Nucleophilic Reactivity towards 'Normal' and Ambidentate Electrophiles Bearing the Nitroso Group

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Bimolecular rate constants for the reactions of *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (MNTS) and 2-ethoxyethyl nitrite (EEN) with oxygen nucleophiles [HO^-, $CF_3CH_2O^-$, HO_2^-, $CH_3(CO)NHO^-$ and ClO^-], sulfur nucleophiles (SO_3^{2-}, SCN^-, thiourea, cysteine, $S_2O_3^{2-}$ and HS^-) and I^- have been determined. For MNTS, 'soft' nucleophiles react at the nitroso group, whereas 'hard' nucleophiles react at least in part at the sulfonyl group. A discussion on the validity of nucleophilicity scales (N_+ and n) is carried out and clearly for soft nucleophiles (N- and S-nucleophiles and I^-) there is a good correlation with N_+ with a slope close to 1 which implies a frontier orbital controlled reaction and a markedly diradicaloid transition state. For reactions at the sulfonyl group (O-nucleophiles), nucleophilic reactivity is better explained using the n scale which can be rationalized in terms of a larger electrostatic contribution to the interaction energy.

Prominent among the unfinished tasks of physical organic chemistry is the development of a comprehensive, reliable theory of the relative rates of reactions between nucleophiles and electrophiles. Such a theory must clarify the reactivity–selectivity 'principle', the basis of free energy correlations and the dividing line and relationship between polar and electron-transfer processes, and must explain α-effects and the behaviour of ambidentate electrophiles and nucleophiles.

The reactions of nucleophiles with the nitroso group are of both practical and theoretical interest. Synthetically, they are very versatile, since the nitroso group readily transfers to a wide variety of nucleophiles to give *N*-, *O*-, *C*- or *S*-nitroso-compounds. As regards the theory, the fact that the nitroso group is isoelectronic with the carbonyl group makes differences between their reactivities especially intriguing or revealing.

In acid media, the nitrosating species involved in the nitrosation of a wide range of nucleophiles, including amines, thiols and ketones, are powerful agents such as the nitrosonium ion, N_2O_3 or nitrosyl halides. Exhaustive studies of the reactivities of these reagents with a variety of nucleophiles (especially amines, given the medical importance of the carcinogenic properties of nitrosamines) have shown that NO^+,[1] NOCl,[2] NOBr[1,2] and N_2O_3[3] are extremely efficient in the nitrosation of moderately strong nucleophiles, the overall reaction rate often being totally or partially diffusion controlled. Unfortunately for the theorist, this means that these reactions provide virtually no information on the chemical determinants of nucleophiles for the nitroso group. Such information can, however, be obtained by studying the slower reactions of nitrosating agents with more reluctant leaving groups, such as alkyl nitrites or *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide† (MNTS).[4,5] In acid media the hydrolysis of these reagents (alkyl nitrites especially) precludes direct transfer of the nitroso group,[6] but they are relatively stable at neutral or slightly basic pH, at which they co-exist with useful quantities of the reactive forms of nucleophiles (unprotonated amines,[4] carbanions,[5] thiolates,[7] *etc.*).

We recently reported that the reactivities of a wide range of nitrogen[4] and carbon[5] nucleophiles with alkyl nitrites and MNTS show patterns that are remarkably similar to those exhibited by these nucleophiles in processes which are mechanistically quite different, such as their reactions with carboxylic esters, disulfones or carbocations. (Though these similarities are at first sight surprising, it would appear to be significant that all these electrophiles have a low-lying LUMO, *i.e.* a LUMO of relatively low energy; arguments put forward by Hoz[8] or based on Pross and Shaik's curve-crossing theory[9] suggest that in these circumstances the transition state of the reaction has a marked diradical nature.)

In the above work,[4,5] both N- and C-nucleophiles reacted with MNTS to give the corresponding *N*- or *C*-nitroso-compounds. They therefore appeared to ignore the other electrophilic group in MNTS, $-SO_2-$, which does, however, react with the hydroxy ion and alkoxides.[10] The behaviour of ambidentate nucleophiles and electrophiles in their reactions seems to be related to the relative importance of electrostatic and orbital interactions in the attainment of the transition state. To investigate this point further, we have now studied the reactions of both MNTS and the NO-electrophile 2-ethoxyethyl nitrite (EEN) with O- and S-nucleophiles and with the iodide ion. Note that some of these reactions constitute novel ways of preparing stable solutions of important but elusive species such as $ONOO^-$ or nitrosyl thiosulfate and for this purpose have substantial advantages over conventional methods.

Experimental

2-Ethoxyethyl nitrite (EEN) was prepared from 2-ethoxyethanol and sodium nitrite at acid pH[11] and stored in the dark at low temperature over molecular sieves. MNTS (Merck) was used as supplied. NaClO solutions prepared by passing chlorine through NaOH solution were kindly provided by another of our Department's research groups (Professor J. Antelo and co-workers); the hypochlorite concentration was determined spectrophotometrically at 292 nm (ε_{292} = 350 dm^3 mol^{-1} cm^{-1}). Heavy water (99.77% D) was supplied by CIEMAT (Spain). Other reagents were used as supplied (by Aldrich).

EEN and MNTS stock solutions were made up in dioxane or acetonitrile. A small volume of these solutions was always the last component to be added to reaction mixtures. The final concentration of organic solvent in the reaction mixture is mentioned in each case in the Results section.

All kinetic experiments were carried out at 25 °C under

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† Toluene-*p*-sulfonamide = 4-methylbenzenesulfonamide.

