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ARTICLE

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Spectroscopic Determination of the Acid Dissociation Constants of Some 2-Hydroxy Schiff Base Derivatives[†]

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ABSTRACT: In this study the acidity constants of a series of biologically active pyridyl Schiff bases were calculated from UV−visible spectrophotometric data at (25 ± 0.1) °C. The first acidity constants ($\mathrm{p}K_{\mathrm{a1}}$) of the 2-[2-aza-2-(4-methyl(2-pyridly))vinyl]phenol (**1**), 2-[2-aza-2-(4-methyl(2-pyridly))vinyl]-6-nitrophenol (**2**), 2-[2-aza-2-(4-methyl(2-pyridly))vinyl]-4-nitrophenol (**3**), 2-[2-aza-2-(4-methyl(2-pyridly))vinyl]-4,6-dinitrophenol (**4**), 2-[2-aza-2-(6-methyl(2-pyridly))vinyl]phenol (**5**), 2-[2-aza-2-(6-methyl(2-pyridly))vinyl]-6-nitrophenol (**6**), 2-[2-aza-2-(6-methyl(2-pyridly))vinyl]-4-nitrophenol (**7**), and 2-[2-aza-2-(6-methyl(2-pyridly))vinyl]-4,6-dinitrophenol (**8**) are found to be associated with the protonation of the phenolate oxygen. The second acidity constants ($\mathrm{p}K_{\mathrm{a2}}$) are found to correspond to protonation of a pyridine nitrogen for molecules **5**, **6**, and **7** and oxoprotonation for molecules **1**, **2**, **3**, **4**, and **8**. The third acidity constants ($\mathrm{p}K_{\mathrm{a3}}$) are found to be associated with the protonation of a pyridine nitrogen for molecules **1**, **3**, **7**, and **8** and amino protonation for molecules **2** and **5**. For molecules **4** and **6**, it is associated with oxo protonation. The contribution of the keto-amino tautomeric form was found to be considerably important.

INTRODUCTION

Schiff bases are molecules that contain the azomethine group (—CH═N—) in their structure, and they are generally synthesized by the condensation of primary amines and active carbonyl groups. Possessing this particular biological activity gives them an important place in diverse fields of chemistry and biochemistry.[1−4] Antimicrobial activities of quinolin-2(1H)-one-triazole derived Schiff bases and their Cu(II) and Zn(II) complexes,[5] antibacterial/antifungal/cytotoxic properties of triazole derived Schiff bases and their oxovanadium(IV) complexes,[6] antimicrobial activity of the heptaaza Schiff base macrocyclic complex of Mn(II)[7] have been reported by several groups. Alternatively, the reactive azomethine linkage of a wide range of Schiff bases have displayed inhibitory activity against experimental tumor cells.[8,9] Yang's research group has recently synthesized novel Paeonol Schiff base ligands and their Cu(II) complexes and they presented DNA interaction and tumor cell cytotoxicity activities of Cu(II) complexes with the Paeonol Schiff-base.[10] Complex formation has been another study area of interest based on the properties of ortho hydroxylated Schiff bases in the field of coordination chemistry.[11,12] Through reversible proton transfer from the hydroxyl oxygen atom to the imine nitrogen atom, these particular Schiff bases may display photochromic and thermochromic behavior.[13,14] Furthermore, solvatochromaticity and biological activity against bacterial species and fungi as microorganisms of some transition metal complexes with 2-(R-benzylideneamino)-pyridin-3-ol Schiff base derivatives have also been studied.[15]

Owing to the growing interest in Schiff bases, the number of studies and publications regarding the determination of the chemical behavior, specifically the $\mathrm{p}K_\mathrm{a}$ values has shown a considerable increase.[16−19] Understanding $\mathrm{p}K_\mathrm{a}$ values leads to a better understanding of the distribution, transport behavior, binding to receptors, and mechanism of action of certain pharmaceutical preparations. This knowledge is also important in the quantitative treatment of systems involving acid−base equilibria in solution. Acid dissociation constants are useful physicochemical properties describing the extent of ionization of functional groups with respect to pH. Therefore, knowledge about acid−base properties of chemical substances gives an idea about their toxicity, pharmaceutical activity and analytical roles.

