Reactivity of 1,3-Dipoles in Aqueous Solution. Part 1. Stereospecific Formation of *Z*-Amidoximes in the Reaction of Benzonitrile Oxides with Amines

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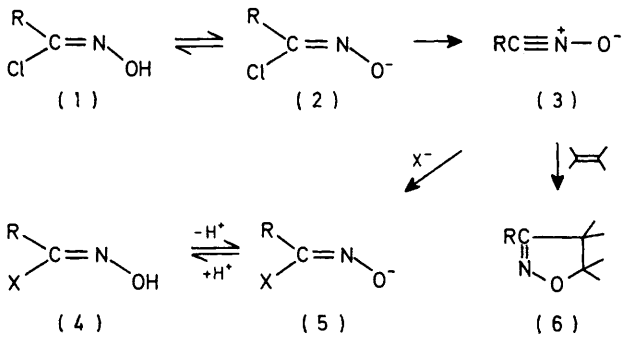
Nitrile oxides (3) are rapidly generated *in situ* on dissolution of the corresponding hydroxamoyl chlorides (1) in aqueous solution at pH > 4; reaction of (3) with the solvent is slow at pH < 10. Primary and secondary amines react stereospecifically to give only the *Z*-amidoximes (11), in which the nucleophile and OH groups are *cis*. With primary amines and ammonia the *Z*-isomer is also thermodynamically favoured but with the more bulky secondary amines subsequent isomerisation to the more stable *E*-isomer (12) occurs. Several criteria (ρ +0.53 for substituent variation in the nitrile oxide; β_{nuc} 0.48 for primary amine variation; small enhancement shown by 'α-effect' amines; small steric effect of *ortho*-substituents in nitrile oxide) are consistent with a transition state for amidoxime formation in which there is little bond formation between the amine and the carbon of the nitrile oxide.

NITRILE OXIDES (3), as typical 1,3-dipoles, undergo a wide range of cycloadditions to unsaturated compounds, leading to heterocyclic systems (6). This reaction has been exploited synthetically and the mechanism of cycloaddition has been both widely studied and discussed.[1,2] Nitrile oxides also react at carbon with nucleophiles leading to open chain oximes (4).[3] Although this reaction has received little study, it is potentially of considerable interest both since (3) can be regarded as a stabilized carbonium ion and since a clearer understanding of a reaction limited to a single site in a 1,3-dipole is expected to clarify the mechanism of the overall cycloaddition processes.



Since nitrile oxides which do not contain bulky R groups [*e.g.* (3; R = adamantyl, 2,6-disubstituted phenyl)] tend to dimerise rapidly in solution or as solids,[4] previous kinetic studies of cycloaddition have been limited either to the dimerisation itself [4] or to the use of bulky monomeric nitrile oxides.[5] We now report that even simple nitrile oxides may be rapidly generated from hydroxamoyl chlorides (1) in aqueous solution; the subsequent reactions of (3) can then be followed without the complicating dimerisation which is minimal in dilute solution. The use of aqueous solutions also simplifies the analysis of the kinetic data and in general a wide range of thermodynamic data is available.

In the present paper we also report on the background reaction of (3) with water and hydroxide ion and in detail on the stereospecific addition of amines to (3) leading to single *Z*-amidoxime isomers (4).

RESULTS AND DISCUSSION

(a) *Nitrile Oxide Formation in Aqueous Solution.*—The dehydrohalogenation of benzohydroxamoyl chloride (1; R = Ph) to (3; R = Ph) was investigated in aqueous solution (μ 1.0; $NaClO_4$) at 21° at low pH. Under these conditions preliminary scans of the u.v. region showed the absence of intermediates or significant subsequent reactions. The kinetic results are summarised in Figure 1, which shows a plot of log of the observed first-order rate against pH. The linearity observed [slope 0.90 (r 0.995)] confirms that the formation of (3) from (1) is inversely proportional to hydrogen

[1] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565.
[2] R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403; R. A. Firestone, *ibid.*, 1972, **37**, 2181.
[3] C. Grundmann and P. Grunanger, 'The Nitrile Oxides,' Springer–Verlag, Berlin, 1971.
[4] G. Barbaro, A. Battaglia, and A. Dondoni, *J. Chem. Soc.* (*B*), 1970, 588.
[5] P. Beltrame, P. L. Beltrame, A. Filippi, and G. Zecchi, *J.C.S. Perkin II*, 1972, 1914; P. Beltrame, P. Sartirana, and C. Vintani, *J. Chem. Soc.* (*B*), 1971, 814.

ion concentration over the pH region 1—3. A mechanism consistent with this is rate-determining loss of chloride ion from the conjugate base (2) which is in equilibrium with (1).

