Potentiometric Determinations of Dissociation Constants and Thermodynamic Parameters of 4-Aminoquinoline in Aqueous, Aqueous-Dioxane, Aqueous EtOH and Aqueous-MeOH Solutions at Various Temperatures

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The dissociation constant (pK_a) and thermodynamic parameters Gibb's free energies of 4-aminoquinoline are measured by potentiometric pH titrations in aqueous solution at 25 to 50°C and in three mixed aqua-organic media (dioxane, EtOH and MeOH) at 25°C ± 0.1°C. It is observed that pK_a^M and pK_a^T (concentration ionization and thermodynamic ionization constants) values of 4-aminoquinoline decrease with the increase in temperature and concentration of organic-water solvent systems. The curve is a parabolic one. It is noted that the pK_a^M and pK_a^T values of this compound are higher than that quinoline and some of its amino derivatives. These results are discussed in terms of solvent characteristics, solvent basicity and stabilization of conjugate acid for base by hydrogen bonding interaction in hydro-organic solvent media. The values of dissociation constant are calculated by a computer program written in GW-BASIC. From pK_a values Gibb's free energies are computed and discussed interms of solute solvent interactions.

Key words: Dissociation constants, Thermodynamic ionization constant, 4-Aminoquinoline

Introduction

The ionization constant K_a are useful criteria of identifying the substances particularly which do not melt. Their principal use is an important parameter in determining the behaviour 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 week bases are widely used in pharmaceutical industries, in spectroscopy, in biological sciences, in preparative chemistry and in structure elucidation of newly isolated species (Barlin and Perrin 1972; Albert 1979; Albert and Sergeant 1984). The term ionization constant is referred to dissociation constant which is a vague expression, not necessarily connected with ionization (Burger 1982). Information about the ionization constant is useful in many ways e.g. different ionic species have different ultra-violet spectra and significant spectrophotometery 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 bioligical properties (Barlin 1972).

The purpose of studies dealing with influence of solvents on acid base equilibria is to obtain a solvent independent acidity or basicity scale and to extend the study of 4-aminoquinoline base strength at different temperatures and in different cosolvent systems. The most important advantage of non-aqueous medium usually an organic solvent is that a large number

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of substances which are insoluble in water are readily soluble in non-aqueous solvents. Another advantage of the use of non-aqueous medium is that a large variety of solvent is available and they have differing acid base properties (Budevsky *et al* 1988).

The aim of the present study is three folds, first to find out the pK_a values of 4-aminoquinoline at high temperature up to 50°C in aqueous solutions and observe the effect of temperature of pK_a values. Secondly to calculate the pK_a^M and PK_a^T values in non aqueous media and analyze the effect of hydro-organic water solvent mixtures on acid base equilibria of the compound at 25°C. The organic solvents chosen are: dioxane, EtOH and MeOH. The percentage composition of organic components with water varies from 10 to 50 % in the step of 5% each. Thirdly to determine the thermodynamic parameters, such as Gibb's free energy ΔG. There has been no detailed work on dissociation constants of 4-aminoquinoline except some work on 5 and 6-aminoquinoline at 18 or 20°C in water (Hearn *et al* 1951; Bari and Khanzada 2000 b).

Quinoline and its derivatives are extensively used in oils, polymer, pharmaceutical industries and as chelating agent for various ions in analytical chemistry. Several important drugs incorporate the quinoline nucleus, notably antimalarials, aminoquinolines, chloroquine (Burger 1982). Many quinoline derivatives of known antibacterial agents have been prepared and tested against micro-organisms (Desai *et al* 1996). The

tautomerism due to prototropy in (4-aminoquinoline $\leftrightarrows$ 4-iminoquinoline) antimalarials are responsible for their antimalarial activity.

