The Chemistry of Nitroso-compounds. Part VI.[1] Direct and Indirect Transnitrosation Reactions of *N*-Nitrosodiphenylamine

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Transfer of the nitroso-function from *N*-nitrosodiphenylamine to *N*-methylaniline, sodium azide, and other nucleophilic species is reported for acidic 50% aqueous ethanol at 25 °C. Neutral *N*-nitrosodiphenylamine is unreactive and protonation is required to initiate these reactions. Transfer to *N*-methylaniline is not catalysed by added Cl^-, which suggests that the nitroso-group is transferred without the intermediacy of nitrous acid (*direct* transnitrosation). Transfer to sodium azide under similar conditions does proceed *via* nitrous acid. For other nucleophiles, however, both direct and indirect transnitrosation reactions may compete. Reaction rates are independent of these nucleophilic species when their concentration is high. Solvent isotope effects for reaction under these circumstances are negligible which suggests that an intramolecular rearrangement of the conjugate acid rather than protonation of the *N*-nitrosodiphenylamine is rate-limiting.

MANY secondary *N*-nitrosamines are powerful chemical carcinogens and their biological properties have been widely examined.[2] It has been suggested [2,3] that they are metabolically converted *via* oxidation of an alkyl substituent into diazoalkanes, which then alkylate the bases of nucleic acids. For several carcinogenic *N*-nitrosamines (*e.g.* *N*-nitrosopiperidine and *N*-nitrosomethylaniline) this alkylation pathway seems unlikely, and the question arises whether they can act as proximate carcinogens by transferring their nitroso-group to other compounds (transnitrosation) either directly or *via* intermediate formation of nitrous acid. Nitrous acid, itself,

[1] Part V, B. C. Challis and A. J. Lawson, *J.C.S. Perkin II*, 1973, 918.

[2] P. N. Magee, *Ann. New York Acad. Sci.*, 1969, **163**, 717; H. Druckrey, R. Preussmann, and S. Ivankovic, *ibid.*, p. 676; P. N. Magee and J. M. Barnes, *Adv. Cancer Res.*, 1967, **10**, 163; H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schmail, *Z. Krebsforsch.*, 1967, **69**, 103.

[3] P. N. Magee and R. Schoental, *Brit. Med. Bull.*, 1964, **20**, 102; D. F. Heath, *Nature*, 1961, **192**, 170.

is not appreciably carcinogenic [4] unless ingested with substantial amounts of secondary amines, which presumably react to form *N*-nitrosamines at stomach pH.[5]

Transnitrosation by secondary *N*-nitrosamines has been reported under two different sets of conditions. In the most common method, the secondary *N*-nitrosamine (*e.g.* *N*-nitrosodiphenylamine,[6] *N*-nitrosocarbazole [7]) is heated with a nucleophilic substrate in an organic solvent. These reactions appear to involve a free radical mechanism.[8] Under heterolytic conditions, transnitrosation *via* nitrous acid would be expected as secondary nitrosamine formation is reversible, especially in the presence of halogen acids.[9] Although *N*-nitrosodiphenylamine, for example, has been used to effect nitrosation in polar solvents, the reaction mechanism is far from clear.[10] It has been suggested, however, that direct transnitrosation (without the intermediacy of nitrous acid) may occur in aqueous acid in connection with the Fischer–Hepp rearrangement of *N*-nitrosomethylaniline.[11]

Because of its relevance to the carcinogenicity of secondary *N*-nitrosamines, we have examined the kinetics and mechanism of the interaction of *N*-nitrosodiphenylamine with various nucleophiles in aqueous solution. This compound is known [12] to undergo the Fischer–Hepp rearrangement, but only under more forcing conditions than we employed.

A preliminary account of some of our findings has been published.[13]

N-*Methylaniline* (NMA).—Transfer of the nitroso-function from *N*-nitrosodiphenylamine to NMA [equation (1)] was examined mainly in dilute acidic 50% aqueous ethanol at 25 °C. The reaction is reversible but the

$$Ph_2NNO + PhNHMe \rightleftharpoons PhMeNNO + Ph_2NH \quad (1)$$

equilibrium lies over to the right; normally initial rates (<7% reaction) were measured to minimise complications due to this reversibility.

With excess of NMA, the rate of formation of diphenylamine follows equation (2), as shown by the consistency of k_0 over 70% reaction for a typical experiment in 0·12M-HCl (Table 1). The variation of k_0 with the

$$\text{Rate} = k_0[Ph_2NNO] \quad (2)$$

stoicheiometric concentration of NMA {(NMA) *} for reaction in 0·12M-HCl is given in Table 2: with (NMA) < 10^{-4}M, a first-order dependence is apparent, but at higher concentrations, k_0 is independent of this reactant.

The acidity dependence of k_0 also depends upon the amount of NMA present in the reaction mixture. With NMA > 10^{-3}M, it is evident from Figure 1 that k_0 has a first-order dependence on [HCl], and the reaction is either catalysed by H^+ or Cl^- but not by both. Experiments in $HClO_4$, however, show that Cl^- is not involved. Thus catalysis by 0·8M-$NaClO_4$ in 0·12M-$HClO_4$ is much larger

TABLE 1

Variation of k_0 [equation (2)] with reaction % for nitrosation of NMA with Ph_2NNO in 50% aqueous ethanol at 25 °C; initial [Ph_2NNO] = 5 × 10^{-5}M; (NMA) = 10^{-2}M; [HCl] = 0·12M

t/s	Reaction (%)	$10^4 k_0$/s^{-1}
0	0	7·6
84	5	7·8
180	12	8·2
276	19	8·2
360	24	8·2
1280	54	7·1
1880	70	7·4

TABLE 2

Dependence of k_0 [equation (2)] on (NMA) for nitrosation by Ph_2NNO in 0·12M-HCl in 50% aqueous ethanol at 25 °C

10^5(NMA)/M	$10^4 k_0$/s^{-1} *	10^5(NMA)/M	$10^4 k_0$/s^{-1} *
5	1·2	200	7·7
7	1·8	500	8·2
10	2·5	1000	7·7
25	3·2		

* Calculated from initial 5% reaction.

