**18.** *Nitrosation, Diazotisation, and Deamination. Part VI.\* Comparative Discussion of Mechanisms of* N- *and* O-*Nitrosation with Special Reference to Diazotisation.*

By E. D. HUGHES, C. K. INGOLD, and J. H. RIDD.

The six discrete kinetic forms in which aqueous diazotisation has been studied diagnose a net-work (scheme 20, p. 95) of inorganic-chemical transformations which produce, and may interconvert, various nitrosation carriers, any of which may nitrosate the amine. Apart from the common basic step of conversion of nitrous acid into its conjugate acid, any one of the steps of production, or interconversion, of the nitrosating agents, or of the attack of any of them on the amine, may be made rate-controlling, the overall kinetics changing accordingly. No step after that which first implicates the amine ever becomes rate-controlling.

In weakly acidic aqueous media, the important carriers are nitrous acidium ion, dinitrogen trioxide, and nitrosyl chloride, bromide, and iodide, but not nitrosonium ion, dinitrogen tetroxide, nitrosyl carboxylates, or nitrous acid. Nitrosonium ions are not produced, and nitrous acid is present but useless. Nitrosyl carboxylates nitrosate nitrite ion more easily than they nitrosate amines, and thus they catalyse nitrosation of the latter by way of dinitrogen trioxide.

Recent literature on the kinetics of *N*- and *O*-nitrosation is reviewed, and some discrepancies are explained. Okano and Ogata's claim for $HN_2O_3^+$ as a main nitrosating agent in aqueous diazotisation arises from their not controlling kinetic form before calculating rate-constants. Most other difficulties can be traced to the fallacy that buffers do nothing except control pH. Dusenbury and Powell's discrepant results for deamination arise, as was previously pointed out, from unrecognised catalysis by their phosphate buffer, which produces the nitrosating species $NOH_2PO_4$ and $NOHPO_4^-$. Anbar and Taube's similarly discrepant results for the nitrosation of water, as followed by oxygen exchange, arise from the same cause. Other modern work is cited which agrees well with that now recorded.

(1) KINETICS AND MECHANISMS OF DIAZOTISATION

(a) *The Kinetic Forms of Diazotisation.*—The immediately preceding four papers have dealt with diazotisation in a number of discrete kinetic forms, which it is convenient here

* Part V, preceding paper.

to bring together. Our convention is again so to write kinetic equations that the entries in brackets are to be given a literal (molecular or ionic) rather than an analytical (stoicheiometric) interpretation; in other words, acids and bases are expressed with exclusion of their conjugate bases and conjugate acids, respectively:

(*a*) *Uncatalysed diazotisation* (cf. Parts II and III):

$$\left\{\begin{array}{l} \text{Rate} = k_3''[\text{amine}][\text{HNO}_2]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1) \\ \text{Rate} = k_2''[\text{HNO}_2]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2) \end{array}\right.$$

(*b*) *Carboxylate-ion catalysed diazotisation* (cf. Part III):

$$\text{Rate} = k_3^{\text{OAc}}[\text{HNO}_2]^2[\text{OAc}^-] \quad . \quad . \quad . \quad . \quad . \quad (3)$$

(*c*) *Hydrogen-ion catalysed diazotisation* (cf. Part IV):

$$\text{Rate} = k_3^{\text{H}}[\text{amine}][\text{H}^+][\text{HNO}_2] \quad . \quad . \quad . \quad . \quad . \quad (4)$$

(*d*) *Halide-ion catalysed diazotisation* (cf. Part V):

$$\left\{\begin{array}{l} \text{Rate} = k_4^{\text{Hal}}[\text{amine}][\text{H}^+][\text{HNO}_2][\text{Hal}^-] \quad . \quad . \quad . \quad . \quad (5) \\ \text{Rate} = k_3^{\text{Hal}}[\text{H}^+][\text{HNO}_2][\text{Hal}^-] \quad . \quad . \quad . \quad . \quad . \quad (6) \end{array}\right.$$

The brace between equations (1) and (2) is a reminder that they are limiting equations. Each alone has a great range of validity, but they enclose between them a band of continuously transitional kinetic forms. In order to accomplish, with a given amine, the transition from limit (1) to limit (2), it is necessary to raise sufficiently the concentration of free-basic amine: the diazotisation rate will then at first rise proportionally, according to equation (1), then less steeply, and finally not at all as a maximum rate is reached, which is given by equation (2).

Similarly, equations (5) and (6) are limiting equations, which bracket a band of transitional kinetic forms; and the conditions for securing a transition from equation (5) to equation (6) are essentially the same as has just been described for the transition from equation (1) to equation (2).

(*b*) *Uncatalysed Diazotisation.*—The experimental proof that kinetic forms (1) and (2) are both valid, and that a transition from form (1) to form (2) can be produced by raising the supply of molecular amine, completely proves the reaction mechanism. The argument is as follows.
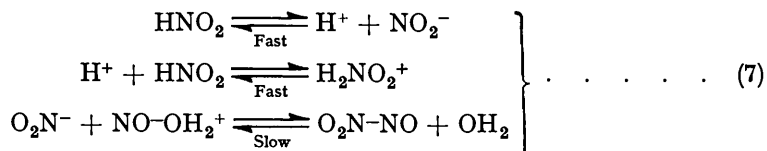
In the first place, the finding shows that there can be no slow step after that step in which the amine is implicated: if there were, we could never get rid of the amine factor from the kinetic equation. That is to say, we have established the conclusion, set down in anticipation in Part I, section 1a, that rate control is complete when primary nitrosation is complete, and that none of the changes undergone by the immediate nitrosation product, or by species formed from it, as set out in outline schemes (1) and (2) of Part I, section 1a, has any influence on the kinetics. It is a part of this conclusion that all kinetic interpretations on the lines of general acid and general base catalysis, explanations of the type of which, as mentioned in Part I, section 2, Kenner's suggestion is an example, are excluded. For it is essential to such interpretations that they contain a slow step of proton transfer subsequent to the nitrosating step.