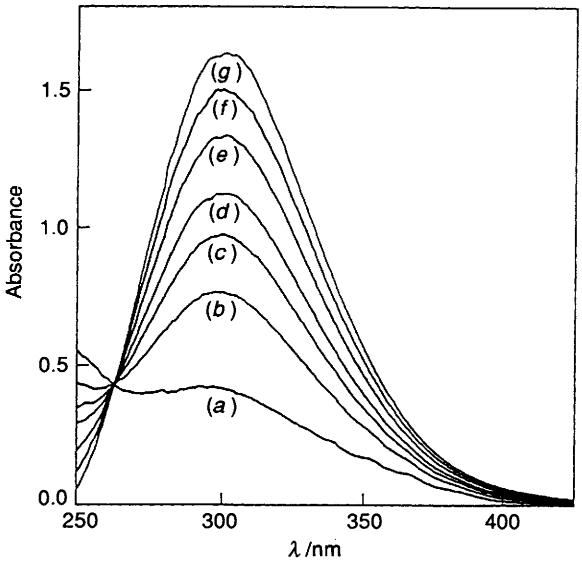


Fig. 1 Typical spectrum series of the reaction between HO_2^- (6×10^{-3} mol dm^{-3}) and EEN (1.03×10^{-3} mol dm^{-3}) in 0.2 mol dm^{-3} NaOH at 25 °C. The spectra were taken (*a*) 6, (*b*) 31, (*c*) 56, (*d*) 81, (*e*) 131, (*f*) 206 and (*g*) 486 s after initiation of the reaction.

pseudo-first-order conditions, *i.e.* with the nucleophile always in at least ten-fold excess with respect to MNTS or EEN. Reactions involving the anions of hydrogen peroxide, 2,2,2-trifluoroethanol and acetohydroxamic acid were buffered by mixtures of NaOH with the nucleophiles themselves and in these experiments both forms of the buffering agent were in at least ten-fold excess with respect to the electrophile; for the reactions involving 2,2,2-trifluoroethanol and hydrogen peroxide, attainment of the desired pH (pH 11–12.5 for H_2O_2 and pH 12 for $CF_3CH_2O^-$) was ensured by adding the appropriate volume of buffer to reaction mixtures which already contained a suitable quantity of NaOH. Reactions with ClO^- were studied with the acidity held at pH 9.91 by 0.13 mol dm^{-3} HCO_3^-–CO_3^{2-} buffer, the excess NaOH of the stock hypochlorite solutions having been neutralized with HCl. The reaction between MNTS and cysteine was carried out in 0.1 mol dm^{-3} NaOH, in which cysteine is totally dissociated. Control of pH was not necessary for the other reactions, but in every case the constancy of the pH was checked by measurement at the end of the reaction. pH was measured with a Radiometer pHM82 pH-meter equipped with a GK2401B combined glass electrode and calibrated using commercial buffers of pH 7.02 (Crison) and pH 12.45 (Beckman).

The ionic strength was found not to affect the rate of any of the reactions studied, and was accordingly not controlled in the kinetic experiments.

Except for the reactions of thiocyanate, thiourea, iodide and cysteine, reaction kinetics were followed spectrophotometrically in Kontron Uvikon 930 or Milton Roy Spectronic 3000 diode array spectrophotometers with thermostatted cell carriers. Series of spectra carried out for each reaction showed no signs of complications and most showed very precise isosbestic points (*e.g.* Fig. 1). Typical working wavelengths were as follows: EEN + OH^-, 245 nm; MNTS + H_2O_2–HO_2^-, 248 nm (isosbestic at *ca.* 330 nm); EEN + H_2O_2–HO_2^-, 302 nm (isosbestic at 262 nm); MNTS + CF_3CH_2OH–$CF_3CH_2O^-$, 250 nm (isosbestic at 234 nm); EEN + CF_3CH_2OH–$CF_3CH_2O^-$, 250 nm (isosbestic at 230 nm); MNTS + $CH_3CONHOH$–CH_3CONHO^-, 280 nm; EEN + $CH_3CONHOH$–CH_3CONHO^-, 274 nm; MNTS + SO_3^{2-}, 278 nm; EEN + SO_3^{2-}, 260 nm; MNTS + $S_2O_3^{2-}$, 305 nm; MNTS + ClO^-, 240 nm; EEN + ClO^-, 238 nm.

The reaction between MNTS and cysteine was studied, following Oh and Williams,[7] by using a stopped-flow apparatus (Applied Photophysics) and monitoring the increase in absorbance at 330 nm due to the S-nitrosated species.

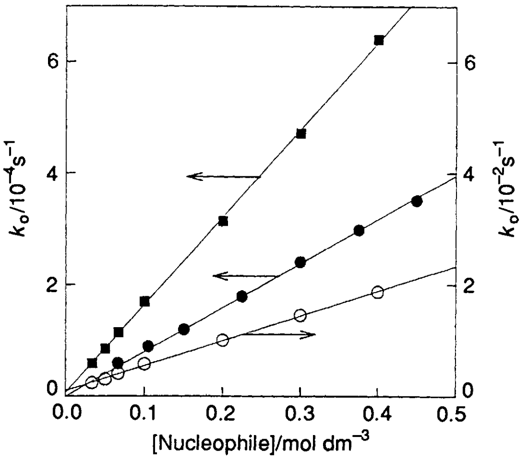


Fig. 2 Influence of total nucleophile concentration on the pseudo-first-order rate constant k_o for the reactions of OH^- with EEN in 5% dioxane (●), $CF_3CH_2O^-$ with EEN in 3.3% dioxane at pH = 12 (■) and $CF_3CH_2O^-$ with MNTS in 10% dioxane at pH = 12 (○). All reactions at 25 °C.