Several attempts were made to extend the pH range to the more alkaline region, for example by the use

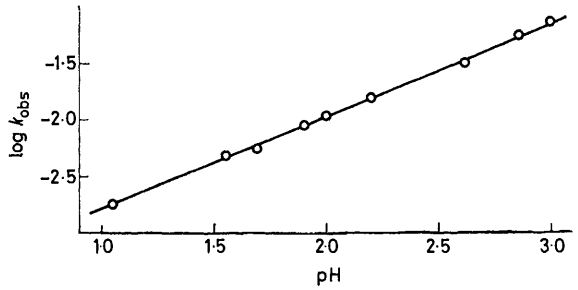


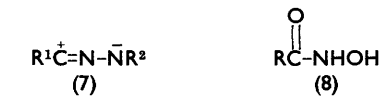
FIGURE 1 Plot of log k_{obs} *versus* pH for the dehydrohalogenation of (1; R = Ph) in the presence of sodium chloride (0.1M) at 21° in water (μ 1.0; $NaClO_4$)

of stopped flow measurements. However this proved difficult since rapid dehydrohalogenation of (1) occurred unless it was maintained as a stock solution in acid solution. Even at the highest pH studied there was no tendency for the observed rate constants to become independent of pH (Figure 1) as expected if a pH close to the pK_a of (1) was being approached.[6] The pK_a values of *syn*- and *anti*-benzaldoxime (4; R = Ph, X = H) are 11.0 and 11.89 respectively;[7] on this basis the pK_a of (1; R = Ph) can be estimated as *ca.* 9 which gives a rate constant for loss of Cl^- from (2) as *ca.* 10^5 s^{-1}. Rate constants of similar magnitudes were previously reported in base catalysed elimination from hydrazonyl chlorides (nitrilimine formation).[8]

Since chloride ion is generated in the conversion of (1) into (3) the possibility arises that the back reaction of Cl^- with (3) to reform (1) (akin to the common-ion effect) is important. This was proved not to be the case since (a) the observed rate of reaction of (1) was independent of the initial concentration of (1) (over the range 10^{-4}—10^{-5}M) and (b) the rate of reaction of (1) (at 21°; μ 1.0; $NaClO_4$) was independent of added chloride ion (k_{obs} 1.23 ± 0.07 × 10^{-2} s^{-1}) over a chloride ion concentration range of 0.00—0.28M (at pH 2.0).

Thus when (1; R = Ph) is added to an aqueous solution at pH >4, the formation of benzonitrile oxide is complete within time of mixing (*ca.* 1 s). Under the dilute conditions used in spectrophotometric studies, dimerisation of the nitrile oxide formed is slow and the only competing process is the reaction with solvent.

(b) *Reaction of Nitrile Oxides with Water.*—Unlike nitrilimines (7) and most other 1,3-dipoles, nitrile oxides react quite slowly with water. The product formed at all pH values was the corresponding benzohydroxamic acid (8) [which is a tautomer of (4; X = OH)]. This was



identified both by actual isolation and by spectrophotometric titration of the products (the benzohydroxamic acids have pK_a *ca.* 8.0 with characteristic spectra for the neutral and anionic forms).

The pH rate profile for the conversion of (3) into (8; R = *p*-$MeOC_6H_4$) at 30° is shown in Figure 2. It is seen that below pH *ca.* 8, the reaction is slow and pH independent ($t_{\frac{1}{2}}$ > 100 min), consistent with water as the nucleophile. Above pH *ca.* 9.5 the principal reaction is between (3) and HO^-, since log k_{obs} is proportional to pH.

