

Complexation Behaviour and Speciation Equilibria of Multimetal Multiligand Complexes of Bioactive Transition Metals Involving $\alpha - \epsilon$ -diaminocaproate and 5-methyl-2,4-dioxypyrimidine

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Abstract

Chelation tendency of α - ϵ -diaminocaproate (lysine=A) to form heterobinuclear complexes with some bioactive transition metal ions (viz. Co^{II} , Ni^{II} , Cu^{II} , Zn^{II}) in the presence of 5-methyl-2,4-dioxypyrimidine (thymine = B) have been examined potentiometrically in aqueous medium. Speciation constants of complexes at $37 \pm 1^\circ$ and at constant ionic strength 0.1 M NaNO_3 have estimated using SCOGS computer program and complex formation equilibria were interpreted. Species distribution curves are finally sketched by running the computer program ORIGIN 4.0. The relevant stability constant of binary, ternary (mixed ligand), quaternary (multimetal, multiligand) (MA, MB, MAB, $\text{M}_1\text{M}_2\text{AB}$) complexes follow Irving William order. The results are discussed to obtain the order of formation constants of the above mentioned complexes and probable solution structures of metal complexes with said ligand have been discussed.

Keywords: Quaternary; Equilibria

Introduction

The complexation of polynuclear metal chelates and multimetal multiligand equilibria are very common in enzymatic process, so mixed-metal, mixed-ligand complexes may help in examining such equilibria found in biological system [1-3]. The metal chelates continues to activate fields of medicinal [4], industrial [5], and analytical [6,7] importance. Biological units comprises of various vital and unimportant or potentially hazardous metal ions [8,9,10] like sodium, calcium, manganese, cobalt, copper, zinc, lead, mercury and cadmium etc. The correlation between metal and amino acids have gain considerable importance as chelation phenomenon prototype for interrelationship between metal and protein. Lysine(α - ϵ -diaminocaproate) is a prime producer of carnitine, chemical which helps body turn fat into energy thereby controlling the level of cholesterol. Humans require lysine for healthy functioning of body. Apart from its role in helping growth and repair of body tissue it also helps the body absorb calcium and restrain its loss by urination. It may also prevent bone deterioration accompanying osteoporosis [11, 12]. Key value of complexes of metal pyrimidine bases in biological context is as model of nucleic acid ion interactions [13]. Thymine (5-methyl-

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2,4-dioxypyrimidine) is associated with biosynthesis of DNA and genetic conductance [14,15]. Product of transition metal and nucleic acid are investigated for examining structure and function of nucleic acid as artificial nuclease metallopharmaceuticals [16] for construction and advancement of restrictive enzymes. In extension to our recent work [17-25] on quaternary (multi-metal multi-ligand) complexes, relative order of stability of quaternary metal complexes of Cu, Ni, Co, and Zn metal ions with Lysine and Thymine as primary and secondary ligand respectively is addressed using pH meter in aqueous medium. The species distribution at different pH, speciation constant, presumed structure and feasible equilibria for the formation of species are communicated in the present paper.

Experimental

All the solutions were prepared in double distilled water. Potentiometric titrations of each ligand with standard carbonate free sodium hydroxide were carried out with an electric digital pH meter (Century-model CP901-S) with glass electrode at $37 \pm 10^\circ \text{C}$ and $I = 0.1 \text{M NaNO}_3$. Relatively low concentrations of metals and ligands are used. A stream of nitrogen was passed through the solutions throughout the titration. All the metal salts used were of A.R. grade (sigma) and were standardised volumetrically by titration with the disodium salt of EDTA in presence of suitable indicators, as described by Schwarzenbach [26]. Binary M:A/M:B (1:1), ternary M:A:B(1:1:1) and quaternary ($M_1:M_2:A:B$) metal-ligand solution mixture have been titrated against standardized NaOH (0.01M) solution, keeping total volume 50ml in each case. Strength of metal and ligand = 0.001M and $I = 0.1 \text{M NaNO}_3$.

