Translated from *Uspekhi Khimii*, **51** 119-152 (1982) U.D.C. 547.317.3

Kinetics and Mechanism of the Oxidation of Aliphatic Amines

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Data on the kinetics and mechanism of the oxidation of aliphatic amines by various oxidants are surveyed and examined critically.
The bibliography includes 205 references

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I. INTRODUCTION

Only that part of the extensive literature on the oxidation of aliphatic amines in which problems of the kinetics and mechanism of the oxidation reaction are considered is surveyed. These studies are of considerable and general interest to organic chemists as an example of the current approach to the problem of the mechanisms of complex reactions. They are of interest also to biochemists in view of the biological importance of aliphatic amines.

Our aim was to find common features in the oxidative reactions of aliphatic amines, to understand the causes of the differences between them, to examine the existing ideas about the mechanism, and to give a critical and general compilation of the entire set of the available data. We do not include studies on photochemical oxidation, electrochemical oxidation, and the interaction of amines with free radicals, since modern reviews of the literature on these problems are available[1-3].

II. INTERMEDIATE OXIDATION PRODUCTS

Non-aromatic ammonium radical-cations $RR'R''\dot{\overset{+}{N}}$ are formed in various reactions of amines, their derivatives, and certain other nitrogen-containing compounds. Their structure and properties have been thoroughly investigated (see the latest review on this problem[4]).

The simplest ammonium radical-cations have a planar structure. They are extremely unstable, but their stability can be made appreciable or increased for radical-cations corresponding to triethylenediamine or olefins with $N(CH_3)_2$ groups at the double bond. In weakly acid, neutral, or basic media the above species rapidly lose a proton at the α-carbon atom and give rise to α-amino-radicals;

$$RCH_2\dot{\overset{+}{N}}R'_2 \xrightarrow[-H^+]{} R\dot{C}H-\overset{+}{N}R'_2 \longleftrightarrow RCH=\overset{+}{N}R'_2 \quad . \qquad (1)$$

This reaction is usually much faster than the abstraction of an $H^\cdot$ atom from the medium by the radical-cation; it is retarded in a strongly acid medium. Species of the type $RR'\dot{\overset{+}{N}}H$ are stronger acids by several orders of magnitude than $RR'\dot{\overset{+}{N}}H_2$.

The existence of α-amino-radicals has been demonstrated and their EPR spectra have been studied[5]. Their chemical properties have not been investigated by direct methods; all the available information about them is hypothetical and is based on indirect data obtained by studying the oxidation of amines in the intermediate stages of which the formation of α-amino-radicals is postulated. In the oxidation of amines α-amino-radicals can be obtained not only via reaction (1) but also as a result of the abstraction of $H^\cdot$ from the α-carbon atom in amines. Under oxidation conditions, the radicals undergo further rapid reactions, probably via two pathways—with electron transfer to the oxidant and the formation of immonium ions:

$$RCH_2\dot{C}H-\ddot{N}R'_2 + Ox \xrightarrow[-Ox^-]{} RCH_2\overset{+}{C}H-\ddot{N}R'_2 \longleftrightarrow RCH_2CH=\overset{+}{N}R'_2$$

or by transition with the oxidation of a hydrogen atom and the formation of an enamine:

$$RCH_2\dot{C}H-\ddot{N}R'_2 + Ox \xrightarrow[-OxH]{} RCH=CH-\ddot{N}R'_2 \quad .$$

Enamines can be obtained also from immonium ions:

$$RCH_2\overset{+}{C}H-\ddot{N}R'_2 \longleftrightarrow RCH_2CH=\overset{+}{N}R'_2 \xrightarrow[-H^+]{} RCH=CH-\ddot{N}R'_2 \quad .$$

Radicals of the type $R\dot{C}H-NHR'$ are also capable of disproportionating:

$$2R\dot{C}H-NHR' \rightarrow RCH=NR' + RCH_2NHR' \quad .$$

The radicals of the last type as well as $RCH_2\dot{N}H$ can give rise to imines also by losing $H^\cdot$ atoms as a result of oxidation.

Among the properties of the immonium ions $RR'C=\overset{+}{N}R''_2$ and imines $RR'C=NR''$, we may mention their tendency to hydrolyse with formation of aldehydes or ketones and dealkylated initial amines. This tendency depends on the structure and the reaction conditions. Sometimes the hydrolysis is slow or does not occur at all and the imines are the main oxidation products. We may also mention the capacity of certain imines for polymerisation, which can lead to tarry products.

Carbinolamines $R_2NCH(OH)CH_2R'$ are formed when secondary amines interact with aldehydes. They are unstable and, as regards their properties, we shall mention their ability to hydrolyse in an acid medium with formation of the initial amine and an aldehyde and to undergo dehydration to the enamines $R_2NCH=CHR'$ (see, for example, Henbest and Stratford[6]).

A significant feature of the properties of enamines (vinylamines)[7] is that these compounds readily hydrolyse in an acid medium to carbonyl compounds and dealkylated initial amines and that enamines containing hydrogen at the nitrogen atom are in tautomeric equilibrium with imines:

$$RR'C=CR''-NHR''' \rightleftharpoons RR'CH-CR''=NR'''.$$

III. THE OXIDATION REACTIONS OF ALIPHATIC AMINES

1. Oxidation by Iodonium Salts

The interaction of iodonium salts $Ar_2I^+X^-$ with amines has been widely investigated[8-12] under various conditions. These reactions give rise to the salts of the initial amines, the

products of the reduction of the iodonium salts (iodoarenes), and the compounds ArH and Ar—Ar. In certain cases a nitrogen-containing resin is also obtained.

This composition of the products serves as an argument in support of a radical reaction mechanism. The latter has been confirmed by the formation of diphenylmercury in the interaction of $(C_6H_5)_2I^+BF_4^-$ with diethyl- or triethyl-amine in the presence of mercury[8,9]; the following reaction mechanism has been proposed:

$$Ar_2I^+X^- + NR_3 \rightleftharpoons [Ar_2I : NR_3]^+ X^- \rightarrow Ar_2\dot{I} + \overset{+}{N}R_3X^-$$
$$Ar_2\dot{I} \xrightarrow{-ArI} \dot{A}r \xrightarrow{+\dot{A}r} Ar—Ar$$
$$\overset{+}{N}R_3X^- + \dot{H} \rightarrow \overset{+}{N}HR_3X^- \ .$$

By analogy with aromatic amines[13] and spectroscopic data[9], it has been suggested that the first stage involves the formation of a donor—acceptor complex, whose homolytic decomposition leads to the products.

This mechanism does not reflect the entire complexity of the reactions of amines with iodonium salts (see below). We may also mention that its last stage requires revision, since ammonium radical-cations rapidly split off protons, particularly in basic media. One can therefore postulate that ammonium salts are formed via the reactions

$$R_2\overset{+}{N}HX^- + R_2NH \rightarrow R_2\dot{N} + R_2\overset{+}{N}H_2X^- \text{ (for primary and secondary amines);} \quad (2a)$$
$$R_3\overset{+}{N}CH_2R'X^- + R_3N \rightarrow R_2N\dot{C}HR' + R_3\overset{+}{N}HX^- \text{ (for tertiary amines).} \quad (2b)$$

Apparently the main pathway, leading to the formation of biaryls, consists in the addition of radicals Ar$^\cdot$ to the compounds ArH and the splitting off of H$^\cdot$ from the resulting cyclohexadienes.

An alternative reaction mechanism, possible only in an aqueous medium, namely homolytic decomposition of diaryliodonium hydroxide, has been rejected[11] on the grounds that the decomposition of $Ar_2I^+OH^-$ is slower than the interaction of iodonium salts with amines and gives rise to other products.

The formation of arylated amines (which are the main products according to some data, for example, those of Beringer et al.[14]) in the reactions considered has also been explained by a radical mechanism[10]):

$$Ar_2\dot{I} + \ddot{N}H_2R \xrightarrow{-ArI} ArNHR + \dot{H}$$

However, one cannot rule out the possibility that nucleophilic substitution of iodonium salts by amines takes place simultaneously with the homolytic reaction[14] and that the arylated amines are formed via this mechanism. We may note that the simultaneous occurrence of nucleophilic and radical reactions has been established in the interaction of iodonium salts with alkoxides[15].

An unambiguous proof of the involvement of radicals in the reactions of amines with iodonium salts has been obtained with the aid of chemically induced nuclear polarisation (CIDNP) and EPR. Chemically induced nuclear polarisation arises in radical pairs and is manifested by anomalies in the NMR spectra of the reaction products of the radicals in these pairs. The reaction kinetics can be inferred from the CIDNP kinetics[16]. In the case considered CIDNP was observed in the benzene obtained by the interaction of iodonium salts with *N,N'*-tetramethyl-*p*-phenylenediamine (TMPA) or triethylamine. At the same time the TMPA radical-cations were detected[17,18]. These data have been treated[17,18] as evidence proving electron transfer from the amine to the iodonium salt in the key stage of the reaction. However, kinetic studies have shown that the mechanism is much more complex.

The kinetics of the oxidation of amines by diphenyliodonium chloride have been investigated in several studies. Reactions with di-n-butylamine[19], ethanolamine[20], and triethylamine[21] proved to have a radical-chain mechanism. They have an inductive period the duration of which is increased by the addition of inhibitors of radical-chain processes. CIDNP in the resulting benzene and iodobenzene is observed under certain conditions. The kinetic equations for the reactions with ethanolamine and triethylamine have the same form (here Am = amine):

$$w = k[Ph_2I^+Cl^-][Am] \ . \quad (3)$$

However, this form changes for dibutylamine, for which the following equation is valid in the presence of an excess of the amine:

$$w = k[Ph_2I^+Cl^-]^2, \ w_0 = k_0[Ph_2I^+X^-] \ , \quad (4)$$

where w_0 and k_0 are the rate of initiation and the initiation rate constant†.

The following mechanism of the reaction with triethylamine corresponds to Eqn.(3).

(5)

$$(C_6H_5)_2I^+ + (C_2H_5)_3N \xrightarrow[S]{\text{fast}} [(C_6H_5)_2I : N(C_2H_5)_3]^+ \xrightarrow[S]{k_0} \rightarrow (C_6H_5)_2\dot{I}\overset{+}{N}(C_2H_5)_3 \xrightarrow{-C_6H_5I} C_6H_5\overset{+}{N}(C_2H_5)_3 \rightarrow \dot{C}_6H_5 + \overset{+}{N}(C_2H_5)_3 \quad \text{(initiation)}$$

$$\dot{C}_6H_5 + (C_2H_5)_3N \xrightarrow[\text{slow}]{k_1} C_6H_6 + (C_2H_5)_2N—\dot{C}HCH_3$$
$$(C_6H_5)_2I^+ + CH_3\dot{C}H—N(C_2H_5)_3 \xrightarrow[-C_6H_5,\,-C_6H_5I]{k_2}$$
$$\rightarrow CH_3\overset{+}{C}H—N(C_2H_5)_2 \longleftrightarrow CH_3CH=\overset{+}{N}(C_2H_5)_2$$
$$\downarrow$$
$$CH_2=CH—N(C_2H_5)_2 + H^+ \quad \text{(chain propagation)}$$

$$\dot{C}_6H_5 + \text{inhibitor} \xrightarrow{k_3} \text{inactive products (chain termination)}$$

Mechanism (5) explains the formation of benzene, biphenyl, and the triethylammonium salt on oxidation: it agrees with the formation of the compounds $RCH = \overset{+}{N}R_2$ or vinylamines, frequently observed in the oxidation of aliphatic amines (see below), and also with the formation of the radicals $CH_3\dot{C}HN.(C_2H_5)_2$ identified in the photochemical oxidation reaction[22].

The reaction with ethanolamine differs only by the fact that in the rate-limiting chain propagation stage the phenyl radical abstracts hydrogen not from a carbon atom of the amine but from the nitrogen atom to give the radical $\dot{N}HCH_2CH_2OH$, which participates in the chain propagation process.