Both reactions show a small sensitivity to the nature of the substituent in (3; R = Ar) with ρ +0.88 for HO^- attack and ρ +0.57 for the water reaction.[9] We can therefore define quite closely the pH regions (10 > pH > 4) where the hydroxamoyl chlorides (1) can be used as a rapid source of the nitrile oxides (3) and where the background reaction of (3) with the solvent has a half-life >10 min. In general the measurements were made

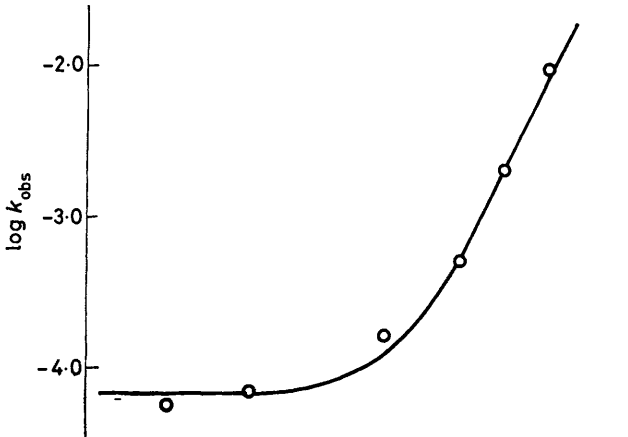


FIGURE 2 Plot of log k_{obs} *versus* pH for the hydrolysis of (3; R = *p*-$MeOC_6H_4$) in water (μ 1.0) at 30°

within these pH limits so that corrections due to the solvent reaction were unnecessary.

(c) *Reaction of Nitrile Oxides with Amines.*—(i) *Primary and secondary amines.* Primary and secondary amines react with nitrile oxides at carbon to produce amidoximes (4; X = R'NH or R'_2N). Figure 3 summarises the kinetic data for the reaction of a typical amine, morpholine, in water at 25° with (3; R = *p*-$NO_2C_6H_4$).

[6] This is consistent with previous work (J. Armand, *Bull. Soc. chim. France*, 1966, 882; P. Souchay, J. Armand, and F. Valentini, *Compt. rend.*, 1966, 985; P. Souchay and J. Armand, *ibid.*, 1963, **256**, 4907) carried out at lower temperature.

[7] A. Raoult and M. Vikao, *Bull. Soc. chim. France*, 1968, 3315.

[8] A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J.C.S. Perkin II*, 1972, 44.

[9] A. F. Hegarty, K. J. Dignam, and P. Quain, unpublished observations.

The pH dependence shows that a simple second-order reaction between the amine free base and (3) is occurring. No upwards curvature in plots of k_{obs} *versus* total amine

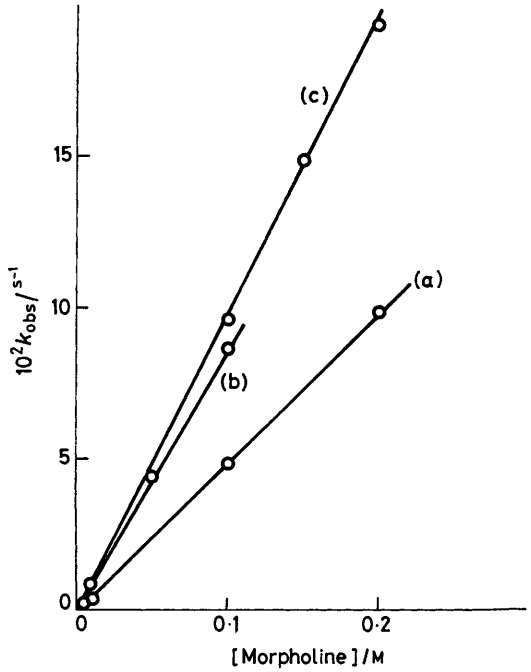


FIGURE 3 Plots of observed rate constants *versus* total morpholine concentration at (a) pH 8.04, (b) pH 8.33, (c) pH 8.82 for the reaction with (3; R = p-$NO_2C_6H_4$) in water (μ 1.0) at 25°

concentration (which are frequently observed with ester aminolysis [10] and indicative of catalysis by a second mol of amine) was observed. Extrapolation to zero amine concentration confirmed that the rate of reaction with water was negligible.

