Chemical Speciation of Mixed-Ligand Complexes of Co(II), Ni(II) and Cu(II) with MSA and L-Dopa in Acetonitrile -Water Mixtures

P. Lakshmi Kishore[1,2], V. Tejeswara Rao[1,2], Prof. G. Nageswara Rao[1]

[1]School of Chemistry, Andhra University, Visakhapatnam-530003, India
[2] MVR Degree & PG College, Gajuwaka, Visakhapatnam

Abstract: A computer assisted pH-metric investigation has been carried out on the speciation of complexes of Co(II), Ni(II) and Cu(II) with MSA and L-Dopa. The titrations were performed in the presence of different relative concentrations (M:L:X = 1.0:2.5:2.5; 1.0:2.5:3.75; 1.0:3.75:2.5) of metal (M) to MSA (L) to L-Dopa (X) with sodium hydroxide in varying concentrations (0–60% v/v) of acetonitrile–water mixtures at an ionic strength of 0.16 mol L^{-1} and at a temperature of 303.0 K. Stability constants of the ternary complexes were refined using MINIQUAD75. The species MLX, MLX$_2$, MLX$_2$H and MLXH$_2$ for Co(II), Ni(II) and Cu(II) were detected. Influence of the solvent on the speciation was discussed based on the dielectric constant of the medium. The stabilities of the mixed ligand complexes are discussed in terms of the molecular structure of MSA and L-Dopa as well as the nature of the metal ion. The species distribution with pH at different compositions of acetonitrile–water mixtures and plausible equilibria for the formation of species were also presented. The bioavailability of the metal ions is explained based on the speciation.

Index Terms: Mercaprosuccinic acid, Ternary Complexes, Acetonitrile, Speciation.

1. Introduction:

In all living systems, the biochemical functions of both essential and toxic metals are mediated through specific chemical species or complexes and the concentrations of these particular species are important for the biochemical reactions but not just the total concentration of the metal in the system. Hence, extensive attention has been paid in recent years to the study of the chemical speciation of ligands with metal ions [1–4].

Mercaptosuccinic acid (MSA) or thiomalic acid (HOOC-CH(SH)-CH$_2$- COOH) is a dicarboxylic acid containing a thiol functional group (-SH group) instead of an -OH group in malic acid [5]. It is an important organic compound with multifunctional intermediate in organic synthesis. MSA is a tridentate ligand which has the ability to form strong complexes with many metal ions in natural environment and within cells and it has three replaceable hydrogen ions (two from the carboxylic and one from the sulfhydryl functional groups).

L-3,4-Dihydroxyphenylalanine (dopa) has been clinically used for the treatment of Parkinson's disease since it is a helpful neurotransmitter. L-Dopa is easily converted into dopamine by the enzyme dopa decarboxylase during passage through the intestine and liver, and accordingly only a small percentage of the originally administered amount of dopa becomes available for transport to the brain [6].

Cobalt complexes have gained importance for their applicability in the biological field [7-12]. In the race of synthesizing new drugs, cobalt complexes have attracted a great deal of attention amongst the scientific community due to their therapeutic uses as tumor imaging agent [13], antitumor [14], transport protein transferrin [15], antimycobacterial [16], antiischaemic [17], antiviral [18], antiparasitic [19], antithrombolytic [20], enzymatic therapeutics [21], anti-inflammatory activities [22] and as metabolic modifier [23].

Nickel is used in a wide variety of metallurgical processes such as electroplating and alloy production as well as in nickel cadmium batteries. Besides it plays a well defined role in the biological system and plants [24-26] Nickel is necessary for the biosynthesis of the hydrogenase, carbon monoxide dehydrogenase [27] and found in a number of genera of bacteria. A nickeltetrapyrrole coenzyme, Cofactor F430, is present in the methyl coenzyme M reductase, which powers methanogenic archaea [28]. One of the carbon monoxide dehydrogenase enzymes consists of an Fe-Ni-S cluster [29] .Urease from jack beans and several species of plants is also a nickel protein. The plant enzyme urease : an enzyme that assists in the hydrolysis of urea contains nickel. These plant enzyme systems can affect animals via the microbiological digestion of food in the rumen. Low nickel offers reduce growth, this is particularly true of intra-uterine development. Nickel deficiency is accompanied by histological and biochemical changes and reduced iron resorption and leads to anemia. Its deficiency also results in lower activities of different dehydrogenases and transaminases and, affects carbohydrate metabolism. Nickel can have an impact on human health through infectious diseases arising from nickel dependent bacteria [30].

Copper is distributed widely in the body and occurs in liver, muscle and bone. Copper is transported in the blood stream on a plasma protein called ceruloplasmin. When copper is first absorbed in the gut it is transported to the liver bound to albumin. Copper

metabolism and excretion is controlled delivery of copper to the liver by ceruloplasmin, where it is excreted in bile. Copper is found in a variety of enzymes, like cytochrome C oxidase and superoxide dismutase. The recommended dietary allowance for copper in normal healthy adults is 0.9 mg/day [31]. Because of its role in facilitating iron uptake, copper deficiency can often produce anemia-like symptoms. In humans, the symptoms of Wilson's disease are caused by an accumulation of copper in body tissues. In addition to its enzymatic roles, copper is used for biological electron transport. The blue copper proteins that participate in electron transport include azurin and plastocyanin.

Acetonitrile (AN) is a weak base [32] and a much weaker acid [33] than water. Anions have lower solvation energies in AN than in water, except in those cases where there is specific interaction with the solvent, thus cations are reduced at considerably more positive potential [34] in AN than in water. It is a protophobic dipolar aprotic solvent and it does not form any hydrogen bond with solute species. The protophobic character of AN may arise from the possible formation of dimers which are shown to exist from IR studies [35]. Acid-base equilibria and dissociation behavior of various acids in AN medium have been studied using spectrophotometer and conductivity meter [36]. Proton acceptor power and homo conjugation of mono- and diamines in AN as solvent was studied [37]. Dielectric constants of water + AN have been measured from 308.15 to 278.15 K over the entire composition range. Their deviations from ideality have been determined [38].

The protonation equilibria and complex forming properties of L-Dopa and MSA with Co(II), Ni(II) and Cu(II) were studied in this laboratory[39-42]. Subsequently the stability and bonding conditions relating to the complexes formed in the ternary systems of L-Dopa and MSA were also dealt with results. Basing on these it is concluded that the L-dopa ligand is an ambidentate ligand in these ternary complexes which can bound to the metal ion via the (N,O) donor groups at physiological pH.
In this work we report speciation of the ternary complexes of Co(II), Ni(II) and Cu(II) with MSA and L-Dopa in AN-water mixtures. The pH-metric method was used to determine the stoichiometries and stability constants of the ternary complexes.

