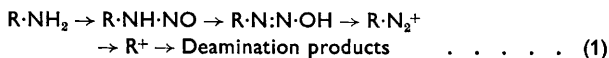# NITROSATION, DIAZOTISATION, AND DEAMINATION

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THE three reactions linked by the title of this Review can be considered as stages on the common reaction path:

$$R \cdot NH_2 \rightarrow R \cdot NH \cdot NO \rightarrow R \cdot N:N \cdot OH \rightarrow R \cdot N_2^+$$
$$\rightarrow R^+ \rightarrow \text{Deamination products} \quad \ldots \ldots \quad (1)$$

With secondary amines, the reaction stops at the nitrosamine stage; with aromatic amines the reaction effectively stops at the diazonium ion stage; and with primary aliphatic amines the reaction extends to the formation of a wide variety of deamination products. However, although this scheme accounts for most of the observations, it appears possible that other mechanisms of deamination may be significant; these complications are briefly discussed after the main evidence for path (1) has been presented.

The total material included in the title is too great for a single review; the following discussion is therefore limited to those observations that throw light on the mechanism of the reactions concerned. Only the simpler aromatic and aliphatic amines are considered, to exclude the many complications which arise from special structural features.

The discovery of deamination by Piria[1] in 1846* (in the conversion of aspartic into malic acid) slightly preceded the isolation of the aliphatic amines[2] but was soon applied both to them and to the aromatic amines.[3] The deamination of the aliphatic amines was shown to give, not only the corresponding alcohol, but a considerable range of other products; thus the reaction of n-propylamine gave n-propyl alcohol, isopropyl alcohol, propene, and some of the nitroso-derivative of di-n-propylamine.[4] The formation of isopropyl alcohol was first explained as due to hydration of the propene but Linnemann showed[5] that propene did not react with water under the conditions of deamination. Further work showed that the rearrangements in deamination could include the carbon skeleton, as in the formation of t-pentyl alcohol from neopentylamine[6] and in the inter-conversion of alicyclic rings termed the Demjanov rearrangements.[7]

The first observed reaction of aromatic amines with nitrous acid was the conversion of aniline into phenol,[3] but this was followed by the isolation

* The 1846 publication was in a little known Italian journal (*Il Cimento*) but the results were soon made generally available by publication[1] elsewhere.

[1] R. Piria, *Ann. Chem. Phys.*, 1848, **22**, 160; *Annalen*, 1848, **68**, 343; cf. report in *J.*, 1849, **1**, 342.

[2] A. Wurtz, *Annalen*, 1849, **71**, 330.

[3] A. W. Hofmann, *Annalen*, 1850, **75**, 356.

[4] V. Meyer and F. Forster, *Ber.*, 1876, **9**, 535; L. Henry, *Comp. rend.*, 1907, **145**, 899.

[5] E. Linnemann, *Ber.*, 1877, **10**, 1111.

[6] M. Freund and F. Lenze, *Ber.*, 1890, **23**, 2865; 1891, **24**, 2150.

[7] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell Ltd., London, 1953, p. 486.

by Griess[8] of diazotised picramic acid (I) (a neutral diazo-oxide), and a little later by the isolation of true diazonium salts.[9] Many of the reactions of diazonium ions and the controversies over the structure of diazo-compounds have been well summarised by Saunders[10] and by Zollinger,[11] and form one of the best known fields of organic chemistry.

        (I)   (II)   (III)
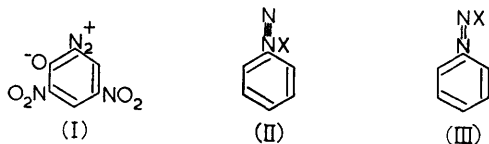
Before discussing the mechanism of the reactions, it is useful to compare the early structural assignments with the results of more recent investigations. One of the early problems concerned the difference between the highly reactive diazonium salts and the less reactive diazo-compounds (both with the empirical formula $Ar.N_2X$). The explanation is now known to lie in the difference between an ionic and a covalent bond, but Arrhenius's theory of ionic dissociation was not proposed until 1887 and so the difference in reactivity had then to be expressed as a difference in the valencies of the atoms concerned. Of the several proposed structures for the diazonium salts, that (II) first put forward by Blomstrand[12] and later supported by Hantzsch[13] is most in accord with modern views (cf. III for the diazo-compounds). If the N–X bond in structure (II) is written as ionic, then this structure becomes equivalent to (IVa), the valence-bond structure frequently used to represent the diazonium ion. Other structures contributing to the resonance hybrid include (IVb), and structures with the

        (IVa)   (IVb)   (IVc)
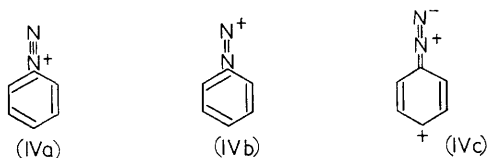
positive charge on the aromatic ring (e.g., IVc). The contribution of structures of type (IVc) increases the order of the C–N bond and thus stabilises the diazonium ion against decomposition by loss of nitrogen; such structures can also be considered to give rise to the strong electron-withdrawal by the $-N_2{}^+$ group.[14] The related structures in aliphatic

[8] P. Griess, *Annalen*, 1858, **106**, 123; 1860, **113**, 201.
[9] P. Griess, *Annalen*, 1861, **120**, 125.
[10] K. H. Saunders, "The Aromatic Diazo-Compounds," Arnold and Co., London, 1949.
[11] H. Zollinger, "Chemie der Azofarbstoffe," Birkhäuser Verlag, Basle, 1958.
[12] C. W. Blomstrand, "Chemie der Jetztzeit," C. Winter, Heidelberg, 1869, p. 272.
[13] A. Hantzsch, *Ber.*, 1895, **28**, 1743.
[14] E. S. Lewis and M. D. Johnson, *J. Amer. Chem. Soc.*, 1959, **81**, 2070.

diazonium ions (e.g., $H^+CH_2=N^+=N^-$) would involve hyperconjugation,[*] a less effective form of electron release.

The two isomeric diazotates formed by diazonium salts in alkaline media were formulated by Hantzsch[16] as geometrical isomers (Va and b) by analogy with the oximes; the cis(syn)-compound is formed rapidly and

$$\text{(Va)} \quad \begin{matrix} \text{Ar—N} \\ \parallel \\ \text{KO—N} \end{matrix} \qquad\qquad \begin{matrix} \text{Ar—N} \\ \parallel \\ \text{N—OK} \end{matrix} \quad \text{(Vb)}$$

is converted into the trans(anti)-compound on storage. This geometrical isomerisation was not at first accepted but has been supported with reference to the diazotate ions by modern physical studies.[11,17] In contrast, there is still a certain amount of disagreement[18] concerning the formation of the corresponding diazohydroxides (Ar·N:N·OH) and the isomeric primary nitrosamine (Ar·NH·NO). These compounds have not been isolated and recent work suggests that the syn-diazo-hydroxide is never formed to a significant extent in the reaction of diazonium salts[11] with alkali.

By the end of the nineteenth century the products of aliphatic deamination were known in considerable detail and the main structural features of the compounds formed on aromatic diazotisation were at least partly understood. However, the factors determining the reaction rate had not been studied and the mechanism of the complex rearrangements in aliphatic deamination were unknown. The main part of this Review is concerned with the more recent work on these two topics.

The rate-determining stage

It is difficult to describe the development of the kinetic studies in strict chronological order. The kinetic form of diazotisation depends very much on the conditions, but this was not appreciated by the early workers, and so several different kinetic forms were reported and considered to be generally valid; this led to considerable controversy. The initial nitrosation stage [cf. reactions (1)] is now recognised to be rate-determining at low acidities, both for diazotisation and for aliphatic deamination; the kinetic complexity, therefore, arises from the several mechanisms of nitrosation, some of which include two potentially rate-determining steps. In the following historical survey, the earlier papers are assigned according to the predominant nitrosation mechanism to which they refer. Only the more

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[*] In Mulliken's terminology,[15] this would be sacrificial hyperconjugation, and therefore less important than the hyperconjugation in the corresponding carbonium ions (isovalent hyperconjugation).

[15] N. Muller and R. S. Mulliken, J. Amer. Chem. Soc., 1958, **80**, 3489.

[16] A. Hantzsch, Ber., 1894, **27**, 1702.

[17] R. J. W. LeFèvre and J. B. Sousa, J., 1955, 3154.

[18] E. S. Lewis and H. Suhr, J. Amer. Chem. Soc., 1958, **80**, 1367; R. J. W. LeFèvre, R. Roper, and I. H. Reece, J., 1959, 4104, cf. B. A. Porai-Koshits, Tetrahedron, 1960, **11**, 30.

important papers have been considered; a very detailed account of the early work is available elsewhere.[10]

The Nitrous Anhydride Mechanism.—Under the conditions of the early kinetic studies, this is the predominant mechanism for the diazotisation of amines similar in basicity to aniline, in dilute perchloric acid ($<0.5M$), dilute sulphuric acid ($<0.5M$), and in very dilute hydrochloric acid ($<0.1M$); it is also the predominant mechanism for the deamination of aliphatic amines. The evidence for this mechanism has developed gradually from 1899 until the present day.

