

Temperature, Medium and Structural Effects on the Acid Dissociation Constants of Certain Schiff Bases Derived from Isatin with Some Amino Acids and Aroylhydrazines

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The acid dissociation constants of certain Schiff bases derived from isatin with p-substituted benzoyl hydrazines and some amino acids of glycine, β - and α -alanine, valine, β -phenyl- α -alanine and anthranilic acid have been determined potentiometrically at different temperatures in different aquo-organic solvent mixtures (ethanol, dioxane, dimethyl formamide, methanol, acetone and tetrahydrofuran). The pKa values were demonstrated on the light of the different electronic and steric effects of the substituents and the solvent characteristics. In all the mixed media used, ionization of the compounds decreased by increasing the mole fraction of the organic cosolvent. Thermodynamic parameters (ΔH° , ΔG° , ΔS°) were evaluated. The structural effects of the investigated compounds on these parameters were reported and discussed.

Key words: Isatin, Amino acids, Aroylhydrazines, Dissociation constants

INTRODUCTION

Isatin and its derivatives showed diverse and marked biological activities such as antiviral (Holzbecher, 1950), antibacterial (Varma *et al.*, 1975), anthelmintic (Knotz, 1973), herbicidal (Mambsch, 1957), cysticidal (Varma and Khan, 1978), hypotensive and anticonvulsant properties. However condensation of isatin with substituted hydrazines leads to the formation of the corresponding biologically active hydrazones (Bauer *et al.*, 1961; Khueb *et al.*, 1981; Bhardwaj *et al.*, 1989; Abu *et al.*, 1991). In view of these important applications and in continuation to our previous works (Hassan *et al.*, 1989; Hassan, 1990; Hassan and Soliman, 1991), we report, in the present paper, the effects of temperature, medium solvents and structures of the investigated compounds of certain Schiff bases derived from isatin with some amino acids and aroylhydrazines on their acid dissociation constants and thermodynamic parameters.

MATERIALS AND METHODS

Materials and solvents

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All materials used were of A.R. Grade products. The selected organic solvents were of highly purity (A.R. or spectrograde products). Isatin-aroylhydrazones or N-methyl isatin were prepared as published elsewhere (Tacconi *et al.*, 1973; Snavely and Sun, 1981; Bhardwaj *et al.*, 1989; Abu *et al.*, 1991). Isatin-amino acid Schiff bases were prepared according to our previous work (Hassan, 1990; Hassan and Soliman, 1991).

Procedures

A 10^{-2} mol·dm⁻³ stock solutions of isatin-Schiff bases under investigation were prepared by dissolving an accurate amount of each compound in the selected organic solvent (EtOH, DMF, Dioxane, MeOH, THF, Acetone). A 0.2 mol·dm⁻³ NaOH solution was prepared by dissolving the granular NaOH pellets in CO₂-free bidistilled water and was standardized by standard 0.2 mol·dm⁻³ potassium hydrogen phthalate. A 2.0 mol·dm⁻³ stock solution of KCl was used as supporting electrolyte. Generally, dilute solutions were prepared by appropriate dilution of the stock.

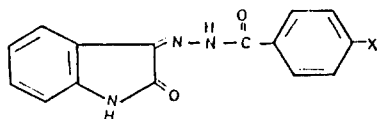
The pH measurements were carried out using an Accumet pH-Meter Model 825 MP. The instrument was calibrated before and after each series of pH readings under the same conditions using two buffer solutions at 4.01 and 9.18.

The pKa values of isatin-Schiff bases in the different organic solvents-water mixtures of different proportions (80, 60, 50, 40, 20% V/V organic solvent-water) were determined at different temperatures (25-40°C) by adopting the Irving and Rossotti pH-titration technique (Irving and Rossotti, 1993).

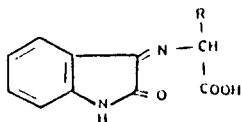
All the titration experiments were done by introducing 5 ml of 10^{-2} mol·dm⁻³ of each Schiff base solution into the thermostated titration cell followed by 1 ml of 2.0 mol·dm⁻³ KCl as ionic background. The total volume was completed to 50 ml with the required amount of water and cosolvent, then titrated against a standard carbonate-free NaOH solution at the desired temperature. Purified nitrogen gas was bubbled through the titrated solution ensure stirring and neutral inert atmosphere. Furthermore, the solution was stirred magnetically to mixing. The pH-meter readings have been corrected in accordance with the method described by Douheret (Douheret, 1967; Douheret, 1968). This was carried out to account for the difference in acidity, basicity, dielectric constant and ion activities in partially aqueous solutions relative to the pure one.

