

## Dependence of Ionization Constants of Ephedrine in Aqueous and Non – aqueous Media

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(Received 12<sup>th</sup> August, 2003, revised 2<sup>nd</sup> June, 2004)

**Summary:** Ionization constants of ephedrine are measured at different temperatures (25,30,35, 40,45 & 50°C ) and in mixed organic-water solvent mixtures (dioxane-water, acetic acid-water, ethanol-water, methanol-water, acetonitrile-water and propylene carbonate-water) at 25°C. Data were obtained for the dissociation of ephedrine with particular emphasis on the effect of temperature and nature of solvent on  $pK_b$  values. Potentiometric data obtained were analysed by computer program. Results shows that as temperature increases,  $pK_b$  values decreases. Also  $pK_b$  values are higher in mixed solvent systems than in aqueous media.

### Introduction

Among the physico-chemical properties of molecules, the acidity constants are of vital importance both in the analysis of drugs as well as in the interpretation of their mechanism of action [1]. Evaluation of acidity constants of organic reagents is also of great value in planning analytical work [2] e.g the acidity constants can be employed in the design of titration procedures and examining the possibility of separation of mixtures of compounds by extraction. The complexing properties of a molecule depend on the number and steric disposition of its donor centres as well as on its acid base properties.

$\beta$ -Adrenergic agonists have been utilized in many chemical settings but now play major roles in the treatment of bronchoconstriction in patients with asthma (reversible airway obstruction) or as cardiac stimulants. Epinephrine was first used as a bronchodilator at the beginning of this century and ephedrine was introduced into western medicine in 1924. Although it had been used in China for thousands of years [3,4,5]. The more recent development of selective  $\beta_2$  agonists has provided drugs with even more valuable characteristics, adequate oral bioavailability, lack of  $\alpha$ -adrenergic activity and diminished likelihood of adverse cardio vascular effects.

Ephedrine is both  $\alpha$  &  $\beta$  adrenergic agonists, in addition it enhances release of morepinephrine from sympathetic nervous. Ephedrine contains two asymmetrical carbon atoms. This drug stimulates heart rate and cardiac output and variably increases

peripheral resistance as a result ephedrine usually increases blood pressure. Stimulation of  $\alpha$ -adrenergic receptors in the lungs promotes bronchodilation. Ephedrine is a patent stimulator of the central nervous system [5].

The purpose of this work is to extend the study of acid strength at different temperature and in different co-solvent systems. Because of ion-pair formation in different medium, the incomplete dissociation of the salt formed in the titration has been taken into account in computing the  $pK_b$  values (dissociation constant of bases is referred as  $pK_b$ ). Potentiometric method proved more useful and quick than other methods for determination of ionization constants [6-12].

Potentiometric data obtained was treated with computer program written in GW-BASIC for calculation of  $pK_b$  values.

### Results and Discussion

The ionization constants of ephedrine were determined in aqueous media at 25, 30, 35, 40, 45 and 50°C and in 10, 20, 30, 40 and 50% organic-water solvent mixtures (dioxane, ethanol, methanol, acetic acid, acetonitrile and propylene carbonate in water) at 25°C.

Table 1 shows the effect of temperature on concentration ionization constant ( $pK_b^c$ ), thermodynamic ionization constant ( $pK_b^T$ ) and thermodynamic constant ( $\Delta G$ ).

Table.1 Effect of Temperature on  $pK_b$  Values and  $\Delta G$  Values of Ephedrine.

Temp. °C	$pK_b^c$	$pK_b^T$	$pK_b$ values reported	$\Delta G$ values KJ/mol
25	9.517±0.01	9.559±0.01	9.6 *	54.505
30	9.417±0.009	9.450±0.01		54.836
35	9.282±0.006	9.315±0.009		54.948
40	9.160±0.008	9.193±0.01		55.107
45	9.014±0.008	9.048±0.01		55.103
50	8.975±0.006	9.009±0.009		55.731

\* Ref [23]

 $pK_b^c$  concentration ionization constant $pK_b^T$  thermodynamic ionization constant

Fig. 1 further elaborates the effect of temperature. When temperature increases from 25 to 50°C then  $pK_b$  values decreases from 9.517 to 8.975 and total decrease is 0.542 unit. This figure clearly indicates that there is sharp decrease in  $pK_b$  values when temperature increases from 25 to 45°C, while there is no sizable decrease in  $pK_b$  values when temperature further increases upto 50°C. A change in temperature causes a shift in equilibrium point which is both of practical and theoretical interest.