On the other hand, the mechanism of the oxidation of dibutylamine differs significantly from mechanism (5)—the chain propagation is controlled by the second and not the first reaction:

$$\dot{C}_6H_5 + (C_4H_9)_2NH \xrightarrow{k_1} C_6H_6 + (C_4H_9)_2\dot{N} \ ;$$

$$(C_6H_5)_2I^+ + (C_4H_9)_2N^\cdot \xrightarrow[\text{slow}]{k_2} \dot{C}_6H_5 + PhI + (C_4H_9)_2\overset{+}{N} \ . \quad (6)$$

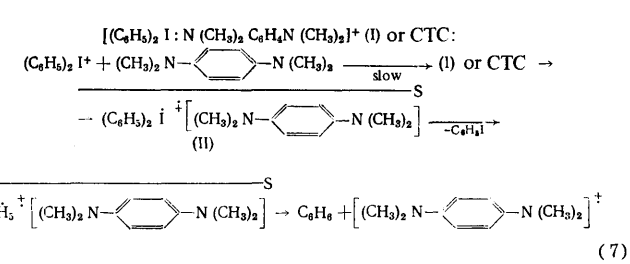
This leads to the change in the kinetic equation already mentioned above.

The differences discussed are apparently caused by the fact that the radicals $(C_2H_5)_2N\dot{C}HCH_3$ and $\dot{N}HCH_2CH_2OH$ are less stable and are formed more slowly than the radicals

† The last equation was obtained from data for CIDNP kinetics in the benzene formed in the initiation stage. The addition of hydroquinone alters the form of the kinetic equation for the oxidation of dibutylamine; the mechanism of the effect of hydroquinone is obscure[19].

$(C_4H_9)_2\dot{N}$. On the other hand, it may be that the first two radicals give up their electrons to the iodonium cation more rapidly than $(C_4H_9)_2\dot{N}$, because the ionisation potential of the last radical is higher than those of the first two. This alters the ratio of the rates of the two chain propagation stages and the form of the kinetic equation.

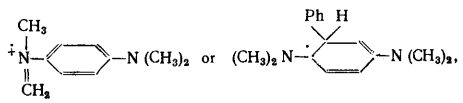
The interaction of $(C_6H_5)_2I^+Cl^-$ with *N,N'*-tetramethyl-*p*-phenylenediamine (TMPA) [23] also obeys Eqn.(3) but differs radically from the three reactions considered. This is a radical and not a chain process. The CIDNP of the benzene formed is observed in the reaction, but there is no induction period and inhibitors of radical-chain reactions do not lead to its appearance and do not alter the rate of reaction. The reaction considered probably procceeds via a mechanism whose slow stage [and not the fast stage as in mechanism (5)] involves the formation of the complex



(7)

However, one cannot rule out the possibility that the complex or the charge-transfer complex (CTC) are formed reversibly and that the homolytic decomposition of the complex or electron transfer in the CTC with formation of the pair (II) take place in the slow stage.

Reaction (7) is analogous to the initiation stage in mechanism (5) but, in contrast to mechanism (5), it is followed by the chain propagation stage. This can be explained by the fact that the radicals

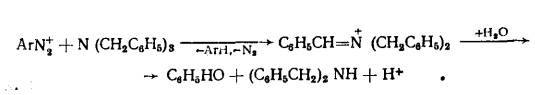


which are probably formed when phenyl radicals interact with TMPA and which may be expected to be very stable, are incapable of transferring electrons rapidly to the Ph_2I^+ ions. This is why the chain propagation process cannot compete with reaction (7) as regards rate.

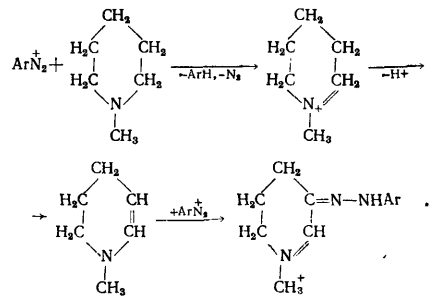
Thus the non-chain mechanism of the reaction considered is determined by the properties of the radicals formed from TMPA. It is clear from the foregoing that the properties of the radicals corresponding to amines determine the characteristics of the kinetics and mechanisms also of the other reactions considered.

2. Oxidation by Diazonium Salts

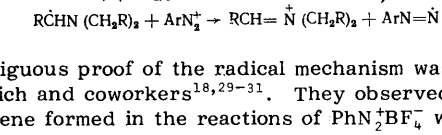
The interaction of the salts $ArN_2^+BF_4^-$ with tertiary amines has been studied[25,26]. The reactions with tribenzylamine or benzyldimethylamine lead to the compounds ArH and immonium salts, which have been identified from the hydrolysis products. These results have been explained by the transfer of a hydride ion from the α-carbon atom to the ArN_2^+ ion:



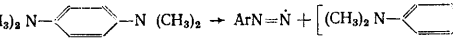
N-Methyl- or *N*-benzyl-piperidine and *N*-benzylpyrrolidine react via a mechanism of the first type, which, however, is more complex



There are data in conflict with the above mechanism which indicate the involvement of radicals in the reactions. Thus the reaction induces the polymerisation of acrylonitrile[27] and is inhibited by oxygen and added bromotrichloromethane. A radical-chain mechanism was therefore proposed[28]:



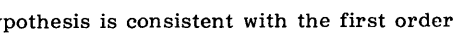
Unambiguous proof of the radical mechanism was obtained by Bilevich and coworkers[18,29-31]. They observed CIDNP in the benzene formed in the reactions of $PhN_2^+BF_4^-$ with aliphatic tertiary amines and the formation of the TMPA radical-cations and the polarisation of the protons of the substituted benzenes formed in the oxidation of TMPA by diazonium salts; the rate of the last reaction is proportional to the concentrations of both reactants. Substituents in the *para*-position in the ring of the salt alter by several orders of magnitude the rate of reaction (the oxidation is accelerated by the withdrawal of electrons by substitutents); the influence of the substituents obeys the Hammett equation ($\rho = 1.92$). The data presented served as the basis for the following mechanism of the slow stage:



which includes electron transfer from the amine to the cation ArN_2^+.

The kinetics of the oxidation of trimethyl-, triethyl-, and tri-n-butyl-amines by the salts $p\text{-}XC_6H_4N_2^+BF_4$ have been investigated by Gragerov and coworkers[32,33] on the basis of the CIDNP kinetics in the compounds C_6H_5X formed. The reactions proved to be of the non-chain type and obeyed a first-order equation. Both electron-accepting and electron-donating substituents X accelerate the reaction by a factor of only 2–3 and the nature of the amine hardly affects its rate, although the basicities of the amines differ considerably.

The results differ sharply from those obtained by the oxidation of TMPA. To account for them, the authors assumed that the slow stage involves the decomposition into free radicals of the intermediate, possibly $Ar-N=N-\dot{N}R_3$, formed via the mechanism

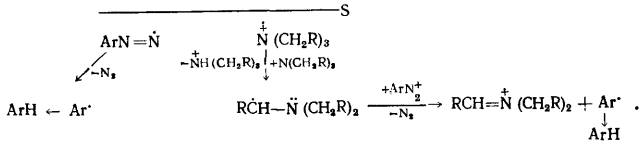


This hypothesis is consistent with the first order of the reaction and explains the weak dependence of the reaction rate on the nature of X and the acceleration of the reaction by both electron-donating and electron-accepting substituents (these features are characteristic of many reactions involving decomposition into radicals—see, for example,

Walling[34]) and agrees with the independence of the rate of reaction of the nature of the amine.

The significant difference between the reactions of diazonium salts with TMPA and aliphatic tertiary amines is apparently caused by the stability of the TMPA radical-cations and the ease of electron transfer from TMPA. Thus, like the oxidation of amines by iodonium salts, it is caused by the nature of the radical species formed. The difference shows how unjustified can be a hypothesis concerning the details of the reaction mechanism arrived at by analogy.

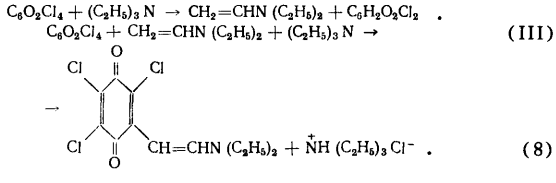
The reactions of the radical pairs arising in the decomposition of the above intermediate can be represented schematically as follows:



The presence of ammonium salts may be expected in the reaction products.

3. Oxidation by Quinonoid Compounds

The reactions of aliphatic tertiary amines with quinones have been investigated[35,36] and it has been found that, for example, triethylamine interacts with chloroanil in benzene via the mechanism

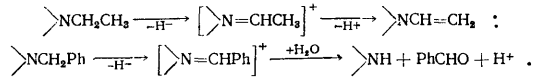


(III)

(8)

Other halogen-containing quinones react similarly, but the rate of reaction diminishes with decrease of the electron affinity of the quinone. Compounds of type (III) ("blue quinone") are formed only from amines containing the residue $\rangle NCH-CH_2-$. Amines with a different structure give rise to aldehydes among other products.

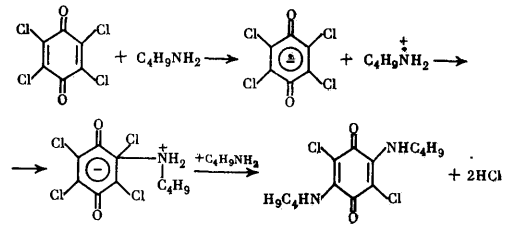
The authors[35,36] suggest that the key stage involves the transfer of a hydride ion from the amine to the quinone, which is followed rapidly by proton transfer from the β-position relative to the nitrogen atom. If there is no such proton in the molecule then the process stops at the stage involving the formation of immonium salts, whose hydrolysis gives rise to aldehydes:



A hydride ion is transferred in the CTC of quinones with amines. The existence of such complexes has been confirmed by spectroscopic data. The details of the hydride shift remain obscure.

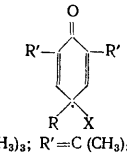
The above mechanisms involve the formation of semiquinone radical-anions preceding the formation of the "blue quinone". This was demonstrated by spectroscopic methods for reaction (8) in solution in chloroform or acetonitrile and the rate and activation energy and entropy for the formation of the semiquinone and compound (III) were determined[38]. The kinetic and activation parameters have also been obtained for electron transfer from tri-isopropylamine and tri-n-butylamine to chloranil. In these cases the process stops at the semiquinone radical-ion formation stage. In methanol or ethanol reaction (8) leads to trichlorohydroquinone and not to the "blue quinone"; the reason for this change has not been elucidated.

The formation of semiquinone radicals has been established in the interaction of quinones with amines of different structure. It is promoted by a low ionisation potential of the amine, a high electron affinity of the quinone, and a high solvent polarity[39]. These radicals proved to be intermediates in the nucleophilic substitution of quinones by amines[40]. In the first stages of the substitution reaction semiquinones accumulate and are then consumed as the products accumulate:



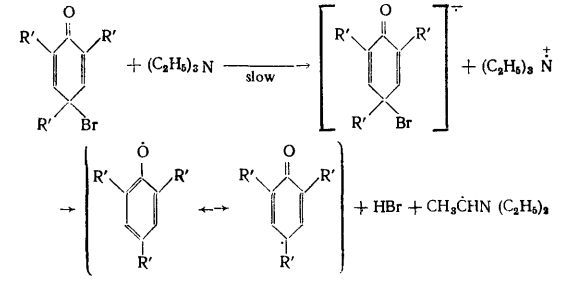
The reaction kinetics have been investigated.

The reactions of amines with other compounds having a quinonoid structure were investigated in a number of studies. Thus it has been established[41] that the reactions of sterically hindered quinobromides or quinonitrols



R=CH_3 or $C(CH_3)_3$; R′=$C(CH_3)_3$; X=Br or NO_2

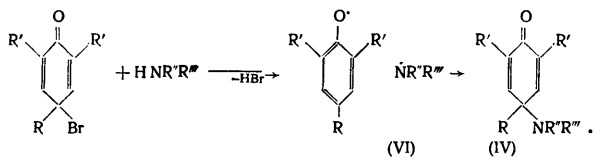
with triethylamine, piperidine, or pyridine give rise to phenoxy-radicals. The reaction in the presence of an excess of amines obeys a first-order kinetic equation; its rate and activation parameters have been found. It proceeds via the mechanism:



It has also been shown that the reaction of phenoxy-radicals with amines results in the formation of phenols.

