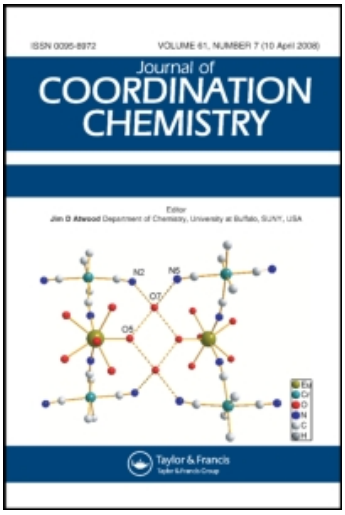

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Solution and solid studies of some metal complexes with cytosine and its derivatives

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SOLUTION AND SOLID STUDIES OF SOME METAL COMPLEXES WITH CYTOSINE AND ITS DERIVATIVES

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Stability constants for the binary (1 : 1) complexes of CoII, NiII, CuII, ZnII, CdII, CaII, SrII and BaII with cytosine, cytidine, 5-bromocytosine, 5-azacytosine and 5-fluorocytosine were determined in aqueous solution (Ionic strength, $\mu = 0.1\,\text{mol}\,\text{dm}^{-3}$ $NaNO_3$) potentiometrically at 25, 35 and 45°C. Experimental pH titration data were analyzed using the BEST computer program in order to evaluate formation constants of various intermediate species formed in the above binary systems. Enthalpy and entropy changes for the formation of binary complexes were calculated. On the basis of solution studies, efforts were made to prepare the binary complexes with 5-azacytosine ligand. Isolated solid complexes were characterized by different techniques and spectroscopic studies suggested a polymeric nature for the complexes, with OH and 5-azacytosine acting as bridging ligands.

Keywords: Solution studies; Solid complexes; Cytosine; Species distribution

INTRODUCTION

Cytosine (C) is the organic base of the pyrimidine family and forms three hydrogen bonds with guanine in both RNA and DNA. The 5-halopyrimidines exhibit remarkable chemotherapeutic, biochemical and biophysical properties. For example, 5-fluorocytosine (5FC), a fluorinated pyrimidine (Fig. 1) [1] has been widely used as an antifungal agent. It is well absorbed from the gastrointestinal tract and 85 to 95 percent is excreted as unchanged form in the urine within 24 h of being taken orally [2]. Of clinical importance is that 5FC readily penetrates the blood-brain-barrier with 64 to 88 percent of serum levels achievable in cerebrospinal fluid. Although 5FC is an inhibitor of both RNA and DNA synthesis [3,4] in exponentially growing cells, it does not influence the germination in serum. Unlike other fluorinated pyrimidines such as 5-fluorouracil (5FU), it has little direct toxicity to human cells. It is also completely inactive against

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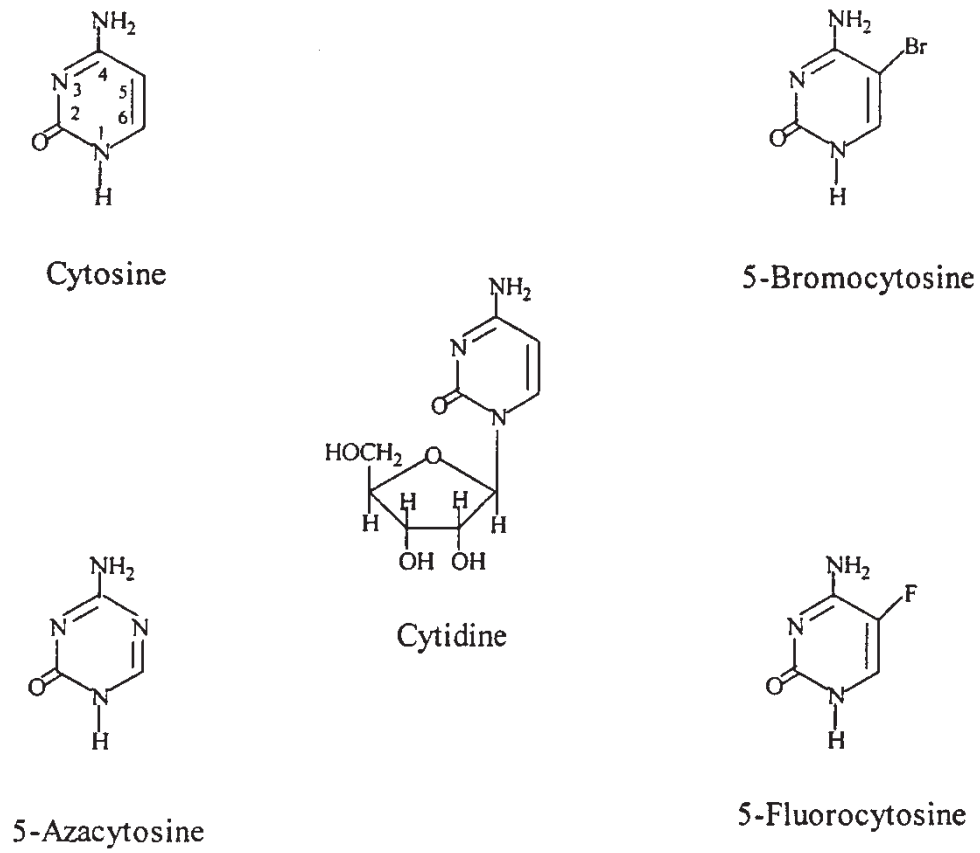


FIGURE 1 Structures of cytosine, cytidine, 5-bromocytosine, 5-azacytosine and 5-fluorocytosine.

bacteria. Because of the increasing clinical use of 5FC and its reported lack of metabolism in mammalian cells, investigation of its effect on human and murine hematopoietic precursors and of the possible biochemical basis for its interaction with these cells has been done *in vitro* [5]. The results strongly suggested that hematopoietic toxicity of 5FC is mediated through cellular metabolism of the drug, as reversal of cytotoxic effects of 5FC by uracil appeared to be competitive. 5FC is weakly immunosuppressive when given in lethal doses to mice and inhibits the response of mouse and human lymphoid cells to plant lectins at concentration of 1.0 mg/cm^3 or more due to the conversion of 5FC to 5FU or other toxic metabolites [6].

Because of the interesting biological properties of cytosine and its halo derivatives, many workers have studied the complexation behavior of cytosine in simple as well as mixed ligand complexes both in the solid state and solution [7–26] but there is no report available on solution studies of halogenated cytosine complexes and their thermodynamic properties. The present article deals with the systematic studies of the interaction of C, cytidine (CD), 5-bromocytosine (5BrC), 5-azacytosine (5AC) and 5FC with cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), calcium(II), barium(II) and strontium(II) ions in solution by using Bjerrum–Calvin's pH-titration technique [27] as adopted by Irving–Rossotti [28] followed by some solid complex

synthesis, i.e., with 5AC, in order to suggest the proposed binding site of the ligand and possible structure of complexes. Thermodynamic parameters at different temperatures i.e., 25, 35 and 45°C, have also been calculated and the presence of different complex species at different pH in solution were determined through species distribution plots by using computer p^{KAS} and BEST programs [29].

