Formation Constants of Transition Metal Mixed Ligand Ternary Complexes with Biologically Significant Ligands

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Abstract: Coordination of ternary complexes of biologically active ligands with transition metals were investigated in aqueous media at 37 ± 1 °C under ionic strength I = 0.1 M $NaNO_3$. Amino acid asparagine (primary ligand =A) and nucleic acid thiouracil (secondary ligand=B) were applied for complex formation with Cu(II), Ni(II), Zn(II) and Co(II) in aqueous solution (1:1:1). The plausible equilibria have been deduced on the basis of speciation curves obtained through BEST computer program and species are also presented and discussed. The Protonation constant and metal ligand stability constant has been determined through the method suggested by Irving & Rossotti and further refined through BEST computer program. The mixed ligand ternary complexes were occurring simultaneously in most cases generally at high pH with gradually declination of binary complexes of particular metal complexes. The order of mixed ligands ternary system were found A-Cu(II)-B>A-Ni(II)-B> A-Zn(II)-B> A-Co(II)-B. The percentage of species formation curves have been demonstrated with the help of computer program ORIGIN 6.1 and possible structure of metal complexes with said ligands have been discussed.

Keywords: Solution equilibria, Stability constants, Transition metals

Introduction

Complexation behavior of metal ions with ligand has significance interest in field of coordination chemistry due to potential activity of complexes formation. In this phenomenon metal acts a central role in chelates formation with ligand[1]. The chelates formation occurs in biological fluids through transition metals with one or more than one coordination site of ligands of different functional group has a significant role in detoxification and remediation of metal pollutants[2]. Mixed metal mixed ligand quaternary complexes containing two or more metal ions with two or more ligands are frequently formed in solutions and their study has reveled new aspects for the further complexation occurring along with the binary and ternary species[3]. Several literature reports have been devoted to the study of stability constants of metal- asparagine (Asp) complexes. Sinha *et al.*,[4] reported the potentiometric

studies on ternary system complex formation with Co(II), Ni(II), Cu(II) and Zn(II) with asparagine (Asp) and uracil. The complexation behavior and stability constant of transition metal complex of thiouracil has been reported in previous literature[5]. The stability constant and complexation behavior of Co(II), Zn(II) and Cu(II) complexes with various ligand has also been studied extensively[6-8]. Asparagine is one of the 20 most common natural amino acids and synthesized from central metabolic pathway intermediates in human being yet not essential for human diet. It has carboxamide as the side-chain's functional group. Asparagine is a bidentate ligand contains one NH_2 group and one COO^- group[9]. Thiouracil is a nucleic acid base posses N, O and S donor ligands and exhibits anti-tumour and anti-thyroid activity[5].

Copper is an essential component of several endogenous antioxidant enzymes and oxidative process. The role of cobalt in biological systems was investigated[10] in series of coenzyme and vitamin B_{12}. The complexes of cobalt with methionine, lysine and serine are plays significant role in bacteriostatic and inhibition of virus replication. Cobalamine is necessary for DNA synthesis, formation of red blood cells, and maintenance of the nervous system, growth and development of children[11]. Zinc plays either a predominantly catalytic role or a solely structural role to maintain the protein configuration. It is a versatile ion as it can bind to different combinations of ligand types resulting in a broad range of stability, reactivity and functions[12]. Nickel is one of the most important trace elements in the world of animals and plays numerous roles in the biology of microorganisms and plants[13].

The present work describe the speciation, nature and extent of coordination studies of the metal ligand systems have been undertaken based on their involvement in various physiological reactions. The transition metals such as Cu(II), Ni(II), Zn(II) and Co(II) were applied at active site cavities in bioactive molecules like asparagine acid and thiouracil as these made a model for many ternary complexes system in biological fluid.

Experimental

All chemicals and reagents used were of analytical grade without any further purification. The solution of metal nitrate and ligands were prepared as described in previous reported literature[14]. All the solutions were prepared in double distilled water. The aqueous solutions of metals nitrate were standardized by sodium salt of EDTA in present of suitable indicator, where as the stocks solution of each ligand standardized against a standard oxalic acid solution. Solution (0.01 M) of asparagine and thiouracil (G.R., E-Merck, Germany) were prepared in double distilled water. Aqueous solutions of Cu(II), Ni(II), Zn(II) and Co(II) nitrates (0.01M) were prepared by maintaining 0.02 M of acid (HNO_3) concentration, to suppress the hydrolysis of metal salts. 1.0 M Sodium nitrate was used to maintain the ionic strength in the titrand. 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 ±1 °C and I= 0.1 M $NaNO_3$.

