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

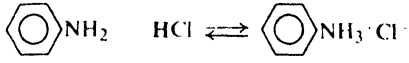
1. Basicity. Salt formation. Discussed in Secs. 22.5 and 23.2–23.4.

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

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

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

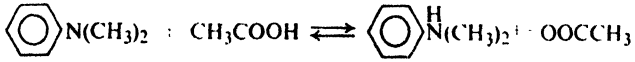
Examples:



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:

$$(n\text{-}C_4H_9)_2NH + C_6H_5CH_2Cl \longrightarrow (n\text{-}C_4H_9)_2NCH_2C_6H_5$$

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

$$n\text{-}C_3H_7NH_2 \xrightarrow{CH_3I} n\text{-}C_3H_7NHCH_3 \xrightarrow{CH_3I} n\text{-}C_3H_7N(CH_3)_2 \xrightarrow{CH_3I} n\text{-}C_3H_7N^+(CH_3)_3I^-$$

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

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

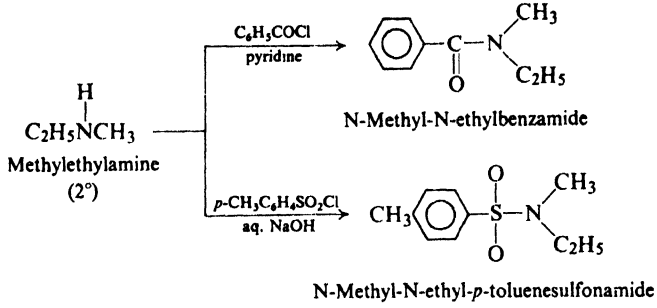
Primary: RNH_2
- $\xrightarrow{R'COCl}$ $R'CONHR$ An N-substituted amide
- $\xrightarrow{ArSO_2Cl}$ $ArSO_2NHR$ An N-substituted sulfonamide

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:

Aniline (1°)
- $\xrightarrow{(CH_3CO)_2O}$ Acetanilide (N-Phenylacetamide)
- $\xrightarrow[\text{aq. NaOH}]{C_6H_5SO_2Cl}$ Benzenesulfonanilide (N-Phenylbenzenesulfonamide)

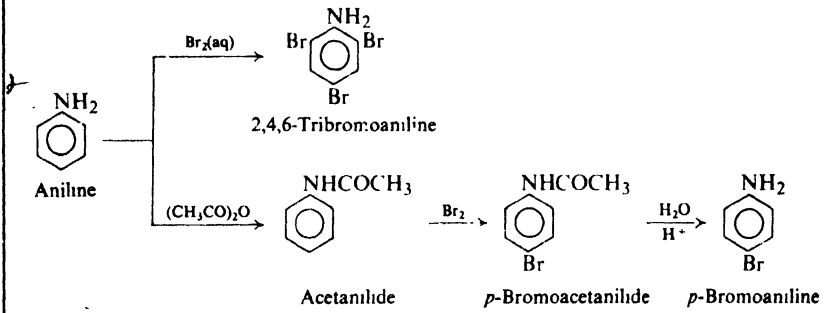


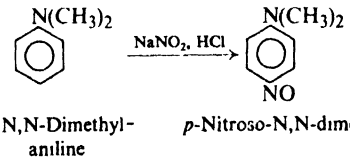
♥ **4. Ring substitution in aromatic amines.** Discussed in Secs. 23.7, 23.10, and 23.17.

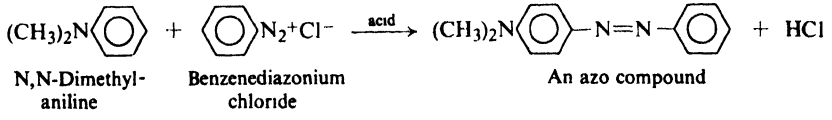
—NH_2, —NHR, —NR_2: Activate powerfully, and direct *ortho, para* in electrophilic aromatic substitution

—NHCOR: Less powerful activator than —NH_2

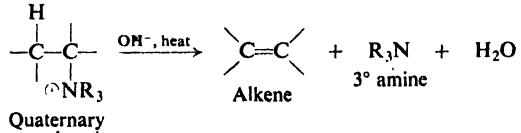
Examples:







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

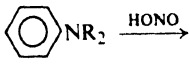


6. Reactions with nitrous acid. Discussed in Secs. 23.10–23.11.

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}

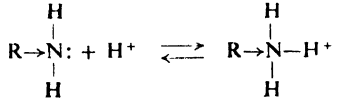
	K_b		K_b		K_b
p-NH_2	140×10^{-10}	*m*-NH_2	10×10^{-10}	*o*-NH_2	3×10^{-10}
p-OCH_3	20	*m*-OCH_3	2	*o*-OCH_3	3
p-CH_3	12	*m*-CH_3	5	*o*-CH_3	2.6
p-Cl	1	*m*-Cl	.3	*o*-Cl	.05
p-NO_2	.001	*m*-NO_2	.029	*o*-NO_2	.00006

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.

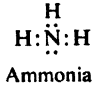
An aliphatic amine is more basic than ammonia because the electron-releasing alkyl groups tend to disperse the positive charge of the substituted ammonium ion, and therefore stabilize it in a way that is not possible for the unsubstituted ammonium ion. Thus an *ammonium* ion is stabilized by electron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



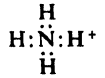
R *releases electrons:* *makes unshared pair more available*

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:

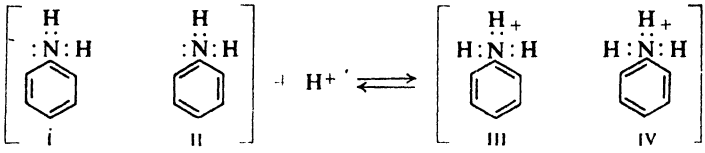


Ammonia



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

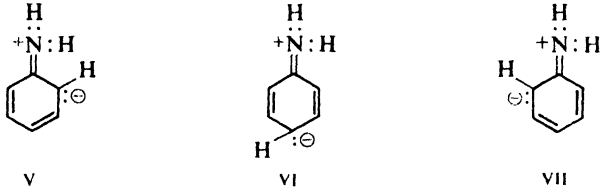


Aniline Anilinium ion

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.

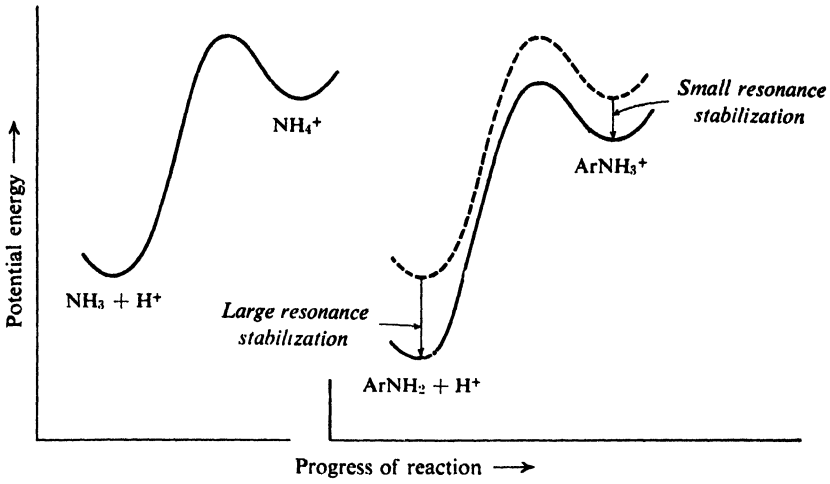


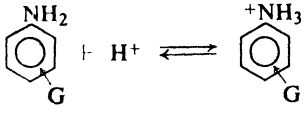
Figure 23.1. Molecular structure and position of equilibrium. Resonance-stabilized aromatic amine is weaker base than ammonia. (Plots aligned with each other for easy comparison.)

23.4 Effect of substituents on basicity of aromatic amines

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

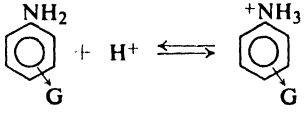
In Table 23.1 (p. 749) we see that an electron-releasing substituent like $-CH_3$ increases the basicity of aniline, and an electron-withdrawing substituent like $-X$ or $-NO_2$ decreases the basicity. These effects are understandable. Electron release tends to disperse the positive charge of the anilinium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

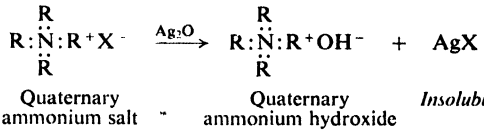
$$\underset{1^\circ}{RNH_2} \xrightarrow{RX} \underset{2^\circ}{R_2NH} \xrightarrow{RX} \underset{3^\circ}{R_3N} \xrightarrow{RX} \underset{4^\circ}{R_4N^+X^-}$$

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.