EXPERIMENTAL

The ligands C and CD were purchased from SRL, Mumbai and 5BrC, 5AC, 5FC from Fluka, Switzerland, and were used as supplied. Ligand solutions (0.01 M) were prepared by dissolving the required amount of ligands in the minimum volume of freshly doubly-distilled CO_2-free water with vigorous shaking at 40°C and subsequently diluting to final volume. The metal nitrates (E Merck, India) were used to prepare solutions (0.01 M) and were standardized by EDTA titrations using suitable indicators [30]. CO_2-free NaOH solutions (0.2 M) was prepared and standardized against a standard oxalic acid solution [31]. All reagents used were of AR grade.

Titrations were performed at 25, 35 and 45 ± 0.1°C in a double-walled cell, fitted with a thermostat (Julabo F-10). The ionic strengths (μ) of all the titration mixtures were adjusted to 0.1 M by adding the requisite volume of $NaNO_3$ solution (1.0 M). In all titrations, oxygen-free N_2 gas was passed into the solution before and during the pH measurements. Titrant (CO_2-free standard NaOH) was added to the titration cell and the pH changes were monitored with a Schott CG 841 pH meter using a glass electrode (Schott Gerate 6280), calibrated with standard buffer solutions (pH 4.0 and 10.0). The pH regions below 3.5 and above 10.5 were calibrated using standard HCl and NaOH solutions, respectively.

Methods

To determine the proton dissociation constants (pK^n) of the free ligands, the following mixtures (i) and (ii) were prepared for each ligand (L) and titrated separately with the CO_2-free standard alkali solution (0.2 M NaOH); (i): HNO_3 (0.02 M, 5.0 cm^3) + $NaNO_3$ (1.0 M, 5.0 cm^3); (ii): (i) + L (0.01 M, 5.0 cm^3). In the study of binary (1 : 1) systems, the following mixture (iii) was prepared for each metal ion and titrated as above: (iii): (ii) + MII (0.01 M, 5.0 cm^3). In each case the total volume of the cell was maintained to 50 cm^3 and the metal ions as well as ligand concentrations were 1.0×10^{-3} M. Nitric acid was used to lower the pH of the initial solution mixture. The pH titrations were terminated when either the pH readings became unstable, showing a downward drift, or precipitation occurred. The pH-metric titration curves were plotted in terms of pH *vs* a (where a is the number of moles of alkali required per mol of ligand) for acid (curve a), C (curve b), CD (curve c), CuII–C (curve d), CuII–CD (curve e) (Fig. 2a, a–e); for 5BrC (curve a), 5AC (curve b), 5FC (curve c), CuII–5BrC (curve d), CuII–5AC (curve e), CuII–5FC (curve f) (Fig. 2b, a–f) systems, respectively. In analyzing the titration data for the determination of proton dissociation constants of free ligands and formation constants of binary metal complexes species using computer p^{KAS} and BEST programs [29], several complex equilibria were studied. Standard deviations were also evaluated for the corresponding equilibrium constants. Enthalpy and entropy

values associated with various proton–ligand and metal–ligand equilibria were calculated using Eqs. (i), (ii) and (iii)

$$\Delta H_f^0 = \frac{2.303RT_1T_2\log(K_2/K_1)}{(T_2 - T_1)} \quad \text{(i)}$$

$$\Delta G_f^0 = -RT\ln K \quad \text{(ii)}$$

$$\Delta S_f^0 = \frac{(\Delta H_f^0 - \Delta G_f^0)}{T} \quad \text{(iii)}$$

where ΔH_f^0 = standard enthalpy change, R = gas constant, T = absolute temperature, K = equilibrium constant, ΔG_f^0 = standard free energy change and ΔS_f^0 = standard entropy change.

Synthesis of MII-5-Azacytosine Complexes

Some 1.0 mmol of the hydrated metal nitrate was refluxed for about 10 h in a mixture of 35.0 cm^3 of ethyl alcohol and 15.0 cm^3 of triethylorthoformate. Then, 1.0 mmol of

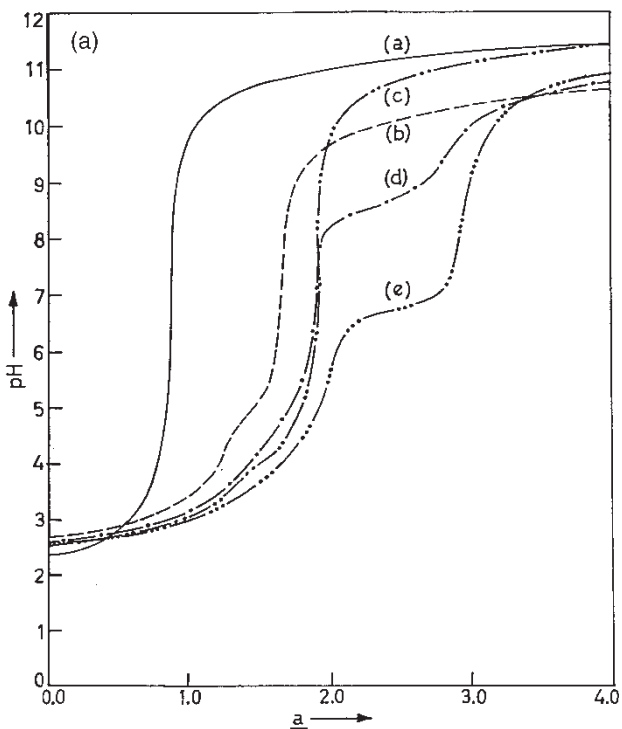


FIGURE 2 (a) pH-Metric titration curves of (a) acid solution (0.002 mol HNO_3), (b) cytosine solution (0.001 mol), (c) cytidine (0.001 mol), (d) copper(II) solution (0.001 mol) + [b], (e) copper(II) solution (0.001 mol) + [c] at $T = 25 \pm 0.1^\circ C$ and ionic strength $\mu = 0.1$ mol $NaNO_3$ in aqueous solution; a is number of mols of alkali per mol of ligand. (b) pH-Metric titration curves of (a) 5-bromocytosine solution (0.001 mol), (b) 5-azacytosine (0.001 mol), (c) 5-fluorocytosine (0.001 mol), (d) copper(II) solution (0.001 mol) + [a], (e) copper(II) solution (0.001 mol) + [b], (f) copper(II) solution (0.001 mol) + [c] under the same conditions as above.

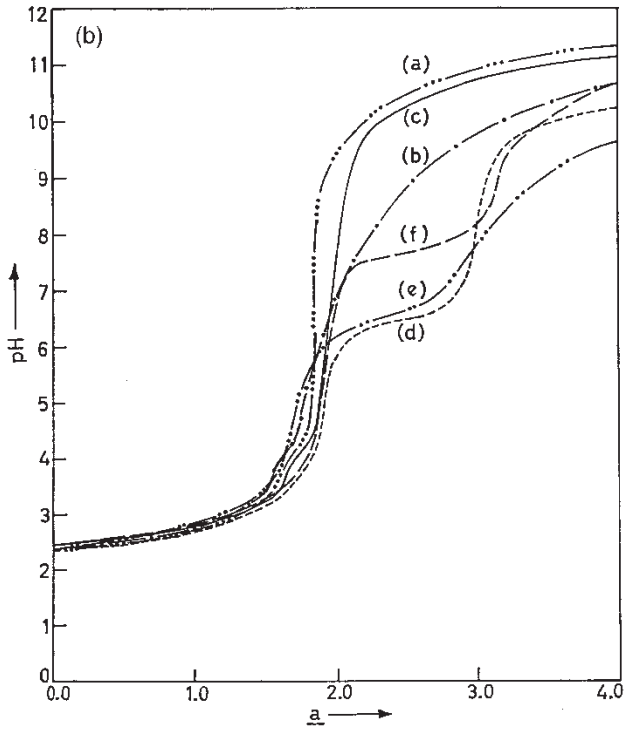


FIGURE 2 Continued.