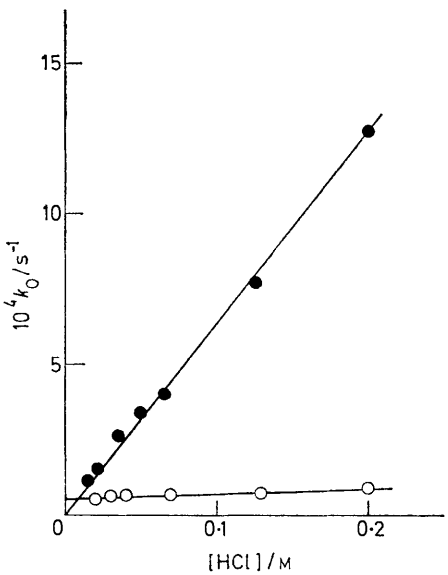


FIGURE 1 Reaction of Ph_2NNO with NMA in 50% aqueous ethanol at 25 °C: effect of acidity on initial rate; initial [Ph_2NNO] = 5 × 10^{-5}M: (NMA) = 5 × 10^{-3}M, [DPA] = 5 × 10^{-6}M; ○ (NMA) = 5 × 10^{-5}M, [DPA] = 2·5 × 10^{-5}M

* Amine and other bases are partially protonated under our conditions and it is necessary to differentiate between stoicheiometric and actual concentrations of those species: the former are denoted by initials in parentheses, the latter by chemical formulae in square brackets. Rate coefficients dependent on stoicheiometric concentrations are identified by a superscript bar.

[4] H. Druckrey, D. Steinhoff, H. Beuthner, H. Schneider, and P. Klärner, *Arzneimittel Forsch.*, 1963, **13**, 320.

[5] N. P. Sen, D. C. Smith, and L. Schwinghamer, *Fd. Cosmet. Toxicol.*, 1969, **7**, 301; J. Sander, *Arch. Hyg. Bakt.*, 1967, **151**, 22.

[6] P. Welzel, *Chem. Ber.*, 1971, **104**, 808.

[7] C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Amer. Chem. Soc.*, 1961, **83**, 4417.

[8] B. C. Challis and M. R. Osborne, to be published.

[9] R. Zahradnik, *Coll. Czech. Chem. Comm.*, 1958, **23**, 1529.

[10] C. H. Schmidt, *Angew. Chem. Internat. Edn.*, 1963, **2**, 101; H. Sieper, *Chem. Ber.*, 1967, **100**, 1646; D. B. Parihar and S. P. Sharma, *Chem. Ind.*, 1966, 1227.

[11] T. D. B. Morgan and D. L. H. Williams, *J.C.S. Perkin II*, 1972, 74.

[12] B. T. Balinga, *J. Org. Chem.*, 1970, **35**, 2031.

[13] B. C. Challis and M. R. Osborne, *J.C.S. Chem. Comm.*, 1972, 518.

than that by 0·8M-NaCl (see Table 3). Since $NOClO_4$ is known to be ionic [14] whereas NOCl is covalent,[15] this suggests that salt effects, but not specific catalysis by Cl^-, are important. Nitrosation reactions are well known to

TABLE 3

Effect of added neutral salts on k_0 [equation (2)] for nitrosation of NMA by Ph_2NNO in 50% aqueous ethanol at 25 °C; initial $[Ph_2NNO] = 5 \times 10^{-5}$M

10^5(NMA)/M	10^6(DPA)/M	[Acid]/M	[Salt]/M	$10^4k_0/s^{-1}$
1000	5	0·12 $HClO_4$		8·8
1000	5	0·12 $HClO_4$	0·8 $NaClO_4$	22
1000	5	0·12 $HClO_4$	0·8 NaCl	13
5	12·5	0·12 HCl		0·72
5	12·5	0·12 $HClO_4$		0·67
25		0·12 $HClO_4$	2·0 NaBr	32
500		0·12 $HClO_4$	0·35 NaSCN	69

be very sensitive to salt effects [16] but the larger effect of $NaClO_4$ observed here probably stems from its influence on the acidity of the medium.[17] At low (NMA), the effect of added acid on the reaction rate is less clear owing to experimental difficulties in assessing the slow rates under these conditions. However, results for (NMA) = 5×10^{-5}M in Figure 1 show that the degree of acid catalysis is much lower at this concentration. The data in Table 3 show further that Cl^- catalysis is also unimportant under these conditions. Our results therefore suggest that the reaction rate is independent of Cl^- and dependent on $[H^+]$ at high (NMA) but not at very low (NMA). Although Cl^- catalysis is not observed under any conditions,