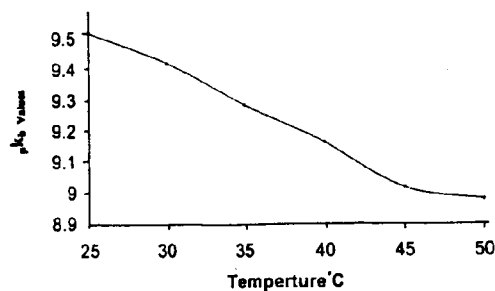
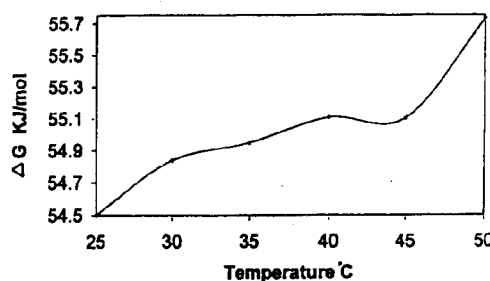
Fig.2 shows the effect of temperature on  $\Delta G$  values.  $\Delta G$  is related with temperature by equation [13,14].

$$\Delta G = - RT \ln K$$

$$\Delta G = - 2.303 RT \log K_a$$

Actually change in thermodynamic constant Gibb's free energy ( $\Delta G$ ) associated with acid-base reaction can be found from the variation of its equilibrium constant with temperature, this thermodynamic property offer interesting insight into acid-base behaviour, particularly with regard to solvation effects [13,14]

Acid-base titration in non-aqueous media is relatively new method in analytical chemistry, but its widespread use for the determination of organic and inorganic substance is still increasing. The most important advantage of non-aqueous (organic solvent) is that a large number of substance which are insoluble in water are readily soluble in non-aqueous solvents. This is very important because almost every analytical reaction (quantitative and qualitative) is carried out after the substance has been dissolved. Another advantage of the use of non-aqueous medium is that a large variety of solvent are available and they have differing acid-base properties, since

Fig. 1: Effect of temperature on  $pK_b$  values of ephedrine.Fig. 2: Effect of temperature on  $\Delta G$  values of ephedrine.

the behaviour of substance may be influenced by the polarity (dielectric constant) of the solvent [15].

In this study we are interested to obtain information about the solute-solvent & solvent-solvent interaction. We have chosen to study solution equilibria by potentiometric titration in mixed solvents, particularly in dioxane, methanol, ethanol, acetic acid, acetonitrile and propylene carbonate. This choice is justified by the fact that each solvent has its own dielectric constant value and solvents are also different in terms of developing hydrogen bonding in solution equilibria. This study help to view the effect of nature of solvent on  $pK_b$  values. The alcohols are similar to the water in the nature of their protolytic behaviour and can be studied by the same experimental technique, though they differ in physical properties (dielectric constant, lipophilicity etc) [16].

Dioxane is also popular solvent for studying acid-base behaviour because of having very low dielectric constant value ( $\epsilon = 2.209$ ).

