

## Determination of Dissociation Constants and Thermodynamic Parameters of 8-Aminoquinoline by Potentiometry in Aqueous and Mixed Organic-Water Solvent Systems

HAFIZ A. BARI INDHAR AND A. W. K. KHANZADA\*

*National Centre of Excellence in Analytical Chemistry University of Sindh,  
Allama I.I. Kazi Campus, Jamshoro, Sindh, Pakistan*

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**Summary:** The dissociation constant ( $pK_a$ ) and thermodynamic parameters ( $\Delta G$ ) of 8-aminoquinoline are determined in aqueous and in mixed organic-water (dioxane, EtOH and MeOH) solvent systems. It is observed that ionization constant of 8-aminoquinoline in aqueous system increases with the increase of temperature. The curve is a parabolic one. It is to be noted that  $pK_a$  values of this compound are lower than those of quinoline and some of its amino derivatives. For mixed organic-water solvent systems  $pK_a^M$  and  $pK_a^T$  values versus percent composition decrease slowly with increase in percent of EtOH, MeOH and dioxane. The curve of the  $pK_a$  versus percent composition is a distorted parabola.

The data have been obtained potentiometrically by titrating aqueous 8-aminoquinoline solution with hydrochloric acid. The values of dissociation constant were obtained from these data by a computer program written in GW-BASIC. From  $pK_a$  values Gibb's free energies ( $\Delta G$ ) have also been calculated.

### Introduction

The dissociation constant is an important parameter in determining the behavior of compounds in various applications. It is used to measure the strength of acids and bases. The dissociation constants ( $pK_a$ ) of weak acids and bases are widely used in pharmaceutical industries, in spectroscopy, in biological sciences, in preparative chemistry and in structure elucidation of newly isolated species. The  $pK_a$ 's are useful criteria of identifying particularly the substances, which do not melt [1-3]. Their principal use is for the establishment of the structure of unknown substances e.g., for deciding which form predominates at equilibrium in the tautomeric or potentially tautomeric substances. Information about the ionization constant is useful in many ways e.g. different ionic species have different ultra-violet spectra and significant spectrophotometry can be done only at a chosen pH at which ionic species are present. The ionic species of a given substance may differ in their physical, chemical and biological properties as well [2]. Among the physico-chemical properties of molecules the ionization constants are of vital importance, both in analysis of drugs as well as in the interpretation of their mechanism of action. Evaluation of ionization or acidity constants can be employed in the design of titration procedures and

examining the possibility of separation of mixtures of compounds by extraction [4].

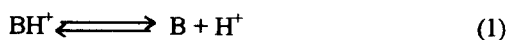
Quinoline derivatives are extensively used in oils, polymer, and pharmaceutical industries and as chelating agent for various ions in analytical chemistry. There are different methods [3,5-8] that are being used for the determination of dissociation constants of weak bases and acids. These methods have certain limitations, such as solubility, range of  $pK_a$  and time requirements etc. [5-9]. The quick method for this purpose is potentiometry [3-11] while spectrophotometry is very accurate but it is time consuming [5-9]. The purpose of this work is to extend the study of 8-aminoquinoline base strength at different temperatures and in different co-solvent systems such as dioxane-water, EtOH-water and MeOH-water. Acid-base titration in non-aqueous media is a relative new method in analytical chemistry but its wide spread use for determination of organic and inorganic substances is still increasing. The most important advantage of non-aqueous medium usually an organic solvent is that a large number of substances, which are insoluble in water, are readily soluble in non aqueous solvents. Another advantage of the use of non-aqueous

\*To whom all correspondence should be addressed.

medium is that large variety of solvents is available and they have differing acid base property [8]. Consequently, the use of mixed water-dioxane solvents was introduced by Calvin and Wilson [12]. The solvent effect on the dissociation of aliphatic acids was measured by potentiometric titration in acetonitrile, propylene, acetone, N-N dimethyl formamide and dimethyl sulphoxide by Bartnicka [13]. The method of comparison of the capacity of polar and non aqueous solvents to differentiate between the strength of cationic acid, based on the magnitude, of slope in correlation of non aqueous and aqueous  $pK_a$  values have been found inapplicable to acids obtained by protonation of substituted pyriele-N-oxide. The magnitude of a slope in this correlation has been suggested as a criterion for comparison of differentiation properties of non-aqueous solvents with respect to the strength of cationic acid [14].

