Acid-catalysed aryl hydroxylation of phenylazopyridines: reaction intermediates, kinetics and mechanism[1]

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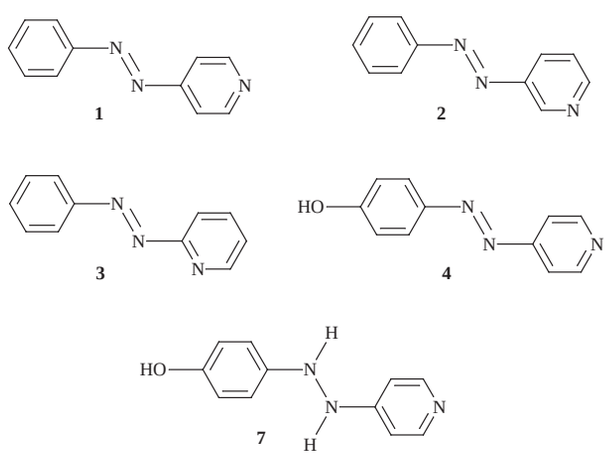
A kinetic and product analysis study of the reactions of the three isomeric phenylazopyridines (PAPys) in aqueous sulfuric acid media (30–97 wt% H_2SO_4) is reported. The final products obtained from the reaction of 4-(phenylazo)pyridine (4-PAPy) are the hydroxylated product 4-(4-hydroxyphenylazo)pyridine, the reduction products 4-aminophenol and 4-aminopyridine, and a small amount of a dimerized product. 3-(Phenylazo)pyridine is unreactive, but 2-(phenylazo)pyridine gives the equivalent 2-(4-hydroxyphenylazo)pyridine, 4-aminophenol and 2-aminopyridine products. This product pattern, an oxidized azo-compound and two reduced amines, is similar to that found in the disproportionation of di-*p*-substituted hydrazinobenzenes observed in benzidine rearrangement studies. Consequently it has been proposed that the corresponding [*N*′-(4-hydroxyphenylhydrazino)]pyridines were formed as reaction intermediates in the present system; this is confirmed by showing that [*N*′-4-(4-hydroxyphenylhydrazino)-pyridine synthesized independently gave the same products as 4-PAPy under the same conditions. The kinetic study shows that the 4-isomer reacted faster than the 2-isomer at all the acid concentrations investigated (the 3-isomer being inert). Rate maxima are observed, at ~72 wt% H_2SO_4 for 4-PAPy and ~86 wt% H_2SO_4 for 2-PAPy. To facilitate the kinetic analysis, values of $pK_{BH_2^{2+}}$ for the protonation of the substrates and the possible hydroxy products at the azo-group were determined, using the excess acidity method; the first protonation occurs on the pyridine nitrogen in the pH region. An excess acidity analysis of the observed pseudo-first-order rate constants as a function of acidity indicate an A2 mechanism, with the diprotonated substrate and either one HSO_4^- ion or one H_2O molecule in the activated complex. The proposed mechanism thus involves nucleophilic attack of HSO_4^- or H_2O at an aryl carbon of the diprotonated substrate in the slow step, resulting in an intermediate hydrazo species which gives the observed products in a subsequent fast step (*cf.* benzidine rearrangement).

Our previous studies of azo and azoxy dye molecules have revealed a remarkable range of structure–activity relationships and a wealth of mechanistic variety.[2–14] As background to the present study the following can be highlighted: (*i*) elucidation of the mechanisms of the Wallach rearrangement of azoxyarenes,[2–5,9] including the role of mono-, di- and tri-protonation processes with changes in mechanism as a function of structure,[3,5,6] the $>10^4$ reactivity difference of the isomeric α- and β-phenylazoxypyridines[6] and the varied tautomeric behaviour of the derived hydroxyphenylazopyridines,[7] (*ii*) the remarkably facile hydrolysis of aryl azo ethers in acid media, with protonation on nitrogen, oxygen or carbon centres occurring as fast equilibria or as the rate-determining step[10,13] and (*iii*) the synthesis and electronic spectral characteristics of novel azo merocyanine dyes.[11] The latter exhibit solvatochromism, which has led to the establishment of the π^*_{azo} solvent polarity scale.[12]

The present study is concerned with our observation that, unexpectedly, phenylazopyridine itself is unstable in acid media, undergoing aryl hydroxylation† as one of the primary processes. However, reactivity varies markedly as a function of structure, in the order 4-phenylazopyridine (4-PAPy, **1**) > 2-phenylazopyridine (2-PAPy, **3**) ≫ 3-phenylazopyridine (3-PAPy, **2**). A kinetic and product analysis study has shown that, in the case of **1**, alongside the hydroxylated product 4-(4-hydroxyphenylazo)pyridine (**4**), 4-aminophenol and 4-aminopyridine are formed as well. This pattern—an oxidized azo product and two reduced amino products–is reminiscent of that found in the benzidine rearrangement,[14] disproportionation of hydrazinobenzene substrates being found in some cases.[14,15] Elucidation of the mechanism of the disproportionation process, and its relationship to the classical benzidine rearrangement,[2,14,16] is the subject of this and the accompanying paper.[17] Central to the discussion is the evidence we have obtained for the formation of phenylhydrazinopyridines, *e.g.* **7**, as transient intermediates in the disproportionation.



† One of the referees has suggested that this reaction should be referred to as a hydration rather than as a hydroxylation, since the latter term implies a positively charged reagent. Although this is formally correct, we prefer to use the term hydroxylation to distinguish this reaction from the quite different ones usually associated with the term hydration (carbonyl hydration, alkene hydration) where the added atoms are adjacent. Here the added H and OH from the water molecule end up 5 (or 6) atoms apart (**1**→**7**, Scheme 2).

The technique used to analyse the observed rate constants is the excess acidity method,[18] which has seen extensive use in recent years for the determination of reaction mechanisms in aqueous strong acid media; for instance, aromatic hydrogen exchange processes,[19] imidazoline cyclizations,[20] alkene hydrations,[21] ether hydrolyses,[13,22] thioacetal hydrolyses[23] and many other reactions have been studied. Most recently it has been used to determine the acid hydrolysis mechanisms of alkylnitramines[24] and nitramide,[25] several *N*-nitro amides[26] and acylimidazoles.[27] The equilibrium version of the excess acidity method[28–30] was used in the determination of the $pK_{BH_2^{2+}}$ values, avoiding the use of acidity functions.[31]

Experimental

Characterization

The compounds synthesized were characterized by a combination of ^1H and ^{13}C NMR, UV, IR and mass spectroscopic methods, by melting point and, in the case of new compounds, elemental analysis. The NMR spectra were obtained on a Bruker AM400 (^1H, 400.1 MHz; ^{13}C, 100.6 MHz) or a Bruker AC-F200 spectrometer (^1H, 200.1 MHz; ^{13}C, 50.3 MHz). Normally $CDCl_3$ and [$^2H_6$]DMSO were used as the solvents and served as deuterium lock standards. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (δ 7.24) and DMSO (δ 2.50) in the solvent. Integral ratios supported the NMR assignments reported. IR spectra were recorded on a Bomen MB-120 spectrophotometer with samples prepared as KBr disks. GC results were obtained using a Carlo Erba GC 8000 instrument. The MS results were recorded using a Fison's VG Quattro (Triple-Quadrupole MS/MS) spectrometer; several techniques were used, electron impact, chemical ionization (CI), electrospray (ES) and fast atom bombardment (FAB). The ES mass results were obtained by flow injection analysis using a Carlo Erba HPLC 20 instrument; for CI the reagents used were isobutene, methane and ammonia; for FAB a matrix of either glycerol or nitrobenzyl alcohol was used. UV–VIS absorption spectra were obtained using a Hewlett–Packard HP8452A Diode Array spectrophotometer fitted with a thermostatted cell compartment. Melting points were measured with a Thomas Hoover apparatus and are uncorrected.

