Reactivity of 1,3-Dipoles in Aqueous Solution. Part 4.[1] Kinetics and Mechanism of Isomerisation of Amidoximes in Aqueous Solution [2]

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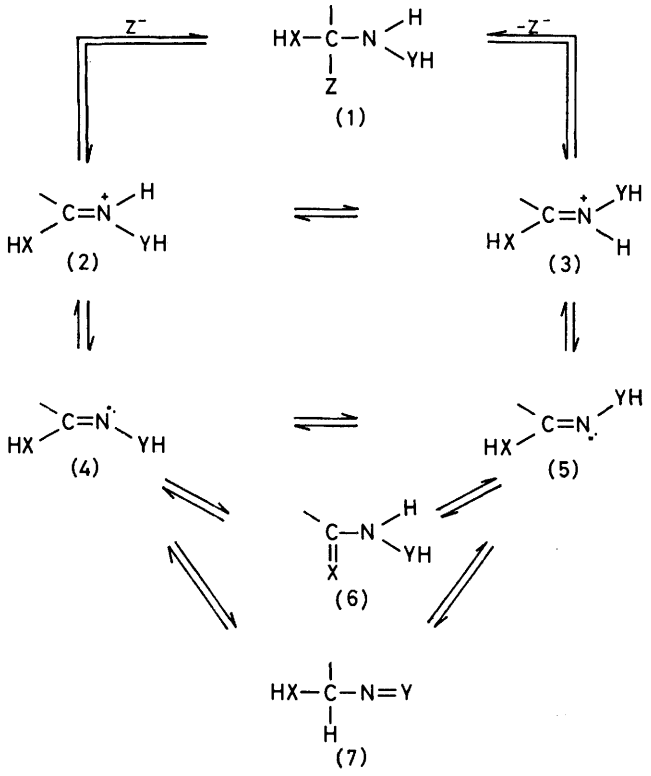
The isomerisation of *Z*-amidoximes (8) to the *E*-form (9) has been examined in aqueous solution as a function of pH and amidoxime structure. Marked acidic catalysis is observed and, in general, the protonated amidoxime reacts $>10^5$-fold faster than the neutral form; at 25 °C, $t_{\frac{1}{2}}$ for the conversion of *Z* into *E* amidoximes is in the region of 0.01—1.0 s. Isomerisation is not catalysed by buffer species, ruling out an addition–elimination pathway. Since *O*-alkylamidoximes (26) isomerise at rates which are similar to those for the unalkylated oxime, it is concluded that the neutral oxime, rather than the nitrone tautomer, is the reactive species at high pH. The results are considered in terms of the mechanism of oxime isomerisation.

SEVERAL mechanisms have been identified [3-12] for the geometric interconversion of imine derivatives (4) (Scheme 1). These include the uncatalysed direct interconversion involving overall nitrogen inversion, which is thought to occur generally by movement of the group YH through a transition state where it becomes colinear with the C=N group (the lateral shift mechanism).[6,7] However, other processes such as the initial conversion into an enamine (6) or to an alternative imine (7) are also possible and,[5] being proton transfers, are expected to be subject to catalysis.[8] These pathways can however be minimised by a suitable choice of substituents (most readily by only using groups attached to nitrogen or carbon which do not have an ionisable proton). Catalysis can also be envisaged as occurring *via* initial protonation at nitrogen to form (2) which can undergo rotation to (3) [and thus yield (5)]; however, whether this provides a genuine catalytic route or whether (2) undergoes rotation *more slowly* than (4) undergoes inversion or rotation has been controversial.[9-12] A variation of this is the addition–elimination path *via* (1) where Z is both a good nucleophile and leaving group.[9]

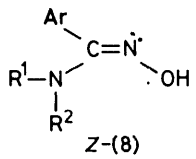


SCHEME 1

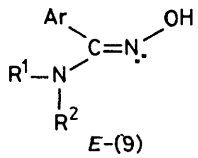
The oxime (4; Y = O) is probably the imine system which is most resistant to uncatalysed isomerisation.[13-15] Oximes are also relatively slowly hydrolysed under acidic or basic conditions so that they present a suitable system for the direct study of catalysed processes in aqueous solution. Acid-catalysed reactions of oximes are also of interest in synthetic sequences, including the classical Beckman rearrangement. We have used the amidoximes (8); the presence of the amino-group increases the basicity of the imine system so that this oxime can be fully protonated in aqueous solution in the pH range studied. The results clearly show for the first time both uncatalysed, (4) ⟶ (5), and acid catalysed [*via* (2) rather than (1)] paths in this medium and also that the fully protonated species (2) undergoes isomerisation $>10^5$ fold faster than (4).

