Heteroaromatic Azo-activated Substitutions. Part 4.[1] Kinetics and Mechanism of the Hydrolysis of 3-(4-Methoxyphenylazo)-5-methylisoxazole in Aqueous Sulphuric Acid Media

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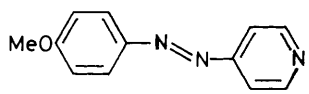
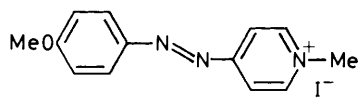
The kinetics of the hydrolysis of the title compound, (**3**), have been investigated in moderately concentrated aqueous sulphuric acid media at 30 °C. Activation parameters have also been determined. Rate correlation by the Cox–Yates excess acidity method shows that hydrolysis occurs from the monoprotonated substrate by the A-S_E2 mechanism of the S_NAr type. Nucleophilic attack by water at the aryl carbon and a subsequent proton-transfer equilibrium are fast processes which precede the electrophilically catalysed separation of the leaving group, in which the functional catalysts are all general acids in solution. An abnormal value of 1.4 is obtained for the slope parameter $m^{\ddagger}$ ($\equiv$Kresge's α_A); this is discussed in terms of differential solvation of the initial and transition states. The Bunnett–Olsen slope parameter ($\varphi_{\ddagger} - \varphi_e$) of −2.0 indicates that the transition state of the reaction is substantially less solvated than its initial state. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ vary to compensate each other and the decreasing $\Delta S^{\ddagger}$ values accord with the ordered transition state proposed.

Although aryl alkyl ethers are relatively insensitive to hydrolysis in acidic media, activation of the ring through phenylazo substitution renders these substrates susceptible to nucleophilic attack.[2–4] Our recent work[5] has shown that azopyridinyl substitution has a remarkable influence on the reactivity of these compounds, most especially when the protonated ring nitrogen is appropriately situated for conjugative interaction with the reaction site as in (**1**). Subsequently, we were able to demonstrate[5,6] that quaternization of the aza nitrogen in (**1**) to give (**2**) makes these compounds susceptible to normal aromatic nucleophilic substitution (S_NAr) reactions in neutral media, thus dispensing with the necessity to activate these substrates through protonation of the ring and/or azo nitrogen(s). Further to our interest in heteroaromatic azo-activated nucleophilic substitutions, we have synthesized the isoxazole-based azophenyl ether (**3**) and have investigated its hydrolysis in acid media. This substrate is also interesting to us in view of our recent interest in the construction of molecules with suitably disposed heteroatomic centres to act as templates for metal-ion co-ordination, with their potential utility in extraction processes and qualitative and quantitative analytical procedures. The results of the metal-ion co-ordination experiments as well as pK_a studies involving (**3**) and its derivative will be published at a later date.



(**1**)



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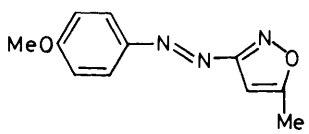


(**3**)

Results and Discussion

The kinetics of the hydrolysis of (**3**) were followed by monitoring spectrophotometrically of the appearance of the product, 3-(4-hydroxyphenylazo)-5-methylisoxazole in the range 39–78 wt% aqueous sulphuric acid. Formation of the product was quantitative. The kinetic data, along with other relevant information, are assembled in Table 1 and presented graphically in Figure 1. Unlike our earlier results for the hydrolysis of (**1**) and its 3-isomer in aqueous sulphuric acid[5] and Bunnett's results for the hydrolysis of 4-(*p*-sulphophenylazo) naphthyl and 4-(*p*-sulphophenylazo)phenyl methyl ethers in aqueous hydrochloric and perchloric acids,[4] no rate maximum was observed in the range of acidity examined. Thus for the acidity range 39.2–78.4 wt% sulphuric acid, the first-order rate con-