Common reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified. Compounds were purified by several techniques, recrystallization, column and thin layer chromatography (TLC) using silica gel 60 F_{254} plates (BDH) in various eluting solvent systems.

Syntheses

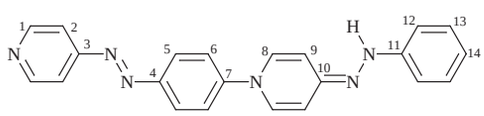
The isomeric phenylazopyridines **1**–**3** were prepared by the condensation of nitrosobenzene with 4-, 3- and 2-aminopyridine, respectively, according to the method of Brown and Granneman.[32] In this work the procedure was modified by using tetramethylammonium hydroxide as a base instead of 50% aq. NaOH, allowing workup under homogeneous conditions. The yields obtained were: **1**, 73.1%, mp 97–98 °C (lit.,[32] 98–99 °C); **2**, 50.0%, mp 50–51 °C (lit.,[32] 52 °C); **3**, 38.0%, mp 32–33 °C (lit.,[32] 33–34 °C).

4-(4-Hydroxyphenylazo)pyridine **4** was prepared by a modified diazo coupling procedure (*in situ* diazo coupling). A solution of $NaNO_2$ (4.0 g, 0.058 mol) in water (20 ml) was added to a solution of phenol (5.0 g, 0.053 mol) in 10% aq. NaOH (45 ml) and the mixture cooled to 0 °C. The resulting solution was then added slowly with stirring to a solution of 4-aminopyridine (6.0 g, 0.064 mol) in aqueous HCl (25 ml conc. HCl in 16 ml water) while keeping the temperature at 0 °C. The pH was then adjusted to ~6 using 1 M aq. Na_2CO_3. The yellowish precipitate that formed was filtered off and the crude product recrystallized from ethanol to give 2.3 g (22% yield) of reddish yellow crystals, mp 255–256 °C (decomp.) (lit.,[33] mp 252–253 °C). 3-(4-Hydroxyphenylazo)pyridine (**5**) was prepared by coupling the diazonium salt of 3-aminopyridine with phenol. The product was purified by recrystallization from ethanol, yield 87%, mp 220–222 °C (Found: C, 66.0; H, 4.3; N, 20.4. Calc. for $C_{11}H_9N_3O$: C, 66.3; H, 4.5; N, 21.1%). 2-(4-Hydroxyphenylazo)pyridine (**6**) was prepared by the oxidative coupling reaction of 2-hydrazinopyridine with *p*-benzoquinone according to the method of Betteridge and John;[34] the pure compound was obtained by recrystallization from ethanol, yield 77.4%, mp 230–231 °C (lit.,[34] 230–231 °C).

[*N*′-4-(4-Hydroxyphenylhydrazino)]pyridine **7** was prepared by a method similar to that used for the preparation of hydrazinobenzene,[35] *in situ* generation of the highly reactive diimide by the cupric ion-catalysed oxidation of hydrazine with hydrogen peroxide and reacting this with 4-(4-hydroxyphenylazo)-pyridine, giving the product in 33.0% yield, mp 258–259 °C.

Product analysis

Direct isolation was employed for product identification for the reactions of **1**, **3** and **7** in 65 wt% aq. H_2SO_4. The example of **1** is given: **1** (0.50 g, 0.0027 mol) was added slowly to 50 ml 65 wt% aq. H_2SO_4 in a round-bottom flask with stirring, giving a substrate concentration of 0.05 M. An aliquot of the reaction mixture was added to a UV cell containing 2.5 ml 65 wt% aq. H_2SO_4, in order to enable the progress of the reaction at 25 °C to be followed. After the reaction was complete according to UV–VIS spectroscopy, the reaction mixture was diluted fourfold with water, and the solution neutralized (pH 7) with sodium carbonate, cooling throughout. The precipitate which formed was filtered off and the filtrate extracted three times with ethyl acetate. The ethyl acetate layer was dried ($MgSO_4$), evaporated on a rotary evaporator, and the residue dried under reduced pressure. The dried extract and the precipitate were combined and dissolved in methanol (5 ml), and the concentrated solution developed on a preparative TLC plate (0.25 mm thickness) with 200 ml of a mixture of 9 parts chloroform to 1 part ethanol. Some of the methanolic solution was also taken for GC–MS analysis. Several bands were visible on the TLC plate after development was complete. Each band was scraped off, added to a solvent (ethanol or ethyl acetate) which was expected to dissolve the component, and the slurry filtered to remove the silica gel. Each fraction was subjected to rotary evaporation and reduced pressure drying overnight, and the isolated products identified by UV–VIS, NMR and MS analysis.



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The structural identification of the dimeric product **8**, formed during the reaction of **1**, was achieved using ^1H and ^{13}C NMR spectroscopy, and MS. δ_H([$^2H_6$]DMSO) 8.74 (H^1), 7.66 (H^2), 7.88 (H^5), 7.16 (H^6), 8.16 (H^8), 6.74 (H^9), 7.45 (H^{12}), 7.45 (H^{13}), 7.21 (H^{14}), 9.78 (NH). δ_C([$^2H_6$]DMSO) 151.41 (C^1), 115.90 (C^2), 146.05 (C^3), 143.60 (C^4), 125.51 (C^5), 115.40 (C^6), 153.14 (C^7), 150.16 (C^8), 106.60 (C^9), 157.00 (C^{10}), 150.70 (C^{11}), 122.94 (C^{12}), 129.80 (C^{13}), 125.57 (C^{14}); *m*/*z* (CI^+) 367.2 (M + 1).

