The Kinetics and Mechanism of the Aminolysis of Phenethyl Nitrite

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Kinetic studies on the ammonolysis and aminolysis of phenethyl nitrite were carried out in 61% dioxan-water. Good second-order rate constants were obtained for the reactions except that with trimethylamine which is autocatalysed by the trimethylammonium ion formed. The rate of the trimethylammonium ion catalysed reaction was obtained from the slope of the plots of apparent second-order rate constants against concentration of trimethylammonium ion. There was no general base catalysis in any of the reactions. Solvent kinetic deuterium isotope effects were found to be 1.96 and 2.21 for the reactions with methylamine and morpholine, respectively, and 2.44 for the trimethylammonium ion catalysed reaction with trimethylamine. Brönsted plots are scattered, since substitution of hydrogen by a methyl group on NH_3 markedly increases the nucleophilicity, *e.g.* the relative rates $NH_3 : MeNH_2 : Me_2NH : Me_3N$ were $1 : 5.5 \times 10^2 : 5.1 \times 10^5 : 5.3 \times 10^6$. However, logarithms of the rate constants are correlated linearly with the vertical ionization potentials of these amines. All these results suggest that the reaction is ' orbital controlled ' and proceeds *via* concerted displacement of alkoxide by amine rather than addition–elimination. The results are rationalized in terms of the high electronegativity of nitrogen and the presence of a lone pair of electrons on nitrogen.

THE quantitative investigations of nucleophilic substitution on trivalent sp^2 hybridized nitrogen which have been reported are nitrosation by nitrosyl halide, acid-catalysed nitrosation by nitrous acid,[1] and acid-catalysed denitrosation of *N*-nitrosamines.[2] These reactions are complicated by the intervention of catalysis by protons, halide ions, *etc.* and involve many steps. The variety of nucleophiles is also limited because of the occurrence of acid catalysis. We have chosen the reaction between alkyl nitrites and various nucleophiles as a model for the systematic investigation of nucleophilic substitution on trivalent sp^2 nitrogen.[3] In previous work on the alkaline hydrolyses of alkyl nitrites, we made the following observations.[3] (1) Carboxylic esters react much faster than the corresponding alkyl nitrites. (2) Polar substituent effects on the leaving alkoxide of alkyl nitrites are larger than those for carboxylic esters. (3) The steric effect for alkyl nitrites is smaller than for the carboxylic esters. (4) There is no oxygen exchange between the nitroso oxygen and OH^- during the alkaline hydrolysis of n-hexyl nitrite, unlike the situation for the analogous carboxylic ester.

These observations suggest that the alkaline hydrolysis is better expressed by a nearly concerted nucleophilic substitution rather than the addition–elimination mechanism which has been accepted for the alkaline hydrolysis of carboxylic esters.[3] The different behaviour of alkyl nitrites was suggested to be due to the lone pair–lone pair repulsion between OH^- ion and the nitrogen atom of the alkyl nitrite and also to the higher electronegativity of nitrogen than of carbon.[3] In order to examine these characteristic features of the nucleophilic substitution of alkyl nitrites, the reaction between phenethyl nitrite and various amines, each of which has only one reacting lone pair and cannot undergo any unfavourable interaction with the lone pair on the nitroso nitrogen atom, has been investigated.

RESULTS AND DISCUSSION

All the reactions between phenethyl nitrite and amines were carried out in evacuated tubes using 61% dioxan–water as solvent. The reaction between phenethyl nitrite and n-hexylamine gave phenethyl alcohol, n-hexyl alcohol, and hexenes. Friedman *et al.* reported that the first step of the reaction between alkyl nitrite and primary amine is nucleophilic attack of amine on the nitroso nitrogen atom to give an *N*-nitrosamine, which affords ultimately hydrocarbons *via* the formation of a

$$R'O{-}N{=}O + RNH_2 \longrightarrow R'OH + RNHN{=}O \qquad (1)$$

$$RNHN{=}O \rightleftharpoons RN{=}NOH \qquad (2)$$

$$RN{=}NOH \longrightarrow R({-}H) + H_2O/ROH + N_2 \qquad (3)$$

cationic or carbene species [equations (1)—(3)]. However, under basic aprotic conditions, base-catalysed

$$R''CH_2ONO \xrightarrow{:B} R''CHO + 1/2H_2O + 1/2N_2O \qquad (4)$$

elimination of HNO takes place to give the corresponding aldehyde, N_2O, and water [equation (4)].[4] In our reaction conditions, there is no such unfavourable side

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[1] (*a*) M. N. Hughes and G. Stedman, *J. Chem. Soc.*, 1963, 2824; (*b*) C. K. Ingold, ' Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, 1967, 2nd edn., p. 618; (*c*) T. D. B. Morgan, G. Stedman, and M. N. Hughes, *J. Chem. Soc.* (*B*), 1968, 344; (*d*) M. A. Hussain, G. Stedman, and M. N. Hughes, *ibid.*, p. 597; (*e*) M. Hutchinson and G. Stedman, *J.C.S. Perkin II*, 1973, 93; (*f*) J. R. Perrott, G. Stedman, and M. N. Uysal, *ibid.*, 1977, 274.