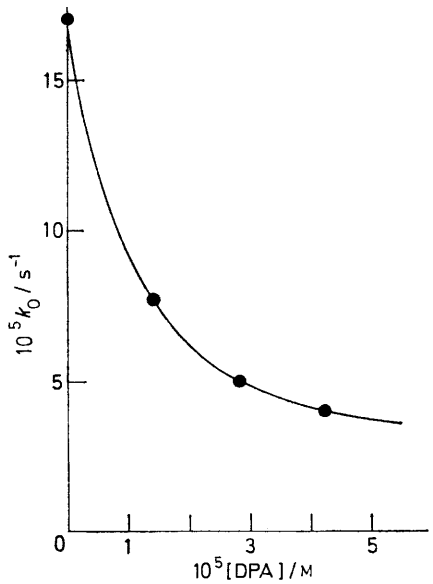


FIGURE 2 Reaction of Ph_2NNO with NMA in 50% aqueous ethanol at 25 °C: effect of added DPA on initial rate; initial $[Ph_2NNO] = 5 \times 10^{-5}$M, (NMA) = 7×10^{-5}M, [HCl] = 0·12M

the reaction is apparently catalysed by the more nucleophilic Br^- and SCN^- species (see Table 3).

Further information as to the mechanism of transnitrosation comes from the effect of added diphenylamine (DPA) on the various rate coefficients. It is evident from Figure 2 that k_0 [equation (2)] decreases with addition of DPA. Such anticatalysis is not unexpected since transnitrosation is reversible and addition of DPA must increase the rate of the reverse reaction.

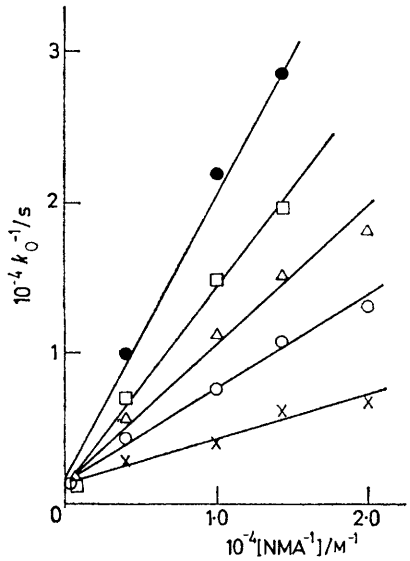


FIGURE 3 Reaction of Ph_2NNO with NMA in 50% aqueous ethanol at 25 °C: variation of initial rate with NMA concentration; initial $[Ph_2NNO] = 5 \times 10^{-5}$M, [HCl] = 0·12M; × [DPA] = 0, ○ $1·0 \times 10^{-5}$M, △ $2·0 \times 10^{-5}$M, □ $3·0 \times 10^{-5}$M, $5·0 \times 10^{-5}$M

The various kinetic dependences show that transfer of the nitroso-group from *N*-nitrosodiphenylamine to *N*-methylaniline occurs at a rate given by equation (3),

$$\text{Rate} = \frac{\bar{k}_3[H^+][Ph_2NNO](NMA)}{K'[H^+](DPA) + K''[H^+] + (NMA)} \quad (3)$$

where K′ and K″ are constants. These and $\bar{k}_3$ are most easily evaluated from kinetic data obtained with constant DPA and HCl concentrations. Under these conditions it can be shown that the dependence of k_0 [equation (2)] on (NMA) is given by equation (4) where $K''' = K' + K''$ and

$$1/k_0 = 1/\bar{k}_3[H^+] + K'''/\bar{k}_3(NMA) \quad (4)$$

this is verified by the linear plots of initial rate $1/k_0$ *versus* 1/(NMA) obtained in Figure 3 for HCl = 0·12M and (DPA) = 0—$5·0 \times 10^{-5}$M. The common intercept for these lines (*ca.* 1300 s) shows that $1/\bar{k}_3[H^+]$ is independent of (DPA) with $k_3 = 6·4 \times 10^{-3}$ l mol^{-1} s^{-1} for [HCl] = 0·12M. The slopes in Figure 3 give the ratios $K'''/\bar{k}_3$ which are plotted as a function of (DPA) in Figure 4. A linear dependence of $K'''/\bar{k}_3$ on (DPA) is evident with $K'''/\bar{k}_3 = 0·30 + 3·1 \times 10^4$(DPA) mol s l^{-1}: it follows that $K''' = 1·9 \times 10^{-3} + 200$(DPA) and that K′ = 200 l mol^{-1} and $K'' = 1·9 \times 10^{-3}$.

A similar, but less detailed, analysis of the reaction rate was carried out for another solvent mixture (25% dioxan

[14] W. R. Angus and A. H. Leckie, *Proc. Roy. Soc.*, 1935, *A*, **150**, 615; *Trans. Faraday Soc.*, 1935, **31**, 958.

[15] H. Schmid and A. Maschka, *Z. Phys. Chem.*, 1941, **B49**, 171.

[16] B. C. Challis and J. H. Ridd, *J. Chem. Soc.*, 1962, 5197.

