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Dissociation Constants of Substituted Aryl Azo Barbituric and Thiobarbituric Acids

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The acid dissociation constants of 5-(substituted phenylazo) barbituric and thiobarbituric acids were determined in aqueous media and in 25%–75% (v/v) ethanol–water and dioxane–water mixtures potentiometrically in the temperature range 25–40 °C, in presence of 0.5 M KCl. The values of the enthalpy change ΔH ($\mathrm{kJ\,mol^{-1}}$), entropy change ΔS ($\mathrm{J\,K^{-1}\,mol^{-1}}$) and the free energy change ΔG ($\mathrm{kJ\,mol^{-1}}$) of these compounds were evaluated at 25 °C. The data were explained from the electronic character of the substituent.

1. Introduction

N-Heterocyclic compounds containing amide linkage are widely used in medicine, principally as hypnotic drugs and produce depressive effects on the central nervous system [1]. The therapeutic applications of barbituric and thiobarbituric acids are reported [2, 3]. Most of the pyrimidines are with antimicrobial, anti-inflammatory and antitumoral activities [2, 3]. Guanidine or its salts is treated with barbituric and thiobarbituric acids or their derivatives to give guanidine barbiturate and thiobarbiturate which are used as fire proofing agents for plastics, polyamides, polyurethane or polyacrylonitrile [4]. Serum lipid peroxidation was measured by thiobarbituric acid reactive material method during physical exercise of different duration [5]. Azo compounds are concerned with a number of important biological reactions such as protein synthesis inhibition cytostatic, carcinogenesis, azo reduction mono-amine oxidase inhibition mutagenic, immunochemical affinity labeling, nitrogen fixation and act as alkylating

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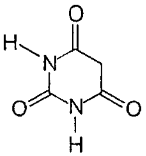
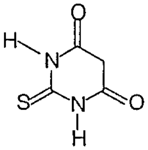
agents with carcinogenic properties where they induce tumors in rats [6–8] and possess inhibitory effects on the biosynthesis of DNA, RNA and proteins [9]. In our laboratory, Masoud *et al.* [10–46] published a series of papers to throw light on the chemistry of azo pyrimidine compounds and their complexes. The 5-(substituted phenylazo) barbituric and thiobarbituric acids are studied through this paper. The main purpose is three-folds:

(i) evaluation of the acid dissociation constants potentiometrically in 25%–75% (v/v) ethanol–water and dioxane–water mixtures,
(ii) explanation of the mechanism of dissociation from solvation and aquation views,
(iii) evaluation of the thermodynamic parameters. The data are discussed from the electronic character of the substituent and the nature of the hydrogen bond views.

2. Experimental

Barbituric(I) and thiobarbituric acids(II) were obtained from BDH. Dyestuff chromogenic azo barbituric and thiobarbituric acids (III, IV) were prepared by the usual diazotization process [47]. The corresponding amines (0.1 mole) were dissolved in 0.2 mole HCl and 25 ml distilled water. The hydrochloride compounds were diazotized below 5 °C with 0.1 mole $NaNO_2$ solution and 20 ml distilled water. The diazonium chlorides were coupled with an alkaline solution (0.1 mole NaOH) of barbituric and thiobarbituric acids. The crude dyes were filtered and were crystallized from ethanol. The analytical data done at the Central Laboratory, Faculty of Science, Alexandria University, Egypt, are given in Table 1.


(I)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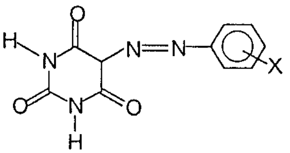
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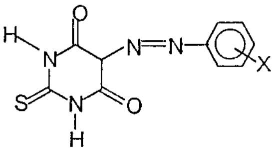

(IV)

X= H,3-CH$_3$,3-Cl,4-COOH X= H,2-Cl,3-Cl,4-COOH

Table 1. Analytical data for 5-(substituted phenylazo) barbituric and thiobarbituric acids*.

