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STUDIES OF AZO AND AZOXY DYESTUFFS—16†

INVESTIGATIONS OF THE PROTONATION AND TAUTOMERIC EQUILIBRIA OF 4-(*p'*-HYDROXYPHENYLAZO)PYRIDINE AND RELATED SUBSTRATES

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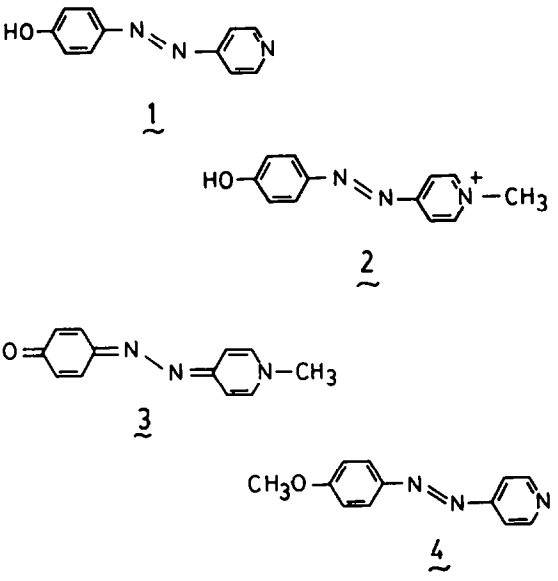
Abstract—A study of the protolytic equilibria undergone by the title compound **1** and the related substrates **2–4** has been carried out by spectrophotometric methods. Compound **1** is associated with two macroscopic protolytic equilibrium constants ($pK_{a_1} = 7.73$, $pK_{a_1} = 4.65$) while compounds **2**, **3** and **4** are associated with a single protolytic equilibrium in each case ($pK_{a_2} = 6.31$, $pK_{a_3} = 6.31$, $pK_{a_4} = 4.53$). Compounds **2** and **3** exhibit identical spectral behaviour as function of pH, which provides clues to interpretation of the equilibria involved in this series. Further consideration of possible protolytic and tautomeric equilibria (Schemes 1–3) has allowed the various microscopic equilibrium constants to be assigned, the first instance in the hydroxyphenylazopyridine series. It is concluded that hydrazone tautomeric forms are not important in these systems. The equilibrium between the neutral (HA) and zwitterionic ($AH^{\pm}$) forms of **1** is predominantly on the former side, whereas the equilibrium between 4-hydroxypyridine and 4-pyridone greatly favours the latter form. Discussion of various equilibrium constants is given in terms of structural and electronic effects.

The discovery of the tautomerism of aromatic hydroxyazo compounds dates back almost 100 years.[1] Of the numerous studies of this phenomenon since then with a variety of structural types,[2–4] using spectroscopic as well as other methods of detection,[5–15] pyridine substituted hydroxyazoarenes have received only cursory attention. Indeed, there is as yet no report of a complete investigation of the tautomeric equilibria for a pyridine containing hydroxyazoarene, including analysis of the microscopic equilibrium constants.[16] This is somewhat surprising in view of the pronounced chelating properties of such compounds towards various metal cations with consequent utility in extraction processes as well as in qualitative and quantitative analytical procedures.[17–19] Also, in addition to their potential utility in the dye industry,[20–22] the pyridine azo compounds are of considerable interest from the theoretical point of view, for example with respect to solvatochronic and photo-imaging characteristics.[23–26] A more thorough understanding of their chemical properties is called for.

We have been interested in hydroxyazoarenes for some years, in part due to their relationship to the acid catalyzed Wallach rearrangement of azoxyarenes.[27–32] It became of interest to extend study of the latter process to azoxyarenes containing the pyridine moiety. It was expected that this would provide a stringent test of our proposed reaction mechanism, which in the case of azoxybenzene was shown to involve two proton transfer steps; an additional protonation process, at least, would then be required in the pyridine series. In that connection it became necessary to examine first the spectroscopic properties and protonation equilibria of the hydroxyazopyridine derivatives, as the expected products of the rearrangement.

In the present study we have examined the UV-visible spectral properties and the protonation equilibria undergone by the compounds **1**, **2**, **3** and **4**, that is 4 - (*p'* - hydroxyphenylazo)pyridine, 4 - (*p'* - hydroxyphenylazo)pyridinium methiodide, *p* - hydrazobenzoquinone - 4 - (N - methyl)pyridone, and 4 - (*p'* - methoxyphenylazo)pyridine, respectively, which have been prepared by unambiguous methods (Experimental).