### Apparatus and measuring techniques

All the potentiometric titrations were carried out under at room temperature through the electric digital pH meter with a glass electrode working on 220 V/50 cycles stabilized by A.C. mains. 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 Sitz, 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 (0.01 M) solution, keeping the total volume 50 mL in following manner.

(i) 5 mL NaNO$_3$ (1.0M) + 5 mL HNO$_3$ (0.02 M) + H$_2$O

(ii) 5 mL NaNO$_3$ (1.0M) + 5 mL HNO$_3$ (0.02 M) + 5 mL M (0.01) + H$_2$O

(iii) 5 mL NaNO$_3$ (1.0M) + 5 mL HNO$_3$ (0.02 M) + 5 mL M (0.01) + 5 mL A (0.01 M) + H$_2$O

(iv) 5 mL NaNO$_3$ (1.0M) + 5 mL HNO$_3$ (0.02 M) + 5 mL M (0.01) + 5 mL A (0.01 M) + 5 mL B (0.01M) H$_2$O

(i), (ii), (iii) & (iv) are represents the total concentration of acid, acid+ metal, acid+ligand (A) + metal and acid + metal + ligand (A) + ligand (B), respectively taken the solution for titration. M is metal ions such as Cu(II)/Ni(II)/Zn(II)/Co(II) and A and B are ligands asparagine and thiouracil, respectively. The titration curves of pH of solution *versus* volume of NaOH for each set of solutions were plotted for potentiometric behavior of solution at different pH. The species distribution curves were obtained by plotting percentage concentration of the species obtained through BEST computer programme against pH.

Results and Discussion

Ionic product of water (K$_w$) at the experimental temperature and the activity coefficient of hydrogen ion at the experimental ionic strength were obtained from the literature. The protonation constants of the ligand were calculated from the potentiometric pH titrations data of solutions according to Irving and Rossetti's method[15]. The dissociation constant of asparagine of associated proton were determined potentiometrically in aqueous solution under the experimental conditions. The protonation constant of asparagine and thiouracil agree well with previous reported literature[4]. The second dissociation of the proton from the N group of asparagine and thiouracil takes place at 3 pH. The pH value of solution regulate the equilibria of metal-ligand complex formation due to protonation of respective ligand which participate in complexes formation, At high pH it was observed that 1:1:1 ternary complex titration curves strongly overlap with the titration curves of the 1:1 binary complexes due to dissociation of binary complexes which also depend the nature of both metal and ligand. The formation of ternary complexes in an aqueous solution may be conveniently expressed by the equilibrium:

$$pM_1 + qM_2 + rA + sB + tOH \leftrightarrow (M_1)_p (M_2)_q (A)_r (B)_s (OH)_t \qquad (1)$$
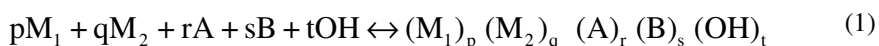
The overall stability constant is given by:

$$\beta pqrst = (M_1)_p (M_2)_q (A)_r (B)_s(OH)_t/[M_1]^p [M_2]^q[A]^r[B]^s[OH]^t \qquad (2)$$

Where A, stands for the primary and B, for the secondary ligand and the stoichiometric number 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 deprotonated species and zero for a neutral species. The overall stability constant (βpqrst) defined may be used to calculate the species distribution curves that provides the clues for the formation equilibria of the complexes showing in Table 1. On the basis of speciation curves obtained through BEST[16], following equilibria have been proposed:

$$[A^-] + [M^{2+}] \leftrightarrow [MA] \qquad (3)$$

$$[AH]^- + M^{2+} \leftrightarrow [MA] + H^+ \qquad (4)$$

$$[AH]^- + M^{2+} \leftrightarrow [MHA] \qquad (5)$$

$$[BH] + M^{2+} \leftrightarrow [MB] + [H^+] \qquad (6)$$

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

$$[MA] + [BH] \leftrightarrow [MHAB]^- + M[OH]_2 \qquad (7)$$

$$[MHA] + [BH] \leftrightarrow [MAB]^- + 2H^+ \qquad (8)$$
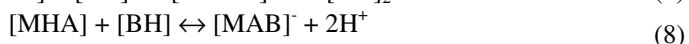
Other general hydrolytic equilibria as:

$$M^{2+} + H_2O \leftrightarrow M(OH)^+ + H^+ \tag{9}$$
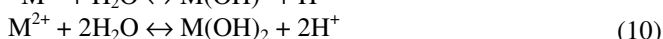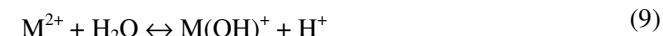$$M^{2+} + 2H_2O \leftrightarrow M(OH)_2 + 2H^+ \tag{10}$$