[2] (*a*) B. C. Challis and M. R. Osborne, *J.C.S. Chem. Comm.*, 1972, 518; (*b*) C. N. Berry and B. C. Challis, *ibid.*, p. 627; (*c*) B. C. Challis and M. R. Osborne, *J.C.S. Perkin II*, 1973, 1526; (*d*) C. N. Berry and B. C. Challis, *ibid.*, 1974, 1638; (*e*) B. C. Challis and S. P. Jones, *ibid.*, 1975, 153; (*f*) T. D. B. Morgan and D. L. H. Williams, *ibid.*, 1972, 74; (*g*) T. D. B. Morgan, D. L. H. Williams, and J. A. Willson, *ibid.*, 1973, 437; (*h*) D. L. H. Williams and J. A. Willson, *ibid.*, 1974, 13; (*i*) D. L. H. Williams, *J.C.S. Chem. Comm.*, 1974, 324; (*j*) I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107; (*k*) D. L. H. Williams, *ibid.*, p. 655; (*l*) I. D. Biggs and D. L. H. Williams, *ibid.*, 1976, 601; (*m*) *ibid.*, 1977, 47; (*n*) D. L. H. Williams, *ibid.*, 1976, 1838; (*o*) *ibid.*, 1977, 128; (*p*) S. S. Singer, W. Lijinsky, and G. M. Singer, *Tetrahedron Letters*, 1977, 1613.

[3] S. Oae, N. Asai, and K. Fujimori, *J.C.S. Perkin II*, 1978, 571.

[4] (*a*) J. H. Bayless, F. D. Mendicino, and L. Firedman, *J. Amer. Chem. Soc.*, 1965, **87**, 5790; (*b*) L. Friedman and J. H. Bayless, *ibid.*, 1969, **91**, 1790; (*c*) L. Friedman, A. T. Jurewiiz, and J. H. Bayless, *ibid.*, p. 1790.

reaction, since phenethyl alcohol was obtained in a quantitative yield.

The reaction between phenethyl nitrite and secondary amines gave phenethyl alcohol and the corresponding *N*-nitrosamine in quantitative yield [equation (5)].

$$\mathrm{R'O{-}N{=}O + R_2NH \longrightarrow R'OH + R_2N{-}N{=}O} \quad (5)$$

Although tertiary amine is usually considered to be unreactive to nitrosating reagents, it may act as a nucleophilic catalyst in the hydrolysis of phenethyl nitrite as shown in equations (6)—(9). In fact, the reaction

$$\mathrm{R'O{-}N{=}O + R_3N + H_2O \longrightarrow R'OH + R_3\overset{+}{N}{-}N{=}O + OH^-} \quad (6)$$

$$\mathrm{R_3\overset{+}{N}{-}N{=}O + OH^- \longrightarrow R_3N + HO{-}N{=}O \longrightarrow R_3NH^+ + NO_2^-} \quad (7)$$

$$\mathrm{R'O{-}N{=}O + R_3N + R_3''NH^+ \longrightarrow R'OH + R_3\overset{+}{N}{-}N{=}O + R''_3N} \quad (8)$$

$$\mathrm{R_3\overset{+}{N}{-}N{=}O + H_2O \longrightarrow R_3N + H_2NO_2^+ \xrightarrow{R''_3N} R_3NH^+ + R''_3NH^+ + NO_2^-} \quad (9)$$

between phenethyl nitrite and trimethylamine or tri-n-propylamine gave the corresponding trialkylammonium nitrite and phenethyl alcohol in quantitative yields.

Nitrosation of hydroxylamine is known to give N_2O and H_2O [equations (10) and (11)].[1a]

$$\mathrm{R'O{-}N{=}O + HONH_2 \longrightarrow R'OH + HONHN{=}O} \quad (10)$$

$$\mathrm{HONHN{=}O \rightleftharpoons HON{=}NOH \longrightarrow H_2O + N_2O} \quad (11)$$

All these reactions are nucleophilic substitutions on the sp^2 hybridized nitrogen of phenethyl nitrite and one mole of phenethyl nitrite consumes one mole of amine.

Rates of aminolyses of phenethyl nitrite were determined by following the consumption of amine by titration of the remaining amine with a standard solution of hydrochloric acid as in the alkaline hydrolyses of alkyl nitrites.[3] The results are summarized in Table 1.

Good second-order rate constants were obtained in the reactions of both primary and secondary amines up to 50% completion of the reaction (Tables 2 and 3). This is quite different from aminolyses of carboxylic esters, in which a substantial decrease of the second-order rate constant is usually observed during the reaction due to general base-catalysis by amines.[5] An increase in the initial concentration of the amine did not increase but decreased very slightly the rate of the reaction between phenethyl nitrite and both primary and secondary amines, suggesting that there is no general base catalysis in these reactions. Addition of sodium nitrite, ammonium perchlorate, or sodium perchlorate, changed the rate only a very little due to the change in ionic strength. Apparently, nitrite ion does not behave as a nucleophilic catalyst unlike its behaviour in nitrosation reactions[1] and there is no general acid catalysis by the conjugate acids of amines.