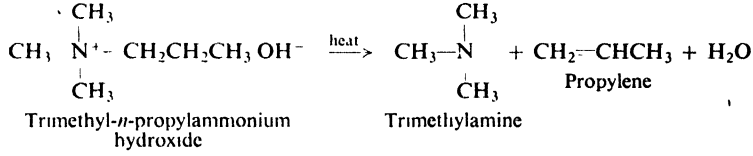
Quaternary ammonium salts are the products of the final stage of alkylation of nitrogen. They have the formula $R_4N^+X^-$. Four organic groups are covalently bonded to nitrogen, and the positive charge of this ion is balanced by some nega-

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.

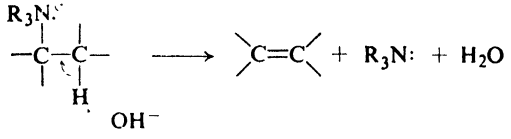


When a solution of a quaternary ammonium halide is treated with silver oxide, silver halide precipitates. When the mixture is filtered and the filtrate is evaporated to dryness, there is obtained a solid which is free of halogen. An aqueous solution of this substance is strongly alkaline, and is comparable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

$$CH_3CH_2CH_2\underset{\underset{N(CH_3)_3}{|}}{CH}CH_3 \xrightarrow[C_2H_5OH]{C_2H_5ONa} \underset{\text{1-Pentene}}{CH_3CH_2CH_2CH{=}CH_2} + \underset{\text{2-Pentene}}{CH_3CH_2CH{=}CHCH_3}$$

2-Pentyltrimethylammonium ion

96% 4%

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.

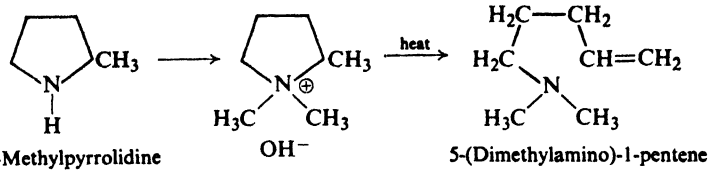
Problem 23.3 Predict the major products of E2 elimination from: (a) 2-methyl-3-pentyltrimethylammonium ion; (b) diethyldi-*n*-propylammonium ion; (c) dimethylethyl(2-chloroethyl)ammonium ion; (d) dimethylethyl-*n*-propylammonium ion.

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?

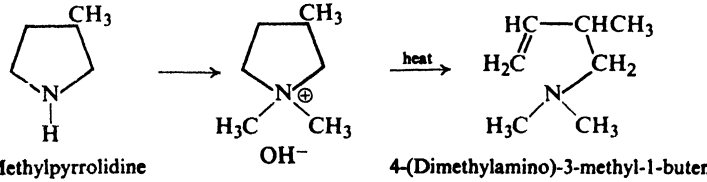
The formation of quaternary ammonium salts, followed by an elimination of the kind just described, is very useful in the determination of the structures of certain complicated nitrogen-containing compounds. The compound, which may be a primary, secondary, or tertiary amine, is converted into the quaternary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

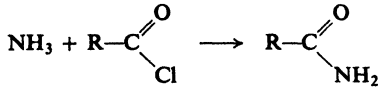
II

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?

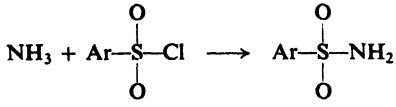
Problem 23.6 What products would be expected if I and II were subjected to exhaustive methylation and elimination?

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:

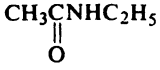
Primary: RNH_2
- $\xrightarrow{R'COCl}$ $R'CONHR$ An N-substituted amide
- $\xrightarrow{ArSO_2Cl}$ $ArSO_2NHR$ An N-substituted sulfonamide

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

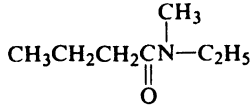
Tertiary: R_3N
- $\xrightarrow{R'COCl}$ No reaction
- $\xrightarrow{ArSO_2Cl}$ No reaction under conditions of Hinsberg test (*but see* Sec. 23.18).

