Reactions in Strongly Basic Media. Part 7.[1] Correlation of the Rates of Alkaline Hydrolysis of 2-Substituted 3- and 5-Nitropyridines, 4-Nitropyridine *N*-Oxide, and 2- and 4-Substituted Pyridine Methiodides in Aqueous Dimethyl Sulphoxide with an Acidity Function

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The rate coefficients for the alkaline hydrolysis of a series of 2-substituted 3- and 5-nitropyridines, 4-nitropyridine *N*-oxide, and 2- and 4-substituted pyridine methiodides in aqueous dimethyl sulphoxide have been measured at 30.0 °C. The halogenonitropyridines react by ring fission, whereas all the other substrates react by substitution. The rates have been correlated with an acidity function for the medium and the slopes of the linear relations are discussed. The observation of Meisenheimer intermediates, and its lack, is related to the structures of the substrates.

Previous studies[2,3] have been made of the correlation of the rate of hydrolysis of 1-substituted 2- and 4-nitrobenzenes, 4-substituted 1-methoxy-2-nitrobenzenes, and 1-substituted 2,4-dinitrobenzenes in aqueous dimethyl sulphoxide (DMSO) containing base with an acidity function for the medium. For the substituted nitrobenzenes, linear relations were found. For the substituted 2,4-dinitrobenzenes, linear relations were found to exist at lower DMSO content. The later relations pass through a maximum in the region of 55—70 mol% DMSO. The latter coincided with the formation of relatively stable and observable Meisenheimer complexes. These results were discussed in terms of both detailed mechanistic paths and reactivity–selectivity relationships.

In the present study, we have extended our investigations to the rates of hydrolysis of activated heteroaromatic systems. The results are discussed in terms of the structure of the substrates and reactivity–selectivity relationships.

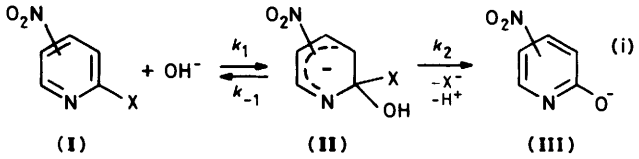
Experimental

Materials.—DMSO and tetramethylammonium hydroxide (TMAH) were prepared and used as described previously.[2,3] 2-Chloro-5- and -3-nitropyridines and 4-nitropyridine *N*-oxide were available commercially and were recrystallised before use. 2-Methoxy-5- and -3-nitropyridines were prepared by the reaction of the corresponding chloro compound with sodium methoxide in methanol.[4,5] The 2-(3-substituted phenoxy)-5-nitropyridines were formed by the action of the sodium salt of the corresponding phenoxide in water on 2-chloro-5-nitropyridine. The reaction of the corresponding sodium halide in acetic acid on 2-chloro-5-nitropyridine gave 2-bromo- and -iodo-5-nitropyridine.[6,7]

The corresponding hydroxynitropyridines (nitropyridones) were made by the action of concentrated hydrochloric and acetic acids on 2-chloro-5- and -3-nitropyridines.[8,9] Alkylation of the substituted pyridines with methyl iodide gave the corresponding 2- and 4-substituted pyridine methiodides. All substrates had physical properties in good agreement with literature values.

Kinetic Measurements.—These were carried out exactly as previously described.[2,3]

Reaction Products.—Isolation of the reaction products gave, upon acidification, quantitative yields of the hydroxypyridines (pyridones) for *all* substrates. For the nitropyridines having