The next conclusion to which the observation of the kinetic transition gives rise is that the process leading to primary nitrosation itself consists of more than one step. For only a last step in any such sequence can involve the amine, and the kinetic transition shows that, whilst that step may be rate-controlling, when, in this situation, we increase its speed by feeding more amine, some earlier step not involving amine will eventually become the bottle-neck. In other words, some inorganic-chemical process, which is slow enough to be rate-controlling, when other rate restrictions are removed, must first produce the nitrosation carrier. Then this can attack the amine.

Reference to Part I, section 1c, and particularly to equations (5)—(11) of that section, will show that the nitrosation carrier can be nothing else than dinitrogen trioxide. That carrier should lead to the two limiting kinetic forms (1) and (2), and to a kinetic transition from form (1) to form (2) under a sufficiently free supply of molecular amine. This prediction has been verified in its entirety.

The kinetic equation for the preliminary self-dehydration of nitrous acid to form dinitrogen trioxide is equation (2), and we measure this inorganic-chemical process when we follow diazotisation kinetics in the form of equation (2).

The most plausible scheme for the self-dehydration, though its actual support is only that of analogy with reactions of nitrous acid discussed later, is the scheme of equations (7), which assumes slow attack by the nitrite ion on the conjugate acid of nitrous acid:
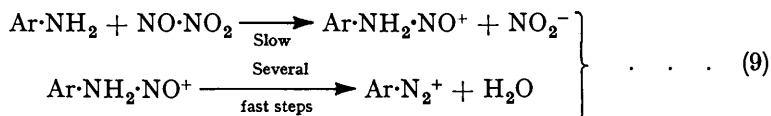
$$\left.\begin{array}{c} HNO_2 \underset{Fast}{\rightleftharpoons} H^+ + NO_2^- \\[2mm] H^+ + HNO_2 \underset{Fast}{\rightleftharpoons} H_2NO_2^+ \\[2mm] O_2N^- + NO\text{--}OH_2^+ \underset{Slow}{\rightleftharpoons} O_2N\text{--}NO + OH_2 \end{array}\right\} \quad \ldots \ldots (7)$$

The slow step here might be a strictly one-stage, bimolecular, nucleophilic substitution $S_N2$, or it might involve an additive intermediate of low stability, such as Bender first demonstrated for reactions of substitution in the carboxyl group.

The rate-equation (2) applies to the combined three steps of scheme (7). The rate-constant $k_2''$ for the formation of dinitrogen trioxide, at 0° in water, from two molecules of nitrous acid according to this equation is 0·85 sec.$^{-1}$ mole$^{-1}$ l., according to the experiments of Part II in perchloric acid at low ionic strength, or is 0·78 sec.$^{-1}$ mole$^{-1}$ l., according to the work of Part III in buffers at the ionic strength 0·1M. For comparison with carrier-forming reactions considered later, it is convenient to write a kinetic equation for the combined second and third steps of scheme 7: this is equation (8):

$$\text{Rate} = k_3^{Nit}[H^+][HNO_2][NO_2^-] \quad \ldots \ldots (8)$$

The rate-constant of this equation, $k_3^{Nit}$, represents the rate of attack of supplied nitrite ion on pre-equilibria nitrous acidium ion. It differs from $k_2''$ by the factor of the acidity constant of nitrous acid, which we take as $4\cdot5 \times 10^{-4}$ mole l.$^{-1}$. The values of $k_3^{Nit}$ are 1890 sec.$^{-1}$ mole$^{-2}$ l.$^2$, according to the experiments of Part II, or 1740 sec.$^{-1}$ mole$^{-2}$ l.$^2$, according to those of Part III.

When the supply of molecular amine is sufficiently restricted, the last step of scheme (7) becomes fast in comparison with the first of scheme (9):

$$\left.\begin{array}{c} Ar\cdot NH_2 + NO\cdot NO_2 \xrightarrow[Slow]{} Ar\cdot NH_2\cdot NO^+ + NO_2^- \\[2mm] Ar\cdot NH_2\cdot NO^+ \xrightarrow[\text{fast steps}]{\text{Several}} Ar\cdot N_2^+ + H_2O \end{array}\right\} \quad \ldots (9)$$
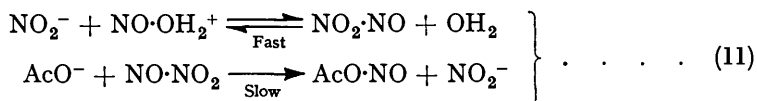
The kinetic equation is now equation (1), which we can, if we choose, rewrite in form (10). Equations (10) and (8) are then in the same forms as equations (5) and (6), respectively.

$$\text{Rate} = k_4^{Nit}[\text{amine}][H^+][HNO_2][NO_2^-] \quad \ldots \ldots (10)$$
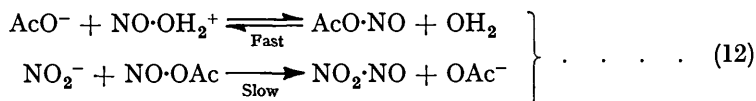
(c) *Carboxylate-ion Catalysed Diazotisation.*—The rate-equation (3) shows that the measured process is one of the formation of a nitrosation carrier, which is taken up by the amine as fast as it is produced. It also shows that two molecules of nitrous acid, plus one of the carboxylate ion, plus or minus undetermined water molecules, are required to build the transition state of the process which leads to the carrier.

