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Metal Complexes of Substituted Pyrimidines

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Abstract

The interaction of Cu(II), Ni(II), Zn(II), Co(II), Mg(II) and Ca(II) ions with substituted pyrimidines, such as 2-mercaptopyrimidine, 4,5-diamino-6-hydroxypyrimidine and 2,4-diamino-6-hydroxypyrimidine, has been investigated by potentiometric studies. The proton dissociation constants of the ligands and the stability constants of the complexes containing 1:1 and 2:1 molar ratios of the ligand to the metal ions have been reported at 45 °C and 0.1 M(KNO_3) ionic strength.

Introduction

Purines and pyrimidines are the main constituents of nucleic acids and play an important role in many biological systems. Substituted purines and pyrimidines are also biologically important; pyrimidine thions were found to inhibit the synthesis of t-RNA under certain conditions and thus act as antitumor and antithyroid agents [1–8]. During recent years there has been an upsurge of interest in new drugs for cancer treatment, and the use of metal coordination compounds in this regard has attracted the attention of chemists. In addition, substituted pyrimidines also serve as model compounds for a range of important biological molecules. Although considerable work has been carried out on the complexes of substituted purines and pyrimidines with a number of metal ions in the solid state [9–12], very little chemistry is known for these complexes in aqueous media. It was therefore considered important to investigate the metal complexes of substituted pyrimidines with Cu(II), Ni(II), Zn(II), Co(II), Mg(II) and Ca(II) ions in aqueous solution. In the present investigation the proton dissociation and stability constants of 2-mercaptopyrimidine, 4,5-diamino-6-hydroxypyrimidine and 2,4-diamino-6-hydroxypyrimidine (Fig. 1) with the above-mentioned metal ions have been determined in a 1:1 and 2:1 ratio, and the metal binding sites of these ligands have been proposed.

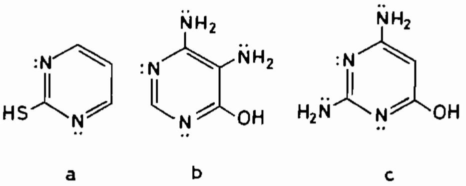

Fig. 1. The sketch of molecules used as ligands: (a) 2-mercaptopyrimidine; (b) 4,5-diamino-6-hydroxypyrimidine; (c) 2,4-diamino-6-hydroxypyrimidine.

Experimental

The experimental method consisted of the potentiometric titration of each ligand with standard sodium hydroxide solution in the absence and presence of the metal ions being investigated. The ionic strength of the solution was maintained constant in the course of the titration by 0.1 M (KNO_3) and a relatively low concentration of the ligand and metal ions. Pre-saturated nitrogen was passed through the solution throughout the course of the titration and the temperature was maintained at 45 ± 0.1 °C. A Digisun pH-meter with combination of glass and Calomel electrodes was used to measure the hydrogen ion concentration. The electrode system was calibrated by direct titration with acetic acid, and the observed pH-meter reading was compared with the actual hydrogen ion concentration as calculated from the data tabulated by Harned and Owen [16]. The pH regions below 3.5 and above 10.5 were calibrated by direct measurement of the hydrogen ion concentration in hydrochloric acid and sodium hydroxide solutions, respectively. The equilibrium constants reported in this investigation correspond to the reference state of infinitely dilute reaction species in a medium of 0.1 M (KNO_3) and thus all equilibrium constants determined are very close to the thermodynamic constants.