$pK_{BH_2^{2+}}$ determination

The $pK_{BH_2^{2+}}$ values of the azo substrates **1**–**3**, and the three possible hydroxylated products, **4** and the corresponding 3- and 2-pyridine isomers, **5** and **6**, in aqueous sulfuric acid were determined using UV–VIS spectroscopy. Sulfuric acid solutions of known concentration were prepared by carefully adding appropriate weights of conc. H_2SO_4 with cooling to a 250 ml

Table 1 Isolated products and yields in the reactions of **1**, **3** and **7** in 65 wt% H_2SO_4

Substrate	Product	Yield (%)	Total Yield (%)
1	4-(4-Hydroxyphenylazo)pyridine **4**	22	92
	4-Aminopyridine	19	
	4-Aminophenol	20	
	Dimeric product **8**	31	
3	2-(4-Hydroxyphenylazo)pyridine **6**	30	91
	2-Aminopyridine	29	
	4-Aminophenol	32	
7	4-(4-Hydroxyphenylazo)pyridine **4**	26	72
	4-Aminopyridine	22	
	4-Aminophenol	24	

reagent bottle containing preweighed distilled deionized water, determining their accurate concentrations by titration with sodium hydroxide solution which had been standardized with potassium hydrogen phthalate.

Stock solutions of the compounds were prepared from accurate mass samples (10–15 mg), dissolved in freshly distilled ethanol in 5 ml volumetric flasks, giving concentrations of 0.010–0.018 M. The flasks were wrapped in aluminium foil to avoid the possible occurrence of photochemical processes. A 10 μl aliquot of the stock solution was transferred to a 1 cm quartz UV cell containing 2.5 ml of the appropriate sulfuric acid which had been thermostatted at 25 °C for at least 10 min to allow thermal equilibration. The final substrate concentration in the cell was ~$6–7 \times 10^{-5}$ M. After shaking the UV cell the spectrum was recorded within 10 s, since the absorbance of the azo compounds examined in this study was found to be time-dependent.

Kinetic studies

All reactions were followed spectrophotometrically using a Hewlett–Packard HP8452A diode array UV–VIS spectrophotometer fitted with a thermostatted cell holder. Reactions were monitored by repetitive wavelength scanning (200–700 nm), for the presence or absence of an observable intermediate during the course of the reaction. All kinetic runs were performed in duplicate.

A 10 μl aliquot of the relevant stock solution was transferred by syringe into the thermostatted cuvette containing 2.5 ml of the relevant sulfuric acid solution, the cell shaken vigorously and placed in the instrument, and overlay scanning begun. Rate constants were obtained mainly by following the disappearance of the absorption due to the substrate; in some cases the appearance of products was also monitored, to elucidate the complexity of the reaction. Each reaction was followed for at least three half-lives, and an infinity absorbance value (A_∞) was obtained after 10. Pseudo-first-order rate constants (k_Ψ) were obtained by least-squares linear regression; the goodness of the first-order fit was first evaluated by examining a plot of absorbance *vs.* time, and then k_Ψ values obtained from slopes of plots of ln ($A_\infty - A_t$) *vs.* time.

Results

Products

Scheme 1 contains all of the observed products for all of the reactions. The products from the reactions of **1**, **3** and **7** in 65 wt% H_2SO_4, substrate concentration ~0.05 M, isolated and characterized as explained in the Experimental section, are given in Table 1, together with the isolated yields of each one. Although reaction was complete according to UV–VIS monitoring, some starting material remained in the cases of **1** and **3**, and so the yields in Table 1 are calculated from the actual amount of substrate reacted; losses during the preparative TLC separation would account for the less than 100% recovery.

In the case of **1**, the percent yield of the hydroxy product **4** and of the dimeric product **8** as a function of acid concentration could be obtained directly from the final UV–VIS kinetic scans, using the known λ_{max} values of the authentic compounds. These are summarized in Table 2; the yields of the amine products (4-aminophenol and 4-aminopyridine) could not be obtained directly due to their overlapping λ_{max} values. However, the yield of **4** decreases with increasing acidity, which means that other processes must become more important as the acidity increases; this point will be discussed in a following paper.[17] Interestingly the dimeric product **8** is only formed in the range of 2–9% at concentrations used in the UV–VIS study, whereas it is generated in much higher amounts (~30%) at the 0.05 M concentration used for Table 1 results; this is reasonable for a bimolecular reaction. The yield of **8** also decreases with increasing acidity. We will discuss the mechanism of the formation of **8** elsewhere.[36]

Table 2 Percent yield of products **4** and **8** formed from **1** as a function of H_2SO_4 concentration[a]

$[H_2SO_4]$ (wt%)	Yield of **4** (%)	Yield of **8** (%)
53.69	48.2	9.4
59.96	43.7	9.2
64.99	43.2	9.8
71.67	43.6	7.1
75.86	37.5	8.4
81.36	21.9	4.7
85.98	12.1	2.7

[a] Initial substrate concentration: 6.13×10^{-5} M.

Table 3 $pK_{BH_2^{2+}}$ values obtained using the excess acidity method[a]

Compound	$pK_{BH_2^{2+}}$	m^*
1	−4.97 ± 0.22	0.807 ± 0.045
2	−6.59 ± 0.49	1.100 ± 0.098
3	−8.90 ± 0.89	1.07 ± 0.12
4	−3.07 ± 0.21	0.994 ± 0.089
5	−3.90 ± 0.16	1.246 ± 0.067
6	−4.09 ± 0.26	0.887 ± 0.077

[a] Errors quoted are standard deviations.

$pK_{BH_2^{2+}}$ values

The substrates **1**–**3** and the possible hydroxy products **4**–**6** are all protonated on the pyridine nitrogen in the pH range,[7] so the protonation of interest in this work is the second protonation at the azo group. UV–VIS spectra were obtained as a function of sulfuric acid concentration and absorbances were measured at wavelengths appropriate for the peak maxima of the protonated and diprotonated forms, A_{BH^+} and $A_{BH_2^{2+}}$. These were converted to extinction values and the differences ($\delta\varepsilon = \varepsilon_{BH^+} - \varepsilon_{BH_2^{2+}}$) calculated; this is the Davis–Geissman method,[37] preferred because errors due to small differences between the individual samples tend to cancel out when the difference is taken (these may cause irregular isosbestic point behaviour, for instance), and spectra of both forms contribute to the resulting $pK_{BH_2^{2+}}$ values. The latter were obtained using the excess acidity method; for equilibria the relevant equation is $\log I - \log C_{H^+} = pK_{BH_2^{2+}} + m^*X$, where C_{H^+} is the proton concentration in the sulfuric acid solution and X is the excess acidity, both obtained from published sources.[28] The slope parameter m^* is characteristic of the substrate, having values of 1.0 for primary nitroanilines, 0.6 for amides, 1.4 for thio compounds, *etc.*[28] The ionization ratio I is given in terms of $\delta\varepsilon$ by $I = (\delta\varepsilon_{BH^+} - \delta\varepsilon)/(\delta\varepsilon - \delta\varepsilon_{BH_2^{2+}})$,[29] where $\delta\varepsilon_{BH^+}$ and $\delta\varepsilon_{BH_2^{2+}}$ apply to the pure monoprotonated form and the pure diprotonated form, respectively; this was substituted in the excess acidity equation and the resulting expression recast in terms of $\delta\varepsilon$ and curve-fitted directly, as before.[29] Previous experience[30] shows that this method gives reliable protonation constants; these molecules are actually simple cases, medium effects being negligibly small,