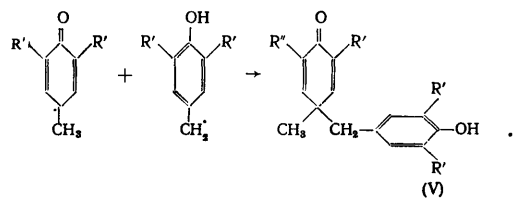
The reactions of the above quinobromides with primary and secondary amines have been investigated[42,43] and it has also been concluded that phenoxy-radicals are formed as intermediates. Apart from phenols and ammonium salts, the main products include quinamines (IV) and quinol (V). The reactions obey a second order kinetic equation and their rates and activation parameters have been found. The authors

believe that electron transfer from the amine to the quinobromide is the key stage in the processes:



(VI) (IV)

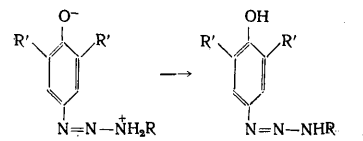
The formation of quinol (V) has been explained by the recombination of the phenoxy-radicals liberated from the pair (VI) with their isomerisation products[44]—hydroxybenzyl radicals:



(V)

The reactions of amines with *p*-benzoquinone diazides have been investigated. These reactions proceed rapidly with primary amines even at room temperature, giving rise to phenol, the quinone, and diphenoquinone corresponding to the quinone diazide used. The same products are obtained slowly in the reaction of quinone diazides with secondary amines or in the decomposition of the triazenes formed by the reaction of quinone diazides with secondary amines. Oxidation products are formed from amines, while with tertiary amines the reaction does not proceed.

The authors[45] suggest that triazenes are formed as intermediates. The triazenes corresponding to primary and secondary amines differ sharply in their stabilities. They are capable of decomposing into radicals (see, for example, Rozantsev and Sholle[46]). Radicals were indeed detected by EPR and with the aid of CIDNP. The CIDNP method made it possible to investigate their reaction pathways and thus to elucidate a series of details of the mechanisms of the processes[47,48]. The reaction mechanism taking into account all the data obtained is presented below in relation to the interaction of 2,6-di-t-butyl-*p*-benzoquinone diazide with primary amines (Scheme 1). Here the letters (A) and (E) denote positive and negative chemically induced nuclear polarisation, an asterisk represents a polarised atom, and (RP) is a radical pair (see below). The reaction begins with the addition of the electrophilic quinone diazide to the amine, which leads to the formation of a compound analogous to the product of the interaction of diazonium salts with tertiary amines (see above). Proton transfer to the oxygen results in the formation of a hydroxyphenyltriazene:



The nuclear polarisation in the latter indicates the reversibility of its decomposition and the sign of the polarisation in the azophenol (VIII) indicates its formation on disproportionation in $(RP_1)^S$. The sign of the polarisation shows that the main reaction product—the phenol (IX)—is formed mainly on disproportionation in $(RP_2)^S$.

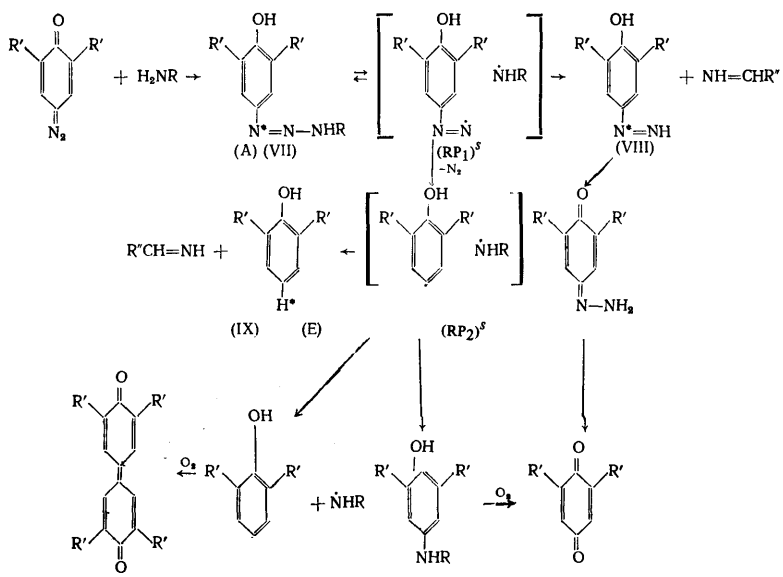
4. Oxidation with Chlorine Dioxide and Hypochlorous Acid

The oxidation of amines with chlorine dioxide in aqueous solutions has been studied[49–52]. Under conditions where side reactions are suppressed, two moles of ClO_2 are consumed per mole of the amine in the presence of an excess of the latter and amine dealkylation products and aldehydes are formed, for example:

$$(C_2H_5)_3N + 2ClO_2 + H_2O \rightarrow CH_3CHO + (C_2H_5)_2NH + 2H^+ + 2ClO_2^- .$$

The rate is proportional to the amine and ClO_2 concentrations. It decreases in the sequence $(C_2H_5)_3N > (CH_3)_3N > (C_2H_5)_2NH$; the rates fall very rapidly on passing from tertiary to secondary and primary amines. The rates are correlated with the values of $\Sigma\sigma^*$ for the substituents at the nitrogen atom; $\rho = -5.24$. The rate constants for *meta*- and *para*-substituted benzyldimethylamines are satisfactorily correlated with

Scheme 1



the pK_a of the amines (the Brønsted parameter $\alpha = 0.812$) and with the σ constants ($\rho = -0.924$). The dealkylation is relatively unselective: formaldehyde and benzaldehydes are formed in proportions of ~3 : 1. The formation of amine radical-cations in the oxidation of $[(CH_3)_2N-C_6H_4-]_3N$ or $(CH_3)_2-C_6H_4-N(CH_3)_2$ was established by EPR.

The authors[49-52] suggest that the rate-limiting stage involves electron transfer from the amine to the oxidant with formation of ammonium radical-cations and ClO_2^- ions and not the abstraction of a hydrogen atom. This is confirmed by the finding that the $\Sigma\sigma^*$ for the residues at the nitrogen atom in secondary or tertiary amines are correlated not only with the rate of oxidation but also with the half-wave potential for the polarographic oxidation of amines, for which a similar mechanism is valid.

However, this mechanism does not account for all the observed features of the reaction. It has been shown that the addition of ClO_2^- ions diminishes the rate of oxidation without altering the kinetic equation and electron transfer is thus reversible. The decrease of the rate is proportional to the amounts of added ClO_2^- for $(C_2H_5)_3N$, $(CH_3)_3N$, and $[(CH_3)_2CH]_2NH$, but its dependence on the concentration of additives is more complex in the case of $C_6H_5CH_2NH_2$, $(C_6H_5CH_2)_2NH$, and $C_6H_5CH_2NHC(CH_3)_3$. Analysis of these relations leads to the conclusion that the last three amines react simultaneously via two mechanisms: with reversible electron transfer in the rate-limiting stage and with irreversible transfer of H^- from the α-carbon atom to the oxidant molecule in the slow stage of the reaction. The contribution of the reaction via the second pathway is 31% (at 41 °C) for $C_6H_5CH_2NHC(CH_3)_3$, 35% for $(C_6H_5CH_2)_2NH$, and 73% (at 25 °C) for $C_6H_5CH_2NH_2$. It is considerable for the amines under consideration because the C–H bonds in the CH_2 groups are weakened by the interaction with the benzene ring, and increases with increasing ionisation potentials of the amines, which hinders the competitive electron transfer. The transfer of H· in the slow stage was confirmed by the observation of primary kinetic isotope effects in the oxidation of $C_6H_5CD_2NHC(CH_3)_3$ and $C_6H_5CD_2NH_2$.

Thus amines which do not contain a CH_2 group next to the benzene ring react with ClO_2 by electron transfer in the slow stage:

$$ClO_2 + RCH_2N(R')R' \underset{}{\overset{\text{slow}}{\rightleftharpoons}} ClO_2^- + RCH_2\overset{+}{N}(R')R' \quad ;$$
$$RCH_2\overset{+}{N}(R')R' \xrightarrow{\text{fast}} H^+ + RCH{\cdots}N(R')R' \quad ;$$
$$RCH{\cdots}N(R')R' + ClO_2 \xrightarrow{\text{fast}} RCH{=}\overset{+}{N}(R')R' + ClO_2^- \quad . \qquad (9)$$

The proton elimination stage cannot be excluded from this mechanism and the latter cannot be replaced by

$$ClO_2 + RCH_2N(R')R' \underset{}{\overset{\text{slow}}{\rightleftharpoons}} ClO_2^- + RCH_2\overset{+}{N}(R')R' \quad ;$$
$$RCH_2\overset{+}{N}(R')R' + ClO_2 \xrightarrow{\text{fast}} HClO_2 + RCH{=}\overset{+}{N}(R')R' \quad ;$$
$$HClO_2 \rightleftarrows H^+ + ClO_2^- \quad ,$$

since analysis showed that the added ClO_2^- would infringe the first order of the reaction with respect to ClO_2 without the proton elimination stage, which is not observed.

Amines containing CH_2 groups linked to the benzene ring react with ClO_2 both via mechanism (9) and with transfer of H· in the slow stage:

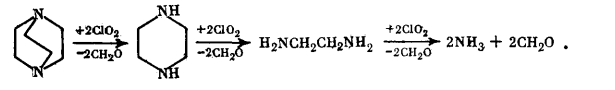
$$ClO_2 + RCH_2N(R')R' \xrightarrow{\text{slow}} RCH{\cdots}N(R')R' + HClO_2 \rightleftarrows H^+ + ClO_2^- \quad ;$$
$$RCH{\cdots}N(R')R' + ClO_2 \xrightarrow{\text{fast}} RCH{=}\overset{+}{N}(R')R' + ClO_2^- \qquad (10)$$

Hydrolysis of the immonium salts formed via both mechanisms leads to the observed reaction products—the aldehydes RCHO and the amines R'_2NH.

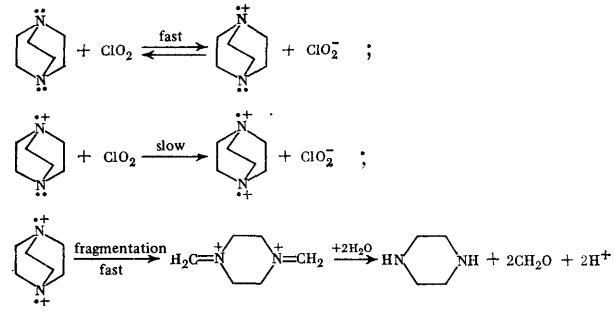
The results of Kudesia[53], who found that the replacement of water in the oxidation of benzylamine by D_2O (the replacement of $C_6H_5CH_2NH_2$ by $C_6H_5CH_2ND_2$) slows down the reaction by a factor of 5, are in conflict with the mechanisms described above and with experimental kinetic isotope effect data.

The amine dealkylation reactions under the influence of ClO_2 discussed above proceed with dissociation of C–N bonds. Reactions of another type, with dissociation of C–C bonds, are observed in the interaction of ClO_2 or HClO with β-amino-, β-hydroxy-, or β-oxo-amines, for example:

$$H_2NCH_2CH_2OH + 2ClO_2 \rightarrow NH_3 + 2CH_2O \quad ;$$



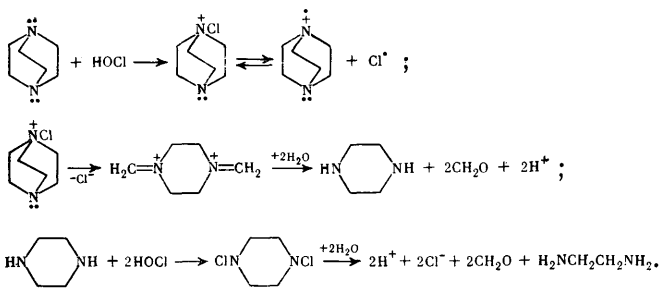
Such "oxidative fragmentation" has been studied[54-56] and the rate constants have been determined in many instances. The kinetics and mechanism of oxidative fragmentation have been investigated in relation to triethylenediamine. The reaction with this substance obeys a first-order kinetic equation with respect to the amine and a second-order equation with respect to the oxidant and is retarded by ClO_2^- ions in proportion to their concentration. The formation of triethylenediamine radical-cations in the course of the reaction has been demonstrated by EPR and the following mechanism has been proposed:



It involves the formation of the amine biradical-dication in the slow stage and not of a radical-cation as in mechanism (9). This difference is responsible for a change in the kinetic equation, which arises owing to the high stability of the triethylenediamine radical-cation. The triethylenediamine biradical-dication is unstable and rapidly fragments.