#### Theory

Any monoacidic base  $BH^+$  dissociates as follows.



$$K_a^M = \frac{[B][H^+]}{[BH^+]} \quad (2)$$

$$pK_a^M = pH + \log \frac{[BH^+]}{[B]} \quad (3)$$

where the terms in square brackets [ ] represent molar concentrations and  $pK_a^M$  is the concentration ionization constant. The thermodynamic ionization constant  $pK_a^T$  for a base is:

$$K_a^T = \frac{a_{H^+} \cdot a_B}{a_{BH^+}} \quad (8)$$

$$a_B = [B]Y_B \quad (5)$$

$$a_{BH^+} = [BH^+]Y_{BH^+} \quad (6)$$

$$-\log Y_i = \frac{Az^2\sqrt{I}}{I + B_{ai}\sqrt{I}} \quad (7)$$

in which the term  $Y_B$  and  $Y_{BH^+}$  are the respective activity coefficients calculated by means of eq. (7) and the terms  $a_{BH^+}, a_B$  are activities of respective ions. A and B are constants, z is the valency of ion and I is the ionic strength [15] given by:

$$I = 0.5 \sum C_i z^2 \quad (8)$$

where  $C_i$  is the molar concentration of ion i and  $\sum$  is summation. These approximate activity coefficients are then used to calculate the hydrogen ion or hydroxyl ion concentration (i.e.  $[H^+] = a_{H^+}/Y_{H^+}$  or  $[OH^-] = a_{OH^-}/Y_{OH^-}$ ) by eq. (7) and also ratios of activities of the non-protonated to protonated species. For bases the ratio is [3]:

$$\frac{a_B}{a_{BH^+}} = \frac{(C - C_A - [OH^-] + [H^+])}{(C_A + [OH^-] - [H^+])Y_{BH^+}} \quad (9)$$

where C = Concentration of the substance i.e., 8-Aminoquinoline

$C_A$  is the concentration of acid i.e., HCl

The values for thermodynamic functions are obtained from the following equations:

$$\Delta G = -RT \ln K_a^T \quad (10)$$

$$pK_a^T = \frac{1}{\ln 10} \left( \frac{\Delta G}{RT} \right) \quad (11)$$

#### Results and Discussions

The dissociation constants of 8-aminoquinoline are determined in water at 20, 25, 30, 35, 40, 45 and 50°C and in percent composition from 10, 15, 20, 25, 30, 35, 40, 45 and 50 percent organic-water solvent mixtures at 25°C. The dissociation constant of this compound was obtained by refining the experimental data with the aid of computer program PKAS [15] written in GW-BASIC language. Table 1 gives the titration data used in computer program PKAS to get the results of calculations for  $pK_a^M$  and their parameters at various temperatures and percent composition of monoacidic base. The dissociation constants of aminoquinolines furnish useful information for the interpretation of the properties of

Table-1: Titration data used in computer program to calculate  $pK_a^M$  and  $pK_a^T$  of Monoacidic base

Substance = 8-Aminoquinolin in ethanol  
 Molecular Weight = 144.48  
 0.1442 Gram Dissolved in 100 ml of Water  
 Volume of Base Taken = 20 ml  
 Concentration of Acid =  $C_a = 0.01M$   
 Concentration of Substance (Base) =  $C_s = 0.077 M$   
 Temperature =  $25^\circ C$

Percentage of Dioxane = 10%

S.No.	Volume of HCl added	pH	BH <sup>+</sup>	B	Log(BH <sup>+</sup> /B)	% ION	$pK_a^M$	$pK_a^T$	Delta ( $\Delta$ )
1	0.00	7.65	-	-	-	-	-	-	-
2	0.25	4.89	0.001	0.09	-0.978	90.792	3.912	3.896	-0.016
3	0.50	4.53	0.002	0.008	-0.630	81.782	3.900	3.787	-0.022
4	0.75	4.30	0.003	0.007	-0.401	72.826	3.899	3.872	-0.027
5	1.00	4.12	0.004	0.006	-0.217	63.870	3.903	3.873	-0.031
6	1.25	3.96	0.004	0.005	-0.051	54.901	3.909	3.875	-0.034
7	1.50	3.80	0.005	0.004	0.107	45.961	3.907	3.870	-0.037
8	1.75	3.64	0.006	0.003	0.269	37.108	3.909	3.869	-0.040
9	2.00	3.46	0.007	0.002	0.439	28.625	3.899	3.957	-0.042
10	2.25	3.28	0.007	0.002	0.628	20.696	3.908	3.863	-0.045
11	2.50	3.08	0.008	0.001	0.828	14.204	3.908	3.861	-0.047
12	2.75	2.89	0.008	0.001	1.026	9.529	3.916	3.867	-0.049
13	3.00	2.73	0.008	0.000	1.216	6.397	3.946	3.895	-0.051
14	3.25	2.59	0.008	0.000	1.320	5.129	3.910	3.857	-0.053
15	3.50	2.50	-	-	-	-	-	-	-

