Thermodynamic Proton – ligand Stability Constants in Dioxane – Water Media, pk$_a$, ΔG°, ΔH° and ΔS°, Values for 1,3-Disubstituted Barbituric Acid

MANOJ KUMAR and B.R. SINGH

Department of Chemistry, Sahu Jain (PG) College, Najibabad. – 246763, India
*Corresponding author E-mail: vs21040@gmail.com

ABSTRACT

Thermodynamic protonation constants of dimethyl barbituric acid [DMBA], Diphenyl barbituric acid [DPBA], di-o-tolyl barbitiuric acid[D-O-TBA], di-m-tolyl barbituric acid [D-m-TBA], di-p-tolyl, barbituric acid [D-p-TBA], di-o-xylyl barbituric acid [D-o-XBA], di-m-xylyl barbituric acid [D-m-XBA], di-p-xylyl barbituric acid [D-p-XBA], di-± napthyl barbituric acid [D-±-NBA] and di-p-anisyl barbituric acid [D-p-ABA] have been determined in different mole fraction of deoxane [0.175 – 0.350] at 20, 30, and 40 ± 0.10⁰C. The thermodynamic protonation constant [pK^T_a] values do not vary linearly with reciprocal of dielectric constant of medium, but a plot of pk^T_a versus the mole fraction of dioxane is linear at all given temperatures. The mean ionic radii are for barbiturates ions, being in the region of 2.12 – 2.72 A⁰, slightly increases with dioxane percentages. The values of ΔG⁰, ΔH⁰ and ΔS⁰ have been evaluated. The effect of temperature as well as medium effect are briefly discussed.

Key words: Stability constant, Dioxane water system, Barbituric acid.

INTRODUCTION

Barbituric acid are have found immense analytical and medicinal applications[1-6]. However, such applications necessitate a precise knowledge of their protonation constants. Recently, several analogous compounds have been synthesised by the introduction of substituent groups in different positions for improved analytical characteristics. This empirical approach, although sometimes inescapable , is generally wasteful and it is more fruitful to determine the physicochemical properties of the reagents and their resulting metal complexes, and in particular their protonation constants, which could lead to a better understanding of the cause of specificity and selectivity of relevant medicinal and analytical reactions. With this value, the thermodynamic protonation constant [pK^T_a] of 1, 3 di substituted barbituric acids in different mole fraction of dioxane at 20, 30, and 40 ± 0.10⁰C have

been determined. The thermodynamic functions, associated with protonation processes have also been evaluated.

EXPERIMENTAL

The substituted barbituric acids were synthesised by the usual procedure reported in the literature[7] and recrystallized before use and the purity was checked by analytical analysis, UV and IR spectra. All other chemicals were of Anala R and G.R grades of B.D.H or E. Merck unless otherwise stated. Dioxane was purified using the method of Weissberger et al[8] or carbonate free sodium hydroxide was prepared by the electrolytic method of Vogel[9].

The protonation constant were determined by the pH-titration method employing a pH-meter cell of type.

Ag, AgCl HCl, glass, KCl, Acids, $HClO_4$ – $NaClO_4$
NaOH KCl, Hg_2Cl_2
[To maintain I = 0.1 M]

The pH values measured with an expanded scale pH- meter were corrected from the calibration curves to obtain the true pH values. From the potentiometric titrations of $HClO_4$ in the absence and presence of barbituric acids, the formation

curves in which $n_{\bar{H}}$ [the average number of protons bound per free ligand] plotted against pH were constructed in accordance with the procedure of Irving and Rossotti[10]. By applying Bjerrum's[11] 10 half integral method, the protonation constants at three temperatures were determined, the correction for activity coefficient were applied on the basis of Davies equation[12] and the thermodynamic protonation constants were evaluated. The change in free energy ΔG^0, enthalpy ΔH^0 and entropy ΔS^0 associated with the protonation equilibrium, i.e

$$H^+ + A^- \rightleftharpoons HA$$
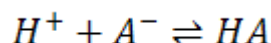
can be readily evaluated on the basis of the equations (1) – (3)

$$-\Delta G^0 = 2.303 \ RT \ \ log \ K_T \quad ...(1)$$

$$\frac{d \ log \ K_T}{d \ [1/T]} = \frac{-\Delta H^0}{4.57} \quad ...(2)$$

$$\Delta G^0 = \Delta H^0 - T \Delta S^0 \quad ...(3)$$

RESULT AND DISCUSSION

The thermodynamic protonation constant $[pK^T_a]$ at temperatures -20, 30 and 40ºC are given in table-1. The average $[pK^T_a]$ generally falls within a