The complex decomposition reactions of nitrosyl thiocyanate and nitrosourea prevented the formation of these species from being followed spectrophotometrically. The reaction of thiocyanate and thiourea with MNTS were followed by monitoring the disappearance of the latter by HPLC (Beckman System Gold); known volumes of the reaction mixture taken at various times after the initiation of the reaction were run on a Beckman Reverse Phase 5 μm Ultrasphere C18 column with 50:50 (v/v) methanol–water as mobile phase (flow rate 2 cm^3 min^{-1}) and UV detection at 250 nm. The integrated area for MNTS peak was related to the concentration by a previous calibration with known amounts of MNTS. The reaction between MNTS and I^- was studied similarly.

For all the reactions studied, the absorbance–time or concentration–time data were fitted with great precision by first-order integrated equations. In what follows we denote the pseudo-first-order rate constant by k_o. Reaction products were in most cases identified and quantified using HPLC or UV–VIS spectroscopy for comparison with authentic samples. For certain reactions, released nitrite was quantified spectrophotometrically by a modified version of Shinn's method which is described elsewhere.[4]

Results

All the bimolecular rate constants determined in this work are listed in Table 1 together with analogous data for N-nucleophiles obtained in previous work.[4,10]

O-Nucleophiles.—OH^- and $CF_3CH_2O^-$. The reactions of OH^- and $CF_3CH_2O^-$ with EEN were both first-order with respect to the nucleophile (*e.g.*, see Fig. 2).

$$k_o = k[\text{nucleophile}] \qquad (1)$$

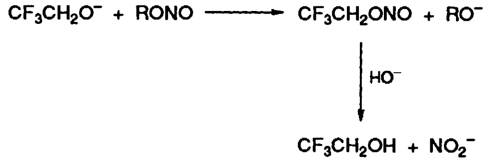
The occurrence of transnitrosation was confirmed by analysis of the final reaction mixtures by Shinn's method,[4] which showed quantitative (> 90%) formation of nitrite (deriving, in the case of $CF_3CH_2O^-$, from hydrolysis of initially formed 2,2,2-trifluoroethyl nitrite; Scheme 1).

For OH^-, the value obtained for the bimolecular rate

Table 1 Bimolecular rate constants of the reactions of nucleophiles with MNTS or EEN at 25 °C

Number	Nucleophile	Electrophile	% (v/v) Organic solvent	k/dm^3 mol^{-1} s^{-1}
1	HO^-	MNTS[a]	23 ethanol	0.127
		EEN	5 dioxane	7.92×10^{-4}
2	$CF_3CH_2O^-$	MNTS	10 dioxane	0.111
		EEN	3.3 dioxane	4.05×10^{-3}
3	HO_2^-	MNTS	4.3 dioxane	17.3
		EEN	1.3 dioxane	2.17
4	$CH_3(CO)NHO^-$	MNTS	10 dioxane	$k_S = 0.73$ $k_N = 0.34$
		EEN	10 dioxane	1.09
5	ClO^-	MNTS	1 acetonitrile	$k_S = 0.131$ $k_N = 1.46 \times 10^{-2}$
		EEN	1 acetonitrile	8.34×10^{-3}
6	SO_3^{2-}	MNTS	15 dioxane	7.94×10^{-2}
		EEN	3.3 dioxane	0.232
7	SCN^-	MNTS	5 dioxane	2.17×10^{-4}
8	$H_2N(CS)NH_2$	MNTS	3.3 dioxane	5.42×10^{-3}
9	$^-SCH_2CH(CO_2^-)NH_3^+$	MNTS	6 dioxane	21.5
10	$S_2O_3^{2-}$	MNTS	15 dioxane	2.46×10^{-2}
11	I^-	MNTS	3.3 acetonitrile	3.12×10^{-4}
12	Ammonia	MNTS[a]	17 ethanol	*ca.* 2.2×10^{-5}
13	Ethylamine	MNTS[b]	3.3 dioxane	6.78×10^{-3}
14	Diethylamine	MNTS[b]	3.3 dioxane	5.81×10^{-2}
15	Triethylamine	MNTS[b]	3.3 dioxane	1.84×10^{-2}
16	Hydroxylamine	MNTS[a]	17 ethanol	4.36×10^{-3}
17	2-Methoxyethylamine	MNTS[b]	3.3 dioxane	9.81×10^{-4}
18	Glycine	MNTS[a]	17 ethanol	8.94×10^{-4}
19	Glycylglycine	MNTS[b]	15 dioxane	5.30×10^{-5}
20	Azide	MNTS[b]	15 dioxane	1.35×10^{-2}
21	Hydrazine	MNTS[a]	17 ethanol	2.18×10^{-2}
22	Semicarbazide	MNTS[b]	10 dioxane	7.49×10^{-5}
23	Piperidine	MNTS[a]	17 ethanol	0.160
24	Pyrrolidine	MNTS[b]	3.3 dioxane	0.830

[a] Ref. 10. [b] Ref. 4.



Scheme 1

constant (Table 1) agrees well with the value reported by Challis and Shuker,[12] 8.26×10^{-4} dm^{-3} mol^{-1} s^{-1}.

OH^-, like alkoxides, reacts with the sulfur atom of MNTS, a reaction that is commonly used for the generation of diazomethane for synthetic purposes[13] and whose rate constant was obtained in previous work.[10] The reaction of MNTS with 2,2,2-trifluoroethanol is first-order with respect to the nucleophile [eqn. (1); *e.g.* Fig. 2], and likewise involves the MNTS SO_2 group rather than the NO group (analysis of acidified final reaction mixtures by Shinn's method showed a < 2% yield of the nitrite that should be formed by attack on the NO group).