methoxy or phenoxy leaving groups and all other substrates, confirmation of the reaction products as being the anions of the corresponding hydroxypyridine (pyridone) was made spectroscopically as previously described.[2] The reaction is considered to proceed as shown in equation (i). However, the spectrophotometric identification of the hydrolysis product of the 2-halogeno-5-nitropyridines and 2-chloro-3-nitropyridine indicated species having $\lambda_{max.}$ 377 and 400 nm, respectively. The corresponding products from other 2- or 3-substituted substrates *and* the isolated products in base solution had $\lambda_{max.}$ 388 and 420 nm, respectively. Examination of the *in situ* hydrolysis products of the halogenonitropyridines by ^{1}H n.m.r. spectroscopy indicated that they were different to the isolated products redissolved in base, *i.e.* (**III**). The *in situ* products gave spectra which clearly showed a formyl hydrogen, as well as two olefinic hydrogens. These products appeared to be the result of a primary addition to the 6-position,[10] followed by ring fission, as shown in equation (ii). After acidification and normal work-up, involving cyclisation and hydrolysis, the 2-hydroxypyridine (2-pyridone) is isolated.

Results

The reactions between the substituted pyridines and hydroxide anions were confirmed to be overall of the second order, first order in each species. TMAH was always in large excess and thus the reactions approximated to first-order behaviour. The rate coefficients were calculated as previously described[2] as first-order rate coefficients, $k_{obs.}$. Values of the H_- acidity function for aqueous DMSO containing 1.10×10^{-2}M-TMAH were interpolated graphically from the values of Dolman and Stewart.[11] The values of log a_w were calculated as described previously.[2]

The acidity function and the rate coefficients for the reactions are shown in Table 1. The rate coefficients were reproducible to ±3% and solvent compositions to ±0.2%.

The only reaction that gave evidence of the formation of a persistent coloured complex was the reaction of 2-methoxy-3-nitropyridine with base. An orange intermediate was formed

Table 1. Rate coefficients for the alkaline hydrolysis of substituted nitropyridines, 4-nitropyridine *N*-oxide, and substituted pyridine methiodides in aqueous DMSO containing 1.10×10^{-2}M-TMAH at 30.0 °C, together with the acidity functions

2-Methoxy-5-nitropyridine

mol% DMSO	35.04	44.57	50.35	57.12	65.07	69.55	74.47	79.93		
$H_- + \log a_w$	15.74	16.52	16.95	17.58	18.21	18.57	18.92	19.36		
$10^3 k_{obs}/s^{-1}$	0.112	0.284	0.556	1.09	2.57	4.59	8.81	15.8		

2-Phenoxy-5-nitropyridine

mol% DMSO	27.58	35.04	44.57	50.35	57.12	65.07	69.55	74.47	79.93	85.88
$H_- + \log a_w$	15.15	15.74	16.52	16.95	17.58	18.21	18.57	18.92	19.36	19.91
$10^3 k_{obs}/s^{-1}$	0.0226	0.0639	0.236	0.537	1.16	3.42	6.24	12.6	25.6	53.2

2-(*m*-Methylphenoxy)-5-nitropyridine

mol% DMSO	27.58	35.04	44.57	50.35	57.12	65.07	69.55	74.47	79.93	85.88
$H_- + \log a_w$	15.15	15.74	16.52	16.95	17.58	18.21	18.57	18.92	19.36	19.91
$10^3 k_{obs}/s^{-1}$	0.0219	0.0569	0.215	0.403	1.02	2.49	4.39	10.5	19.6	45.8

2-(*m*-Chlorophenoxy)-5-nitropyridine

mol% DMSO	44.57	50.35	57.12	60.12	65.07	69.55	74.47	79.93
$H_- + \log a_w$	16.52	16.95	17.58	17.88	18.21	18.57	18.92	19.36
$10^3 k_{obs}/s^{-1}$	0.567	1.30	3.69	5.91	10.4	19.1	36.6	61.5

2-(*m*-Nitrophenoxy)-5-nitropyridine

mol% DMSO	35.04	44.57	50.35	57.12	60.92	65.07	69.55
$H_- + \log a_w$	15.74	16.52	16.95	17.58	17.88	18.21	18.57
$10^3 k_{obs}/s^{-1}$	0.451	1.94	4.42	10.3	17.1	29.1	53.7

