Thermochimica Acta, 96 (1985) 49–57
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

THERMODYNAMIC STUDY OF THE COMPLEXATION PROCESSES BETWEEN 6,7-DIHYDRO-3(*H*)-6-METHYL-5-METHOXY-7-OXO-VIC-TRIAZOLO (4,5-*d*) PYRIMIDINE AND Cu(II), Zn(II), Cd(II) AND Hg(II)

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(Received 4 June 1985)

ABSTRACT

The compound 6,7-dihydro-3(*H*)-6-methyl-5-methoxy-7-oxo-vic-triazolo (4,5-*d*) pyrimidine (LH) has been characterized by IR, ^{1}H-NMR and UV-visible spectroscopy. Furthermore, its acid behaviour in aqueous solutions at variable temperatures and ionic strengths have been studied.

The stability constants of the complexes formed by LH with Cu(II), Zn(II), Cd(II) and Hg(II) metal ions at different ionic strengths and temperatures have been calculated by the method of Chabereck and Martell. From these data, the thermodynamic functions for the corresponding complexation processes have been obtained.

INTRODUCTION

In the past thirty years, experimental studies in Coordination Chemistry and Bioinorganic Chemistry have highlighted the essential role of metal ions in many general biological processes and particularly in the biochemistry of nucleic acids [1]. There is much evidence on the importance of Zn(II) and Cu(II) in biological processes [2–5] and also on the involvement of Cd(II) and Hg(II) ions in metal poisoning as soluble organo complexes [2,6,7]. On the other hand, it is known that 8-azapurines can act as antitumour and antiallergic agents [8–10], which is why we found it interesting to study the complex formation of Cu(II) and Zn group IIB metal ions with some 8-azapurine derivatives.

In the present study, we report the spectral characterization of 6,7-dihydro-3(*H*)-6-methyl-5-methoxy-7-oxo-vic-triazolo (4,5-*d*) pyrimidine (LH). The acid character of LH and the interactions between Cu(II) and the zinc group IIB metal ions and LH have also been studied.

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0040-6031/85/$03.30

EXPERIMENTAL

LH was synthesized according to a method reported by one of the authors [11]. The compound obtained was analysed in the National Institute of Organic Chemistry (CSIC, Madrid).

All the inorganic chemicals used in this work were analytical-reagent grade. In all the solutions, double-distilled carbon dioxide-free water was used as solvent. When it was necessary, solutions of LH were obtained by diluting suitable volumes of a 10^{-3} M solution of LH, previously prepared by direct weighing from a pure sample. 0.125 M solutions of $Cu(NO_3)_2$, $ZnCl_2$, $Cd(NO_3)_2$ and $HgCl_2$ were prepared and standardized. To maintain the necessary ionic strength, a standardized solution of KNO_3 (0.1 M) was used. Standardized and carbonate-free solutions of KOH were also used in this work.

UV-visible spectra of LH were obtained on a Spectronic 2000 spectrophotometer and the IR spectrum in a Beckman 4250 spectrophotometer (from KBr pellets); whereas the ^{1}H-NMR spectrum was obtained using a Hitachi Perkin-Elmer (model FT-NMR R-600) and DMSO-d_6 as solvent.

A Radiometer TTT-60 pH-meter, fitted with glass and calomel electrodes, was used to record the pH.

In the study of the acid behaviour of LH, Bjerrum's method was employed [12]. In all cases, a 10^{-3} M solution of LH (initial volume 35 ml) was titrated against a standard alkali (0.01 M KOH) after adjusting the ionic strength and temperature in a thermostated bath.

In order to calculate the corresponding K_1 and K_2 values of the complexes formed in the systems M^{2+}/LH, the method of Chabereck and Martell was employed [12]. According to this method, the ratios of metal ion to ligand concentrations were kept at 1/2. In each case, 35 ml of the corresponding solution ($LH = 5 \times 10^{-4}$ M when $M^{2+} =$ Cu(II), Zn(II) or Cd(II); $LH = 10^{-4}$ M when $M^{2+} =$ Hg(II)) was titrated against KOH (5×10^{-3} and 10^{-3} M, respectively) at the appropriate temperature and ionic strength.