HO_2^-. The reaction of EEN with H_2O_2–HO_2^- mixtures was studied at various pH values in the range 11–12 (see the Experimental), *i.e.* using mixtures with various proportions of H_2O_2 and HO_2^-. Fig. 1, a typical series of spectra of the reaction mixture, shows a clean isosbestic point at 262 nm and the formation of a stable final product, with no signs of kinetic complications. The final product has an absorption peak at 300–303 nm in good agreement with reported data for solutions of peroxynitrite (λ_{max} = 302 nm),[14] the expected product of nucleophile attack by HO_2^- on the EEN nitroso group. In view of the reported extinction coefficient for peroxynitrite (ε_{302} = 1670 ± 50 dm^3 mol^{-1} cm^{-1}),[14] the last spectrum shown in Fig. 1 reflects practically quantitative (97%) formation.

$$HO_2^- + RO{-}N{=}O \longrightarrow ROH + ONOO^- \quad (2)$$

Note that this route to peroxynitrite will be of interest to those studying ONO_2^- in relation to environmental protection,[15] photochemistry (*e.g.* in the photolysis of nitrates),[16] the biological implications of its possible formation *in vivo* through reaction (3)[17] or its involvement in such processes as the oxidation of H_2O_2[18] and the self-oxidation of chloramine and hydroxylamine.[19] As reported previously,[20] preparation in a basic medium as above is an efficient alternative to traditional methods, in which formation in an acidic medium is followed by basification to stabilize the anion.[14] The short half-life of HOONO in acidic media (a few seconds) means that the traditional method affords final yields of no more than *ca.* 50%,[14] the rest of the initial product being converted into undesired nitrites and nitrates that cannot be removed without destroying the $ONOO^-$, whereas the new procedure described here affords yields close to 100% with no significant nitrite or nitrate impurities. Furthermore, the new method does not require the use of a buffer other than the reagents themselves (see the Experimental).

$$NO + O_2^- \longrightarrow ONOO^- \quad (3)$$

The kinetics of eqn. (2) were studied in two series of reactions. In the first, the pseudo-first-order rate constant k_o increased linearly with the total concentration of nucleophile ($[H_2O_2] + [HO_2^-]$) at constant pH (Fig. 3). In the second, pH was increased while the total concentration of nucleophile was kept fixed; plotting k_o against pH produced a sigmoid curve (Fig. 4), showing that only the basic form of the nucleophile, HO_2^-, is involved in the reaction. These findings imply the rate

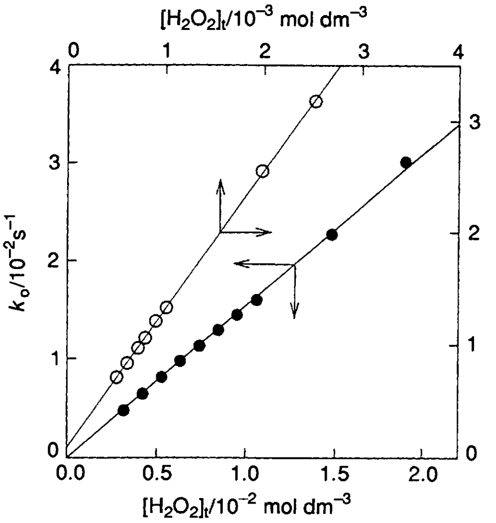


Fig. 3 Influence of total concentration of H_2O_2–HO_2^- on the pseudo-first-order rate constant k_o for the reactions of HO_2^- with EEN in 1.3% dioxane (●) and with MNTS in 4.3% dioxane (○). All reactions at 25 °C and pH = 12.

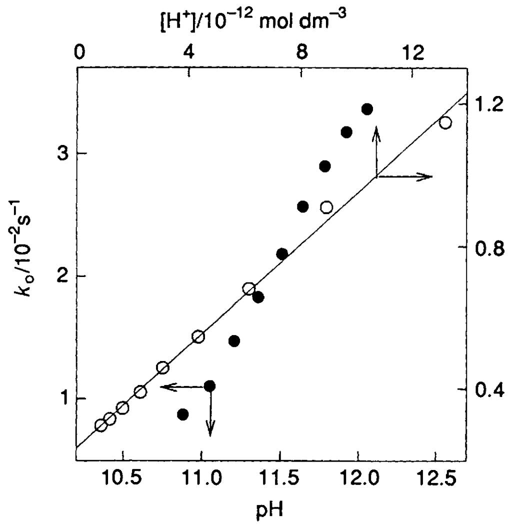


Fig. 4 Influence of acidity on the pseudo-first-order rate constant k_o in the reaction of EEN with HO_2^- ($[H_2O_2]_t = 1.98 \times 10^{-2}$ mol dm^{-3}) in 1.3% dioxane at 25 °C. (●) k_o plotted against pH; (○) $1/k_o$ plotted against $[H^+]$.

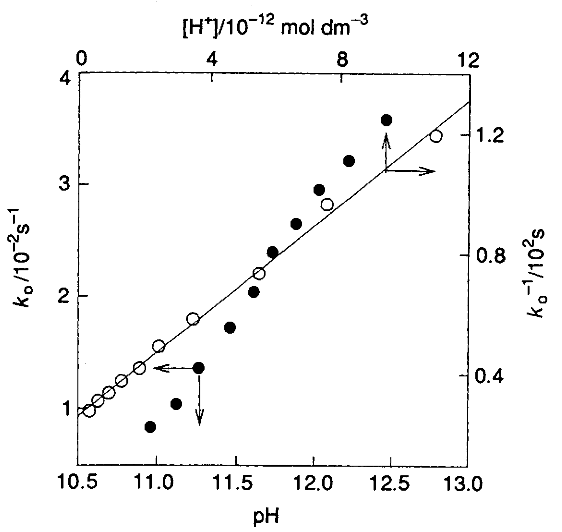


Fig. 5 Influence of acidity on the pseudo-first-order rate constant k_o in the reaction of MNTS with HO_2^- ($[H_2O_2]_t = 2.22 \times 10^{-3}$ mol dm ^{3}) in 4.7% dioxane at 25 °C. (●) k_o plotted against pH; (○) $1/k_o$ plotted against $[H^+]$.