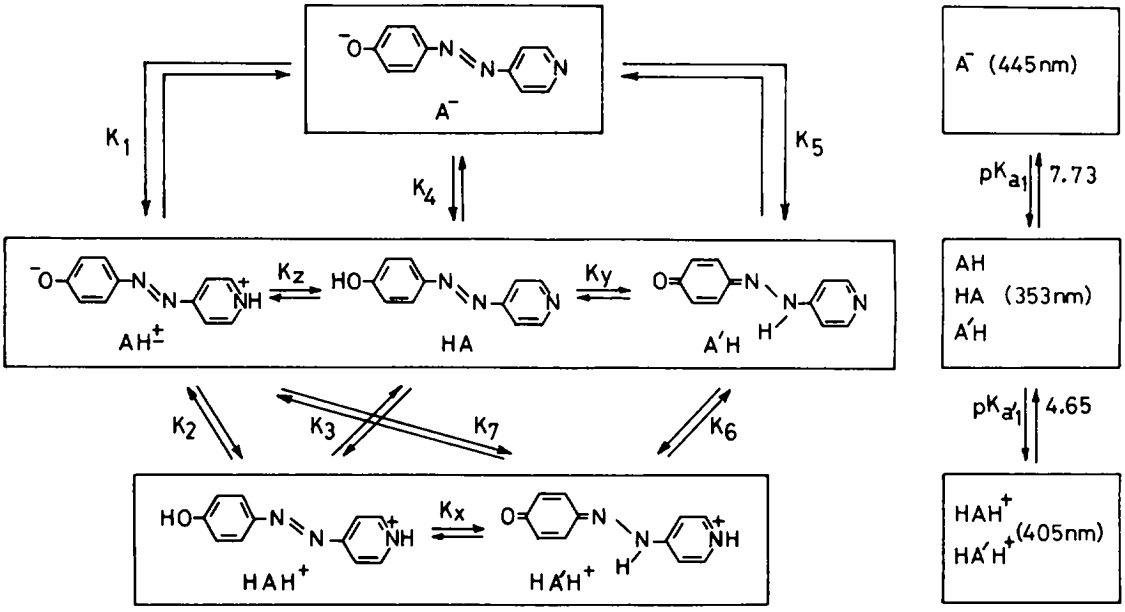


It will be shown that the structural relationships among these compounds allow a unique interpretation of their spectroscopic and protolytic behaviour. A number of unusual features have been revealed in this study, which includes an estimate or the importance of zwitterionic species and the assignment of microscopic equilibrium constants.

RESULTS AND DISCUSSION

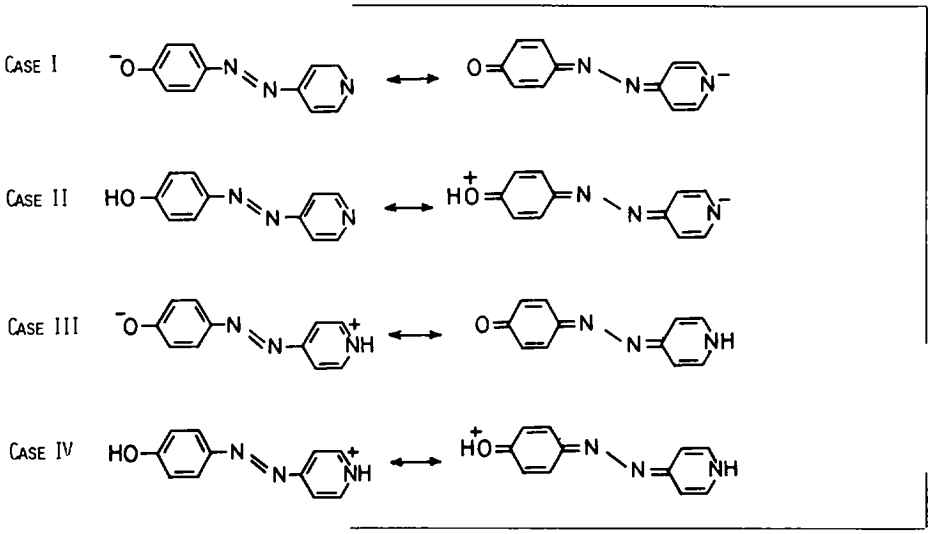
The protolytic equilibria which compound **1** can potentially undergo are shown in Scheme 1. This in-

†This series is an extension of our previous studies on the Wallach rearrangement of azoxyarenes. Part 15: E. Buncel, R. A. Cox and A. Dolenko, *Tetrahedron Letters* 215 (1975).



Scheme 1.

cludes examples of both azo-hydrazone tautomerism ($HA \rightleftarrows A'H$ and $HAH^+ \rightleftarrows HA'H^+$), and equilibria between zwitterionic species ($AH^{\pm} \rightleftarrows HA$). In addition there are interesting possibilities for resonance in this series, some of which can be represented as follows:



Other resonance structures, e.g. with negative charge on a N atom of the azo function, are also possible. The relative importance of the various contributing forms will, of course, vary widely depending on structure and charge type. For example in case I the quinoid form should be contributing relatively more than in case II, since in the latter there is separation of charge but not in the former. Mesomerism in case III is particularly interesting since the zwitterionic as well as the quinoid canonical forms possess characteristic structural features which are associated with special stability. Moreover, among other factors, solvation will be important in contributing to preferential stabilization of one or other of the canonical forms in case III. Thus we have embodied here the possibility of solvatochromic behaviour[26,33–35] in a new series of compounds. The results described below shed some light on these phenomena.

Spectral behaviour of **1–4** *as function of pH.* Spectrophotometric examination of the protolytic equilibria of **1** revealed the behaviour shown in Fig. 1. The spectra were taken in buffer solutions of varying pH, starting with spectrum 1 at the highest pH and continuing through spectrum 9 at the lowest pH value. It is seen that, initially, as the pH is decreased from 9.1 to 7.0, there is a hypsochromic shift with the starting absorption at 445 nm decreasing and an absorption at 353 nm increasing, the curves passing through an isosbestic point at 383 nm. Further decrease in pH from 7.0 to 3.6 results in a bathochromic shift, the absorption at 353 nm giving place to a more intense max at 405 nm. The latter set of spectra are characterized by an isosbestic point at 367 nm.

The spectral changes in Fig. 1 show that two pro-

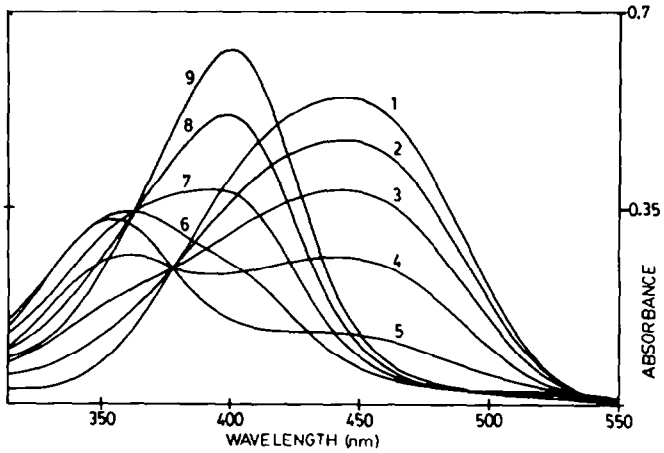


Fig. 1. Spectral behaviour of compound 1 in media of varying pH: 1, 9.12; 2, 8.35; 3, 8.10; 4, 7.60; 5, 7.00; 6, 5.10; 7, 4.75; 8, 4.35; 9, 3.60.

tonation equilibria are involved over this pH range. In Fig. 2 is given a plot of absorbance vs pH corresponding to the data in Fig. 1, for absorbances at 445, 405 and 353 nm. Inflection points occur at pH values of 7.73 ± 0.02 and 4.65 ± 0.03, yielding the two apparent pK_a's i.e. $pK_{a_1} = 7.73 \pm 0.03$ and $pK_{a_1} = 4.65 \pm 0.03$ (Tables 1, 2 and 6).