There are different methods (Albert and Sergeant 1984; Gampp *et al* 1985; Budvesky *et al* 1988; Muhvri and Hazara 1991) which 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 (Ramette 1967; Gampp *et al* 1985; Muhvri and Hazara 1991). The quick method for this purpose is potentiometery (Ramette 1967; Albert and Sergeant 1984; Asuero and Jamenz-Trillo 1984 and 1986; Gampp *et al* 1985; Budvesky *et al* 1988; Muhvri and Hazara 1991) while spectrophotomerty is very accurate but it is time consuming (Ramette 1967; Gampp *et al* 1985; Muhvri and Hazara 1991). The potentiometric titration has been improved by elimination of carbon dioxide using dried and purified nitrogen gas (Barlin and Perrin 1972; Albert and Seargeant 1984). The temperature is controlled to an accuracy of $\pm$ 0.1 °C. pK_a values were obtained by analyzing the experimental data with a computer programme written in GW-BASIC to work on IBM PC.

Theory. The Method of calculation of ionization (K_a^M) is as under. Any monoacidic base BH^+ dissociates as follows.

$$BH^+ \xleftrightarrow{\hspace{1cm}} B + H^+ \quad \text{...............................(1)}$$

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

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

Where the terms in square brackets [ ] represent molar concentration, pK_a^M is concentration ionization constant pK_a^T for a base in term of active concentration is:

$$pK_a^T = \frac{\{H^+\} \{B\}}{\{BH^+\}} \quad \text{...............................(4)}$$

In potentiometer, activity rather than concentration term is used. The conversion of concentration of ionized species into activity is given by equation:

$$\{B\} = [B] Y_B \quad \text{...............................(5)}$$

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

$$-\log Y_i = \frac{AZ^2 \sqrt{I}}{I + Ba_i \sqrt{I}} \quad \text{...............................(7)}$$

In which the term Y_B and Y_{BH}^+ are the respective activity coeffficients calculated by means of eq. (7) and the term in { } are activities of respective ions. A and B are the constants, z is valency of ion and I is ionic strength given by:

$$I = 0.5 \sum C_i z_i^2 \quad \text{...............................(8)}$$

Where C_i is molar concentration of ion i, z is its valency and $\sum$ is summation. Activity coefficients are calculated by eq. (7). These approximate activity coefficient are then used to calculate the hydrogen ion or hydroxyl ion concentration i.e. $[H] = H^+/Y_i\{H^+\}Y_i$ or $[OH^-] = \{OH^-\}/Y_i$) by eq. (7) and also ratios of activities of the non-protonated to protonated species for bases is.

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

There is an empirically derived approximation, suitable for results obtained with a set calibrated in 0.02 pH unit, e.g. for bases:

$$pK_a^T = pH + \log \frac{[BH^+] Y_i - \{H^+\}}{[B] + \{H^+\}} \quad \text{...............................(10)}$$

Where Y_i can be obtained from eq. (7).

Experimental

All the chemicals used in the preparation of solution were of analytical grade and doubly distilled water was used throughout. An approximate 0.1 M solution of HCl was prepared which was further diluted up to 0.01M standardized with primary standard solution of sodium carbonate. The solution of 4-aminoquinoline compound was prepared by weighing it with accurate digital balance (SARTORIUS BAL IO S). The potentiometric titrations were performed in a thermostated double walled glass cell containing 20 ml of sample solution of HCl. The pH was determined with Philips PW 9420 digital pH meter. The temperature was controlled by circulating water through the jacketed measuring cell. JULABO HC thermostated bath accurate to $\pm$ 0.1°C was used to control the temperature prior to experiment. The glass electrode was calibrated with buffers pH of 4.05 at 25°C and pH 6.98 at 25 °C (Barlin and Perrin 1972). The sample solution was kept mixed by stirring with magnetic stirrer and inert by nitrogen gas. For dispensing titrant Mettler burette DV-10 accurate to 0.01 ml was used. The data obtained at different temperatures were analyzed by a computer program written in GW-BASIC for calculation of dissociation constants of monoacidic base (4-aminoquinoline).