Solution A: 5ml NaNO_3 (1.0M) + 5ml HNO_3 (0.02M) + Water

Solution B: 5ml NaNO_3 (1.0M) + 5ml HNO_3 (0.02M) + 5ml A (0.01M) + Water

Solution C: 5ml NaNO_3 (1.0M) + 5ml HNO_3 (0.02M) + 5ml A (0.01M) + 5ml M_1 (II) (0.01) + Water

Solution D: 5ml NaNO_3 (1.0M) + 5ml HNO_3 (0.02M) + 5ml A (0.01M) + 5ml M_1 (II) (0.01) + 5ml B (0.01) + water

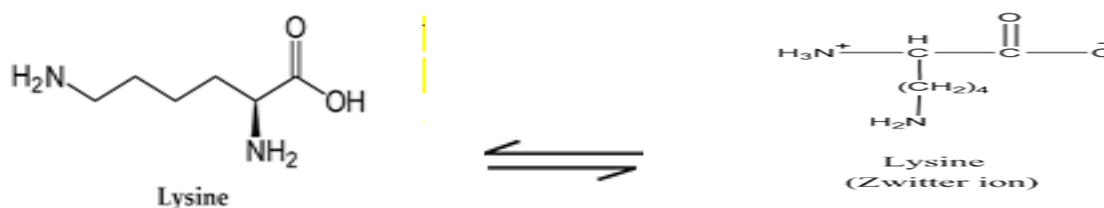
Solution E: 5ml NaNO_3 (1.0M) + 5ml HNO_3 (0.02M) + 5ml A (0.01M) +

5ml M_1 (II) (0.01) + 5ml B (0.01) + 5ml M_2 (II) (0.01M) + water

Where M_1 (II) and M_2 (II) are Co/Ni/Cu and Zn, A = Primary ligand and B = Secondary ligand. The pH meter reading with progressive addition of alkali to the titration mixtures were noted, when the reading of pH meter stabilized. The titration was discontinued at the appearance of turbidity. The pH values were plotted against the volume of NaOH and titration curves were obtained.

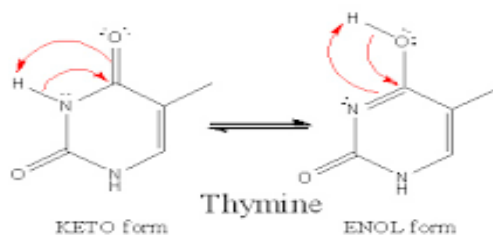
Result and Discussion

The lysine dianion offers to an incoming ligand both a functional group which is a potential hydrogen bond acceptor, the coordinated oxygen and two primary amine groups which are potential hydrogen bond donor. Thus lysine is a potentially tridentate ligand.

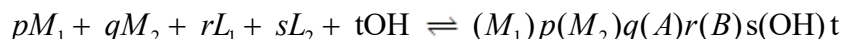


The side $\epsilon\text{-NH}_2$ group of lysine residue in peptides and proteins is one of the potential donor sites for metal especially copper ion complexation. However, its coordination to the metal centre generally involves the formation of usually large chelate rings [27,28].

Proton ionization for thymine in the strongly acidic region has been reported based on spectrophotometric data. Metal complexation observed in thymine is unusual due to absence of free lone pairs. Coordination in thymine is reported to take place through ring nitrogen and carbonyl oxygen or from both the ring nitrogen making it bidentate ligand. UV and Ultrasonic absorption studies indicate that in aqueous medium thymine primarily exist in lactum form, α -hydroxyl and γ -hydroxyl ionizes in alkaline medium corresponding to two pK values 9.9 and >13



For evaluation of stability constants by the SCOGS computer program [26] in a system of the two different metal ion M_1 and M_2 and two different ligands A and B in aqueous medium, speciation may be described according to equilibrium.



The overall stability constant (β_{pqrst}) is defined as:

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

may be used to calculate the species distribution curves that provides the clues for the formation equilibria of the complexes. Values of constants were supplied to the computer as input data to obtain distribution curves of the complexes occurring at different pH. Ionic product of water (k_w) and activity coefficient of hydrogen ion under the experimental conditions were obtained from literature.

