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Thermodynamical study on the formation of some bivalent metal complexes of biologically active *N*,*N*′-di-*p*-tolyl-5-nitro-2-thiobarbituric acid (DTNTBA) in aqueous solutions

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Abstract

Thermodynamic proton–ligand stability constants of *N*,*N*′-di-*p*-tolyl-5-nitro-2-thiobarbituric acid (DTNTBA) and the thermodynamic metal ligand stability constants of complexes of DTNTBA with some bivalent metal ions were determined by potentiometric measurements in 75% (v/v) aqueous dioxan medium at different temperatures, ranging from 20 to 50°C. The order of stability constants was found to be $Cu^{2+} > Ni^{2+} > Co^{2+} > Zn^{2+} > Cd^{2+} > Mn^{2+} > Mg^{2+}$. The values of S_{min} (χ^2) have also been calculated. The thermodynamic functions along with the error range for the stepwise complexation processes were calculated at 20°C (error range ±0.5°C). The process is predominantly an enthalpy-driven process.

Keywords: DTNTBA; Ligand; Proton–ligand stability; Stability constant

1. Introduction

Thiobarbiturates are among the drugs used frequently in toxicology. Various simple or N-substituted thiobarbiturates possess hypnotic, anaesthetic, intravenous narcotic and antibacterial activity [1–4]. They are classified as ultrashort acting, attaining maximal concentration in the brain in <30 s after intravenous administration [5]. The widespread interest in thiobarbiturates is largely due to their

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pharmacological activity which, in turn, is due mainly to their enhanced lipid solubility compared with that of the corresponding parent barbiturates [6].

1,3-Di-aryl-5-substituted-2-thiobarbituric acids show considerable anti-inflammatory activity but less toxicity [7]. Derivatives having one methyl group each in both phenyl rings are capable of the prevention and therapy of diseases caused by viruses [8]. 5-Substituted derivatives on screening were found to be useful as insecticides, acricides, nematocides, molluscicides and agricultural fungicides [9].

Keeping in view the importance of 2-thiobarbiturates in therapy, as well as in the textile industry [10], and encouraged by the findings of an extended study undertaken by us on the thermal behaviour of metal complexes of biologically active ligands, we report here the results of pH-metric studies on the thermal stabilities of bivalent metal complexes with DTNTBA at different temperatures in 75% (v/v) aqueous dioxan medium.

2. Experimental

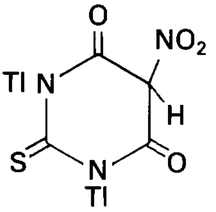
2.1. Apparatus

A digital pH-meter (ECIL, model pH 5653) with a combined glass electrode (0–14 pH range) was used for pH measurements. The pH-meter was standardised with potassium hydrogen phthalate and phosphate buffers before the performance of the titrations. All the measurements were made at a definite temperature which was maintained constant using an MLW (West Germany) (NBE type) thermostat. A personal computer PC/AT was used for most of the calculations.

2.2. Chemicals

N,N′-Di-*p*-tolyl-5-nitro-2-thiobarbituric acid (DTNTBA) was prepared in three steps. In the first step, *N,N′*-di-*p*-tolyl-thiourea was prepared from *p*-toluidine and carbon disulphide by the method given by Vogel [11]. In the second step, 1,3-di-*p*-tolyl-2-thiobarbituric acid was synthesised from the above-mentioned thiourea and malonic acid by refluxing the two with acetyl chloride on a steam bath for 20 min. After cooling and on addition of ice, the mixture gave the required light-yellow product which was recrystallised from acetic acid. In the third stage, the above-formed thiobarbituric acid (0.5 g) was dissolved in conc. H_2SO_4 (1 ml) and to this solution conc. HNO_3 (dl. 52, 0.25 ml) was added dropwise at room temperature. After 30 min, the reaction mixture was poured over crushed ice to yield DTNTBA. The compound was dull yellow in colour and had a decomposition temperature of 162°C. The purity of the product was checked by IR and ^1H NMR spectroscopy, TLC and elemental analysis.

On the basis of the above analysis and the spectral study of Miyazawa [12] and Ahluvalia et al. [13], structures I and II may be assigned to DTNTBA and its metal chelates.



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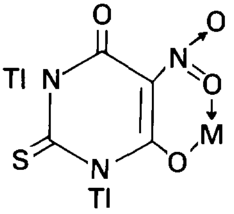

II

The solution of DTNTBA was prepared in freshly distilled dioxan. The solutions of bivalent metal ions, namely Cu(II), Ni(II), Co(II), Zn(II), Cd(II), Mn(II) and Mg(II), were standardised by conventional methods.