Results and Discussion

a) Temperature effect on ionization constants. The 4-aminoquinoline has greatest basicity (attraction for protons) of various mono amino derivatives of quinoline. The aromatic nuclei of 4-aminoquinolines also accept a single proton in dilute aqueous solutions. These compounds possess various degrees of antimalerial activity. The chemical properties of the 2-and 4-aminoquinolines have frequently been found to contrast with those of other isomers of aminoquinolines.

The ionization constants varies with the temperature. The correlation curve is usually a parabola with a flat maximum. A change in temperature causes a shift in equilibrium point, which is of both practical and theoretical interest. Nitrogen bases (Albert and Sergeant 1984) are highly temperature sensitive and become weaker as temperature is increased.

Mostly reported pK_a values are determined at 25°C or 18°C to see the effect of temperature variation on pK_a values. We extended the temperature range from 20 °C to 50°C with the interval of 5°C.

The protonation constant of 4-aminoquinolines were determined in water at 20-50°C at the interval of 5°C and are presented in Table 1 together with reported values (at 20 or 25°C). These values agree reasonably with reported values ((Burger 1982). Generally increase in temperature causes decrease in dissociation constant values in 4-aminoquinolines. As the temperature increases from 20 to 50 °C the pK_a^M value drops 8.691 ± 0.003 to 7.760 ± 0.006 in 4-aminoquinoline and the total decrease in the value is 0.931 unit. The dissociation constants of amino derivatives of quinoline furnish the useful information for the interpretation of the properties of the substances. From summarized acidity constants table, it is observed that pK_a^M values of amino derivatives of quinoline fall into three categories.

(1) The pK_a^M values of 3-aminoquinoline (Bari and Khanzada 1999 a) are not more than one unit high than that of quinoline which therefore be considered as normal amino-quinoline.

(2) The pK_a^M value of 4-aminoquinoline are considerable larger than that of quinoline.

(3) The pK_a^M values of 8-aminoquinoline (Bari and Khanzada 2000 b) are considerably lower than that of quinoline, it may be due to hydrogen bonding or to an ortho effect(depression of pK_a^M) which hinders the approach of hydronium ion. The 4-aminoquinoline shows greater elevation of pK_a^M 8.691 ± 0.005. The spectra of 2-amino and 4-aminoquinolines differ quite readily from those of other aminoquinolines. The absorption in acidic solution is greater than the basic (Elderfield 1952).

A closer inspection of Fig 1 shows the effect of pK_a^M and pK_a^T versus temperature, the curve is a parabolic one.

The changes in the thermodynamic parameters (∆G) Gibb's free energies associated with acid base reaction can be found from the variation of its equilibrium constant with temperature. These thermodynamic properties offer interesting insights into acid base behaviour particularly with regards to solvation effects (King 1965). Fig 2 shows the effect of temperature on Gibb's free energy (∆G) values of 4-aminoquinoline. The graph of ∆ G of pK_a^M and ∆G of pK_a^T versus temperature is distorted parabola. There is regular increase in Gibbs' free energy values from 20 to 60°C as shown in Fig 2.

Effect of solvent system of pK_a^M, pK_a^M and Gibb's free energy values. Many chemist require to know the dissociation constants of organic acids and bases in non-aqueous media. Therefore much attention has been paid to a quantitative explanation of the medium on pK_a values (Saeeduddin *et al* 1996). In recent years many non aqueous solvents have been increasingly used in analytical chemistry, in pharmaceutical industries, poorly soluble substances are much titrated in partly aqueous solvents. They are organic solvents and may be used as mixture with each other or with water, for this reason it is interested to compare their behaviour with that of water. One of the most important properties of solvent is its dielectric constant, which defines to a considerable degree of the solvating ability of the medium (Budevsky *et al* 1988). The concentration ionization constant pK_a^M and thermodynamic ionization constant pK_a^T values of 4-amino-quinolines decrease with an increase in composition of dioxane, EtOH and MeOH solvent mixtures. The correlation curve is usually parabola with a flat maximum. It is observed that the strength rises when amino group is inserted in 4th position and distinctly weakened if this group is in the 8th position (ortho effect) (Bari and Khanzada 2000b) The data of each solvent dioxane-water, EtOH-water and MeOH-water are shown in Tables 2, 3 and 4. The trend of decrease of pK_a^M and pK_a^T from 10% to 50% composition is similar in all the three solvents but the magnitude of pK_a^M and pK_a^T is different. As pK_a^M value in 10% dioxane is 8.640 ± 0.005, in 10% EtOH 8.620 ± 0.007 and 10% MeOH is 8.63 ± 0.002 again the values for 4-aminoquinoline in 50% dioxane 7.550 ± 0.008, in 50% EtOH 7.470 ± 0.010 and 50% MeOH is 7.531 ± 0.012.

