

## Chemical Distribution, Stability and Structures of Ternary Metal Chelates in Ethyleneglycol – Water Media Involving Mercaptosuccinicacid and Some Essential Amino Acids

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### Abstract

*There has been focus upon the study of stability constants of amino acids with metal ions since they processes antibacterial activities. Mixed-ligand complexes generated between Mercaptosuccinicacid (MSA), L-Histidine (His), and L-Valine (Val) with transition metals (Co(II), Ni(II), Cu(II), and Zn(II)) were examined pH metrically in aqueous solution at 25.0 °C and = 0.1M NaCl to determine stability constants. From potentiometric data, "MINIQUAD75" computer program created a complexation model for each system. Based on equilibrium and stability constants, the most likely binding mode for each ternary species was discussed. And also investigated solution concentration distributions of various species. Complex stability follows Irving-Williams' order of metal ions: Cu(II) > Ni(II) > Co(II) > Zn(II). The plausible structures for each species detected were proposed.*

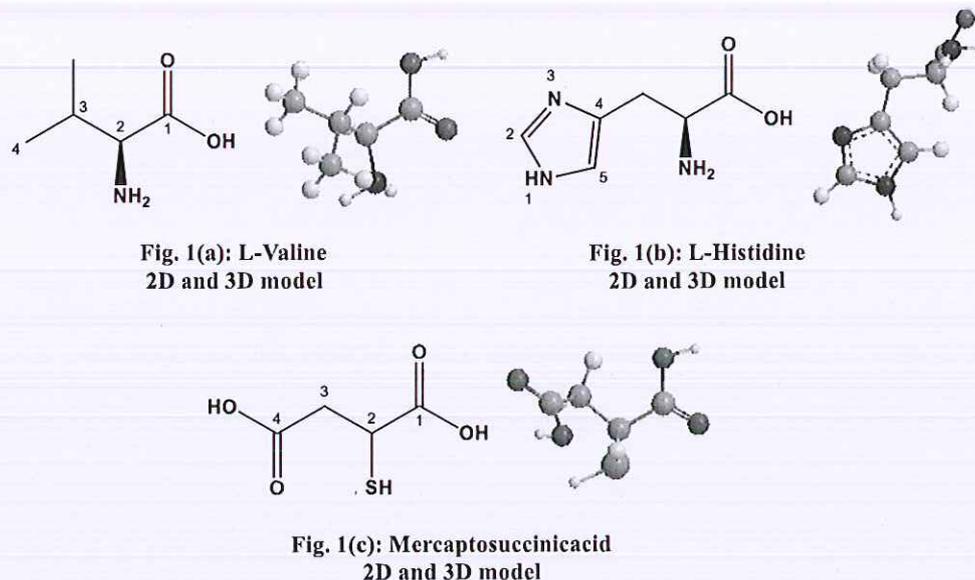
**Key Words:** L-Histidine, L- Valine, Best Fit, Ternary Complexes, Irving-Williams Series

## INTRODUCTION

Metal complexes have become importance in recent years especially at design from repository, release slow or long acting medicine in nutrition and by the study of metabolism [Akalpita et al,2012]. It is known that metal ions to accelerate the action of the drug [Sunil et al,2009]. Mixed ligand complexes are well known to play an important role in biological processes [Adkhis et al ,2000, Shivankar et al ,2003&Nomiya & Yokoyama ,2002]. Many researchers have extensively investigated metal complexes of biologically active ligands [Regupathy & Sivasankaran Nair ,2014 &Abdel-Rahman et al,2017]. The literature survey revealed that mixed ligand complexes of some transition metals with amino acids have been studied for their synthesis, characterization, biological significance and metabolic enzymatic [Choudhary et al,2011&Sharma et al,2018]. Amino acids containing  $-NH_2$  and  $-COOH$  active groups are well known that, can form strong complexes with metals and have great significance at biological as well as pharmaceutical [Selvaganapathy & Raman,2016 &Liao et al,2013] domains. In last year's transition metals amino acids complexes were received lots of interest because they have proven to be beneficial antibacterial and antifungal agents used on *Staphylococcus aureus*, *Escherichia Coli* with humans and animals, etc[Liao et al,2007 &Liao et al,2010]

