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Medium Effect on the Acid Dissociation Constants of Some Heterocyclic Azo Compounds

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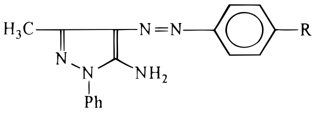
The effect of different organic solvent + water mixtures on the acid dissociation constants of protonated 5-amino-4-(arylazo)-3-methyl-1-phenylpyrazole derivatives were studied. The organic solvents used are methanol, ethanol, acetone, and dimethylformamide. The results obtained were discussed in terms of the solvent characteristics.The pK_{BH^+} values of the dyes in question were determined and found to depend on both the amount and nature of the organic cosolvent. The decrease of the pK_{BH^+} values as the amount of organic solvent in the medium is increased can be accounted for in terms of the high stabilization of the protonated form of the compounds by dispersion forces rather than by hydrogen bonding. Also the effect of solvent polarizability and hydrogen-bonding interaction on the pK_{BH^+} values and thus on the spectra of the charge-transfer band observed have been discussed. The absolute pK_{BH^+} value for each compound despite the presence of more than one basicity center has also been discussed.

Introduction

The widespread applications of the azo compounds in various fields have attracted the attention of many researchers, prompting them to study their spectral and acid−base properties (Issa et al.,1972; Hammam et al., 1979; El-Haty et al., 1991). Aminopyrazoles are of considerable interest as intermediates in many useful biochemical reactions (El-Nagdi et al., 1983). Skipper et al. (1957) have shown that aminopyrazole derivatives are potential drugs for schistosomiasis. The literature reveals that few studies have been made on the medium effects on the basicity of such compounds. In continuation of our studies on the acid−base properties of azo compounds (Mahmoud et al., 1983; Hammam et al.,1993; Rageh, 1998) we investigate the medium effect on the basicity of the NH_2 group belonging to the 1-phenylpyrazole moiety by the study of the electronic spectra of the compounds in aqueous acetate buffer solutions containing varying proportions of organic solvents of different polarities, such as methanol, ethanol, acetone, and dimethylformamide (DMF). The pK_{BH^+} values have been determined and discussed in terms of solvent characteristics. The studied compounds have the following structure.



R = H(I), OCH_3 (II); $COCH_3$(III); NO_2(IV)

I- 5-Amino-4-[(phenyl)azo]-3-methyl-1-phenyl pyrazole (PAP).

II- 5-Amino-4-[(4-methoxyphenyl)azo]-3-methyl-1-phenyl pyrazole (MAP)

III-5-Amino-4-[(4-acetylphenyl)azo]-3-methyl-phenyl pyrazole (AAP)

IV- 5-Amino-4-[(4-Nitrophenyl)azo]-3-methyl-1-phenyl pyrazole (NAP)

Experimental Section

5-Amino-3-methyl-1-phenylpyrazole prepared according to the procedure previously described by Vergl Michaelis (1905). 5-Amino-4-(arylazo)-3-methyl-1-phenylpyrazole derivatives were prepared according to the following procedure: The appropriate amine (aniline, *p*-anisidine, *p*-acetylaniline, or *p*-nitroaniline, 0.054 mol) was dissolved in diluted HCl (32 mL; 5.49 mol), and the resulting solution was cooled in an ice bath to 5 °C. This solution was added dropwise with stirring to a cold solution of sodium nitrite (4 g; 0.058 mol/(20 mL of H_2O)).

The resulting diazonium salt was added slowly with stirring to a cold solution (9.3 g; 0.05 mol) of 5-amino-3-methyl-1-phenylpyrazole in 20 mL of diluted HCl (this compound was prepared by the reaction of aminocrotonitrile with phenylhydrazine). After the completion of the addition, stirring was continued for 15 min and then a solution of sodium acetate (20 g/(60 mL of H_2O)) was added until complete precipitation of the dye was achieved. The solid precipitate was filtered, washed with cold water, and recrystallized from ethanol to give the corresponding azo derivatives. The purity of these compounds was checked by microanalysis and by IR spectroscopy. Stock solutions (10^{-3} mol dm^{-3}) 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 acetate buffer solution (Britton, 1952). To account for the difference in acidity, basicity, relative permittivity, and ion activities in partially aqueous media relative to pure aqueous solutions, where the pH meter is standardized using aqueous buffers at 25 °C, the pH values in the former media were corrected by using the procedure described by Douheret (1967).