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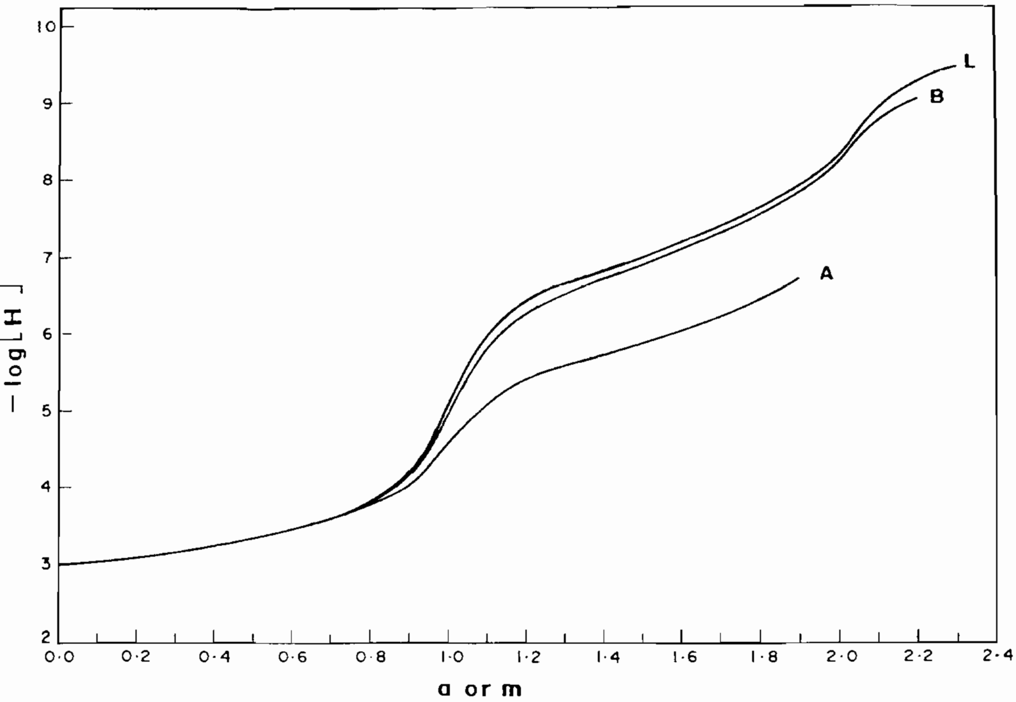

Fig. 2. Potentiometric titration curves of 2-mercaptopyrimidine with Ni(II) and Ca(II) in 1:1 ratio of the ligand to the metal ion at 45 °C, $\mu = 0.10$ M (KNO_3). L = free ligand; A = Ni(II); B = Ca(II); a = mol of base added per mol of ligand; m = mol of base added per mol of metal ion.

Reagents

Chromatographically pure samples of 2-mercaptopyrimidine, 4,5-diamino-6-hydroxypyrimidine and 2,4-diamine-6-hydroxypyrimidine purchased from Sigma Chemical Company (U.S.A.) were employed in this work. Fresh solid ligand was weighed out for each titration to ensure no loss by hydrolysis or photochemical decomposition. The metal salt solutions were standardized by titration with the disodium salt of EDTA, as described by Schwarzenbach [17]. Carbonate-free sodium hydroxide was prepared by the method of Schwarzenbach and Biedermann [18] and was standardized by titration with pure potassium acid phthalate.

Results

2-Mercaptopyrimidine

The potentiometric titration curves of monoprotonated 2-mercaptopyrimidine shown in Fig. 2 indicate a steep inflection at $a = 1$ followed by a buffer region at higher pH. The pK_a and pK_{2a} values calculated [13] in the lower and upper buffer regions are presented in Table I. The first dissociation of 2-mercaptopyrimidine probably involves the removal of a proton from $\overset{+}{N}_3H$ of the pyrimidine ring [19, 20]. The second dissociation is obviously due to the dissociation of a proton from the C_2–SH group of the pyrimidine (Fig. 3a).

TABLE I. Equilibrium Constants Associated with the Interaction of 2-Mercaptopyrimidine with Bivalent Metal Ions; $T = 45$ °C; $\mu = 0.10$ M (KNO_3)

Metal ion	2-Mercaptopyrimidine ($pK_a = 2.11 \pm 0.01$; $pK_{2a} = 7.01 \pm 0.01$) log K	6-Mercaptopurines[a] ($pK_a = 2.2 \pm 0.01$; $pK_{2a} = 6.9 \pm 0.1$; $pK_{3a} = 9.1 \pm 0.1$) log K
Cu(II)	–	7.0
Ni(II)	4.43 ± 0.06	6.8 ± 0.3
Zn(II)	3.92 ± 0.04	6.6 ± 0.2
Co(II)	3.61 ± 0.05	6.5 ± 0.3
Mg(II)	2.76 ± 0.02	6.0 ± 0.2
Ca(II)	2.41 ± 0.04	6.4 ± 0.2

[a] These values have been previously reported [13].

