exerts the *same* effect in both cases; it stabilizes—and thus weakens—the base: amine or phenoxide ion.)

In Table 24.1 (p. 788) we see that electron-attracting substituents like —X or $-NO_2$ increase the acidity of phenols, and electron-releasing substituents like $-CH_3$ decrease acidity. Thus substituents affect acidity of phenols in the same way that they affect acidity of carboxylic acids (Sec. 18.14); it is, of course, opposite to the way these groups affect basicity of amines (Sec. 23.4). Electron-attracting substituents tend to disperse the negative charge of the phenoxide ion, whereas electron-releasing substituents tend to intensify the charge.

Problem 24.6 How do you account for the fact that, unlike most phenols, 2,4-dinitrophenol and 2,4,6-trinitrophenol are soluble in aqueous sodium bicarbonate?

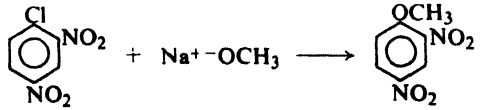
We can see that a group attached to an aromatic ring affects *position of equilibrium* in reversible reactions in the same way that it affects *rate* in irreversible reactions. An electron-releasing group favors reactions in which the ring becomes more positive, as in electrophilic substitution or in the conversion of an amine into its salt. An electron-withdrawing group favors reactions in which the ring becomes more negative, as in nucleophilic substitution (Chap. 25) or in the conversion of a phenol or an acid into its salt.

24.8 Formation of ethers. Williamson synthesis

As already discussed (Sec. 17.5), phenols are converted into ethers by reaction in alkaline solution with alkyl halides; methyl ethers can also be prepared by reaction with methyl sulfate. In alkaline solutions a phenol exists as the phenoxide ion which, acting as a nucleophilic reagent, attacks the halide (or the sulfate) and displaces halide ion (or sulfate ion).

$$ArOH \xrightarrow{OH^-} ArO^- \begin{cases} \xrightarrow{RX} Ar{-}O{-}R \cdot X^- \\ \xrightarrow{(CH_3)_2SO_4} Ar{-}O{-}CH_3 \cdot CH_3OSO_3^- \end{cases}$$

Certain ethers can be prepared by the reaction of unusually active aryl halides with sodium alkoxides. For example:

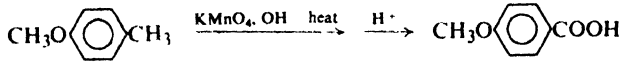


2,4-Dinitrochlorobenzene

2,4-Dinitroanisole
(2,4-Dinitrophenyl methyl ether)

While alkoxy groups are activating and *ortho,para*-directing in electrophilic aromatic substitution, they are considerably less so than the —OH group. As a result ethers do not generally undergo those reactions (Secs. 24.10–24.12) which require the especially high reactivity of phenols: coupling, Kolbe reaction, Reimer-Tiemann reaction, etc. This difference in reactivity is probably due to the fact that, unlike a phenol, an ether cannot ionize to form the extremely reactive phenoxide ion.

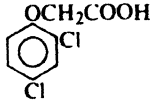
As a consequence of the lower reactivity of the ring, an aromatic ether is less sensitive to oxidation than a phenol. For example:



p-Methylanisole Anisic acid

We have already discussed the cleavage of ethers by acids (Sec. 17.7). Cleavage of methyl aryl ethers by concentrated hydriodic acid is the basis of an important analytical procedure (the *Zeisel procedure*, Sec. 17.16).

Problem 24.7 2,4-Dichlorophenoxyacetic acid is the important weed-killer known as 2,4-D. Outline the synthesis of this compound starting from benzene or toluene and acetic acid.



2,4-Dichlorophenoxyacetic acid
(2,4-D)

Problem 24.8 The *n*-propyl ether of 2-amino-4-nitrophenol is one of the sweetest compounds ever prepared, being about 5000 times as sweet as the common sugar sucrose. It can be made from the dinitro compound by reduction with ammonium bisulfide. Outline the synthesis of this material starting from benzene or toluene and any aliphatic reagents.

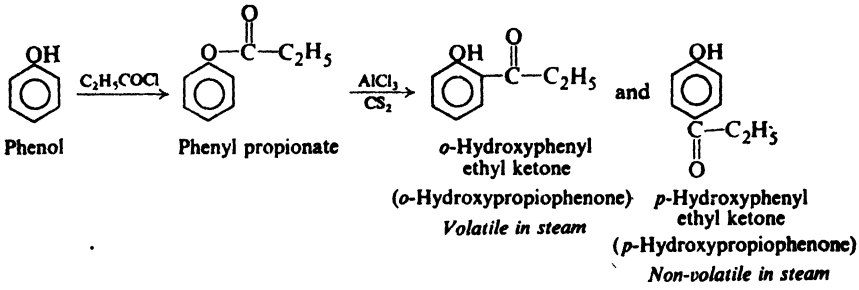
24.9 Ester formation. Fries rearrangement

Phenols are usually converted into their esters by the action of acids, acid chlorides, or anhydrides as discussed in Secs. 18.16, 20.8, and 20.15.

Problem 24.9 Predict the products of the reaction between phenyl benzoate and one mole of bromine in the presence of iron.

When esters of phenols are heated with aluminum chloride, the acyl group migrates from the phenolic oxygen to an *ortho* or *para* position of the ring, thus yielding a ketone. This reaction, called the *Fries rearrangement*, is often used

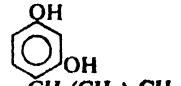
instead of direct acylation for the synthesis of phenolic ketones. For example:



In at least some cases, rearrangement appears to involve generation of an acylium ion, RCO^+, which then attacks the ring as in ordinary Friedel-Crafts acylation.

Problem 24.10 A mixture of *o*- and *p*-isomers obtained by the Fries rearrangement can often be separated by steam distillation, only the *o*-isomer distilling. How do you account for this?

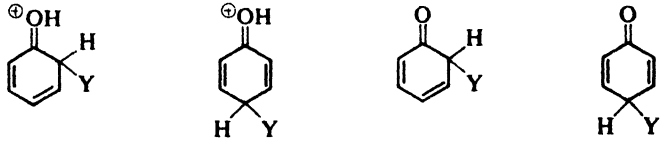
Problem 24.11 4-*n*-Hexylresorcinol is used in certain antiseptics. Outline its preparation starting with resorcinol and any aliphatic reagents.



4-*n*-Hexylresorcinol

24.10 Ring substitution

Like the amino group, the phenolic group powerfully activates aromatic rings toward electrophilic substitution, and in essentially the same way. The intermediates are hardly carbonium ions at all, but rather oxonium ions (like I and II), in which every atom (except hydrogen) has a complete octet of electrons;

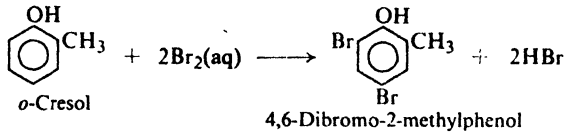


I II III IV

they are formed tremendously faster than the carbonium ions derived from benzene itself. Attack on a phenoxide ion yields an even more stable—and even more rapidly formed—intermediate, an unsaturated ketone (like III and IV).

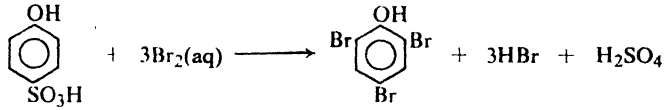
With phenols, as with amines, special precautions must often be taken to prevent polysubstitution and oxidation.

Treatment of phenols with aqueous solutions of bromine results in replacement of every hydrogen *ortho* or *para* to the —OH group, and may even cause displacement of certain other groups. For example:



o-Cresol

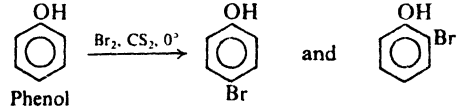
4,6-Dibromo-2-methylphenol



p-Phenolsulfonic acid

2,4,6-Tribromophenol

If halogenation is carried out in a solvent of low polarity, such as chloroform, carbon tetrachloride, or carbon disulfide, reaction can be limited to monohalogenation. For example:

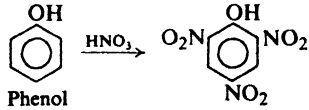


Phenol

p-Bromophenol
Chief product

o-Bromophenol

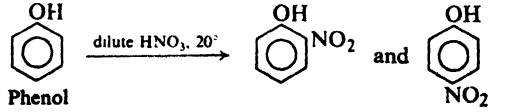
Phenol is converted by concentrated nitric acid into 2,4,6-trinitrophenol (*picric acid*), but the nitration is accompanied by considerable oxidation. To



Phenol

2,4,6-Trinitrophenol
(Picric acid)

obtain mononitrophenols, it is necessary to use dilute nitric acid at a low temperature; even then the yield is poor. (The isomeric products are readily separated by



Phenol

o-Nitrophenol
40% yield

p-Nitrophenol
13% yield

steam distillation. *Why?*)

Problem 24.12 Picric acid can be prepared by treatment of 2,4-phenoldisulfonic acid with nitric acid. (a) Show in detail the mechanism by which this happens. (b) What advantage does this method of synthesis have over the direct nitration of phenol?

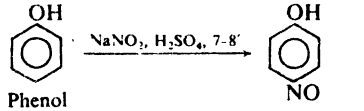
Alkylphenols can be prepared by Friedel-Crafts alkylation of phenols, but the yields are often poor.

Although phenolic ketones can be made by direct acylation of phenols, they are more often prepared in two steps by means of the Fries rearrangement (Sec. 24.9).

Problem 24.13 The product of sulfonation of phenol depends upon the temperature of reaction: chiefly *ortho* at 15-20°, chiefly *para* at 100°. Once formed, *o*-phenolsulfonic acid is converted into the *p*-isomer by sulfuric acid at 100°. How do you account for these facts? (*Hint:* See Sec. 8.22.)

In addition, phenols undergo a number of other reactions that also involve electrophilic substitution, and that are possible only because of the especially high reactivity of the ring.

Nitrous acid converts phenols into nitrosophenols:



Phenol

p-Nitrosophenol
80% yield

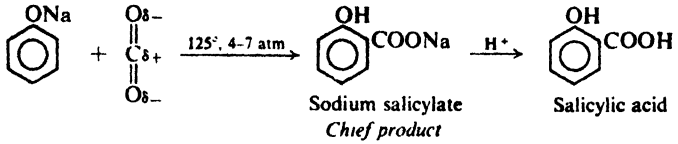
Phenols are one of the few classes of compounds reactive enough to undergo attack by the weakly electrophilic nitrosonium ion, ^+NO.

Problem 24.14 The —NO group is readily oxidized to the $—NO_2$ group by nitric acid. Suggest a better way to synthesize *p*-nitrophenol than the one given earlier in this section

As we have seen, the ring of a phenol is reactive enough to undergo attack by diazonium salts, with the formation of azo compounds. This reaction is discussed in detail in Sec. 23.17.

24.11 Kolbe reaction. Synthesis of phenolic acids

Treatment of the salt of a phenol with carbon dioxide brings about substitution of the carboxyl group, —COOH, for hydrogen of the ring. This reaction is known as the **Kolbe reaction**; its most important application is in the conversion of phenol itself into *o*-hydroxybenzoic acid, known as *salicylic acid.* Although some *p*-hydroxybenzoic acid is formed as well, the separation of the two isomers can be



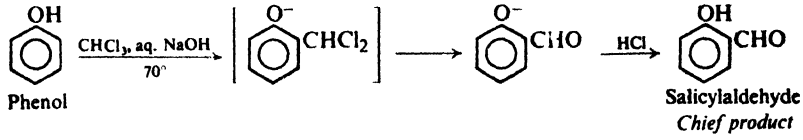
carried out readily by steam distillation, the *o*-isomer being the more volatile. (Why?)

It seems likely that CO_2 attaches itself initially to phenoxide oxygen rather than to the ring. In any case, the final product almost certainly results from electrophilic attack by electron-deficient carbon on the highly reactive ring.

Problem 24.15 *Aspirin* is acetylsalicylic acid (*o*-acetoxybenzoic acid, *o*-CH_3COO-C_6H_4COOH); *oil of wintergreen* is the ester, methyl salicylate. Outline the synthesis of these two compounds from phenol.

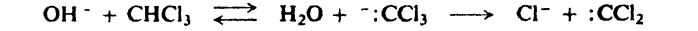
24.12 Reimer-Tiemann reaction. Synthesis of phenolic aldehydes. Dichlorocarbene

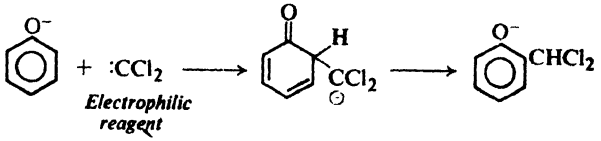
Treatment of a phenol with chloroform and aqueous hydroxide introduces an aldehyde group, —CHO, into the aromatic ring, generally *ortho* to the —OH. This reaction is known as the **Reimer-Tiemann reaction**. For example:



A substituted benzal chloride is initially formed, but is hydrolyzed by the alkaline reaction medium.

The Reimer-Tiemann reaction involves electrophilic substitution on the highly reactive phenoxide ring. The electrophilic reagent is dichlorocarbene, $:CCl_2$, generated from chloroform by the action of base. Although electrically neutral, dichlorocarbene contains a carbon atom with only a sextet of electrons and hence is strongly electrophilic.





We encountered dichlorocarbene earlier (Sec. 9.16) as a species adding to carbon–carbon double bonds. There, as here, it is considered to be formed from chloroform by the action of a strong base.

The formation of dichlorocarbene by the sequence

(1) $CHCl_3 + OH^- \rightleftharpoons CCl_3^- + H_2O$

(2) $CCl_3^- \rightleftharpoons Cl^- + :CCl_2$

$\xrightarrow{\text{fast}}$ products (addition to alkenes, Reimer-Tiemann reaction, hydrolysis, etc.)

is indicated by many lines of evidence, due mostly to elegant work by Jack Hine of the Ohio State University.

Problem 24.16 What bearing does each of the following facts have on the mechanism above? Be specific.

(a) $CHCl_3$ undergoes alkaline hydrolysis much more rapidly than CCl_4 or CH_2Cl_2.

(b) Hydrolysis of ordinary chloroform is carried out in D_2O in the presence of OD^-. When the reaction is interrupted, and unconsumed chloroform is recovered, it is found to contain deuterium. (*Hint:* See Sec. 20.17.)

(c) The presence of added Cl^- *slows down* alkaline hydrolysis of $CHCl_3$.

(d) When alkaline hydrolysis of $CHCl_3$ in the presence of I^- is interrupted, there is recovered not only $CHCl_3$ but also $CHCl_2I$. (In the absence of base, $CHCl_3$ does not react with I^-.)

(e) In the presence of base, $CHCl_3$ reacts with acetone to give 1,1,1-trichloro-2-methyl-2-propanol.

24.13 Analysis of phenols

The most characteristic property of phenols is their particular degree of acidity. Most of them (Secs. 24.3 and 24.7) are stronger acids than water but weaker acids than carbonic acid. Thus, a water-insoluble compound that dissolves in aqueous sodium hydroxide but *not* in aqueous sodium bicarbonate is most likely a phenol.

Many (but not all) phenols form colored complexes (ranging from green through blue and violet to red) with ferric chloride. (This test is also given by *enols*.)

Phenols are often identified through bromination products and certain esters and ethers.

