Evaluation of Dissociation and Thermodynamic Constants of Quinoline Using Potentiometric Method in Aqueous and Mixed Organic-Water Solvents

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The dissociation constant (pK_a) and thermodynamic parameters Gibb's free energies (ΔG) of quinoline compound are determined by potentiometric pH titrations in aqueous solutions at 25 to 50°C and in various mixtures of water and organic solvent systems at 25°C ± 0.1°C.

It is observed that the mixed ionization constant (pK_a^M) and thermodynamic ionization constant (pK_a^T) values of quinoline decrease with the increase of temperature and concentration of organic-water solvent systems. The curve is a parabolic one. 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 programme written in GW-BASIC. From pK_a values Gibb's free energies ΔG for the respective pK_a values are computed and discussed in terms of solute solvent interactions.

Key words: Dissociation constants, Potentiometry, Quinoline, Thermodynamic-parameters.

Introduction

The ionization constant is an important parameter for determining the behaviour of compounds in various applications. It is used to measure the strength of acids and bases (Barlin and Perrin 1972; Albert 1979; Albert and Sergeant 1984). The dissociation constants (pK_a) of weak acids and bases are widely used in pharmaceutical industries, spectroscopy, biological sciences, preparative chemistry and structure elucidation of newly isolated species. The pK_a's are useful criteria for identifying the substances which do not melt (Barlin and Perrin 1972; Albert 1979; Burger 1982; Albert and Sergeant 1984). The ionization constants are of vital importance, both in analysis of drugs as well as in the interpretation of their mechanism of action (Asuero *et al* 1986). Ionization constant also help to discover the structure of newly isolated substance (Albert and Sergeant 1984).

The aim of the present study is three fold, i) to find out the pK_a values of quinoline at high temperature up to 50°C in aqueous solutions and observe the effect of temperature on pK_a values. ii) to calculate the pK_a values in non-aqueous media and analyse the effect of hydro-organic water solvent mixtures on acid base equilibria of the compound at 25°C. The solvent systems chosen are: dioxane-water, EtOH-water and MeOH-water. The percentage composition of organic components varies from 10 to 50 percent in the step of 5% each. iii) to determine the thermodynamic parameters, such as enthalpy ΔH and Gibb's free energy (ΔG). There has been no significant

work on dissociation constants of quinoline and its derivatives except some work on amino derivatives of quinoline. Dissociation constants can therefore help us in better way to understand the structure of the compounds (Albert 1979). The most important advantage of non-aqueous media lies not only in the better solubility, but rather in the differentiating power of the acidic and basic strength of the solutes that many solvents show (Budevsky *et al* 1988).

Quinoline is colourless, hygroscopic basic liquid, which has a pK_a value of 4.94 at 20°C and displays many chemical properties associated with tertiary amines. The quinoline is ten π electron heterocycle and some times used as a high B.P. (237°C) basic solvent (Wilson *et al* 1977). The nitrogen atom of quinoline bears a lone pair of electron not involved in aromatic bonding which can be protonated, alkylated or complexed to Lewis acids (Codrell 1981).

Quinolines constitute an important class of heterocyclic molecules, firstly it plays an important part in the metabolism of all living cells and secondly increases availability of intermediates suitable for large scale production of heterocyclic substances or drugs, many of which are finding important new uses in chemical as well as in pharmaceutical industries (Wilson *et al* 1977).

There are different methods (Albert 1984; Gampp *et al* 1985; Budevsky *et al* 1988; Muhvri and Hazra 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

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etc. (Ramette 1979; Gampp *et al* 1985; Muhvri and Hazra 1991). The quick method for this purpose is potentiometery (Ramette 1979; Albert and Sergeant 1984; Asuero and Jamez-Trillo *et al* 1984; Sergeant 1984; Gampp *et al* 1985; Budvesky *et al* 1988; Muhvri and Hazra 1991) whereas spectrophotometry is very accurate but time consuming (Ramette 1979; Gampp *et al* 1985; Muhvri and Hazra 1991). The potentiometric titration has been improved by elimination of CO_2 using dried and purified nitrogen gas (Barlin and Perrin 1972). 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 (Meloun *et al* 1988; Bari and Khanzada 1999).

