Heteroaromatic Azo-activated Substitutions. Part 3.[1,2] Catalysis in the Reaction of 4-(4-Methoxyphenylazo)pyridinium Methiodide with Amines in Dipolar Aprotic Solvents. Kinetic Form and the Mechanism of the Uncatalysed Reaction in Nucleophilic Aromatic Substitution

Ikenna Onyido * and Collins I. Ubochi
Department of Chemistry, University of Ibadan, Ibadan, Nigeria

The kinetics of the reaction of the title compound with piperidine, n-butylamine, morpholine, and benzylamine have been studied in dimethyl sulphoxide and, for piperidine and n-butylamine only, in acetonitrile. The predominant reaction in all cases was nucleophilic displacement at the aryl carbon (S_NAr reaction), accompanied by an S_N2 attack at the alkyl carbon when secondary amines were the nucleophiles. The S_N2 rate constants were independent of amine concentration. The S_NAr reactions were all base-catalysed independent of whether the nucleophile was a primary or secondary amine, indicating that decomposition of the first formed intermediate was rate limiting in all cases. The activating influence of the azopyridinium function is discussed. The hitherto observed dichotomy in the reactions of the two amine types is considered. It is shown that in the absence of an *ortho*-nitro group in the substrate, as in the present case, both the catalysed and uncatalysed reactions occur by the specific base–general acid (SB–GA) mechanism.

Recently, we reported[1] that the heteroaromatic azo-activated phenyl methyl ether (**1**) undergoes concurrent nucleophilic attack by piperidine in dimethyl sulphoxide (DMSO) at impressive rates at the aryl carbon to give 4-(4-piperidinylphenylazo)pyridinium methiodide (**2**) and at the alkyl carbon to yield *N*-methylpiperidine and 4-(4-hydroxyphenylazo)pyridinium methiodide (**3**). The displacement at the aryl carbon is a nucleophilic aromatic substitution (S_NAr) reaction activated by the azopyridinium function and was susceptible to catalysis by added piperidine. We have now extended the kinetic study to the solvent acetonitrile and have also studied the reaction with n-butylamine in both solvents. Additionally the kinetics of the reactions of morpholine and benzylamine with (**1**) have been determined in DMSO. The objectives of the present study are set out below.

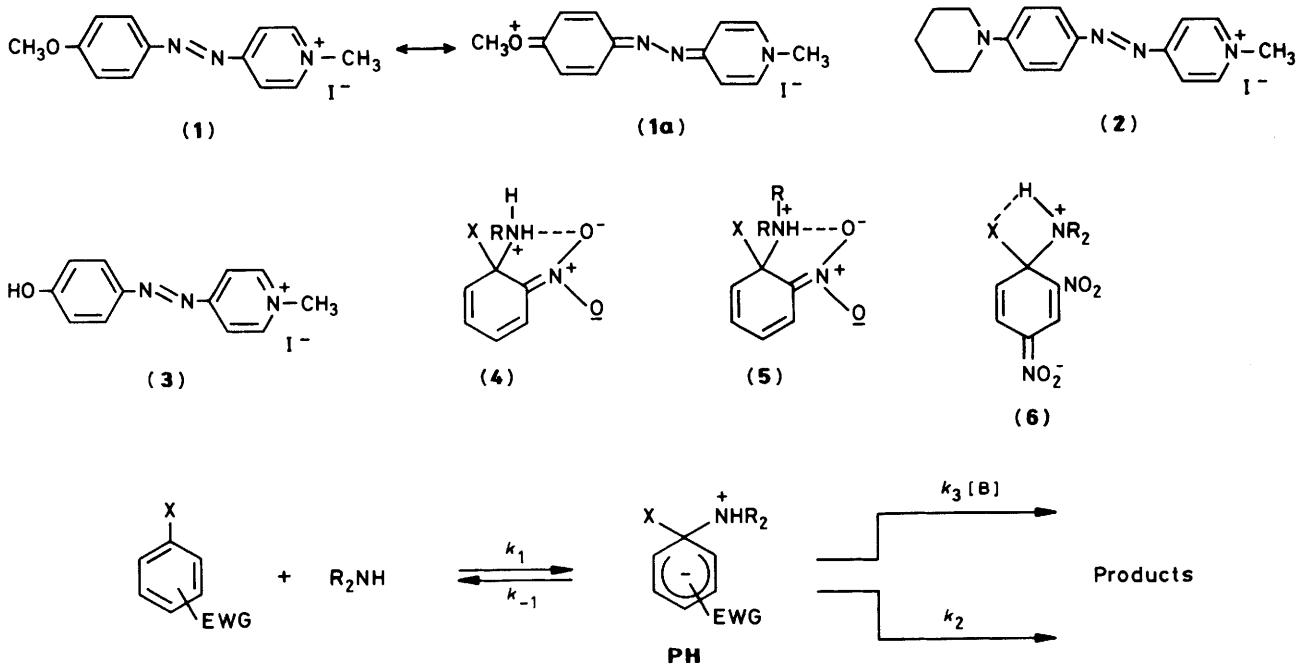
The intermediate complex mechanism of S_NAr reactions involving primary and secondary amines as nucleophiles is given in Scheme 1 (EWG = electron-withdrawing group), while equation (i) gives the steady-state rate expression for this mechanism, k_A being the observed second-order rate constant. Studies from this and other laboratories[3–11] have shown that in polar solvents the reactions of secondary amines are prone to base catalysis whereas those of primary amines of comparable basicity are usually not. There is an indication that this dichotomy also exists in the non-polar solvents ethyl acetate and