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

where pH* is the corrected reading and pH(R) is the meter reading obtained in water−organic solvent mixtures.

The values of δ of the aqueous buffer solutions containing varying proportions of each of the organic solvents used were determined by Douheret (1967, 1968). The solutions were thermostated at (25 ± 0.2) °C before their spectra were measured. The absorption spectra were recorded on a Shimadzu 2401PC spectrophotometer, containing a ther-

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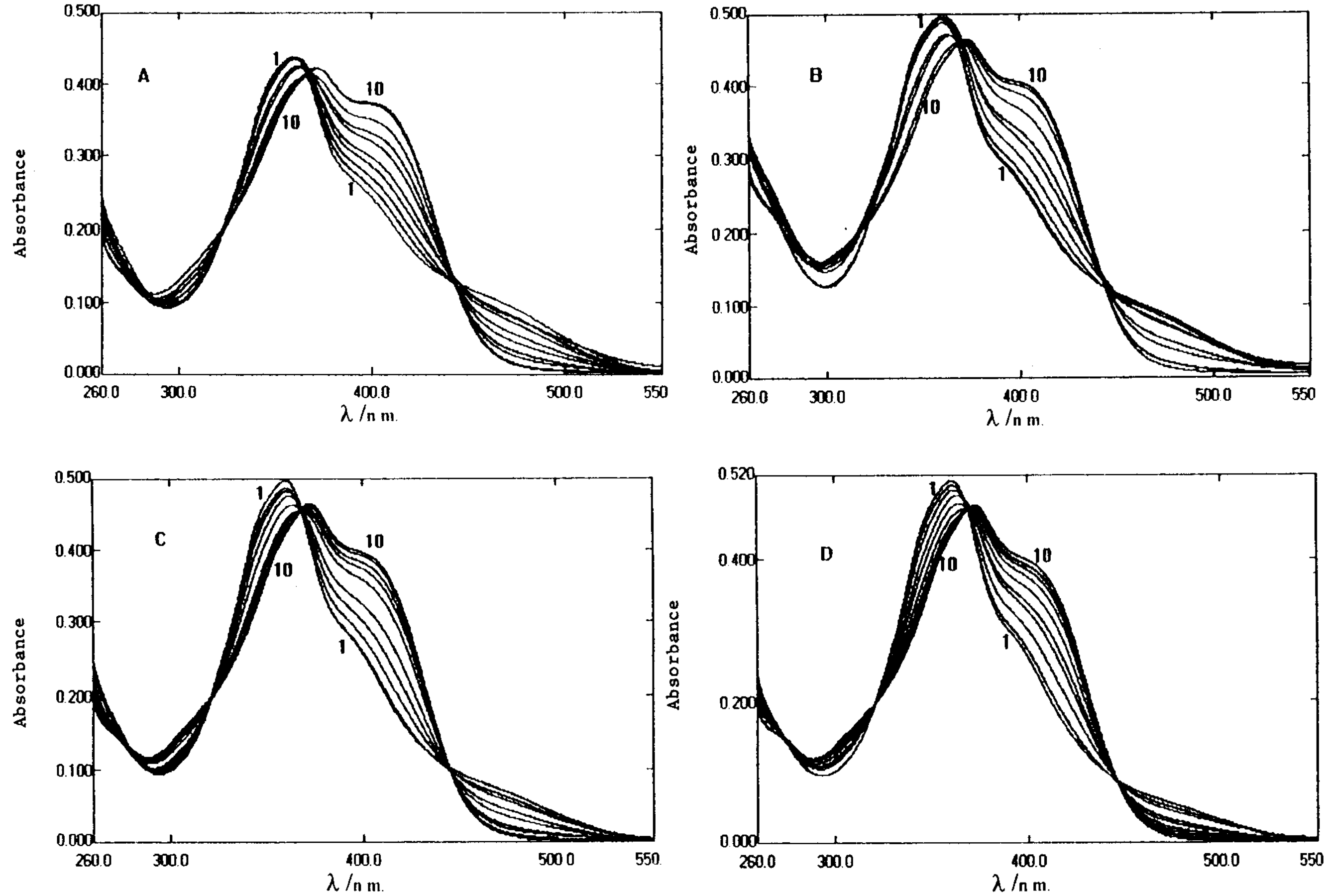