Interaction of Metal Ions with 2-Mercaptopyrimidine

Titration curves of 2-mercaptopyrimidine in the presence of Ni(II) and Ca(II) in 1:1 ratio is represented in Fig. 2; similar titration curves were obtained in the case of the other metal ions being investigated. Since there is no metal interaction up to

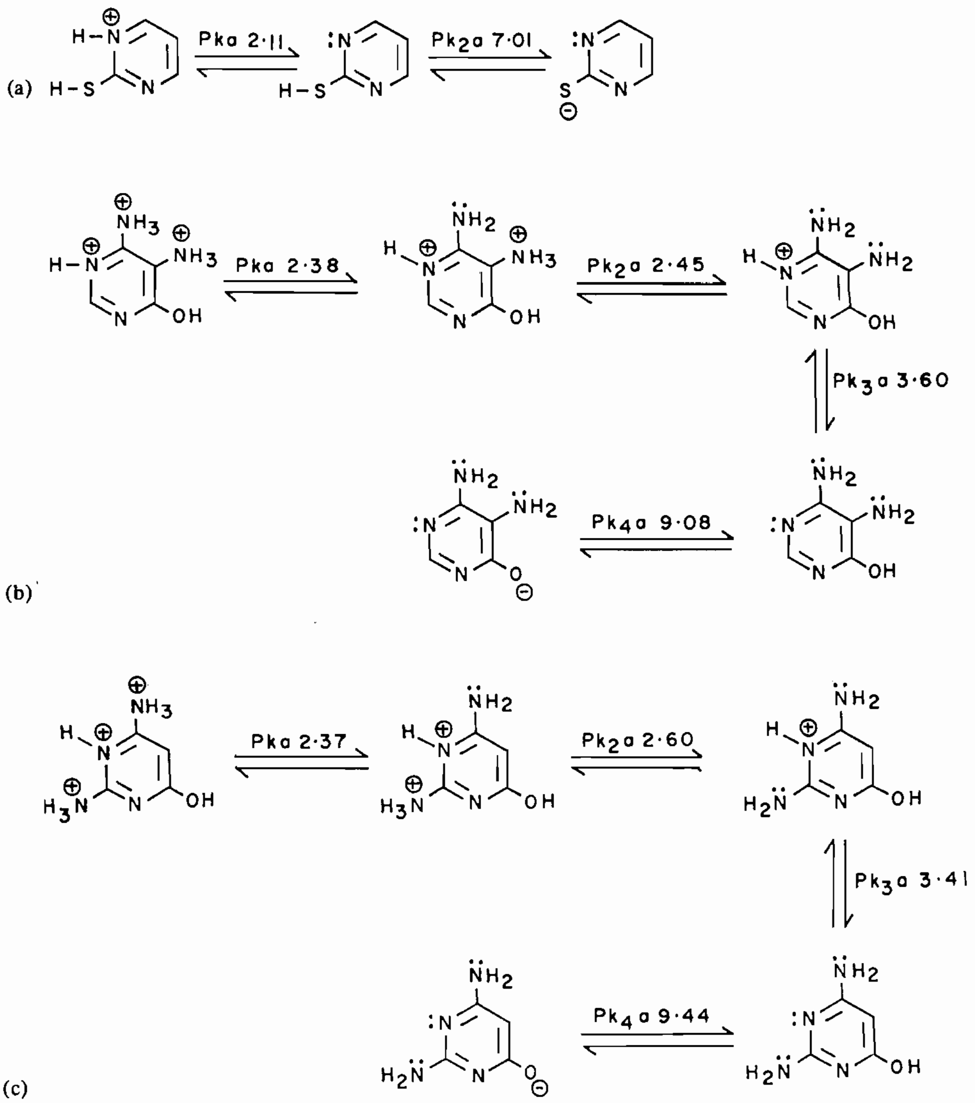

Fig. 3. Proton dissociation of the ligands: (a) monoprotonated 2-mercaptopyrimidine; (b) triprotonated 4,5-diamino-6-hydroxypyrimidine; (c) triprotonated 2,4-diamino-6-hydroxypyrimidine.