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \qquad \text{(i)}$$

tetrahydrofuran.[12] Thus, while the reactions of secondary amines proceed by way of rate-determining breakdown of the intermediate **PH** corresponding to the kinetic condition $k_{-1} \gg k_2 + k_3[B]$ or $k_{-1} \sim k_2 + k_3[B]$, those of primary amines occur with rate-limiting formation of **PH** in which case the condition $k_{-1} \ll k_2 + k_3[B]$ holds. Typical substrates studied in this class of reactions usually carry one or two *ortho*-nitro groups and the difference in the behaviour of primary and secondary amines noted above is thought[3,7–11] to arise from the hydrogen bonding known to occur[13,14] between the ammonium proton and the oxygen of the nitro group in **PH**. As there is a free transferable proton in (**4**) for primary amines while for secondary amines the hydrogen bond in (**5**) first has to be broken before further reaction can occur, the ratio $(k_2 + k_3[B])/k_{-1}$ is usually smaller for secondary amines than for primary ones, thus making the reactions of the former more prone to base catalysis than those of the latter.[3,7,10]

A dichotomy in the mechanism of the uncatalysed pathway has also been noted in the reactions of primary and secondary amines. The base-catalysed pathway is usually discussed in terms of the mechanism proposed by Bunnett and Davies[15] given in Scheme 2, in which **PH** is rapidly deprotonated by a base to give $\mathbf{P}^-$ and the conjugate acid of the base, BH^+, which in turn electrophilically assists the removal of the nucleofuge from $\mathbf{P}^-$. This mechanism is also known as the specific base–general acid (SB–GA) mechanism. Two mechanisms, on the other hand, have been proposed for the uncatalysed reaction. Orvik and Bunnett[16] have suggested that the uncatalysed pathway in effect occurs *via* the SB–GA mechanism in which a solvent molecule replaces the base in Scheme 2, while Kirby and Jencks[17] favour the unimolecular decomposition of **PH** depicted in (**6**). We have earlier employed the variation of solvent basicity as a probe to show that while primary amines react by the SB–GA mechanism in the uncatalysed pathway,[10,18] the reactions of secondary amines are explicable in terms of the unimolecular mechanism.[7,8,10,19] The objective of the present paper is to employ the heteroaromatic azo-activated substrate (**1**), which is reasonably disposed towards nucleophilic substitution[1] but devoid of the electronic, electrostatic, and possibly steric complications arising from the presence of *ortho* substituents, as a model compound in seeking further information regarding the differing behaviour of primary and secondary amines highlighted above with a view to providing a unified explanation.