There are only two possibilities for producing such a transition state. Either,

dinitrogen trioxide is formed in pre-equilibrium, and is then converted in a rate-controlling way into the acyl nitrite, which becomes the effective nitrosating agent:

$$NO_2^- + NO\cdot OH_2^+ \underset{Fast}{\rightleftharpoons} NO_2\cdot NO + OH_2$$
$$AcO^- + NO\cdot NO_2 \underset{Slow}{\longrightarrow} AcO\cdot NO + NO_2^-$$

$$\left.\right\} \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (11)$$

Or, the acyl nitrite is formed in pre-equilibrium, and is then converted in a rate-controlling manner into dinitrogen trioxide, which is still the nitrosating agent, just as in the uncatalysed reaction:

$$AcO^- + NO\cdot OH_2^+ \underset{Fast}{\rightleftharpoons} AcO\cdot NO + OH_2$$
$$NO_2^- + NO\cdot OAc \underset{Slow}{\longrightarrow} NO_2\cdot NO + OAc^-$$

$$\left.\right\} \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (12)$$

Of the two schemes (11) and (12), both consistent with the kinetic form, only (12) can lead to catalysis. Supposing diazotisation, in the absence of carboxylate ions, to be proceeding at its maximum uncatalysed rate, that which is given by the amine-independent equation (2), then, since, under scheme (11), carboxylate ions could only intercalate a step which is slower than the one which was the slowest before, they could not divert any dinitrogen trioxide from direct uptake by the amine; and therefore they could have no kinetic effect, not even a retarding one. On the other hand, the carboxylate ions could be accelerating under scheme (12), because they would then provide a new, and possibly faster, route for the formation of dinitrogen trioxide.

We conclude that this is essentially how carboxylate ions do act: they catalyse the formation of the original nitrosation carrier: they do not change the carrier. That was part of the value to us of carboxylate buffers in the experiments recorded in Part III: many buffers would just as adequately have controlled the pH; but some at least would have changed the nitrosating agent.
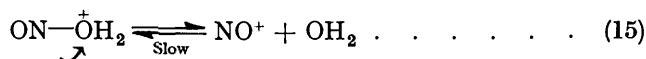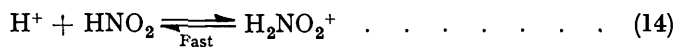
The kinetics of scheme (12) are expressed by equation (13), which is, of course, equivalent to equation (3):

$$Rate = k_4^{OAc}[OAc^-][H^+][HNO_2][NO_2^-] \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (13)$$

The rate constant $k_4^{OAc}$, calculated with $4\cdot 5 \times 10^{-4}$ mole l.$^{-1}$ as the value of the acidity constant of nitrous acid, is 85,000 sec.$^{-1}$ mole$^{-3}$ l.$^3$ for acetate ions, and 360,000 sec.$^{-1}$ mole$^{-3}$ l.$^3$ for phthalate ions.

(d) *Hydrogen-ion Catalysed Diazotisation (Introduction).*—The kinetic equation (4) shows that a cationic nitrous species is being formed in some relatively rapid pre-equilibrium, and is then nitrosating the amine in a rate-controlling fashion. Reference to Part I, section 1c, and particularly to the set of equations (5)—(11) in that section, will show that two carriers could account for the observed kinetics. They are the nitrous acidium ion and the nitrosonium ion.

The relation between these alternative carriers is the same as that between the nitric acidium ion and the nitronium ion in nitration, and between the hypochlorous acidium ion and the chlorinium ion in chlorination. The nitrous acidium ion is the product of a pre-equilibrium process (14), which is inevitably rapid, whilst the nitrosonium ion is formed from the acidium ion by a heterolytic bond-fission (15), which is in principle slow, and could conceivably be made rate-controlling—just as the analogous formation of the nitronium ion, and that of the chlorinium ion, have in fact been made rate-controlling in nitration and chlorination, respectively:

$$H^+ + HNO_2 \underset{Fast}{\rightleftharpoons} H_2NO_2^+ \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (14)$$

$$ON\overset{+}{-}OH_2 \underset{Slow}{\rightleftharpoons} NO^+ + OH_2 \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (15)$$

If the cationic nitrosation carrier is indeed the nitrous acidium ion, then the kinetic equation is, universally, equation (4). If, however, the carrier is the nitrosonium ion, then kinetics of form (4) might still be observed, but now only as a limit, a change to kinetic form (16), in which the rate becomes independent of amine concentration, being in principle possible:

$$\text{Rate} = k_2{}^{\text{H}}[\text{H}^+][\text{HNO}_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

If we can observe such a kinetic change, we establish the nitrosonium ion as carrier unambiguously. In order to make the observation we must intercept the reversal of process (15), by the efficient trapping of nitrosonium ion with amine, so making the forward process (15) rate-controlling. We tried to do this, but could see no sign of a change from kinetic form (4) to form (16). At this point, then, we were left with an ambiguous conclusion: either the carrier is the nitrous acidium ion, and our kinetic observation is already complete; or it is the nitrosonium ion, but our trapping system was not efficient enough to prove it.

