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THE STABILITY AND THERMODYNAMIC FUNCTIONS OF 4-AMINO-1,6-DIHYDRO-1-METHYL-2-METHYLTHIO-5-NITROSO-6-OXO-PYRIMIDINE COMPLEXES WITH Mn(II), Fe(II), Co(II), Ni(II) AND Cu(II)

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ABSTRACT

The acidic constants for 4-amino-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-pyrimidine (LH) and the formation constants for ML^+ and ML_2 (where M = Mn(II), Fe(II), Co(II), Ni(II) and Cu(II)) complexes, at variable ionic strengths and temperatures, are reported.

INTRODUCTION

It is known that the pyrimidine derivatives containing sulphur act as inhibitors and antimetabolites [1–4]. Although the biological action mechanisms of these compounds are not generally well known, it seems probable that they would form complex compounds. That is why the study of the formation of metal complexes of such ligands has aroused growing interest.

In a previous paper [5] we reported some thermodynamic data of the complex formation processes between 4-amino-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-pyrimidine (LH) and the IIB group bivalent metal ions, in aqueous media. As a continuation of that work we now report a study of the complex formation processes, in aqueous media, between LH and a series of metal ions of particular biological interest [6]: Mn(II), Fe(II), Co(II), Ni(II) and Cu(II).

EXPERIMENTAL

Reagents

The solutions were prepared in double-distilled, carbon dioxide-free water. All the chemicals used in this work were analytical reagent grade.

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Solutions of LH (2×10^{-4} M) were prepared by diluting a 4×10^{-4} M solution of the compound which was previously prepared by direct weighing from a pure solid sample [7]. Solutions (5×10^{-3} M) of Mn(II) (chloride), Fe(II) (Mohr's salt), Co(II), Ni(II) and Cu(II) (nitrates) were prepared by diluting suitable volumes of the corresponding previously prepared and standardised 5×10^{-2} M solutions.

In order to maintain the ionic strength at the appropriate values, a 1 M standardised KCl solution was used in all cases.

As titrating reagent for all LH and LH/M(II) solutions, a 0.01 M carbonate-free NaOH standardised solution was used.

Apparatus and methods

To record pH, a Radiometer TTT-60 pH-meter fitted with glass and calomel electrodes was used. All the potentiometric titrations were carried out under nitrogen atmosphere.

For each LH/M(II) system, 25 ml of the corresponding solutions, in which [LH]/[M(II)] values were always kept at 2:1 ($LH = 10^{-4}$ M), were titrated against a standardised 10^{-2} M NaOH solution. The ionic strength and temperature were adjusted in each case to the appropriate value.

RESULTS AND DISCUSSION

Values of the deprotonation process constants of LH at different ionic strengths were obtained by applying Bjerrum's method to the pH titration data obtained from 2×10^{-4} M aqueous LH solutions at 25°C. These values are practically unaffected by the ionic strength (Table 1), and they have been used, together with those previously reported for LH at different temperatures [8], to calculate the stability constants of the complexes studied.

On the other hand, $\bar{n}$ values for all the systems under study were obtained by applying the method of Chaberek and Martell [9] to the potentiometric titration data of the LH/M(II) solutions. In all the LH/M(II) systems studied, the maximum $\bar{n}$ values obtained are about 1.7, indicating that the species formed are those defined by LH/M(II) stoichiometries 1/1 and 2/1. Likewise, by plotting $\bar{n}$ vs. pA values, the formation curves were obtained and by interpolating at $\bar{n} = 0.5$ and 1.5 the logarithmic values of

TABLE 1

Deprotonation constants of LH at different ionic strength ($T = 25$ °C)

I (mol l^{-1})	0.01	0.02	0.04	0.06	0.1
$K_A \times 10^{10}$ (mol l^{-1})	1.14	1.12	0.98	1.02	1.21

TABLE 2

Stability constants of 4-amino-1,6-dihydro-1-methyl-2-methylthio-5-nitroso-6-oxo-pyrimidine complexes with Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) at different temperatures and ionic strengths