In 1899, Hantzsch and Schümann[19] published the first kinetic results on diazotisation. They showed that the diazotisation of aniline and several similar amines in dilute ($\sim 0.002M$) hydrochloric acid was overall of the second order, and, since there were only two reactants, they assumed that the order was unity with respect to each and expressed their results by equation (2):*

$$\text{Rate} = k[\text{Ar} \cdot \text{NH}_3^+] \, [\text{HNO}_2]. \qquad (2)$$

They did not study the detailed variation of the reaction rate with acidity and so they had no direct evidence that the protonated amine was the reacting species, but they did find that all their amines reacted at about the same rate. Since the amines were almost completely protonated, this equivalence of reaction rates is most simply explained by assuming that the conjugate acids are the reacting species and that these are of equal reactivity. Other workers,[20] using greater concentrations of hydrochloric acid, confirmed the second-order kinetics but found marked differences in the reactivity of different amines.

In contrast to equation (2), the deamination of methylamine was shown by Taylor[21] to give third-order kinetics in a form which can be expressed by equation (3):

$$\text{Rate} = k[\text{R} \cdot \text{NH}_2] \, [\text{HNO}_2]^2. \qquad (3)$$

The same kinetic form was obtained for the reaction of ammonia with nitrous acid[21] and for the reaction of several other amino-compounds including dimethylamine.[22] The last result suggests that the kinetic form of equation (3) can be generally associated with a rate-determining nitrosation.

Some years later, an equivalent kinetic equation was obtained by

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* In all the kinetic equations in this Review, the concentration terms refer to the molecular or ionic concentration of the stated species, not to the stoicheiometric concentration unless [as for the conditions of eqn. (2)] this is effectively equivalent to the former.

[19] A. Hantzsch and M. Schümann, *Ber,*, 1899, **32**, 1691.
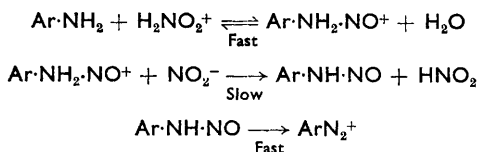[20] J. Boeseken, W. F. Brandsma, and H. A. J. Schoutissen, *Proc. Acad. Sci., Amsterdam*, 1920, **23**, 249.
[21] T. W. J. Taylor, *J.*, 1928, 1099.
[22] T. W. J. Taylor and L. S. Price, *J.*, 1929, 2052.

Schmid[23] for the diazotisation of aniline in sulphuric acid at acidities ($\sim$0·2M) somewhat higher than those used by previous workers. Schmid did not refer to the earlier work leading to equation (2).

It is not easy to reconcile equation (2) with equation (3) and so the early theories of diazotisation were based on the acceptance of one of these kinetic forms and on the rejection of the other. Several groups of workers considered that the second molecule of nitrous acid implied in equation (3) was in some way "spurious", and that only the kinetic form of equation (2) need be considered. This point of view was put forward by Earl and Hills[24] with reference to diazotisation, and by Dusenbury and Powell[25] with reference to deamination; both arguments were illustrated by results which were considered to conflict with equation (3). However, later workers have confirmed this kinetic form for both diazotisation[26] and deamination.[27]

Two interpretations were based on the third-order equation. Kenner[28] suggested a mechanism involving the nitrosation of the free amine followed by a slow proton transfer to a nitrite ion (Scheme 1). This would give the

$$Ar \cdot NH_2 + H_2NO_2{}^+ \underset{\text{Fast}}{\rightleftharpoons} Ar \cdot NH_2 \cdot NO^+ + H_2O$$

$$Ar \cdot NH_2 \cdot NO^+ + NO_2{}^- \underset{\text{Slow}}{\longrightarrow} Ar \cdot NH \cdot NO + HNO_2$$

$$Ar \cdot NH \cdot NO \underset{\text{Fast}}{\longrightarrow} ArN_2{}^+$$

SCHEME 1.

correct kinetic form, for two nitrous acid molecules are effectively involved in the transition state, but the slow proton loss implies that diazotisation should be subject to general base-catalysis. Austin has since shown[29] that the acetate ion cannot take the place of the nitrite ion in aliphatic deamination, and although some buffer catalysis is observed in diazotisation this is associated with a more complex kinetic form (see below). Hammett[30] suggested that the third-order form arose from nitrosation by nitrous anhydride (Scheme 2). This interpretation has now been shown to be correct and has also led to the reconciliation of equations (2) and (3); however, it was not immediately accepted and is not even mentioned in some later Reviews.[31]

[23] H. Schmid, Z. Electrochem., 1936, 42, 579.
[24] J. C. Earl and N. G. Hills, J., 1939, 1089.
[25] J. H. Dusenbury and R. E. Powell, J. Amer. Chem. Soc., 1951, 73, 3266, 3269.
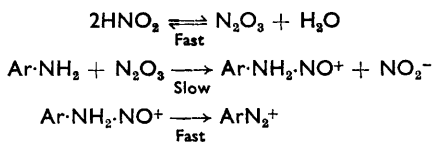[26] L. F. Larkworthy, J., 1959, 3116.
[27] (a) A. T. Austin, E. D. Hughes, C. K. Ingold, and J. H. Ridd, J. Amer. Chem. Soc., 1952, 74, 555; (b) G. J. Ewing and N. Bauer, J. Phys. Chem., 1958, 62, 1449.
[28] J. Kenner, Chem. and Ind., 1941, 19, 443.
[29] A. T. Austin, Ph.D. Thesis, London, 1950.
[30] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Inc., New York, 1940, p. 294.
[31] H. H. Hodgson and W. H. H. Norris, J. Soc. Dyers and Colourists, 1949, 65, 226; J. C. Earl, Research, 1950, 3, 120.

$$2HNO_2 \underset{Fast}{\rightleftharpoons} N_2O_3 + H_3O$$

$$Ar \cdot NH_2 + N_2O_3 \underset{Slow}{\longrightarrow} Ar \cdot NH_2 \cdot NO^+ + NO_2^-$$

$$Ar \cdot NH_2 \cdot NO^+ \underset{Fast}{\longrightarrow} ArN_2^+$$

SCHEME 2.

Unlike the mechanism outlined in Scheme 1, and also unlike those suggested by other workers,[31] the mechanism of Scheme 2 has, as its first stage, a potentially slow inorganic reaction. This distinction provides a simple way of establishing the truth of Hammett's suggestion.

The evidence for this slow stage has been obtained by decreasing the acidity.[32,33] With reactant concentrations of $\sim 10^{-3}$M in 0·002M-perchloric acid, the concentration of the free amine is sufficient to react with the nitrous anhydride before a significant proportion of the nitrous anhydride can undergo hydrolysis: the rate-determining stage then shifts to the rate of formation of nitrous anhydride and the kinetic form is as equation (4):

$$\text{Rate} = k[HNO_2]^2. \tag{4}$$

The reaction rate is then effectively independent of the concentration of the amine, and also, over a limited range of basicity, independent of the nature of the amine. Equations (3) and (4) together indicate that the nitrosating agent is nitrous anhydride, and that the later stages of equation (1) do not influence the reaction rate.[33]

The acidity used in establishing equation (4) is that used by Hantzsch and Schümann,[19] although these authors used hydrochloric acid and would thereby introduce a small amount of chloride ion catalysis. There is little doubt that Hantzsch and Schümann were essentially observing diazotisation according to equation (4), but, since they worked with equal concentrations of the two reactants, they could not distinguish between equations (2) and (4). The analysis of their results in terms of equation (4) explains both the kinetic form and the equal reactivity of the amines.

Studies of ^{18}O-exchange between nitrous acid and water have provided further support for the intermediate formation of nitrous anhydride. The equilibrium concentration of nitrous anhydride in these solutions is very small and so, in the absence of the amine, the nitrous anhydride formed according to equation (4) should rapidly undergo hydrolysis to nitrous acid, exchanging one oxygen atom with the medium in the overall process. The rate of ^{18}O-exchange between nitrous acid and water, there-fore, provides a maximum value* for the possible rate of formation of nitrous anhydride. Bunton, Llewellyn, and Stedman[35] have shown that,

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* A maximum value because exchange could occur by other mechanisms besides the intermediate formation of nitrous anhydride; one other mechanism[34] is known to become important when the nitrite ion concentration is low.

