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Interaction of biologicallyactive metal ions with cytidine 5'-triphosphate and nicotinic acid

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Abstract
Equilibrium study on the mixed ligand complex formation of Cu (II), Cd(II) withCytidine 5'-triphosphate and Nicotinic acid, under experimental conditions (constant ionic strength I =0.1 mol/dm^3, at 37±0.1^{0}C) and potentiometric pH titrations were carried out to determine the stabilities of the binary (1:1) and ternary (1:1:1) complexes, with M(II)= Cu(II), Cd(II) bivalent metal ions, where the self-association of the cytidine 5'-triphosphates (CTP) is negligible. The percentage of species distribution curves have been demonstrated with the help of ORIGIN 6.1 software. Stability constant have been determined through the method suggested by Irving & Rossetti and further refined through Stability Constant of Generalized Species (SCOGS) computer program. Species distribution curves of complexes have been plotted as a function of pH.The mixed ligand (1:1:1) ternary complexes were occurred simultaneously in most cases generally at high pH with gradually declination of binary complexes of particular metal complexes.

Keywords: Bio-metals, Cytidine 5'-triphosphate, Nicotinic acid, Equilibria studies, SCOGS

1. Introduction

We have reported earlier on the metal chelates of Nicotinic acid with bivalent metal ions. The present paper extends the work to bivalent metal ions {Cu(II),Cd(II)}with Cytidine5'-triphosphate(CTP) and Nicotinic acid ($C_6H_5NO_2$). Although the metal complexes of cytidine 5'-triphosphate nucleotides have been the subject of several studies [1-4]. Previous investigation by Eva Wallas [5], with was restricted to the complexes of cytidine 5'- triphosphate. Nicotinic acid (NA), known as vitamin B_3, is essential for cell respiration, metabolism of carbohydrates, fats and proteins, healthy skin and circulation, etc. Furthermore, it has been reported that Nicotinic acid prevents Alzheimer's-like symptoms [6], and it is used in the treatment of schizophrenia and other mental illnesses [7].The ligand nicotinic acids ($C_6H_5NO_2$) are well known vitamin [8]. Nicotinic acid is chiefly used in the treatment of pellagra disease due to diet deficiency.In living systems, almost all the biochemical processes are known to proceed mostly in the solution phase where several metal ions are present in trace quantities. Most of the physiological activities regarding nucleic acid interactions are promoted by metal ions through the formation of ternary (mixed-ligand) complexes. In the blood brain kidney and liver it is converted to the coenzymes nicotinamide adenine dinucleotide (NAD) nicotinamide adenine dinucleotide phosphate (NADP) both of which are involved in the generation of energy in cells. Nicotinic acid also known as niacin (3-pyridine carboxylic acid) is a white translucent crystalline solid with a carboxyl side chain at the 3-position.

Experimental

1. Materials and reagents

Both the ligands i.e. Cytidine 5'-triphosphate and Nicotinic acid ($C_6H_5NO_2$)) was analytical grade reagent commercially available and used without further purification were prepared. The solution of metal nitrate and ligands are obtained from SRL. These ligands were used as such Carbonate free sodium hydroxide solution was prepared by standard method [9]. All other solutions were prepared in doubly distilled water.

The aqueous solutions of metal nitrate were standardized by sodium salt of EDTA in presence of suitable indicator, where as the stock solutions of each ligand standardized against a standard oxalic acid solution. The Potentiometric titration were carried out by carbonate free sodium hydroxide with an electric digital pH meter (Eutech-501) with a glass electrode at 37±0.1 ºC and ionic strength I = 0.1 mol/dm^3 $NaNO_3$.

Apparatus and measuring Techniques

All the Potentiometric titrations were carried out at room temperature through the electric digital pH meter with a glass electrode working on 220V/50 cycles stabilized by A.C. mains. The pH meter was calibrated with standard buffer solutions (pH 4.0, 7.0, and 9.2) before and after each series [10] of pH titration measurements. With reproducibility of ±0.01 pH, the electrode of pH meter was conditioned monthly by saturated potassium chloride (BDH) solution. An ultra thermostat type U10 (VEB MLW Seitz, Freital, Germany) was used to maintain a constant temperature in all the experiments. For all binary and ternary systems following solution mixture have been titrated against standardized NaOH (0.1mol/dm^3) solution, keeping the total volume 50 ml in following methods.