RESULTS AND DISCUSSION

The analytical data found for the compound synthesized were: C, 39.91% (39.78); H, 3.78% (3.89); N, 38.54 (38.66). Values in parentheses are the required percentages for $C_6H_7N_5O_2$(LH).

Given that no bibliographical reference to this compound was found, we proceeded to its spectral characterization.

Table 1 gives the assignations for the most significant bands of the IR spectrum of LH (4000–200 cm^{-1}).

The ^{1}H-NMR spectrum of LH shows three singlet signals at δ values of 3.30, 4.00 and 7.50 (broad) ppm. In accordance with bibliographical data

TABLE 1

IR spectral data of LH (w = weak, m = medium, s = strong, br = broad, d = double)

ν (cm^{-1})	Intensity	Assignments
3200	w	ν(N–H)
3130	m (br)	
2980	w	ν(C–H)
2950	w	
1685	s	ν(C=O)
1610	m, d	ν(C=N)
1560	s, br	ν(C=C)
1520	m	ν(N=N)
1435	m	δ_{asym}(C–H)
1355	m	δ_{sym}(C–H)
1240	m	ν(C–N)
1200	m	
805	m	Skeletal vibrations
780	m	

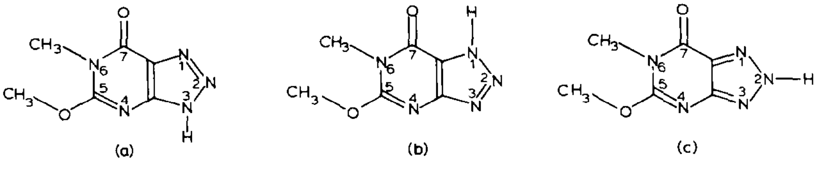
[13,14], signals at 3.30 and 4.00 ppm have been assigned to the acidic hydrogen atom.

The above data are in accordance with the three probable structures shown in Scheme 1.

Nevertheless, of the three proposed structures it should be expected that the most stable is **b**, in which the hydrogen atom linked to N_1 interacts with the O atom of the 7-oxo group via a hydrogen bond.

The UV spectrum of LH in aqueous solution (LH = 5.50×10^{-5} M; 0.1 M KNO_3) shows two bands: at 252 nm ($\epsilon = 6975$) and 205 nm ($\epsilon = 23820$). On the other hand, on varying the pH values of an aqueous solution of LH in the above-mentioned conditions, in the range 2.0–11.70, the UV spectral curves define an isosbestic point at $\lambda = 225$ nm; this fact suggests the existence of an equilibrium between the anionic and neutral forms of the compound, due to the acidic character of LH.

To study the acidic character of LH, Bjerrum's method was applied to the pH titration curves of aqueous solutions of LH at temperatures of 10, 20, 30, 40 and 50°C ($I = 0.1$ M in all cases) and at ionic strength values of 0.01, 0.02, 0.06, 0.1 and 0.2 M of KNO_3 (at 25°C in all cases). By plotting pH



(a) (b) (c)

Scheme 1

TABLE 2

Ionization constants of LH at different ionic strengths and temperatures

I (mol l^{-1})	T (°C)	$\log K_c$
0.01	25	−6.43
0.02	25	−6.30
0.06	25	−5.98
0.10	25	−5.78
0.20	25	−5.62
0.10	10	−5.75
0.10	20	−5.70
0.10	30	−5.55
0.10	40	−5.41
0.10	50	−5.31

versus $\bar{n}$, and interpolating at $\bar{n} = 0.5$, the corresponding $\log K_c$ values were obtained. These are listed in Table 2 and are slightly lower than those of other 8-azapurine derivatives, recently reported: 8-azaxanthine, 1-methyl-8-azaxanthine, 3-methyl-8-azaxanthine and 1,3-dimethyl-8-azaxanthine [14].