2. Experimental:

0.05 mol L^{-1} solutions of MSA (Himedia, India) and L-Dopa (Himedia, India) were prepared in deionised triple-distilled water by maintaining 0.05 mol L^{-1} concentration of hydrochloric acid to increase the solubility. 0.2 mol L^{-1} stock solution was prepared from Hydrochloric acid (Qualigens, India). Acetonitrile (Finar, India) was used as received. 2 mol L^{-1} Sodium chloride (Qualigens, India) was prepared to maintain the ionic strength in the titrand. 0.1 mol L^{-1} solutions of Co(II), Ni(II) and Cu(II) chlorides were prepared by dissolving G.R. Grade (Merck, India) salts in triple distilled water maintaining 0.05 mol L^{-1} concentration of HCl to suppresses the hydrolysis of metal salts. Sodium hydroxide (Qualigens, India) of 0.4 mol L^{-1} and Hydrochloric acid (Qualigens, India) of 0.2 mol L-1 were prepared. All the solutions were standardized by standard methods. To assess the errors that might have crept into the determination of the concentrations, the data were subjected to analysis of variance of one way classification [43]. The strengths of alkali and mineral acid were determined using the Gran plot method [44,45].

2.1 Procedure

ELICO (Model LI-120) pH meter of readability 0.01 was used for pH metric titrations. The effect of variations in asymmetry, liquid junction potential, activity coefficient, sodium ion error and dissolved carbon dioxide on the response of glass electrode were accounted for in the form of correction factor [46-48]. For the determination of stability constants of ternary species, the establishment of equilibration of the glass electrode was checked by titrating strong acid against alkali at regular intervals. The calomel electrode was refilled with AN-water mixture of equivalent composition as that of the titrand. All the titrations were performed pH metrically at 303.0±0.1 K in media containing varying concentrations (0-60% v/v) of AN-water mixtures. Titrations were carried out in the presence of different relative concentrations of the metal ion (M) to MSA (L) and L-Dopa (X) with 0.4 mol L^{-1} sodium hydroxide. The concentrations of the ingredients are given in **Table 1**. The details of experimental procedure and titration assembly are given elsewhere [49].

Table 1: Total initial concentrations of ingredients (in mmol) for mixed-ligand titrations in   0-60% v/v AN-water mixtures.
[NaOH] = 0.4 mol L-1; V0 = 50.0 cm^3; Temperature = 303.0 K; Ionic strength = 0.16 mol L-1; [HCl] = 1 mmol

% V/V AN	TM_0			TL_0		$TM_0{:}TL_0$
	Co(II)	Ni(II)	Cu(II)	MSA	L-Dopa	
0.0	0.099	0.095	0.097	0.250	0.250	2.50
				0.375	0.375	3.75
				0.500	0.500	5.00
10.0	0.099	0.095	0.097	0.250	0.250	2.50
				0.375	0.375	3.75
				0.500	0.500	5.00
20.0	0.099	0.095	0.097	0.250	0.250	2.50
				0.375	0.375	3.75
				0.500	0.500	5.00
30.0	0.099	0.095	0.097	0.250	0.250	2.50
				0.375	0.375	3.75
				0.500	0.500	5.00
40.0	0.097	0.095	0.097	0.250	0.250	2.50
				0.375	0.375	3.75
				0.500	0.500	5.00
50.0	0.097	0.095	0.097	0.250	0.250	2.50
				0.375	0.375	3.75
				0.500	0.500	5.00
60.0	0.097	0.095	0.097	0.250	0.250	2.50
				0.375	0.375	3.75
				0.500	0.500	5.00

3. Results And Discussion

3.1 Modeling of Chemical Speciation

A preliminary investigation of alkalimetric titrations of mixtures containing different mole ratios of MSA and L-Dopa in the presence of mineral acid and inert electrolyte inferred that no condensed species were formed. The best fit models were chosen based on the statistical parameters like χ2, R-factor, skewness and kurtosis given in Table 2. The ternary complex species detected are MLX, MLX_2, MLX_2H and $MLXH_2$ for Co(II) and Ni(II) and MLX, MLX_2, MLX_2H for Cu(II). A very low standard deviation (SD) in log values of overall stability constants (log β) indicates the precision of these parameters. The small values of Ucorr (sum of squares of the deviations in the concentrations of the ligands and the hydrogen ion at all the experimental points corrected for degrees of freedom) indicate that the models represent the experimental data. Small values of mean, standard deviation and mean deviation for these systems corroborate that the residuals are around a zero mean with little dispersion. For an ideal normal distribution, the values of kurtosis and skewness should be three and zero, respectively. The kurtosis values in the present study of Co(II) and Ni(II) indicate that most of the residuals are very nearer to mesokurtic and a few form leptokurtic patterns while Cu(II) indicates leptokurtic patterns. The values of skewness recorded in **Table 2** are between −0.49 and 1.64. These data indicates that the residuals form a part of normal distribution. Hence the least–squares method can be applied to the present data. The sufficiency of the model is further evident from the low crystallographic R-values recorded.

Table 2: Parameters of best fit chemical models of Co(II), Ni(II) and Cu(II) with MSA and   L-Dopa complexes in 0-60% v/v AN-water mixtures

Ucorr = U/ (NP-m) x 10^8; NP = Number of points; m = number of constants; SD = Standard deviation