Unlike the reactions of primary and secondary amines, the second-order rate constant of the reaction of trimethylamine was found to increase as the reaction proceeds (Table 4). Since addition of a small amount of trimethylammonium perchlorate increases the initial rate remarkably while addition of sodium nitrite and sodium perchlorate enhance the rate only slightly, the reaction of the trimethylamine is considered to be autocatalysed by trimethylammonium ion, which is presumed to function as a general acid catalyst to quench $R'O^-$, formed in the initial stage of the reaction.

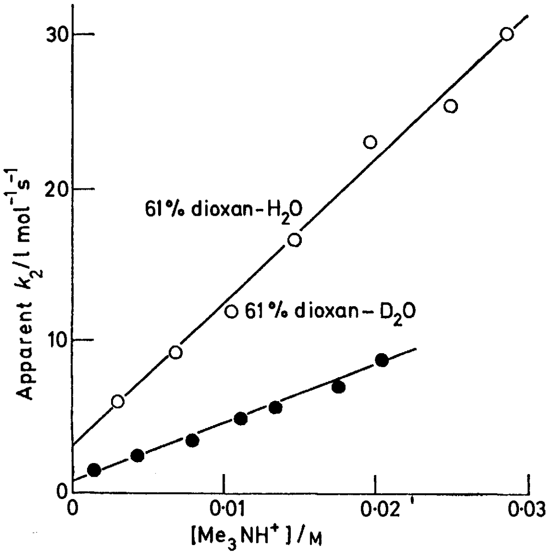

FIGURE 1 Plots of apparent second-order rate constants for the reaction of $(CH_3)_3N$ with $PhCH_2CH_2ONO$ against concentration of trimethylammonium ion at 35.1 °C

According to this mechanism, the rate of the reaction is expressed by equation (12). Actually plots of the

$$-\mathrm{d[Amine]}/\mathrm{d}t = -\mathrm{d[PhCH_2CH_2ONO]}/\mathrm{d}t = (k_2 + k_3[\mathrm{Amine{\cdot}H^+}])[\mathrm{Amine}][\mathrm{RONO}] \quad (12)$$

apparent second-order rate constants against the concentration of trimethylammonium nitrite give a straight line (r 0.995 2) and from the slope and the intercept, the values of k_3 and k_2, respectively, were obtained (Figure 1). On the other hand, in the reaction with a bulky tertiary amine such as tri-n-propylamine, the second-order rate constant did not increase during the reaction. Apparently, the bulky tertiary ammonium ion cannot come close enough to the reaction site to donate a proton to the $R'O^-$ group. Further, there is no general acid catalysis by the conjugate acids of primary and secondary amines. Undoubtedly, the *N*-nitrosomono- or di-alkylammonium ions, which are formed initially by substitution of alkoxide in the alkyl nitrite by the primary or secondary amines give a proton to the leaving alkoxide ion. Consequently, in order to determine the nucleophilicity of amines toward the alkyl nitrite, the second-order rate constants of the reactions

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[5] (*a*) R. L. Betts and L. P. Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1568; (*b*) M. Gordon, J. G. Miller, and A. R. Day, *ibid.*, 1948, **70**, 1946.

of primary and secondary amines and the third-order rate constants of tertiary amines must be compared.