Problem 24.17 Phenols are often identified as their aryloxyacetic acids, $ArOCH_2COOH$. Suggest a reagent and a procedure for the preparation of these derivatives. (*Hint:* See Sec. 24.8.) Aside from melting point, what other property of the aryloxyacetic acids would be useful in identifying phenols? (*Hint:* See Sec. 18.21.)

24.14 Spectroscopic analysis of phenols

Infrared. As can be seen in Fig. 24.2 (p. 806), phenols show a strong, broad band due to O—H stretching in the same region, 3200–3600 cm^{-1}, as alcohols.

O—H stretching, *strong, broad*

Phenols (or alcohols), 3200–3600 cm^{-1}

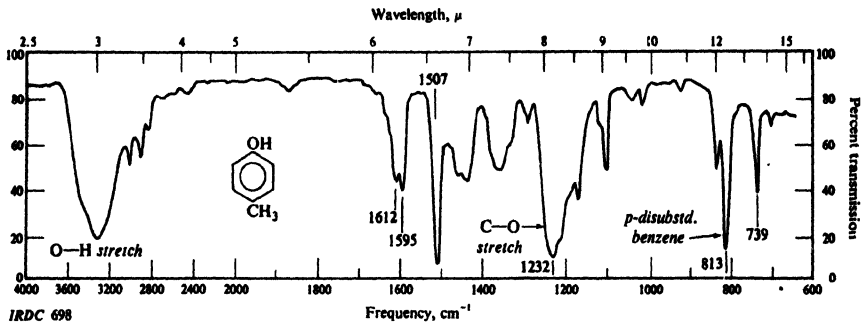


Figure 24.2. Infrared spectrum of *p*-cresol.

Phenols differ from alcohols, however, in the position of the C—O stretching band (compare Sec. 16.13).

C—O stretching, *strong, broad*

Phenols, about 1230 cm^{-1} Alcohols, 1050–1200 cm^{-1}

Phenolic ethers do not, of course, show the O—H band, but do show C—O stretching.

C—O stretching, *strong, broad*

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

Alkyl ethers, 1060–1150 cm^{-1}

(For a comparison of certain oxygen compounds, see Table 20.3, p. 689.)

Nmr. Absorption by the O—H proton of a phenol, like that of an alcohol (Sec. 16.13), is affected by the degree of hydrogen bonding, and hence by the temperature, concentration, and nature of the solvent. The signal may appear anywhere in the range δ 4–7, or, if there is intramolecular hydrogen bonding, still lower: δ 6–12.

PROBLEMS

1. Write structural formulas for.

(a) 2,4-dinitrophenol
(b) *m*-cresol
(c) hydroquinone
(d) resorcinol
(e) 4-*n*-hexylresorcinol
(f) catechol
(g) picric acid
(h) phenyl acetate
(i) anisole
(j) salicylic acid
(k) ethyl salicylate

2. Give the reagents and any critical conditions necessary to prepare phenol from:

(a) aniline
(b) benzene
(c) chlorobenzene
(d) cumene (isopropylbenzene)

3. Outline the steps in a possible industrial synthesis of:

(a) catechol from *guaiacol*, *o*-$CH_3OC_6H_4OH$, found in beech-wood tar
(b) catechol from phenol
(c) resorcinol from benzene
(d) picric acid from chlorobenzene
(e) *veratrole*, *o*-$C_6H_4(OCH_3)_2$, from catechol

4. Outline a possible laboratory synthesis of each of the following compounds from benzene and/or toluene, using any needed aliphatic and inorganic reagents.

(a)–(c) the three cresols
(d) *p*-iodophenol
(e) *m*-bromophenol
(f) *o*-bromophenol
(g) 3-bromo-4-methylphenol
(h) 2-bromo-4-methylphenol
(i) 2-bromo-5-methylphenol
(j) 5-bromo-2-methylphenol
(k) 2,4-dinitrophenol
(l) *p*-isopropylphenol
(m) 2,6-dibromo-4-isopropylphenol
(n) 2-hydroxy-5-methylbenzaldehyde
(o) *o*-methoxybenzyl alcohol

5. Give structures and names of the principal organic products of the reaction (if any) of *o*-cresol with:

(a) aqueous NaOH
(b) aqueous $NaHCO_3$
(c) hot conc. HBr
(d) methyl sulfate, aqueous NaOH
(e) benzyl bromide, aqueous NaOH
(f) bromobenzene, aqueous NaOH
(g) 2,4-dinitrochlorobenzene, aqueous NaOH
(h) acetic acid, H_2SO_4
(i) acetic anhydride
(j) phthalic anhydride
(k) *p*-nitrobenzoyl chloride, pyridine
(l) benzenesulfonyl chloride, aqueous NaOH
(m) product (i) + $AlCl_3$
(n) thionyl chloride
(o) ferric chloride solution
(p) H_2, Ni, 200°, 20 atm.
(q) cold dilute HNO_3
(r) H_2SO_4, 15°
(s) H_2SO_4, 100°
(t) bromine water
(u) Br_2, CS_2
(v) $NaNO_2$, dilute H_2SO_4
(w) product (v) + HNO_3
(x) *p*-nitrobenzenediazonium chloride
(y) CO_2, NaOH, 125°, 5 atm.
(z) $CHCl_3$, aqueous NaOH, 70°

6. Answer Problem 5 for anisole.

7. Answer Problem 5, parts (a) through (o), for benzyl alcohol.

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

(a) benzenesulfonic acid, benzoic acid, benzyl alcohol, phenol
(b) carbonic acid, phenol, sulfuric acid, water
(c) *m*-bromophenol, *m*-cresol, *m*-nitrophenol, phenol
(d) *p*-chlorophenol, 2,4-dichlorophenol, 2,4,6-trichlorophenol

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

(a) phenol and *o*-xylene
(b) *p*-ethylphenol, *p*-methylanisole, and *p*-methylbenzyl alcohol
(c) 2,5-dimethylphenol, phenyl benzoate, *m*-toluic acid
(d) anisole and *o*-toluidine
(e) acetylsalicylic acid, ethyl acetylsalicylate, ethyl salicylate, and salicylic acid
(f) *m*-dinitrobenzene, *m*-nitroaniline, *m*-nitrobenzoic acid, and *m*-nitrophenol

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

10. Describe simple chemical methods for the separation of the compounds of Problem 9, parts (a), (c), (d), and (f), recovering each component in essentially pure form.

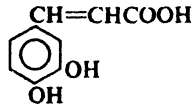
11. Outline all steps in a possible laboratory synthesis of each of the following compounds starting from the aromatic source given, and using any needed aliphatic and inorganic reagents:

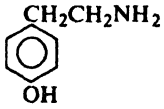
(a) 2,4-diaminophenol (Amidol, used as a photographic developer) from chlorobenzene
(b) 4-amino-1,2-dimethoxybenzene from catechol
(c) 2-nitro-1,3-dihydroxybenzene from resorcinol (*Hint:* See Problem 11.7, p. 350.)
(d) 2,4,6-trimethylphenol from mesitylene
(e) *p-tert*-butylphenol from phenol
(f) 4-(*p*-hydroxyphenyl)-2,2,4-trimethylpentane from phenol
(g) 2-phenoxy-1-bromoethane from phenol (*Hint:* Together with $C_6H_5OCH_2CH_2OC_6H_5$.)
(h) phenyl vinyl ether from phenol

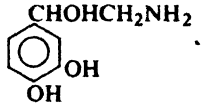
(i) What will phenyl vinyl ether give when heated with acid?
(j) 2,6-dinitro-4-*tert*-butyl-3-methylanisole (synthetic musk) from *m*-cresol
(k) 5-methyl-1,3-dihydroxybenzene (*orcinol*, the parent compound of the litmus dyes) from toluene

12. Outline a possible synthesis of each of the following from benzene, toluene, or any of the natural products shown in Sec. 24.4, using any other needed reagents.

(a) *caffeic acid*, from coffee beans
(b) *tyramine*, found in ergot (*Hint:* See Problem 21.22a, p. 714.)
(c) *noradrenaline*, an adrenal hormone


Caffeic acid


Tyramine

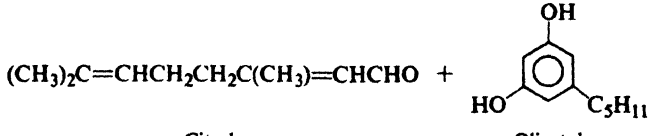

Noradrenaline

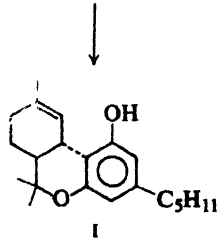
13. The reaction between benzyl chloride and sodium phenoxide follows second-order kinetics in a variety of solvents; the nature of the products, however, varies considerably. (a) In dimethylformamide, dioxane, or tetrahydrofuran, reaction yields only benzyl phenyl ether. Show in detail the mechanism of this reaction. To what general class does it belong? (b) In aqueous solution, the yield of ether is cut in half, and there is obtained, in addition, *o*- and *p*-benzylphenol. Show in detail the mechanism by which the latter products are formed. To what general class (or classes) does the reaction belong? (c) What is a possible explanation for the difference between (a) and (b)? (*Hint:* See Sec. 1.21.) (d) In methanol or ethanol, reaction occurs as in (a); in liquid phenol or 2,2,2-trifluoroethanol, reaction is as in (b). How can you account for these differences?

14. When *phloroglucinol*, 1,3,5-trihydroxybenzene, is dissolved in concentrated $HClO_4$, its nmr spectrum shows two peaks of equal area at δ 6.12 and δ 4.15. Similar solutions of 1,3,5-trimethoxybenzene and 1,3,5-triethoxybenzene show similar nmr peaks. On dilution, the original compounds are recovered unchanged. Solutions of these compounds in D_2SO_4 also show these peaks, but on standing the peaks gradually disappear.

How do you account for these observations? What is formed in the acidic solutions? What would you expect to recover from the solution of 1,3,5-trimethoxybenzene in D_2SO_4?

15. When the terpene *citral* is allowed to react in the presence of dilute acid with *olivetol*, there is obtained a mixture of products containing I, the racemic form of one of the physiologically active components of hashish (marijuana). (C_5H_{11} is *n*-pentyl.) Show all steps in a likely mechanism for the formation of I.


Citral Olivetol


I

Δ^1-3,4-*trans*-Tetrahydrocannabinol

16. Give structures of all compounds below:

(a) *p*-nitrophenol + C_2H_5Br + NaOH (aq) $\longrightarrow$ A ($C_8H_9O_3N$)
A + Sn + HCl $\longrightarrow$ B ($C_8H_{11}ON$)
B + $NaNO_2$ + HCl, then phenol $\longrightarrow$ C ($C_{14}H_{14}O_2N_2$)
C + ethyl sulfate + NaOH (aq) $\longrightarrow$ D ($C_{16}H_{18}O_2N_2$)
D + $SnCl_2$ $\longrightarrow$ E ($C_8H_{11}ON$)
E + acetyl chloride $\longrightarrow$ *phenacetin* ($C_{10}H_{13}O_2N$), an analgesic ("pain-killer") and antipyretic ("fever-killer")

(b) β-(*o*-hydroxyphenyl)ethyl alcohol + HBr $\longrightarrow$ F (C_8H_9OBr)
F + KOH $\longrightarrow$ *coumarane* (C_8H_8O), insoluble in NaOH

(c) phenol + $ClCH_2COOH$ + NaOH (aq), then HCl $\longrightarrow$ G ($C_8H_8O_3$)
G + $SOCl_2$ $\longrightarrow$ H ($C_8H_7O_2Cl$)
H + $AlCl_3$ $\longrightarrow$ *3-cumaranone* ($C_8H_6O_2$)

(d) *p*-cymene (*p*-isopropyltoluene) + conc. H_2SO_4 $\longrightarrow$ I + J (both $C_{10}H_{14}O_3S$)
I + KOH + heat, then H^+ $\longrightarrow$ *carvacrol* ($C_{10}H_{14}O$), found in some essential oils
J + KOH + heat, then H^+ $\longrightarrow$ *thymol* ($C_{10}H_{14}O$), from oil of thyme
I + HNO_3 $\longrightarrow$ K ($C_8H_8O_5S$)
p-toluic acid + fuming sulfuric acid $\longrightarrow$ K

(e) anethole (p. 791) + HBr $\longrightarrow$ L ($C_{10}H_{13}OBr$)
L + Mg $\longrightarrow$ M ($C_{20}H_{26}O_2$)
M + HBr, heat $\longrightarrow$ *hexestrol* ($C_{18}H_{22}O_2$), a synthetic estrogen (female sex hormone)

17. The adrenal hormone (−)-*adrenaline* was the first hormone isolated and the first synthesized. Its structure was proved by the following synthesis:

catechol + $ClCH_2COCl$ $\xrightarrow{POCl_3}$ N ($C_8H_7O_3Cl$)
N + CH_3NH_2 $\longrightarrow$ O ($C_9H_{11}O_3N$)
O + H_2, Pd $\longrightarrow$ (±)-adrenaline ($C_9H_{13}O_3N$)
N + NaOI, then H^+ $\longrightarrow$ 3,4-dihydroxybenzoic acid

What is the structure of adrenaline?

18. (−)-*Phellandral*, $C_{10}H_{16}O$, is a terpene found in eucalyptus oils. It is oxidized by Tollens' reagent to (−)-phellandric acid, $C_{10}H_{16}O_2$, which readily absorbs only one mole of hydrogen, yielding dihydrophellandric acid. $C_{10}H_{18}O_2$. (±)-Phellandral has been synthesized as follows:

isopropylbenzene + H_2SO_4 + SO_3 $\longrightarrow$ P ($C_9H_{12}O_3S$)
P + KOH, fuse $\longrightarrow$ Q ($C_9H_{12}O$)
Q + H_2, Ni $\longrightarrow$ R ($C_9H_{18}O$)
R + $K_2Cr_2O_7$, H_2SO_4 $\longrightarrow$ S ($C_9H_{16}O$)
S + KCN + H^+ $\longrightarrow$ T ($C_{10}H_{17}ON$)
T + acetic anhydride $\longrightarrow$ U ($C_{12}H_{19}O_2N$)
U + heat (600°) $\longrightarrow$ V ($C_{10}H_{15}N$) + CH_3COOH
V + H_2SO_4 + H_2O $\longrightarrow$ W ($C_{10}H_{16}O_2$)
W + $SOCl_2$ $\longrightarrow$ X ($C_{10}H_{15}OCl$)
X $\xrightarrow{\text{reduction}}$ (±)-phellandral

(a) What is the most likely structure of phellandral? (b) Why is synthetic phellandral optically inactive? At what stage in the synthesis does inactivity of this sort first appear? (c) Dihydrophellandric acid is actually a mixture of two optically inactive isomers. Give the structures of these isomers and account for their optical inactivity.

19. Compound Y, C_7H_8O, is insoluble in water, dilute HCl, and aqueous $NaHCO_3$; it dissolves in dilute NaOH. When Y is treated with bromine water it is converted rapidly into a compound of formula $C_7H_5OBr_3$. What is the structure of Y?

20. Two isomeric compounds, Z and AA, are isolated from oil of bay leaf; both are found to have the formula $C_{10}H_{12}O$. Both are insoluble in water, dilute acid, and

dilute base. Both give positive tests with dilute $KMnO_4$ and Br_2/CCl_4. Upon vigorous oxidation, both yield anisic acid, *p*-$CH_3OC_6H_4COOH$.