The dissociation of proton from thymine is from N_3H [29,30]. Since thymine is the nucleoside of thymine, so it may be assumed that the first dissociation from thymine is from N_3H group. Thymine shows only single dissociation since hydrogen in N_1 position of the pyrimidine is substituted by sugar moiety [31]. Protonation constants for the ligands have been determined by Irving-Rossotti titration technique [32] and are presented in the table provided:

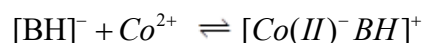
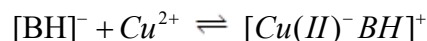
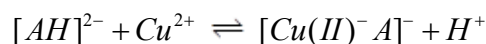
Table 1: Stability constants and other related constants of Binary, Ternary, and Quaternary complex of α - ϵ -diaminocaproate (lysine = A) and 5-methyl-2,4dioxypyrimidine (thymine=B) with different metal ions in aqueous solution at $37 \pm 1^\circ C$, $I = 0.1M NaNO_3$.

(A) Proton-ligand formation constants ($\log\beta_{00rst}$)				
AH3	-	21.84		
AH2	-	19.77		
AH	-	10.69		
BH	-	9.94		
(B) Hydrolytic constants ($\log\beta_{p000t} / \log\beta_{0q00t}$)				
	Cu	Ni	Zn	Co
$M(OH)^+$	-6.29	-8.10	-7.89	-8.23
$M(OH)_2$	-13.10	-16.87	-14.92	-17.83
(C) Metal – ligand constants ($\log\beta_{p0r00} / \log\beta_{0qr00} / \log\beta_{p00s0} / \log\beta_{0q0s0}$) : Binary systems				
	Cu	Ni	Zn	Co
MA	11.56	8.30	8.22	6.12
MB	8.83	8.20	7.06	6.34

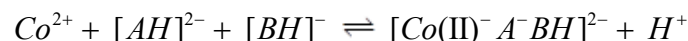
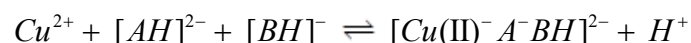
(D) Metal – ligand constants ($\log\beta_{p0rs0} / \log\beta_{0qrs0}$) : Ternary systems						
	Cu	Ni	Zn	Co		
MAB	15.92	13.58	12.67	11.89		
(E) Metal – ligand constants ($\log\beta_{pqrs0}$) : Quaternary systems						
	Cu-Ni	Cu-Zn	Cu-Co	Ni-Zn	Ni-Co	Zn-Co
M ₁ M ₂ AB	23.83	22.96	21.67	20.85	19.94	18.37

Cu(II)-Co(II) –Lysine-Thymine (1:1:1:1) system

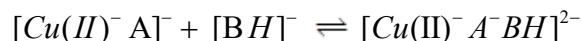
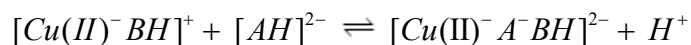
Deflection of titration curve E (quaternary) from curve D (ternary) clearly indicates formation of multinuclear complex at $\text{pH} \approx 7.8$ consumes ≈ 1.5 ml alkali. In present system, protonated species AH_3 , AH_2 , AH , BH , multimetal-multiligand complex i.e. quaternary complex species, ternary, and binary complex species, exist in sufficient concentration. The hydroxo species and free metal ions are also present throughout the entire pH range. Speciation curves (**FIG. 1**) clearly indicate that the concentration of AH_3 , AH_2 , AH , and BH species of both ligands are found to be decreasing with increase in pH range $\approx 3.0-7.5$ whereas species AH increases with increase in pH and attains maximum concentration $\approx 42\%$ at $\text{pH} \approx 3.5$, it further decreases in pH range $\approx 3.5-7.6$, which shows their involvement in the complex formation. Binary complexes show their remarkable presence according to the following equilibria.