Capillary electrophoresis,[20] UV−vis absorption,[21−23] fluorescence spectrophotometry,[24] potentiometry,[25,26] and similar methodologies have been proposed for the experimental determination of acid dissociation constants. Among all these methods listed above, spectroscopic methods are, in general, highly sensitive and are therefore suitable for chemical equilibria studies.

In our previous work, the $\mathrm{p}K_\mathrm{a}$ values were reported for similar Schiff bases with the methyl group in the pyridine ring at the o and p positions according to the azomethine group.[26] Following this study, we currently report the acidity constants for the 8 Schiff base series with the methyl group in the pyridine ring at the m position according to the azomethine group using the same spectroscopic method. As a joint result of both studies, the $\mathrm{p}K_\mathrm{a}$ values of a total of 16 biologically active Schiff bases are reported in the literature. Taking the vast application areas where Schiff bases are useful into consideration, we think that knowledge of the $\mathrm{p}K_\mathrm{a}$ values of a wide series of molecules will prove to be important for many researchers in various types of studies.

EXPERIMENTAL SECTION

Materials and Solutions. The studied molecules (Table 1) were synthesized and the procedures of the synthesis are

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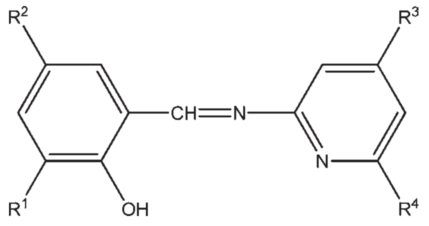
[†] This work is dedicated to the memory of our colleague Prof. Dr. Cemil Öğretir, who died on January 19, 2011.

Table 1. Formulas and IUPAC Names for the Studied Molecules 1 to 8



molecule	IUPAC name	R^1	R^2	R^3	R^4
1	2-[2-aza-2-(4-methyl(2-pyridly))vinyl]phenol	H	H	CH_3	H
2	2-[2-aza-2-(4-methyl(2-pyridly))vinyl]-6-nitrophenol	NO_2	H	CH_3	H
3	2-[2-aza-2-(4-methyl(2-pyridly))vinyl]-4-nitrophenol	H	NO_2	CH_3	H
4	2-[2-aza-2-(4-methyl(2-pyridly))vinyl]-4,6-dinitrophenol	NO_2	NO_2	CH_3	H
5	2-[2-aza-2-(6-methyl(2-pyridly))vinyl]phenol	H	H	H	CH_3
6	2-[2-aza-2-(6-methyl(2-pyridly))vinyl]-6-nitrophenol	NO_2	H	H	CH_3
7	2-[2-aza-2-(6-methyl(2-pyridly))vinyl]-4-nitrophenol	H	NO_2	H	CH_3
8	2-[2-aza-2-(6-methyl(2-pyridly))vinyl]-4,6-dinitrophenol	NO_2	NO_2	H	CH_3

Table 2. UV Spectral Data and Acidity Constants (pK_{a1}) of 1 to 8 for the Proton Loss (or Phenolate Protonation) Process