Table 4 Kinetic data for 4-PAPy, **1**

$[H_2SO_4]$ (wt%)	$k_\Psi/10^{-4}$ s^{-1} [a]	X [b]	log C_{H^+} [b]	log a_{H_2O} [c]	log $C_{HSO_4^-}$	PCT [d]	log k_Ψ − PCT
32.59	0.0621	1.179	0.718	1.553	0.476	−3.299	−1.908
	0.0625						−1.905
43.80	0.537	1.884	0.876	1.362	0.642	−2.572	−1.698
	0.535						−1.700
53.69	3.16	2.648	0.984	1.088	0.778	−1.852	−1.648
	3.17						−1.647
59.96	12.5	3.234	1.039	0.840	0.864	−1.339	−1.564
	12.3						−1.571
64.99	34.8	3.793	1.078	0.576	0.932	−0.888	−1.570
	34.1						−1.579
68.22	51.8	4.208	1.100	0.367	0.975	−0.597	−1.689
	52.8						−1.680
71.67	86.7	4.708	1.122	0.105	1.020	−0.324	−1.738
	85.4						−1.745
73.01	98.0	4.919	1.130	−0.009	1.037	−0.239	−1.770
	99.5						−1.763
75.86	88.5	5.397	1.144	−0.276	1.071	−0.112	−1.941
	88.0						−1.944
78.28	42.4	5.830	1.154	−0.537	1.096	−0.052	−2.321
	42.9						−2.316
81.36	23.6	6.407	1.157	−0.921	1.118	−0.018	−2.609
	23.8						−2.605
81.67	15.4	6.465	1.157	−0.962	1.119	−0.017	−2.795
	15.1						−2.804
85.98	6.6	7.274	1.118	−1.581	1.102	−0.004	−3.176
	6.6						−3.176
89.40	1.78	7.881	1.020	−2.113	1.019	−0.002	−3.748
	1.78						−3.748

[a] Observed pseudo-first-order rate constants; both duplicate determinations given. [b] From ref. 28. [c] From ref. 38, converted to molarity units (log 55.34 = 1.734 for pure water). [d] Protonation Correction Term; log $[C_{SH_2^{2+}}/(C_{SH^+} + C_{SH_2^{2+}})]$. Calculated using p$K_{BH_2^{2+}} = -4.97$ and $m^* = 0.807$ from Table 3.

Table 5 Kinetic data for 2-PAPy, **3**

$[H_2SO_4]$ (wt%)	$k_\Psi/10^{-4}$ s^{-1} [a]	X [b]	log C_{H^+} [b]	log $C_{HSO_4^-}$	PCT [c]	log k_Ψ − PCT
75.86	2.9	5.397	1.144	1.071	−2.003	−1.535
	2.7					−1.566
78.28	5.6	5.830	1.154	1.096	−1.539	−1.713
	5.7					−1.705
81.36	11.5	6.407	1.157	1.118	−0.958	−1.981
	11.7					−1.974
81.67	17.7	6.465	1.157	1.119	−0.904	−1.848
	17.9					−1.843
85.98	29.0	7.274	1.118	1.102	−0.312	−2.226
	29.2					−2.223
	29.3					−2.221
	29.0					−2.226
89.40	18.4	7.881	1.020	1.019	−0.113	−2.622
	18.6					−2.617
89.85	16.9	7.959	1.002	1.002	−0.098	−2.674
	16.7					−2.679
96.59	1.6	9.493	0.456	0.456	−0.009	−3.787
	1.5					−3.815

[a] Observed pseudo-first-order rate constants; all replicate determinations given. [b] From ref. 28. [c] Protonation Correction Term; log $[C_{SH_2^{2+}}/(C_{SH^+} + C_{SH_2^{2+}})]$. Calculated using p$K_{BH_2^{2+}} = -8.90$ and $m^* = 1.07$ from Table 3.

corresponding to Case 0 in ref. 29. The parameters given by the curve fit are $\delta\varepsilon_{BH^+}$, $\delta\varepsilon_{BH_2^{2+}}$, p$K_{BH_2^{2+}}$ and m^*; the latter two are listed for **1**–**6** in Table 3. The experimental data obtained and the values of X and log C_{H^+} used for **1**–**6** are given in Tables S1–S6 of the Supplementary material,‡ and the observed spectra as a function of acidity for **1**, **3** and **4** are given as Figs. S1–S3.

Kinetics

The kinetics of the reaction of the isomeric phenylazopyridines 4-PAPy (**1**) and 2-PAPy (**3**) were monitored spectrophotometrically by following the disappearance of the reactants, and occasionally by following product appearance. 3-PAPy (**2**) was found to be inert at any acid concentration. The observed pseudo-first-order rate constants as a function of acidity, and other parameters relevant to the kinetic analysis, are given in Tables 4 and 5. The behaviour of the rate constants as a function of sulfuric acid concentration is illustrated in Fig. 1.

The rate constants for 4-PAPy (Table 4) were obtained by following the disappearance of the substrate in either its monoprotonated SH^+ form, at 340 nm, or its diprotonated SH_2^{2+} form, at 414 nm, as appropriate at the acidity used. Similarly 2-PAPy was followed at 360 or 440 nm (Table 5). All the kinetic plots of ln $(A_\infty - A_t)$ *vs.* time showed excellent linearity over the typically three half-lives for which the reaction was followed. In the case of **1**, the 2–9% of the dimerization product found,

‡ Available as supplementary data (SUPPL. NO 57360, pp. 11) from the British Library. For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC Web page (http://www.rsc.org/authors).

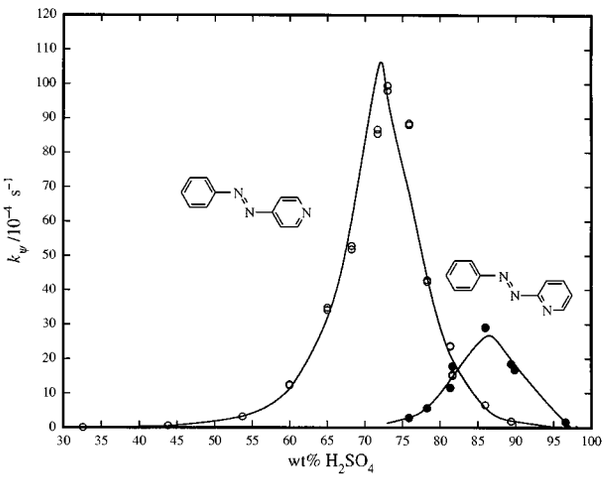


Fig. 1 Rate constants for the reactions of **1**, 4-PAPy (○) and **3**, 2-PAPy (●) as a function of sulfuric acid concentration. The points are experimental and the curves theoretical, see text.

