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Note

TEMPERATURE AND SUBSTITUENT EFFECTS ON THE IONIZATION OF SOME DISUBSTITUTED ARYLAZO BARBITURIC AND THIOBARBITURIC ACID COMPOUNDS

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The dissociation constants for the 5-(disubstituted phenylazo)-barbituric and -thiobarbituric acid compounds were determined potentiometrically over the temperature range 25–40 °C, in the presence of 0.3 M KCl and 50% v/v dioxane–water. The values of the enthalpy ΔH (kcal mol^{-1}), entropy ΔS (e.u.) and the free energy ΔG (kcal mol^{-1}) of these compounds were evaluated at 25 °C. The ΔH values of the compounds are affected by the electronic character of the substituents, controlled by the ortho effect and by steric hindrance of the groups. The type of hydrogen bonding present is determined from the sign of ΔS [1].

INTRODUCTION

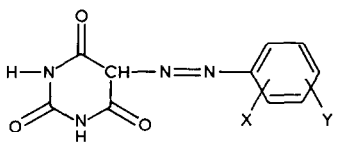
The barbiturates and the thiobarbiturates are classified as substituted pyrimidines and are components of the biologically important nucleic acids. They have been shown to exert a pronounced physiological effect [3–5]. In general, barbiturates and thiobarbiturates are widely used in medicine as hypnotic drugs, especially for their depressive effects on the central nervous system [6]. 5-(Phenylazo)barbituric acid has clear anticonvulsive effects which are absent in the corresponding barbiturates. Azo dyes form the largest group of synthetic dyestuffs and feature prominently in many types of application. The azo group is involved in a number of important biological reactions such as protein synthesis inhibition, carcinogenesis and azo reduction monoamine oxidase inhibition. Some azo compounds are used for histochemical detection of compounds containing–SH groups [8].

Equilibrium studies have led to the proposal that the 5,6 enol structure is involved in the ionization of barbituric and thiobarbituric acids [9]. In this study, the thermodynamic dissociation constants of ionization of 5-(disubstituted phenylazo)-barbituric and -thiobarbituric acid compounds with

different substituents possessing different polar and steric effects are evaluated.

EXPERIMENTAL

The ligands were prepared by diazotization of barbituric and thiobarbituric acid [10]. The general formula of the azo compounds prepared is illustrated below.



The starting amines used were 2,4-dichloro-, 2,5-dichloro-, 2,4-dinitro-, 2,5-dimethyl-, 2-methyl-4-chloro- and 2-nitro-4-methyl-aniline.

The potentiometric measurements were carried out using a Radiometer pH-meter model PHM 62 fitted with a combined glass electrode (type GK 2401 C). The pH-meter was calibrated by standard Radiometer buffers having pH values of 4.0 and 7.0. The instrument was accurate to 0.01 pH unit. The titrations were carried out in a 150 ml thermostated cell. Carbonate-free potassium hydroxide titrant (0.01 M) was added in small amounts from a micro-burette. During the whole titration, purified nitrogen gas was slowly bubbled into the solution. The nitrogen gas was purified by being passed through a chain of bubblers containing, in succession, vanadium solution (to remove any traces of oxygen), copper sulphate solution and alkaline pyrogallol (to remove oxygen). The gas was then passed through a tube containing calcium chloride to remove moisture and CO_2.

The pH-metric titration was carried out in (50% v/v) dioxane–water media to evaluate the dissociation constants of the azo compounds over the temperature range 25–40 °C, and the data were used to calculate the thermodynamic quantities. In these titrations, 5 ml of a 10^{-3} M azo compound solution were introduced into the titration cell followed by 3 ml of 0.5 M KCl to increase the ionic strength, the solution was made up to 50 ml and titrated against standard KOH at the desired temperature. The solution in the titration cell was left for about 15 min to attain the desired constant temperature, which was achieved using a thermostatic device (model Ultra thermostate U-10, GDR). The pH-meter reading B recorded in 50% v/v dioxane–water was converted to hydrogen ion concentration $[H^+]$ by means of the widely used relation of van Uitert and Haas [10], namely

$$-\log[H^+] = B + \log U_H$$

where U_H is the correction factor for the particular solvent composition and ionic strength at which B is read.

RESULTS AND DISCUSSION

The potentiometric titration of the compounds investigated against NaOH in the presence of 0.03 M KCl as a supporting electrolyte at different temperatures was studied over the temperature range 25–40 °C. The pK values of these compounds were evaluated according to a published procedure [11]. The following points are apparent.

(i) The pK values decrease with increasing temperature except for that of the 5-(2,5-dichlorophenylazo)barbituric acid compound where the pK values increase with increasing temperature.

