Direct Nitrosation of Aniline Derivatives and Other Nucleophilic Species by *N*-Nitrosodiphenylamine

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In the presence of a relatively high concentration of added sodium azide, *N*-nitrosodiphenylamine undergoes denitrosation in aqueous acid solution to give diphenylamine irreversibly. Reaction can be effected by Cl^-, Br^-, SCN^-, I^-, $SC(NH_2)_2$, or H_2O, and the reactivity can be reasonably well correlated with the Pearson nucleophilicity parameter *n*, except for I^- and $SC(NH_2)_2$, where it is thought a steric effect may operate. *N*-Nitrosodiphenylamine is more reactive than *N*-methyl-*N*-nitrosoaniline by a factor of *ca.* 10^2. Denitrosation is acid-catalysed and shows a solvent isotope effect (at low concentration of added nucleophile), $(k_0)_{D_2O} : (k_0)_{H_2O}$, of 2.0. These facts are consistent with a mechanism involving rate-determining attack by the nucleophile on the protonated form of the nitroso-amine. At high $[Br^-]$ the rate constant is no longer dependent on $[Br^-]$ and the observed solvent isotope effect changes to $(k_0)_{D_2O} : (k_0)_{H_2O} = 0.8$, suggesting that under these conditions proton transfer to the nitroso-amine becomes rate-limiting. A direct reaction occurs between *N*-nitrosodiphenylamine (again in aqueous acid solution) and aniline (and its ring-substituted derivatives), but not with the primary amines n-butylamine and cyclohexylamine. The acidity dependence, together with the substituent effects, can be interpreted in terms of a reaction between the protonated form of the nitroso-amine and the anilinium ion, initial attack occurring at the ring rather than at the amino-nitrogen atom, as has been suggested for diazotisation of aniline derivatives in 3M-perchloric acid. The solvent-promoted denitrosation is acid catalysed with $k_0 \propto h_0^{1.0}$. Generally the rate of denitrosation is reduced by the addition of diphenylamine, and from an analysis of the variation of the rate constant with [diphenylamine] in the presence of various nitrite traps, it is possible to confirm the overall reactivity sequence of some nitrite traps towards a free nitrosating agent as $HN_3 > NH_2SO_3H > \overset{+}{N}H_3OH$.

THE direct nitrosation of various nucleophilic species by *N*-nitroso-amines and -amides is a topic of current interest,[1,2] particularly with regard to the possibility that those reactions may have a bearing on the carcinogenic properties of *N*-nitroso-amines and -amides.[3] In aqueous acid solution, reaction usually occurs between the nucleophile and the protonated form of the nitroso-amine in the rate-determining step, but when strongly electron-withdrawing groups are present in the nitroso-amine proton transfer to the nitroso-amine is believed to be rate-limiting. Such a situation arises in the reactions of nitroso-amides [4] and -sulphonamides.[5] For *N*-methyl-*N*-nitrosoaniline (NMNA) the following order of reactivity of nucleophiles was established quantitatively:[2,6] $H_2O < Cl^- < Br^- < SCN^- < SC(NH_2)_2 < I^-$. A surprisingly good correlation existed between these reactivities and the nucleophilicity parameter *n* put forward by Pearson [7] on the basis of S_N2 reactions at carbon. On the basis of this correlation it is not to be expected that direct nitrosation of amines would occur readily, since in these acid solutions the concentration of free amine is very low. Although aniline has a Pearson *n* value comparable with that of bromide ion, it is to be expected that the value for the anilinium ion would be much smaller. No such reaction was observed [2] with aniline and NMNA, although the range of aniline concentration studied was not very large. Earlier however, Challis and Osborne [1] reported the results of a study of nitrosations brought about by *N*-nitrosodiphenylamine (NNDA) and concluded that a direct reaction between NNDA and *N*-methylaniline did occur, whereas for HN_3, hydrolysis of the nitroso-amine (or solvent-promoted denitrosation) was the preferred reaction. This direct reaction with *N*-methylaniline may involve the anilinium ion rather than the free base. A similar reaction scheme has been suggested [8] to account for the observed results in the diazotisation of aniline and the *N*-nitrosation of *N*-methylaniline by nitrous acid in 3M-perchloric acid. Here it is claimed (see Scheme 1) that the nitrous acidium ion $H_2\overset{+}{N}O_2$ reacts directly with the protonated form of the aniline, not in the first instance by attack at the amino-nitrogen atom, but rather as a transfer of NO^+ to the aromatic ring, before the intermediate undergoes a rearrangement to give the *N*-nitroso-compound (concurrently with a proton transfer to the solvent), which then forms the diazonium ion (if the amine is primary) by a series of fast steps. The evidence for such a mechanism was obtained from a detailed study of the variation of the rate constant with acidity, and also from the observed ring-substituent kinetic effects, which were not compatible with a reaction of the free amine. Some support for this mechanism was presented recently,[2,9] for the reverse reaction, *i.e.* denitrosation of NMNA in the absence of added nucleophiles, for which the kinetic results suggested a direct reaction between H_3O^+ and the protonated form of the nitroso-amine $C_6H_5\overset{+}{N}H(CH_3)NO$.