[17] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

in water) from the experimental data given in Table 4. This generates a similar relationship to equation (3) with K″ doubled in size, but $\bar{k}_3$ and K′ almost unchanged. The

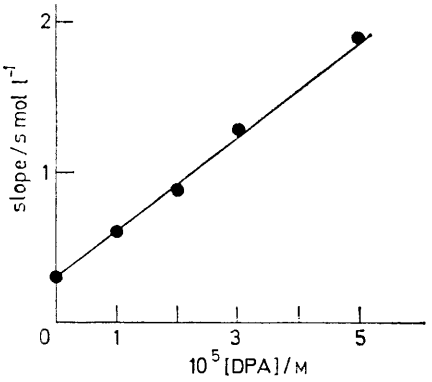


FIGURE 4 Variation of the slopes in Figure 3 with DPA concentration

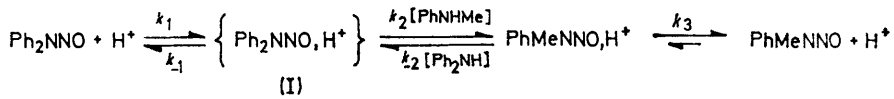
TABLE 4

Variation of k_0 [equation (2)] with (NMA) and (DPA) for the nitrosation of NMA by Ph_2NNO in 75% aqueous dioxan at 25 °C; initial $[Ph_2NNO] = 5 \times 10^{-5}$M; [HCl] = 0·10M

10^4(NMA)/M	10^5(DPA)/M	$10^4k_0/s^{-1}$
1·0		3·9
1·0	2·0	1·16
5·0		7·6
5·0	2·0	3·5
25		9·8
25	2·0	9·2

kinetics of the reaction in either solvent mixture, and in particular the acid catalysis, indicate that it is heterolytic; a radical pathway for the same reaction does take place under very different conditions and will be described elsewhere.[8]

The observed kinetics [equation (3)] suggest a mechanism by which the nitroso-group is transferred directly from an activated complex (I) derived by protonation of *N*-nitrosodiphenylamine to *N*-methylaniline without being released as nitrous acid or covalent nitrosyl chloride (Scheme 1). The steady-state kinetic expression for this



SCHEME 1 Direct transnitrosation between *N*-nitrosodiphenylamine and *N*-methylaniline

pathway is given by equation (5). In the dilute acidic

$$\text{Rate} = \frac{k_1k_2k_3[H^+][Ph_2NNO][PhNHMe]}{k_{-1}k_{-2}[Ph_2NH] + k_{-1}k_3 + k_2k_3[PhNHMe]} \quad (5)$$

medium used, the *N*-methylaniline [pK_A (50% EtOH–H_2O) = 3·90] [18] is almost completely protonated, whereas the diphenylamine is largely (*ca.* 90%) unprotonated.[19] So to a first approximation, the stoicheiometric concentrations of these amines can be expressed by (DPA) ≃ Ph_2NH and (NMA) = $[PhNHMe][H^+]/K_A$, where K_A = acid dissociation constant of $PhMeNH_2^+$ in this medium. In terms of stoicheiometric amine concentrations, equation (5) is therefore transposed to equation (6). This is

$$\text{Rate} = \frac{K_Ak_1k_2k_3[H^+][Ph_2NNO](NMA)}{k_{-1}k_{-2}[H^+](DPA) + k_{-1}k_3[H^+] + k_2k_3K_A(NMA)} \quad (6)$$

of the same form as the rate expression derived experimentally [equation (3)], with $k_1 = k_3 = 6{\cdot}2 \times 10^{-3}$ l mol^{-1} s^{-1}, $k_{-1}/k_2K_A = K'' = 1{\cdot}9 \times 10^{-3}$ and $k_{-2}/k_3 = K'/K'' = 1{\cdot}0 \times 10^5$ l mol^{-1}. It is apparent that any of the steps in Scheme 1 may be rate-limiting, depending on the concentrations of *N*-methylaniline and diphenylamine. When (NMA) is large, the first step (k_1) is slowest and the reaction is acid-catalysed; with lower (NMA), the second step (k_2) is rate-limiting and the degree of acid catalysis is much reduced because protonation of the *N*-nitrosodiphenylamine is counteracted by a lowering of the concentration of unprotonated *N*-methylaniline. Thus the experimental observations meet the kinetic expectations of Scheme 1 in a sensible way.

Hydrazoic Acid.—Aqueous nitrous acid is well known to react with hydrazoic acid and azide salts with the evolution of N_2 and N_2O [equation (7)].[20] The observation of a similar reaction with *N*-nitrosamines has not

$$HNO_2 + HN_3 \longrightarrow N_2 + N_2O + H_2O \quad (7)$$

been explicitly reported before, although it would be expected in as much as secondary *N*-nitrosamine formation is a reversible process.[9]

Our investigation concerned the interaction of *N*-nitrosodiphenylamine with sodium azide in the presence and absence of other added neutral salts. The reactions proceeded readily in acidic 50% aqueous ethanol at 25 °C with the evolution of nitrous gases, and were followed by the appearance of diphenylamine.

In many respects, the reaction kinetics were similar to those for NMA. Thus in the presence of excess of sodium azide, the rate followed equation (2). The kinetic order in azide depended on its concentration. Data in Table 5 confirm that k_0 is independent of the sodium azide concentration when this is relatively large. At lower concentrations, however, more complex kinetics are observed because the product diphenylamine inhibits further decomposition of the *N*-nitrosodiphenylamine by competing with the azide for the released nitrous acid. This complication can be circumvented if a known stoicheiometric concentration of diphenylamine is introduced into the

[18] S. Gutbezahl and E. Grunwald, *J. Amer. Chem. Soc.*, 1953, **75**, 559.

[19] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965, p. 92.