Table 1: pK^T_a values of 1, 3 – di substituted Barbituric acids at different Temperatures

Acids	Mole fraction of dioxane (n_2)											
	0[a]			0.175			0.250			0.350		
	20º C	30º C	40º C	20º C	30º C	40º C	20º C	30º C	40º C	20º C	30º C	40º C
DMBA	3.85	3.74	3.65	4.18	4.00	3.92	4.25	4.12	4.02	4.33	4.21	4.10
DPBA	4.07	3.98	3.92	4.35	4.22	4.09	4.44	4.35	4.24	4.60	4.48	4.39
D-p-TBA	4.29	4.18	4.08	4.54	4.45	4.35	4.70	4.58	4.46	4.85	4.74	4.63
D-m-TBA	3.98	3.88	3.79	4.23	4.14	4.03	4.34	4.23	4.10	4.48	4.36	4.24
D-o-TBA	3.57	3.48	3.40	3.82	3.69	3.58	3.86	3.77	3.66	3.96	3.88	3.78
D-o-XBA	3.66	3.57	3.46	3.85	3.76	3.64	3.96	3.84	3.71	4.04	3.95	3.85
D-m-XBA	4.38	4.28	4.19	4.68	4.57	4.45	4.79	4.68	4.56	4.97	4.85	4.74
D-p-XBA	3.94	3.83	3.72	4.16	4.05	3.92	4.27	4.15	4.03	4.39	4.27	4.15
D-p-ABA	4.12	4.00	3.89	4.46	4.35	4.25	4.57	4.45	4.32	4.70	4.58	4.45
D-α-NBA	4.33	4.22	4.13	4.58	4.48	4.37	4.74	4.62	4.52	4.80	4.68	4.57

O[a] Extrapolated values at 0 % dioxane.

spread of 0.02 but not beyond 0.03 in any case. The empirical data for the mole fraction of dioxane (n_2) and ΔG^0, ΔH^0 and ΔS^0 values are given in the table 2 and 3 respectively. The pK_a^T values increase in dioxane content because of the decrease in the dielectric constant of bulk solvent. As the dielectric constant decreases, the ion interaction involving the proton and anionic oxygen on the ligand decrease to a greater extent than the ion dipole interaction between the proton and the solvent molecule. A plot of pK_a^T against mole fraction of dioxane [Fig.1] shows a linear relationship of the form. $pK_a^T = mn_2 + c$.

Gurney[13] and others [14, 15] have shown that the standard free energy change associated with the proton transfer, ΔG^0_{diss}, may be split into two distinct parts: electrostatic [el.] and none electrostatics [nonel].

$$\Delta G^0_{diss} = \Delta G^0_{el} + \Delta G^0_{nonel} \qquad ...(4)$$

Table 2: Empirical correlation of   with mole fraction of dioxane (pK_a^T)

Acids	Temp.(°C)	$pK_a^T = m\ n_2 + c$				
		Last square method			Graphically	
		m	c	r	m	c
DPBA	20	5.66	3.96	1.00	5.63	3.98
	30	5.64	3.88	0.99	5.61	3.90
	40	5.63	3.80	1.00	5.62	3.82
DMBA	20	5.56	3.81	1.00	5.54	3.82
	30	5.53	3.72	1.00	5.52	3.74
	40	5.52	3.64	1.00	5.50	3.65
D-p-TBA	20	5.69	4.20	1.00	5.68	4.18
	30	5.68	4.11	1.00	5.67	4.10
	40	5.66	4.05	1.00	5.65	402
D-m-TBA	20	5.09	3.65	1.00	5.08	3.68
	30	5.09	3.60	0.99	5.08	3.63
	40	5.08	3.52	1.00	5.05	3.57
D-o-TBA	20	5.03	3.44	0.99	5.02	3.45
	30	5.03	3.39	1.00	5.02	3.40
	40	5.02	3.33	1.00	5.00	3.34
D-o-XBA	20	5.78	3.60	1.00	5.76	3.59
	30	5.75	3.53	1.00	5.74	3.52
	40	5.73	3.48	0.99	5.72	3.46
D-m-XBA	20	5.14	4.00	0.99	5.12	4.02
	30	5.14	3.94	1.00	5.12	3.96
	40	5.12	3.88	1.00	5.10	3.90
D-p-XBA	20	5.25	3.65	1.00	5.23	3.62
	30	5.25	3.55	1.00	5.23	3.54
	40	5.24	3.50	0.99	5.22	3.48
D-α-NBA	20	5.36	3.57	1.00	5.35	3.56
	30	5.37	3.52	1.00	5.35	3.50
	40	5.36	3.46	0.99	5.34	3.44
D-p-ABA	20	5.44	3.50	0.99	5.42	3.48
	30	5.43	3.43	1.00	5.42	3.42
	40	5.43	3.37	1.00	5.40	3.35