RESULTS AND DISCUSSION

We have previously described the isolation of the thermodynamically unstable *Z*-amidoxime isomer by stereoelectronically controlled reaction of nitrile oxides with secondary amines.[16] Similar *Z*-amidoximes are formed on reaction with primary amines and with



Z-(8)



E-(9)

	R^1	R^2	Ar
a;	$-(CH_2)_2-O-(CH_2)_2-$		p-$NO_2C_6H_4$
b;	$-(CH_2)_2-O-(CH_2)_2-$		p-ClC_6H_4
c;	$-(CH_2)_4-$		p-$NO_2C_6H_4$
d;	$-(CH_2)_2-O-(CH_2)_2-$		Ph
e;	Me	Ph	p-$NO_2C_6H_4$

ammonia,[17,18] but since the *Z*-form is also the thermodynamically more-stable isomer in acidic, neutral and basic conditions, further geometric isomerisation cannot be readily studied. With most secondary amidoximes,

the equilibrium position lies almost entirely to the side of the *E*-isomer so that no correction is required for the back reaction; only with *N*-aryl, *N*-alkyl-amidoximes [such as (8e)] is an equilibrium mixture reached with detectable amounts of (8) present.

The rates of *Z* to *E* isomerisation were followed by u.v. spectroscopy (see ref. 16 for typical u.v. spectra) and confirmed in a number of cases by n.m.r. The reaction medium used in all cases was water at 25 or 57 °C, the ionic strength being maintained at 1.0 by the addition of $NaClO_4$ where necessary. The amidoximes principally studied were (8a)—(8c). Owing to the wide range of reactivities encountered, it was found necessary to use the stopped-flow technique for some measurements while others had to be done at elevated temperature. Figure 1 shows plots of the observed rate constants as a function of pH; closed symbols are used to represent the data at higher temperature. Hydrolysis of the amidoxime was not observed under these conditions.

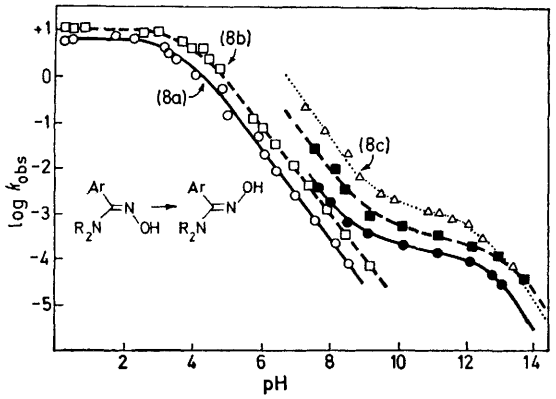


FIGURE 1 Plot of the log of the observed rate constants for the *Z* to *E* isomerisation of amidoximes (8a), (8b), and (8c) as a function of pH. The open symbols represent data obtained at 25 °C, the closed symbols at 57 °C. The lines are theoretical, being derived from Scheme 2 with values of constants given in Table 1

The pH-rate profiles show two distinct pH regions (pH *ca.* 0—3 and *ca.* pH 10) where the rate of isomerisation is essentially pH independent. These represent (see below) the rates of isomerisation of the fully protonated amidoxime and the neutral amidoxime respectively.

Acid-catalysed Isomerisation.—In acidic solution the amidoximes are clearly protonated. This is shown by a change in the u.v. spectrum which occurs immediately on dissolution but prior to isomerisation. Because of the high reactivity of the *Z*-isomers it was not possible to determine accurately the pK_a values of the amidoxime conjugate acids, although this was possible for the stable *E*-isomers (9). Figure 2 shows a typical plot for the variation in absorbance at 300 nm for the amidoxime (9b); from these data a pK_a of 3.91 has been estimated. This is close to the value required to fit the kinetic data in Figure 2, assuming the kinetic Scheme 2, where $(8)H^+$ and $(9)H^+$ are the protonated *Z*- and *E*-amidoximes respectively. With k_1 rate determining the observed rate constant should describe a simple ' titration curve ' [equation (1)] and this closely fits the observed data [solid line for (8b), Figure 1] with $k_1 = 10.6\ s^{-1}$, $K_{a_1} = 1.15 \times 10^{-4}$. Values for the other amidoximes are summarised in Table 1.