5-azacytosine was added to each metal solution separately and the resulting mixtures (1 : 1) were refluxed for several hours. The volume was reduced to about one third of the volume and the pH adjusted to about 7–8 by adding sodium hydroxide solution (0.5 M) with continuous stirring. The solid complexes were separated by filtration, washed several times with ethanol and finally with ether, and dried at 50–60°C in the oven.

Metal ions were determined volumetrically by dissolving the complexes in very dilute nitric acid and titrating against EDTA [30]. Carbon, hydrogen and nitrogen were analyzed with a Vario EL III instrument. Infrared spectra were obtained on a Perkin-Elmer 1600 spectrophotometer using KBr discs. Electronic spectra were recorded in Nujol with a Perkin Elmer Lambda 35 spectrophotometer at room temperature. The magnetic susceptibility measurements (298 K) were performed on a Cahn Faraday magnetic balance.

RESULTS AND DISCUSSION

Solution Studies

Proton–Ligand Systems

The pH-metric titration curves drawn between pH *vs* $\underline{a}$ clearly shows an inflection at $0 < \underline{a} < 2$ for almost all ligand used, indicating the dissociation of two

protons from each ligand. The proton dissociation equilibria involved are shown in (iv) and (v)

$$H_2L \rightleftharpoons HL^- + H^+; \qquad K^1 = \frac{[HL^-][H^+]}{[H_2L]} \tag{iv}$$

$$HL^- \rightleftharpoons L^{2-} + H^+; \qquad K^2 = \frac{[L^{2-}][H^+]}{[HL^-]} \tag{v}$$

Values for proton dissociation constants of various ligands are presented in Table I and are in good agreement with reported values of C and CD in the literature [32]. Figure 2(a) and (b) show the initial stages of the titration where the medium is strongly acidic. The ligand curve shifts to the left of (or above) the acid curve depending on the basic properties of N_1 and N_3 [33]. Cytosine is generally represented in the lactim–lactam form (Fig. 3, Ia and Ib) both as a free molecule and in its nucleosides or nucleotides. The lactim–lactam form is also considered to be involved in base-pairing in DNA. IR studies show that the dominant tautomer of the cytosine in aqueous solution is the lactim–lactam form and that the protonated cation has the structure II (Fig. 3).

Raman spectroscopy studies [34,35] indicate that the neutral molecule has the structure I. These studies also suggest that removal of a proton from the free base leads to an anion of type (III) and that, in the cation, N_3 is the site of protonation. Calculations of distribution of π-, σ- and total electron density reveal that 5-fluoro substitution changes π- and total electronic charges mainly at and near the C-5 and C-6 atoms. Ionization potentials and electron affinities are of π-type for C and 5FC. It has been found that halogen substitution at C-5 in 2-oxo-pyrimidine does not influence the relative stabilities of keto–enol tautomers [36]. Thus in C, CD and 5-substituted cytosine, the

TABLE I Proton dissociation constants ($pK^a = -\log K \pm 3\sigma^b$) and corresponding thermodynamic parameters at ionic strength, $\mu = 0.1$ mol $NaNO_3$ in aqueous solution

Ligand	T°C			ΔH_f^0 (kcal/mol)	ΔG_f^0 (kcal/mol)	ΔS_f^0 (e.u.)
	25	*35*	*45*			
Cytosine						
pK^1	4.22 ± 0.04	4.09 ± 0.08	4.00 ± 0.11	-4.73 ± 0.02	-5.73 ± 0.04	$+3.37 \pm 0.03$
pK^2	11.58 ± 0.03	11.50 ± 0.05	11.05 ± 0.08	-11.83 ± 0.08	-15.74 ± 0.08	$+13.14 \pm 0.06$
Cytidine						
pK^1	4.21 ± 0.10	4.05 ± 0.07	3.99 ± 0.08	-4.69 ± 0.06	-5.72 ± 0.05	$+3.46 \pm 0.08$
pK^2	11.22 ± 0.03	11.08 ± 0.02	10.70 ± 0.07	-11.30 ± 0.05	-15.25 ± 0.04	$+13.23 \pm 0.07$
5-Bromocytosine						
pK^1	3.48 ± 0.08	3.32 ± 0.14	3.30 ± 0.05	-3.69 ± 0.09	-4.72 ± 0.03	$+3.46 \pm 0.07$
pK^2	11.05 ± 0.04	10.74 ± 0.09	10.54 ± 0.06	10.96 ± 0.05	-15.01 ± 0.06	$+13.61 \pm 0.06$
5-Azacytosine						
pK^1	3.45 ± 0.08	3.32 ± 0.05	3.28 ± 0.06	-3.61 ± 0.06	-4.69 ± 0.03	$+3.61 \pm 0.07$
pK^2	10.85 ± 0.09	10.72 ± 0.05	10.36 ± 0.11	10.65 ± 0.09	-14.74 ± 0.04	$+13.74 \pm 0.05$
5-Fluorocytosine						
pK^1	3.38 ± 0.05	3.30 ± 0.03	3.22 ± 0.09	-3.46 ± 0.11	-4.59 ± 0.05	$+3.80 \pm 0.08$
pK^2	10.75 ± 0.03	10.50 ± 0.08	10.70 ± 0.06	10.03 ± 0.03	-14.61 ± 0.07	$+15.35 \pm 0.04$

[a] $pK^1 = -\log K^1$, $K^1 = [HL^-][H^+]/[H_2L]$, $pK^2 = -\log K^2$, $K^2 = [L^{2-}][H^+]/[HL^-]$; [b] σ = standard deviation.