TABLE 1

Kinetic data of aminolyses of phenethyl nitrite in 61% dioxan–water

Amine	$[\text{Amine}]_0$/ M	$[\text{PhCH}_2\text{CH}_2\text{ONO}]_0$/ M	T/°C	Salt	10^4k_2/l mol^{-1} s^{-1}	pK_a [a]
CH_3NH_2	0.0831	0.0606	35.1		0.961 ± 0.018	10.66
	0.0811	0.0502	45.0		1.91 ± 0.07	
	0.0862	0.0639	55.0		3.55 ± 0.06	
	0.0873	0.0625	35.1	$NaClO_4$ (0.0304M)	1.06 ± 0.02	
	0.0761	0.0593	35.1	$CH_3NH_2,HClO_4$ (0.0324M)	1.28 ± 0.01	
	0.0621	0.0525	35.1		0.477 ± 0.007 [f]	
Pr^nNH_2	0.0900	0.0700	35.1		0.292 ± 0.003	10.89
Bu^nNH_2	0.0883	0.0634	35.1		0.366 ± 0.007	10.61
	0.0771	0.0656	35.1		0.0398 ± 0.004 [b]	
$(CH_3)_2NH$	0.0799	0.0615	35.1		89.6 ± 1.4	10.73
	0.0712	0.0582	35.1	$(CH_3)_2NH,HClO_4$ (0.0323M)	88.8 ± 1.2	
Pyrrolidine	0.0399	0.0192	35.1		174 ± 6	11.27
Piperidine	0.0417	0.0315	35.1		35.0 ± 1.2	11.12
	0.0420	0.0319	25.0		18.3 ± 0.4	
	0.0409	0.0208	45.0		57.5 ± 1.8	
Morpholine	0.0824	0.0617	35.1		0.865 ± 0.008	8.33
	0.2620	0.0616	35.1		0.816 ± 0.012	
	0.4040	0.0565	35.1		0.732 ± 0.039	
	0.0746	0.0585	35.1	$NaClO_4$ (0.0315M)	0.987 ± 0.02	
	0.0794	0.0601	35.1	Morpholine,$HClO_4$ (0.0317M)	1.29 ± 0.01	
	0.0820	0.0654	35.1	$NaNO_2$ (0.0312M)	1.20 ± 0.03	
	0.0832	0.0650	35.1		0.391 ± 0.05 [f]	
Pr^n_2NH	0.0469	0.0352	35.1		9.89 ± 0.12	11.00
	0.1880	0.0308	35.1		8.41 ± 0.27	
	0.0477	0.0374	35.1		0.326 ± 0.017 [b]	
Bu^n_2NH	0.0771	0.0609	35.1		8.56 ± 0.15	11.25
$(CH_2{=}CHCH_2)_2NH$	0.0837	0.0616	35.1		0.680 ± 0.025	9.29
$(HOCH_2CH_2)_2NH$	0.0851	0.0606	35.1		1.48 ± 0.03	8.88
$(NCCH_2CH_2)_2NH$	0.596	0.0217	35.1		0.00444 [illegible] 0.0002 [c]	5.26
$(CH_3)_3N$	0.0456	0.0367	35.1		3.0 (k_2)	9.81
	0.0456	0.0367	35.1		935 (k_3)	
	0.0585	0.0390	35.1	$Me_3N,HClO_4$ (0.0128M)	15 [e]	
	0.0445	0.0338	35.1	$NaClO_4$ (0.0144M)	5 [e]	
	0.0405	0.0296	35.1	$NaNO_2$ (0.0142M)	8 [e]	
	0.0458	0.0402	35.1		0.66 (k_2) [f]	
	0.0458	0.0402	35.1	$NaNO_2$ (0.0142M)	383 (k_3) [f]	
Pr^n_3N	0.0682	0.0551	35.1		0.106 ± 0.004	10.26
NH_3	0.510	0.122	35.1		0.00176 ± 0.00006	9.20
NH_2OH	0.0828	0.0635	35.1		14.1 ± 0.07	6.17
OH^-	0.0870	0.0692	35.1		1.85 ± 0.01 [d]	15.8

[a] At 25.0 °C in water, D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworth Scientific Publications, London, 1965; Z. Rappoport, 'Handbook of Tables for Organic Compound Identification,' The Chemical Rubber Co., Cleveland, 1967; W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622. [b] In dioxan. [c] Measured by u.v. [d] Ref. 3. [e] Apparent initial k_2. [f] In 61% dioxan–D_2O.

TABLE 2

Typical kinetic run of the reaction of phenethyl nitrite with a primary amine ($MeNH_2$) in 61% dioxan–water at 35.1 °C

t/min	0	300	420	545	1 305	1 790	∞
0.05N-HCl (ml) [a]	8.14	7.39	7.11	6.90	5.74	5.52	2.21
10^4k_2/l mol^{-1} s^{-1}		0.948	0.975	0.938	0.957	0.973	av. 0.961 ± 0.0018

[a] Volume of standard HCl solution required to titrate 5 ml of reaction mixture.

TABLE 3

Typical kinetic run of the reaction of phenethyl nitrate with a secondary amine (Me_2NH) in 61% dioxan–water at 35.1 °C

t/min	0	14	24	34	44	54	65	84	∞
0.05N-HCl (ml) [a]	4.650	3.250	2.730	2.375	2.160	1.950	1.785	1.585	1.073
10^4k_2/l mol^{-1} s^{-1}		88.4	89.4	89.3	90.1	87.2	89.9	92.7	av. 89.6 ± 1.4

[a] Volume of standard HCl solution required to titrate 5 ml of reaction mixture.

The possible occurrence of proton transfer either in the concerted or stepwise process is discussed later.

In accord with our previous work,[3] the data in Tables 1 and 5 revealed that the lone pair on nitrogen in the alkyl nitrite plays an important role in nucleophilic substitution on nitrogen. For example, the nucleophilic reactivity of OH^- in the hydrolysis of carboxylic esters is remarkably greater than for alkyl nitrites. However, the nucleophilic reactivity of amine in the aminolysis of esters is remarkably less than for alkyl nitrites. Therefore, the amine is a better nucleophile than OH^- in the reaction with alkyl nitrites, but much weaker in the reaction with carboxylic esters. For example, the reaction of piperidine with phenethyl nitrite is 19 times faster than alkaline hydrolysis in 61% dioxan–water. On the other hand, under the same conditions the reaction of piperidine with phenethyl benzoate is at least 10^2 fold slower than alkaline hydrolysis, the major product being that of hydrolyses and the corresponding amide a minor product.[3] This is due to the smaller activation enthalpy for aminolyses than for alkaline hydrolysis for alkyl nitrites. These observations are rationalized in terms of an unfavourable lone pair–lone pair interaction between the nucleophiles and the nitroso nitrogen atom in the reaction with OH^-, while there is no such repulsion in the reaction with amine.[3]

TABLE 4

Typical kinetic run of phenethyl nitrite with trimethylamine in 61% dioxan–water at 35.1 °C

t/min	0	51	103	152	210	276	399	441	∞
0.05N-HCl (ml) [a]	4.420	4.150	3.785	3.430	2.985	2.505	1.940	1.795	0.860
10^4k_2/l mol^{-1} s^{-1}		5.84	7.56	8.94	11.1	13.9	17.4	18.6	

[a] Volume of standard HCl solution required to titrate 5 ml of reaction mixture.