The study of the coordinated systems metal ion - amino acids has become increasingly important in recent years. The "Bio coordination Chemistry" was confirmed as one of seven priority research fields during 1990's [14]. L-Valine (abbreviated as Val) is an  $\alpha$ -amino acid with the chemical formula  $HO_2CCH(NH_2)CH(CH_3)_2$  (Fig. 1(a)). It is one of 20 proteinogenic amino acids [Yuichi Shimazaki et al] widely distributed but rarely occurs in amount exceeding 10%. It is branched chain amino acid and can be derived from alanine by the introduction of two methyl group present on  $\alpha$ -carbon atom [Aliyu and Isyaku ,2010, Deschamps et al,2005, Creighton et al,1999, Guo et al,1999, Vinnikova et al,1992, Sitton et al,1998, Hitomi-Ohmura et al,1992 & Aoyama et al,1992] L-Histidine (His) is one of the most powerful metal coordinating ligands among amino acids, and it is essential for protein metal ion binding. Histidine is one of the amino acid residues found in the majority of biomolecule active sites. It has three potential metal-binding sites, namely, carboxylate oxygen ( $O_{\text{carboxyl}}$ ), imidazole imidone nitrogen ( $N_{\text{im}}$ ) and aminonitrogen ( $N_{\text{am}}$ ) [Cai et al,1995] (Figure 1(b)).

Mercaptosuccinic acid (MSA) is a potentially important tridentate ligand capable of forming strong complexes with a variety of metal ions and having chemotherapeutic applications in a variety of solvents [Muthusamy & Natarajan,2016,Pharr et al,2011, Wilson et al,1970&Lahsasni et al,2012,]Fig. 1(c)). Metals including cobalt, nickel, copper, and zinc are vital in biological activities.



**Fig. 1: 2D and 3D structures of a) Mercaptosuccinic Acid; b) L-Valine; c) L-Histidine.**

The speciation study of ternary metal ion complexes of MSA with both essential and non – essential amino acids with transition metal ions have been studied in aqua – organic media have. In this paper, we report the stability constants of all complexes which form in Ethylene glycol - Water media, including the most probable structures of all mixed species of Mercaptosuccinic acid (MSA) as primary ligand and L-Histidine and L-Valine as secondary ligands. Thus, in the present study, a systematic study of complex formation between some transition metal ions (Co(II), Ni(II), Cu(II), and Zn(II)) and ligands (MSA, His, Val) was carried out using a pH metric titration technique over a wide pH range at  $(25.0 \pm 0.1)^\circ\text{C}$  and  $\mu = 0.16\text{M}(\text{NaCl})$ , with a view to determining the stability constants.

Under the current experimental conditions, the types of complexes produced and their relative concentrations represent the potential forms of metal ions in biological fluids, and speciation symbolises the biological activity of these metals in the presence of diverse complexing agents. Because the dielectric constant at the active site cavities is low in comparison to biofluids, the authors attempted to simulate it by employing a water soluble organic solvent such as ethylene glycol.

## MATERIALS AND METHODS

All compounds utilised in this study were analytical grade and unpurified. Alkali strength and lack of carbonate were frequently evaluated by pH-metry against oven-dried sodium hydrogen phthalate [Gran et al,1950 & Rossotti & Rossotti,1965,]. Merck's acid solutions were titrated against sodium hydroxide [Khan et al,1996]. NaCl was used to modify each solution's ionic strength to 0.16 M. Himedia india sold MSA, L-Histidine, and L-Valine. Analytical-grade chlorides were used to make 0.1 M stock solutions of Co(II), Ni(II), Cu(II), and Zn(II). Complexometric EDTA titration was used to standardise metal(II) stock solutions [Schwarzenbach et al,1969].

## MEASUREMENTS

The ternary stability constants of MSA as primary ligand, L-Histidine and L-Valine as secondary ligands were determined by pH- titration and the total volume was  $(50.00 \pm 0.01)$   $\text{cm}^{-3}$  at the beginning of each pH metric titration. The following mixtures containing proton, metal(II) chloride and the two ligands (at different ratios 1:1:1, 1:1:1.5 and 1:1.5:1) were titrated by incremental additions of carbonate-free and standard NaOH.