The spectra of compound 2 taken as a function of pH are shown in Fig. 3. This spectral behaviour is characteristic of a simple one-stage protolytic equilibrium. Plots

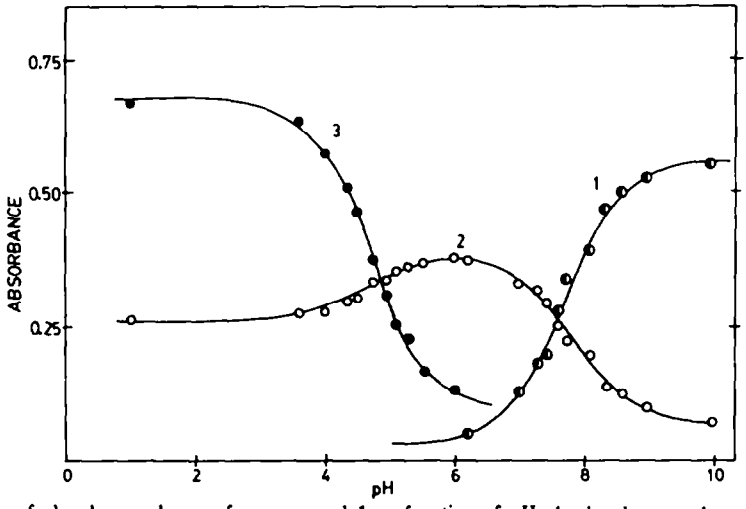


Fig. 2. Plots of absorbance changes for compound 1 as function of pH: 1, absorbance values at 445 nm; 2, absorbance values at 353 nm; 3, absorbance values at 403 nm.

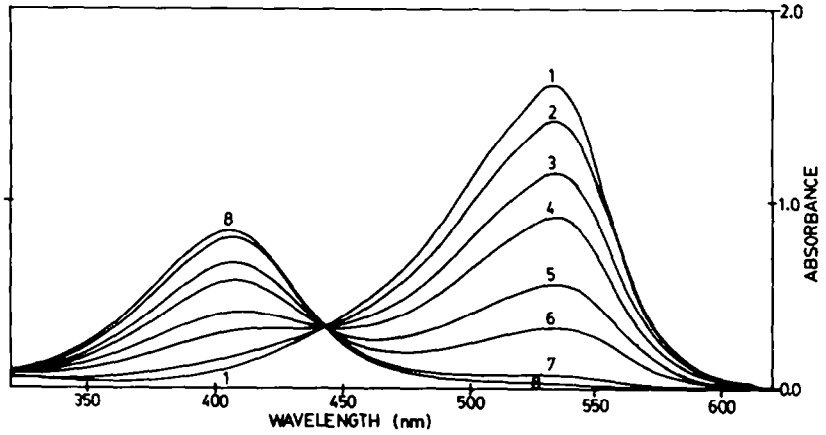


Fig. 3. Spectral behaviour of compound 2 in media of varying pH: 1, pH 8.70; 8, pH 4.10.

Table 1. Absorbance data for compound 1 as function of pH for determination of pK_{a_1}

pH	$A_{B^-}^{445}$ [a]	A_{BH}^{353} [b]	$(A_{BH}^{353} - A_{B^-}^{445})$ [c]
10.00	0.543	0.070	-0.473
8.96	0.520	0.098	-0.422
8.60	0.490	0.122	-0.368
8.35	0.459	0.133	-0.326
8.10	0.384	0.195	-0.189
7.74	0.333	0.220	-0.113
7.60	0.275	0.248	-0.027
7.42	0.192	0.292	0.100
7.28	0.177	0.312	0.135
7.00	0.128	0.324	0.196
6.20	0.050	0.364	0.314

[a] Absorbance at λ_{max} (nm) of basic species.

[b] Absorbance at λ_{max} (nm) of neutral species.

[c] Absorbance differences used to determine pK_a value by Davis-Geissman method (C.T. Davis and T.A. Geissman, J. Am. Chem. Soc. 76, 3507 (1954)).

Table 2. Absorbance data for compound 1 as function of pH for determination of pK_{a_3}

	A_{BH}^{353} [a]	$A_{BH_2^+}^{403}$ [b]	$(A_{BH}^{353} - A_{BH_2^+}^{403})$ [c]
6.00	0.372	0.126	0.246
5.52	0.360	0.163	0.197
5.30	0.354	0.222	0.132
5.10	0.346	0.246	0.100
4.95	0.330	0.302	0.028
4.75	0.326	0.365	-0.039
4.50	0.297	0.448	-0.151
4.35	0.291	0.499	-0.208
4.00	0.272	0.562	-0.290
3.60	0.269	0.624	-0.355
1.00	0.258	0.656	-0.398

[a] Absorbance at λ_{max} (nm) of neutral species.

[b] Absorbance at λ_{max} (nm) of conjugate acid.

[c] As Table 1

of absorbance changes at 533 and at 405 nm vs pH exhibit sigmoid curves with inflection points at pH 6.31 ± 0.01 yielding the apparent pK_a value, i.e. $pK_{a_2} = 6.31 \pm 0.01$ (Tables 3 and 6).

