

Medium Effects on the Ionization Constants of Some Quinoline Derivatives

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Summary. The deprotonation and acid ionization constants of some quinoline derivatives in aqueous organic solvents were determined. The organic solvents used include methanol and ethanol as amphiprotic solvents and *DMF* and *DMSO* as dipolar aprotic solvents. The obtained pK_1 and pK_2 values are discussed with respect to the nature and the amount of the organic component. The high stabilization of the non-protonated form by dispersion forces and of the proton by its interaction with the solvent are the main factors responsible for the increase in the ionization constants of the protonated forms of the quinolines under investigation. On the other hand, H-bonding interactions (in addition to the electrostatic effect) seem to play the major role in determining the second acid-base equilibrium of 8-hydroxyquinoline. The deprotonation constants of the examined quinolines are correlated with their experimentally determined lone-pair ionization potential values.

Keywords. Acid Ionization Constants; Ionization of Quinoline Derivatives; Medium Effects.

Lösungsmittelleffekte auf die Ionisationskonstanten einiger Chinolinderivate

Zusammenfassung. Die Deprotonierungs- und Ionisationskonstanten einiger Chinolinderivate wurden in wäßrigen organischen Medien, darunter Methanol und Ethanol als amphiprotische und *DMF* und *DMSO* als dipolare aprotische Lösungsmittel, bestimmt. Die gemessenen pK_1 - und pK_2 -Werte werden im Hinblick auf die Art und Menge der organische Komponente diskutiert. Die hohe Stabilisierung der nichtprotonierten Form durch Dispersionskräfte und des Protons durch Wechselwirkungen mit dem Lösungsmittel sind die wesentlichen Faktoren, die für den Anstieg der Ionisationskonstanten der protonierten Formen der untersuchten Chinoline verantwortlich sind. Andererseits scheinen Wasserstoffbrückenbindungen – zusätzlich zum elektrostatischen Effekt – das zweite Säure-Basen-Gleichgewicht von 8-Hydroxychinolin entscheidend zu beeinflussen. Die Deprotonierungskonstanten aller untersuchten Chinoline werden mit ihren experimentell bestimmten *lone-pair*-Ionisationspotentialen korreliert.

Introduction

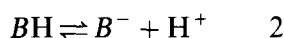
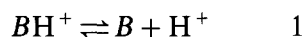
Due to their importance in biology, the properties of molecules containing non-bonding electrons are very interesting. In this respect, the azaaromatics, particularly substituted quinolines, are considered as an important class of compounds in many fields (mainly chelatometry, separation methods [1] and some biological applications [2]). Moreover, quinoline derivatives represent the effective moiety in some antimalarial drugs such as pamaquine and chloroquine [3].

Though dissociation constants of acids and bases in mixed and nonaqueous solvents have been extensively investigated, little work has been done to study the dissociation constants of quinoline derivatives in different water-organic solvent mixtures. *Vasil'ev et al.* [4, 5] studied the dissociation constant of 8-hydroxyquinoline in aqueous solutions containing different proportions of dimethylformamide, dimethylsulfoxide, and dioxane potentiometrically. The results, discussed on the basis of dielectric constants and solvation effects, showed that the pK_1 (pK_{NH^+}) values decrease, whereas pK_2 (pK_{OH}) values increase with rising amount of nonaqueous component. *Reynaud* [6] determined the ionization constants of some nitrogen bases including quinoline and isoquinoline in different aquo-organic solvents. It was found that the ionization constant of quinoline increases with increasing nonaqueous proportion in the medium. Accordingly, this article is devoted to study the medium effect on the acidity ionization constant of quinoline derivatives (quinoline (1), 6-methyl-quinoline (2), 6-methoxyquinoline (3), 2,6-dimethylquinoline (4), and 8-hydroxyquinoline (5) in water-organic solvent mixtures. The organic solvents used are methanol and ethanol as amphiprotic solvents and N,N-dimethylformamide, DMF, and DMSO as dipolar aprotic solvents.

