Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 129 (2014) 209–218

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Acidity constant and solvatochromic behavior of some pyrazolo[1,5-a]pyrimidin-2-amine derivatives

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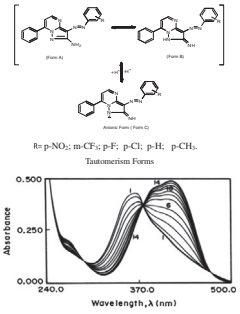
HIGHLIGHTS

- Novel pyrazolo[1,5-a]pyrimidin-2-amine derivatives have been synthesis and characterized.
- p*Ka* values depended largely on both the amount and basicity of organic solvent.
- The λ_{max} exhibits a red shift in order cyclohexane → CCl_4 → $CHCl_3$ → C_2H_5OH → DMF.

GRAPHICAL ABSTRACT

Electronic spectra, solvatochromic behavior and p*Ka* values of some [1,5-a] pyrimidin-2-amine derivatives have been studied. Absorption spectra of 1.0×10^{-5} M compound **VI** in water (1) + methanol (2) at different pH's.



ARTICLE INFO

Article history:
Received 27 November 2013
Received in revised form 5 March 2014
Accepted 18 March 2014
Available online 28 March 2014

Keywords:
Pyrazolo[1,5-a]pyrimidin-2-amine
Solvatochromic behavior
p*Ka* determined

ABSTRACT

The UV–visible electronic spectra of some azo compounds of pyrazolo[1,5-a]pyrimidin-2-amine have been studied. The solvatochromic behavior of these compounds was investigated by studying their spectra in pure organic solvents of different polarities such as cyclohexane carbon tetrachloride, chloroform, ethanol and DMF. These exhibits a red shift in its λ_{max} with increase relative permittivity of medium changing from cyclohexane → carbon tetrachloride → chloroform → ethanol → DMF. The acid dissociation constants of these compounds were determined in aqueous–organic solvent mixtures such as acetone, methanol, ethanol and DMF. The ionization constants of the dyes in question depend largely on both the proportion and the nature of the organic solvent basicity contribute the major effects on the ionization process. In general, p*Ka* values in all compounds decrease with increase relative permittivity of the medium. The acidity of studied azo compounds increases in the following order:

p-NO_2 < m-CF_3 < p-F < p-Cl < p-H < p-CH_3.

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http://dx.doi.org/10.1016/j.saa.2014.03.029
1386-1425/

Introduction

The widespread application of azo compounds as dyes, acid–base, redox, and metallochrome indicators, or histological stains has attracted the attention of many researchers to study their acid–base properties [1–4].

Innovations in azo dye based on heterocyclic systems have been made as a result of intensive studies stimulated by the mounting need for bright dyes. Generally, many of heterocyclic azo dyes shows dramatic bathochromic shifts combined with brilliance of shade and high tinctorial strength compared with conventional anthraquinone dyes and amino benzene azo dyes [5–8]. One of the most important azo dye series are arylazopyrazolopyrimidines derivatives that used in silk screen and heat transfer printing techniques on polyester and polyamide fabrics [9]. These dyes were also used in manufacture of clothing and products with antibacterial properties [9].

On the other hand, the knowledge of p*K*a is considered to be of great interest in organic and inorganic compounds, because it has a significant role in many chemical reactions; therefore, numerous works has been devoted to the determination of p*K*a values of different azo compounds [10–13]. However, some azo dyes have toxicological properties and therefore require sensitive and selective methods to determine their physicochemical characteristics [14].

The literature lacks studies on the acid–base properties or medium effects on the acid dissociation constants of azo compounds containing the pyrazolo[1,5-a]pyrimidines moiety, which are thought to be special interest owing to their biological and therapeutical importance [15,16].

This paper presents an investigation of the electronic spectra of some azopyrazolo[1,5-a]pyrimidine-2-amine derivatives in pure organic solvents of different polarities such as cyclohexane carbon tetrachloride, chloroform, ethanol and DMF.

We have investigated the medium effect on the ionization constants of azo compounds by the study of the electronic spectra of the compounds in aqueous buffer solutions containing varying proportions of organic solvents of different polarities, such as acetone, methanol, ethanol, and *N*,*N*-dimethyl formamide (DMF). The p*K*a values have been determined and discussed in terms of solvent characteristics.

Experimental

Materials

All spectrograde organic solvents were purchased from Aldrich and used as received unless otherwise stated. *E*-3-dimethylamino-1-phenylprop-2-en-1-one **(1)** [17] and 4-(Aryldiazenyl)-1H-pyrazole-3,5-diamine derivatives **2a–f** [18] were prepared according to the reported literature.

Instruments

Thin-layer chromatography (TLC) was performed on percolated Merck 60 GF254 silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. The melting points were measured with a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart TR, which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet IS10 FT-IR spectrophotometer. The NMR spectra were recorded on a Bruker Avance III 400 (9.4 T, 400.13 MHz for ^{1}H) spectrometer with a 5-mm BBFO probe, at 298 K. Chemical shifts (δ in ppm) are given relative to internal solvent, DMSO-d_6 2.50 for ^{1}H. Software (Topspin 3.2). Mass spectra were recorded on a Thermo ISQ Single Quadruple GCeMS. Elemental analyses were carried out on a Euro Vector instrument C, H, N, S analyzer EA3000 Series.

Microwave experiments were performed using CEM Discover & Explorer SP microwave apparatus (300 W), utilizing 35 ml capped glass reaction vessels automated power control based on temperature feedback.

The absorption spectra were recorded on a Shimatzu 2401PC spectrophotometer at 25 °C using 1 cm matched silica cells. The pH measurements were carried out using an Orion 501 digital analyzer accurate to ±0.01 pH units. All measurements were carried out at 25 °C, and temperature control was achieved using an ultra thermostat of accuracy ±0.05 °C.