%V /V	Log β_{MLXH}(SD)				NP	U_{Corr} x10^{-8}	Skewnes s	Kurto sis	χ^2	R-Factor	pH Range
	1110	**1120**	**1121**	**1112**							
Co(II)											
0.0	9.62(22)	12.13(19)	22.61(17)	27.94(22)	105	3.21	0.85	3.70	52.61	0.020	2.3-10.0
10	10.40(24)	12.46(06)	23.42(08)	28.54(06)	121	5.57	-1.40	3.56	63	0.025	2.5-10.0
20	11.59(05)	13.88(33)	23.28(45)	28.13(14)	261	7.29	0.91	2.77	137.02	0.022	2.2-10.0
30	12.88(11)	14.33(07)	24.35(10)	29.23(38)	148	1.54	0.67	3.00	116.17	0.040	2.3-10.0
40	13.09(08)	15.80(11)	25.82(15)	29.75(19)	188	2.14	-1.29	5.19	118.77	0.012	2.2-10.0
50	13.11(08)	16.22(09)	-	30.18(14)	136	5.80	-1.79	10.50	32.78	0.013	2.3-10.0
60	14.92(27)	16.91(14)	27.86(17)	31.87(09)	199	2.82	-1.03	29.56	169.89	0.018	2.3-10.0
Ni(II)											
0.0	14.35(09)	18.15(08)	27.74(08)	29.32(24)	136	4.96	-1.59	4.17	129.38	0.024	2.5-9.0
10	14.52(11)	17.50(39)	27.08(15)	29.56(04)	218	4.01	-1.14	3.10	111.2	0.010	2.5-8.5
20	13.49(09)	19.09(04)	-	30.96(12)	247	2.90	1.81	1.64	63.16	0.016	2.5-9.0
30	16.54(08)	19.19(31)	29.45(11)	30.75(04)	240	1.10	0.39	1.13	56.10	0.020	2.5-9.0
40	17.02(08)	20.58(18)	29.72(34)	31.14(06)	150	1.50	1.00	3.15	99.25	0.015	2.2-9.0
50	17.93(12)	20.05(14)	30.25(13)	32.03(07)	162	1.59	0.12	2.23	23.70	0.016	2.2-9.0
60	18.62(04)	21.01(15)	30.64(08)	32.97(07)	222	2.98	1.29	9.12	106.58	0.019	2.5-9.0
Cu(II)											
0.0	27.75(15)	32.23(11)	39.97(04)		99	2.80	-0.15	2.80	19.56	0.032	2.5-8.0
10	26.49(06)	31.65(09)	38.12(08)		167	1.43	-0.22	4.12	27.16	0.073	2.6-8.0
20	25.48(29)	31.19(14)	38.39(10)		193	8.59	0.21	3.68	10.41	0.011	2.2-8.5
30	25.84(18)	30.86(27)	37.33(05)		121	5.41	-1.26	3.11	63	0.032	2.5-8.5
40	24.30(36)	30.74(08)	37.19(36)		271	4.58	-2.25	3.89	76.14	0.015	2.6-8.5
50	24.58(15)	29.11(23)	36.77(25)		113	1.16	0.01	3.23	8.71	0.015	2.7-8.0
60	23.41(44)	28.04(21)	36.11(34)		195	4.24	-0.75	17.92	99.16	0.025	2.5-8.0

3.2 Effect of Dielectric Constant on the Stability of Ternary Complexes

AN is a polar aprotic and coordinating solvent. It is a structure former and it enhances the water structure in AN-water mixtures. Hence it removes water from the coordination sphere of the metal ions, making them more reactive towards the ligands. As a result, the stability of the complexes is expected to increase. At the same time, it is a coordinating solvent which competes with the ligands for coordinating with the metals. This decreases the stability of the complexes. Hence, the stability of the complexes is expected to either increase or decrease linearly. The variation of overall stability constants with co-solvent content depends upon the electrostatic and the non-electrostatic factors. Born's classical treatment holds good in accounting for the electrostatic contribution to the free energy change [**50**]. According to this treatment, the energy of electrostatic interaction is related to dielectric constant. Hence, the log β values should vary linearly as a function of reciprocal of the dielectric constant (1/D) of the medium, which is observed in the present study (Figure 1). The linear variation indicates that the electrostatic forces are dominating the equilibrium process under the present experimental conditions. The linear variation in the stability of the complexes of Co(II), Ni(II) and Cu(II) indicates the dominance of structure forming nature of AN over its complexing ability. The cation stabilizing nature of co solvents, specific solvent-water interactions, charge dispersion and specific interactions of co solvent with solute (indicated by the changes in the solubility of different species in the aqua-organic mixtures) account for the little deviation of linear relationship.
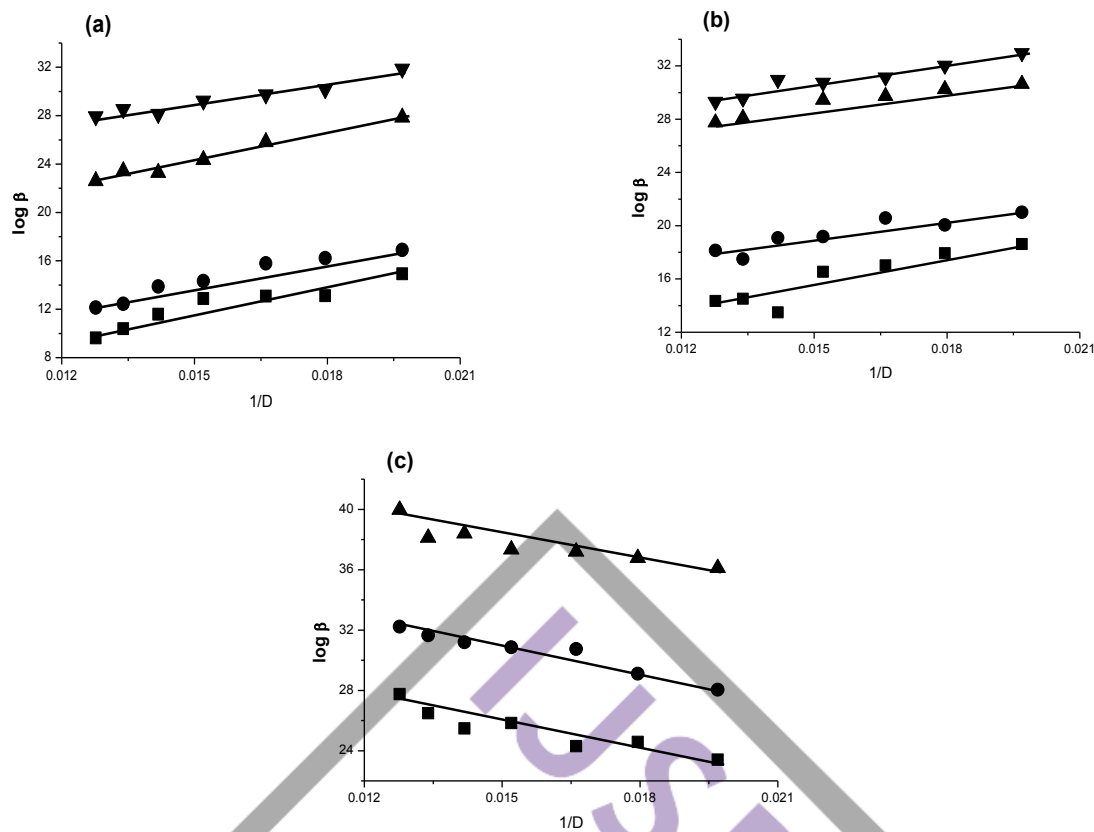
Figure 1: Variation of magnitude of stability constant (log β) of ternary complexes of M(II), with MSA and L-Dopa with reciprocal of dielectric constant (1/D) of AN: (■) logβMLX,   (●) logβMLX$_2$, (▲) logβMLX$_2$H, (▼) logβMLXH$_2$. (a) M = Co(II), (b) M = Ni(II) and (c) M = Cu(II).