Results and Discussion

The obtained mean pK_a values for quinolines 1–5 under investigation by application of two different methods (average value and straight line methods) are collected in Tables 1 and 2. All calculations were carried out by applying the least squares method. The results listed in these tables clearly indicate that both the proportion and nature of the organic co-solvent have a profound influence on the pK_a values of the studied compounds. Generally, the ionization constant for compounds 1–4 as well as the first one for compound 5 increase with increasing amount of organic solvent in the medium, while the second ionization constant for compound 5 decreases in the same direction.

The acid-base equilibria of the first and the second ionization steps can be represented by the following equations:



The acidity constants in aqueous medium (K) corresponding to the above steps, are related to that in partially aqueous medium (K') by means of equations 3 and 4.

$$K_1 = K'_1 \cdot \gamma_{H^+} \gamma_B / \gamma_{H^+B} \quad 3$$

$$K_2 = K'_2 \cdot \gamma_{B^-} \gamma_{H^+} / \gamma_{HB} \quad 4$$

Here γ is the activity coefficient of the subscripted species in a partially aqueous medium relative to that in a pure one [11]. It is known that the electrostatic effect resulting from the change in the dielectric constant of the medium will operate only on the activity coefficient of the charged species. However, the magnitude of this effect is inversely proportional to the radius of the ionic species considered [12]. Consequently, the electrostatic effect is expected to influence H^+ heavily. Thus, according to equations 3 and 4, the ionization constants of the compounds are expected to decrease with increasing percentage of the organic solvent in the

Table 1. Mean pK_1 values for quinolines **1–5** in different organic solvent-water mixtures at 25 °C

% wt of organic solvent	Mole fraction of organic solvent	Dielectric constant of the medium (D)	$1/\bar{D} \times 10^2$	pK_1 values			
				1	2	3	4
0.0	0.0	80.20	1.24	4.94*	5.18	5.05*	6.00
Methanol							
10	0.059	77.39	1.29	4.45	5.16	5.02	5.68
20	0.123	74.34	1.34	4.28	4.92	4.98	5.54
30	0.194	70.96	1.40	4.08	4.69	4.91	5.23
40	0.279	66.92	1.49	3.92	4.52	4.73	5.13
50	0.360	63.06	1.58	3.74	4.20	4.56	5.00
Ethanol							
10	0.040	77.96	1.28	4.59	5.17	5.00	5.78
20	0.089	75.22	1.33	4.38	4.91	4.90	5.52
30	0.143	72.20	1.38	4.27	4.58	4.85	5.26
40	0.206	68.68	1.45	3.93	4.39	4.63	5.01
50	0.281	64.49	1.55	3.36	4.07	4.40	4.87
DMF							
10	0.027	79.03	1.26	4.33	4.65	4.89	5.51
20	0.058	77.69	1.28	4.16	4.33	4.76	5.17
30	0.095	76.09	1.31	3.92	4.14	4.56	4.96
40	0.141	74.11	1.35	3.70	3.93	4.35	4.63
50	0.197	71.69	1.39	3.45	3.77	4.13	4.41
DMSO							
10	0.025	79.36	1.26	4.94	4.98	5.04	5.77
20	0.054	78.39	1.27	4.65	4.79	5.00	5.58
30	0.086	77.32	1.30	4.42	4.51	4.82	5.21
40	0.133	75.74	1.32	4.17	4.29	4.62	4.99
50	0.187	73.93	1.35	3.87	3.95	4.31	4.68

* The published values in aqueous solutions for compounds **1** and **3** are 4.90 and 5.03 at 20 °C, respectively [20]

aqueous medium resulting from an increasing activity coefficient of the proton, *i.e.* pK_a is high. This is not the case for the observed behaviour for the first ionization constant of the studied compounds as it is evident from the results in Tables 1 and 2. Accordingly, one can deduce that solvent effects rather than the electrostatic one are likely to play the major role in determining the acid dissociation process of the HN⁺ moiety of the subjected quinolines. Generally, specific solute-solvent interactions and dispersion forces play an important role in the ionization of weak acids. Accordingly, the observed decrease in pK_1 values of the various quinolines under investigation can be mainly interpreted on the principle of the expected relatively high stabilization of the free base of each compound by dispersion forces in the