To this end we have studied the kinetics of the reactions of (**1**) with the following secondary–primary amine pairs in DMSO: piperidine–n-butylamine, morpholine–benzylamine, and in MeCN: piperidine–n-butylamine. The pK_a values for these amines in water, MeCN, and DMSO (where available) are given in Table 1. We have been unable to find a complete set of pK_a



Scheme 1.

Table 1. pK_a Values of amines in different solvents

Amine	$pK_a(H_2O)$[a]	$pK_a(MeCN)$[b]	$pK_a(DMSO)$[c]
Piperidine	11.20	18.92	
n-Butylamine	10.65	18.26	
Morpholine	8.61	16.62	11.0
Benzylamine	9.38	16.76	

[a] Taken from ref. 21. [b] Values taken from ref. 22. [c] See ref. 23.

data for these amines in DMSO and have assumed that the similarity in the values of the primary–secondary amine pairs that exist in water and MeCN also holds in solvent DMSO.

Results

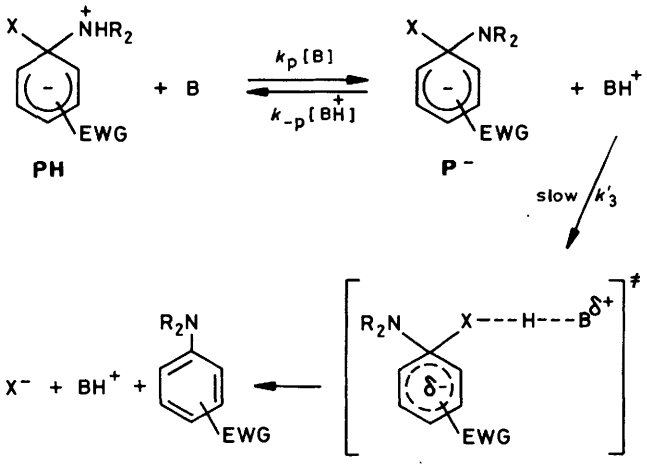
The reactions were followed by monitoring the appearance of the products spectrophotometrically under conditions in which the amines were present in large enough excess to ensure pseudo-first-order kinetics. The reactions of morpholine and benzylamine were studied in DMSO only because the rates of reactions involving these amines were very slow in MeCN. As previously discussed,[1] the reactions of the secondary amines gave infinity absorbance values which were less than the calculated ones at low nucleophile concentrations and we ascribe this behaviour to a competing S_N2 attack by the nucleophile to give (**3**) and the corresponding tertiary amine. Good agreement between the experimental and theoretical infinity values was obtained at higher nucleophile concentrations. The spectral characteristics of (**3**) are known from the work of Buncel and Keum,[20] and the following S_N2 rate constants (l mol^{-1}) were calculated for the formation of (**3**): piperidine 4.0×10^{-4} (DMSO),[1] 1.7×10^{-4} (MeCN), morpholine 3.2×10^{-5} (DMSO). These rate constants were more or less independent of amine concentration.

The reactions of the primary amines proceeded smoothly to completion at low nucleophile concentrations but gave decreasing infinity absorbances at high nucleophile concentrations. The unidentified side product has a u.v.-visible spectrum that is markedly different from that due to (**3**), showing $\lambda_{max.}$ *ca.* 490 nm [$\lambda_{max.}$ for (**3**) 530 nm]. All rate constants were however calculated using experimental infinity values and the argument that follows is based mainly on the kinetic forms of the reactions and the derived rate ratios. For the cases in which there was disparity between calculated and observed infinity values, data were treated as described in the Experimental section. The results for the S_NAr reactions are assembled in Table 2.

Discussion

The detailed mechanism of the S_NAr reaction of (**1**) with primary and secondary amines is restated in Scheme 3, while Scheme 4 shows the mechanism of the S_N2 displacement. The schemes clearly depict the fact that both modes of reaction involve highly delocalized intermediates and/or transition states thereby highlighting the fact that the azopyridinium function activates the aryl ether towards nucleophilic attack by acting as an electron sink, as shown by the resonance-contributing structure (**1a**).

