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Acidity Constants of Some Hydroxy Azopyrazolopyridines in Mixed Aqueous-Organic Solvents

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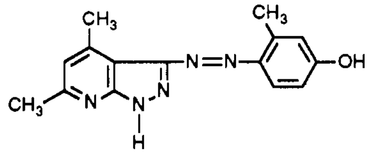
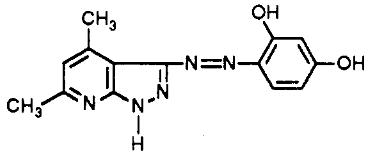
The acid dissociation constants of some hydroxy azopyrazolopyridine derivatives are determined in aqueous-organic solvent mixtures. The organic solvents are methanol, ethanol, acetone, and DMF. The results obtained are discussed in terms of the solvent characteristics. The ionization constants of the dyes in question depend largely on both the proportion and nature of the organic cosolvent. Hydrogen-bonding interactions of the conjugate base with solvent molecules as well as the solvent basicity contribute the major effects on the ionization process. The effect of molecular structure of the azo compound on the pK_a value is discussed.

Introduction

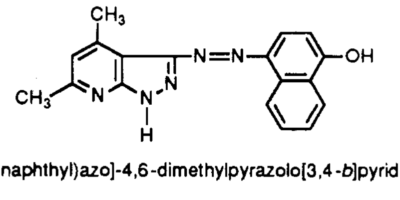
The widespread applications of azo compounds as dyes, acid-base, redox, and metallochrome indicators, or histological stains have attracted the attention of many researchers to study their acid-base properties (*1-5*). However, the literature is lacking studies concerning the acid-base properties of azo compounds containing the pyrazolopyridine moiety which are thought of special interest due to their biological and therapeutical importance (*6, 7*). In continuation of our studies on the acid-base properties of azo compounds (*4,8-10*), we have investigated the medium effect on the ionization constants of some hydroxy azopyrazolopyridine derivatives by the study of the visible spectra of the compounds in aqueous buffer solutions containing varying proportions of organic solvents of different polarities, such as methanol, ethanol, acetone, and dimethylformamide. The pK_a values have been determined and discussed in terms of solvent characteristics. The hydroxy azopyrazolopyridine derivatives studied have the following structures:



3-[(4-hydroxy-2-methylphenyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine (HMPAPP)



3-[(2,4-dihydroxyphenyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine (HPAPP)



3-[(4-hydroxynaphthyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine (HNAPP)

Experimental Section

Hydroxy azopyrazolopyridines were prepared as described previously (*11,12*). Stock solutions (10^{-3} M) of the compounds were prepared by dissolving a known mass of the solid in the required volume of the solvent. The pH control was achieved by using the modified universal buffer solution (*13*).

To account for the difference in acidity, basicity, dielectric constant, and ion activities in partially aqueous media relative to pure aqueous solutions, where the pH meter is standardized using aqueous buffers, the pH values in the former media were corrected making use of the procedure described by Douheret (*14*):

$$\mathrm{pH}^* = \mathrm{pH(R)} - \delta \qquad (1)$$

where pH* is the corrected value, and pH(R) is the pH meter reading obtained in water-organic solvent mixtures. Values of δ for various aqueous-organic solvent mixtures were determined as recommended by Douheret (*14, 15*).

The absorption spectra were recorded on a CECIL 599 spectrophotometer within a wavelength range of 300-600 nm using 1-cm matched silica cells. The pH measurements were carried out using an Orion 501 digital ionalyzer accurate to ±0.01 pH unit. All measurements were carried out at room temperature (~25 °C).

Results and Discussion

The visible absorption spectra of the hydroxy azopyrazolopyridines in buffer solutions containing different proportions of an organic solvent (methanol, ethanol, acetone, or DMF) show mainly two bands (Figure 1). The shorter wavelength band, appearing at low pH values (pH <8.0), represents absorption by the nonionized species, whereas the longer wavelength band, observed at higher pH's (>9.0), is due to the absorption by ionized species. On increasing the pH of the medium, the absorbance of the former band decreases while that of the latter band increases, where a fine isosbestic point is achieved, denoting the existence of an equilibrium of the type

$$\mathrm{HA} \rightleftharpoons \mathrm{H}^+ + \mathrm{A}^- \qquad (2)$$

The sigmoidal absorbance-pH* curves are typical dissociation ones confirming the establishment of an acid-base equilibrium in each case. Representative curves are shown in Figure 2.