Synthesis of pyrazolo[1,5-a]pyrimidin-2-amine derivatives

Method A: To a mixture of *E*-3-dimethylamino-1-phenylprop-2-en-1-one **(1)** (2 mmol) and the appropriate 4-(Aryldiazenyl)-1H-pyrazole-3,5-diamine **2a–f** (2 mmol) in glacial acetic acid (25 mL), concentrated sulfuric acid is added (0.5 ml); the reaction mixture was refluxed for about 9 h (as examined by TLC) and then left to cool. The solid product was filtered off, washed with ethanol, dried, and finally recrystallized from DMF/H_2O to afford the corresponding pyrazolo[1,5-a]pyrimidine derivatives **I–VI**.

Method B: This process was performed using microwave irradiation (300 W, 120 °C) on the same scale described above. Here the reactants were dissolved in acetic acid; concentrated sulfuric acid also was added (0.5 ml) and subjected to microwave irradiation for about 15–20 min until the starting materials were no longer detectable by TLC. The products were obtained and purified as described above in conventional reaction.

*7-Phenyl-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (**I**)*

m.p.: 296–298 °C; FT-IR υ_{max} [cm^{-1}]:3321, 3154 (NH_2), 1592(C=N); ^{1}H NMR (DMSO-d_6) δ [ppm]: 7.25–8.05 (m, 10H, Ar—H), 7.31 (d, 1H, *J* = 4.2 Hz, pyrimidine), 8.19 (d, 1H, *J* = 4.2 Hz, pyrimidine), 10.75 (br. S, 2H, NH_2, D_2O-exchangeable); MS *m/z* [%]:314 [M^+], Anal. Calced. For $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74. Found: C, 69.06; H, 4.36; N, 26.59.

*7-Phenyl-3-(4-tolyldiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (**II**)*

m.p.: >300 °C; FT-IR υ_{max} [cm^{-1}]:3316, 3149 (NH_2), 1599(C=N); ^{1}H NMR (DMSO-d_6) δ [ppm]: 2.11 (s, 3H, CH_3), 7.19–8.02 (m, 9H, Ar—H), 7.37 (d, 1H, *J* = 4.5 Hz, pyrimidine), 8.63 (d, 1H, *J* = 4.5 Hz, pyrimidine); 10.63 (br. s, 2H, NH_2, D_2O-exchangeable), MS *m/z* [%]:328 [M^+], Anal. Calced. For $C_{19}H_{16}N_6$: C, 69.50; H, 4.91; N, 25.59. Found: C, 69.73; H, 4.83; N, 25.44.

*7-Phenyl-3-((4-chlorophenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (**III**)*

m.p.: 252–254 °C; FT-IR υ_{max} [cm^{-1}]:3333, 3169 (NH_2), 1591(C=N); ^{1}H NMR (DMSO-d_6) δ [ppm]: 6.23 (br. s, H, NH, D_2O-exchangeable), 7.21–8.09 (m, 9H, Ar—H), 7.42 (d, 1H, *J* = 4.2 Hz, pyrimidine), 8.68 (d, 1H, *J* = 4.2 Hz, pyrimidine), 10.61 (br. s, 2H, NH_2, D_2O-exchangeable); MS *m/z* [%]:348 [M^+], Anal. Calced. For $C_{18}H_{13}ClN_6$: C, 61.98; H, 3.76; N, 24.09. Found: C, 62.23; H, 3.65; N, 23.97.

*7-Phenyl-3-((4-flurophenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (**IV**)*

m.p.: 290–292 °C; FT-IR υ_{max} [cm^{-1}]:3314, 3148 (NH_2), 1600(C=N); ^{1}H NMR (DMSO-d_6) δ [ppm]: 5.78 (br. s, H, NH, D_2O-exchangeable), 7.14–8.09 (m, 9H, Ar—H), 7.54 (d, 1H, *J* = 4.2 Hz,

pyrimidine), 8.33 (d, 1H, J = 4.2 Hz, pyrimidine), 10.78 (br. S, 2H, NH_2, D_2O-exchangeable); MS m/z [%]:332 [M^+], Anal. Calced. For $C_{18}H_{13}FN_6$: C, 65.05; H, 3.94; N, 25.29. Found: C, 65.28; H, 3.86; N, 25.14.

*7-Phenyl-3-((3-trifluromethylphenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (**V**)*

m.p.: >300 °C; FT-IR υ_{max} [cm^{-1}]:3328, 3161 (NH_2), 1591(C=N); ^{1}H NMR (DMSO-d_6) δ [ppm]: 7.15 –8.13 (m, 9H, Ar—H), 7.39 (d, 1H, J = 4.2 Hz, pyrimidine), 8.41 (d, 1H, J = 4.2 Hz, pyrimidine), 10.68 (br. S, 2H, NH_2, D_2O-exchangeable); MS m/z [%]:382 [M^+], Anal. Calced. For $C_{19}H_{13}F_3N_6$: C, 59.69; H, 3.43; N, 21.98. Found: C, 59.91; H, 3.36; N, 21.83.

*7-Phenyl-3-((4-nitrophenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (**VI**)*

m.p.: >300 °C; FT-IR υ_{max} [cm^{-1}]:3312, 3154 (NH_2), 1600(C=N); ^{1}H NMR (DMSO-d_6) δ [ppm]: 6.15 (br. s, H, NH, D_2O-exchangeable), 7.08–7.95 (m, 9H, Ar—H), 7.25 (d, 1H, J = 4.2 Hz, pyrimidine), 8.51 (d, 1H, J = 4.2 Hz, pyrimidine), 11.01 (br. s, 2H, NH_2, D_2O-exchangeable); MS m/z [%]:359 [M^+], Anal. Calced. For $C_{18}H_{13}N_7O_2$: C, 60.16; H, 3.65; N, 27.29. Found: C, 60.42; H, 3.58; N, 27.10.

Solutions

Stock solutions (10^{-3} mol dm^{-3}) of the compounds were prepared by dissolving a known mass of the azo dyes solid in the required volume of the solvent. The pH control was achieved by using the modified universal buffer solution [19]. 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 at 25 °C. The pH values of the former media were corrected by using the procedure described by Douheret [20], where:

$$pH^* = pH(R) - \delta \quad (1)$$

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 [20,21]. The solutions were thermostated at 25 °C before measuring their spectra.