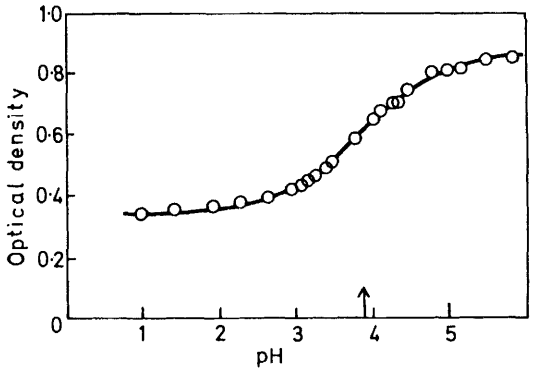


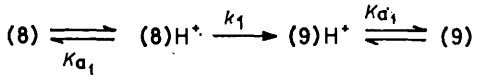
FIGURE 2 Plot of optical density of (9b) at 300 nm as a function of pH in water at 25 °C ($\mu = 1.0$, $NaClO_4$); the solid line has been drawn assuming that $pK_{a_1} = 3.91$

Substituents in Ar have a small effect on the rate of isomerisation of $(8)H^+$; an approximate ρ value of

$$k_{obs} = \frac{k_1 a_{H^+}}{a_{H^+} + K_{a_1}} \qquad (1)$$

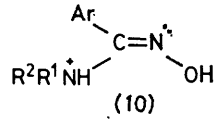
+0.28 can be estimated from the data in Table 1 (using just two substituents).

Although there are two possible sites for protonation on an amidoxime (the amino- and imino-nitrogens) it is

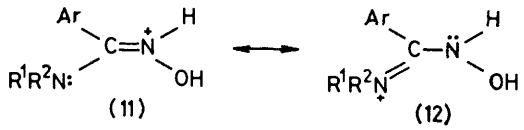


SCHEME 2

difficult to envisage protonation on the amino-group [to give (10)] leading to such enhanced isomerisation rates. However, protonation on the imino-group does allow delocalisation of the charge onto the amino-group while reducing the bond order of the C–N bond, *i.e.* resonance structures such as (12) should be major contributors to the stabilisation of the protonated form, by reducing the degree of charge localisation on the ' hydroxylamine type ' nitrogen in (11). Using i.r.



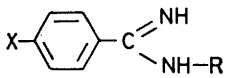
(10)



(11) (12)

absorption intensities as a guide, it has been concluded [19] that the ' amino '-nitrogen in (8) or (9) is very nearly sp^2 hybridised and conjugated with the π system of the imino-bond. This is also consistent with several *X*-

ray studies [20-23] which show that amidoximes have a coplanar structure and that the Ar group may be rotated out of the plane to accommodate the amino-groups. Amidoximes have, therefore, pronounced amidine-type character and would be expected to have similar protonation site [to give (11), (12) rather than (10)]. In fact a Hammett plot of pK_{a_1} for (8a, b, d),* *vs.* the σ value of *para*-substituent in Ar gives a slope (or ρ value) of −0.91, which is the same as that reported [25] for the amidine



(13)

system (13) (variation of X) where protonation is known to occur on the imino nitrogen.

On this basis the rate of isomerisation of the protonated amidoxime would be dependent on the ability of the R^1, R^2 groups to act as electron donors [*i.e.* stabilisation of form (12)]. This is, in fact, observed as shown by the direct relationship between log k_1 and the pK_a values of

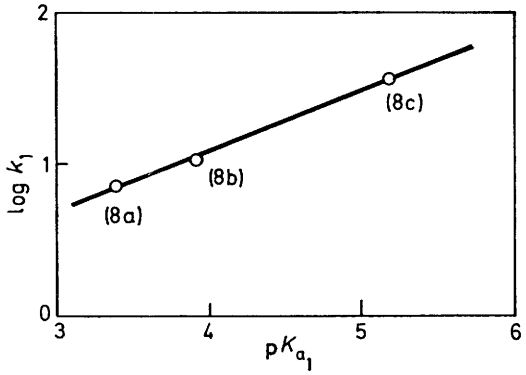


FIGURE 3 Log plot of pH-independent rate of $Z \rightarrow E$ isomerisation of (8a—e) in acidic solution (k_1) against pK_{a_1} (slope = 0.41)

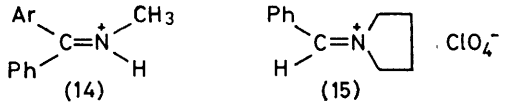
the corresponding amines $R^1R^2\overset{+}{N}H_2$. The rates of isomerisation of the protonated amidoximes also show a simple relationship with the variation in the pK_{a_1} value of the amidoxime itself (see Figure 3). The slope (0.41) shows that the pK_{a_1} and log k_1 values are affected in the same direction by substituents but that the transition state for isomerisation is *ca.* 40% as sensitive as is the (equilibrium) protonation.

