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EFFECT OF IONIC STRENGTH AND TEMPERATURE ON IONIZATION CONSTANTS AND STABILITY CONSTANTS OF 4-AMINO-1,6-DIHYDRO-2-METHYLTHIO-5-NITROSO-6-OXO-PYRIMIDINE AND ITS COMPLEXES WITH Fe(II), Co(II), Ni(II) AND Cu(II)

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ABSTRACT

The influence of ionic strength and temperature on the ionization constants of 4-amino-1,6-dihydro-2-methylthio-5-nitroso-6-oxo-pyrimidine (MTH) has been determined.

Stability constants for Fe(II), Co(II), Ni(II) and Cu(II) complexes of MTH at different ionic strengths and temperatures have also been calculated.

INTRODUCTION

Numerous sulphur-substituted pyrimidines and purine bases have found application as clinically useful drugs [1–6], and many sulphur derivatives of nucleic acids have shown anticarcinogenic properties [7,8]. On the other hand, some mercaptopyrimidine derivatives, such as 2-thiouracil [9], 4-amino-6-hydroxy-2-mercapto-5-nitroso-pyrimidine [10], 4,5-diamino-6-mercaptopyrimidine [11] and other 2- or 6-mercaptopyrimidine derivatives [12], have been used as analytical reagents.

We have studied the interactions of some pyrimidine and purine bases with metal ions in solution and in the solid phase in order to obtain information about the stability constants of the isolated complexes and the binding sites of these bases [13–15]. Thus, in a previous paper [16] we reported the ionization constants of some purine and pyrimidine derivatives and values of the stability constants of their Zn(II) and Cd(II) complexes.

For all the above reasons, we have found it interesting to continue the study of pyrimidine derivatives, choosing 4-amino-1,6-dihydro-2-methylthio-

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5-nitroso-6-oxo-pyrimidine (MTH) and its complexes with Fe(II), Co(II), Ni(II) and Cu(II) ions, in order to obtain the values of the respective ionization and stability constants.

EXPERIMENTAL

Solutions of MTH (2×10^{-4} M) were prepared by direct weighing from a pure sample, which was synthesized according to a previously reported method [17].

Analytical grade nitrate salts of Co(II), Ni(II) and Cu(II) and Fe(II) sulphate were used to prepare solutions in double-distilled carbon dioxide-free water. These solutions were conveniently standardized.

All potentiometric titrations were performed using a Radiometer TTT-60 pH-meter, fitted with glass and calomel electrodes. To maintain a constant temperature a thermostated bath was used. A standardized solution of sodium nitrate was used to maintain the required ionic strength.

RESULTS AND DISCUSSION

In order to obtain information about the influence of ionic strength and temperature on the dissociation process of 4-amino-1,6-dihydro-2-methylthio-5-nitroso-6-oxo-pyrimidine (MTH), we recorded the potentiometric curves of aqueous solutions of MTH (2×10^{-4} M) at various temperatures (25, 30, 40 and 50°C) and ionic strengths (0.01, 0.02, 0.06, 0.1, 0.2, 0.3, 0.4 and 0.5 M in $NaNO_3$).

From these curves and by application of Bjerrum's method [18] we obtained the pK values reported in Table 1. These results indicate that (i) the effect of ionic strength on pK_1 values is only considerable for high

TABLE 1

Influence of ionic strength and temperature on pK_1 values for MTH

I (mol l^{-1})	T (°C) = 25	30	40	50
0.01	6.45	6.38	6.30	6.24
0.02	6.47	6.44	6.34	6.30
0.06	6.48	6.43	6.36	6.27
0.10	6.52	6.45	6.37	6.24
0.20	6.50	6.48	6.42	6.38
0.30	6.77	6.45	6.39	6.33
0.40	6.48	6.47	6.43	6.40
0.50	6.69	6.66	6.59	6.55

TABLE 2

Thermodynamic constants and free energy (kJ mol^{-1}) of MTH at 25, 30, 40 and 50°C

T (°C)	pK	ΔG
25	6.42	36.6
30	6.33	36.7
40	6.27	37.6
50	6.19	38.3

values of I (0.4–0.5 M) and (ii) the values of the acidity constants decrease with increasing temperature in accordance with the weak acid nature of MTH.

The log K values for MTH at the four temperatures were plotted against $\sqrt{I}$ and extrapolated to zero ionic strength to get thermodynamic data. Values of thermodynamic constants and free energy (ΔG) for the dissociation process are summarized in Table 2.

Plotting ΔG values vs. T we obtained a straight line which was adjusted by least squares. From the slope and ordinate of this line, values of enthalpy and entropy were calculated. These values were: $\Delta H = 15.8$ kJ mol^{-1}; $\Delta S = -69.5$ J K^{-1} mol^{-1}.

On the other hand, Table 1 shows that the acidity constants of MTH decrease with increasing temperature. In order to obtain the corresponding thermodynamic function of the dissociation process, log K has been plotted vs. $1/T$ for each ionic strength value. In all cases, straight lines were obtained, which were also adjusted by least squares. From these lines, we obtained the data summarized in Table 3.

The enthalpy values are positive, as for the dissociation of a weak acid, and the entropy values are negative due to the increased order produced by the solvation process.

The potentiometric titration curves of solutions containing Fe(II), Co(II), Ni(II) or Cu(II) and MTH in a 1 : 1 ratio at 25, 30, 40 or 50°C and 0.01, 0.02, 0.06, 0.1, 0.2 or 0.5 M ionic strength were recorded. The stability constants obtained by application of Bjerrum's method to these curves are presented in Table 4.