(a) At this point what structures are possible for Z and AA?
(b) Catalytic hydrogenation converts Z and AA into the same compound, $C_{10}H_{14}O$. Now what structures are possible for Z and AA?
(c) Describe chemical procedures (other than synthesis) by which you could assign structures to Z and AA.
(d) Compound Z can be synthesized as follows:

p-bromoanisole + Mg + ether, then allyl bromide $\longrightarrow$ Z

What is the structure of Z?
(e) Z is converted into AA when heated strongly with concentrated base. What is the most likely structure for AA?
(f) Suggest a synthetic sequence starting with *p*-bromoanisole that would independently confirm the structure assigned to AA.

21. Compound BB ($C_{10}H_{12}O_3$) was insoluble in water, dilute HCl, and dilute aqueous $NaHCO_3$; it was soluble in dilute NaOH. A solution of BB in dilute NaOH was boiled, and the distillate was collected in a solution of NaOI, where a yellow precipitate formed.

The alkaline residue in the distillation flask was acidified with dilute H_2SO_4; a solid, CC, precipitated. When this mixture was boiled, CC steam-distilled and was collected. CC was found to have the formula $C_7H_6O_3$; it dissolved in aqueous $NaHCO_3$ with evolution of a gas.

(a) Give structures and names for BB and CC. (b) Write complete equations for all the above reactions.

22. *Chavibetol*, $C_{10}H_{12}O_2$, is found in betel-nut leaves. It is soluble in aqueous NaOH but not in aqueous $NaHCO_3$.

Treatment of chavibetol (a) with methyl sulfate and aqueous NaOH gives compound DD, $C_{11}H_{14}O_2$; (b) with hot hydriodic acid gives methyl iodide; (c) with hot concentrated base gives compound EE, $C_{10}H_{12}O_2$.

Compound DD is insoluble in aqueous NaOH, and readily decolorizes dilute $KMnO_4$ and Br_2/CCl_4. Treatment of DD with hot concentrated base gives FF, $C_{11}H_{14}O_2$.

Ozonolysis of EE gives a compound that is isomeric with vanillin (p. 792).

Ozonolysis of FF gives a compound that is identical with the one obtained from the treatment of vanillin with methyl sulfate.

What is the structure of chavibetol?

23. *Piperine*, $C_{17}H_{19}O_3N$, is an alkaloid found in black pepper. It is insoluble in water, dilute acid, and dilute base. When heated with aqueous alkali, it yields *piperic acid*, $C_{12}H_{10}O_4$, and the cyclic secondary amine *piperidine* (see Sec. 31.12), $C_5H_{11}N$.

Piperic acid is insoluble in water, but soluble in aqueous NaOH and aqueous $NaHCO_3$. Titration gives an equivalent weight of 215 ± 6. It reacts readily with Br_2/CCl_4, without evolution of HBr, to yield a compound of formula $C_{12}H_{10}O_4Br_4$. Careful oxidation of piperic acid yields *piperonylic acid*, $C_8H_6O_4$, and *tartaric acid*, HOOCCHOHCHOHCOOH.

When piperonylic acid is heated with aqueous HCl at 200° it yields formaldehyde and *protocatechuic acid*, 3,4-dihydroxybenzoic acid.

(a) What kind of compound is piperine? (b) What is the structure of piperonylic acid? Of piperic acid? Of piperine?

(c) Does the following synthesis confirm your structure?

catechol + $CHCl_3$ + NaOH $\longrightarrow$ GG ($C_7H_6O_3$)
GG + CH_2I_2 + NaOH $\longrightarrow$ HH ($C_8H_6O_3$)
HH + CH_3CHO + NaOH $\longrightarrow$ II ($C_{10}H_8O_3$)
II + acetic anhydride + sodium acetate $\longrightarrow$ piperic acid ($C_{12}H_{10}O_4$)
piperic acid + PCl_5 $\longrightarrow$ JJ ($C_{12}H_9O_3Cl$)
JJ + piperidine $\longrightarrow$ piperine

24. *Hordinene*, $C_{10}H_{15}ON$, is an alkaloid found in germinating barley. It is soluble in dilute HCl and in dilute NaOH; it reprecipitates from the alkaline solution when CO_2 is bubbled in. It reacts with benzenesulfonyl chloride to yield a product KK that is soluble in dilute acids.

When hordinene is treated with methyl sulfate and base, a product, LL, is formed. When LL is oxidized by alkaline $KMnO_4$, there is obtained anisic acid, *p*-$CH_3OC_6H_4$-COOH. When LL is heated strongly there is obtained *p*-methoxystyrene.

(a) What structure or structures are consistent with this evidence? (b) Outline a synthesis or syntheses that would prove the structure of hordinene.

25. The structure of the terpene *α-terpineol* (found in oils of cardamom and marjoram) was proved in part by the following synthesis:

p-toluic acid + fuming sulfuric acid $\longrightarrow$ MM ($C_8H_8O_5S$)
MM + KOH $\xrightarrow{\text{fusion}}$ NN ($C_8H_8O_3$)
NN + Na, alcohol $\longrightarrow$ OO ($C_8H_{14}O_3$)
OO + HBr $\longrightarrow$ PP ($C_8H_{13}O_2Br$)
PP + base, heat $\longrightarrow$ QQ ($C_8H_{12}O_2$)
QQ + C_2H_5OH, HCl $\longrightarrow$ RR ($C_{10}H_{16}O_2$)
RR + CH_3MgI, then H_2O $\longrightarrow$ α-terpineol ($C_{10}H_{18}O$)

What is the most likely structure for α-terpineol?

26. *Coniferyl alcohol*, $C_{10}H_{12}O_3$, is obtained from the sap of conifers. It is soluble in aqueous NaOH but not in aqueous $NaHCO_3$.

Treatment of coniferyl alcohol (a) with benzoyl chloride and pyridine gives compound SS, $C_{24}H_{20}O_5$; (b) with cold HBr gives $C_{10}H_{11}O_2Br$; (c) with hot hydriodic acid gives a volatile compound identified as methyl iodide; (d) with methyl iodide and aqueous base gives compound TT, $C_{11}H_{14}O_3$.

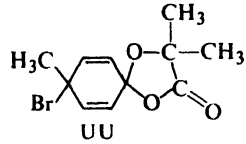
Both SS and TT are insoluble in dilute NaOH, and rapidly decolorize dilute $KMnO_4$ and Br_2/CCl_4.

Ozonolysis of coniferyl alcohol gives vanillin.

What is the structure of coniferyl alcohol?

Write equations for all the above reactions.

27. When α-(*p*-tolyloxy)isobutyric acid (prepared from *p*-cresol) is treated with Br_2, there is obtained UU.



UU

(a) To what class of compounds does UU belong? Suggest a mechanism for its formation.

(b) Give structural formulas for compounds VV, WW, and XX.

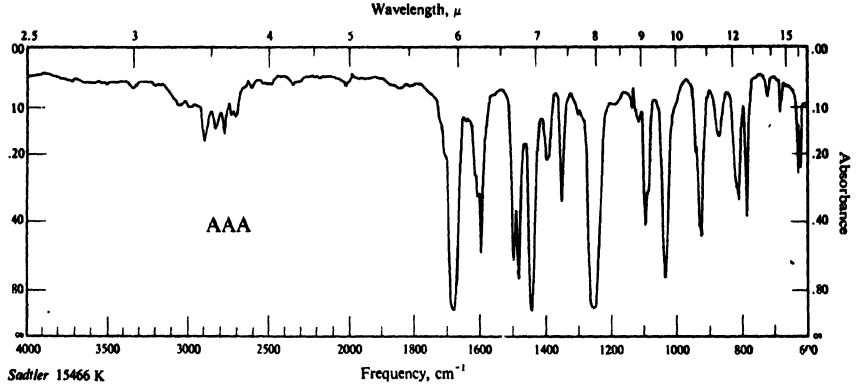
UU + $AgNO_3$, CH_3OH $\longrightarrow$ VV ($C_{12}H_{16}O_4$)
VV + H_2, Rh $\longrightarrow$ WW ($C_{12}H_{20}O_4$)
WW + H_2O, OH^- $\longrightarrow$ XX ($C_8H_{14}O$)

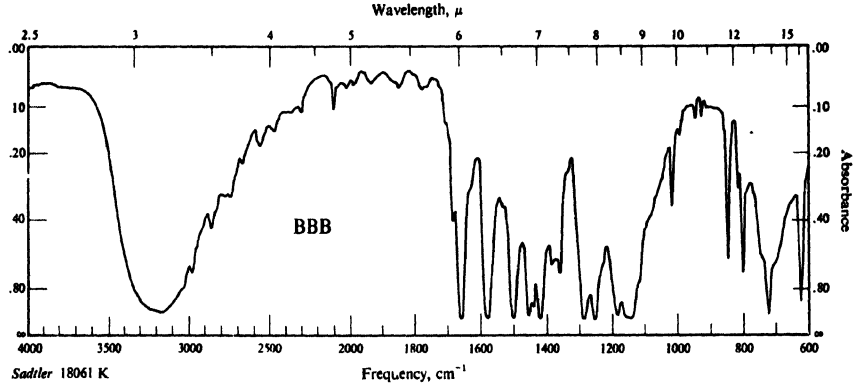
(c) The reactions outlined in (b) can be varied. Of what general synthetic utility do you think this general process might be?

28. Compounds AAA–FFF are phenols or related compounds whose structures are given in Problem 19, p. 650, or Sec. 24.4. Assign a structure to each one on the basis of infrared and/or nmr spectra shown as follows.

AAA, BBB, and CCC: infrared spectra in Fig. 24.3 (p. 812)
nmr spectra in Fig. 24.4 (p. 813)
DDD: nmr spectrum in Fig. 24.5 (p. 814)
EEE and FFF: infrared spectra in Fig. 24.6 (p. 814)

(*Hint:* After you have worked out some of the structures, compare infrared spectra.)





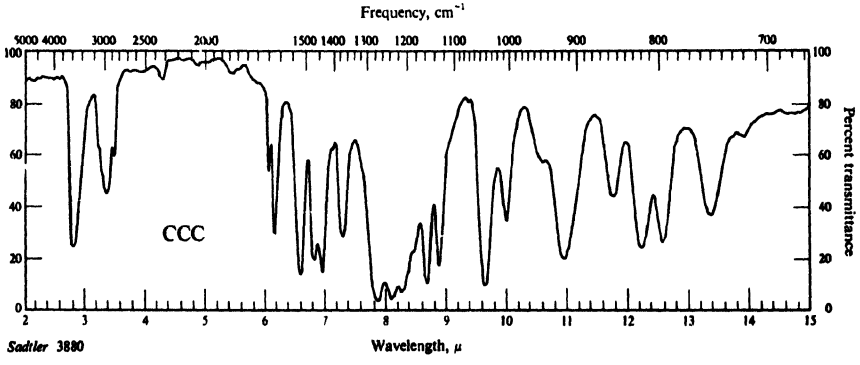


Figure 24.3. Infrared spectra for Problem 28, p. 811.

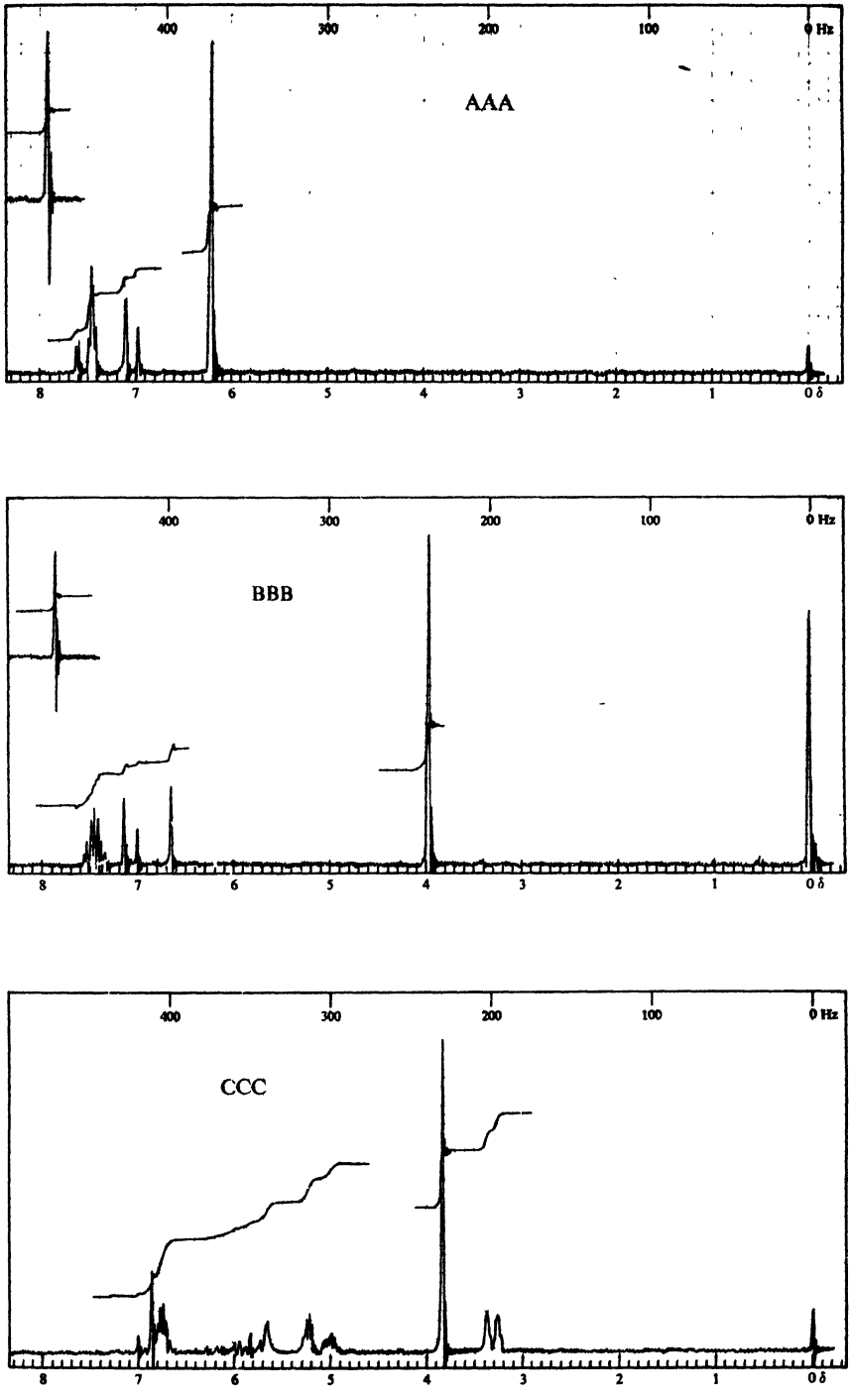


Figure 24.4. Nmr spectra for Problem 28, p. 811.