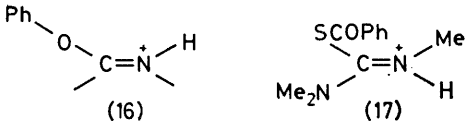
At pH values greater than pK_{a_1}, the rate of isomerisation is inversely proportional to hydrogen ion concentration [as required by equation (1)]; however, since k_1 and K_{a_1} vary in the reverse direction as the substrate structure is changed there is an increase in the overall substituent effect in this region at a given pH. Because of the high reactivity of (8c) it was thus possible to measure a complete pH-rate profile at higher pH (see Figure 1) at 25 °C.

* The pK_a of (9d) is a literature value of 4.11;[24] because of the method of preparation and purification of (9d) it is assumed that the pK_a measured was for the thermodynamically more stable isomer.

Catalysis by Addition–Elimination.—The rate of conversion of (8a) into (9a) was also measured in the presence of added sodium acetate–acetic acid buffer at constant pH. The results ($k_{obs} = 1.62 \pm .28 \times 10^{-2}$ s^{-1} at pH 6.50 when the total buffer concentration is varied from 0 to 0.5M) clearly show that in the region where the rate of isomerisation is proportional to specific acid concentration, that acetate ion does not act as a catalyst [as it might *via* the addition–elimination mechanism involving (1; $Z^- = AcO^-$). Experiments using other buffers (such as phosphate, imidazole, carbonate, and borate) and controls in the absence of buffers (using the pH-stat) [26] also showed no significant buffer catalysis.

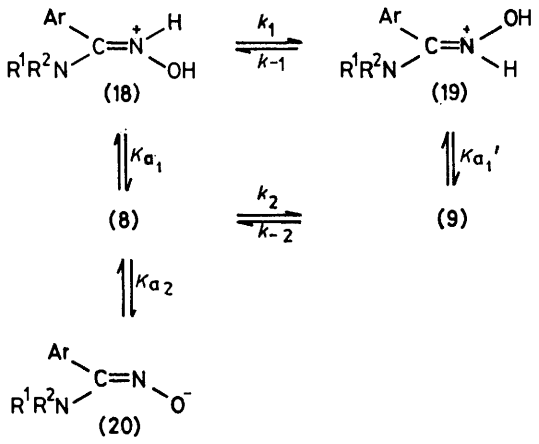
This result shows that isomerisation in acid occurs by rotation of the protonated species (11), and contrasts with previous results for simple iminium ions [such as (14) or (15)] which seem to indicate that in diphenyl





ether solution [19] significant rotation about the $C=\overset{+}{N}$ bond does not occur even at 220 °C but that isomerisation is markedly catalysed (presumably *via* the addition–elimination pathway) by the addition of small quantities of benzoic acid. Isomerisation of protonated imine derivatives has however been reported in the imidate (16) and *S*-acylisothiourea (17) systems. Perhaps significantly, in common with the present work, both of these studies were carried out in aqueous solution.[5,11]

Z/E *Isomerisation in Neutral and Basic Media.*—At pH *ca.* 10 the rate of isomerisation becomes pH independent, before decreasing again at higher pH. This latter decrease corresponds to the ionisation of the oxime to the oximate anion (20) and the curves in Figure 1



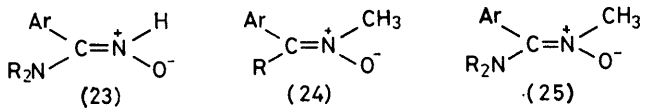
SCHEME 3

have been drawn assuming the spectrophotometrically determined pK_a values for the equilibrium (8) $\rightleftharpoons$ (20) (K_{a_2}). This indicates that the neutral oxime itself (8)

undergoes isomerisation, but that the anion (20) is inert. This is consistent with recent findings which show [27] that the oximate anion (21) is configurationally more stable than the corresponding oxime with a k_1 value estimated at 1.3×10^{-5} s^{-1} at 135 °C.

The observed rate constants are consistent with the mechanistic Scheme 3, with k_{-1} and $k_{-2} = 0$; the values of k_2, the rate of uncatalysed oxime isomerisation derived from the data are summarised in the Table. Acidity constants (K_{a_2} derived spectrophotometrically) are also included in the Table. Although the substituent effects on the rate of isomerisation of the neutral oxime are by no means systematic, they do indicate (see Table) that electron withdrawal in Ar slows the rate of isomerisation; *e.g.* there is a three-fold decrease in the rate of isomerisation of (8a) relative to (8b) and the same trend is obvious when data for (8a) and (8c) are compared. Thus the substituent effects on the rates of isomerisation of the protonated and neutral oxime are parallel.