When such ambiguities arise, it is a good general rule to introduce mechanistic competition, even though this involves making the system more complicated. That was why we took up the study of halide-ion catalysis. We shall consider that subject next, and then return to close the gap in the present argument.
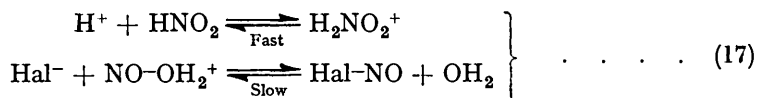
(e) *Halide-ion Catalysed Diazotisation.*—Fluoride-ion catalysis seems not to occur. In catalysis by the other halide ions, we observe, overall, both the limiting kinetic forms (5) and (6), though there is a distinction between the cases, in that form (6) could not be observed with chloride ion, but was particularly easily observed with iodide ion.

The first conclusion to be drawn from the observation of kinetic form (6) is that halide ions are not participating in general-acid–general-base catalysis. By an argument similar to one used in sub-section (1b), we can show that no element of rate-control enters later than the step of attack on the amine.

Again, by an argument similar to another of those employed in sub-section (1b), we can show that primary nitrosation of the amine is itself the result of a succession of steps. First, a purely inorganic-chemical process produces the nitrosating agent; then this attacks the amine; and, according to the conditions, either of these steps may become rate-controlling.

The rate of the inorganic-chemical carrier-forming process is that which is measured as diazotisation rate in the form of equation (6). This equation unambiguously identified the carrier as the nitrosyl halide.

Equation (6) represents a nucleophilic substitution by supplied halide ion in pre-equilibrium nitrous acidium ion. This process, represented in scheme (17), is completely analogous to the second and third steps of scheme (7), for the formation of dinitrogen trioxide:

$$\left.\begin{array}{l} \text{H}^+ + \text{HNO}_2 \underset{\text{Fast}}{\rightleftharpoons} \text{H}_2\text{NO}_2{}^+ \\[2mm] \text{Hal}^- + \text{NO-OH}_2{}^+ \underset{\text{Slow}}{\rightleftharpoons} \text{Hal-NO} + \text{OH}_2 \end{array}\right\} \quad . \quad . \quad . \quad (17)$$

Correspondingly, the kinetic equation (6) for the formation of nitrosyl halides is analogous to kinetic equation (8) for the formation of dinitrogen trioxide.

It is of interest to compare our rate-constants, $k_3{}^{\text{Hal}}$ and $k_3{}^{\text{Nit}}$, of formation of nitrosyl halides and dinitrogen trioxide (nitrosyl nitrite) from supplied halide or nitrite ion and pre-equilibrium nitrous acidium ion. The values for $0°$ in water are as follows:

$$\text{NOBr, 1170; NOI, 1370; NONO}_2\text{, 1890 (sec.}^{-1}\text{ mole}^{-2}\text{ l.}^2)$$

(f) *Hydrogen-ion Catalysed Diazotisation (Conclusion).*—There is another way, than that of the second step of scheme (17), through which a nitrosyl halide could, and certainly would, be formed, were nitrosonium ion available, *viz.*, through the simple ionic association (18):

$$\text{Hal}^- + \text{NO}^+ \longrightarrow \text{Hal·NO} \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

No bond is broken in this process, which would therefore be fast, indeed, for practical purposes, instantaneous.

By measurements of diazotisation in accordance with the kinetic equation (6), we have found the rates of formation of nitrosyl bromide and iodide. Apart from a reservation mentioned below, these observed rates will be upper limits to any possible rate at which nitrosonium ion could appear in the solutions under the conditions of the measurements.
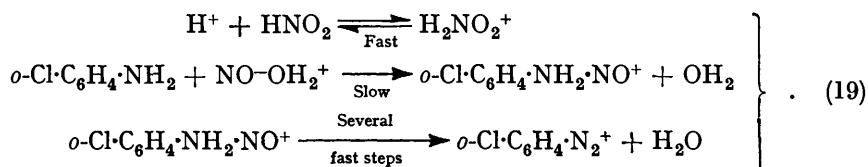
At the end of sub-section (1d), the mechanism of hydrogen-ion catalysed diazotisation was left unsettled, insofar as the nitrosation carrier might be nitrous acidium ion or nitrosonium ion. We can now carry the matter further. For, as described in Part V, we have run two processes of diazotisation of o-chloroaniline in competition, *viz.*, diazotisation under hydrogen-ion catalysis, and under bromide-ion catalysis. The rates of the concurrent reactions were compared. Moreover, the bromide-ion reaction, for its part, was run under such conditions that its rate was the rate of formation of nitrosyl bromide, and therefore, according to the suggestion in the preceding paragraph, an upper limit to any possible rate of appearance of nitrosonium ion. Therefore, if the hydrogen-ion reaction were to depend on nitrosonium ion, it could never go faster than the bromide-ion reaction. But, in fact, the rate laws show that the two reactions are not kinetically tied together, and that the rates themselves can stand in either order. Each rate follows its own kinetic law, the hydrogen-ion rate increasing proportionally to amine, but not bromide, concentration, and the bromide-ion reaction proportionally to bromide, but not amine, concentration. If the amine concentration is high enough, and the bromide concentration low enough, the hydrogen-ion reaction will go faster than the bromide-ion reaction (cf. for example, Part V, Table 4, Run 188). The inference is that the hydrogen-ion reaction does not involve the nitrosonium ion, and that, therefore, its carrier must be the nitrous acidium ion.