3.3 Stability of Ternary Complexes

The complexes formed can be characterized with the following general equilibrium process and stability constant:

$$M_m + L_l + X_x + H_h \rightleftharpoons M_m L_l X_x H_h \qquad (1)$$

Where M is the central metal ion, H is proton, L and X are primary and secondary ligands, respectively in the complex and m, l, x, h are stoichiometric coefficients. The corresponding stability constant is defined as

$$\beta = \frac{[M_m L_l X_x H_h]}{[M_m][L_l][X_x][H_h]} \qquad (2)$$

The stability constants defined by Eq. (2) were calculated from the pH-metric titration curves in the usual way with the aid of the computer programme MINIQUAD75 [**51**]. The computer program SCPHD [**52**] was used to calculate the correction factor. During the refinement of ternary systems, the correction factor, protonation constants and binary formation constants of MSA and L-Dopa were fixed. The variation of stability constants with the dielectric constant of the medium was analyzed on the basis of electrostatic/non-electrostatic, solute-solute and solute –solvent interactions.

The formation of mononuclear unprotonated binary and ternary complexes from a mixture of metal ion (M) and primary (L) and secondary (X) ligands can be shown as the equilibria given in Equilibria (3)
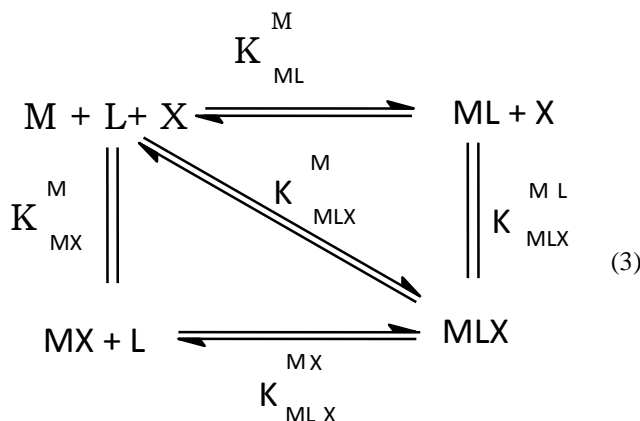
The change in the stability of the ternary complexes as compared to their binary analogues was quantified based on the disproportion constant (log X) given by Equation[**53-56**] which corresponds to equation (4).

$$\log X = 2\log K_{MLX}^M - \log K_{ML_2}^M - \log K_{MX_2}^M \tag{4}$$

This corresponds to the equilibrium

$$ML_2 + MX_2 \rightleftharpoons 2\,MLX$$

Under the equilibrium conditions one can expect the formation of 50% ternary complexes and 25% each of the binary complexes statistically and the value of log X shall be 0.6 [**57**] a value greater than these accounts for the extra stability of MLX.

Another approach to quantify the stability of ternary complexes was based on the difference in stability (Δ log K) for the reactions ML with X and M(aq) with L and X [**54-58**] where L is the primary ligand (MSA) and X is the secondary ligand (L-Dopa). It is compared with that calculated purely on the statistical grounds as given in Equation (5)

$$\Delta\log K = \log K_{MLX}^M - \log K_{ML}^M - \log K_M^M \tag{5}$$

The electrostatic theory of binary complex formation and statistical arguments suggest the availability of additional coordination positions of the hydrated metal ion for the first ligand than for the second. Hence, the usual order of stability $K_{ML}^M > K_{MLX}^{ML}$ applies. This suggests that Δ log K should be negative, although several exceptions have been found [**59**].

The statistical values of Δ log K for bi-dentate ligands L and X are –0.4, –0.6 and between –0.9 and –0.3 for octahedral, square planar and distorted octahedral complexes, respectively. Negative values of Δ log K can be understood as the secondary ligand forms a more stable complex with ML than hydrated metal ion. Whenever the experimental values of Δ log K exceed the statistical values, it can be inferred that the ternary complex is formed as a result of interaction of ML with X or MX with L. Δ log K values of ternary complexes are positive for O-donors (malonic acid, pyrocatechol etc.),[**54**] negative for N-donors (ethylene diamine) and intermediate or negative for amino acids with both N and O coordination sites [**60,61**]. However, a very high negative value (–2.3) for Cu(ethylene diamine)(iminodiacetic acid) and a positive value (0.82) for Cu(o-phen)-(6,7-dihydroxynaphthalene-2-sulphonate) were also observed.

The log X and Δ log K values calculated from binary and ternary complexes are included in **Table 3**. The equations for the calculation of Δ log K and log X are given in **Table 4**. These values could not be calculated for some systems due to the absence of relevant binary species. In the present study, the log X values range from -1.93 to 23.48 and these values are found to be higher than those expected on the basis of statistics (0.6). These higher values account for the extra stability of the ternary complexes. Δ log K values are in the range from -4.11 to 11.62 which indicate that the ternary complexes formed by the Co(II) and Ni(II) were more stable compared to Cu(II). The reason for the extra stability of these complexes may be due to interactions outside the coordination sphere such as the formation of hydrogen bonds between the coordinated ligands, charge neutralization, chelate effect and stacking interactions [**62**].

3.4 Effect of Influential parameters on stability Constants

Any variation in the parameters like concentration of ingredients affects the magnitude of equilibrium constants. Such parameters are called influential parameters. In order to rely upon the best chemical model for critical evaluation and application under varied experimental conditions with different accuracies of data acquisition, an investigation was made by introducing pessimistic errors in the concentrations of alkali, acid, ligands, metal ions and correction factors. The results of typical samples given in **Table 5** emphasise that the errors in the concentrations of alkali and acid affect the stability constant more than those of the ligands and metal ion.

4. Chemical Speciation

Distribution diagrams drawn using the formation constants of the best fit model are shown in Figure 2 which contain protonated and unprotonated species like MLX₂H, MLXH₂, MLX and MLX₂ for Co(II) and Ni(II) and MLX₂H, MLX and MLX₂for Cu(II). The distribution diagrams indicate the relative abundance of various forms of metal (chemical speciation) at different pH and dielectric conditions. A stable ternary complex shall be responsible for metal ion transportation in biological systems and the weak binary metal complexes make the essential metals bioavailable. The increased concentrations of complexing agents make the essential metal ions unavailable due to the formation of stable binary metal complexes. The formation of the complex species can be represented by the following equilibria.