Isomerisation via *Neutral Oxime or Nitrone?*—Because of the known resistance of neutral oximes to isomerisation,[13] an alternative pathway *via* the tautomeric nitrone (23) must also be considered. Simple aldo- and keto-nitrones (24; R = H, alkyl) are known to undergo



Z/E isomerisation,[27-29] moreover, if (23) were the reactive species [rather than (8)] then the same type of pH–rate profile would be observed. Although amino-substituted nitrones (25) have not been studied [these would provide a good model for (23)] the amino-group would be expected to enhance the rate of Z/E isomerisation (relative to R = H or alkyl).

This was investigated by using two models where tautomerism to (23) was blocked by alkylation of the oxime oxygen. Alkylation (with *p*-nitrobenzyl bromide in base) of the pure *Z*-amidoxime (8a) initially gave the (*Z*)-*O*-alkyl amidoxime (26) without significant isomerisation (see Figure 4). On heating or treatment with acid the *O*-alkyl amidoxime underwent isomerisation to the *E*-isomer, and spectral data u.v. and n.m.r. (see Figure 4) parallel that for the corresponding amidoximes, confirming that alkylation has occurred on oxygen rather than on nitrogen. The downfield shift of 0.15 p.p.m. noted for the methylene protons on *Z* to *E* isomerisation (see Figure 4) is comparable to that observed with other *O*-benzyl oxime systems (27; X = OAc,[30] OMe,[31] or Cl.[32])

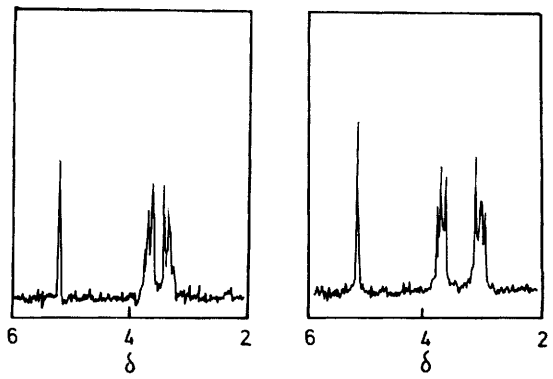
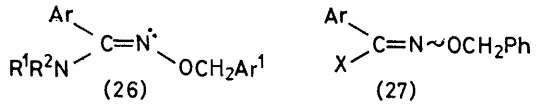


FIGURE 4 N.m.r. spectra (in deuterioacetone) of (a) (*Z*)-*O*-(*p*-nitrobenzyl)-*p*-nitrobenzamidoxime (26a) and (b) the corresponding *E*-isomer

Rate constants for the *Z* to *E* isomerisation of amidoximes and acidity constants

Amidoxime	t/°C	k_1/s^{-1}	k_2/s^{-1}	K_{a_1}	K_{a_1}'	k_1/K_{a_1}/s^{-1}	K_{a_2}
(8a)	25	6.8		3.98×10^{-4}			
	57		1.32×10^{-4}			1.25×10^{-5}	6.6×10^{-13}
(8b)	25	10.6		1.15×10^{-4}	1.23×10^{-4}		
	57		3.71×10^{-4}			1.12×10^{-6}	1.98×10^{-13}
(8c)	25	35.6	1.05×10^{-3}		6.61×10^{-6}		7.9×10^{-13}

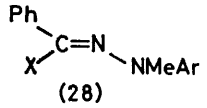
Kinetic data for the oxime ether (26c; $Ar^1 = p$-$NO_2C_6H_4$) are summarised in Figure 5 (because of the low solubility of this amidoxime in water, 80 : 20 water–dioxan was used as solvent). It is seen that the major



difference is that the rate of isomerisation of amidoxime ether does not decrease at high pH, confirming the oximate anion (20) is unreactive. More importantly this also confirms that the neutral *O*-alkyl amidoxime does isomerise at a rate comparable (actually 5.5-fold more slowly) to that observed for the corresponding amidoxime.