The graph drawn in Fig 3 shows effect of organic water solvent system on pK_a^M and pK_a^T values in dioxane-water. The behaviour in EtOH-water and MeOH-water is similar.

The thermodynamic parameter viz. Gibb's free (∆G) associated with proton dissociation constants were calculated utilizing the standard equations. The values of Gibb's free energies are shown in Table 2-4.
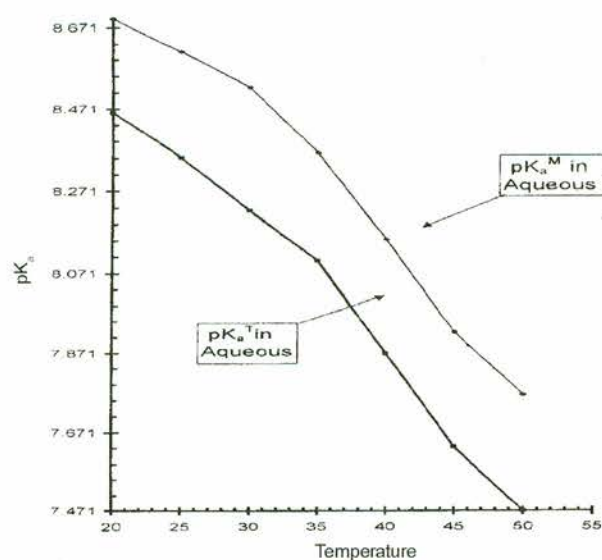
Fig 1. Effect of pK_a^M and pK_a^T Vs Temp in a aqueous solution of 4-aminoquinoline.
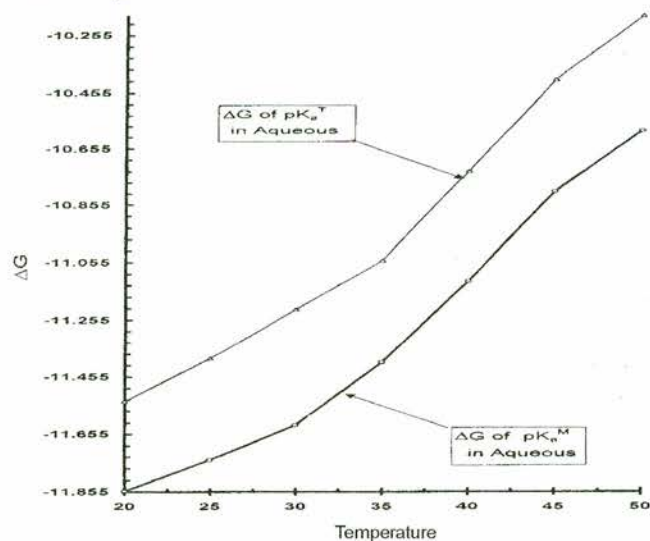