Similar results were obtained (at a minimum of two pH values for each amine) for other amines; the results are summarised in the Table as second-order rate constants (k_B) for the reaction of (3; Ar = p-$NO_2C_6H_4$) with free amine. These results show that the reaction of the nitrile oxide is relatively insensitive to the structure of the amine. This is best shown in Figure 4, which is a Brønsted plot of log k_B against the pK_a of the conjugate acid of the amine. The slope (or β_{nuc} value) for primary amines is +0.48 (r 0.990). The datum points for secondary amines (triangles) lie quite close to this line (with the possible exception of piperazine monocation); data for the secondary amines, taken alone, give β_{nuc} +0.37 (r 0.990).

The low β_{nuc} value contrasts with typical values in the region 0.8—1.0 reported for the aminolysis of esters; for such a reaction at a carbonyl centre a maximum β value of +1.74, representing complete N–C bond formation in the transition state, has been estimated.[11] However, the results are similar to those recently reported for the reaction of phenyl isocyanate (9; R = Ph) and cyanic

RN=C=O
(9)

acid (9; R = H) with amines. Interestingly the isocyanates are isomeric with the nitrile oxides (3) and the transition states for the reaction of both materials with amines appear to be quite similar with little N–C bond formation in the transition state.

Reaction of amines with p-nitrobenzonitrile oxide (1; R = p-$NO_2C_6H_4$) at 25° in water (μ 1.0; NaCl or $NaClO_4$)

No.	Amine	pK_a [a]	k_B/l mol^{-1} s^{-1}
1	Methoxyamine	4.75	0.053
2	Hydroxylamine	6.00	0.250
3	Hydrazine	8.27	3.59
4	Piperazine [b]	5.46	0.137
5	Imidazole	6.95	0.340
6	Morpholine	8.32	1.97
7	Piperazine [c]	9.84	5.61
8	Piperidine	11.35	18.90
9	Trifluoroethylamine	5.84	0.038
10	Glycine ethyl ester	7.90	0.830
11	Glycylglycine	8.25	1.16
12	Glycine	9.80	7.52
13	Cyclohexylamine	10.63	11.34
14	Ethylamine	10.88	13.20
15	Methylamine	11.00	13.60

[a] A. Williams and W. P. Jencks, *J.C.S. Perkin II*, 1974, 1753. [b] Monocation. [c] Neutral species.

(ii) *α-Effect amines.* The three 'α-effect' amines, hydrazine, hydroxylamine, and methoxyamine, all show positive deviations from the Brønsted line for the other primary amines, but form a separate line of slightly

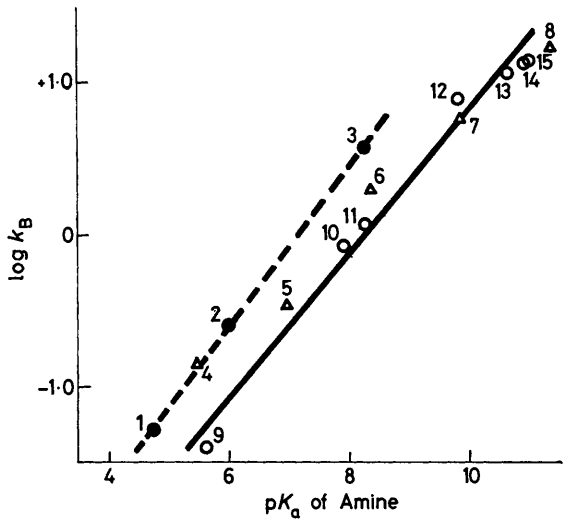


FIGURE 4 Brønsted type dependence of reactivity of amines with (3; R = p-$NO_2C_6H_4$) on the pK_a of the aminium ion: ○, primary amines, β + 0.48; △, secondary amines, β + 0.37; ●, α-effect amines, β + 0.52

greater slope (β_{nuc} +0.52). The enhanced reactivity shown by these amines (*ca.* 4-fold) is small when compared with that observed in, say, ester aminolysis.

[10] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969.
[11] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

However, this is in line with Dixon and Bruice's [12] observation that the magnitude of the α-effect is greatest when the corresponding β value for the reaction is large. In the present instance, this confirms that the transition state is reached with little charge build-up on the amine nitrogen; delocalization of charge onto the α-atom is thus relatively less important.