The acid dissociation constants, pK_a, of the compounds are determined from the variation of the absorbance with

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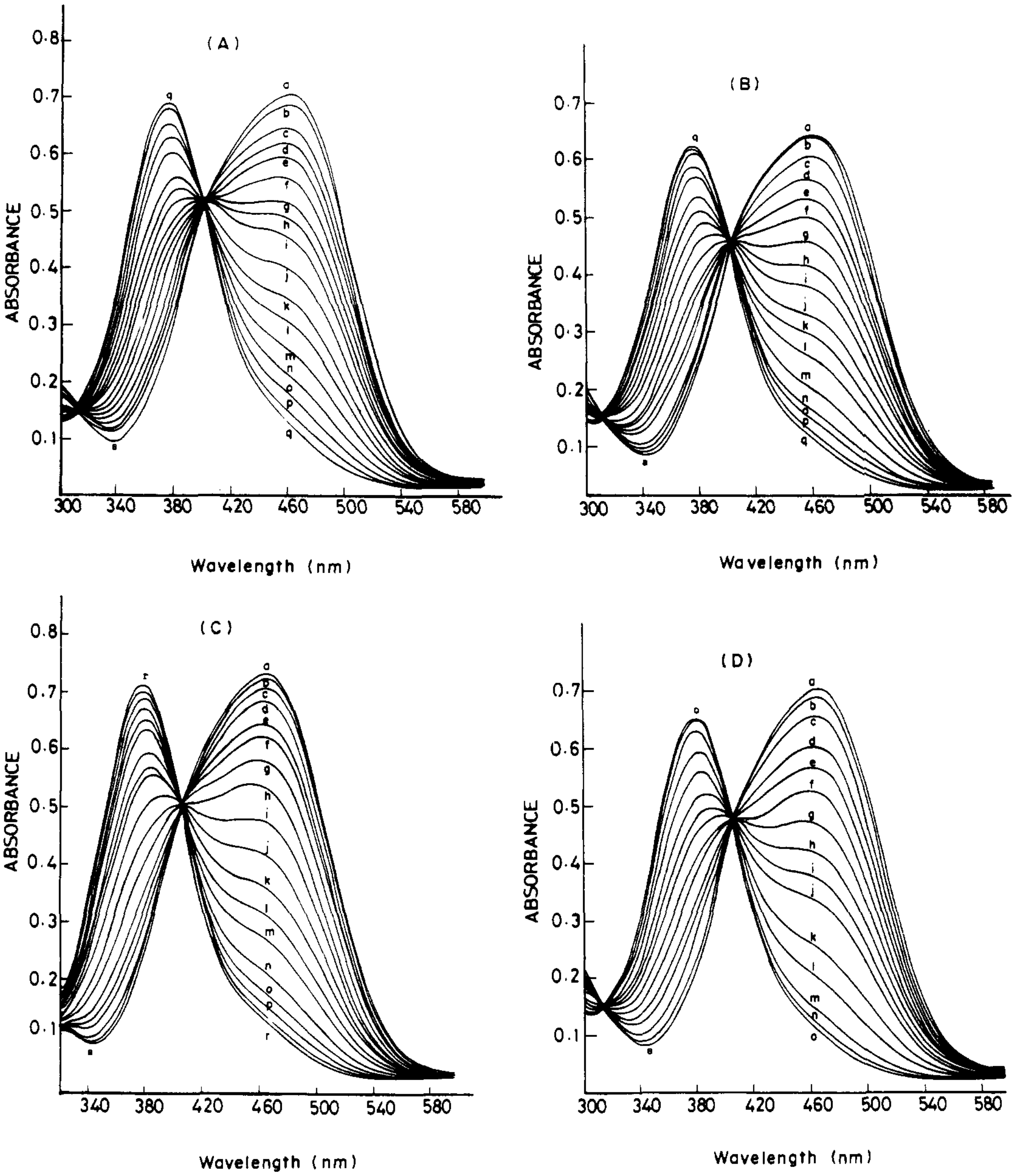