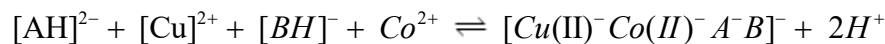
The concentration of binary complexes CuA and CuB are maximum at $\text{pH} \approx 4.5$. The species $[\text{Co(II)}^- \text{BH}]$ attains maximum value $\approx 25\%$ at higher $\text{pH} \approx 9.1$, while $[\text{Co(II)}^- \text{A}]$ complex species does not exist throughout entire pH range. The concentration of all binary species are decreasing with further increase in pH, probably due to the formation of ternary and quaternary complexes. Mixed ligand complexes with Cu^{2+} (aq.) and Co^{2+} (aq.) are found to be the remarkable species in the pH range $\approx 6.5-10.0$, as follows:



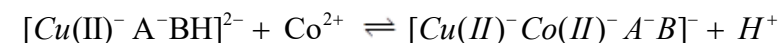
The alternative equilibria may also be indicated as follows:



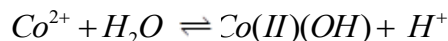
It is clearly evident from the distribution curves that the $[\text{Cu(II)}^- \text{A}^- \text{BH}]$ is the major ternary species attaining $\approx 40\%$ at higher $\text{pH} \approx 10.0$ whereas $[\text{Co(II)}^- \text{A}^- \text{BH}]$ does not exist in the present system. The speciation curves indicate the formation of heterobinuclear complex according to the following equilibria:



The another form of multinuclear equilibrium can be written as:

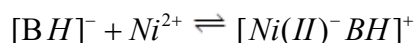
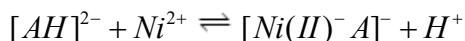


Formation curves shows that there is concomitant decline in the concentration of Cu^{2+} and Co^{2+} aqueous ions with the incline in the concentration of quaternary complex species . The concentration of multinuclear complex is increasing gradually with the gradual increase in pH and attains a maximum value $\approx 76\%$ in the pH range $\approx 7.5-8.5$. The metal hydroxo species Co(II)(OH)^+ , Co(II)(OH)_2^+ exist in the pH range $\approx 8.0-10.0$ involving the following equilibrium:

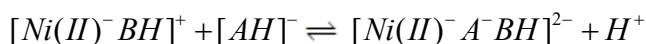


Ni (II)-Zn (II)- Lysine-Thymine (1:1:1:1) system:

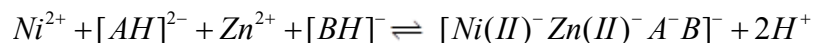
Potentiometric curves clearly indicate that the complexation starts at $\text{pH} \approx 8.0$. According to Speciation curve (**FIG. 2**) following species are assumed to prevail in the present system: AH_3 , AH_2 , AH , BH , Ni(OH) , Ni(OH)_2 , Zn(OH) , Zn(OH)_2 , $[\text{Ni(II)-A}]$, $[\text{Ni(II)-B}]$, $[\text{Zn(II)-A}]$, $[\text{Zn(II)B}]$, $[\text{Ni(II)-A-B}]$, $[\text{Zn(II)-A-B}]$ and $[\text{Ni(II)-Zn(II)-A-B}]$. The protonated ligand species of both the ligands and free metal ions Ni^{2+} (aq.) and Zn^{2+} (aq.) have been found to a declining pattern of their concentration with rise in pH. The concentration of AH_3 , AH_2 , AH and BH species of both the ligands are found to be decreasing with increase in the pH range $\approx 3.0-7.0$, which shows their involvement in the complex formation. The binary complexes show their remarkable presence according to the following equilibria:



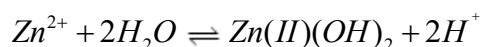
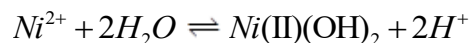
Binary complexes NiA and NiB shows their existence in the present system. Their formation start right from the beginning of the titration and after a gradual incline, their concentration becomes maximum at higher $\text{pH} \approx 10.0$ and 9.0 respectively. At still higher pH, these follow a declining pattern of their concentrations. Mixed ligand complexes with Ni^{2+} (aq.) and Zn^{2+} (aq.) are found to be remarkable species in the pH range $\approx 8.3-10.5$ as follows:



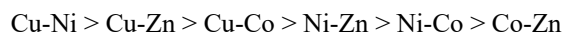
For quaternary system, the species distribution curve indicates the formation of heterobinuclear complex according to the following equilibria:



It is clear from the speciation curves , that there is gradual rise in the concentration of multimetal-multiligand complex with the progressive addition of alkali. Maximum concentration of the complex is $\approx 93\%$ at $\text{pH} \approx 8.0$. There is concomitant decline in the concentration of Ni^{2+} and Zn^{2+} aqueous ions with the incline in the concentration of quaternary complex species. The multinuclear complex species are predominant species in the present system. The metal hydroxo species are formed in the system which indicates the dissociation of multinuclear species.



