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Mononuclear Binary Complex Formation Equilibria of L-Ornithine with Biologically Essential Metals in TBAB Micellar Media

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Investigation of mononuclear complex of L-ornithine in tetrabutylammonium bromide (TBAB, a cationinc surfactant) micelle media has been made pH metrically at constant temperature and ionic strength in different percentage of micellar solutions (0.0-2.5 %). Stability constants and best fit model for metal complexes were obtained by MINIQUAD75 computer program on the basis of the analysis of residues and other statistical parameters. Accordingly, ML, ML_2, MLH and ML_2H for both Co(II) and Cu(II) and ML_2 and ML_2H for Ni(II) mononuclear chemical models were obtained. The stabilization/destabilization equilibria of the binary system for the model species with percentage composition of micelles at constant ionic strength and temperature could be attributed to dielectric constant and other intrinsic interaction properties of tetrabutylammonium bromide micelle with ligands and metal ions. The plot of percentage of species against pH values has been generated from SIM refined data using origin85 software.

Keywords: Complex equilibria, Metal ions, L-Ornithine, TBAB, MINIQUAD75.

INTRODUCTION

Complexes of metal ions play an important catalytic role in various enzymatic reactions where the reaction mechanism involves the formation of metal-enzyme species. The action of metal ions in biological systems which contain several complex forming molecules like amino-acids, peptides, proteins, carboxylic acids, *etc.* is closely related to selective formation of complexes with these ligands. Therefore, determination of stability constants of metal-ligand complexes is very important in biosystem or coordination chemistry [1-6].

When a metal ion is in contact with single/several ligands, there is a chance of formation of a number of species depending on the concentrations of metal ions, concentrations of ligand and other environmental conditions of the biosystem surrounding it [3,4]. The activity of a metal ion or a ligand depends on the actual form of the chemical species in which the metal ion exists [5,6]. The term chemical species refers to this specific form of an element in a particular oxidation state or molecular structure and chemical speciation study is the analytical study of identifying/measuring the quantity of one or more individual chemical species in a sample [3]. Information regarding the nature and extent of formation of species as a function of pH can be obtained from speciation study [7,8].

L-Ornithine (L-Orn) is a non-protein 2,5-diaminopentanoic acid whose metal complexes are insoluble in water and soluble in most organic solvents [9]. It is a tridentate ligand [10,11] and known to form several stable metal ion complexes in a variety of solvents differing in the degree of solubility: with Co(II), Ni(II) and Cu(II) [12-22]; Cd(II), Sn(IV), Ce(IV) and Pd(II) in different solvents [23-27]. L-Ornithine complexes of bio-essential metals play an important role in chemotherapeutic applications [28,29]. For instance Orn-Cu(II) complexes showed excellent antimicrobial activity [30], Orn-Cd(II) and Orn-Cu(II) proteasome inhibitors and apoptosis inducers in human cancer cells [31]. L-Ornithine also helps to build muscles, reduces body fats, removes toxic ammonia in urea cycle from liver [32] and is the source of polyamines in maintaining physiological system.

EXPERIMENTAL

All chemicals used were of analytical reagent grade from which corresponding solutions were prepared in triply distilled

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water free of dissolved oxygen or carbon dioxide *via* purging nitrogen gas in to it. Solutions of ~0.05 mol dm^{-3}, L-ornithine (Sigma-Aldrich, India), ~ 0.4 mol dm^{-3} of sodium hydroxide and 0.2 mol dm^{-3} hydrochloric acid (both Merck, India) were prepared. Carbonates were removed from NaOH through regular Gran titration. NaOH was standardized against potassium hydrogen phthalate and used to standardize HCl solution before use. A ~ 0.1 mol dm^{-3} solutions of Cu(II), Co(II) and Ni(II) (all E-Merck, Germany) were prepared from the corresponding chloride salts and standardized by complexometric titration method. The ligand solutions (to increase their solubility) and metal solutions (to repress their hydrolysis) were maintained in 0.05 mol dm^{-3} HCl. Tetrabutylammonium bromide (TBAB) (Merck, India) were used as received. 0.5-2.5 % percentage solutions were successively prepared for TBAB. The ionic strength of the titration mixture was maintained to be 0.16 mol dm^{-3} sodium chloride (Merck, India) in a total volume of 50 mL.

