Reactivity of Nucleophilic Nitrogen Compounds towards the Nitroso Group

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We discuss the reactivity of 43 nucleophilic nitrogen compounds towards the nitroso group of *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (MNTS), and in some cases with alkyl nitrites. The series of nucleophiles considered is structurally very varied, includes members exhibiting the alpha effect, and covers 8 pK_a units and a range of reactivities of almost five orders of magnitude. The values of solvent isotope effects and activation parameters have been measured and throw light on the structure of the transition states involved. Reactivities do not correlate well with the basicity of the nucleophile, largely owing to the behaviour of primary amines, ammonia and nucleophiles with an alpha effect. Application of the curve crossing model suggests a relationship with vertical ionization potentials. The relationship with Ritchie's N_+ scale is discussed, and interesting correlations with the reactivities of the same nucleophiles in various other chemical processes are noted.

One of the main unachieved goals of chemistry is the quantitative understanding of chemical reactivity. Marcus' theory of the relationship between kinetic and thermodynamic barriers to chemical reaction has explained the empirical findings concerning a certain number of reaction processes, including proton transfer [1] and S_N2 reactions,[2] but in most cases the best available tools for the systematization and prediction of reactivity are qualitative approaches such as Pearson's theory of hard and soft acids [3] or empirical reactivity scales.[4]

Various quantum mechanical methods have been developed which may help to explore the root cause of the correlations noted above. Particularly relevant are Klopman's theory of frontier orbitals [5] and Pross and Shaik's developments based on the 'curve crossing model'.[6] Application of these theories to anion–cation combination,[7] reactions between nucleophiles and esters,[8] and other reactions suggests that, in some of the most important kinds of chemical process, the physical parameter governing the relative reactivities of a family of nucleophiles with a given electrophile is the vertical ionization potential (vE_i). These studies also attribute to single electron transfer an important role in the activation process, thus resolving long-standing quantum problems [9] and reestablishing the importance of single electron transfer as a fundamental process in organic chemistry.[10]

In previous work,[11] we found that the vE_i values of a number of nucleophilic nitrogen compounds correlated reasonably well with their reactivities with *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (MNTS) in aqueous solution, even though the available vE_i data referred to the gas phase. Similar behaviour has been reported by Oae *et al.*[12] for the reactions of various nitrogen compounds with an alkyl nitrite. Both these kinds of reaction involve nucleophilic attack on the N=O group. To investigate whether these results are generally valid for reactions between nucleophiles and nitroso compounds, and to explore possible relationships with other, better-understood chemical processes, we have now carried out an exhaustive study of the reactivities of numerous nucleophilic nitrogen compounds with the N=O group of MNTS (and in some cases with that of alkyl nitrites, especially 2-ethoxyethyl nitrite, EEN), and of the factors affecting nucleophilic behaviour in these and related systems. We consider data obtained under similar conditions for the reaction between MNTS and the 15 nucleophiles discussed in our previous paper [11] and for 28 nucleophiles for which no data were previously available. Our results relate the behaviour of nucleophiles in apparently unrelated chemical processes.

Experimental

Alkyl nitrites were prepared in an acid medium from sodium nitrite and the parent alcohol, following standard procedures,[13] and stored over molecular sieves. *N*-Methylbenzylamine (Aldrich) was distilled under argon and used shortly afterwards. Thiomorpholine was precipitated as its perchlorate salt, which was recrystallized from isopropanol–diethyl ether mixtures. Heavy water (99.77% D) was supplied by C.I.E.M.A.T. (Spain). All other reagents were Merck or Aldrich products of the maximum commercially available purity, and were used without further purification.

All kinetic experiments were performed with a great excess of the nucleophile over MNTS or the alkyl nitrite. In most reactions, pH was controlled using buffer solutions of the nucleophile itself, which were made up with amine and hydrochloric acid, ammonium salts, or amino acid and NaOH. For the reaction between azide and EEN this procedure was ruled out by the low pK_a of HN_3, which led to considerable acid hydrolysis of EEN at pH near its pK_a;[14] in this case, a 0.5 mol dm^{-3} sodium carbonate/0.5 mol dm^{-3} sodium hydrogencarbonate buffer was used.

Reaction kinetics were generally studied by following the change in absorbance (generally in the range of 250–270 nm) using Uvikon 930 or Milton Roy Spectronic 3000 array spectrophotometers. Absorbance–time data always fitted the first-order integrated equation, and k_0, the corresponding first-order pseudoconstant, was reproducible to within 3%. In the case of thioproline, owing to the instability of the *N*-nitroso compound under the working conditions and the resulting complex absorbance–time profiles, we studied the reaction by following the decrease in MNTS concentration by HPLC, using Beckman System Gold equipment. Known volumes of a thermostatted reaction mixture containing MNTS and thioproline at pH 6.2 (maintained by the amine itself) were analysed at different times using 50:50 (v:v) CH_3OH/H_2O as the mobile phase and with a Beckman Reverse Phase 5 μm

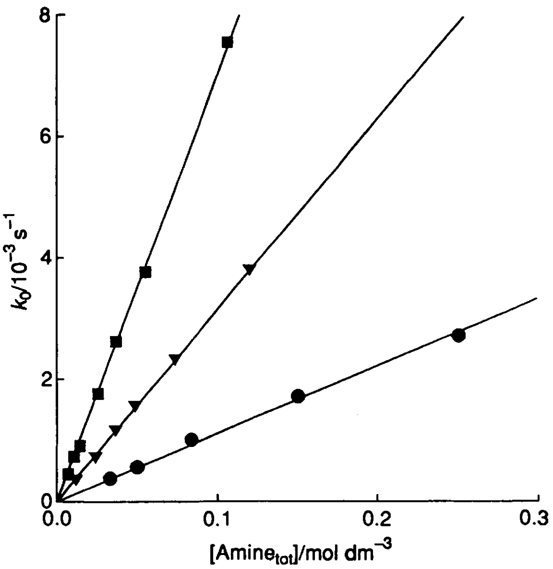


Fig. 1 Influence of the total amine concentration upon the pseudo-first-order rate constant k_0 for reaction with MNTS in 3.3% dioxane. (■) *N,N'*-dimethylethylenediamine, [free amine]/[ammonium salt] = 1. (▼) Dipropylamine, [free amine]/[ammonium salt] = 0.99. (●) Thiomorpholine, [free amine]/[ammonium salt] = 15.