5ml $NaNO_3$ (1.0 mol/dm^3) + 5ml HNO_3 (0.02 mol/dm^3) + H_2O
5ml $NaNO_3$ (1.0 mol/dm^3) + 5ml HNO_3 (0.02 mol/dm^3) + 5ml L_1 (0.01mol/dm^3) + H_2O
5ml $NaNO_3$ (1.0 mol/dm^3) + 5mlHNO_3 (0.02 mol/dm^3) + 5ml L_2 (0.01mol/dm^3) + H_2O
5ml $NaNO_3$ (1.0 mol/dm^3) + 5ml HNO_3 (0.02 mol/dm^3) + 5ml M (0.01mol/dm^3) + H_2O
5ml $NaNO_3$(1.0 mol/dm^3) + 5ml HNO_3(0.02 mol/dm^3) + 5mlM (0.01mol/dm^3) + 5ml L_1 (0.01mol/dm3) + H_2O
5ml $NaNO_3$ (1.0 mol/dm^3) + 5ml HNO_3 (0.02 mol/dm^3) + 5ml M (0.01mol/dm^3) + 5ml L_2 (0.01mol/dm3) + H_2O
5ml $NaNO_3$ (1.0 mol/dm^3) + 5ml HNO_3 (0.02 mol/dm^3) + 5ml M (0.01mol/dm^3) + 5ml L_1 (0.01mol/dm^3) + 5 ml L_2 (0.01mol/dm^3) + H_2O

Where M is Cu(II)/Cd(II) metal ions and L_1 is Cytidine 5'-triphosphate and L_2 Nicotinic acid ($C_6H_5NO_2$). The titration curves of pH solution verses volume of NaOH for each set of solutions were plotted for Potentiometric behaviour of solution at different pH.The species distribution curves were obtained by plotting % concentration of the species obtained through Stability Constant of Generalize Species (SCOGS) computer program against pH.

Results and Discussions

The Protonation constants of the ligand were calculated from the potentiometric pH titration data of solutions according to Irving and Rossetti's method [11] and the acid dissociation constants for the sodium salt of Cytidine 5'-tri phosphate anion ($H_3L_1^-$) are related to the dissociation equilibrium as follows:

$$H_3L_1^- \Leftrightarrow HL_1^{3-} + 2H^+$$
$$HL_1^{3-} \Leftrightarrow L_1^{4-} + H^+$$

The constant pK_1, pK_2 were calculated by the graphical solution of Schwarzenbach and Martell [12] and pK_3 by the usual algebraic method. The experimental data of the potentiometric pH titration for both Cd(II) and Cu(II) binary systems are completely described by the following equations:

$$M^{2+} + HL_1^{3-} \rightleftharpoons MHL_1^-$$
$$K_1 = [MHL_1^-]/[M^{2+}][HL_1^{3-}]$$
$$M^{2+} + L_1^{4-} \rightleftharpoons ML_1^{2-}$$
$$K_2 = [ML_1^{2-}]/[M^{2+}][L_1^{4-}]$$
$$ML_{1aq}^{2-} \rightleftharpoons ML_1(OH)^{3-} + H^+$$
$$K_3 = [ML_1(OH)^{3-}][H^+]/[ML_{1(aq)}^{2-}]$$

The formation of ternary complexes in an aqueous solution may be conveniently expressed by the equilibrium:

$$pM_1+qM_2+rL_1+sL_2+tOH \Leftrightarrow (M_1)_p(M_2)_q(L_1)_r(L_2)_s(OH)_t$$

The overall stability constant is given by the equation:

$$\beta_{pqrst} = [(M_1)_p(M_2)_q(L_1)_r(L_2)_s(OH)]_t/[M_1]^p[M_2]^q[L_1]^r[L_2]^s[OH]^t$$

Where L_1 stands for the Cytidine 5'-triphosphate and L_2 stand for nicotinic acid ($C_6H_5NO_2$) and the stoichiometric numbers p, q, r, s are either zero or positive integer and't' is a negative integer for a protonated species, positive values for a hydroxo or de-protonated species and zero for a neutral species.
The overall stability constant (β_{pqrst}) defined may be used to calculate the species distribution curves that provides the clues for the formation equilibria of the complexes. After the description of species distribution curve through SCOGS, following equilibria have been proposed:

$$L_2^- + M^{2+} \Leftrightarrow ML_2^+$$

The formation of ternary complex may be explained as per the following equilibrium:

$$ML_1 + L_2H^- \Leftrightarrow MHL_1L_2^-$$
$$ML_1H^+ + L_2H^- \Leftrightarrow ML_1L_2^{2-} + 2H^+$$

