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Acidity Constants and Thermodynamic Parameters of Barbituric and Diethylbarbituric Acids in Water, (Water + Tetrahydrofuran), and (Water + Triton X-100) Systems

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Using potentiometric measurements, dissociation constants of barbituric and diethylbarbituric acid (BA and DEBA) were determind in water, in a tetrahydrofuran + water mixture, and in a water + Triton X-100 micellar system. Results show that the pK_a value of these acids increases as the percentages of the tetrahydrofuran increase. Similar results were obtained upon addition of a neutral surfactant such as Triton X-100 to the solution of these acids. Thermodynamic parameters of these acids were obtained by determination of the acidity constants of barbituric and diethylbarbituric acids in water at five different temperatures ranging from (15.0 to 55.0) °C and at an ionic strength of 0.100 M KCl.

The predication of acidity constants of weak electrolyte drugs is important in estimating their physical and biological activity. Binary solvent systems are often used in the preparation of liquid dosage forms of these drugs, in liquid chromatographic analysis, and in the estimation of relative dissociation constants of compounds which are less soluble in water. Generally these weak electrolytes become even weaker as a nonaqueous solvent replaces the water.

Barbituric acid (BA) represents the parent compound of barbiturates, which are important in the pharmaceutical industry due to their hypnotic and sedative properties. These substituted acids in low doses have a tranquilizing effect, and high doses act as anticonvulsants and anesthetics. Therefore, investigation of such a compound from an analytical point of view is interesting. Barbituric acid behaves as a monobasic acid of moderate strength with a pK_a value of about 4 (in 0.04 M KCl) that was given by Krahl[1] in 1940. Rubino[2] reported pK_a values of barbituric acid and barbital (DEBA) in different mass fractions of ethanol + water. They observed no significant change in the pK_a values of these acids upon addition of ethanol.

The application of micelles in analytical chemistry has grown since 1976.[3] The effect of micelles on the equilibrium of a variety of indicator acids was noted by Hartley[4] in 1934 and expanded upon by Hartley and Roe[5] in 1940. Micelles can affect the apparent pK_a values of the acids due to a combination of electrostatic and microenvironmental affects of the micelle.[6−9] Staroscik[10] et al. reported the acid−base titration of barbiturates in cationic micelles in water. The cationic attraction of the surface groups for hydroxide ions from the bulk aqueous solution effectively lowers the apparent pK_a of the barbiturates, making them stronger acids and thus more amenable to titrametric analyses.

Experimental Section

Reagents. All reagents were of analytical grade from Merck except the barbituric acid, which was from Fluka. These reagents were used without further purification. The KOH solution was standardized by potassium hydrogen phetalate. Triply distilled water was used in the preparation of all solutions.

Apparatus. The pH measurements were carried out with a 654 Metrohm pH-meter (Metrohm Ltd, CH-9100-Hersau, Switzerland) using a combined glass electrode. Temperature was maintained at each specific temperature ($t \pm 0.1$) °C by circulation of thermostated water through the jacket. Nitrogen purge gas was used to remove CO_2. An Eppendorf micropipet (±0.6%) was used for the addition of a standard base to the solution.

Cell for Potentiometric Measurements. The reaction solution was introduced in a cell equipped with a magnetic stirrer. The temperature was controlled by a thermostat, and the solution was sealed from the atmosphere through the use of O-rings. The inert gas (N_2) for removing CO_2 and O_2 must be pure. The standard base is added by a micropipet tip beneath the surface of the solution. There was a sufficient number of openings in the cap to take care of the electrodes and all materials to be introduced into the reaction mixture. The capacity of the cell which is recommended is about 70−80 mL, so that a volume of 50.00 mL for the experimental solution can be easily accommodated.

Calibration.[11] Before each experiment, it is necessary to calibrate the pH-meter and electrode system in terms of p[H]. To calibrate the pH-meter system in terms of p[H], in a water system, the cell was charged with 5.00 mL of 0.100 M HCl, 5.00 mL of 1.000 M KCl, and 40.00 mL of water. Increments of standard base solution (KOH) are then added, up to a meter reading about 11.5. By drawing the pH reading versus the calculated pH, the calibration line is obtained. The calibration line thus determined provides the factors (usually a constant factor) necessary to convert the meter reading to p[H].

In each mixture solution we prepare the KOH titrant in the appropriate percentage of tetrahydrofuran (or Triton X-100) + water, make up the test solution (similar in water solution) by using appropriate dilutions to achieve the appropriate volume fraction of tetrahydrofuran (or Triton X-100), and then titrate as if dealing with a water solution.