$m = 1$ for all the metal ions, the stability constants of 1:1 normal complexes were calculated well ahead of the precipitation point. In case of Cu(II) it is not possible to determine the stability of the complex because of the immediate separation of a solid phase on mixing the metal solution to the ligand. The stability constants of the 1:1 complexes reported in Table I decrease in the order: Ni(II) > Zn(II) > Co(II) > Mg(II) > Ca(II).

4,5-Diamino-6-hydroxypyrimidine

The potentiometric titration curve of 1:1 triprotonated 4,5-diamino-6-hydroxypyrimidine shown in Fig. 4 indicates a steep inflection at $a = 3$ followed by a buffer region at higher pH. The four pK values calculated in the lower and upper buffer regions are presented in Table II. In triprotonated 4,5-diamino-6-hydroxypyrimidine the dissociation of the first three protons occurs in overlapping steps; hence the dissociation constants K_a and K_{2a} were calculated to be between $a = 0$ to 2, and the constants K_{2a} and K_{3a} at $a = 1$ to 3, respectively, by the graphic method [21]. The value of K_{2a} is the same in both cases (Fig. 3b).

Interaction of Metal Ions with 4,5-Diamino-6-hydroxypyrimidine

Titration curves of 4,5-diamino-6-hydroxypyrimidine in the presence of Cu(II), Zn(II) and Mg(II) in 1:1 ratio are represented in Fig. 4. The titra-

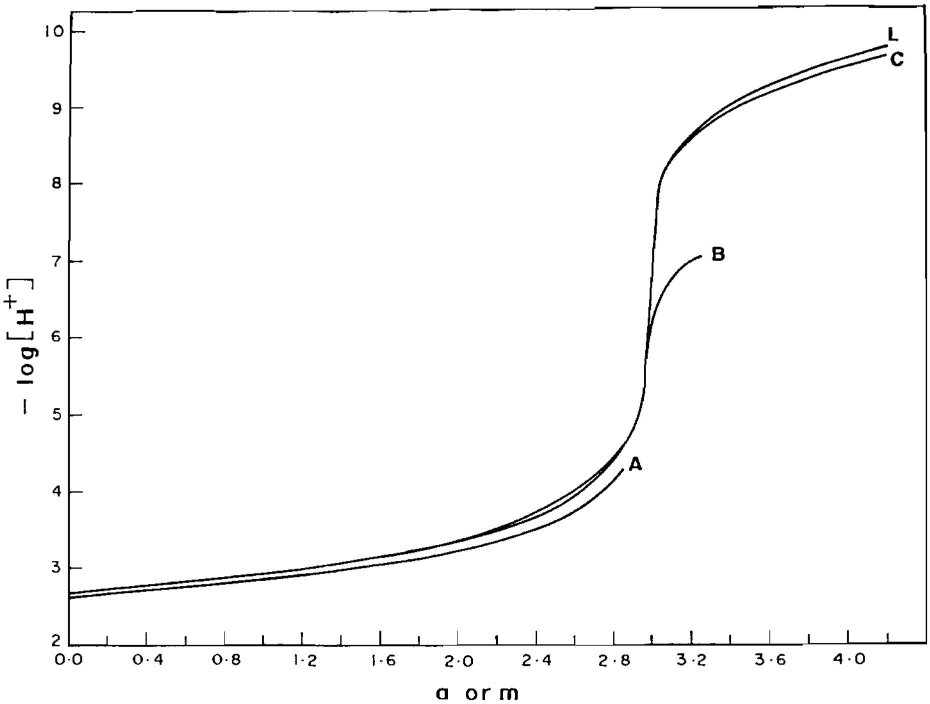

Fig. 4. Potentiometric titration curves of 4,5-diamino-6-hydroxypyrimidine with Cu(II), Zn(II) and Mg(II) in 1:1 ratio of the ligand to the metal ion at 45 °C, $\mu = 0.10$ M (KNO_3). L = free ligand; A = Cu(II), B = Zn(II); C = Mg(II); a = mol of base added per mol of ligand; m = mol of base added per mol of metal ion.