Metal ion	I (mol l^{-1})	T (°C)	Log K_1	Log K_2	Log β_2
Mn(II)	0.01	25	3.57	4.06	7.63
	0.02	25	3.55	4.05	7.60
	0.04	25	3.54	4.02	7.56
	0.06	25	3.54	4.03	7.57
	0.10	25	3.55	4.02	7.57
	0.10	30	3.56	4.05	7.61
	0.10	40	3.69	4.11	7.80
	0.10	50	3.79	4.19	7.98
Fe(II)	0.01	25	7.00	7.05	14.05
	0.02	25	7.13	7.12	14.25
	0.04	25	7.12	7.08	14.20
	0.06	25	7.07	7.01	14.08
	0.10	25	7.36	7.09	14.46
	0.10	30	7.06	7.08	14.14
	0.10	40	7.13	7.22	14.35
	0.10	50	7.03	7.13	14.16
Co(II)	0.01	25	4.79	4.64	9.43
	0.02	25	4.81	4.62	9.43
	0.04	25	4.83	4.56	9.39
	0.06	25	4.77	4.54	9.31
	0.10	25	4.70	4.51	9.21
	0.10	30	4.91	4.66	9.57
	0.10	40	4.92	4.58	9.50
	0.10	50	5.00	4.65	9.65
Ni(II)	0.01	25	4.25	4.43	8.68
	0.02	25	4.32	4.47	8.79
	0.04	25	4.22	4.38	8.60
	0.06	25	4.16	4.41	8.57
	0.10	25	4.19	4.44	8.63
	0.10	30	4.29	4.52	8.81
	0.10	40	4.47	4.68	9.15
	0.10	50	4.58	4.75	9.33
Cu(II)	0.01	25	8.44	7.58	16.02
	0.02	25	8.65	7.64	16.29
	0.04	25	8.34	7.50	15.84
	0.06	25	8.31	7.57	15.88
	0.10	25	8.39	7.32	15.71
	0.10	30	8.50	7.30	15.80
	0.10	40	8.31	7.31	15.62
	0.10	50	8.25	7.15	15.40

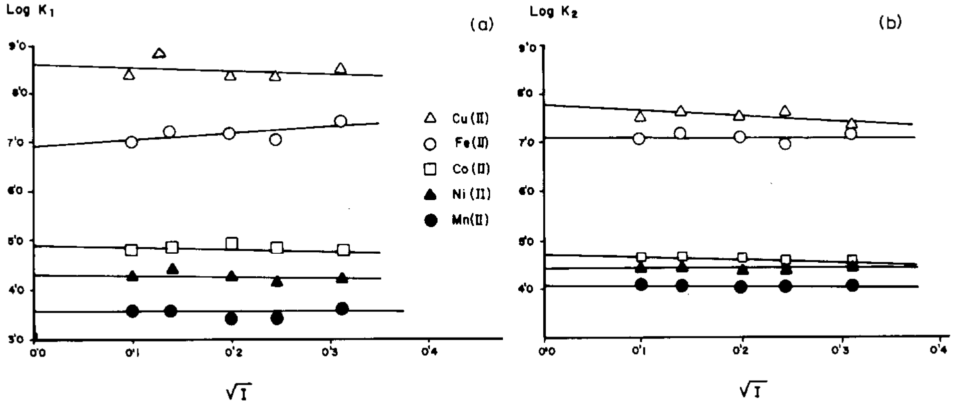

Fig. 1. Plots of (a) log K_1 and (b) log K_2 vs. $\sqrt{I}$ for M(II)–LH complexes at 25°C.

the corresponding stability constants, log K_1 and log K_2, were evaluated. These values, at different ionic strengths and temperatures, are listed in Table 2.

The stability constants of both 1/1 and 1/2 complexes are practically unaffected by both ionic strength and temperature, in the range of values studied in this work. The log K_1 and log K_2 values obtained at 0.1 M ionic strength and 45°C are higher than those of the corresponding metal complexes of uracil, thymine and cytosine [10]; this is probably due to the fact that in the complexes studied here, LH acts as a five-membered [11] or a six-membered [12] chelating agent, whereas in the complexes cited the corresponding ligands probably act as four-membered chelating agents.

The plots of both log K_1 and log K_2 values vs. $\sqrt{I}$ define straight lines in all cases (Fig. 1). In order to calculate the corresponding thermodynamic stability constants, we applied the Debye–Hückel limiting equation for 1 : 1 electrolytes [13] to these plots. The values obtained, together with those corresponding to the free energy changes, ΔG_i, calculated by the relation $\Delta G = -2.303RT \log K$, are listed in Table 3.

The ΔG_1 and ΔG_2 values are all negative, thus indicating that the formation processes of both $[ML]^+$ and $[ML_2]$ species are spontaneous.

On the other hand, the K_1 and K_2 stability constants for Fe(II) and Cu(II) complexes are in a similar range, following the Irving–Williams rule. This fact suggests that in such Fe(II) and Cu(II) complexes the ligand molecules are similarly coordinated to the respective central ions; this type of coordination is probably the same as that found for the ligand under study, LH, in the octahedral solid complex $Cu(L)_2(H_2O)_2$, that is, through the N atom of the 5-NO group and the O atom of the 6-oxo group [11]. This type of coordination would imply the formation of a five-membered ring on coordination of L to the central ion.