[20] G. Stedman, *J. Chem. Soc.*, 1959, 2949.

reaction mixture and the initial rate measured. Under such conditions, the rate becomes proportional to

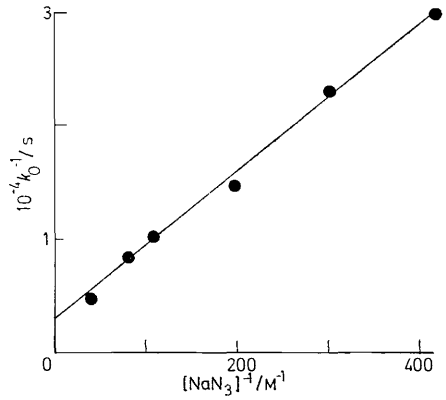


FIGURE 5 Denitrosation of Ph_2NNO by HN_3 in 50% aqueous ethanol at 25 °C: variation of rate with NaN_3 concentration; initial $[Ph_2NNO] = 5 \times 10^{-5}$M, [DPA] = 2×10^{-5}M, [HCl] = 0·10M

$[NaN_3]$ when this is low (Table 5). Also the plot of $1/k_0$ *versus* $1/[NaN_3]$ under these conditions (Figure 5) is

TABLE 5

Variation of k_0 [equation (2)] with (NaN_3) and [NaCl] for reaction with Ph_2NNO in 50% aqueous ethanol at 25 °C; initial $[Ph_2NNO] = 5 \times 10^{-5}$M

$10^3(NaN_3)$/M	10^5(DPA)/M	[Acid]/M	[Salt]/M	10^4k_0/s^{-1}
52		0·1 HCl	1·9 NaCl	17
26		0·1 HCl	1·9 NaCl	16
2·4	2	0·1 HCl		0·33
5·1	2	0·1 HCl		0·68
25		0·1 $HClO_4$	0·065 NaCl + 0·96 $NaClO_4$	2·9
25		0·1 $HClO_4$	0·091 NaCl + 0·934 $NaClO_4$	4·2

linear. When sodium azide is in excess, the reaction is also acid-catalysed (Figure 6) but not when the azide

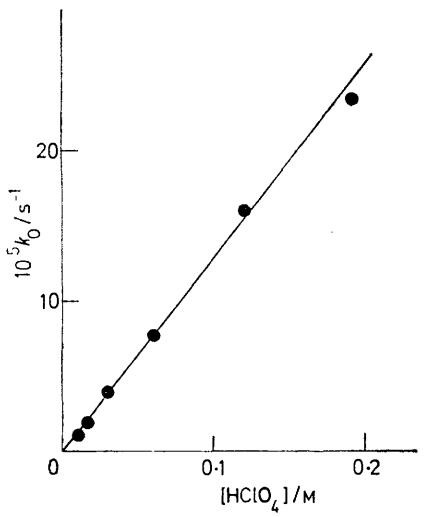


FIGURE 6 Denitrosation of Ph_2NNO by HN_3 in 50% aqueous ethanol at 25 °C: effect of acidity on initial rate; initial $[Ph_2NNO] = 5 \times 10^{-5}$M, $[NaN_3] = 0·025$M, [NaCl] = 0·1M

concentration is reduced. As for *N*-methylaniline before, the acidity independence must stem from protonation of the nitrous acid trap; the reactive entities are HN_3 and N_3^- but the concentration of the latter diminishes with increasing acidity.

Unlike the reaction with *N*-methylaniline, however, transfer of the nitroso-group to azide is Cl^- catalysed. Thus in 0·1M-$HClO_4$, even with excess of sodium azide, the transfer is immeasurably slow in the absence of Cl^- or other nucleophilic anions. The degree of Cl^- catalysis depends upon its concentration and this observation has an important bearing on the reaction mechanism. The rate is independent of $[Cl^-]$ at high concentrations (>1M), whereas a first-order dependence prevails at lower concentrations. The behaviour is demonstrated in Figure 7

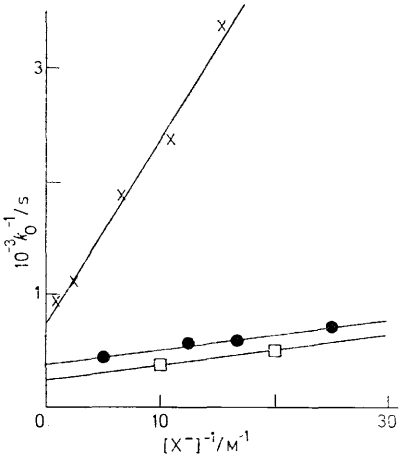


FIGURE 7 Denitrosation of Ph_2NNO by HN_3 in 50% aqueous ethanol at 25 °C: variation of rate with halide ion concentration; $[Ph_2NNO] = 5 \times 10^{-5}$M, $[NaN_3] = 0·025$M, $[HClO_4] = 0·1$M, [NaX] + $[NaClO_4] = 1$M; × X = Cl, ● X = Br, □ X = SCN

from which equation (8) is obtained. Catalyses were also observed for added bromide and thiocyanate ion, and

$$1/k_0 = 730 + 165/[Cl^-] \text{ s} \qquad (8)$$

linear correlations similar to equation (8) were obtained (see Figure 7). In these cases, the catalyst was effective at lower concentrations and the rate became independent of catalyst at >0·1M-Br^- and -SCN^-: both observations are consistent with a greater nucleophilic reactivity of these species relative to Cl^-.

