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THERMODYNAMIC STUDY OF THE COMPLEXATION OF 1,6-DIHYDRO-1-METHYL-2-METHYLTHIO-5-NITROSO-6-OXO-4-XYLOPYRANOSYLAMINOPYRIMIDINE WITH SOME METAL IONS

R. LÓPEZ GARZÓN *, E. CAZALILLA CANTERO, M.D. GUTIERREZ VALERO, M. NOGUERAS MONTIEL, A. SÁNCHEZ RODRIGO and M.L. QUIJANO LOPEZ

Department of Inorganic and Organic Chemistry, University College, 23071-Jaén (Spain)

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ABSTRACT

The acidic constant of 1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-4-xylopyranosylaminopyrimidine and the formation constants of its $[ML^-]^+$ and $[ML_2]$ complexes ($M \equiv$ Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II)) at variable ionic strengths and temperatures, were determined and their values compared with those of 4-amino-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-pyrimidine.

INTRODUCTION

The interest in the study of metal complexes of heterocyclic thione compounds stems from the biological activity of many of them [1]. The bacteriostatic activity of some thione imidazoline, thiazoline and pyridine thione derivatives has been related to their coordination ability [2,3]. Other thione derivatives have thyrotoxic [4], anti-convulsant or central-nervous-system depressant capacity [5]. Moreover, the carcinostatic activity of some of their heavy metal complexes has been reported [6], e.g. a platinum pyridine thione complex has been patented for use in cancer treatment [7].

Thiopyrimidine derivatives are also very important heterocyclic compounds because of their wide range of biological activity, e.g. some of them can act as inhibitors [8,9] and anti-metabolites [10,11], whereas 2-thiopyrimidine shows a strong in vitro bacteriostatic activity on *E. coli* [12]. 6-amino-2-thiouracil is well known for its anti-viral [13] and chemi-therapeutic activities [13–15]. In many of these cases, it seems probable that metal complexes are formed in their biological action mechanisms [16].

In view of the above, we are interested in the study of the complex formation processes between metal ions and 2-methylthiopyrimidine deriva-

* Author to whom correspondence should be addressed.

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tives, on which several papers have been previously published [17–26]. In continuation of these, the present paper reports the study of the acidic character of the compound 1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-4-xylopyranosylaminopyrimidine (L–H), as well as the study of the interactions of the anion L^- with some bivalent ions from the first row of the transition elements (Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II)).

EXPERIMENTAL

Reagents

The compound 1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-4-xylopyranosylaminopyrimidine (L–H) was prepared by a previously reported method [27]; the sample obtained was water-recrystallised several times and dried over P_4O_{10}; the analytical data of the sample were in accordance with the formula of anhydrous L–H. All the remaining chemicals used were commercial analytical grade reagents. Solutions were prepared in double distilled, carbon-dioxide-free water.

Solutions of 10^{-3} M L–H were prepared by diluting a 2×10^{-3} M solution of the compound previously prepared by direct weighing from the pure solid sample, and were then used for potentiometric titrations of the ligand. Potentiometric titrations of solutions of L–H/M(II) systems in which L–H is 10^{-3} M and [L–H] : [M(II)] = 2 were also made. To prepare these, 5×10^{-2} M solutions of Mn(II) (chloride), Fe(II) (Mhor's salt), Co(II), Ni(II), Cu(II) and Zn(II) (nitrates) were prepared by diluting suitable volumes of previously prepared and standardized 0.5 M solutions.

To maintain the ionic strength at the appropriate values, a 1 M standardized KCl solution was used in all cases.

0.01 M carbonate-free NaOH solutions were used as titrating agent for all L–H and L–H/M(II) solutions.

Apparatus and methods

UV spectra of L–H solutions at different pH values were obtained using a Spectronic 2000 spectrophotometer.

All the potentiometric titrations were carried out under nitrogen atmosphere using a Radiometer TTT60 pH-meter fitted with glass and calomel electrodes.

To study the acidic character of L–H, 25 ml of a 10^{-3} M solution of this compound were titrated against standardized 0.01 M NaOH solutions. Similarly, 25 ml of solutions containing L–H/M(II) systems in which [L–H] : [M(II)] = 2 (L–H = 10^{-3} M) were also titrated against standardized 0.01 M NaOH solutions, in order to obtain the apparent formation con-

stants of the complexes. The ionic strength and temperature were adjusted in each case to the appropriate value.