Table 2. Mean pK values for 8-hydroxyquinoline (compound **5**) in different organic solvent-water mixtures at 25 °C

% wt of organic solvent	Mole fraction of organic solvent	Dielectric constant of the medium (D)	$1/D \times 10^2$	pK_1	pK_2
0.0	0.0	80.20	1.24	4.91*	9.68*
Methanol					
10	0.059	77.39	1.29	4.86	9.88
20	0.123	74.34	1.34	4.74	10.05
30	0.194	70.96	1.40	4.65	10.40
40	0.279	66.92	1.49	4.37	10.51
55	0.407	60.83	1.64	4.20	10.90
Ethanol					
10	0.040	77.96	1.28	4.85	9.84
20	0.089	75.22	1.33	4.72	10.33
30	0.143	72.20	1.38	4.43	10.66
40	0.206	68.68	1.45	4.22	11.04
55	0.323	62.14	1.61	4.00	
DMF					
10	0.027	79.03	1.26	4.66	10.02
20	0.058	77.69	1.28	4.39	10.17
30	0.095	76.09	1.31	4.25	10.63
40	0.141	74.11	1.35	4.00	10.63
50	0.197	71.69	1.39	3.78	
DMSO					
10	0.025	79.36	1.26	4.87	9.80
20	0.054	78.39	1.27	4.65	9.92
30	0.086	77.32	1.30	4.45	10.10
40	0.133	75.74	1.32	4.19	10.30
55	0.220	72.83	1.37	3.99	10.56

* The published values are 5.01 and 9.81 at 20 °C for pK_1 and pK_2 , respectively [20]

different solvent-water mixtures compared to that in pure aqueous media. Therefore, an increase in organic solvent content in the aqueous medium will lead to a decrease in the activity coefficient of the free base, thereby causing an increase in the acid dissociation constant of the protonated form of each compound, *i.e.* a low pK_a value (equation 3). The dispersion interaction is established between the delocalized oscillator dipole of the free base and the delocalized oscillator dipole of the solvent. The high stabilization of the base by dispersion forces in partially aqueous media is due to the fact that the effective density of dispersion centers of the solvents under study is higher than that of water [13].

Furthermore, the high stabilization of the proton by its interaction with organic solvent and water molecules in the mixture compared to that with water molecules

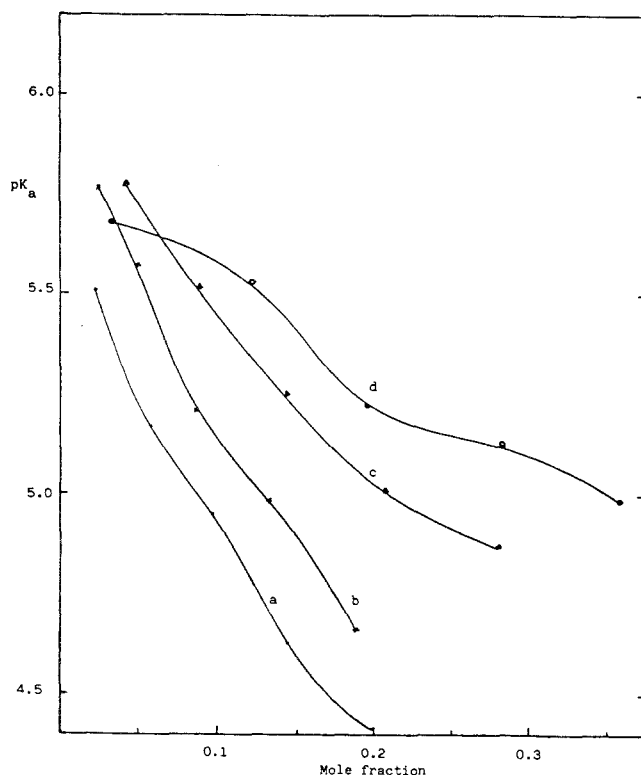
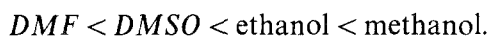