We must deal with an apparent loop-hole in this argument. This is as follows. We can admit that the combination of formed nitrosonium ion with bromide ion would be practically instantaneous; but we might assume that its combination with all bond-forming nucleophiles, even the neutral ones, amine and water, is also practically instantaneous. Then, in order to account for the mutual independence of the kinetics of the hydrogen-ion and bromide-ion reactions, we should have to assume that the recombination of formed nitrosonium ion with water is its most immediate reaction of all, so that amine and bromide ion are able, additively and independently, to " tap off " nitrosonium ion from a fully maintained stationary concentration. In other words, we must assume that nearly all the nitrosonium ion, primarily formed from nitrous acidium ion, goes back into nitrous acidium ion, and that only very small fractions of it are caught by amine and by bromide ion. In still other words, we must assume that the rate of the primary dehydration of nitrous acidium ion to nitrosonium ion is almost equal to the rate of rehydration of the latter, and is thus very much greater than either of the measured rates of diazotisation, and, in particular, very much greater than that measured rate which is identified with the rate of formation of nitosyl bromide. This has further implications. It was shown in sub-section (1e) that the rates of formation of nitrosyl bromide, nitrosyl iodide, and dinitrogen trioxide are all the same to well within a factor of 2. Therefore the assumption, to which we are forced, when we try to get over the difficulty of making the nitrosonium ion an intermediate in hydrogen-ion catalysed diazotisation by adopting it as an extra intermediate in halide-catalysed, and, as would then follow, in all forms of diazotisation, includes the particular assumption that the rate of the primary dehydration of nitrous acidium ion to nitrosonium ion is very much greater than the second-order rate of self-dehydration of nitrous acid to dinitrogen trioxide. Now we know the latter rate: it is the upper limiting rate of uncatalysed diazotisation in weakly acidic aqueous conditions. We also know—for this has been shown by Bunton, Llewellyn, and Stedman, as will be noted in sub-section (2c)—that, in such conditions, there is no faster mechanism

for oxygen exchange between nitrous acid and water than that of the second-order self-dehydration of nitrous acid to dinitrogen trioxide. Therefore the assumption, to which our attempt to drag the nitrosonium ion into the picture has led us, that of a very fast, reversible, acidic dehydration of nitrous acid to nitrosonium ion, necessarily much faster than the limiting rate of uncatalysed diazotisation, is false. Thus the apparent loop-hole in the previous argument is unreal.

Our final conclusion is, then, that the nitrous acidium ion, not the nitrosonium ion, is the carrier in hydrogen-ion catalysed diazotisation. It has also emerged in the discussion that the nitrosonium ion does not intervene in any of the forms in which diazotisation has been observed to take place in weakly acid solution. It follows that the nitrous acidium ion substitutes, whether by organic or inorganic, and whether by anionic or molecular, nucleophiles, always by an $S_N2$ mechanism, and never by an $S_N1$ mechanism, in the range of conditions which our investigation covers.

It follows from this interpretation that, in the study of the hydrogen-ion reaction described in Part IV, we were measuring the rate of attack of supplied *o*-chloroaniline on pre-equilibrium nitrous acidium ion:

$$\left. \begin{array}{c} \text{H}^+ + \text{HNO}_2 \underset{\text{Fast}}{\rightleftharpoons} \text{H}_2\text{NO}_2{}^+ \\[6pt] o\text{-Cl·C}_6\text{H}_4\text{·NH}_2 + \text{NO–OH}_2{}^+ \underset{\text{Slow}}{\longrightarrow} o\text{-Cl·C}_6\text{H}_4\text{·NH}_2\text{·NO}^+ + \text{OH}_2 \\[6pt] o\text{-Cl·C}_6\text{H}_4\text{·NH}_2\text{·NO}^+ \xrightarrow[\text{fast steps}]{\text{Several}} o\text{-Cl·C}_6\text{H}_4\text{·N}_2{}^+ + \text{H}_2\text{O} \end{array} \right\} \quad . \quad (19)$$

The first two steps of scheme (19) are exactly like scheme (17), and like the last two steps of scheme (7), except that a neutral, rather than an anionic, nucleophile is attacking the nitrous acidium ion. The overall rate-constant $k_3{}^{\text{H}}$ of process (19) is 175 sec.$^{-1}$ mole$^{-2}$ l.$^2$, a figure to be compared with those given at the end of the preceding sub-section.

As we do not know the acidity constant of the nitrous acidium ion, we cannot give absolute values for the rates of substitution in it of the various nucleophiles considered. The relative values of these rates are as follows:

$$o\text{-Cl·C}_6\text{H}_4\text{·NH}_2, \ 1; \ \text{Br}^-, \ 6\cdot7; \ \text{I}^-, \ 7\cdot8; \ \text{NO}_2{}^-, \ 10\cdot8$$
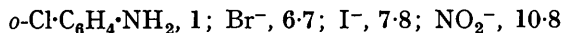
(g) *The Mechanisms of Diazotisation.*—Our investigation of diazotisation has been confined to weakly acidic aqueous media. Of the possible carriers of the nitrosation process, which were listed for consideration in Part I, section 1b, the following have been found effective in these conditions:

$$\text{H}_2\text{NO}_2{}^+ \qquad \text{NOI} \qquad \text{NOBr} \qquad \text{NOCl} \qquad \text{N}_2\text{O}_3$$

The following possible carriers have been found to be much less effective, or ineffective, *viz.*,

$$\text{NO}^+ \qquad \text{N}_2\text{O}_4 \qquad \text{NO}_2\text{Ac} \qquad \text{NO}_2\text{H}$$

though this may be either because, as in the case of NO$^+$, they are not formed in the conditions, or because, as with NO$_2$H, they are formed, but are useless as direct nitrosating agents.

