

## Equilibrium studies on binary and ternary Cu(II) complexes containing ethylenediaminediacetic acid and a series of $O^- - O^-$ , $N - O^-$ and $N - N$ donor ligands

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MS received 7 December 1991; revised 7 March 1992

**Abstract.** The formation constants for ternary metal complexes (MLA) where L = ethylenediaminediacetic acid (EDDA), M = Cu(II) and A = glycine, alanine, leucine, serine, threonine, methionine, proline, phenylalanine, tryptophan, histidine, aspartic acid, ethylenediamine, histamine, 2,2'-bipyridyl, 1,10-phenanthroline, imidazole, oxalic acid, malonic acid, pyrocatechol and nitropyrocatechol have been investigated by pH-metric method at 35°C and  $\mu = 0.2$  M ( $KNO_3$ ). With respect to the donor atoms on ligand A, the stabilities of the ternary complexes increase in the order  $O^- - O^- < N - O^- \approx N - N$ . The stabilities of the various ternary complexes decrease with the increasing number of carboxylate groups on the ligand in the order ethylenediamine (EN) < ethylenediamine monoacetic acid (EDMA) < EDDA. Various factors influencing the formation and stabilities of ternary complexes are discussed.

**Keywords.** Stability constants; ternary complexes; ethylenediaminediacetic acid; ethylenediamine.

### 1. Introduction

In view of the fact that ternary metal complexes play a pivotal role in various fields such as biological systems (Eichhorn 1973; Sigel 1989), chemotherapy (Sherman and Lippard 1987), catalysis (Martell 1973) etc, the formation, stabilities and reactivities of these complexes have been an active field of research (Bhattacharya 1981; Banarjee 1990). In continuation of our previous work in this field (Srinivas Mohan *et al* 1979; Prasad and Srinivas Mohan 1987; Koteswar Rao 1990), we have investigated the formation of binary and ternary Cu(II) complexes involving ethylenediaminediacetic acid [EDDA] whose metal complexes have been shown to possess anti-inflammatory activity (Katz and March 1986). The ternary complexes investigated involved EDDA as one ligand [L], Cu(II) as the metal ion (M) and glycine (Gly), alanine (Ala), leucine (Leu), phenylalanine (Phe), tryptophan (Trp), serine (Ser), threonine (Thr), methionine (Met), proline (Pro), histidine (His), histamine (Hin), 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (Phen), imidazole (Im), oxalic acid (Ox), malonic acid (Mal),

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pyrocatechol (Pyr) and 4-nitrocatechol (NPyr) as the second ligand [A]. The stability constants of these ternary complexes are reported at 35°C and  $\mu = 0.2$  M (KNO<sub>3</sub>). The mutual influence of two ligands (L and A) in the coordination sphere of the metal ion has been quantitatively assessed in terms of the parameter  $\Delta \log K$ . The formation constants of binary and ternary Cu(II) complexes containing ethylenediaminemonoacetic acid (EDMA) and the amino acids Gly, Ala, Trp and Phe were reported earlier at 25.0°C and  $\mu = 0.5$  M (KCl) (Leporati 1986). The stability of various ternary metal complexes containing the parent ligand ethylenediamine (EN) and the substituted analogues EDMA and EDDA have been compared and the differences discussed.

## 2. Experimental

The amino acids Gly, DL-Ala, Leu, Ser, Thr, Met, Pro, Phe, Trp, His and Hin, and EDDA were obtained from the Sigma Chemical Company, USA. Bipy, Phen, Ox, Mal, Pyr, NPyr, Im, potassium nitrate, Cu(II) nitrate trihydrate and sodium hydroxide were of BDH analar grade. A stock solution of Cu(II) was prepared and standardised by titrating with standard EDTA (Flashka 1964). Carbonate free sodium hydroxide was prepared and standardised by titrating with potassium hydrogen phthalate (Schwarzenbach and Biederman 1948).