Fig. 1. Variation of pK_1 of compound 4 with the mole fraction of the organic solvent present in the aqueous medium at 25 °C; a) DMF, b) DMSO, c) Ethanol, d) Methanol

alone (ion-solvent interaction) can be considered, in part, responsible for the observed decrease in pK_{a1} values as the organic solvent content in the aqueous medium is increased.

Careful examination of the pK_1 values of the subjected compounds in different organic solvent-water media of more or less the same organic solvent mole fraction (Tables 1 and 2; Fig. 1) reveals that the pK_1 value varies with the nature of the applied organic solvent according to the following sequence:



This is expected as a result of the decrease in solvent polarizability on going from DMF to methanol within the above sequence [14].

With respect to the solvent effect on the second acid dissociation constant value pK_2 (pK_{OH}) of 8-hydroxyquinoline, one observes that the pK_2 value increases as the amount of each of the used organic solvents in the aqueous medium is increased. This behaviour can be ascribed to the electrostatic effect. Generally, by increasing the amount of the organic solvent in the aqueous medium, the dielectric constant of the medium is lowered. This in turn results in increasing the activity coefficient of both the free base and the proton, yielding high pK_2 values as it is evident from equation 4. However, in the light of the relation given by Charlot and Tremillon [15] giving the variation of pK_a with the dielectric constant (D), the plots of pK_2 values vs. $1/D$ are not strictly linear (Fig. 2). This indicates that the decrease in the second ionization constant of compound 5—though governed by the dielectric constant effect—is strongly influenced also by other solvent effects. It is recognized that effects

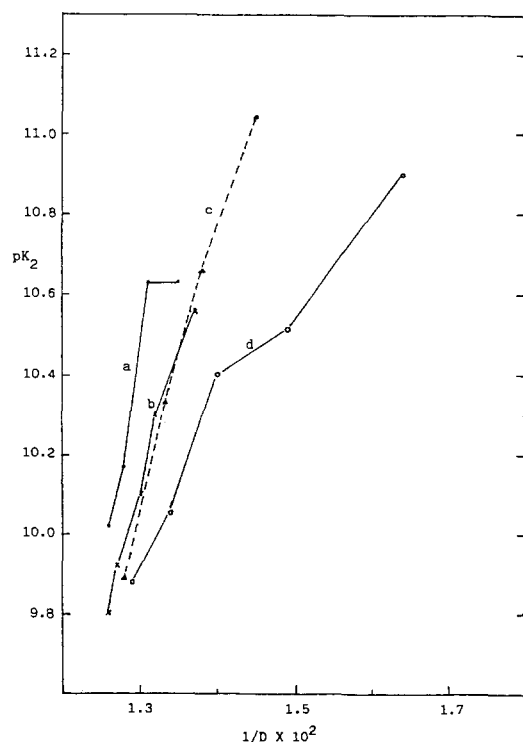


Fig. 2. Variation of pK_2 of compound **5** in aqueous-organic phase with $1/D$ of the medium at 25°C; a) DMF, b) DMSO, c) Ethanol, d) Methanol

such as hydrogen bonding and solvent polarity play vital roles in the ionization processes in different solvents [11]. Thus, the observed increase in pK_2 of compound **5** with increasing amount of organic solvent can also be ascribed to the effect of the possible hydrogen bonding interactions between the conjugate base (B^-) and solvent molecules in addition to the electrostatic effect discussed above. So it is expected that the conjugate base B^- is less stabilized by hydrogen bonding interaction with solvent molecules as the amount of the organic solvent in the medium is increased (*i.e.*, γB^- increases). This is based on the principle that water molecules have a high tendency to develop hydrogen bonds compared with other solvents [16]. However, the unexpected high acidity in presence of the poorer hydrogen bond donor DMSO relative to ethanol or methanol (Table 2 and Fig. 2) can be presumably ascribed to the high basic character of the former solvent. This is expected to lead to the formation of stronger bonds between solute (BH) and DMSO, thereby facilitating the second ionization process of compound **5**.