TABLE 5

Activation parameters for aminolyses and alkaline hydrolysis of phenethyl nitrite in 61% dioxan–water

Nucleophile	E_a/ kcal mol^{-1}	$\Delta H^‡$/ kcal mol^{-1}	$\Delta S^‡$/cal mol^{-1} K^{-1}	Correlation coefficient
Piperidine	10.8	10.2	−36.8	0.9987
Methylamine	13.2	12.6	−36.2	0.9999
OH^- [a]	16.5	15.8	−24.3	0.9985

[a] Ref. 3.

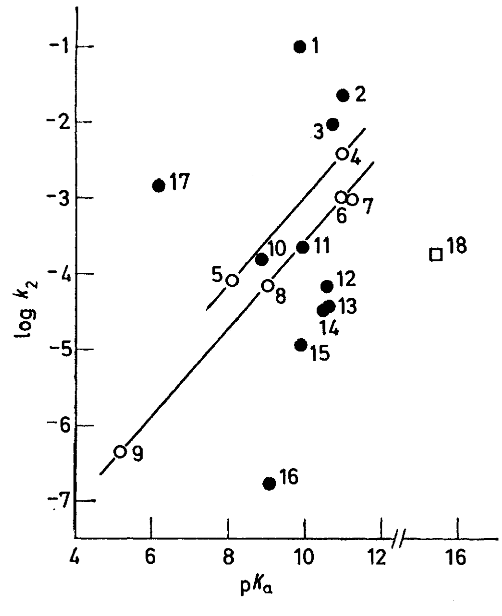

FIGURE 2 Plots of log k_2 of the aminolyses of phenethyl nitrite in 61% dioxan–water at 35.1 °C *versus* pK_a of amine in H_2O at 25 °C: 1, Me_3N (k_3); 2, pyrrolidine; 3, Me_2NH; 4, piperidine; 5, morpholine; 6, Pr^n_2NH; 7, Bu^n_2NH; 8, $(CH_2{=}CHCH_2)_2NH$; 9, $(NCCH_2CH_2)_2NH$; 10, $(HOCH_2CH_2)_2NH$; 11, Me_3N (k_2); 12, $MeNH_2$; 13, Bu^nNH_2; 14, Pr^nNH_2; 15, Pr^n_3N; 16, NH_3; 17, NH_2OH; 18, OH^-

In order to examine the effect of the basicity of the amine on the rate of aminolysis, the logarithms of the second-order rate constants were plotted against the pK_a values of the amines in H_2O at 25 °C (Figure 2). Inspection of the Brönsted plot of phenethyl nitrite reveals the following features. The points for the sterically similar amines, Pr^n_2NH, Bu^n_2NH, $(CH_2{=}CHCH_2)_2NH$, and $(NCCH_2CH_2)_2NH$ fall on a straight line and β (0.58) is substantially smaller than for the aminolysis of phenyl acetate (0.8).[6a] However, the points for NH_3 and primary amines deviate from the line for the secondary amines. Although the pK_a values of primary amines, $MeNH_2$ and Pr^nNH_2, and the secondary amines, Me_2NH, Pr^n_2NH, Bu^n_2NH, piperidine, and pyrrolidine are nearly the same, the reactions of the secondary amines are much faster than those of primary amines by factors of 10—470. The pK_a values of $(CH_2{=}CHCH_2)_2NH$ and NH_3 are quite similar, and yet the reaction of the former is faster than the latter by a factor of 390. However, the Brönsted plots of aminolyses of phenyl acetate including ammonia, primary amines, and secondary amines give roughly a straight line.[6]

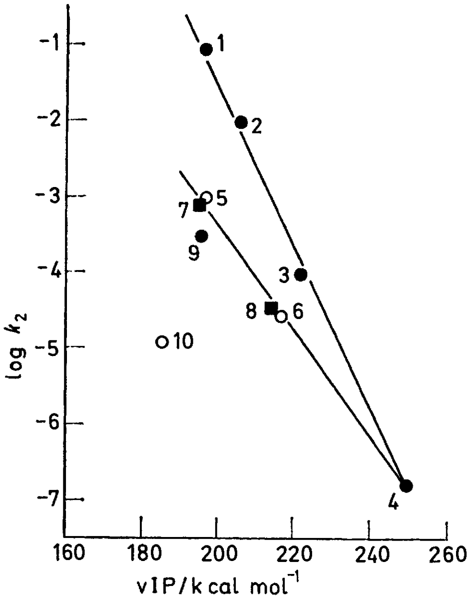

FIGURE 3 Plots of log k_2 of the aminolysis of phenethyl nitrite in 61% dioxan–water at 35.1 °C *versus* vIP of amine: 1, Me_3N (k_3); 2, Me_2NH; 3, $MeNH_2$; 4, NH_3; 5, Pr^n_2NH; 6, Pr^nNH_2; 7, Bu^n_2NH; 8, Bu^nNH_2; 9, Me_3N; 10, Bu^n_3N

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[6] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, (*a*) 675; (*b*) 1778.