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.)

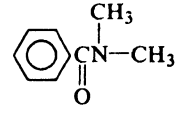
Substituted amides are generally named as derivatives of the unsubstituted amides. For example:



N-Ethylacetamide

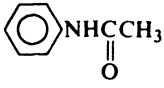


N-Methyl-N-ethylbutyramide

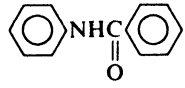


N,N-Dimethylbenzamide

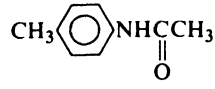
In many cases, and particularly where aromatic amines are involved, we are more interested in the amine from which the amide is derived than in the acyl group. In these cases the substituted amide is named as an acyl derivative of the amine. For example:



Acetanilide

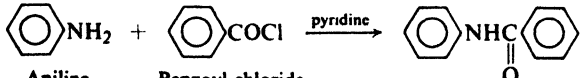


Benzanilide

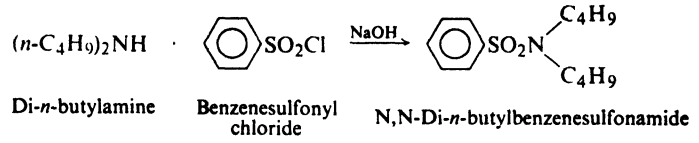


Aceto-*p*-toluidide

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:

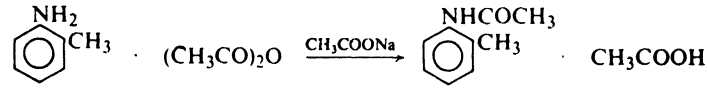


Aniline + Benzoyl chloride $\xrightarrow{\text{pyridine}}$ Benzanilide



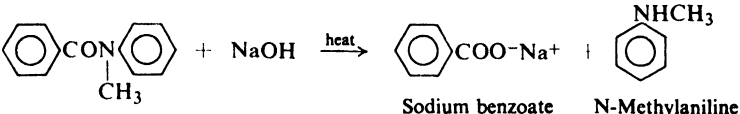
Di-*n*-butylamine | Benzenesulfonyl chloride | N,N-Di-*n*-butylbenzenesulfonamide

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

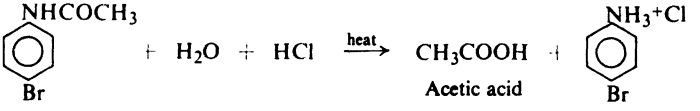


o-Toluidine | Acetic anhydride | Aceto-*o*-toluidide

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.

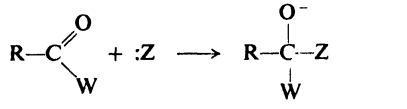


N-Methylbenzanilide | Sodium benzoate | N-Methylaniline



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

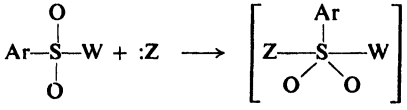
Sulfonamides are hydrolyzed more slowly than amides of carboxylic acids; examination of the structures involved shows us what probably underlies this difference. Nucleophilic attack on a trigonal acyl carbon (Sec. 20.4) is relatively unhindered; it involves the temporary attachment of a fourth group,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



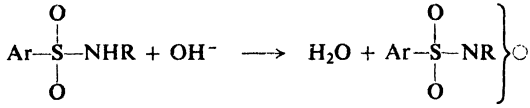
Tetrahedral S | Pentavalent S

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?

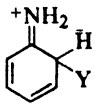
Problem 23.8 In contrast to carboxylic esters, we know, alkyl sulfonates undergo nucleophilic attack at alkyl carbon. What *two* factors are responsible for this difference

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

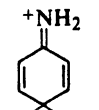
The conversion of an amine into a sulfonamide is used in determining the class of the amine; this is discussed in the section on analysis (Sec. 23.18).

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.

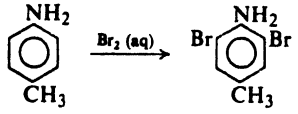
In such structures nitrogen shares more than one pair of electrons with the ring, and hence carries the charge of the "carbonium ion." Thus the basicity of nitrogen accounts for one more characteristic of aromatic amines.

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.)