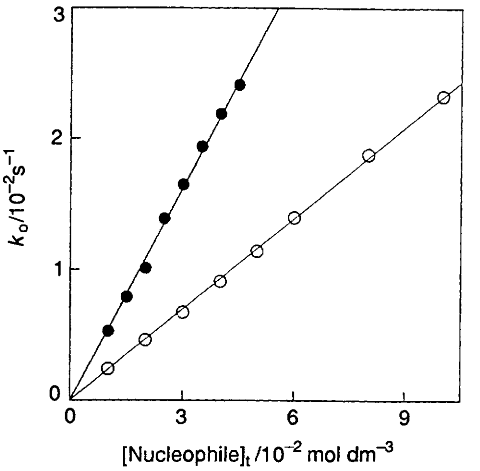


Fig. 6 Influence of total nucleophile concentration on the pseudo-first-order rate constant k_o for the reactions of EEN with $CH_3(CO)NHO^-$ ($[CH_3(CO)NHO^-]:[CH_3(CO)NHOH] = 1$) in 10% dioxane (●) and with SO_3^{2-} in 3.3% dioxane (○). All reactions at 25 °C.

equation [eqn. (4)] where K_a is the dissociation constant of

$$k_o = \frac{kK_a[\text{nucleophile}]_t}{K_a + [H^+]} \quad (4)$$

H_2O_2, k is the bimolecular rate constant and $[\text{nucleophile}]_t$ is the total concentration of nucleophile. Fitting this equation to the experimental data affords values of 11.5 for pK_a (in good agreement with the previously published value, 11.6)[21] and 2.17 dm^3 mol^{-1} s^{-1} for k (Table 1).

Similar studies of the reaction between HO_2^- and MNTS at a pH in the range 11.0–12.5 showed that in this case too the reaction is first-order with respect to the total nucleophile concentration (Fig. 3) and involves HO_2^- as the effective reagent (Fig. 5). Fitting eqn. (4) again afforded a value of 11.5 for pK_a, together with a value of 17.3 dm^3 mol^{-1} s^{-1} for the bimolecular rate constant (Table 1). However, the spectra of the reaction mixtures recorded when reaction was complete showed $<2\%$ yield of peroxynitrite ion (which would be stable under the working conditions), and hence that the nucleophile attacked only the MNTS sulfur atom. This was confirmed by HPLC analysis of the mixture of products, which detected no *N*-methyltoluene-*p*-sulfonamide.

Acetohydroxamic and hypochlorite ions. The reaction between the acetohydroxamic acid anion and EEN was found to be first-order with respect to both EEN and the reagent in excess (Fig. 6), with a bimolecular rate constant of 1.09 dm^3 mol^{-1} s^{-1}. A rate equation of the same form was also found for the reaction between the acetohydroxamic acid anion and MNTS, with k = 1.07 dm^3 mol^{-1} s^{-1}. However, unlike the O-nucleophiles discussed above, which exclusively attacked the MNTS sulfur atom, the acetohydroxamic acid anion appeared to react with both the sulfonyl and nitroso groups, since HPLC analysis of the mixture of products detected a (32 ± 5)% yield of *N*-methyltoluene-*p*-sulfonamide, the expected product of the denitrosation of MNTS. This was corroborated by detection of a (58 ± 5)% yield of sulfonic acid in the mixture of products, which is attributed to attack on the sulfonyl group being followed by hydrolysis. Hence the observed bimolecular rate constant, 1.07

$dm^3\ mol^{-1}\ s^{-1}$, is the sum of the rate constants for the reactions with the sulfonyl and nitroso groups. The observed value of

$$k_o = (k_S + k_N)[\text{nucleophile}] \qquad (5)$$

$k_S + k_N$, together with the relative proportions of the products of each route, affords the values of k_S and k_N listed in Table 1.

Similar behaviour was exhibited by the hypochlorite ion, except that in this case the observed bimolecular rate constant for the reaction with MNTS was more than an order of magnitude greater than that for EEN (0.146 $dm^3\ mol^{-1}\ s^{-1}$ as against $8.34 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$). Furthermore, analysis of the mixtures of products showed that the behaviour of MNTS was rather less ambidentate than with $CH_3(CO)NHO^-$, 90% of the reaction taking place at the sulfur atom and only 10% at the nitroso N atom. The corresponding rate constants k_S and k_N are listed in Table 1 showing clearly the preference of this O-nucleophile for reaction at the S atom of the MNTS.

S-Nucleophiles.—SO_3^{2-}. Fig. 6 shows the influence of sulfite concentration on the pseudo-first-order rate constant of its reaction with EEN. The reaction is first-order with respect to both the nucleophile and the alkyl nitrite, with a bimolecular rate constant of 0.232 $dm^3\ mol^{-1}\ s^{-1}$ (Table 1). The nitrosation of sulfite (as bisulfite) in acid media is a well known reaction of great environmental relevance that is thought to involve the formation of an unstable intermediate, SO_3NO^-, which rapidly decomposes to give a variety of products, including free radicals.[22] The same unstable intermediate may be assumed to be formed in the reaction with EEN.

The same kinetic behaviour was observed when sulfite reacted with MNTS and the fact that the bimolecular rate constant differed little from that of the reaction with EEN (especially if the difference in the dioxane content of the medium is borne in mind) suggests that it is the MNTS nitroso group that is attacked. This hypothesis was corroborated by HPLC analysis of the mixtures of products, which showed quantitative formation of *N*-methyltoluene-*p*-sulfonamide.