2-Chloro-5-nitropyridine*

mol% DMSO	12.49	14.47	19.00	21.57	24.42	27.58	31.11	35.04	39.44
$H_- + \log a_w$	13.44	13.64	14.16	14.46	14.76	15.12	15.42	15.74	16.08
$10^3 k_{obs}/s^{-1}$	0.396	0.708	2.46	4.44	7.57	10.6	19.2	27.4	70.9

2-Bromo-5-nitropyridine*

mol% DMSO	5.97	8.99	14.47	19.00	24.42	27.58	35.04
$H_- + \log a_w$	12.52	12.84	13.64	14.16	14.76	15.12	15.74
$10^3 k_{obs}/s^{-1}$	0.465	0.685	2.24	3.65	8.64	12.2	36.0

2-Iodo-5-nitropyridine*

mol% DMSO	14.47	19.00	21.57	24.42	27.58	31.11	35.04	39.44
$H_- + \log a_w$	13.64	14.16	14.46	14.76	15.12	15.42	15.74	16.08
$10^3 k_{obs}/s^{-1}$	0.751	2.36	3.52	4.96	8.84	13.2	22.9	45.2

2-Methoxy-3-nitropyridine

mol% DMSO	74.47	79.93	85.88	92.60	98.45
$H_- + \log a_w$	18.92	19.36	19.91	20.62	21.29
$10^3 k_{obs}/s^{-1}$	0.549	1.21	3.05	19.4	35.8

2-Chloro-3-nitropyridine*

mol% DMSO	19.00	27.58	35.04	44.57	50.35	57.12
$H_- + \log a_w$	14.16	15.12	15.74	16.52	16.95	17.58
$10^3 k_{obs}/s^{-1}$	0.249	1.45	5.07	20.3	59.1	112

4-Nitropyridine *N*-oxide

mol% DMSO	35.04	44.57	50.35	57.12	65.07
$H_- + \log a_w$	15.74	16.52	16.95	17.58	18.21
$10^3 k_{obs}/s^{-1}$	0.186	0.402	0.552	1.27	2.31

4-Chloropyridine methiodide

mol% DMSO	5.97	9.83	14.46	20.26	27.57	32.05
$H_- + \log a_w$	12.52	13.05	13.67	14.34	15.05	15.44
$10^3 k_{obs}/s^{-1}$	0.594	1.12	2.42	7.25	26.3	54.3

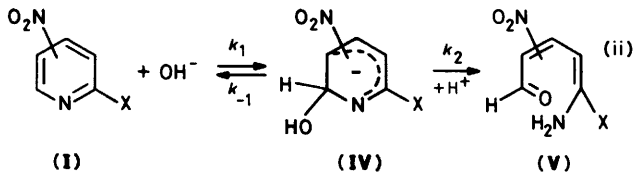
2-Methoxypyridine methiodide

mol% DMSO	0.0	2.70	5.97	9.83	14.46	20.26
$H_- + \log a_w$	11.64	12.05	12.52	13.05	13.67	14.34
$10^3 k_{obs}/s^{-1}$	0.733	1.35	2.70	6.10	15.6	53.8

Table (*continued*)

				2-Chloropyridine methiodide		
mol% DMSO	0.0	2.70	5.97	9.83		
H_- + log a_w	11.64	12.05	12.52	13.05		
$10^3k_{obs}/s^{-1}$	15.2	27.2	51.2	107		
				2-Bromopyridine methiodide		
mol% DMSO	0.0	2.70	5.97	9.83	14.46	
H_- + log a_w	11.64	12.05	12.52	13.05	13.67	
$10^3k_{obs}/s^{-1}$	10.9$_5$	19.5	32.5	67.0	168	
				2-Iodopyridine methiodide		
mol% DMSO	0.0	2.70	5.97	9.83	14.46	20.26
H_- + log a_w	11.64	12.05	12.52	13.05	13.67	14.34
$10^3k_{obs}/s^{-1}$	2.59	3.62	6.54	14.0	31.6	113

* Products of kinetic reaction, not normal hydrolysis product (see Experimental section).