Compound 3 was found to exhibit spectral behaviour as a function of pH which corresponds exactly to that seen in the case of 2 and as shown in Fig. 3. Even the isosbestic points occur at the same wavelength (440 nm) in the two cases. One thus obtains for 3, $pK_{a_3} = 6.31 \pm 0.01$ (Tables 4 and 6). The identity in the two protolytic behaviours is considered further in the next section.

The spectral behaviour of compound 4 as a function of pH was found to be characteristic of a one-stage protolytic equilibrium as well. The absorption present at 353 nm in media of high pH diminished in intensity as the pH was lowered, while another absorption at 388 nm simultaneously increased in intensity, an isosbestic point occurring at 363 nm. Plots of the absorbance at 353 nm and 388 nm as a function of pH gave typical sigmoid curves from which $pK_{a_4} = 4.53 \pm 0.01$ was obtained (Tables 5 and 6).

Identification of protolytic equilibria. Unambiguous structural assignment of spectral species is possible in

Table 3. Absorbance data for compound 2 as function of pH for determination of pK_{a_2}

pH	A_{BH}^{405} [a]	$A_{B^-}^{533}$ [b]	$(A_{BH}^{405} - A_{B^-}^{533})$ [c]
3.00	0.843	0.001	0.843
4.10	0.841	0.021	0.820
4.82	0.808	0.074	0.734
5.60	0.676	0.328	0.348
5.93	0.575	0.629	-0.054
6.30	0.411	0.926	-0.515
6.56	0.308	1.159	-0.851
7.10	0.169	1.438	-1.269
8.00	0.104	1.627	-1.523
10.00	0.065	1.643	-1.578

[a] Absorbance at λ_{max} (nm) of neutral species.

[b] Absorbance at λ_{max} (nm) of basic species.

[c] As Table 1

Table 4. Absorbance data for compound 3 as function of pH for determination of pK_{a_3}

pH	$A_{BH^+}^{405}$ [a]	A_{B}^{533} [b]	$(A_{B}^{533} - A_{BH^+}^{405})$ [c]
3.00	0.420	0.014	-0.406
4.10	0.419	0.025	-0.394
4.82	0.402	0.051	-0.351
5.60	0.336	0.181	-0.155
5.93	0.286	0.330	0.044
6.30	0.203	0.478	0.275
6.56	0.152	0.595	0.443
7.10	0.082	0.735	0.653
8.00	0.049	0.830	0.781
9.00	0.032	0.835	0.803
10.00	0.030	0.838	0.808

[a,b,c] As in Table 3

Table 5. Absorbance data for compound 4 as function of pH for determination of pK_{a_4}

pH	A_{B}^{352} [a]	$A_{BH^+}^{388}$ [b]	$(A_{B}^{352} - A_{BH^+}^{388})$ [c]
6.97	0.274	0.115	0.159
5.70	0.271	0.126	0.145
5.00	0.253	0.157	0.096
4.70	0.235	0.187	0.048
4.50	0.231	0.207	0.024
4.30	0.206	0.227	-0.021
4.00	0.197	0.251	-0.054
3.78	0.190	0.266	-0.076
3.10	0.178	0.287	-0.109
1.40	0.175	0.292	-0.117

[a] Absorbance at λ_{max} (nm) of neutral species.

[b] Absorbance at λ_{max} (nm) of conjugate acid.

[c] As Table 1

Table 6. Summary of macroscopic pK_a values obtained by various methods

Compound		Method of pK_a determination			pK_a[d]
		A_{BH}[a] vs. pH	$A_{BH_2}^+$[b] or A_B^-[c] vs. pH	Davis-Geissman	
1	pK_{a_1}	7.70	7.73	7.75	7.73 ± 0.01
	pK_{a_1}'	4.60	4.72	4.07	4.65 ± 0.03
2	pK_{a_2}	6.30	6.33	6.30	6.31 ± 0.01
3	pK_{a_3}	6.30	6.31	6.20	6.27 ± 0.03
4	pK_{a_4}	4.54	4.52	4.52	4.53 ± 0.01

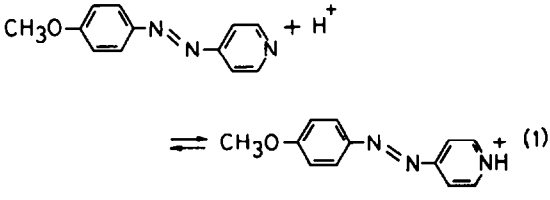
[a] Absorbance at λ_{max} of phenolic species.

[b] Absorbance at λ_{max} of conjugate acid.

[c] Absorbance at λ_{max} of conjugate base.

[d] Average values including standard error.

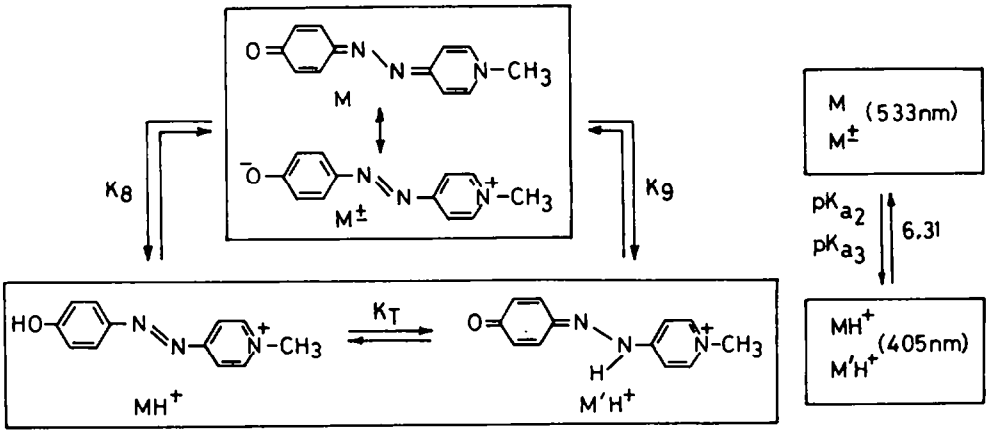
the case of the protolytic equilibrium undergone by 4. The 353 nm species present at high pH corresponds to the neutral substrate and the 388 nm species formed in acidic media to the conjugate acid, protonation having occurred on the pyridine N according to eqn (1), for which a pK_{a_4} value of 4.53 is obtained.