Compound	Colour	% Calculated (% Found)		
		H	C	N
5-(Phenylazo) barbituric acid	Yellowish green	3.4 (3.1)	51.7 (51.5)	24.1 (23.8)
5-(Phenylazo) thiobarbituric acid	Yellow	3.2 (3.0)	48.4 (48.6)	22.6 (22.8)
5-(*m*-Tolylazo) barbituric acid	Orange	4.0 (3.8)	53.7 (53.3)	22.8 (23.0)
5-(*m*-Chloro phenylazo) barbituric acid	Orange	2.6 (2.5)	45.0 (44.9)	21.0 (21.2)
5-(*p*-Chloro phenylazo) barbituric acid	Yellow	2.6 (2.8)	45.0 (44.8)	21.0 (20.8)
5-(*p*-Carboxy phenylazo) barbituric acid	Yellow	2.9 (3.0)	47.8 (47.5)	20.3 (20.2)
5-(*o*-Chloro phenylazo) thiobarbituric acid	Brown	2.5 (2.4)	42.5 (42.2)	19.8 (20.0)
5-(*m*-Chloro phenylazo) thiobarbituric acid	Yellowish brown	2.5 (2.3)	42.5 (42.3)	19.8 (19.5)
5-(*p*-Carboxy phenylazo) thiobarbituric acid	Yellow	2.7 (2.6)	45.2 (45.0)	19.2 (19.0)

* m.p for all compounds $> 300\,^{\circ}$C

Acidity and stability constants were determined by using acid-base titration technique. A standard 10^{-2} M KOH solution was prepared in CO_2 free distilled water. 0.5 M KCl was used as a supporting electrolyte. A stream of purified nitrogen gas was passed through the solution during the whole titration. BDH spectroscopic quality solvents (dioxane and ethanol) were used. The correction factor, δ, for measuring the pH values in different dioxane–water and ethanol–water concentration was calculated [48]. The δ values are -0.1 in the dioxane–water solvents in the concentration ranges 25%–50% and $+0.3$ in 75% concentration. These values are 0.05 and $+0.2$ in ethanol–water media, respectively. The dissociation constants of the organic compounds were determined by introducing 50 ml10^{-3} M of the organic compound into the titration cell in presence of 5 ml 0.5 M KCl solution and different %'s (v/v) of ethanol–water at different temperatures (25–45 °C). The same experiment was done in presence of different %'s (v/v) of dioxane–water at 25 °C. Cole Palmer pH-meter model 60 648 was used. The electrode system was calibrated before and after each titration using standard buffers of pH's 4.01 and 9.14. The titrations were carried out in 150 ml thermostated cell. The cell compartment was kept constant at the desired temperature using a thermostat model U10.

3. Results and discussion

The potentiometric measurements depend on the evaluation of the average number of protons associated with the ligand [49], $\bar{n}_A$. This was determined at different pH's using the simplified following equation [11].

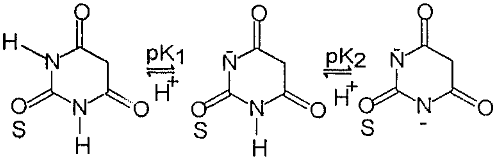
$$\bar{n}_A = Y - \frac{V_t N^\circ}{V_\circ C_L{}^\circ} \tag{1}$$

Where V_t denotes the volume of alkali required to reach a given pH on the titration curve, $V_\circ$ is the initial volume of the ligand, N° is the alkali concentration, $C_L{}^\circ$ is the total concentration of the ligand and Y is the number of displaceable hydrogen atoms in the ligand. The dissociation constants are obtained by plotting $\bar{n}_A$ against pH for the free ligands which gave two pK's values at $\bar{n}_A = 0.5$ and 1.5. The data are collected in Tables 2–5. The point-wise method [50] gave almost same values with 0.02 deviation.