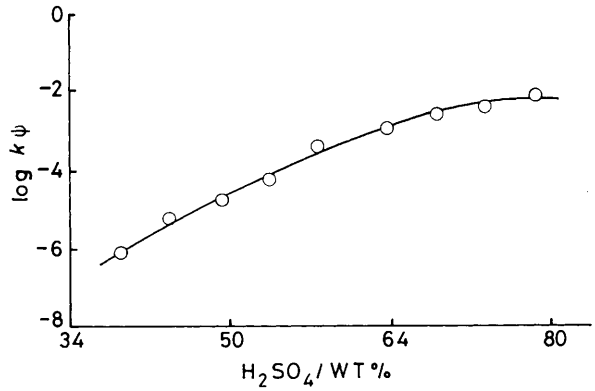


Figure 1. Plot of log k_ψ vs. % H_2SO_4 for the hydrolysis of (**3**) at 30 °C.

Table 1. Rate, equilibrium, and other relevant data for the hydrolysis of (3) in aqueous sulphuric acid media at 30 °C.

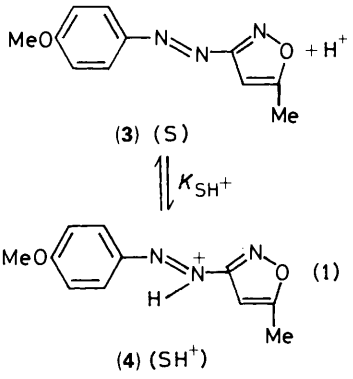
H_2SO_4/wt%	H_0[a]	^aH_2O[b]	$\frac{c_S}{c_S + c_{SH^+}}$	$\frac{c_{SH^+}}{c_S + c_{SH^+}}$[c]	$C^d_{H^+}$/M	X[d]	k_ψ/s^{-1}
39.20	−2.35	0.582	0.9993	0.0007	6.53	1.58	8.09×10^{-7}
44.10	−2.77	0.475	0.9981	0.0019	7.60	1.92	5.93×10^{-6}
49.00	−3.20	0.373	0.9950	0.0050	8.60	2.27	1.51×10^{-5}
53.90	−3.69	0.270	0.9847	0.0153	9.65	2.67	4.63×10^{-5}
58.80	−4.24	0.180	0.9479	0.0521	10.63	3.12	3.54×10^{-4}
63.70	−4.86	0.103	0.8136	0.1864	11.50	3.63	9.36×10^{-4}
68.60	−5.60	0.055	0.4427	0.5573	12.35	4.25	2.24×10^{-4}
73.50	−6.38	0.016	0.1165	0.8835	13.08	5.01	3.27×10^{-3}
78.40	−7.19	0.004	0.0200	0.9800	13.75	5.88	5.87×10^{-3}

[a] Values taken from the data of ref. 26. [b] Values taken from the data of ref. 27. [c] pK_{SH^+} for (3) = −5.50 (see text). [d] Values taken from the data of ref. 13.

Table 2. Rate data at different temperatures and activation parameters[a] for the hydrolysis of (3) in different aqueous sulphuric acid media.

H_2SO_4 (wt%)	$k_\psi^{30\,°C}$/s^{-1}	$k_\psi^{60\,°C}$/s^{-1}	$\Delta G^\ddagger$/kcal mol^{-1}	$\Delta H^\ddagger$/kcal mol^{-1}	$\Delta S^\ddagger$/e.u.
44.10	5.93×10^{-6}	4.83×10^{-4}	20.2	29.4	30.3
49.00	1.51×10^{-5}	1.10×10^{-3}	23.2	28.7	18.0
53.90	4.63×10^{-5}	1.94×10^{-3}	23.1	25.0	6.0
58.80	3.54×10^{-4}	4.31×10^{-3}	21.9	16.7	−17.2
63.70	9.36×10^{-4}	6.70×10^{-3}	21.4	13.2	−27.0