(1)

In the case of 1, 2 and 3, however, assignment of the spectral species as a function of pH is not readily possible since a number of tautomeric as well as zwitterionic structures can form in principle (Schemes 1 and 2). However, the task of identification of the various spectral species, and the assignment of various equilibrium constants, can be approached through comparison of the spectral behaviours exhibited in these systems, coupled with other pertinent evidence.

The complete correspondence in the spectrophotometric behaviour of 2 and 3 as a function of pH shows that the same types of protolytic equilibria are involved in both cases, as represented in Scheme 2. The symbol M in this scheme denotes substrate 3 while $M^{\pm}$ denotes the



Scheme 2.

species obtained on deprotonation of 2. This notation is of course arbitrary since the same chemical species is involved in both cases as the two structures are related as resonance forms. However, the notation emphasizes the circumstance that the chemical origins of M and $M^{\pm}$ are different, the former (i.e. corresponding to 3) being prepared directly as the neutral substrate,[36] while the latter is obtained on deprotonation of the hydroxyazopyridinium methiodide (i.e. 2) when the pH is changed appropriately. Thus the same spectral behaviour in the two cases is to be expected.

We can now return to Scheme 1 in order to glean better understanding of the more important processes that are involved and to attempt a species assignment to be made, making use of comparisons within the series 1, 2, 3 and 4. A striking aspect of the results is the correspondence of the 405 nm absorption in the "proton-gained" equilibrium of 1 with the same absorption seen on protonation of 2 and 3. However, this spectral correspondence can readily be understood on the basis of the structural analogy between the species involved in these protolytic processes, i.e. $AH^{\pm} + H^{+} \rightleftarrows (HAH^{+} \rightleftarrows HA'H^{+})$ and $M^{\pm} + H^{+} \rightleftarrows (MH^{+} \rightleftarrows M'H^{+})$, with corresponding species differing only through $^{+}$N–Me replacing $^{+}$N–H. Comparison of related compounds in the azo-pyridine series shows that the UV-vis spectra of structural analogues, which differ only in an N-Me substituent vs the protonated pyridine moiety, are virtually identical. It follows also that the positions of the tautometric equilibria in the two systems ($HAH^{+} \rightleftarrows HA'H^{+}$ and $MH^{+} \rightleftarrows M'H^{+}$) will be closely similar, though we cannot as yet decide which tautomers are dominant in these systems.

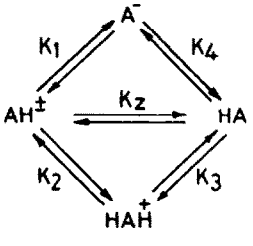
Relating the spectral behaviour of 1 with the species shown in Scheme 1, the 445 nm absorption (Fig. 1) can clearly be identified as corresponding to the anion A^{-}. However, assignment of the 353 nm absorption to particular species presents a problem. One can eliminate the hydrazone tautomer A'H as the major species present, and this can probably also be eliminated as a minor species on the basis of the following evidence. In the first place, quinoid hydrazone tautomers are expected to exhibit an absorption at appreciably longer wavelength compared to the fully aromatic azo tautomer form; this has been found in those cases where the hydrazone structure has been obtained as the methylated form, on a N of the azo function.[37] Comparison can also be made with *p*-hydroxyazobenzene which has λ_{max} at 367 nm in aqueous ethanol and which is known to exist virtually exclusively in the fully aromatic form; in fact there is no evidence that the hydrazone tautomer is present in detectable concentration in this case.[15]

Even more direct evidence is provided by the spectral behaviour of 4 since protonation in this case can occur only on the pyridine N, the hydrazone form being precluded by the blocking O-Me group. Accordingly, the absorption max of the neutral 4 which occurs at 353 nm corresponds exactly to the 353 nm absorption exhibited by 1. The absorption max of the conjugate acid of 4 (388 nm) differs somewhat from that of 1 (402 nm) but this could follow from the anticipated different degrees of contribution of quinoidal resonance forms towards stabilization of the conjugate acids of 4 and 1, as may be seen by referring to case IV above and its O–Me analogue. An alternative explanation, however, would invoke different types of H-bonding possibilities in the two cases. Thus in the conjugate acid (NH^{+} form) of 1 the phenolic OH will readily partake in H-bonding as a result of polarisation of the O–H bond, since the resulting electronic displacement imparts a degree of zwitterionic character to the molecule. This type of interaction is not possible for the conjugate acid of 4. Although the OMe group in 4 could act as an H-bond acceptor, this is expected to be a weaker interaction. Further aspects of H-bonding as well as aggregation phenomena in these systems will be discussed in a future paper.†

The available NMR evidence supports the conclusion drawn on the basis of the UV-VIS spectral data, that the hydrazone tautomer A'H can be neglected as a contributing species. Thus the NMR spectrum of 1 in DMSO exhibits a signal at δ 10.67 which is characteristic of phenolic OH and similarly 2 exhibits a corresponding signal at δ 11.22. Additionally, the aromatic protons furthest downfield, which can be ascribed as adjacent to the O function, appear at δ 7.10 in 1, at δ 7.08 in 2, and δ 7.02 in 4. In a quinoid structure these protons would be expected to lie upfield, in the region δ 6.0–6.3; thus in 3 they appear at δ 6.30. Although the change in medium could have an effect on the position of the tautomeric equilibria in 1, the combined evidence weighs against the hydrazone tautomer A'H being of any importance in this system. By analogy, it seems plausible to assume that in the second protonation step in Scheme 1, the hydrazone tautomer $HA'H^{+}$ is once again not an important contributing species. Furthermore, it would follow also that neither is $M'H^{+}$ an important contributor in Scheme 2.†

Evaluation of equilibrium constants. Scheme 1 can now be simplified in the form of Scheme 3, which retains only five of the microscopic equilibrium constants present in the former, i.e. the acidity constants K_1 through K_4 and the constant K_Z for the equilibrium between the zwitterionic species $AH^{\pm}$ and HA. Protomeric equilibria involving zwitterionic species in the aromatic series containing acidic and basic centers have been considered previously,[16,38] for example in the case of 4-aminobenzoic acid,[39] and in the pyridine series with nicotinic acid[40] and 3(4)-hydroxypyridine.[41,42] These systems, as well as the familiar amino-acids in the aliphatic series, form precedents for our work, though the present is the first application to the pyridine azo dyes.