Refined values of binary,ternary and quaternary constants are listed in **TABLE 1**, which are in good agreement with those in literature. The overall stability constants of mixed metal-mixed ligand $[\text{Lysine-Thymine-M}_1\text{-M}_2]$ systems have been found to follow the following order.



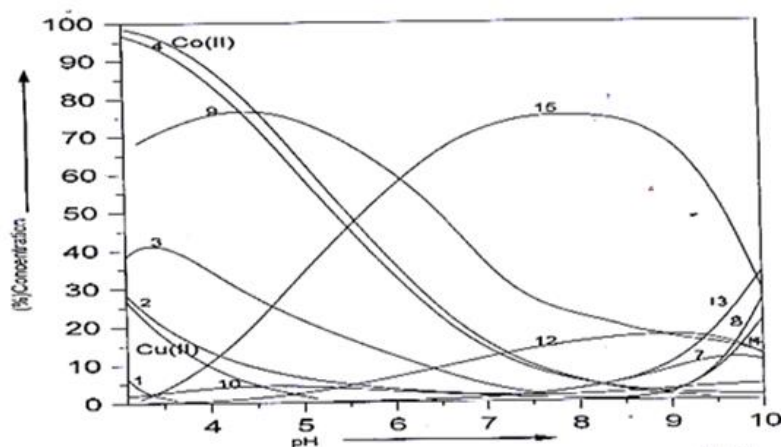


FIG.1 Distribution curves of 1:1:1 Cu(II)-Co(II)-Lysine-Thymine System; (1) AH_3 (2) AH_2 (3) AH (4) BH (5) $Cu(OH)^+$ (6) $Cu(OH)_2$ (7) $Co(OH)^+$ (8) $Co(OH)_2$ (9) CuA (10) CoA (11) CuB (12) CoB (13) $CuAB$ (14) $CoAB$ (15) $CuCoAB$.

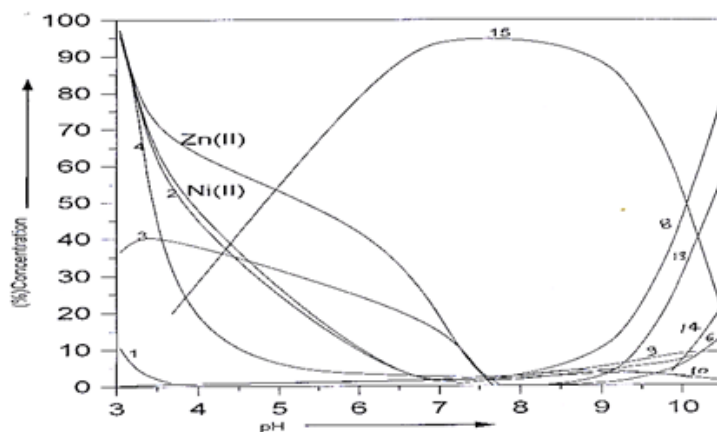


FIG.2 Distribution curves of 1:1:1 Ni(II)-Zn(II)-Lysine-Thymine System; (1) AH_3 (2) AH_2 (3) AH (4) BH (5) $Ni(OH)^+$ (6) $Ni(OH)_2$ (7) $Zn(OH)^+$ (8) $Zn(OH)_2$ (9) NiA (10) NiB (11) ZnA (12) ZnB (13) $NiAB$ (14) $ZnAB$ (15) $NiZnAB$.