The following points are recorded:

1. The pK values of barbituric and thiobarbituric acids are increased with increasing the % of the co-solvent ethanol in ethanol–water mixture and also with increasing the % of dioxane in dioxane–water mixture. Meanwhile, the values of pK for barbituric acid in the dioxane media are higher than that in the presence of the ethanolic media. The high polarity of ethanol facilitates the ionization of H^+ leading to a relative decrease in the pK values. In dioxane–water mixtures, increasing the dioxane % leads to increase the extent of intramolecular hydrogen bonding, retarding the ionization of H^+ leading to increase the pK values. For thiobarbituric acid, the pK values in 25% and 35% dioxane–water mixtures are lower than those in the presence of the same concentration of ethanol–water mixtures.
2. The compounds with *o*-, *m*- and *p*-chloro groups of the entitled series are with higher pK's values while the *p*-carboxy derivatives have lower pK's values probably due to that the carboxy group in the *p*-position can act as an electron acceptor rather than electron donor [51]. The electronegativity property of the substituent is a major factor for controlling the behaviour of these compounds. The pK values of 5-(substituted phenylazo) barbituric and thiobarbituric acids in presence of 75% (v/v) dioxane–water media are relatively higher than that in presence of 75% (v/v) ethanol–water media due to the high polarity of ethanol that facilitates the ionization of H^+ leading to increase in the pK values. 5-(*p*-carboxy phenylazo) derivatives of both barbituric and thiobarbituric acids gave three pK values in 75% (v/v) dioxane–water media while and two pK values in 75% (v/v) ethanol–

water media, Tables 4, 5. The scheme of ionization is represented as follows:



4. Thermodynamic parameters of ionization

The ΔG, ΔH and ΔS values are evaluated in the temperature range 25–45 °C, Tables 2–5. The equation $K = A\,\mathrm{e}^{-\Delta H/RT}$ is applied for studying the effect of temperature on the pK's values. Plotting the pK values versus $1/T$, straight lines are obtained with a slope of $\Delta H/2.3R$, from which the ΔH values ($\mathrm{kJ\,mol^{-1}}$) are computed. The free energy values ΔG ($\mathrm{kJ\,mol^{-1}}$) are calculated using the equation $\Delta G = 2.3RT$ pK. The ΔS ($\mathrm{J\,K^{-1}\,mol^{-1}}$) values are calculated from the relation $\Delta G = \Delta H - T\Delta S$. In general, the pK values are decreased with increasing temperature. The values of ΔH based on $\mathrm{pK_1}$ and $\mathrm{pK_2}$ values for barbituric acid are independent on the %'s of ethanol–water mixture. The sequence of ΔH values for the barbituric acid compounds based on the pK values decreases in the following order: m-Cl > H > p-Cl > m-$\mathrm{CH_3}$ $\cong$ p-COOH. Thus, the ΔH values of the barbituric acid compounds depend on the electronic requirements of the substituent. The values are increased with increasing electron-withdrawal property. The order of the ΔH values based on $\mathrm{pK_2}$ values is as follows: H $\cong$ p-Cl > m-Cl > m-$\mathrm{CH_3}$ > p-COOH, i.e. increased with increasing electron withdrawal property. The sequence of ΔH values for the series of thiobarbituric acid compounds computed from $\mathrm{pK_1}$ is as follows: m-Cl > o-Cl > H > p-COOH. However, those values based on $\mathrm{pK_2}$ are as follows: o-Cl > m-Cl > p-COOH > H. On the other hand, the ΔH values for the series of thiobarbituric acid compounds depend on the electronic character of the substituents rather than the steric hindrance of the group. The intramolecular hydrogen bonding gives rise to a positive entropy change whereas the hydrogen bonding to solvent leads to a higher degree of solvent ordering with a negative entropy change [52]. The ΔS values for barbituric acid in different %'s of ethanol–water mixture and for 5-(substituted phenylazo) barbituric acid in 75% ethanol–water media are attributed to the predominant presence of intermolecular hydrogen bonding. The same conclusions are obtained for thiobarbituric acid in different %'s of ethanol–water mixture and for 5-(substituted phenylazo) thiobarbituric acid in 75% ethanol–water media. The $+\Delta S$ for barbituric and thiobarbituric acids in aqueous media and 50% (v/v) ethanol–water proved the presence of both intramolecular and intermolecular hydrogen bonding [53].