- a — HCl + metal(II) + MSA + L-Histidine;  
 b — HCl + metal(II) + MSA + L-Valine;  
 Metal(II) = Co(II) or Ni(II) or Cu(II) or Zn(II).

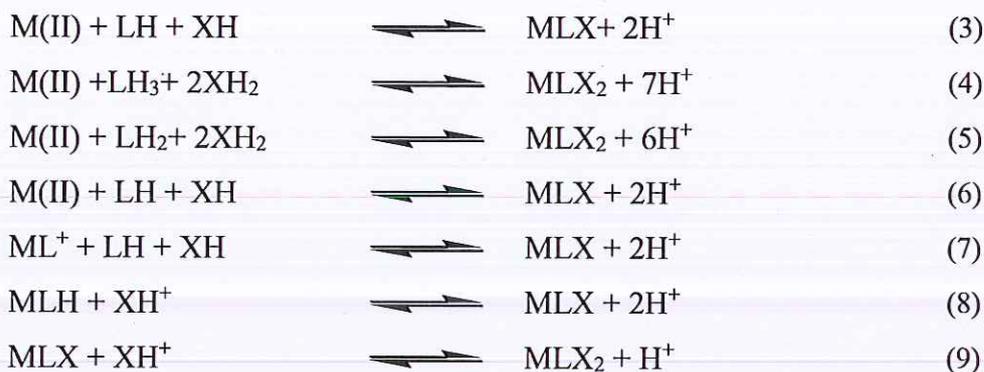
## APPROACH

pH metric titrations were performed in 0-60 percent v/v EG-Water using an auto-titrator Metrohm 877 titrino plus Switzerland and pH sensitive electrode at 298 K [Shoukry et al,1995].

## Metal-Ligand Ternary Systems

The stability constants were calculated using the MINIQUAD75 computer programme [Gans et al,1976&Khan et al,1996]. A set of typical distribution curves for the different 1:1:1 M(II):MSA:His and M(II):MSA:Val systems at  $(25.0 \pm 0.1)^\circ\text{C}$  and  $\mu = 0.16\text{M}$  NaCl is shown in **Fig. 2**. Similar behaviour was observed for all metal ions (Co(II), Ni(II), Cu(II) and Zn(II)) studied.





**Fig. 2:** The plausible forms of equilibria and their distribution of protonated and un-protonated complexes observed in the present study.

## RESULTS AND DISCUSSION

### MODELLING OF CHEMICAL SPECIES

The metal-ligand stability constants of ternary complexes were evaluated assuming that the formation of polynuclear complexes and hydrolyzed products were not formed. In this ternary (M-L-X) complex, the metal forms the complex first with the primary ligand (L) at lower pH and then with the secondary ligand (X) to form the mixed ligand complex at higher pH. At lower pH, the secondary ligand does not come into contact with metal ions. In other words, when M-L complex formation is complete, mixed ligand complex formation occurs. The best fit models for ternary complexes with MSA and chosen amino acids (His, Val) have been given in **Table 1 and 2**. Species like MLX and MLX<sub>2</sub> were detected for M(II)-MSA-X (X = His or Val). Overall stability constants (log β) with minimal standard deviation (SD) in specifies the exactness of these constraints.

**Table-1:** Best fit model of M(II)-MSA- L-Histidine ternary complexes in 0-60% v/v EG-water mixtures

% V/V	log β <sub>MLXH</sub> (SD)		log β <sub>MLXH</sub> (SD)	
	MLX	MLX <sub>2</sub>	MLX	MLX <sub>2</sub>
	Co(II) pH Range: 2.5 – 9.5		Ni(II) pH Range: 2.5 – 9.5	
0.0	13.03	23.75	15.76	28.51
10	13.29	24.23	16.04	29.01
20	13.56	24.71	16.33	29.52
30	13.83	25.20	16.63	30.04
40	14.10	25.71	16.93	30.57
50	14.39	26.22	17.23	31.11