Average of  $pK_a^M = 3.867 \pm 0.008$  at 95% Confidence Level

Average of  $pK_a^T = 3.829 \pm 0.003$  at 95% Confidence Level

Gibb's Free Energy of  $pK_a^M = 5.275 \pm 0.010$  kcal/mol at 95% Confidence Level

Gibb's Free Energy of  $pK_a^T = 5.233 \pm 0.018$  kcal/mol at 95% Confidence Level

these substances [16]. The ionization constant varies with the temperature. The graph between ionization constant and temperature is usually a parabola with a flat maximum. Increase in temperature causes decrease in  $pK_a$  values. At  $20^\circ C$   $pK_a^M$  is  $4.021 \pm 0.012$  and at  $50^\circ C$  it is  $3.694 \pm 0.006$ . The  $pK_a$  values calculated are given in Table 2 together with reported values. The  $pK_a$  value of 8-aminoquinoline is considerable lower than that of quinoline [16,19]. It may be due to hydrogen bonding or due to an ortho effect (depression of  $pK_a$ ) which hinders the approach of hydronium ion [16]. Amino group near to quinoline nitrogen increases the dissociation value. The total decrease is 0.186 unit for  $pK_a^M$ .

Considerable interest exists today in determination of proton dissociation or association properties of water insoluble compounds. This information is useful in itself as a measure of acid base characteristics of such compounds [17]. The use of dioxane, ethanol and methanol solvents rises the question of interpretation of the potential obtained in partially non-aqueous solvent from a cell containing

Table-2:  $pK_a^M$  and  $pK_a^T$  Thermodynamic Constant Values of 8-Aminoquinoline at various temperatures in aqueous solution

S.No.	T in $^\circ C$	$pK_a^M$	$pK_a^T$	$\Delta G$ from $pK_a^M$	$\Delta G$ from $pK_a^T$
1	20	$4.021 \pm 0.012$	$3.983 \pm 0.017$	$5.393 \pm 0.016$	$5.342 \pm 0.023$
2	25	$3.954 \pm 0.014$	$3.916 \pm 0.018$	$5.394 \pm 0.018$	$5.342 \pm 0.024$
3	30	$3.909 \pm 0.006$	$3.871 \pm 0.011$	$5.422 \pm 0.008$	$5.368 \pm 0.015$
4	35	$3.850 \pm 0.019$	$3.811 \pm 0.023$	$5.428 \pm 0.027$	$5.373 \pm 0.030$
5	40	$3.795 \pm 0.009$	$3.756 \pm 0.014$	$5.437 \pm 0.013$	$5.381 \pm 0.010$
6	45	$3.742 \pm 0.010$	$3.702 \pm 0.014$	$5.447 \pm 0.015$	$5.389 \pm 0.022$
7	50	$3.694 \pm 0.006$	$3.654 \pm 0.012$	$5.461 \pm 0.008$	$5.402 \pm 0.017$

Note: The report  $pK_a$  value of 8-Aminoquinoline at  $20^\circ C$  is 3.98 [19].

a glass electrode and possessing liquid junction error. Determinations of the  $pK_a$  values of an organic acids and bases that it self sparingly soluble in water and may be expedient to measure its magnitude in a series of dioxane-water mixture and to extrapolate to the zero mole fraction of dioxane [18]. Many chemists are interested in calculating the  $pK_a^M$  and  $pK_a^T$  values of organic acids and bases in non aqueous media. The effect of solvent on acid base equilibria of the compound is studied in different organic water mixtures at  $25^\circ C$ . The solvent systems

chosen are: dioxane-water, EtOH-water and MeOH-water. The percentage composition of organic components varies from 10% to 50% in the step of 5% each. The ionization constant  $pK_a^M$  and  $pK_a^T$  of 8-aminoquinoline decreases with the increase of percent composition in all the three solvent systems.

The data of each solvent mixture i.e., dioxane-water, EtOH-water and MeOH-water are shown in Table 2 to 4. These tables show that  $pK_a$  value in 50% dioxane-water is  $3.228 \pm 0.006$ , in 50% EtOH, it is  $3.489 \pm 0.005$  and in 50% MeOH-water system it is  $3.475 \pm 0.004$ . The graph of  $pK_a$  versus percent composition is a parabola.  $\Delta G$  values of 8-aminoquinoline decrease with the increase of percent composition (as we go to high percentages).