Table 2. pK values and thermodynamic parameters of ionization of barbituric acid in ethanol–water and dioxane–water media.

Solvent	$\bar{n}$-pH					Point-wise method					$\Delta G_{25\,°C}$	$\Delta H_{25\,°C}$	$\Delta S_{25\,°C}$
	25 °C	30 °C	35 °C	40 °C	45 °C	25 °C	30 °C	35 °C	40 °C	45 °C	kJ mol^{-1}	kJ mol^{-1}	J K^{-1} mol^{-1}
aqueous solution	4.40 (9.94)	4.26 (9.48)	4.14 (9.73)	4.03 (9.67)	3.93 (9.57)	4.40 (9.93)	4.25 (9.84)	4.13 (9.72)	4.04 (9.67)	3.93 (9.56)	6.03 (13.63)	9.62 (7.95)	12.04 (−19.06)
25% (*v*/*v*) ethanol–water	4.42 (10.40)	4.38 (10.26)	4.31 (10.11)	4.26 (9.99)	4.17 (9.86)	4.43 (10.39)	4.39 (10.26)	4.32 (10.10)	4.27 (9.99)	4.17 (9.86)	6.06 (14.26)	5.85 (10.87)	−0.69 (−11.35)
35% (*v*/*v*) ethanol–water	4.67 (10.70)	4.58 (10.58)	4.53 (10.48)	4.48 (10.37)	4.41 (10.24)	4.66 (10.69)	4.60 (10.57)	4.56 (10.47)	4.48 (10.37)	4.41 (10.24)	6.40 (14.67)	5.44 (8.87)	−3.24 (−19.75)
50% (*v*/*v*) ethanol–water	4.84 (10.98)	4.75 (10.87)	4.65 (10.75)	4.54 (10.67)	4.45 (10.56)	4.84 (10.89)	4.74 (10.86)	4.64 (10.75)	4.55 (10.67)	4.46 (10.55)	6.63 (15.05)	8.78 (9.20)	7.21 (−19.64)
75% (*v*/*v*) ethanol–water	5.47 (11.50)	5.40 (11.39)	5.33 (11.28)	5.25 (11.18)	5.17 (11.07)	5.50 (11.50)	5.40 (11.39)	5.33 (11.27)	5.24 (11.18)	5.16 (11.07)	7.50 (15.76)	6.27 (9.20)	−4.11 (−22.03)
25% (*v*/*v*) dioxane–water	4.79 (10.58)	4.71 (10.46)	4.58 (10.35)	4.49 (10.26)	—	4.80 (10.58)	4.71 (10.46)	4.59 (10.34)	4.48 (10.26)	—	—	—	—
35% (*v*/*v*) dioxane–water	4.82 (10.85)	—	—	—	—	4.82 (10.85)	—	—	—	—	—	—	—
50% (*v*/*v*) dioxane–water	5.25 (11.64)	—	—	—	—	5.25 (11.47)	—	—	—	—	—	—	—
75% (*v*/*v*) dioxane–water	7.0 (13.14)	—	—	—	—	7.02 (13.14)	—	—	—	—	—	—	—

Values in parentheses are for pK_2.

Table 3. pK values and thermodynamic parameters of ionization of thiobarbituric acid in ethanol–water and dioxane–water media.