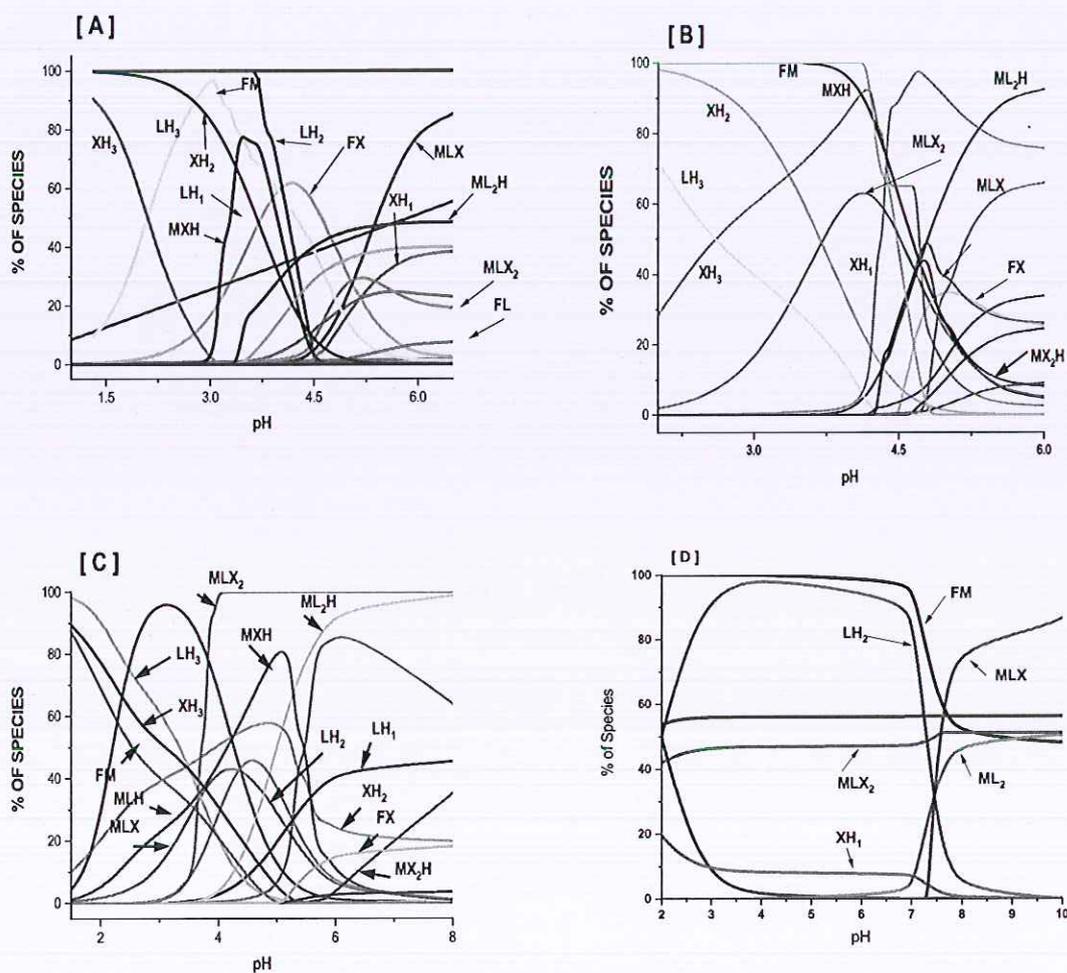
60	14.67	26.75	17.54	31.66
<b>Cu(II) pH Range: 2.5 – 9.5</b>			<b>Zn(II) pH Range: 2.5 – 9.5</b>	
0.0	19.74	34.59	12.33	22.84
10	20.14	35.11	12.58	23.11
20	20.55	35.63	12.84	23.39
30	20.97	36.16	13.10	23.67
40	21.40	36.70	13.36	23.96
50	21.84	37.24	13.63	24.24
60	22.28	37.80	13.91	24.53