The incidence of halide ion catalysis indicates that transfer of the nitroso-group must proceed *via* nitrosyl halides or nitrous acid (Scheme 2). The formation of nitrosyl azide (NON_3) is believed to be irreversible,

$$Ph_2NNO + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \{Ph_2NNO_2H^+\} + H_2O \underset{k_{-2}}{\overset{k_2[X^-]}{\rightleftharpoons}} Ph_2NH + NOX$$

(I)

$$NOX + N_3^- \overset{k_3}{\rightleftharpoons} X^- + NON_3 \longrightarrow N_2O + N_2$$

SCHEME 2 Transnitrosation *via* nitrosyl halides between *N*-nitrosodiphenylamine and azide ion

because it quickly decomposes to nitrogen and nitrous oxide.[20] Thus the 'steady state' rate expression in

terms of *actual* reactant concentrations for Scheme 2 is given by equation (9). Assuming as before that diphenylamine is largely unprotonated [19] whereas the

$$\text{Rate} = \frac{k_1k_2k_3[H^+][Ph_2NNO][N_3^-][Cl^-]}{k_2k_3[N_3^-][Cl^-] + k_{-1}k_{-2}[Ph_2NH] + k_{-1}k_3[N_3^-]} \quad (9)$$

azide ion is almost fully protonated and therefore $(HN_3) = 1/K_A[H^+][N_3^-]$ (where K_A = acid dissociation constant of $HN_3 = 6{\cdot}3 \times 10^{-6}$ mol l^{-1}),[21] the rate expression in terms of *stoicheiometric* concentrations is given by equation (10).

All the experimental observations are consistent with equation (10), although insufficient data are available to evaluate all the coefficients. For conditions under

$$\text{Rate} = \frac{K_Ak_1k_2k_3[H^+][Ph_2NNO](HN_3)[Cl^-]}{K_Ak_2k_3(HN_3)[Cl^-] + k_{-1}k_{-2}[H^+](Ph_2NH) + k_{-1}k_3K_A(HN_3)} \quad (10)$$

which the halide ion catalysis was examined {*i.e.* $(Ph_2NH) = 0$, $[Ph_2NNO] < (HN_3)$}, however, equation (10) simplifies to equation (11). Comparison with equation (8) then gives $k_1 = 0{\cdot}014$ l mol^{-1} s^{-1} and

$$\text{Rate} = \frac{k_1k_2[Ph_2NNO][H^+][Cl^-]}{k_2[Cl^-] + k_{-1}} \quad (11)$$

$k_2/k_{-1} = 4{\cdot}4$ l mol^{-1} This figure for k_1 is about twice that obtained previously with *N*-methylaniline ($k_1 = 6{\cdot}2 \times 10^{-3}$ l mol^{-1} s^{-1}), but the difference may be accounted for by the higher ionic strength ($\mu = 1{\cdot}1$ *versus* 0·12) of the azide reaction solutions. The k_2/k_{-1} parameter is also of interest. When $[Cl^-]$ becomes large, $k_2[Cl^-] > k_1$ (Scheme 2) and denitrosation of $\{Ph_2NNO,H^+\}$ then becomes faster than its collapse to reactants (k_{-1}).

This phenomenon can also be observed by a decrease in the degree of Cl^- catalysis with increasing $[Cl^-]$ for the nitrosation of diphenylamine with nitrous acid [equation (12)]. The rate of nitrosamine formation is given by

$$Ph_2NH + NOCl \underset{k_2}{\overset{k_{-2}}{\rightleftharpoons}} \{Ph_2NNO,H^+\} + Cl^- \overset{k_{-1}}{\rightleftharpoons} Ph_2NNO \quad (12)$$

equation (13) where $K_{NOCl} = [NOCl]/[HNO_2][H^+][Cl^-]$ and the rate coefficients have the same significance as in Scheme 2. The plot of $1/k_0$ (Rate $= k_0[Ph_2NH][HNO_2]$) *versus* $1/[Cl^-]$ [equation (14)] is reasonably linear (Figure 8) and, despite difficulties in measuring the very fast

$$\text{Rate} = k_{-2}K_{NOCl}[Ph_2NH][HNO_2][H^+][Cl^-]\frac{k_{-1}}{k_2[Cl^-] + k_{-1}} \quad (13)$$

reaction rates, a decrease in Cl^- dependence at high $[Cl^-]$ is clearly indicated by the significant positive intercept. From the ratio of the intercept of the plot

$$1/k_0 = \{k_2/k_{-1} + 1/[Cl^-]\}/k_{-2}K_{NOCl}[H^+] \quad (14)$$

($4{\cdot}2 \times 10^{-4}$ mol s l^{-1}) to its slope ($9{\cdot}6 \times 10^{-5}$ s l^{-2} mol^{-2}) a value of $k_2/k_{-1} = 4{\cdot}4$ l mol^{-1} is obtained, in good agreement with the value of this ratio derived from data for the reaction of *N*-nitrosodiphenylamine with azide under similar conditions.

Similar behaviour was observed for Cl^- catalysed nitrosation of diphenylamine in the absence of ethanol (95% aqueous dioxan as solvent) and for bromide ion catalysis.

Other Nucleophiles.—The interaction of *N*-nitrosodiphenylamine with several other nucleophilic species in 50% aqueous ethanol at 25 °C was also examined. The kinetics and mechanism resemble those for either *N*-methylaniline or azide ion.