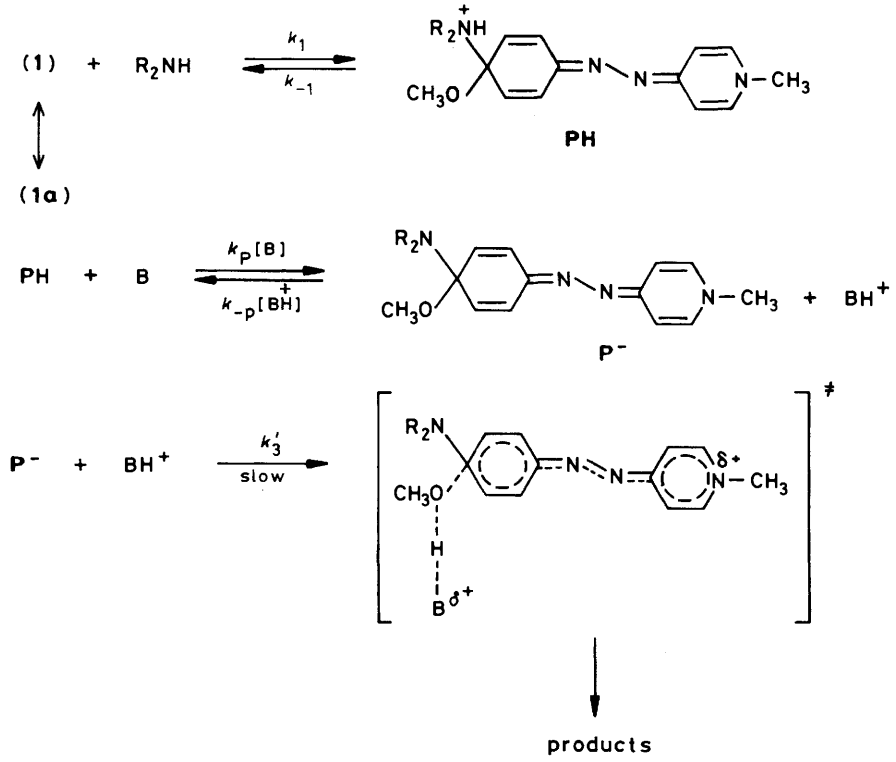
Kinetic Form and Mechanism—The S_NAr reactions of (**1**) with piperidine and n-butylamine in both solvents and with benzylamine in DMSO are curvilinearly dependent on [amine], indicating that the condition $k_{-1} \sim k_2 + k_3[B]$ obtains, hence decomposition of **PH** to products is rate limiting, at least at low amine concentrations. A typical plot of this kinetic behaviour is given in the Figure for the reaction of (**1**) with piperidine in both solvents. The reaction with morpholine in DMSO gives a good linear plot (not shown) indicating that the condition $k_{-1} \gg k_2 + k_3[B]$ holds and decomposition of **PH** to products is rate limiting across the entire range of amine concentration studied. Thus, in all cases, the reactions of primary and secondary amines of comparable basicities proceed *via* rate-limiting breakdown of **PH** to products. This is contrary to the widely documented difference in the behaviour of both classes of amines [3–12] noted above. Hence in the absence



Scheme 2.

of an *ortho* substituent the observed dichotomy is removed, thereby confirming our earlier hypothesis.[7,10]

The Activating Influence of the Azopyridinium Moiety.—In discussing the activating effect of the azopyridinium function in nucleophilic substitution reactions, we compare our present results with those involving 2,4-dinitroanisole (DNA)[10] where possible. For the S_NAr reaction data are available only for the reaction of DNA with piperidine[10] and the ratio of the S_NAr rate constants $k(1)/k(DNA)$ at 30 °C is *ca.* 65 in both DMSO and MeCN. The bond broken in the transition state is C–O in each case and one would expect the rate differences to mirror mainly the stabilities of the leaving groups as anions, which, in turn, should be related to the pK_a of the conjugate acids of the leaving group. The pK_a values of (3) and 2,4-dinitrophenol in water are 6.31[20] and 4.09[24] respectively, and it is obvious that the reactivity order noted above is in reverse order of the anticipated nucleofugality of the phenoxide ions. We suggest that this is a result of differential solvent effects on the initial and