[32] E. D. Hughes, C. K. Ingold, and J. H. Ridd, *J.*, 1958, 65.
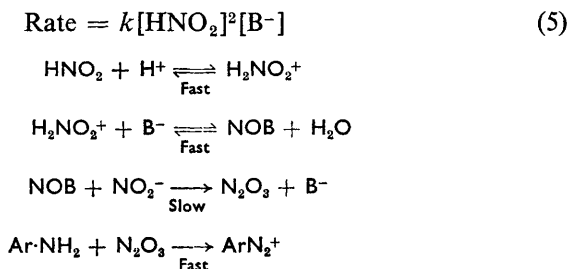
[33] E. D. Hughes, C. K. Ingold, and J. H. Ridd, *J.*, 1958, 88.

[34] C. A. Bunton and G. Stedman, *J.*, 1959, 3466.

[35] C. A. Bunton, D. R. Llewellyn, and G. Stedman, *Chem. Soc. Special Publ.*, 1957, No. 10, 113; *J.*, 1959, 568.

at very low acidities and at high concentrations of nitrite ion, the rate of this oxygen exchange is second-order with respect to nitrous acid and in fair agreement with the rate of diazotisation according to equation (4). More recently, diazotisation and oxygen exchange have been compared under identical conditions;[36] the reaction rates are then almost identical. Hence the nitrosation of the amine is preceded by a reaction in which two molecules of nitrous acid come together with the breaking of one N–O bond to form an intermediate, the concentration of which is proportional to $[HNO_2]^2$ (cf. eqn. 3). These observations establish the intermediate as nitrous anhydride.

The absence of the amine concentration from equation (4) was first illustrated[37] in studies of diazotisation in buffer solutions containing an excess of sodium nitrite; the plot of the percentage reaction against time is then linear because the concentration of molecular nitrous acid in the solution is maintained constant by the ready prototropic equilibration. However, the reaction in buffer solutions is complicated by base-catalysis of the formation of nitrous anhydride; this apparently operates[33,38] through the sequence of reactions shown in Scheme 3 (where B^- is the buffer base) and leads to the kinetic form shown in equation (5).

$$\text{Rate} = k[HNO_2]^2[B^-] \qquad (5)$$

$$HNO_2 + H^+ \underset{\text{Fast}}{\rightleftharpoons} H_2NO_2^+$$

$$H_2NO_2^+ + B^- \underset{\text{Fast}}{\rightleftharpoons} NOB + H_2O$$

$$NOB + NO_2^- \underset{\text{Slow}}{\longrightarrow} N_2O_3 + B^-$$

$$Ar \cdot NH_2 + N_2O_3 \underset{\text{Fast}}{\longrightarrow} ArN_2^+$$

SCHEME 3.

The timing of the stages in Scheme 3 is that observed for diazotisation in phthalate buffers. In acetate buffers, and with higher concentrations of nitrite ions, there is some evidence that the kinetic form of equation (6) is obtained, corresponding to a change whereby the second stage of Scheme 3 becomes rate-determining:[39,40]

$$\text{Rate} = k[HNO_2][B^-][H^+] \qquad (6)$$
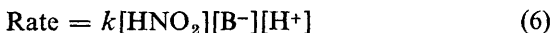
Other authors[40] have suggested that equation (6) corresponds to a general

[36] C. A. Bunton, J. E. Burch, B. C. Challis, and J. H. Ridd, unpublished work.
[37] E. D. Hughes, C. K. Ingold, and J. H. Ridd, Nature, 1950, 166, 642.
[38] E. D. Hughes and J. H. Ridd, J., 1958, 70.
[39] G. Stedman, J., 1960, 1702.
[40] J. O. Edwards, J. R. Abbott, H. R. Ellison, and J. Nyberg, J. Phys. Chem., 1959, 63, 359.

acid-catalysed formation of the nitrosonium ion, but this is inconsistent*
with experiments involving ^{18}O-exchange.[41] The direct nitrosation of the
amine by the mixed anhydrides (NOB) may make a small contribution to
the reaction rate.

Most of the available results on the reaction of amines with nitrous
anhydride according to equation (3) are summarised in Table 1. They
show that, for the aromatic amines, there is a fair correlation between
reactivity and basicity (cf. ref. 26) but that this does not hold if the aliphatic
amines are included; the latter are far less reactive than their high basicity
would suggest. The equilibrium constant for the formation of nitrous
anhydride $(K = [N_2O_3]/[HNO_2]^2)$ is known[42] to be about 0·2 at 20° and
so the true rate coefficient for the interaction of the free amine with mole-
cular nitrous anhydride can be estimated. For aniline, this rate coefficient
[defined by equation (7)] is about 10^7 mole^{-1} sec.$^{-1}$ l. at 25°; i.e., it is
considerably less than the encounter rate of the two species.[43] This result
is of interest in connexion with the reaction of the amines with nitrosyl
halides described below.

$$\text{Rate} = k[\text{R·NH}_2][\text{N}_2\text{O}_3] \qquad (7)$$

TABLE 1. *Nitrosation by nitrous anhydride.*[21,22,26,44]

Aniline deriv.	Temp.	$10^{-5}k$ (eqn. 3)^a	Amine^b	Temp.	$10^{-5}k$ (eqn. 3)^a
p-H	25°	27	Ammonia	25°	0·04
p-H	0	3·11	Methylamine	25	4·8
p-OMe	0	5·56	Propylamine	25	2·8
p-Cl	0	0·92	Dimethylamine	25	4·0
p-NMe$_3$$^+$	0	0·14			

^{a} Rate coefficients in mole^{-2} sec.$^{-1}$ l.^{2}.
^{b} Some authors have emphasised the experimental difficulties in studying these
reactions because of the decomposition of nitrous acid (cf. ref. 27*b*). These figures are
therefore likely to be less accurate than those for the aromatic amines.

The Nitrosyl Halide Mechanism.—Nitrosation by the nitrosyl halides
becomes important first in the presence of rather low concentrations of
halide ions; thus, nitrosation by nitrosyl chloride is the predominant
mechanism for the diazotisation of aniline in concentrations of hydro-

* The interpretation of equation (6) by a new reaction path is also inconsistent with
an interesting kinetic principle. The transition from equation (5) to equation (6) is
apparently brought about by increasing the concentration of nitrite ions and therefore
also that of nitrous acid. If the order with respect to a chemical species is reduced when
the concentration of that species is increased, this cannot result from the incursion of a
new mechanism of lower order because the relative contribution of such a mechanism
would be decreased by the change in concentration. The change in kinetic form must
therefore result from a shift of the rate-determining step to an earlier stage of the same
reaction path.

[41] C. A. Bunton and M. Masui, *J.*, 1960, 304.
[42] T. A. Turney, *J.*, 1960, 4263; C. A. Bunton and G. Stedman, *J.*, 1958, 2440.
[43] Cf. S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Co.
Inc., New York, 1960, p. 497.
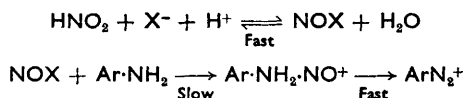[44] H. Schmid, *Monatsh.*, 1954, **85**, 424.

chloric acid exceeding about 0·1M.* These mechanisms can also operate for aliphatic deamination,[45] although they must be unimportant in the feebly acidic solutions usually employed.

Several of the early papers contain evidence that diazotisation is catalysed by hydrochloric acid,[46] but the kinetic form of this catalysis was first elucidated by Schmid[47] in 1937. He found that the effect of the halide ion (X^-) was to add the kinetic term shown in equation (8) (where $X = Br$ or Cl) to the background rate of diazotisation given by equation (3):

$$\text{Rate} = k[\text{Ar·NH}_2][\text{H}^+][\text{HNO}_2][\text{X}^-]. \qquad (8)$$

For bromide ions, the catalytic coefficient [k in eqn. (8)] is more than 100 times as great as for chloride ions. Hammett[30] pointed out that this catalytic term is equivalent to the concentration product $[\text{Ar·NH}_2][\text{NOX}]$ and that the catalysis can therefore be considered to operate as shown in Scheme 4.

As with the nitrous anhydride mechanism (Scheme 2), the first stage of Scheme 4 is a potentially rate-determining inorganic reaction in which the amine is not involved. However, it has not yet been found possible to

$$\text{HNO}_2 + \text{X}^- + \text{H}^+ \underset{\text{Fast}}{\rightleftharpoons} \text{NOX} + \text{H}_2\text{O}$$

$$\text{NOX} + \text{Ar·NH}_2 \underset{\text{Slow}}{\longrightarrow} \text{Ar·NH}_2\text{·NO}^+ \underset{\text{Fast}}{\longrightarrow} \text{ArN}_2^+$$

SCHEME 4.

adjust conditions such that the rate of formation of nitrosyl chloride is rate-determining in diazotisation,† but the corresponding stage can be made rate-determining in bromide-ion catalysis[49] and more easily in iodide-ion catalysis;[49] the kinetic form is then as equation (9):

$$\text{Rate} = k[\text{HNO}_2][\text{H}^+][\text{X}^-]. \qquad (9)$$

This equation has been interpreted[33] as a rate-determining attack of the halide ion on the nitrous acidium ion (H_2NO_2^+). It is interesting that the normal oxidation of iodide ions by nitrous acid is not observed when diazotisation occurs under the conditions of equation (9); this suggests that the oxidation also involves nitrosyl iodide and that the nitrosyl iodide reacts so rapidly with the amine that the alternative possibility of homolysis (leading to oxidation) is not observed.