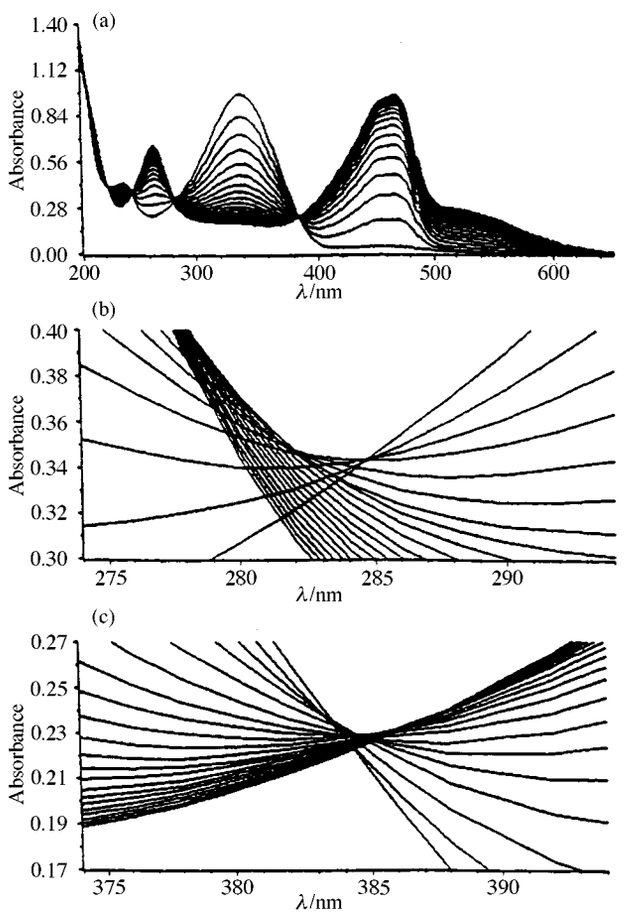


Fig. 2 UV–VIS overlay spectra for the reaction of **1** (a) in 53.69 wt% H_2SO_4, (b) enlargement of 285 nm region and (c) enlargement of 385 nm region, illustrating the diffuse isosbestic points

presumably second-order in the substrate, did not affect the linearity of the first-order plots, and the kinetics were treated as first-order throughout. If the first-order kinetic treatment was inappropriate then systematic deviation from the first-order plots would be visible and the observed excellent linearity found would not have been seen. Despite this, tight isosbestic point behaviour for the spectral scans as a function of time was not observed; this is illustrated in Fig. 2 for **1**, and is taken as evidence for the formation of an intermediate during the reaction (*vide infra*).

Discussion

Reaction pathways

We have found that the course of the reactions of 4-(phenylazo)-pyridine (4-PAPy, **1**) and (2-(phenylazo)pyridine (2-PAPy, **3**) in aqueous sulfuric acid gives rise to a diverse set of products, as shown in Scheme 1. Significantly, a similar pattern of products from either substrate is revealed; the hydroxylated azo product, aminophenol and aminopyridine. In contrast, the isomeric 3-(phenylazo)pyridine (3-PAPy, **3**) was unreactive under corresponding conditions.

The pattern of products formed from the reactions of 4-PAPy and 2-PAPy is notably similar to the products formed from the disproportionation of hydrazinobenzenes,[14–16] namely an oxidized azo product and two reduced amine products. On this basis one could propose that the present systems involve the formation of a hydrazino species, *i.e.* [*N*′-4-(4-hydroxyphenylhydrazino)]pyridine (**7**), as a reaction intermediate (from 4-PAPy) and the 2-isomer for 2-PAPy. Hereafter 4-PAPy will become the focus of discussion, since 2-PAPy yields corresponding products with the exception of the dimeric side product.

If, indeed, **7** is formed as an intermediate in the reaction of **1** then its presence might be detectable spectroscopically. In general, the existence of an intermediate can be inferred by the absence of, or lack of clean, isosbestic points during kinetic runs. Fig. 2 shows the isosbestic point regions of UV–VIS repetitive scan kinetics for 4-PAPy in 53.7 wt% H_2SO_4. The isosbestic points are quite unfocussed. The same behaviour was found for 2-PAPy. This can be taken as evidence for the presence of an intermediate in the reactions of 4-PAPy and 2-PAPy in aqueous sulfuric acid.

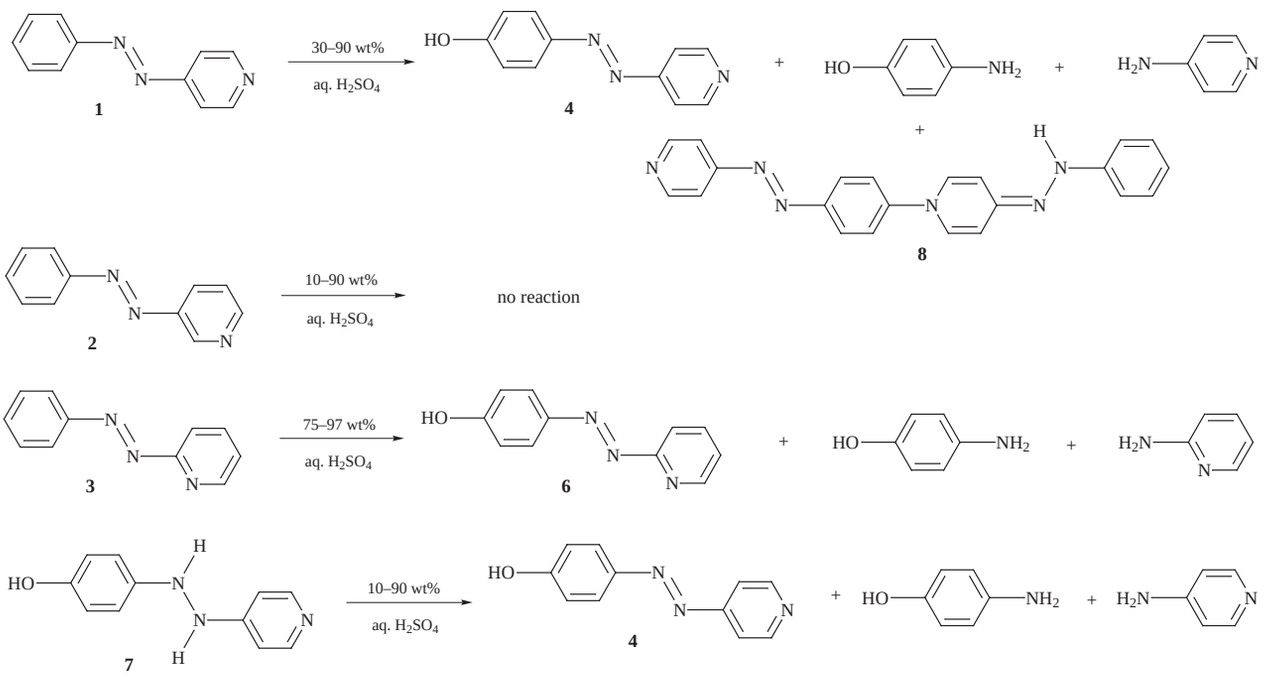
The proposed intermediate, [*N*′-4-(4-hydroxyphenylhydrazino)]pyridine (**7**), was not directly observable in the reaction of **1** as a species with a characteristic UV–VIS spectrum, so it was synthesized separately and investigated under the same acid concentration conditions as used for the reaction of **1**. As can be seen from Table 1, exactly the same products with very similar product distributions are formed from the reactions of both **1** and **7**. Thus the relationship between **1** and **7** must be that shown in Scheme 2. However, there is one notable difference between the reactions of **1** and **7**: the dimeric side product **8** formed during the reaction of **1** was not found in the reaction of **7**. This point will be discussed further elsewhere.[36]