TMAH (Me_4NOH) (Merck) in 75% dioxan (aqueous) was used as titrant. The solution was standardised with oxalic acid, $(COOH)_2 \cdot 2H_2O$. Perchloric acid ($HClO_4$) was standardised with Na_2CO_3 and diluted to the required molarity (0.05 M). $NaClO_4$ (Merck) was used to maintain the ionic strength constant.

Dioxan (Merck) was freed from peroxide by refluxing it with sodium metal for 24 h and was freshly distilled over sodium before use. All other chemicals were of reagent grade.

2.3. *Titration technique*

Investigations were carried out at four temperatures, 20, 30, 40 and 50 ± 0.5°C at 0.02 M $NaClO_4$ ionic strength. For each set of experiments, the final volume was made up to 20 ml, maintaining the 75% aqueous dioxan medium. The following solutions (total volume 19.67 ml instead of 20 ml, due to volume contraction on mixing dioxan and water) was titrated potentiometrically against standard 0.05 M TMAH, in 75% aqueous dioxan (v/v) to determine $\bar{n}$ and p_L values of the complexes formed in the solution.

(1) 3.0 ml $HClO_4$ (0.05 M) + 0.2 ml $NaClO_4$ (2 M) + 0.5 ml KNO_3 or K_2SO_4 (0.02 M) + 1.3 ml H_2O (double distilled) + 15.0 ml dioxan;

(2) 3.0 ml $HClO_4$ (0.05 M) + 0.2 ml $NaClO_4$ (2 M) + 0.5 ml KNO_3 or K_2SO_4 (0.02 M) + 1.3 ml H_2O + 10.0 ml ligand solution (0.01 M) + 5.0 ml dioxan;

(3) 3.0 ml $HClO_4$ (0.05 M) + 0.2 ml $NaClO_4$ (2 M) + 0.5 ml metal solution (0.02 M) + 1.3 ml H_2O + 10.0 ml ligand solution (0.01 M) + 5.0 ml dioxan.

The titrations were carried out in a covered, double-walled glass cell in an atmosphere of nitrogen gas, which was pre-saturated with solvent (75% aqueous dioxan) before being passed into the titration vessel.

From the titration curves of solutions (1) and (2), the values of $\bar{n}_H$ were calculated at various pH values. The pK_a value of the ligand was found by plotting $\log(\bar{n}_H/1-\bar{n}_H)$ vs. pH and the values thus obtained were found to be 7.48, 7.31, 7.17 and 7.01 at 20, 30, 40 and 50°C respectively, with $\mu = 0.02$ M $NaClO_4$. From the titration curves of solutions (1), (2) and (3), $\bar{n}$ (the average number of ligand molecules bound per metal ion) values of the metal complexes were determined at various pH values and the corresponding p_L (the free ligand exponent) values were calculated, using the method of Bjerrum [14] and Calvin and Wilson [15] as modified by Irving and Rossotti [16]. The $\bar{n}$ and p_L data were analysed using the weighted least-squares technique developed by Sullivan et al. [17] on a PC/AT personal computer to yield β_n values. The weighted least-squares treatment determined by the set of β_n values which make the function U

$$U = \sum_{n=0}^{N} (y - x - nz)\beta_n \chi^n$$

nearest to zero, by minimising S

$$S = \sum_{i=1}^{I} W_i U^2(x_i, y_i, z_i)$$

with respect to variation in β_n. $S_{\min}$ has the same statistical distribution as χ^2 with K degrees of freedom and the weight defined in accordance with Sullivan et al. [18]. $S_{\min}$ can be equated to χ^2. The stability constants thus calculated are given in Table 1. The values of ΔH were calculated by the graphical method of Yatsimirskii and Vaslev [19], while values of ΔG and ΔS were calculated by conventional methods.

The reliability of the data was checked by calculating the error range [20] of the ΔG and ΔH functions of the complexation process for different systems. The category of errors which is difficult to detect and also difficult to handle, includes systematic errors, i.e. errors which are not random but inherent in the reaction studied or the methods employed. In such studies, errors due to small amounts of secondary reactions are the most frequent type of systematic error encountered.

In the completely general case of a dependent variable $y = f(x_1, x_2, \ldots, x_n)$ which is a known function of the n independent variables $x_1, x_2, \ldots, x_n$, the expected relative error in y due to the relative errors in $x_1, x_2, \ldots, x_n$ is given by

$$\left(\frac{\Delta y}{y}\right)^2 = \sum_{i=1}^{n} \left(\frac{\delta \ln f}{\delta \ln x_i}\right)^2 \left(\frac{\Delta x_i}{x_i}\right)^2$$

The error range calculated for the ΔG and ΔH functions is presented in Table 3, below.