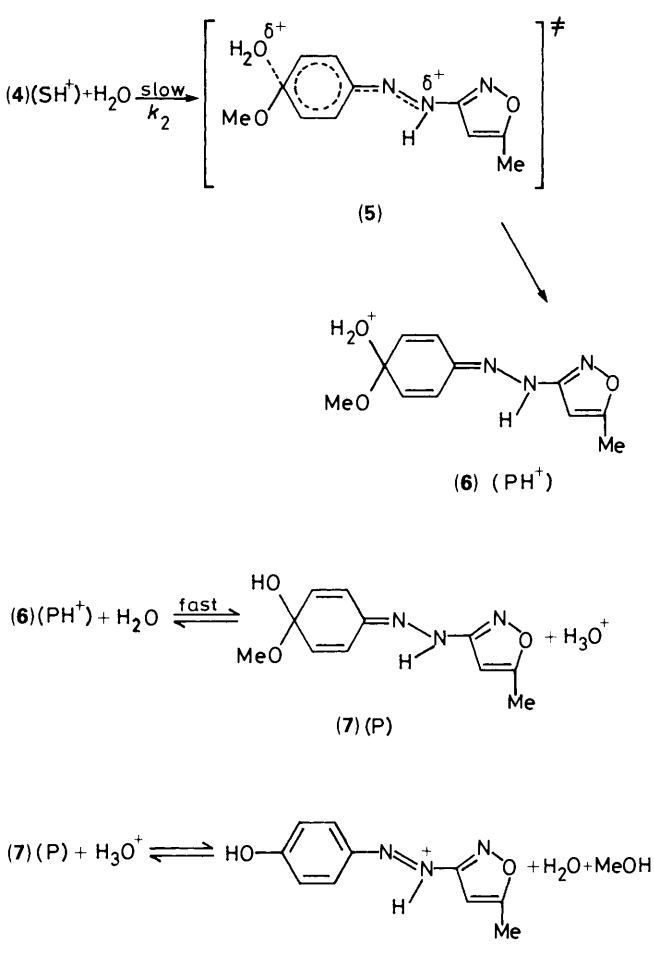
[a] Obtained at 30 °C.



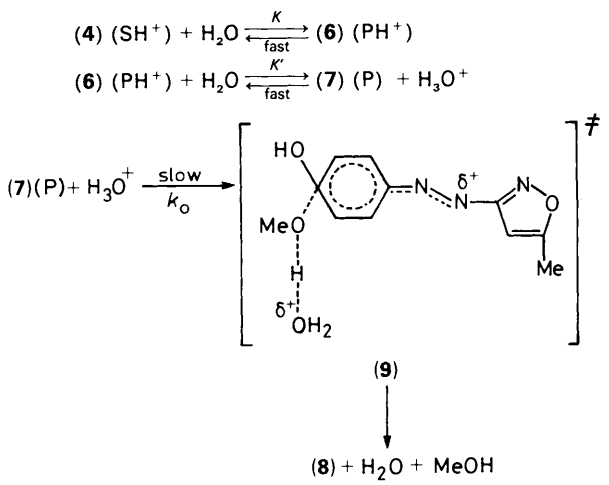
stant, k_ψ, increased by *ca.* 7 250 times. Activation parameters were also determined for some of the acid solutions. Rate data at different temperatures and the corresponding activation parameters are given in Table 2..

A study of the monoprotonation behaviour of (3) in aqueous sulphuric acid solutions according to equation (1) has been undertaken.[7] No evidence for additional protonation equilibria was obtained from the spectroscopic data and a pK_{SH^+} value of −5.50 was evaluated.

Rate Correlations and Mechanism.—The A1 mechanism of hydrolysis is generally disfavoured for methyl aryl ethers of the type under consideration owing to the involvement of high energy Me^+ species in the rate-limiting step of the reaction.[5] Bunnett *et al.*[4] have shown that the protonated azo linkage is a strong activating group for S_NAr reactions and the following discussion is predicated on the S_NAr mechanism, since structurally similar substrates have been shown to hydrolyse by the same mechanism.[4,5] Thus, the mechanisms under consideration are the A2 and A-S_E2 mechanisms of the S_NAr-type involving monoprotonated substrate species. These mechanisms are shown in Schemes 1 and 2, respectively. It should be pointed out at the onset that in Scheme 2, addition of H_2O to (4) might be subject to general base catalysis, analogous to the general acid-



Scheme 1.



Scheme 2.