Table 3: Variation of stability of ternary complexes of MSA and L-Dopa in AN-water mixtures

% v/v	Δ log K			log X
	MLX	MLX$_2$	MLX$_2$H	MLX
Co(II)				
0.0	-2.55	-2.89	1.02	4.43
10.0	-3.27	-4.43	0.53	4.84
20.0	--	--	--	--
30.0	-2.01	-6.98	-3.41	4.71
40.0	-4.34	-6.75	-2.12	3.56
50.0	-5.49	-	--	3.93
60.0	-4.62	-2.44	--	5.50
Ni(II)				
0.0	-2.44	-1.88	--	0.17
10.0			--	-2.26
20.0	-5.74	-4.65	--	-2.29
30.0	-	--	--	--
40.0	-5.48	--	--	--
50.0	-4.09	-4.80	--	6.11
60.0	-4.61	-6.15	--	7.87
Cu(II)				
0.0			--	--
10.0	-1.37	3.93	--	--
20.0	-4.93	-4.27	--	10.74
30.0	-5.98	--	--	--
40.0	--	--	--	--
50.0	--	--	--	--
60.0	-7.76	-7.08	--	13.28

Table 4: Equations for the calculation of Δ log K and log X

Δ log K$_{MLX}$	=	log β$_{MLX}$ - log β$_{ML}$ - log β$_{MX}$
Δ log K$_{MLXH}$	=	log β$_{MLXH}$ - log β$_{MLH}$ - log β$_{MX}$
Δ log K$_{MLX2H}$	=	log β$_{MLX2H}$ - log β$_{MLH}$ - log β$_{MX2}$
Δ log K$_{ML2X}$	=	log β$_{ML2X}$ - log β$_{ML2}$ - log β$_{MX}$
logX$_{MLXH}$	=	2logX$_{MLXH}$ - log β$_{ML2H2}$ - log β$_{MX2}$
logX$_{MLX}$	=	2logX$_{MLX}$ - log β$_{ML2}$ - log β$_{MX2}$

$M(II) + LH_3 + XH_3$	$\rightleftharpoons$	$MLXH_2 + 4H^+$	-----(1)
$MLXH_3$	$\rightleftharpoons$	$MLXH_2 + H^+$	-----(2)
$MLH + XH_3$	$\rightleftharpoons$	$MLX + 4H^+$	-------(3)
$MXH + LH_3$	$\rightleftharpoons$	$MLX + 4H^+$	-------(4)
$M(II) + LH_3 + 2XH_3$	$\rightleftharpoons$	$MLX_2H + 8H^+$	-------(5)
$M(II) + LH_2 + 2XH_2$	$\rightleftharpoons$	$MLX_2H + 5H^+$	-------(6)
$MLH + 2XH_3$	$\rightleftharpoons$	$MLX_2H + 6H^+$	-------(7)
$MXH + LH_3 + XH_3$	$\rightleftharpoons$	$MLX_2H + 6H^+$	-------(8)
$MX_2H_2 + LH_2$	$\rightleftharpoons$	$MLX_2H + 3H^+$	-------(9)

$$M(II) + LH_2 + 2XH_2 \longrightarrow MLX_2 + 6H^+ \quad \text{------(10)}$$

$$M(II) + LH + 2XH \longrightarrow MLX_2 + 3H^+ \quad \text{------(11)}$$

$$MLXH + XH_2 \longrightarrow MLX_2 + 3H^+ \quad \text{------(12)}$$

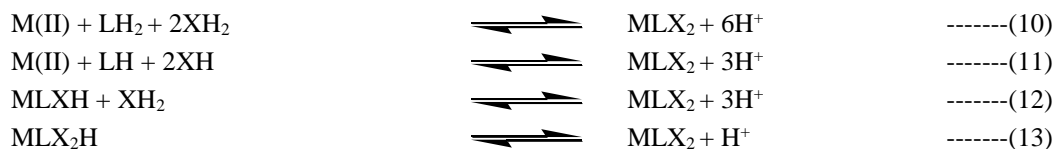$$MLX_2H \longrightarrow MLX_2 + H^+ \quad \text{------(13)}$$

Table 5: Effect of errors on influential parameters on the stability constants of ternary complexes of Co(II) with MSA and L-Dopa in 40% (v/v) AN-water mixture

Ingredient	% Error	Logβ(SD)			
		MLX	**MLX$_2$**	**MLX$_2$H**	**MLXH$_2$**
	0	13.09(08)	15.80(11)	25.82(15)	29.75(19)
	-5	12.69(08)	Rejected	25.63(15)	Rejected
Alkali	-2	12.91(08)	15.71(11)	25.74(15)	29.61(19)
	2	13.11(08)	15.85(11)	25.91(15)	29.86(19)
	5	13.21(08)	15.92(11)	Rejected	30.01(19)
	-5	Rejected	15.72(11)	Rejected	29.48(19)
Acid	-2	13.03(08)	15.77(11)	25.65(15)	29.62(19)
	2	13.10(08)	15.83(11)	25.81(15)	29.91(19)
	5	13.14(08)	15.88(11)	26.01(15)	Rejected
	-5	13.07(08)	Rejected	25.66(15)	29.51(19)
MSA	-2	13.09(08)	15.81(11)	25.70(15)	29.62(19)
	2	13.10(08)	15.79(11)	25.88(15)	29.84(19)
	5	13.11(08)	15.82(11)	25.96(15)	29.98(19)
	-5	13.08(08)	15.71(11)	25.57(15)	29.65(19)
L-Dopa	-2	13.09(08)	15.79(11)	25.69(15)	29.71(19)
	2	13.10(08)	15.82(11)	25.91(15)	29.79(19)
	5	13.13(08)	15.85(11)	26.02(15)	29.86(19)
	-5	13.08(08)	15.72(11)	25.73(15)	29.62(19)
Metal	-2	13.09(08)	15.75(11)	25.79(15)	29.69(19)
	2	13.10(08)	15.81(11)	25.83(15)	29.61(19)
	5	13.12(08)	15.84(11)	25.86(15)	29.74(19)

Some typical distribution diagrams in 40% AN-water mixture are shown in Figure 2. Figure 2a shows the formation of MSA-Co(II)-L-Dopa complexes, MLX$_2$H, MLXH$_2$, MLX and MLX$_2$ in the pH range 2.5-9.5. At lower pH concentration of MLXH$_2$ species is high (Equilibria 1 and 2). As the concentration of MLXH$_2$ decreases with increasing the concentration of MLX$_2$H (Equilibtium 5-9). As the pH increases the concentration of MLXH$_2$ and LH$_2$ decreased and the concentration of MLX and MLX$_2$ are increased (Equilibria 3, 4, 10, 11 and 12).