Table 1 Influence of the polarity of the medium on the first-order pseudoconstant k_0 in the reaction of MNTS with *N*-methylbenzylamine

Cosolvent	% Cosolvent	k_0/s^{-1}
Dioxane[a]	15.0	1.87×10^{-3}
	21.6	1.34×10^{-3}
	28.3	8.84×10^{-4}
	35.0	5.82×10^{-4}
	41.6	3.77×10^{-4}
	48.3	2.42×10^{-4}
	55.0	1.35×10^{-4}
	61.6	8.11×10^{-5}
	71.6	3.94×10^{-5}
Ethanol[b]	20.0	4.82×10^{-3}
	26.6	3.58×10^{-3}
	33.0	2.39×10^{-3}
	40.0	1.55×10^{-3}
	53.0	7.01×10^{-4}
	60.0	5.35×10^{-4}
	66.6	3.96×10^{-4}
	73.3	2.97×10^{-4}
	80.0	2.26×10^{-4}
	90.0	1.50×10^{-4}

[a] [*N*-methylbenzylamine] = 4.56×10^{-2} mol dm^{-3}. [b] [*N*-methylbenzylamine] = 9.30×10^{-2} mol dm^{-3}.

Ultrasphere C_{18} column. Flow rate was 2 cm^3 min^{-1}. Peak areas for MNTS were obtained by electronic integration of the UV absorbance at 250 nm.

pH was measured with a Radiometer 82 pH-meter equipped with GK2401C or GK2401B (for pH > 11) combined glass electrodes.

Because of its poor solubility in water, MNTS was dissolved in a small quantity of organic solvent (usually dioxane) prior to preparation of aqueous solutions. The final concentration of organic solvent in the medium was usually 3.3% (v/v), but was 10 or 15% when higher concentrations of MNTS (*ca.* 10^{-3} mol dm^{-3}) were necessary in order to follow the reaction at 330 nm, at which wavelength its molar absorptivity is less than at 250–270 nm. EEN, which is unstable in water,[14] was dissolved in dioxane and reactions were initiated by addition of a small volume of this solution to the reaction mixture. All results reported below are accompanied by a statement of the volume percentage of organic solvent in the medium.

Nitrite ions produced by reactions between tertiary amines and MNTS were determined using a modification of Shinn's method.[15] The reaction mixture was brought to pH *ca.* 2 and mixed with sulfanilamide (Merck) and naphthylethylenediamine (Carlo Erba), absorbance at 550 nm by the dye formed was measured, and nitrite was quantified using the value 4.6×10^4 dm^3 mol^{-1} cm^{-1} for the molar absorptivity of the dye.

Results

Reaction with Secondary Amines.—Reactions between MNTS or alkyl nitrites and secondary amines produce *N*-nitrosamines in quantitative yield.[11–16] In most cases, we confirmed this spectroscopically. The reaction spectra, with clear isosbestic points, are typical of kinetically uncomplicated processes. Plotting k_0 against total amine concentration (free base plus conjugate acid) generally yielded good straight lines (see Fig. 1 for some examples) showing that the reaction was of first order with respect to the amine. For thiomorpholine, however, such plots deviate slightly downwards from linearity at total amine concentrations greater than 0.25 mol dm^{-3} (typically by 20% at a total thiomorpholine concentration of 0.5 mol dm^{-3}); this behaviour is considered to be an effect of the medium. *N*-Methylbenzylamine was the other exception, since its poor solubility in water meant that large concentrations of dioxane were necessary in order to study the behaviour of high concentrations of the amine; in 40% dioxane, k_0–[amine$_{tot}$] plots began to deviate from linearity at amine concentrations of about 0.1 mol dm^{-3}. As in the case of thiomorpholine, the observed non-linear behaviour is tentatively attributed to an effect of the medium; the possibility of association between amine molecules at high amine concentrations appears to be ruled out by the fact that *N*-methylbenzylamine complies with Beer's law up to concentrations of at least 0.7 mol dm^{-3}, while the hypothesis of a medium effect is supported by the effect of the polarity of the medium on the reaction rate (Table 1). The influence of ionic strength on the reaction rate must be negligible in each case, since there was perfect agreement between the results of experiments performed with no control of ionic strength and others in which ionic strength was controlled with NaCl.

Plotting k_0 against pH for constant total amine concentration produced sigmoid curves that could be put in linear form by plotting $1/k_0$ against [H$^+$] (see Fig. 2 for an example). This behaviour is in keeping with the assumption that reaction takes place directly with the basic form of the amine, without involvement of general acid or base catalysis,[11] since this assumption leads to the rate equation in eqn. (1) where k is the

$$k_0 = \frac{kK_a[\text{amine}_{tot}]}{K_a + [\text{H}^+]} \qquad (1)$$

bimolecular rate constant for reaction between free amine and MNTS, and K_a is the acidity constant of the protonated amine. Values of K_a obtained from these plots are always in good agreement with literature values. Table 2 lists the values of k obtained for the different secondary amines and amino acids studied, as well as values for several secondary amines obtained in a previous work.[11] Table 3 lists k values obtained in this work or by others[17,18] for reaction with EEN or the similar reagent 2-hydroxyethyl nitrite. In general, the reactivities of the nucleophiles with MNTS are very similar to their reactivities with EEN. Table 4 lists k for the reaction of morpholine with several alkyl nitrites, a strong accelerating effect produced

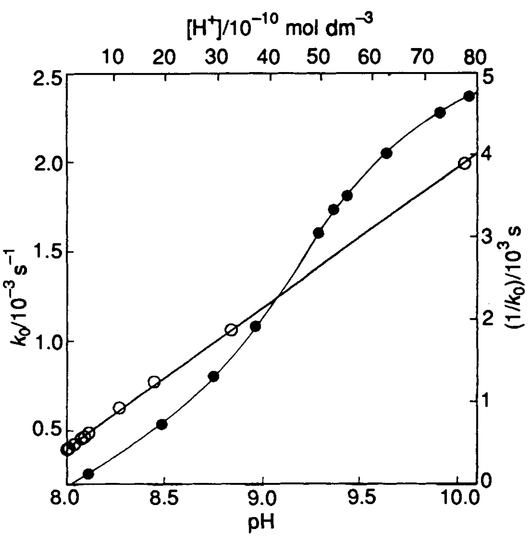
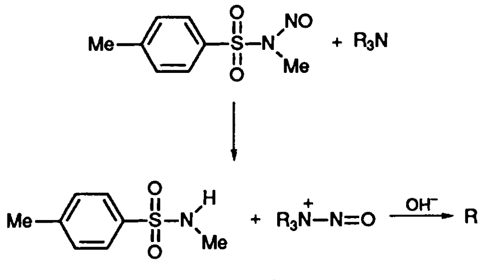


Fig. 2 Influence of acidity on the pseudo-first-order rate constant k_0 for the reaction between MNTS and thiomorpholine at 3.3% dioxane; [thiomorpholine$_{tot}$] = 0.24 mol dm^{-3}; (●) k_0 *vs.* pH; (○) $1/k_0$ *vs.* [H$^+$]

by the presence of electron-withdrawing substituents in the alcoholic moiety being observed.