†The present interpretation is further supported by the finding that 4 undergoes slow acid-catalyzed hydrolysis to 1 in more strongly acidic media (10–20% H_2SO_4) and that the spectral characteristics of the reaction product are completely concordant with the data reported here. This result argues against the possibility that while the 388 nm absorption corresponds to protonation on the pyridine nitrogen of 4, the 405 nm absorption would represent protonation on the hydrazone N. It also provides evidence for our assertion that hydrazone tautomers are not important contributors in acidic media.



Scheme 3.

The microscopic equilibrium constants are related to the measured macroscopic constants K_{a_1} and $K_{a_1'}$ by way of the expressions in eqns (2)–(4)[41]

$$K_{a_1} = K_2 + K_3 \quad (2)$$

$$\frac{1}{K_{a_1'}} = \frac{1}{K_1} + \frac{1}{K_4} \quad (3)$$

$$K_Z = \frac{K_2}{K_3} = \frac{K_4}{K_1}. \quad (4)$$

Solution of these equations requires that one of the microscopic constants be known, in addition to the macroscopic constants K_{a_1} and $K_{a_1'}$. By drawing on the analogous aspects between Schemes 1 and 2, and from the previous discussion, one can predict the approximate equality of K_2 and K_8, assuming that methyl substitution has negligible effect on the equilibrium constants. Now K_8 can be taken as the experimentally determined K_{a_4} (or K_{a_3}) value, since the species $M'H^+$ has been effectively eliminated from Scheme 3. In this way we obtain the following values for the microscopic constants pertaining to Scheme 1: $pK_1 = 6.07$, $pK_2 = 6.31$, $pK_3 = 4.66$, $pK_4 = 7.72$ and $pK_Z = 1.65$. For ready referral in the following discussion, these values are recorded in Table 7.

The calculated microscopic constant pK_3 should be very closely similar to the experimentally determined pK_{a_4} value since substitution of *p*-methoxy for *p*-hydroxy on one ring should have little effect on protonation of the pyridine N of the other ring. The two values (4.66 and 4.53 respectively) do compare favorably, bearing out our expectation.

Another estimate of K_Z can be made from the ratio of the ionization constants of the N-alkylated 2 and the O-alkylated 4, i.e. $K_{a_2}/K_{a_4} = 1.66 \times 10^{-2}$ and $pK_Z = 1.78$. It has been considered[43] that in this way any errors introduced in assigning the pK_a of one alkylated form to one of the microscopic constants will tend to cancel, although some exceptions to this have been found.[44] The pK_Z value of 1.78 agrees reasonably with the previously calculated value of 1.65 and also with the experimentally determined value as described below.

Estimate of the tautomeric equilibrium constant, K_Z. It has been found possible to obtain direct information concerning the magnitude of the tautomeric equilibrium constant K_Z. Thus close inspection of Fig. 1 reveals a hint of a minor, long-wavelength absorption which we deduce is attributable to the zwitterionic species $AH^{\pm}$. This minor absorption is more clearly apparent in the spectra in Fig. 4, which correspond to the portion of Fig. 1 covering the equilibrium between the neutral and the acidic species, i.e. the spectra for the low pH region (3.6–5.1) passing through the isosbestic point at 367 nm. The remaining spectra in Fig. 1 corresponding to the equilibrium between the basic and neutral species (isosbestic at 383 nm) tend to obscure the absorption due to $AH^{\pm}$ as a result of the appreciable end absorption of the anionic species A^- (λ_{max} 450 nm). As expected, the 530–540 nm absorption is highest in spectrum 6 corresponding to the case that the species AH predominates and decreases as conversion to A^- becomes effective at

Table 7. The macroscopic and microscopic equilibrium constants

Compound	Macroscopic		Microscopic				
	pK_{a_1}	$pK_{a_1'}$	pK_1	pK_2[a]	pK_3	pK_4	pK_Z[b]
1	7.73	4.65	6.07	6.31	4.66	7.72	1.65

[a] Value for compound 2 or 3

[b] $K_Z = K_2/K_3$

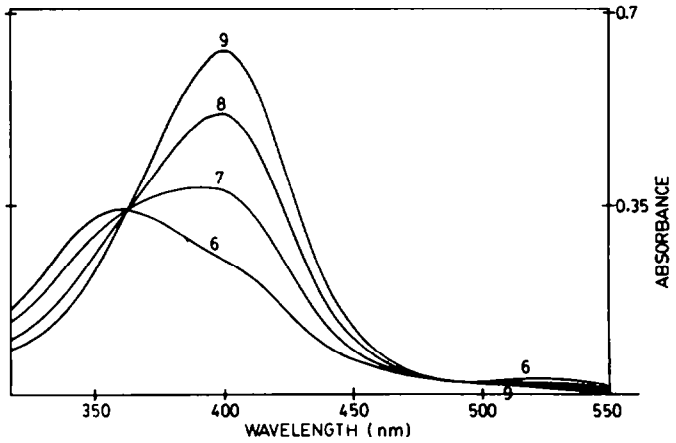


Fig. 4. Spectra for compound 1 in low pH region showing minor longwavelength absorption assignable to zwitterionic species.