Figure 2b shows the formation of MSA-Ni(II)-L-Dopa Complexes, MLX$_2$H, MLXH$_2$, MLX and MLX$_2$ in the pH range 2.0-9.0. At lower pH the concentration of MLXH$_2$ is high (Equilibria 1 and 2). As the pH increases the concentration of MLXH$_2$ decreases with increasing concentration of MLX$_2$H, MLX, and MLX$_2$ species (Equilibria 3, 4, 10, 12 and 13).

Figure 2c shows the formation of MSA-Cu(II)-L-Dopa Complexes, MLX$_2$H, MLX and MLX$_2$ in the pH range 1.8-8.0. At lower pH the species MLX$_2$H has high concentration (Equilibria 5, 6, 7, 8 and 9). As the pH increases the concentration of MLX$_2$H, LH$_3$ and XH$_3$ decreased and the concentration of MLX and MLX$_2$ are increased (Equilibria 3, 4, 10 and 11).

Figure 2: Species distribution diagrams of ternary complexes of M(II) with MSA and L-Dopa in 40% AN-water mixture. (a) M = Co(II), (b) M = Ni(II) and (c) M = Cu(II).

Depending upon the nature of the ligands and the metal ions and based on the basic chemical knowledge the structures of the ternary complexes are proposed as shown in Figure 3. MSA and L-Dopa form strong bidentate complexes with transition metals. L-Dopa at higher pH favors the (O,O) coordination. At physiological pH it is bound only through the amino acid side chain [**29-32**].
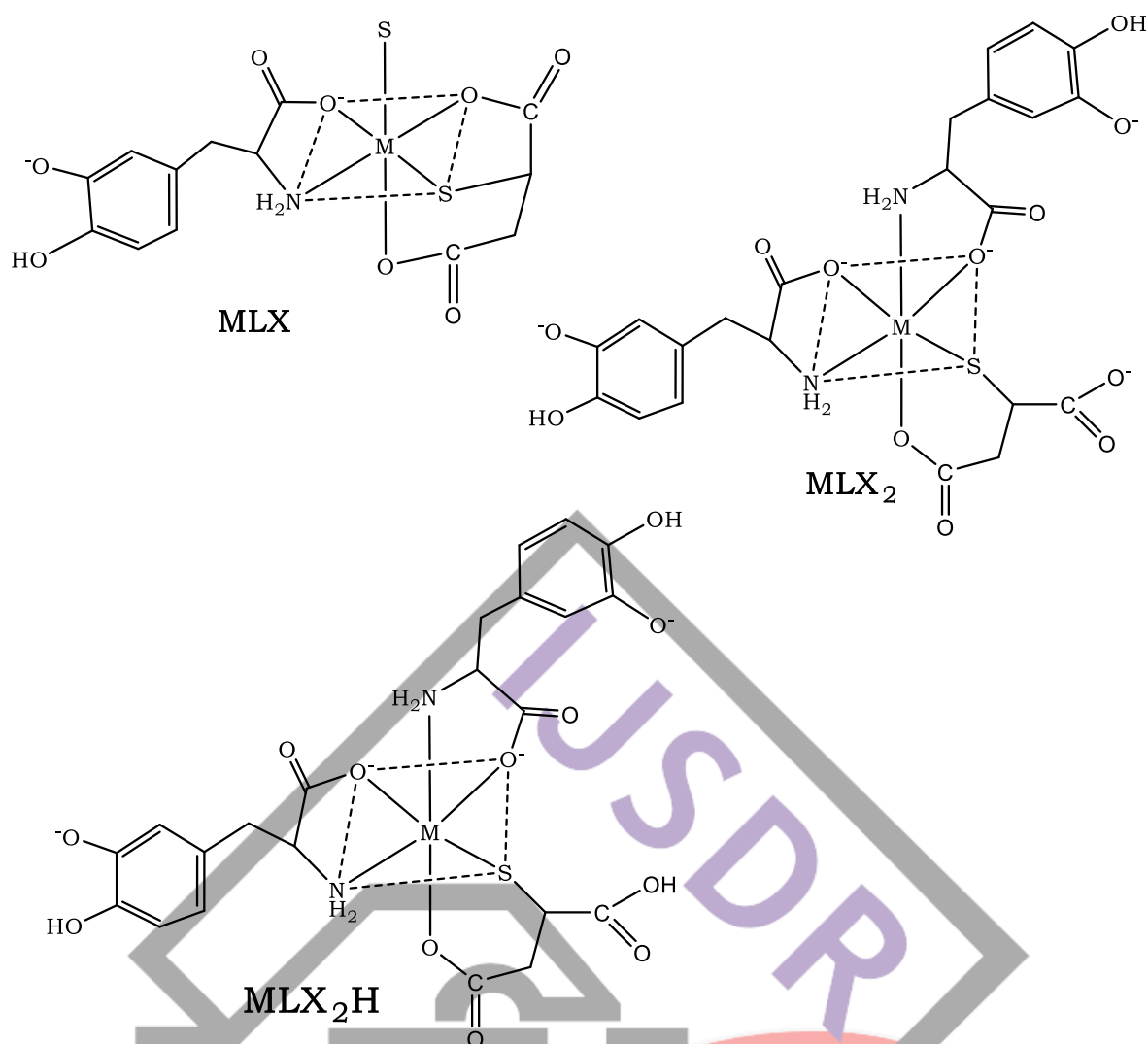
Figure 3: Structures of ternary complexes, where S=solvent or water molecule; M= Co(II), Ni(II) or Cu(II) Structure of complexes

5. Conclusions

A study of the speciation of ternary complexes of Co(II), Ni(II) and Cu(II) with MSA and L-Dopa AN−water media reveals the compartmentalization of metabolic reactions. The following conclusions have been drawn from the modeling studies:

The species detected are MLX_2H, $MLXH_2$, MLX and MLX_2 for Co(II) and Ni(II) and MLX_2H, MLX and MLX_2 for Cu(II). Where L = MSA and X = L-Dopa. Only these species are refined due to the restricted pH ranges and the possible active forms of ligands like LH_3^+, LH_2 and LH^- for MSA and L-Dopa.

The values of $\Delta \log K$ indicate that the ternary species have extra stability compared to their binary species, may be due to the interactions outside the coordination sphere, such as the formation of hydrogen bonds between the coordinated ligands, charge neutralization, chelate effect, stacking interactions and the electrostatic interaction between non-coordinated charge groups of the ligands.

The linear increase in the stabilities of ternary complexes with decreasing dielectric constants is due to the dominance of electrostatic forces.