The mechanisms by which the effective carriers act are not all independent. The first step of all of them is the formation of the nitrous acidium ion. In this ion, a water molecule is holding the place that has eventually to be taken by the amine molecule. The amine molecule may substitute itself for water directly, and so become nitrosated. This is hydrogen-ion catalysed diazotisation. Alternatively, an anion may first displace the water, and become itself subsequently displaced by the amine, which thus becomes nitrosated. In the special case in which the substituting anion is nitrite ion, the intermediate product is dinitrogen trioxide, which is now the nitrosating agent towards the amine. This is uncatalysed diazotisation. In the general case in which some other anion

first substitutes and then becomes displaced, the intermediate is a general nitrosyl compound, which nitrosates the amine. We call this anion-catalysed diazotisation. If a general anion introduces itself, and is then displaced by nitrite ion, which is finally displaced by the amine, we have a catalysed formation of dinitrogen trioxide, which is still the nitrosating carrier for the amine. These relations are summarised in the annexed scheme.
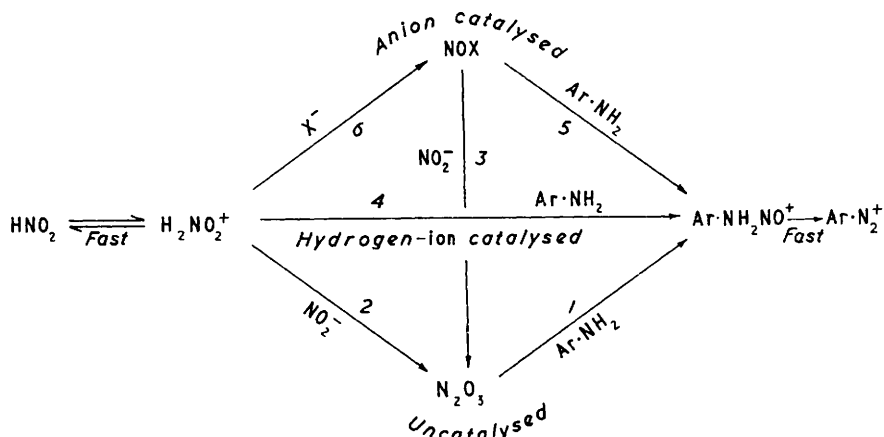


*Mechanisms of aqueous diazotisation* . . . . . . (20)

In scheme 20, every process except the two marked " fast " has separately been made rate-controlling, and has had its kinetics determined. The figures against the arrows are the numbers of the relevant kinetic equations, as listed in sub-section (1a). All these processes are bimolecular nucleophilic substitutions $S_N2$.

### (2) RECENT REPORTS ON THE KINETICS OF NITROSATION

The first of several summaries of the findings now particularised was published in 1950. Since then, a number of papers have appeared, which our work seems to have influenced, on the kinetics and mechanism of one or another of the forms of nitrosation. Some of these reports confirm our conclusions, whilst others leave discrepancies, which need consideration.

(a) N-*Nitrosation: Concordant Reports.*—There have been several by Schmid. He and Woppmann repeated the diazotisation of aniline at low acidities, which they set with added nitric acid.[2] They confirmed equation (2), and the transition between equations (1) and (2); and they obtained, for the rate constant $k_2''$ of equation (2) at 0°, a value 0·92 sec.$^{-1}$ mole$^{-1}$ l., in good agreement with our comparable value given in Part II. Schmid and Muhr's early work on chloride catalysis has been extended by Schmid and Pfeiffer to include deamination,[3] and by Schmid and Hallaba within the field of diazotisation.[4] These kinetics always followed equation (5). Schmid and his co-workers were evidently unable, just as we were in chloride-catalysis, to realise the transition to equation (6).

(b) N-*Nitrosation: Discrepant Reports.*—Okano and Ogato have reported [5] on the diazotisation of aniline in sulphuric acid over the pH range 0·6—3·3. According to our conclusions, the reaction should follow at first the third-order equation (1), and later the second-order equation (2), as acidity is decreased over this range. It is curious that, although Okano and Ogata refer to our paper of 1950, in which the main point was the

[1] Hughes, Ingold, and Ridd, *Nature*, 1950, **166**, 642; Ingold, *Bull. Soc. chim. France*, 1952, **19**, 667; " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953, p. 398; cf. Ridd, Thesis, London, 1951.
[2] Schmid and Woppmann, *Monatsh.*, 1952, **83**, 346; cf. Schmid, *ibid.*, 1954, **85**, 424.
[3] Schmid and Pfeiffer, *ibid.*, 1953, **84**, 829, 842.
[4] Schmid and Hallaba, *ibid.*, 1956, **87**, 560.
[5] Okano and Ogata, *J. Amer. Chem. Soc.*, 1953, **75**, 5175.

change from third-order to second-order kinetics within their pH range, they make no reference to the point itself, and continue their paper as if in ignorance of it. Without citing any of their own experimental readings, or offering any new evidence as to the extent to which equation (1) is obeyed in their conditions, they record, for their whole pH range, third-order constants $k_3''$, calculated with the integrated form of equation (1). Then, in just that part of the range, pH 2·0—3·3, in which the real kinetic order will be well away from three, they find that their calculated constants (which cannot in fact have been constant) decrease with diminishing acidity; and therefrom they draw the conclusion that the true rate-equation is a fourth-order one,

$$\text{Rate} \propto [\text{H}^+][\text{Ph·NH}_2][\text{HNO}_2]^2$$

and that the real nitrosating entity is, not $\text{N}_2\text{O}_3$, but $\text{HN}_2\text{O}_3{}^+$.