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* This value is for diazotisation with 10^{-3}M-nitrous acid. With greater concentrations of nitrous acid, the relative importance of the nitrous anhydride mechanism is increased because the corresponding kinetic term involves $[\text{HNO}_2]^{-2}$.

† This has been achieved in the related reaction of nitrous acid with azide ions[48] (see ref. 48).

[45] H. Schmid and R. Pfeifer, *Monatsh.*, 1953, **84**, 829, 842.

[46] *E.g.*, H. A. J. Schoutissen, *J. Amer. Chem. Soc.*, 1936, **58**, 259.

[47] H. Schmid, *Z. Electrochem.*, 1937, **43**, 626; H. Schmid and G. Muhr, *Ber.*, 1937, **70**, 421.

[48] G. Stedman, *J.*, 1959, 2949.

[49] E. D. Hughes and J. H. Ridd, *J.*, 1958, 82.

Some evidence is available on the reaction of molecular nitrosyl halides with amines. The rate coefficients of equation (8) contain implicitly the equilibrium constants for the formation of the nitrosyl halides, and these equilibrium constants are known for both nitrosyl chloride and nitrosyl bromide at several temperatures. From the rate coefficients [eqn. (8)] and the equilibrium constants, Schmid and his co-workers[50] have obtained the true rate coefficients for the reaction of the free amines with the molecular nitrosyl halides, i.e., the rate coefficients (k) in equation (10):

$$\text{Rate} = k[\text{Ar·NH}_2][\text{NOX}]. \tag{10}$$

Some of these values for the reaction of amines with nitrosyl chloride are given in Table 2. Schmid et al. stressed the dependence on the basicity of the amine but this is very slight (for comparison, p-toluidine is more basic than o-chloroaniline by a factor of 250) and the most interesting features of these results lie in their similarities to encounter reactions. The values of the rate-coefficients approach that expected for the frequency of bi-molecular encounters in aqueous solution (leading to a rate coefficient of $\sim 10^{10}$ mole^{-2} sec.$^{-1}$ l.^{2})[43] and the activation energy calculated from the temperature dependence of k [eqn. (10)] is also consistent with this inter-pretation. The value obtained for the diazotisation of aniline is 4560 cal. mole^{-1} and that for the diazotisation of p-chloroaniline is 4950 cal. mole^{-1}. In comparison, the temperature-dependence of the viscosity of aqueous solutions gives diffusion-controlled reactions[43] an apparent activation energy of about 4 kcal. mole^{-1} at 25°. The results for the reaction of amines with nitrosyl bromide are less complete but very similar; for aniline, the rate coefficient k [of eqn. (10)] is $3 \cdot 2 \times 10^9$ mole^{-2} sec.$^{-1}$ l.^{2}. Although the calculation of these rate coefficients requires several approximations, the consistency of the results makes it probable that the reaction of these amines with the nitrosyl halides approaches closely to a diffusion-controlled process.

TABLE 2. *Nitrosation by nitrosyl chloride.*[50]

Amine	$10^{-9}k$ (eqn. 10)^a	Amine	$10^{-9}k$ (eqn. 10)^a
o-Chloroaniline	1·16	o-Toluidine	2·44
m-Chloroaniline	1·63	m-Toluidine	2·70
p-Chloroaniline	1·89	p-Toluidine	3·0
Aniline	2.60		

^{a} In mole^{-1} sec.$^{-1}$ l. at 25°.

Acid-catalysed Mechanisms of Nitrosation.—If the mechanisms of diazotisation were limited to those just described, the reaction of most amines with nitrous acid would occur very slowly in molar concentrations of perchloric or sulphuric acid, for the perchlorate ion and the sulphate
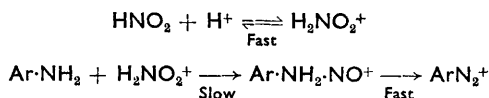
[50] H. Schmid and E. Hallaba, *Monatsh.*, 1956, **87**, 560; H. Schmid and M. G. Fouad, *ibid.*, 1957, **88**, 631; H. Schmid and C. Essler, *ibid.*, p. 1110.

ion do not form covalent nitrosating agents and, as implied in equation (3), the rate of diazotisation by the nitrous anhydride mechanism decreases rapidly with acidity, because of the protonation of the free amine. In fact, for amines such as aniline, the reaction rate first decreases and then increases with acidity; the subsequent increase comes from the incursion of new acid-catalysed mechanisms of diazotisation.

The first of the acid-catalysed mechanisms to be identified[51] had the kinetic form shown in equation (11):

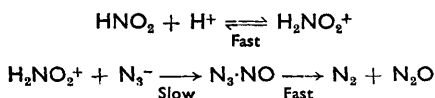$$\text{Rate} = k[\text{Ar·NH}_2][\text{HNO}_2][\text{H}^+]; \qquad (11)$$

this result has been interpreted[33] as a rate-determining reaction of the free amine with the nitrous acidium ion ($H_2NO_2^+$) (Scheme 5):

$$\text{HNO}_2 + \text{H}^+ \underset{\text{Fast}}{\rightleftharpoons} \text{H}_2\text{NO}_2^+$$

$$\text{Ar·NH}_2 + \text{H}_2\text{NO}_2^+ \underset{\text{Slow}}{\longrightarrow} \text{Ar·NH}_2\text{·NO}^+ \underset{\text{Fast}}{\longrightarrow} \text{ArN}_2^+$$

SCHEME 5.

Of several other possible interpretations, that involving a reaction of the free amine with an equilibrium concentration of the nitrosonium ion (formed by the reaction $HNO_2 + H^+ \rightleftharpoons NO^+ + H_2O$) was rejected[33] from a consideration of the rate of ^{18}O-exchange between nitrous acid and water. In rejecting this mechanism, it is implied that the ON–OH bond is not completely broken until the interaction with the amine. This mechanistic detail has recently received support from a study of the reaction of azide ions with nitrous acid.[34] The reaction has the kinetic form of equation (12) and apparently occurs as shown in Scheme 6; the suggested intermediate (N_3·NO) can be isolated at low temperatures.[52]

$$\text{Rate} = k[\text{N}_3^-][\text{HNO}_2][\text{H}^+] \qquad (12)$$

$$\text{HNO}_2 + \text{H}^+ \underset{\text{Fast}}{\rightleftharpoons} \text{H}_2\text{NO}_2^+$$

$$\text{H}_2\text{NO}_2^+ + \text{N}_3^- \underset{\text{Slow}}{\longrightarrow} \text{N}_3\text{·NO} \underset{\text{Fast}}{\longrightarrow} \text{N}_2 + \text{N}_2\text{O}$$

SCHEME 6.

The rate coefficient of equation (12) is about ten times greater than that observed with a number of amines according to equation (11); the nucleophilic powers of azide ions and of such amines as o-chloroaniline towards the nitrous acidium ion are therefore not very different. When the azide reaction is carried out in water containing an excess of ^{18}O, the nitrous oxide produced does not contain the equilibrium concentration of isotopic oxygen;[34] this shows that the nitrosation stage is not preceded by the

[51] E. D. Hughes, C. K. Ingold, and J. H. Ridd, *J.*, 1958, 77.
[52] H. W. Lucien, *J. Amer. Chem. Soc.*, 1958, **80**, 4458.

formation of the nitrosonium ion in a fast equilibrium step. This conclusion should apply also to the amine reaction.

The nitrous acidium ion appears to be a more reactive nitrosating agent than nitrous anhydride, for Larkworthy[53] has shown that the rate of reaction according to equation (11) is much less sensitive to the basicity of the amine than that according to equation (3). Diazotisation by the nitrous acidium ion is, therefore, observed most easily with the less basic amines: equation (11) accounts completely for the diazotisation of p-nitroaniline in concentrations of perchloric acid between 0·01 and 0·5M.[53] At higher acidities, certain new factors complicate the kinetic form and the reaction rate increases above that given by equation (11).

The analysis of kinetics in terms of reaction mechanisms becomes considerably more difficult at acidities above 0·5M; the conventional assumptions concerning acidity functions are proving inadequate,* but there is, as yet, no simple alternative approach. Diazotisation should be more suitable than most reactions for mechanistic analysis, because the protonation of the primary aromatic amines should generally follow H_0 (since H_0 is defined from examples of this equilibrium) and because the equilibrium concentration of the nitrosonium ion in perchloric acid media has been shown[55] to follow J_0†. Nevertheless, the following discussion is restricted to the two main factors involved.