**Table-2:** Best fit model of M(II)-MSA- L-Valine ternary complexes in 0-60% v/v EG-water mixtures

% V/V	log $\beta_{MLXH}(SD)$		log $\beta_{MLXH}(SD)$	
	MLX	MLX2	MLX	MLX2
<b>Co(II) pH Range: 2.5 – 9.5</b>			<b>Ni(II) pH Range: 2.5 – 9.5</b>	
0.0	10.75	19.26	12.55	23.34
10	10.94	19.61	12.73	23.78
20	11.14	19.96	12.91	24.24
30	11.34	20.32	13.10	24.70
40	11.55	20.68	13.28	25.17
50	11.75	21.06	13.47	25.64
60	11.96	21.44	13.67	26.13
<b>Cu(II) pH Range: 2.5 – 9.5</b>			<b>Zn(II) pH Range: 2.5 – 9.5</b>	
0.0	17.59	30.93	10.57	19.48
10	17.91	31.24	10.76	19.83
20	18.23	31.55	10.96	20.19
30	18.56	31.87	11.16	20.55
40	18.90	32.19	11.36	20.92
50	19.24	32.51	11.57	21.30
60	19.59	32.83	11.78	21.68

### SPECIES DISTRIBUTION PLOTS

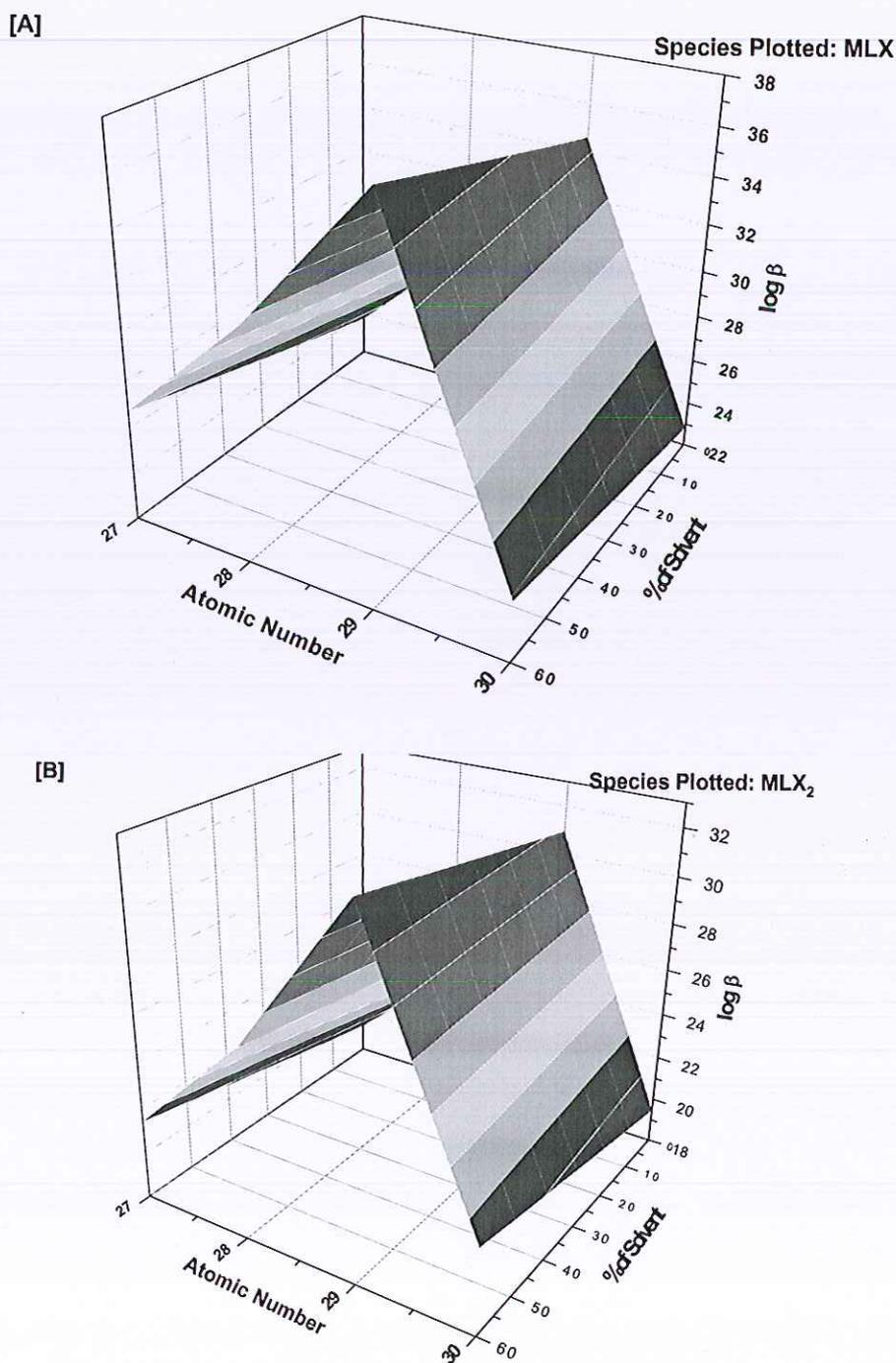
The weak binary metal complexes render the essential metals accessible, while the stable ternary complexes transport metal ions in biological systems. The plausible forms and their distribution of protonated and un-protonated complexes observed in 20% v/v EG – water mixtures that suit best for ternary complex hypothesis and their respective relative distribution plots of several species was plotted using computer program ORIGIN 8.5 and shown in **Fig. 3**. The present study found MLX, MLX<sub>2</sub> species were found for M(II)-MSA-L-His and M(II)-MSA-L-Val in the pH range 2.0-9.5. At lower pH concentration of MLX species is high (Equilibria 1, 2, 3, 6, 7 and 8). As the concentration of MLX decreases with increasing pH and the concentration of MLX<sub>2</sub> (Equilibria 4, 5 and 9) increases gradually.