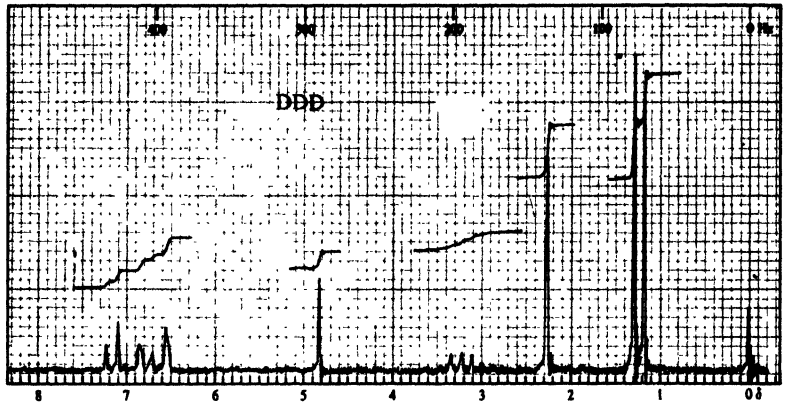
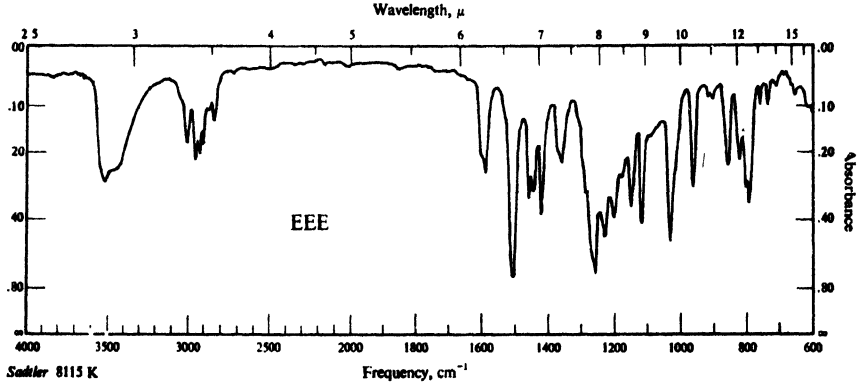


Figure 24.5. Nmr spectrum for Problem 28, p. 811.



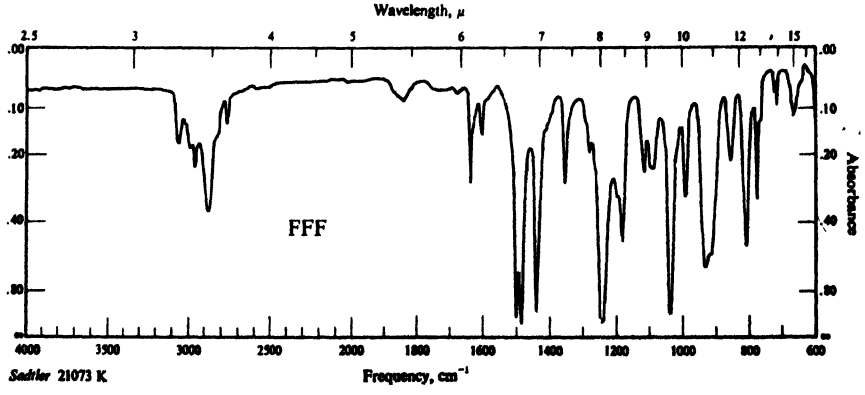


Figure 24.6. Infrared spectra for Problem 28, p. 811.

PART II

Special Topics

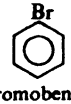
Chapter 25

Aryl Halides

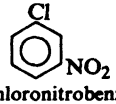
Nucleophilic Aromatic Substitution

25.1 Structure

Aryl halides are compounds containing halogen attached directly to an aromatic ring. They have the general formula ArX, where Ar is phenyl, substituted phenyl, or one of the other aryl groups that we shall study (e.g., naphthyl, Chap. 30):



Bromobenzene



m-Chloronitrobenzene

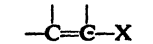
p-Iodotoluene

o-Chlorobenzoic acid

An aryl halide is not just any halogen compound containing an aromatic ring. Benzyl chloride, for example, is not an aryl halide, for halogen is not attached to the aromatic ring; in structure and properties it is simply a substituted alkyl halide and was studied with the compounds it closely resembles (Chap. 14).

We take up the aryl halides in a separate chapter because they differ so much from the alkyl halides in their preparation and properties. Aryl halides as a class are comparatively unreactive toward the nucleophilic substitution reactions so characteristic of the alkyl halides. The presence of certain other groups on the aromatic ring, however, greatly increases the reactivity of aryl halides; in the absence of such groups, reaction can still be brought about by very basic reagents or high temperatures. We shall find that **nucleophilic aromatic substitution** can follow two very different paths: the *bimolecular displacement mechanism*, for activated aryl halides; and the *elimination-addition mechanism*, which involves the remarkable intermediate called *benzyne*.

It will be useful to compare aryl halides with certain other halides that are not aromatic at all: *vinyl halides*, compounds in which halogen is attached directly



A vinyl halide

to a doubly-bonded carbon.

Vinyl halides, we have already seen, show an interesting parallel to aryl halides. Each kind of compound contains another functional group besides halogen: aryl halides contain a ring, which undergoes electrophilic substitution; vinyl halides contain a carbon–carbon double bond, which undergoes electrophilic addition. In each of these reactions, halogen exerts an anomalous influence on reactivity and orientation. In electrophilic substitution, halogen deactivates, yet directs *ortho,para* (Sec. 11.21); in electrophilic addition, halogen deactivates, yet causes Markovnikov orientation (Problem 11.13, p. 367). In both cases we attributed the influence of halogen to the working of opposing factors. Through its inductive effect, halogen withdraws electrons and deactivates the entire molecule toward electrophilic attack. Through its resonance effect, halogen releases electrons and tends to activate—but only toward attack *at certain positions.*

Problem 25.1 Drawing all pertinent structures, account in detail for the fact that: (a) nitration of chlorobenzene is slower than that of benzene, yet occurs predominantly *ortho,para*; (b) addition of hydrogen iodide to vinyl chloride is slower than to ethylene, yet yields predominantly 1-chloro-1-iodoethane.

The parallel between aryl and vinyl halides goes further: both are unreactive toward nucleophilic substitution and, as we shall see, for basically the same reason. Moreover, this low reactivity is caused—partly, at least—by the same structural feature that is responsible for their anomalous influence on electrophilic attack: partial double-bond character of the carbon–halogen bond.

We must keep in mind that aryl halides are of "low reactivity" only with respect to certain sets of familiar reactions typical of the more widely studied alkyl halides. Before 1953, aryl halides appeared to undergo essentially only one reaction—and that one, rather poorly. It is becoming increasingly evident that aryl halides are actually capable of doing many different things; as with the "unreactive" alkanes (Sec. 3.18), it is only necessary to provide the proper conditions—and to have the ingenuity to *observe* what is going on. Of these reactions, we shall have time to take up only two. But we should be aware that there *are* others: free-radical reactions, for example, and what Joseph Bunnett (p. 478) has named the *base-catalyzed halogen dance* (Problem 23, p. 845).

25.2 Physical properties

Unless modified by the presence of some other functional group, the physical properties of the aryl halides are much like those of the corresponding alkyl halides. Chlorobenzene and bromobenzene, for example, have boiling points very nearly the same as those of *n*-hexyl chloride and *n*-hexyl bromide; like the alkyl halides, the aryl halides are insoluble in water and soluble in organic solvents.

Table 25.1 ARYL HALIDES

			Ortho		*Meta*		*Para*	
	M.p., °C	B.p., °C	M.p., °C	B.p., °C	M.p., °C	B.p., °C	M.p., °C	B.p., °C
Fluorobenzene	− 45	85						
Chlorobenzene	− 45	132						
Bromobenzene	− 31	156						
Iodobenzene	− 31	189						
Fluorotoluene				115	−111	115		116
Chlorotoluene			− 34	159	− 48	162	8	162
Bromotoluene			− 26	182	− 40	184	28	185
Iodotoluene				206		211	35	211
Difluorobenzene			− 34	92	− 59	83	− 13	89
Dichlorobenzene			− 17	180	− 24	173	52	175
Dibromobenzene			6	221	− 7	217	87	219
Diiodobenzene			27	287	35	285	129	285
Nitrochlorobenzene			32	245	48	236	83	239
2,4-Dinitro-chlorobenzene	53	315						
2,4,6-Trinitro-chlorobenzene (picryl chloride)	83							
Vinyl chloride	−160	− 14						
Vinyl bromide	−138	16						

The physical constants listed in Table 25.1 illustrate very well a point previously made (Sec. 12.3) about the boiling points and melting points of *ortho*, *meta*, and *para* isomers. The isomeric dihalobenzenes, for example, have very nearly the same boiling points: between 173° and 180° for the dichlorobenzenes, 217° to 221° for the dibromobenzenes, and 285° to 287° for the diiodobenzenes. Yet the melting points of these same compounds show a considerable spread; in each case, the *para* isomer has a melting point that is some 70–100 degrees higher than the *ortho* or *meta* isomer. The physical constants of the halotoluenes show a similar relationship.

Here again we see that, having the most symmetrical structure, the *para* isomer fits better into a crystalline lattice and has the highest melting point. We can see how it is that a reaction product containing both *ortho* and *para* isomers frequently deposits crystals of only the *para* isomer upon cooling. Because of the strong intracrystalline forces, the higher melting *para* isomer also is less soluble in a given solvent than the *ortho* isomer, so that purification of the *para* isomer is often possible by recrystallization. The *ortho* isomer that remains in solution is generally heavily contaminated with the *para* isomer, and is difficult to purify.

25.3 Preparation

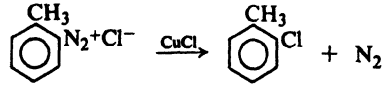
Aryl halides are most often prepared in the laboratory by the methods outlined below, and on an industrial scale by adaptations of these methods.

PREPARATION OF ARYL HALIDES

1. From diazonium salts. Discussed in Secs. 23.12 and 25.3.

$$ArH \xrightarrow[H_2SO_4]{HNO_3} ArNO_2 \xrightarrow{\text{redn.}} ArNH_2 \xrightarrow[0°]{HONO} \underset{\text{Diazonium salt}}{ArN_2^+} \begin{cases} \xrightarrow{BF_4^-} ArF \\ \xrightarrow{CuCl} ArCl \\ \xrightarrow{CuBr} ArBr \\ \xrightarrow{I^-} ArI \end{cases} + N_2$$

Example:



o-Toluenediazonium chloride — *o*-Chlorotoluene

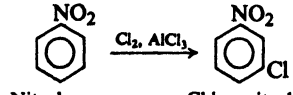
2. Halogenation. Discussed in Secs. 11.11 and 12.12.

$$ArH + X_2 \xrightarrow{\text{Lewis acid}} ArX + HX$$

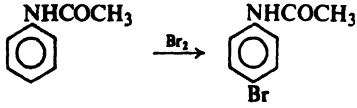
$X_2 = Cl_2, Br_2$

Lewis acid = $FeCl_3$, $AlCl_3$, $Tl(OAc)_3$, etc.

Examples:



Nitrobenzene — *m*-Chloronitrobenzene



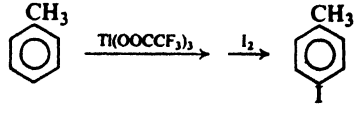
Acetanilide — *p*-Bromoacetanilide *Major product*

3. From arylthallium compounds. Discussed in Sec. 25.3.

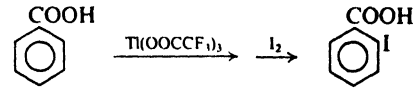
$$[ArH + Tl(OOCCF_3)_3 \longrightarrow] \underset{\text{Arylthallium trifluoroacetate}}{ArTl(OOCCF_3)_2} + I_2 \longrightarrow ArI$$

For iodides only

Examples:



Toluene — *p*-Iodotoluene



Benzoic acid *o*-Iodobenzoic acid

These methods, we notice, differ considerably from the methods of preparing alkyl halides. (a) Direct halogenation of the aromatic ring is more useful than direct halogenation of alkanes; although mixtures may be obtained (e.g., *ortho* + *para*), attack is not nearly so random as in the free-radical halogenation of aliphatic hydrocarbons. Furthermore, by use of bulky thallium acetate (Sec. 11.7) as the Lewis acid, one can direct bromination *exclusively* to the *para* position. (b) Alkyl halides are most often prepared from the corresponding alcohols; aryl halides are not prepared from the phenols. Instead, aryl halides are most commonly prepared by replacement of the nitrogen of a **diazonium salt**; as the sequence above shows, this ultimately comes from a nitro group which was itself introduced directly into the ring. *From the standpoint of synthesis, then, the nitro compounds bear much the same relationship to aryl halides that alcohols do to alkyl halides.* (These reactions of diazonium salts have been discussed in detail in Secs. 23.11–23.12.)

The preparation of aryl halides from diazonium salts is more important than direct halogenation for several reasons. First of all, fluorides and iodides, which can seldom be prepared by direct halogenation, can be obtained from the diazonium salts. Second, where direct halogenation yields a mixture of *ortho* and *para* isomers, the *ortho* isomer, at least, is difficult to obtain pure. On the other hand, the *ortho* and *para* isomers of the corresponding nitro compounds, from which the diazonium salts ultimately come, can often be separated by fractional distillation (Sec. 11.7). For example, the *o*- and *p*-bromotoluenes boil only three degrees apart: 182° and 185°. The corresponding *o*- and *p*-nitrotoluenes, however, boil sixteen degrees apart: 222° and 238°.

Aryl *iodides* can be prepared by simple treatment of arylthallium compounds with iodine. As in the synthesis of phenols (Sec. 24.5) the thallation route has the advantages of speed, high yield, and orientation control (see Secs. 11.7 and 11.13)

Problem 25.2 Using a different approach in each case, outline all steps in the synthesis of the following from toluene: (a) *p*-bromotoluene; (b) *p*-iodotoluene; (c) *m*-bromotoluene; (d) *m*-iodotoluene; (e) *o*-bromotoluene.

25.4 Reactions

The typical reaction of alkyl halides, we have seen (Sec. 14.5), is nucleophilic substitution. Halogen is displaced as halide ion by such bases as OH^-, OR^-, NH_3, CN^-, etc., to yield alcohols, ethers, amines, nitriles, etc. Even Friedel-Crafts alkylation is, from the standpoint of the alkyl halide, nucleophilic substitution by the basic aromatic ring.

$$R{:}X + {:}Z \longrightarrow R{:}Z + {:}X^-$$

$$Z = OH^-, OR^-, NH_3, CN^-, \text{etc.}$$

It is typical of **aryl halides** *that they undergo nucleophilic substitution only with extreme difficulty.* Except for certain industrial processes where very severe conditions are feasible, one does not ordinarily prepare phenols (ArOH), ethers (ArOR), amines ($ArNH_2$), or nitriles (ArCN) by nucleophilic attack on aryl halides. We cannot use aryl halides as we use alkyl halides in the Friedel-Crafts reaction.

However, aryl halides do undergo nucleophilic substitution readily if the aromatic ring contains, in addition to halogen, certain other properly placed groups: electron-withdrawing groups like $-NO_2$, —NO, or —CN, located *ortho* or *para* to halogen. For aryl halides having this special kind of structure, nucleophilic substitution proceeds readily and can be used for synthetic purposes.

The reactions of unactivated aryl halides with strong bases or at high temperatures, which proceed via benzyne, are finding increasing synthetic importance. The Dow process, which has been used for many years in the manufacture of phenol (Sec. 24.4), turns out to be what Bunnett (p. 478) calls "benzyne chemistry on the tonnage scale!"

The aromatic ring to which halogen is attached can, of course, undergo the typical electrophilic aromatic substitution reactions: nitration, sulfonation, halogenation, Friedel-Crafts alkylation. Like any substituent, halogen affects the reactivity and orientation in these reactions. As we have seen (Sec. 11.5), halogen is unusual in being deactivating, yet *ortho,para*-directing.