In some cases the solvent isotope effect on the reaction was studied (Table 5). For reactions with MNTS the ratio k_H/k_D was always near unity, in contrast to the considerably higher value found for the reactions of hydroxyproline and morpholine with EEN and with other alkyl nitrites, in agreement with some earlier reports.[12] Activation parameters were also determined in some cases, and again there was a marked difference between MNTS and EEN: in spite of their having very similar overall reactivities, the entropy of activation is considerably less favourable for EEN than for MNTS, while the reverse holds for the enthalpy of activation (Table 6).

Reaction with Tertiary Amines.—The difficulty of nitrosation of tertiary amines in acid media[19] is the basis of a well-known test for distinguishing between primary, secondary and tertiary amines. In neutral or basic media, however, tertiary amines readily react with MNTS, the final result being the generation of nitrite and the recovery of the amine, as shown in Scheme 1[11]



Scheme 1

(the fact that in some cases[11] the yield of nitrite is less than quantitative is attributed to alternative pathways followed by the protonated nitrosamine intermediate, which likewise complicated the reaction in acid media[20]).

In this work we studied the reactions of five tertiary amines with MNTS. In all cases, the validity of Scheme 1 was supported by analysis of the reaction mixtures at the end of the reaction, which showed a nitrite yield of ≥90% (Table 7). The observed kinetic behaviour was in general very similar to that of secondary amines: the reactions were of first order with respect to the amine and were unaffected by ionic strength, and the pH-dependence of k_0 showed that the reaction took place through the basic form of the amine, free of complications. Table 2 lists the values determined for the bimolecular rate constants of reaction between MNTS and the unprotonated amine, and Table 5 includes the solvent isotope effect for reaction of MNTS with 1,4-diazabicyclo[2.2.2]octane (DABCO).

Table 2 Bimolecular rate constants for the reaction of MNTS with various nitrogen nucleophiles at 25 °C

Number	Nucleophile	pK_a[f]	k/dm^3 mol^{-1} s^{-1}
Primary amines			
1	Glycylglycine[a]	8.25	5.30×10^{-5}
2	Methionine[a]	9.28[g]	1.51×10^{-4}
3	2-Methoxyethylamine[b]	9.43	9.81×10^{-4}
4	Ethanolamine[a]	9.50	7.70×10^{-4}
5	Glycine[c]	9.78	8.94×10^{-4}
6	2-Aminobutyric acid[a]	9.83	3.24×10^{-4}
7	Ethylenediamine[b]	9.93	5.39×10^{-3}
8	Isobutylamine[b]	10.48	7.06×10^{-3}
9	*sec*-Butylamine[b]	10.56	1.34×10^{-3}
10	Propylamine[b]	10.57	9.16×10^{-3}
11	Butylamine[c]	10.64	5.46×10^{-3}
12	Ethylamine[b]	10.64	6.78×10^{-3}
13	Methylamine[c]	10.64	1.80×10^{-2}
14	Isopropylamine[b]	10.67	1.40×10^{-3}
15	*tert*-Butylamine[b]	10.68	*ca.* 5×10^{-4}
Secondary amines			
16	Thioproline[d]	6.20[h]	2.33×10^{-4}
17	Sarcosine ethyl ester[b]	8.12	4.82×10^{-3}
18	Morpholine[c]	8.49	4.96×10^{-3}
19	*N*-Methylpiperazine[c]	8.98	7.81×10^{-3}
20	Thiomorpholine[b]	9.06[i]	1.23×10^{-2}
21	4-Hydroxyproline[b]	9.66	7.52×10^{-2}
22	*N*-Methylbenzylamine[a]	9.71[j]	4.10×10^{-2}
23	Piperazine[c]	9.73	2.98×10^{-2}
24	Sarcosine[c]	10.2	4.87×10^{-2}
25	*N*,*N*′-Dimethylethylenediamine[b]	10.29[g]	0.141
26	Proline[c]	10.64	0.129
27	Dimethylamine[c]	10.77	0.384
28	Diethylamine[b]	10.93	5.81×10^{-2}
29	Dipropylamine[b]	11.00	6.32×10^{-2}
30	Piperidine[c]	11.12	0.160
31	Diisopropylamine[b]	11.20	1.12×10^{-2}
32	Pyrrolidine[b]	11.30	0.830
Tertiary amines			
33	DABCO[b]	8.82[g]	2.87×10^{-2}
34	Trimethylamine[e]	9.80	0.240
35	Quinuclidinol[d]	9.86	4.90×10^{-2}
36	*N*-Methylpiperidine[e]	10.08	2.80×10^{-2}
37	Diethylmethylamine[b]	10.54[j]	5.08×10^{-2}
38	Triethylamine[b]	10.71	1.84×10^{-2}
39	Quinuclidine[b]	11.15	0.440
Other nitrogen nucleophiles			
40	Semicarbazide[d]	3.86[k]	7.49×10^{-5}
41	Azide[a]	4.69[l]	1.35×10^{-2}
42	Hydrazine[c]	7.96[g]	2.18×10^{-2}
43	Ammonia[c]	9.24[g]	2.20×10^{-5}

[a] This work, at 15% dioxane. [b] This work, at 3.3% dioxane. [c] Ref. 11, 17% ethanol. [d] This work, 10% dioxane. [e] Ref. 11, 13% ethanol. [f] In water, at 25 °C, from *Critical Stability Constants*, vols. 1, 2, 5; Plenum Press, New York, unless otherwise stated. [g] J. J. Christensen, R. M. Izatt, D. P. Wrathall and L. D. Hansen, *J. Chem. Soc. A*, 1969, 1212. [h] S. Ratner and H. T. Clarke, *J. Am. Chem. Soc.*, 1937, **59**, 200. [i] Obtained from fitting of the kinetic data to eqn. (1) and confirmed by pH measurements of a half-neutralized thiomorpholine solution. [j] Obtained from pH measurements of partially neutralized solutions. [k] Ref. 39. [l] Mean of the values discussed by G. Stedman, *J. Chem. Soc.*, 1959, 2943.

Reaction with Primary Amines, Azide Ion and Semicarbazide.—Primary amines react with MNTS considerably more slowly than secondary or tertiary amines of similar basicity. As a result,

Table 3 Bimolecular rate constants for the nitrosation of various nucleophiles by 2-ethoxyethyl nitrite (EEN) or 2-hydroxyethyl nitrite (HEN) at 25 °C

Nucleophile	k(EEN)/dm^3 mol^{-1} s^{-1}	k(HEN)^a/dm^3 mol^{-1} s^{-1}
Morpholine	—	3.03×10^{-3}
N-Methylpiperazine	—	6.90×10^{-3}
4-Hydroxyproline	$6.85 \times 10^{-2\,b}$	—
N-Methylbenzylamine	$4.01 \times 10^{-2\,c}$	
Piperazine	—	3.00×10^{-2}
Sarcosine	0.165^d	—
Proline	$4.2 \times 10^{-2\,d}$	—
Dimethylamine	—	0.5
Diethylamine	—	0.125
Dipropylamine	—	8.73×10^{-2}
Piperidine	—	0.28
Pyrrolidine	—	0.49
N_3^-	$3.10 \times 10^{-3\,e}$	—

[a] Ref. 18. [b] This work, 5% dioxane. [c] This work, 3.3% dioxane. [d] Ref. 17. [e] This work, 6% dioxane.