Table 1. Stability constant and other related constants of binary, ternary complexes of Asparagine (A) and Thiouracil (B) with different metal ions in aqueous solution at 37 ± 1 °C, I=0.1 MNaNO$_3$

Proton-ligand formation constant (Log β pqrst)						
Proton-ligand formation constant (Log β pqrst)	p	q	r	s	t	logβ
H$_2$A	0	0	1	0	-3	10.86
HA	0	0	1	0	-2	08.72
HB	0	0	1	0	-1	8.28
Hydrolytic constants (Log β pqrst)						
Complexes	Copper		Nikel	Zinc		Cobalt
M(OH)$^+$	-6.29		-8.10	-7.89		-8.23
M(OH)2$^+$	13.10		-1783	14.92		-17.83
Metal-Ligand constants (Log βpqrst) Binary System						
Complexes	Copper		Nikel	Zinc		Cobalt
MA	9.27		7.76	6.14		6.25
MB	7.83		4.86	5.81		5.24
Metal-Ligand constants (Log β pqrst) Ternary System						
Complexes	Copper		Nikel	Zinc		Cobalt
M-A-B	12.83		11.83	11.75		11.15

In the present study the dominancy of ternary complexes is traced at pH ranges between 3.0 to 10 which is about 80% of all the species. It is evident from the concentration profiles that the concentrations of H$_3$A, H$_2$A and HA species are found to decrease within the pH range 3.0-9.5, representing the metal-ligand complexation. Species distribution curve of A-Cu(II)-B shown in Figure 1 reveal that protonated species H$_3$A, H$_2$A, HA and HB decrease with increase in pH in the range 3.0-10.0.

The binary complex species Cu-A and Cu-B exist in appreciable amount. The free metal ion is found to declining pattern and metal hydroxo species Cu(OH)$_2$ and Cu(OH)$^+$ are also seen the higher pH range. The concentration of H$_3$A H$_2$A and HA species of both the ligands are found to be decreasing with increase in pH where as the species HA is increasing in the pH range 3.20-5.0 while decreasing in the pH range 5.0-10.00 indicating the metal ligand complex formation. At pH 6.5 the complexes of Cu(II)-B obtain a maximum 42.8% meanwhile ternary complex species formation is found to be start with reducing the Cu(II)-B concentration (Figure 1A). When the pH increases up to pH 8.5 the concentrations of ternary species obtain maximum concentration 88%. The result is somewhat supported by literature[17]. In Figure 1B the A-Ni(II)-B system at increasing pH the concentration of protonated species formation H$_2$A<HA increases. After at pH 5.1 the obtained 97% HA concentration going to decreased. Protonated species of secondary ligand *i.e*. HB is also decrease with increasing pH. The concentration of binary species of Ni(II)-B were found maximum than Ni(II)-A. The curve demonstrate that at the starting point ternary complex formation is slow and both the binary species is dominated that time but when the concentration