Acetonitrile (AN) is one of the most important dipolar aprotic solvent. It is used extensively as a

reaction medium in synthesis and for mechanistic studies, as well as in electrochemistry, spectrophotometry and liquid chromatography [17]. In common with all other dipolar aprotic solvents acetonitrile typically behaves as a very weak electrophile. It is a much weaker hydrogen bond donor than water ( $\alpha = 0.19$ ) [18] but unlike protophilic aprotic solvent it is also a weak hydrogen bond acceptor ( $\beta = 0.31$ ). In consequence many solutes have high and strong differentiated reactivities (both kinetically and thermodynamically) in acetonitrile. Acetonitrile is a much more differentiated solvent than water, reflected by its much smaller autoprotolysis constant ( $pK_{ap}=33.6$ ). Nevertheless, the dielectric constant of acetonitrile is high enough ( $\epsilon = 36.0$ ) to allow extensive electrolytic dissociation of ionic solutes [17].

Acetic acid is the most popular solvent for titrimetric assay of bases in pharmaceutical formulations, because of the high purity of commercial product, its good physical characteristics, low basicity and good solvating power [19]

Propylene carbonate (PC) has drawn much attention in recent years as a solvent medium for electrochemical studies relating to the high energy batteries and free radical species. It is a stable solvent of moderately high relative permittivity (64.40 at 25°C) and has good solvent properties for a variety of organic and inorganic salts. Hence it is of much interest to study the behaviour of electrolytes in such a solvent media [20].

Fig. 3 shows the graph of  $pK_b$  values of ephedrine versus percent composition of mixed solvents (organic-water). As composition of organic solvent increases from 10 to 50% v/v then  $pK_b$  values of ephedrine increases in all solvent systems (dioxane-water, acetic acid-water, EtOH-water, MeOH-water, acetonitrile-water and propylene carbonate-water) but this effect is not same.

In case of dioxane-water solvent system as composition of dioxane increases from 10 to 20% and 20 to 30% the  $pK_b$  values increases from 9.73 to 9.79 and 9.79 to 9.86, total increase in  $pK_b$  values are 0.06 and 0.07 unit respectively but as composition further increases from 30 to 40% and 40 to 50% v/v than sizable increase in  $pK_b$  values marked. Total increase in  $pK_b$  values i.e. 0.4 unit is marked when overall composition increases from 10 to 50%.

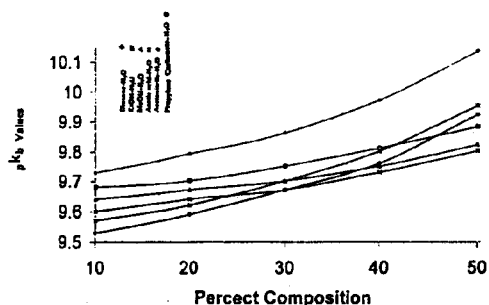


Fig. 3: Effect of percent composition of mixed solvent systems on  $pK_b$  values of ephedrine.

Nearly same trend is observed in case of acetonitrile-water and propylene carbonate-water solvent systems.

In (AN-H<sub>2</sub>O) solvent system when composition of organic solvent increases from 10 to 50% then  $pK_b$  values increases from 9.57 to 9.95 and total increase in  $pK_b$  values is 0.38 unit. Minimum increase in  $pK_b$  values is marked between 10 to 20% while maximum increase is marked when composition increase from 40 to 50%.

In (PC-H<sub>2</sub>O) solvent system composition of solvent in water also influence on  $pK_b$  values. As composition increase from 10 to 50% then  $pK_b$  values increase from 9.53 to 9.92 and total increase in  $pK_b$  values is 0.39 which is very close to the (AN-H<sub>2</sub>O) solvent system.

In case of (MeOH-H<sub>2</sub>O) solvent system  $pK_b$  values increases from 9.60 to 9.80 as composition of organic solvent increases from 10 to 50% while in case of (EtOH-H<sub>2</sub>O) solvent system  $pK_b$  values increases from 9.64 to 9.82 and total increase in  $pK_b$  values is 0.18 unit.

Acetic acid-water solvent mixture shows nearly same pattern as in case of (alcohols-water) solvent system.