Figure 1. Absorption spectra of 3-[(4-hydroxy-2-methylphenyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine in organic solvent (1)–water (2) at different pH's: (A) w_1 = 0.2535 methanol, pH* (a) 9.81, (b) 9.60, (c) 9.37, (d) 9.26, (e) 9.15, (f) 9.03, (g) 8.90, (h) 8.80, (i) 8.70, (j) 8.60, (k) 8.44, (l) 8.30, (m) 8.10, (n) 7.90, (o) 7.70, (p) 7.42, (q) 6.76; (B) w_1 = 0.2542 ethanol, pH* (a) 10.96, (b) 10.59, (c) 10.36, (d) 10.14, (e) 9.86, (f) 9.72, (g) 9.57, (h) 9.42, (i) 9.20, (j) 9.05, (k) 8.88, (l) 8.73, (m) 8.57, (n) 8.30, (o) 8.04, (p) 7.8, (q) 7.34, (r) 6.84; (C) w_1 = 0.2535, pH* (a) 10.37, (b) 10.14, (c) 9.90, (d) 9.63, (e) 9.48, (f) 9.34, (g) 9.21, (h) 9.05, (i) 8.92, (j) 8.76, (k) 8.64, (l) 8.48, (m) 8.21, (n) 7.96, (o) 7.73, (p) 7.24, (q) 6.72; (D) w_1 = 0.2896 DMF, pH* (a) 10.58, (b) 10.14, (c) 9.83, (d) 9.53, (e) 9.38, (f) 9.20, (g) 9.04, (h) 8.88, (i) 8.76, (j) 8.62, (k) 8.35, (l) 8.10, (m) 7.61, (n) 6.70, (o) 5.70.

pH*, making use of three different spectrophotometric methods, namely, the half-curve height, isosbestic point, and limiting absorbance (*16, 17*). The obtained results are given in Tables I–III.

The results listed in these tables show that the pK_a values of all the compounds are dependent upon both the nature and proportion of the organic cosolvent. In general, increasing the organic cosolvent content in the medium results in an increase in the pK_a value. This can be explained as follows. According to Coetzee and Richie (*18*), the acidity constant in a pure aqueous medium (K_{a_1}) can be related to that in water–organic solvent mixtures (K_{a_2}) by the equation

$$K_{a_1} = K_{a_2}(\gamma_{H^+}\gamma_{A^-}/\gamma_{HA}) \qquad (3)$$

where γ is the activity coefficient of the subscripted species in a partially aqueous medium relative to that in a pure aqueous one. Since it is known that the electrostatic effects of solvents operate only on the activity coefficients of charged species (*18*), one can expect that the increase in the amount of the organic cosolvent in the medium will increase the activity coefficients of both H^+ and A^- ions. According to eq 3, this will result in a decrease in the acid dissociation constant K_{a_1} (high pK_a value), which is consistent with the results reported in Tables I–III.

However, methanol and DMF have approximately similar dielectric constants (32.6 and 36.7, respectively, at 25 °C) so that electrostatic effects in aqueous solutions containing the same mole fraction of these two solvents are expected to be virtually indentical (i.e., pK_a values of a compound in such solutions should be the same). The general trend is that HPAPP and HNAPP are less and HMPAPP is more acidic in the presence of methanol than in DMF (cf. Tables I–III

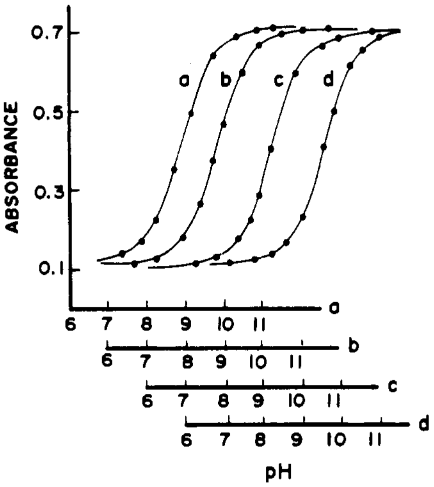


Figure 2. Absorbance–pH* curves for 3-[(4-hydroxy-2-methylphenyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine in dimethylformamide (1)–water (2).

Table I. pK_a Values of 3-[(4-Hydroxy-2-methylphenyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine (4.0 × 10^{-5} M) in Various Mass Fractions w_1 of Water–Organic Solvent Mixtures

		pK_a			
$100w_1$	D_m[a]	method 1	method 2	method 3	mean value
			Methanol (1)–Water (2)		
0.1653	73.72	8.65	8.60	8.65	8.63
0.2535	71.03	9.00	9.05	8.95	9.00
0.3456	67.88	9.10	9.25	9.20	9.18
0.4421	64.27	9.40	9.45	9.42	9.42
			Ethanol (1)–Water (2)		
0.1659	74.46	8.50	8.57	8.42	8.49
0.2542	72.00	8.65	8.76	8.65	8.68
0.3465	69.08	8.88	8.95	8.85	8.89
0.4430	65.54	9.09	9.10	9.05	9.08
			Acetone (1)–Water (2)		
0.1654	74.92	8.80	8.87	8.75	8.80
0.2535	72.87	9.10	9.20	9.10	9.13
0.3456	70.25	9.60	9.40	9.30	9.43
0.4421	66.99	9.60	9.65	9.55	9.60
			DMF (1)–Water (2)		
0.1921	76.06	8.90	8.75	8.65	8.76
0.2896	74.56	8.85	8.95	8.90	8.90
0.3881	72.73	9.15	9.23	9.20	9.19
0.4875	70.45	9.55	9.53	9.55	9.54

