Chemistry of Nitroso-compounds.[1] The Reaction of *N*-Nitrosodiphenylamine with *N*-Methylaniline—a Direct Transnitrosation

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Summary In dilute acidic media, *N*-nitrosodiphenylamine can transfer the nitroso-group to other amines directly and without the intermediacy of nitrous acid, suggesting that secondary nitrosamines may act as proximate carcinogens in this way.

THE carcinogenic properties of secondary nitrosamines have been widely examined.[1] It has been suggested[2] that they are metabolically converted into diazoalkanes which then alkylate the bases of DNA. Some carcinogenic nitrosamines are known, however, for which this alkylation pathway seems unlikely (*e.g.* *N*-nitrosopiperidine, *N*-nitrosomethylaniline) and the question arises whether they can act as proximate carcinogens by transferring their nitroso-group to other compounds. Since nitrous acid is not appreciably carcinogenic,[2] this process may occur without the release of nitrous acid.

Transnitrosation has been reported under two different sets of conditions: in the most common method a secondary aromatic nitrosamine is heated with a nitroso-acceptor in an organic solvent,[3,4] which apparently involves a free-radical mechanism,[5] and it has been suggested that transnitrosation also occurs in aqueous acid in connection with the Fischer–Hepp rearrangement.[6] To establish the conditions under which nitrosamines may act in this way and the mechanism of these reactions, we have examined in detail the interaction of *N*-nitrosodiphenylamine with *N*-methylaniline [equation (1)] and with other substrates.

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

This reaction proceeds readily to equilibrium in dilute acid. We have studied it in 0·12M-HCl in 50% aqueous ethanol at 25°; the appearance of diphenylamine was followed by u.v. spectrometry and the initial rate of the forward reaction ($v = k_0[Ph_2NNO]$) was measured, to minimise complications due to its reversibility. The data listed in the Table show several characteristics. In particular, the rate appears to be (i) independent of [Cl^-], (ii) independent of

[PhNHMe] when this is high, and (iii) decreased by the addition of Ph_2NH to a much smaller extent than would be expected for a reaction proceeding *via* the liberation of HNO_2. [Relative reactivity towards HNO_2 in 0·1M-HCl, $k(Ph_2NH)/k(PhNHMe)$ = *ca.* 200].[4] The effects of sodium chloride and sodium perchlorate on the reaction rate are consistent with changes in the acidity of the medium and not with reaction *via* covalent nitrosyl salts.[7]

Transnitrosation, both with and without the intermediacy of nitrous acid, is observed for similar reactions of other aromatic amines and nucleophiles with *N*-nitrosodiphenylamine. For instance, the denitrosation of *N*-nitrosodiphenylamine by hydrazoic acid under similar conditions to those above (0·1M-$HClO_4$ in 50% ethanol + NaCl or $NaClO_4$ up to 1·02M concentration) is chloride ion-catalysed, and proceeds at a rate close to that calculated on the basis

Reaction of N-*nitrosodiphenylamine with* N-*methylaniline in* 50% *EtOH at* 25°

Initial $[Ph_2NNO] = 5 \times 10^{-5}$M

[Catalyst]/M	$10^5 \times$ [PhNHMe]/M	$10^6 \times [Ph_2NH]$/M	$10^3 \times k_0$/min^{-1}
0·12M-HCl	5	0	7·4
0·12M-HCl	5	50	1·4
0·12M-HCl	500	5	49
0·12M-HCl	1000	5	53
0·06M-HCl	500	5	20
0·12M-$HClO_4$	1000	5	53
0·12M-$HClO_4$ + 0·8M-NaCl	1000	5	78
0·12M-$HClO_4$ + 0·8M-$NaClO_4$	1000	5	130

These features are incompatible with transnitrosation proceeding *via* free nitrous acid. Instead they suggest that transfer of the nitroso-group occurs directly between the nitrosamine and the amine [equation (2)], for which the rate is given by equation (3), where $k_1 = 0{\cdot}37$ min^{-1}, $k_{-1}/k_2 = 2{\cdot}2 \times 10^{-5}$ mol l^{-1}, and $k_3/k_{-2} = 1{\cdot}1 \times 10^{-5}$. It is apparent that any of the steps in equation (2) may be rate-limiting, depending on the relative concentrations of

$$Ph_2NNO + HX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (Ph_2NNO{\cdot}H)^+X^- \underset{k_{-2}\,(Ph_2NH)}{\overset{k_2\,(PhNHMe)}{\rightleftharpoons}} (PhMeNNO{\cdot}H)^+X^- \xrightarrow{k_3} PhMeNNO + HX \quad (2)$$

$$v = \frac{k_1[H^+][Ph_2NNO] \times k_2k_3[PhNHMe]}{k_2k_3[PhNHMe] + k_{-1}k_3 + k_{-1}k_{-2}[Ph_2NH]} \quad (3)$$

diphenylamine and *N*-methylaniline. With excess of *N*-methylaniline, and without added diphenylamine, the first step is slow [equation (4)]. Although this appears to

$$v = k_1[H^+][Ph_2NNO] \quad (4)$$

represent the rate of protonation of the nitrosamine, no solvent isotope effect was observed for the reaction [$k(H_2O)/k(D_2O)$ = 1·0 with 0·025M-PhNHMe]. A more complex transformation is therefore indicated for this step, possibly involving a hydrate or π-complex of the nitrosamine as an intermediate.

of equation (5), with $k_1 = 0{\cdot}6$ min^{-1}; $k_{-1}/k_4 = 0{\cdot}23$; and

$$Ph_2NNO + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (Ph_2NNO{\cdot}H)^+ \underset{k_{-4}}{\overset{k_4\,(Cl^-)}{\rightleftharpoons}} Ph_2NH + NOCl$$
$$NOCl + N_3^- \xrightarrow{k_5} NON_3 \rightarrow N_2 + N_2O \quad (5)$$

k_{-4}/k_5 = *ca.* 600. Again the rate becomes independent of $[HN_3]$ when this is high, but in this case added diphenylamine inhibits the reaction much more than in the case of *N*-methylaniline. In the absence of chloride ion, reaction is extremely slow and probably proceeds *via* the nitrous acidium ion.

Transnitrosation involving the release of nitrous acid is also observed between aliphatic amines (*e.g.* piperidine + *N*-nitrosomorpholine), but more forcing conditions are needed (4M-HCl at 80°).

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