The order of the rates of aminolyses, $NH_3 < MeNH_2 < Me_2NH < Me_3N$, is the reverse of that of the ionization potentials of these amines.[7] As shown in Figure 3, good linear dependences of the logarithms of specific rates of aminolyses on the vertical ionization potentials (vIP) are observed in the NH_3–$MeNH_2$–Me_2NH–Me_3N, NH_3–Pr^nNH_2–$Pr^n{}_2NH$, and NH_3–Bu^nNH_2–$Bu^n{}_2NH$ series. Although unfortunately vIPs of $(CH_2{=}CHCH_2)_2NH$ and $(NCCH_2CH_2)_2NH$ are not available, the pK_a values of structurally similar secondary amines with straight-line Brönsted plots are in general linearly correlated with vIP values. Since the vIP reflects the energy level of the highest occupied orbital (lone pair) of the amine, the rate of aminolysis is determined by the energy level of the highest occupied orbital of the nucleophile. Since the electronegativity of nitrogen is greater than that of carbon, one can expect that the nitroso group of an alkyl nitrite is less polarized than the carbonyl group of a carboxylic ester and the energy level of the π* orbital of a nitroso group is lower than that of a carbonyl group. In fact a simple Hückel MO calculation shows that not only is the nitroso nitrogen in an alkyl nitrite less positive than the carbonyl carbon in a carboxylic ester but also the lowest unoccupied molecular orbital of an alkyl nitrite is substantially lower than that of a carboxylic ester. The energy levels of four amine nucleophiles and the lowest unoccupied molecular orbitals of the electrophiles are qualitatively represented in Figure 4.

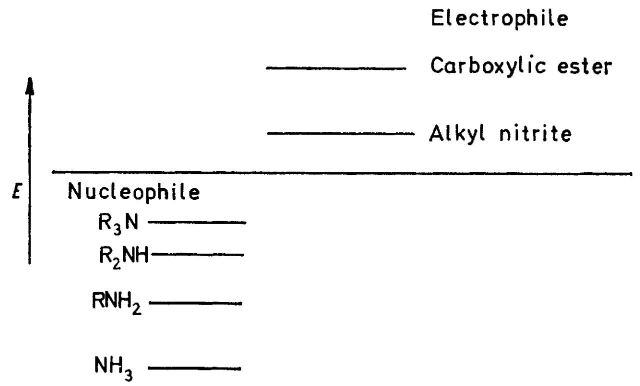
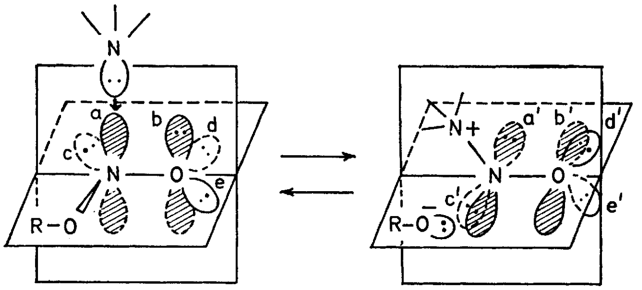


FIGURE 4 Qualitative representation of energy levels of nucleophiles and electrophiles

According to current perturbation theory, the bonding interaction between a nucleophile and an electrophile can be divided into an electrostatic term and a covalent term,[8] and often one dominates the other. One case is a 'charge controlled reaction' in which a large energy gap exists between the highest occupied orbital of the nucleophile and the lowest unoccupied orbital of the electrophile and the electrostatic term plays a major role.[8] The other extreme is an 'orbital controlled reaction' in which the two orbitals are nearly degenerate and hence the covalent term is important.[8]