Materials and Methods

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

The solution was prepared for quinoline compound by weighing it with accurate digital balance (SARTORIUS BA110S). 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 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 for controlling the temperature. Prior to experiment, the glass electrode was calibrated with buffers of pH 4.05 at 25°C and 6.98 at 25°C. 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 0.01ml was used. The data obtained at different temperatures were analyzed by a computer programme written in GW-BASIC for calculation of dissociation constants of monoacidic base (quinoline).

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

$$BH^+ \rightleftharpoons B + H^+ \quad \text{.. (1)}$$

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

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

Where the terms square bracket [ ] represent molar concentration, pK_a^M is the concentration or mixed ionization con-

stant. The thermodynamic ionization constant pK_a^T for a base in term of active concentration is:

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

The activity concentration (concentration of ionized species) applied on the data of potentiometrically is an activity rather than concentration term. The conversion of concentration of ionized species into the equations:

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

$$[BH^+] = [BH^+]y_{HB^+} \quad \text{................. for basis .... (6)}$$

$$-\log y_i = \frac{AZ^2\sqrt{I}}{1+Ba_i\sqrt{I}} \quad \text{.. (7)}$$

The term Y_b and Y_{BH+} are the respective activity coefficients 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 (Burger 1982) given by:

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

Where C_i is molar concentration of ion i, z is its valency and symbol Σ is summation. Activity coefficients are calculated by eq. (7). These approximate activity coefficients are then used to calculate the hydrogen ion or hydroxyl ion concentration i.e. ($[H^+] = [H^+]/y_i$ or $[OH^-] = [OH^-]/y$). Ratios of the activities of the non-protonated to protonated species for bases is (Asuero and Jamenz-Trillo 1984):

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

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)

Results and Discussion

Temperature effect on ionization constants of quinoline. The ionization constants vary 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 both practical and theoretical interest. Nitrogenous bases are highly temperature sensitive, become weaker as temperature is increased, (Albert and Sergeant 1984).

Mostly reported pKa values are determined at 25°C or 18°C, so efforts have been made to see the effect of temperature variation on pK_a values. The temperature range was extended from 20°C to 50°C at the interval of 5°C. The changes in the thermodynamic parameters (ΔG) Gibb's free energies associated with acid base reaction can be determined 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). Thus pK_a^M and pK_a^T (concentration and thermodynamic ionization constant) of quinoline are 4.969 ± 0.004 and 4.934 ± 0.009 at 20°C but at 30°C pK_a^M and pK_a^T are 4.734 ± 0.003 and 4.698 ± 0.010 at 95% confidence level (Bari and Khanzada 1997). The temperature effect is much greater with the stronger than the weaker bases Table 1.

Again at 50°C the pK_a^T of quinoline reaches up to 4.124 ± 0.012. The pK_a^M and pK_a^T values decrease with increase of temperature.

A general equation, governing the temperature variation for the ionization of mono acidic bases, is well supported by experimental evidence

$$\frac{-d(pK_a)}{dT} = \frac{pK_a - 0.9}{T} \quad \text{...................................... (11)}$$

This equation assumes that the standard entropy change for nitrogenous bases is about -4 Cal °C mol^{-1} and this yields the expression for temperature coefficient. Where T temperature is in K°.

It has been observed that the pK_a^M values are temperature dependent, but there is no rule whether the pK_a^M values will increase or decrease with the increase of temperature (Mufti et al 1995). The organic bases have overall much greater temperature coefficient than organic acids. Temperature effect is much greater with the stronger bases as compared with weaker ones.

Gibb's free energies ΔG have been calculated from the value of pK_a^M and pK_a^T at 20 °C to 50°C with the increment of 5°C. The curve of ΔG of pK_a^M and ΔG of pK_a^T versus percent composition is a distorted parabola. It is observed that there is a regular increase in ΔG of pK_a^M and ΔG of pK_a^T with increase of temperature. At 20°C ΔG of pK_a^T value is 6.664 ± 0.006 kcal mol^{-1} where as at 50 °C ΔG value of pK_a^M is 6.152 ± 0.008 kcal mol^{-1}.