The pKa values were calculated by using the graphical method (average value method) and the linear plot method. The average pKa values of these two different calculation methods are listed in Tables I-IV.

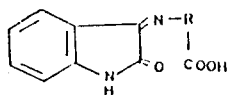
The general structural formulas of the Schiff bases derived from isatin with aroylhydrazines and amino acids are represented as follow:



1, X=Cl, NO₂, H, OCH₃



2, R=H, -CH₃, -CH(CH₃)₂, -CH₂-C₆H₅ for glycine, α -alanine, valine and β -phenyl- α -alanine-isatin Schiff bases respectively.



3, R=(CH₂)₂, o-C₆H₄ for β -alanine and anthranilic acid-isatin Schiff bases respectively.

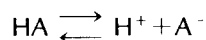
RESULTS AND DISCUSSION

The acid dissociation constant (pKa) of the com-

pounds under this study were determined by plotting the $\bar{n}A$ (the average number of protons attached to the compound) against the pH of the titrated solution corresponding to each addition of alkali. Only one pKa could be obtained by recording the pH value at $\bar{n}A=0.5$ indicating that only one proton is titrated. This is consistent with the appearance of one inflection point on the titration curves.

Titration curves of 1, X=H and its N-methyl derivative in 50%(V/V) ethanol-water at room temperature give the same value of pKa (9.50) indicating that this value of pKa is due to the N-proton adjacent to keto group of the hydrazone moiety whereas the N-proton of isatin moiety in position 1 may be dissociated at higher region of pH.

For simplicity, the investigated compounds would be abbreviated with a general simple formula (HA) and the mode of ionization is given as follows



The acid dissociation constants (pKa) of the compounds under investigation have been affected and demonstrated by the following factors:

Effect of the selected organic solvents

It is apparent that the pKa values (Table I-III), at the same concentration of the organic cosolvent, have the higher magnitude in ethanol than in dioxane or DMF.

The pKa values of 1, X=H in 50% (V/V) ethanol, dioxane, DMF, acetone, THF or methanol-water at room temperature are 9.50, 8.60, 8.35, 9.21, 9.4 and 6.98, respectively. Although methanol and DMF have quite similar dielectric constants (32.6 and 36.7, respectively at 25°C), the pKa values corresponding to these two solvents are highly different. The general

Table I. The pKa values for Schiff bases of isatin with amino acids and aroyl-hydrazines at room temperature in different (V/V) ethanol-water media

Compound	pKa				
	20%	40	50%	60%	80%
1, X=NO ₂	7.93	8.40	8.88	9.08	9.43
Cl	*	8.72	9.10	9.33	9.73
H	*	9.35	9.50	10.40	10.95
OCH ₃	*	9.93	10.47	10.87	11.40
2, X=H	8.50	9.55	10.03	10.45	10.70
CH ₃	9.30	10.00	10.18	10.30	10.70
CH(CH ₃) ₂	9.28	9.95	10.20	10.55	10.95
CH ₂ -C ₆ H ₅	*	*	10.65	10.98	11.10
3, R=(CH ₂) ₂	9.00	9.60	9.8	10.20	10.60
o-C ₆ H ₄	9.25	9.80	10.10	10.25	10.55

*Precipitation occur

Table II. The pKa values for Schiff bases of isatin with amino acids and aroyl-hydrazines at room temperature in different (V/V) dioxane-water media

Compound	pKa 20%	40	50%	60%
1, X=NO ₂	6.73	7.17	7.37	7.82
Cl	*	8.05	8.50	8.90
H	*	8.15	8.60	9.00
OCH ₃	*	8.30	8.75	9.15
2, X=-H	8.45	9.00	9.30	9.75
CH ₃	8.60	9.20	9.35	9.85
CH(CH ₃) ₂	8.80	9.43	9.80	10.18
CH ₂ -C ₆ H ₅	*	9.60	10.00	10.35
3, R=(CH ₂) ₂	8.40	9.00	9.15	9.45
o-C ₆ H ₄	8.50	9.05	9.35	9.58