The *O*-(*p*-nitrobenzyl)morpholinoamidoxime (26a; $Ar^1 = p$-$NO_2C_6H_4$) showed similar acid-catalysed isomerisation but, like (26c), the rate of isomerisation observed at any pH was *ca.* 10-fold less than that for the parent amidoxime. A decrease in the pH independent rate at high pH also occurred since k_{obs} was $\leqslant 10^{-5}$ s^{-1} at pH 10 even at 57 °C. This decrease is almost certainly due, not to a change in mechanism, but to the presence of the electron-withdrawing *p*-nitrobenzyl group. This was confirmed using (26a; Ar^1 = Ph) which isomerised from pH 10—14 at a rate of 6.3×10^{-5} s^{-1}, which is only *ca.* 2.0 fold less than the unsubstituted

oxime (8a). The reduction in the rate of isomerisation of the *O*-benzyl amidoxime ethers on the introduction of an electron-withdrawing group is consistent both with previous work [33] on the hydrazonyl system (28; X =



(28)

OAc or OMe) and the predictions of the Walsh–Bent rules for amine inversions.[3]

The *N*-methylanilino-amidoxime (8e) was more resistant to thermal isomerisation than the morpholino- or pyrrolidino-amidoximes and, moreover, reacted in the

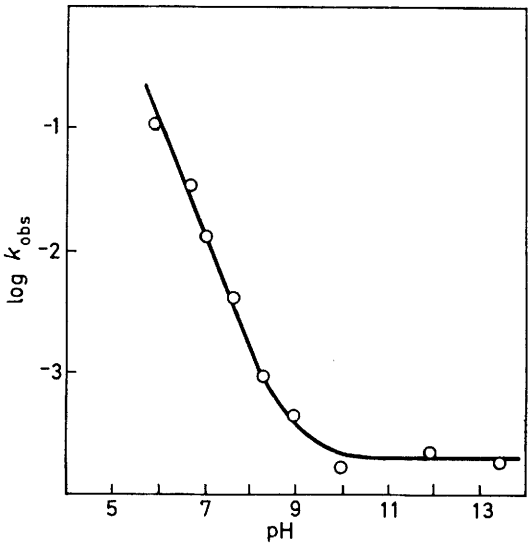
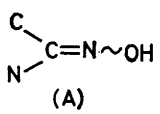


FIGURE 5 Rate of $Z \rightarrow E$ isomerisation of *O*-(*p*-nitrobenzyl)-pyrrolidino-*p*-nitrobenzamidoxime (26c; $Ar^1 = p\text{-}NO_2C_6H_4$) as a function of pH in water–dioxan (80 : 20) (μ = 1.0, $NaClO_4$) at 25 °C

presence of acid to give a 2 : 1 equilibrium mixture of *E*- and *Z*-isomers (rather than pure *E*-isomer). The rates of isomerisation from the pure *Z*-isomer to the *E*/*Z* mixture are summarised in Figure 6; the reduced rate of isomerisation is due both to lower basicity of the amidoxime (K_{a_1}) coupled with a *ca.* 10-fold lower rate of isomerisation (k_1) of the protonated amidoxime. The fact that the *N*-methylanilino-amidoxime (8e) gives an equilibrium mixture of *E*- and *Z*-isomers under thermodynamic conditions (rather than pure *E*-isomers as with other *N*-dialkylamidoximes) can readily be appreciated by inspection of space-filling molecular models; the skeleton (A) was maintained coplanar as indicated



(A)

by *X*-ray studies,[20] but the *C*-aryl ring (Ar) was allowed to rotate out of this plane. Other effects, such as the importance of non-bonded interactions between lone pairs or between unsaturated bonds (which can be attractive rather than repulsive) as described by Epiotis,[34] may also be operative.

An equilibrium mixture of isomers of (8; Ar = Ph, R^1 = Me, R^2 = Ph) has previously been reported by Dondoni and his co-workers,[35] on the basis of n.m.r. measurements. These were assigned [17,35] to isomers obtained by slow rotation about the C–amino [C–NR^1R^2 bond in (8)], rather than to *E*- and *Z*-isomers as in the present work. It was assumed that the energy barrier for *ZE*-isomerisation in amidoximes would be high which clearly from the present work is not the case. Moreover, the kinetic behaviour of (8a—d) (where, because of the symmetrical nature of the R^1 and R^2 groups, it is not possible to have isomers due to slow rotation about the C–NR^1R^2 bond) parallels that of (8e). We have also measured the OH resonance of (8a) in Me_2SO and find a difference of 0.74 p.p.m. between the *E*- and *Z*-isomers, which is similar to that reported for the isomers observed by Dondoni and his co-workers.[35] We therefore conclude that the latter were also most likely *E*- and *Z*-isomers, due to slow rotation about the C=N bond; restricted rotation about the C–NR^1R^2 bond can also occur but is observed by dynamic n.m.r. methods at much lower temperatures.[36]