We thought it of interest to examine further the direct

[1] B. C. Challis and M. R. Osborne, *J.C.S. Perkin II*, 1973, 1526.
[2] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107.
[3] P. N. Magee and J. M. Barnes, *Adv. Cancer Research*, 1967, **10**, 163; U. Schutz and D. R. McCalla, *Canad. J. Chem.*, 1969, **47**, 2021.
[4] C. N. Berry and B. C. Challis, *J.C.S. Perkin II*, 1974, 1638; B. C. Challis and S. P. Jones, *ibid.*, 1975, 153.
[5] D. L. H. Williams, *J.C.S. Perkin II*, 1976, 1838.
[6] D. L. H. Williams, *J.C.S. Perkin II*, 1977, 128.
[7] R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, 1968, **90**, 319.
[8] E. Kalatzis and J. H. Ridd, *J. Chem. Soc.* (*B*), 1966, 529; E. C. R. de Fabrizio, E. Kalatzis, and J. H. Ridd, *ibid.*, p. 533.
[9] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1976, 691.

reaction of nitroso-amines with amines generally, in order to establish the mechanism firmly. This paper presents the results of our study, in which the reactivities of NNDA and NMNA are compared directly.

EXPERIMENTAL

N-Nitrosodiphenylamine (NNDA) was prepared by the usual procedure.[10] Stock solutions were made up in AnalaR methanol for the kinetic studies. All other materials used were obtained commercially, and were purified by recrystallisation, sublimation, or distillation before use. In each case m.p.s or b.p.s agreed with those given in the literature. Reactions were carried out in the cell of a Pye–Unicam SP 8000 spectrophotometer at 31.0 °C, and were started by the addition of a small portion (usually 1.00 ml) of the nitroso-amine solution to the aqueous acid solution containing all the other reagents (total volume usually 32 ml). The rate constant was calculated from absorption measurements at 310 nm (due to the reactant). Good first-order behaviour was normally found, except in some cases (see Discussion section) when there were complications due to the reversibility of the reaction; in such cases the initial rate constant was determined. A typical run is given for the reaction of NNDA (1×10^{-4}M) in sulphuric acid (0.6M) containing sodium azide (0.16M) and sodium bromide (0.104M). Generally k_0 values obtained had a

t/s	0	30	60	90	120	150	180	210
OD	0.857	0.742	0.734	0.687	0.641	0.605	0.573	0.542
10^3k_0/s^{-1}		4.23	4.25	4.14	4.20	4.13	4.08	4.10
t/s	240	270	300	∞				
OD	0.517	0.492	0.471	0.311				
10^3k_0/s^{-1}	4.06	4.09	4.09					