REACTIONS OF ARYL HALIDES

1. Formation of Grignard reagent. Limitations are discussed in Sec. 15.15.

$$ArBr + Mg \xrightarrow{\text{dry ether}} ArMgBr$$

$$ArCl + Mg \xrightarrow{\text{tetrahydrofuran}} ArMgCl$$

2. Substitution in the ring. Electrophilic aromatic substitution. Discussed in Sec. 11.21.

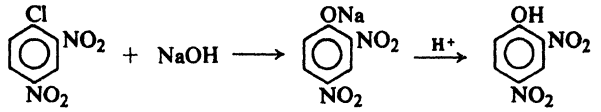
X: Deactivates and directs *ortho,para* in electrophilic aromatic substitution.

3. Nucleophilic aromatic substitution. Bimolecular displacement. Discussed in Secs. 25.7–25.13.

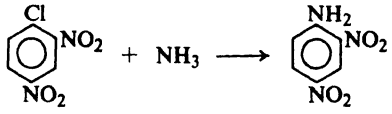
$$Ar{:}X + {:}Z \longrightarrow Ar{:}Z + {:}X^-$$

Ar *must contain strongly electron-withdrawing groups ortho and/or para to* —X.

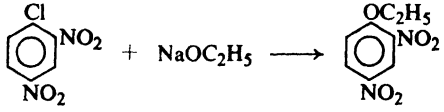
Examples:



2,4-Dinitrochlorobenzene 2,4-Dinitrophenol

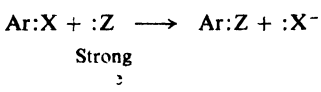


2,4-Dinitrochlorobenzene 2,4-Dinitroaniline



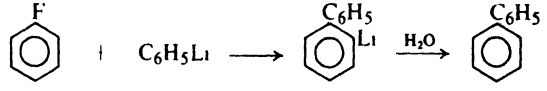
2,4-Dinitrochlorobenzene 2,4-Dinitrophenyl ethyl ether

4. Nucleophilic aromatic substitution. Elimination-addition. Discussed in Sec. 25.14.

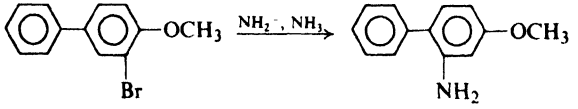


Ring not activated toward bimolecular displacement

Examples:



Fluorobenzene Phenyllithium Biphenyl

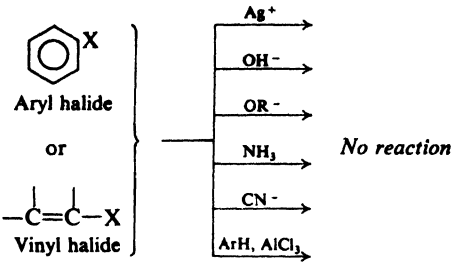


3-Bromo-4-methoxybiphenyl 2-Amino-4-methoxybiphenyl

25.5 Low reactivity of aryl and vinyl halides

We have seen (Sec. 14.24) that an alkyl halide is conveniently detected by the precipitation of insoluble silver halide when it is warmed with alcoholic silver nitrate. The reaction occurs nearly instantaneously with tertiary, allyl, and benzyl bromides, and within five minutes or so with primary and secondary bromides. Compounds containing halogen joined directly to an aromatic ring or to a doubly-bonded carbon, however, do not yield silver halide under these conditions. Bromobenzene or vinyl bromide can be heated with alcoholic $AgNO_3$ for days without the slightest trace of AgBr being detected. In a similar way, attempts to convert aryl

or vinyl halides into phenols (or alcohols), ethers, amines, or nitriles by treatment with the usual nucleophilic reagents are also unsuccessful; aryl or vinyl halides cannot be used in place of alkyl halides in the Friedel-Crafts reaction.



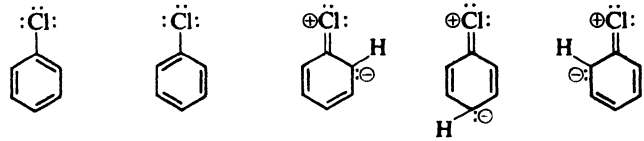
How can the low reactivity of these halides be accounted for? To find possible answers, let us look at their structures.

25.6 Structure of aryl and vinyl halides

The low reactivity of aryl and vinyl halides toward displacement has, like the stabilities of alkenes and dienes (Secs. 8.17–8.19), been attributed to two different factors: (a) delocalization of electrons by resonance; and (b) differences in (σ) bond energies due to differences in hybridization of carbon.

Let us look first at the resonance interpretation.

Chlorobenzene is considered to be a hybrid of not only the two Kekulé structures, I and II, but also of three structures, III, IV, and V, in which chlorine is



joined to carbon by a double bond; in III, IV, and V chlorine bears a positive charge and the *ortho* and *para* positions of the ring bear a negative charge.

In a similar way, vinyl chloride is considered to be a hybrid of structure VI (the one we usually draw for it) and structure VII, in which chlorine is joined to carbon by a double bond; in VII chlorine bears a positive charge and C-2 bears

a negative charge. Other aryl and vinyl halides are considered to have structures exactly analogous to these.

Contribution from III, IV, and V, and from VII stabilizes the chlorobenzene and vinyl chloride molecules, and gives double-bond character to the carbon–

chlorine bond. Carbon and chlorine are thus held together by something more than a single pair of electrons, and the carbon–chlorine bond is stronger than if it were a pure single bond. The low reactivity of these halides toward nucleophilic substitution is due (partly, at least) to resonance stabilization of the halides (by a factor that in this case does not stabilize the transition state to the same extent); this stabilization increases the E_{act} for displacement, and thus slows down reaction. For aryl halides, another factor—which may well be the most important one—is stabilization of the molecule by resonance involving the Kekulé structures.

The alternative interpretation is simple. In alkyl halides the carbon holding halogen is sp^3-hybridized. In aryl and vinyl halides, carbon is sp^2-hybridized; the bond to halogen is shorter and stronger, and the molecule is more stable (see Sec. 5.4).

What evidence is there to support either interpretation, other than the fact that it would account for *the low reactivity of aryl and vinyl halides*?

The carbon–halogen bonds of aryl and vinyl halides are unusually short. In chlorobenzene and vinyl chloride the C—Cl bond length is only 1.69 A, as compared with a length of 1.77–1.80 A in a large number of alkyl chlorides (Table 25.2). In bromobenzene and vinyl bromide the C—Br bond length is only 1.86 A, as compared with a length of 1.91–1.92 A in alkyl bromides.

Now, as we have seen (Sec. 5.2), a double bond is shorter than a single bond joining the same pair of atoms; if the carbon–halogen bond in aryl and vinyl halides has double-bond character, it should be shorter than the carbon–halogen bond in alkyl halides. Alternatively, a bond formed by overlap of an sp^2 orbital should be shorter than the corresponding bond involving an sp^3 orbital.

Dipole moments of aryl and vinyl halides are unusually small. Organic halogen compounds are polar molecules; displacement of electrons toward the more electronegative element makes halogen relatively negative and carbon relatively positive. Table 25.2 shows that the dipole moments of a number of alkyl chlorides and bromides range from 2.02 D to 2.15 D. The mobile π electrons of the benzene ring and of the carbon–carbon double bond should be particularly easy to displace; hence we might have expected aryl and vinyl halides to have even larger dipole moments than alkyl halides.

However, we see that this is not the case. Chlorobenzene and bromobenzene have dipole moments of only 1.7 D, and vinyl chloride and vinyl bromide have dipole moments of only 1.4 D. This is consistent with the resonance picture of these molecules. In the structures that contain doubly-bonded halogen (III, IV,

Table 25.2 BOND LENGTHS AND DIPOLE MOMENTS OF HALIDES

	Bond Lengths, A		Dipole Moments, D	
	C—Cl	C—Br	R—Cl	R—Br
CH_3—X	1.77	1.91	—	—
C_2H_5—X	1.77	1.91	2.05	2.02
n-C_3H_7—X	—	—	2.10	2.15
n-C_4H_9—X	—	—	2.09	2.15
$(CH_3)_3C$—X	1.80	1.92	2.13	—
CH_2=CH—X	1.69	1.86	1.44	1.41
C_6H_5—X	1.69	1.86	1.73	1.71

V, and VII) there is a positive charge on halogen and a negative charge on carbon; to the extent that these structures contribute to the hybrids, they tend to oppose the usual displacement of electrons toward halogen. Although there is still a net displacement of electrons toward halogen in aryl halides and in vinyl halides, it is less than in other organic halides.

Alternatively, sp^2-hybridized carbon is, in effect, a more electronegative atom than an sp^3-hybridized carbon (see Sec. 8.10), and is less willing to release electrons to chlorine.

As was discussed in Secs. 11.21 and 25.1, contribution from structures in which halogen is doubly bonded and bears a positive charge accounts for *the way halogen affects the reactions of the benzene ring or of the carbon–carbon double bond to which it is joined.*

The counterargument is that this simply indicates that resonance of this kind can occur—but not how important it is in the halide molecules.

Finally, the *existence of cyclic halonium ions* (Sec. 7.12) certainly shows that halogen *can* share more than a pair of electrons.

It is hard to believe that the stability of these molecules is not affected by the particular kind of hybridization; on the other hand, it seems clear that there is resonance involving halogen and the π electrons. The question, once more, is one of their relative importance. As in the case of alkenes and dienes, it is probable that *both* are important.

As we shall see, in the rate-determining step of nucleophilic aromatic substitution a nucleophile attaches itself to the carbon bearing halogen; this carbon becomes tetrahedral, and the ring acquires a negative charge. Such a reaction is made more difficult by the fact that it destroys the aromaticity of the ring and disrupts the resonance between ring and halogen; and, if Dewar is correct (Sec. 8.19), because energy is required to change the hybridization of carbon from sp^2 to sp^3

Problem 25.3 In Sec. 25.3 we learned that, unlike alkyl halides, aryl halides are not readily prepared from the corresponding hydroxy compounds. How might you account for this contrast between alcohols and phenols? (*Hint:* See Sec. 24.7.)

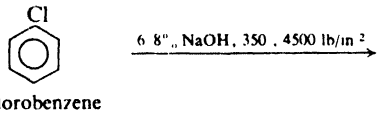
25.7 Nucleophilic aromatic substitution: bimolecular displacement

We have seen that the aryl halides are characterized by very low reactivity toward the nucleophilic reagents like OH^-, OR^-, NH_3, and CN^- that play such an important part in the chemistry of the alkyl halides. Consequently, nucleophilic aromatic substitution is much less important in synthesis than either nucleophilic aliphatic substitution or electrophilic aromatic substitution.

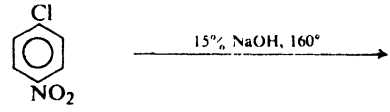
However, the presence of certain groups at certain positions of the ring markedly activates the halogen of aryl halides toward displacement. We shall have a look at some of these activation effects, and then try to account for them on the basis of the chemical principles we have learned. We shall find a remarkable parallel between the two kinds of aromatic substitution, electrophilic and nucleophilic, with respect both to mechanism and to the ways in which substituent groups affect reactivity and orientation.

Chlorobenzene is converted into phenol by aqueous sodium hydroxide only at temperatures over 300°. The presence of a nitro group *ortho* or *para* to the

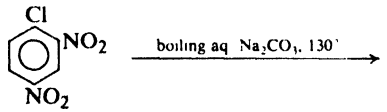
chlorine greatly increases its reactivity: *o*- or *p*-chloronitrobenzene is converted into the nitrophenol by treatment with aqueous sodium hydroxide at 160°. A nitro group *meta* to the chlorine, on the other hand, has practically no effect on reactivity. As the number of *ortho* and *para* nitro groups on the ring is increased, the reactivity increases: the phenol is obtained from 2,4-dinitrochlorobenzene by treatment with hot aqueous sodium carbonate, and from 2,4,6-trinitrochlorobenzene by simple treatment with water.



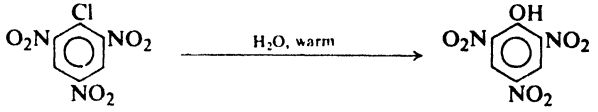
Chlorobenzene — Phenol



p-Chloronitrobenzene — *p*-Nitrophenol

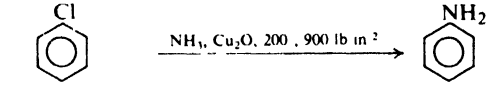


2,4-Dinitrochlorobenzene — 2,4-Dinitrophenol



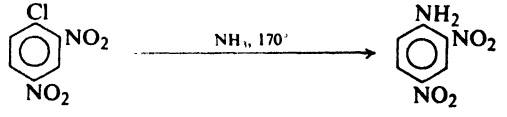
2,4,6-Trinitrochlorobenzene — 2,4,6-Trinitrophenol (Picric acid)

Similar effects are observed when other nucleophilic reagents are used. Ammonia or sodium methoxide, for example, reacts with chloro- or bromobenzene only under very vigorous conditions. For example:

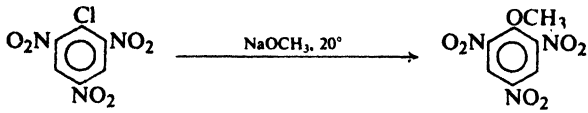


Chlorobenzene — Aniline

Yet if the ring contains a nitro group—or preferably two or three of them—*ortho* or *para* to the halogen, reaction proceeds quite readily. For example:



2,4-Dinitrochlorobenzene — 2,4-Dinitroaniline



2,4,6-Trinitrochlorobenzene 2,4,6-Trinitroanisole

Like $-NO_2$, certain other groups have been found to activate halogen located *ortho* or *para* to them: $-N(CH_3)_3^+$, $-CN$, $-SO_3H$, $-COOH$, $-CHO$, $-COR$. This is a familiar list. All these are electron-withdrawing groups, which are deactivating and *meta*-directing toward *electrophilic* substitution (see Table 11.3, p. 342).

Although our concern here is primarily with displacement of halogen, it is important to know that these electron-withdrawing substituents activate many groups other than halogen toward nucleophilic substitution. (Hydrogen is generally not displaced from the aromatic ring, since this would require the separation of the very strongly basic hydride ion, $:H^-$.)

Problem 25.4 When *p*-nitroso-N,N-dimethylaniline is heated with aqueous KOH, dimethylamine is evolved; this reaction is sometimes used to prepare pure dimethylamine, free from methylamine and trimethylamine. (a) What are the other products of the reaction? (b) To what class of organic reactions does this belong? (c) Upon what property of the nitroso group does this reaction depend? (d) Outline all steps in the preparation of pure diethylamine starting from nitrobenzene and ethyl alcohol.

Problem 25.5 How do you account for the following observations?

(a) Although most ethers are inert toward bases, 2,4-dinitroanisole is readily cleaved to methanol and 2,4-dinitrophenol when refluxed with dilute aqueous NaOH.

(b) Although amides can be hydrolyzed by either aqueous acid or aqueous alkali, hydrolysis of *p*-nitroacetanilide is best carried out in acidic solution.

(c) Treatment of *o*-chloronitrobenzene by aqueous sodium sulfite yields sodium *o*-nitrobenzenesulfonate. Give the structure of the reagent involved. How does this reagent compare with the one in ordinary sulfonations?

(d) Would you expect the method of (c) to be a general one for preparation of sulfonic acids? Could it be used, for example, to prepare benzenesulfonic acid?