The stability constant values decrease with increasing ionic strength, as could be expected according to the Debye–Hückel limiting equation [15] for 1/1 electrolytes

$$\log K_c = \log K_d + C_t\sqrt{I}$$

In order to obtain the thermodynamic dissociation constant K_d of LH, $\log K_c$ values were plotted versus $\sqrt{I}$. The straight line obtained was extrapolated to zero ionic strength and the value $K_d = 2.45 \times 10^{-7}$ mol l^{-1} was obtained. To calculate ΔG^0 for the dissociation process, the equation

$$\Delta G^0 = -2.303RT \log K_d$$

was used. The value obtained was $\Delta G^0 = 4.54$ kJ mol^{-1}.

On the other hand, as can be seen in Table 2, $\log K_c$ values increase with increasing temperature. We have calculated the corresponding enthalpy and entropy changes for the dissociation process following the equation

$$\log K = -\frac{\Delta H}{2.303RT} + \frac{\Delta S}{2.303R}$$

The plot of $\log K_c$ versus $1/T$ leads to a straight line, from which we obtained the values $\Delta H = 19.3$ kJ mol^{-1} and $\Delta S = -18.37$ J mol^{-1} K^{-1}. These indicate that the dissociation process is endothermic and exoentropic. With entropy, two effects must be considered; the increase in entropy due to the dissociation process of LH, and its decrease as a result of solvation of ions from the dissociation. Given that in the process under study, dissociation also occurs in a side reaction, the negative value of ΔS suggests that the second effect predominates over the first.

The first and second formation constants of the complexes formed between LH and Cu, Zn, Cd and Hg divalent ions were calculated according to the method proposed by Chaberek and Martell [12]. Values of ionization constants of LH (given in Table 2) were used. Log K_1 and log K_2 values were obtained in each metal–ligand system, by interpolation at $\bar{n} = 0.5$ and 1.5, respectively, in the formation curves $\bar{n}$ versus pH previously plotted.

TABLE 3

Stability constants of LH complexes with Cu(II), Zn(II), Cd(II) and Hg(II) at different temperatures and ionic strengths

Metal ion	I (mol l^{-1})	T (°C)	log K_1	log K_2	log β_2
Cu(II)	0.01	25	5.44	5.44	10.88
	0.02	25	5.35	5.34	10.69
	0.06	25	5.01	4.99	10.00
	0.10	25	4.52	4.54	9.06
	0.10	10	4.60	4.58	9.18
	0.10	20	4.62	4.60	9.22
	0.10	30	4.48	4.49	8.97
	0.10	40	4.39	4.45	8.84
	0.10	50	4.34	4.50	8.84
Zn(II)	0.01	25	4.62	4.37	8.99
	0.02	25	4.48	4.26	8.74
	0.06	25	4.13	4.02	8.15
	0.10	25	3.71	3.29	7.00
	0.10	10	3.75	3.33	7.08
	0.10	20	3.72	3.30	7.02
	0.10	30	3.69	3.28	6.97
	0.10	40	3.70	3.28	6.98
	0.10	50	3.64	3.31	6.95
Cd(II)	0.01	25	4.43	4.09	8.52
	0.02	25	4.19	3.85	8.04
	0.06	25	4.00	3.87	7.87
	0.10	25	3.79	3.50	7.29
	0.10	10	3.83	3.35	7.18
	0.10	20	3.78	3.34	7.12
	0.10	30	3.77	3.32	7.09
	0.10	40	3.76	3.34	7.10
	0.10	50	3.75	3.31	7.06
Hg(II)	0.01	25	5.24	5.19	10.43
	0.02	25	5.21	5.25	10.46
	0.06	25	5.18	5.23	10.41
	0.10	25	5.19	5.10	10.29
	0.10	10	5.33	5.12	10.45
	0.10	20	5.28	5.07	10.35
	0.10	30	5.20	5.05	10.25
	0.10	40	5.16	5.14	10.30
	0.10	50	5.08	5.01	10.09