One of these appears to be a medium effect, caused equally by perchloric acid and sodium perchlorate. With the less basic amines this is the only important factor up to acidities of 3·0M; thus the diazotisation of p-nitroaniline in aqueous perchloric acid, containing sodium perchlorate to maintain the ionic strength (and hence the medium effect) constant, follows equation (11) with the substitution of h_0 for [H⁺] up to [H⁺] = 3·0M.[57] The exponential dependence of this medium effect on the concentration of sodium perchlorate and the dependence on the nature of the metal ion[57] show that the effect is not an example of specific perchlorate-ion catalysis, analogous to the specific halide-ion catalysis discussed above.

The other factor is the incursion of a new kinetic term of the form given in equation (13):[57]

$$\text{Rate} = k[\text{Ar·NH}_3{}^+][\text{HNO}_2]h_0 \qquad (13)$$

This term has only been observed with the more basic amines, and it has been interpreted as the effective nitrosation of the *protonated* amine in

* This is shown most clearly in recent discussions of protonation and hydrogen-isotope exchange in aromatic rings (cf. ref. 54).

† The acidity function nomenclature in this Review follows that of Paul and Long. (ref. 56).

[53] L. F. Larkworthy, *J.*, 1959, 3304.

[54] A. J. Kresge and Y. Chiang, *Proc. Chem. Soc.*, 1961, 81.

[55] N. C. Deno, H. E. Berkheimer, W. L. Evans, and H. J. Peterson, *J. Amer. Chem. Soc.*, 1959, **81**, 2344.
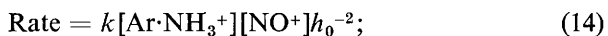
[56] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

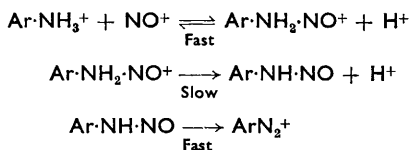[57] B. C. Challis and J. H. Ridd, *Proc. Chem. Soc.*, 1961, 173.

such a way that the proton being displaced is still present in the transition state.[57] The details of this mechanism remain to be established. The above interpretation is not a return to the old idea that the protonation of the amine is necessary before diazotisation will occur: reaction takes place much more readily through the free amine but, if the amine is almost entirely protonated, the interaction of the nitrosating agent with the protonated amine can apparently become significant.

Nitrosation by the nitrosonium ion would be expected to become more important as the acidity is increased and the incursion of this mechanism should be first observed with the less basic amines, for the nitrosonium ion should be the most reactive nitrosating agent. The kinetic form of the reaction of benzamide with nitrous acid in strong sulphuric acid has been explained in this way.[58]

Diazotisation at High Acidities.—Diazotisation in about 60% perchloric acid and that in about 60% sulphuric acid have to be considered separately, partly because the stoicheiometric nitrous acid is then essentially present as ionised nitrosonium salts,[59] and partly because the kinetic form is very different from any previously discussed. In the perchloric acid media, diazotisation of aniline, *p*-toluidine, and *p*-nitroaniline follows equation (14):[60]

$$\text{Rate} = k[\text{Ar·NH}_3{}^+][\text{NO}^+]h_0{}^{-2}; \qquad (14)$$

the reaction rate therefore decreases very rapidly with acidity (*e.g.*, by a factor of 10 between 9M- and 9·5M-perchloric acid). The results in sulphuric acid media are similar, although the decrease with acidity (when expressed by the H_0 acidity function) is slightly greater. In contrast to diazotisation in dilute acid, the reaction at high acidities shows a large solvent isotope effect with deuterium[60] ($k_H/k_D = 10$). It is difficult to reconcile the kinetic form and the isotope effect observed at high aciditieswith any mechanism for the rate-determining nitrosation of the amine; it seems probable that a rapid reversible nitrosation is followed by a later slow stage involving a proton transfer to the medium, and one such mechanism is shown in Scheme 7. The isotope effect could then be derived partly from a change in the position of the initial equilibrium and partly from the subsequent slow stage.

$$\text{Ar·NH}_3{}^+ + \text{NO}^+ \underset{\text{Fast}}{\rightleftharpoons} \text{Ar·NH}_2\text{·NO}^+ + \text{H}^+$$

$$\text{Ar·NH}_2\text{·NO}^+ \underset{\text{Slow}}{\longrightarrow} \text{Ar·NH·NO} + \text{H}^+$$

$$\text{Ar·NH·NO} \underset{\text{Fast}}{\longrightarrow} \text{ArN}_2{}^+$$

SCHEME 7.

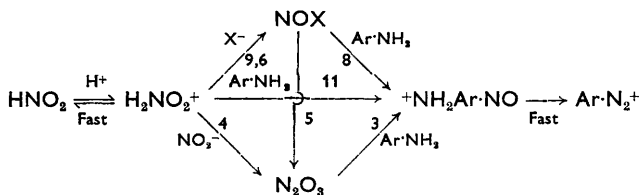[58] H. Ladenheim and M. L. Bender, *J. Amer. Chem. Soc.*, 1960, **82**, 1895.
[59] K. Singer and P. A. Vamplew, *J.*, 1956, 3971; N. S. Bayliss and D. W. Watts, *Austral. J. Chem.*, 1956, **9**, 319.
[60] B. C. Challis and J. H. Ridd, *Proc. Chem. Soc.*, 1960, 245.

It is easy to see why the rate-determining step should change in this way as the acidity is increased. The rate of proton transfer from positive nitrogen to the medium is known to decrease with increasing acidity;[61] thus at high acidities the N-protons of the anilinium ion contribute a separate peak to the proton magnetic resonance spectrum.[62] In contrast, the rate of displacement of the nitrosonium ion from $Ar \cdot NH_2 \cdot NO^+$ by a proton may well increase with acidity, for the transition state associated with the nitrosation of the protonated amine must provide a path for the corresponding reverse reaction. The proportion of the protonated nitrosamine ($Ar \cdot NH_2 \cdot NO^+$) reverting to the reactants should therefore increase with acidity, and this would tend to change the rate-determining step in the direction discussed above.

This change in the rate-determining step makes it possible to understand why some of the more basic amines undergo C-nitrosation instead of diazotisation at somewhat higher acidities.[63] A slow proton transfer at high acidities must provide a barrier to diazotisation analogous to that of the N-methyl group in the reaction of secondary amines with nitrous acid. It is therefore reasonable that, at high acidities, a process analogous to the Fischer–Hepp rearrangement (leading to C-nitrosation) should be observed with primary aromatic amines.

Nitrosation Mechanisms: General Survey.—The suggested mechanisms for diazotisation and deamination at low acidities ($[H^+] < 0.5M$) can be simply illustrated by the network of reaction paths in Scheme 8;[33] in this representation the symbol X^- stands for any Brönsted base in the medium, except the amine molecule, the nitrite ion, and bases derived from the solvent. The six numbered arrows correspond to the six types of rate-

SCHEME 8.

determining step detected in the kinetic study, and the numbers designate the corresponding kinetic equations.

This network of reaction paths has been of value in interpreting the kinetics of other nitrosations as well as diazotisation and deamination. The corresponding forms of a number of the kinetic equations listed in Scheme 8 have been observed by Stedman[39] in the reaction of nitrous acid

[61] C. G. Swain, J. T. McKnight, M. M. Labes, and V. P. Kreiter, *J. Amer. Chem. Soc.*, 1954, **76**, 4243.
[62] B. N. Figgis, personal communication.
[63] L. Blangey, *Helv. Chim. Acta*, 1938, **21**, 1579.

with hydrazoic acid, and by Bunton, Dahn, and their co-workers[64] in the oxidation of ascorbic acid by nitrous acid (this appears to involve a preliminary O-nitrosation). These related studies confirm the complexity of nitrosation kinetics and extend the range of possible substrates.

The first stage of Scheme 8, the protonation of nitrous acid, appears necessary for all nitrosation reactions. The nature of the next stage depends on the concentrations of the different nucleophiles present in the solution and on the discrimination shown by the nitrous acidium ion. Rate co-efficients for the reaction of different nucleophiles with the nitrous acidium ion are given in Table 3 in terms of the rate coefficient (k) of equation (15) [this generalises equations (4), (9), and (11) to include all possible substrates (S)]:

$$\text{Rate} = k[\text{S}][\text{HNO}_2][\text{H}^+]. \qquad (15)$$

Some of the values of k in Table 3 may require correction because of uncertainties in the equilibrium constants used in the calculations (cf. ref. 48), but the results are sufficient to show that the nitrous acidium ion does not discriminate markedly between different nucleophiles. When the values of k are considered as a function of the basicity or nucleophilicity of the substrate, the results for neutral nucleophiles* appear to be approaching a limiting value and the results for negative nucleophiles may also be near a limiting value, the latter limit being about 10 times the former.