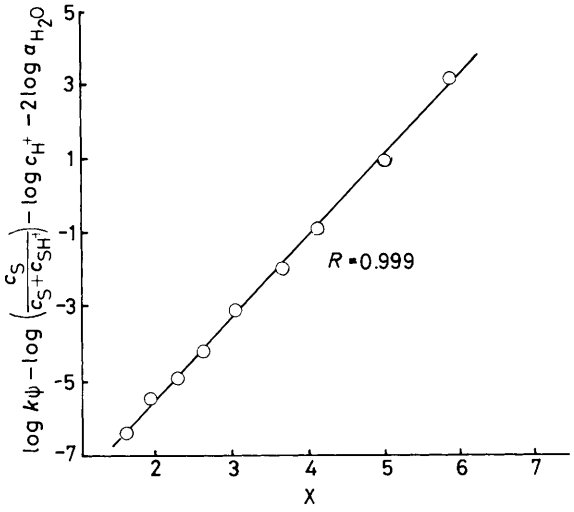


Figure 2. Cox–Yates plot for the A-S_E2 mechanism of hydrolysis of (**3**) in which the electrophilic catalyst is H_3O^+.

catalysed detachment of MeOH from (**7**). As there are no satisfactory criteria for establishing such a process in moderately concentrated acid, we have not considered this possibility any further.

Several methods for the correlation of rates with acidity functions exist in the literature. These include the Edward–Meacock correlation,[8] Bunnett–Olsen treatment,[9,10] Modena–Scorrano treatment,[11] the M_C function of Marziano *et al.*,[12] and the Cox–Yates excess acidity method.[4c,13–15] In our earlier discussion of the mechanism of hydrolysis of (**1**) and its 3-isomer in aqueous sulphuric acid, we showed that the Cox–Yates method is a valid criterion for the mechanism of azo ether hydrolysis.[5] The following discussion of the present data, therefore, will focus on the Cox–Yates excess acidity treatment.

Equation (2) is derived from the A2 mechanism of Scheme 1

$$\log k_\psi - \log \frac{c_{SH^+}}{c_S + c_{SH^+}} = (m^\ddagger - 1)m^*X + r \log a_{H_2O} + \log k_2 \quad (2)$$

in which the reactive species is the monoprotonated substrate. A diagnostic feature of the A2 mechanism is that a plot of the left-hand side of equation (2) *vs.* X should give a downward curve.[14] Such a curve is not obtained (plot not shown), hence we conclude that the mechanism is not A2. This leaves the A-S_E2 mechanism for further consideration.

The A-S_E2 mechanism involves rapid nucleophilic attack by water followed by a fast, proton-transfer equilibrium to give the intermediate (**7**), from which the nucleofuge is separated under general acid catalysis in the rate-limiting step (Scheme 2). Equation (3) is derived for this mechanism. The quantity $a_{SH^+} = a_S a_{H^+}/K_{SH^+}$, hence equations (4) and (5) are obtained. A plot of the left-hand side of equation (5) *vs.* X should

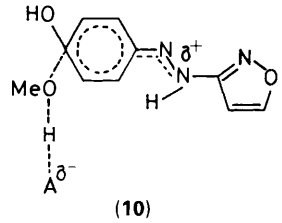
$$k_\psi(c_S + c_{SH^+}) = k_0 a_{PH^+} \cdot a_{H_3O^+}/f^\ddagger = k_0 K K' a_{SH^+} a_{H_2O}^2/f^\ddagger \quad (3)$$

$$k_\psi(c_S + c_{SH^+}) = \frac{k_0 K K'}{K_{SH^+}} a_S a_{H^+} \cdot a_{H_2O}^2/f^\ddagger = k' c_S c_{H^+} a_{H_2O}^2 f_S f_{H^+}/f^\ddagger \quad (4)$$

$$\log k_\psi - \log \frac{c_S}{c_S + c_{SH^+}} - \log c_{H^+} - 2 \log a_{H_2O} = \log k' + m^\ddagger m^* X \quad (5)$$

be linear with slope = $m^*m^\ddagger$ if an A-S_E2 mechanism operates. Such a plot is indeed obtained (Figure 2). Using the value of $m^* = 1.1$ calculated from protonation studies,[7] the value of $m^\ddagger = 1.9$ is evaluated. Although the linearity of the plot of equation (5) displayed in Figure 2 gives qualitative evidence for an A-S_E2 mechanism, the magnitude of the slope parameter $m^\ddagger$ lies outside the limits of 0 and 1 expected for a rate-limiting proton-transfer mechanism.[5,14] This is further considered below.