There are two main steps proposed in Scheme 2, hydroxylation with concurrent reduction, and disproportionation. Hydroxylation is the slow step in the reaction of **1**, which is consistent with the fact that **7** was not observed spectrally in the repetitively scanned UV–VIS spectra of **1** in aqueous H_2SO_4. On the contrary, if hydroxylation was fast and disproportionation was the rate-determining step, the hydrazino intermediate would accumulate and be spectrally observable. In fact the kinetic experiments with authentic (separately prepared) **7**[17] show that k_d, the rate constant for disproportionation, is at least 150 times greater than k_h, the rate constant for hydroxylation, determined for **1** in this work.

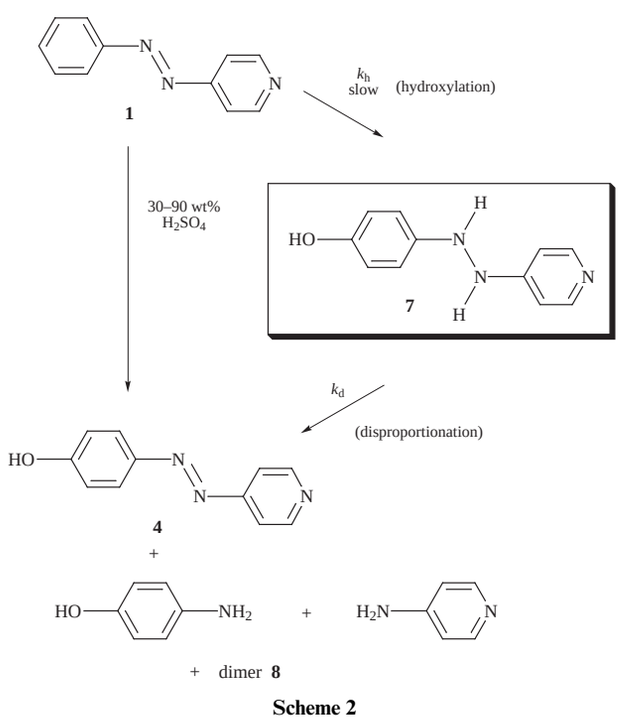
Based on the fact that the disproportionation of **7** is much faster than the hydroxylation of **1**, a qualitative energy profile for the **1**→**4** process can be constructed (Scheme 3). The higher activation energy barrier for **1**→**7** (hydroxylation) than for **7**→**4** (disproportionation) reflects the much greater rate of the second process. This energy profile is in accord with Scheme 2, *i.e.* the hydrazino species **7** is an unobservable transient intermediate in the **1**→**4** hydroxylation.

$pK_{BH_2^{2+}}$ values

The values given in Table 3 for **1**, **2** and **3**, −5, −6.5 and −9 respectively, are in accord with the expectation that diprotonation will become increasingly difficult with increasing proximity of the positive charges on the pyridinium ring and the



Scheme 1



Scheme 2

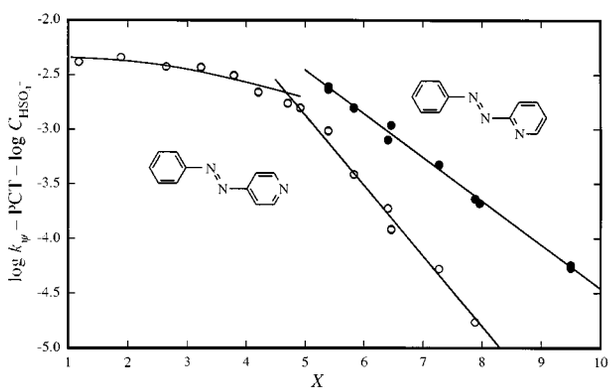


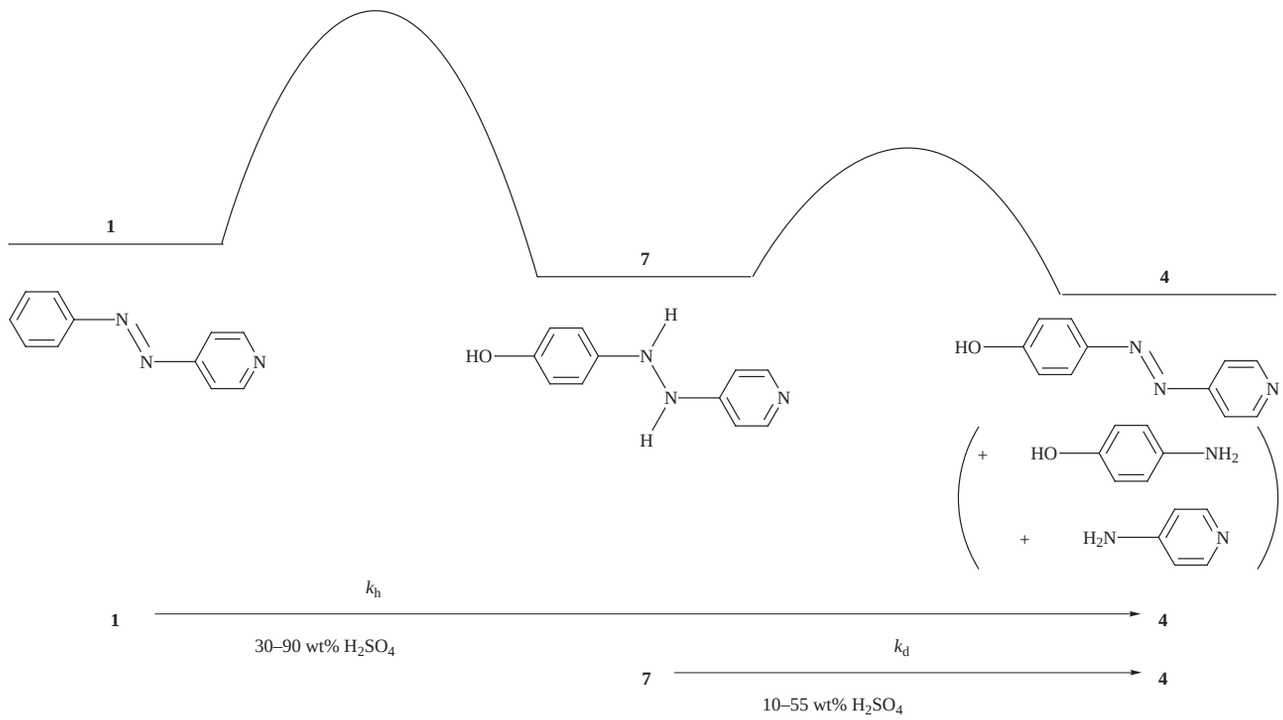
Fig. 3 Excess acidity plots for the reactions of **1**, 4-PAPy (○) and **3**, 2-PAPy (●) in aqueous sulfuric acid, assuming reaction with one HSO_4^- ion. See text.