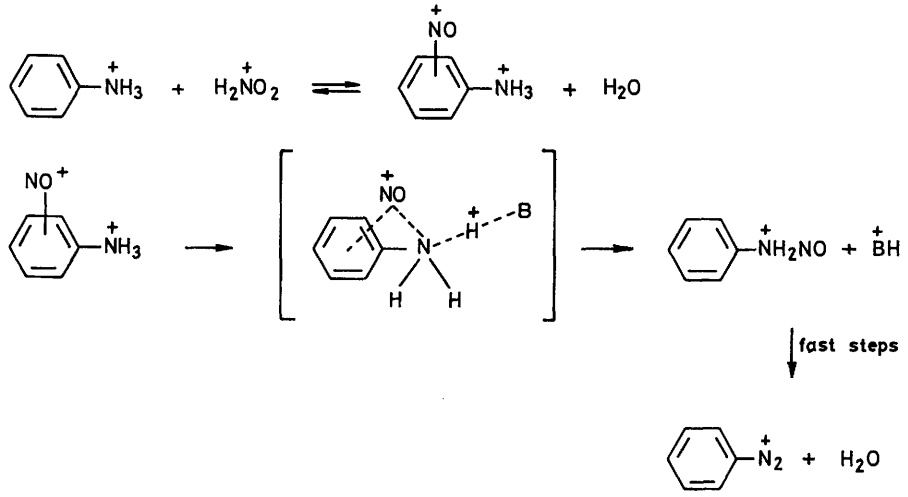
Mean $10^3k_0 = 4.14 \pm 0.07$ s^{-1}.

standard deviation of *ca.* ±2%, and duplicates agreed to within ±4%.

[10] A. I. Vogel, 'Textbook of Practical Organic Chemistry,' Longman, London, 1954, p. 547.
[11] D. L. H. Williams, *J.C.S. Perkin II*, 1975, 655.

RESULTS AND DISCUSSION

One of the difficulties encountered in denitrosation of nitroso-amines is the general reversibility of such reactions *i.e.* *N*-nitrosation of the secondary amine produced. In previous work [2,9,11] we have overcome this problem by carrying out the reactions in the presence of a sufficient concentration of a trap for the free nitrosating species thus formed (*e.g.* HNO_2 or NOCl) so that the rate of destruction of the free nitrosating species is much greater than the rate of its reaction with the secondary amine produced. Added sodium azide, hydrazine,



SCHEME 1

hydroxylamine, sulphamic acid, aniline, and urea have been used and the relative efficiencies of these traps established quantitatively.[11] Under these conditions the reactions are zero order in the trapping species To establish the limiting condition for the denitrosation

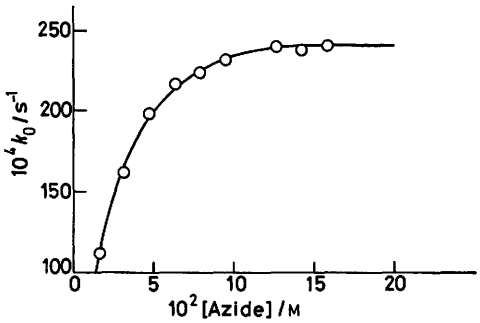


FIGURE 1 Variation of k_0 with [Azide]

of NNDA in sulphuric acid containing added sodium bromide, we measured the first-order rate constant k_0 (defined by $-d[NNDA]/dt = k_0[NNDA]$) as a function of the concentration of added sodium azide. The results are shown in Figure 1; k_0 increases with [NaN_3] added until at *ca.* 0.1M-NaN_3, k_0 levels off and the reaction becomes zero order in added NaN_3. This had earlier been demonstrated by Challis and Osborne [1] for reaction of NNDA in 50% ethanol–water and by us [2] for reaction

of NMNA in water with HN_3 and other nitrite traps. This behaviour is to be expected from the mechanism outlined in Scheme 2. HN_3 is one of the more efficient

$$Ph_2NNO + H_3O^+ \underset{}{\overset{K}{\rightleftharpoons}} Ph_2\overset{+}{N}HNO \underset{k_{-1}}{\overset{Br^-,k_1}{\rightleftharpoons}} Ph_2NH + NOBr$$