(e) Washing crude *m*-dinitrobenzene with aqueous sodium sulfite removes contaminating *o*- and *p*-dinitrobenzene.

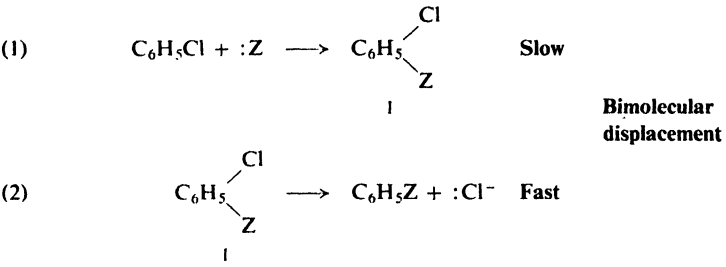
If electron-withdrawing groups activate toward nucleophilic substitution, we might expect electron-releasing groups to *deactivate*. This is found to be so. Furthermore, the degree of deactivation depends upon how strongly they release electrons: $-NH_2$ and $-OH$ deactivate strongly; $-OR$, moderately; and $-R$, weakly.

In nucleophilic as in electrophilic aromatic substitution, then, a substituent group affects reactivity by its ability to attract or release electrons; in nucleophilic as in electrophilic aromatic substitution, a substituent group exerts its effect chiefly at the position *ortho* and *para* to it. The kind of effect that each group exerts, however, is exactly opposite to the kind of effect it exerts in electrophilic aromatic substitution. *In* **nucleophilic aromatic substitution** *electron withdrawal causes activation, and electron release causes deactivation.*

To account for these effects, we must look at the mechanism for the kind of nucleophilic aromatic substitution we have been talking about.

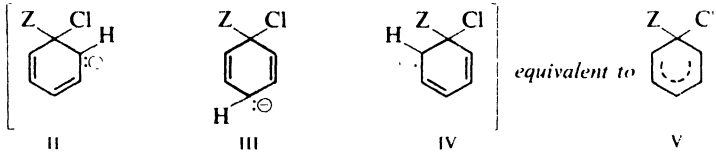
25.8 Bimolecular displacement mechanism for nucleophilic aromatic substitution

The bimolecular displacement mechanism for nucleophilic aromatic substitution (shown here for chlorobenzene) is:

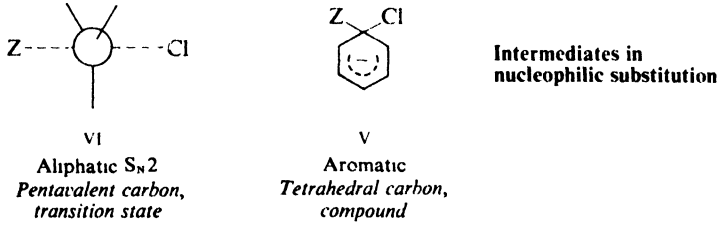


There are two essential steps: attack of a nucleophilic reagent upon the ring to form a carbanion (I), and the expulsion of halide ion from this carbanion to yield the product.

The intermediate carbanion (I) is a hybrid of II, III, and IV; this hybrid is sometimes represented by the single structure V:



In nucleophilic aliphatic substitution (S_N2), the intermediate in which carbon is bonded to both the attacking group and the displaced group is considered to be a transition state; a structure (VI) containing carbon bonded to five atoms must be



unstable and so corresponds to the top of an energy hill (Fig. 25.1). In nucleophilic aromatic substitution, on the other hand, the intermediate is an actual compound; a structure (V) containing tetrahedral carbon and having the negative charge distributed about the ring is comparatively stable, and corresponds to an energy valley (Fig. 25.2).

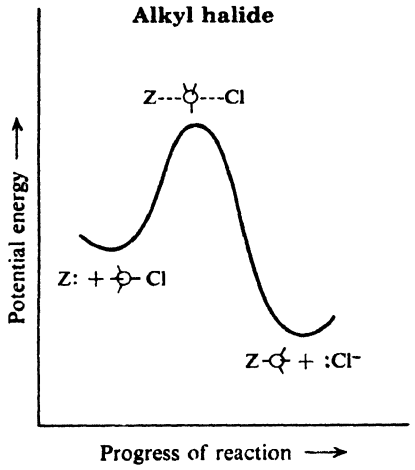


Figure 25.1. Energy curve for nucleophilic aliphatic (S_N2) substitution. One-step reaction: intermediate is a transition state.

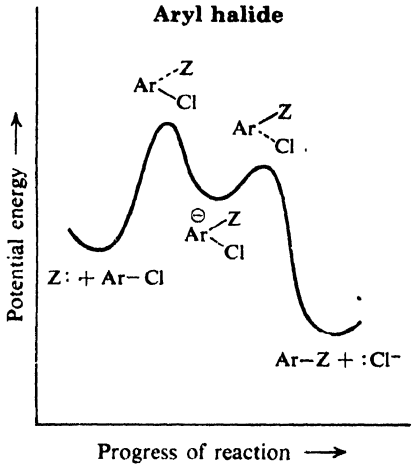
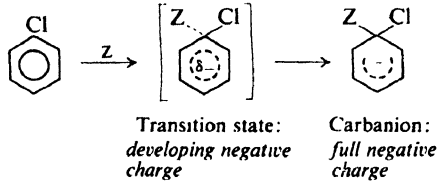


Figure 25.2. Energy curve for nucleophilic aromatic substitution. Two-step reaction: intermediate is a compound.

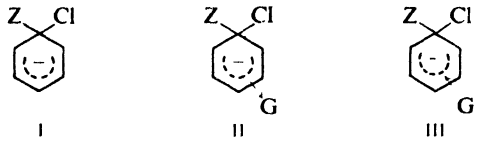
25.9 Reactivity in nucleophilic aromatic substitution

For reactions involving an intermediate carbonium ion, we have seen that the overall rate depends only on the rate of formation of the carbonium ion. In nucleophilic aromatic substitution an analogous situation seems to exist: the first step, formation of the carbanion, largely determines the overall rate of reaction; once formed, the carbanion rapidly reacts to yield the final product.

For closely related reactions, we might expect a difference in rate of formation of carbanions to be largely determined by a difference in E_{act}, that is, by a difference in stability of the transition states. Factors that stabilize the carbanion by dispersing the charge should for the same reason stabilize the incipient carbanion of the transition state. Just as the more stable carbonium ion is formed more rapidly, so, we expect, the more stable carbanion should be formed more rapidly. We shall therefore concentrate our attention on the relative stabilities of the intermediate carbanions.



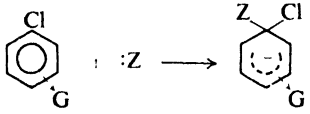
To compare the rates of substitution in chlorobenzene itself, a chlorobenzene containing an electron-withdrawing group, and a chlorobenzene containing an electron-releasing group, we compare the structures of carbanions I, II, and III.



I II III

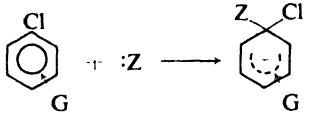
A group that withdraws electrons (II) tends to neutralize the negative charge of the ring and so to become more negative itself; this dispersal of the charge stabilizes the carbanion. In the same way, electron withdrawal stabilizes the transition state with its developing negative charge, and thus speeds up reaction. A group that releases electrons (III) tends to intensify the negative charge, destabilizes the carbanion (and the transition state), and thus slows down reaction.

Nucleophilic Aromatic Substitution



G withdraws electrons stabilizes carbanion, activates

G = $-N(CH_3)_3^+$, $-NO_2$, $-CN$, $-SO_3H$, $-COOH$, $-CHO$, $-COR$, $-X$



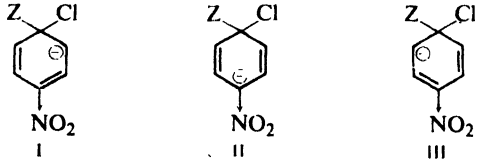
G releases electrons destabilizes carbanion, deactivates

G = $-NH_2$, $-OH$, $-OR$, $-R$

It is clear, then, why a given substituent group affects nucleophilic and electrophilic aromatic substitution in opposite ways: it affects the stability of negatively and positively charged ions in opposite ways.

25.10 Orientation in nucleophilic aromatic substitution

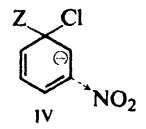
To see why it is that a group activates the positions *ortho* and *para* to it most strongly, let us compare, for example, the carbanions formed from *p*-chloronitrobenzene and *m*-chloronitrobenzene. Each of these is a hybrid of three structures, I–III for *para* attack, IV–VI for *meta* attack. In one of these six structures, II,

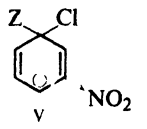


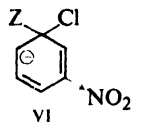
I II III

***Para* attack**

Especially stable: charge on carbon bearing substituent


IV

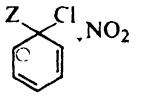

V

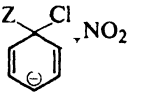

VI

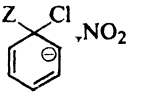
Meta attack

the negative charge is located on the carbon atom to which $-NO_2$ is attached. Although $-NO_2$ attracts electrons from all positions of the ring, it does so most from the carbon atom nearest it; consequently, structure II is a particularly stable one. Because of contribution from structure II, the hybrid carbanion resulting from attack on *p*-chloronitrobenzene is more stable than the carbanion resulting from attack on *m*-chloronitrobenzene. The *para* isomer therefore reacts faster than the *meta* isomer.

In the same way, it can be seen that attack on *o*-chloronitrobenzene (VII–IX) also yields a more stable carbanion, because of contribution from IX, than attack on *m*-chloronitrobenzene.


VII


VIII


IX

Especially stable: charge on carbon bearing substituent

Ortho attack

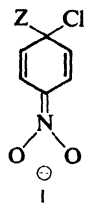
By considerations similar to those of Sec. 11.19, we can see that deactivation by an electron-releasing group should also be strongest when it is *ortho* or *para* to the halogen.

Nucleophilic and electrophilic aromatic substitution are similar, then, in that a group exerts its strongest influence—whether activating or deactivating—at the positions *ortho* and *para* to it. This similarity is due to a similarity in the intermediate ions: in both cases the charge of the intermediate ion—whether negative or positive—is strongest at the positions *ortho* and *para* to the point of attack, and hence a group attached to one of these positions can exert the strongest influence.

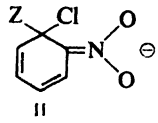
25.11 Electron withdrawal by resonance

The activation by $-NO_2$ and other electron-attracting groups can be accounted for, as we have seen, simply on the basis of inductive effects. However, it is generally believed that certain of these groups withdraw electrons by resonance as well. Let us see what kind of structures are involved.

The intermediate carbanions formed by nucleophilic attack on *o*- and *p*-chloronitrobenzene are considered to be hybrids not only of structures with negative charges carried by carbons of the ring (as shown in the last section), but also of structures I and II in which the negative charge is carried by oxygen of the $-NO_2$ group. Being highly electronegative, oxygen readily accommodates a negative charge, and hence I and II should be especially stable structures. The carbanions to which these structures contribute are therefore much more stable than the ones



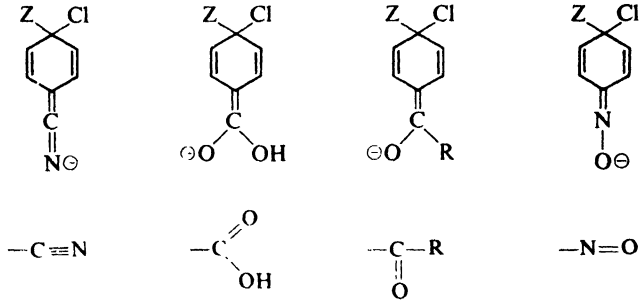
I



II

formed by attack on chlorobenzene itself or on *m*-chloronitrobenzene, for which structures like I and II are not possible. Thus resonance involving the $-NO_2$ group strengthens the activation toward nucleophilic substitution caused by the inductive effect.

The activating effect of a number of other electron-attracting groups is considered to arise, in part, from the contribution of similar structures (shown only for *para* isomers) to the intermediate carbanions.



Problem 25.6 There is evidence to suggest that the nitroso group, $-\ddot{N}=\ddot{O}:$, activates *ortho* and *para* positions toward *both* nucleophilic and electrophilic aromatic substitution; the group apparently can either withdraw or release electrons upon demand by the attacking reagent. Show how this might be accounted for. (***Hint:*** See Sec. 11.20.)

25.12 Evidence for the two steps in bimolecular displacement

Our interpretation of reactivity and orientation in nucleophilic aromatic substitution has been based on one all-important assumption that we have not yet justified: *displacement involves two steps, of which the first one is much slower than the second.*

(1) $\mathrm{Ar{-}X + :Z \longrightarrow Ar(X)(Z)}$ *Slow*

(2) $\mathrm{Ar(X)(Z) \longrightarrow Ar{-}Z + :X^-}$ *Fast*

The problem here reminds us of the analogous problem in electrophilic aromatic substitution (Sec. 11.16). There the answer was found in the absence of

an isotope effect: although carbon–deuterium bonds are broken more slowly than carbon–hydrogen bonds, deuterium and hydrogen were found to be displaced at the same rate. Reactivity is determined by the rate of a reaction that does not involve the breaking of a carbon–hydrogen bond.

But in nucleophilic aromatic substitution, we are dealing with displacement, not of hydrogen, but of elements like the halogens; as was discussed in connection with dehydrohalogenation, any isotope effects would be small, and hard to measure.

The answer came from Joseph Bunnett (p. 478), who is responsible for much of what we understand about nucleophilic aromatic substitution. It was while studying this reaction that he first conceived the idea of *element effect* (Sec. 14.20), and showed how it gave evidence for the two-step mechanism.

In S_N1 and S_N2 displacement, we recall, the reactivity of alkyl halides follows the sequence

$$R{-}I > R{-}Br > R{-}Cl > R{-}F$$

The ease of breaking the carbon–halogen bond depends upon its strength, and the resulting differences in rate are quite large.

Yet, in nucleophilic *aromatic* substitution, there is often very little difference in reactivity among the various halides and, more often than not, the fluoride—containing the carbon–halogen bond hardest to break—is the *most* reactive. If reactivity is independent of the strength of the carbon–halogen bond, we can only conclude that the reaction *whose rate we are observing* does not involve breaking

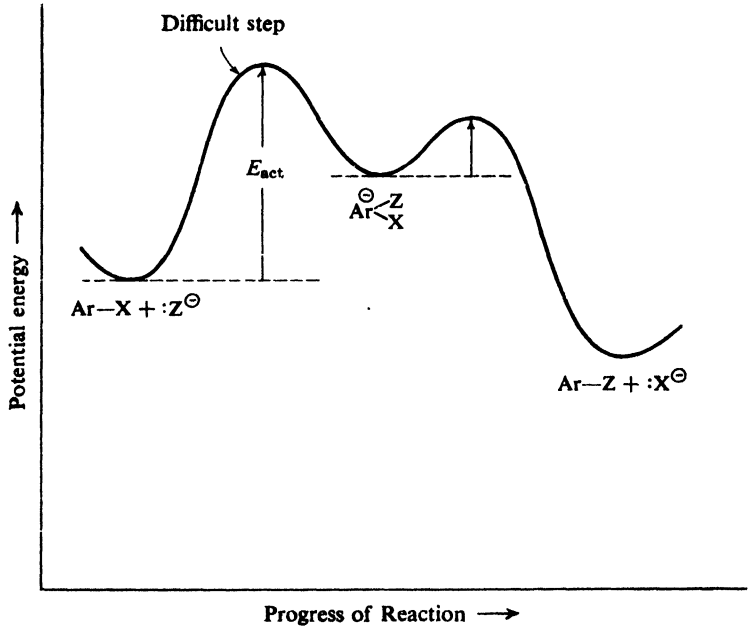


Figure 25.3. Potential energy changes during course of reaction: nucleophilic aromatic substitution. Formation of carbanion is rate-controlling step; strength of C–X bond does not affect over-all rate.