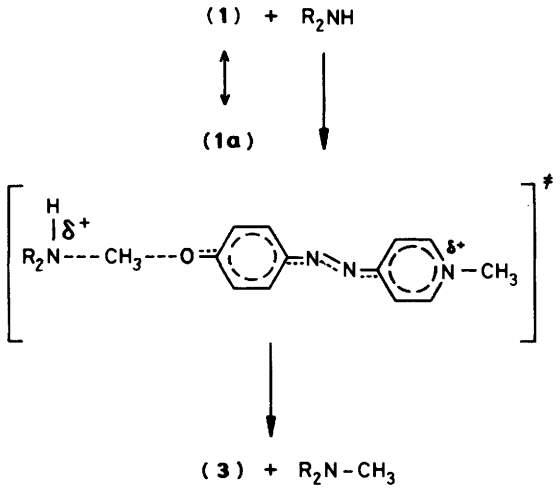


Scheme 3.

Table 2. Rate constants (l mol^{-1}) for the S_NAr reactions of (**1**)[a] with primary and secondary amines in DMSO and MeCN at 30 °C

Solvent	Amine									
DMSO	Piperidine[b]	10^3[amine]/M	7.0	10.0	20.0	40.0	80.0	100.0		
		10^3k_A	1.92	2.79	4.79	7.83	11.4	12.8		
	n-Butylamine	10^3[amine]/M	4.0	7.0	10.0	20.0	30.0	40.0		
		10^3k_A	2.62	2.94	2.85	3.90	4.03	3.89		
	Morpholine	10^2[amine]/M	4.0	6.0	8.0	10.0	12.0	14.0		
		10^4k_A	2.99	4.23	5.10	6.33	7.64	8.68		
	Benzylamine	10^2[amine]/M	1.5	2.5	4.0	5.0	6.0	7.0	8.0	10.0
		10^4k_A	8.24	8.57	9.19	9.21	9.57	9.57	9.70	9.91
MeCN	Piperidine	10^3[amine]/M	5.0	10.0	30.0	60.0	70.0	80.0	90.0	100.0	120.0
		10^4k_A	2.76	4.54	14.8	37.4	38.4	46.6	45.8	49.4	52.1
	n-Butylamine	10^3[amine]/M	3.0	4.0	10.0	20.0	30.0	40.0	50.0		
		10^5k_A	9.77	11.6	13.4	16.0	17.8	17.9	17.8		

[a] Initial [(**1**)] 1.5—3.0 × 10^{-4}M. [b] Revised data taken from ref. 1.



Scheme 4.

transition states of the reactions involving (**1**) and DNA. It is noted in particular that the transition state for the S_N2 reaction of (**1**) (Scheme 4) is bulkier and more likely to be much better stabilized by polarizability effects than the corresponding transition state involving DNA.

The S_NAr reaction of DNA with n-butylamine in DMSO is not base catalysed[10] showing that for this amine the rate-limiting step is the formation of **PH**, hence $k_A = k_1$. Using k_1 data for this system and k_1 obtained for the reaction of (**1**) with n-butylamine by standard procedures,[4] it is calculated that k_1(**1**)/k_1(DNA) is *ca.* 0.2, showing that DNA is only marginally more activated than (**1**) towards nucleophilic attack at the aryl carbon. Since *ortho*-substituents are absent in (**1**) and if we assume that nucleophilicity would approximately parallel nucleophile basicity, a similar ratio is expected for piperidine. The second-order rate constant k_A for the reaction of piperidine with (**1**) is, however, considerably higher than that for DNA by factors of *ca.* 10^2 or more in DMSO and MeCN, respectively. On the other hand, the reactions of (**1**) and DNA with n-butylamine are base catalysed in MeCN and k_A for both substrates is of the same order of magnitude. The results show that while (**1**) and DNA have comparable reactivity towards primary amines, for secondary amines (**1**) reacts considerably faster. As the second-order rate constant k_A is a composite quantity, it would be imprudent to attempt to locate the origin of this difference. This notwithstanding, the results indicate that the azopyridinium function has a powerful activating effect.