Methods and equipments: Potentiometric titrations were conducted in micellar media by using Metrohm 877 titrino plus auto-titrator (Switzerland) (readability 0.001) in conjunction with electrode of 0-14 pH reading at the temperature of 298 K and purified nitrogen atmosphere as described elsewhere [33]. The electrode was calibrated with 0.1 mol dm^{-3} potassium hydrogen phthalate (pH 4.01) and 0.05 mol dm^{-3} borax solutions (pH 9.18). It was also equilibrated in well stirred solvent with regular checking *via* initial titration of strong acid with alkali solution. After equilibration of the electrode, the data obtained by the three replicate titration measurements were reproducible and found to differ by not more than 0.02 units.

Data processing for selection of best fit models: In this study, the relative compositions of chemical species (their complexes and free forms) formed by the interactions between metal ions and ligand (L-ornithine) at the given set of experimental conditions (pH, temperature and ionic strength) have been determined using the modified [34] Calvin-Wilson titration technique.

A total volume of 50 mL titration mixtures containing different percentage of surfactants, ligand and fixed concentration of metal ions in an ionic strength of 0.16 mol dm^{-3} NaCl and 298 K has been carried out to study the formation of binary complexes. Determination of metal ligand stability constants was performed by the titration of metal ion-ligand mixtures with 0.05 mL sodium hydroxide (0.4 mol dm^{-3}) at regular interval. For each experimental data point, the metal to ligand ratios were kept to be 1:1, 1:2 and 1:3 (M:L) to form mononuclear complexes. The titrimetric data generated were automatically saved in the instrument (Metrohm 877 titrino plus auto-titrator). The effect of variations in liquid junction potential, asymmetry potential, dielectric constant, sodium ion error, dissolved carbon dioxide and activity coefficient on the response of the electrode were accounted for by correction factor which was calculated using SCPHD [35] program. The stability constants of the binary complexes were determined by MINIQUAD75 computer program [35,36] using value of correction factor as initial imputes and fixed values of Kw and protonation constants of the ligand during refinement.

RESULTS AND DISCUSSION

Modeling of chemical species: The outcomes of the best fit models that represent the different types of chemical species and their stochiometric ratio and stability constant values are given in Table-1. The detection of all plausible species in the form of non-protonated and protonated complexes that best fit with the model for metal-ligand system is also given in Fig. 1. The validity and sufficiency of the chemical models