Table 3: ΔG°, ΔH° and ΔS°values for 1,3 – di substituted barbituric acids at 30⁰C

Acids	Mole fraction of dioxane (n_2)											
	0[a]			0.175			0.250			0.350		
	ΔH°	-ΔG°	+ΔS°	ΔH°	-ΔG°	+ΔS°	ΔH°	-ΔG°	+ΔS°	ΔH°	-ΔG°	+ΔS°
DMBA	3.74	5.16	4.68	4.05	5.53	4.88	4.15	5.69	5.08	4.23	5.82	5.25
DPBA	3.92	5.50	5.21	4.21	5.83	5.34	4.32	6.01	5.57	4.45	6.18	5.70
D-p-TBA	4.53	5.77	4.09	4.85	6.15	4.29	4.98	6.32	4.42	5.15	6.55	4.62
D-m-TBA	3.69	5.36	5.51	3.99	5.72	5.70	4.07	5.84	5.84	4.20	6.02	6.00
D-o-TBA	3.18	4.80	5.34	3.41	5.09	5.54	3.48	5.21	5.70	3.58	5.36	5.87
D-o-XBA	3.06	4.93	6.17	3.28	5.19	6.30	3.34	5.30	6.45	3.44	5.45	6.63
D-m-XBA	4.16	5.91	5.77	4.52	6.31	5.90	4.62	6.46	6.07	4.80	6.70	6.27
D-p-XBA	3.68	5.29	5.32	3.94	5.59	5.44	4.03	5.73	5.61	4.14	5.89	5.77
D-p-ABA	4.05	5.52	4.85	4.48	6.01	5.04	4.56	6.14	5.20	4.68	6.33	5.44
D-α-NBA	4.45	5.83	4.55	4.75	6.19	4.75	4.90	6.38	4.88	5.07	6.60	5.05

ΔG° and ΔH° in Kcal $^{-1}$mole^{-1} , in Cal mole $^{-1}$ K^{-1}

aextrapolated values at 0% dioxane.

Table 4: $pK_a^T (S - W) = pK_a^T(S) - pK_a^T(W)$

Acids	Mole fraction of dioxane (n_2)								
	0.175⁰C			0.250			0.350		
	20°C	30°C	40°C	20°C	30°C	40°C	20°C	30°C	40°C
DMBA	0.33	0.26	0.27	0.40	0.38	0.37	0.48	0.47	0.45
DPBA	0.28	0.24	0.17	0.37	0.37	0.32	0.53	0.50	0.47
D-p-TBA	0.25	0.27	0.27	0.41	0.40	0.38	0.56	0.56	0.55
D-m-TBA	0.25	0.26	0.24	0.36	0.35	0.31	0.50	0.48	0.45
D-o-TBA	0.26	0.21	0.18	0.29	0.29	0.26	0.39	0.40	0.38
D-o-XBA	0.19	0.20	0.19	0.30	0.27	0.25	0.38	0.38	0.39
D-m-XBA	0.30	0.29	0.26	0.41	0.40	0.37	0.59	0.57	0.55
D-p-XBA	0.22	0.23	0.20	0.33	0.32	0.31	0.45	0.44	0.43
D-p-ABA	0.35	0.34	0.36	0.45	0.44	0.43	0.58	0.58	0.56
D-α-NBA	0.25	0.26	0.24	0.41	0.40	0.39	0.47	0.46	0.54

The electrostatic contribution to the free energy change is often estimated using Born equation[16].

$$...(6)$$

Further, as , the equation simplifies as

$$...(5)$$

$$....(7)$$

Where R$_+$ and R$_-$ are radii of solvated ions and D is the dielectric constant of the medium[17, 18]. Hence

against 1/D assuming ΔG^0_{nonel}. to be independent of the solvent. When the values of substituted barbituric acids are plotted against 1/D it is observed

that the plots possess a distinct curvature. It seems evident that non-electrostatic factors exert a considerable influence on the deprotonation of barbituric acids.

For barbituric acids, the change in pK_a^T with mole fraction of dioxane (n_2) is of considerable magnitude. Generally, the difference in in aqueous medium (n_2= 0) and aqueous dioxane medium (n_2= 0.350) is of the order of 1.45 – 1.95 pK_a^T units. When pK_a^T values of these barbituric acids are plotted against n_2, the straight line relationship are encountered [Fig 1]. The experimental values of pK_a^T here indicate a maximum deviation from linearly of the order of 0.05 or about 0.5% in pK_a^T .