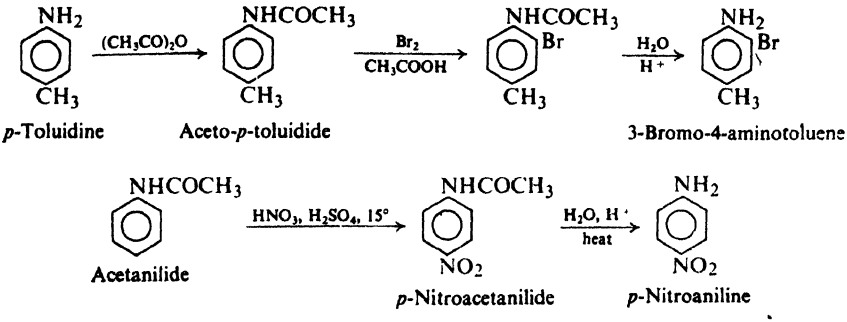
In electrophilic substitution, the chief problem encountered with aromatic amines is that they are *too* reactive. In halogenation, substitution tends to occur at every available *ortho* or *para* position. For example:



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.

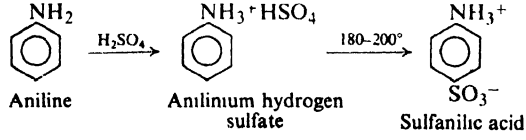
There is, fortunately, a simple way out of these difficulties: We *protect* the amino group: we acetylate the amine, then carry out the substitution, and finally hydrolyze the amide to the desired substituted amine. For example:



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

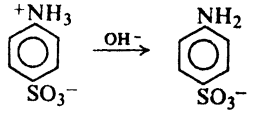


known to be reversible, and the *p*-isomer is known to be the most stable isomer; it may well be that the product obtained, the *p*-isomer, is determined by the position of an equilibrium and not by relative rates of formation (see Sec. 8.22 and Sec. 12.11). It also seems likely that, in some cases at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

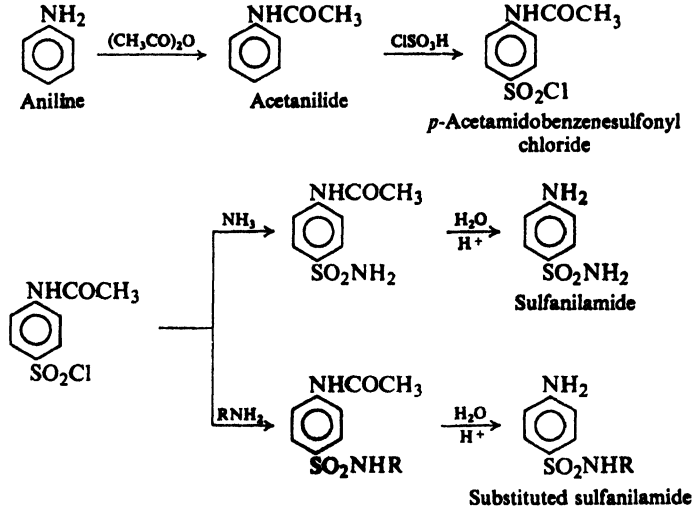
We can expect to encounter dipolar ions whenever we have a molecule containing both an amino group and an acid group, providing the amine is more basic than the anion of the acid.

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?

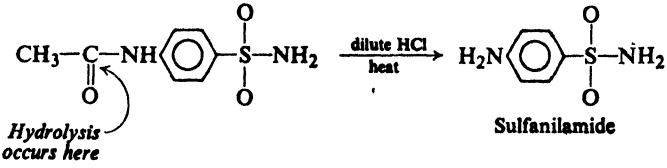
23.9 Sulfanilamide. The sulfa drugs

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:

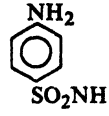


The selective removal of the acetyl group in the final step is consistent with the general observation that amides of carboxylic acids are more easily hydrolyzed than amides of sulfonic acids.



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

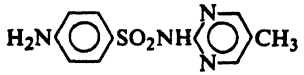
p-Aminobenzoic acid



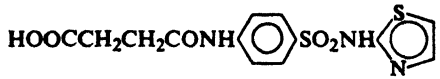
Substituted sulfanilamide

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

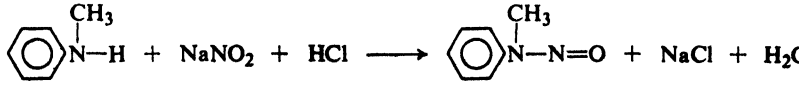
$$\underset{\substack{1^\circ \text{ aliphatic}\\ \text{amine}}}{RNH_2} + NaNO_2 + HX \longrightarrow \underset{\textit{Unstable}}{[RN_2^+X^-]} \xrightarrow{H_2O} N_2 + \text{mixture of alcohols and alkenes}$$

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.