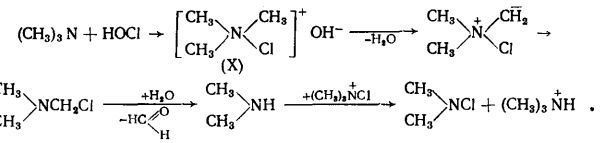
The oxidation of triethylenediamine by HOCl requires three moles of the acid per mole of the amine and probably obeys a first-order kinetic equation with respect to both the amine and the oxidant. Here too it was concluded that an ammonium radical-cation is formed in this reaction but the above investigators suggest that it is formed as a side product, since

HOCl is a two-electron oxidant. The mechanism is different:



The products contain 1,4-dichloropiperazine, since its hydrolysis is slow.

The oxidation of trimethylamine with HOCl in aqueous solutions gives rise to dimethylchloroamine and formaldehyde[57]:

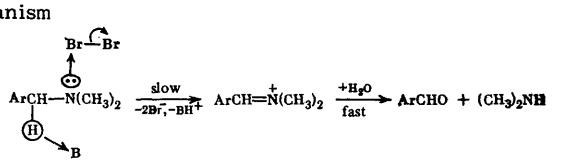


It proceeds via a mechanism analogous to mechanism (11). A proton is probably split off from compound (X) also in the reaction with the initial amine.

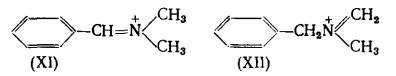
5. Oxidation with Bromine, Chlorine, and *N*-Halogenoamino-Compounds

The oxidation of amines with an aqueous solution of bromine at pH 5–7 in the presence of an excess of the amine has been studied[58]. Under these conditions, amines lose one alkyl group. Secondary alkyl groups are split off in the form of ketones and the fate of primary alkyls depends on the structure of the initial amine. The rate of oxidation of tripropylamine is proportional to the concentrations of both reagents, depends on pH in a complex manner, and is independent of illumination. The Hammett relation between the rate and the σ constants of the ring substituents holds for substituted benzyldimethylamines; $\rho = -0.84$. The reaction mechanism can consist in the elimination of an α-hydrogen atom in the form of H^+ with simultaneous abstraction of the electron pair at the nitrogen atom by the bromine. However, this mechanism does not account for the differences between the reaction products of primary, secondary, and tertiary amines. It has been confirmed and specified in greater detail by studies of the kinetics of the oxidation of *para*- and *meta*-substituted benzyldimethylamines with a bromine solution in 50% aqueous acetic acid[59].

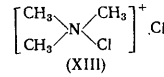
The reaction is of first order with respect to each reactant and its rate is correlated with the pK_a of the amines (the Brønsted parameter $\alpha = 0.67$) and obeys the Hammett relation ($\rho = -0.95$). The addition of sodium acetate or benzoate accelerates the oxidation; $C_6H_5CD_2N(CH_3)_2$ reacts more slowly than $C_6H_5CH_2N(CH_3)_2$. Irradiation with light does not affect the rate of reaction. The oxidation proceeds very selectively with formation of a high yield of benzaldehyde (in contrast to the radical oxidation of benzyldimethylamine with ClO_2). All these features of the reaction can be accounted for by the mechanism



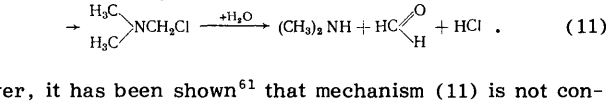
(where B is a base). The selectivity of the oxidation is associated with the preferential formation in the limiting stage of the ions (XI), which, in contrast to the ions (XII), are stabilised by the conjugation of the C=N bond with the ring:



When trimethyl- or triethyl-amine interacts with an aqueous solution of an equimolar amount of chlorine, the hydrochloride of the corresponding secondary amine is formed. In solution in CCl_4, trimethylamine forms with chlorine a compound which probably has the following structure:

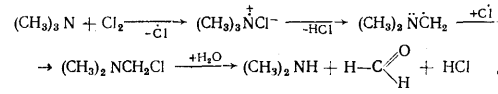


On hydrolysis, this compound is converted into the products formed on reaction of trimethylamine with an aqueous chlorine solution. On this basis, the following heterolytic mechanism has been proposed[60]:

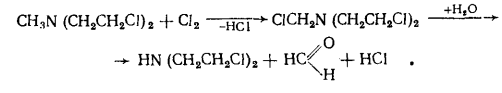


(11)

However, it has been shown[61] that mechanism (11) is not consistent with the kinetic data and that compound (XIII) or the reaction mixture in the interaction of trimethylamine with chlorine cause the polymerisation of acrylonitrile. The authors[61] therefore propose the radical mechanism



The oxidation of amines of the type $RN(CH_2CH_2Cl)_2$ with chlorine and *N*-chloroimides, leading to the dealkylation of the amine, has been studied[62], for example:



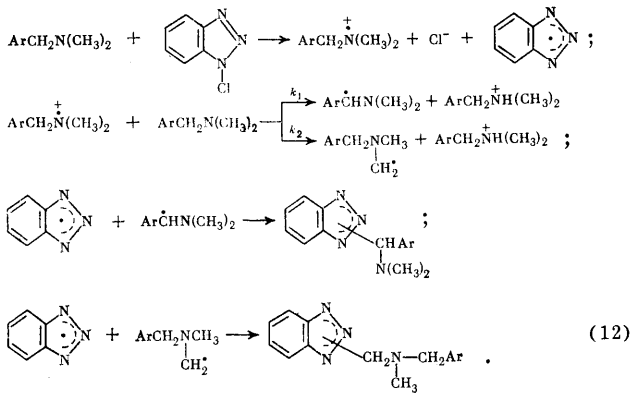
The reaction mechanism was not investigated.

The oxidation of amines by 1-chlorobenzotriazole has been investigated[63]. In the case of *para*-substituted benzyldimethylamines the reaction leads to 1- and 2-aminoalkylbenzotriazoles, the hydrochlorides of the initial amines, and compounds containing active (positive) chlorine. The rate of formation of products, not containing active chlorine, in benzene is proportional to the concentrations of both reactants and is correlated with the pK_a of the amines (the Brønsted parameter $\alpha = 0.63$). The influence of substituents in the benzene rings of the amines is described by the Hammett equation ($\rho = -0.71$). An induction period is not observed in the reaction and its rate is independent of illumination and the presence of oxygen or radical-chain process inhibitors. $C_6H_5CH_2N(CH_3)_2$ is oxidised faster than $C_6H_5CD_2N(CH_3)_2$. The reaction is accelerated by the addition of methanol. *para*-Substituted benzaldehydes, p-$XC_6H_4CH_2NHCH_3$ and formaldehyde, formed from aminoalkylbenzotriazoles, were identified after acid hydrolysis.

The oxidation of triethylenediamine yields 1,4-bis(benzotriazolylmethyl)piperazine—the product of the oxidative fragmentation of the amine. It has been established by EPR

that ammonium radical-cations are formed in the reaction. The radical-cations have been identified also in the oxidation of *N,N'*-tetramethyl-*p*-phenylenediamine. Primary amines give rise to monochloroamines.

The formation of aminoalkylbenzotriazoles has been explained by a radical non-chain mechanism, which agrees with all the data described above:



(12)

The authors[63] rejected two variants of the ionic mechanism—with transfer of H^- or Cl^+—on the grounds of not very reliable criteria—the inconsistency of the values of ρ and the kinetic isotope effects with values usually observed for such mechanisms.

The ratio of the yields of the hydrolysis products of aminoalkylbenzotriazoles, namely substituted benzaldehydes and $p\text{-}XC_6H_4CH_2NHCH_3$, is determined by the rates of abstraction of H^+ from the CH_2 or CH_3 groups of the ammonium radical-cations and is equal to the ratio k_1/k_2 [see mechanism (12)]. This mechanism depends on the nature of X and decreases with increasing solvent polarity. For reactions in methanol, it is close to the statistical value, as in the oxidation of benzyldimethylamines by a solution of ClO_2 in water.

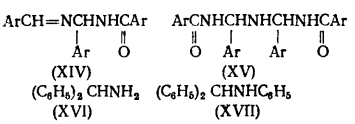
When tertiary amines are acted upon by *N*-bromosuccinimide, the C–N bonds are broken and secondary amines and aldehydes are formed (see, for example, Dunstan and Henvest[64] and Filler[65]). A radical mechanism has been proposed for the reaction on the basis of general considerations[66].

Studies on the oxidation of amines by "chloramine-T" ($CH_3C_6H_4SO_2NNaCl$) have been undertaken for synthetic purposes. The problems of the reaction mechanism have been investigated only in relation to diethanolamine[67] and monoethanolamine[68]. Both compounds undergo oxidative fragmentation with formation of formaldehyde, formic acid, and ammonia. The details of the mechanism are obscure.

6. Oxidation with Potassium Permanganate, Periodic Acid, and Chromic Acid

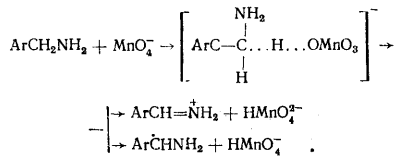
The mechanism of the oxidation of amines by potassium permanganate has not so far been thoroughly elucidated. A brief review of early studies has been published[69]; the investigations in recent years are considered below.

Substituted benzylamines give rise to compounds (XIV) and (XV) on oxidation with $KMnO_4$ in a 1 : 1 aqueous t-butyl alcohol in the presence of an excess of $CaSO_4$:



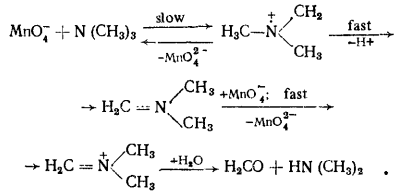
The reaction mechanism has not been established, but the aldimines ArCH=NH are probably formed in the initial stages; the initial amines then add to them, giving rise to products whose oxidation leads to compounds (XIV) and (XV).[72] The oxidation of compound (XVI), dibenzylamines, and compound (XVII) apparently proceeds similarly. Tertiary amines, incapable of being converted into aldimines, are oxidised differently. Thus tributylamine gives rise to dibutylamine, butyraldehyde, butyric acid, and the *N,N*-dibutylamide of butyric acid, which are products of subsequent interactions of the enamine $(C_4H_9)_2NCH{=}CHCH_2CH_3$ formed initially. Tribenzylamine is oxidised to benzaldehyde and benzoic acid; dibenzylamine is not formed. The mechanism of this reaction has not been established[70].

It has been observed[71] that in the reaction of substituted benzylamines with $KMnO_4$ in water, the amines and not their salts are oxidised. At pH 10 the rate of reaction is described by a first-order equation with respect to the amine and the oxidant. The rate is independent of the ionic strength of the solution. The activation energy and entropy are 10.4–11.7 kcal mol^{-1} and from −21.6 to −24.8 e.u. respectively. Benzylamine is oxidised seven times faster than $C_6H_5CD_2NH_2$ but at the same rate as $C_6H_5CH_2ND_2$. The influence of substituents is correlated with σ^+ ($\rho = -0.28$). At high pH yet another reaction takes place whose mechanism has not been established. The following mechanism has been proposed for the reaction in weakly alkaline media:



Here the activated complex decomposes with transfer of a hydride ion or H·. The radicals are then (after the loss of the proton) oxidised to benzaldimine.

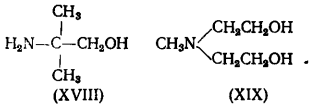
It has been found[73] that the rate of oxidation of amines at pH 7.5–8 is proportional to the concentration of the oxidant and the substrate and decreases in the sequence $(C_2H_5)_3N > (C_2H_5)_2NH > C_2H_5NH_2$; it has also been found that $(CH_3)_3N$ is oxidised to formaldehyde 1.84 times faster than $(CD_3)_3N$. According to the authors[73], an electron is transferred in the slow stage of the oxidation of trimethylamine and the abstraction of hydrogen is not the main reaction pathway. The reaction proceeds preferentially via a mechanism analogous to that of the oxidation by ClO_2:



On passing to secondary or tertiary amines, the abstraction of hydrogen in the slow reaction stage assumes increasing importance, as in the oxidation by ClO_2.

The oxidation of $(CH_3)_3N$ and $(C_2H_5)_3N$ with aqueous $KMnO_4$ at pH 6–8 has been studied[74] and a mechanism has been proposed in which the ammonium radical-cations are formed when amines interact with manganese complexes. The latter are obtained in the first stages from complexes of the amines with manganese (VII) and manganese(V) compounds.

On treatment with periodic acid; ethanolamine, diethanolamine, triethanolamine, ethylenediamine, and the amines (XVIII) and (XIX) undergo oxidative fragmentation[75], the reactions with ethanolamine and ethylenediamine being quantitative[76].