azo-group in this series. The same trend is evident in **4**–**6**, but the second protonation is easier, due to the presence of the mesomerically stabilizing OH group, dispersing the positive charge more and reducing the electrostatic repulsion to the proton. The *m** values are all in the range 0.8–1.2, values which are very similar to those of primary aromatic amines,[28] which seems reasonable.

Kinetics and mechanism

The kinetics in this paper concern the k_h step discussed above, **1**→**7** and the equivalent reaction of **3**; the subsequent k_d step is discussed in the following paper.[17] The excess acidity method[18] was used to analyse the kinetic data. The reaction does not involve rate-determining proton transfer (A-S_E2 reaction); if it did one would expect the rate constants to continue to increase as the acidity increases, but Fig. 1 shows that this is not the case. Consequently the protonation must be a pre-equilibrium process, and so the p$K_{BH_2^{2+}}$ and *m** values given in Table 3 were used to calculate protonation correction terms (PCT) on the basis of full substrate protonation, log [$C_{SH_2^{2+}}/(C_{SH^+} + C_{SH_2^{2+}})$], or log [$I/(1 + I)$] after division by C_{SH^+}; these correct for less than full substrate protonation at the acidity under investigation. The equation log I − log C_{H^+} = p$K_{BH_2^{2+}}$ + *m***X* was used to calculate the ionization ratios *I*. Graphs of log k_ψ − PCT *vs. X* showed downward curvature, indicating that the reaction is not an A1 process.[18]

An A2 mechanism is plausible, with another species reacting with the protonated substrate in the rate-determining step, and this species was identified by examining plots of log k_ψ − PCT − log a_{H_2O} and log k_ψ − PCT − log $C_{HSO_4^-}$ *vs. X* (Fig. 3).[18] For 4-PAPy, one water molecule is reacting with the diprotonated substrate at acidities below 70 wt% H_2SO_4 (curve at the left in Fig. 3; for these points log k_ψ − PCT − log a_{H_2O} *vs. X* is linear), and one HSO_4^- ion at acidities higher than this (line to the right in Fig. 3, which displays log k_ψ − PCT − log $C_{HSO_4^-}$ as a function of *X*). For 2-PAPy, reaction occurs with one HSO_4^- at all acidities, as the excellent linearity observed in Fig. 3 makes clear. It is to be expected that HSO_4^- would take over from water in the concentration range covered by the rate measurements, as the HSO_4^- concentration is at its maximum



Scheme 3

and the water activity is very low, and decreasing rapidly, in the ~80 wt% H_2SO_4 region.[3]

Water activities in aqueous sulfuric acid media for these correlations are readily available,[38] and the values of X and log C_{H^+} used were obtained from published sources.[28] However, HSO_4^- ion activities are not available, and so HSO_4^- concentrations below the 0.5 mole fraction point were calculated on the basis of available degrees of dissociation of HSO_4^- as a function of sulfuric acid concentration,[39] and the reasonable assumption that the first proton of sulfuric acid is fully dissociated. Above this value it was assumed that all the water present is fully protonated, *i.e.* the first proton of sulfuric acid remains fully dissociated, which gives accurate HSO_4^- concentrations up to ~98 wt% H_2SO_4, when sulfuric acid autoprotolysis begins to be important.[40]

Deriving an excess acidity rate equation for an A2 mechanism is relatively straightforward.[18] Absolute rate theory requires that eqn. (1) applies, where the pseudo-first-order observed rate

$$k_\Psi(C_{SH^+} + C_{SH_2^{2+}}) = k_0 a_{Nu^-} a_{SH_2^{2+}}/f_\ddagger \quad (1)$$

constants are k_Ψ and the substrate concentration is written as a sum of protonated and diprotonated forms because the state of protonation changes over the range of sulfuric acid concentrations covered by the measurements. The rate constant for the rate-determining step in the standard state (a hypothetical ideal 1 M acid solution)[28] is k_0; this is multiplied by the activities of the species in the transition state (SH_2^{2+} and Nu^- here), and divided by the transition state activity coefficient to allow equation of concentrations with activities. If $a_{SH_2^{2+}}$ is replaced by $C_{SH_2^{2+}} f_{SH_2^{2+}}$, the equation rearranged and logs taken, we obtain eqn. (2).

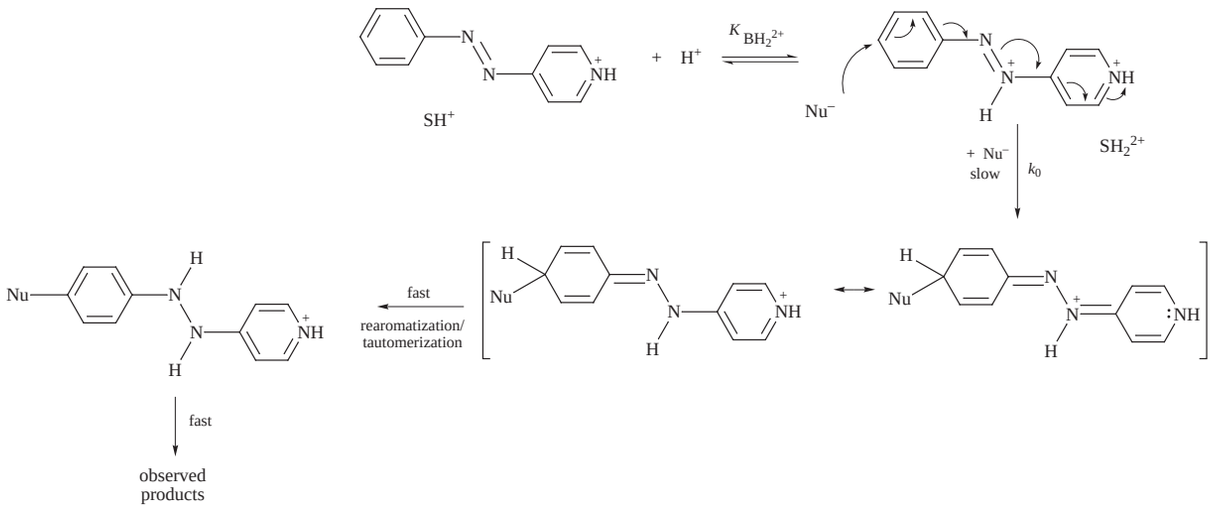
$$\log k_\Psi - \log [C_{SH_2^{2+}}/(C_{SH^+} + C_{SH_2^{2+}})] - \log a_{Nu^-} = \log k_0 + \log (f_{SH_2^{2+}}/f_\ddagger) \quad (2)$$