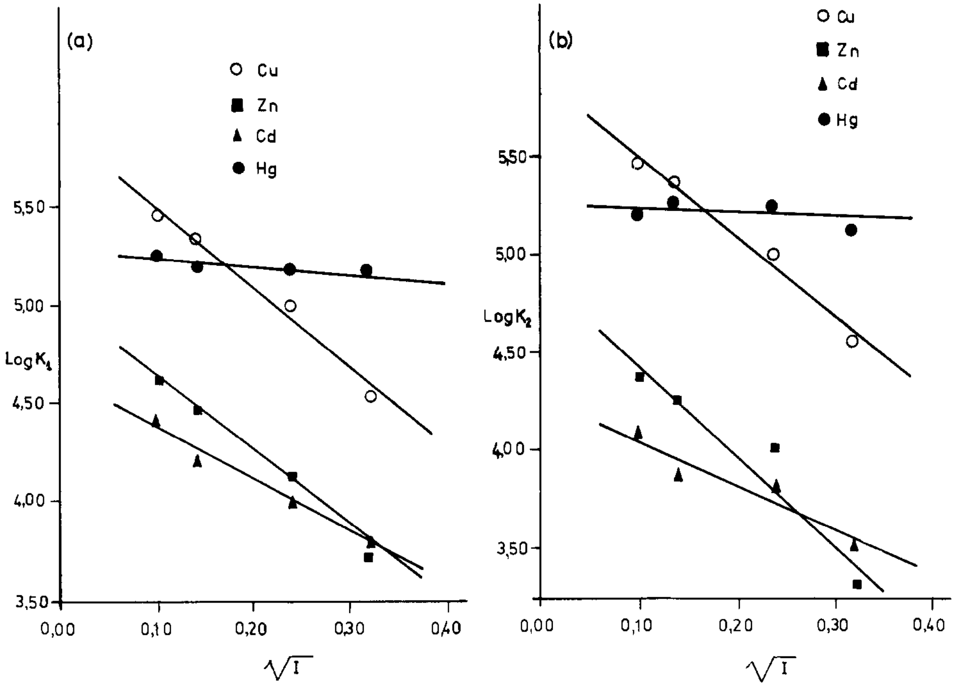


Fig. 1. Plots of (a) log K_1 and (b) log K_2 versus I for metal–LH complexes at 25°C.

These values, at different temperatures and ionic strengths, are given in Table 3.

From the data listed in this table, it is evident that K_1 and K_2 values decrease with increasing ionic strength of the medium, in all cases. This fact can be explained on the basis of the hindrance to metal–ligand interactions produced by the negatively charged atmosphere around the cation; this atmosphere increases in density with increasing ionic strength of the medium.

The plots of log K_1 and log K_2 versus $\sqrt{I}$ leads, in all cases, to straight lines (Fig. 1). According to the Debye–Hückel limiting equation, we have obtained the corresponding thermodynamic stability constants of the com-

TABLE 4

Thermodynamic stability constants and free energy (kJ mol^{-1}) of metal ion–LH complexes at 25°C

Metal ion	log K_1	log K_2	log β_2	$-\Delta G_1$	$-\Delta G_2$	$-\Delta G$
Cu(II)	5.91	5.88	11.79	33.72	33.55	67.27
Zn(II)	5.05	4.91	9.96	28.82	28.01	56.83
Cd(II)	4.64	4.26	8.90	26.48	24.31	50.79
Hg(II)	5.25	5.28	10.53	29.96	30.13	60.09

plexes, K_1 and K_2, by extrapolation to zero ionic strength. These data are shown in Table 4.

The stability constants of Cu(II) and Zn(II) complexes are lower than those found for 4-amino-1,6-dihydro-1-methyl-2-methoxy-5-nitrosopyrimidine [16], and similar to those of glycylglycine and 1,10-phenanthroline [2]. In contrast, they are slightly higher than those of Cu(II), Zn(II) and Cd(II) complexes of 2-(aminomethyl) pyridine, 2-(2′-aminoethyl) pyridine, 2-(methylaminoethyl) pyridine and 6-methyl-2-(aminomethyl) pyridine, at 40°C [17]. The data listed in Table 4 show that both K_1 and K_2 values are in the order Cu(II) > Hg(II) > Zn(II) > Cd(II). Thus, the K_1 and K_2 values of Cu(II) and Zn(II) complexes follow the foreseen sequence predicted by Irving-Williams [18]. Besides, the stability constants of the complexes of group IIB metal ions are in accordance with Van Panthaleon's empirical relation [19]; they increase in the same order as the corresponding ionization potential values, as would be expected on the basis that there must be a higher attraction over the electrons of the donor atoms of the ligand for a higher ionization potential of the metal. Thus, the above-discussed sequence may indicate that the ligand molecules in the two series of complexes studied are bound to the metal ions in the same way.