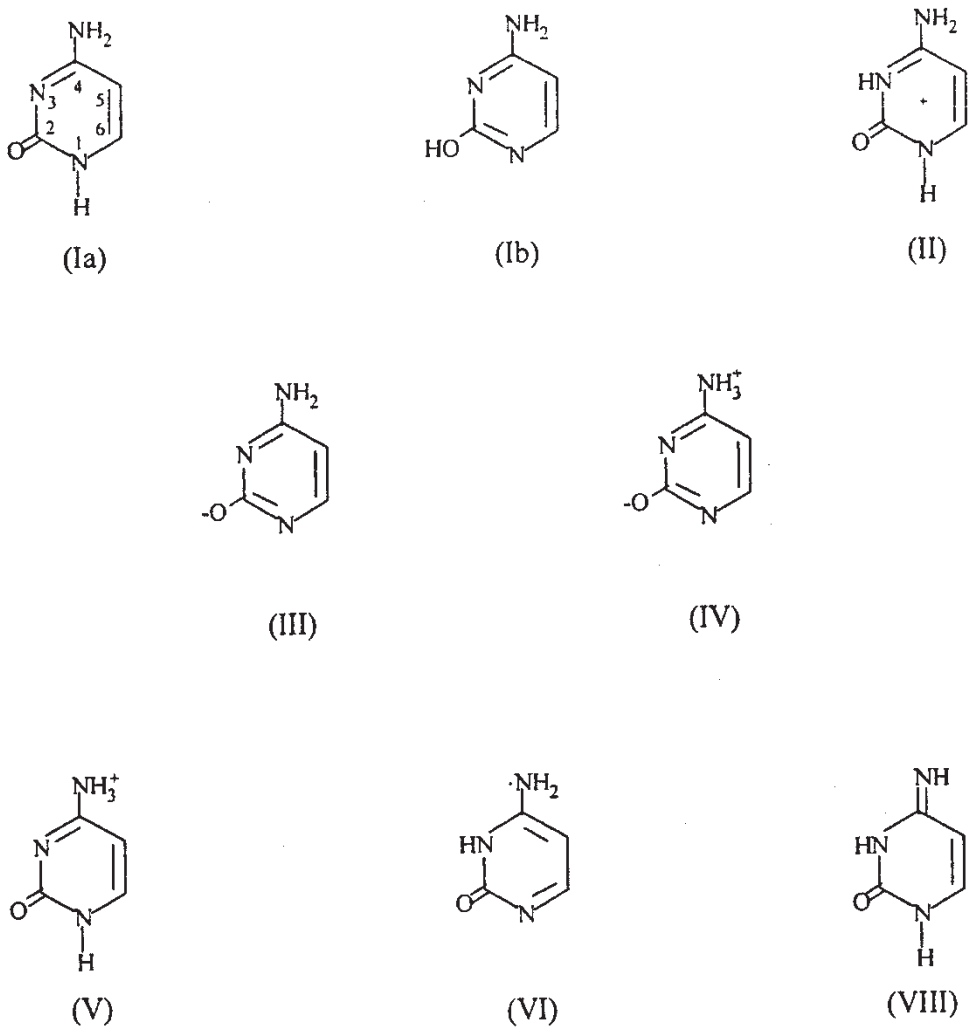


FIGURE 3 Tautomeric structures of cytosine.

first protonation corresponds to the N_3 position of cationic structure II whereas the second protonation constant corresponds to the N_1 position of neutral molecule. Order of protonation constants for the ligands in the present study is C > CD > 5BrC > 5AC > 5FC and depends on the electronegativity of the 5-substituent group. As the size of the 5-substituent atom increases, acidity decreases, i.e., protonation capacity decreases and the protonation constant increases. Enthalpy and entropy changes for the first proton dissociation of all the ligands are exothermic and positive, respectively. ΔH_f^0 and ΔS_f^0 values are comparable for all the ligand systems. The trend is more pronounced for the second proton dissociation of the ligands. The more negative values of enthalpy and favourable entropy effects make 5-substituted cytosine more acidic than C and CD. Thermodynamic parameters associated with proton dissociation constants are in good agreement with reported values [32].

Binary Metal–Ligand (1 : 1) Systems

The curves (Fig. 2a and b) obtained for pH *vs* volume of alkali added from the titration mixture (ii) and (iii) at $25 \pm 0.1^{\circ}C$ were utilized for the evaluation of metal–ligand equilibrium constants. At various pH values, the important complex species formed are supposed to be protonated (MHL^+ at $\underline{a} = 1$), non-protonated (ML at $\underline{a} = 2$), protonated-hydroxo (MHL(OH) at $\underline{a} = 2$), non-protonated-hydroxo $(ML(OH)^-$ at $\underline{a} = 3$ and $ML(OH)_2^{2-}$ at $\underline{a} = 4$). Titration data were analyzed for various possible equilibria (vi–xii), which are supposed to exist at $\underline{a} = 1$–4 and the corresponding equilibrium constants, K_1–K_4 are given as follows.

$$M^{2+} + HL^- \rightleftharpoons MHL^+; \qquad K_1 = \frac{[MHL^+]}{[M^{2+}][HL^-]} \tag{vi}$$

$$M^{2+} + L^{2-} \rightleftharpoons ML; \qquad K_2 = \frac{[ML]}{[M^{2+}][L^{2-}]} \tag{vii}$$

$$M^{2+} + HL^- + OH^- \rightleftharpoons MHL(OH); \qquad K_2' = \frac{[MHL(OH)]}{[M^{2+}][HL^-][OH^-]} \tag{viii}$$

$$MHL^+ + OH^- \rightleftharpoons MHL(OH); \qquad K_2'' = \frac{[MHL(OH)]}{[MHL^+][OH^-]} \tag{ix}$$

$$M^{2+} + L^{2-} + OH^- \rightleftharpoons ML(OH)^-; \qquad K_3 = \frac{[ML(OH)^-]}{[M^{2+}][L^{2-}][OH^-]} \tag{x}$$

$$M^{2+} + L^{2-} + 2OH^- \rightleftharpoons ML(OH)_2^{2-}; \qquad K_4 = \frac{[ML(OH)_2^{2-}]}{[M^{2+}][L^{2-}][OH^-]^2} \tag{xi}$$

$$ML(OH)^- + OH^- \rightleftharpoons ML(OH)_2^{2-}; \qquad K_4' = \frac{[ML(OH)_2^{2-}]}{[ML(OH)^-][OH^-]} \tag{xii}$$

Formation constants were calculated using the BEST program [29] for pH-titration analysis and results are summarized in Table II (in terms of $\log K$). Typical distribution diagrams for various complex species drawn by plotting percentage distribution *vs* pH with equimolar amounts of metal ion and ligands are displayed in Fig. 4(a)–(d).

All ligands under present investigation have two binding sites. Titration curves in Fig. 2(a) and (b) suggest that the ligands form 1 : 1 metal–ligand complexes. Depending upon chelation processes, the formation of various stable complex species in solution is possible. The pH *vs* $\underline{a}$ curves (Fig. 2a and b) show several inflections at $\underline{a} = 1$, 2, 3 and 4, suggesting the formation of protonated (MHL^+), non-protonated (ML) or protonated-hydroxo (MHL(OH)), non-protonated-hydroxo $(ML(OH)^-)$ and $(ML(OH)_2^{2-})$ species in solution. The inflection at $\underline{a} = 1$ (pH $\sim$ 3.0 to 5.0) indicates the formation of MHL^+. All metal ions gave rise to titration curves with significant inflections at $\underline{a} = 2$, due to the formation of a mixed protonated-hydroxo (MHL(OH)) species or non-protonated complex (ML) [37]. The reaction involves OH^- ion association with metal ions along with ligand interaction (viii). Protonated (MHL^+) species may involve OH^- ion association (ix) in order to stabilize the coordination sphere of the MHL^+ species. Further, formation constant data presented in

TABLE II Equilibrium constants ($\log K \pm 3\sigma$[a]) for reactions[b] of various metal–ligand (1 : 1) systems at $T = 25 \pm 0.1^{\circ}C$ and ionic strength, $\mu = 0.1$ mol $NaNO_3$ in aqueous solution