[a] Dielectric constant of the medium.

and Figure 2). Moreover, though ethanol and acetone have comparable dielectric constants also (24.3 and 20.7, respectively, at 25 °C), all the compounds are more acidic in water–ethanol than in water–acetone, where the same mole fraction of each is used. This behavior indicates that other solvent effects beside the electrostatic one have a contribution in the ionization process of the investigated compounds. This fact is further substantiated by the nonlinear relations obtained by plotting pK_a against $1/D_m$ of the medium (Figure 3) according to the equation given by Denison and Ramsey (*19*), as well as by Gilkerson (*20*), which relates the variation of the pK_a of the acid with the dielectric constant of the medium (D_m). The dielectric constant of the medium, D_m, is obtained from the relation

$$D_m = D_{(w)}m_{f(w)} + D_{(s)}m_{f(s)} \qquad (4)$$

where D and m_f are the dielectric constant and mole fraction and the subscripts w and s refer to water and organic solvent, respectively.

Table II. pK_a Values of 3-[(2,4-Dihydroxyphenyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine (4.0 × 10^{-5} M) in Various Mass Fractions w_1 of Water–Organic Solvent Mixtures

		pK_a			
$100w_1$	D_m[a]	method 1	method 2	method 3	mean value
			Methanol (1)–Water (2)		
0.1653	73.73	6.53	6.55	6.53	6.54
0.2535	71.03	6.65	6.70	6.72	6.69
0.3456	67.88	6.80	6.88	6.80	6.83
0.4421	64.27	7.10	7.12	7.12	7.11
			Ethanol (1)–Water (2)		
0.1659	74.46	6.60	6.70	6.50	6.60
0.2542	72.00	6.85	6.95	5.80	6.87
0.3465	69.08	7.22	7.25	7.20	7.22
0.4430	65.54	7.52	7.60	7.50	7.54
			Acetone (1)–Water (2)		
0.1653	74.92	6.73	6.85	6.73	6.78
0.2535	72.87	7.10	7.22	7.10	7.14
0.3456	70.25	7.40	7.48	7.40	7.43
0.4421	66.99	7.80	7.88	7.75	7.81
			DMF (1)–Water (2)		
0.1921	76.06	5.28	5.35	5.33	5.32
0.2896	74.56	5.10	5.15	5.13	5.13
0.3881	72.73	5.20	5.20	5.20	5.20
0.4875	70.45	5.40	5.43	5.37	5.40

[a] Dielectric constant of the medium.

Table III. pK_a Values of 3-[(4-Hydroxynaphthyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine (4.0 × 10^{-5} M) in Various Mass Fractions w_1 of Water–Organic Solvent Mixtures

		pK_a			
$100w_1$	D_m[a]	method 1	method 2	method 3	mean value
			Methanol (1)–Water (2)		
0.1653	73.72	7.60	7.35	7.60	7.52
0.2535	71.03	7.70	7.50	7.70	7.63
0.3456	67.88	7.78	7.68	7.80	7.75
0.4421	64.27	7.98	7.77	7.95	7.90
			Ethanol (1)–Water (2)		
0.1659	74.46	7.50	7.30	7.50	7.43
0.2542	72.00	7.75	7.57	7.70	7.67
0.3465	69.08	8.15	7.90	8.10	8.05
0.4430	65.54	8.36	8.15	8.33	8.28
			Acetone (1)–Water (2)		
0.1653	74.92	7.55	7.35	7.50	7.47
0.2535	72.87	7.80	7.55	7.80	7.72
0.3456	70.25	8.10	7.85	8.05	8.00
0.4421	66.99	8.40	8.20	8.33	8.31
			DMF (1)–Water (2)		
0.1921	76.06	7.40	7.20	7.38	7.33
0.2896	74.56	7.52	7.30	7.54	7.45
0.3881	72.73	7.70	7.25	7.65	7.53
0.4875	70.45	7.80	7.25	7.80	7.62

[a] Dielectric constant of the medium.