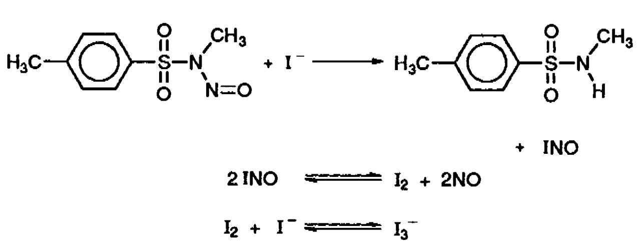
SCN^- *and thiourea.* For the reasons mentioned in the Experimental section, the reactions of SCN^- and thiourea with MNTS were studied by HPLC. The bimolecular rate constants of the reactions with MNTS, $2.17 \times 10^{-4}\ dm^3\ mol^{-1}\ s^{-1}$ for thiocyanate and $5.42 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$ for thiourea, are in keeping with other reports of thiourea being more nucleophilic than thiocyanate for the nitroso group.[23] Attack on the nitroso group was confirmed by HPLC, which showed quantitative formation of *N*-methyltoluene-*p*-sulfonamide.

Cysteine. The reaction between MNTS and concentrations of cysteine anion in the range $0.3\text{–}3 \times 10^{-2}\ mol\ dm^{-3}$ was studied in a medium containing 0.1 $mol\ dm^{-3}$ NaOH. The pseudo-first-order rate constant depended linearly on cysteine concentration, with a low reaction rate at [cysteine] = 0 that is attributable to alkaline hydrolysis of MNTS. The slope of the line fitted to the k_o[cysteine] data implies a second-order rate constant of 21.5 $dm^3\ mol^{-1}\ s^{-1}$, which, since the working medium was 6% dioxane, agrees reasonably well with the previously published value of 25 $dm^3\ mol^{-1}\ s^{-1}$ for the reaction in 25% ethanol at pH 12.6.[7]

Thiosulfate and HS^-. The reactions of thiosulfate with both MNTS and EEN yielded yellow products whose spectral characteristics ($\lambda_{max} = 419$ nm, $\varepsilon = 130\ dm^3\ mol^{-1}\ cm^{-1}$) are virtually identical to those attributed by Garley and Stedman to the relatively unstable species nitrosyl thiosulfate ($\lambda_{max} = 418.4$ nm, $\varepsilon = 131\ dm^3\ mol^{-1}\ cm^{-1}$).[24] As with the other nucleophiles studied, the reaction of MNTS with freshly prepared solutions of thiosulfate in deoxygenated water was first-order with respect to both MNTS and the nucleophile, and its rate constant is listed in Table 1. Even under these conditions, however, the recorded absorbance–time data sometimes deviated slightly from the integrated first-order equation during the initial period of the reaction and when the thiosulfate solutions were not fresh the kinetics of the reaction were erratic. Similarly, the kinetics of the reaction with EEN were unreproducible under any conditions, with non-exponential (sometimes sigmoid) absorbance–time curves. The observation that the absorbance–time curve of the reaction between $5 \times 10^{-4}\ mol\ dm^{-3}$ EEN and $5 \times 10^{-2}\ mol\ dm^{-3}$ thiosulfate became less markedly sigmoid upon addition of the free radical trap 2-methyl-2-nitrosopropane suggested that the presence of free radicals (possibly $S_2O_3^{\bullet -}$) was causing the reaction to deviate from the nucleophilic substitution mechanism of the reactions studied previously. Sulfur-bearing species are known to form free radicals readily and alkyl nitrites are known to produce NO by homolytic cleavage,[23] a mechanism that has been invoked to explain the behaviour of several of their reactions, especially in the photochemical field. In this case, it seems possible that the $S_2O_3^{\bullet -}$ radical and thiosulfate may be competing for the NO group.

MNTS also reacted readily with HS^- in media buffered at *ca.* pH 7 by HS^-–S^{2-}. Again, the yellow colouration of the reaction mixtures suggested[24] the formation of an S-nitrosated product (presumably HSNO or ONS^-), and hence that the nucleophile reacted with the MNTS nitroso group, but the absorbance–time records were too complex for kinetic analysis (in fact, sequential spectra of the reaction mixtures indicated the occurrence of several successive reactions with similar timescales). This complexity is to be expected of a reaction producing HSNO or ONS^-, since most S-nitroso compounds are very unstable.

Iodide Ion.—The reaction between I^- and MNTS was studied in 3.3% (v/v) acetonitrile–water mixtures, the use of dioxane employed in most of the other experiments being precluded by the observation of the reaction between the commercial dioxane and iodide. HPLC of the mixture of products showed quantitative formation of *N*-methyltoluene-*p*-sulfonamide, and hence that the iodide attacked the MNTS NO group. This was further confirmed by detection of triiodide, which must have been formed by rapid decomposition of the initial reaction product INO (see Scheme 2);[23,25] the triiodide was quantified by measuring the absorbance of reaction mixtures at 460 nm and using the published extinction coefficients of I_3^- [$\varepsilon_{460}(I_3^-) = 975$; $\varepsilon_{460}(I_2) = 746\ dm^3\ mol^{-1}\ cm^{-1}$].[26] Monitoring the course of the reaction by HPLC afforded a value of $3.1 \times 10^{-4}\ dm^3\ mol^{-1}$ for the bimolecular rate constant (Table 1).



$$2\,INO \rightleftharpoons I_2 + 2NO$$

$$I_2 + I^- \rightleftharpoons I_3^-$$

Scheme 2

Discussion

Relative Reactivities of Nucleophiles with the Nitroso Group.—In those of the above MNTS reactions in which it is the nitroso group that is attacked, the bimolecular rate constant differs little (generally by less than a factor of two) from that of the reaction between EEN and the same nucleophile. This similarity between MNTS and EEN was also observed in our studies of their reactivities with a large number of structurally diverse N-nucleophiles (including primary, secondary and