(XVIII) (XIX)

The study of the kinetics of the oxidation of ethanolamine[77] and *N*-methylethanolamine[77,78] did not yield sufficient data for the determination of the reaction mechanism. It is not even clear whether ethanolamine or their protonated forms and which of the ions $H_4IO_6^-$ and $H_3IO_6^{2-}$, $H_2IO_5^-$, or HIO_5^{2-} are involved in the reaction.

The mechanism of the oxidation of amines with chromic acid has not been studied. Data on the kinetics of the oxidation of a number of amines to CO_2, H_2O, and NH_3 by $K_2Cr_2O_7$ in an acid medium have been published in only one communication[79].

7. Oxidation by $K_3Fe(CN)_6$, $Pb(OCOCH_3)_4$, Silver(II) Picolinate, and $AgNO_3$

Smith and coworkers studied the oxidation of tertiary amines by $K_3Fe(CN)_6$ in aqueous solutions at pH > 12. In the presence of an excess of the substrate, two moles of the oxidant are consumed per mole of the amine and mainly oxidative dealkylation products are formed. The reaction obeys a first-order kinetic law with respect to the oxidant and the amine. Tertiary *N*-methyl- and *N*,*N*-dimethyl-amines are mainly demethylated[80]. The secondary amines formed are not oxidised further. The rate of reaction is correlated with the $\Sigma\sigma^*$ of the substituents at the nitrogen atom; $\rho^* = -5.45$ and is close to $\rho^* = -5.24$ found for the oxidation of amines by ClO_2, where an electron is transferred in the rate-limiting stage. The addition of $K_4Fe(CN)_6$ does not affect the rate of oxidation. The salt effect of cations is observed. All these data can be accounted for by a mechanism involving the irreversible transfer of an electron from the amine to the oxidant in the slow stage#:

$$RCH_2NR'_2 + Fe(CN)_6^{3-} \xrightarrow[-Fe(CN)_6^{4-}]{slow} RCH_2\overset{+}{N}R'_2 \xrightarrow{-H^+}$$

$$\rightarrow RCH{=}NR'_2 \xrightarrow[-Fe(CN)_6^{4-}]{+Fe(CN)_6^{3-}} RCH{=}\overset{+}{N}R'_2 \xrightarrow{+OH^-}$$

$$\rightarrow RCH(OH)NR'_2 \rightarrow RCHO + R'_2NH \quad . \qquad (13)$$

An alternative mechanism, in which the first two stages have been replaced by the concerted loss of an electron and an α-proton by the amine, i.e.

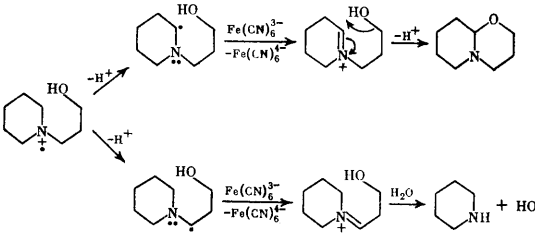
$$RCH_2NR'_2 + Fe(CN)_6^{3-} \rightarrow RCH\dot{N}R'_2 + Fe(CN)_6^{4-} + H^+ \ ,$$

is in poor agreement with the high value of ρ^* and the small kinetic isotope effect (see below). The possibility of the simultaneous occurrence of the reaction via both mechanisms is ruled out by the finding that a linear relation between $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ holds for a series of the amines investigated.

It has been found[82] that at pH 8.8 the rate of oxidation of triethylamine by $K_3Fe(CN)_6$ diminishes following the addition of $K_4Fe(CN)_6$ in proportion to the concentration of the additive. It was therefore concluded that the electron transfer in the slow stage is reversible. The discrepancy between these data and the findings described above was explained by differences in the pH.

The oxidation of *para*-substituted benzyldimethylamines[81] also proceeds via mechanism (13). The rate of reaction is correlated with the Hammett σ constants of the ring substituents, with the $\Sigma\sigma^*$ of the substituents at the nitrogen atom, and with the pK_a of the amines. The values of ρ, ρ*, and α (−0.989, −4.24, and 0.990 respectively) are close to those found for the oxidation of benzyldimethylamines by ClO_2. The ratio of the demethylation and debenzylation products (formed after the loss of H^+ from the CH_3 or CH_2 group in the amines) differs from the statistical ratio. According to mechanism (13), it is determined by the relative acidity of the *N*-methyl or *N*-benzyl hydrogen atoms and the number of these atoms.

Mechanism (13) has been confirmed in the oxidation of trialkylaminoalcohols and trialkylaminoamines[83]. Thus 3-piperidino-1-propanol gives rise to a cyclisation product and piperidine, which can be explained by the intermediate formation of a radical-cation and of immonium ions:



The electron transfer in the rate-limiting stage is confirmed by the low kinetic isotope effect in the oxidation of $CH_3N(C_4H_9)_2$ and $CD_3N(C_4H_9)_2$ ($k_H/k_D = 1.04$). The ratio of the demethylation and debutylation products changes greatly on isotope substitution—the isotope effect is 3.6.[84]

It has also been shown[84] that the characteristics of the rate of oxidation of tertiary amines with a nitrogen atom in the ring or bicyclic tertiary amines can be satisfactorily explained by mechanism (13). The radical-cations $R_3\overset{+}{N}$ have a planar structure and the transition state for their formation is a structure close to that of radical-cations. The rate of oxidation is therefore controlled by the changes in ring strain and the barriers to changes in conformation which arise when the molecules are converted into radical-cations. This treatment has been confirmed[85] in relation to trialkylaminoalcohols, their ethers, trialkylaminoamines, phenetylamines, and cyclic, bicyclic, and tricyclic amines.

In contrast to tertiary amines, diethanolamine undergoes oxidative fragmentation in oxidation by $K_3Fe(CN)_6$ in aqueous alkali[86–88]:

$$NH(CH_2CH_2OH)_2 + 4OH^- + 4Fe(CN)_6^{3-} \rightarrow 4HCHO + + NH_3 + 4Fe(CN)_6^{4-} + 2H_2O \ .$$

The process is analogous to the oxidation of β-hydroxyamines by ClO_2, but its mechanism has been studied inadequately. At low $K_3Fe(CN)_6$ concentrations the rate of oxidation is proportional to the concentrations of alkali, the substrate, and the oxidant, but the reaction order with respect to the oxidant decreases with increasing concentration of the latter and may become zero. The addition of salts, including $K_4Fe(CN)_6$, accelerates the reaction, while the addition of methanol retards it. The following mechanism has been proposed:

$$NH(CH_2CH_2OH)_2 + OH^- \underset{-H_2O}{\rightleftharpoons} HOCH_2CH_2NHCH_2CH_2O^- \xrightarrow{+Fe(CN)_6^{3-}}$$

$$\rightarrow complex \xrightarrow{+Fe(CN)_6^{3-}} 2Fe(CN)_6^{4-} + products.$$

At low oxidant concentrations the rate of reaction is limited

by the formation of a complex, which explains the third order of the reaction, while at high oxidant concentration it is limited by the ionisation of ethanolamine.

The oxidation of primary amines with a methylene group by $Pb(OCOCH_3)_4$ in boiling benzene[89,90] leads to the formation of nitriles in yields up to 60%. The reaction is believed to be a two-stage dehydrogenation process with the intermediate formation of aldimines. The mechanism has been confirmed by the formation of 2–4% of benzaldehyde in the oxidation of benzylamine and subsequent hydrolysis, since the aldehyde is probably formed from the aldimine $C_6H_5CH{=}NH$. Aliphatic aldehydes are not formed in the reaction, since their aldimines are unstable. They rapidly polymerise, which lowers the yield of nitriles and increases the yield of resins.

In specifying the details of the mechanism, the authors[89,90] postulated the intermediate formation of the products (XX) and (XXI) of the aminolysis of lead tetra-acetate [see mechanism (14)] and their homolytic decomposition. This is based on the analogy with the alcoholysis of $Pb(OAc)_4$ and the photochemical oxidation of benzylamine to benzonitrile by $Pb(OAc)_4$. The reaction mechanism is as follows:

$$RCH_2NH_2 + Pb(OAc)_4 \overset{a}{\rightleftarrows} RCH_2NHPb(OAc)_3 + AcOH$$
$$\overset{c}{\searrow} \quad \overset{b}{\downarrow} \ (XX)$$
$$RCH_2\dot{N}H + \dot{P}b(OAc)_3 \rightarrow RCH{=}NH + Pb(OAc)_2 + AcOH \ ;$$

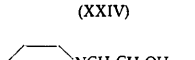
$$RCH{=}NH + Pb(OAc)_4 \overset{a}{\rightleftarrows} RCH{=}NPb(OAc)_3 + AcOH$$
$$\overset{c}{\searrow} \quad \overset{b}{\downarrow} \ (XXI)$$
$$RCH{=}\dot{N} + \dot{P}b(OAc)_3 \longrightarrow RC{\equiv}N + Pb(OAc)_2 + AcOH \ . \qquad (14)$$

Compounds (XX) and (XXI) are converted into an imine or a nitrile either directly (pathway *b*) or with the intermediate formation of radical pairs (pathway c). Mechanisms involving the formation of side products have also been proposed.

The oxidation of dibenzylamine gives rise to benzaldehyde, benzonitrile, benzylamine, and the compounds $C_6H_5CH_2N = CHC_6H_5$ (XXII) and $C_6H_5CH(COCH_3)NH = CHC_6H_5$ (XXIII). A reaction mechanism has been proposed in which compound (XXII) is formed in the first stage via a mechanism analogous to mechanism (14); its subsequent reactions explain the formation of the other products mentioned.

Triethylamine is very slowly oxidised by lead tetra-acetate in glacial acetic acid, while the amines (XXIV)–(XXVII) are rapidly oxidised. After hydrolysis, the amines (XXIV)–(XXVI) give high yields of diethylamine, while compound (XXVII) gives rise to piperidine. The hydroxylamines (XXVIII) and (XXIX) are oxidised much more slowly than compounds (XXIV)–(XXVII) but faster than the mixture of $(C_2H_5)_3N$ and 1-propanol, which is in its turn oxidised faster than triethylamine[91]. The oxidation of the amines (XXIV) and (XXVII) results in the formation of glyoxal.

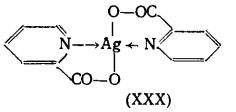
$(C_2H_5)_2NCH_2CH_2OH$ (XXIV); $(C_2H_5)_2NCH_2CHCH_3$ (XXV) (OH); $(C_2H_5)_2NCH_2C(CH_3)_2$ (XXVI) (OH);


NCH_2CH_2OH (XXVII); $(C_2H_5)_2NCH_2CH_2CH_2OH$ (XXVIII); $(C_2H_5)_2NCH_2CH_2CH_2CH_2OH$ (XXIX) .

The above data show that the C–N bonds are cleaved in the reaction. The authors quoted above proposed the following process mechanism:

$$(C_2H_5)_2NCH_2CH_2OH \xrightarrow[-CH_3COOH]{+CH_3COO^-} (C_2H_5)_2N\dot{C}HCH_2OH \xrightarrow{+CH_3COO^-}$$
$$\rightarrow (C_2H_5)_2NCH(OCOCH_3)CH_2OH \xrightarrow{+H_2O} (C_2H_5)_2NH + CH_3COOH + O{=}CHCH_2OH$$

The oxidation of primary and secondary amines with an α-hydrogen atom by a suspension of silver(II) picolinate (XXX) in water or polar solvents[93] leads to the formation of aldehydes or ketones and apparently proceeds via an imine formation stage.