Fig 2. Effect of ΔG of PK_a^M and pK_a^T Vs Temp in a aqueous solution of 4-aminoquinoline
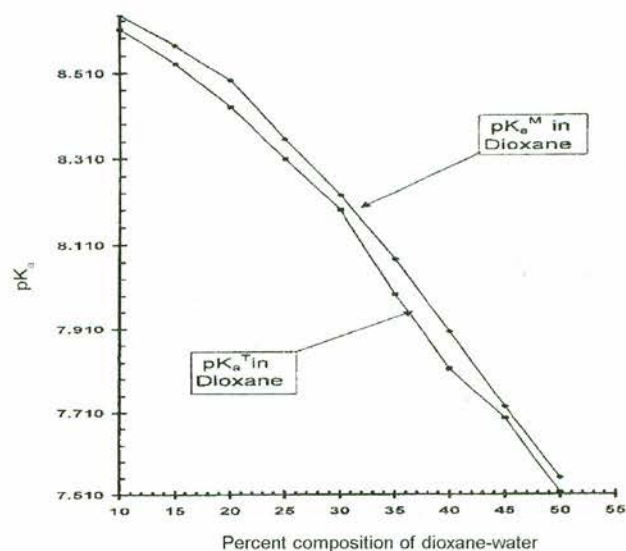

Fig 3. Effect of organic-water solvent mixture on PK_a^M and PK_a^T Vs % composition of 4-aminoquinoline in dioxane-water solvent system
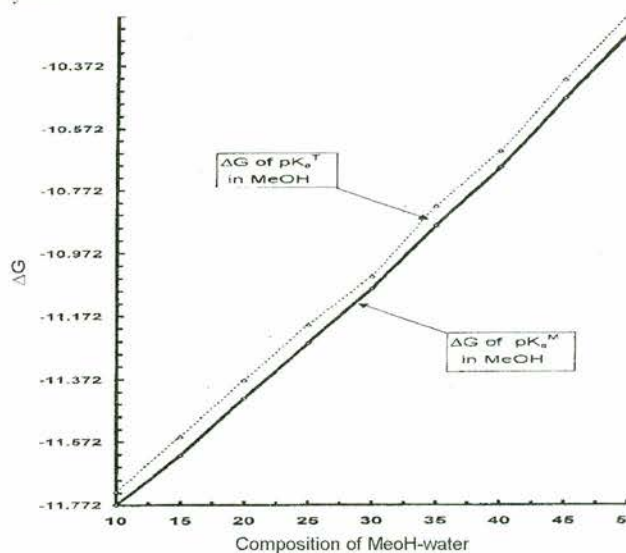

Fig 4. Effect ΔG of PK_a^M and pK_a^T Vs % composition of 4-aminoquinoline in-MeOH-water solvent system

Table 1

Effect of temperature of pK_a^M, pK_a^M and thermodynamic constants of 4-aminoquinoline in aqueous solution

S.no	Temp. °C	pK_a^M	pK_a^T	ΔG of pK_a^T	ΔG of PK_a^M
1	20	8.691 ±0.005	8.462 ±0.001	-11.854 ±0.002	-11.541 ± 0.005
2	25	8.612 ± 0.009	9.352 ± 0.004	-11.746 ± 0.005	-11.391 ± 0.006
3	30	8.523 ± 0.001	8.225 ± 0.005	-11.624 ± 0.002	-11.218 ± 0.005
4	35	8.362 ± 0.006	8.102 ± 0.003	-11.405 ± 0.006	-11.050 ± 0.004
5	40	8.154 ± 0.002	7.871 ± 0.009	-11.121 ± 0.007	-10.735 ± 0.003
6	45	7.924 ± 0.010	7.635 ± 0.006	-10.807 ± 0.006	-10.411 ± 0.002
7	50	7.765 ± 0.003	7.471 ± 0.008	-10.591 ± 0.018	-10.189 ± 0.007

Table 2

Effect of percent composition on pK_a^M, pK_a^M and thermodynamic constants of 4-aminoquinoline in dioxane-water solvent system