The Slope Parameter, $m^\ddagger$.— Inspection of Scheme 2 reveals the implicit assumption that the only electrophilic species capable of catalysing the departure of the nucleofuge is the hydronium ion, H_3O^+, which may not necessarily be true. In principle, all general acids in solution can fulfil this role. It is known that moderately concentrated sulphuric acid media of the range employed in the present study contain a complex mileu of species in equilibrium.[16–18] The principal species capable of acting as electrophilic catalysts apart from the actual hydronium ion are $H(H_2O)_n^+$ and HSO_4^-. A model of the transition state for the electrophilic catalysis of the departure of the leaving group involving all general acids in solution is depicted as (**10**).



(**10**)

To account for the involvement of all species capable of electrophilically assisting the expulsion of the nucleofuge, the terms for the activities of $H(H_2O)_n^+$ and HSO_4^- are further subtracted from the left-hand side of equation (5). A linear plot is obtained with an excellent correlation coefficient, r (Figure 3), and a value of the slope parameter $m^*m^\ddagger = 1.53$, from which the value of $m^\ddagger = 1.4$ is calculated.

According to the excess acidity concept,[13–15] $m^\ddagger$ for an A-S_E2 mechanism is identical with α_A as defined by Kresge,[19] and should vary between 0 and 1 depending on whether the

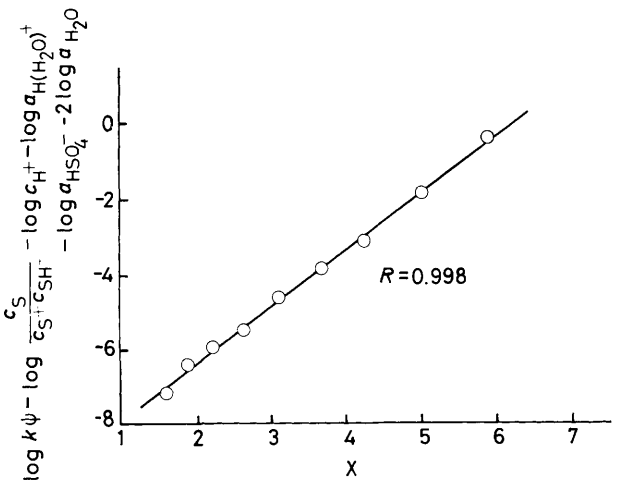


Figure 3. Cox–Yates plot for the A-S_E2 mechanism of hydrolysis of (**3**) in which all general acids in solution [H_3O^+, $H(H_2O)_n^+$, and HSO_4^-] function as electrophilic catalysts.

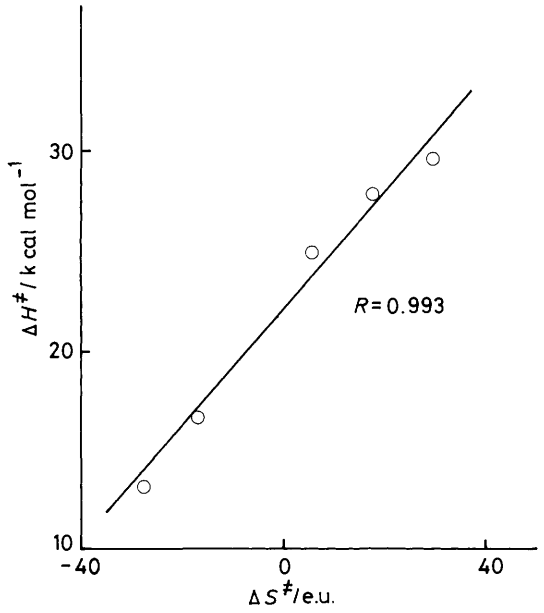


Figure 4. Plot of $\Delta H^‡$ *vs.* $\Delta S^‡$ (at 30 °C) for the hydrolysis of (**3**).