Procedure for Calculation of K_w in Different Tetrahydrofuran/Water Mixtures. For determination of K_w in various tetrahydrofuran + water mixtures, at an ionic strength of 0.100 M KCl and $t = 25.0$ °C, the cell was

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Table 1. Thermodynamic Functions of Diethylbarbituric (DEBA) and Barbituric Acid (BA) ($HA \rightarrow H^+ + A^-$) in 0.100 M KCl

	pK_a (±0.04)					$-\Delta H$	$-\Delta S$
	t/°C = 15	t/°C = 25	t/°C = 35	t/°C = 45	t/°C = 55	kJ mol^{-1}	J mol^{-1} K^{-1}
BA	3.69	3.78	3.84	3.93	4.01	14.28 (±0.13)	120.2 (±3.5)
DEBA	7.58	7.64	7.70	7.76	7.83	11.19 (±0.16)	183.8 (±4.5)

charged with 5.00 mL of 0.100 M HCl, 5.00 mL of 1.000 M KCl, and the appropriate volume of tetrahydrofuran and water until the total volume was equal to 50.00 mL. The cell was capped (letting inert gas flow), equilibrated until pH drifts < 0.001 unit/5 min (usually between 5 min and 0.5 h), and titrated with standard KOH (which is prepared in a given percentage of tetrahydrofuran). The ion product ($K_w = [H^+][OH^-]$) was determined in various percentages of mixture by several series of [OH] and p[H] measurements. The p[H] was measured with a pH-meter, while $[OH^-]$ was calculated from the amount of base added to the solution. K_w and then pK_w were calculated.

Procedure for Calculation of pK$_a$. In the present study Martell's computer[11] program has been used to calculate the acidity constants (in different media) of the barbital and barbituric acid. The acidity constants were determined by titrating 50.00 mL of (2.000×10^{-3} to 2.000×10^{-2}) M analyte with KOH in each medium, and the ionic strength of the solution was adjusted with 0.100 M KCl. The temperature was maintained at each specific temperature ($t \pm 0.1$) °C by circulation of thermostated water through the jacket. Before doing each titration, the solution was allowed to equilibrate until pH drifts < 0.001 unit/5 min (usually between 5 min and 0.5 h) were obtained at each specific temperature. N_2 gas was pumped through the solution to remove CO_2. During the titration the pumping of N_2 was continued above the solution. The titroprocessor was calibrated to read hydrogen ion concentration. To obtain each pK_a value, at least five titrations were made and each titration had almost 30 points (at the pH range 3 to 11 for barbituric acid and 5 to 11 for diethylbarbituric acid).

Results and Discussion

The refinement of the acidity constant is the process where the computer adjusts parameter(s) with a programmed algorithm to obtain the best possible least-squares fit of the calculated data to the observed data. σ_{fit}, which is a measure of the weighted sum of the squares of pH(cal) − pH(obs), is a measure of the goodness of fit. The purpose is to minimize σ_{fit} through refinement of the parameter(s). The BEST[11] computer program was used to obtain pK_a values of barbituric acid and barbital. This program is a new algorithm for the simultaneous determination of any number of acidity constants from potentiometric data.

The pK_w values obtained for various tetrahydrofuran + water mixtures at $\mu = 0.100$ M and $t = 25.0$ °C are 13.78, 13.97, 14.36, 14.74, and 15.13 at 0.0, 0.09, 0.27, 0.47, and 0.67 mass fraction of tetrahydrofuran, respectively. Similar experiments in different Triton X-100 + water systems were done, and results show that pK_w values in these media do not change significantly relative to those in pure water.

To check the possibility of complex formation between K^+ ion (from KCl) and analyte,[12] first the titration curves of barbituric acid in two different media, KCl and $(Et)_4NBr$ (as supporting electrolyte), were obtained. These two titration curves almost superimpose, indicating that there is no strong interaction between barbituric acid and K^+ ion, so 0.100 M KCl was chosen as a supporting electrolyte. The pK_a values of barbituric acid and barbital were calculated in water. The results are given in Table 1.

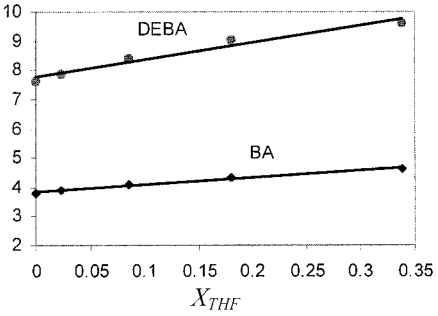

Figure 1. Relationship between pK_a values of diethylbarbituric (DEBA) and barbituric (BA) acid with the mole fraction of tetrahydrofuran in water.