**Fig. 3:**Species distribution plots of [A]: Co(II) – MSA – His; [B] : Ni(II) – MSA – His; [C] : Cu(II) – MSA – Val; [D]: Zn(II) – MSA - Val in 20% v/v EG – water media.

## INTER COMPARISON OF STABILITY CONSTANTS

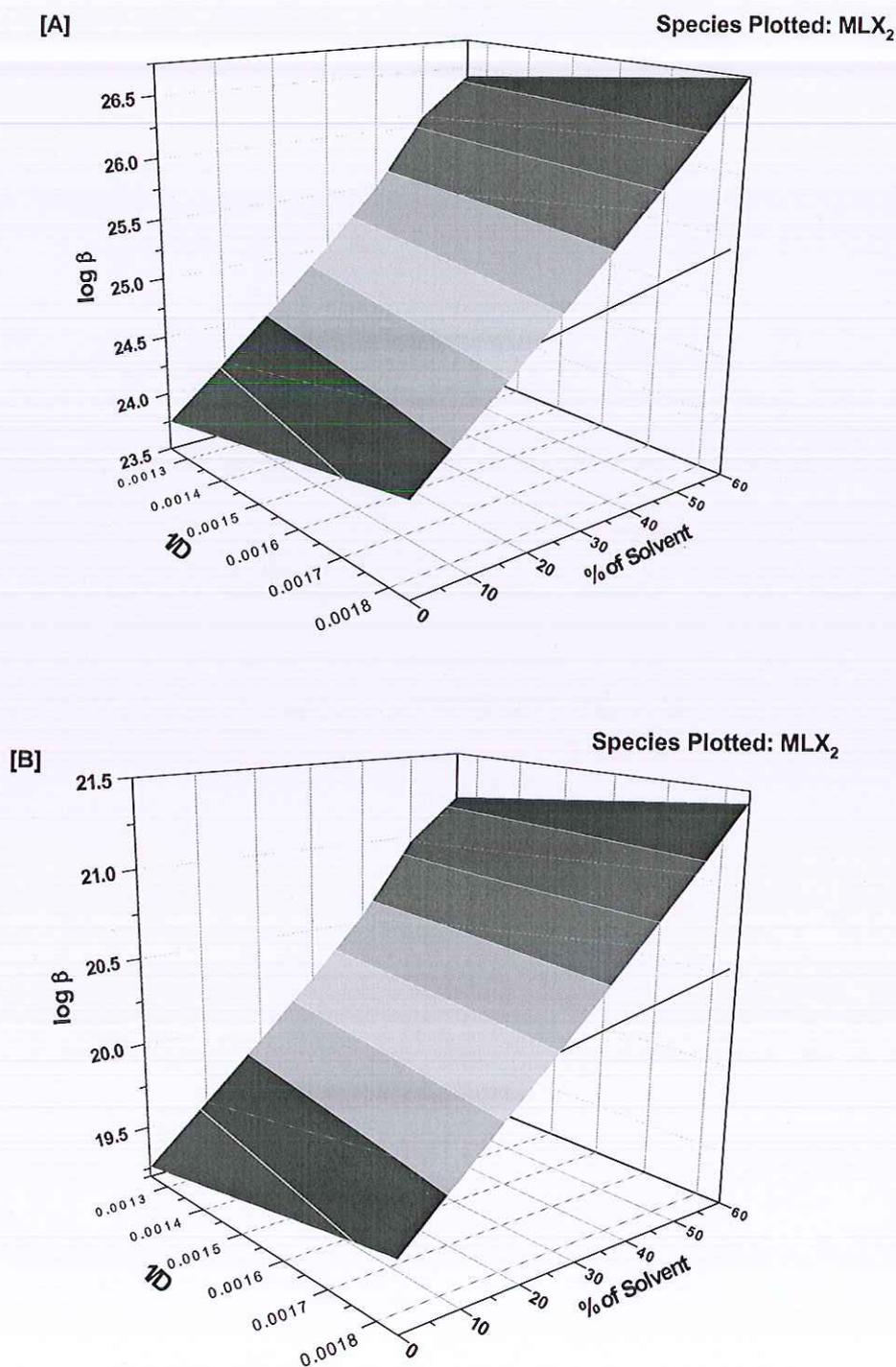
Having inspected **Tables 1 and 2**, we can say that the stability constants of Cu(II) ternary complexes are higher than those of the other studied metal complexes due to the smaller size of Cu(II) and shown in **Fig. 4**. This behaviour is in line with Irving–Williams order [Irving & Williams ,1953s].



**Fig. 4:** Variation of  $\log \beta$  with Atomic Number for [A]: M(II) – MSA – His; [B]: M(II) – MSA – Val in 0 – 60% v/v EG – water media.