TABLE-1
PARAMETERS OF BEST FIT CHEMICAL MODELS OF Co(II), Ni(II) AND Cu(II)-L-ORNITHINE COMPLEXES IN TBAB-WATER MIXTURES

TBAB (%)	log β_{MLH}				NP	U_{corr}	Skewness	Kurtosis	χ^2	R
	ML	MLH	ML_2	ML_2H						
Co(II) (pH 2.0-9.5)										
0.0	7.86(17)	10.3(20)	15.91(31)	23.59(37)	104	3.04	-0.33	4.63	25.08	0.0110
0.5	7.68(18)	9.98(23)	15.25(30)	23.02(31)	115	8.48	-0.49	2.77	12.22	0.0155
1.0	7.03(12)	9.34(13)	14.80(25)	22.57(26)	143	5.47	-0.07	2.91	23.68	0.0125
1.5	6.52(9)	9.41(21)	14.17(20)	22.53(16)	81	4.29	0.10	3.43	4.28	0.0091
2.0	6.27(7)	8.72(10)	12.81(12)	21.68(11)	96	3.72	0.29	3.38	12.95	0.0136
2.5	5.93(15)	8.33(17)	12.71(22)	21.62(16)	74	6.41	-0.09	2.39	3.65	0.0214
Cu(II) (pH 1.8-7.5)										
0.0	17.65(6)	20.18(14)	30.87(29)	36.18(18)	143	6.35	-0.15	3.28	43.56	0.019659
0.5	16.93(12)	19.79(20)	27.99(55)	34.23(25)	96	5.76	0.08	2.53	8.56	0.015053
1.0	16.51(9)	19.80 (9)	26.79 (75)	33.52 (14)	73	1.37	0.06	1.73	77.73	0.006239
1.5	16.95(9)	18.93(41)	28.35(33)	34.47(13)	69	3.23	-0.05	2.66	9.08	0.016845
2.0	17.48(9)	19.21(45)	28.27(70)	34.90(14)	91	1.24	-0.25	2.50	29.27	0.022362
2.5	16.47(9)	19.93(6)	26.54(64)	33.16(16)	91	1.87	0.05	1.97	95.85	0.006528
Ni(II) (pH 2.4-10.5)										
0.0	–	–	14.67(35)	23.43(23)	45	22.39	0.21	5.01	19.61	0.0539
0.5	–	–	13.91(15)	22.95(10)	109	6.46	-0.72	4.34	10.44	0.0244
1.0	–	–	12.97(18)	22.56(12)	89	10.21	-0.77	3.36	7.55	0.0284
1.5	–	–	12.81(16)	22.46(12)	101	9.62	-0.88	4.18	16.29	0.0285
2.0	–	–	12.42(14)	22.22(11)	104	8.29	-0.88	3.76	11.79	0.0259
2.5	–	–	11.82(15)	21.95(12)	102	9.86	-0.89	3.60	13.48	0.0285

$U_{corr} = U/(NP-m) \times 10^8$, where m = number of species; NP = number of experimental points

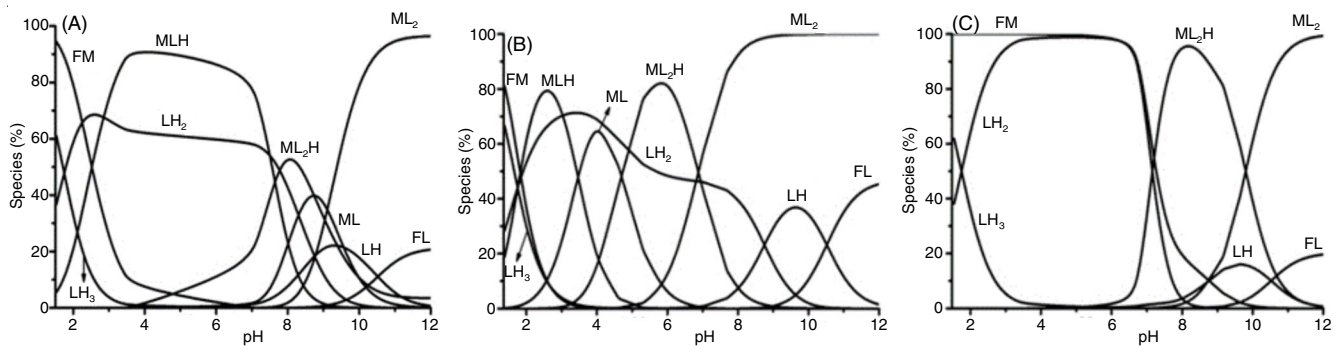

Fig. 1. Concentration distribution diagrams of L-ornithine complexes in 1.5 % v/v TBAB-water mixture. (A) Co(II) (B) Cu(II) and (C) Ni(II). The analytical concentrations of metal and ligand are: M(II): ~ 0.1 and L-ornithine: 0.05. (mol L^{-1})