The experimental method consisted of the potentiometric titration of a 1:1:1 molar ratio of EDDA-metal ion-ligand A with standard carbonate-free sodium hydroxide. The concentration of Cu(II) was about  $2 \times 10^{-3}$  M. Titrations were carried out in a double jacketed cell maintained at  $35^\circ\text{C} \pm 0.1$  and  $\mu = 0.2$  M (KNO<sub>3</sub>). The pH measurements were carried out with a Digisun digital pH meter fitted with a combination glass electrode assembly. The electrode system was calibrated by direct titration of acetic acid, the observed pH meter readings being compared with the actual hydrogen ion concentration calculated from data tabulated by Harned and Owen (1952). The pH regions below 3.5 and above 10.5 were calibrated by measurements in HCl and NaOH solutions respectively.

## 3. Calculations

The protonation constants and formation constants  $\beta_{pqrs}$  for the complex  $M_p L_q A_r H_s$  (where  $p$ ,  $q$ ,  $r$  and  $s$  are the numbers of metal ions, ligand L, ligand A, and protons respectively) formed according to the equilibrium



where

$$\beta_{pqrs} = \frac{[M_p L_q A_r H_s]}{[M]^p [L]^q [A]^r [H]^s}, \quad (2)$$

were calculated from the potentiometric data obtained for the free ligand, binary and ternary systems by using the computer programme SCOGS (Sayce 1968). The species  $H_3L$ ,  $H_2L$ , HL, L and A were considered for computing the protonation constants,

H<sub>2</sub>L, HL, L, H, M, ML and ML<sub>2</sub> for computing the binary constants and H<sub>2</sub>L, HL, L, H, H<sub>2</sub>A, HA, A, M, ML, MA, ML<sub>2</sub>, MA<sub>2</sub> and MLA for computing the ternary constants. The stepwise protonation constants ( $\beta_{0101}$ ,  $\beta_{0102}$ , and  $\beta_{0103}$ ) the binary constants ( $\beta_{1100}$ ,  $\beta_{1200}$ ) and the ternary constants ( $\beta_{1110}$ ) were then calculated from the overall formation constant  $\beta_{pqrs}$  by using the appropriate relationships (Srinivas Mohan *et al* 1979).

#### 4. Results and discussion

The protonation constants, the binary constants and the various ternary constants are listed in tables 1 and 2. To facilitate comparison the formation constants for the binary Cu(II) complexes (MA) determined by us earlier (Prasad *et al* 1987) under identical experimental conditions are listed in table 1 along with ternary constants for Cu(II) complexes containing ethylenediamine (EN) or EDMA (Leporati 1986).

The influence of ligand L (or A) on the binding of the second ligand A (or L) has been quantitatively expressed in terms of the parameter  $\Delta \log K$  obtained by comparing the stepwise formation constants for the ternary complexes with the corresponding binary metal complexes as below:

$$\Delta \log K = \log K_{MLA}^{ML} - \log K_{MA}^M \quad (3)$$

or

$$\Delta \log K = \log K_{MLA}^{MA} - \log K_{ML}^M. \quad (4)$$

The stepwise formation constants for the various ternary metal complexes and the corresponding  $\Delta \log K$  values are listed in table 2. Using the relevant protonation constants and the formation constants for the mono and *bis* binary complexes as well as the ternary stability constants listed in tables 1 and 2, the percentage variation of the various metal complex species as a function of pH were calculated by using the computer programme BEST (Martell and Motekaitis 1988) and these pH-species profiles are shown in figures 1–3. In all these systems it is observed that the percentage of the ternary complexes (MLA) increased with an increase in pH.