(XXX)

The imines were isolated in those instances of the oxidation of secondary amines where the imines were stable. Stable imines, corresponding to primary amines, are oxidised further to nitriles. The stoichiometry of the reaction is described by the equations

$$\rangle CHNH_2 + 2Ag^{2+} + H_2O \rightarrow \rangle CO + NH_3 + 2Ag^+ + 2H^+ \ ;$$
$$\rangle CHNHR + 2Ag^{2+} \rightarrow \left(\rangle C{=}NR + 2Ag^+ + 2H^+\right) \overset{H_2O}{\rightleftarrows} \rangle CO + RNH_2 + 2Ag^+ + 2H^+ \ .$$

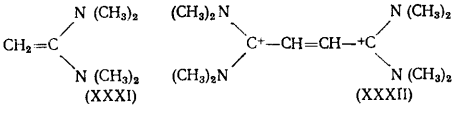
The authors[93] suggest that the amines substitute picolinic acid in the complex (XXX), after which they give up an electron to silver(II). This is followed by the oxidation of the resulting radical by a second picolinate molecule, which leads to an imine either directly or via a hydroxyamine formation stage:

$$RCH_2NHR' \rightarrow Ag(I) + RCH_2\overset{+}{N}HR' \rightarrow R\dot{C}HNHR' + H^+ \ ;$$
$$\downarrow Ag(II)$$
$$Ag(II) + R\dot{C}HNHR' \begin{cases} \longrightarrow Ag(I) + H^+ + RCH{=}NR' \\ \xrightarrow{H_2O} Ag(I) + H^+ + RCH(OH)NHR' \rightleftarrows RCHO + R'NH_2 \ . \end{cases}$$

One cannot rule out the possibility that imines are formed in the disproportionation of α-amino radicals:

$$2R\dot{C}HNHR' \rightarrow RCH{=}NR' + RCH_2NHR' \ .$$

The interaction of vinylidenebisdialkylamines with silver nitrate in acetonitrile leads to oxidative dimerisation with formation of diamidinium salts[94,95]. Thus compound (XXXII) and metallic silver are formed from compound (XXXI).


(XXXI) (XXXII)

If the initial amine contains two double bonds, there is a possibility of the formation of cyclic or bicyclic products. It has been suggested that the reaction proceeds with participation of radical-cations. In certain cases their formation was established by EPR.

8. Oxidation with Molecular Oxygen and Ozone

When triethylamine is oxidised with oxgen in the gas phase at 200 °C,[96,97] mainly ethylamine, acetaldehyde, and diethylamine are formed. The diethylamine concentration initially increases, but rapidly attains a limiting value. It has been suggested that oxygen abstracts H· from the CH_2 group, after which another oxygen molecule adds to the resulting radical to form a peroxy-radical; ethylamine is formed in the intramolecular decomposition of this radical, while diethylamine arises in consequence of the decomposition of the hydroperoxide. The details of the mechanism have not been determined.

The kinetics of the radical-initiated liquid-phase oxidation of amines by oxygen have been studied[98–109]. These reactions proceed at a lower temperature than the gas-phase

oxidation, but their products have not been investigated. In most cases the oxidation involves radical-chain processes and proceeds via the following mechanism with both primary and secondary amines:

$$\text{Initiator} \xrightarrow{+RH,+O_2} \dot{R} \xrightarrow{+O_2} RO_2^{\cdot} \xrightarrow{+RH} ROOH + \dot{R} \quad ;$$
$$2RO_2^{\cdot} \rightarrow O_2 + \text{molecular products.}$$

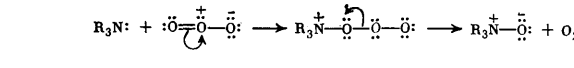
Here $\dot{R}$ = α-amino-radical. Tertiary amines are oxidised more readily than primary and secondary amines. The involvement of enamines in the reaction and in certain cases linear chain termination have been postulated[102].

The specific features of the reactions consist in the fact that α-aminoperoxy-radicals have not only oxidative but also reductive properties. They are capable of regenerating the inhibitors of radical-chain processes, which explains the observed high stoichiometric inhibition coefficients.

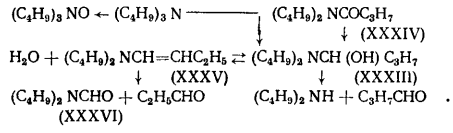
The liquid-phase autoxidation of enamines with a complex structure has been studied[110]. The reaction proceeds via a radical-chain mechanism. In the initiation stage the amine gives up an electron to the oxygen with formation of ammonium radical-cations. The Fe^{3+} and Cu^{2+} ions react similarly and greatly accelerate the autoxidation.

It has been found[111] that $RuCl_3$ catalyses the homogeneous liquid-phase oxidation of amines by oxygen. In toluene at 100 °C benzylamine is converted into benzonitrile and benzamide, while butyronitrile and butyramide are formed from n-butylamine. 2-Aminohexane gives rise to the corresponding ketone (formed in the hydrolysis of the imine) and the product of the condensation of the ketone with the initial amine. Variants of the mechanism involving ruthenium(III)—amide and ruthenium(III)—hydride complexes have been proposed.

In their interaction with ozone in chloroform at low temperatures, tertiary amines are converted with high yields into *N*-oxides[112]. The reaction probably proceeds via the mechanism[112,113]



The reaction has been studied in detail in relation to tri-n-butylamine[6,114]. Apart from its *N*-oxide, compounds (XXXIV) and (XXXVI) and dibutylamine are formed. The ratio of their yields is influenced by the nature of the solvent and temperature. In chloroform or methanol at −45 °C the main product is the *N*-oxide, while in hydrocarbons or 1-chlorobutane the products are dibutylamine at −45° or −78 °C and compound (XXVI) at +15 °C. It has also been shown that, for a tributylamine : ozone ratio of 1 : 1 at −78 °C in pentane, subsequent heating to 20 °C results in the formation of the enamine (XXXV), which is oxidised by ozone to compound (XXXVI). The following process mechanism has been proposed:



The formation of an *N*-oxide is apparently favoured by the tendency of the solvent to form hydrogen bonds; the carbinolamine (XXXIII) is obtained in solution in hydrocarbons or 1-chlorobutane. It is oxidised to compound (XXXIV), hydrolyses to butylamine and butyraldehyde, and is dehydrated to compound (XXXV) with subsequent ozonolysis at the double bond. Heating, which promotes dehydration, lowers the yield of dibutylamine and increases that of dibutylformamide. Hydrolysis of the carbinolamine, leading to dibutylamine and butyraldehyde, predominates in the oxidation of a suspension of tributylamine in water. The mechanism discussed does not, however, explain the formation of carbinolamine.

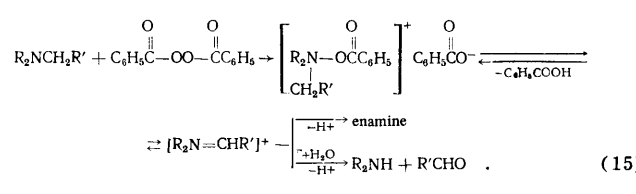
Primary amines are oxidised by ozone to nitro-compounds. At low temperatures the yields are 25–50%.[115] Alkylhydroxyamines and nitroso-compounds are probably formed initially, which is confirmed by the presence in the reaction mixture of alkylhydroxylamines when the oxidation is interrupted, after the introduction of one equivalent of ozone, by the conversion of alkylhydroxylamines into nitro-compounds under the influence of ozone and by the colour characteristic of nitroso-compounds appearing in the course of the reaction.

Since oximes are not converted into nitro-compounds on being oxidised with ozone, it is to be expected, in conformity with the mechanism discussed, that amines with tertiary hydrocarbon groups, which are converted into nitroso-compounds incapable of isomerising to oximes, would give rise to higher yields of nitro-compounds than amines with primary or secondary hydrocarbon groups. This prediction has been confirmed. However, it is noteworthy that the mechanism of the formation of alkylhydroxylamines and of their conversion into nitroso-compounds and then nitro-compounds remains obscure.

9. Oxidation by Peroxy-Compounds

The oxidation of amines by peroxy-compounds frequently depends on the nature of the solvent and the mechanism is often different for primary, secondary, and tertiary amines. These reactions apparently include both heterolytic and homolytic processes. The study of their kinetics is complicated by the inhibition or acceleration of the oxidation by reaction products, which is frequently encountered, and by the widespread occurrence of radical-chain processes. The oxidation mechanisms are by no means always satisfactorily justified and their details are frequently unknown.

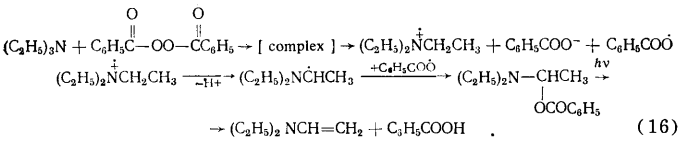
The interaction of benzoyl peroxide with tertiary amines has been investigated[116]. In benzene, in the presence of an excess of the amine, the stages involving the oxidation of amines with the $R_2NCH_2CH_2$ group yield enamines, which have been identified from the formation of compounds of the "blue quinone" type (see Section III, 2) when the reaction is carried out in the presence of quinones. The enamine $(C_2H_5)_2.NCH{=}CH_2$ has been isolated[117]. Amines of the type $(CH_3)_2.NCH_2Ar$, which are incapable of forming enamines, give rise to immonium salts, which hydrolyse to secondary amines and carbonyl compounds. These data can be accounted for by a mechanism analogous to that of the interaction of benzoyl peroxide with dimethylaniline[118]:



(15)

The first stage involves nucleophilic substitution with formation of a quaternary salt, corresponding to the ether of the substituted hydroxylamine. Mechansim (15) has been confirmed by the isolation of a compound of this type in the oxidation of triethylamine by acetyl peroxide[119]; however, it conflicts with the formation of radicals giving rise to polymerisation (see, for example, Margaritova and coworkers[120,121]).

The involvement of radicals in the stages where amines are oxidised by benzoyl peroxide, the intermediates, and the kinetics and mechanisms of the reactions have been investigated[122–128]. The authors used a method based on the chemiluminescence which arises in the course of the recombination of radicals: its appearance is a sign of a radical mechanism and the variation of its intensity makes it possible to infer the reaction kinetics. It has been established that the oxidation of triethylamine by benzoyl peroxide obeys a first-order kinetic equation with respect to each reactant and has a radical but not chain mechanism. Benzoic acid retards while pyridine accelerates the reaction as a result of the formation of complexes with the amines or the peroxide respectively. In the presence of an excess of the peroxide, chemiluminescence, corresponding to the oxidation of an intermediate, probably an enamine, is observed. On hydrolysis, the enamine gives rise to diethylamine and acetaldehyde. The following mechanism has been proposed:



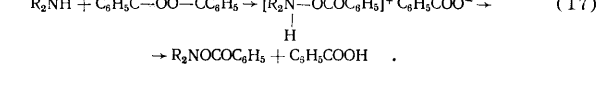
(16)

It is closer to Horner's mechanism of the oxidation of *N*,*N*-dialkylanilines (see, for example, Horner and Junkermann[129]). It may be that the intermediate complex is a quaternary salt, corresponding to an ether of the substituted hydroxylamine[130], which rapidly decomposes into radicals. It is also possible that the salt decomposes simultaneously via a non-radical mechanism (see, for example, Walling and Inductor[117]).

According to the authors of the studies quoted, the oxidation of aminoalcohols $R'R''NCH_2CH_2OH$ [123,128,131] proceeds via a mechanism analogous to mechanism (16). The oxidation of triethanolamine[132–134] is a radical-chain reaction.

The structure factors which determine the mode of dealkylation of tertiary amines have been studied[135].

The secondary amine oxidation reactions[122,126,127,133,136–140] are also usually second-order reactions. Radicals are probably not formed in these reactions or not in the initial stages, being produced in the oxidation of the intermediates [for example, of $(C_2H_5)_2NCH{=}CH_2$, obtained in the oxidation of diethylamine[143]]. The radical mechanisms proposed previously (see, for example, Horner and Kirmse[194]) are probably incorrect[142]. Apparently the cations of the quaternary salts obtained from hydroxylamine derivatives are formed in these reactions and then rapidly lose protons:

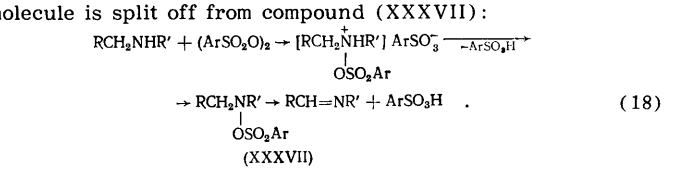


(17)

Nor can one rule out the possibility[139] that secondary amines react with an amine–peroxide complex rather than the peroxide itself.

The oxidation of primary amines by benzoyl peroxide has been investigated only in relation to propylamine[127], butylamine[140], and benzylamine[144–146]. The ideas concerning the mechanisms of these reactions have been only slightly elaborated.