Results and discussion

Synthesis and characterization

The enaminone **1** was treated with 4-(Aryldiazenyl)-1H-pyrazole-3,5-diamine derivatives **2a–f** in glacial acetic acid, and presence of 2 drops of concentrated sulfuric acid under microwave irradiation, it afforded in each case, the corresponding pyrazolo[1,5-a]pyrimidine derivatives **I–VI** in almost quantitative yield (Scheme 1).

The mass spectrum of compound I have taken as an example of the prepared series, revealed a molecular ion peak at m/z 314. Its ^{1}H NMR spectrum revealed a single signal at δ 7.06 (CH-3) and two doublet signals at δ 7.21, 8.61 (J = 4.2 Hz) due to pyrimidine protons (CH-6, CH-5), respectively, in addition to aromatic protons as a multiple at δ 7.26–7.75. The IR spectrum of **I** revealed the absence of any band due to carbonyl function.

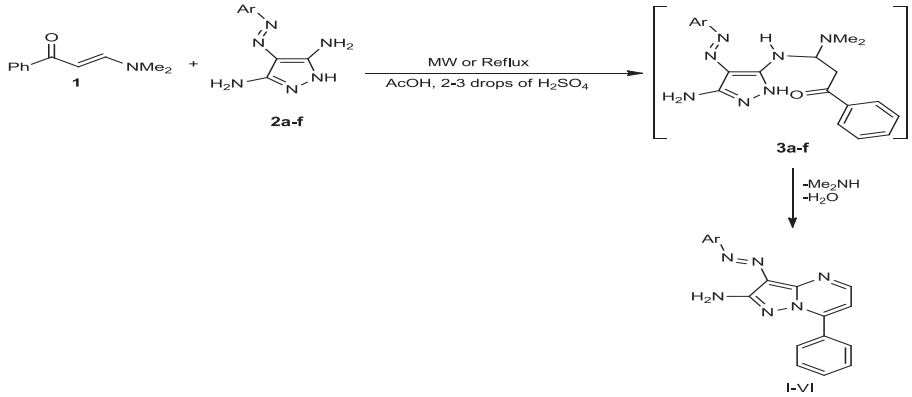
The formation of the products **I–VI** is assumed to take place *via* an initial addition of the exocyclic amino group in the aminopyrazoles **2** to the α,β-unsaturated moiety in the enaminone **1** to yield the corresponding acyclic non-isolable intermediates **3a–f** which undergo intramolecular cyclization and aromatization to give the final products **I–VI** (Scheme 1).

To find the specific effect of microwave on this reaction, the mentioned reaction was carried out under the same conditions in the absence of microwave irradiation (Table 1), and it was observed that the reaction time increased considerably and yield of the products decreased.

Thus, microwave was found to have a beneficial effect on the synthesis of pyrazolopyrimidine derivatives in which decrease time of the above reactions from 9 h in the conventional procedure to less than 30 min, also, a noticeable improvement in yields of reactions under microwave irradiations.

It is noteworthy to mention here that, the azo-hydrazo tautomerism is not only of importance to the dyestuff manufacturer but also another area of chemistry. Azo-hydrazo tautomerism not only have different colors, but also have different tinctorial strengths (and hence economics) and different properties, e.g. light fastness. Azo dyes (**I–VI**) exist in two possible tautomerism forms, namely the azo-enamine from A and the hydrazo-online form **B** as shown in Scheme 2.

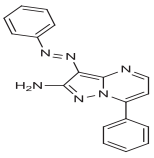
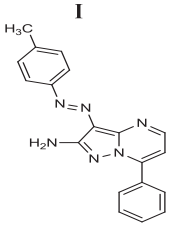
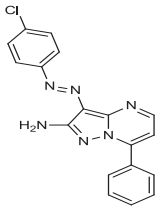
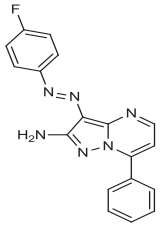
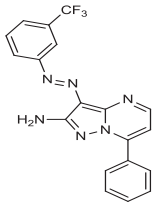
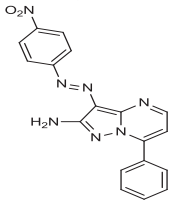
The FT-IR spectra of dyes **I–VI** showed intense amino (NH_2) bands in region 3312–3148 cm^{-1}. This suggests that these dyes are predominantly in the azo – enamine form, as opposed to the hydrazo imine form, in the solid state.



Ar = C_6H_5 (I), C_6H_4-4-CH_3 (II), C_6H_4-4-Cl (III), C_6H_4-4-F (IV), C_6H_4-3-CF_3 (V), C_6H_4-4-NO_2 (VI)

Scheme 1. Synthesis of pyrazolo[1,5-a]pyrimidin-2-amine derivatives.

Table 1
Synthesis of pyrazolo[1,5-a]pyrimidin-2-amine derivatives I–VI under both microwave irradiation and conventional method.

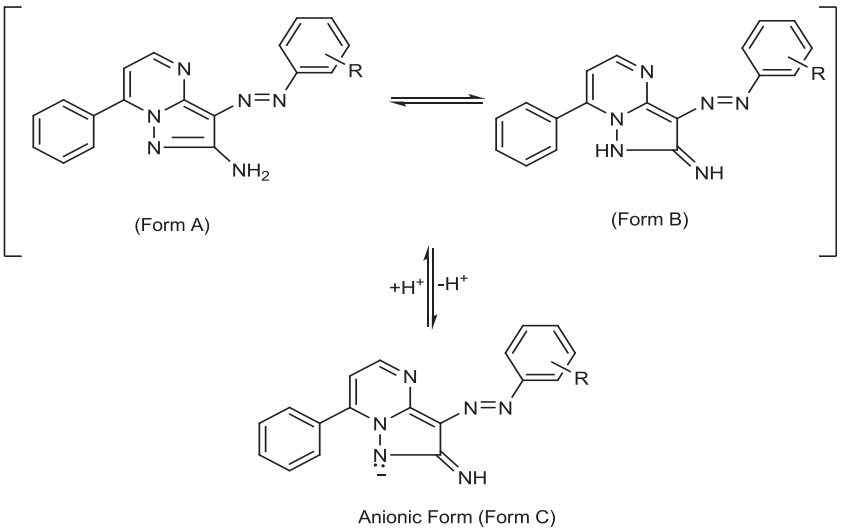
Entry	Product	*Microwave irradiation*		*Conventional condition*	
		Time (min)	*Yield %*	*Time (h)*	*Yield %*
1	 **I**	17	93	9	72
2	 **II**	15	93	9	70
3	 **III**	20	93	9	71
4	 **IV**	15	95	9	82
5	 **V**	15	90	9	75
6	 **VI**	20	95	9	82