transition state is reactant (or product) like. Thus the value of 1.4 calculated for this quantity is considered abnormal for an A-S_E2 mechanism, since earlier reports of values of $m^‡$ lie within the prescribed limits. This situation is clearly analogous to Bordwell's observation[20,21] of abnormal Brønsted α values for proton transfers for which a number of explanations are available.[20–22] Pending accumulation of further information regarding processes in moderately concentrated acid media as they pertain to the Cox–Yates excess acidity concept, we tentatively ascribe the abnormal value of $m^‡$ observed in this study as a consequence of differential solvation of the ground and transition states of the reaction. Experimental support for this interpretation comes from the Bunnett–Olsen plot[9] for an A-S_E2 mechanism (plot not shown) which closely resembles the Cox–Yates plot of Figure 2. A good straight line is obtained when the left-hand side of equation (5) is plotted against (H_0 + log c_{H^+}), with slope ($\varphi_‡ - \varphi_e$) = −2.0, showing that the transition state of the reaction is substantially less solvated than the initial state. In this regard, it is noted that the formation of the A-S_E2 transition state involves charge delocalisation and redistribution, processes which have been known, in some cases, to have energetic consequences.[23,24]

Activation Parameters.—The activation parameters displayed in Table 2 show $\Delta H^‡$ and $\Delta S^‡$ values that vary in a more or less compensating manner. Thus, while $\Delta H^‡$ progressively decreased as the acid medium became more concentrated, $\Delta S^‡$ became more negative, the overall effect resulting in little variation in $\Delta G^‡$. Although a plot of $\Delta H^‡$ *vs.* $\Delta S^‡$ is approximately linear (correlation coefficient 0.993) as shown in Figure 4, its significance is not pursued further considering the controversy regarding the validity of such plots and their interpretation.[25] The decreasing values of $\Delta S^‡$ point to ordered transition-state structures in accord with charge development and consequent electrostriction of solvent molecules.

Experimental

Materials.—Sulphuric acid solutions were made up with water distilled twice from $KMnO_4$ and commercial concentrated sulphuric acid (BDH) and were standardised by titration. Compound (**3**) was prepared by direct coupling of 3-amino-5-methylisoxazole and anisole. *t*-Butyl nitrite (0.02 mol, 2.1 g) was added dropwise with stirring to a solution of 3-amino-5-methylisoxazole (0.02 mol, 2 g) in H_3PO_4 (20 cm^3) at temperatures below 5 °C. Dropwise addition of anisole (0.02 mol, 2.2 g) at 0 °C, followed by neutralisation with ice-cold NaOH solution (10%) gave a yellow solid which was filtered and washed copiously with water and recrystallised from methanol–water 5:1 (v/v). The yellow crystals obtained were dried in vacuum, m.p. 125–127 °C (decomp.), 1.1 g (30%); λ_{max}(EtOH) 340 nm (17 700 dm^3 mol^{-1} cm^{-1}) (Found: C, 61.3; H, 4.9. Calc. for $C_{11}H_{11}O_2N_3$: C 60.83; H 5.07%). The hydrolysis product of (**3**), 3-(4(hydroxyphenylazo)-5-methylisoxazole was prepared by diazotization of 3-amino-5-methylisoxazole and coupling with phenol. The yellow precipitate was washed thoroughly with water and recrystallised from 5:1 (v/v) methanol–water, m.p. 196–198 °C (decomp.), yield 66%; λ_{max}(EtOH) 350 nm (18 900 dm^3 mol^{-1} cm^{-1}). Calc. for $C_{10}H_9O_2N_3$: C 59.11, H 4.43%; Found: C 59.31, H 4.57%.

Kinetics.—The rates of the formation of the product were monitored spectrophotometrically by the indirect method described previously.[5] Rate constants were reckoned by plotting $\ln(A_\infty - A_t)$ *vs.* time. Excellent linearity was obtained in all cases.

Acknowledgements

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