Thus the denitrosation of *N*-nitrosodiphenylamine with hydroxylamine [equation (15)] is chloride ion-catalysed, and shows kinetics similar to those observed

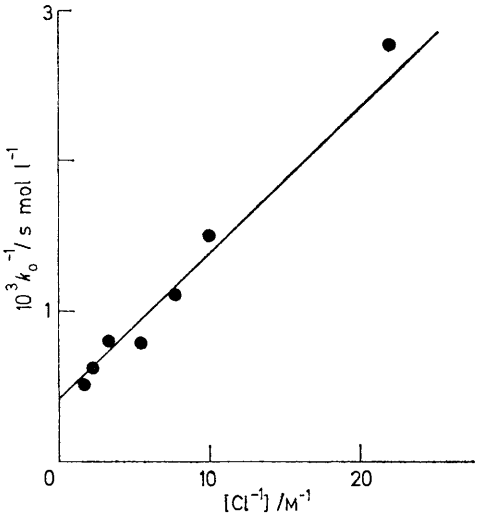


FIGURE 8 Nitrosation of Ph_2NH with nitrous acid in 50% aqueous ethanol at 25 °C: variation of rate with chloride ion concentration; initial $[Ph_2NH] = 1{\cdot}5 \times 10^{-5}$M, initial $[HNO_2] = 7{\cdot}5 \times 10^{-6}$M, $[HClO_4] = 0{\cdot}10$M, $[NaCl] + [NaClO_4] = 1$M

for azide ion [equations (8) and (9)]. The reaction with urea [equation (16)] probably proceeds similarly, but is

$$Ph_2NNO + NH_2OH \xrightarrow{HCl} Ph_2NH + H_2O + N_2O \quad (15)$$

$$Ph_2NNO + CO(NH_2)_2 \xrightarrow{HCl} Ph_2NH + CO_2 + NH_3 + N_2 \quad (16)$$

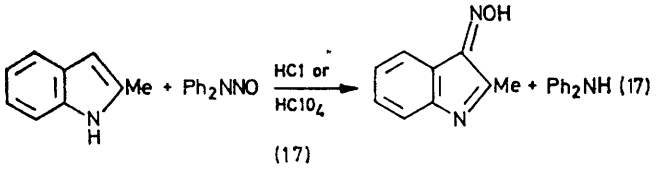
very slow in 0·1M-HCl; urea may compete poorly with diphenylamine for nitrosyl halide (or nitrous acid) released from the nitrosamine.

The diazotisation of sulphanilamide by *N*-nitrosodiphenylamine also shows kinetics in accord with an indirect mechanism [*cf.* Scheme 2 and equation (8)] and is catalysed by Cl^-, Br^-, or SCN^-. *N*-1-Naphthylethylenediamine, however, apparently reacts directly with the nitrosamine like *N*-methylaniline as the reaction shows no Cl^- catalysis.

Some substrates show both pathways. For example, aniline in HCl is diazotised by *N*-nitrosodiphenylamine: the reaction is Cl^- catalysed and the kinetics in the

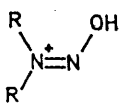
[21] B. C. Challis and G. Bhattacharjee, unpublished results.

presence of added diphenylamine are those predicted by a rate expression similar to equation (9). In 0·1M-$HClO_4$, however, reaction still occurs and a different rate equation is observed. Aniline may therefore react with $\{Ph_2NNO,H^+\}$ directly, but, in the presence of diphenylamine and Cl^-, the pathway involving release of nitrous acid is faster and only this is observed. Similar behaviour is observed for interaction with 2-methylindole to give the 3-nitroso-derivative [equation (17)].

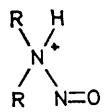


(17)

Conclusion.—Our results suggest that *N*-nitrosodiphenylamine may transfer the nitroso-function directly to other amines. Thus secondary amines, like other bases, appear to act as carriers of the nitrosonium ion (NO^+). Although this *N*-nitrosamine carrier is undoubtedly a protonated species, its explicit structure is not clear. There is considerable ambiguity from earlier investigations as to the conjugate acid structure of *N*-nitrosamines: evidence for *O*-protonation (II) in very strongly acidic media has been obtained from n.m.r. studies,[22] consistent with the dipolar character of neutral *N*-nitrosamines, but Layne *et al.*[23] have deduced from u.v. experiments that several structures, possibly molecular complexes, are formed in dilute acidic media. The *N*-conjugate acid structure (III) for the nitrosamine carrier is not supported by the remarkably different reactivity of *N*-nitrosodiphenylamine and the nitrous acidium ion ($H_2NO_2^+$) towards the nucleophilic species we have examined. There is a slight possibility that the reactivity we observe is complicated because of reaction *via* ethyl nitrite, formed *in situ* from nitrous acid and the co-solvent. Ethyl nitrite, however, is an ineffectual reagent



(II)

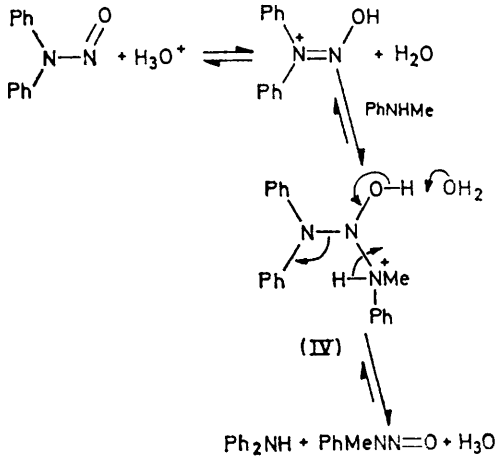


(III)

in aqueous solution unless it is protonated, in which case its reactivity should be similar to that of the nitrous-acidium ion.[24] Also, the results for NMA in aqueous dioxan suggest that the presence of ethanol is not fundamental to the incidence of direct transnitrosation.