RESULTS AND DISCUSSION

The spectroscopic data (IR and ^{1}H-NMR spectra) demonstrate that the compound is to be found (either as a solid or in DMSO-d_6 solutions) in the keto-amino tautomeric form [24].

The UV spectrum of an aqueous solution of L–H is very much like that of 4-amino-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-pyrimidine (A–H). Therefore, the absorption bands at 350 nm ($\epsilon = 18000$ l mol^{-1} cm^{-1}), 285 nm (shoulder, $\epsilon = 5400$ l mol^{-1} cm^{-1}), 235 nm (shoulder, $\epsilon = 6600$ l mol^{-1} cm^{-1}) and 216 nm ($\epsilon = 14400$ l mol^{-1} cm^{-1}) are all assignable to $\pi \rightarrow \pi^{\star}$ transitions [28,29].

The different UV spectra obtained when the pH of an L–H solution varies define an isosbestic point at 237 nm, which occurs at pH values higher than 10.25 (as well as in the case of A–H [17]), which is due to the deprotonation of the NH group, this being in accordance with the above proposed keto-amino tautomeric structure.

The apparent deprotonation constants of L–H at variable ionic strengths and temperatures, appearing in Table 1, were obtained by applying Bjerrum's method [30] to the pH titration data of the L–H solutions. These values (k_a) were calculated from the plots of $\bar{n}$ (the average number of L^- molecules linked to the protons) versus pH, by interpolating at $\bar{n} = 0.5$, and are about ten times lower than those corresponding to the compound A–H; this compound differs structurally from L–H in the absence of the xylosydic residue. Thus, the difference in k_a values of the two compounds could be due to the inductive effect of the glyosydic residue on the C4–NH group which would enhance the covalent character of the N–H bond.

TABLE 1

Ionization constants of L–H at different ionic strengths (KCl) and temperatures

I (mol^{-1})	T (°C)	pK_a
0.01	25	10.80
0.03	25	10.90
0.06	25	10.82
0.10	25	10.85
0.20	25	11.02
0.10	20	10.95
0.10	30	10.77
0.10	35	10.62
0.10	40	10.42

TABLE 2

Stability constants of 1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-4-xylopyranosylaminopyrimidine complexes with Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II)

Metal ion	I (mol l^{-1})	T (°C)	log k_1	log k_2	log β_2
Mn(II)	0.01	25	5.23	5.05	10.28
	0.03	25	5.10	4.90	9.90
	0.06	25	5.35	4.79	10.44
	0.10	25	5.25	4.75	10.00
	0.20	25	5.36	4.70	10.06
	0.10	20	6.77	4.70	11.47
	0.10	30	5.57	4.67	10.24
	0.10	35	5.35	4.68	10.03
	0.10	40	4.45	4.63	9.08
Fe(II)	0.01	25	8.40	8.37	16.74
	0.03	25	8.37	8.32	16.72
	0.06	25	8.32	8.28	16.60
	0.10	25	8.24	8.30	16.64
	0.20	25	8.22	8.07	16.29
	0.10	20	8.37	8.33	16.60
	0.10	30	8.34	8.18	16.52
	0.10	35	8.25	8.06	16.31
	0.10	40	7.96	8.02	15.98
Co(II)	0.01	25	7.32	6.58	13.90
	0.03	25	7.25	6.50	13.75
	0.06	25	7.08	6.46	13.54
	0.10	25	7.14	6.40	13.40
	0.20	25	6.60	6.30	12.85
	0.10	20	– [a]	– [a]	– [a]
	0.10	30	7.00	6.41	13.55
	0.10	35	6.72	6.35	13.07
	0.10	40	6.60	6.22	12.82
Ni(II)	0.01	25	6.92	6.15	13.07
	0.03	25	6.90	6.12	13.02
	0.06	25	6.78	6.10	12.88
	0.10	25	6.72	5.92	12.64
	0.20	25	6.62	5.90	12.52
	0.10	20	6.73	5.97	12.70
	0.10	30	6.55	5.85	12.40
	0.10	35	6.44	5.74	12.18
	0.10	40	6.22	5.59	11.81
Cu(II)	0.01	25	9.10	8.70	17.80
	0.03	25	9.06	8.78	17.84
	0.06	25	8.92	8.74	17.66
	0.10	25	8.88	8.64	17.52
	0.20	25	8.80	8.54	17.34
	0.10	20	8.96	8.70	17.66
	0.10	30	8.84	8.60	17.44
	0.10	35	8.56	8.20	16.76
	0.10	40	8.46	8.06	16.52

TABLE 2 (continued)

Metal ion	I (mol l^{-1})	T (°C)	log k_1	log k_2	log β_2
Zn(II)	0.01	25	6.75	6.66	13.41
	0.03	25	6.48	6.52	13.00
	0.06	25	6.45	6.47	12.92
	0.10	25	6.42	6.43	12.87
	0.20	25	6.41	6.42	12.90
	0.10	20	6.56	6.46	13.20
	0.10	30	6.50	6.46	12.96
	0.10	35	6.46	6.47	12.93
	0.10	40	6.30	6.40	12.70

[a] Complex formation is not detected at this temperature.