	spectral maximum λ/nm		acidity measurements				
molecule	neutral species[a] λ ($\log \varepsilon_{max}$)	anion[b] λ ($\log \varepsilon_{max}$)	λ_{max} (nm)[c]	$H^{1/2}$[d]	m[e]	pK_{a1}[f]	corr[g]
1	297.00 (3.81)	376.60 (3.63)	256.60	8.30	0.4713	3.9140 ± 0.98	0.982
	256.40 (3.63)	268.00 (3.79)					
2	307.20 (4.03)	377.40 (3.86)	268.20	7.15	0.4471	3.1978 ± 0.08	0.988
	256.00 (4.15)	268.20 (4.01)					
3	403.20 (3.86)	406.80 (3.87)	286.20	9.02	0.4755	4.2898 ± 0.17	0.977
	291.60 (3.96)	282.40 (3.80)					
4	422.40 (4.03)	416.60 (4.01)	293.60	6.19	0.8515	5.2737 ± 0.11	0.989
	293.60 (4.08)	288.60 (4.17)					
5	387.40 (4.15)	403.00 (4.29)	299.80	6.11	0.5023	3.0699 ± 0.07	0.990
	360.60 (4.14)	276.60 (3.81)					
6	388.60 (4.21)	403.40 (4.27)	228.60	7.33	0.4249	3.1454 ± 0.12	0.971
	309.00 (4.12)	289.20 (3.79)					
7	360.60 (4.28)	361.00 (4.22)	295.60	6.87	0.4406	3.0280 ± 0.07	0.987
	295.60 (4.03)						
8	360.60 (4.29)	360.60 (4.26)	307.80	7.08	0.6283	4.4482 ± 0.08	0.981
	307.80 (4.11)	290.00 (4.01)					

[a] Measured in pH 7 buffer. [b] Measured in pH 14 buffer. [c] Analytical wavelength for pK_a measurements. [d] Half protonation value ± uncertainties refer to the standard error. [e] Slopes for log I as a function of pH (or acidity function H_o) graph. [f] Acidity constant value for the deprotonation. [g] Correlations for log I as a function of the pH graph.

described elsewhere.[27] Methanol, ethanol, KOH, H_2SO_4, HCl, CH_3COOH, CH_3COONa, NaOH, KH_2PO_4, Na_2CO_3, $NaHCO_3$, phenolphthalein indicator, and standard buffer solutions were from Aldrich and were not purified further.

Apparatus. pH measurements were performed using a glass electrode. pH values of the standard buffer solutions were 4, 7, and 9, and they were used in the calibration of the Orion pH/ion analyzer. A Ohaus Advanturer balance and a UNICAM UV2 PC UV—visible scanning spectrometer were used for measurements.

Procedure. Acid solutions were prepared with H_2SO_4 % (w/w) [(0.0049 to 98) % H_2SO_4] in water.[28] The CO_2-free NaOH solutions were prepared with NaOH pellets [(1 to 16.4) $\text{mol}\cdot\text{dm}^{-3}$] in water.[29] Buffer solutions were prepared by using Perrin's descriptions.[30]

Spectrometry is an ideal method[31] when a substance is not soluble enough for potentiometry or when its pK_a value is particularly low or high (e.g., less than 2 or more than 11).

The proton-gain of a weak base can be defined as follows:[28]

$$HX + SH \rightleftharpoons X^- + SH_2^+ \qquad (1)$$

where SH is the solvent. Then the equilibrium constant might be

Table 3. UV Spectral Data and Acidity Constants (pK_{a2} and pK_{a3}) of 1 to 8 for the First and Second Protonations