$$NOBr + HN_3 \xrightarrow{k_2} N_2 + N_2O + H^+ + Br^-$$

SCHEME 2

traps for nitrous acid [2] and reacts irreversibly [12] to form N_2 and N_2O. The general expression for k_0 inferred from Scheme 2 is given by equation (1), which simplifies to equation (2) at high $[HN_3]$ when $k_2[HN_3] \gg k_{-1}[Ph_2NH]$. The equilibrium constant for the initial

$$k_0 = \frac{k_1Kh_0[Y]k_2[HN_3]}{k_{-1}[Ph_2NH] + k_2[HN_3]} \quad (1)$$

$$k_0 = k_1Kh_0[Y] \quad (2)$$

protonation of the nitroso-amine is K, and it is assumed that a Hammett acidity dependence applies and that the protonation is not rate-determining. These assumptions are borne out experimentally (see later) by the observed h_0 dependence, the catalysis by the general nucleophile Y and the solvent isotope effect. It is noteworthy that a much higher concentration of added sodium azide is required in this case to produce the limiting condition of $k_2[HN_3] \gg k_{-1}[Ph_2NH]$, than for the corresponding reaction of NMNA; this is presumably because k_{-1} (which necessarily includes the equilibrium constant for protonation of the secondary amine if reaction occurs *via* the free base) is much greater for the NNDA case, due to the very much lower basicity of diphenylamine than that of *N*-methylaniline.

The measured solvent isotope effect $(k_0)_{D_2O} : (k_0)_{H_2O}$ was 2.0 for reaction in sulphuric acid (0.6M) containing sodium chloride (0.4M) and sodium azide (0.16M). This is consistent with the rapid equilibrium formation of the protonated form of NNDA and compares favourably with the value of 2.9 for the NMNA reaction.[2]

Effect of Added Cl^-, Br^-, I^-, SCN^-, *or* $SC(NH_2)_2$.—In carrying out the denitrosation of NNDA in sulphuric acid (0.6M) containing sodium azide > *ca.* 0.1M, it is a straightforward procedure to establish any catalysis by nucleophiles Y and so obtain the product k_1K for each nucleophile. For each of the nucleophiles Cl^-, Br^-, I^-, SCN^-, and $SC(NH_2)_2$ good straight lines were obtained for the plot of k_0 against [Y], with a common intercept, which represents denitrosation by the solvent. Figure 2 shows (on different scales) the lines for Cl^- and I^-. The results for each nucleophile are presented in terms of the Pearson nucleophilicity n in Figure 3 as a plot of $\log(k_1K)$ against n, together with the earlier data obtained for NMNA.[2] The points for the latter system all lie close to a straight line of slope 1.41, indicating that apparently the same criteria apply to the reactivity of nucleophilic substitution at nitrogen as do for the more conventional S_N2 reactions at carbon. Overall, NNDA is more reactive than NMNA by a factor of *ca.* 10^2. It is difficult to account for this difference exactly since K and k_1 are not separately determinable. However if the analogy with the corresponding aniline derivatives (*N*-phenyl and *N*-methyl) is used, then it is to be expected that K would be much smaller for NNDA than for NMNA. If this is so then k_1 must be several powers of ten greater for the *N*-phenyl than for the *N*-methyl nitroso-amine. This may be interpreted in terms of the electron attraction by a phenyl relative to a methyl