ΔG standard values for all complexation processes have been calculated and are included in Table 4. All the ΔG values are negative, indicating that the processes are spontaneous.

In addition to this, values listed in Table 3 show that log K_1 and log K_2 (at an ionic strength of 0.1 M KNO_3) decrease slightly with increasing temperature, in all cases. The ΔH and ΔS values of the corresponding Cu(II), Zn(II), Cd(II) and Hg(II) complexes of LH have been calculated by

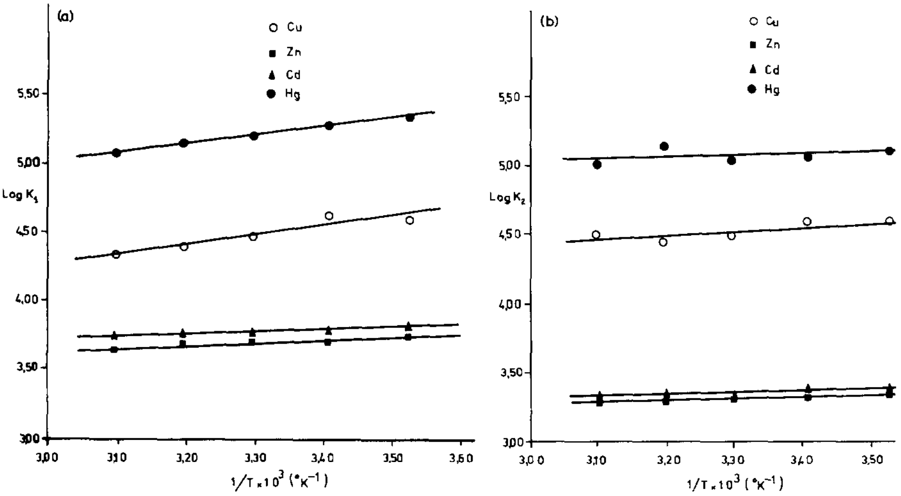


Fig. 2. Plots of (a) log K_1 and (b) log K_2 versus $1/T$ for metal–LH complexes at 0.1 M ionic strength.

TABLE 5

Enthalpy (kJ mol^{-1}) and entropy changes (J mol^{-1}) of metal–LH complexes at 0.1 M ionic strength

Metal ion	ΔH_1	ΔH_2	ΔH	ΔS_1	ΔS_2	ΔS
Cu(II)	−13.32	−5.58	−18.90	41.84	68.17	110.01
Zn(II)	−4.32	−1.19	−5.51	56.49	59.17	115.66
Cd(II)	−2.91	−1.77	−4.68	62.81	58.02	120.83
Hg(II)	−10.94	−2.54	−13.48	63.57	88.85	152.42

plotting log K_t versus $1/T$ (Fig. 2), following the same equation as in the study of the ligand.

The data obtained are shown in Table 5. From this data it can be seen that all the ΔH values are negative; this indicates that all the processes are exothermic. In addition to this ΔH_1 values are much greater than ΔH_2 values in all the systems under study, as could be expected for the enthalpies of the similar stepwise additions. Nevertheless, the great difference between ΔH_1 and ΔH_2 values might indicate the appearance of steric hindrances on coordinating the second molecule of ligand to the central ions, and also the probable appearance of coulombic repulsions between two charged ligands L^-.

The entropy values ΔS_1, ΔS_2 and ΔS, listed in Table 5, are all positive; this fact indicates that the entropy, together with enthalpy, are favourable to all the complexation processes studied. The increase in entropy of the medium can be related to the predominance of the desolvation processes (of both metal ions and the ligands) over the increases in the order occurring during the complexation reactions.

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