Figure 1. Absorption spectra of 2.0 × 10^{-5} M compound II (MAP) in water (1) + methanol (2) at different pH's: (A) $w_2 = 0.1653$ methanol; pH* (1) 0.60, (2) 1.02, (3) 1.24, (4) 1.35, (5) 1.55, (6) 1.85, (7) 2.11, (8) 2.39, (9) 3.00, and (10) 3.5. (B) $w_2 = 0.2535$ methanol; pH* (1) 0.58, (2) 0.71, (3) 0.93, (4) 1.12, (5) 1.3, (6) 1.56, (7) 1.84, (8) 2.07, (9) 2.58, and (10) 3.85. (C) $w_2 = 0.3456$ methanol; pH* (1) 0.65, (2) 0.77, (3) 0.95, (4) 1.17, (5) 1.45, (6) 1.81, (7) 2.06, (8) 2.39, (9) 2.96, and (10) 3.65. (D) $w_2 = 0.4421$ methanol; pH* (1) 0.69, (2) 0.82, (3) 1.09, (4) 1.3, (5) 1.48, (6) 1.72, (7) 2.01, (8) 2.25, (9) 2.42, and (10) 3.4.

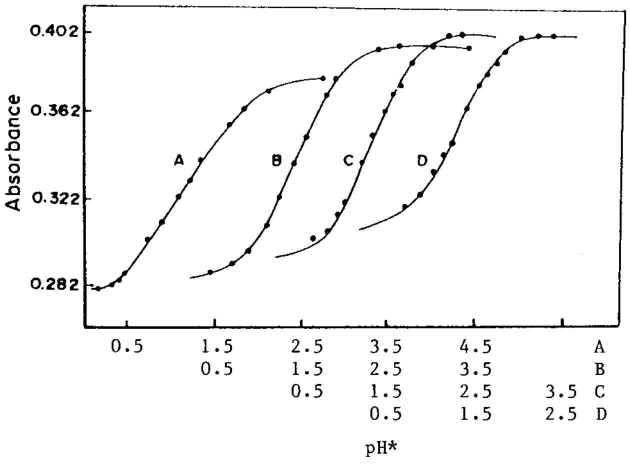


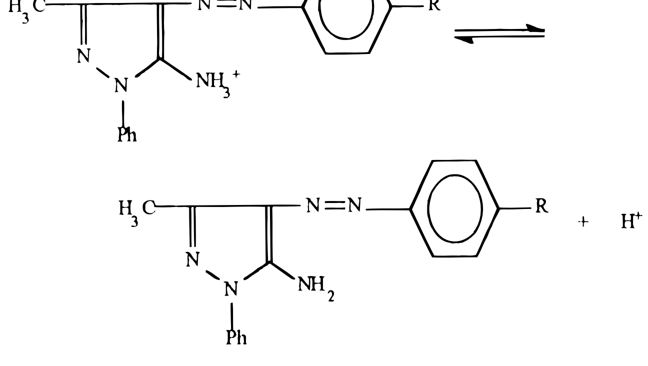
Figure 2. Absorption–pH* curves for compound I (PAP) in water (1) + acetone (2), w_2 = (a) 16.53, (b) 25.42, (c) 34.56, and (d) 44.21.

moelectrically temperature-controlled cell holder, within the wavelength range of 240–580 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 (25 ± 0.2) °C, and temperature control was achieved using an ultrathermostat of accuracy ±0.2 °C.

Results and Discussion

The visible absorption spectra of 5-amino-4-(arylazo)-3-methyl-1-phenylpyrazole derivatives in acetate buffer solutions containing different proportions of an organic solvent (methanol, ethanol, acetone and DMF) show mainly two bands (Figure 1). The shorter wavelength band, appearing at low pH* values (pH* < 1.0), is mainly due to absorption by protonated species, whereas the longer wavelength band, observed at higher pH* values (pH*s > 1.5), is due to the absorption by neutral molecule. 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

$$H_2A^+ \rightleftharpoons HA + H^+ \qquad (2)$$



The absorbance–pH* curves obtained in all cases, as shown

Table 1. pK_{BH^+} Values for 2 × 10^{-5} M of PAP in Various Mass Fractions w_2 of Water (1) + Organic Solvent (2) Mixtures at 25 °C