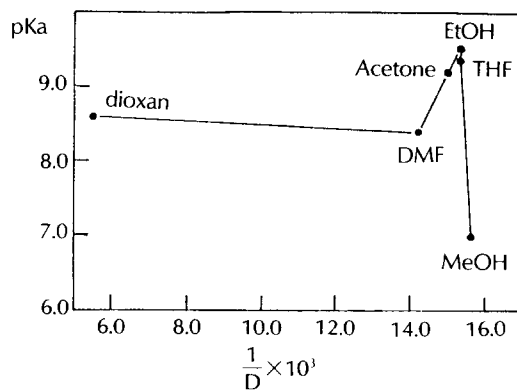
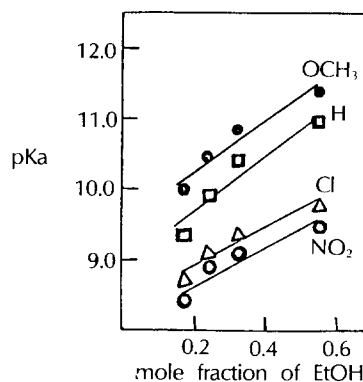
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Table III. The pKa values for Schiff bases of isatin with amino acids and aroyl-hydrazines at room temperature in different (V/V) D.M.F-water media

Compound	pKa 20%	40	50%	60%
1, X=NO ₂	6.63	7.03	7.23	7.65
Cl	*	7.8	7.95	8.58
H	*	8.00	8.35	8.85
OCH ₃	*	8.20	8.60	9.00
2, X=H	8.20	8.85	9.10	9.0
CH ₃	8.38	9.00	9.15	9.60
CH(CH ₃) ₂	8.60	9.20	9.50	9.85
CH ₂ -C ₆ H ₅	*	9.55	9.70	10.05
3, R=(CH ₂) ₂	8.15	8.80	8.95	9.20
o-C ₆ H ₄	8.15	8.78	9.00	9.25

*Precipitation occur

observation is that the compound (1, X=H) is more acidic in presence of methanol than in presence of DMF. Moreover, though ethanol and acetone have quite similar dielectric constants (24.3 and 20.7 respectively at 25°C), the compound (1, X=H) is more acidic in water-acetone mixture than water-ethanol mixture of the same ratio. This behaviour indicates that other solvent effects beside the electrostatic one can act as important factors influencing the ionization process of the investigated compounds. This fact is further substantiated by the obtained nonlinear plot of pKa against 1/D of the medium (Fig. 1) according to the equation given by Denison and Ramsey (1955), Gilkerson (1956) which relates the variation of pKa of the acid with the dielectric constant of the medium. Generally, it is recognized that solvent effects such as hydrogen bonding, dispersion forces, proton-solvent interactions and solvent basicity play vital roles in the ionization process of acids in different solvent (Coet-

**Fig. 1.** pKa-medium dielectric constant relation in 50% (V/V) organic solvent-water.**Fig. 2.** pKa-mole fraction of EtOH relation for compound 1, X=Cl, NO₂, H, OCH₃.

zee and Ritchie, 1969). The observed low acidity for this compound (1, X=H) in ethanol-water mixture relative to in methanol-water where both have the same mole fraction of alcohol is in consistency with the fact that ethanol is characterized by low tendency to donate hydrogen bond than methanol (Franks and Ives, 1966). Thus, the conjugate base (A⁻) is expected to be more stabilized in presence of MeOH (i.e. facilitate the ionization of acidic compound) leading to decrease in pKa. The unexpected high acidity of all compounds in presence of the very poorer hydrogen bond donor solvents (Dioxane, DMF, Acetone) relative to that in presence of ethanol (Table I-III), where the mole fraction of these solvents in the aqueous medium is identical, can be presumably ascribed to the high basic character of DMF and acetone relative to ethanol. This leads to the construction of stronger hydrogen bonds donated by the solutes (HA) to these solvents thereby facilitates the ionization process of the compound (i.e. low pKa). In case of dioxane, the observed high acidity may be attributed to its anomalous behaviour. Though it is considered a weak polar solvent, it, in many cases, behaves as a polar solvents (Bayliss and Mcrae, 1957; Ledger and Suppan, 1967).

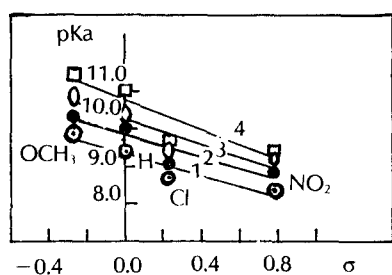


Fig. 3. σ hammett-pKa relation for **1**, X=Cl, NO₂, H, OCH₃ in EtOH-H₂O 40, 50, 60, 80% (V/V) represented by lines 1, 2, 3, 4 respectively.