	spectral maximum λ/nm			acidity measurements					
molecule	neutral species[a] λ_{max} (log ε_{max})	monocation[b] λ_{max} (log ε_{max})	dication[c] λ_{max} (log ε_{max})	λ[d]/nm	$H^{1/2}$[e]	m[f]	pK_{a2}[g]	pK_{a3}[h]	corr[i]
1	291.20 (3.67)	298.40 (3.84)		291.20	7.42	0.5088	3.7759 ± 0.14		0.976
	256.60 (4.00)	256.40 (4.06)							
		298.20 (3.83)	397.40 (3.46)	256.40	−6.3365	0.6366		−4.0338 ± 0.16	0.963
		256.40 (4.06)	290.20 (4.28)						
2	307.20 (4.03)	309.00 (4.09)		299.00	6.65	0.5097	3.3890 ± 0.09		0.974
	256.00 (4.15)	256.20 (4.16)							
		309.00 (4.15)	398.60 (3.68)	255.00	−6.5076	0.5656		−3.6807 ± 0.12	0.989
		256.00 (4.22)	290.40 (4.22)						
3	403.20 (3.86)	295.40 (4.04)		405.80	5.76	0.7161	4.1236 ± 0.17		0.972
	291.60 (3.96)	235.40 (4.29)							
		295.20 (3.95)	389.80 (4.00)	387.00	−7.8225	0.5008		−3.9175 ± 0.12	0.963
		235.40 (4.19)							
4	422.40 (4.03)	345.60 (3.85)		416.60	4.94	0.9348	4.6164 ± 0.08		0.994
	293.60 (4.08)	306.40 (4.19)							
		345.20 (3.93)	265.20 (4.57)	391.00	−7.5154	0.4928		−3.7036 ± 0.07	0.988
		307.20 (4.27)							
5	387.40 (4.15)	299.80 (4.20)		387.40	5.45	0.5579	3.0390 ± 0.16		0.964
	360.60 (4.14)	235.00 (4.34)							
		299.80 (4.26)	273.60 (4.27)	258.40	−9.0954	0.4014		−3.6509 ± 0.07	0.989
		234.60 (4.40)	258.40 (4.32)						
6	388.60 (4.21)	307.00 (4.27)		307.00	6.33	0.4557	2.8865 ± 0.07		0.992
	309.00 (4.12)	233.60 (4.38)							
		307.20 (4.25)	264.20 (4.36)	264.00	−8.5667	0.5844		−5.0064 ± 0.09	0.988
		233.60 (4.36)							
7	360.60 4.28)	346.40 (4.07)		361.00	1.20	0.5624	0.6765 ± 0.05		0.997
	295.60 (4.03)	295.20 (4.25)							
		347.20 (3.80)	337.00 (3.49)	293.00	−7.4615	0.6775		−5.0552 ± 0.13	0.984
		293.60 (4.04)	247.00 (3.99)						
8	360.60 (4.29)	343.80 (4.04)		360.00	2.03	0.6298	1.2766 ± 0.12		0.975
	307.80(4.11)								
		306.20 (4.27)	342.00 (3.72)	309.00	−5.9383	1.1558		−6.8635 ± 0.15	0.965
		231.00 (4.42)	256.60 (4.30)						

[a] Measured in pH 7 buffer solution. [b] Measured in pH 1 buffer solution. [c] Measured in 98 % H_2SO_4. [d] The wavelength for pK_a determination. [e] Half protonation value ± uncertainties refer to the standard error. [f] Slopes for log I as a function of pH (or acidity function H_o) graph. [g] Acidity constant value for the first protonation. [h] Acidity constant value for the second protonation. [i] Correlations for log I as a function of the pH (or H_o) graph.

expressed in terms of concentration and activity coefficient:

$$K_a = \frac{a_{X^-} a_{SH_2^+}}{a_{HX}} = \frac{[X^-][SH_2^+]}{[HX]} \frac{\gamma_{X^-}\gamma_{SH_2^+}}{\gamma_{HX}} \qquad (2)$$

where $a = c\gamma$; a = activity constant, γ = activity coefficient, and c = concentration

$$K_a = \frac{[X^-]}{HX} \frac{\gamma_{X^-}}{\gamma_{HX}} a_{SH_2^+} = h_x \frac{[X^-]}{[HX]} \qquad (3)$$

Therefore, eq 3 can be rearranged as follows:

$$H_x = -\log h_x = pK_a - \log \frac{[HX]}{[X^-]} \qquad (4)$$

A plot of log I (log I = log ([HX]/[X$^-$])) against H_X does not yield the pK_a at log I = 0, unless it is a Hammett base, but yields the pH at half-proton-gain value ($H_X^{1/2}$). The general eq 4 may therefore be applied and the more general eq 5 can be derived.

$$pK_a = mH_X^{1/2} \qquad (5)$$

where $H^{1/2}$ describes the half proton-gain value.