We have calculated Gibb's free energies  $\Delta G$  from the value of  $pK_a^M$  and  $pK_a^T$  in aqueous and in 10 to 50 percent solvent systems. It is observed that there is a regular decrease in Gibb's free energy ( $\Delta G$ ) with increase of temperature and percent composition of mixed organic-water solvents. Same pattern is observed for  $\Delta G$  values of  $pK_a^T$ . The overall change in  $pK_a^M$  and  $pK_a^T$ ,  $\Delta G$  from  $pK_a^M$  and  $pK_a^T$   $\Delta G$  from  $pK_a^T$  of the compound is given in Tables 2, 3, 4 and 5.

Table-3: Effect of percent composition on and thermodynamic constants of 8-aminoquinoline in dioxane-water solvent system at 25°C

S.No.	%age Comp.	$pK_a^M$	$pK_a^T$	$\Delta G$ from $pK_a^M$	$\Delta G$ from $pK_a^T$
1	10	$3.867 \pm 0.008$	$3.829 \pm 0.003$	$5.275 \pm 0.010$	$5.223 \pm 0.018$
2	15	$3.775 \pm 0.004$	$3.737 \pm 0.009$	$5.150 \pm 0.005$	$5.098 \pm 0.012$
3	20	$3.703 \pm 0.005$	$3.665 \pm 0.006$	$5.052 \pm 0.007$	$5.000 \pm 0.009$
4	25	$3.633 \pm 0.005$	$3.595 \pm 0.010$	$4.956 \pm 0.007$	$4.904 \pm 0.014$
5	30	$3.555 \pm 0.008$	$3.517 \pm 0.010$	$4.849 \pm 0.011$	$4.798 \pm 0.014$
6	35	$3.489 \pm 0.003$	$3.451 \pm 0.009$	$4.759 \pm 0.004$	$4.708 \pm 0.013$
7	40	$3.416 \pm 0.005$	$3.378 \pm 0.010$	$4.660 \pm 0.007$	$4.609 \pm 0.009$
8	45	$3.311 \pm 0.008$	$3.273 \pm 0.014$	$4.517 \pm 0.011$	$4.465 \pm 0.019$
9	50	$3.228 \pm 0.006$	$3.190 \pm 0.012$	$4.403 \pm 0.008$	$4.352 \pm 0.016$

Table-4: Effect of percent composition on and thermodynamic constants of 8-aminoquinoline in EtOH-water solvent system at 25°C

S.No.	%age Comp.	$pK_a^M$	$pK_a^T$	$\Delta G$ from $pK_a^M$	$\Delta G$ from $pK_a^T$
1	10	$3.910 \pm 0.008$	$3.872 \pm 0.008$	$5.333 \pm 0.010$	$5.282 \pm 0.011$
2	15	$3.836 \pm 0.015$	$3.799 \pm 0.019$	$5.233 \pm 0.021$	$5.182 \pm 0.026$
3	20	$3.775 \pm 0.005$	$3.738 \pm 0.011$	$5.150 \pm 0.007$	$5.098 \pm 0.014$
4	25	$3.724 \pm 0.005$	$3.686 \pm 0.011$	$5.080 \pm 0.006$	$5.028 \pm 0.015$
5	30	$3.655 \pm 0.005$	$3.617 \pm 0.010$	$4.985 \pm 0.007$	$4.934 \pm 0.014$
6	35	$3.611 \pm 0.006$	$3.573 \pm 0.011$	$4.926 \pm 0.008$	$4.874 \pm 0.016$
7	40	$3.573 \pm 0.005$	$3.535 \pm 0.010$	$4.874 \pm 0.006$	$4.822 \pm 0.013$
8	45	$3.524 \pm 0.003$	$3.487 \pm 0.006$	$4.808 \pm 0.004$	$4.756 \pm 0.008$
9	50	$3.489 \pm 0.005$	$3.451 \pm 0.010$	$4.760 \pm 0.007$	$4.708 \pm 0.014$

Table-5: Effect of percent composition on and thermodynamic constants of 8-aminoquinoline in MeOH-water solvent system at 25°C