Effect of solvents on ionization constants of quinoline. Considerable literature is available for determination of proton dissociation constant of water insoluble compounds. Since many chemists require the knowledge about the dissociation constants of organic acid and bases in non-aqueous media, much attention has been paid to a quantitative explanation of the medium on pK_a values (Saeeduddin et al 1996).

The real problem in non-aqueous solvents is that a very few data are available in the literature. The pK_a values in solvents are very different from those in aqueous, but systematic study of the variations is lacking. In general non-aqueous solvents of dielectric constant less than that of water (Weissberger 1979) will shift the dissociation equilibria in favour of uncharged form. 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, it is therefore, interesting to compare their behaviour with that of water. One of the most important property of solvent its dielectric constant, which defines to a considerable degree of solvating ability of the medium (Budevsky 1988). Solvents may be distinguished according to their dielectric constant value and also their tendency to form hydrogen bonds. Both these properties were taken into consideration and we have selected three solvents i.e., (dioxane, ethanol and methanol) fact that water ethanol and methanol are the solvents having high dielectric constant values 78.5, 32.6 and 24.3 respectively and also ability to form hydrogen bond while dioxane having low dielectric constant 2.21 but no ability to form hydrogen bonds. The acid base titration in non-aqueous media is a relatively new method in analytical chemistry but its widespread use for the determination of organic and inorganic substances is still increasing.

The dissociation constants (in pK_a form) of quinoline have been determined at different compositions of aqueous-dioxane, aqueous-ethanol and aqueous-methanol mixtures.

The pK_a^M and pK_a^T values decrease with the increase in dioxane, ethanol and methanol contents of the solvent mixtures at 25°C. At 10%, the pK_a^M is 4.654 ± 0.005, 4.740 ± 0.002 and 4.677 ± 0.003 in dioxane-water, ethanol-water and methanol-water at 95% confidence level and at 50% pK_a^M is obtained as 3.771 ± 0.006, 3.876 ± 0.003 and 3.843 ± 0.004 respectively (Table 2, 3, 4 Fig. 1 and 2).

Dissociation constant values of quinoline show the reverse trend, thus in passing from water to high percentage of organic solvents the strength of the compound becomes stronger. The pK_a^M and pK_a^T values in ethanol-water and methanol-water are quite close to each other as compared to
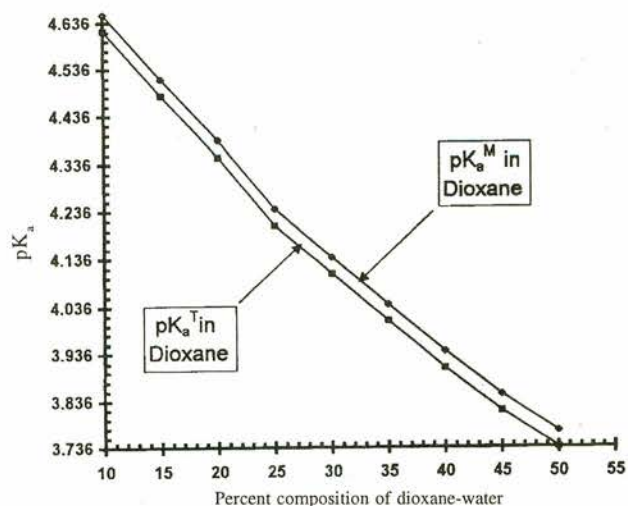
Fig 1. Effect of organic-water solvent mixture on pK_a^M and pK_a^T V_s composition of quinoline in dioxane-water solvent system.
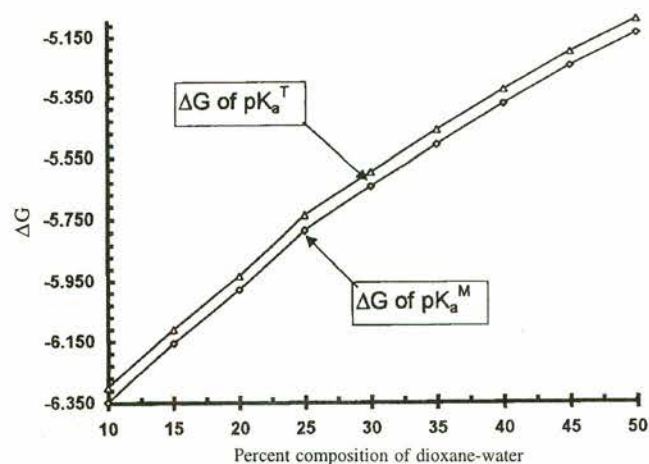