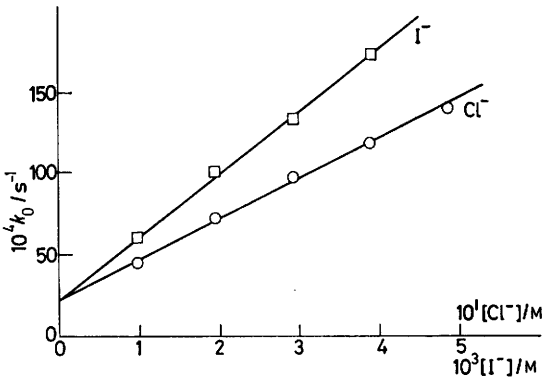


FIGURE 2 Variation of k_0 with $[I^-]$ or $[Cl^-]$

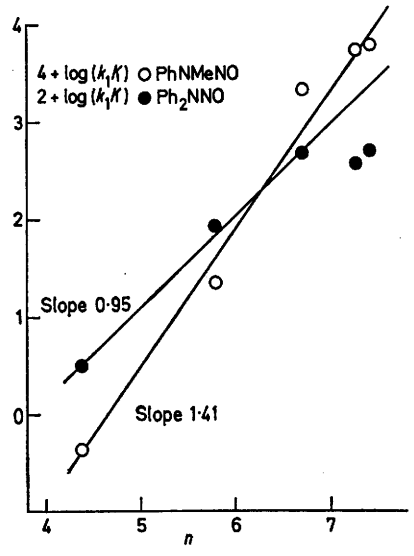


FIGURE 3 Variation of $\log(k_1K)$ with Pearson nucleophilicity n

group, reflected in the σ^* value of +0.60 for a phenyl substituent, although other factors, such as the steric requirements, may be important. The slope of the line is significantly bigger for NMNA than for NNDA, the greater selectivity shown by the former reflecting its lower reactivity. The points for I^- and $SC(NH_2)_2$ depart significantly from the line drawn through the Cl^-, Br^-, and SCN^- points for NNDA. It is possible that a steric effect becomes operative here for these larger nucleophiles, which is not important for NMNA.

At quite high $[Br^-]$ the denitrosation reaction loses its

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

dependence upon the bromide ion (see Table 1). This was also observed earlier by Challis and Osborne.[1] Under these conditions (0.154M-Br^-) the solvent isotope effect $(k_0)_{D_2O} : (k_0)_{H_2O}$ was 0.8, contrasting with the value of 2.0 when reaction was first order in halide ion. This

TABLE 1

Variation of k_0 with $[Br^-]$

$[Br^-]$/M	$10^4k_0/s^{-1}$
0.024	16
0.041	23
0.056	28
0.072	33
0.088	38
0.104	41
0.120	44
0.136	43
0.154	46

requires that at high $[Br^-]$ an earlier step in the reaction sequence becomes rate limiting. The solvent isotope effect suggests that the proton transfer is now the rate-limiting step. It has been argued that this is the case, at all Y concentrations, for the reactions of nitroso-amides [4] and a nitroso-sulphonamide,[5] where there is no halide ion catalysis and the solvent isotope effects $(k_0)_{D_2O} : (k_0)_{H_2O}$ are respectively 0.5 and 0.7. These values, together with the 0.8 found in the present work are perhaps rather large for a primary isotope effect, but it is quite conceivable that the transition state leading to the protonation of these very weak bases is quite unsymmetrical,[13] with a resulting isotope effect not far away from 1. We prefer this interpretation to that given by Challis and Osborne,[1] who suggested an intramolecular rearrangement of the protonated form of the nitroso-amine to some active form, as the rate-limiting step.

However, it can be argued from the Westheimer treatment and the expected pK_a values of the nitroso-compounds concerned, that $(k_0)_{D_2O} : (k_0)_{H_2O}$ should be smaller for NNDA than for the nitroso-amides and nitroso-sulphonamides. It is possible that we are not at the limiting situation at $[Br^-]$ 0.154M, but it may well be that the factors, such as the importance of tunnel effects or steric requirements, are involved. There is currently no general agreement as to the quantitative explanation of variations of this type in the kinetic isotope effect.

The Effect of Added Amines.—Challis and Osborne [1] concluded that a direct reaction occurred between NNDA and *N*-methylaniline, mainly from the evidence that the reaction was not catalysed by chloride ion. In that case, reaction was complicated by the reversibility of the reaction, so that only initial rates of reaction (<7%) were measured. In order to avoid this complication, we undertook to examine this reaction with primary amines, where it is to be expected that the initially formed *N*-nitroso-amine would react rapidly and irreversibly to form the diazonium ion. The results for aniline, n-butylamine, and cyclohexylamine are shown in Figure 4, and refer again to reaction in *ca.* 0.6M-H_2SO_4 containing 0.16M added sodium azide. Clearly the reaction is first order in aniline, and within experimental error independent of the concentrations of both other amines. There was also no evidence for a direct reaction with adenine and 5-methylcytosine over a concentration range of both these amines of 0—0.02M. The slope of the line gives a k_1K value for aniline which is significantly greater than that for chloride ion in this reaction, which is rather surprising (but in accord with the findings of Challis and Osborne [1]), considering that aniline is protonated in this acid solution to an extent >99.9%. Aniline itself has a Pearson *n* value of 5.70 (close to that of bromide ion), but because of the much reduced concentration of the free base, if reaction were to occur *via* the free base, then it is ' too reactive ' (compared with the other nucleophiles and using the nucleophilicity-reactivity correlation of Figure 3) by a factor of *ca.* 10^3. This direct reaction appears to be a property of the