Mechanism of the Catalysed and Uncatalysed Pathways in the S_NAr Reactions.—Following standard procedures,[4] k_3/k_2 ratios for all the S_NAr reactions have been calculated and are given in Table 3. According to Bunnett's criterion[25] values of this ratio ≥ 50 indicate genuine base catalysis, hence for all reactions studied the decomposition of **PH** is rate limiting.

The mechanism of the base-catalysed step in dipolar aprotic solvents is usually discussed in terms of the SB–GA mechanism although the existence of this mechanism in protic solvents has been questioned by Bernasconi.[26] Good evidence for this mechanism was provided by Bunnett and Orvik[16] in the reaction of n-butylamine with 2,4-dinitro-1-naphthyl ethyl ether in DMSO. We predicate our discussion of the mechanism of the reaction of the ether (**1**) with primary and secondary amines in dipolar aprotic solvents on this model, hence k_3 [equation (i)] = k'_3K_B, where $K_B = [P^-][BH^+]/[PH][B] = k_p/k_{-p}$ in Schemes 2 and 3. If it is assumed that the uncatalysed pathway also occurs by the SB–GA mechanism with a solvent molecule S replacing the base, then k_2 [equation (i)] = k'_2K_S, where

Table 3. Values of k_3/k_2 at 30 °C in DMSO and MeCN for the reactions of different primary and secondary amines with (**1**)

Solvent	Amine	k_3/k_2
DMSO	Piperidine	620
	n-Butylamine	408.8
	Morpholine	81.8
	Benzylamine	206.6
MeCN	Piperidine	∞ [a]
	n-Butylamine	∞ [a]

[a] Plots of k_A *versus* [amine] for these amines in MeCN are curvilinear, passing through the origin. This is equivalent to the condition $k_{-1} \sim k_3[B]$, *i.e.* k_2 is negligible and equation (i) becomes $k_A = k_1k_3[B]/(k_{-1} + k_3[B])$. In the catalysed region k_3/k_2 therefore approaches ∞.

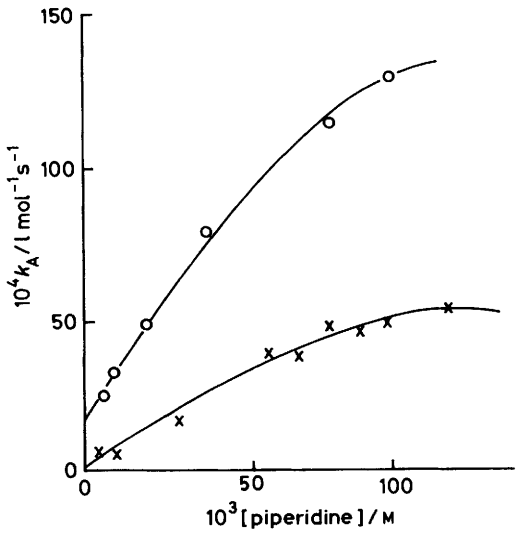


Figure. Plot of k_A *versus* [amine] for the reaction of (**1**) with piperidine in DMSO (○) and MeCN (×) at 30 °C

$K_S = [P^-][SH^+]/[PH] = k_s/k_{-s}$. We have earlier shown that since K_S defines the acid strength of the conjugate acid of an amine in a particular solvent there should be a very large difference in the value of $k_3/k_2 = k'_3K_B/k'_2K_S$ in solvents of widely differing basicity, since the quantity K_S is very sensitive to the basicity of the solvent in which it is measured.[7,18,19] For example, DMSO is *ca.* 10^{10}-times more basic than MeCN[27] and the ratio of the acid dissociation constant of tri-n-butylammonium ion[24] is 5×10^9.

The very large change in the values of k_3/k_2 for the reactions of piperidine and n-butylamine as the solvent is changed from DMSO to MeCN is in good agreement with this expectation and indicates that both amine types react by the same mechanism in the uncatalysed step.