Table 4 Comparison of the reactivity of different alkyl nitrites and MNTS with morpholine at 25 °C

Electrophile	k/dm^3 mol^{-1} s^{-1}
MNTS[a]	4.96×10^{-3}
2-Hydroxyethyl nitrite[b]	3.03×10^{-3}
2-Bromoethyl nitrite[c]	3.62×10^{-2}
2,2-Dichloroethyl nitrite[c]	1.37

[a] Ref. 11, 17% ethanol. [b] Ref. 18. [c] This work, 0.5% dioxane.

Table 5 Solvent isotope effects for the reaction of various nitrogen nucleophiles with MNTS or alkyl nitrites

Reaction	k_H/k_D
MNTS + *N*-Methylbenzylamine	1.09
MNTS + 4-Hydroxyproline	1.10
MNTS + Diethylamine	1.05
MNTS + Diisopropylamine	0.92
MNTS + Propylamine	1.20
MNTS + DABCO	0.99
MNTS + N_3^-	0.96
EEN + 4-Hydroxyproline	1.70
EEN + N_3^-	1.70
2,2-Dichloroethyl nitrite + morpholine	1.70
2-Bromoethyl nitrite + morpholine	1.82

Table 6 Activation parameters of some of the reactions studied

Reaction	$\Delta H^\ddagger$/kJ mol^{-1}	$\Delta S^\ddagger$/J mol^{-1} K^{-1}
MNTS + 4-Hydroxyproline	55.3	−81
MNTS + 3-Quinuclidinol	55.5	−87
MNTS + N_3^-	60.2	−78
EEN + 4-Hydroxyproline	39.8	−134
EEN + N_3^-	55.0	−112

Table 7 Yield of nitrite obtained in the reaction of tertiary amines with MNTS at basic pH, as measured by Shinn's method

Amine	[Amine$_{tot}$]/mol dm^{-3}	pH	% nitrite
Triethylamine	8.33×10^{-2}	10.7	92
Triethylamine	0.120	10.7	90
Diethylmethylamine	0.185	10.5	96
Diethylmethylamine	0.074	10.5	97
DABCO	0.11	8.8	94
DABCO	0.18	8.8	93
Quinuclidine	9.2×10^{-3}	10.95	99
Quinuclidine	2.75×10^{-2}	10.95	99
Quinuclidine	6.42×10^{-2}	10.95	100
Quinuclidine	0.180	10.95	98
Quinuclidinol	1.5×10^{-2}	9.86	98.6
Quinuclidinol	6.7×10^{-2}	9.86	100
Quinuclidinol	0.12	9.86	100
Quinuclidinol	0.40	9.86	100

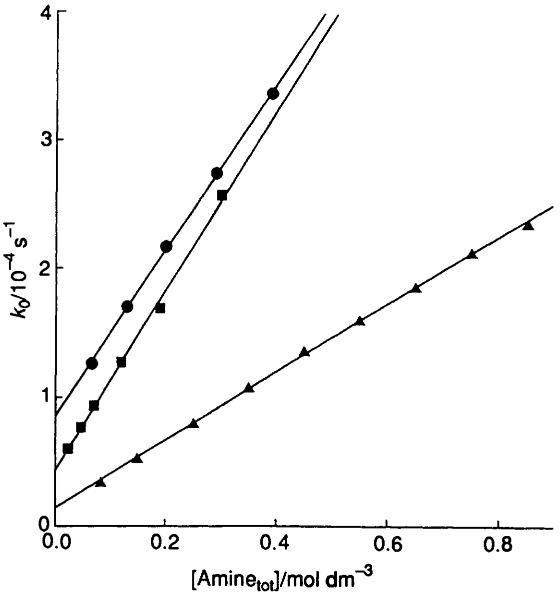


Fig. 3 Influence of the total amine concentration upon the pseudo-first-order rate constant k_0 for reaction with MNTS: (●) *sec*-butylamine, [free amine]/[ammonium salt] = 0.93, 3.3% dioxane; (■) isopropylamine, [free amine]/[ammonium salt] = 1, 3.3% dioxane; (▲) 2-aminobutyric acid, [free amine]/[ammonium salt] = 4.4, 15% dioxane

the transnitrosation process may suffer from competition with the basic hydrolysis of MNTS at its sulfur atom, a reaction whose kinetics are well understood.[11] Under these conditions, the rate equation is eqn. (2) where k_{OH} is the rate constant for

$$k_0 = k_{OH}[OH^-] + k[RNH_2] \qquad (2)$$

the hydrolysis of MNTS and k the bimolecular constant for reaction between free amine and MNTS. Eqn. (2) explains the non-zero intersection on the y-axis of plots of k_0 against total amine concentration (Fig. 3); a similar effect was observed in the case of the relatively unreactive secondary amine diisopropylamine. The values of k determined from such plots are listed in Table 2. The solvent isotope effect for the reaction of MNTS with propylamine is listed in Table 5.

Having previously[11] observed that nucleophiles with an alpha effect underwent nitrosation at anomalously fast rates, in this work we studied two further nucleophiles of this kind, the azide ion (reacted with both MNTS and EEN) and semicarbazide. Table 2 lists the corresponding rate constants, and Tables 5 and 6 the solvent isotope effects and activation parameters for reaction of the azide ion with MNTS and EEN.

Discussion

Mechanisms of Reaction with MNTS *and Alkyl Nitrites.*— Oae *et al.*[12] and Casado *et al.*[21] suggested that alkyl nitrites transfer their nitroso group to amines *via* a concerted mechanism with a four-centre transition state in which the amine aids removal of the –OR group by partial protonation [Scheme 2(*a*)], although the possibility of a six-membered ring

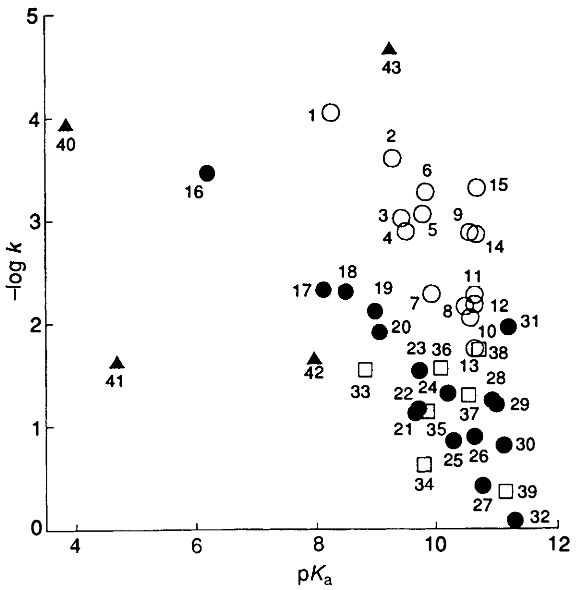
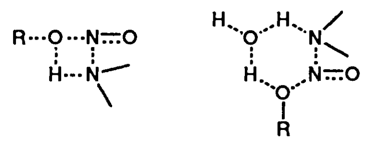


Fig. 4 Brønsted plot for the reaction between MNTS and nucleophilic nitrogen compounds: (○) primary amines; (●) secondary amines; (□) tertiary amines; (▲) other nitrogen nucleophiles



2a **2b**

Scheme 2

[Scheme 2(*b*)] was also considered. This hypothesis was based chiefly on the observation of (i) solvent isotope effects greater than unity interpreted as evidence of a rate-controlling step that in some way involved proton transfer, and (ii) large negative entropies of activation.