Now this is not sensible. It should be clear from our paper, which they cited, that when acidity is reduced, and the fraction of molecular amine is thereby increased, the rate rises at first proportionally, and then less than proportionally to the amine, until, finally, it stops rising; wherefore, when one calculates third-order constants, so dividing absolute rate *inter alia* by the amine concentration, one divides by a quantity which becomes progressively too large, and so one produces answers which become progressively too small, as the acidity is diminished. That is the origin of Okano and Ogata's apparent order of unity in hydrogen ions. We are not saying, of course, that $\text{HN}_2\text{O}_3{}^+$ does not exist, or never would nitrosate. But we do say that these authors had no evidence for either its existence or its effectiveness; and that, neither under their conditions, nor under any hitherto investigated conditions, does it function comparably in extent to $\text{N}_2\text{O}_3$ in the diazotisation of aniline.

The other discrepancies can mostly be traced to the all too common idea that one buffer is as good as another, so long as both give the same pH. Specific effects of buffer anions should be expected in our reactions, and we have emphasised the need for circumspection in the selection of buffers, and for the careful control of their specific effects (Part III). Difficulties through the neglect of such precautions first arose in a paper by Dusenbury and Powell, who claimed that T. W. J. Taylor's original observation of kinetic equation (1) in deamination was incorrect,[6] a claim which led us to publish a statement that we had repeated Taylor's work and had found it perfectly correct.[7] Dusenbury and Powell, using a phosphate buffer, were replacing the normal deaminating agent, dinitrogen trioxide, by a new one, a nitrosyl phosphate. They gave equation (4) as their kinetic expression, but there can be no doubt that it should have contained a phosphate-concentration factor, corresponding formally to the halide factor in equation (5).

Li and Ritter report [8] that the decomposition of nitrosyldisulphonate ion, $\text{NO(SO}_3)_2{}^-$, follows equation (2). But they were working in concentrated acetate solution, though without regard for its specific effects; and so the more important kinetic equation in their conditions must really have been equation (3). This seems to be the more certain, inasmuch as the rate constant $k_2''$, calculated for equation (2) from their results, is about 6 times larger than our value of that quantity. The conclusion that dinitrogen trioxide was the reagent remains, though it was formed, not by self-dehydration, but by a catalytic mechanism, and its primary reaction cannot have been a simple $N$-nitrosation. Li and Ritter also report that the deamination of sulphamate ion, $\text{NH}_2\text{·SO}_3{}^-$, follows equation (4). Here again the work was done in acetate buffers, the specific effects of which were disregarded. It is therefore not known whether the kinetic equation should have contained an acetate-concentration factor, like the halide-concentration factor of equation (5). The open question here is whether the nitrosating agent was the nitrous acidium ion or nitrosyl acetate. It is unlikely that it was, as they assume, the nitrosonium ion.

[6] Dusenbury and Powell, *J. Amer. Chem. Soc.*, 1951, **73**, 2269.
[7] Austin, Hughes, Ingold, and Ridd, *ibid.*, 1952, **74**, 555.
[8] Li and Ritter, *ibid.*, 1953, **75**, 3024.

(c) *O-Nitrosation: Concordant Reports.*—Bunton, Llewellyn, and Stedman [9] have noted that isotopically marked oxygen is exchanged between nitrous acid and water in accordance with kinetic equation (2). This means that dinitrogen trioxide is the carrier of the isotopic exchange. The equilibrium in the dehydration of nitrous acid in water being on the side of nitrous acid, the dinitrogen trioxide is formed slowly, and nitrosates water rapidly—just as it nitrosates aniline rapidly, when we supply sufficient molecular aniline. The rate of formation of dinitrogen trioxide, as measured at 0° through the diazotisation of aniline, is 0·85 sec.$^{-1}$ mole$^{-1}$ l. at low ionic strengths, and 0·78 sec.$^{-1}$ mole$^{-1}$ l. at the ionic strength 0·1M, these values (Parts II and III) being somewhat dependent on the figure taken for the acidity constant of nitrous acid. Bunton, Llewellyn, and Stedman used 0·4—1·0M-sodium nitrite, to which they added a somewhat small proportion of perchloric acid, thereby liberating an equivalent quantity of practically undissociated nitrous acid in the excess of nitrite; and for the rate-constant of exchange at 0°, they found 0·53 sec.$^{-1}$ mole$^{-1}$ l., a firm figure not dependent on the acidity constant of nitrous acid. These rates may all be consistent to within the somewhat small uncertainty of the acidity constant. For at low ionic strengths, when the nitrous acid is considerably ionised, its self-dehydration must be subject to a negative salt effect; which will die out, as indeed Bunton, Llewellyn, and Stedman verified for their conditions, when enough of a common ion, whether hydrogen or nitrite, is added to suppress ionisation of nitrous acid; but which will, before that stage is reached, have reduced the rate of self-dehydration to well below its value at low ionic strengths.