Fig 2. Effect of ΔG of pK_a^M and ΔG of pK_a^T V_s % composition of quinoline in dioxane-water solvent system.

dioxane. Possible reason is that the dielectric constant of ethanol and methanol are higher and close enough while for dioxane it is smaller i.e., 2.21. More over EtOH and MeOH have similar properties. The effect of ionization constant versus percent composition in all the three mixed organic water sol-

vent systems are detailed in Tables 2-4 for dioxane water, for EtOH-water and for MeOH-water respectively.

The thermodynamic parameters viz. Gibb's free energies ΔG associated with proton dissociation constants were calculated utilizing the standard equations. The values of Gibb's free energies are shown in Tables 2-4.

Table 1
Effect of temperature on pK_a^M, pK_a^T and thermodynamic constants of quinoline 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	4.969 ±0.004	4.934±0.009	-6.617 ±0.012	-6.664± 0.006
2	25	4.865 ± 0.005	4.830±0.011	-6.589±0.014	-6.637±0.007
3	30	4.734 ±0.003	4.698 ±0.010	-6.517±0.014	-6.566±0.005
4	35	4.559 ±0.006	4.524 ±0.014	-6.378±0.019	-6.428±0.009
5	40	4.365 ± 0.002	4.329±0.009	-6.202±0.013	-6.253±0.003
6	45	4.273 ±0.009	4.237±0.009	-6.167±0.013	-6.220±0.013
7	50	4.161 ±0.006	4.124±0.012	-6.097±0.018	-6.152±0.008

Table 2
Effect of percent composition on pK_a^M, pK_a^T and thermodynamic constants of

quinoline in dioxane-water solvent system

S.No	% Compt	PK_a^M	pK_a^T	ΔG of pK_a^M	ΔG of pK_a^T
1	10	4.654 ±0.005	4.619±0.012	-6.349±0.007	-6.301±0.017
2	15	4.514±0.008	4.479±0.016	-6.157±0.012	-6.110±0.021
3	20	4.385±0.008	4.350±0.014	-5.981±0.010	-5.934±0.018
4	25	4.241±0.030	4.206±0.037	-5.785±0.041	-5.737±0.005
5	30	4.139±0.007	4.105±0.010	-5.646±0.010	-5.599±0.014
6	35	4.041±0.007	4.006±0.013	-5.512±0.009	-5.464±0.018
7	40	3.941±0.004	3.906±0.009	-5.376±0.005	-5.329±0.013
8	45	3.850±0.011	3.815±0.017	-5.252±0.015	-5.205±0.023
9	50	3.771±0.006	3.736±0.015	-5.144±0.010	-5.097±0.020

Table 3
Effect of percent composition on pK_a^M, pK_a^T and thermodynamic constants of quinoline in EtOH-water solvent system

S.No	% Compt	PK_a^M	pK_a^T	ΔG of pK_a^M	ΔG of pK_a^T
1	10	4.740±0.002	4.705±0.010	-6.466±0.002	-6.419±0.013
2	15	4.620±0.005	4.585±0.011	-6.302±0.007	-6.254±0.016
3	20	4.505±0.006	4.47±0.008	-6.145±0.008	-6.099±0.011
4	25	4.429±0.004	4.395±0.010	-6.042±0.005	-5.995±0.014
5	30	4.365±0.002	4.330±0.010	-5.954±0.003	-5.906±0.013
6	35	4.233±0.026	4.198±0.032	-5.774±0.035	-5.727±0.043
7	40	4.117±0.006	4.083±0.006	-5.616±0.008	-5.569±0.008
8	45	4.024±0.008	3.989±0.012	-5.489±0.011	-5.442±0.016
9	50	3.876±0.003	3.841±0.010	-5.288±0.004	-5.240±0.013