Where M = Metal ions, L_1 represents the sodium salt of cytidine 5'-triphosphate and L_2 represents the Nicotinic acid ($C_6H_5NO_2$) .The Ternary (1:1:1) complexes have been used in this study to ensure the exclusive formation of the $[M(C_6H_5NO_2)(CTP)]^{3-}$ type complex,

Table 1: Proton ligand formation constant of cytidine 5'-triphosphate and nicotinic acid, Hydrolytic constant of bivalent metal ion, Metal-ligand constants ($Log_{10}\beta_{pqrst}$) binary and ternary system

System	p	q	r	s	t	$Log_{10}\beta_{pqrst}$
H_3L_1	0	0	1	0	-3	9.99
H_2L_1	0	0	1	0	-2	4.22
HL_1	0	0	1	0	-1	2.62
HL_2	0	0	0	1	-1	4.67
M(OH)	1	0	0	0	1	-6.29
$M(OH)_2$	1	0	0	0	2	-13.10
ML_1	1	0	1	0	0	6.03
ML_2	1	0	0	1	0	6.94
ML_1L_2	1	0	1	1	0	9.96

p, q, r, s, and t are the stoichiometric coefficient corresponding to ternary system which is mention above.

Table 2: Proton ligand formation constant, Stability constant and other related constants of the binary and ternary species of Bio-metal Cu (II) complexes with cytidine 5'-triphosphate and nicotinic acid at different pH

pH	H_3L_1	HL_1	HL_2	M(OH)	$M(OH)_2$	ML_1	ML_2	ML_1L_2
2.63	27.5	0.21	9.17	-	-	8.87	27.6	63.2
2.77	33.7	0.49	15.7	-	-	14.9	34	50.1
2.82	35.9	0.66	18.9	-	-	17.7	36.2	44.6
2.88	34.4	0.84	20.9	-	-	19.7	35.2	43.6
2.95	30.8	1.04	22.2	-	-	21.1	32.6	44.8
3.05	24.3	1.30	22.8	-	-	22.1	27.9	48.8
3.15	18.2	1.54	21.3	-	-	22.5	24	52.6
3.31	9.70	1.72	19.3	-	-	21.5	19.2	58.6
3.47	4.39	1.63	14.2	-	-	19.9	17.1	62.5
3.79	0.61	1.00	9.05	-	-	15.7	16.1	67.8
4.18	-	0.45	4.85	-	-	11.7	16.8	71.2
4.62	-	0.17	2.50	-	-	8.95	17.7	73.1
5.01	-	-	1.15	-	-	7.76	18.5	73.6
5.41	-	-	0.78	-	-	7.24	19.2	73.4
5.60	-	-	0.44	-	-	7.26	19.8	72.7
5.87	-	-	0.20	-	-	7.27	20.4	72.1
6.23	-	-	0.11	0.18	-	7.26	20.8	71.4
6.52	-	-	-	0.36	0.18	5.94	21.2	70.8
7.16	-	-	-	1.24	2.77	-	20.1	69.8
9.44	-	-	-	0.22	9.72	-	-	-

Table 3: Proton ligand formation constant, Stability constant and other related constants of the binary and ternary species of Bio-metal Cd (II) complexes with cytidine 5'-triphosphate and nicotinic acid at different pH

pH	H_3L_1	HL_1	HL_2	$M(OH)_2$	ML_1	ML_2	ML_1L_2
2.66	11.6	0.10	5	-	2.83	9.66	85.3
2.69	23.3	0.23	11.9	-	4.65	16.4	71.5
2.75	25.6	0.34	14.9	-	5.54	16.9	68
2.80	26.1	0.44	16.7	-	6.22	16.6	66.5
2.86	24.6	0.55	17.4	-	6.85	15.3	67
2.92	22.4	0.66	17.6	-	7.41	14	68.1
3.02	17.3	0.80	16.3	-	7.97	11.4	71.9
3.12	12.7	0.94	15.1	-	8.30	9.43	75.1
3.28	6.62	1.02	12.8	-	8.17	7.21	79.5
3.45	2.78	0.94	10.8	-	7.57	6.17	82.3
3.78	0.34	0.53	7.59	-	5.82	5.85	85.6
4.24	-	0.19	4.34	-	3.97	6.30	87.7
4.69	-	-	2.24	-	3	6.76	88.7
5.14	-	-	1.01	-	2.57	7.12	88.9
5.72	-	-	0.30	-	2.38	7.42	88.8
6.69	-	-	-	-	2.35	7.66	88.6
7.19	-	-	-	0.10	2.37	7.85	88.2
7.59	-	-	-	0.61	2.28	7.87	87.8
9.13	-	-	-	29.4	0.27	2.04	68.2
10.07	-	-	-	83	-	0.2	16.8
10.42	-	-	-	95.4	-	-	4.51