3. Results and discussion

In the present investigations, it was noted that the values of the acid dissociation constant pK_a and the stability constants decrease with increasing temperature of the medium and with increasing acidity of metal ions. The order of stability constants

Table 1
Stability constants of bivalent metal complexes of *N,N'*-di-*p*-tolyl-5-nitro-2-thiobarbituric acid (DTNTBA) at constant ionic strength $\mu = 0.02$ M $NaClO_4$ at different temperatures

Metal ion	Weighted least-squares method			
	$\log K_1$	$\log K_2$	$\log \beta_2$	S_{min}
Temperature, 20 ± 0.5°C				
H^+	7.48	–	–	–
Cu(II)	4.78	4.55	9.33	0.0245
Ni(II)	4.58	4.32	8.90	0.0138
Co(II)	4.41	4.07	8.48	0.0121
Zn(II)	3.60	2.90	6.50	0.0019
Cd(II)	2.98	2.47	5.45	0.0002
Mn(II)	2.63	2.38	5.01	0.0000
Mg(II)	2.50	2.33	4.83	0.0001
Temperature, 30 ± 0.5°C				
H^+	7.31	–	–	–
Cu(II)	4.59	4.29	8.88	0.0374
Ni(II)	4.34	4.27	8.61	0.0442
Co(II)	4.10	4.00	8.10	0.0186
Zn(II)	3.18	3.14	6.32	0.0032
Cd(II)	2.67	2.53	5.20	0.0002
Mn(II)	2.57	2.36	4.93	0.0002
Mg(II)	2.40	2.13	4.53	0.0000
Temperature, 40 ± 0.5°C				
H^+	7.17	–	–	–
Cu(II)	4.26	4.11	8.37	0.0130
Ni(II)	4.12	3.97	8.09	0.0248
Co(II)	3.85	3.77	7.62	0.0155
Zn(II)	3.07	3.03	6.10	0.0024
Cd(II)	2.60	2.34	4.94	0.0002
Mn(II)	2.44	2.13	4.57	0.0000
Mg(II)	2.26	1.95	4.21	0.0014
Temperature, 50 ± 0.5°C				
H^+	7.01	–	–	–
Cu(II)	4.03	3.99	8.02	0.0241
Ni(II)	3.91	3.61	7.52	0.0052
Co(II)	3.67	3.28	6.95	0.0074
Zn(II)	2.95	2.86	5.81	0.0009
Cd(II)	2.51	2.18	4.69	0.0001
Mn(II)	2.28	2.04	4.32	0.0021
Mg(II)	2.13	1.66	3.79	0.0005

($\log K_1$) of metal complexes of DTNTBA is found to be Cu > Ni > Co > Zn > Cd > Mn > Mg. The order is in good agreement with the order found by Mellor and Maley [21] and Irving and Williams [22,23]. The decrease in stabilities with increasing temperature is in accord with the results of Pitzer [24]. The $\log K_1$, $\log K_2$, $\log \beta_2$ and S_{min} values at different temperatures