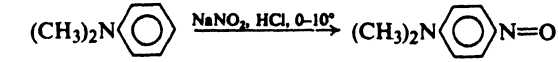
Secondary amines, both aliphatic and aromatic, react with nitrous acid to yield N-nitrosoamines.



N-Methylaniline

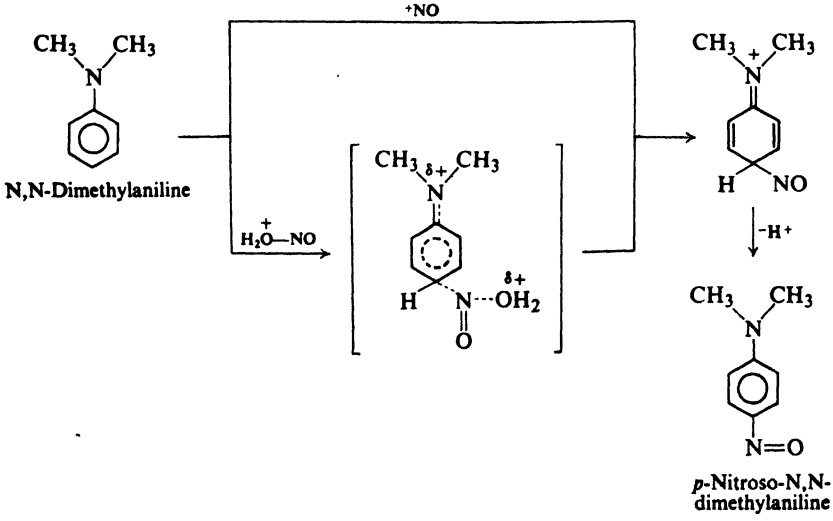
N-Nitroso-N-methylaniline

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

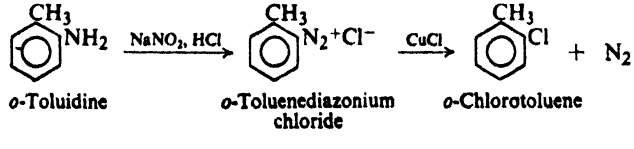
1. Replacement of nitrogen

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

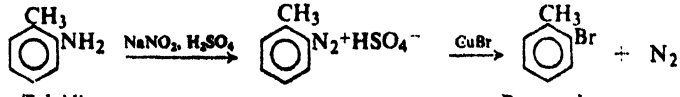
(a) **Replacement by —Cl, —Br, and —CN. Sandmeyer reaction.** Discussed in Secs. 23.12–23.13.

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

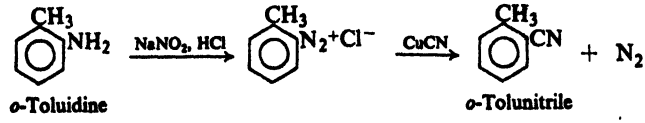
Examples:



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



o-Toluidine — *o*-Bromotoluene

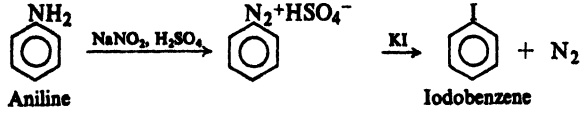


o-Toluidine *o*-Tolunitrile

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

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

Example:

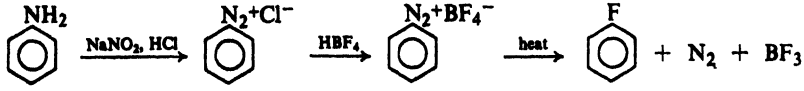


Aniline Iodobenzene

(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

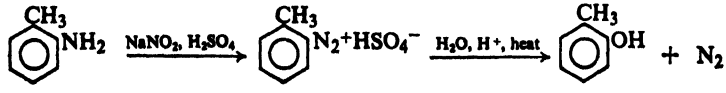
Isolated as crystalline salt

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

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

A phenol

Example:

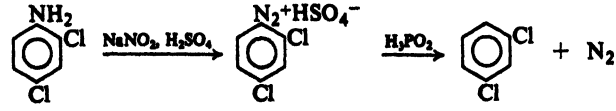


o-Toluidine *o*-Cresol

(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.