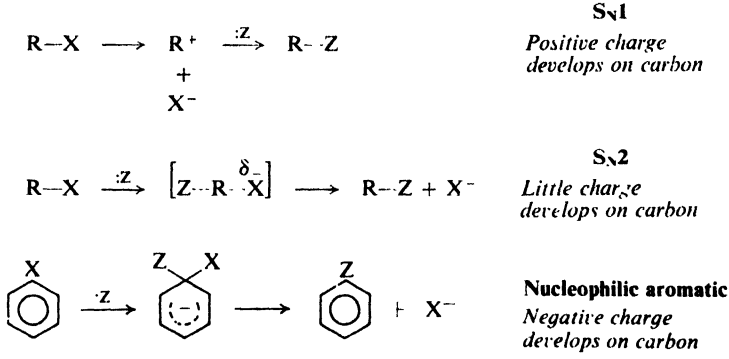
of the carbon–halogen bond. In nucleophilic aromatic substitution, as in electrophilic aromatic substitution, the rate of reaction is determined by the rate of attachment of the attacking particle to the ring (Fig. 25.3).

The *faster* reaction of aryl fluorides is attributed to the very strong inductive effect of fluorine; by withdrawing electrons it stabilizes the transition state of the first step of a reaction that will ultimately lead to its displacement.

Problem 25.7 When 2,4,6-trinitroanisole is treated with sodium ethoxide, a product of formula $C_9H_{10}O_8N_3^-Na^+$ is formed. A product of the same formula is formed by the treatment of trinitrophenetole by sodium methoxide. When treated with acid, both products give the same mixture of trinitroanisole and trinitrophenetole. What structure (or structures) would you assign to these products?

25.13 Nucleophilic substitution: aliphatic and aromatic

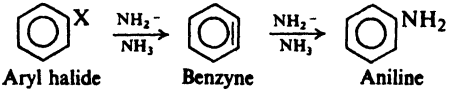
We can see a regular progression in the three kinds of nucleophilic substitution that we have studied so far. The departing group leaves the molecule *before* the entering group becomes attached in an S_N1 reaction, *at the same time* in an S_N2 reaction, and *after* in nucleophilic aromatic substitution. A *positive charge* thus develops on carbon during an S_N1 reaction, *no particular charge* during an S_N2 reaction, and a *negative charge* during nucleophilic aromatic substitution. As a result, an S_N1 reaction is favored by *electron release*, an S_N2 reaction is relatively *insensitive to electronic factors*, and nucleophilic aromatic substitution is favored by *electron withdrawal*.



25.14 Elimination-addition mechanism for nucleophilic aromatic substitution. Benzyne

We have seen that electron-withdrawing groups activate aryl halides toward nucleophilic substitution. In the absence of such activation, substitution can be *made* to take place, by use of very strong bases, for example. But when this is done, substitution does not take place by the mechanism we have just discussed (the so-called *bimolecular mechanism*), but by an entirely different mechanism: the *benzyne* (or *elimination-addition*) *mechanism*. Let us first see what this mechanism is, and then examine some of the evidence for it.

When an aryl halide like chlorobenzene is treated with the very strongly basic amide ion, NH_2^-, in liquid ammonia, it is converted into aniline. This is not the simple displacement that, on the surface, it appears to be. Instead, the reaction involves two stages: *elimination* and then *addition*. The intermediate is the molecule called *benzyne* (or *dehydrobenzene*).



Benzyne has the structure shown in Fig. 25.4, in which an additional bond is formed between two carbons (the one originally holding the halogen and the one

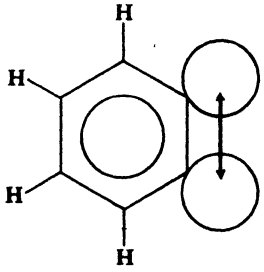
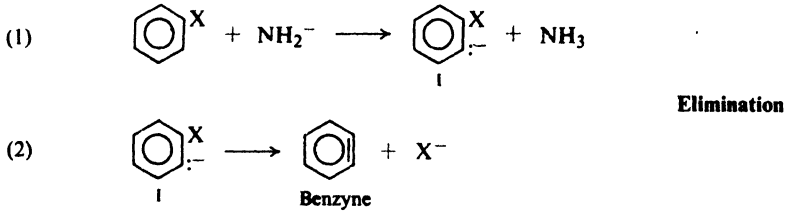


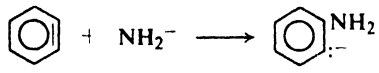
Figure 25.4. Benzyne molecule. Sideways overlap of sp^2 orbitals forms π bond out of plane of aromatic π cloud.

originally holding the hydrogen) by sideways overlap of sp^2 orbitals. This new bond orbital lies along the side of the ring, and has little interaction with the π cloud lying above and below the ring. The sideways overlap is not very good, the new bond is a weak one, and benzyne is a highly reactive molecule.

The elimination stage, in which benzyne is formed, involves two steps: abstraction of a hydrogen ion (step 1) by the amide ion to form ammonia and carbanion I, which then loses halide ion (step 2) to form benzyne.



The addition stage, in which benzyne is consumed, may also involve two steps: attachment of the amide ion (step 3) to form carbanion II, which then reacts with an acid, ammonia, to abstract a hydrogen ion (step 4). It may be that step (3) and step (4) are concerted, and addition involves a single step; if this is so, the transition state is probably one in which attachment of nitrogen has proceeded to a greater extent than attachment of hydrogen, so that it has considerable carbanion

(3) 

Benzyne II

Addition

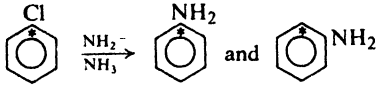
(4) 

II Aniline

character. (This is analogous to hydroboration (Sec. 15.11), in which the transition state has considerable carbonium ion character.)

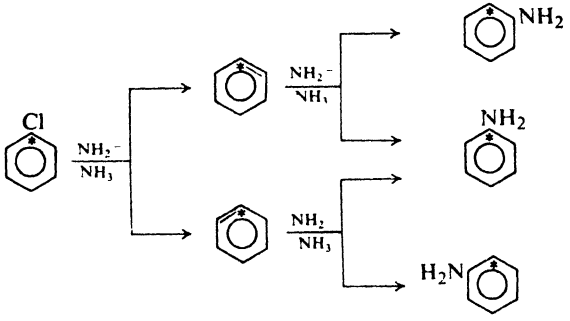
Let us look at the facts on which the above mechanism is based.

(a) *Fact.* Labeled chlorobenzene in which ^{14}C held the chlorine atom was allowed to react with amide ion. In *half* the aniline obtained the amino group was held by ^{14}C and in *half* it was held by an adjacent carbon.



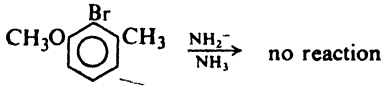
(47%) (53%)

Interpretation. In benzyne the labeled carbon and the ones next to it become equivalent, and NH_2^- adds randomly (except for a small isotope effect) to one or the other.



Although foreshadowed by certain earlier observations, this experiment, reported in 1953 by John D. Roberts of the California Institute of Technology, marks the real beginning of benzyne chemistry.

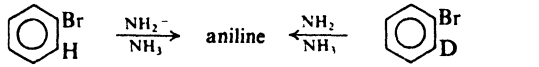
(b) *Fact.* Compounds containing two groups *ortho* to halogen, like 2-bromo-3-methylanisole, do not react at all.



Interpretation. With no *ortho* hydrogen to be lost, benzyne cannot form.

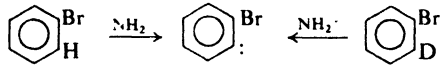
(c) *Fact.* When a 50:50 mixture of bromobenzene and *o*-deuteriobromobenzene is allowed to react with a limited amount of amide ion, recovered unreacted

material contains more of the deuteriobromobenzene than bromobenzene; the deuterated compound is less reactive and is consumed more slowly.



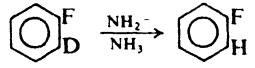
o-Deuteriobromobenzene
Reacts more slowly: more left unconsumed

Interpretation. This isotope effect (Sec. 11.15) shows not only that the *ortho* hydrogen is involved, but that it is involved in a rate-determining step. Deuterium is abstracted more slowly in the first step (equation 1, p. 836), and the whole reaction sequence is slowed down.



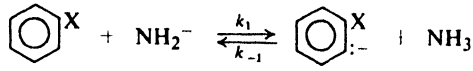
Bond to D broken more slowly

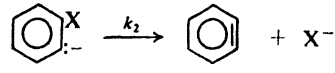
(d) *Fact.* *o*-Deuteriofluorobenzene is converted into aniline only very slowly, but loses its deuterium rapidly to yield ordinary fluorobenzene.



Interpretation. Abstraction of hydrogen (step 1) takes place, but before the very strong carbon–fluorine bond can break, the carbanion reacts with the acid—which is almost *all* NH_3 with only a trace of NH_2D—to regenerate fluorobenzene, but without its deuterium.

In the case of *o*-deuterio*bromo*benzene, on the other hand, breaking of the weaker carbon–bromide bond (step 2) is much faster than the protonation by ammonia (reverse of step 1): as fast as a carbanion is formed, it loses bromide ion. In this case, isotopic exchange is not important. (It may even be that here steps (1) and (2) are concerted.)

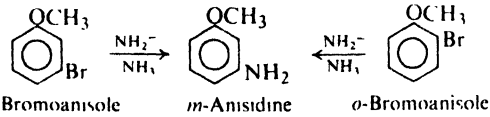
(1) 

(2) 

for X = F, $k_{-1} \gg k_2$

X = Br, $k_2 \gg k_{-1}$

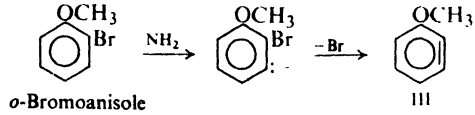
(e) *Fact.* Both *m*-bromoanisole and *o*-bromoanisole yield the same product: *m*-anisidine (*m*-aminoanisole).



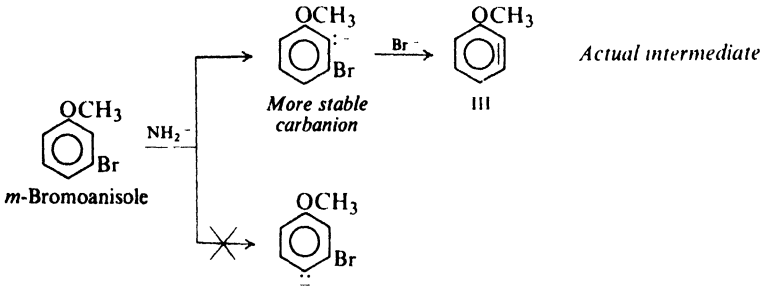
Interpretation. They yield the same product because they form the same intermediate benzyne.

Which benzyne is this, and how is it that it yields *m*-anisidine? To deal with orientation—both in the elimination stage and the addition stage—we must remember that a methoxyl group has an electron-withdrawing inductive effect. Since the electrons in carbanions like I and II (pp. 836–837) are out of the plane of the π cloud, there is no question of resonance interaction; only the inductive effect, working along the σ bonds (or perhaps through space), is operative.

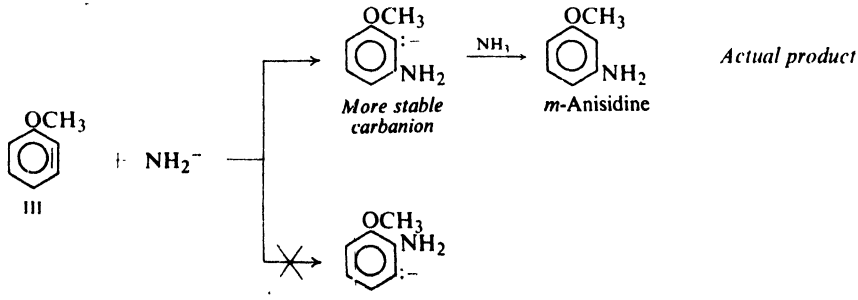
o-Bromoanisole yields the benzyne shown (III, 2,3-dehydroanisole) because it has to. *m*-Bromoanisole yields III because, in the first step, the negative charge



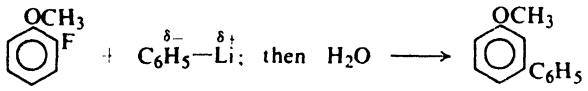
appears preferentially on the carbon that can best accommodate it: the carbon next to the electron-withdrawing group. Whatever its source, III yields *m*-anisidine



for the same reason: addition of NH_2^- occurs in such a way that the negative charge appears on the carbon next to methoxyl.

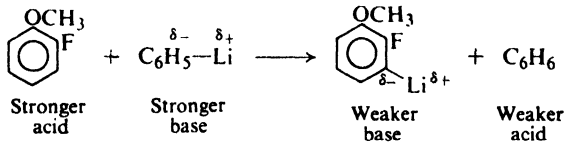


Another common way to generate benzyne involves use of organolithium compounds. For example:

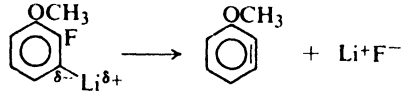


Here benzyne formation involves abstraction of a proton (reaction 5) by the base $C_6H_5^-$ to form a carbanion which loses fluoride ion (reaction 6) to give benzyne.

(5)



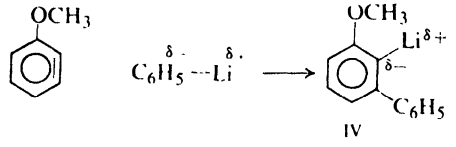
(6)



Problem 25.8 Account for the relative strengths of these acids and bases.

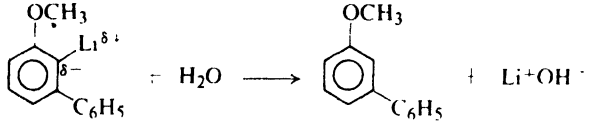
Addition of phenyllithium (reaction 7) to the benzyne gives the organolithium compound IV. From one point of view, this is the same reaction sequence observed for the amide ion–ammonia reaction (above), but it stops at the carbanion stage for want of strong acid. (Alternatively, the Lewis acid Li^+ has completed the sequence.) Addition of water—in this company, a very strong acid—yields (reaction 8) the final product. (The strong acid H^+ has displaced the weaker acid Li^+.)