In the reaction of carboxylic esters not only is the energy gap between the donor orbitals of the amines and the acceptor orbitals of the ester substantial (Figure 4) but also the carbonyl group is highly polarized. Accordingly, the aminolysis of a carboxylic ester is considered to be a 'charge-controlled reaction.'[8] Moreover, the Brönsted β value represents the extent of bond formation in the transition state.[9] Indeed the rates of aminolyses of carboxylic esters are nicely correlated with the Brönsted base-catalysis relationship with a large β value (0.8). In the reaction of alkyl nitrites, however, not only the energy gap between the donor orbitals and the acceptor orbital but also the positive charge on the nitroso-nitrogen is small. Thus aminolysis of phenethyl nitrite is considered to be an 'orbital-controlled reaction', in which the rates of aminolyses depend on the energy levels of the highest occupied orbitals of the amines but not on their pK_a values. In other words, the sp^2 hybridized trivalent nitrogen in the alkyl nitrite is a soft electrophile. This is consistent with the nucleophilic order, $Cl^- < Br^- < SCN^- < (NH_2)_2C{=}S < I^-$, in the acid-catalysed denitrosation of *N*-nitroso-*N*-methylaniline.[2c] Figure 3 indicates that the slope of the straight line for the methyl series is steeper than those of the n-propyl and n-butyl series due mainly to steric effects. The small Brönsted β value for the aminolyses of these secondary amine series suggests that the transition state of the aminolysis is at an earlier stage than that for the aminolysis of phenyl acetate. All these experimental results suggest that the aminolysis of alkyl nitrites is nearly concerted as illustrated in Figure 5. The nucleophile attacks the π* orbital of the nitroso group in a direction perpendicular to the trigonal plane of the nitrogen. In the transition state, the electrons of the nitroso group are localized mainly into a *p* orbital (b) of the oxygen of (1), which is finally changed to a lone pair (d′) of (2), while the lone pair (d) simultaneously attacks the nitrogen atom from the back side of the OR′ group to remove the $R'O^-$ group. As a result, the trigonal plane of the nitroso group rotates 90° during the reaction of (1) to (2).[10]



(1) (2)

FIGURE 5 Stereoelectronic course in the aminolysis of alkyl nitrite

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[7] D. H. Aue, H. M. Webb, and M. T. Bowers, *J. Amer. Chem. Soc.*, 1976, **98**, 311.

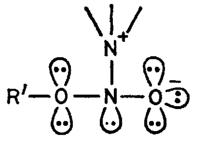
[8] G. Klopman, (*a*) *J. Amer. Chem. Soc.*, 1968, **90**, 223; (*b*) 'Chemical Reactivity and Reaction Paths,' Wiley–Interscience, New York, 1974, ch. 4.

[9] R. F. Hudson, ref. 8*b*, ch. 5.

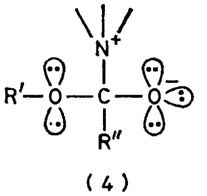
[10] (*a*) D. Y. Curtin and M. L. Poutsma, *J. Amer. Chem. Soc.*, 1962, **84**, 4892; (*b*) D. Y. Curtin and L. L. Miller, *ibid.*, 1967, **89**, 637; (*c*) S. Oae, Y. Uchida, K. Fujimori, and S. Kozuka, *Bull. Chem. Soc. Japan*, 1973, **46**, 174.

If the aminolysis of the alkyl nitrite proceeds *via* a tetrahedral addition intermediate (3) as in the aminolysis of carboxylic esters,[11] the intermediate (3) would be destabilized by the lone pair–lone pair repulsion between the nitrogen and oxygen atoms. However, there is no such unfavourable interaction in the intermediate (4). Therefore the transition state for the aminolysis of alkyl nitrites should be at a later stage than for carboxylic esters. If the reaction occurs *via* addition–elimination, the Brönsted β value for the reaction with alkyl nitrites should be greater than that for the reaction with carboxylic esters.[9]

However, this is not the case. Thus, the possibility of an addition–elimination mechanism can be ruled out.



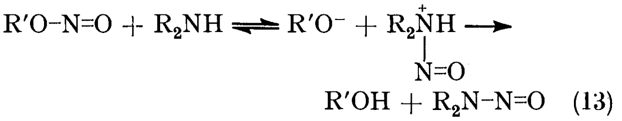
(3)



(4)

This conclusion is in keeping with the results we found for the alkaline hydrolyses of the alkyl nitrites.[3] Thus, the *high electronegativity* of the nitrogen atom and the *presence of a lone pair* characterize nucleophilic substitution on sp^2 hybridized trivalent nitrogen.

A question still remains whether the reaction includes the stepwise proton transfer represented by equations

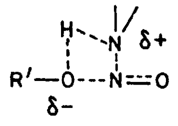


$$R'O\text{-}N{=}O + R_2NH \rightleftharpoons R'O^- + R_2\overset{+}{N}H(N{=}O) \longrightarrow R'OH + R_2N\text{-}N{=}O \quad (13)$$

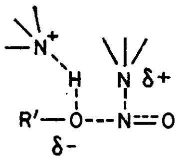
$$R'O\text{-}N{=}O + R_3N \rightleftharpoons$$
$$R'O^- + R_3\overset{+}{N}\text{-}N{=}O \xrightarrow{+H_2O} R'OH + R_3\overset{+}{N}\text{-}N{=}O$$
$$\xrightarrow{+ R''_3NH^+} R'OH + R''_3N + R_3\overset{+}{N}\text{-}N{=}O \quad (14)$$
$$R_3\overset{+}{N}\text{-}N{=}O + H_2O \longrightarrow R_3N + H_2NO_2^+ \xrightarrow{+ R_3N} 2R_3NH^+ + NO_2^-$$

(13) and (14) or a concerted proton transfer process as illustrated by (5)—(8).