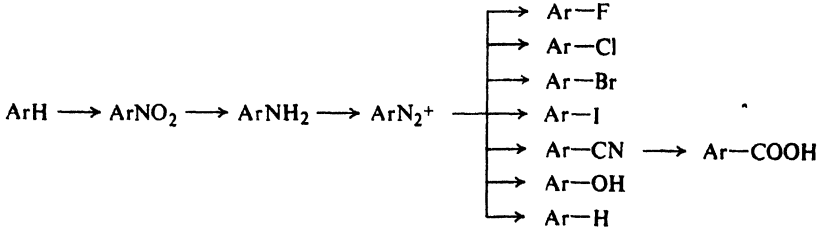
An azo compound

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, $ArN_2^+PF_6^-$.

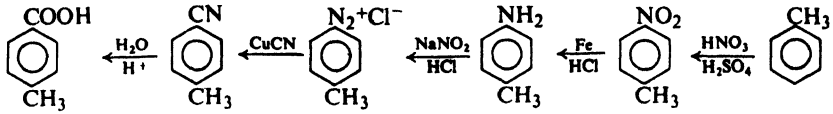
The advantages of the synthesis of aryl halides from diazonium salts will be discussed in detail in Sec. 25.3. Aryl fluorides and iodides cannot generally be prepared by direct halogenation. Aryl chlorides and bromides can be prepared by direct halogenation, but, when a mixture of *o*- and *p*-isomers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

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

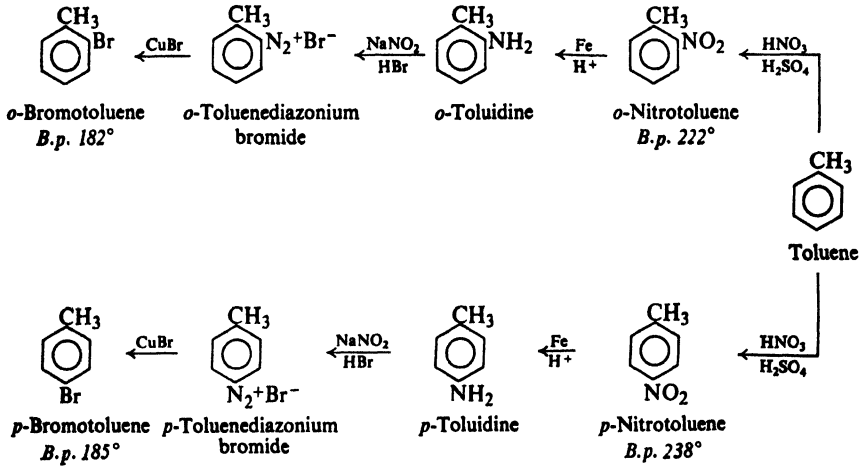
An especially elegant way of carrying out this replacement is to use hypophosphorous acid as the diazotizing acid. The amine is dissolved in hypophosphorous acid, and sodium nitrite is added; the diazonium salt is reduced as fast as it is formed.

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

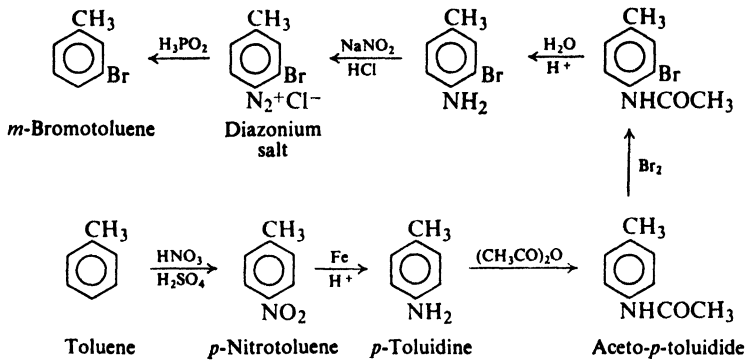
Let us look at a few examples of how diazonium salts can be used in organic synthesis.

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.