TABLE 3.   *Nitrosation by the nitrous acidium ion.*

Neutral substrates			Negative substrates		
	k (eqn. 15)[a]	Ref.		k (eqn. 15)[a]	Ref.
o-Chloroaniline	175	33	Azide ion	2340	48
p-Nitroaniline	161	53	Acetate ion	2200	39
o-Nitroaniline	145	53	Ascorbate ion	~2000	64
Ascorbic acid	63	64	Nitrite ion	1893	33
Hydrazoic acid	33·7	65	Thiocyanate ion	1460	48
Water[b]	4	34	Iodide ion	1370	33
2,4-Dinitroaniline	3·7	53	Bromide ion	1170	33
			Chloride ion	975	48
			Nitrate ion[c]	0·26	66

[a]In mole^{-2} sec.$^{-1}$ l.^{2} at 0°.   [b]From ^{18}O-exchange.   [c]This value refers to 25°.

It is interesting to speculate on whether this difference between the two limits comes largely from the effect of charge on the encounter rate of the two reactants (the difference is of the right order; cf. ref. 67), but the little

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* The value for aniline is not given because of complications arising from the nitrous anhydride mechanism, but this value cannot be significantly greater than that for o-chloroaniline.

[64] C. A. Bunton, H. Dahn, and L. Loewe, *Nature*, 1959, **183**, 163; H. Dahn, L. Loewe, E. Lüscher, and R. Menassé, *Helv. Chim. Acta*, 1960, **43**, 287, and following papers.
[65] G. Stedman, *J.*, 1959, 2943.
[66] E. Abel and H. Schmid, *Z. phys. Chem.*, 1928, **136**, 430, and preceding papers.
[67] P. Debye, *Trans. Electrochem. Soc.*, 1942, **82**, 265.

information at present available on activation energies does not permit a definite decision. Indeed, very little is known about the details of these nitrous acidium ion reactions. Lidstone[68] has suggested that N-protonation is involved, making the nitrous acidium ion isoelectronic with formic acid, but it is still possible that the proton transfer is part of the rate-determining step.

The Product-determining stage

The stability of aromatic diazonium ions enables them to be considered as the end-product in the reaction of aromatic amines with nitrous acid. However, in the aliphatic series, the corresponding diazonium ions are only hypothetical intermediates; the final products are a mixture of compounds derived by substitution, elimination, and rearrangement. The kinetic studies show that the first stage of deamination involves N-nitrosation: it remains to consider the conversion of the resulting nitros-amine into the final products.

Until recently, primary aliphatic nitrosamines were unknown, but monomethylnitrosamine has now been obtained by reaction of methyl-amine with an ethereal solution of nitrosyl chloride at low temperatures.[69] The compound was identified from the similarity of its ultraviolet spectrum to that of dimethylnitrosamine and was shown to decompose into di-azomethane at higher temperatures. This mode of decomposition cannot be generally important for the simpler aliphatic amines* in water or acetic acid for the direct substitution products are formed without significant isotopic exchange between the α-hydrogen atoms and the solution.[70] In aqueous media at normal temperatures, the primary nitrosamine almost certainly rearranges to give, first, the diazohydroxide, then the diazonium ion, and finally a carbonium ion (cf. eqn. 1).

The carbonium ion interpretation of deamination was being discussed as early as 1928,[71] when very little detailed information was available on the properties of carbonium ion reactions. By the early 1950's the correct-ness of the carbonium ion interpretation was generally accepted and since then the main interest has come from an analysis of the differences between deamination and related S_N1 reactions. In discussing the present position, it is convenient first to survey those characteristics of deamination that suggest a carbonium ion interpretation and then to discuss some special features which distinguish deamination from other carbonium ion reactions.

Evidence for Carbonium Ion Intermediates.—Since the nitrosation is

* This decomposition by proton loss is important with amines containing an activat-ing group ($C=O$, $C\equiv N$, etc.) in the α-position: the diazo-compound is then the major product.
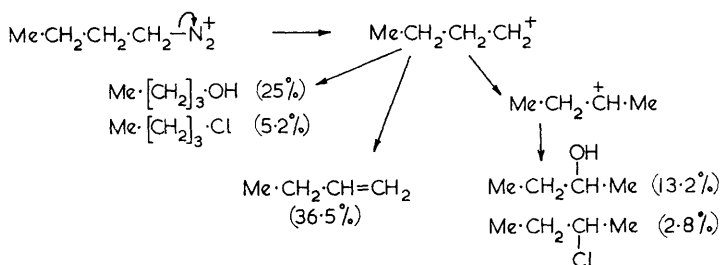
[68] A. G. Lidstone, *Chem. and Ind.*, 1959, 1316.
[69] E. Müller, H. Haiss, and W. Rundel, *Chem. Ber.*, 1960, **93**, 1541.
[70] A. Streitwieser and W. D. Schaeffer, *J. Amer. Chem. Soc.*, 1957, **79**, 2888.
[71] J. W. Baker, K. E. Cooper, and C. K. Ingold, *J.*, 1928, 426.

rate-determining, the kinetic method cannot be used to elucidate the mechanism of later reaction stages; the evidence for carbonium ion intermediates has therefore to come from the nature and stereochemistry of the products. The multiplicity of these products is illustrated for one typical amine (n-butylamine) in Scheme 9; the results suggest the intermediate formation of a carbonium ion that can react with a nucleophile, rearrange, or eliminate a proton. A recent discussion of the deamination of methylamine[72] has led to a similar conclusion. The stereochemistry of the direct substitutions shows that the reaction usually involves racemisation, accompanied by some inversion,[73] a result indicating the intermediate formation of a carbonium ion, followed rapidly by reaction with a nucleophile while one side of the carbonium ion is still partly shielded by the departing nitrogen molecule. As might be expected, the amount of racemisation increases with the stability of the carbonium ion;[70] the formation of [1-²H] butyl acetate from [1-²H]butylamine by nitrous acid in acetic acid leads to 31% racemisation (69% inversion) while the corresponding reaction of secondary butylamine leads to 72% of racemisation. Retention

$$Me \cdot CH_2 \cdot CH_2 \cdot CH_2 \overset{\frown}{-} \overset{+}{N_2} \longrightarrow Me \cdot CH_2 \cdot CH_2 \cdot CH_2^+$$

$$Me \cdot [CH_2]_3 \cdot OH \ (25\%)$$
$$Me \cdot [CH_2]_3 \cdot Cl \ (5 \cdot 2\%)$$

$$Me \cdot CH_2 \cdot \overset{+}{C}H \cdot Me$$

$$Me \cdot CH_2 \cdot CH = CH_2$$
$$(36 \cdot 5\%)$$

$$Me \cdot CH_2 \cdot \overset{OH}{\underset{|}{C}H} \cdot Me \ (13 \cdot 2\%)$$

$$Me \cdot CH_2 \cdot \overset{}{\underset{\underset{Cl}{|}}{C}H} \cdot Me \ (2 \cdot 8\%)$$

SCHEME 9.

Product composition in the deamination of n-butylamine in aqueous hydrochloric acid.[74] A later analysis[70] of the olefin fraction for deamination in acetic acid has shown that 29% of the olefin is but-2-ene (9% cis; 20% trans); this but-2-ene is presumably derived from the rearranged carbonium ion.

of configuration has been observed in the deamination of α-amino-acids,[73] as in other S_N1 reactions involving a neighbouring carboxyl group.[75]

The rearrangements of the carbon skeleton observed in deamination (e.g., the conversion of neopentylamine into t-pentyl alcohol) generally correspond to those in other S_N1 reactions.[7] Where several products are formed, the comparison of product composition with that from related S_N1 reactions has sometimes provided evidence for the same carbonium

[72] A. T. Austin, *Nature*, 1960, **188**, 1086.
[73] P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, 1950, **166**, 179.
[74] F. C. Whitmore and D. P. Langlois, *J. Amer. Chem. Soc.*, 1932, **54**, 3441.
[75] Ref. 7, p. 383.

ion intermediate; examples include some reactions of t-butyl compounds,[76] and the aqueous deamination* of allylic amines.[77]

Related comparisons involving the products formed by elimination are more difficult because of the reaction of nitrous acid with the olefins formed in deamination, but the reaction of t-butylamine with nitrous acid has been shown to give the same yield of olefin as the decomposition of the corresponding dimethylsulphonium salt under similar conditions;[79] for other substrates, some discrepancies have been reported.[79,80]

To summarize, the comparison of deamination and S_N1 reactions provides strong evidence that some deaminations involve a carbonium ion intermediate and presumptive evidence that such intermediates are generally formed.

Special Characteristics of Deamination.—The evidence for carbonium ion intermediates makes it particularly interesting to study those reactions where significant differences exist between the products of deamination and those of other S_N1 reactions, e.g., solvolysis of toluene-p-sulphonates. In part, these differences appear to arise from a lower discrimination in the deamination, so that rearrangement products that are unimportant in solvolysis become significant in deamination. Thus the deamination of n-butylamine gives a considerable amount of secondary substitution products owing to a hydrogen migration (Scheme 9), but no secondary product is obtained on solvolysis of the corresponding toluene-p-sulphonate, although studies with [1-^{2}H]butylamine show that deamination and solvolysis involve similar amounts of racemisation.[70] Primary carbonium ions rearrange to give secondary products under more drastic conditions (e.g., in Friedel–Crafts reactions) but normally discriminate in favour of direct substitution and elimination. Another apparent example of this lack of discrimination comes from the migration aptitudes of the p-methoxyphenyl and the phenyl group:[81] in the pinacol rearrangement the former migrates more rapidly by a factor of 500, but in pinacolic deamination the factor is only 1·56.