Experimental

Details of the synthesis of (**1**) have already been given.[1] Piperidine, n-butylamine, morpholine, and benzylamine were commercial samples purified by distilling from either potassium hydroxide pellets or sodium wire, followed by fractionation. DMSO was distilled from calcium hydride under reduced pressure. MeCN was distilled from several batches of phosphorus pentaoxide until the drying agent was no longer coloured, and finally distilled from anhydrous potassium carbonate.

All reactions were monitored by spectrophotometric determination of reaction products under first-order conditions using the pipette procedure already described.[28] Rate constants were calculated by plotting ln $A_\infty - A_t$ *versus* time using experimental infinity values of absorbance. In all cases such plots gave excellent linearity. In situations where experimental and infinity absorbance values differed, the S_NAr rate constants were obtained according to the method of Bunnett and his co-workers[29] by multiplying the k_{obs} values by the ratio A_∞(experimental)/A_∞(theoretical). S_N2 Rate constants were reckoned from the expression $k(S_N2) = k_{obs} - k(S_NAr)$.

Acknowledgements

We thank Professors E. Buncel and J. Hirst for discussions, and a referee for pointing out an error in the evaluation of some of the rate data.

References

1 Part 1, I. Onyido and C. I. Ubochi, *Heterocycles*, 1987, **26**, 313.
2 Part 2, E. Buncel and I. Onyido, *Can. J. Chem.*, 1986, **64**, 2115.
3 C. F. Bernasconi, *MTP Int. Rev. Sci. Org. Chem. Ser. One*, 1973, **3**, 33.
4 J. F. Bunnett and C. F. Bernasconi, *J. Am. Chem. Soc.*, 1965, **87**, 5209.
5 F. Pietra, *Tetrahedron Lett.*, 1975, 2405.
6 D. Ayediran, T. O. Bamkole, and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1396.
7 D. Ayediran, T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1580.
8 T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1201.
9 T. O. Bamkole, J. Hirst, and G. Hussain, *J. Chem. Soc., Perkin Trans. 2*, 1984, 681.
10 J. Hirst, G. Hussain, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1986, 397.
11 E. Buncel, C. Innis, and I. Onyido, *J. Org. Chem.*, 1986, **51**, 3680.
12 I. Onyido, J. Hirst, and E. T. Akinyele, unpublished results.
13 C. F. Bernasconi, *J. Phys. Chem.*, 1971, **75**, 3636.
14 C. F. Bernasconi and F. Terrier, *J. Am. Chem. Soc.*, 1975, **97**, 7458.
15 J. F. Bunnett and G. T. Davies, *J. Am. Chem. Soc.*, 1960, **82**, 655.
16 J. A. Orvik and J. F. Bunnett, *J. Am. Chem. Soc.*, 1970, **92**, 2417.
17 A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, 1965, **87**, 3217.
18 T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1317.
19 D. Ayediran, T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1977, 597.
20 E. Buncel and S. R. Keum, *Tetrahedron*, 1983, **39**, 1091.
21 D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Supplement 1972, IUPAC, Butterworths, London.
22 J. F. Coetzee, *Prog. Phys. Org. Chem.*, 1967, **4**, 45.
23 I. M. Kolthoff, M. K. Chantooni, and S. Bhownik, *J. Am. Chem. Soc.*, 1968, **90**, 23.
24 G. Kortum, W. Vogel, and K. Andrussov, 'Dissociation Constants of Organic Acids in Aqueous Solution,' 1961, Butterworths, London.
25 J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1.
26 C. F. Bernasconi, R. H. deRossi, and P. Schmid, *J. Am. Chem. Soc.*, 1977, **99**, 4090.
27 E. M. Arnett, *Prog. Phys. Org. Chem.*, 1963, **1**, 223.
28 T. O. Bamkole, C. W. L. Bevan, and J. Hirst, *Nigerian J. Sci.*, 1968, **2**, 11.
29 J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruit, *J. Am. Chem. Soc.*, 1957, **79**, 385.

Received 28*th April* 1986; *Paper* 6/805