Cu^{2+} in aqueous solution is coordinated by six water molecules. However, tetragonal coordination is possible as two water molecules lie at longer distance. Hydrated nickel ion usually show regular octahedral configuration unless tetragonal distortion is forced by some strong field ligand which ultimately leads to square planar configuration. Isomeric complex species of hexacoordinated nickel is expected to have in greater number in comparison to copper, with predominant geometry of four equatorial bonds. Depending upon the nature of ligand bounded configuration of zinc can easily move from tetrahedral to octahedral geometry. Metal –A complex which has higher value of $\log \beta$ will be the first to attach ligand A, which further attaches to ligand B to satisfy its coordination number. Uncoordinated sites of ligands will then be occupied by another metal ion. (FIG. 3 and 4)

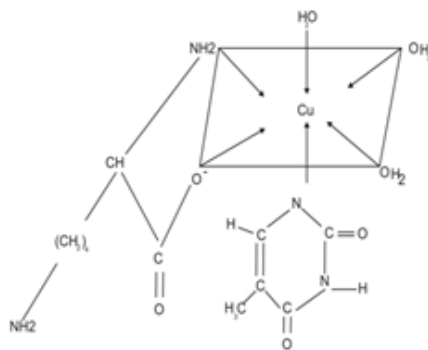


FIG.3. Proposed structure of ternary Cu(II) Lysine-Thymine.

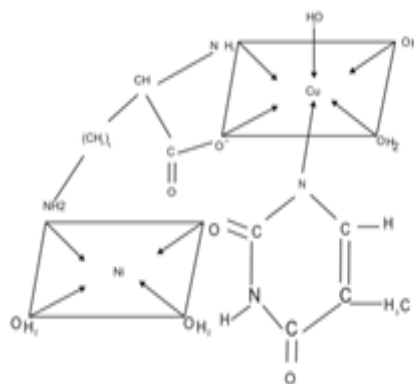


FIG.4. Proposed structure of Quaternary Cu(II)-Ni(II)-Lysine-Thymine.

REFERENCES

1. Sigel H, Sigel A, editors. Metal ions in biological systems. Dekker; 1983.
2. Martell A, editor. Critical Stability Constants: Volume 2: Amines. Springer Sci. Bus. Media; 2012 Dec 6.
3. Moratal JM, Jiménez HR, Castells J, et al. ¹H NMR and UV-vis spectroscopic characterization of sulfonamide complexes of nickel (II)-carbonic anhydrase. Resonance assignments based on NOE effects. *J inorg biochem.* 1992 Mar 1;45(4):231-43.
4. Behari Jr, Gupta S, Srivastava S, et al. LETTERS TO THE EDITOR Influence of Size of Liposomes in Potentiating the Efficacy of Encapsulated Triethylenetetramine-hexaacetic Acid (TTHA) Against Cadmium Intoxication. *Ind. health.* 1993;31(1):29-33.
5. Jin JY, Xu F, Miwa T. Cathodic Stripping Voltammetry for Determination of Trace Manganese with Graphite/Styrene-Acrylonitrile Copolymer Composite Electrodes. *Electroanal.: Int. J. Devoted Fundam. Pract. Asp. Electroanal.* 2000 May;12(8):610-5.
6. Yang XJ, Pin C. Determination of trace zirconium and hafnium in basaltic rocks by inductively coupled plasma atomic emission spectrometry after chemical separation: an evaluation of two methods based on extraction chromatography. *Analyst.* 2000;125(3):453-7.
7. Miles DL, Cook JM. Geological applications of plasma spectrometry. *Inductively Coupled Plasma Spectrometry and its Applications.* 2007 Feb 5:277
8. Jones MM, Cherian MG. The search for chelate antagonists for chronic cadmium intoxication. *Toxicology.* 1990 May 14;62(1):1-25.
9. De, A.K. *Environmental chemistry* 3 ed. India: Wiley Eastern Limited. 1994;26(24)
10. Williams DR. *The Metals of Life*, van Nonstrand Reinhold Company. London, UK. 1971.
11. Fürst P. Dietary L-lysine supplementation: a promising nutritional tool in the prophylaxis and treatment of osteoporosis. *Nutr. (Burbank Angeles Cty. Calif.).* 1993 Jan 1;9(1):71-2
12. Flodin NW. The metabolic roles, pharmacology, and toxicology of lysine. *J. Am. Coll. Nutr.* 1997 Feb 1;16(1):7-21
13. Magda D, Crofts S, Lin A, et al. Synthesis and kinetic properties of ribozyme analogues prepared using phosphoramidite derivatives of dysprosium (III) texaphyrin. *J. Am. Chem. Soc.* 1997 Mar 5;119(9):2293-4
14. Wempen I, Duschinsky R, Kaplan L, et al. Thiation of Nucleosides. IV. The Synthesis of 5-Fluoro-2'-deoxycytidine and Related Compounds 1, 2. *J. Am. Chem. Soc.* 1961 Dec;83(23):4755-66
15. Izatt RM, Christensen JJ, Rytting JH. Sites and thermodynamic quantities associated with proton and metal ion interaction with ribonucleic acid, deoxyribonucleic acid, and their constituent bases, nucleosides, and nucleotides. *Chem. rev.* 1971 Oct;71(5):439-81
16. Amico P., Arena G., Danille G, et al. *Environ. Inorg. Chem.* 1985
17. Singh M, Sinha S, Krishna V. Computed Distribution of Quaternary Complexes of Cu (II), Zn (II) Co (II) and Ni (II) with Citrulline and Tryptophan as Primary Ligand and Thymine as Secondary Ligand. *Proc. Natl. Acad. Sci. India A: Phys. Sci.* 2021 Mar;91(1):1-7.