(ii) *Tertiary amines.* Tertiary amines cannot form stable amidoximes, the intermediates (4 and 5; X = $R'_3\overset{+}{N}$) reverting to the nitrile oxide (3). Addition of the tertiary amine, *N*-ethylmorpholine, however increased the rate of conversion of (3; R = *p*-$NO_2C_6H_4$) into *p*-nitrobenzohydroxamic acid (8; R = *p*-$NO_2C_6H_4$) [13] (see Figure 5). The second-order rate constant calculated from these data (1.32×10^{-2} l mol^{-1} s^{-1}) is *ca.* 10^2 fold less than the rate of reaction of a secondary amine (of similar pK_a) with the nitrile oxide (see Figure 4). Thus general base catalysed hydration of the nitrile oxide contributes

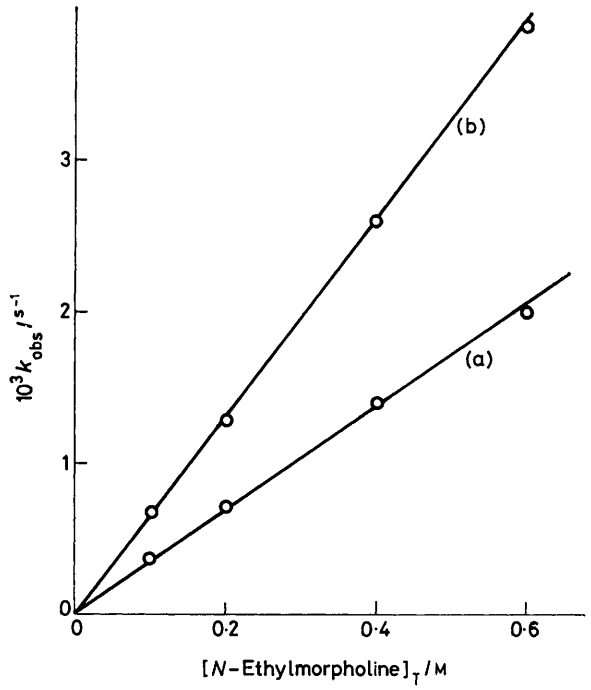


FIGURE 5 Effect of *N*-ethylmorpholine concentration on the rate of hydrolysis of (3; R = *p*-$NO_2C_6H_4$) in water (μ 1.0) at (a) pH 7.20, (b) pH 7.70 at 25°

≤1% to the observed rates of reaction with primary and secondary amines.

(iv) *Variation of nitrile oxide structure.* The rates of reaction of a series of nitrile oxides (3; R = Ar) at constant amine concentration and pH are summarised in the form of a Hammett plot (see Figure 6). The ρ

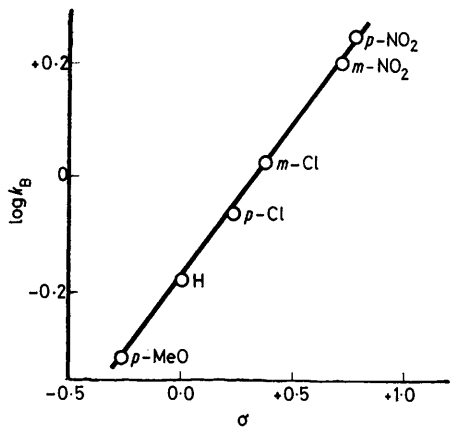
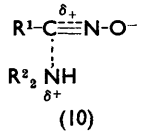


FIGURE 6 Hammett plot of log of the second-order rate constant *versus* σ for the reaction of (3; R = XC_6H_4) with morpholine in water (μ 1.0) at 25°