In this work too we observed large solvent isotope effects and large negative entropies of activation (Tables 5 and 6). However, we also obtained similar results with the azide ion, a nucleophile for which the transition states of Scheme 2 are impossible. This finding makes it less likely that the isotope effects and activation entropies observed with secondary amines are due to partial transfer of the amine proton assisting removal of the alcohol. There are other possibilities which would equally give rise to the observed solvent isotope effects. A first explanation would be that a water molecule were present in the transition state partially protonating the alkoxide moiety, *i.e.* protonation of the leaving group taking place *via* the solvent, without involvement of cyclic structures such as those in Scheme 2. This explanation is however at odds with the results in Table 5, which show similar values for the solvent isotope effects independently of the nature of the alkyl nitrite, protonation being more necessary the more basic the leaving alkoxide. A more likely explanation comes in terms of the fractionation factor theory,[22] if we assume a simple concerted mechanism with a substantial development of negative charge on the O atom in the transition state. The leaving alkoxide would be expected to be strongly hydrogen-bonded to solvent and the fractionation factors for the hydrogen-bonded protons on the solvating molecules could give rise to the observed solvent isotope effects. We can compare our situation with that of a reaction in which OH^- is released. Since the fractionation factor for the hydroxide ion, due to three solvating water molecules, is 0.48,[22] a reaction with a late transition state would be expected to exhibit a solvent isotope effect of 2.08. Our value, *ca.* 1.7 in every case, is therefore understandable in terms of simple solvation of the leaving group being responsible for the positive solvent isotope effect, concerted protonation being no longer necessary. Strong solvation could also be responsible for the highly negative value of $\Delta S^{\ddagger}$.

Our earlier hypothesis[11] that reactions with MNTS involve a simple concerted mechanism in which the leaving group is not aided by any kind of proton transfer is supported by the present findings: isotope effects close to unity for primary, secondary and tertiary amines and for the azide ion rule out proton transfer from either the amine or the solvent in the rate-controlling step.

The possibility that in the case of bisamines there may be transition states different from those of simple amines is ruled out by the results listed in Table 2; the primary amine ethylenediamine, for example, reacts at a rate very similar to that of ethylamine, while the fact that the secondary amine *N,N′*-dimethylethylenediamine reacts twice as fast as sarcosine (which has similar basicity) is partially accounted for by the statistical advantage possessed by the molecule with two equivalent reaction centres.

Reaction of Ambident Nucleophiles.—Three of the amines studied in this work, thiomorpholine, methionine and thioproline contain sulfur and, in acid media, undergo nitrosation much more rapidly than sulfurless analogues.[23–25] This phenomenon has been attributed[25] to their ambidentate character: initial nitrosation of the S atom is assumed to be immediately followed by fast internal rearrangement to the thermodynamically stable *N*-nitroso compound. Such behaviour has important implications for estimation of endogenous formation of nitroso compounds and of the risk deriving from their carcinogenic properties.[26]

The advantage of the possibility of initial *S*-nitrosation is obvious for reaction in acid media, in which the nitrogen atom is protonated. This does not mean that S is, *per se*, a better nucleophilic centre than N for the N=O group. In fact, S must have considerably less nucleophilic attraction than N, for in the basic media used in this work, in which the N atoms of a large proportion of the molecules present are unprotonated, it is only this unprotonated form that reacts with the electrophile (Fig. 2). Furthermore, in these experiments the reaction rate of the unprotonated form was similar to that of sulfurless analogues, showing that nitrosation takes place directly at the N atom rather than *via* the S atom; methionine, for example, has a reactivity similar to (in fact, slightly less than) that of 2-aminobutyric acid, and the reactivity of thiomorpholine is similar to that of other secondary amines of similar basicity, such as morpholine.

Relative Reactivities with MNTS.—In Fig. 4, $-\log k$ is plotted against pK_a for the nucleophilic nitrogen compounds studied in this and our previous work;[11] all values are for reaction mixtures with a dioxane content of 3.3%, appropriate slight corrections (based on data on medium effects in Table 8) having been applied to the values listed in Table 2 for nucleophiles studied in reaction mixtures with greater dioxane contents (the corrections are in fact negligible considering that the range of reactivities considered covers more than four orders of magnitude). In several cases, values obtained previously[11] in reaction mixtures containing 17% of ethanol were found to agree well with the values obtained using 3.3% of dioxane.

It is clear that, taken all together, the data of Fig. 4 show no correlation or clear trend. In spite of our studies covering eight powers of ten in pK_a and almost five in $\log k$, no definite tendencies are observed. A more detailed analysis of the plot shows that α-nucleophiles, ammonia and primary amines are the reagents with higher responsibilities for the overall dis-

Table 8 Medium effects upon the reaction of MNTS with several nitrogen nucleophiles

Reaction	% Dioxane (v:v)	k/dm^3 mol^{-1} s^{-1}
MNTS + 4-Hydroxyproline	3.3	7.52×10^{-2}
	5.0	7.48×10^{-2}
	6.7	7.07×10^{-2}
	10	6.25×10^{-2}
	15	5.10×10^{-2}
MNTS + DABCO	3.3	2.87×10^{-2}
	10	1.63×10^{-2}
MNTS + Quinuclidinol	10	4.90×10^{-2}
	15	3.45×10^{-2}