Solvent	$\bar{n}$-pH					Point–wise method					$\Delta G_{25\,°\mathrm{C}}$	$\Delta H_{25\,°\mathrm{C}}$	$\Delta S_{25\,°\mathrm{C}}$
	25 °C	30 °C	35 °C	40 °C	45 °C	25 °C	30 °C	35 °C	40 °C	45 °C	kJ mol^{-1}	kJ mol^{-1}	J K^{-1} mol^{-1}
aqueous solution	3.86 (9.65)	3.70 (9.55)	3.60 (9.46)	3.50 (9.33)	3.41 (9.20)	3.86 (9.65)	3.70 (9.54)	3.59 (9.45)	3.49 (9.32)	3.41 (9.19)	5.29 (13.23)	8.36 (9.20)	10.31 (−13.52)
25% (*v*/*v*) ethanol–water	3.98 (10.17)	3.86 (10.05)	3.78 (9.90)	3.65 (9.72)	3.50 (9.62)	3.99 (10.17)	3.86 (10.05)	3.79 (9.90)	3.66 (9.72)	3.50 (9.61)	5.46 (13.94)	8.78 (11.71)	11.16 (−7.49)
35% (*v*/*v*) ethanol–water	3.99 (10.50)	3.90 (10.40)	3.83 (10.29)	3.77 (10.15)	3.71 (10.09)	3.97 (10.50)	3.91 (10.40)	3.83 (10.28)	3.78 (10.15)	3.71 (10.09)	5.47 (14.39)	5.02 (8.78)	−1.51 (−18.83)
50% (*v*/*v*) ethanol–water	4.08 (10.53)	3.98 (10.41)	3.92 (10.35)	3.85 (10.21)	3.78 (10.13)	4.09 (10.52)	3.98 (10.40)	3.92 (10.34)	3.86 (10.20)	3.78 (10.12)	5.59 (14.43)	5.85 (8.36)	0.88 (−20.37)
75% (*v*/*v*) ethanol–water	4.27 (10.75)	4.13 (10.64)	3.98 (10.55)	3.88 (10.46)	3.81 (10.40)	4.27 (10.74)	4.14 (10.64)	3.98 (10.54)	3.88 (10.45)	3.82 (10.41)	5.85 (14.74)	10.45 (7.95)	15.44 (−22.79)
25% (*v*/*v*) dioxane–water	3.87 (10.20)	3.80 (10.11)	3.70 (10.01)	3.61 (9.88)	—	3.89 (10.19)	3.80 (10.11)	3.71 (10.01)	3.62 (9.88)	—	—	—	—
35% (*v*/*v*) dioxane–water	3.92 (10.54)	—	—	—	—	3.93 (10.54)	—	—	—	—	—	—	—
50% (*v*/*v*) dioxane–water	4.26 (11.23)	—	—	—	—	3.93 (11.23)	—	—	—	—	—	—	—
75% (*v*/*v*) dioxane–water	5.44 (12.66)	—	—	—	—	4.62 (12.65)	—	—	—	—	—	—	—

Table 4. pK values of 5-(substituted phenylazo) barbituric acid in 75% (v/v) ethanol–water and 75% (v/v) dioxane–water media.