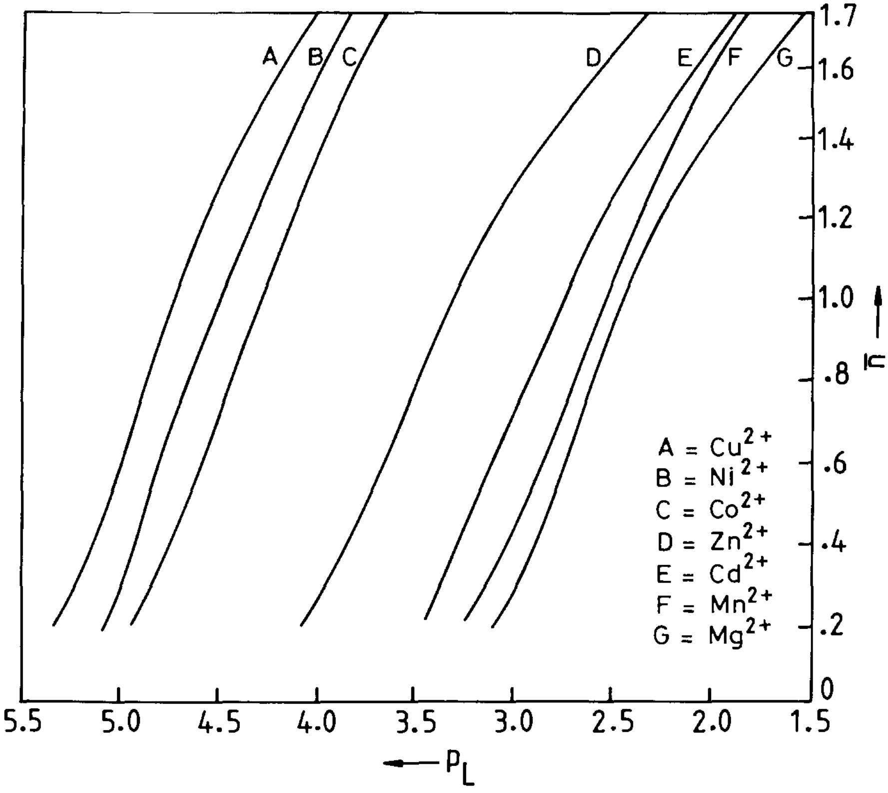

Fig. 1. Formation curves of bivalent metal complexes of DTNTBA at ionic strength $\mu = 0.02$ M $NaClO_4$ in 75% (v/v) dioxan-water medium and at a temperature of 20 ± 0.5°C: $\bar{n}$, average number of ligand molecules bound per metal ion; p_L, the free ligand exponent.

($\mu = 0.02$ M $NaClO_4$) are given in Table 1. In all the cases, the values of log K_1 are greater than those of log K_2 as is evident from Fig. 1, which shows the formation curves (plots of $\bar{n}$ and p_L) of various metal complexes of DTNTBA at $\mu = 0.02$ M $NaClO_4$ and at a temperature of 20 ± 0.5°C.

Table 2
Thermodynamic parameters of bivalent metal complexes of *N*,*N*′-di-*p*-tolyl-5-nitro-2-thiobarbituric acid (DTNTBA) at ionic strength $\mu = 0.02$ M $NaClO_4$ and a temperature of 20 ± 0.5°C

Metal ion	$\Delta G/(\mathrm{kJ\ mol^{-1}})$	$-\Delta H/(\mathrm{kJ\ mol^{-1}})$	$\Delta S/(\mathrm{J\ mol^{-1}\ K^{-1}})$
Cu(II)	25.83	32.31	−18.83
Ni(II)	25.70	32.45	−23.01
Co(II)	24.75	52.72	−95.39
Zn(II)	20.20	71.42	−174.89
Cd(II)	16.73	52.72	−122.59
Mn(II)	14.76	10.20	+15.48
Mg(II)	14.03	17.01	−10.04

Table 3
Error range (±) for ΔG and ΔH values of the bivalent metal complexes of DTNTBA at ionic strength $\mu = 0.02$ M $NaClO_4$ and a temperature of 20 ± 0.5°C

Metal ion	Error range (±)/(kJ mol^{-1})		Metal ion	Error range (±)/(kJ mol^{-1})	
	ΔG	ΔH		ΔG	ΔH
Cu(II)	0.12	0.55	Cd(II)	0.10	0.34
Ni(II)	0.11	0.49	Mn(II)	0.10	0.34
Co(II)	0.11	0.35	Mg(II)	0.10	0.34
Zn(II)	0.11	0.34			

The regularity in stability constants can be correlated with a monotonic decrease in the ionic radii and a monotonic increase in the second ionisation potential, which, in passing from Mn to Cu, may be taken to indicate that either the coordination has not altered the electronic ground state of the metal ions or that any modifications are of secondary importance. For these chelates, $\bar{n}$ values greater than 2.0 have not been obtained. We, therefore, conclude that not more than two chelates, i.e. 1 : 1 and 1 : 2 (M : L) are found in each system.

Finally, in view of the very low (5.0×10^{-4} M) concentration of metal ions used in the titration, it has been assumed that the possibility of formation of polynuclear complexes is negligible.

The thermodynamic parameters (ΔG, ΔH and ΔS) were calculated using the relationships

$$\Delta G = -RT \ln K$$

$$\mathrm{d}(\log K)/\mathrm{d}(1/T) = -\Delta H/2.303R$$

$$\Delta S = (\Delta H - \Delta G)/T$$

The overall free energy change, and the enthalpy and entropy changes at 20 ± 0.5°C are reported in Table 2. The negative free energy change (ΔG) in each case indicates that the chelation is spontaneous. Furthermore, ΔG becomes more negative with decrease in temperature suggesting an increase in the extent of complex formation at lower temperatures. The enthalpy changes are exothermic. The change in entropy upon complexation is related both to changes in the number of particles in the system and to changes in the mode of vibration of particles in the system. A very small error range for the ΔG and ΔH values indicates complete reliability and reproducibility of data (Table 3).

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