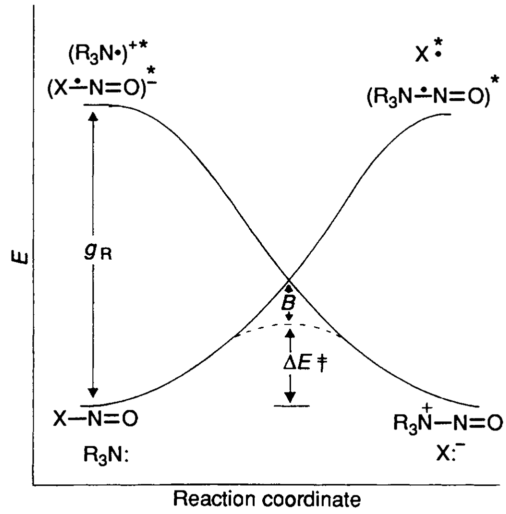


Fig. 5 State correlation diagram for nucleophilic attack on a nitroso compound X–N=O

persion. Analysis of each type of amines leads to some interesting conclusions. In the case of secondary amines (filled circles) a rough linear relationship can be found between basicity and reactivity (slope = 0.50 ± 0.08, r = 0.85). However, when the point corresponding to the sterically-hindered diisopropylamine is excluded from the regression, correlation improves (slope = 0.57 ± 0.06, r = 0.93). Data for tertiary amines (open squares) show in general a reactivity quite close to that found for secondary amines of similar basicity. In fact, if we add the values corresponding to all our tertiary amines to the previous correlation (excluding the point for triethylamine, which seems abnormally unreactive), the results of the fitting do not change significantly (slope = 0.55 ± 0.06, r = 0.90). However, the behaviour of primary amines is surprising: they all react at significantly lower rates than those of secondary or tertiary amines of similar basicity. Attempts to correlate reactivity and basicity in this case yielded rather poor results if we consider all the reagents (slope = 0.66 ± 0.17, r = 0.73). Better correlation can be found if we selectively exclude some points from the plot. For example, if the points corresponding to the reactivity of the four butylamines and of isopropylamine are omitted, the correlation improves, with a significant increase in slope (slope = 0.91 ± 0.14, r = 0.92). However, it is difficult to rationalize *a priori* why primary amines should be more sensitive to basicity (higher β value) than secondary or tertiary amines. The general trend in reactivity (tertiary amines = secondary amines > primary amines) is likewise difficult to understand. The behaviour of ammonia is particularly noteworthy in that its reactivity is more than three powers of ten lower than a secondary or tertiary amine of similar basicity. Thus the overall dispersion of the data of Fig. 4 is due largely to the primary amines, ammonia and the nucleophiles with an alpha effect. The latter (azide ion, hydrazine and semicarbazide) are much more reactive than any nucleophiles of similar basicity. It may therefore be concluded that pK_a (which quantifies the affinity of the nucleophile for protons in water, and is heavily influenced by specific interactions with the solvent) does not reflect the intrinsic nucleophilicity of amines for the N=O group, and that other physical parameters must be resorted to for better rationalization of the experimentally observed behaviour.

The factors governing reactivity in a number of different kinds of chemical reaction have recently been studied in terms of the 'curve crossing model'.[6] Fig. 5 shows the application of this model to the concerted reaction between a nitroso compound XNO and an amine. According to the curve crossing model, the reaction barrier is a fraction f of the electron transfer energy gap, g_R, minus an 'avoided crossing' term B [eqn. (3)]

$$\Delta E = f g_R - B \qquad (3)$$

Here, g_R corresponds to the transfer of an electron from the nucleophile to the electrophile as in eqn. (4) where EA refers to

$$g_R = vE_i^*(\text{nucleophile}) - \text{EA}^*\,(\text{XNO}) \qquad (4)$$

the electron affinity of the nitroso compound and the asterisks indicate vertical processes that do not affect geometry or solvation (and hence lead to a non-equilibrium solvation state). Thus the parameter determining the relative reactivities of a series of nucleophiles with the same electrophile is the vertical ionization potential.

For some nucleophiles, including the azide ion,[27] the vE_i* in water has been determined experimentally. For many amines and other nucleophilic nitrogen compounds for which this has not been done, gas phase vE_i values are available[28] which allow vE_i* values in solution to be estimated, after Shaik,[7] by considering the following simple thermodynamic cycle (for simplicity, charges are not shown). Desolvation of the nucleophile is followed by electron loss in the gas phase, solvation of the radical so formed, and a transition from a state of equilibrium solvation of the radical to a state of solvation of the original nucleophile.

$$R_3N\!:\!(s) \longrightarrow R_3N\!:\!(g) \quad -\Delta G_s{}^\circ(R_3N\!:)$$

$$R_3N\!:\!(g) \longrightarrow R_3N^\bullet(g) + e \quad vE_i$$

$$R_3N^\bullet(g) \longrightarrow R_3N^\bullet(s) \quad \Delta G_s{}^\circ(R_3N^\bullet)$$

$$R_3N^\bullet(s) \longrightarrow R_3N^\bullet(s^*) \quad \Delta G_{SR}{}^\circ$$

Desolvation energies and gas phase vE_i values have been reported[28,29] for many amines; solvation energies of species $B^{\bullet+}$ have been shown by Ritchie[30] to be equal to the free energies of solution of the corresponding species BH^+, *i.e.* in our case to the free energies of solution of protonated amines, which have been published by Aue *et al.*;[29] and Marcus' theory of non-equilibrium polarization[31] can be used to estimate the energy of reorganization of the solvent by eqn. (5) where ρ = 0.56 for water at 25 °C. The aqueous

$$\Delta G_{SR}{}^\circ = -\rho \Delta G_s{}^\circ(R_3N^\bullet) \qquad (5)$$

solution vE_i* values so calculated are listed in Table 9.

Though the plot of −log k against vE_i* exhibits considerable dispersion (Fig. 6), it is clearly promising in that it does appear to explain some of the aspects of reactivity mentioned earlier. In particular, vE_i*, *via* its effect on the energy barrier, seems

Table 9 Gas and solution vertical ionization potentials (vE_i) for various nucleophiles

Nucleophile	vE_i(gas)[a]/kcal mol^{-1}	vE_i^*(water)[b]/kcal mol^{-1}
Propylamine	216.8	192
Butylamine	214[c]	189
Ethylamine	218.4	193
Methylamine	222.8	196
Dimethylamine	205.9	181
Diethylamine	199	179
Dipropylamine	196.9	175
Piperidine	199.7	176
Pyrrolidine	202.2	178
Trimethylamine	196.7	174
N-Methylpiperidine	198.2	176.5
Triethylamine	186.7	166
Azide ion		176[e], 172[d]
Hydrazine		198[e]
Ammonia	250.2	218

[a] Ref. 28 and 29 (1 cal = 4.184 J). [b] Calculated in the present work, unless otherwise stated. [c] The value for butylamine is assumed to be the same as that of isobutylamine and *sec*-butylamine, which are both 214 kcal mol^{-1}. [d] Ref. 27. [e] Ref. 7.