The order of the ingredients that influence the magnitudes of stability constants due to incorporation of errors is alkali > acid > MSA > L-Dopa> metal.

The study also gives an insight into the metal availability/metal transport in biofluids and toxicity of these metals. The ternary complexes are more amenable for 'metal transport' because of their extra stability and the binary complexes make the 'metal available' in biological systems due to their decreased stability.

References:

[1]. Rao S P, Srikanth B, Rao V S S, Sastry C K and Rao G N., Micellar Effect on Metal-Ligand Complexes of Co(II), Ni(II), Cu(II) and Zn(II) with Citric Acid, *Bull. Chem. Soc. Ethiop*., 23(3), **2009**, 347-358.

[2]. Kishore P L, Tejeswara Rao V, and Rao G N., Chemical Speciation of Binary Complexes of Co(II), Ni(II) and Cu(II) with 1,10 Phenanthroline in Acetonitrile-Water and DMF- Water Mixtures, *ijresm,* volume 2 (2). **2019**. 1-8.

[3]. Padmaja N and Rao G N., Speciation of ternary complexes of lead(II), cadmium(II) and mercury(II) with L-dopa and phenanthroline in propanediol–water mixtures., *Chemical Speciation and Bioavailability,* 24(4), **2012**, 234-240

[4]. Ramanaiah M, Gouthama S, Sailaja BBV. Effect of non ionic micelles on the chemical speciation of binary complexes of Pb(II), Cd(II) and Hg(II) with L-phenylalanine. *Chem. Speciation Bioavailability.* 25, **2013**, 285–290.

[5]. **S.** Patai, *The Chemistry of the Thiol Group*, Vol. 15, *Wiley-Interscience, London*, **1974**, pp. 569.

[6]. Lavanya, K.V., Rao, V. M. and Rao, G. N. *Oxidat. Commun*., **31**, **2008**, 398-409

[7]. Li Q.L., Huang J., Wang Q., Jiang N., Xia C.Q., Lin H.H., Wu J. and Yu X.Q., *Bioorg. Med. Chem.,* 14, **2016**, 415.

[8]. Silver G.C. and Trogler W.C., *J. Am. Chem. Soc.,* 117, **1995**, 3983.

[9]. Huang Q., Pan Z., Wang P., Chen Z., Zhang X. and Xu H., *Bioorg. Med. Chem. Lett.,* 16, **2006**, 3030.

[10]. Oliveira M.C.B., Couto M.S.R., Severino P.C., Foppa T., Martins G.T.S., Szpoganicz B., Peralta R., Neves A. and Terenzi H., *Polyhedron*, 24, **2005**, 495.

[11]. Hettich R. and Schneider H.J., *J. Am. Chem. Soc*., 119, **1997**, 563.

[12]. Dixon N.E., Geue R.J., Lambert J.N., Moghaddas S., Pearce D.A. and Sargeson A.M., *Chem. Commun*., **1996**, 1287.

[13]. Livermore D.M., *Clin. Infect. Dis*., 36, **2003,** 11.

[14]. Liang F., Wang P., Zhou X., Li T., Li Z., Lin H., Gao D., Zhang C. and Smith T.A.D., *Bioorg. Med. Chem.,* 13, **2005,** 4576.

[15]. Maccari R., Ottana R., Bottari B., Rotondo E. and Vigorita M.G.*, Bioorg.Med. Chem. Lett*., 14, **2004,** 5731.

[16]. Unitt J.F., Boden K.L., Wallace A.V., Nall A.H., Coombs M.E. and Ince F., *Bioorg. Med. Chem*., 7, **1999,** 1891.

[17]. Takeuchi T., Bottcher A., Quezada C.M., Meade T.J. and Gray H.B., *Bioorg.Med. Chem*., 7, **1999,** 815.

[18]. Rawlings N.D. and Barrett A.J., *Methods Enzymol*., 244, **1994,** 19.

[19]. McKerrow J.H., Sun E., Rosenthal P.J. and Bouvier J., *Annu. Rev. Microbiol*., 47, **1993,** 821.

[20]. Bury A, Underhill A.E., Kemp D.R., Oshea N.J., Smith J.P. and Gomm P.S., *Inorg. Chim. Acta,* 138, **1987,** 85.

[21]. Witczak J.Z. and Boryczewski D., *Bioorg. Med. Chem. Lett*., 8, **1998**, 3265.

[22]. Vigato P.A. and Tamburinii S., *Coord. Chem. Rev*., 248, **2004,** 1717.

[23]. Collman J.P., Zeng L. and Brauman J.I., *Inorg. Chem*., 43, **2004**, 2672.

[24]. Sigel A., Sigel H. and Sigel R.K.O. Nickel and Its Surprising Impact in Nature. In: *Metal Ions in Life Sciences 2 (Eds*) Sigel A., Sigel H. *John Wiley & Sons*, Ltd. Chichester, U.S.A, **2008**

[25]. Sydor Andrew M. and Zamble Deborah B. "Chapter 11 Nickel Metallomics: General Themes Guiding Nickel Homeostasis".In: Metallomics and the Cell. *Metal Ions in Life Sciences 12. (Eds.) Banci, Lucia . Springer*. U.S.A., **2013.**

[26]. Dixit R., Wasiullah, Malaviya D., Pandiyan K., Singh Udai B., Sahu A., Shukla R., Singh B.P., Rai J.P., Sharma Pawan K., Lade H. and Paul D., *Bioremediation of Heavy Metals from Soil and Aquatic Environment:* An Overview of Principles and Criteria of Fundamental Processes Sustainability. 7, **2015**, 2189-2212.

[27]. Can M., Armstrong F.A. and Ragsdale S.W. Structure, Function, and Mechanism of the Nickel Metalloenzymes, CO Dehydrogenase, and Acetyl-CoA Synthase. *Chemical Reviews*. 114(8), **2014**, 4149-4174.

[28]. Stephen W.R. "Chapter 6. Biochemistry of Methyl-Coenzyme M Reductase: The Nickel Metalloenzyme that Catalyzes the Final Step in Synthesis and the First Step in Anaerobic Oxidation of the Greenhouse Gas Methane". In: *The Metal-Driven Biogeochemistry of Gaseous Compounds in the Environment. Metal Ions in Life Sciences 14*.(Eds.) Peter, M.H. Kroneck and Martha, E. Sosa Torres. Springer.U.S.A. **2014**, Pp. 125-145.