Allen [10] has investigated the hydrogen-ion catalysed hydrolysis of several alkyl nitrites by dilute ($\sim$10$^{-3}$M) perchloric acid in aqueous dioxan. As nitrosyl–oxygen fission was established, the reaction is a nitrosation of water. Allen's kinetic equation corresponds to our hydrogen-ion-catalytic equation (4), but with alkyl nitrite replacing nitrous acid, and water replacing amine. This shows that the nitrosating agent is either the nitrous esterium ion, NO·OHR$^+$, or the nitrosonium ion, NO$^+$, formed from it. As in our case of hydrogen-ion catalysis, as discussed in sub-sections 1d and 1f, the crux of the problem is to distinguish between these possibilities. Allen proceeded as we have done: he studied halide-ion catalysis, and showed that this could be used to measure the rate of bimolecular substitution of the halide ion in the nitrous esterium ion to give nitrosyl halide; and then, by arguments of comparison, he was able to conclude that, in the absence of halide ion, water reacts with the nitrous esterium ion, and not with the nitrosonium ion. Thus the nitrous esterium ion, like the nitrous acidium ion, does its nitrosating by $S_N2$, and not by $S_N1$, substitutions. Certainly, we should expect these two conjugate acids to behave quite similarly, and thus Allen's conclusions and ours, concerning hydrogen-ion catalysis in nitrosation, are mutually confirmatory.

(d) *O-Nitrosation: Discrepant Report.*—Anbar and Taube have also examined oxygen exchange between nitrous acid and water.[11] They claim kinetics which are at variance with equation (2), and are even incompatible with the occurrence of the self-dehydration which that equation represents, but are, on the other hand in agreement with equation (4)—with the difference that water replaces amine. They also claim that this result is not an artefact of the phosphate buffer used; and they interpret it as due to nitrosation by the nitrosonium ion, though they did nothing to distinguish this from the nitrous acidium ion, and insufficient to distinguish these from nitrosyl dihydrogen and mono-hydrogen phosphate. However, they deduce that our conclusions concerning the reactions of nitrous acid with amines are " incomplete if not incorrect," and that their results " indicate the necessity for re-examining the reactions in question." This necessity is, in their opinion, made the more apparent by the " paradoxes " among amine reactions, particularly the " direct contradiction " that in some circumstances they are of first and

[9] Bunton, Llewellyn, and Stedman, *Nature*, 1955, **175**, 83.
[10] Allen, *J.*, 1954, 1968.
[11] Anbar and Taube, *J. Amer. Chem. Soc.*, 1954, **76**, 6243.

E

in some of second order in nitrous acid. They argue that Dusenbury and Powell's first-order result (like their own) is not due to phosphate catalyses, but that, on the other hand, our second-order reaction (2) is fallacious. Two of their reasons for these conclusions are, first, that Li and Ritter's rate-constant for the decomposition of nitrosyldisulphonate ion would make reaction (2) obvious in Dusenbury and Powell's (and their own) conditions, and, secondly, that Li and Ritter, and Schmid and Woppmann, obtained disagreeing rate-constants for reaction (2).

Now the most obvious point about the actual figures given by Anbar and Taube is that their constants for the equation corresponding to (4) are not even approximately constant. They vary widely with the pH. They vary with the concentration of the buffer, and become changed in the experiments in which the usual phosphate buffer was replaced by an acetate or a phthalate buffer of similar pH. It appears, then, that there is some invalidity in the allowance for the dependence of rate on hydrogen ion in Anbar and Taube's rate-expression, in which, also, a buffer-ion concentration should have appeared. In a forthcoming paper by Bunton, Llewellyn, and Stedman, it will be shown [12] more quantitatively that Anbar and Taube's rates are phosphate-catalysed, and that the observed reductions of kinetic order in nitrous acid below two are due to the production of a nitrosyl phosphate, which, when in sufficient concentration, takes over the nitrosating function. In the same paper it will be shown that even acetate buffers will act similarly if their concentration is high enough. It is also shown that the relative efficiency of dinitrogen trioxide and of a general nitrosyl compound, as nitrosating agents, depends on what is being nitrosated, *e.g.*, water or amine. Furthermore, we have seen that the relative efficiency with which a general nitrosyl compound nitrosates water, amine, and nitrite ion depends on the nature of the nitrosyl compound. In this somewhat involved situation, which the use of buffers creates, the arguments of Anbar and Taube mean nothing: they were doing what Dusenbury and Powell had previously been criticised for doing, *viz.*, treating buffers as chemically immaterial except for the control of pH. That is why it did not strike them that Li and Ritter's rate was a buffer-catalysed rate, whereas Schmid and Woppmann's rate was not; and that the former rate has nothing to do with the *self*-dehydration of nitrous acid. It would be useful to have a buffer, whose anions were basic, yet not otherwise nucleophilic,[13] but the phosphate buffer does not happen to be such.

Anbar and Taube offer a third objection to equation (2) and its interpretation with respect to amine nitrosations. This is based on the results of their examination of oxygen exchange accompanying the diazotisation of aniline, in conditions which they considered would ensure exclusive diazotisation according to equation (2), supposing that this equation had any validity. They noted that, since the re-hydration of the formed dinitrogen trioxide would in that case be completely intercepted by its reaction with aniline, no oxygen exchange between nitrous acid and water should be observed. Actually, they found an especially rapid exchange in the conditions of these experiments.

But the conditions were wrong: in these particular experiments, Anbar and Taube changed their usual phosphate buffer for a phthalate buffer, using such a concentration that most of the diazotisation must have followed equation (3), rather than equation (2). And when we examine the detailed meaning of equation (3), as expressed by scheme (12) in sub-section (1c), we see that it requires oxygen exchange to be much faster than the formation of dinitrogen trioxide, and therefore much faster than the already buffer-accelerated diazotisation. Again, Anbar and Taube were not realising clearly that they were dealing with a buffer-catalysed reaction, having no relation to the self-dehydration of nitrous acid.

[12] Bunton, Llewellyn, and Stedman, *Chem. Soc. Special Publ.*, No. 10, to be published.
[13] Cf. Pritchard and Long, *J. Amer. Chem. Soc.*, 1957, **79**, 2365.