The ^{1}H NMR spectra of dyes **I, II** and **V** showed a broad signal of amino group in the region 10–11.01 ppm. This result suggests that dyes **I, II** and **V** are present as a single tautomerism form in DMSO, namely azo-enamine form A as shown in Scheme 2.

On the other hand, ^{1}H NMR spectra of dyes **III, IV** and **VI** showed a broad signal of amino group at **10–11** ppm and a broad signal due to the NH group at 5–6.5 ppm. These results suggest that dyes **III, IV** and **VI** are present as a mixture of two tautomerism forms in DMSO, namely the azo-enamine (Form **A**) and hydrazo-imine (Form **B**) as shown in Scheme 2.

The electronic absorption spectral characteristics

λ_{max} and ε_{max} values of the investigated compounds **I–VI** in ethanol, in the wavelength range 200–500 nm, are reported in Table 2. The results show that the solvent effect on UV absorption spectra of investigate azo compounds in very complex and strongly depend on the nature of the substituent on phenyl ring. This phenomenon is caused by the difference in the conjugational or migrating ability of electron lone pair on nitrogen atoms and azo-enamine; hydrazo-imine tautamerism of azo compounds.



Scheme 2. Tautomerism forms.

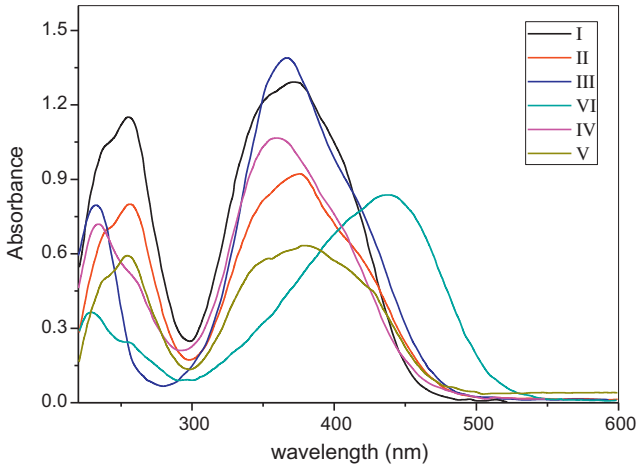


Fig. 1. Electronic spectra of compounds **I–VI** in ethanol.

These results are in accordance with structure of these dyes (Table 1). This also indicates that the electronic behavior of nitrogen atoms of azo group in some what different between derivatives with electron donating substituent's.

The compounds comprise mainly three bands in ethanol (Fig. 1). The shortest wavelength absorption appearing in the range 230–260 nm is assignable to a π–π^* transition of the benzoid system of the compounds. This assignment is quite reasonable since λ_{max} of this band is slightly altered on transfer from on derivative to another indicating the local nature of such a transition.

The bands in spectra observed, in region 356–395 nm can be assigned to π–π^* transition involving to a whole electronic system of the compounds with consider charge transfer nature of this band is achieved from its broadness as well as the sensitivity of its λ_{max} to the type of substitute (R) to azo group. Examination of the data reported in Table 2 reveals that this band acquires an appreciable shift toward lower energy (red shift) where R is an electron acceptor (compounds **III–VI**), relative to its position in case of R is an electron donor (compound **II**). This behavior can be interpreted on the basis of the expected high delocalization of the electrons in the former compounds due to the antagonizing effect of the electron accepting (R) groups.

The band appeared as a shoulder in the spectra of the compounds except compounds **VI** in the visible region 415–430 nm can be assigned to a n–π^* transition involving the lone pairs of electrons localized on the azo group nitrogen.

Solvatochromic behavior

The Solvatochromic behavior of the azo compounds used is investigated by studying their electronic absorption spectra in different organic solvents (*viz.* cyclohexane, carbon tetrachloride, chloroform, ethanol and DMF). The λ_{max} and ε_{max} bands observed are listed in Table 2. It is evident from this table that the visible bands appeared in the range 405–460 nm are very sensitive to the nature of the solvent used. This band exhibits a red shift in its λ_{max} with increase relative permittivity of the medium changing from cyclohexane (2.02) → carbon tetrachloride (2.24) → chloroform (4.81) → ethanol (24.50) → DMF (36.70), this trend is in harmony with the increasing polarity of the solvent. This behavior can be explained on the principle that the excited state of such a type of transitions is polar and consequently it is expected to be more stabilized in higher polar solvent (*viz.* ethanol or DMF relative to cyclohexane) and thus low excitation energy required for this band with the former solvent relative to the latter one. From idealized theories, the solvent dielectric constant (i.e. The relative permittivity ε_r) is often predicted to serve as a quantitative

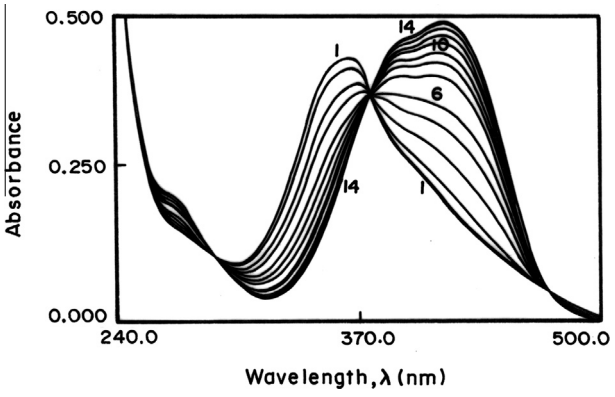


Fig. 2. Absorption spectra of 1.0×10^{-5} M compound **VI** in water (1) + methanol (2) at different pH's. ω_2 = 16.53 methanol, pH* (1) 4.53, (2) 5.13, (3)5.90, (4) 6.50, (5) 6.92, (6) 7.21, (7) 7.45, (8) 7.7, (9) 7.92, (10) 8.3, (11) 8.45, (12) 8.60, (13) 9.50, (14) 10.53.