When primary or secondary amines interact with *p*-nitrobenzenesulphonyl peroxide with subsequent hydrolysis, carbonyl compounds are obtained, frequently in good yields. Imines are formed in the intermediate oxidation stages and can sometimes be isolated. The process apparently begins with nucleophilic attack by the amine on the peroxide, analogous to reaction (17), and then yet another sulphonic acid molecule is split off from compound (XXXVII):

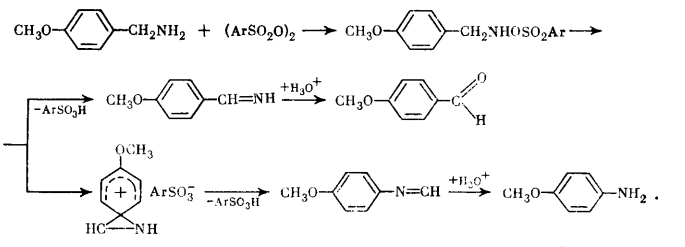


(18)

(XXXVII)

The electrophilic nature of the peroxide and its tendency to split off the $ArSO_3^-$ residue favour this two-electron mechanism.

The "anomalous" course of the reaction has been studied[148]. In the oxidation of, for example, *p*-methoxybenzylamine or diphenylmethylamine the products are *p*-methoxyaniline or benzaldehyde instead of *p*-methoxybenzaldehyde or benzophenone expected on the basis of mechanism (18). These results have been explained by the migration of the aryl residue from the carbon atom to the positively charged nitrogen atom arising on ionisation of a compound of type (XXXVII):



It has been shown[148] that the radical variants of the mechanism are less probable.

The oxidation of amines by dicyclohexyl peroxydicarbonate $(C_6H_{11}OCOO)_2$ has been investigated[141]. In the presence of an excess of the amine, the reactions with triethylamine, *N*-diethylethanolamine, and *N*-ethyldiethanolamine obey a second-order kinetic equation and are accompanied by chemiluminescence. A radical mechanism analogous to mechanism (16) has been proposed.

The oxidation of amines by potassium persulphate in water has been studied[149–156]. According to the characteristics of the rate and the reaction mechanism, the authors divided amines into two groups[149,150]. Primary and secondary amines were assigned to the first group. Their oxidation products have not been determined, but the rate obeys a second-order kinetic equation and is proportional to the KOH concentration. Primary amines are oxidised more slowly than secondary amines. The initial rates of oxidation of amines in this group are proportional to their pK_a, which has been explained by complex formation between the amine and the peroxide in the slow stage. The reaction mechanism has not been established, but it is probably of a non-radical type[149–152].

Tertiary amines and aminoalcohols were assigned to the second group. The oxidation of tertiary amines[149,150,153–156] results in the formation of secondary amines and carbonyl compounds. Diethylvinylamine, which gives rise to diethylamine and acetaldehyde on hydrolysis, was detected among the products of the reaction with triethylamine. The oxidation of tertiary and secondary aminoalcohols[149–150,152,154–166] leads to secondary or primary aminoalcohols and carbonyl compounds respectively. In the case of triethylamine, diethanolamine, and *N*-ethyldiethanolamine, formaldehyde is present among the products, i.e. oxidative fragmentation takes place. The kinetics of the above reactions are fairly complex; fractional reaction orders, the acceleration of the consumption of the oxidant by the reaction products, and the dependence of the rate of oxidation on the presence of radical chain process inhibitors are observed. The rate is not

simply related to the basicity of the amines; the addition of KOH has a different and more complex effect on the rate than for amines in the first group. These data can be accounted for by the involvement of radicals in the reaction, which is consistent with the finding that some of the reactions of this type induce radical polymerisation.

The mechanism of the oxidation of amines of the second group remains obscure. We believe that the proposed mechanisms[150,153,154,156,158,159] are inadequately founded and are unconvincing. They do not explain or only explain poorly the dependence of the rates of the reactions on the concentration of alkali, their orders, etc. and are not detailed.

The oxidation of amines by potassium persulphate is catalysed by variable-valence metals. These reactions with amines and aminoalcohols have been studied[167–173]. The catalytic effect of metal ions increases in the sequence Co^{2+} < Cu^{2+} < Ag^{+}.[170,172] In most cases the rate of oxidation falls with increasing basicity of the amines[167,172], which the authors explained by a decrease of the activity of the metal ions as a result of the increase of the stability of their complexes with the amines. A reaction mechanism involving the formation of a complex comprising the amine, Ag^+ ions, and persulphate, in which the metal ion behaves as an agent transferring an electron from the amine to the persulphate, has been proposed[170,172]. The reaction products were not determined in the above investigations.

The interaction of persulphate with primary amines in the presence of Ag^+ ions is of preparative value[174]. Amines of the type RCH_2NH_2 are converted into aldimines $RCH{=}NCH_2R$, amines of the type $RR'CHNH_2$ give rise to ketones, while the amines R_3CNH_2 are not oxidised. In contrast to the results of Bacon and Stewart[174], Babu et al.[175] isolated hydroxylamine derivatives and oximes as intermediates in the above reaction. In the presence of an excess of the amine (Am), the rate of reaction is proportional to the concentrations of persulphate and Ag^+, the order with respect to the amine falls with increasing Ag^+ concentration, and the reaction is of first order with respect to the amine in the absence of the catalyst. Neutral salts retard the reaction. These data have been explained by the fact that non-catalysed and catalysed reactions take place simultaneously. Ions of opposite sign react in the slow stage of the latter. The overall rate of the process is expressed by the equation

$$\frac{d[S_2O_8^{2-}]}{dt} = k_1[Am][S_2O_8^{2-}] + k_2[Ag^+][S_2O_8^{2-}] \quad .$$

At a high Ag^+ concentration the quantity $k_1[Am]$ becomes much smaller than $k_2[Ag^+]$ and the order of the reaction with respect to the amine becomes zero. The rate constant k_2 is higher the smaller the stability of the complexes of the amines with Ag^+. The catalysed reaction proceeds via the mechanism

$$S_2O_8^{2-} \rightleftarrows 2SO_4^{\cdot-} \quad ,$$
$$2SO_4^{\cdot-} + Ag^+ \xrightarrow[k_M]{\text{slow}} 2SO_4^{2-} + Ag^{3+} \quad ,$$
$$Ag^{3+} + RNH_2 + H_2O \rightarrow RNHOH + Ag^+ \quad , \qquad (19)$$

according to which $w = k_M[SO_4^{\cdot-}]^2[Ag^+]$. Bearing in mind that $[SO_4^{\cdot-}]^2 = K[S_2O_8^{2-}]$ (where K is the equilibrium constant of the reaction $S_2O_8^{2-} \rightleftharpoons 2SO_4^{\cdot-}$), then $w = k_M K[Ag^+][S_2O_8^{2-}]$ and $k_2 = k_M K$. We may note that the last stage in mechanism (19) is not specified in detail and that an analogous mechanism explains the formation of aldimines.

Secondary amines of the type $(RCH_2)_2NH$ react with persulphate and Ag^+ ions to form aldehydes, while those of the type $(RR'CH)_2NH$ give rise to ketones. Primary amines are formed simultaneously. α-Aminoacids give rise to aldehydes while *N*-methylpiperidine and *N*-methylpyridine are not oxidised. These reactions are more complex than the oxidation of primary amines[176].

In contrast to the data presented above, it has been found[177] that di-isopropylamine and the aminoalcohol $HN(CH_2CHOHCH_3)_2$ are oxidised to hydroxylamine derivatives; the mechanism of these reactions has not been established.

Among the reactions of dialkyl peroxides, only the interaction of di-t-butyl peroxide with tri-n-butylamine, di-isopropylamine, and 4-methyl-2-pentylamine has been investigated[178,179]. t-Butyl alcohol and compounds with −C=N− bonds are formed almost quantitatively. The rate of reaction is determined by the stage involving the decomposition of the peroxide into radicals, which dehydrogenate the amine. Two variants of the mechanism have been proposed:

$$(CH_3)_3C\dot{O} + R_2CH{-}NHR' \xrightarrow[-(CH_3)_3COH]{} R_2\dot{C}{-}NHR' \xrightarrow{+(CH_3)_3C\dot{O}} \rightarrow (CH_3)_3COH + R_2C{=}NHR'$$

$$(CH_3)_3C\dot{O} + R_2CH{-}NHR' \rightarrow (CH_3)_3CO^- + R_2CH{-}\dot{\overset{+}{N}}R' \xrightarrow[-(CH_3)_3COH]{} R_2\dot{C}{-}\ddot{N}HR' \rightarrow$$

$$\xrightarrow{(CH_3)_3C\dot{O}} R_2C{=}\overset{+}{N}HR' + (CH_3)_3CO^- \rightarrow R_2C{=}NR' + (CH_3)_3COH \quad .$$

The interaction of hydroperoxides with amines has been studied more widely. It has been shown[180] that these reactions lead to satisfactory yields of the alcohols coresponding to the peroxides. Their mechanism has been studied[179] in relation to the reactions of t-butyl hydroperoxide with an excess of 4-methyl-2-pentylamine, di-isopropylamine, tri-n-propylamine, and 2,4,4-trimethyl-2-pentylamine. All these amines form hydrogen-bonded complexes with the hydroperoxide; t-butyl alcohol was detected among the products. The last of the above amines, which does not contain a hydrogen atom in the α-position relative to the amino-group, reacts at a higher temperature than the other amines and gives rise to 2,4,4-trimethyl-2-nitropentane and the products of the thermal decomposition of the hydroperoxide. The reaction mechanism is unknown. The first three amines are converted respectively into the ketimine (XXXVIII), ammonia, and water, into acetone, isopropylamine, water, and the ketimine (XXXIX), and into dipropylamine, propionaldehyde, and its aldol condensation products. Compounds (XL)–(XLIII) are probably formed in addition from tri-n-propylamine.

$(CH_3)_2CHCH_2C(CH_3)_2{=}NCHCH_2CH(CH_3)_2$ (XXXVIII)

$(CH_3)_2C{=}NCH(CH_3)_2$ (XXXIX)

$C_3H_7NHCHCH_2CH_3$ | OC_4H_9 (XL)

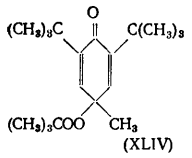
$(C_5H_7)_2NCHCH_2CH_3$ | OC_4H_9 (XLI)

$C_3H_7NHCHCH_2CH_3$ | $C_3H_7NHCHCH_2CH_3$ (XLII)

$(C_3H_7)_2NCHCH_2CH_3$ | $(C_3H_7)_2NCHCH_2CH_3$ (XLIII)

One may therefore assume that the first three amines give rise to dealkylation products and carbonyl compounds, which can be converted into imines by reacting with the initial amine or the amine formed in the reaction. The products (XL)–(XLIII) probably arise from intermediate radicals. The involvement of radicals is confirmed by the retardation of the reactions by radical chain process inhibitors, for example ionol. The formation of the radicals $(CH_3)_3C\dot{O}$ has been demonstrated by the isolation of compound (XLIV)—the product of their interaction with radicals corresponding to

ionol.



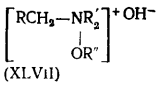
(XLIV)



(XLV)

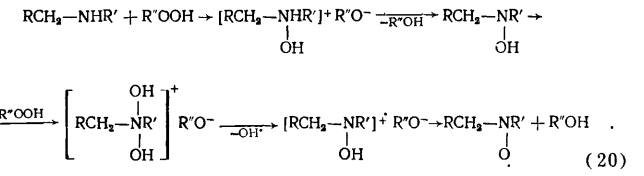


(XLVI)



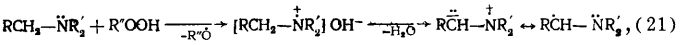
(XLVII)

De La Mare[179] explained the set of results obtained in terms of a radical-chain mechanism. The radicals (XLV) or (XLVI) arise in the initiation stage. The formation of the radicals (XLV) in the oxidation of tertiary and secondary amines by t-butyl hydroperoxide has been demonstrated by EPR.[181] The mechanism of their formation is obscure in the case of tertiary amines and that in the reaction with secondary and primary amines is



(20)

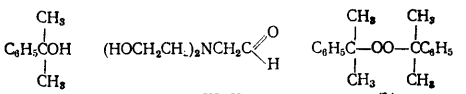
The radicals (XLVI) are obtained via the mechanism



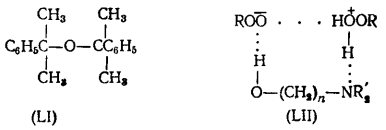
(21)

possibly with the intermediate involvement of the quaternary ammonium salt (XLVII). The chain propagation and termination mechanisms proposed by De La Mare[179] easily explain the mechanisms of the formation of all the reaction products.