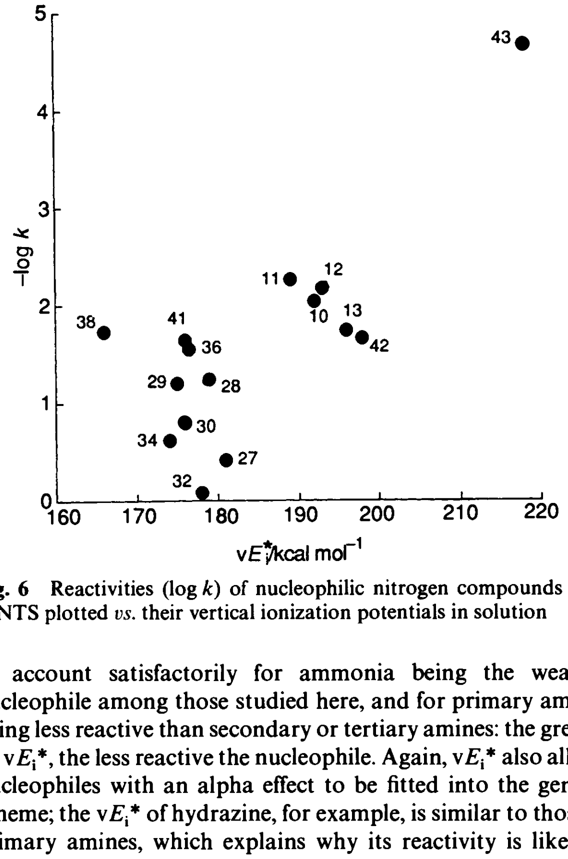


Fig. 6 Reactivities (log *k*) of nucleophilic nitrogen compounds with MNTS plotted *vs.* their vertical ionization potentials in solution

to account satisfactorily for ammonia being the weakest nucleophile among those studied here, and for primary amines being less reactive than secondary or tertiary amines: the greater its vE_i^*, the less reactive the nucleophile. Again, vE_i^* also allows nucleophiles with an alpha effect to be fitted into the general scheme; the vE_i^* of hydrazine, for example, is similar to those of primary amines, which explains why its reactivity is likewise similar to theirs in spite of its much lower basicity, and the same is true for azide ion in comparison with secondary amines.

To explain the considerable dispersion unaccounted for by vE_i^* in Fig. 6, we note that for strict linearity of the data it would be necessary for the coefficient *f* to be constant in eqn. (3). This coefficient, however, depends on a variety of factors that are not expected to remain constant over the wide range of reactivities being considered. In particular, *f* depends on the curvature of the potential energy surfaces, which appears to be related to charge delocalization in the reagents, and on the thermodynamic reaction barrier.[6] These considerations may explain, for example, why bulky amines show a low reactivity. The presence of bulky groups in $(R_3N^{\cdot})^+$, for example, probably hinders its coupling with $(X\dot{-}NO)^-$, causing a less pronounced descent of the energy curve along the reaction coordinate, with a consequent increase in *f*. This view of our reaction is in keeping with its strong sensibility to the alpha effect, since according to Hoz's ideas, the alpha effect is due to the radicaloid nature of the nucleophile in the transition state conferring extra stability upon this state.[32]

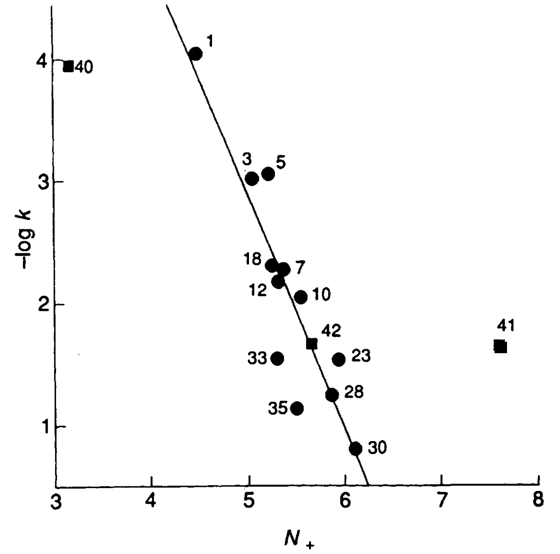


Fig. 7 Reactivities (log *k*) of nucleophilic nitrogen compounds with MNTS plotted *vs.* Ritchie's N_+ parameter: (●) 'normal' nucleophiles; (■) α-effect nucleophiles

A physically more obscure approach to understanding the relative reactivities of nucleophiles is in terms of empirical reactivity parameters. Ritchie's[33] N_+ index, for example, which has been determined for a wide variety of nucleophiles on the basis of data for nucleophile–carbocation recombination and other chemical processes allows prediction of reactivity from eqn. (6) where log k_0 depends solely on the electrophile and N_+

$$\log k = \log k_o + \mathrm{N}_+ \qquad (6)$$

on the nucleophile and the solvent. With relatively few unexplained exceptions, the single parameter N_+ assigned to each nucleophile for a given solvent has surprisingly proved capable of predicting reactivities with electrophiles as varied as triarylmethyl cations, arylidiazonium ions, aryltropylium ions, metal-complexed π-hydrocarbons, 2,3-dinitrohalobenzenes and even esters (though for the latter there is more discrepancy among different authors[34]).[35] In view of the variety of mechanisms and transition states involved in these reactions, the consistency and coherence of the results strongly suggest that N_+ must be a measure of some important intrinsic physical property. More surprising still is the constancy of the selectivity of the electrophiles used,[33,36] which appears to contradict the traditional reactivity–selectivity principle.

Plotting log *k* against N_+ for nucleophiles considered in this work, using N_+ values from ref. 35† (see ref. 34 regarding the reliability of some values) reveals remarkably good correlation (Fig. 7), showing that the validity of the N_+ values extends to the prediction of reactivity with the N=O group. Note that now primary, secondary and tertiary amines all fall on the same line. The only nucleophiles to deviate greatly from the line obtained are N_3^- and semicarbazide, for which similar unexplained deviations have been reported for other kinds of reaction.[35] Note that instead of the slope of unity predicted by eqn. (6), the

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† The value for diethylamine was taken from C. D. Ritchie and P. O. I. Virtanen, *J. Am. Chem. Soc.*, 1973, **95**, 1882.

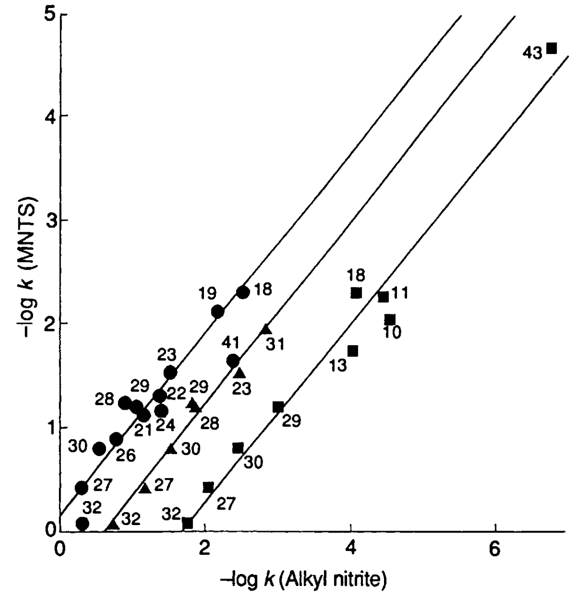

Fig. 8 log–log plots of rate constants for reactions of nucleophiles with MNTS *vs.* those for reactions with (■) 2-phenylethyl nitrite, (▲) propyl nitrite, (●) 2-hydroxyethyl nitrite or 2-ethoxyethyl nitrite