Table 2
Electronic spectral data of the pyrazolo[1,5-a]pyrimidin-2-amine derivatives in various organic solvents.

Compound	Cyclohexane		CCl_4		$CHCl_3$		EtOH		DMF	
	(λ_{max}) nm	$(\varepsilon^a_{max}) \times 10^{-3}$	(λ_{max}) nm	$(\varepsilon^a_{max}) \times 10^{-3}$	(λ_{max}) nm	$(\varepsilon^a_{max}) \times 10^{-3}$	(λ_{max}) nm	$(\varepsilon^a_{max}) \times 10^{-3}$	(λ_{max}) nm	$(\varepsilon^a_{max}) \times 10^{-3}$
I	235	12.00	250	11.00	240	15.00	250	15.60	245	11.30
	360	14.00	375	12.00	365	16.50	365	17.00	375	14.60
	430sh	11.00	435sh	14.00	435sh	14.00	430sh	15.30	440sh	12.00
II	250	11.50	225	11.30	245	12.50	260	12.00	235	13.00
	395	12.00	375	14.00	385	14.00	375	15.60	390	15.30
	420sh	11.00	420sh	4.50	425sh	6.00	430sh	5.30	460sh	10.00
III	265	12.20	260	10.00	275	12.20	255	13.50	270	12.10
	375	13.30	370	13.00	380	14.00	360	14.00	385	14.00
	410sh	01.50	415sh	4.00	415sh	5.00	415sh	6.20	425sh	10.30
IV	230	16.00	225	15.30	225	15.10	230	15.00	240	16.30
	410	13.20	415	17.50	420	16.50	420	17.20	460	17.50
V	245	14.00	255	12.00	270	14.00	250	16.10	275	15.30
	350	11.50	350	15.60	355	16.30	355	16.60	360	16.00
	390	11.70	390	3.00	370	16.00	390	17.00	395	16.30
	400sh	3.00	–	–	410sh	4.60	430sh	6.00	425sh	11.00
VI	255	13.00	265	14.00	250	14.20	245	14.60	260	13.10
	360	12.00	370	16.70	360	16.00	360	16.10	365	14.00
	415sh	3.20	415	5.20	420sh	6.20	425sh	5.30	425sh	10.00

a, $cm^2\ mol^{-1}$.

measure of solvents as a non-structured isotropic continuum, not composed of individual solvent molecules with their own solvent–solvent interactions and they do not into account specific solute–solvent interaction which often play a dominant role in solute–solvent interactions.

On changing the medium from cyclohexane to ethanol and DMF (Table 2), the splitting of the CT band becomes more pronounced. These dramatic spectral changes on changing the dielectric constant of the medium can be attributed to the existence of compounds in a tautomerism equilibrium [22] of the type as stated in Scheme 2.

Azo-enamine ⇌ Hydrazo-imine ⇌ Anionic from

A compound (**IV**) gave a single dominate absorption peak without a shoulder in all used solvents at 405–460 nm. It was also observed that the λ_{max} value of this dye was the largest in DMF (460 nm) when compared with those in other solvents. These results suggest that this dye is present as an anionic form (**C**) in DMF [22], as a tautomerism form azo-enamine (**A**) in ethanol or chloroform and as a different tautomerism form hydrazo-imine (**B**) in carbon tetrachloride and cyclohexane [18].

The electronic absorption spectra of the 3-arylazo-7-phenylpyrazolo[1,5-a]pyrimidin-2-amine derivatives in buffer solutions containing different proportions of an organic solvent (ethanol, methanol, acetone and DMF) show mainly two bands (Fig. 1). The shorter wavelength band appearing at low pH values represents the absorption of the non-ionized species, whereas the longer wavelength band, observed at higher pH's, is due to the absorption by ionized species. With increase in the pH of the medium, the absorbance of the former band decrease which that of the latter band increases where a fine isobestic point is achieved, denoting the existence of and equilibrium of the type.

Table 3
p*Ka* values for 1×10^{-5} M of 7-phenyl-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (I) in different water (1) + organic solvent (2) mixtures at 25 °C.

Mass% 100 W_2[a]	*E*	p*Ka*			Mean value ± SD
		Method 1	Method 2	Method 3	
		Water (1) + acetone (2)			
16.53	74.92	7.40	7.40	7.40	7.40 ± 0.02
25.35	72.87	7.50	7.50	7.55	7.51 ± 0.02
34.56	70.25	7.55	7.70	7.60	7.61 ± 0.02
44.21	66.99	7.75	7.80	7.75	7.76 ± 0.02
		Water (1) + methanol (2)			
16.53	73.72	7.25	7.25	7.20	7.23 ± 0.02
25.35	71.03	7.35	7.30	7.35	7.33 ± 0.02
34.56	67.88	7.30	7.50	7.40	7.40 ± 0.02
44.21	64.27	7.50	7.50	7.60	7.53 ± 0.02
		Water (1) + ethanol (2)			
16.59	74.46	7.35	7.35	7.30	7.33 ± 0.02
25.42	72.00	7.30	7.40	7.40	7.36 ± 0.02
34.65	69.08	7.40	7.40	7.55	7.45 ± 0.02
44.30	65.54	7.55	7.50	7.60	7.55 ± 0.02
		Water (1) + DMF (2)			
19.21	76.06	7.20	7.15	7.15	7.16 ± 0.02
28.96	74.56	7.30	7.22	7.30	7.27 ± 0.02
38.81	72.73	7.25	7.32	7.35	7.31 ± 0.02
48.75	70.45	7.30	7.35	7.40	7.35 ± 0.02

[a] Mass fraction of component I.