The values obtained are analogous to those found for other metal complexes of pyrimidine derivatives [19]. Values of the stability constants (Table

TABLE 3

Thermodynamic functions of MTH at different ionic strengths

	I (mol l^{-1}) = 0.01	0.02	0.06	0.1	0.2	0.3	0.4	0.5
ΔH (kJ mol^{-1})	15.10	13.22	15.02	19.70	9.09	10.41	6.09	10.57
$-\Delta S$ (J K^{-1} mol^{-1})	72.34	79.42	73.49	58.56	93.97	88.99	103.72	92.63

TABLE 4

Stability constants, log K, of 1:1 M^{2+}/MTH complexes at different ionic strengths and temperatures

I (mol l^{-1})	Fe	Co	Ni	Cu	Fe	Co	Ni	Cu
	At 25°C				*At 30°C*			
0.01	5.90	4.65	5.09	6.36	5.84	4.39	4.96	6.24
0.02	5.86	4.64	4.95	6.27	5.78	4.58	4.88	6.10
0.06	5.78	4.63	4.84	6.09	5.71	4.55	4.82	5.97
0.1	5.80	4.61	4.76	5.97	5.73	4.50	4.69	5.83
0.2	5.70	4.40	4.60	5.86	5.66	4.35	4.57	5.79
0.5	5.44	4.35	4.50	5.62	5.33	4.29	4.50	5.52
	At 40°C				*At 50°C*			
0.01	5.66	4.50	4.80	6.06	5.52	4.40	4.66	5.94
0.02	5.64	4.50	4.70	5.86	5.51	4.39	4.60	5.70
0.06	5.63	4.41	4.65	5.77	5.53	4.28	4.50	5.63
0.1	5.62	4.38	4.58	5.63	5.51	4.19	4.48	5.52
0.2	5.54	4.24	4.53	5.60	5.42	4.10	4.46	5.41
0.5	5.21	4.21	4.47	5.35	5.08	4.09	4.45	5.26

4) show, in all cases, a decrease with a rise in temperature from 25 to 50°C. This suggests that the formation of Fe(II), Co(II), Ni(II) and Cu(II) complexes with MTH is favourable at lower temperatures. On the other hand, the activity of a metal ion for complexation with a ligand decreases in the presence of other ions in the system. This fact can be seen in Table 4, where values of log K decrease with increasing ionic strength of the medium and, hence, the metal ion is screened by the other ions. This is in accordance with the similar findings reported by Hückel [20] that the stability decreases with increasing ionic strength of the medium.

The thermodynamic stability constants were obtained at 25, 30, 40 and 50°C by plotting log K against $\sqrt{I}$ and extrapolating to zero ionic strength. These values are reported in Table 5.

The corresponding values of free energy (ΔG) for the complexation processes were calculated by the relation $\Delta G = -2.303RT\log K$, and these values are given in Table 6.

TABLE 5

Thermodynamic constants log K_1, of complexes with MTH at 25, 30, 40 and 50°C

Metal ion	T (°C) = 25	30	40	50
Fe(II)	5.98	5.92	5.78	5.66
Co(II)	4.73	4.70	4.55	4.42
Ni(II)	5.09	4.99	4.78	4.63
Cu(II)	6.41	6.27	6.05	5.90

TABLE 6

Free energy, ΔG (kJ mol^{-1}), of metal ion–MTH complexes at 25, 30, 40 and 50°C

Metal ion	T (°C) = 25	30	40	50
Fe(II)	34.10	34.33	34.62	34.99
Co(II)	26.98	27.25	27.26	27.32
Ni(II)	29.03	28.94	28.63	28.62
Cu(II)	36.56	36.36	36.24	36.47

In all cases, ΔG is negative which means that the complexation processes are spontaneous. By comparing the values of ΔG for Fe(II), Co(II), Ni(II) and Cu(II) it is seen that its value is lowest for Cu(II) which suggests that this ion has the highest tendency for interaction with the ligand MTH.

The stability order of the complexes Cu(II) > Fe(II) > Ni(II) > Co(II), is in accordance with the Irving–Williams rule [21] with the exception of the Fe(II) complex. This higher stability of the Fe(II) complex has been observed in other analogous cases [22,23]. The values of stability constants collected in Table 4 are similar to those found by other authors for complexes of Ni(II) with 5-methyl-2-thiouracil [24], Fe(II), Co(II), Ni(II) and Cu(II) with 5-arylazo-2-methylthio-4-hydroxy-6-methyl-pyrimidine [22], and Co(II), Ni(II) and Cu(II) with nucleoside derivatives [25].

From the values in Table 4 and using the relation

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

by plotting log K vs $1/T$, we have calculated the corresponding enthalpy and entropy changes for each complexation process. These values are listed in Table 7.

TABLE 7

Enthalpy (kJ mol^{-1}) and entropy (J K^{-1} mol^{-1}) of metal–MTH complexes at different ionic strengths

Metal ion	I (mol l^{-1}) = 0.01	0.02	0.06	0.1	0.2	0.5
	$-\Delta H$					
Fe(II)	21.89	24.69	17.15	20.29	21.82	4.69
Co(II)	17.43	17.22	24.73	29.51	21.17	18.45
Ni(II)	29.86	26.56	26.03	20.36	9.88	3.96
Cu(II)	30.79	41.64	33.87	33.07	33.40	26.77
	ΔS					
Fe(II)	20.09	28.90	52.82	42.49	36.36	45.36
Co(II)	30.43	30.81	5.36	−10.91	13.21	21.24
Ni(II)	−3.25	5.55	5.74	22.58	54.93	72.72
Cu(II)	17.80	−20.29	2.49	2.68	0.42	1.72

The enthalpy values are negative, which supports the idea that the lower temperature is favourable for complexation. On the other hand, entropy values, for all complexes, are positive, which suggests that, on account of the complexation process, the disorder of the system increases much more rapidly than the increase in the order taking place in the complexation reactions.

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