value is small and positive [+0.53 (*r* 0.990)]. This implies the neutralization of just a small fraction of the charge on carbon in the transition state. Moreover *ortho*-substituents in the nitrile oxides do not appear to slow down reaction *via* a steric effect. Thus (a) *o*-chlorobenzonitrile oxide reacts with morpholine at about the same rate (at 25°) as does *p*-chlorobenzonitrile oxide and (b) the rate constant for the reaction of the mesityl compound (3; R = 2,4,6-$Me_3C_6H_2$) is only *ca.* 6-fold less than that for (3; R = *p*-ClC_6H_4) (the actual rate constants observed were 4.26×10^{-3} and 26.5×10^{-3} s^{-1} respectively at 60° in the presence of 0.01M-morpholine (μ 1.0) in 1 : 4 dioxan–water]. Assigning a σ value of −0.51 for the 2,4,6-Me_3 substituent (*i.e.* 3 × 0.17, where −0.17 is the σ value for *p*-Me) and using the data in Figure 6, the expected rate difference is *ca.* 3-fold (with the *p*-chloro-compound reacting faster). On this basis, it is clear that *ortho*-substituents, including even 2,6-disubstitution do not decrease greatly the second-order rate constants for reaction of (3) with amines.

Taken together these data are consistent with a transition state (10) in which C–N bond formation has not progressed greatly in the transition state. As such the



(10)

small substituent effects observed are similar to those typically observed in cycloadditions to 1,3-dipolar ions.[14] Since the amidoximes have pK_a values of *ca.* 12, protonation of (5; X = R'_2N) to give (6) occurs in a rapid subsequent step and there is no thermodynamic advantage in partial donation of proton from water to oxygen in the transition state.

[12] J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94**, 2052.

[13] Tertiary amines also catalyse the conversion of nitrile oxides into 3,6-diaryl-1,4,2,5-dioxadiazines (F. De Sarlo, *J.C.S. Perkin I*, 1974, 1951; F. De Sarlo and A. Guarna, *ibid.*, 1976, 626). However at low concentrations of nitrile oxide (as we have used) the dimerisation becomes third order (rate = k_{obs}[ArCNO]^2[R_3N]) and we estimate that the rate of catalysed dimerisation would be *ca.* 10^3-fold less than the rate of catalysed hydrolysis observed.

[14] A. Battaglia and A. Dondoni, *Roczniki Sci.*, 1968, **38**, 201; A. Dondoni, *Tetrahedron Letters*, 1967, 2397.

(d) *Product Analysis: Initial Formation of Z-Amidoximes.*—That the products formed with primary amines were the corresponding amidoximes was confirmed by independent synthesis; the u.v. spectrum of the reaction mixture was identical with that of the authentic sample of the amidoxime (under the same conditions) while t.l.c. analysis was also consistent with this.

However, a discrepancy arose with secondary amines. An example is shown in Figure 7; the u.v. spectrum of the reaction product from (3; Ar = *p*-$NO_2C_6H_4$) and morpholine is shown as the solid line. The expected amidoxime (which was prepared from *p*-nitrobenzonitrile oxide and morpholine and purified by recrystallisation) has a distinctly different u.v. spectrum (broken line, Figure 7), measured under the same conditions (0.1M-morpholine; pH 8.09; 25°; substrate concentration 7×10^{-5}M).

Moreover, a slow subsequent reaction occurred with amidoximes from secondary amines. This latter reaction was greatly accelerated by heating or the addition of acid. On completion of this secondary reaction the u.v. spectrum was then identical with that of the 'authentic' amidoxime. This suggested that these

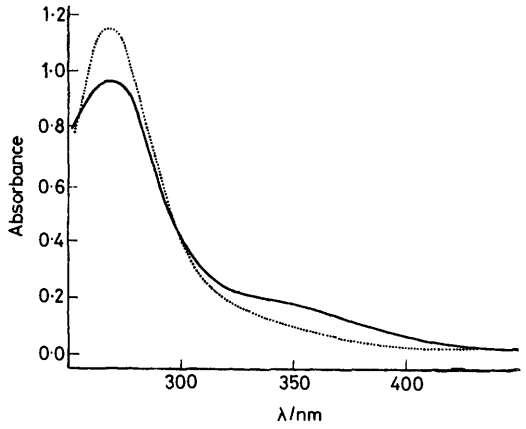
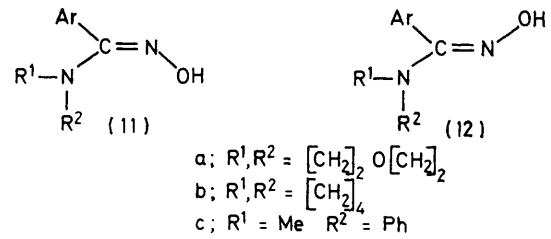


FIGURE 7 U.v. spectra of reaction product of (3; R = *p*-$NO_2C_6H_4$) at low temperature (solid line); and at high temperature (broken line), in 10^{-1}M-morpholine in water (μ 1.0) at 25° at pH 8.09. Substrate concentration in each case 7×10^{-5}M. These correspond to the spectra of the *Z*- and *E*-isomers (11a and 12a; Ar = *p*-$NO_2C_6H_4$) respectively

amidoximes were initially formed in a 'labile' form which then isomerised to a 'stable' form.