The k_a values of L–H, are practically unaffected by ionic strength but undergo a slight increase with temperature. In fact, the values define a straight line when plotted against $1/T$ (the apparent thermodynamic constants for the deprotonation process are found to be: $\Delta H = -55.52$ kJ mol^{-1} and $\Delta S = -21.42$ J K^{-1} mol^{-1}).

These k_a values were used to calculate the apparent formation constants corresponding to the processes

$$M(II) + L^- \rightleftharpoons ML^{-+}, \qquad k_1 = [ML]^+/[M(II)][L^-]$$

and

$$ML^{-+} + L^- \rightleftharpoons ML_2, \qquad k_2 = [ML_2]/[ML^-]^+[L^-],$$

for which the Chaberek and Martell method was used [31]. From the potentiometric data, the formation curves are obtained by plotting $\bar{n}$ (the average number of ligand molecules, L^-, linked to each metal ion) against pL. In all cases the curves level off at about $n = 1.8$, which suggests that the highest species formed in solution is ML_2. Thus, the apparent formation constants of $[ML^-]^+$, k_1, and $[ML_2]$, k_2, were obtained by interpolating, in the formation curves, the ordinates corresponding to $\bar{n} = 0.5$ and $\bar{n} = 1.5$, respectively; their values are summarized in Table 2, together with the overall apparent formation constants, β_2. The values of k_1, k_2 and β_2 decrease slightly when the ionic strength increases due to a higher intensity in the solvation of M(II) ions which inhibits metal–ligand interactions.

For all the systems, the linearity in the plots of log k_1 and log k_2 versus $\sqrt{I}$ was demonstrated by the least squares method (Fig. 1). This enabled us to calculate the values of the thermodynamic formation constants appearing in Table 3 by application of the Debye–Hückel limiting equation for weak 1/1 electrolytes ($\log k_c = \log k + c\sqrt{I}$, where k_c are the apparent constants and k, the thermodynamic ones). Comparing these values with the corresponding values for similar complexes of the compound A–H, it can be seen that the sequence of the thermodynamic constant values are similar for the two