The general procedure was applied as follows: a stock solution of the molecule under investigation was prepared by dissolving the molecule (about (10 to 20) mg) in water of known volume (25 mL). Aliquots (1 mL) of this solution were transferred into 10 mL volumetric flasks and diluted to the mark with buffers of various pH (or H_o or $H\_$). The pH (or H_o or $H\_$) values were measured before and after addition of the new solution. The absorbance of each solution was then measured in 1 cm cells, against solvent blanks, using a constant temperature cell-holder (UNICAM UV2 PC UV−visible). A scanning spectrometer was thermostatted at 25 °C (to within ± 0.1 °C). The wavelengths were chosen such that the fully cationic or anionic form of the

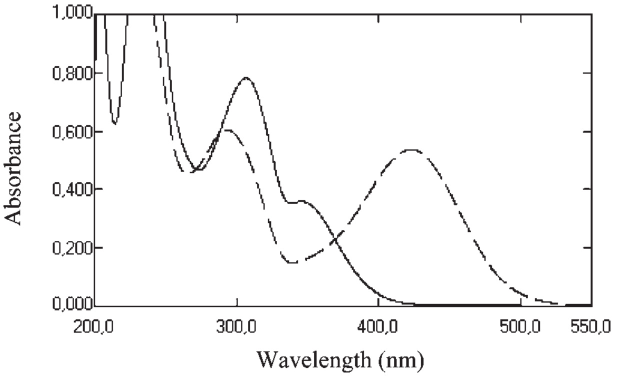


Figure 1. UV−visible spectrum of molecule **8** in pH 1 and pH 7 solutions. (Neutral ---, ionic — —).

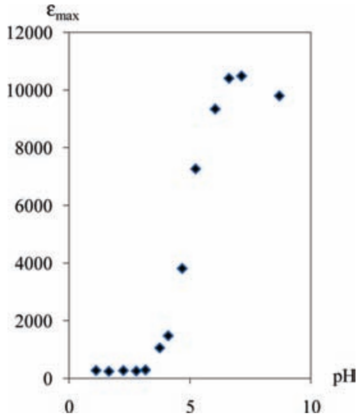


Figure 2. λ_{max} as a function of pH (416.60 nm) plot of molecule **8** for the first protonation.

substrate had a much greater or a much smaller extinction coefficient than the neutral form (this procedure was applied for both super acidic, H_o, and super basic, $H_\_$, solutions). The analytical wavelengths, the half-proton-gain values, and the UV−vis. absorption maxima for each substrate are depicted in Tables 2 and 3.

Calculations of half-proton-gain values were carried out as follows; the sigmoid curve of absorbance or extinction coefficients at the analytical wavelength (A, λ) was first obtained (Figure 1 and 2). The absorbance of the fully protonated molecule (A_{ca}, absorbance of conjugated acid) and the pure free base (A_{fb}, absorbance of free base) at an acidity were then calculated by linear extrapolation of the arms of the curve. Equation 6 provides the ionization ratio where the A_{obs} (the observed absorbance) was in turn converted into molar extinction ε_{obs} using Beers law of $A = \varepsilon bc$ (b = cell width, cm; c = concentration, mol·dm^{-3}):

$$I = \frac{[HX]}{[X]} = \frac{(A_{obs} - A_{fb})}{(A_{ca} - A_{obs})} = \frac{(\varepsilon_{obs} - \varepsilon_{fb})}{(\varepsilon_{ca} - \varepsilon_{obs})} \qquad (6)$$

A linear plot of log I against pH, using the values $-1.0 < \log I < 1.0$, had slope m, yielded the half-proton-gain value as pH$^{1/2}$ at $\log I = 0$. The pK_a values were calculated by using eq 7 (Figure 3).