Compound	75% (v/v) ethanol–water								75% (v/v) dioxane–water		$\Delta G_{25\,^{\circ}\mathrm{C}}$ kJ mol^{-1}	$\Delta H_{25\,^{\circ}\mathrm{C}}$ kJ mol^{-1}	$\Delta S_{25\,^{\circ}\mathrm{C}}$ J K^{-1} mol^{-1}
	$\bar{n}$-pH				Point-wise method				$\bar{n}$-pH	Point-wise method			
	25 °C	30 °C	35 °C	40 °C	25 °C	30 °C	35 °C	40 °C					
5-(phenylazo) barbituric acid	9.11 (11.20)	8.99 (11.10)	8.90 (10.97)	8.82 (10.89)	9.12 (11.20)	8.99 (11.10)	8.89 (10.97)	8.82 (10.89)	10.10 (13.39)	10.1 (13.39)	12.49 (15.35)	8.78 (8.78)	−12.44 (−22.05)
5-(*m*-tolylazo) barbituric acid	9.02 (11.93)	8.94 (11.31)	8.85 (11.23)	8.78 (11.14)	9.02 (11.39)	8.94 (11.31)	8.85 (11.23)	8.78 (11.14)	10.01 (13.23)	10.01 (13.23)	12.36 (15.61)	6.69 (7.11)	−19.04 (−28.54)
5-(*p*-carboxy phenylazo) barbituric acid	8.55 (11.14)	8.46 (11.07)	8.40 (11.00)	8.30 (10.94)	8.55 (11.14)	8.47 (11.07)	8.41 (11.00)	8.30 (10.94)	6.96 (10.68) (12.96)	6.96 (10.68) (12.96)	11.72 (15.27)	6.69 (5.44)	−16.88 (−33.00)
5-(*p*-chloro phenylazo) barbituric acid	10.91 (11.49)	10.80 (11.41)	10.71 (11.32)	10.63 (11.21)	10.90 (11.49)	10.80 (11.42)	10.70 (11.32)	10.64 (11.21)	12.18 (13.46)	12.18 (13.46)	14.97 (15.75)	7.13 (8.87)	−26.21 (−23.39)
5-(*m*-chloro phenylazo) barbituric acid	10.32 (11.32)	10.20 (11.24)	10.10 (11.06)	9.96 (11.00)	10.30 (11.32)	10.18 (11.24)	10.02 (11.06)	9.96 (10.99)	9.60 (13.15)	9.60 (13.15)	14.15 (15.52)	10.04 (8.36)	−13.79 (−24.01)

Table 5. pK values of 5-(substituted phenylazo) thiobarbituric acid in 75% (v/v) ethanol–water and 75% (v/v) dioxane–water media.

Compound	75% (v/v) ethanol–water								75% (v/v) dioxane–water		$\Delta G_{25\,^\circ\mathrm{C}}$ kJ mol^{-1}	$\Delta H_{25\,^\circ\mathrm{C}}$ kJ mol^{-1}	$\Delta S_{25\,^\circ\mathrm{C}}$ J K^{-1} mol^{-1}
	$\bar{n}$-pH				Point-wise method				$\bar{n}$-pH	Point-wise method			
	25 °C	30 °C	35 °C	40 °C	25 °C	30 °C	35 °C	40 °C					
5-(phenylazo) thiobarbituric acid	8.62 (11.22)	8.45 (11.12)	8.45 (11.03)	8.36 (10.93)	8.62 (11.22)	8.55 (11.13)	8.47 (11.02)	8.38 (10.93)	9.26 (12.70)	9.26 (12.71)	11.82 (15.38)	7.11 (7.95)	−15.80 (−24.95)
5-(*o*-chloro) barbituric thiobarbituric acid	8.40 (11.57)	8.27 (11.45)	8.15 (11.33)	8.03 (11.17)	8.40 (11.55)	8.28 (11.44)	8.14 (11.33)	8.03 (11.16)	9.11 (12.91)	9.11 (12.89)	11.51 (15.86)	10.04 (11.71)	−4.96 (−13.93)
5-(*m*-chloro phenylazo) thiobarbituric acid	8.88 (11.24)	8.71 (11.11)	8.51 (10.98)	8.83 (10.87)	8.90 (11.24)	8.72 (11.12)	8.49 (10.96)	8.38 (10.88)	8.92 (12.54)	8.92 (12.55)	12.17 (15.41)	13.80 (10.04)	5.46 (−18.02)
5-(*p*-carboxy phenylazo) thiobarbituric acid	8.57 (11.88)	8.50 (11.75)	8.44 (11.76)	8.35 (11.56)	8.54 (11.88)	8.50 (11.73)	8.42 (11.54)	8.33 (11.54)	6.64 (9.15) (12.47)	6.48 (9.16) (12.64)	11.75 (16.29)	6.27 (8.78)	−18.37 (−25.18)

Values in parentheses are for pK_2.