TABLE II. Equilibrium Constants Associated with the Interaction of Substituted Pyrimidines with Bivalent Metal Ions; $T = 45$ °C; $\mu = 0.10$ M (KNO_3)

Metal ion	4,5-Diamino-6-hydroxypyrimidine ($pK_a = 2.38$; $pK_{2a} = 2.45$; $pK_{3a} = 3.60$; $pK_{4a} = 9.08 \pm 0.02$)			Cytosine[a] ($pK_a = 4.2 \pm 0.1$; $pK_{2a} = 10.0 \pm 0.1$)			2,4-Diamino-6-hydroxypyrimidine ($pK_a = 2.37$; $pK_{2a} = 2.60$; $pK_{3a} = 3.41$; $pK_{4a} = 9.44 \pm 0.04$)	
	1:1		1:2	1:1		1:2	1:1	
	$\log K^{M}_{MHL}$	$\log K^{M}_{ML}$	$\log K^{MHL}_{MH_2L_2}$	$\log K^{M}_{MHL}$	$\log K^{M}_{ML}$	$\log K^{MHL}_{MH_2L_2}$	$\log K^{M}_{MHL}$	$\log K^{M}_{ML}$
Cu(II)	4.52 ± 0.07		4.3 ± 0.1	3.1 ± 0.1		2.48 ± 0.06	3.20 ± 0.05	
Ni(II)	3.06 ± 0.05		3.3 ± 0.1	2.9 ± 0.1		3.40 ± 0.06		
Zn(II)	2.75 ± 0.03		3.7 ± 0.1	2.8 ± 0.1		3.14 ± 0.08		
Co(II)		4.06 ± 0.05		2.8 ± 0.1		3.11 ± 0.03		
Mg(II)		3.14 ± 0.03		2.4 ± 0.1	2.7 ± 0.1	3.54 ± 0.08		2.7 ± 0.1
Ca(II)		2.93 ± 0.02		2.2 ± 0.1	2.5 ± 0.1	3.48 ± 0.05		2.5 ± 0.1

[a] The values have been reported previously [14, 15].

tion curve of Ni(II) follows the Zn(II) curve up to $m = 3$ and it precipitates before $m = 4$. Therefore, in the case of Cu(II), Ni(II) and Zn(II), the formation of a 1:1 protonated complex was assumed. In the case of Co(II) and Ca(II), the titration curves were similar to the Mg(II) curve, but Co(II) precipitates before $m = 4$. In such cases the formation of 1:1 normal complexes was assumed in the upper buffer regions, and the corresponding stability constants were calculated. The stability of the 1:1 protonated complexes of 4,5-diamino-6-hydroxypyrimidine decrease in the order of Cu(II) > Ni(II) > Zn(II), and the stabilities of normal complexes decrease in the order: Co(II) > Mg(II) > Ca(II).

The titration curves of 2:1 triprotonated 4,5-diamino-6-hydroxypyrimidine in the absence and presence of Cu(II), Zn(II) and Co(II) metal ions are shown in Fig. 5. The titration curve of Ni(II)