Table 4
p*K*a values for 1×10^{-5} M of 7-phenyl-3-((4-methylphenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine in different water (1) + organic solvent (2) mixtures at 25 °C.

Mass% 100 W_2[a]	*E*	p*K*a			Mean value ± SD
		Method 1	Method 2	Method 3	
		Water (1) + acetone (2)			
16.53	74.92	7.50	7.50	7.55	7.51 ± 0.02
25.35	72.87	7.60	7.62	7.50	7.57 ± 0.02
34.56	70.25	7.70	7.78	7.75	7.74 ± 0.02
44.21	66.99	7.80	7.82	7.77	7.80 ± 0.02
		Water (1) + methanol (2)			
16.53	73.72	7.20	7.35	7.30	7.28 ± 0.02
25.35	71.03	7.35	7.35	7.30	7.33 ± 0.02
34.56	67.88	7.35	7.35	7.40	7.37 ± 0.02
44.21	64.27	7.45	7.45	7.40	7.43 ± 0.02
		Water (1) + ethanol (2)			
16.59	74.46	7.25	7.35	7.26	7.29 ± 0.02
25.42	72.00	7.40	7.35	7.30	7.35 ± 0.02
34.65	69.08	7.45	7.40	7.45	7.43 ± 0.02
44.30	65.54	7.45	7.53	7.50	7.49 ± 0.02
		Water (1) + DMF (2)			
19.21	76.06	7.10	7.20	7.00	7.10 ± 0.02
28.96	74.56	7.20	7.15	7.07	7.14 ± 0.02
38.81	72.73	7.12	7.21	7.13	7.15 ± 0.02
48.75	70.45	7.17	7.32	7.22	7.23 ± 0.02

[a] Mass fraction of component II.

Azo-enamine ⇌ Hydrazo-imine

The acid dissociation constants, p*K*a, of the compounds are determined from the variation of the absorbance with pH*, making use of three different spectrophotometric methods, namely: the half-curve height [23,24], plot the absorbance–pH curve, p*K*a = pH at $A_{1/2}$;

$$A_{1/2} = (A_{max} - A_{min})/2 + A_{min} \quad (2)$$

where A_{min} and A_{max} are the maximum and minimum absorbance on the absorbance–pH curve (Fig. 2).

In the isobestic point method [24], the isobestic point represents the equilibrium between the (**B**) and (**C**) specie. By plotting pH against absorbance for anion form and hydrazo-imine form, the pH corresponding to the isobestic point equals the p*K*a value.

In the limiting absorbance method [24], thus, p*K*a can be determined from the plot of log $(A - A_{min})/(A_{max} - A)$ against the pH, where a straight line is obtained Eq. (3).

$$pH = pKa + log(A - A_{min})/(A_{max} - A) \quad (3)$$

The pH value where $(A - A_{min})$ equals $(A_{max} - A)$ gives the values of p*K*a. The p*K*a values were calculated by using a simple program. The experimental error in determining p*K*a values was checked by using the least-squares method. The obtained results are given in Tables 3–8. The results listed in tables show that the p*K*a values of all the compounds are dependent upon both the nature and the proportion of the organic co-solvent. In general, increasing the organic co-solvent content in the medium results in an increase in the p*K*a value. This can be explained as follows.

Table 5
p*K*a values for 1×10^{-5} M of 7-phenyl-3-((4-chlorophenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (III) in different water (1) + organic solvent (2) mixtures at 25 °C.

Mass% 100 W_2[a]	*E*	p*K*a			Mean value ± SD
		Method 1	Method 2	Method 3	
		Water (1) + acetone (2)			
16.53	74.92	7.38	7.37	7.40	7.35 ± 0.02
25.35	72.87	7.45	7.50	7.54	7.45 ± 0.02
34.56	70.25	7.54	7.70	7.60	7.60 ± 0.02
44.21	66.99	7.74	7.85	7.70	7.75 ± 0.02
		Water (1) + methanol (2)			
16.53	73.72	7.20	7.27	7.20	7.20 ± 0.02
25.35	71.03	7.32	7.30	7.35	7.30 ± 0.02
34.56	67.88	7.25	7.45	7.45	7.35 ± 0.02
44.21	64.27	7.45	7.52	7.60	7.50 ± 0.02
		Water (1) + ethanol (2)			
16.59	74.46	7.32	7.30	7.35	7.30 ± 0.02
25.42	72.00	7.35	7.35	7.39	7.35 ± 0.02
34.65	69.08	7.55	7.44	7.44	7.45 ± 0.02
44.30	65.54	7.50	7.45	7.65	7.50 ± 0.02
		Water (1) + DMF (2)			
19.21	76.06	7.19	7.20	7.10	7.15 ± 0.02
28.96	74.56	7.26	7.20	7.32	7.23 ± 0.02
38.81	72.73	7.24	7.30	7.37	7.30 ± 0.02
48.75	70.45	7.28	7.40	7.35	7.33 ± 0.02

[a] Mass fraction of component III.

Table 6
p*Ka* values for 1×10^{-5} M of 7-phenyl-3-((4-flurolphenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (IV) in different water (1) + organic solvent (2) mixtures at 25 °C.