(I) (IV) (V)

above 80 mol% aqueous DMSO that absorbed in the region 350—370 nm. The rates of decay of the immediate were measured at 360 nm and the rate coefficients are given in Table 2.

The reaction rates and acidity function were correlated by a least-squares method. The acidity function, H_- + log a_w, approximates to J_-.[12] Constants of equation (iii) are given in Table 3.

$$\log k_{obs} = l(H_- + \log a_w) + c \qquad \text{(iii)}$$

Discussion

Good linear relationships are observed between log k_{obs} and H_- + log a_w for the reactions between the substituted pyridines and hydroxide anions. The reactions are of two types: ring fission and substitution. These will be discussed separately. However, for both reactions, k_{obs} can be equal to the rate of formation of the intermediate or to the product of the pre-equilibrium forming the intermediate and its rate of decomposition. It seems very likely that, for these activated substrates, the addition step is rate determining.[2,3]

The ring fission occurs for halogeno-substituted nitropyridines. It is known that Meisenheimer complexes can be readily formed by highly activated pyridines.[13] The halogeno groups assist in activation of the 6-position and must switch the reactivity in favour of formation of 6-adduct (**II**). This can protonate at the nitrogen to give the neutral intermediate (**VI**), a covalent hydrate. The latter can suffer base-catalysed tautomerisation to give the aldehyde (**III**). The addition of hydroxide anion to substituted pyridinium salts, followed by ring fission to form derivatives of glutaconic aldehyde, have been studied in detail by Kavalek *et al.*[14] Reversible hydration has been investigated in many nitrogen heterocycles.[15]

The substitution reaction occurs for methoxy- and phenoxy-substituted nitropyridines, 4-nitropyridine *N*-oxide, and substituted pyridine methiodides. For the 2-substituted 5-nitropyridine series the reactivities are in the order: *m*-nitrophenoxy > *m*-chlorophenoxy > methoxy ~ phenoxy > *m*-methylphenoxy. For the 2-substituted pyridine methiodides the reactivities are in the order: chloro > bromo > iodo > methoxy. The reactivity trends agree well with those quoted for similar

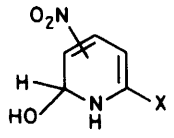
Table 2. Rate coefficients for the decay of the intermediate from 2-methoxy-3-nitropyridine in aqueous DMSO containing 1.10 × 10^{-2}M-TMAH at 30 °C, together with the acidity functions

mol% DMSO	85.88	89.78	92.60	98.45
H_- + log a_w	19.91	20.26	20.62	20.92
$10^3k_{obs}/s^{-1}$	4.45	10.2	16.0	20.0

Table 3. Regression analysis for equation (iii) correlating the reactions of substituted pyridines in aqueous DMSO containing 1.10 × 10^{-2}M-TMAH at 30.0 °C

Substrate	*l*	*c*	Correlation coefficient
2-Methoxy-5-nitropyridine	0.60	−13.37	0.995
2-Phenoxy-5-nitropyridine	0.71	−15.34	0.999
2-(*m*-Nitrophenoxy)-5-nitropyridine	0.72	−14.68	0.997
2-(*m*-Methylphenoxy)-5-nitropyridine	0.69	−15.13	0.998
2-(*m*-Chlorophenoxy)-5-nitropyridine	0.72	−15.16	0.998
2-Chloro-5-nitropyridine*	0.80	−13.99	0.983
2-Bromo-5-nitropyridine*	0.57	−10.48	0.995
2-Iodo-5-nitropyridine*	0.69	−12.46	0.992
2-Chloro-3-nitropyridine*	0.81	−15.03	0.993
2-Methoxy-3-nitropyridine	0.90	−20.36	0.984
4-Nitropyridine *N*-oxide	0.45	−10.81	0.993
4-Chloropyridine methiodide	0.60	−10.63	0.982
2-Methoxypyridine methiodide	0.68	−11.12	0.999
2-Chloropyridine methiodide	0.60	−8.79	1.000
2-Bromopyridine methiodide	0.58	−8.67	0.999
2-Iodopyridine methiodide	0.61	−9.73	0.994

* Products of kinetic reaction, not normal hydrolysis product (see Experimental section). Rate at highest DMSO content omitted.