(ii) The familiar equation $K = A\ e^{-\Delta H/RT}$ can be applied for studying the effect of temperature on the pK values by reformulating it to give

$$pK = \frac{\Delta H}{2.3RT} + \text{constant}$$

On plotting the pK values versus $1/T$, straight lines are obtained with a slope of $\Delta H/2.3R$, from which the ΔH values (kcal mol^{-1}) are computed (Tables 1 and 2).

(iii) The free energy values ΔG (kcal mol^{-1}) are calculated using the equation

$$\Delta G = 2.3RTpK$$

TABLE 1

Thermodynamic parameters of ionization of 5-(disubstituted arylazo)barbituric acid

Substituents	pK_1/pK_2					ΔG at 25 °C (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔS at 25 °C (e.u.)
	20 °C	25 °C	30 °C	35 °C	40 °C			
2,4-dichloro-	7.12	7.05	6.95	6.87	–	9.60	7.18	8.12
	(8.85)	(8.66)	(8.42)	(8.22)	–	(11.79)	(18.28)	(21.70)
2,5-dichloro-	6.85	7.0	7.20	7.3	–	9.53	13.3	12.6
	(8.32)	(9.0)	(9.42)	(9.32)	–	(12.26)	(45.71)	(11.2)
2-methyl-4-chloro-	–	7.1	6.96	6.70	6.6	9.67	16.15	21.74
	–	(9.10)	(8.60)	(8.10)	(7.8)	(12.39)	(38.47)	(87.5)
2-nitro-4-methyl-	–	7.25	7.07	6.90	6.80	9.87	12.92	10.23
		(8.95)	(8.58)	(8.20)	(7.95)	(12.19)	(29.09)	(56.7)
2,5-dimethyl-	–	7.20	6.95	6.65	6.44	9.81	22.39	42.2
		(9.35)	(8.80)	(8.33)	(7.9)	(12.73)	(45.2)	(10.90)

TABLE 2

Thermodynamic parameters of ionization of 5-(disubstituted arylazo)thiobarbituric acid

Substituents	pK_1/pK_2					ΔG at 25 °C (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔS at 25 °C (kcal mol^{-1})
	20 °C	25 °C	30 °C	35 °C	40 °C			
2,5-dichloro-	–	6.77	6.63	6.5	6.67	9.22	11.87	8.88
	–	(8.9)	(8.77)	(8.62)	(8.87)	(12.12)	(11.65)	(−1.64)
2-methyl-4-chloro-	–	6.55	6.45	6.38	6.30	8.92	7.54	−4.6
	–	(8.16)	(7.99)	(7.84)	(7.75)	(11.11)	(11.43)	(1.05)
2-nitro-4-methyl-	–	6.83	6.75	6.59	6.4	15.43	15.43	20.5
	–	(8.9)	(8.55)	(8.4)	(8.15)	(12.12)	(13.77)	(5.5)
2,5-dimethyl-	–	7.17	7.00	6.87	6.65	9.77	14.22	14.9
	–	(9.5)	(9.1)	(8.67)	(8.2)	(12.94)	(36.56)	(79.26)

(iv) The ΔS (e.u.) values are calculated using the relation

$$\Delta G = \Delta H - T\Delta S$$

(v) The sequence of ΔH values for the series of barbituric acid compounds (based on the pK_1 values) decreases in the following order of the substituents: 2,5-di-CH_3 > 2-CH_3-4-Cl > 2,5-di-Cl ≈ 2-NO_2-4-CH_3 > 2,4-di-Cl. The ΔH values of the barbituric acid compounds thus depend on the electronic requirements of the substituents. The values increase with increasing electron donation by the substituents and decrease with increasing electron withdrawal. However, the order for the ΔH values based on pK_2 values is as follows: 2,5-di-Cl ≥ 2,5-di-CH_3 > 2-CH_3-4-Cl > 2-NO_2-4-CH_3 > 2,4-di-Cl. On the other hand, the sequence of ΔH values for the series of thio compounds computed from pK_1 is as follows: 2-NO_2-4-CH_3 > 2,5-di-CH_3 > 2,5-di-Cl > 2-CH_3-4-Cl. However, the order for the ΔH values based on the pK_2 values is as follows: 2,5-di-CH_3 > 2-NO_2-4-CH_3 > 2,5-di-Cl ≈ 2-CH_3-4-Cl. From the sequence of ΔH values of the thio compounds, the following conclusions are reached. The ΔH values for the series of thio compounds depend on the electronic character of the substituents, which is influenced by the ortho effect and by steric hindrance of the groups, in the following manner: 2-NO_2-4-CH_3 > 2-CH_3-4-Cl. This order is attributed to the property of the O–CH_3 group which is larger than the O–NO_2 group. This hinders hydrogen bond formation, giving more acidity (smaller pK values and smaller ΔH values).

The positive ΔS values for the barbituric acid compounds indicate the presence of intramolecular hydrogen bonds [1], and the negative ΔS values for the thio compounds are attributed to the predominant presence of intermolecular hydrogen bonding.

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