$$pK_a = m\mathrm{pH}^{1/2} \qquad (7)$$

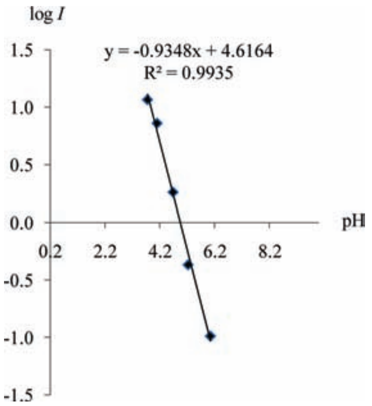


Figure 3. pH as a function of log I (416.60 nm) plot of molecule **8** for the first protonation.

RESULTS AND DISCUSSION

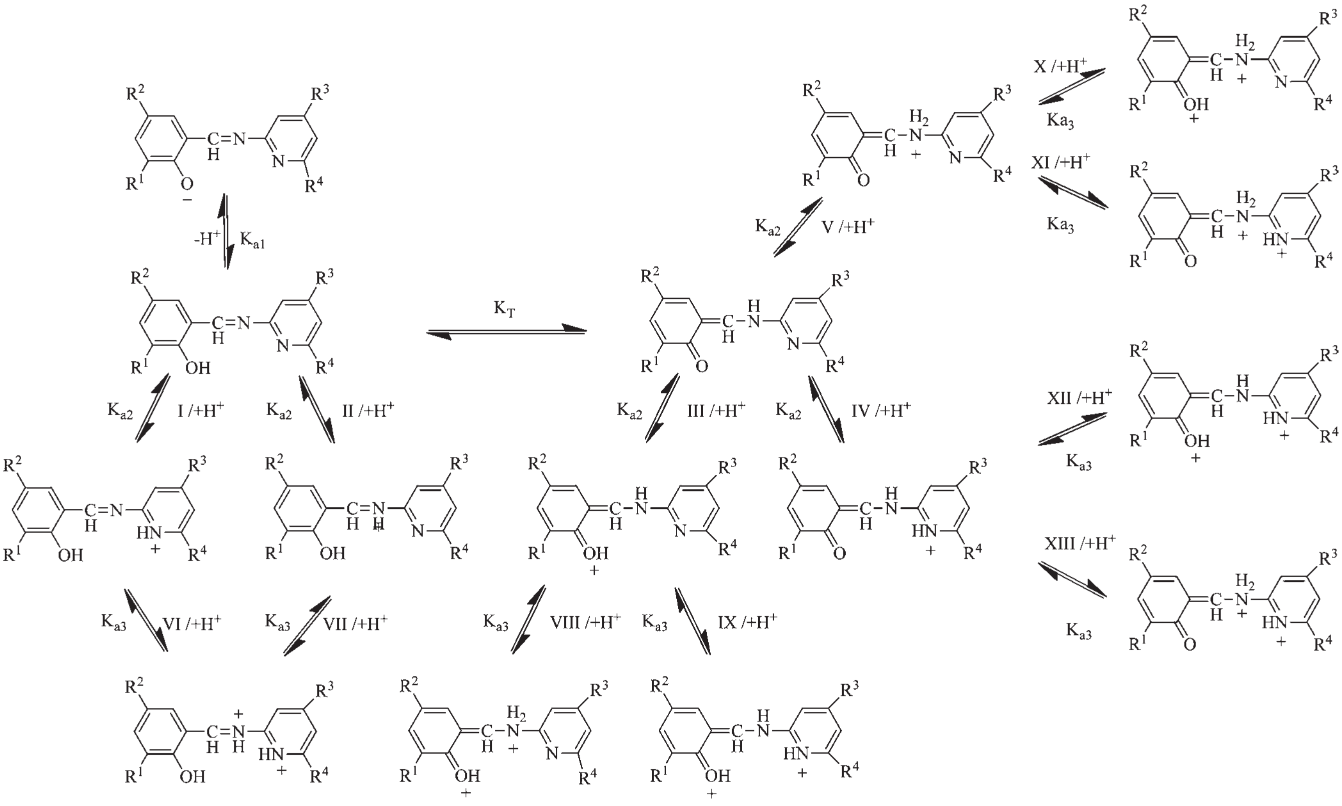
A major difficulty in obtaining reliable values for the protonation constants of the Schiff bases of salicylaldehyde with heteroaromatic amines is due to their low solubility and possible hydrolysis in aqueous solutions. Therefore, it is necessary to work at low concentrations and pH values should be neither extremely low nor extremely high. This poses some limitations on the choice of the method. The spectrophotometric method seems to be the most convenient one. The names and possible protonation patterns of the studied molecules **1** to **8** are depicted in Table 1 and in Scheme 1, respectively.