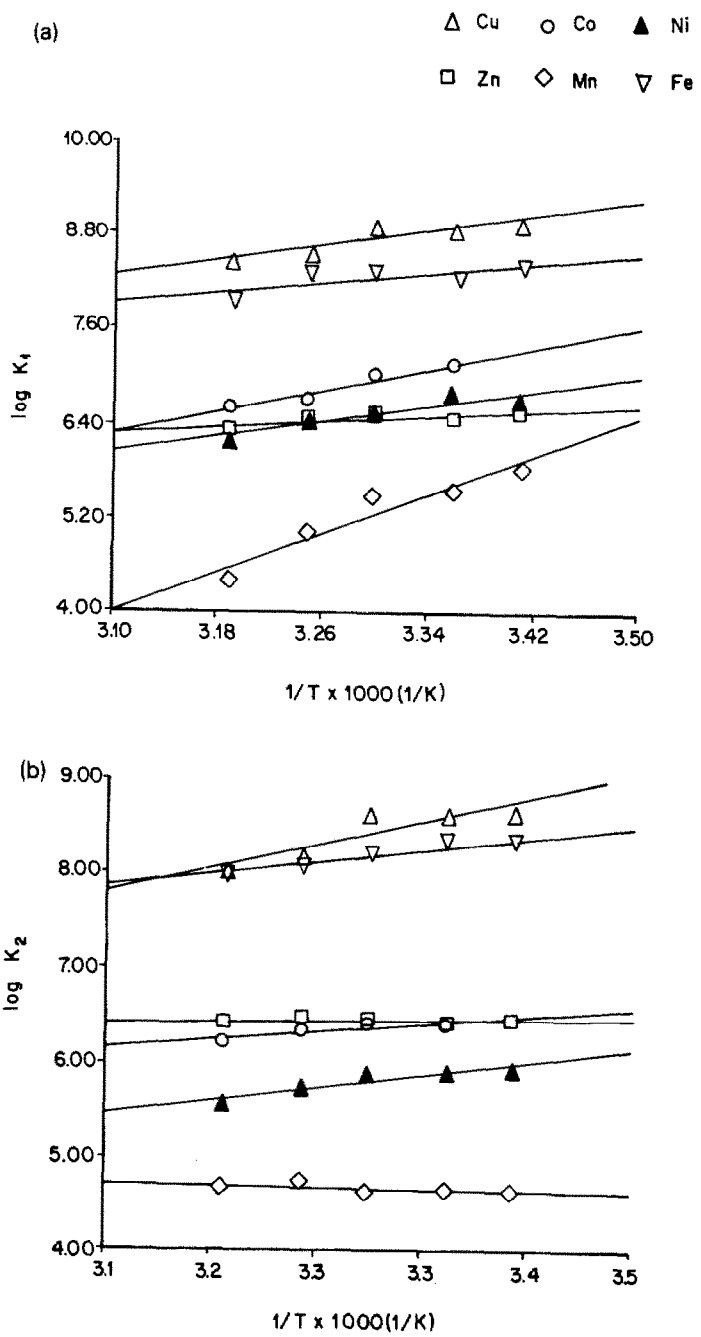

Fig. 1. Plots of (a) log k_1 and (b) log k_2 versus $\sqrt{I}$ for L–H---M(II) complexes at 25 °C.

compounds [32]; that is, Mn(II) < Fe(II) > Co(II) > Ni(II) < Cu(II) which suggests that in complexes with the same metal ion the coordination of the two organic bases is similar (thus, this shows that the OH groups of the

TABLE 3

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	$-\Delta G_1$	$-\Delta G_2$	$-\Delta G$
Mn(II)	5.20	5.09	10.29	29.67	29.04	58.72
Fe(II)	8.45	8.47	16.92	48.22	48.33	96.55
Co(II)	7.51	6.65	14.16	42.85	37.95	80.80
Ni(II)	7.02	6.25	13.27	40.06	35.66	75.72
Cu(II)	9.18	8.83	18.01	52.38	50.38	102.77
Zn(II)	6.71	6.66	13.37	38.29	38.00	76.29

glycosydic rest in L–H do not act as donors). Nevertheless, the great variability in the possible mode of coordination of the A–H and L–H bases (the potential donor groups in both compounds are: C2–SCH_3, N3, C4–NH, C5–NO and C6=O, as well as the OH groups of the xylosydic residue in the case of L–H) is confirmed by the fact that neither k_1 nor k_2 values follow the Irving–Williams rule; in fact, structural studies on solid complexes of these bases have demonstrated the coordination mode is very variable [24,33].

In addition, the values of the thermodynamic constants of the L–H complexes are considerably higher than those in the corresponding A–H ones (between 10^2 and 10^3 times higher for the former base); thus, in spite of the similar structures of complexes with the same cation but different base, the formation energies of L–H complexes are higher than those of A–H, probably due to the role played by the OH groups of the glycosydic rest in the formation of strong intramolecular hydrogen bridges stabilizing the L–H–metal chelates; although the inductive effect of the glycosydic rest on the pyrimidine could enhance the basicity of the donor atoms of L^-, this also results in an enhancement of the complex stability.

The apparent ΔH and ΔS values for the formation processes let us compare the thermodynamic behaviour of the different L–H/M(II) systems. The values, summarized in Table 4, were obtained from the apparent formation constants at different temperatures. The plots of log k_1 and log k_2 versus $1/T$ are straight lines in all cases, as proved by the least square method (Fig. 2); this enabled us to obtain the apparent ΔH and ΔS values on the basis of the equation $\log k = -\Delta H/2.303RT + \Delta S/R$.