This figure clearly indicates that increase in  $pK_b$  values is related to mainly their dielectric constant values. Minimum increase in  $pK_b$  values is marked in case of (CH<sub>3</sub>COOH-H<sub>2</sub>O, MeOH-H<sub>2</sub>O, EtOH-H<sub>2</sub>O) while maximum increase is marked in case of (dioxane-water, AN-H<sub>2</sub>O and PC-H<sub>2</sub>O). Possible reason is that acetic acid and especially alcohols

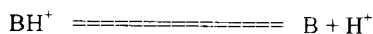
establish hydrogen bonding in solution so, there is minimum increase in  $pK_b$  values while rest of the solvents do not form hydrogen bonding so, increase in  $pK_b$  values is maximum.

This Fig. 3 also helps to view the effect of dielectric constant in a way that the dielectric constant values of EtOH & MeOH are close i.e. 24.3 and 32.7 so,  $pK_b$  values are also close. As dioxane has very low dielectric constant value ( $\epsilon = 2.209$ ) so  $pK_b$  values are also high as compare to rest of the solvent-water systems.

Increase in  $pK_b$  values with increasing organic solvent concentration in binary mixture can be explained by the dielectric constant change. Lower the dielectric constant value of solvent higher will be the  $pK_b$  values [21] and same is observed in this Fig. 3. Increase in  $pK_b$  value with increasing solvents concentration from 10 to 50% is in accordance with the theory. The dielectric constants of a solvent is a measure of how well that solvent separate oppositely charged ions. According to Colomb's law the attraction force (F) between two ions of charged  $q^-$  &  $q^+$  separated by a distance 'r' [22]

$$F = 8.988 \times 10^9 \frac{q^- q^+}{\epsilon r^2}$$

where  $\epsilon$  is the dielectric constant of the solvent. The attraction forces is inversely proportional to the dielectric constant. The larger the value of the dielectric constant, the smaller the attraction between two ions ( $H^+$  & B for dissociation reaction of base) and thus larger the acidity constant or  $pK_b$  values decrease[21]



Solvents can indeed influence the equilibria in solution by long range electrostatic interaction and through short range factors such as solute-solvent interaction. Binary mixed solvents containing water as one component are able to react protolytically both with protic acids and their conjugate bases. The acid-base behaviour of many of these mixed solvents is qualitatively comparable with that of water, even though wide quantitative differences are observed.

#### Experimental

All chemicals were of analytical grade (Merck) and were used without further purification.

Double distilled deionized water was used in preparation of all solutions. Freshly distilled dioxane, ethanol, methanol, acetic acid, acetonitrile and propylene carbonate were also used. Following solutions were prepared.

1. Stock solution of 0.01 mol.dm<sup>-3</sup> ephedrine in water.
2. 0.1 mol.dm<sup>-3</sup> hydrochloric acid solution in water.
3. 0.1 mol.dm<sup>-3</sup> hydrochloric acid solution containing 10,20,30,40 and 50% dioxane, ethanol, methanol, acetic acid, acetonitrile and propylene carbonate.

The potentiometric titration was performed in a thermostated double walled glass cell containing 50ml of sample solution with hydrochloric acid. The pH was determined with PHILIPS PW 9420 digital pH meter which was coupled with ingold combined glass and reference electrode dipped in sample solution whose temperature was controlled by circulating water through the jacket of measuring cell. JULABO HC thermostated bath accurate of  $\pm 0.1^\circ\text{C}$  was used for controlling the temperature.

Prior to experiment the glass electrode was calibrated with buffers [23,24]. Sample solution was kept mixed by stirring with magnetic stirrer and inert atmosphere was created in a reaction cell by bubbling nitrogen gas. For dispensing titrant, Mettler Burette DV-10 accurate to  $\pm 0.01\text{ml}$  was used. The potentiometric titration were performed on sample solution at different temperatures, in different solvents and their different composition (10,20,30, 40 and 50%). Potentiometric data obtained were analysed by computer program written in GW-BASIC for calculation of ionization constants of monoacidic bases.

#### Conclusions

After going through the experimental data it is concluded that both temperature and solvent's nature and their polarity in mixed solvent systems has significant effect on  $pK_b$  values of ephedrine.

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