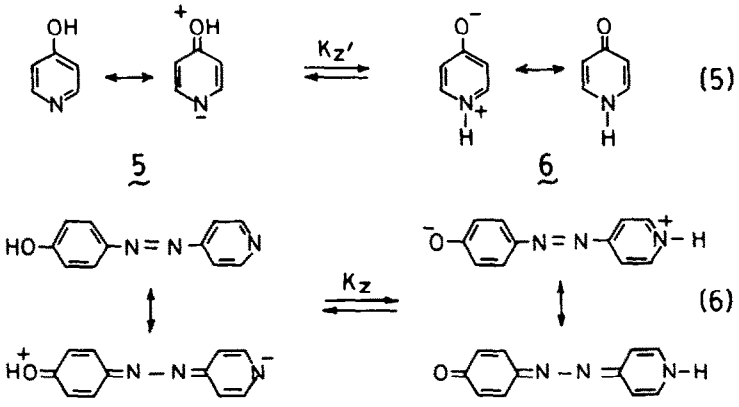
higher pH; there is also an isosbestic point at ~495 nm. It is recalled that the structurally analogous compound $M^{\pm}$ has λ_{max} at 533 nm, which is in agreement with our assignment of the 530–540 nm absorption in Fig. 4 to $AH^{\pm}$.

An estimate of K_Z can be made by assuming that the molar extinction coefficient of $AH^{\pm}$ at 533 nm will be equal to that of $M^{\pm}$ at this wavelength, which is known to be $6.74 \times 10^4 M^{-1} cm^{-1}$. Using this value and the observed absorbance (0.0187) at 533 nm in spectrum 6, one obtains $K_Z = [AH^{\pm}]/[AH] = 1.41 \times 10^{-2}$. A more accurate value of K_Z was obtained on performing another set of experiments with a larger number of spectra taken in the pH region 3.1–6.3 and using an expanded absorbance scale in the 450–600 nm region. This yielded $K_Z = 1.54 \times 10^{-2}$. The mean value of pK_Z by the two determinations is 1.83, which agrees reasonably well with $pK_Z = 1.65$ calculated via eqns (2)–(4) and with the value $pK_Z = 1.78$ calculated subsequently. The good agreement between the experimentally determined pK_Z value and the calculated value via eqns (2)–(4) lends confidence to the methods and assumptions involved in evaluating the microscopic equilibrium constants in Table 7.

Structural effects on equilibria. The results for the microscopic constants in Scheme 3 allow several interesting comparisons to be made. Considering first proton loss from the phenolic OH, the ionization constants for the analogous processes $HA \rightleftarrows H^+ + A^-$ and $HAH^+ \rightleftarrows H^+ + AH^{\pm}$ differ appreciably, that is $pK_4 = 7.72$ and $pK_2 = 6.31$ respectively. The greater acidity in the latter case can be explained by charge delocalization in the zwitterionic azo-phenolate anion $AH^{\pm}$ as depicted by the structures indicated in case III as well as the resonance form in which an azo nitrogen would bear the negative charge. Resonance stabilization in A^- via analogous contributing structures will be relatively less important.†

Considering next the basicities of the pyridine moieties, the two analogous equilibria are $A^- + H^+ \rightleftarrows AH^{\pm}$ and $HA + H^+ \rightleftarrows HAH^+$, with $pK_1 = 6.07$ and $pK_3 = 4.66$ respectively. That the pyridine N is more strongly basic in the former case is explained through contribution of the resonance structure shown in case I which increases the electron density on the pyridine nitrogen in the ground state. Conversely in the conjugate acid $AH^{\pm}$ charge is effectively delocalized through contribution of structures indicated under case III. Corresponding delocalization in HA (case II) and HAH^+ (case IV) will be less effective.†

Of further interest is the K_Z value for the equilibrium between the neutral form AH and the zwitterionic form $AH^{\pm}$. That this equilibrium is predominantly on the side of the hydroxyazopyridine form, can be contrasted with the equilibrium between 4-hydroxypyridine (5) and 4-pyridone (6) where the latter form greatly predominates; $K_{Z'} = [6]/[5] = 2000$ in aqueous solution.[45] In discussing the two equilibria, we may re-write these in analogous fashion as follows:



One can consider the hydroxyphenylazopyridine system as an extension, through the phenylazo moiety, of the hydroxypyridine structure; then wherein lies the origin of the contrasting equilibrium constants, with $K_Z/K_{Z'} \sim 10^5$? It appears that K_Z is disfavored relative to $K_{Z'}$ primarily in that the extended quinoid canonical form, contributing to the structure of $AH^{\pm}$, will be associated with a destabilizing effect. The strong preference of the benzenoid relative to the quinoid form manifests itself in many situations, for example in the absence of the hydrazone tautomer with *p*-hydroxyazobenzene. In contrast it has been estimated that the aromatic stabilization energy of 4-pyridone is only 8 kcal less than that of pyridine.[46] However, a different situation will arise on introducing structural changes, such as with 4 - (*o'* - hydroxyphenylazo)pyridine, or on replacing phenyl by naphthyl, and such systems will be considered in future papers in this series.

It should be emphasized that the present considerations and comparisons are limited to results obtained in solution. However, comparisons of energies of tautomeres should strictly be made in the gas phase, as has been emphasized by the recent work of Beak *et al.*,[47] as well as of Katritzky *et al.*[48] Solvation has been found to play an important role in protomeric equilibria of the type in eqn (5).[47,48] Corresponding information concerning the equilibria considered in the present work (Schemes 1 and 2) are not available, however. Although it will be difficult to apply vapor phase techniques to the present series of compounds, their suitability for examination of solvatochromic effects should enable pertinent information on solvent effects to be obtained and such studies are under active consideration.