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

S.No	% Compt	PK_a^M	pK_a^T	ΔG of pK_a^M	ΔG of pK_a^T
1	10	4.677±0.003	4.642±0.008	-6.273±0.004	-6.226±0.011
2	15	4.566±0.006	4.531±0.011	-6.229±0.008	-6.181±0.016
3	20	4.460±0.004	4.426±0.010	-5.982±0.006	-5.906±0.002
4	25	4.359±0.007	4.324±0.015	-5.946±0.010	-5.898±0.020
5	30	4.274±0.002	4.239±0.010	-5.732±0.003	-5.686±0.017
6	35	4.168±0.008	4.133±0.012	-5.685±0.011	-5.638±0.017
7	40	4.070±0.012	4.035±0.018	-5.458±0.016	-5.412±0.024
8	45	3.948±0.007	3.913±0.014	-5.385±0.009	-5.338±0.019
9	50	3.843±0.004	3.808±0.012	-5.154±0.005	-5.108±0.016

$$\Delta G = - RT \ln K_a^T \text{...} (12)$$

$$pK_a^T = \frac{1}{\ln_{10}} \left(\frac{\Delta G}{RT} \right) \text{.................................} (13)$$

The Gibb's free energies ΔG from the value of pK_a^M and pK_a^T in three-mixed solvent system 10 to 50. At 10% ΔG of pK_a^M in dioxane-water, EtOH-water and MeOH-water is 6.349 ± 0.007, -6.466 ± 0.002 and -6.273 ± 0.004 at 95% confidence level but at 50% the ΔG of pK_a^M value becomes higher i.e., (less negative) -5.144 ± 0.010, -5.288 ± 0.004 and -5.154 ± 0.005 respectively at 25°C. The negative value of ΔG suggests that proton dissociation reactions are favorable and spontaneous. It is clear from Tables/graphs drawn for ΔG of pK_a^M and ΔG of pK_a^T values versus percent composition which are parabola for dioxane-water and EtOH-water. The ΔG of pK_a^M and ΔG of pK_a^T values in case of MeOH-Water solvent system, there is no regular increase or decrease with the temperature.

The overall change in pK_a^M and pK_a^T, of ΔG of pK_a^M and ΔG of pK_a^T of this compound is given in detail (Tables 2, 3 and 4).

Conclusion

After going through the experimental data (Tables 1-4 and Fig 1-2) is noted that both temperature and solvent have significant effect on pK_a^M and pK_a^T values of quinoline base. It is also observed that effect of temperature is not the same as the effect of solvent systems but it depends upon the nature of solvent and dielectric constant. The trend of decrease by increasing the temperature and addition of solvent composition is the same in both the case, but the ionization values are much different (low and high). For example: at 25°C in aqueous system pK_a^M is 4.865 ± 0.005, at the same temperature in 50% dioxane pK_a^M is 3.771 ± 0.006, in 50% EtOH is 3.876 ± 0.006 and in 50% MeOH the pK_a^M is 3.843 ± 0.004. It means degree of dissociation of quinoline compound varies with percent composition of solvent water system and temperature. So it is observed that dissociation

constant values in EtOH and MeOH are closer to each other as compared with dioxane.

In case of water the $pK_a^M = 4.969 \pm 0.004$, at 20°C and at 50°C pK_a^M is 4.161 ± 0.006 which implies that quinoline dissociates faster at high temperature. The graph of pK_a^M and pK_a^T versus temperature and percent composition is a parabola. The Gibb's free energy (ΔG) values of quinoline increase with the temperature and at higher composition of dioxane, EtOH and MeOH. (Less negative at high temperature).

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