Mass% 100 W_2[a]	*E*	p*Ka*			Mean value ± SD
		Method 1	Method 2	Method 3	
		Water (1) + acetone (2)			
16.53	74.92	7.35	7.35	7.42	7.32 ± 0.02
25.35	72.87	7.40	7.52	7.52	7.40 ± 0.02
34.56	70.25	7.70	7.54	7.60	7.60 ± 0.02
44.21	66.99	7.74	7.70	7.80	7.70 ± 0.02
		Water (1) + methanol (2)			
16.53	73.72	7.20	7.25	7.20	7.18 ± 0.02
25.35	71.03	7.30	7.32	7.30	7.25 ± 0.02
34.56	67.88	7.25	7.40	7.45	7.30 ± 0.02
44.21	64.27	7.42	7.55	7.60	7.50 ± 0.02
		Water (1) + ethanol (2)			
16.59	74.46	7.30	7.32	7.35	7.30 ± 0.02
25.42	72.00	7.40	7.30	7.40	7.35 ± 0.02
34.65	69.08	7.50	7.45	7.45	7.42 ± 0.02
44.30	65.54	7.46	7.50	7.40	7.46 ± 0.02
		Water (1) + DMF (2)			
19.21	76.06	7.10	7.20	7.20	7.15 ± 0.02
28.96	74.56	7.23	7.20	7.32	7.20 ± 0.02
38.81	72.73	7.20	7.35	7.31	7.25 ± 0.02
48.75	70.45	7.25	7.45	7.30	7.30 ± 0.02

[a] Mass fraction of component IV.

According to Coetzee and Richie [25], the acid dissociation constant in aqueous medium (Ka) is related to that in partially aqueous (K'_a) by Eq. (4):

$$Ka = K'_a(\gamma_H + \gamma_{A^-})/\gamma_{HA} \quad (4)$$

where γ is the activity coefficient of the subscripted species in a partially aqueous medium relative to that in a pure aqueous one. It is known that the electronic effect resulting from the change in relative permittivity of the medium operates on the activity coefficients of a charged species [25] and one can expect that the increase in the amount of the organic co-solvent in the medium will increase the activity coefficient of both hydrazo-imine and anionic form. According to Eq. (4), this will result in a decrease in the acid dissociation constant *Ka* (high p*Ka* value), which is consistent with the results reported in Tables 3–8.

However, methanol and DMF have similar relative permittivity (32.6 and 36.7 respectively, at 25 °C) and all the compounds are more acidic in water + DMF than in water + methanol, despite that the same mole fraction of each is used (Tables 3–8). Moreover, although ethanol and acetone have comparable relative permittivity 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. In general, p*Ka* values in all compounds decrease with increase relative permittivity of the medium (*i.e.* the p*Ka* values of a compound in water + organic solvent are arranged according to the following sequence: DMF < methanol < ethanol < acetone (see Fig. 3).

This behavior indicates that other solvent effects beside the electrostatic one have a contribution to the ionization process of the investigated compounds. This fact is further substantiated by

Table 7
p*Ka* values for 1×10^{-5} M of 7-phenyl-3-((3-trifluromethylphenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (V) in different water (1) + organic solvent (2) mixtures at 25 °C.

Mass% 100 W_2[a]	*E*	p*Ka*			Mean value ± SD
		Method 1	Method 2	Method 3	
		Water (1) + acetone (2)			
16.53	74.92	7.10	7.15	7.15	7.17 ± 0.02
25.35	72.87	7.30	7.25	7.30	7.28 ± 0.02
34.56	70.25	7.32	7.25	7.35	7.30 ± 0.02
44.21	66.99	7.45	7.55	7.45	7.45 ± 0.02
		Water (1) + methanol (2)			
16.53	73.72	7.60	7.15	7.15	7.13 ± 0.02
25.35	71.03	7.15	7.18	7.18	7.17 ± 0.02
34.56	67.88	7.25	7.27	7.25	7.26 ± 0.02
44.21	64.27	7.25	7.30	7.32	7.29 ± 0.02
		Water (1) + ethanol (2)			
16.59	74.46	7.06	7.15	7.09	7.10 ± 0.02
25.42	72.00	7.10	7.16	7.20	7.15 ± 0.02
34.65	69.08	7.30	7.20	7.25	7.25 ± 0.02
44.30	65.54	7.25	7.30	7.30	7.28 ± 0.02
		Water (1) + DMF (2)			
19.21	76.06	7.05	7.00	6.90	6.98 ± 0.02
28.96	74.56	7.00	6.93	6.95	6.96 ± 0.02
38.81	72.73	6.90	7.08	7.00	6.99 ± 0.02
48.75	70.45	7.00	6.95	7.05	7.00 ± 0.02

[a] Mass fraction of component V.

Table 8
pKa values for 1×10^{-5} Mass% M of 7-phenyl-3-((4-nitrophenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (VI) in different water (1) + organic solvent (2) mixtures at 25 °C.

Mass% 100 W_2[a]	E	pKa			Mean value ± SD
		Method 1	Method 2	Method 3	
		Water (1) + acetone (2)			
16.53	74.92	7.25	7.28	7.15	7.22 ± 0.02
25.35	72.87	7.30	7.40	7.45	7.38 ± 0.02
34.56	70.25	7.45	7.53	7.20	7.46 ± 0.02
44.21	66.99	7.60	7.50	7.60	7.57 ± 0.02
		Water (1) + methanol (2)			
16.53	73.72	7.05	7.10	7.10	7.08 ± 0.02
25.35	71.03	7.15	7.20	7.20	7.15 ± 0.02
34.56	67.88	7.20	7.25	7.20	7.18 ± 0.02
44.21	64.27	7.25	7.25	7.25	7.22 ± 0.02
		Water (1) + ethanol (2)			
16.59	74.46	7.13	7.23	7.20	7.18 ± 0.02
25.42	72.00	7.10	7.30	7.30	7.23 ± 0.02
34.65	69.08	7.20	7.30	7.35	7.26 ± 0.02
44.30	65.54	7.25	7.35	7.25	7.28 ± 0.02
		Water (1) + DMF (2)			
19.21	76.06	6.90	7.05	6.90	6.95 ± 0.02
28.96	74.56	6.90	7.07	6.95	6.97 ± 0.02
38.81	72.73	6.95	7.05	7.00	6.99 ± 0.02
48.75	70.45	7.00	7.10	7.00	7.03 ± 0.02

[a] Mass fraction of component (VI).