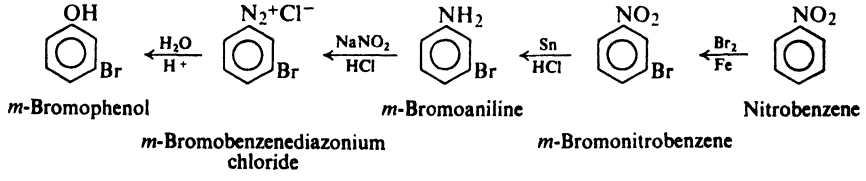
Synthesis of *m*-bromotoluene is a more complicated matter. The problem here is one of preparing a compound in which two *ortho,para*-directing groups are situated *meta* to each other. Bromination of toluene or methylation of bromobenzene would not yield the correct isomer. *m*-Bromotoluene is obtained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

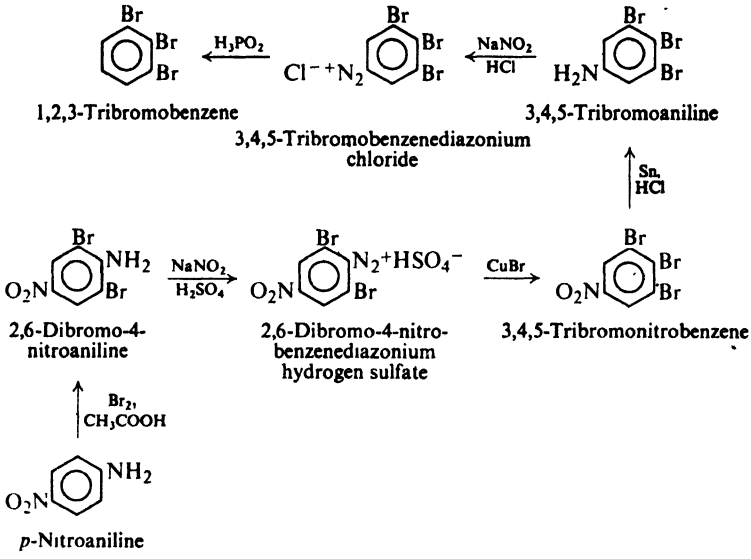
In the synthesis of *m*-bromotoluene, advantage was taken of the fact that the diazonium group is prepared from a group that is strongly *ortho,para*-directing. Ultimately, however, the diazonium group is prepared from the $-NO_2$ group, which is a strongly *meta*-directing group. Advantage can be taken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

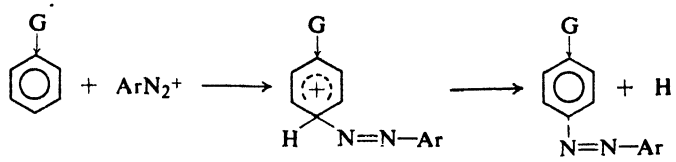
23.17 Coupling of diazonium salts. Synthesis of azo compounds

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.

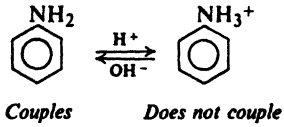
The electrophilic reagent is the diazonium ion, ArN_2^+. In the presence of hydroxide ion, the diazonium ion exists in equilibrium with an un-ionized compound, Ar—N=N—OH, and salts (Ar—N=N—O^-Na^+) derived from it:

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

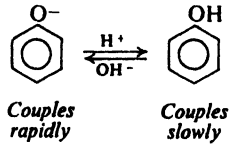
For our purpose we need only know that hydroxide tends to convert diazonium ion, which couples, into compounds which do not couple. In so far as the electrophilic reagent is concerned, then, coupling will be favored by a low concentration of hydroxide ion, that is, by high acidity.

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.



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



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.

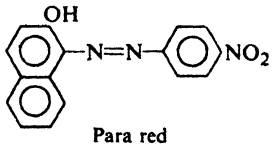
The conditions under which coupling proceeds most rapidly are the result of a compromise. The solution must not be so alkaline that the concentration of diazonium ion is too low; it must not be so acidic that the concentration of free amine or phenoxide ion is too low. It turns out that amines couple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

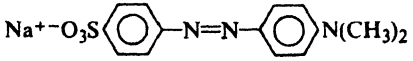
Problem 23.20 (a) Coupling of diazonium salts with primary or secondary aromatic amines (but not with tertiary aromatic amines) is complicated by a side reaction that yields an isomer of the azo compound. Judging from the reaction of secondary aromatic amines with nitrous acid (Sec. 23.10), suggest a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