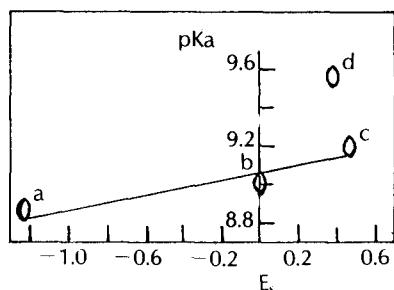


Fig. 4. Taft E_s-pKa relation for **2**, R=H, CH₃, CH(CH₃)₂, CH₂-C₆H₅, represented by a, b, c, d, respectively, in DMF-H₂O 40% (V/V).

Effect of the organic cosolvent-water ratio

In this context, since the water molecules are characterized by a high tendency to give rise to hydrogen bonds as compared with the other solvent molecules (Franks and Ives, 1966), the conjugate base (A⁻) is expected to be more stabilized by the hydrogen bonding donated by water leading to facilitate the ionization of the acidic compounds (i.e. low pKa and high acidity) as the mole fraction of water increases (Tables I-III and Fig. 2). On the other hand, the conjugate base (A⁻) would be less stabilized as the amount of the organic cosolvent in the medium increases (i.e. suppression of ionization) i.e. high pKa and low acidity as shown by Tables I-III and Fig. 2.

Structural effect

Careful inspection of the pKa values in Tables I-IV clearly indicates that these values are greatly influenced by the nature of the substituents. For compounds **1**, X=Cl, NO₂, H, OCH₃, the effect of substituents (**10**) can be adequately represented by Hammett's equation. This equation can provide a quantitative measure of the electronic effects (δ) of different substituents in the aromatic systems. For compounds **2**, R=H, -CH₃, -CH(CH₃)₂, -CH₂-C₆H₅, the effect of substituents (R) is illustrated by Taft's equation which gives a quantitative measure of the electronic (δ^*) and steric

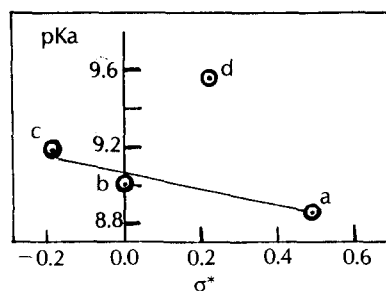


Fig. 5. Taft σ^* -pKa relation for **2**, R=H, CH₃, CH(CH₃)₂, CH₂-C₆H₅, represented by a, b, c, d, respectively, in DMF-H₂O 40% (V/V).

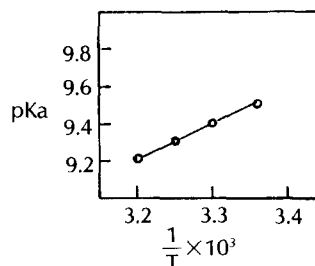


Fig. 6. pKa-1/T relation for **3**, R=o-C₆H₄ in EtOH-H₂O 50% (V/V).

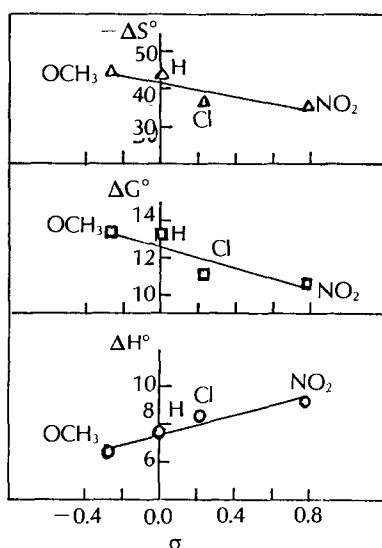
(E_s) effects of different substituents in the aliphatic systems. It has been found that the electron withdrawing substituents (**1**, X=Cl, NO₂) result in increase the acidity of the compounds and decrease their pKa values. The electron withdrawing ability facilitates the ionization of proton in the acidic compounds. The reverse situation is observed in case of the electron donating substituents (**1**, X=H, OCH₃). This fact is graphically represented in Fig. 3.