(VI)

substrates in the literature.[16–18] It is clear that the substrates are reacting with hydroxide by the S_NAr pathway.[16] The mechanism is that shown in reaction (i) with the rate-determining step being the addition of the nucleophile to the ring, k_1. The effect of substituents in the phenoxy group for the 2-phenoxy-5-nitropyridine system has been examined. The Hammett equation correlations are shown in Table 4. The ρ value found of *ca.* 1.3 is significantly greater than that of *ca.* 0.7 found for the same reaction of 1-(substituted phenoxy)-2,4-dinitrobenzenes.[3] This appears to indicate that the reaction is significantly advanced for the nitropyridine system.

Table 4. Hammett correlations for the substitution in the phenoxy group of 2-phenoxy-5-nitropyridine*

Solvent	ρ	$\log k_0$	s	r	n
57.12 mol% DMSO–water	1.31	−3.22	0.03	0.998	4
69.55 mol% DMSO–water	1.37	−2.60	0.05	0.996	4

* r is the correlation coefficient, s the standard deviation, and n the number of substituents.

The justification of the linear relationships between log k_{obs} and the acidity function has been examined previously.[2] In this study,[2] the slopes of the linear relationships have been interpreted to indicate to what extent the transition state resembles the indicator anions constructing the scale and/or to the extent the transition state has advanced. It has been suggested that the slopes are a function of a reactivity–selectivity relation.[2] The evidence for such principles has been reviewed[19] and a lack of support has been found. The present results, in conjunction with the previous ones,[2,3] do *not* show a general relationship of this type. Thus the pyridine methiodides, which are significantly more reactive than the 5-nitropyridine systems undergoing substitution, have comparable slopes (see Table 3). Likewise the 2,4-dinitrobenzene system[3] is more reactive than the 5-nitropyridines, but comparison of similarly substituted examples indicate larger slopes for the 2,4-dinitrobenzene system. The slopes of the correlations appear to be determined, in the main, by the requirements for protic solvation in going from the initial to the transition state. An advanced transition state will give rise to an increase in l as less protic solvation will be required. A less advanced transition state can arise from either a reactive substrate or a substrate having steric interactions in and around the reaction site. A substrate can have substituents which require significantly different protic solvation in the transition state than did the defining indicator anions. The present study indicates that there appears to be little dependence of the slope l on substrate reactivity.

Meisenheimer intermediates[20] have been observed in related systems. Only for 2-methoxy-3-nitropyridine has a Meisenheimer intermediate been observed in this study. The latter substrate also shows some curvature of the rate–acidity function correlation at high basicity. In a previous study[3] of the 2,4-dinitrobenzene system such intermediates and curvatures were observed above *ca.* 50 mol% DMSO; while, for the nitrobenzene systems, no such behaviour occurs. The conditions necessary for the observation of such intermediates appear to be two-fold. First, sufficient strongly activating substituents must be present to stabilise the intermediates. Second, the reaction must be occurring in a solvent system capable of sustaining the intermediates, *i.e.* aqueous DMSO rich in DMSO. The 2-methoxy- and -phenoxy-5-nitropyridines appear to be too reactive for the observation of Meisenheimer intermediates in this system; reaction occurring rapidly at a low DMSO contents. The pyridine *N*-oxide and pyridine methiodide systems are not sufficiently substituted with activating substituents for such observations.

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