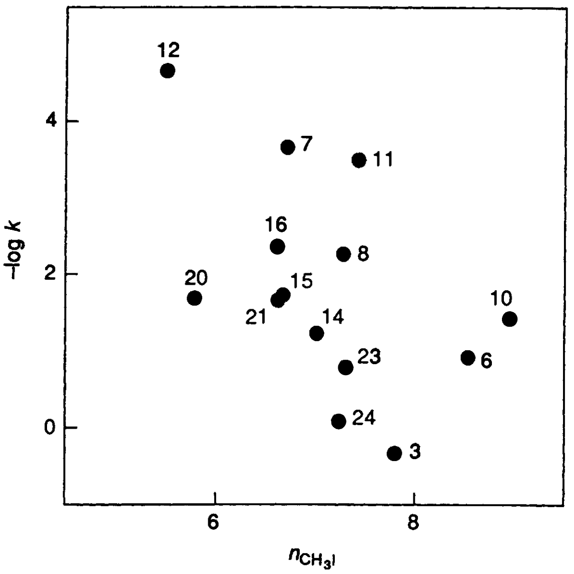


Fig. 7 Reactivities of nucleophiles (–log k of their reactions with MNTS or, for O-nucleophiles, EEN) plotted against their nucleophilicities according to Pearson's n_{CH_3I} scale

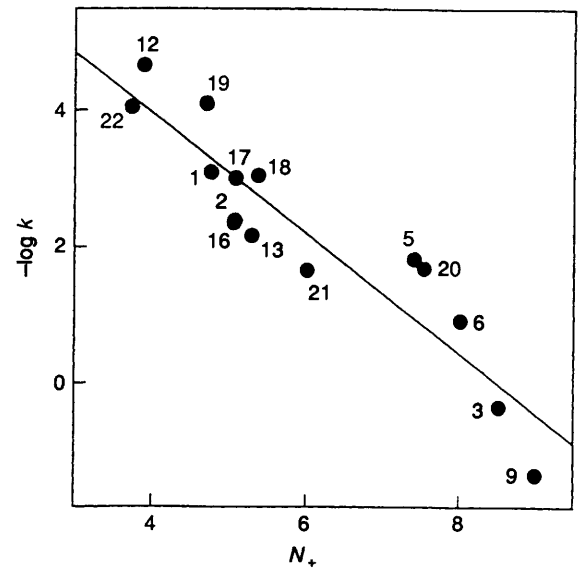


Fig. 8 Reactivities of nucleophiles (–log k of their reactions with MNTS or, for O-nucleophiles, EEN) plotted against their nucleophilicities according to Ritchie's N_+ scale

tertiary amines, azide and hydrazine)[4] and of several carbanions;[5] the results reported here therefore may be generalized to S- and O-nucleophiles.

Pearson *et al.*[27] defined the index n_{CH_3I}, as a measure of nucleophilicity based on nucleophilic substitution in CH_3I as a standard reference reaction. This index has often been used to compare nucleophilic reactivities in the acid denitrosation of *N*-nitrosamines, *i.e.* in reactions with protonated *N*-nitroso compounds.[28] Unfortunately, few nucleophiles can be used in this kind of reaction (in practice, only Cl^-, Br^-, SCN^- and thiourea, in ascending order of nucleophilicity). The reactions carried out in neutral or basic media in this and previous[4,10] work allow correlation between n_{CH_3I} and the reactivity with the MNTS NO group to be investigated for a number of other nucleophiles for which n_{CH_3I} values are available: iodide, the S-nucleophiles employed (except cysteine), most of the N-nucleophiles discussed in refs. 4 and 10 and HO_2^- (an approximate value may be derived by extrapolating to the unobserved reaction of HO_2^- with the MNTS nitroso group; the similarity between the reactivities of MNTS and EEN was pointed out in the previous paragraph). Fig. 7 shows that there is no correlation for the set of nucleophiles considered. Azide, for example, has an n_{CH_3I} value of 5.8 and is *ca.* 100 times more reactive than iodide ($n_{CH_3I} = 7.4$); while the species with the highest n_{CH_3I} value, thiosulfate ($n_{CH_3I} = 9.0$), is less reactive than, *e.g.*, diethylamine, for which $n_{CH_3I} = 7.0$.

Azide is also more nucleophilic than OH^- towards NO (Table 1). This order is not the expected one for a reaction following the n scale (the Swain–Scott's n values for azide and OH^- being 4 and 4.2, respectively), but it is the order predicted by Ritchie's N_+ scale, with which our reactivity data correlate much better than with n_{CH_3I} (Fig. 8; the values of N_+ were obtained[29] for reactions with electrophiles of the form Ar_3C^+, namely malachite green or tri-*p*-anisoylmethyl cation; we have included the value of k for the cysteine anion, obtained by Oh and Williams,[7] using the approximate value $N_+ = 9$ typical of alkylthiolates in water). The high degree of correlation ($r = 0.92$; most of the reactivities are within a factor of 10 of the regression line) is remarkable considering that it involves N-, O- and S- nucleophiles, that some of these nucleophiles (azide, HO_2^-, hydrazine and semicarbazide) exhibit α-effects and that for some of them the rate constant for the reaction with EEN has been used as an approximation to the constant for reaction with the MNTS nitroso group ($k_{EEN} \cong k_{MNTS}$), measurement of the latter being impossible owing to the overwhelming predominance of the reaction with the sulfonyl group. It is also significant that the slope of the regression line in Fig. 8 is very close to the theoretical value of unity, showing that the electrophile–nucleophile reactions fulfilling Ritchie's equation include the concerted[4] reaction of nucleophiles with the nitroso group. In previous work,[4] in which the values of N_+ were less reliable and covered a smaller range (they concerned only N-nucleophiles, and were obtained by statistical treatment of a large number of reactions),[30] the slope of a log k *vs.* N_+ plot was near two, and the nucleophiles showing an α-effect deviated considerably from the fitted line.