Ligand	*Log K for reaction*						
	1	*2*	*3*	*4*	*5*	*6*	*7*
CoII							
C		18.23 ± 0.14	12.27 ± 0.06	14.38 ± 0.01		24.23 ± 0.02	6.24 ± 0.09
CD		17.54 ± 0.08	11.32 ± 0.02	14.21 ± 0.06	20.13 ± 0.06	23.38 ± 0.06	6.11 ± 0.12
5BrC		17.32 ± 0.09	11.91 ± 0.11	14.00 ± 0.04		23.00 ± 0.19	7.02 ± 0.05
5AC		17.44 ± 0.08	11.92 ± 0.18	14.05 ± 0.15		22.92 ± 0.10	5.23 ± 0.18
5FC		17.21 ± 0.02	11.00 ± 0.04	13.89 ± 0.11			
NiII							
C	10.11 ± 0.04	18.26 ± 0.04	12.30 ± 0.07	14.42 ± 0.18	19.88 ± 0.05	24.28 ± 0.04	6.32 ± 0.19
CD		18.22 ± 0.02	12.28 ± 0.03	14.40 ± 0.14		23.31 ± 0.05	6.00 ± 0.04
5BrC		18.10 ± 0.18	12.21 ± 0.05	14.41 ± 0.21		23.23 ± 0.03	5.97 ± 0.07
5AC		17.98 ± 0.14	12.24 ± 0.11	14.32 ± 0.04		23.11 ± 0.02	5.68 ± 0.02
5FC	10.18 ± 0.03	18.00 ± 0.03	12.23 ± 0.14	14.28 ± 0.03	19.97 ± 0.06	23.10 ± 0.07	4.23 ± 0.15
CuII							
C		18.50 ± 0.04	12.28 ± 0.03	14.48 ± 0.03		24.51 ± 0.04	6.50 ± 0.03
CD		18.00 ± 0.03	12.28 ± 0.09	13.98 ± 0.05	20.30 ± 0.04	24.58 ± 0.09	5.98 ± 0.06
5BrC		18.02 ± 0.07	12.11 ± 0.05	13.99 ± 0.04		24.32 ± 0.03	5.78 ± 0.05
5AC		17.88 ± 0.16	12.21 ± 0.15	14.01 ± 0.08		24.00 ± 0.05	5.81 ± 0.11
5FC		17.85 ± 0.11	12.13 ± 0.21	14.28 ± 0.03	20.03 ± 0.03	24.11 ± 0.11	5.85 ± 0.02
ZnII							
C	10.01 ± 0.06	18.32 ± 0.04	12.36 ± 0.06	14.44 ± 0.04		24.42 ± 0.04	6.38 ± 0.03
CD		17.98 ± 0.09	12.33 ± 0.02	14.11 ± 0.09	20.18 ± 0.21	21.98 ± 0.05	6.32 ± 0.01
5BrC		17.19 ± 0.03	12.32 ± 0.18	14.32 ± 0.02		23.24 ± 0.09	6.28 ± 0.04
5AC		17.91 ± 0.05	12.28 ± 0.11	14.24 ± 0.11		23.11 ± 0.11	6.27 ± 0.05
5FC		17.94 ± 0.07	12.27 ± 0.07	14.23 ± 0.08	20.11 ± 0.03	23.00 ± 0.23	6.31 ± 0.10
CdII							
C		18.28 ± 0.04	12.33 ± 0.01	14.40 ± 0.03		24.32 ± 0.16	6.22 ± 0.03
CD		18.21 ± 0.09	12.32 ± 0.09	14.32 ± 0.02		22.88 ± 0.06	6.21 ± 0.07
5BrC		18.20 ± 0.13	12.28 ± 0.04	14.28 ± 0.06	20.16 ± 0.11	24.30 ± 0.14	6.18 ± 0.04
5AC		17.69 ± 0.02	12.08 ± 0.07	14.22 ± 0.03		24.22 ± 0.18	6.17 ± 0.06
5FC		18.18 ± 0.17	11.98 ± 0.11	14.24 ± 0.05		24.20 ± 0.21	6.20 ± 0.02
CaII							
C		18.23 ± 0.04	12.29 ± 0.03	14.45 ± 0.03		24.30 ± 0.04	6.18 ± 0.06
CD		17.88 ± 0.02	12.32 ± 0.07	14.32 ± 0.02	19.89 ± 0.02	24.22 ± 0.08	6.02 ± 0.02
5BrC		17.76 ± 0.09	12.28 ± 0.04	14.31 ± 0.07	19.86 ± 0.07	24.24 ± 0.11	5.88 ± 0.01
5AC		17.71 ± 0.14	12.26 ± 0.03	14.80 ± 0.01	19.88 ± 0.03	24.21 ± 0.16	5.87 ± 0.07
5FC		17.72 ± 0.11	12.11 ± 0.06	14.08 ± 0.03	19.78 ± 0.01	24.17 ± 0.05	5.78 ± 0.11
SrII							
C	8.32 ± 0.03	18.20 ± 0.10	12.27 ± 0.03	14.37 ± 0.03	19.78 ± 0.06	24.18 ± 0.02	6.11 ± 0.03
CD	8.08 ± 0.05	18.18 ± 0.04	12.18 ± 0.01	13.88 ± 0.04	19.98 ± 0.03	24.10 ± 0.09	6.08 ± 0.05
5BrC		17.98 ± 0.03	12.15 ± 0.04	13.86 ± 0.01	19.85 ± 0.02	24.08 ± 0.05	6.07 ± 0.19
5AC		18.22 ± 0.02	12.14 ± 0.11	13.84 ± 0.11	19.82 ± 0.07	24.18 ± 0.03	6.06 ± 0.13
5FC		18.16 ± 0.06	12.08 ± 0.10	13.82 ± 0.24	19.80 ± 0.09	24.11 ± 0.11	6.12 ± 0.06
BaII							
C	8.18 ± 0.09	18.18 ± 0.02	12.55 ± 0.12	14.38 ± 0.04	19.99 ± 0.01	24.12 ± 0.03	6.00 ± 0.02
CD		18.12 ± 0.04	12.22 ± 0.18	14.08 ± 0.02	19.18 ± 0.05	24.08 ± 0.09	5.88 ± 0.05
5BrC		18.11 ± 0.02	12.08 ± 0.15	14.05 ± 0.14	19.11 ± 0.03	24.11 ± 0.11	5.23 ± 0.04
5AC		18.08 ± 0.05	12.17 ± 0.12	13.89 ± 0.25	19.05 ± 0.07	24.10 ± 0.10	5.44 ± 0.08
5FC		18.05 ± 0.03	12.15 ± 0.21	13.88 ± 0.23	19.08 ± 0.02	24.05 ± 0.18	5.51 ± 0.03

[a]σ = standard deviation; [b]reactions: (1) $M^{2+} + HL^{-} \rightleftharpoons MHL^{+}$, (2) $M^{2+} + HL^{-} + OH^{-} \rightleftharpoons MHL(OH)$, (3) $MHL^{+} + OH^{-} \rightleftharpoons MHL(OH)$, (4) $M^{2+} + L^{2-} \rightleftharpoons ML$, (5) $M^{2+} + L^{2-} + OH^{-} \rightleftharpoons ML(OH)^{-}$, (6) $M^{2+} + L^{2-} + 2OH^{-} \rightleftharpoons ML(OH)_2^{2-}$, (7) $ML(OH)^{-} + OH^{-} \rightleftharpoons ML(OH)_2^{2-}$.

Table II shows that the $\log K^{M}_{MHL(OH)}$ values are around 4 to 5 units greater than $\log K^{M}_{ML}$ values and hence the formation of MHL(OH) species is more favored than the non-protonated ML species (vii). Reaction (ix) should be more favored electrostatistically as compared to reaction (viii) (Table II). The reason is that the electron density around the metal ions in $[MHL^{+}]$ systems would be more than in $[M(H_2O)_n^{2+}]$ systems owing to ligand being more strongly coordinating than H_2O. However, in the case of $[MHL^{+}]$ systems, the M–N bond is influenced not only by L→M σ-interaction but there also occurs to some extent a M→L dπ–pπ interaction which does not allow electron density around the metal ions to increase significantly [38] and hence lowers $\log K^{MHL^{+}}_{MHL(OH)}$ values. Of course, concentration of both species resulting in ML formation (vii) and association of OH^{-} ion with MHL^{+} forming MHL(OH) (ix, Table II) would be equal.