When ΔS values for L^----M(II) complexation processes are compared with those for A^----M(II) [32], it is clear that the first are considerably lower than the second, which is probably due to the ability of the glycosydic rest of the L^--coordinated molecules to intervene in the formation of inter- (as well as intra-) molecular hydrogen bridges which inhibits the enhancement of the disorder accompanying the complexation processes (due to the ionic atmosphere around the metal ion). On the other hand, the L–H---

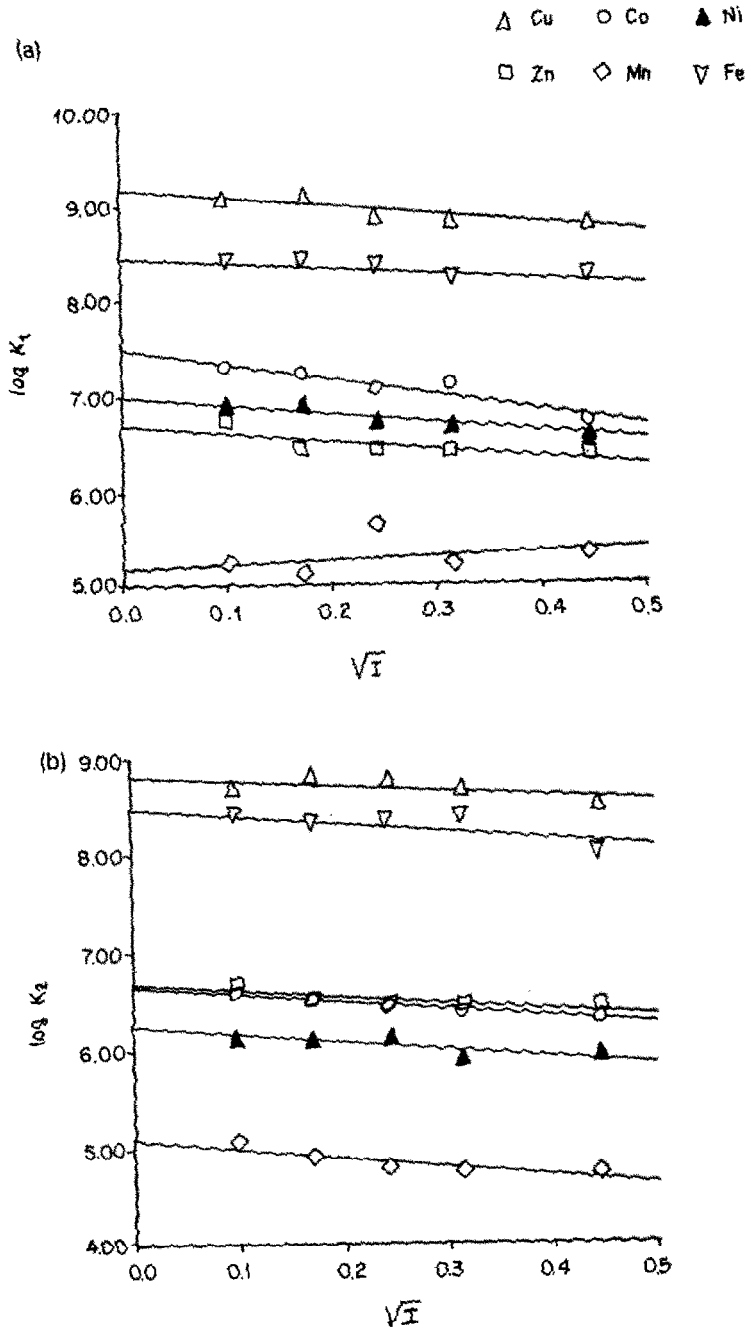

Fig. 2. Plots of (a) log k_1 and (b) log k_2 versus $1/T$ for L–H---M(II) complexes at 0.1 M (KCl) ionic strength.

TABLE 4

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

Metal ion	ΔH_1	ΔH_2	ΔH	ΔS_1	ΔS_2	ΔS
Mn(II)	−119.31	2.64	−116.67	−293.03	98.11	−194.92
Fe(II)	−28.30	−29.92	−58.22	64.01	57.78	121.79
Co(II)	−64.52	−20.49	−85.01	−79.84	54.39	−25.45
Ni(II)	−45.52	−32.79	−78.31	−25.22	3.04	−22.18
Cu(II)	−45.78	−59.69	−105.47	16.18	−35.50	−19.32
Zn(II)	−16.69	−2.82	−19.51	68.57	114.08	182.65

M(II) complexation processes are all exothermic (except that corresponding to the formation of $[ML_2]$ which is slightly endothermic), the ΔH values being more widely spread than those corresponding to the A–H---M(II) complexation processes. This shows that the enthalpy (which is related to the strength of the formed L^-–M bonds) is mainly responsible for the L–H---M(II) complexation processes and supports the above-mentioned probable role of the intramolecular hydrogen bridges of the OH groups of the glycosydic rest in the stability of the formed chelates.

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