These were shown to be the *Z*- and *E*-amidoxime isomers (11) and (12) respectively, by the actual isolation of the kinetic product (11; R^1R^2NH = morpholine, pyrrolidine, *N*-methylaniline) by carrying out the reaction of (1) and the amine at 0—5°. The *Z*-isomer [15] could be crystallised from non-acidic solvents at <25° but was readily converted into (12) on heating, addition of acid, or when chromatography was attempted. The two isomers showed distinct differences in their u.v. and n.m.r. spectra; the latter was a particularly useful criterion since the NCH_2 protons in (11) were deshielded



by *ca.* 0.3 p.p.m. relative to (12), rendering small amounts of (11) or (12) detectable.

That the *Z*-isomer (11a; Ar = *p*-$NO_2C_6H_4$), was formed initially in aqueous solution at 25° (the conditions used to study the kinetics) was shown by the identity of the u.v. spectrum of an authentic sample of (11a) and the reaction product (Figure 7, solid line; measured at the same concentration and conditions). Although a small amount of (12a) (whose u.v. spectrum is given by the broken line in Figure 7) could have remained undetected by this method (because of the similarity in the u.v. spectra of the *E*- and *Z*-isomers), no *E*-isomer (12) could be detected (<2%) by n.m.r. when the reaction was carried out in non-aqueous solution.

With primary amines, the *Z*-isomer (11; R^1 = H) is also the thermodynamically more stable isomer so that the kinetic and thermodynamic products were identical in this case and no subsequent reactions were encountered. In one case, with *N*-methylaniline, (11c) was initially isolated, uncontaminated by (12c). Equilibration of the isomers (heat or acid) gave 60 : 40 mixture of (11c) and (12c) (Ar = *p*-$NO_2C_6H_4$).

We therefore conclude that the reaction of secondary and primary amine nucleophiles with the 1,3-dipoles (3) in aqueous solution leads to the *Z*-isomers (11) in which the nucleophile and OH group are adjacent. These isomerise to the more stable *E*-isomers (12) when the amidoxime nitrogen is disubstituted, showing that the *Z*-isomers represent kinetic control. We have previously reported [16] that nitrilium ions ($-C\equiv\overset{+}{N}-$) react with nucleophiles at carbon to give only the isomer in which the entering nucleophile and forming lone pair on the adjacent nitrogen are mutually *trans*. Clearly there is a formal similarity between nitrilium ions and the 1,3-dipolar ions (3) since the latter show the same stereospecificity towards nucleophiles (which is determined early, rather than late, on the reaction co-ordinate).

EXPERIMENTAL

General.—M.p.s were determined on an Electrothermal apparatus and are uncorrected. U.v. spectra for product analysis were run on either a Unicam SP 800B or a Perkin-Elmer 124 spectrophotometer. A Perkin-Elmer model R20A instrument was used for n.m.r. spectra using deuterio-

[15] A. F. Hegarty, K. J. Dignam, and M. J. Begley, in preparation.

[16] A. F. Hegarty and M. T. McCormack, *J.C.S. Chem. Comm.*, 1975, 168; *J.C.S. Perkin II*, 1976, 1701.

chloroform as solvent. All inorganic salts were AnalaR grade. Aqueous sodium hydroxide solutions were made up from Volucon (M and B) standard ampoules and the perchloric acid solutions from 60—62% AnalaR perchloric acid. Dioxan was AnalaR grade and was used without further purification. Liquid amines were distilled from potassium hydroxide immediately before use and solid amines were recrystallised from alcohol.