$100w_2$	ϵ	mole fraction of organic solvent	pK_{BH^+} method 1	pK_{BH^+} method 2	pK_{BH^+} method 3	pK_{BH^+} mean value	SD
			Water (1) + Methanol (2)				
0.1653	73.7 2	0.1000	1.85	1.84	1.81	1.83	±0.017
0.2535	71.03	0.1602	1.75	1.73	1.65	1.71	±0.043
0.3456	67.88	0.2288	1.57	1.57	1.52	1.55	±0.42
0.4421	64.26	0.3080	1.40	1.43	1.40	1.41	±0.014
			Water (1) + Ethanol (2)				
0.1659	74.46	0.0720	1.67	1.67	1.65	1.66	±0.009
0.2542	72.00	0.1175	1.30	1.30	1.32	1.31	±0.009
0.3465	69.08	0.176	1.10	1.10	1.10	1.10	±0.000
0.4430	65.54	0.2371	1.07	1.10	1.10	1.09	±0.014
			Water (1) + Acetone (2)				
0.1653	74.92	0.0525	1.65	1.70	1.67	1.67	±0.021
0.2535	72.87	0.0952	1.55	1.55	1.45	1.52	±0.047
0.3456	70.25	0.1407	1.40	1.42	1.42	1.41	±0.009
0.4421	66.99	0.1972	1.35	1.40	1.40	1.38	±0.024
			Water (1) + DMF (2)				
0.1921	76.06	0.0553	1.28	1.30	1.24	1.27	±0.025
0.2896	74.56	0.09123	1.10	1.07	1.04	1.07	±0.025
0.3881	72.73	0.1351	0.92	1.00	1.06	0.99	±0.057
0.4875	70.45	0.1898	0.88	0.90	0.92	0.90	±0.016

Table 2. pK_{BH^+} Values for 2.0 × 10^{-5} M of MAP in Various Mass Fractions w_2 of Water (1) + Organic Solvent (2) Mixtures at 25 °C

$100w_2$	ϵ	mole fraction of organic solvent	pK_{BH^+} method 1	pK_{BH^+} method 2	pK_{BH^+} method 3	pK_{BH^+} mean value	SD
			Water (1) + Methanol (2)				
0.1653	73.72	0.1000	1.70	1.73	1.70	1.71	±0.014
0.2535	71.03	0.1602	1.50	1.50	1.65	1.55	±0.071
0.3456	67.88	0.2288	1.45	1.48	1.48	1.47	±0.014
0.4421	64.26	0.3080	1.40	1.42	1.45	1.42	±0.021
			Water (1) + Ethanol (2)				
0.1659	74.46	0.0720	1.54	1.50	1.52	1.52	±0.016
0.2542	72.00	0.1175	1.48	1.46	1.46	1.47	±0.010
0.3465	69.08	0.176	1.24	1.30	1.32	1.29	±0.034
0.4430	65.54	0.2371	1.28	1.25	1.28	1.27	±0.014
			Water (1) + Acetone (2)				
0.1653	74.92	0.0525	1.50	1.51	1.52	1.51	±0.008
0.2535	72.87	0.0952	1.40	1.40	1.40	1.40	±0.000
0.3456	70.25	0.1407	1.20	1.23	1.20	1.21	±0.014
0.4421	66.99	0.1972	1.15	1.18	1.18	1.17	±0.014
			Water (1) + DMF (2)				
0.1921	76.06	0.0553	1.40	1.37	1.40	1.39	±0.014
0.2896	74.56	0.09123	1.15	1.15	1.15	1.15	±0.000
0.3881	72.73	0.1351	1.07	1.10	1.05	1.07	±0.021
0.4875	70.45	0.1898	0.88	0.90	0.98	0.92	±0.043

in Figure 2, are sigmoidal curves, confirming the establishment of an acid−base equilibrium in each case.

The acid dissociation constant of the protonated form of the compounds were determined from the variations of the absorbance with pH*, making use of three different spectrophotometric methods, namely, the half-curve height, isosbestic point, and limting absorbance (Issa et al., 1971, 1972). The values were calculated by using a simple program. The experimental error in detrmined pK_{BH^+} values was checked by using the least-squares method. The obtained results are given in Tables 1−4.

Examination of the results cited in Tables 1−4 reveals that pK_{BH^+} values of all compounds are largely dependent upon both the nature and the proportion of the organic cosolvent. Generally, pK_{BH^+} values decrease with an increase of the organic cosolvent content in the medium. This can be interpreted on the principle of the expected relatively high stabilization of the protonated form (H_2A^+) by dispersion force in the different solvent−water mixtures.