(7)



IV

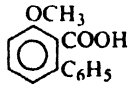
(8)



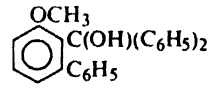
Organolithium compounds, RLi, resemble Grignard reagents, RMgX, in their reactions. As in Grignard reagents (Sec. 3.16), the carbon–metal bond can probably best be described as a highly polar covalent bond or, in another manner of speaking, as a bond with much *ionic character* (a resonance hybrid of R⁻ M and R M⁺). Because of the greater electropositivity of lithium, the carbon–lithium bond is even more ionic than the carbon–magnesium bond and, partly as a result of this, organolithium compounds are more reactive than Grignard reagents. As we have done with Grignard reagents, we shall for convenience focus our attention on the carbanion character of the organic group in discussing these reactions as acid base chemistry. In the reactions

involving $K^+NH_2^-$ we indicated free carbanions as intermediates, although even here the attractive forces- whatever they are--between carbon and potassium may be of great importance.

Problem 25.9 Account for the following facts: (a) treatment of the reaction mixture in reaction (8) with carbon dioxide instead of water gives V; (b) treatment of



V



VI

the reaction mixture in reaction (8) with benzophenone gives VI; (c) benzyne can be generated by treatment of *o*-bromofluorobenzene with magnesium metal.

25.15 Analysis of aryl halides

Aryl halides show much the same response to characterization tests as the hydrocarbons from which they are derived: insolubility in cold concentrated sulfuric acid; inertness toward bromine in carbon tetrachloride and toward permanganate solutions; formation of orange to red colors when treated with chloroform and aluminum chloride; dissolution in cold fuming sulfuric acid, but at a slower rate than that of benzene.

Aryl halides are distinguished from aromatic hydrocarbons by the presence of halogen, as shown by elemental analysis. Aryl halides are distinguished from most alkyl halides by their inertness toward silver nitrate; in this respect they resemble vinyl halides (Sec. 25.5).

Any other functional groups that may be present in the molecule undergo their characteristic reactions.

Problem 25.10 Describe simple chemical tests (if any) that will distinguish between: (a) bromobenzene and *n*-hexyl bromide; (b) *p*-bromotoluene and benzyl bromide; (c) chlorobenzene and 1-chloro-1-hexene; (d) α-(*p*-bromophenyl)ethyl alcohol (*p*-$BrC_6H_4CHOHCH_3$) and *p*-bromo-*n*-hexylbenzene; (e) α-(*p*-chlorophenyl)ethyl alcohol and β-(*p*-chlorophenyl)ethyl alcohol (*p*-$ClC_6H_4CH_2CH_2OH$). Tell exactly what you would *do* and *see*.

Problem 25.11 Outline a procedure for distinguishing by chemical means (not necessarily simple tests) between: (a) *p*-bromoethylbenzene and 4-bromo-1,3-dimethylbenzene; (b) *o*-chloropropenylbenzene (*o*-$ClC_6H_4CH{=}CHCH_3$) and *o*-chloroallylbenzene (*o*-$ClC_6H_4CH_2CH{=}CH_2$).

PROBLEMS

1. Give structures and names of the principal organic products of the reaction (if any) of each of the following reagents with bromobenzene:

(a) Mg, ether
(b) boiling 10% aqueous NaOH
(c) boiling alcoholic KOH
(d) sodium acetylide
(e) sodium ethoxide
(f) NH_3, 100°
(g) boiling aqueous NaCN
(h) HNO_3, H_2SO_4
(i) fuming sulfuric acid
(j) Cl_2, Fe

(k) I_2, Fe
(l) C_6H_6, $AlCl_3$
(m) CH_3CH_2Cl, $AlCl_3$
(n) cold dilute $KMnO_4$
(o) hot $KMnO_4$

2. Answer Problem 1 for *n*-butyl bromide.

3. Answer Problem 1, parts (b), (c), (f), and (g) for 2,4-dinitrobromobenzene.

4. Outline a laboratory method for the conversion of bromobenzene into each of the following, using any needed aliphatic and inorganic reagents.

(a) benzene
(b) *p*-bromonitrobenzene
(c) *p*-bromochlorobenzene
(d) *p*-bromobenzenesulfonic acid
(e) 1,2,4-tribromobenzene
(f) *p*-bromotoluene
(g) benzyl alcohol
(h) α-phenylethyl alcohol
(i) 2-phenyl-2-propanol
(j) 2,4-dinitrophenol
(k) allylbenzene (*Hint:* See Problem 16, p. 281.)
(l) benzoic acid
(m) aniline

5. Give the structure and name of the product expected when phenylmagnesium bromide is treated with each of the following compounds and then with water:

(a) H_2O
(b) HBr (dry)
(c) C_2H_5OH
(d) allyl bromide
(e) HCHO
(f) CH_3CHO
(g) C_6H_5CHO
(h) p-$CH_3C_6H_4CHO$
(i) CH_3COCH_3
(j) cyclohexanone
(k) 3,3-dimethylcyclohexanone
(l) $C_6H_5COCH_3$
(m) $C_6H_5COC_6H_5$
(n) (−)-$C_6H_5COCH(CH_3)C_2H_5$
(o) acetylene

Which products (if any) would be single compounds? Which (if any) would be racemic modifications? Which (if any) would be optically active as isolated?

6. Arrange the compounds in each set in order of reactivity toward the indicated reagent. Give the structure and name of the product expected from the compound you select as the most reactive in each set.

(a) NaOH: chlorobenzene, *m*-chloronitrobenzene, *o*-chloronitrobenzene, 2,4-dinitrochlorobenzene, 2,4,6-trinitrochlorobenzene
(b) HNO_3/H_2SO_4: benzene, chlorobenzene, nitrobenzene, toluene
(c) alcoholic $AgNO_3$: 1-bromo-1-butene, 3-bromo-1-butene, 4-bromo-1-butene
(d) fuming sulfuric acid: bromobenzene, *p*-bromotoluene, *p*-dibromobenzene, toluene
(e) KCN: benzyl chloride, chlorobenzene, ethyl chloride
(f) alcoholic $AgNO_3$: 2-bromo-1-phenylethene, α-phenylethyl bromide, β-phenylethyl bromide

7. In the preparation of 2,4-dinitrochlorobenzene from chlorobenzene, the excess nitric acid and sulfuric acid must be washed from the product. Which would you select for this purpose: aqueous sodium hydroxide or aqueous sodium bicarbonate? Why?

8. Give structures and names of the principal organic products expected from each of the following reactions:

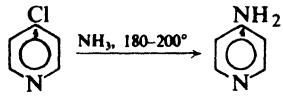
(a) 2,3-dibromopropene + NaOH(aq)
(b) *p*-bromobenzyl bromide + NH_3(aq)
(c) *p*-chlorotoluene + hot $KMnO_4$
(d) *m*-bromostyrene + Br_2/CCl_4
(e) 3,4-dichloronitrobenzene + 1 mole $NaOCH_3$
(f) *p*-bromochlorobenzene + Mg, ethyl ether
(g) *p*-bromobenzyl alcohol + cold dilute $KMnO_4$
(h) *p*-bromobenzyl alcohol + conc. HBr
(i) α-(*o*-chlorophenyl)ethyl bromide + KOH(alc)

(j) *p*-bromotoluene + 1 mole Cl_2, heat, light
(k) *o*-bromobenzotrifluoride + $NaNH_2/NH_3$
(l) *o*-bromoanisole + $K^+ {}^-NEt_2/Et_2NH$

9. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene and/or toluene, using any needed aliphatic or inorganic reagents:

(a) *m*-chloronitrobenzene
(b) *p*-chloronitrobenzene
(c) *m*-bromobenzoic acid
(d) *p*-bromobenzoic acid
(e) *m*-chlorobenzotrichloride
(f) 3,4-dibromonitrobenzene
(g) *p*-bromobenzal chloride
(h) 2,4-dinitroaniline
(i) *p*-bromostyrene
(j) 2,4-dibromobenzoic acid
(k) *m*-iodotoluene
(l) *p*-bromobenzenesulfonic acid
(m) *p*-chlorobenzyl alcohol
(n) 2-(*p*-tolyl)propane

10. Halogen located at the 2- or 4-position of the aromatic heterocyclic compound *pyridine* (Sec. 31.6) is fairly reactive toward nucleophilic displacement. For example:



4-Chloropyridine 4-Aminopyridine

How do you account for the reactivity of these compounds? (Check your answer in Sec. 31.10.)

11. The insecticide called DDT, 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl(ethane, $(p\text{-}ClC_6H_4)_2CHCCl_3$, is manufactured by the reaction between chlorobenzene and trichloroacetaldehyde in the presence of sulfuric acid. Outline the series of steps by which this synthesis most probably takes place; make sure you show the function of the H_2SO_4. Label each step according to its fundamental reaction type.

12. In the Dow process for the manufacture of phenol, two by-products are diphenyl ether and *p*-phenylphenol. It has been suggested that these two compounds are formed via the same intermediate. How might this happen?

13. In KNH_2/NH_3, protium-deuterium exchange takes place at the following relative rates:

$o\text{-}C_6H_4DF$	>	$m\text{-}C_6H_4DF$	>	$p\text{-}C_6H_4DF$	>	C_6H_5D
4,000,000		4,000		200		1

How do you account for this sequence of reactivity?

14. Reduction of 2,6-dibromobenzenediazonium chloride, which would be expected to give *m*-dibromobenzene, actually yields chiefly *m*-bromochlorobenzene. How do you account for this?

15. The reaction of 2,4-dinitrofluorobenzene with N-methylaniline to give N-methyl-2,4-dinitrodiphenylamine is catalyzed by weak bases like acetate ion. The reaction of the corresponding bromo compound is faster, and is not catalyzed by bases. How do you account for these observations? (*Hint:* Examine in detail every step of the mechanism.)

16. (a) The labeled ether $2,4\text{-}(NO_2)_2C_6H_3{}^{18}OC_6H_5$ reacts more slowly than the unlabeled ether with the secondary amine piperidine (Sec. 31.12). How do you account for this?

(b) The isotope effect in part (a) becomes weaker as the piperidine concentration is raised. Account in detail for this observation. (*Hint:* See the preceding problem.)

17. The rate of reaction between *p*-fluoronitrobenzene and azide ion (N_3^-) is affected markedly by the nature of the solvent. How do you account for the following relative rates: in methanol, 1; in formamide, 5.6; in N-methylformamide, 15.7; in dimethylformamide, 2.4×10^4.

18. The dry diazonium salt I was subjected to a flash discharge, and an especially

I

adapted mass spectrometer scanned the spectrum of the products at rapid intervals after the flash. After about 50 microseconds there appeared simultaneously masses 28, 44, and 76. As time passed (about 250 microseconds) mass 76 gradually disappeared and a peak at mass 152 approached maximum intensity.

(a) What are the peaks at 28, 44, and 76 due to? What happens as time passes, and what is the substance of mass 152? (b) From what compound was the diazonium salt I prepared?

19. When a trace of KNH_2 is added to a solution of chlorobenzene and potassium triphenylmethide, $(C_6H_5)_3C^-K^+$, in liquid ammonia, a rapid reaction takes place to yield a product of formula $C_{25}H_{20}$. What is the product? What is the role of KNH_2, and why is it needed?

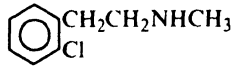
20. How do you account for each of the following observations?

(a) When *p*-iodotoluene is treated with aqueous NaOH at 340°, there is obtained a mixture of *p*-cresol (51%) and *m*-cresol (49%). At 250°, reaction is, of course, slower, and yields only *p*-cresol.

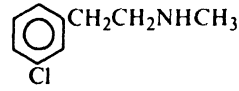
(b) When diazotized 4-nitro-2-aminobenzoic acid is heated in *tert*-butyl alcohol, there is obtained carbon dioxide, nitrogen, and a mixture of *m*- and *p*-nitrophenyl *tert*-butyl ethers.

(c) When *o*-chlorobenzoic acid is treated with $NaNH_2/NH_3$ in the presence of acetonitrile (CH_3CN) there is obtained a 70% yield of *m*-$HOOCC_6H_4CH_2CN$ and 10–20% of a 1:2 mixture of *o*- and *m*-aminobenzoic acids.

21. When either II or III is treated with $KN(C_2H_5)_2/HN(C_2H_5)_2$, there is obtained in



II

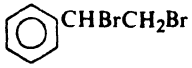


III

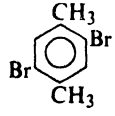
good yield the same product, of formula $C_9H_{11}N$. What is the product, and how is it formed?

22. 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. Where necessary, make use of Table 18.1, p. 580.

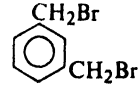
(a) $C_6H_5CH{=}CHBr$ (b.p. 221°), *o*-$C_6H_4Br_2$ (b.p. 221°), $BrCH_2(CH_2)_3CH_2Br$ (b.p. 224°)
(b) *o*-$CH_3C_6H_4Br$ (b.p. 182°), *m*-$CH_3C_6H_4Br$ (b.p. 184°), *p*-$CH_3C_6H_4Br$ (b.p. 185°)
(c) *o*-$ClC_6H_4C_2H_5$ (b.p. 178°), $C_6H_5CH_2Cl$ (b.p. 179°), *o*-$C_6H_4Cl_2$ (b.p. 180°)
(d) $ClCH_2CH_2OH$ (b.p. 129°), 4-octyne (b.p. 131°), isopentyl alcohol (b.p. 132°), C_6H_5Cl (b.p. 132°), ethylcyclohexane (b.p. 132°), 1-chlorohexane (b.p. 134°)

(e) 

(m.p. 73°)

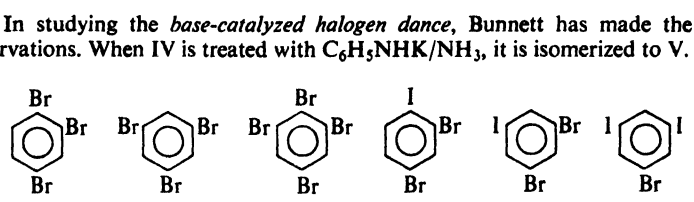


(m.p. 74°)



(m.p. 76°)

23. In studying the *base-catalyzed halogen dance*, Bunnett has made the following observations. When IV is treated with C_6H_5NHK/NH_3, it is isomerized to V. There is



IV V VI VII VIII IX

found, in addition, VI, *m*- and *p*-dibromobenzenes, and unconsumed IV. Similar treatment of VII gives chiefly VIII, along with IX, IV, and V. When IV labeled at the 1-position with radioactive bromine is allowed to react, the recovered IV had the label statistically distributed among all three positions.

(a) Bunnett first considered a mechanism involving intermediate benzynes. Show how you could account for the above observations on this basis.

(b) When IV is allowed to isomerize in the presence of much KI, no iodobromobenzenes are found. On this and other grounds, Bunnett rejected the benzyne mechanism. Explain.

(c) From the isomerization of IV, some unconsumed IV is *always* obtained. Yet the reaction of V gives IV *only if* there is present a small amount of VI to start with. (This is a *real* effect; highly purified materials give the same results.) In the presence of a little VI, the same mixture (about 50:50) of IV and V is formed whether one starts with IV or with V.

Suggest a complete mechanism for the base-catalyzed halogen dance, and show how it accounts for all the facts. It may help to go at the problem in this way. First, start with V and the base, in the presence of VI, and show how IV can be formed. Show how, under the same conditions, V can be formed from IV.

Next, start with *only* IV and base, and show how all the products are formed (V, VI, *m*- and *p*-dibromobenzenes), and account for the scrambling of the bromine label.

Finally, the hardest part: why must VI be added to bring about isomerization of V but not the isomerization of IV? (*Hint:* Simply write for V equations analogous to those you have written for IV, and keep in mind Problem 13, p. 843.)