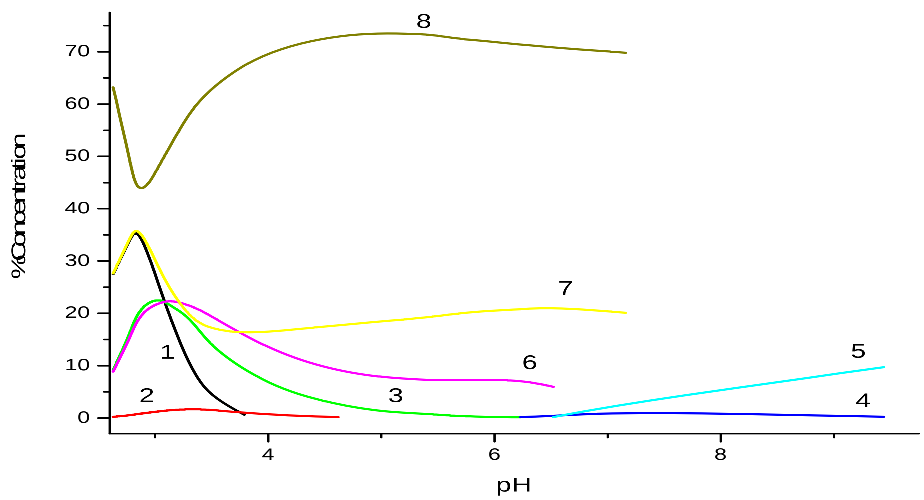

Fig1: Species distribution curve of 1:1:1 ternary Cu(II)L_1L_2-system (1)H_3L_1 (2)HL_1 (3)HL_2(4)Cu(II)L_1 (5)Cu(II)L_2 (6)Cu(II)L_1L_2

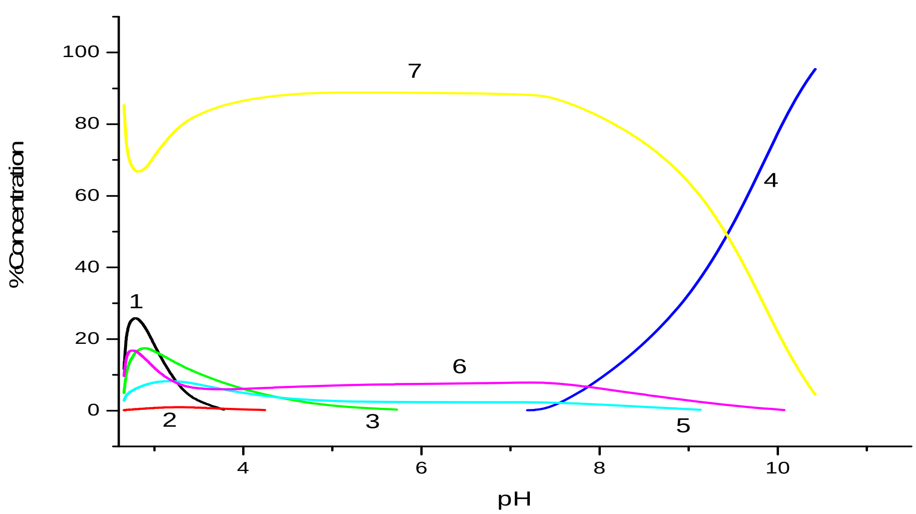

Fig 2: Species distribution curve of 1:1:1 ternary Cu(II)L_1L_2-system (1)H_3L_1 (2)HL_1 (3)HL_2(4)Cu(II)L_1 (5)Cu(II)L_2 (6)Cu(II)L_1L_2

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