Table 2. Acidity Constants of Diethylbarbituric (DEBA) and Barbituric Acid (BA) in Different Mass Fractions *w* for (*w*)Tetrahydrofuran + (1 − *w*)Water Systems at 25.0 ± 0.1 °C

	pK_a (±0.04)	
w	BA	DEBA
0.00	3.78	7.64
0.09	3.88	7.87
0.27	4.07	8.42
0.47	4.34	9.05
0.67	4.60	9.61

The thermodynamic parameters are also listed in Table 1. Values of enthalpies and entropies of ionization were calculated using a Van't Hoff analysis. In all cases plots of ln K_a versus $1/T$ were linear with correlation coefficients of 0.999 (line equation $Y = 1717.6X - 14.458$) and 0.998 (line equation $Y = 1346X - 22.114$) for barbituric acid and barbital, respectively.

Table 2 shows pK_a values in different mass fractions (w) of tetrahyrofuran (THF). The pK_a values increase as the percent (or mass fraction) of THF increases. The solvating ability and relative permittivity play a fundamental role in dissociation reactions. The energy required to separate the opposite charges of an acid in a solvent is inversely proportional to the relative permittivity of the solvent. This energy requirement can be supplied by solvation of the ions, and in addition the proton transfer from acid to the solvent molecule also supplies some energy. Since the relative permittivity and solvating ability of the mixture decrease as the percentage of THF increases ($\epsilon_{H_2O} = 78.36$ and $\epsilon_{THF} = 7.6$), the energy required for separation of charges will increase and thus the extent of the dissociation constant will be lowered. This explains that the pK_a value of each acid will increase as the percentage (or mole fraction) of tetrahydrofuran in the mixture increases.

The relationship between pK_a values (of BA and DEBA) and mole fraction of tetrahydrofuran is shown in Figure 1. As results show, there is a linear relationship between pK_a and mole fraction of THF with correlation coefficients of 0.987 ($y = 2.41x + 3.83$) and 0.979 ($y = 5.80x + 7.79$) for BA and DEBA, respectively.

Many papers and reviews have discussed the effect of micelle on the apparent pK_a values of the acids. Usually

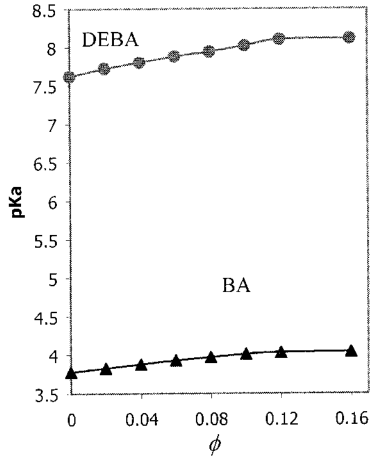

Figure 2. Relationship between pK_a values of diethylbarbituric (DEBA) and barbituric (BA) acid with the volume fraction ϕ of Triton X- 100 in water.

Table 3. Acidity Constants of Barbital and Barbituric Acid (DEBA and BA) in Different Volume Fractions ϕ of Triton X-100 in Water at 25. 0 ± 0.1 °C

	pK_a (±0.04)	
ϕ Triton X-100	BA	DEBA
0.00	3.78	7.64
0.02	3.83	7.72
0.04	3.88	7.80
0.06	3.93	7.88
0.08	3.97	7.94
0.10	4.01	8.02
0.12	4.03	8.10
0.16	4.04	8.11

they explain the shift of the pK_a values either theoretically or by the estimation from the titration curve(s).[13−17] In the present work we observed the shifts in titration curves of the barbital and barbituric acid in a nonionic micellar system, and then we calculated the pK_a values of these acids. Results show that, for up to $\phi = 0.1$ (where ϕ is the volume fraction) of the micelle, the pK_a values increase and, beyond that, pK_a values are almost not changed. pK_a values in different volume fractions of the micelle (Triton X-100) are given in Table 3 and also shown in Figure 2.

Conclusion

Linear relationships were observed between ln K_a and $1/T$ for barbituric acid and barbital (DEBA) in water. Thermodynamic parameters of BA and DEBA were obtained at five different temperatures ranging from (15.0 to 55.0) °C and at an ionic strength of 0.100 M KCl.

The shifts in pK_a values of barbituric acid and barbital in binary solvent mixture and nonionic micellar systems were derived. Similar behaviors were observed in both media.

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