Mechanism of Isomerisation.—Attempts have recently been made to identify the reactive amidoxime species undergoing isomerisation in a variety of non-aqueous solvents.[22] This is an uncertain procedure since there is such a large difference (>10^5 fold) between the rate of reaction of the protonated and neutral form that catalysis is observed even in ' neutral ' solution. Moreover, since amidoximes can act as weak acids and bases, the equilibrium of equation (2) can furnish (in more

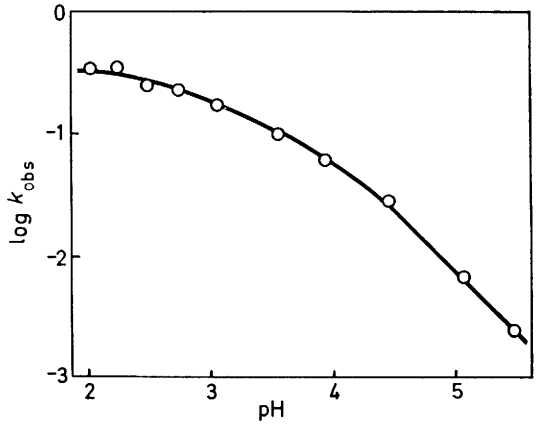


FIGURE 6 Plot of log of rates (in s^{-1}) of $Z \rightarrow E$ isomerisation of (8e) against pH [in water, μ = 1.0 ($NaClO_4$) at 25 °C]

concentrated solution) sufficient quantities of the highly reactive (18) so that all the reaction is chanelled *via* this path; the existence of such a pre-equilibrium would

$$(8) \rightleftharpoons (18) + (20) \qquad (2)$$

then have to be taken into account in any discussion of substituent effects. The use of a basic solvent such as

pyridine [22] does not alleviate this problem since the oximate anion (which is shown to be less reactive than the neutral oxime) may be formed under these conditions. As shown in Figure 1 the pH range over which the neutral amidoxime is the reactive species in water is very narrow. Neither have we found evidence for a bimolecular pathway [22] involving simultaneous transfer of two protons between the amidoximes prior to isomerisation under our conditions of solvent and concentration.

Conclusion.—The conversion of *Z-N,N*-dialkyl-amidoximes into *E*-isomers is strongly acid catalysed; the protonated amidoxime undergoes rapid spontaneous rotation and the rate of this reaction is increased by electron-donating substituents on carbon (Ar) or nitrogen (R^1, R^2) which help to reduce the double-bond character of the $>\overset{+}{N}<_{OH}$ group. Amidoximes, unlike simple oximes, undergo uncatalysed isomerisation at a measurable rate in aqueous solution at high pH. Although substituents act on this reaction in the same direction as they do on the rotation of the protonated amidoxime, the data as yet do not allow a definitive assignment of mechanism for *ZE*-isomerisation of the neutral oxime. The oximate anion is inert under these conditions.

EXPERIMENTAL

General.—M.p.s were determined on an Electrothermal apparatus and are uncorrected. A Perkin-Elmer PE 124 was used for u.v. work while n.m.r. were measured using a Perkin-Elmer–Hitachi R-20A using deuteriochloroform as solvent unless otherwise indicated. All inorganic salts and buffers used were AnalaR grade. Dioxan for kinetic work was purified using a standard literature procedure.