In addition to the above inflections at $\underline{a} = 1$ and 2, some binary systems show one more prominent inflection at $\underline{a} = 3$ in the range pH ~ 5.0 to 9.0 (Fig. 2a and b), indicating the formation of non-protonated-hydroxo species $(ML(OH)^{-})$ by direct association of various component ions (x). Further, the copper(II) complex has been found to be more stable with $\log K$, whose values range from 19.05 to 20.03 for all metal ligand systems. Almost all the metal ions show an additional inflection at $\underline{a} = 4$ (pH ≥ 9) with all the ligands, indicating the formation of non-protonated-dihydroxo species $ML(OH)_2^{2-}$ (xi and xii, Table II). In the high alkaline region the metal ions start precipitating as metal hydroxides at pH ≥ 10.0.

Species distributions are presented in Fig. 4(a)–(d). It is observed that the percentage of free metal ion decreases gradually on increasing the pH of the solution, which suggests that a very low pH (~ 2.0 to 5.0) MHL^{+} is formed; the latter then decreases with increasing pH and is converted into MHL(OH). The metal ions are present as MHL(OH) species (90%) for all metal–ligand systems at pH ~ 4.0 to 9.0 but this decreases as it starts converting into $ML(OH)^{-}$ at pH ~ 7.0. Finally, most metal is distributed (about 90%) in $ML(OH)_2^{2-}$ species at higher pH (≥ 10.0). It is notable that metal hydroxides form in this (very high pH) region. Species distribution plots are in agreement with the Irving–Williams order [38] for various metal ions. Cadmium(II) complexes with all ligands have the lowest stability among the transition metal ions studied and copper(II) complexes the highest. Stabilities of copper(II) complexes (Table III) are higher than might be expected from ionic radius and electronegativity considerations [39]. This may be attributed to additional stabilization due to Jahn–Teller distortion [40]. Further, stability constants increase with increasing basicity of anions of the various ligands, in the order C > CD > 5BrC > 5AC > 5FC.

In all systems, stability constants decrease with increasing temperature. Though the stability order of the various species formed in different systems are not strictly according to the Irving–Williams order due to various other factors such as heat of hydration, overall stability constants for each binary system evaluated using the modified Irving–Rossotti technique [28] shows an order which is more or less in conformity with the Irving–Williams trend, i.e., CoII < NiII ≪ CuII ≫ ZnII > CdII. Stability constants of the various metal–ligand systems were determined at 25, 35 and 45 ± 0.1°C. The enthalpy change for the formation of 1 : 1 MII–ligand (except calcium(II), strontium(II) and barium(II)) systems is exothermic and entropy values are positive (Table IV). Calcium(II), strontium(II) and barium(II) complexes also exhibit large positive entropy values. Higher entropy values in all the systems support bidentate behavior of the ligands in the binary (1 : 1) complexes. Positive enthalpy values for

CaII–ligand systems are due to a higher heat of hydration of calcium(II) as compared to other alkaline earth metals [7]. The heat of hydration of a metal ions in general is inversely proportional to its ionic radii and calcium(II), with the smallest ionic radius of 0.94 Å, has the highest value ΔH_f^0. Enthalpy changes for calcium(II), strontium(II) and barium(II) complexes are in accord with corresponding heats of hydration of the relative ions [7,12]. Entropy values for metal–cytosine systems are somewhat higher than those for other metal–ligand systems. Values decrease as the acidity of the ligand and the ionic radius of the metal ions increases [12]. This trend was observed for almost all the systems in the present study. Small values of ΔH_f^0 coupled with large positive values of ΔS_f^0 offer evidence for the role of entropy as the primary factor favoring the formation of the 1 : 1 species in solution.

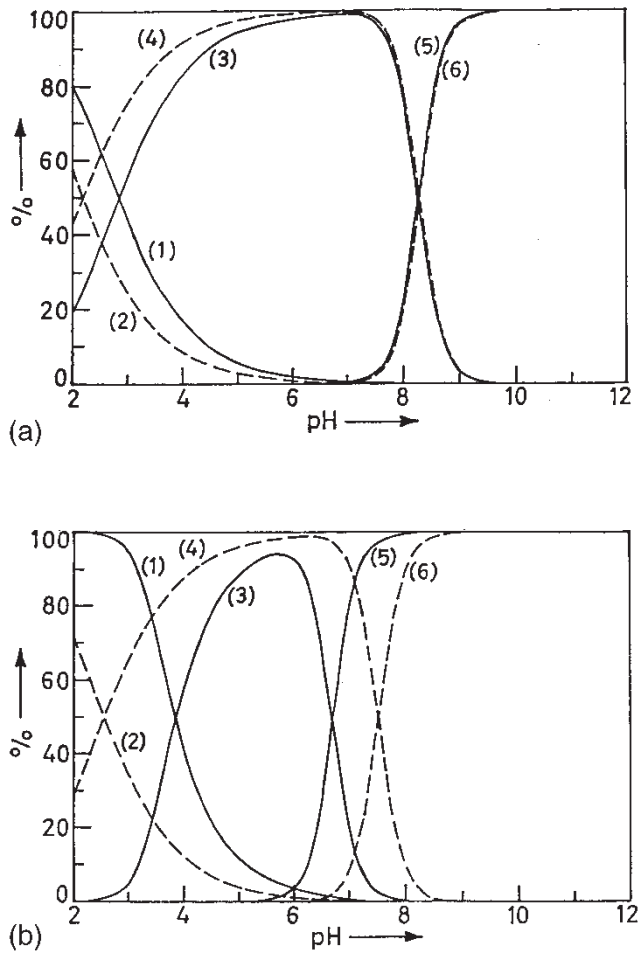
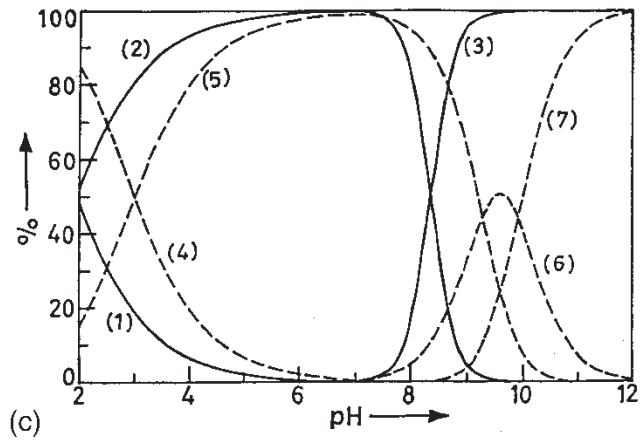


FIGURE 4 (a) Species distribution curve for the MII : 5AC (1 : 1) binary system; (1) CoII, (2) NiII, (3) Co(5AC), (4) Ni(5AC), (5) $Co(5AC)(OH)_2$, (6) $Ni(5AC)(OH)_2$. (b) Species distribution curve for the MII : 5AC (1 : 1) binary system; (1) CuII, (2) ZnII, (3) Cu(5AC), (4) Zn(5AC), (5) $Cu(5AC)(OH)_2$, (6) $Zn(5AC)(OH)_2$. (c) Species distribution curve for the MII : 5AC (1 : 1) binary system; (1) CdII, (2) CaII, (3) Cd(5AC), (4) Ca(5AC), (5) Ca(5AC)(OH), (6) $Ca(5AC)(OH)_2$, (7) $Ca(5AC)(OH)_2$. (d) Species distribution curve for the MII : 5AC (1 : 1) binary system; (1) SrII, (2) BaII, (3) Sr(5AC), (4) Ba(5AC), (5) Sr(5AC)(OH), (6) Ba(5AC)(OH), (7) $Sr(5AC)(OH)_2$, (8) $Ba(5AC)(OH)_2$.