The interaction of amines with cumenyl hydroperoxides in water has been studied[182–185]. Two parallel reactions take place with triethanolamine. The rate of one of them is proportional to the concentrations of the amine and the hydroperoxide. The rate of the second reaction is proportional to the square of the concentration of the hydroperoxide and depends on the dielectric constant and the presence of neutral salts. The reaction products—the alcohol (XLVIII), the aldehyde (XLIX), the peroxide (L), oxygen, and possibly the ether (LI)—are believed to be formed on decomposition of complexes of the amine with the hydroperoxide or its dimer. The latter complex is formed only by aminoalcohols, which has been explained by the structure (LII).



(XLVIII) (XLIX) (L)



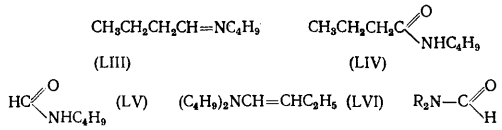
(LI)

(LII)

The mechanism of the decomposition of the complexes is unknown.

Metal compounds catalyse the oxidation of amines by hydroperoxides. Tertiary amines and aminoalcohols are converted into *N*-oxides in high yields, piperidine is converted into 2-piperidinone, and primary amines are converted into oximes. Vanadium, molybdenum, titanium, and tungsten compounds are particularly active. The reaction mechanism has not been established[186]. A study has been made of the kinetics of the reactions of triethylamine and morpholine with cumenyl hydroperoxide catalysed by metal ions[187].

The oxidation of amines by hydrogen peroxide has been little investigated. Only isolated data are available concerning its kinetics and mechanism. Thus it has been shown[188] that in acetonitrile the intermediate in the oxidation of n-butylamine is the aldimine (LIII), which is converted by the peroxide into the amides (LIV) and (LV).



(LIII) (LIV) (LV) (LVI) (LVII)

In addition the corresponding hydroxylamine and oxime are formed. The reaction with di-n-butylamine leads to dibutylhydroxylamine, the aldimine (LIII), and its oxidation products. Tri-n-butylamine gives rise to an amine oxide and the enamine (LVI), which hydrolyses to dibutylamine and butyraldehyde. It has been established[189] that the hydroxylamines formed in the oxidation of secondary amines on treatment with an aqueous H_2O_2 solution always contain an admixture of the corresponding *N*-formyldialkylamines (LVII) and a mechanism of their formation has been proposed. The kinetics of the oxidation of triethylamine by hydrogen peroxide have been investigated[190].

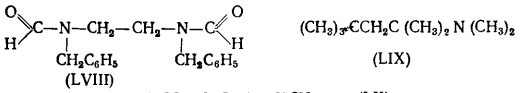
The characteristics of the catalytic oxidation of amines by hydrogen peroxide in the presence of $NaWO_4$ or $NaMoO_4$ have been studied[191,192]. The rate of reaction is proportional to the concentrations of the amine and the catalyst, decreasing on passing from tertiary to secondary amines and with increasing branching of the hydrocarbon residues at the nitrogen atom. It has been suggested that the primary products are amine oxides or amine oxide hydrates. Those obtained from ammonia and primary and secondary amines isomerise to hydroxylamines, which have been identified. Among other products, oximes and in certain cases carbonyl compounds have been detected. The formation of oxides from tertiary amines and of *N*,*N*-dialkylhydroxylamines from secondary amines on treatment with hydrogen peroxide in the presence of $NaWO_4$ has also been established in another study[193]. t-Butylamine is converted into a nitro-compound, while amines in which a primary or secondary carbon atom are linked to the NH_2 group give rise to aldoximes or ketoximes (isomerisation products of nitroso-compounds). It is believed that the above reactions involve electrophilic substitution at the nitrogen atom.

It is noteworthy that, despite the incompleteness of the data presented, one can postulate that radicals are involved in the reactions. It may be that radical processes take place simultaneously with electrophilic substitution. This is indicated by the formation of imines, enamines, and carbonyl compounds, usually obtained in the radical oxidation reactions of amines. One cannot rule out the possibility that radical reactions involving oxidation by hydrogen peroxide begin with reactions of types (20) and (21).

10. Other Oxidation Reactions

The oxidation of tri-n-alkylamines with $N-CH_2-CH_2$ residues by a suspension of hydrated manganese dioxide ($HOMnO_x$) in cyclohexane[114,195] leads to the formation of dialkylformamides. The hydrolysis of the reaction mixture gives rise also to dialkylamines. It has been suggested that the "$HOMnO_x$" surface generates HȮ radicals, which oxidise the adsorbed amines to carbinolamines. As in the reaction of amines with ozone, the latter hydrolyse to dialkylamines or are dehydrated to enamines, whose oxidation gives rise to dialkylformamides.

The formation of carbinolamines and their reactions account for the nature of the products of the reactions of various tertiary amines with "$HOMnO_x$". Thus benzaldehyde has been obtained from benzyldimethyl-, benzyldiethyl-, and tribenzyl-amines. 1,4-Dibenzylpiperazine gives rise to compound (LVIII). Cyclohexyldimethyl- and cyclohexyldiethylamines are converted into cyclohexanone, while the latter amines also give rise to acetaldehyde. Triethylenediamine and 1,2-dipiperidinoethane are converted into 1,4-diformylpiperazine and 1-formylpiperidine respectively. The amine (LIX) is converted into compound (LX).[195,196]



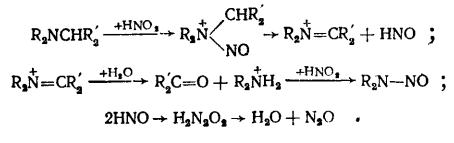
(LVIII)

$(CH_3)_3CCH_2C(CH_3)_2N(CH_3)_2$ (LIX)

$(CH_3)_3CCH_2C(CH_3)_2NHCH_3$ (LX)

Nitrous acid in aqueous acetic acid reacts with tertiary amines via the mechanism $R_2NCHR'_2 + HNO_2 \rightarrow R_2N{-}NO + R'_2C{=}O$.

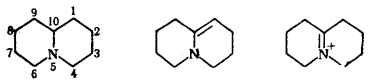
Nitrous oxide is present among the products. The introduction of substituents in the *meta*- or *para*-positions in one of the tribenzylamine rings influences the process: the fractions of unsubstituted benzaldehyde and substituted nitrosamine are given by the Hammett equation with a small negative value of ρ. The rate of reaction decreases with decrease of the basicity of the amines. Quinuclidine does not react. Substituents in one of the α-positions of tribenzylamine or benzyldiethylamine lead to the preferential formation of benzaldehyde or acetaldehyde regardless of the nature of the substituents. The amine $C_6H_5CD_2N(CH_2C_6H_5)_2$ is converted into deuterated and non-deuterated benzaldehyde in proportions of 1 : 8 ($k_H/k_D = 3.78$). The results have been explained by a heterolytic mechanism[197,198]:



It has been suggested that the elimination of HNO takes place intramolecularly in the reaction with a cyclic transition state. The mechanism involving the intermediate formation of ammonium radical-cations and nitric oxide as one of the reaction products[199] does not explain the formation of nitrous oxide, while the nucleophilic dealkylation mechanism[200] is inconsistent with the isotope effect. Nor can one rule out a mechanism in which NO^+ abstracts a hydride ion from the α-carbon atom of the amine[198].

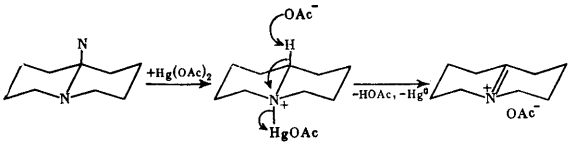
In the oxidation of triethylamine by iron(III) complexes of phenanthroline derivatives or the molybdenum(V) octacyanide complex[80] an electron is transferred from the amine to the oxidant with formation of ammonium radical-cations.

The oxidation of cyclic tertiary amines by mercury(II) acetate has been investigated[92,201-205]. The reaction leads to the formation of enamines. For example, the enamine (LXII) is formed from quinolizidine (LXI) and is converted into a salt.



(LXI) (LXII) (LXIII)

The oxidation apparently proceeds via a heterocyclic mechanism involving structure (LXIII):



$Hg(OAc)_2 + Hg^0 \longrightarrow Hg_2(OAc)_2$.

Quinolizidine-10-*d* is oxidised 2.3 times more slowly, so that the rate is limited by the decomposition and not the formation of the complex illustrated in the scheme above. The C–H bond involving the eliminated proton must be located in the *trans*-position relative to the N–Hg bond. A one-electron reaction mechanism is also not ruled out.

The data described above show that most of the reactions considered have radical or radical chain mechanisms. However, in only a few instances has direct evidence been obtained for the involvement of the radicals and their decisive role in the formation of the main reaction products established. We include in evidence of this type the observation of chemically induced nuclear polarisation in the products, the observation of EPR and optical spectra of the radicals or radical-cations involved in the formation of the products, the observation of the chemiluminescence of the reaction mixture and the initiation of polymerisation processes by the reaction mixture, and the presence of an induction period, which depends on the presence of inhibitors or initiators of radical chain reactions. Such evidence has been obtained for the oxidation of amines by diazonium and iodonium salts, ClO_2, quinonoid and peroxide compounds, etc., but in such cases there is no certainty that the main reaction products are obtained solely via the radical mechanism.

In other instances the radical mechanism has been justified indirectly. The relevant evidence has been obtained by considering kinetic data (in particular, the nature of the dependence of the rate of oxidation on the substituents in the substrate and the oxidant), the nature of the products formed, etc. Such combined indirect evidence constitutes a serious argument in support of the proposed mechanisms but cannot be regarded as their unambiguous confirmation.

The radical mechanisms examined can be classified in terms of the mode of generation and the nature of the radicals formed in the key stages. In most reactions the key role is due to the ammonium radical-cations, but direct evidence for their involvement in the reactions is available in only rare instances. These radicals can be obtained on electron transfer from the amines to the oxidants. If the transfer is reversible and limits the rate of oxidation, then the rates of reaction of a specified amine with a series of oxidants are correlated with their oxidation potentials E^0 and the rates of oxidation of different amines are correlated with the E^0 and the sum of the σ^* constants of the substituents at the nitrogen atom of the amine or with the E^0 and the photoionisation potentials of the amines[82]. The validity of these correlations may serve as a criterion of reversible electron transfer from the amine to the oxidant in the slow stage of the reaction. (Its other features were frequently discussed above.)

Yet another way of forming ammonium radical-cations consists in the decomposition of an intermediate compound or complex of the amine with the oxidant. The choice between this pathway and electron transfer is important for the understanding of the mechanism; however, frequently, such choice is based on indirect data in view of the lack of detailed information about the reaction kinetics. In only relatively

rare instances (see Section III, 2) has it been shown clearly that there is no direct electron transfer in the slow stage of the reaction.

In certain reactions (see, for example, Sections III, 4 and III, 6) the primary formation of α-amino radicals or the competitive formation of these radicals and ammonium radical-cations has been postulated. The rates of such reactions do not obey the above correlations. However, one should note that the involvement of α-amine radicals in the reactions, which can be regarded as likely on the basis of the available experimental data, has not been demonstrated directly. The observation of the primary isotope effect of deuterium cannot be regarded as direct evidence, since it can arise in the transfer of protons or hydride ions in the slow stage.

The formation of nitroxy-radicals has been established in the interaction of amines with t-butyl hydroperoxide. It is natural to postulate their key role in radical reactions of hydroperoxides and possibly of hydrogen peroxide with amines, particularly in those cases where compounds with nitrogen–oxygen bonds are formed.

As can be seen from the data presented above, the non-radical (molecular and ionic) amine oxidation mechanisms have been specified in less detail and are less well founded than the radical mechanisms. This applies particularly to mechanisms where the shift of a hydride ion is postulated. We may note that doubts have arisen in recent years as to whether the hydride ion shift is an elementary step and not consecutive transfer of an electron and a hydrogen atom or of two electrons and a proton[24,37].

We emphasise the importance of the results obtained in the study of the mechanism of the oxidation of amines with the aid of CIDNP. This method not only permits an unambiguous solution of the problem of the involvement of radicals in the formation of the reaction products but also allows one to derive information about the fine details of the mechanism, in particular to identify the radical pairs whose radicals are converted into the products (see Section III, 2 and Section III, 4).

In conclusion we may note that, despite the considerable advances in the study of individual amine oxidation reactions, this field has still not been adequately studied.

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