that represent the metal-ligand system to qualify as best fit model to experimental data have been tested based on sum of squares of residuals in mass balance equations 'U', the standard deviations in refined overall stability constants, chi-square, skewness, kurtosis and crystallographic R-factor. These statistical parameters satisfy the requirements for the least square method to be applied to the data presented. The small values of standard deviations ensure that the parameters employed are precise. The residuals with skewness values of -0.49 to 0.29 for Co(II)-Orn, -0.03 to 0.08 for Cu(II)-Orn and -1.41 to 0.21 for Ni(II)-Orn systems form part of the guassian (normal) distribution for M(II)-Orn system. The values of kurtosis shows both meso and slight leptokurtic pattern for Co(II)-Orn and leptokurtic pattern (> 3.0) for Ni(II)-Orn systems and platykurtic pattern for Cu(II)-Orn (< 3 except in aqueous) in the model distribution. The very small values of crystallographic R-factor (less than the critical value) further strengthen the adequacy of the model to represent the chemical species.

Chemical speciation and species distribution plots: Chemical speciation is determined through various analytical methods in conjunction with mathematical model in order to get the number, types, compositions and distributions as a function of pH and to assess stability of the species under specified experimental conditions of constant temperature and ionic strength. In this connection, metal-ornithine complexes were studied by determining the overall stability constants and data were subjected to refinement to arrive at the chemically reasonable speciation model that provide satisfactory best fit to the experimental data.

L-Ornithine is a tridentate ligand having two associable amino protons and one dissociable carboxylate proton. It exists as LH_3^{2+}, LH_2^+, LH and L^- in the pH ranges of 2.0-3.5, 2.0-9.0, 8.0-11.0 and 10.0-12.0, respectively. Based on the ligand information and metal-ornithine interactions, the plausible chemical species predicted and refined are ML, ML_2, MLH, ML_2H for both Co(II) and Cu(II) and ML_2 and ML_2H for Ni(II) in micelles-water mixture between 2.0-9.5, 1.8-7.5 and 2.0-10.5 pH ranges, respectively. The electron pair donor N-atom on α-amino and terminal amine functional group of L-ornithine has strong affinity towards hydrogen ions in the physiological pH ranges. As a result of the high competition between the metal ion and hydrogen ion for electron pair donar N-site, protonated species were likely formed as well. The most likely equilibria for the binary species formation are given as follows for which charges of species are omitted for simplicity:

$$M(II) + LH_3 \rightleftharpoons MLH + 2H^+ \quad (1)$$

$$M(II) + LH_2 \rightleftharpoons MLH + H^+ \quad (2)$$

$$M(II) + 2LH_3 \rightleftharpoons ML_2H + 5H^+ \quad (3)$$

$$M(II) + 2LH_2 \rightleftharpoons ML_2H + 3H^+ \quad (4)$$

$$MLH + LH_2 \rightleftharpoons ML_2H + 2H^+ \quad (5)$$

$$M + LH_3 \rightleftharpoons ML + 3H^+ \quad (6)$$

$$M + LH_2 \rightleftharpoons ML + 2H^+ \quad (7)$$

$$M + LH \rightleftharpoons ML + H^+ \quad (8)$$

$$MLH \rightleftharpoons ML + H^+ \quad (9)$$

$$ML_2H \rightleftharpoons ML_2 + H^+ \quad (10)$$

$$MLH + LH \rightleftharpoons ML_2 + 2H^+ \quad (11)$$

$$ML + LH \rightleftharpoons ML_2 + H^+ \quad (12)$$

The relative abundance, types and nature of chemical species are obtained from SIM refined data in the form of distribution diagrams drawn by origin 85. The interaction of the metal ions of interest with L-ornithine ligand progressively depleted the essential metal ions resulting in the formation of stable M(II)-Orn binary complex species. The concentration distribution diagrams of M(II)-Orn binary complexes for Co(II), Cu(II) and Ni(II) in Micellar–water mixtures are given in Fig. 1.

ML, MLH, ML_2 and ML_2H plausible chemical models have been found to exist for both Co(II)-Orn and Cu(II)-Orn systems in the pH ranges of 1.5-9.5. The ML_2 and ML_2H models were converged and refined for Ni(II)-Orn system in the pH ranges of 2.4-11.0.

