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TEMPERATURE AND SUBSTITUENT EFFECTS ON THE DISSOCIATION CONSTANTS OF SOME 5-(*p*-SUBSTITUTED PHENYLAZO) BARBITURIC ACID COMPOUNDS

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ABSTRACT

The dissociation constants of the title compounds were determined potentiometrically in the range 25–40 °C. The thermodynamic quantities ΔH, ΔG and ΔS were evaluated. The variation in the pK values were ascribed to the differences in the chemical potentialities of the substituents. The imide–imidol tautomerism in the barbituric acid nuclei was visualized. Trials to correlate the values of pK with ν(N=N) were made.

INTRODUCTION

The azo group has great interest for various reasons. It gains much attention for use as models of biological systems [1], antifungals [2,3] and dyes. Furthermore, the azo compounds occupy an important position as analytical reagents [4–6]. As an extension to our area of interest with the azo system [7–12], and because of the pronounced chemotherapeutic importance [13,14] of barbituric acid, it seemed desirable to undertake this investigation. The dissociation constants were evaluated potentiometrically at different temperatures to calculate the thermodynamic parameters. The data were explained in the light of molecular structure of the compounds.

EXPERIMENTAL

Barbituric acid was of Koch–Light grade. The 5-(*p*-substituted phenylazo)barbituric acids were prepared by dissolving the corresponding amines (0.1 mole) in HCl (0.2 mole per 25 ml distilled water) and diazotizing below 5 °C with a solution of $NaNO_2$ (0.1 mole per 30 ml distilled water). The

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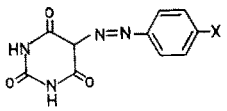
TABLE 1

The crystallizing solvents

Substituent	Solvent
$-CH_3$, $-OCH_3$, $-Cl$ and $-NO_2$	Acetic acid
$-Br$	Dioxane
$-SO_3H$	Methanol

diazonium chlorides were coupled with an alkaline solution of barbituric acid (0.1 mole) [15]. The crude azo dyes were separated by filtration, crystallized and then dried in a vaccum desiccator over P_2O_5. The crystallizing solvents are shown in Table 1.

A general skeleton for the azo compounds prepared was as follows



$X = -CH_3, -OCH_3, -Cl, -Br, -NO_2, -SO_3H.$

Instruments and reagents

The pH measurements were made using a Pye Unicam pH-Meter Model 291 MK_2. The electrode system was calibrated before and after each series of pH measurements under the same conditions using standard buffer of pH 4.0 and 9.0. The calibration of pH was also done by direct titration of 10^{-3} M HCl with 0.1 M KOH in the presence of 0.05 M KCl as supporting electrolyte. The titration cell consisted of a water-jacketed 150 ml cell fitted with a polyethylene stopper with appropriately located holes, one of them allowing the insertion of a 10 ml microburette accurate to 0.02 ml. The burette was filled by gentle suction exerted by a water pump. Another hole was used to insert the combined electrode. There were holes for the entry and exit of purified nitrogen to eliminate CO_2 dissolved in the medium throughout the course of titration. The pH titration was carried out in 50% (v/v) dioxane–water media, to evaluate pK values for the ligands in the range 25–40 °C; the data were used to calculate their thermodynamic quantities. In these titrations, 5 ml of 10^{-2} M ligand solution was introduced into the titration cell followed by 5 ml of 0.5 M KCl solution as ionic background, made up to 50 ml and titrated against standard KOH at the desired temperature. The constant temperature value was achieved by using a thermostatic device model (Ultra Thermostat U-10, GDR). The accuracy

TABLE 2

The pK values and thermodynamic parameters of 5-(p-substituted phenylazo) barbituric acid compounds in 50% (v/v) dioxane–water media at 25 °C

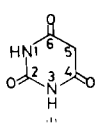
Substituent	pK				ΔG (kcal. mol^{-1})	ΔH (kcal. mol^{-1})	ΔS (eu)
	25 °C	30 °C	35 °C	40 °C			
$-CH_3$	6.05	5.95	5.85	5.75	8.29	8.36	+0.23
$-OCH_3$	9.85	9.75	9.65	9.55	13.50	8.36	−17.25
$-Cl$	9.30	9.20	9.10	9.00	12.75	8.36	−14.71
$-Br$	9.00	8.90	8.80	8.70	12.34	8.36	−13.34
$-NO_2$	8.40	8.30	8.20	8.10	11.51	8.57	−9.88
$-SO_3H$	9.70	9.60	9.50	9.40	13.30	8.36	−16.55

of the temperature measurements was ±0.5 °C. The values of the pH meter reading were corrected using the method described [16,17].

The KBr-IR spectra of the ligands were recorded on an Sp 1025 Pye Unicam Spectrophotometer covering the range 3800–625 cm^{-1}.

RESULTS AND DISCUSSION

The pK values of the ligands were determined in the temperature range 25–40 °C in presence of 0.5 M KCl as a supporting electrolyte. The values of the enthalpy, ΔH (kcal mol^{-1}), of the ionization were determined by plotting pK versus $1/T$; straight lines were obtained with a slope $\Delta H/2.3R$. The free energy, ΔG (kcal mol^{-1}), was calculated from the relation $\Delta G = 2.3RT\text{p}K$, whereas the entropy term ΔS (eu) is given as $\Delta G = \Delta H - T\Delta S$. The data are collected in Table 2. The pK values were obtained from the formation curve constructed by plotting $\bar{n}_A$ (average number of protons associated with the ligand) against the pH of a solution corresponding to each addition of the alkali [18]. Concordant results were obtained on applying the point-wise calculation [8,19]. Different structures have been proposed for explaining the acidic nature of barbituric acid. The more representative structures are I and II. The former was favoured where methylation of 2,4,6-trihydroxy pyrimidine (II) with CH_3I in the presence of alkali results in the formation of the N-methyl derivative.