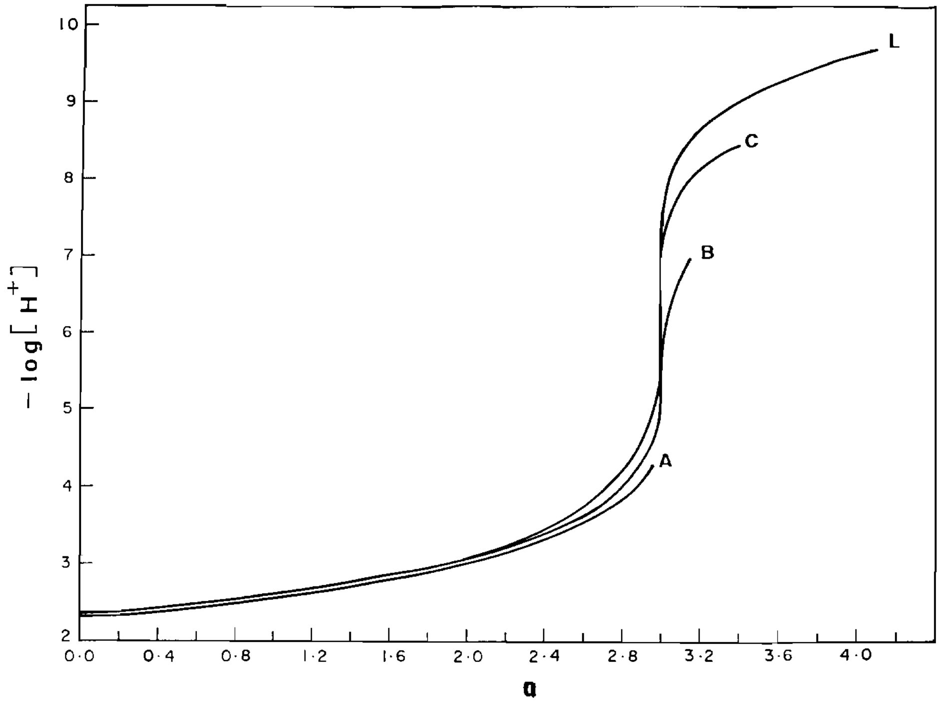

Fig. 5. Potentiometric titration curves of 4,5-diamino-6-hydroxypyrimidine with Cu(II), Zn(II) and Co(II) in 2:1 ratio of the ligand to the metal ion at 45 °C, μ = 0.10 M (KNO_3). L = free ligand; A = Cu(II); B = Zn(II); C = Co(II); a = mol of base added per mol of ligand.

is similar to the Zn(II) curve. The formation of 2:1 diprotonated complexes was assumed in the cases of Cu(II), Zn(II) and Ni(II) ions, and the stability constants were calculated. With Ca(II) and Mg(II) there is no interaction with the metal ions.

2,4-Diamino-6-hydroxypyrimidine

The potentiometric titration curve of triprotonated 2,4-diamino-6-hydroxypyrimidine presented in Fig. 6 shows a steep inflection at $a = 3$ followed by a buffer region. The four pK values calculated as in the case of 4,5-diamino-6-hydroxypyrimidine are presented in Table II (Fig. 3c).

Interaction of Metal Ions with 2,4-Diamino-6-hydroxypyrimidine

The titration curves of 2,4-diamino-6-hydroxypyrimidine in the presence of Cu(II), Zn(II) and Mg(II) in 1:1 ratio is represented in Fig. 4. Except for Cu(II), there is no interaction between m = 2 to 3 with all the other metal ions. The formation of a 1:1 protonated complex for Cu(II) was assumed in the said buffer range, and the corresponding constants were calculated. Since there is no formation of precipitate in Ca(II) and Mg(II), the formation of a 1:1 normal complex is assumed and the stability constants calculated are presented in Table II.

Discussion

2-Mercaptopyrimidine can be compared with 6-mercaptopurine, where the –SH group is present in the pyrimidine ring. In both cases, the pK_a and pK_{2a} values are almost the same; the presence of an imidazole ring in 6-mercaptopurine does not affect the dissociation of protons in both the positions. The extra stability of 6-mercaptopurine complexes may be due to the formation of a 5-membered chelate ring with the $C_6-\bar{S}$ and N_7 positions, whereas 2-mercaptopyrimidine acts as a monodentate ligand coordinating to the metal ion through the $C_2-\bar{S}$ group.

The sum of the pK_a values of 4,5-diamino-6-hydroxypyrimidine is slightly lower than that of 2,4-diamino-6-hydroxypyrimidine; this difference may be due to the intramolecular hydrogen bonding. In contrast to the lower pK_a values of 4,5-diamino-6-hydroxypyrimidine, the stabilities of the metal complexes are comparatively higher than those of 2,4-diamino-6-hydroxypyrimidine. This is because of the fact that 4,5-diamino-6-hydroxypyrimidine forms a chelate coordinating to the metal ion through the C_5-NH_2 and $C_6-\bar{O}$ groups, whereas 2,4-diamino-6-hydroxypyrimidine acts as a monodentate ligand coordinating through the $C_6-\bar{O}$ group.