### ROLE OF DIELECTRIC CONSTANT,

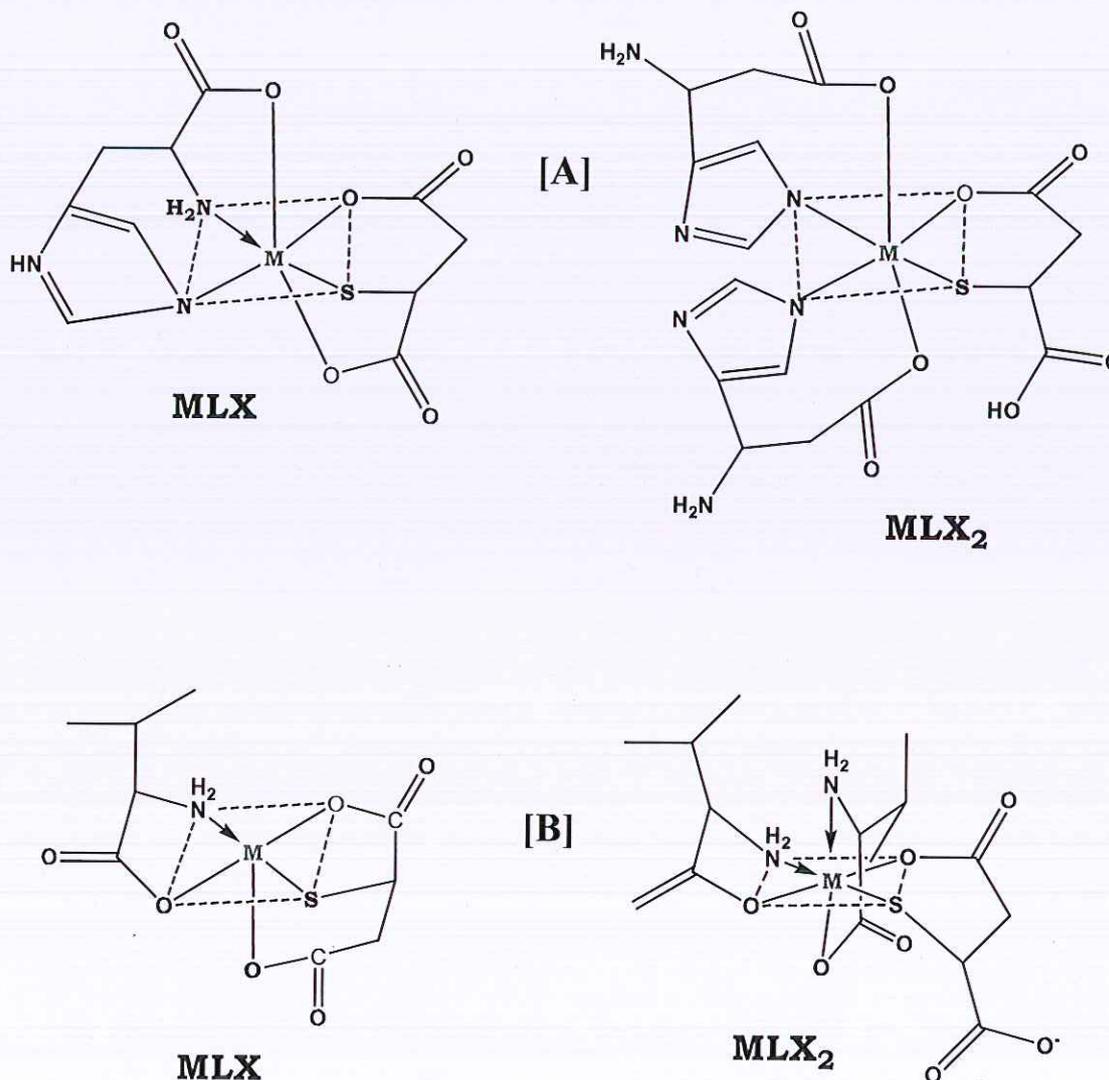
EG's protophilic and structure forming nature removes water from metal ion coordination spheres, making complexes more stable. As indicated in the study, log values should be connected to the medium's dielectric constant ( $1/D$ ). (Fig. 5).



**Fig. 5:** 3D Surface plot for Variation of  $\log \beta$  against reciprocal of Dielectric constant and percentage of solvent for [A]: M(II) – MSA – His; [B]: M(II) – MSA – Val; M(II): Co(II), Ni(II), Cu(II) and Zn(II).

### PROPOSED STRUCTURE

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 and sketched using Chem Draw 18.1 computer program and shown in **Fig. 6**. MSA form strong bidentate complexes with transition metals. MSA at higher pH favors the (O, S) coordination and at physiological pH amino acids bound only through the amino acid side chain [Wang et al, Peter et al, 2014, Zambelli et al, 2013, Padmaja et al, 2011, Vashi, & Shelat, 2011, Raman et al, 2004 & Kumar & Kiremire, 2007].



**Fig. 6:** Proposed Structures of Ternary Complexes of [A]: M(II) - MSA - His; [B]: M(II) - MSA - Val. M(II) : Co(II), Ni(II), Cu(II) or Zn(II); S = either H<sub>2</sub>O or Solvent.

## CONCLUSION

In this study, the results of a pH-metric study of ternary systems of MSA and three essential amino acids (Val and His) with transition metal ions were used to figure out the constants. It was clear that MSA could form stable ternary complexes with studied metal ions, L-Valine and L-Histidine as the secondary ligands. Due to the effect of the N- and O- donors, the formation of mixed-ligand complexes probability is more than binary

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## CONFLICTS OF INTEREST

There are no conflicts to declare.

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