S.No.	%age Comp.	$pK_a^M$	$pK_a^T$	$\Delta G$ from $pK_a^M$	$\Delta G$ from $pK_a^T$
1	10	$3.890 \pm 0.005$	$3.852 \pm 0.007$	$5.306 \pm 0.006$	$5.254 \pm 0.010$
2	15	$3.831 \pm 0.005$	$3.793 \pm 0.010$	$5.226 \pm 0.007$	$5.175 \pm 0.013$
3	20	$3.775 \pm 0.004$	$3.737 \pm 0.009$	$5.150 \pm 0.005$	$5.098 \pm 0.012$
4	25	$3.680 \pm 0.008$	$3.642 \pm 0.013$	$5.019 \pm 0.011$	$4.968 \pm 0.016$
5	30	$3.642 \pm 0.006$	$3.605 \pm 0.011$	$4.969 \pm 0.009$	$4.917 \pm 0.018$
6	35	$3.588 \pm 0.008$	$3.550 \pm 0.013$	$4.894 \pm 0.011$	$4.842 \pm 0.018$
7	40	$3.555 \pm 0.008$	$3.517 \pm 0.010$	$4.849 \pm 0.011$	$4.798 \pm 0.014$
8	45	$3.513 \pm 0.005$	$3.475 \pm 0.008$	$4.792 \pm 0.007$	$4.740 \pm 0.010$
9	50	$3.475 \pm 0.004$	$3.437 \pm 0.006$	$4.740 \pm 0.006$	$4.689 \pm 0.008$

The degree of dissociation of the compound varies with percent composition of solvent-water system and temperature. Solvents are distinguished from their dielectric constants and hydrogen bonding capabilities. Water, EtOH, and MeOH have greater hydrogen bonding capacity and dielectric constant of 78.5, 32.6 and 24.3 respectively. In pure water  $pK_a$  values are highest and MeOH-water has lowest values. Dioxane has lowest dielectric constant of 2.21 and no ability to form H-bond. The  $pK_a$  values in this system are therefore the lowest.

### Experimental

In solution preparation chemicals used were of analytical grade and doubly degassed distilled water was used throughout. An approximate 0.1M solution of HCl was prepared which is diluted by successive dilution method up to 0.01M (Table 1) standardized with primary standard solution of sodium carbonate.

The solution of 8-aminoquinoline was prepared by weighing the compound with accurate digital balance (SARTORIUS BA110S). The percentage composition of organic components varies from 10% to 50% in the step of 5% each. The potentiometric titrations were performed in a thermostated double walled glass cell containing 20 ml of sample solution with HCl. The pH was determined with a Philips PW 9420 digital pH meter. Circulating water through the jacketed measuring cell controlled the temperature. JULABO HC thermostated bath accurate to  $\pm 0.1^\circ\text{C}$  was used for controlling the temperature. Prior to experiment, the glass electrode was calibrated with buffers of pH 4.05 and 6.98 at 25°C respectively [2]. The sample solution was kept mixed by stirring with magnetic stirrer and inert by bubbling nitrogen gas. For

dispensing titrant a Mettler burette DV-10 accurate to 0.01ml was used. The potentiometric titration has been improved by elimination of carbon dioxide using dried and purified nitrogen gas [2].  $pK_a$  values were obtained by analyzing the experimental data with a computer program written in GW-BASIC to work on IBM PC for calculations of ionization constants of monoacidic base (8-aminoquinoline) [15].

### Conclusion

Ionization constant of 8-aminoquinoline in aqueous solutions agrees to the values reported in literature. Real problem in non-aqueous solvents lies in the fact that a very few data are available in the literature at 18 or 20°C. The present work gives  $pK_a$  values at high temperatures (up to 50°C) in aqueous and in dioxane, EtOH and MeOH-water mixed solvent systems at 25 °C. The  $pK_a$  values of solvents other than water are very different from those which are in aqueous solutions e.g.  $pK_a$  of 8-aminoquinoline in water at 20°C is  $4.021 \pm 0.012$ , in 50% dioxane is  $3.228 \pm 0.006$ , in 50% EtOH is  $3.489 \pm 0.005$  and in 50% MeOH is  $3.475 \pm 0.004$ . Due to ortho effect or 8th position of 8-aminoquinoline and hydrogen bonding the  $pK_a$  is considerably lower than quinoline and amino derivatives of quinoline. It is observed that concentration ionization constant  $pK_a^M$  and thermodynamic ionization constant  $pK_a^T$  values in aqueous solutions decrease with rise of temperature. The curve of  $pK_a$  versus temperature is a parabolic one. In case of dioxane-water, EtOH-water and MeOH-water solvent systems  $pK_a^M$  and  $pK_a^T$  versus percent composition decrease slowly by increasing the addition of the solvents. The curve of the mixed and thermodynamic constants ( $pK_a^M$  and  $pK_a^T$ ) versus percent composition is a distorted parabola. These findings leads to conclude that the solvents which establish hydrogen bonding (Water, EtOH and MeOH) decrease in  $pK_a$  are minimum but dioxane which do not show hydrogen bonding effect,  $pK_a$  value decrease is maximum.

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