Deprotonation. The electronic absorption spectra and obtained acidity constants for deprotonation (i.e., protonation of phenoxide ion) process are depicted in Table 2. The proton-loss acidity constants of these Schiff bases (pK_{a1}) vary between 3 and 5. The presence of strong electron-withdrawing nitro groups in the para position of the phenol ring leads to a decrease in the basic character of molecule **5** and **6**. On the other hand the basicity of molecule **8** and **6** with an o-nitro substituted according to the −OH group are higher than the basicity of these molecules, since the strong electron withdrawing effect of the nitro group prevented the formation of hydrogen bonding between the hydrogen atom of the hydroxyl (−OH) group. Taking the first protonation (i.e., phenolate anion) or deprotonation values into account, we can put the studied molecules in a decreasing basicity order as follows:

Molecule :	4	8	3	1	2	6	5	7
pK_{a1} :	5.27 >	4.45 >	4.30 >	3.91>	3.20 >	3.15 >	3.10 >	3.03

Decreasing basicity ⟶

Protonation. The UV spectral and protonation data of the studied molecules **1** to **8** are shown in Table 3. Obviously, substitution of the imino nitrogen on the pyridine ring at position 2 leads to a drastic decrease in the basic character of this group due to the close proximity of the electron-withdrawing pyridine nitrogen and the basicity of pyridine increases. The sequence of protonation changes and the first acidity constant (pK_{a1}) of **1** to **8** may be associated with the protonation of the phenolate oxygen, the second acidity constant (pK_{a2}) may be associated with the protonation of the pyridine nitrogen and the third acidity constant (pK_{a3}) may be associated with the protonation of the imino group of enolimine. Looking at the m value, of the log I acidity graphs, Scheme 1. Possible Protonation Pattern for Studied Molecules 1 to 8



which are about 0.5, we can predict that the contribution of the ketoamino tautomeric form is important in molecules **1**, **2**, **3**, **4**, and **8** and that these molecules protonate primarily at the oxo group (path III). For molecules **5**, **6**, and **7**, the slopes of the log *I* acidity values are about unity and are indicative of the pyridine nitrogen atom (path I). For the third pronation (pK_{a3}), the slopes of log *I* acidity groups (Table 3) are about unity for molecules **1**, **3**, **7**, and **8**, indicating the pyridine nitrogen atom (path IX). They are about 1.30 for molecules **2** and **5**, indicating amino protonation (path XIII). For molecules **4** and **6**, however, the slope at about 0.50 is indicative of oxo protonation (path XII).

■ CONCLUSION

The acidity constants of Schiff bases were calculated via an UV−vis spectrophotometric method at (25 ± 0.1) °C. The pK_{a1} of the all molecules (**1** to **8**) are found to be associated with the protonation of the phenolate oxygen. The pK_{a2} are found to correspond to protonation of the pyridine nitrogen for molecules **5**, **6**, and **7** and oxoprotonation for molecules **1**, **2**, **3**, **4**, and **8**. The pK_{a3} are found to be associated with the protonation of pyridine nitrogen for molecules **1**, **3**, **7**, and **8** and amino protonation for molecules **2** and **5**. For molecules **4** and **6**, it is associated with oxo protonation.

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