In the excess acidity method, activity coefficient ratios of the form log $(f_{SH_2^{2+}}/f_\ddagger)$ are found to be linear in the excess acidity X according to log $(f_{SH_2^{2+}}/f_\ddagger) = (m^\ddagger - 1)m^*X$.[18,41] Here m^* refers to ionization of the substrate, while $m^\ddagger$ refers to the transition state, having values of >1 for an A1 reaction, <1 for an A-S_E2 reaction and ~1 for an A2 reaction with water.[18] The term which corrects for less than full substrate protonation is readily calculated from the $pK_{BH_2^{2+}}$ and m^* values given in Table 3, as explained above. Thus the rate equation that gives the good linear behaviour in Fig. 3 is eqn. (3) with Nu^- being HSO_4^-, or one water molecule in more dilute acid.

$$\log k_\Psi - \log [C_{SH_2^{2+}}/(C_{SH^+} + C_{SH_2^{2+}})] - \log a_{Nu^-} = \log k_0 + (m^\ddagger - 1)m^*X \quad (3)$$

Linear regression analysis for the reaction of **1** with water gives log k_0 (intercept) = −3.981 ± 0.035 and $m^*(m^\ddagger - 1)$ (slope) = 0.473 ± 0.012, or $m^\ddagger$ = 1.586 ± 0.036. For the reaction of **1** with HSO_4^-, log k_0 = 0.36 ± 0.11 and $m^*(m^\ddagger - 1)$ = −0.645 ± 0.018, *i.e.* $m^\ddagger$ = 0.201 ± 0.050. For the reaction of **3** with HSO_4^-, log k_0 = −0.449 ± 0.069 and $m^*(m^\ddagger - 1)$ = −0.4012 ± 0.0095, *i.e.* $m^\ddagger$ = 0.624 ± 0.044. The curves shown in Fig. 1 are theoretical curves calculated using these parameters.

In the sulfuric acid reaction media used the 4-pyridinium isomer **1** reacts more quickly than the 2-pyridinium isomer **3**, as is apparent from Fig. 1. In the standard state (which in this case is a hypothetical ideal 1 M acid solution which is also 1 M in HSO_4^-) **1** reacts with HSO_4^- some six times faster than does **3** (from the log k_0 intercept values). Both reactions are considerably faster than is the reaction of **1** with water. This is an interesting reversal of the normal situation, which has water reacting substantially faster than HSO_4^-,[24,41] although HSO_4^- has been found to be the preferred reactant in some cases of the one-proton Wallach rearrangement.[5] For **1** the difference between the reaction media and the standard state rates arises from the substantially different $m^\ddagger$ values for water and HSO_4^-, 1.59 and 0.20, respectively. This is probably attributable to solvation differences;[42] since charge destruction occurs at the transition state for HSO_4^- but not for water, solvation of the two transition states would be expected to be quite different. It is difficult to predict $m^\ddagger$ values for reaction with HSO_4^-, as there is at present very little data to use for comparison. In the case of protonated benzamide a value of 1.1 was found for nucleophilic attack of HSO_4^- at the carbonyl group,[41] and for a number of substituted alkylnitramines values of $m^*m^\ddagger$ between 0.9 and 1.2 were found for S_N2 displacement by HSO_4^-, the value of m^*

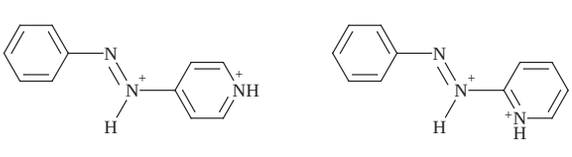


Scheme 4

being unknown.[24] Neither case corresponds very well to the situation in this reaction, nucleophilic attack at a benzene ring.

Scheme 4 shows the overall mechanism proposed for the formation of **7** from **1**; **3** is proposed to give the equivalent product by the same mechanism. The rate-determining step is nucleophilic attack by Nu^- upon SH_2^{2+}; Nu^- is either one water molecule or one HSO_4^-, depending on the sulfuric acid concentration, as shown by the kinetic behaviour. Fast rearomatization of the resulting intermediate gives the product as shown. (For simplicity the resonance adduct in Scheme 4 is shown with the imino nitrogen unprotonated, although it would surely be protonated at these acidities. The isolated products will always contain an OH group, even if the original attack is by HSO_4^-; we have shown previously[43] that sulfate ester products like these hydrolyse quickly to the phenol in dilute acid, which will occur during workup; this effectively prevents their isolation.)

The reactive form of the substrate, SH_2^{2+} in Scheme 4, is shown with the nitrogen nearer the pyridinium moiety being protonated, since this will allow the electron-pair from the incoming nucleophile to be discharged onto the azonium moiety as well as the pyridinium moiety. This may not be the most basic nitrogen in an equilibrium sense, however; the values in Table 3 probably refer to protonation at the nitrogen further away from the pyridinium ring. The through-conjugation to the pyridinium N^+ is probably the reason why these molecules are reactive at the *p*-position of the phenyl ring, particularly when the second proton is present. The values in Table 3 show why **3** is less reactive than **1**; it is ~4 p*K* units less basic, and thus the concentration of the reactive diprotonated form of **3** is only 10^{-4} times that of **1** at a given acidity. However, intrinsically $\mathbf{3}H_2^{2+}$ will be more reactive than will $\mathbf{1}H_2^{2+}$ (see Fig. 3), because



$\mathbf{1}H_2^{2+}$ $\mathbf{3}H_2^{2+}$

of the proximity of the positive charges (structures above); this is relieved upon reaction. Thus overall **3** is only a factor of 3–5 less reactive than **1** (Fig. 1), rather than a factor of 10^4.

In conclusion, the present study has shown that hydroxylation of the isomeric phenylazopyridines has occurred as a consequence of the powerful electron-withdrawing protonated pyridylazo moiety, which activates the phenyl ring to nucleophilic attack in moderately concentrated aqueous sulfuric acid. This type of nucleophilic attack for the isomeric phenylazopyridines in strongly acidic media is unique, since nucleophilic processes are generally carried out in basic media. It would be interesting to determine how activated towards nucleophilic attack a substrate has to be before this sort of reaction becomes possible. The relationship between this reaction and the benzidine rearrangement is explored in the following paper.[17]

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