[29]. Wang V.C.-C., Ragsdale S.W. and Armstrong F.A. Investigations of the Efficient Electrocatalytic Inter conversions of Carbon Dioxide and Carbon Monoxide by Nickel Containing Carbon Monoxide Dehydrogenases In: The Metal Driven Biogeochemistry of Gaseous Compounds in the Environment ; *Metal Ions in Life Sciences 14. (Eds.)* Peter M.H., Kroneck, Martha E. and Sosa Torres. *Springer,* U.S.A., **2014**, Pp. 71–97.

[30]. Zambelli B. and Ciurli S. Nickel and Human Health" In *Metal Ions in Life Sciences* 13 "Interrelations between Essential Metal Ions and Human Diseases" (Eds.), **2013.**

[31]. National Research Council, Food Nutrition Board Recommended Dietary Allowances,*National Research Council*, *Food Nutrition Board,* NRC/NAS: Washington, D.C.; **1980**; p 151.

[32]. Laubengayer AW, Sears DS, Donor-acceptor bonding. III. Methyl cyanide addition compounds of boron trichloride and boron trifluoride. *J Am Chem Soc*, 67, **1945,** p164

[33]. Fritz JS, Yamamura SS, Rapid microtitration of sulphate. *Anal Chem*, 27, **1955,** p1461

[34]. Kolthoff I. M., Lingane J. J., *Polarography, Interscience Publisher Inc*. New York, **1952**

[35]. De A. L., *Electrochim. Acta*, *29*, **1984**, p471.

[36]. Kolthoff I.M., Bruckenstein S, and Chantooni M. K. Jr, *J. Am. Chem. Soc.*, *83* (19), **1961,** p3927

[37]. Coetzee J. F., and Padmanabhan G. R. *J. Am. Chem. Soc.*, *87* (22), **1965,** p5005

[38]. Colette Moreau, and Gérard Douhéret *The Journal of Chemical Thermodynamics*, 8(5), **1976**, p403

[39]. Kishore P L, Tejeswara Rao V, and Rao G N,*ijrar*.,vol 5 (4), **2018**, 217-223

[40]. Tejeswara Rao V, Kishore P L, , and Rao G N, *jetir*.,vol 5 (12), **2018**, 452-458

[41]. Kishore P L, Tejeswara Rao V, and Rao G N,*ijrar*.,vol 6 (1), **2019**, 858-868

[42]. Tejeswara Rao V, Kishore P L, , and Rao G N, *jetir.*,vol 6 (1), **2019**, 607-616

[43]. Rao RS, Rao GN, *Computer Applications in Chemistry*, Himalaya Publishing House, Mumbai: India, **2005**.

[44]. Gran G. Determination of the equivalence point in potentiometric titrations. *Analyst*. 77, **1952**, 661-671.

[45]. Gran G. Equivalence volumes in potentiometric titrations. *Anal Chim Acta*, 206, **1988,** 111-123.

[46]. Raju BR, Devi KVS, Rao GN. Chemical speciation of Ternary Complexes of L-dopa and 1, 10-Phenanthroline with Co(II), Ni(II) and Cu(II) in low dielectric media. *Chem Speciation Bioavail.*, 24, **2012**, 89-96.

[47]. Raju BR, Devi KVS, Rao GN. Chemical Speciation of Ternary Complexes of Co(II), Ni(II) and Cu(II) with L- dopa and 1,10-phenanthroline in low dielectric media. *Chin J Inorg Chem.*, 28, **2012**, 785-794.

[48]. Srikanth B, Rao PS, Rao VSS, Sastry CK, Rao GN. Effect of micelles on chemical speciation of binary complexes of Co(II), Ni(II), Cu(II) and Zn(II) with succinic acid. *J Serb Chem Soc.,* 74, **2009,** 745-754.

[49]. Lavanya KV, Rao GN, Rajesh M, Babu MS. Micellar effect on protonation equilibria of   L-arginine and L-histidine. *J Indian Chem Soc.*, 81, **2004,** 384-387.

[50]. Born M. Volume and hydration heat of ions. *Z Phys.,* 1, **1920,** 45-48.

[51]. Gans P, Sabatini A, Vacca A. An improved computer program for the computation of formation constants from potentiometric data. *Inorg Chim Acta.*, 18, **1976,** 237-239.

[52]. Rao GN. Complex Equilibria of Biological importance in Aquo-organic media-Computer augmented modeling studies. *Ph.D. Thesis*, *Andhra University;Visakhapatnam:India* **1989**.

[53]. Griesser R, Sigel H. Ternary complexes in solution. VIII. Complex formation between the copper(II)-2,2'-bipyridyl 1:1 complex and ligands containing oxygen and/or nitrogen donor atoms. *Inorg Chem.*, 9, **1970,** 1238-1243.

[54]. Griesser R, Sigel H. Ternary complexes in solution. XI. Complex formation between the cobalt(II)-, nickel(II)-, copper(II)-, and zinc(II)-2,2'-bipyridyl 1:1 complexes and ethylenediamine, glycinate, or pyrocatecholate. *Inorg Chem.* , 10, **1971,** 2229-2232.

[55]. Sigel H, Caraco R, Prijs B.Ternary complexes in solution. XVI. Influence of the size of the chelate rings on the stability of mixed-ligand copper(II) complexes containing aliphatic ligands. *Inorg Chem.*, 13, **1974,** 462-465.

[56]. Sigel H, Huber PR, Greisser R, Prijs B. Ternary complexes in solution. XV. Mixed-ligand copper(II) complexes with 2,2'-bipyridyl or 1,10-phenanthroline and pyrocatecholate or derivatives thereof. *Inorg Chem.,* 12, **1974,** 1198-1200.

[57]. Kida S. Investigation on Mixed Complex. I. Spectrophotometric Study of Mixed Complexes Formed by Cupric Ion and Bidentate Ligands., *Bull Chem Soc Jpn*., 29, **1956,** 805-811.

[58]. Martin RB, Prados RJ. Some factors influencing mixed complex formation. *Inorg Nucl Chem.,* 36, **1974,** 1665-1670.

[59]. Sigel H. Ternary Cu^{2+} Complexes: Stability, Structure and Reactivity. *Angew Chem Int Ed Engl.,* 14, **1975,** 394-402.

[60]. Sigel H. Ternare Komplexe in Losung., *Chimia*., 21, **1967,** 489-500.

[61]. Griesser R, Sigel H. Ternare Komplexe in Losung II†. Einfluss von 2,2′-Bipyridyl auf die Stabilitat des Cu^{2+}-Glycin-1:1-Komplexes. *Helv Chim Acta*., 50, **1967,** 1842-1845.

[62]. Sakurai T, Yamauchi O, Nakahara A. Mixed Ligand Copper(II) Complexes of α-Amino Acids with Ligand-Ligand Interactions. *Bull Chem Soc Jpn*., 49, **1976,** 169-173.