Hoz[8] has pointed out that when reactivities correlate well with N_+ the substrate generally has a low-energy LUMO, typically being an unsaturated species (which of course includes nitroso compounds). This observation allows the reaction for which N_+ is effective (especially those involving S- or N-nucleophiles or I^-, which as 'soft' nucleophiles have high-energy HOMOs) to be characterized in Klopman's[31] terms as frontier-controlled reactions. According to Klopman's theory, the total energy perturbation when the orbitals of a nucleophile overlap those of an electrophile is given by eqn. (6), where q_n and q_e are

$$\Delta E = -\frac{q_n q_e}{\varepsilon R_{ne}} + \frac{2c_n^2 c_e^2 \beta_{ne}^2}{E_{HOMO} - E_{LUMO}} \tag{6}$$

the charges on the nucleophile and the electrophile, respectively, R_{ne} is the distance between them, E_{HOMO} and E_{LUMO} are the energies of the frontier orbitals, c_n and c_e are the molecular orbital coefficients, β_{ne} is the bonding integral and ε is the relative permittivity of the medium. The first term on the right-hand side of eqn. (6) represents electrostatic interaction and the second the interaction between orbitals. If the LUMO of the substrate has low energy, as appears to be the case when N_+ 'works well', then $E_{HOMO} - E_{LUMO}$ is small (especially for high HOMO nucleophiles) and the orbital interaction term dominates eqn. (6), *i.e.* the reaction is frontier-controlled.

A more detailed explanation of the predictive efficacy of N_+ has been given by Shaik,[32] who used a curve-crossing model[9] to conclude that for reactions with any given electrophile the N_+ values of nucleophiles are proportional to their vertical ionization potentials relative to a standard nucleophile. Since the vertical ionization potential is a measure of the energy of the HOMO, this analysis is in keeping with that of the previous paragraph. Hoz[8] infers that when N_+ is an effective measure of nucleophilicity, ready electron transfer between the nucleophile and the electrophile leads to a markedly diradicaloid transition state.

Relative Reactivities of Nucleophiles with the MNTS Sulfonyl Group.—As was noted above, whilst good correlation with n[29] requires the azide to be less nucleophilic than OH^- [n(azide) = 4, $n(OH^-)$ = 4.2], good correlation with N_+ requires the azide to be more nucleophilic than OH^- [N_+(azide) = 7.54, $N_+(OH^-)$ = 4.75]. As we have seen above, it is the latter behaviour that is observed when the nucleophiles react with the nitroso group, but the reverse seems to hold for the reaction with the MNTS sulfonyl group. Although no direct measurement of the rate constant is possible for azide in this case, the fact that analysis of the products of reaction between MNTS and azide shows a >97% yield of *N*-methyltoluene-*p*-sulfonamide means that the reaction with the sulfonyl group must be at least 20 times slower than the reaction with the nitroso group, for which the bimolecular rate constant is 1.35×10^{-2} dm^3 mol^{-1} s^{-1} (Table 1). Thus the reaction of the sulfonyl group with the azide must be at least 100 times slower than its reaction with OH^-, for which the bimolecular rate constant is 0.127 dm^3 mol^{-1} s^{-1} (Table 1). This strongly suggests that the proper scale for prediction of nucleophilicity for the sulfonyl group is not N_+, but possibly some scale resembling n.

Given the considerations of the previous section, the inefficacy of N_+ for prediction of nucleophilicity for the sulfonyl group suggests that the transition state of these reactions is not markedly diradicaloid and that the reactions are not frontier-controlled. The latter conclusion certainly seems reasonable in view of the strong charge-withdrawing effect of the two sulfonyl oxygen atoms on the sulfur atom, since the resulting concentration of positive charge on the sulfur atom must lead to a large electrostatic term in eqn. (6).

Ambidentate Behaviour of MNTS.—The work reported here and in previous articles[4,5,10] shows that the nucleophiles which in their reactions with MNTS attack only the nitroso group include iodide and all the N-, C- and S-nucleophiles. O-nucleophiles (OH^-, alkoxides and HO_2^-) also, or exclusively, attack the MNTS sulfonyl group. The nitroso-attackers are, in Pearson's terminology,[27] 'soft' nucleophiles, and their reacting with the nitroso rather than the sulfonyl group shows the former to be softer than the latter (certain theoretical studies also suggest that the nitroso group is relatively soft, *i.e.* is only weakly positively charged).[33] The sulfonyl-attackers, on the other hand, are 'hard' nucleophiles in which charge is concentrated on a highly electronegative atom and their reaction with the MNTS sulfonyl group shows the sulfur atom to be the hardest in the MNTS molecule.

The reactions of soft nucleophiles with the soft nitroso group, upon which the LUMO of MNTS must be localized, are frontier-controlled, while the reactions of hard nucleophiles with the hard sulfonyl group are charge-controlled. The conflict that can arise between these two mechanisms is illustrated by the reaction of the acetohydroxamic acid anion with both the electrophilic groups of MNTS. Although this anion is an O-nucleophile and might therefore be expected to take part only in a charge-controlled reaction with the sulfonyl group, it is also an α-nucleophile and perhaps, owing to the presence of the –C(O)N group, fairly polarizable; it may even feature a considerable degree of indirect charge delocalization. Charge delocalization and polarizability must both make the anion more readily ionizable, *i.e.* reduce its hardness, while the presence of a lone pair α to the O atom must stabilize the diradicaloid transition state involved in an electron-transfer reaction.[34] As a result, the acetohydroxamic acid anion is able to react with the MNTS nitroso group as well as with the sulfonyl group. This contrasts with the behaviour of HO_2^-, in which the electrostatic interaction favoured by the hard oxygen predominates over the α-effect.

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