Dependance of pK_1 on the structure of quinolines

Generally, pK_1 values of compounds **2–4** are higher than that of **1** ($pK_1 = 4.94, 5.18, 5.05, 6.00$ for compounds **1–4**, respectively). This can be ascribed to the expected high electron density at the aromatic system as a result of the electron donor character of the substituents. This in turn will result in high charge density on the heterocyclic nitrogen atom and therefore stronger bonding of the proton. Accordingly, this will lead to a difficult deprotonation of this nitrogen atom, *i.e.* a high pK_1 value. This behaviour can be substantiated by correlating the solution-phase

basicities of the examined quinolines with their lone pair ionization potentials [17, 18]. The experimental lone pair ionization potential values of compounds **1–4** are 9.46, 9.24, 9.23, and 9.09 eV, respectively. It is evident that the pK_1 values of these compounds run according to the order $\mathbf{1} < \mathbf{2} < \mathbf{3} < \mathbf{4}$, which is generally in accordance with the observed decrease in lone pair ionization potentials in the direction $\mathbf{1} \rightarrow \mathbf{4}$. The observed decrease in the lone pair ionization potential on going from compound **1** to compound **4** is in accordance with the high basicity of the nitrogen atom as a result of the electron donor character of the substituents in compounds **2**, **3**, and **4**, respectively.

On the other hand, it is evident that though compound **5** has a higher lone pair ionization potential value (9.85 eV) than that of compound **1** [19], the two compounds have more or less the same pK_1 value (pK_1 of compound **5** is 4.91). This behaviour can be understood by the suggestion that the high ionization potential value of the lone-pair electrons of compound **5** can be likely attributed to the expected strong intramolecular hydrogen bond in the gas phase compared to that in the aqueous one.

Experimental

Materials and Solutions. All materials used were of a.r. grade (Aldrich and Janssen companies for fine chemicals). The organic solvents utilized were of high purity (a.r. or spectrograde).

Stock solutions (10^{-2} mole·dm $^{-3}$) of the compounds were prepared by dissolving the appropriate amount of each substance in bidistilled water. CO $_2$ -free NaOH solution (0.2 mole·dm $^{-3}$) was prepared and standardized against a standard solution of potassium hydrogen phthalate. A 0.2 mole·dm $^{-3}$ stock solution of KCl was used as supporting electrolyte. More dilute solutions were prepared by accurate dilution.

Procedure. The pK_a values of the quinoline derivatives in different organic solvents-water mixtures were determined by adopting the *Irving–Rossotti* [7, 8] *pH*-titration technique. *pH*-Titrations were carried out using an Orion model 701A digital *pH*-meter (accurate to $pH = \pm 0.005$ units) with a glass calomel electrode assembly at constant temperature ($25 \pm 0.10^\circ\text{C}$) with a standard carbonate-free NaOH solution of following compositions:

- 0.17–0.20 mole·dm $^{-3}$ HClO $_4$ + 0.1 mole dm $^{-3}$ KCl and
- Solution (a) in presence of 5×10^{-3} mole·dm $^{-3}$ quinoline base and different proportions (% w/w) of the organic solvent used.

To account for the differences in acidity, basicity, dielectric constants and ion activities for partially aqueous solutions relative to pure aqueous ones, the *pH* values of the former solutions were corrected making use of the procedure described by *Douhéret* [9]. If the *pH*-meter is standardized using aqueous buffers, the meter reading pH_R obtained in a partially aqueous medium differs by an amount δ from the corrected reading pH^* : $pH^* = pH_R - \delta$. The values of δ for the various proportions of each of the organic solvents under investigation were determined by *Douhéret* [9, 10].

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