At lower pH, MLH and ML_2H chemical models are formed by the interactions of LH_3 and LH_2 with the free metal ions [Equilibria (1-4)]. ML_2H can also be formed by the reaction of MLH and LH_2 [Equilibria (5)]. With increasing pH, deprotonation of MLH and ML_2H species gives their corresponding ML and ML_2 species [Equilibria (9) and (10)], respectively. This co-existence of MLH/ML and ML_2H/ML_2 with deprotonation/protonation dynamic equilibrium might be ensured by the increase in concentration of ML and ML_2 progressively with decreasing concentration of MLH and ML_2H in all the M(II)-Orn system.

ML species could be formed by the interactions of the free metal with LH_3, LH_2 and LH [Equilibria (6-8)]. Similarly ML_2 species has also been formed by the reactions of LH with MLH and LH at higher pH [Equilibria (11) and (12)]. The decrease in concentration of the free metal to lower values

and to zero values at extreme higher pH indicates its strong participation in the complex formation equilibria. With the complete depletion of the metal ions in the post active pH regions of the complex formation equilibria, the concentration of the free ligand drastically increases.

Interpretation of systematic errors: Changing experimental conditions and the concentrations of ingredients of the titration mixture alter the position of acid-base equilibria between the metal ion and the ligand. It in turn, significantly affects the magnitudes of stability constants. Deliberate introduction of pessimistic errors in concentrations of alkali, mineral acid, ligand and metal ions, most commonly known as influential parameters in the study of M(II)-Orn system in 1.5 % v/v micelle –water mixture has been made to ensure the appropriateness of the experimental conditions and the choice of the best fit models (Table-2).

TABLE-2
EFFECT OF ERRORS IN INFLUENTIAL PARAMETERS ON THE CO-ORNITHINE COMPLEX STABILITY CONSTANTS IN 1.5 % (v/v) TBAB-WATER MIXTURE

Ingredient	Error (%)	log β_{MLH} (SD)			
		ML	MLH	ML_2	ML_2H
Acid	0	6.52(09)	9.41(21)	14.17(20)	22.52(16)
	-5	Rejected	Rejected	Rejected	Rejected
	-2	6.06(09)	Rejected	15.57(20)	Rejected
	+2	7.24(19)	9.71(24)	12.17(32)	20.18(26)
	+5	5.21(20)	10.32(21)	11.17(14)	18.45(25)
Alkali	-5	8.96(20)	13.71(35)	Rejected	22.69(23)
	-2	7.92(30)	11.32(41)	16.02(47)	21.18(31)
	+2	5.36(41)	Rejected	12.17(20)	23.43(36)
	+5	Rejected	Rejected	Rejected	Rejected
Ligand	-5	6.32(10)	10.12(02)	14.05(36)	22.70(38)
	-2	6.45(08)	10.00(12)	14.13(38)	21.87(23)
	+2	6.42(10)	9.61(18)	14.20(36)	22.07(32)
	+5	6.48(13)	9.37(25)	13.83(34)	21.26(37)
Metal	-5	6.51(12)	9.52(21)	14.47(40)	22.15(16)
	-2	6.43(05)	9.36(08)	14.27(38)	21.68(25)
	+2	6.30(10)	9.25(11)	14.05(32)	21.83(20)
	+5	6.31(07)	9.23(21)	14.23(31)	21.89(35)

The destabilization/stabilization complex equilibria have been assessed from the magnitude of the overall stability constants their corresponding standard deviation and acceptance/rejection of certain species refined by MINIQUAD75. The values of the stability constants due to incorporation of the errors resulted from change in concentration of ingredients were found to be more significantly affected by alkali and acid but less affected by concentration of ligand and metal ions (Table-3). This is noted from the high standard deviation in the log β values and rejection of more species in the alkali and acids compared to the metal and ligands. The resulted high standard deviation in log β values and species rejection with introduction of errors signifies the appropriateness of the model and relative precision of the analytical concentrations.