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)	3.57	4.08	7.65	20.38	23.29	43.67
Fe(II)	6.88	7.08	13.96	39.26	40.41	79.67
Co(II)	4.87	4.71	9.58	27.80	26.89	54.69
Ni(II)	4.34	4.42	8.76	24.78	25.23	50.01
Cu(II)	8.59	7.76	16.35	49.04	44.30	93.34

The K_1 and K_2 values for Mn(II), Co(II) and Ni(II) complexes are clearly in a lower range than that corresponding to the Fe(II) and Cu(II) complexes, probably indicating a different coordination model for these three metal ions. On the basis of literature data concerning some Co(II)/LH and Ni(II)/LH solid complexes [12], it could be supposed that in the Mn(II), Co(II) and Ni(II) complexes under study coordination occurs via the O atoms of the 5-NO and 6-oxo groups; thus the ligand is acting as a six-membered chelating ligand. So, the greater stability of the five-membered ring in the case of Fe(II) and Cu(II) complexes, as compared with that of the six-membered ring in Mn(II), Co(II) and Ni(II) complexes, could explain the different range of K_i values in both series of complexes.

Moreover, the more negative formation enthalpies of Fe(II) and Cu(II) complexes (Table 4) compared to those for the remaining three ions, indicates stronger L–M bonds in the first two cases than in the other three; this fact is also in accordance with the above hypothesis.

In contrast to the above data, the stability constant values given in a recent paper [14] for complexes of the type $[MX]^+$ and $[MX_2]$ (where M = Fe(II), Co(II), Ni(II) and Cu(II); X = 6,7-dihydro-3(*H*)-6-methyl-5-methylthio-7-oxo-vic-triazolo(4,5-*d*)pyrimidine) are in a lower range than those corresponding to the Mn(II), Co(II) and Ni(II) complexes of LH studied here. This might be due to the fact that X probably acts as a four-membered, N_4–N_3, chelating ligand [15]. Alternatively, it might be that

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	$-\Delta H_1$	$-\Delta H_2$	$-\Delta H$	ΔS_1	ΔS_2	ΔS
Mn(II)	−19.2	−12.8	−32.0	132.0	120.0	252.0
Fe(II)	18.1	−5.2	12.9	78.1	153.3	231.4
Co(II)	−18.3	−6.7	−25.0	152.7	109.9	262.6
Ni(II)	−23.1	−28.8	−51.9	162.8	177.2	340.0
Cu(II)	14.7	11.3	26.0	112.4	102.5	214.9

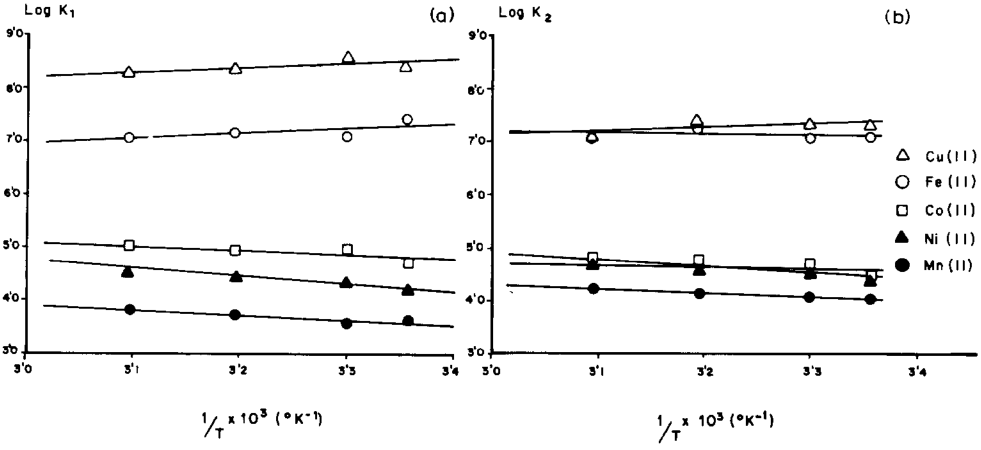

Fig. 2. Plots of (a) log K_1 and (b) log K_2 vs. $1/T$ for M(II)–LH complexes at 0.1 M (KCl) ionic strength.

only one of the two available N_4–N_3 donor nitrogen atoms coordinates with the metal atom and a chelate ring might not be formed.

The plots of log K_i vs. $1/T$ define straight lines in all cases (Fig. 2). Thus, we used the relation

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

to calculate ΔH_i and ΔS_i values at 0.1 M ionic strength (KCl) in the 25–50°C range. These values are also listed in Table 4.

In Fig. 2 it can be observed that the plots corresponding to LH/Mn(II), LH/Co(II) and LH/Ni(II) are all of negative slope, whereas those for LH/Fe(II) and LH/Cu(II) are of positive slope.

The enthalpy values for Fe(II) and Cu(II) complexes are negative, indicating that the corresponding formation processes are exothermic, whereas those corresponding to Mn(II), Co(II) and Ni(II) complexes are endothermic. Thus, in the last cases the enthalpy is unfavourable for complexation processes. Nevertheless, the entropy changes are all high, positive values; therefore, the entropy in all cases favours complexation processes. In particular in the LH/Mn(II), LH/Co(II) and LH/Ni(II) systems, the entropy is responsible for the corresponding complexation processes being spontaneous.

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