In the following, the effect of ethanol and dioxane solvents on the behaviour of such compounds is explained from another view. Assume that the j factor, representing a solvent-transfer number characteristic of the tested chemical reaction, can be attributed to the transfer of the solvent. The following relation is tested [54, 55].

$$(j\ \log[\mathrm{S}]+\log K^{*})-\log K=-\Delta Gt(2.303RT)-W\ \log([\mathrm{H_2O}]_\mathrm{s}/[\mathrm{S}])$$
$$+\,j\ \log[\mathrm{H_2O}]$$
$$\text{Where}\quad \log[\mathrm{H_2O}]_\mathrm{s}/[\mathrm{S}]=X\ ;\quad (j\ \log[\mathrm{S}]+\log K^{*})-\log K=Y.$$

[S] and ΔG represent the solvent concentration and the free energy, respectively. $[H_2O]$, $[H_2O]_s$ are the concentration of water, and that of the co-solvent molecule. Y is plotted against X. Trail values of $j = 1, 2, 3, 4, \ldots$ are used to find values of W for the gradients of Y vs. X. Fig. 1 is taken as a representative example. Table 6 includes the slopes of the X–Y relation to give the values for water in the molecules (W). The obtained data may throw light on the role of aquation and solvation during the course of dissociation. For barbituric acid in different %'s of ethanol–water mixtures, the W values for $j = 1$ and $j = 2$ at temperatures from 25–45 °C are higher than that of j values to pinpoint more aquation by increasing the temperature. The values of W are smaller than that of $j = 3$ and $j = 4$ which suggests more solvation. In the temperature range from 35–45 °C, the values of W for different values of j from 1 to 4 are nearly constant which means that the aquation process is independent on temperature. For barbituric acid in different %'s of ethanol–water mixtures at 25 °C, the W values are greater than that the values of j which suggest more aquation. For thiobarbituric acid in different %'s of ethanol–water, the W values are higher than that of j which suggests more aquation. As a result, the effect of solvent is of major importance in aquation and solvation during the dissociation.

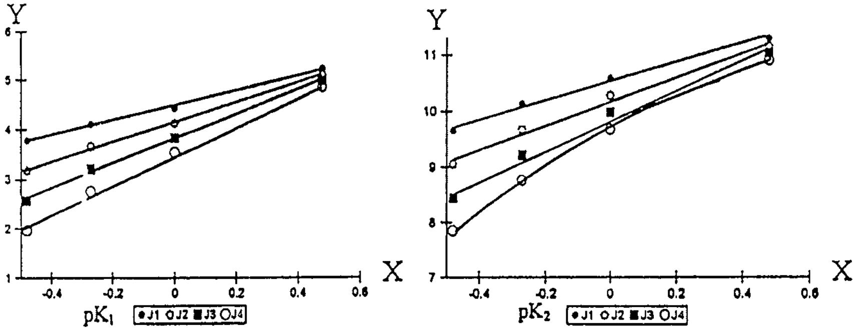


Fig. 1. X–Y relationship for pK_1 and pK_2 of barbituric acid in different %'s of ethanol–water at 25 °C.

Table 6. Values of (W) in ethanol–water at (25–45 °C) and in dioxane–water at 25 °C for different values of (j).

Temperatures	Barbituric acid				Thiobarbituric acid			
	$j=1$	$j=2$	$j=3$	$j=4$	$j=1$	$j=2$	$j=3$	$j=4$
25 °C	1.67 (1.65)	2.08 (2.03)	2.60 (2.48)	3.13	0.80	1.29	1.80	2.29
30 °C	1.56 (1.67)	1.98	2.40	2.92	0.78	1.27	1.78	
35 °C	1.56 (1.52)	2.05	2.56	3.05	0.71	1.25		
40 °C	1.53 (1.74)	2.02	2.53	3.02				
45 °C	1.54	2.03	2.54	3.00				
dioxane–water at 25 °C			(4.17)	(4.66)	(3.06)	(3.55)	3.14 (4.06)	3.63 (4.55)

Values in parentheses are for pK_2.

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