Effects of surfactants: Dielectric constant is one of the most and prominent solvent properties that could be altered by surfactants in the given titration mixtures. The anisotropic water distribution within micellar structure causes non-uniform micropolarity, microviscosity and degree of hydration within the micellar media [37,38]. The degree of stability of complexes could be measured in terms of the magnitude of the overall stability constant of each species formed in metal ligand dynamic equilibria. The linear and non-linear variations in the magnitude of the stability constants of metal-ligand complexes are due to electrostatic and non-electrostatic opposing factors, respectively. In the present study results of the stability constants were found to be linearly decreasing as the percentage of surfactants increases progressively. The destabilization of the metal ligand complexes could be attributed mainly to the low dielectric constant of the surfactant mediated solvent compared to aqueous medium. Moreover, the destabilization effect of the low dielectric constant is synergized by the cationic surfactant, TBAB, which causes the log β values to decrease linearly as shown in Fig. 2. On the other hand, the proton accepting ability of the ligand increases in acidic environment (in TBAB). Hence, the metal ion, the protons and TBAB, as a cationic surfactant, compete for the ligand decreasing the full availability of the electron pairs of the ligand making difficult to easily donate to vacant shell of the metal ion. As a result of these competing processes, the stability of the complex and values of the stability constant seems to decrease in TBAB-water mixture. This concept is in good agreement with the linearity of plots of log β values *vs.* % TBAB (low dielectric constant effect of surfactant modified medium).

Structure: It is noted in the literature that octahedral structure has been proposed for Co(II) and Ni(II) complexes by different authors. Unlike Co(II) and Ni(II), Cu(II) complexes has been suggested to have square planar or distorted octahedral structure. The distorted structure for Cu(II) complexes is accounted for the Jahn-Teller distortion effect [15,16]. It is also evident that amino nitrogen electron donor sites have high

TABLE-3
COMPARISON WITH PREVIOUSLY REPORTED LITERATURE VALUES OF Co(II), Ni(II) AND Cu(II)-L-ORNITHINE COMPLEXES IN TBAB–WATER MIXTURES

Metal ion	Medium (mol L^{-1})	log β_{MLH}				Temp. (K)	Instrumental method used	Ref.
		ML	ML_2	MLH	ML_2H			
Co(II)	1.00	5.60	–	3.54	6.84	298	Potentiometry	[10]
	0.10	5.01	8.49	14.16	27.77	298	Potentiometry	[12]
	0.16	–	12.71	–	21.62	298	Potentiometry	Current work
Ni(II)	1.00	7.04	–	4.72	9.06	298	Potentiometry	[10]
	0.16	–	11.82	–	21.95	298	Potentiometry	Current work
Cu(II)	1.00	11.30	–	7.87	14.05	298	Potentiometry	[10]
	0.10	–	–	17.81	–	298	Potentiometry	[12]
	1.00	–	15.53	–	34.44	298	Potentiometry	–
	0.16	16.47	19.93	26.54	33.16	298	Potentiometry	Current work