Substrates.—Hydroxamoyl chlorides were prepared by low temperature chlorination of the appropriate benzaldoxime in chloroform, except for benzohydroxamoyl chloride which was prepared in aqueous hydrochloric acid at 0 °C. The following benzohydroxamoyl chlorides were synthesised: unsubstituted, m.p. 47—48° (lit.,[17] 48°); *p*-nitro, m.p. 124—125° (lit.,[18] 123.5—124°); *m*-nitro, m.p. 98—100° (lit.,[17] 96°); *p*-chloro, m.p. 88.5—89.5° (lit.,[17] 82—86°); *o*-chloro, m.p. 53—54° (lit., [19] 56°); *m*-chloro, m.p. 69—70° (lit.,[17] 75—80°); *p*-methoxy, m.p. 87.5—89° (lit.,[20] 88—89°). *p*-Nitrobenzohydroxamic acid, m.p. 182—184° [lit.,[21] 177, 186° (decomp.)], mesitaldoxime, m.p. 124—126° (lit.,[22] 124—127°), and mesitylnitrile oxide, m.p. 110—112° (lit.,[22] 110—112°), were prepared by standard literature methods.

Z-*Morpholino*-p-*nitrobenzamidoxime* was prepared by the dropwise addition of *p*-nitrobenzohydroxamoyl chloride (1 equiv.) in dry benzene to dry morpholine (2 equiv.) also in dry benzene at 0—5°. On stirring for 30 min the precipitated morpholine hydrochloride was filtered off and washed until colourless with dry benzene. The combined benzene washings were evaporated under vacuum at room temperature and the resultant yellow solid recrystallised from chloroform–pentane (at room temperature), m.p. 158—160° (Found: C, 52.1; H, 5.5; N, 16.4. $C_{11}H_{13}N_3O_4$ requires C, 52.6; H, 5.2; N, 16.7%), δ 3.67 (4 H) and 3.27 (4 H), $\lambda_{max.}$ (MeOH) 267 (log ε 3.93) and 340 nm (3.30). E-*Morpholino*-p-*nitrobenzamidoxime* was prepared similarly but the reaction mixture was refluxed for 3 h to ensure 100% conversion, m.p. 158—160° (Found: C, 52.3; H, 5.4; N, 16.5%), δ 3.64 (4 H) and 2.91 (4 H), $\lambda_{max.}$ 264 (log ε 4.10) and 340 nm (3.08). Z-*Pyrrolidino*-p-*nitrobenzamidoxime* had m.p. 176—178° (Found: C, 56.7; H, 5.7; N, 18.3. $C_{11}H_{13}N_3O_3$ requires C, 56.2; H, 5.5; N, 17.9%), δ 3.41 (4 H) and 1.80 (4 H); $\lambda_{max.}$ 262 nm (log ε 3.96). E-*Pyrrolidino*-p-*nitrobenzamidoxime* had m.p. 176—178° (Found: C, 56.3; H, 5.6; N, 18.4%), δ 3.05 (4 H) and 1.80 (4 H); $\lambda_{max.}$ 259 nm (log ε 4.09), Z-*morpholino*-p-*chlorobenzamidoxime* had m.p. 110—112° (Found: C, 55.0; H, 5.7; N, 11.5. $C_{11}H_{13}ClN_2O_2$ requires C, 54.9; H, 5.4; N, 11.6%), δ 3.63 (4 H) and 3.26 (4 H), and E-*morpholino*-p-*chlorobenzamidoxime* had m.p. 110—112° (Found: C, 55.2; H, 5.6; N, 11.6%), δ 3.58 (4 H) and 2.89 (4 H).

Kinetic Method.—All rate data were measured on a Unicam SP 800B spectrophotometer fitted with a scale expansion accessory by following the decrease in absorbance at the following wavelengths: benzonitrile oxide, 250, *p*-methoxy, 260; *o*-chloro, 255, *m*-chloro, 252; *p*-chloro, 260, *m*-nitro, 315; *p*-nitro, 300, and mesityl, 257 nm. Substrates were made up 10^{-2}M in dioxan (AnalaR). pH Values were measured using a Radiometer model PHM 26 or a Beckmann model 3550 digital pH meter both fitted with a Metrohn EA-125U glass combination electrode. The techniques used for following the kinetics have already been fully described.[23]

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