Substrates.—Most of the amidoximes were available from a previous study.[16] (Z)-N-*methylanilino*-p-*nitrobenzamidoxime* (8e) however was prepared by the same general method from the corresponding nitrile oxide using one equivalent of dry triethylamine and five equivalents of freshly distilled *N*-methylaniline. The precipitated triethylamine hydrochloride was filtered off and washed with ether. On evaporation of the combined solvent the amidoxime (together with unchanged *N*-methylaniline) was obtained. The aniline was removed by washing with pentane and the amidoxime remaining was recrystallised from chloroform–pentane, and had m.p. 158—160 °C (Found: C, 61.8; H, 4.9; H, 15.4. $C_{14}H_{13}N_3O_3$ requires C, 62.0; H, 4.8; N, 15.5%); n.m.r.: δ 8.36—7.73 [m, 4 H, (A_2B_2), aromatic H], 7.43—6.76 (m, 5 H, aromatic H), 3.39 (s, 3 H, NCH_3). (*Z*)-*O*-(*p*-Nitrobenzyl) morpholino-*p*-nitrobenzamidoxime (26a; $Ar^1 = p\text{-}NO_2C_6H_4$) was prepared by treating the oxime (8a) (1 equiv.) with *p*-nitrobenzyl bromide (1 equiv.) in ethanol in the presence of sodium hydroxide (1 equiv.) at room temperature overnight. The *O*-alkylamidoxime was precipitated by pouring the reaction mixture onto ice and on recrystallisation from chloroform–light petroleum (b.p. 40—60 °C) had m.p. 136—138 °C (Found: C, 55.8; H, 4.9; N, 14.3. $C_{18}H_{18}N_4O_6$ requires C, 56.0; H, 4.7; N, 14.5%); n.m.r. [$(CD_3)_2CO$], δ 8.43—7.23 (m, 8 H), 5.29 (s, 2 H), 3.77 (m, 4 H), and 3.42 (m, 4 H). The E-*isomer* was similarly prepared starting with (9a) and had m.p. 136—138° (Found: C, 55.6; H, 4.8; N, 14.1. $C_{18}H_{18}N_4O_6$ requires C, 56.0; H, 4.7; N, 14.7%); n.m.r. [$(CD_3)_2CO$] δ 8.50—7.54 (m, 8 H), 5.12 (s, 2 H), 3.68 (m, 4 H), and 3.02 (m, 4 H). Similarly prepared were: (*Z*)-*O*-(*p*-nitrobenzyl) pyrrolidino-*p*-nitrobenzamidoxime (26c; $Ar^1 = p\text{-}NO_2C_6H_4$), m.p. 146—148 °C (Found: C, 57.6; H, 5.4; N, 14.4. $C_{18}H_{18}N_4O_5$ requires C, 58.4; H, 2.9; N, 15.1%); n.m.r. δ 8.38—7.34 (m, 8 H), 5.13 (s, 2 H), 3.50 (m, 4 H), and 1.86 (m, 4 H); (*E*)-*O*-(*p*-nitrobenzyl) pyrrolidino-*p*-nitrobenzamidoxime, m.p. 146—148 °C (Found: C, 57.5; H, 5.2; N, 14.5. $C_{18}H_{18}N_4O_5$ requires C, 58.4; H, 4.9; N, 15.1%); n.m.r. δ 8.47—7.36 (m, 8 H), 4.98 (s, 2 H), 3.13 (m, 4 H), and 1.87 (m, 4 H).

Kinetic Measurements.—Rate data were measured using a Unicam SP 800B or Perkin-Elmer 124 u.v. spectrophotometer at wavelengths preselected from initial repetitive scans of the spectra (see ref. 16 for an example). Since the spectral changes were small, scale expansion (0.2 absorbance full-scale) was necessary throughout. For runs at high temperature, the cells were equilibrated for 30 min before addition of the substrate [which was made up (in 10^{-2} M-solution) in dioxan]. The temperature within the cells was recorded using a thermocouple attached to a Pye Scalamp galvanometer, which was calibrated using an external water-bath. Tight-fitting Teflon stoppers were used with quartz cells and plastic film (Parafilm) was used to minimise solvent loss. For the more rapid reactions ($t_{\frac{1}{2}}$ <5 s) a Durrum–Gibson D-110 stopped-flow spectrophotometer attached to an Advance storage oscilloscope was used. The pH measurements were carried out using a Metrohm 125U glass electrode with a Beckmann model 3550 pH meter, and standardised using Radiometer aqueous buffer solutions. The pH values quoted for dioxan–water (20 : 80) (see Figure 5) are those measured directly using this standardised electrode. The pH was measured both before and after reaction and runs showing a change in >0.05 unit were discarded.

pK_a *Determinations.*—A pH-stat assembly mounted in a Cary 14 spectrophotometer was used to carry out pK_a determinations. A 36 ml thermostatted cell which was magnetically stirred and fitted with quartz windows was used. The pH was maintained constant by a Radiometer pH-stat assembly consisting of a pHM-26 pH-meter, a TTT 116 titrator and ABU 1c autoburette. A Metrohm 125U electrode measured the pH of the solution in the cell. The dissociation constants were determined in water at 25 °C (μ = 1.0, $NaClO_4$) at wavelengths previously determined from spectra of substrates in neutral/acidic/basic solution. The pH of the solution was initially lowered using 4N-perchloric acid and the absorbance at the chosen wavelength being recorded at various pH values until no further change occurred. Near the pK_a, readings were

$$Abs_{obs.} = Abs_{max.} \cdot \frac{K_a}{a_H + K_a} \qquad (3)$$

taken at 0.1 unit intervals or less. Theoretical titration curves were plotted from equation (3) and the plot of absorbance *versus* pH was compared with the theoretical curve to give the pK_a (see Table 1 for results).

[8/1322 *Received*, 17*th July*, 1978]

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