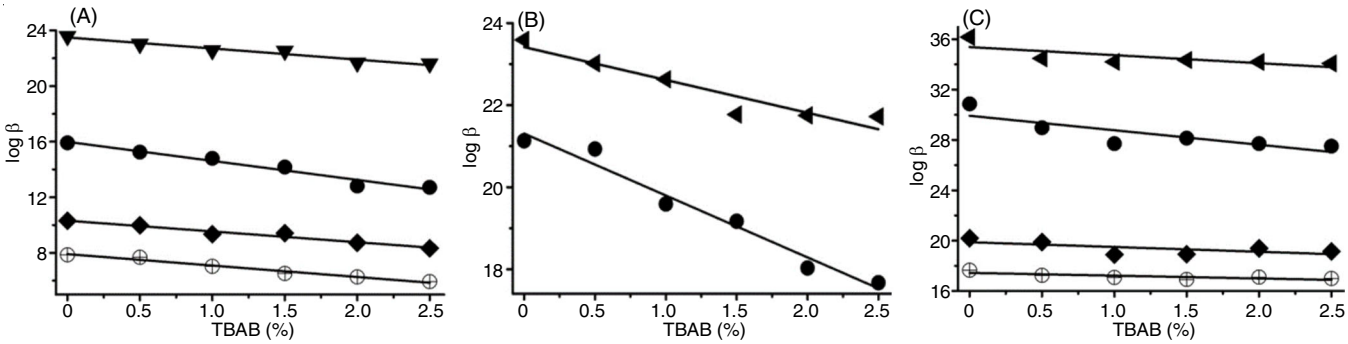

Fig. 2. Variation of stability constants of L-ornithine complexes of (A) Co(II), (B) Ni(II), (C) Cu(II) with percentage of surfactants in TBAB-water mixtures: (⊗) log β_{110}, (■) log β_{111}, (●) log β_{120} and (▲) log β_{121}

tendency to associate with potential electron pair acceptors (hydrogen ion) in the pH range of physiological spots. The metal and hydrogen ions are, therefore, in competition for these donor sites. As a result, several protonated and non-protonated complex species co-exist in the acid base equilibria of metal ligand system.

L-Ornithine has two associable amino and one dissociable (exchangeable) carboxylate protons which makes it to act as tridentate chelating agent. At higher pH region, both the α-amino and terminal nitrogen atoms and oxygen atom of the carboxylate functional group have participated in coordinating preferentially with the metal ion resulting the formation of unprotonated complexes. While at lower pH, only the terminal N- and carboxylate O-atoms preferentially coordinated with the metal ion leaving lone pair electrons in α-amino N-atom donated to H-ion. This situation ensured the formation of MLH, ML_2H complexes at lower pH and ML, ML_2 complexes at higher pH. Thus, on the basis of integrated chemical knowledge (educational speculation) and literature reported data, the most likely structure of these detected complexes resulted from lone pair-lone pair, lone pair-bond pair and bond pair-bond pair electronic repulsions and Jahn-Teller distortion effect are given in Fig. 3.

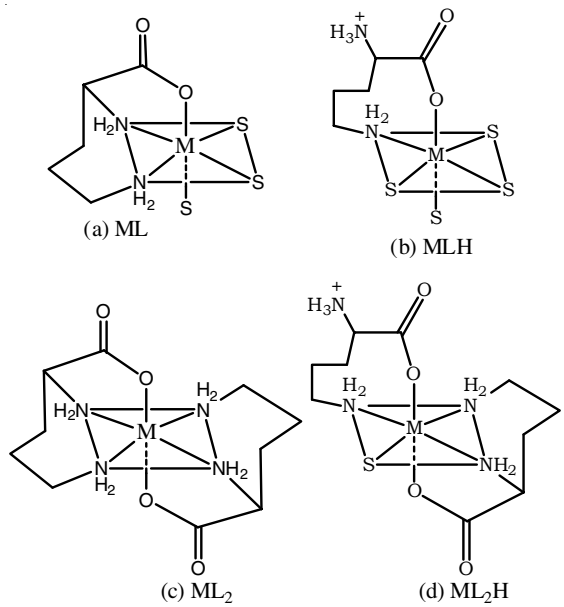

Fig. 3. Most likely structures of M(II)-Orn complexes where M is ether Co(II), Ni(II) or Cu(II) and S is either solvent or water molecule

Conclusion

In this study, L-ornithine forms protonated species (MLH and ML_2H) at low pH and non-protonated species (ML and ML_2) at higher pH. The species detected were validated by statistical data

Protonated species were found to deprotonated to give non-protonated species with increasing pH of titration mixture.

Systematic errors in the influential parameters shows that the errors in the concentrations of alkali and mineral acid were found to affect the overall stability constants of the complex more significantly than that of ligand and metal.

log β values of stability constant were found to decrease linearly with increasing percentage of tetrabutylammonium bromide suggesting the dominance of electrostatic interactions over the non-electrostatic interactions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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