Any mechanistic scheme has to account, in the first instance, for the abnormally high reactivity of NMA towards the *N*-nitrosodiphenylamine carrier. Enhanced reactivity is not evident, for example, on reaction with NOCl: thus values of $\bar{k}_2$ {Rate = $\bar{k}_2$(Substrate)[HNO_2]} for the nitrosation of NaN_3 and *N*-methylaniline with 0·1M-HCl in 50% aqueous ethanol are 105 and 200 l mol^{-1} s^{-1}, respectively.[8] A possible explanation (Scheme 3) is that NMA interacts with the *O*-protonated *N*-nitrosodiphenylamine to form the tetrahedral intermediate (IV), which then collapses to products. It is unclear, however, why this pathway should be favourable for NMA, but not for NaN_3 or Cl^-.

With high concentrations of either NaN_3 or NMA, the reaction rate becomes independent of these nucleophilic reagents. A decrease in kinetic order of this nature with increasing concentration of the nucleophile is consistent only with a shift of the slow step to an *earlier* stage on the reaction path. Evidently, the interaction of the nucleophile with the nitrosating agent is so rapid that formation of the latter becomes rate-limiting. This deduction is confirmed by the onset of significant acid catalysis only when the concentration of added NaN_3 or NMA is high. Furthermore, the close correspondence of rates under



SCHEME 3 Transnitrosation to NMA *via* a tetrahedral intermediate

these conditions for NaN_3, NMA, and other nucleophiles suggests that the rate-limiting step is a common one, dependent only on the solvent acidity. This could be either protonation of the *N*-nitrosodiphenylamine or an intramolecular rearrangement of this conjugate acid to form the active nitrosating species. Earlier studies of aromatic nitrosation (essentially the reverse process of our transnitrosation reaction) imply that either of these steps could be slow under the appropriate conditions. For example, proton transfer from the protonated nitrosamine is thought to be rate-limiting for the diazotisation of aniline in methanolic HCl.[25] In our case, however, preliminary examination of solvent isotope effects for both NMA and NaN_3 show that proton transfer to *N*-nitrosodiphenylamine is probably rapid: thus $k_0(H_2O)/k_0(D_2O) = 0{\cdot}83 \pm 0{\cdot}1$ for reaction of 5×10^{-5}M-Ph_2NNO with $5{\cdot}2 \times 10^{-2}$M-NaN_3 in 0·1M-HCl and 2·0M-NaCl in 50% aqueous ethanol at 25 °C and $k_0(H_2O)/k_0(D_2O) = 1{\cdot}0 \pm 0{\cdot}1$ for the reaction of $2{\cdot}5 \times 10^{-4}$M-Ph_2NNO with 0·025M-NMA in 75% aqueous

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ethanol at 25 °C. Thus unless the transition state for this proton transfer is exceedingly asymmetric,[26] this step must be rapid under our conditions and an intramolecular rearrangement of this conjugate to an active nitrosating agent must therefore be rate limiting. Slow rearrangement of the π-complex from the nitrosating agent and the substrate has been suggested to explain the diazotisation kinetics of anilinium ions in concentrated acids,[27] and a related process may be rate limiting in our case.

EXPERIMENTAL

Substrates and Reagents.—*N*-Nitrosodiphenylamine was prepared by the action of nitrous acid in diphenylamine,[28] and purified by crystallisation from methanol, m.p. 67·5 °C (lit.,[28] m.p., 68 °C). *N*-Methylaniline and aniline were distilled at reduced pressure and 2-methylindole was sublimed *in vacuo*, m.p. 58 °C (lit.,[29] m.p. 59 °C). Other substances were obtained from commercial sources and purified.

Kinetics.—The denitrosation of *N*-nitrosodiphenylamine was normally followed by direct observation of the optical density of the reaction mixture at 286 nm. The medium and substrate were mixed and the solution warmed to 25 °C; at zero time the nitrosamine (dissolved in 95% ethanol) was added, and the volume adjusted to 50 ml. The optical density of a sample of this solution in a 1 cm cell thermostatted at 25 °C was continuously recorded, using a Unicam SP 1800 spectrophotometer. The absorbance increased during denitrosation [ε (286 nm) in 0·1M-HCl in 50% aqueous ethanol: Ph_2NNO 6800, Ph_2NH 16,600]. The transnitrosation to NMA could also be followed by this method; the absorbance of NMA was low at the acidities used and the absorption by the product *N*-nitrosomethylaniline could be allowed for [ε (286 nm) 5000].

Direct observation of the nitrosated product was possible for some substrates. Thus 2-methylindole gave a coloured product which could be estimated by direct spectrophotometry of the reaction solution [2-methyl-3-nitrosoindole; $\lambda_{max.}$ 347 nm (ε 5800)]. Diazotised sulphanilamide was estimated by treating samples of the reaction mixture with *N*-1-naphthylethylenediamine solution and measuring the dye formed by visible spectroscopy, $\lambda_{max.}$ 541 nm (ε 51,000).[30]

The nitrosation of diphenylamine was followed by the addition of excess of sulphanilamide solution to a sample of the reaction mixture. The amount of unchanged nitrous acid present could then be estimated as diazotised sulphanilamide as above.

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