The goodness of fit in these instances was judged by calculating the correlation coefficient, , defined by--

Where x and y are mean values of x ($_)$ and y (pK_a^T), respectively. The summations are extended to all pairs (x, y) a variable. Linear
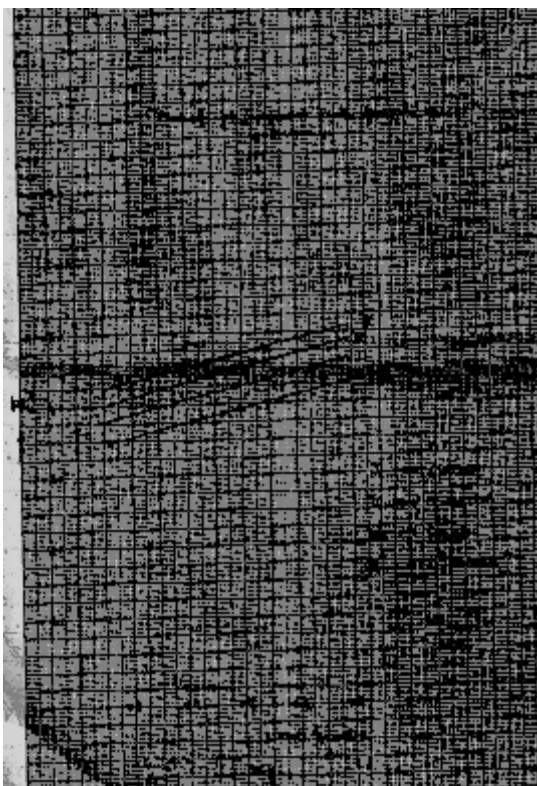
proportionality is readily indicated between the variables when the value of is +1.0.

Since the value of is approximately +1.0 at 20, 30 and 40⁰C for all the substituted barbituric acids. [Table-2], it implies that there is quite a high probability of a linear relationship between (pK_a^T) and $_2$. A similar behaviour is found for several other acids such as benzoic, acetic propionic and formic acids[19]. 18 in aqueous dioxane medium. Likewise, linear proportionality is also obtained for some other mixed water solvents, e.g: acetic, propionic, butyric and benzoic acids in methanol-water mixtures[20].

The values have been determined with a precision of 0.02 to 0.03 and hence the error in ΔG^0 is believed to be close to 0.03 and 0.04 Kcal/mole. The values of ΔS^0 given in table -3 are accurate to 0.02 cal.mole^{-1}K^{-1}.

The negative value of ΔH^0 found in aqueous as well as dioxane mixtures for all barbituric acids proves that their protonation at temperatures up to 40⁰c is exothermic. The negative values of ΔH^0 encountered here may be described to the formation of the covalent bond between proton and anionic oxygen on the barbituric acids. Further, It is evident that the magnitude of Change in, " H^0 with solvent composition is relatively small and falls with in the range of experimental error. it is because of this that the slopes of straight lines in the plots of   against n_2 (Fig – 1) do not differ markedly and are nearly the same and parallel at the three temperatures for all the barbituric acids. The values of ΔS^0 are found to increase with increase in dioxane content of the solvent medium for all barbituric acids, there by proving that it is dependent of solvent composition. The net entropy changes associated with protonation process can be attributed to a combination of the following:

(i). Change neutralisation; (ii) Subsequent liberation of ordered water molecules; and (iii) loss of rotational and vibrational degrees of freedom of the legend only (iii) gives a small negative contribution to entropy, but the contributions of (i) and (ii) together more than offset that due to (iii) and hence the protonation process has large positive " S^0 values. The protonation of these acids then appears to be entropy driven as expected from

Fig. 1:

the degree of change neutralisation and polarizability of the resulting anions.

When the acid protonates in two media, the free energy change for the transfer reaction from one medium to the other is given by 2.303 RT . For instance with DPBA, $\Delta G^0_{(aq.)}$ and $\Delta G^0_{(=0.175)}$ are 5.50 and 5.83 Kcal mole^{-1}, respectively at 30^0 and " G^0 changes by 0.33 Kcal mole^{-1} in the transfer reaction.

and this result in a change of 0.20 Cal mole $^{-1}$ in entropy. Δ (S – W) values, ie; (S) – (W) (where S and W refer to mixed solvents and water respectively) of barbituric acids are given in table 4.

The change in (S – W) which is found to be different for the different acids for the same percentage of dioxane is probably due to the presence of different substituents which cause a great change in the distribution of electron density in the ring and hence the electron density at any particular point is also affected.

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