On the other hand, methanol and DMF have approximately similar relative permittivity constants (32.6 and 36.7, respectively, at 25 °C), so that the electrostatic effects in aqueous solutions containing the same mole fraction of these two solvents are expected to be virtually identical (i.e, pK_{BH^+} values of a compound in such solutions should be the same). The general trend observed is that these values in all compounds are higher in the presence of methanol than with DMF. (cf. Tables 1−4 and Figure 2).

Moreover, though ethanol and acetone have comparable relative permittivity constants too (24.3 and 20.7, respectively, at 25 °C), NAP and MAP have pK_{BH^+} values in the water + ethanol mixture more than in the water + acetone mixture, where the same mole fraction of each is used. This trend is the converse for PAP and AAP. This behavior

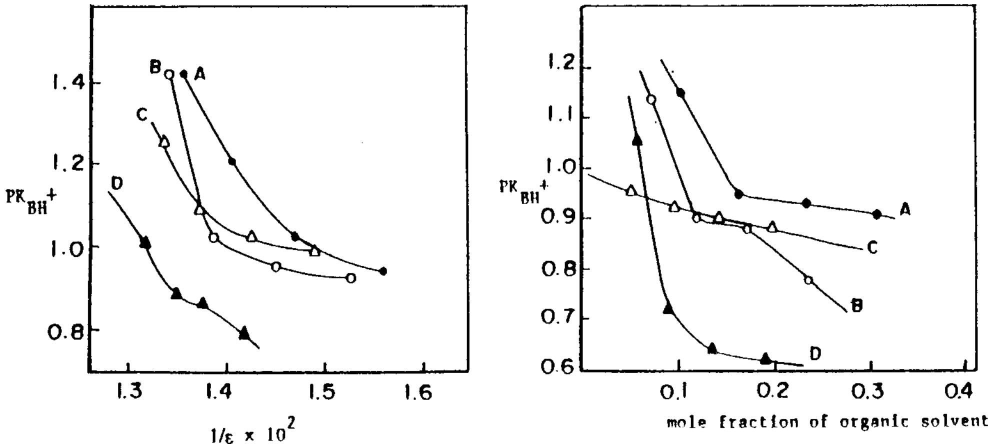


Figure 3. (a, left) Variation of pK_{BH^+} of compound IV (NAP) in water (1) + organic solvent (2) with $1/\epsilon \times 10^2$ of the medium at 25 °C: (A) methanol, (B) ethanol, (C) acetone, and (D) DMF. (b, right) Variation of pK_{BH^+} of compound III (AAP) with the mole fraction of the organic solvent present in the aquous medium: (A) methanol, (B) ethanol, (C) acetone, and (D) DMF.

Table 3. pK_{BH^+} Values for 2.0×10^{-5} M of AAP in Various Mass Fractions w_2 of Water (1) + Organic Solvent (2) Mixtures at 25 °C

100w_2	ϵ	mole fraction of organic solvent	pK_{BH^+}				SD
			method 1	method 2	method 3	mean value	
			Water (1) + Methanol (2)				
0.1653	73.72	0.1000	1.40	1.45	1.40	1.42	±0.024
0.2535	71.03	0.1602	1.20	1.25	1.15	1.20	±0.041
0.3456	67.88	0.2288	1.03	0.97	1.00	1.00	±0.025
0.4421	64.27	0.3080	0.92	0.95	0.92	0.93	±0.014
			Water (1) + Ethanol (2				
0.1659	74.46	0.0720	1.40	1.45	1.40	1.42	±0.024
0.2542	72.00	0.1175	1.00	1.02	1.02	1.01	±0.009
0.3465	69.08	0.176	0.95	0.95	1.02	0.97	±0.033
0.4430	65.54	0.2371	0.92	0.92		0.92	±0.000
			Water (1) + Acetone (2)				
0.1653	74.92	0.0525	1.22	1.25	1.20	1.22	±0.021
0.2535	72.87	0.0952	1.05	1.10	1.10	1.08	±0.024
0.3456	70.25	0.1407	1.00	1.05	1.04	1.03	±0.022
0.4421	66.99	0.1972	0.97	1.01		0.99	±0.020
			Water (1) + DMF (2)				
0.1921	76.06	0.0553	1.00	1.00	0.95	0.98	±0.024
0.2896	74.56	0.09123	0.88	0.85	0.90	0.88	±0.021
0.3881	72.73	0.1351	0.83	0.87	0.88	0.86	±0.022
0.4875	70.45	0.1898	0.77	0.79		0.76	±0.010