EXPERIMENTAL

General methods. The solvents used in the preparative work were freshly distilled. Reagents used were of the highest quality

†The discussion concerning the dependence of pK_a's on electron densities, and the influence of charge delocalization thereon, should be complemented through consideration of solvent effects on the neutral and on the protonated (deprotonated) species. We have little information concerning the effect of this factor in the present systems.

commercially available. The pyridine derivatives used in this work were purchased from the Aldrich Chemical Company. Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario. M.Ps were determined on a Fisher–Johns apparatus and are uncorrected. The products were purified by means of preparative tlc with the exception of the ionic 2. NMR spectra were recorded on a Brooker CXP 200 MHz high resolution instrument operating under FT mode.

4 - (p' - *Hydroxyphenylazo)pyridine* (1). This compound was examined for its antiparasitic properties by Hayashi *et al.*[49] but no description of its method of preparation was given. In the present work 1 was prepared by a modified coupling procedure starting with diazotized 4-aminopyridine. The method used minimized decomposition or conversion of the diazonium salt to 4-pyridone via nucleophilic displacement. Previous attempts at synthesis of arylazopyridinyl compounds via coupling with 4-pyridinodiazonium salts were generally unsuccessful due to competition from these side reactions. In the following procedure the diazotization is carried out in presence of the phenol, which allows the subsequent coupling to proceed smoothly to yield the desired product.

A soln of $NaNO_2$ (4.0 g) in water (20 ml) was added to phenol (5 g) in 10% NaOH aq (45 ml) and cooled to 0°. The resulting soln was added slowly with stirring to a soln of 4-aminopyridine (6 g) in HCl aq (25 ml conc HCl: 16 ml water) keeping the temp. at 0°. Following the addition (10 min) the pH of the mixture was adjusted to *ca* 6 and the ppt which formed was filtered off, purified by preparative tlc and recrystallized from EtOH to give 7.6 g (71%) of yellow crystals m.p. 256–257° (dec), lit.[49] m.p. 252–253°. (Found: C, 65.96; H, 4.56; N, 20.92. Calc. for $C_{11}H_9N_3O$: C, 66.33; H, 4.52; N, 21.11%.) λ_{max} (ϵ) in EtOH: 363 nm (24,500 M^{-1} cm^{-1}).

4 - (p' - *Hydroxyphenylazo)pyridinium methiodide* (2). This compound was prepared by methylation of 1. A soln of 1 (2.0 g) in EtOH (30 ml) was heated with MeI (5.7 g) under reflux for 8 hr. On cooling yellow crystals of product formed and were filtered off; more product was obtained from the filtrate on concentration. The combined product was recrystallized from EtOH to give brownish yellow crystals (3.0 g, 88%) m.p. 220–221° (dec). (Found: C, 42.17; H, 3.50; N, 12.46; I, 36.98. Calc. for $C_{12}H_{12}N_3OI$: C, 42.24; H, 3.52; N, 12.32; I, 37.22%.) λ_{max} (ϵ) in EtOH: 415 nm (34800 M^{-1} cm^{-1}).

p - *Hydrazobenzoquinone* - 4 - (N - *methyl)pyridone* (3). The preparation of 3 followed a modified oxidative coupling procedure adapted from Hünig and Köbrich.[36] N - methyl - 4 - chloropyridinium iodide[50] was prepared by reaction of 4-chloropyridine (16 g) with MeI (67 g) at 0° for 4 days in the dark. The product separated as a yellow solid (25.6 g, 80%), m.p. 151–155° (dec). Reaction of the pyridinium iodide with benzoyl hydrazine, followed by condensation with benzoquinone, was essentially according to the lit. method.[36] Recrystallization of the product from aqueous ethyleneglycol monomethyl ether gave 3 as violet crystals, m.p. 215°, lit.[36] 218°. λ_{max} (ϵ) in EtOH: 547 nm (67400 M^{-1} cm^{-1}).

4 - (p' - *Methoxyphenylazo)pyridine* (4). This compound was also examined by Hayashi *et al.*[49] for its antiparasitic properties but no details of its preparation were given. In the present work 4 was obtained in low yield from *p*-nitroanisole and *p*-aminopyridine by the general method given by Faessinger and Brown.[51] To a soln of *p*-nitroanisole (7.6 g, 0.05 mole) and 4-aminopyridine (4.7 g, 0.05 mole) in dry toluene (100 ml) was added freshly cut Na (2.3 g, 0.1 mole) while stirring vigorously under N_2. The mixture was carefully warmed and then heated under reflux for 3 hr with continued stirring. After filtration of the hot mixture, the cooled filtrate was extracted twice with 25 ml portions of 17% HCl aq and then made basic with cold 20% NaOH aq. Extraction with ether followed by evaporation of the solvent *in vacuo* yielded a solid which was purified by preparative tlc (toluene/MeOH, 1:1). Recrystallization from benzene yielded 0.5 g (5%) of product m.p. 96–98°, lit.[49] m.p. 97–98°. λ_{max} (ϵ) in EtOH: 355 nm (20,150 M^{-1} cm^{-1}).

pK_a Determinations. Buffer solns of constant ionic strength (I = 0.01) were made up according to the procedure given by Bates[52] and checked with a Metrohm E512 pH meter. Triply redistilled demineralized water was used throughout. The buffers used together with their pH range are phthalate, pH 2.2–3.6; succinate, 3.6–6.2; dihydrogen phosphate, 6.4–8.0; boric acid, 8.0–8.4; tris(hydroxymethyl)aminoethane, 8.4–9.2. UV-visible absorption spectra were taken on a Beckman DU-8 spectrophotometer at 25°.

Stock solns of the substrates 1–4 in EtOH (10^{-2}–10^{-3} M) were prepared and 10 μl added to 2 ml of the buffer soln contained in a 1.0 cm cuvette. The spectra for compounds 2, 3 and 4 as a function of pH were taken by the overlay method using distilled water in the reference cell. In the case of 1 the overlay spectra were run in two series: (1) covering the pH region 3.6 to 6.0 using the succinate buffer of pH 6.00 in the reference cell; and (2) 7.0–10.0 in which the dihydrogen phosphate buffer of pH 7.00 was used in the reference cell.

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