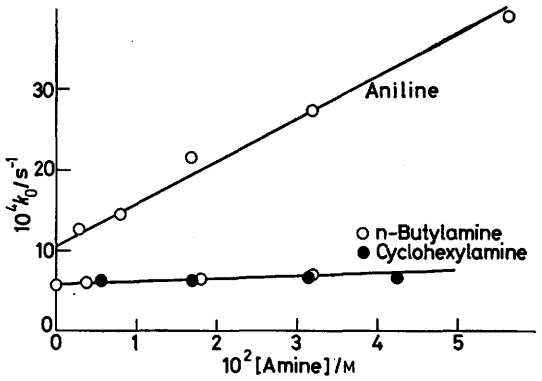


FIGURE 4 Variation of k_0 with [Amine]

aromatic amine, since n-butylamine and cyclohexylamine are virtually inert under the same conditions.

The reaction with aniline was examined in more detail over a range of acidity. Linear plots of k_0 against [Aniline] were obtained at each acidity with both the intercepts and slopes of the lines increasing with increasing acidity. The intercept represents the solvent-promoted reaction and would be expected to increase with acidity for reaction *via* the protonated nitroso-amine species. The increasing slopes, given in Table 2,

TABLE 2

Slopes of k_0 against $[PhNH_2]$ plots as a function of the acidity

$[H_2SO_4]$/M	Slope/l mol^{-1} s^{-1}
0.42	0.044
0.52	0.053
1.04	0.11
1.94	0.19

show clearly that the direct reaction with aniline is also acid catalysed, suggesting that the reacting species is the anilinium ion rather than the free base, for if reaction occurred between the protonated nitroso-amine and aniline itself, then as a first approximation the reaction

[13] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265.

rate should be independent of the acidity since [protonated nitroso-amine] should increase and [free aniline] decrease as the acidity is increased. Support for this view comes from a study of the substituent effects shown in Table 3 where the relative rate constants $(k_0)_X : (k_0)_H$

TABLE 3

Substituent effects

Amine	$Ph_2\overset{+}{N}HNO$ reaction $(k_0)_X : (k_0)_H$	$H_2\overset{+}{N}O_2$ reaction $(k_1)_X : (k_1)_H$
Aniline	1	1
p-Toluidine	9.1	7.4
m-Toluidine		6.8
p-Chloroaniline	0.8	0.2
m-Methoxyaniline	4.4	18.6

for the reaction of NNDA with some substituted anilines are given, together with, for comparison, the same rate constant ratios for diazotisation [8] by $H_2\overset{+}{N}O_2$ in 3M-perchloric acid. Whilst the two sets of results do not exactly parallel each other there are notable similarities. Particularly significant is the appreciable rate enhancement brought about by an *m*-methoxy substituent for both reactions. This was interpreted for the $H_2\overset{+}{N}O_2$ reactions in terms of a mechanism in which the NO group is transferred to the anilinium ion, not as an *N*-nitrosation but rather by initial electrophilic attack at the π-electron system of the aromatic nucleus. This was thought to be followed by a migration of the NO group to the amino-nitrogen atom, concurrently displacing a proton to the solvent (Scheme 1). Our results support such a scheme and suggest that the protonated forms of nitroso-amines can also effectively transfer NO^+ directly to an aromatic system.