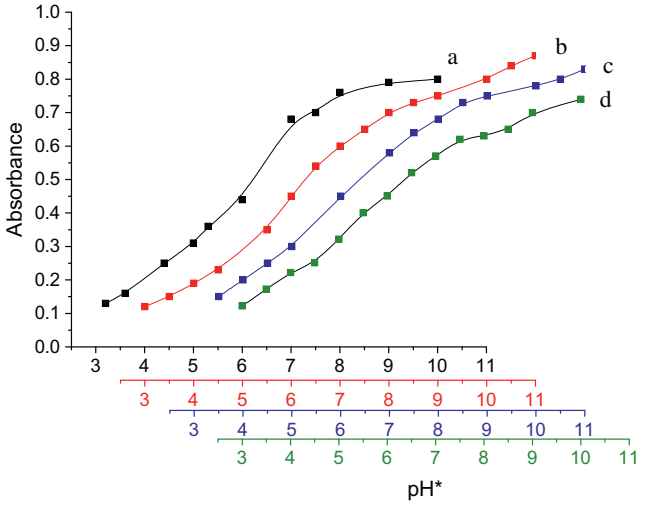


Fig. 3. Absorbance–pH* curves of 2×10^{-5} M compound **VI** in water + DMF; ω_2 = 19.21 (a); 28.96 (b); 38.81 (c); 48.75 (d).

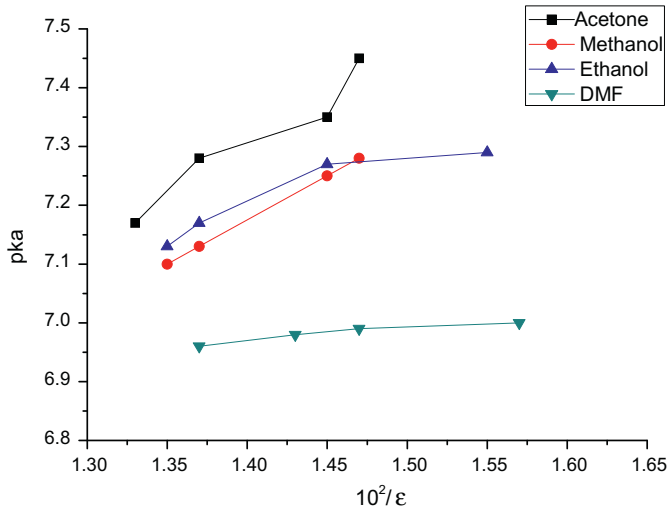


Fig. 4. Variation of pKa (compound **V**) in water + organic solvent with $10^2/\varepsilon$ of the medium at 25 °C.

the nonlinear relations obtained by plotting pKa against $1/\varepsilon_m$ of the medium (Fig. 4) according to Eq. (5), which relates the variation of pKa of the acid with the relative permittivity of the medium, ε_m, is obtained from the relation [26] respectively:

$$\varepsilon_m = \varepsilon_\omega m_{f(\omega)} + \varepsilon_{(s)} m_{f(s)} \quad (5)$$

ε and m_f are the relative permittivity and mole fraction and the subscripts ω and s refer to water and organic solvent.

In general, effects such as hydrogen bonding, solvent basicity, dispersive forces, and proton solvent interactions play vital roles in the ionization process of acids in the presence of organic solvents [27]. Thus, the observed increase in the pKa of the compounds as the proportion of the organic co-solvent in the medium is increased can be ascribed, in addition to the electrostatic effect, to the hydrogen-bonding interaction between the conjugate base (anionic form C) and solvent molecules since water molecules have a higher tendency to donate a hydrogen bond than other solvent molecules [27]. The conjugate base anionic form (**C**) is expected to be less stabilized by hydrogen-bonding interaction with solvent molecules as the amount of the organic co-solvent in the medium is increased (*i.e.* γ_A^- increase). This will tend to increase the pKa value of the compound as Eq. (5) implies. It indicates also that the difference in the stabilization of the ionic form by hydrogen-bond donor solvent molecules plays an important role in the increase in the pKa value as the amount of the organic co-solvent in the medium increases.

Examination of the results in Tables 3–8 reveals that the pKa 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 [27].

There are dispersive forces, which possibly exist in the medium used, between the delocalized charge on the conjugate base of the dye (A^-) and the localized dispersion center in near solvent molecules. The proton-solvent interactions have important effects on the ionization process the compounds studied, one should expect

that by increasing the amount of the organic co-solvent both A^- and H^+ will be highly stabilized by DMF molecules (*i.e.* $\gamma_{\bar{A}}$ and γ_H^+ decrease), since the effective density of dispersion centers in each of the organic solvents used is higher that of water [28]. Thus, in light of Eq. (4), the acid dissociation constant of the dyes studied would increase (p*K*a decrease) with the increase in the amount of the organic co-solvent in the medium. This is not the case obtained from the results (*cf.* Tables 3–8).

Effect of molecular structure on the values of p*K*a reported in Tables 3–8 shows that the acidity of studied azo compounds increases in the following order:

$$p\text{-}NO_2 < m\text{-}CF_3 < p\text{-}F < p\text{-}Cl < p\text{-}H < p\text{-}CH_3$$

This trend is in accordance with the increase in the electron's donor's ability of the substituent azo compounds.

Conclusions

In summary, solvatochromic behavior of these compounds exhibits a red shift in the order cyclohexane, carbon tetrachloride, chloroform, ethanol, DMF. The p*K*a values of the dyes studied were determined and found depend largely on the amount and nature of organic solvents. p*K*a values in all compounds decrease with increase relative permittivity of the medium and are arranged according to the following sequence: DMF < methanol < ethanol < acetone. p*K*a values of the studied azo compounds increase in the following order $p\text{-}NO_2 < m\text{-}CF_3 < p\text{-}F < p\text{-}Cl < p\text{-}H < p\text{-}CH_3$.

Acknowledgements

This paper was funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under grant No. (965-002-D1434). The authors, therefore, thank DSR for technical and financial support.

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