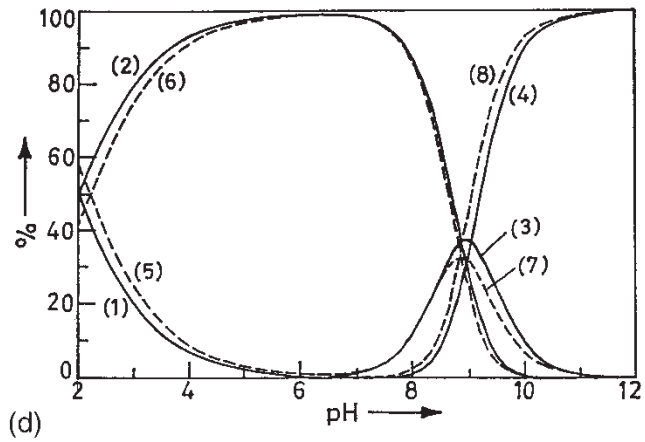


FIGURE 4 Continued.

Characterization of Solid Complexes

The compositions of the complexes isolated and analytical data are listed in Table V. The complexes were obtained according to the general reaction given below in aqueous ethanolic solution.

$$M(NO_3)_2 + 5AC \xrightarrow{2NaOH} [M(OH)_2(5AC) \cdot 2H_2O + 2NaNO_3$$

All complexes display MII : 5AC (1 : 1) stoichiometry and are colored except for those of ZnII and CdII. They are insoluble in almost all common organic solvents as well as water. It may thus be inferred that they are polymeric in nature.

TABLE III Overall stability constants (log $K^{M}_{ML} \pm 3\sigma$[a]) for metal : ligand (1 : 1) system at 25, 35 and 45 ± 0.1°C and ionic strength $\mu = 0.1$ mol $NaNO_3$ in aqueous solution

T°C	*CoII*	*NiII*	*CuII*	*ZnII*	*CdII*	*CaII*	*SrII*	*BaII*
Cytosine								
25	10.40 ± 0.02	10.77 ± 0.03	10.85 ± 0.06	10.55 ± 0.06	10.28 ± 0.06	6.92 ± 0.09	6.50 ± 0.04	6.02 ± 0.14
35	10.15 ± 0.02	10.41 ± 0.04	10.52 ± 0.04	10.19 ± 0.04	9.89 ± 0.08	7.80 ± 0.02	6.00 ± 0.08	6.50 ± 0.12
45	10.04 ± 0.02	10.40 ± 0.05	10.48 ± 0.05	10.18 ± 0.03	9.92 ± 0.05	7.00 ± 0.05	6.50 ± 0.08	6.10 ± 0.15
Cytidine								
25	7.98 ± 0.18	9.56 ± 0.19	10.20 ± 0.05	9.86 ± 0.11	8.26 ± 0.09			8.75 ± 0.15
35	7.81 ± 0.18	9.40 ± 0.20	10.75 ± 0.09	8.41 ± 0.12	8.10 ± 0.14	7.58 ± 0.17	5.40 ± 0.16	8.80 ± 0.16
45	7.78 ± 0.17	9.28 ± 0.14	9.93 ± 0.12	9.47 ± 0.19	8.05 ± 0.18	7.62 ± 0.21	5.50 ± 0.15	
5-Bromocytosine								
25	7.89 ± 0.19	8.36 ± 0.12	9.59 ± 0.16	7.91 ± 0.19	7.45 ± 0.11	6.07 ± 0.08	5.82 ± 0.09	5.65 ± 0.18
35	7.69 ± 0.18	8.15 ± 0.19	9.30 ± 0.14	7.71 ± 0.18	7.30 ± 0.13	5.89 ± 0.11	5.65 ± 0.13	5.42 ± 0.11
45	7.87 ± 0.16	8.12 ± 0.18	9.13 ± 0.17	7.58 ± 0.19	7.28 ± 0.15	6.11 ± 0.07	5.89 ± 0.15	5.74 ± 0.04
5-Azacytosine								
25	6.89 ± 0.04	7.11 ± 0.06	8.89 ± 0.09	7.28 ± 0.12	6.22 ± 0.18	6.05 ± 0.18	5.65 ± 0.15	5.39 ± 0.19
35	6.74 ± 0.06	6.96 ± 0.08	8.64 ± 0.12	7.13 ± 0.14	6.00 ± 0.17	6.00 ± 0.17	5.62 ± 0.16	5.71 ± 0.16
45	7.90 ± 0.09	6.62 ± 0.11	8.76 ± 0.14	7.11 ± 0.11	6.10 ± 0.14	6.08 ± 0.14	5.72 ± 0.12	5.49 ± 0.20
5-Fluorocytosine								
25	6.72 ± 0.23	7.00 ± 0.24	7.92 ± 0.21	6.78 ± 0.19	5.94 ± 0.16	5.80 ± 0.09	4.87 ± 0.05	4.52 ± 0.08
35	6.85 ± 0.24	6.92 ± 0.16	7.90 ± 0.24	6.90 ± 0.20	5.54 ± 0.18	6.00 ± 0.06	4.72 ± 0.06	3.90 ± 0.12
45	6.57 ± 0.26	6.82 ± 0.22	7.70 ± 0.26	6.62 ± 0.28	5.80 ± 0.11	5.82 ± 0.06	4.87 ± 0.09	4.50 ± 0.11

[a]σ = standard deviation.

TABLE IV Thermodynamic parameters associated with formation of (1 : 1) systems

Thermodynamic parameters	*CoII*	*NiII*	*CuII*	*ZnII*	*CdII*	*CaII*	*SrII*	*BaII*
Cytosine								
ΔH_f^0	−7.69	−7.76	−7.80	−7.75	−7.38	+0.55	+0.75	+1.11
$\Delta G_f^0(25^\circ)$	−14.61	−15.13	−15.24	−14.82	−14.44	−9.72	−9.13	−8.46
$\Delta S_f^0(25^\circ)$	+22.46	+23.90	+24.15	+22.95	+22.92	+33.34	+32.06	+31.06
Cytidine								
ΔH_f^0	−4.18	−6.86	−5.92	−6.56	−4.57	+1.79	+4.47	+2.09
$\Delta G_f^0(25^\circ)$	−10.84	−13.87	−12.98	−13.39	−11.23	−10.65	−7.58	−11.89
$\Delta S_f^0(25^\circ)$	+22.33	+23.51	+23.69	+22.92	+22.35	+41.72	+40.44	+46.92
5-Bromocytosine								
ΔH_f^0	−4.08	−4.39	−6.01	−4.04	−3.59	+1.15	+1.80	+2.22
$\Delta G_f^0(25^\circ)$	−10.72	−11.36	−13.03	−10.74	−10.12	−8.25	−7.91	−7.68
$\Delta S_f^0(25^\circ)$	+22.28	+23.37	+23.56	+22.49	+21.94	+31.52	+32.59	+33.22
5-Azacytosine								
ΔH_f^0	−3.32	−3.24	−5.23	−3.14	−2.30	+0.85	+1.67	+1.79
$\Delta G_f^0(25^\circ)$	−9.36	−9.66	−12.08	−9.89	−8.45	−8.22	−7.68	−7.33
$\Delta S_f^0(25^\circ)$	+20.88	+21.54	+22.98	+22.66	+20.63	+30.45	+31.38	+30.63
5-Fluorocytosine								
ΔH_f^0	−3.53	−3.91	−4.88	−3.78	−2.67	+0.17	+0.21	+0.42
$\Delta G_f^0(25^\circ)$	−9.13	−9.51	−10.76	−9.22	−8.08	−7.88	−6.62	−6.14
$\Delta S_f^0(25^\circ)$	+18.79	+18.81	+19.72	+18.25	+18.15	+27.00	+22.91	+22.03