of binary complex decrease ternary complex attained maximum concentration of 80.% at pH 9 which closely related to the literature value[18]. The concentration profile of A-Ni(II)-B system indicates the formation of mixed ligand complex in the pH rage 3.0-10.0 shown in Figure 1 C. Protonated ligand species H_3A H_2A, HA and HB and the binary complex species Zn(II)-B exist in good concentration.
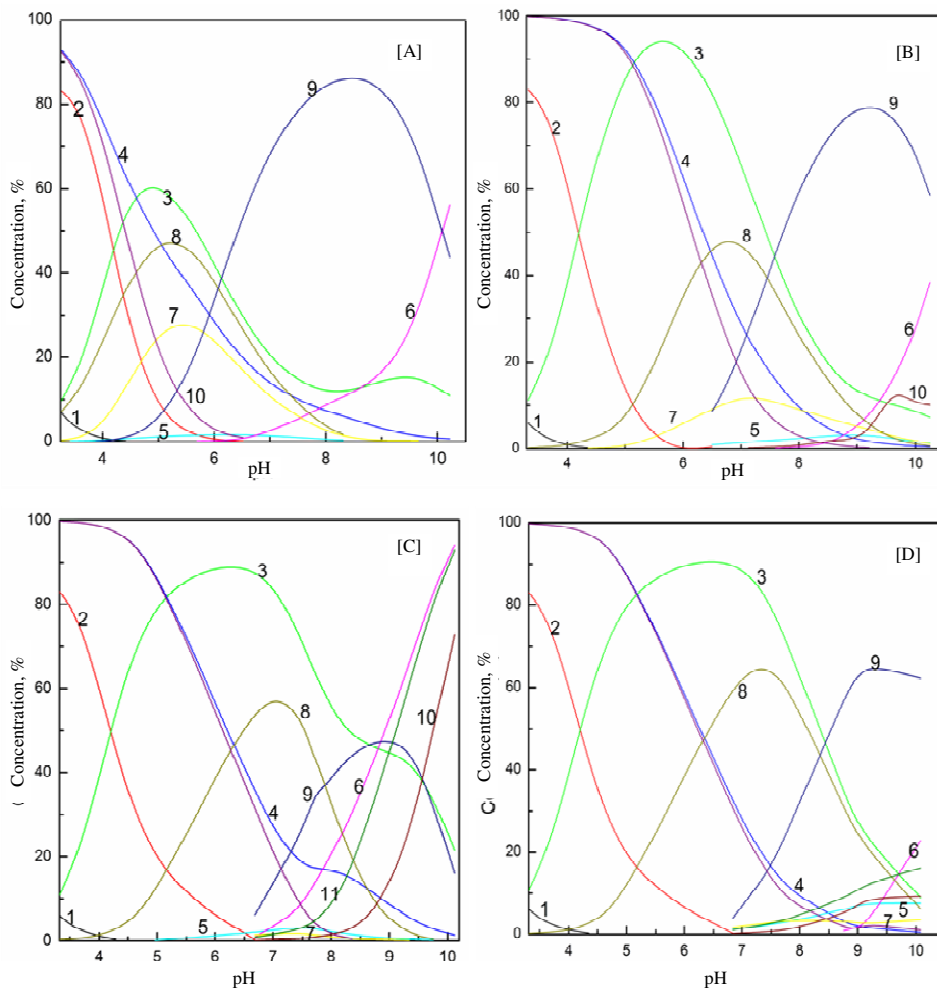

Figure 1. Species distribution curve of (1:1:1) ternary system (A) A-Cu-B, (B) A-Ni-B, (C) A-Zn-B (D) A-Co-B system, where (1) H_3A (2) H_2A (3) HA(4) HB (5) $M(OH)^+$ (6) $M(OH)_2$ (7) MA (8) MB (9) MAB (10) M(II)

The free metal ion is ~99.0% at the start of the titration following declining pattern with the rise in pH. The ternary complex species shows its remarkable presence at higher pH range 6.5-10.0. There is gradual increase in once of A-Zn(II)-B complex species attaining the maximum concentration ~50.18% at pH 9.0 with decrease in binary Zn-A and Zn-B complex species in the same pH range. Both the metal hydroxo species $Zn(OH)_2$ is good concentration at higher pH and $Zn(OH)^+$ is form negligible amount. The system A-Co(II)-B shows its remarkable presence at higher pH range 4.0-10.0. Protonated species H_3A, H_2A,

HA and HB decrease with increase the pH range 3.31-10.0 showing in Figure 1D. The binary complex species Co-B exist in appreciable amount whereas Co-A exist in small amount and the free metal ion is found to be declining pattern and metal hydroxo species $Co(OH)_2$ and $Co(OH)^+$ exist in higher pH. The concentration of H_3A H_2A and HA species of both the ligands are found to be decreasing with increase in pH where as the species HA is increasing in the pH range 3.31-6.5 while decreasing in the pH range 6.5-10.0 indicating the metal ligand complex formation. Speciation curves reveals that the binary species dissociates and formation of the ternary mixed ligand complex occurs. The concentration profile of A-Co(II)-B system indicates the formation of mixed ligand complex in the pH rage 6.8-10.0 There is gradual increase in once of A-Co-B complex species attaining the maximum 63% concentration at pH 9.0 with decrease in binary Co-B complex species in the same pH range[19]. The proposed solution structure of ternary complexes of Cu(II), Ni(II), Zn(II) and Co(II) with asparagine and thiouracil were also suggested which shown in Figure 2 (A&B).
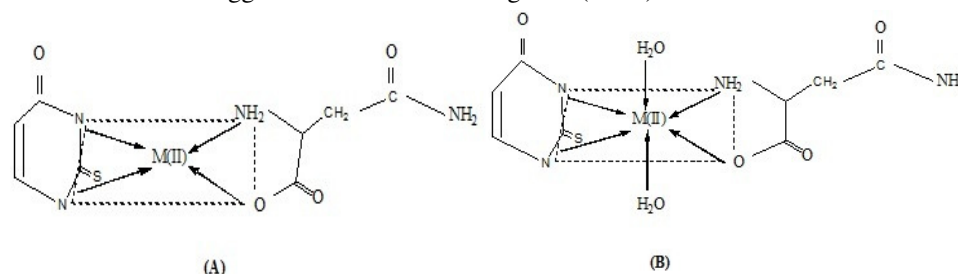