However, this lack of discrimination, which suggests that the carbonium ions derived from deamination are unusually reactive, is not a sufficient explanation of the differences observed. This is shown most clearly by the results of Cram and McCarty[82] for the acetic acid deamination of 1-methyl-2-phenylpropylamine and the acetolysis of the corresponding toluene-p-

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* These allylic deaminations in acetic acid involve less rearrangement than do acetolyses of the corresponding halides. The results have been explained in terms of a "hot" carbonium ion in the deamination,[78] but this result may also be influenced by ion-pair equilibria (cf. p. 440).

[76] L. G. Cannell and R. W. Taft, Abstracts of papers presented at the 129th Meeting of the American Chemical Society, Dallas, 1956, p. 46-N.

[77] R. H. DeWolfe and W. G. Young, *Chem. Rev.*, 1956, **56**, 753.

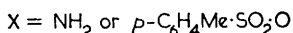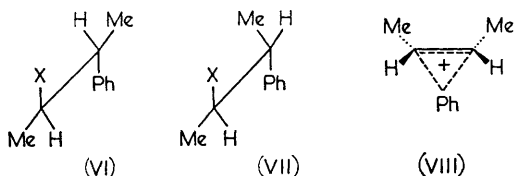[78] D. Semenow, Chin-Hua Shih, and W. G. Young, *J. Amer. Chem. Soc.*, 1958, **80**, 5472.

[79] J. S. Burgess, Ph.D. Thesis, London, 1953.

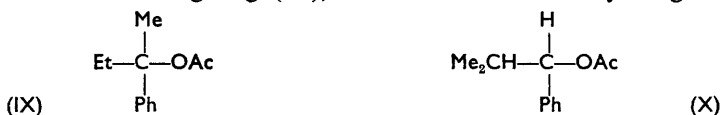[80] A. Streitwieser, *J. Org. Chem.*, 1957, **22**, 861.

[81] D. Y. Curtin and M. C. Crew, *J. Amer. Chem. Soc.*, 1954, **76**, 3719.

[82] D. J. Cram and J. E. McCarty, *J. Amer. Chem. Soc.*, 1957, **79**, 2866.

sulphonate. These compounds exist as two diastereoisomers termed *erythro** (VI) and *threo* (VII), each of which contains three β-groups (Ph, Me, H) capable of undergoing rearrangement during deamination or solvolysis. From the symmetry of the system, the rearrangement of the phenyl group gives the same structural product as the non-rearranged material but the rearrangement does have stereochemical consequences which permit its observation. Acetolysis of the toluene-*p*-sulphonates

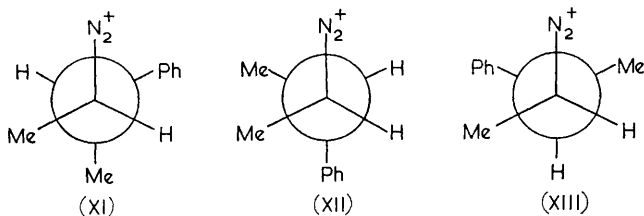$$X = NH_2 \text{ or } p\text{-}C_6H_4Me\cdot SO_2O$$

appears to be accelerated by the phenyl group and to lead to a symmetrical "phenonium" ion (illustrated for the *threo*-isomer by VIII). Some hydrogen migration is observed giving (IX), but none of the methyl migration

leading to (X). In contrast, in the deamination of the *threo*-amine (VII; $X = NH_2$), more methyl than phenyl migration occurs (ratio 1·5:1), and the amount of hydrogen migration is also increased. This result cannot simply arise from a lack of discrimination in the rearrangement for, in the deamination of the *erythro*-amine, phenyl migration exceeds methyl migration by a factor of eight.

The above example is only one of a number of unusual rearrangements observed in deamination,[83] but these can be rationalised by assuming that the mobility of groups in deamination is largely controlled by the conformations of the diazonium ion and that the group *trans* to the diazo-nitrogen atom in the most stable conformation is particularly mobile (ground-state control of migration). The three conformations of the *threo*-diazonium ions
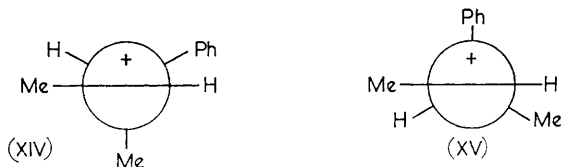
* The *erythro*-diastereoisomer is that which in one eclipsed conformation has at least two sets of similar substituents in line.
[83] Cf. D. Y. Curtin and M. C. Crew, *J. Amer. Chem. Soc.*, 1955, 77, 354; L. S. Ciereszko and J. G. Burr, *ibid.*, 1952, 74, 5431.
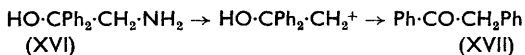
are (XI)—(XIII): conformation (XI) should be the most stable, for each bulky group is flanked on one side by a hydrogen atom. The methyl group is then in the favoured position for rearrangement. A similar argument applied to the *erythro*-isomer would place the phenyl group in the most favoured position for rearrangement.

The importance of this ground-state control can be linked to the low activation energy for the breakdown of the aliphatic diazonium ion. In the solvolysis of the toluene-*p*-sulphonates, the mobility of the β-substituents presumably facilitates the ionisation to an extent which is energetically large in comparison with the energy differences between the ground-state conformations; the relative stability of these conformations is then less revelant and the greater mobility of the phenyl groups is sufficient to determine the product. In comparison with ionisation of the toluene-*p*-sulphonate, the activation energy for heterolysis of the diazonium ion should be very small, and the contribution from the mobility of the β-substituents should be correspondingly decreased; it is, therefore, reasonable that reaction should occur in the most probable ground-state conformation rather than in that which in the sulphonates is energetically the most favourable.

The carbonium ion from (IX) should first assume conformation (XIV) but this can then rearrange to (XV) by partial rotation about the central bond. Although the methyl group should be the most mobile in conformation (XIV) (for the σ-electrons of the C-Me bond are well placed to overlap with the vacant *p*-orbital on the adjacent carbon) this would not be true in conformation (XV). Hence the above explanation requires that migration of the methyl group either occurs at the same time as the C-N$_2^+$ heterolysis or follows this process before rotation about the centre C-C bond becomes significant.

Newman projection (XIV): H and Ph at top, Me and H at sides, Me at bottom.

Newman projection (XV): Ph at top, Me and H at sides, H and Me at bottom.
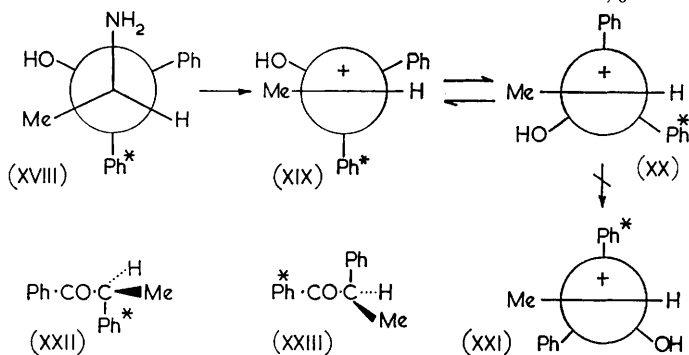
Other studies have provided evidence that some rotation can occur about the central C-C bond after the loss of nitrogen. One example concerns the pinacolic deamination of 2-amino-1,1-diphenylpropan-1-ol (XVI); in this reaction the rearranged carbonium ion is stabilised by proton loss from the hydroxy-group to form the ketone (XVII). The overall

$$HO\cdot CPh_2\cdot CH_2\cdot NH_2 \rightarrow HO\cdot CPh_2\cdot CH_2^+ \rightarrow Ph\cdot CO\cdot CH_2Ph$$
$$\text{(XVI)} \qquad\qquad\qquad\qquad \text{(XVII)}$$

reaction was shown by Bernstein and Whitmore [84] to involve about 88 % of inversion at the migration terminus. More recent work by Benjamin,

[84] H. I. Bernstein and F. C. Whitmore, *J. Amer. Chem. Soc.*, 1939, **61**, 1324.