S. no	% tage comp	pK_a^M	pK_a^T	ΔG of pK_a^T	ΔG of pK_a^T
1	10	8.642 ±0.004	8.610±0.003	-11.790 ±0.003	-11.747 ±0.008
2	15	8.571± 0.008	8.531± 0.004	-11.694±0.005	-11.639± 0.006
3	20	8.492± 0.003	8.429± 0.005	-11.586±0.010	-11.499± 0.005
4	25	8.354± 0.002	8.308± 0.001	-11.397±0.004	-11.335±0.007
5	30	8.223± 0.007	8.189± 0.005	-11.219±0.010	-11.172±0.009
6	35	8.075± 0.007	7.992± 0.006	-10.017±0.009	-10.904± 0.006
7	40	7.901± 0.007	7.813± 0.009	-10.779±0.003	-10.649± 0.010
8	45	7.723± 0.005	7.695± 0.006	-10.536±0.008	-10.498± 0.008
9	50	7.551± 0.008	7.515± 0.003	-10.302±0.010	-10.253± 0.002

Table 3

Effect of percent composition on pK_a^M, pK_a^T and thermodynamic constants of 4-aminoquinoline in EtOH-water solvent system

S. no	%tage comp	pK_a^M	pK_a^T	ΔG of pK_a^M	ΔG of pK_a^M
1	10	8.642 ±0.008	8.591±0.006	-11.765 ±0.004	-11.791 ± 0.008
2	15	8.525± 0.008	8.503± 0.006	-11.629±0.005	-11.599± 0.003
3	20	8.402± 0.008	8.396± 0.004	-11.462±0.004	-11.454± 0.005
4	25	8.271± 0.001	8.223± 0.003	-11.283±0.006	-11.218±0.015
5	30	8.132± 0.007	8.189± 0.005	-11.094±0.004	-11.050± 0.007
6	35	7.992± 0.007	7.100± 0.010	-10.903±0.005	-10.834± 0.006
7	40	7.825± 0.004	7.942± 0.006	-10.675±0.004	-10.544± 0.008
8	45	7.653± 0.004	7.792± 0.007	-10.440±0.015	-10.384± 0.002
9	50	7.476± 0.002	7.421± 0.002	-10.199±0.004	-10.123s± 0.005

Table 4

Effect of percent composition on pK_a^M, pK_a^T and thermodynamic constants of 4-aminoquinoline in MeOH-water solvent system

S. no	%tage comp	pK_a^M	pK_a^T	ΔG of pK_a^M	ΔG of pK_a^T
1	10	8.630±0.003	8.598± 0.003	-11.772 ±0.008	-11.728± 0.005
2	15	8.516± 0.009	8.471± 0.004	-11.616±0.003	-11.555± 0.021
3	20	8.382± 0.010	8.338± 0.005	-11.424±0.005	-11.374± 0.003
4	25	8.253± 0.002	8.210± 0.003	-11.258±0.003	-11.199±0.015
5	30	8.126± 0.005	8.089± 0.002	-11.085±0.010	-11.046± 0.006
6	35	7.981± 0.007	7.935± 0.003	-10.887±0.009	-10.824± 0.006
7	40	7.845± 0.004	7.805± 0.003	-10.701±0.004	-10.647± 0.007
8	45	7.682± 0.008	7.639± 0.005	-10.480±0.002	-10.420± 0.009
9	50	7.531± 0.009	7.485± 0.004	-10.273±0.001	-10.210s± 0.010

$$\Delta G = -RT \ln K_a^T \quad \text{.....................................(11)}$$

The effect of solvent mixture of (ΔG) Gibb's free energy values shows that as composition of organic solvents increases the ΔG of pK_a^M and ΔG of pK_a^T increase at 25°C. It is clear from the graphs drawn for ΔG of pK_a^M and ΔG of pK_a^T versus percent composition as shown in Fig 4 in MeOH-water, similar trend is observed for dioxane-water, EtOH-water system.

We observed that as the percentage composition increases from 10% to 50% at the increment of 5% then ΔG value increases linearly and distorted parabolic curves are obtained. The negative value of ΔG suggest that proton dissociation reactions are favourable and spontaneous. The percentage ionization of the sample is calculated by using the formula (Albert and Sergeant 1984) given the equations:

$$\% \text{ ionized} = \frac{100}{1 + 10^{(pKa-pH)}} \quad \text{for acids.................(12)}$$

$$\% \text{ ionized} = \frac{100}{1 + 10^{(pH-pKa)}} \quad \text{for bases ....(13)}$$

We can calculate maximum percentage ionization of sample at a particular pH. As the temperature or percentage of the solvent increases, pH changes and therefore percentage of the sample ionization alters.