ΔH_f^0 and ΔG_f^0 values in kcal mol^{-1} and ΔS_f^0 values in cal K^{-1} mol^{-1}; 1 cal = 4.184 J.

TABLE V Analytical data and colors of the complexes

Complexes	*Formula weight*	*Colour*	*Calculated (Found)%*				
			M	*C*	*H*	*N*	*Yield %*
$[Co(5AC)(OH_2]\cdot 2H_2O$ ($C_3H_5CoN_4O_3$)	205.04	Violet	28.74 (28.53)	17.57 (17.25)	2.95 (3.01)	27.46 (27.98)	78
$[Ni(5AC)(OH_2]\cdot 2H_2O$ ($C_3H_5N_4NiO_3$)	204.79	Green	28.66 (28.32)	17.59 (17.25)	2.95 (2.98)	27.49 (27.71)	88
$[Cu(5AC)(OH_2]\cdot 2H_2O$ ($C_3H_5CuN_4O_3$)	209.65	Intense green	30.31 (30.35)	17.19 (17.44)	2.88 (2.86)	26.86 (26.39)	85
$[Zn(5AC)(OH_2]\cdot 2H_2O$ ($C_3H_5CuN_4O_3$)	211.49	White	30.92 (30.99)	17.03 (17.13)	2.86 (2.89)	26.62 (26.40)	92
$[Cd(5AC)(OH_2]\cdot 2H_2O$ ($C_3H_5CdN_4O_3$)	258.51	White	43.48 (43.85)	13.94 (14.08)	2.34 (2.31)	21.78 (21.91)	90

Infrared Studies

Characteristic IR frequencies for the ligand and its metal complexes are given in Table VI. In the region 3500–3000 cm^{-1} many bands appear and may be attributed to NH and OH stretching modes. The band corresponding to δN_1–H of 5AC at (1512 cm^{-1}) remain almost at the same position in the metal complexes, suggesting that the N_1 is not involved in bonding. Bands corresponding to νN–H (3175 cm^{-1}) and $\nu C–NH_2 + C{=}N$ (1271 cm^{-1}) of 5AC show considerable shifts in complexes suggesting the participation of N_3 in coordination with metal ions. The $C_2{=}O$ band of

TABLE VI Characteristic infrared data for 5-azacytosine and its metal complexes

Band assignments	*5-Azacytosine*	*CoII*	*NiII*	*CuII*	*ZnII*	*CdII*
ν(N–H) + ν(C–H)	3175 s	3167 m	3172 s	3185 m	3121 m	3180 w
$\delta(NH_2)$ scissoring	1780 s	1709 s	1689 w	1677 m	1682 s	1672 s
$\nu(C_2{=}O)$	1643 m	1640 m	1648 s	1646 s	1647 m	1640 m
ν(C=N) + ν(C=C)	1627 s	1620 s	1578 w	1602 m	1599 s	1585 s
$\delta(N_1{-}H)$ in plane	1512 m	1515 m	1505 s	1511 s	1516 s	1519 s
$\delta(N_3{-}H)$	1420 s	1446 s	1445 m	1444 w	1388 w	1376 s
$\nu(C{-}NH_2) + \nu$(C–N)	1271 m	1264 m	1226 s	1316 s	1259 sh	
ν(N–H) out of plane	796 m	787 m	795 w	811 m	789 m	811 s
δC=O + δC–N in phase + ωNH_2	551 s	548 s	543 w	547 m	518 w	559 s
ν(M–O)		245 m	245 w	242 m	256 w	250 w
ν(M–N)		262 s	240 m	258 w	240 m	240 m

cytosine is shifted to higher frequency on coordination at the N_3 site because there is no electron transfer from N_3 position to C_2=O [41]. Since the C_2=O band here is almost unchanged (1643 cm^{-1}), through C_2=O is indicated.

On the basis of the above, it is tentatively suggested that a number of potential metal binding sites in 5AC, the sites employed for bonding are N_3–H and C_2=O. The presence of νM–O [42] and νM–N [43] bands in the lower frequency region suggests coordination number six for CoII, NiII, CuII, ZnII and CdII. Bridging OH stretching vibrations appear at about 3300–3400 cm^{-1} [44] and the bridging OH bending mode appears at about 950 cm^{-1} in the metal complexes suggesting an OH bridging polymeric structure for them.

Electronic Spectra and Magnetic Studies

The magnetic moment for the CoII–5AC complex is 3.96 BM. Its electronic spectrum exhibits a band at 815 nm ($^4A_2g(F) \leftarrow {}^4T_1g(F)(\nu_2)$) and a strong band at 562 nm ($^4T_1g(P) \leftarrow {}^4T_1g(F)(\nu_3)$) [45]. The $^4T_2g(F) \leftarrow {}^4T_1g(F)(\nu_1)$ transition could not be observed as it is likely to appear beyond 1000 nm. All data suggests an octahedral geometry for this complex.

The electronic spectrum of the NiII–5AC complex shows two bands at 624 and 381 nm assigned to $^3T_1g(F) \leftarrow {}^3A_2g(F)(\nu_2)$ and $^3T_1g(P) \leftarrow {}^3A_2g(F)(\nu_3)$ transitions, respectively [46]. The $^3T_2g(F) \leftarrow {}^3A_2g(F)(\nu_1)$ transition is likely to appear beyond 1000 nm. These data thus favour an octahedral geometry for this compound, which has a magnetic moment of 2.81 BM.

The magnetic moment of the CuII–5AC complex is 1.73 BM, showing the presence of one unpaired electron. A d–d transition at 625 nm indicates hexacoordination [45].

On the basis of the above, the complexes are polymeric, involving 5-azacytosine and –OH groups as bridging ligands. From solution studies it is concluded that all ligands dissociate two protons. The pK^1 and pK^2 values of cytosine and its 5-substituted derivatives have been assigned to the N_3 and N_1–H/C_2=O [33,47,48] groups whereas in the case of cytidine, the first and second proton dissociation sites are the N_3 and sugar moiety [47], respectively. It has been found that substitution at the 5-position does not influence the relative extent of keto–enol tautomerism and the order of protonation constants depends upon the electronegativity of the substituted group at the 5-position. However, the more negative values of enthalpy and favorable entropy effects seem to

make 5-substituted cytosine more acidic than cytosine and cytidine. Formation of 1 : 1 neutral species probably involves the bidentate behavior of the ligands.

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