Table 4. pK_{BH^+} Values for 2.0×10^{-5} M of NAP in Various Mass Fractions w_2 of Water (1) + Organic Solvent (2) Mixtures at 25 °C

100w_2	ϵ	mole fraction of organic solvent	pK_{BH^+}				SD
			method 1	method 2	method 3	mean value	
			Water (1) + Methanol (2)				
0.1653	73.72	0.1000	1.05	1.05	1.02	1.04	±0.014
0.2535	71.03	0.1602	0.95	0.95	0.95	0.95	±0.000
0.3456	67.88	0.2288	0.92	0.93	1.05	0.96	±0.059
0.4421	64.27	0.3080	0.90	0.92		0.91	±0.010
			Water (1) + Ethanol (2)				
0.1659	74.46	0.0720	1.07	1.07	1.00	1.05	±0.033
0.2542	72.00	0.1175	0.87	0.90	0.90	0.89	±0.014
0.3465	69.08	0.176	0.85	0.90	0.90	0.88	±0.240
0.4430	65.54	0.2371	0.82	0.80		0.81	±0.010
			Water (1) + Acetone (2)				
0.1653	74.92	0.0525	0.95	0.96	0.95	0.95	±0.005
0.2535	72.87	0.0952	0.92	0.92	0.92	0.92	±0.000
0.3456	70.25	0.1407	0.87	0.88	0.93	0.89	±0.026
0.4421	66.99	0.1972	0.85	0.80	0.80	0.82	±0.024
			Water (1) + DMF (2)				
0.1921	76.06	0.0553	1.05	1.05	1.00	1.03	±0.024
0.2896	74.56	0.09123	0.70	0.72	0.75	0.72	±0.021
0.3881	72.73	0.1351	0.65	0.63	0.62	0.63	±0.013
0.4875	70.45	0.1898	0.60	0.65		0.62	±0.025

supports that other solvent effects beside the electrostatic one have a contribution in the acid−base process of the investigated compounds. This fact is further substantiated by the nonlinear relationship obtained by plotting pK_{BH^+} against $1/\epsilon$ of the medium (Figure 3), according to the equation given by Denison and Ramsey (1955), as well as by Gilkerson (1956) which relates the variation of the pK_a with the relative permittivity of the medium (ϵ). The relative permittivity of the medium, ϵ, is obtained from the relation

$$\epsilon = \epsilon_w x_{f,w} + \epsilon_s x_{f,s} \tag{3}$$

where ϵ and x_f are the relative permittivity and mole fraction and the subscripts w and s refer to water and organic solvent, respectively.

The observed decrease in pK_{BH^+} of each compound as the proportion of the organic cosolvent in the medium is increased can be attributed, in addition to the relative permittivity, to the high stabilization of the free base HA by hydrogen bonding in pure aqueous medium relative to that in the presence of organic solvents. Since water molecules have a higher tendency to donate hydrogen bonds than other solvent molecules (Franks and Ives, 1966), accordingly the free base of the studied compounds 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 (El-Gyar et al., 1993). In the different media studied, an increase in the pK_{BH^+} values of the compounds under investigation is observed in the presence of the same percentage of the organic cosolvent in the medium according to the following sequence:

$$\text{DMF} < \text{acetone} < \text{ethanol} < \text{methanol}$$

This behavior is expected to occur as a result of decreasing medium polarizability on going from DMF + water to methanol + water within the above sequence (Alfenaar and Deligny, 1967).

The higher pK_{BH^+} values observed in methanol than in ethanol in solutions containing the same mole fraction of alcohol are due to the low tendency of ethanol to donate a hydrogen bond to the free base, since the tendency of alcohol to associate with solute through hydrogen bonding decreases with increasing molecular weight (Skipper et al., 1957). The pK_{BH^+} of the dyes under investigation show a small dependence of the nature of the substituent (cf. Tables 1−4). A similar behavior was observed before (John et al., 1985). The values of pK_{BH^+} of the nitrogen atoms of both the heterocyclic ring and azo group cannot be determined since their protonation does not show any order in the absorbance of the charge-transfer bands. This makes the evaluation of their pK_{BH^+} values inaccurate (El-Taher and Gabr, 1996).

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