Schaeffer, and Collins[85] has involved labelling of the amine (XVI) in one phenyl group with ^{14}C. The compound then exists as two diastereoisomers, one of which is shown in its most stable conformation as (XVIII). As before, the reaction was observed to occur with about 88% of inversion

NH₂
HO   Ph
Me   H
(XVIII)   Ph*

HO   +   Ph
Me   H
(XIX)   Ph*

Ph
+
Me   H
HO   Ph*
(XX)

Ph*
+
Me   H
Ph   OH
(XXI)

Ph·CO·C◀Me
      H
      Ph*
(XXII)

Ph
Ph*·CO·C···H
          Me
(XXIII)

to give the ketone (XXII) and 12% of retention to give the isomer (XXIII). However, the interesting new result is that in the reaction of the diastereoisomer (XVIII) the ketone formed with inversion involved essentially complete migration of the labelled phenyl group, while that formed with retention correspondingly involved migration of the unlabelled phenyl group. The formation of the latter product indicates that the lifetime of the carbonium ion (XIX) is sufficiently long to permit some part of the material to undergo the partial rotation to (XX). However, the absence of labelled-phenyl migration in the ketone of retained configuration indicates that the carbonium ion does not have time to reach conformation (XXI). It appears therefore that the deamination of these compounds produces a reactive, open* carbonium ion whose lifetime is rather less than the period of rotation about the central C–C bond.

This conclusion concerning reactive open carbonium ions has not been universally accepted and it has been suggested[70,80] that a considerable part of the rearrangement and substitution in deamination can occur at the same time as the loss of nitrogen, *i.e.*, that the substitution is at least partly an S_N2 reaction of the diazonium ion. The ready breakdown of aliphatic diazonium ions is considered so to reduce the differences in the activation energy for competing reactions that direct displacement by solvent can become comparable with the unimolecular formation of a carbonium ion. The Reviewer considers that this emphasis on the bimolecular nature of the reaction may give a misleading picture of the transition state, because the argument is based on energetics alone and does not consider the probability factors involved. Since ground-state control operates in the selection of the rearranging group, so that deamination

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* *I.e.*, not a bridged structure analogous to (VIII).
[85] B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J. Amer. Chem. Soc.*, 1957, **79**, 6160.

occurs in the most populated conformation, a similar kind of ground-state control should operate as far as the orientation of the local solvent molecules is concerned. The deamination is, therefore, unlikely to require the special orientation of solvent molecules associated with an S_N^2 substitution or an $E2$ elimination (cf. ref. 82). Benjamin *et al.* pointed out that the "topside" rearrangements (*e.g.*, the formation of XXIII) are difficult to reconcile with a mechanism involving a synchronous rearrangement,[85] and, on the whole, it seems best to consider all these reactions as involving an intermediate carbonium ion. The formation of olefins in deamination has been discussed in terms of an $E2$ reaction,[80] but the arguments can be easily rephrased in terms of ground-state control of elimination from an intermediate carbonium ion.

The material quoted above was selected to illustrate how the special facility of carbonium ion formation by the loss of nitrogen can apparently modify the relative proportions of the products formed. A more detailed consideration of the nature and stability of carbonium ions formed under different conditions belongs more to the general field of carbonium ion chemistry; such matters have been discussed in recent publications.[86]
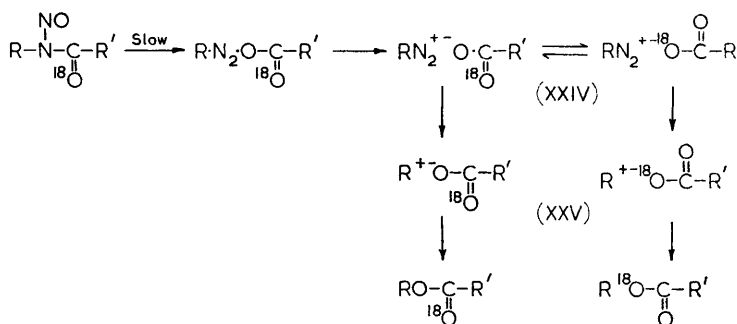
There is one other factor that particularly concerns deamination, namely, the possible influence of ion pairs involving diazonium ions in non-aqueous solvents. Such ion pairs have been discussed by Huisgen and Rüchardt,[87] but recently new evidence has been obtained by White and Aufdermarsh[88] from an oxygen-18 study of the decomposition of *N*-nitrosoamides ($ON \cdot NR \cdot CO \cdot R'$, where R is aliphatic). These nitrosoamides are known to decompose by a preliminary rate-determining rearrangement to the corresponding diazo-ester[89] ($R \cdot N_2 \cdot O \cdot COR'$) which can then undergo a number of reactions depending on the conditions. In such solvents as acetic acid, one of these reactions involves the formation of the ester $R' \cdot CO_2R$ by an intramolecular path requiring mainly retention of configuration. These features would be consistent with a cyclic $S_N i$ transition state but the oxygen-isotope studies show that the two oxygen atoms become partly equivalent before the final product is formed. The degree of mixing depends on the conditions and on the compound in a way that suggests[88] the ion-pair equilibrium (XXIV) shown in Scheme 10. The products with retained and inverted configuration involve essentially the same degree of mixing of the oxygen isotopes; it appears that some rotation of R^+ can occur in the ion-pairs (XXV) without further equilibration of the oxygen atoms.

[86] V. F. Raaen and C. J. Collins, *J. Amer. Chem. Soc.*, 1958, **80**, 1409; C. J. Collins, W. A. Bonner, and C. T. Lester, *ibid.*, 1959, **81**, 466; D. Bethell and V. Gold, *Quart. Rev.*, 1958, **12**, 173; M. S. Silver, *J. Amer. Chem. Soc.*, 1961, **83**, 3482.

[87] R. Huisgen and C. Rüchardt, *Annalen*, 1956, **601**, 1.

[88] E. H. White and C. A. Aufdermarsh, *J. Amer. Chem. Soc.*, 1958, **80**, 2597; 1961, **83**, 1179.

[89] R. Huisgen and C. Rüchardt, *Annalen*, 1956, **601**, 21, and preceding papers; E. H. White, *J. Amer. Chem. Soc.*, 1955, **77**, 6014.

$$\overset{NO}{\underset{\overset{\|}{^{18}O}}{R-N-\overset{|}{C}-R'}} \xrightarrow{\text{Slow}} \overset{}{\underset{\overset{\|}{^{18}O}}{R\cdot N_2O-\overset{|}{C}-R'}} \longrightarrow \underset{\overset{\|}{^{18}O}}{RN_2^{+}\ {}^{-}O\cdot\overset{|}{C}-R'} \rightleftharpoons \underset{}{RN_2^{+}\ {}^{-18}\overset{\overset{O}{\|}}{O-C-R}}$$

(XXIV)

$$R^{+}\ {}^{-}\underset{\overset{\|}{^{18}O}}{O-\overset{|}{C}-R'} \qquad\qquad R^{+}\ {}^{-18}O-\overset{\overset{O}{\|}}{C}-R'$$

(XXV)

$$RO-\underset{\overset{\|}{^{18}O}}{\overset{|}{C}}-R' \qquad\qquad R\ {}^{18}O-\overset{}{\underset{\overset{\|}{O}}{C}}-R'$$

SCHEME 10.

The reaction paths in Scheme 10 do not fully indicate the complexity of these nitrosoamide reactions but the evidence[88] that the loss of nitrogen involves a diazonium–carboxylate ion-pair supports earlier conclusions[87] on the importance of ion-pair equilibria in these reactions and suggests that similar equilibria may influence the course of deamination in media of low polarity. Deamination could lead first to a diazonium–hydroxide ion-pair, but in acetic acid such ion-pairs would be converted into diazonium acetate ion-pairs by proton transfers. The subsequent formation of a carbonium ion would then occur in the neighbourhood of a hydroxide or an acetate ion. This may explain the extensive formation of unrearranged products in the acetic acid deamination of allylic amines[78] and other results previously explained in terms of cyclic S_Ni transition states.[90] It seems increasingly necessary to distinguish between deamination in water and in solvents of low polarity.

The deamination of alicyclic amines has not been included in this Review but two recent papers on this subject add to the general knowledge of deamination mechanisms. Streitwieser and Coverdale[91] have shown that the aqueous deamination of cis-2-deuteriocyclohexylamine proceeds with almost complete retention of configuration so that the carbonium ion, if formed, reacts before reaching conformational equilibrium. This might suggest a cyclic S_Ni transition state but Boutle and Bunton[92] have shown that this is unlikely since the oxygen in the final cyclohexanol is not that present in the initial nitrosation of the amine. An intermediate carbonium ion therefore appears more probable.

From the above discussion, it appears that the simple representation of deamination by equation (1) is still adequate to explain the great majority of the experimental results although consideration must be given to the different mechanisms of nitrosation, to the special facility of carbonium

[90] P. S. Bailey and J. G. Burr, *J. Amer. Chem. Soc.*, 1953, **75**, 2951; cf. discussion in ref. 80.
[91] A. Streitwieser and C. E. Coverdale, *J. Amer. Chem. Soc.*, 1959, **81**, 4275.
[92] D. L. Boutle and C. A. Bunton, *J.*, 1961, 761.

ion formation by loss of nitrogen, and to the influence of diazonium salt ion-pairs in media of low polarity.