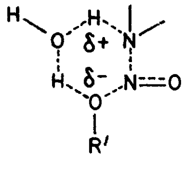
Solvent kinetic deuterium isotope effects were determined as shown in Table 1 and found to be 1.96 for the reaction with methylamine, 2.21 for the reaction with morpholine, and 2.4 for the trimethylammonium ion catalysed reaction with trimethylamine. These values reveal that proton transfer does occur in the rate-determining step. The proton attached to the nitrogen of the amine is displaced by a deuteron in deuterium oxide. In view of the large negative entropy (Table 5) and the relatively large k_H/k_D values, the reactions of primary and secondary amines seems to proceed *via* a cyclic transition process. The absence of general base catalysis appears to rule out process (8). When the solvent is changed from 61% dioxan–water to dioxan, the rate decreased only by factors of 9 and 26 for the reaction of n-butylamine and di-n-propylamine, respectively. On the other hand, aminolysis of a carboxylic ester in dioxan–water is measurable but is immeasurably slow in dioxan,[5b] suggesting that the cyclic structure (5) is most likely in the aminolyses of alkyl nitrites with primary and secondary amines. The relatively large value of k_H/k_D for the reaction of trimethylamine could also be explained by the general acid-catalysed removal of the leaving alkoxide group as illustrated in (6).



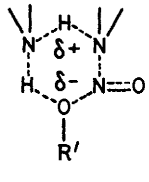
(5)



(6)



(7)



(8)

While the reactivity of hydroxylamine cannot be predicted because its vIP is not known, the very rapid reaction of hydroxylamine could be due to the α-effect.[11,12]

EXPERIMENTAL

Materials.—Dioxan was purified by a method described elsewhere and stored in a refrigerator under argon. Phenethyl nitrite was prepared by treating phenethyl alcohol with $NaNO_2$ in the presence of H_2SO_4 and was distilled under reduced pressure before use. Carbonate-free distilled water was used for all experiments.

Product Analyses.—Reaction of phenethyl nitrite with piperidine. A solution of phenethyl nitrite (0.0803M) and piperidine (0.0101M) in 61% dioxan–water (25 ml) was placed in a Pyrex glass tube connected to a vacuum line, evacuated with cooling by a dry ice–acetone bath, degassed by freeze–thaw cycles, evacuated, and sealed. The tubes were placed in a thermostatted bath at 35.1 °C for 3 days. The tubes were then opened and tetralin (241 mg) was added as the standard for the analysis by g.l.c. on a 2 m stainless steel column packed with a 5% PEG-20M on 80 mesh Celite. The mixture was extracted with ether and dried (Na_2SO_4). The gas chromatogram of the solution, which was recorded on Shimazu GC-6A instrument, gave peaks for phenethyl alcohol and *N*-nitrosopiperidine. The yields of phenethyl alcohol and *N*-nitrosopiperidine were found to be 99 and 101%, respectively.

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[11] (*a*) T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966; (*b*) W. P. Jencks, 'Catalysis in Chemistry and Enzymolozy,' McGraw-Hill, New York, 1969; (*c*) S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.

[12] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1957, **79**, 5969.

Reaction of n-hexylamine and phenethyl nitrite. Product analysis was carried out as described above. A glass column (2 m) packed with OV-1 on 60—80 mesh Celite was used for g.l.c. analysis. The yield of phenethyl alcohol was found to be 99.5% and n-hexyl alcohol and pentenes were identified.

Reaction of tri-n-propylamine with phenethyl nitrite. The reaction was carried out as for piperidine. The yield of phenethyl alcohol was found to be quantitative (g.l.c.). Titration of the reaction mixture with a standard solution of HCl showed that phenethyl nitrite consumed an equimolar amount of the amine.

Kinetics.—The solution for a typical kinetic run was prepared by dissolving the desired amounts phenethyl nitrite and an amine in 61% dioxan–water in a 100 ml volumetric flask so that the final concentration of amine was *ca.* 1.4 times that of phenethyl nitrite. The solution (5 ml portions) was pipetted into Pyrex glass tubes, degassed, evacuated, and sealed. The tubes were placed in a thermostatted bath and after 5 min the first tube was removed and subjected to sudden cooling (*t* 0). The tube was opened and the solution transferred into a 100 ml conical flask containing CCl_4 (30 ml). The tube was rinsed with water (30 ml) which was combined with the reaction mixture. The amine was titrated with a standard solution of HCl using Neutral Red–Bromothymol Blue (9 : 2) or Bromocresol Purple as an indicator. At appropriate intervals, the remaining tubes were treated in the same manner.

In the reaction of bis-β-cyanoethylamine with phenethyl nitrite, since titration of the amine was difficult, the increase of absorption at 245 nm due to bis-β-cyanoethyl-*N*-nitrosoamine was followed by a JASCO UVDEC-1 spectrometer under the pseudo-first-order kinetic conditions.

We are grateful to Dr. O. Kikuchi, University of Tsukuba, for MO calculations and valuable discussions.

[7/2052 *Received*, 22*nd November*, 1977]