In this context, the electronic (σ^*) and steric (E_s) effects of the substituents of compounds **2**, R=H, -CH₃, -CH(CH₃)₂ and -CH₂-C₆H₅ are demonstrated by Taft's equation. It has been found that the acidity decrease in the order **2**, R=H > **2**, R=CH₃ > **2**, R=CH(CH₃)₂ > **2**, R=-CH₂-C₆H₅. This is represented by figures, 4, 5. The deviation of **2**, R=-CH₂-C₆H₅ from the linearity may be ascribed to the greater steric effect of -CH₂-C₆H₅ group relative to the other substituents. Furthermore the expected higher acidic **2**, R=H relative to **3**, R=(CH₃)₂ may be ascribed to the elongation of the hydrocarbon chain in case of the latter compound. In addition, **3**, R=o-C₆H₄ exhibits, in general, a slight higher acidic character more than the other isatin-amino acid Schiff bases. This may be presumably attributed to presence of its carboxylic group attached directly to aromatic ring.

It can be seen from Tables I-IV that the pKa values, in general, are identical approximately to those of the second dissociation constants of the corresponding

Table IV. The pKa values for Schiff bases of isatin with amino acids and aroyl-hydrazines at different temperature (25-40°C) in 50% (V/V) ethanol-water medium

Compound	pKa 25°C	30°C	35°C	40°C	ΔH° Cal/mol	$\Delta G^\circ(2^\circ\text{C})$ Kcal/mol	$-\Delta S^\circ(25^\circ\text{C})$ Cal/mol/deg.
1 X=NO ₂	7.76	7.66	7.5	7.46	9.20	10.64	35.67
	Cl	8.12	8.0	7.96	8.43	11.13	37.32
	H	9.70	9.65	9.55	9.40	7.67	44.59
	OCH ₃	9.80	9.70	9.60	9.55	6.37	45.06
2 , X=H	9.85	9.75	9.50	9.30	14.72	13.50	45.25
	CH ₃	9.85	9.755	9.65	9.35	13.80	45.26
	CH(CH ₃) ₂	9.88	9.78	9.65	9.55	9.20	45.42
	CH ₂ -C ₆ H ₅	10.10	10.00	9.85	9.80	9.20	46.43
3 , R=(CH ₂) ₂	9.60	9.50	9.25	9.00	16.87	13.16	44.10
	o-C ₆ H ₄	9.50	9.40	9.30	9.20	9.20	43.58

**Fig. 7.** σ hammett-thermodynamic parameters (ΔH° , ΔG° , $-\Delta S^\circ$) relations for **1**, X=Cl, NO₂, H, OCH₃ in 50% (V/V) EtOH-H₂O medium.

free amino acids (Mahanoud *et al.*, 1988; Singh *et al.*, 1988). This reveals the limited influence of isatin moiety towards the pKa values obtained for the investigated isatin-amino acid Schiff bases.

Temperature effect and thermodynamic parameters

The pKa values of the investigated compounds are determined in 50% (V/V) ethanol-water at different temperatures (25-40°C). The thermodynamic parameters and pKa values are listed in Table IV. It has been observed that as the temperature increase, the pKa values decrease (Fig. 6) indicating that acidity and ionization of these compounds are increased by temperature.

The values of the enthalpy change (ΔH°) are calculated from the slope of the least square best fitting

line for the plot of pKa versus $\frac{1}{T}$ (Fig. 6) and equation $\text{pKa} = \frac{\Delta H^\circ}{2.3 RT} + \text{const.}$ The free energy change (ΔG°) and the entropy change (ΔS°) are calculated from the equations:

$$\Delta G^\circ = 2.3 RT \text{ pKa}$$

$$\Delta S^\circ = \frac{\Delta H^\circ - \Delta G^\circ}{T}$$

An inspection of the results given in Table IV reveals that the measured values of pKa and therefore of ΔG° for the two series of **1** and **2** compounds exhibit the expected increase in their values with an increase in the donor power of the substituents and an increase in steric effect of the substituents R for the **2** compounds and vice versa (Fig. 7). A similar trend is also observed in the entropy change (Fig. 7) indicating its contribution to the ΔG° values. The less negative ΔS° for **1**, X=NO₂ and **3**, R=o-C₆H₄ indicates less ordering of solvent molecules upon dissociation. This points to greater association (Mui *et al.*, 1974; Masoud *et al.*, 1983). The higher ΔH° values for **1**, X=NO₂ and **3**, R=(CH₂)₂ indicate that the dissociation in the case of these two compounds requires a great amount of energy relative to the other related compounds.

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