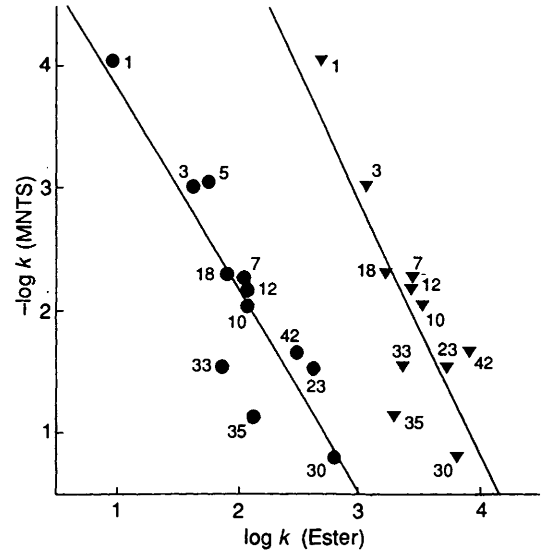

Fig. 9 log–log plots of rate constants for reactions of nucleophiles with MNTS *vs.* those for reactions with (●) 2,4-dinitrophenyl acetate, (▼) 1-acetoxy-4-methoxypyridinium perchlorate

line in Fig. 7 has a slope close to 2, showing that the reactivity of these nucleophiles is more sensitive to N_+ in reactions with N=O than in other types of reaction that have been investigated. In spite of this difference, it still seems likely that N_+ measures some property of the nucleophiles that strongly influences reactivity in our case.

On applying the curve crossing model to cation–anion recombination, Shaik[7] recently concluded that, for a given family, N_+ depends on (and is proportional to) vE_i^* alone, that eqn. (4) and Ritchie's eqn. (6) have a common origin, and that the latter is complied with whenever nucleophilic reactivity depends solely on the ease of transferring an electron to the electrophile. However, the fact that the reactivities considered in our work correlate much better with N_+ than with vE_i^* suggests that N_+ does not depend on vE_i^* alone; rather, since N_+ is determined kinetically, it seems likely that it must contain information on transformations that take place in the nucleophile in the course of chemical reaction, and which are not reflected by any single physical parameter such as vE_i^*. If, in spite of this, it is accepted that the physical basis of correlations between log *k* and N_+ is the curve crossing model, and hence, indirectly, eqn. (4), then the slope of 2 in Fig. 7 implies that the coefficient *f* of eqn. (3) must have a greater value for MNTS than for other electrophiles that have been used in this field. The reason for this difference is far from clear; it may perhaps be related to the lone pair on the nitroso N atom. It can also be attributed to the importance of electronic delocalization through the N=O double bond in $(X\dot{-}NO)^-$. Both factors may hinder coupling of $(R_3N^{\cdot})^+$ and $(X\dot{-}NO)^-$ and therefore smooth the dependence of their energy on the reaction coordinate.

Correlation between Reactivities of Nucleophiles with MNTS *and with other Electrophiles.*—In Fig. 8, log *k* for the reaction of a number of nucleophiles with MNTS is plotted against log *k* for their reactions with 2-ethoxyethyl nitrite (or the very similar 2-hydroxyethyl nitrite), with propyl nitrite[18] and with 2-phenylethyl nitrite (in 61% dioxane).[12] Correlation is good in all three cases (deviations from the lines are in every case less than factors of 2 in *k*), and the three regression lines have very similar slopes of near unity. This is rather surprising, firstly because of the differences among the media in which the alkyl nitrite data were obtained, and secondly because nitrosation by alkyl nitrites involves the leaving group being assisted by strong solvation, whereas the reaction with MNTS does not. It suggests that the relative reactivities of these nucleophiles in processes involving different transition states and different net reaction rates depend entirely on the natures of the nucleophiles themselves, and appears to be another of the growing number of items of experimental evidence against the reactivity–selectivity principle. Though the reasons for non-compliance with this principle may be various,[38] we agree with Jencks[37] that, as a general principle, it should be abandoned.

It is also of interest to compare the reactivities of nitroso compounds with those of esters of carboxylic acids, which are isoelectronic but which, possibly because of the high electronegativity and lone pair of the nitroso N atom, have appreciably different reaction mechanisms: the chemistry of the carbonyl group is dominated by the formation of tetrahedral intermediates, whereas reactions involving the N=O group (hydrolysis, reactions with nucleophiles) appear to occur *via* concerted processes. Plotting the reactivities of nucleophiles with MNTS against their reactivities with the extensively studied esters 2,4-dinitrophenylacetate and 1-acetoxy-4-methoxypyridinium perchlorate[39] (both of which are believed to react with most nucleophiles studied in this work *via* the formation of a tetrahedral intermediate in the slow step[40]) reveals a correlation that is quite acceptable given the difference between the processes and transition states involved (Fig. 9), a result that is not unexpected in view of the correlation of N_+ with both the MNTS reactivities and those of the esters.[35] In both cases the slope of the regression line is *ca.* 2. Again, the nucleophiles deviating most widely from the regression line are two molecules with an alpha effect, semicarbazide and the azide ion; the low reactivities of these weakly basic nucleophiles with the carboxylic esters may be due to the slow step of these reactions being not the formation of the tetrahedral intermediate, but its decomposition.[8,40] Correlations similar to those of Fig. 9 are obtained for other esters, including acetyl-4-methylpyridinium and related compounds,[41] and also for compounds with a sulfonyl group, such as phenyl disulfone[42] (data not shown). A satisfactory correlation is also found with the very recent data[43] for reaction between the carbocation derived from 1-(4-dimethylaminophenyl)-2,2,2-trifluoroethyl azide and a large set of nitrogen nucleophiles.

In conclusion, the reactivities of nucleophiles in a wide range of chemical processes, including reaction at different atoms and (as shown in this work) with nitroso compounds, appear to be governed by some unknown intrinsic characteristic of the nucleophiles themselves. In the particular case of nitroso compounds, their exact nature seems to be largely irrelevant, MNTS and different alkyl nitrites having similar relative reactivities in spite of their structural differences. Ritchie's N_+ parameter appears to be a remarkably good measure of the intrinsic characteristic in question; N_+ may be related to the vertical ionization potential of the nucleophiles, but it also seems to contain additional 'kinetic' information allowing it to predict reactivity better than vE_i^* values themselves do, except in the case of α-nucleophiles. To sum up, our results seem to be in keeping with a pleasingly simplifying generalization of the concept of nucleophilicity to many kinds of chemical process, but at the same time are surprising in view of the complexity of chemical reactions and are difficult to understand in the framework of current theories of chemical reaction.

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