In general, effects such as hydrogen bonding, solvent basicity, dispersion forces, and proton–solvent interactions play vital roles in the ionization process of acids in the presence of organic solvents (*18*). Thus, the observed increase in the pK_a of the compounds as the proportion of the organic cosolvent in the medium is increased can be ascribed, in addition to the electrostatic effect, to the hydrogen-bonding interaction between the conjugate base (A^-) and solvent molecules. Since water molecules have a higher tendency to donate hydrogen bonds than other solvent molecules (*21*), the conjugate base (A^-) is expected to be less stabilized by hydrogen-bonding interaction with solvent molecules as the amount of the organic cosolvent in the medium is increased (i.e., γ_{A^-} increases). This will tend to increase the pK_a value of the compound as eq 3 implies. It indicates also that the

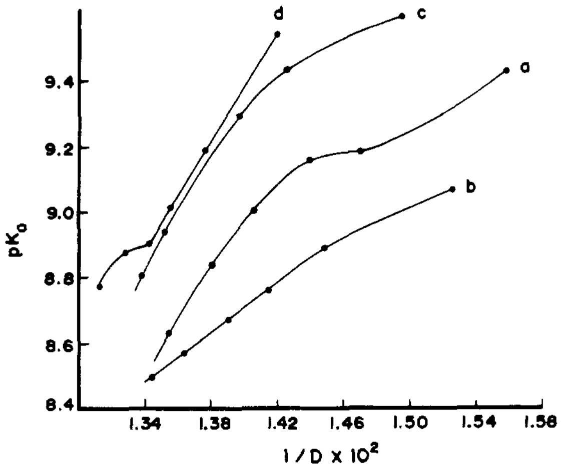


Figure 3. Variation of pK_a of 3-[(4-hydroxy-2-methylphenyl)azo]-4,6-dimethylpyrazolo[3,4-*b*]pyridine in organic solvent–water with $1/D_m$ of the medium at 25 °C: (a) methanol, (b) ethanol, (c) acetone, (d) DMF.

difference in the stabilization of the ionic form by hydrogen bond donor solvent molecules plays an important role for the increase in the pK_a value as the amount of the organic cosolvent in the medium is increased.

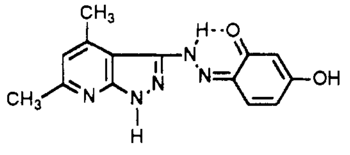
Examination of the results in Tables I–III reveals that the pK_a values in the presence of the poorer hydrogen bond donor DMF are less than those obtained in the presence of corresponding amounts of the other solvents. This behavior can be ascribed to the high basic character of DMF which reflects itself in the construction of a strong hydrogen bond acceptor from the OH group of the nonionized dye molecule and consequently promotes the ionization process (i.e., low pK_a).

If the dispersion forces, which possibly exist in the used media, between the delocalized charge on the conjugate base of the dye (A^-) and the localized dispersion centers in near solvent molecules as well as the proton–solvent interaction have important effects on the ionization process of the studied compounds, one should expect that by increasing the amount of the organic cosolvent both A^- and H^+ will be highly stabilized by DMF molecules (i.e., γ_{A^-} and γ_{H^+} decrease), since the effective density of dispersion centers in each of the organic solvents used is higher than that of water (*22*). Thus, in light of eq 3, the acid dissociation constant of the studied dyes would increase (pK_a decreases) with the increase in the amount of the organic cosolvent in the medium. This is not the case as is evident from the obtained results (cf. Tables I–III). Therefore, one can conclude that both the dispersion forces and proton solvent interaction effects do not have an effective contribution in the ionization process of the azopyrazolopyridine dyes.

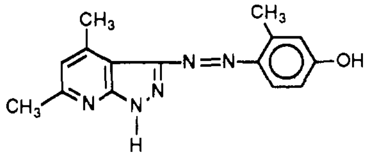
Effect of Molecular Structure. The values of pK_a, reported in Tables I–III, show that the acidity of the studied azo compounds increases in the order

HPAPP < HNAPP < HMPAPP

This trend can be explained on the basis of the fact that HPAPP which exists in the hydrazone form (*12*) has an electron-withdrawing carbonyl group (cf. structure I) which decreases the electron density on the oxygen of the OH group. This in turn weakens the bonding between the oxygen and hydrogen atoms, causing easier ionization. On the contrary, the electron-releasing methyl group of HMPAPP (structure II), which was found to exist in solution in the true azo form (*12*), increases the electron density on the OH group oxygen of this compound and thus retards its ionization.



(I) HPAPP



(II) HNAPP

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