Figure 2. Proposed solution structure of ternary complexes of (A) Tetracoordinated thiouracil and asparagine where M(II) = Co(II), Zn(II) and (B) Hexacoordinated thiouracil and asparagine where M(II) = Co(II),Cu(II), Ni(II)

Conclusion

The overall stability constant of all the analogous complexes was found to follow the following order: Cu > Ni > Zn > Co in case of ternary systems of both the ligands studied *i.e*. Asparagine and Thiouracil with the above used divalent transition metal ions. The marked stabilization of the ternary complexes occurs in larger concentrations at higher pH in each of the systems studied. The extra stability of the ternary complexes is due to the interactions outside the coordination sphere. This may sometimes be the formation of hydrogen bonds between the coordinated ligands. The dissociation of the ternary complex may also be attributed to the formation of hydroxo species as the buffer region corresponding to the complexation equilibria has been found to be overlapping with the hydrolytic equilibria aqueous medium ions.

References

1. Janrao D M, Pathan J, Kayande D D and Mulla J J, *Sci Revs Chem Commun.,* 2014, **4(1)**, 11-24.
2. Chohan Z H, Mohammad S I, Syed K A and Rauf A, *J Enzy Inhib Med Chem.*, 2012 **27(2)**, 223-231; DOI:10.3109/14756366.2011.585135
3. Reddy P R, Radhika M and Manjula P, *J Chem Sci.*, 2005, **117(3)**, 239-246; DOI:10.1007/BF02709293
4. Sinha S, Shukla V P, Singh P P and Krishna V, *Chem Sci Trans.*, 2014, **3(2)**, 576-581; DOI:10.7598/cst2014.746

5.   Singh D, Chandra H and Krishna V, *Int J Inorg Bio Inorg Chem.*, 2013, **3(4),** 65-69.
6.   Kumar N V, Sreekanth B and Rao G N, *Acta Chim Slov.*, 2011, **58**, 342-346.
7.   Devi K V S, Raju B R and Rao G N, *Chem Speciat Bioavail.*, 2010, **22(3)**, 191-199; DOI:10.3184/095422910X12829312795432
8.   Srikanth R B, Rao V S S, Kamala S C and Rao G N, *J Chem.*, 2009, **6(2)**, 561-568; DOI:10.1155/2009/705976
9.   Moyal M and Gupta O D, *Int J Chem Tech Res.*, **4(4)**, 1433-1436.
10. Watabe M, Kai M, Goto K, Ohmuro H, Furukawa S, Chikaraishi N, Takayama T and Koike Y, *J Inorg Biochem.*, 2013, **97(2),** 240-245; DOI:10.1016/S0162-0134(03)00287-3
11. Sigel H, Sigel and Sigel K O R, Metal ions in life Science, John Willey & Sons Ltd., Chichester, U.K., 44, 2006.
12. Rao V S S, Rao P S, Srikanth B, Sastrya C K and Rao G N, *Chem Speciat Bioavailabil.*, 2009, **21(2)**, 71-80; DOI:10.3184/095422909X449508
13. Van J P and Wouwe, *Eur J Pediatr.*, 1989, **149(1)**, 2-8; DOI:10.1007/BF02024322
14. Verma S, Singh D, Kumar R, Shukla B K and Krishna V, *Res J Chem Sci.*, 2015, **5(3)**, 1-5.
15. Chandra P, Singh M, Bartaria D and Krishna V, *J Indian Chem Soc*., 2010, **87**, 955-958.
16. Martell A E, Motekaitis RJ, Determination and Uses of Stability Constants, VCH, NY, 1992.
17. Singh D, Chandra H, Shankar V and Krishna V, *Int J Res Chem Environ.*, 2014, **4(1)**, 48-53.
18. Bartaria D, Chandra P and Krishna V, *Chem Sci Rev Lett.,* 2013, **1(4)**, 201-208.
19. Sakuri T, Yamauchi O and Nakahara A A, *Bull Chem Soc.*, 1976, **49,** 169, *ibid*.,1976, **49,** 1579, *ibid.,* 1977, **50,** 1776, *ibid.,* 1978, **51,** 3203.