18. Bartaria D, Sinha S, Krishna V. Formation and stability of heterobinuclear complexes containing HgII and divalent metal ions with EDTA and CDTA. *J. Indian Chem. Soc.* 2006;83(2):198-200.
19. Shukla VP, Sinha S, Krishna V. Multiple equilibria and chemical distribution of some bio metals with β -amide α -aminosuccinate and α -aminoisoverate as primary ligand and 5-methyl 2, 4 dioxypyrimidine as secondary ligand. *IOSR J. Appl. Chem.* 2013;4(6):21-6.
20. Shukla VP, Sinha S, Krishna V. Multiple equilibria and chemical distribution of some bio metals with β -amide α -aminosuccinate and α -aminoisoverate as primary ligand and 5-methyl 2, 4 dioxypyrimidine as secondary ligand. *IOSR J. Appl. Chem.* 2013;4(6):21-6.
21. Shukla VP, Sinha S, Krishna V. Multiple equilibria and chemical distribution of some bio metals with β -amide α -aminosuccinate and α -aminoisoverate as primary ligand and 5-methyl 2, 4 dioxypyrimidine as secondary ligand. *IOSR J. Appl. Chem.* 2013;4(6):21-6.
22. Sinha, Surabhi, Shukla, V.P., et al. Chemical Distribution and Structure of Quaternary Metal Chelates in Aqueous Solution Involving Asparagine and Uracil. *Chem. Sci. Trans.* 2014;3(2):576-81.
23. Verma Shalini, Singh Dharmeer, Kumar Rajendra, et al. Equilibrium study and Stability constants of mixed Ligand complexes of Biomolecules and Amino acids with Metal ions by Potentiometric method. *Res. J. Chem.Sci.* 2015;5(3):1-5.
24. Sinha Surabhi, Shukla V.P., Krishna, V. et al. *Inorg. Chem.* (2016);11(2):58-64
25. Singh M, Shankar V, Singh D, et al. Chelation and Stabilization Properties of Citrulline and Uracil with Hg (II) as a Heavy Metal Ion in Solution. *Chem. Sci.* 2017;6(4):646-52.
26. Schwarzenbach, G.: *Complexometric Titration in Sciences*, New York, 77 (1951) .
27. Sayce IG. Computer calculation of equilibrium constants of species present in mixtures of metal ions and complexing agents. *Talanta.* 1968 Dec 1;15(12):1397-411.
28. Wilson E W. Jr., Kasperian M.H., Martin R.B., et al. *J.Chem.Soc.*(1990):289.
29. Puspita W.L., Odant A., Yanauchi, O. *J.Inorg.Biochem.*,(1999):203-73.
30. Reddy VR, Rao AR, Reddy KV. Equilibrium Studies on Binary and Ternary Complexes of Transition Metal Ions with Thiouracil as Binary and some N-Donor Ligands as Ternary Ligands. *J Chem Chem Sci.* 2015 May;5(5):285-91.
Khan Taqui, Krishnamoorthy. *J.Inorg.Nucl.Chem.*(1973)25:1285
31. Maskog, Karol.; *Inst.Biochem.Wroclam.uni.*,50-137, Wreclaw; *pol Acta Biochem.pol.*25A, 311 (1978).