Conclusion

In recent years many non aqueous solvents have been increasingly used in analytical chemistry. They are generally organic solvents and may be used as mixtures with each other or with water. For this reason, it is interesting to compare their behaviour with that of water. One of the most important property of the solvent is its dielectric constant, which defines to considerable degree of the solvating ability of the medium. The dissociation constant study on 4-aminoquinoline in pure water and three mixed organic water solvent systems have been carried out. For pure aqueous system the temperature varies from 20 to 50°C and the percent content of organic components varies from 10% to 50% in the step of 5% at 25°C. The amino group substitution of 4th position in quinoline affects as under.

(a) The pK_a^M values of 4-aminoquinoline are considerable larger than that of quinoline. Generally increase in temperature and percent composition causes the decrease in pK_a^M and pK_a^T values in all the three mixed solvents. A change in temperature from 20 to 50°C causes a shift in equilibrium point

which is of both practical and theoretical interest. Amino group near to quinoline nitrogen increase the dissociation. The ΔG of pK_a^M and ΔG of pK_a^T increase with increase in temperature and percent composition and the graphs are parabola.

References

Albert A 1979 *Selective Toxicity* 6th Ed., Chapman and Hall, London.

Albert A, Sergeant E P 1984 *The Determination of Ionization Constants, A Laboratory Manual.* 3rd Ed., Chapman and Hall, London.

Asuero A G, Jamenz-Trilo M J 1984 Spectrophotometric methods for evalution of acidity constants-I. *Talanta* **33** 195.

Asuero A G, Jamenz-Trillo M J 1986 Spectrophotometric methods for evalution of acidity constants-II. *Talanta* **33**

Barlin G B, Perrin D D 11972 *Technique of Organic Chemistry.* Vol. 4 Part I A. Weissberger Ed., Wiley-Interscience, New York

Burger K 1982 *Organic Reactions in Metal Analysis.* Pergaman Press London.

Budevsky O, Zikolova T, Tanjeheva 1988 NABTIT-A Computer Program for non-aqueous acid-base titration. *Talanta* **35** 899

Bari Hafiz A, Khanzada A W K 1999a Ionization and thermodynamic constants of 3-aminoquinoline by potentiometry in aqueous and mixed organic water solvent system, scientific sindh. *Ann Res J* Khairpur University Pakistan (in press).

Bari Hafiz A, Khanzada A W K 2000b Dissociation and thermodynamic constants of 8-aminoquinoline by potentiomerty in aqueous and mixed organic water solvent system. *J Chem Soc Pak* **22** (1).

Desai P K, Desai Pratibha, Petal D 1996 Quinoline derivatives as antitubercular/antibacterial agents. *Indian J Chem* **35B** 871.

Elderfield R C 1952 *Heterocyclic Compounds.* Vol 4 Wiley USA.

Gampp H, Maeder M, Charles J M, Zuberbyhler A D 1985 Calculation of equilibrium constants from multiwavelength spectroscopic data-II. *Talanta* **32** 25.

Hearn J M, Morton R A, Simpson JCE 1951 Spectrophotometric determinations of the second dissociation constants of 5-and 6-aminoquinoline. *J Chem Soc* 3329.

King E J 1965 *Acid Base Equilibria,* Pergaman Press Oxford 225.

Muhvri P K, Hazara D K 1991 Simultaneous determinations of

ionization constants of some amino acids from spectrophotometric and potentiometric data. *J Chem Soc Fraday Trans* **87** 3511

Ramette R W 1979 Equilibrium constants from spectrophoto-

metric data. *J Chem Educ* **44** 647.

Saeeduddin, Khanzada AWK, Mufti At 1996 Determination of ionization constants of overlapping dibasic acids in acetonitrile-water mixture. *J Chem Soc pak* **18**.