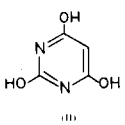
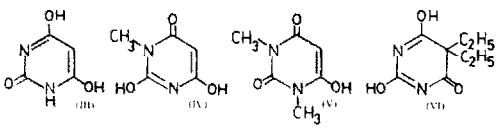


TABLE 3

pK values of barbituric acid and some of its derivatives

	pK_1	pK_2	Enolization
Barbituric acid (III)	3.90	12.5	5,4; 1,6
1-Methyl barbituric acid (IV)	4.20	12.8	5,4; 3,2
1,3-Dimethyl barbituric acid (V)	4.60	–	5,4
5,5-Diethyl barbituric acid (VI)	7.85	12.1	1,6; 3,2

The pK values of barbituric acid and some of its derivatives are given in Table 3 [20,21].



The mode of ionization for barbituric acid [22] (pK = 4.01) was suggested to be initiated by a proton transfer of the active methylene group in position 5 to the neighbouring carbonyl group to give the corresponding –OH group which is subjected to deprotonation.

For the azo series, the electron donating substituents $-CH_3$ and $-OCH_3$ gave pK values of 6.05 and 9.85 respectively, and the electron attracting substituents $-NO_2$, –Br, –Cl and $-SO_3H$ gave pK values of 8.40, 9.0, 9.3 and 9.70 respectively. These high pK values relative to that of barbituric acid could be explained as below.

(i) The great bulk of the *p*-substituted phenylazo group in position 5 may sterically hinder the displacement of the active proton to oxygen in position 4 (5,4 enolization), leading to acid weakening (i.e. higher pK values).

(ii) The stereochemical hindrance of the substituent in position 5 is great enough to bring about 1,6 or 3,2 enolization which is more favourable with pK values between 7.85 and 12.50.

The decrease of the pK value from the *p*-Cl to *p*-Br compounds could be attributed to the electronegativity differences between both. The strong electron attracting $-NO_2$ group affected the smallest pK value (8.40). The electronic withdrawal character of the $-SO_3H$ group is completely diminished. Hence, steric effects may twist this group out of planarity with the rest of the molecule. The pK–σ Hammett relationship [23] gives a straight line including $-OCH_3$, –Cl, –Br and $-NO_2$ groups (Fig. 1) whereas the $-SO_3H$ and $-CH_3$ groups are out of line. More support of the suggestion that the effect of $-SO_3H$ is completely suppressed is obtained when the σ-value of the $-SO_3H$ group is substituted by that of H (0.0) which, corresponding to the pK value of 9.70, will lie on the straight line of the pK–σ relationship. The lower pK value of the *p*-CH_3 compound and its

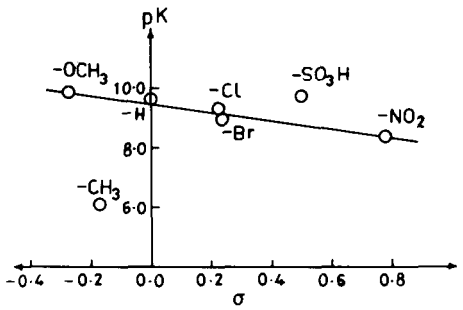
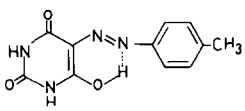


Fig. 1. pK–σ Hammett relationship.

departure from the linear pK–σ relationship (Fig. 1) suggests that its ionization (5,4) is more favourable.

The IR spectra of these compounds showed a broad band in the vicinity of (3570–3450 cm^{-1}) which could be assigned to ν(OH) in an intramolecular hydrogen bond [1]. The lower frequency of the ν(N–H) band (3260–3050 cm^{-1}) which was shifted from its normal position (3460–3400 cm^{-1}) points to the presence of intramolecular hydrogen bonds of the type OH · · · N



The strong band lying between 1410 and 1460 cm^{-1} is due to ν(N=N). The formation of hydrogen bonds between the hydroxylic protons in positions 6 and 4 and the basic azo group explains their stabilities. The pK–ν(N=N) relation indicates that the nature of the substituent has no assignable influence on ν(N=N) due to the weak basicity of the azo group [24].

From Table 2, the following conclusions are drawn.

(i) The pK values are decreased as the temperature increased (i.e. acid strengthening effect) independent of the nature of the substituent.

(ii) All the azo ligands have positive ΔH values with the same magnitude (8.36 kcal mol^{-1}) except the p-NO_2 compound which has a higher value (8.57 kcal mol^{-1}). The same value of ΔH progressively indicates that the entropy term, ΔS contributes significantly to the free energy changes. The slightly higher ΔH value for the $-NO_2$ compound (i.e. more energy is needed for dissociation) implies the probable existence of intermolecular hydrogen bonds of the type OH · · · O. The larger ΔS value (− 9.88 e.u.) given for the $-NO_2$ compound indicates less ordering of solvent molecules upon dissociation leading to greater association [24].

(iii) All the azo compounds have negative ΔS values except in the case of the p-CH_3 compound.

In general, the intramolecular hydrogen bond gives rise to a positive entropy change, whereas the hydrogen bond to solvent promotes a higher degree of solvent ordering and gives rise to a negative entropy change. Hence, positive ΔS values suggest the formation of intramolecular hydrogen bonds, while the formation of intermolecular hydrogen bonds gives rise to negative ΔS values [25].

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