There was evidence of a degree of reversibility in the NNDA–aniline (and derivatives) reaction. Possibly the reverse reaction of a direct nitrosation of diphenylamine by $Ph\overset{+}{N}H_2NO$ competes somewhat with the diazonium ion formation. Recent work [14] on the diazotisation of aniline derivatives by nitrous acid has shown that, particularly at high concentrations of nucleophilic species, the reaction can be significantly reversible.

Denitrosation without Added Nucleophiles.—In the absence of added nucleophiles, denitrosation of NNDA occurs but at a much smaller rate. The reaction is acid catalysed as shown by the results in Table 4, which

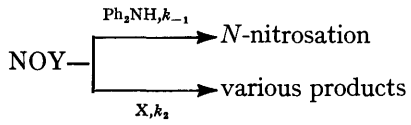
TABLE 4

Variation of k_0 with acidity

$[H_2SO_4]$/M	10^4k_0/s^{-1}
0.60	5.7
1.15	19
1.73	34
2.34	74
2.99	155

again refer to reactions in the presence of 0.16M sodium azide, to ensure the irreversibility of the reaction. A plot of log k_0 against $-H_0$ gives a good straight line of slope 1.0, which means that NNDA behaves here as a Hammett base. No rearrangement to *p*-nitrosodiphenylamine (the Fischer–Hepp rearrangement) was detected in this acidity range. In the absence of added sodium azide or any other nitrite trap, it is to be expected that rearrangement would compete more effectively with denitrosation (*cf.* ref. 2), but in fact blue colours developed rapidly in the reaction solutions. This blue material was not extractable into organic solvents, but was destroyed by the addition of (a) diphenylpicrylhydrazyl, (b) ascorbic acid, (c) sodium azide, or (d) halide ion. It is possible that under these conditions radical cations are formed which are related to the well known Wurster's Blue.[15] The addition of diphenylamine, in the absence of nitrite traps, in order to suppress denitrosation and thus favour the rearrangement reaction [16] also resulted in the formation of blue colours.

Quantitative Effect of Various Nitrite Traps.—As expected from the general form of k_0 [equation (1)] the addition of diphenylamine, at constant acidity, nucleophile concentration and nitrite trap concentration, decreased the value of k_0. This effect had earlier been noted by Challis and Osborne.[1] From the variation of $(k_0)^{-1}$ with $[Ph_2NH]$ added, it is possible to obtain the rate constant ratio k_2/k_{-1} which represents the reactivity



of any nitrite trap X towards a nitrosating agent NOY, relative to its reaction with Ph_2NH. This procedure has been used for the NMNA reaction [6,11] for various nitrosating agents and a range of nitrite traps X. In the present work results were obtained only for NOSCN as the nitrosating agent and for three different X species.

TABLE 5

k_2/k_{-1} Values for different X species

X	NNDA reaction k_2k_{-1}	NMNA reaction k_2k_{-1}
HN_3	1.0×10^{-1}	22
NH_2SO_3H	5.0×10^{-3}	0.25
$\overset{+}{N}H_3OH$	5.4×10^{-4}	1.1×10^{-2}

Good straight lines were obtained in each case for the plot of k_0 against $[Ph_2NH]$ added at constant $[H^+]$, [X], and [Y] (for reaction in 50% methanol–water), and k_2/k_{-1} readily obtained from the slope. The results, together with those for the corresponding NMNA reaction are in Table 5. The two sets of results are not strictly comparable because of the different solvent systems (50% methanol–water, and water), but nevertheless it appears that Ph_2NH is significantly more reactive than PhNMeH towards NOSCN. The order of overall bulk reactivity

[14] M. R. Crampton, J. T. Thompson, and D. L. H. Williams, to be published.

[15] P. A. S. Smith, 'Open Chain Nitrogen Compounds,' Benjamin, New York, 1965, vol. 1, p. 113 and references therein.

[16] D. L. H. Williams, *Tetrahedron*, 1975, **31**, 1343.

of the X species is also the same, $HN_3 > NH_2SO_3H > \overset{+}{N}H_3OH$. Similar results were found [11] for PhNMeH with other nitrosating species NOCl, NOBr, and $H_2\overset{+}{N}O_2$

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