It is also of interest to compare the dissociation and the stability constants of cytosine with that

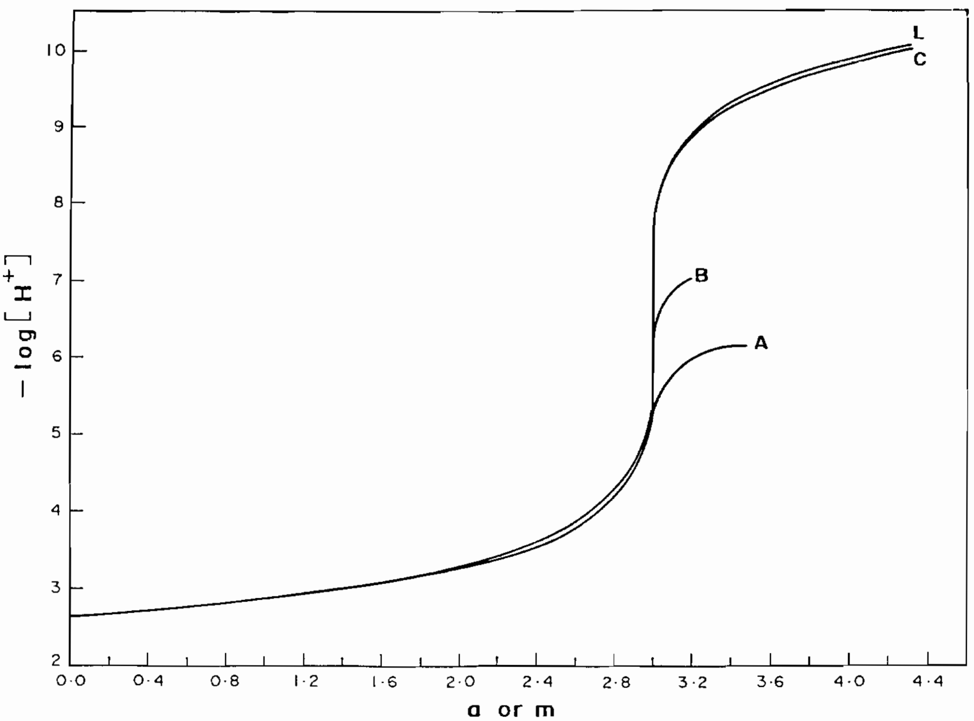

Fig. 6. Potentiometric titration curves of 2,4-diamino-6-hydroxypyrimidine with Cu(II), Zn(II) and Mg(II) in 1:1 ratio of the ligand to the metal ion at 45 °C, μ = 0.10 M (KNO_3). L = free ligand; A = Cu(II); B = Zn(II); C = Mg(II); *a* = mol of base added per mol of ligand; *m* = mol of base added per mol of metal ion.

of 4,5-diamino-6-hydroxypyrimidine. In the case of cytosine the pK_a and pK_{2a} values are 4.2 and 10.0, whereas the pK_{3a} and pK_{4a} values of 4,5-diamino-6-hydroxypyrimidine are 3.60 and 9.08, respectively, corresponding to the dissociation of protons from the $\overset{+}{N}_3H$ and –OH groups. Even though the pK_a values of 4,5-diamino-6-hydroxypyrimidine are slightly less than those of cytosine, the comparatively high stabilities of the metal complexes may be due to chelation. On comparing the stabilities of 1:1 and 2:1 Cu(II) complexes of 4,5-diamino-6-hydroxypyrimidine and cytosine, the extra stability in the former case is due to the formation of a 5-membered chelate ring through the C_5–NH_2 and C_6–$\bar{O}$ positions. The stabilities of the normal 1:1 complexes of Ca(II) and Mg(II) are slightly higher than those of cytosine because of the weak interaction with the C_5–NH_2 group. In the case of Ni(II) and Zn(II), this weak interaction is not as effective; therefore the stabilities of these complexes of 4,5-diamino-6-hydroxypyrimidine are almost the same as that of cytosine.

The stabilities of 1:1 complexes of 2,4-diamino-6-hydroxypyrimidine may be compared with those of cytosine. In 2,4-diamino-6-hydroxypyrimidine, insertion of an extra –NH_2 group in the pyrimidine ring does not affect the stabilities of the complexes, as all the substituents are in a meta position to each other. Therefore, 2,4-diamino-6-hydroxypyrimidine and cytosine act as monodentate ligands having the same stability constant values as most of the metal complexes.

The higher stabilities of 2:1 as compared to 1:1 complexes of 4,5-diamino-6-hydroxypyrimidine may be due to the weak Van der Waals forces between the two 4,5-diamino-6-hydroxypyrimidine rings in the complex which may have a parallel configuration with respect to each other.

Supplementary Material

Has been deposited and is available from the Editor-in-Chief on request.

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