##### 4.1 Protonation constants of EDDA and formation constants for binary metal complexes

Protonation constants for EDDA are lower than the corresponding values for EN determined under identical conditions. The presence of electron-withdrawing carboxylate groups on the nitrogens of EDDA makes the attached protons more acidic. The stability of the Cu(II)-EDDA complex is about four log units higher than the stability of the Cu(II) complex with the unsubstituted parent ligand ethylenediamine (EN) (table 1). The enhanced stability may be attributed to two factors: (1) the two additional five-membered chelate rings formed by the coordination of the carboxylate oxygens of EDDA to the axial sites of the metal ion, and (2) the favourable entropy factor resulting from charge neutralization and consequent release of ordered solvent molecules around the positively charged metal and the negatively charged carboxylate oxygens. It is interesting to note that the stability of the ethylenediaminemonoacetic acid [EDMA]-Cu(II) complex which contains two

**Table 1.** Cumulative formation constants\* for binary and ternary complexes containing Cu(II), ethylenediamine diacetic acid (EDDA), ethylenediaminemonoacetic acid (EDMA)\* and ethylenediamine (EN) and various secondary ligands. Temperature = 35°C;  $\mu = 0.2 \text{ M (KNO}_3\text{)}$

Ligand	<i>pqrs</i>	$\log \beta_{pqrs}$	$\log \beta_{pqrs}$			
			<i>pqrs</i>	EDDA	EDMA	EN
EDMA	1100	12.84				
EDDA	1100	14.50				
	1200	19.45				
Gly	1100	8.00	1110	19.06	18.24	
Ala	1100	7.94	1110	18.67	18.28	17.64
Leu	1100	8.04	1110	18.89		17.60
Ser	1100	7.80	1110	18.63		17.25
Thr	1100	7.92	1110	18.64		17.06
Met	1100	7.70	1110	18.60		
Pro	1100	8.60	1110	19.13		
Phe	1100	7.64	1110	18.42	18.22	17.47
Trp	1100	7.96	1110	18.57	18.83	17.73
His	1100	9.76	1110	19.49		18.63
Asp	1100	8.38	1110	18.94		17.71
EN	1100	10.32	1110	20.97		
Hin	1100	9.02	1110	19.67		
2,2'-Bipy	1100	CF	1110	10.78		
1,10-Phen	1100	CF	1110	10.74		
Im	1100	4.11	1110	17.86		
	1200	7.44	1120	18.81		
Pyr	1100	13.64	1110	23.51		
4-NPyr	1100	11.18	1110	21.47		

CF = completely formed

Protonation constants for EDDA at 35°C and  $\mu = 0.2 \text{ M (KNO}_3\text{)}$ :  $pK_{2a} = 1.83$ ,  $pK_{3a} = 6.41$ ,  $pK_{4a} = 9.35$ .

Protonation constants for EN at 35°C and  $\mu = 0.2 \text{ M (KNO}_3\text{)}$ :  $pK_a = 6.96$ ,  $pK_{2a} = 9.73$

Protonation constants for EDMA at 25°C and  $\mu = 0.5 \text{ M (KCl)}$ :  $pK_a = 1.49$ ,  $pK_{2a} = 6.96$ ,  $pK_{3a} = 9.88$

\*Constants accurate to  $\pm 0.02$ .

\*EDMA constants from Leporati (1986) (25°C and  $\mu = 0.5 \text{ M (KCl)}$ ).

chelate rings is more stable than the Cu(II)–EN complex by about two log units. Hence formation of each additional chelate ring increases the stability by about two log units. The large decrease in the stability associated with the formation of *bis* binary [Cu(II)–(EDDA)<sub>2</sub>] complex (–9.5 log units) indicates that each of the two EDDA molecules may be bound to Cu(II) in a bidentate fashion involving the two nitrogen donor atoms only with the four carboxylate oxygens remaining unbound. The protonation constants for EDDA and its binary Cu(II) constant ( $K_{ML}^M$ ) was reported earlier (Chaberek and Martell 1952) under different experimental conditions.

#### 4.2 EDDA–Cu(II)–Amino acid ternary complexes

(Gly, Ala, Leu, Ser, Thr, Met, Pro, Trp, Phe): Ternary complexes containing EN, Cu(II) and the above amino acids are destabilized to a modest extent. The  $\Delta \log K$  values are

**Table 2.** Stepwise stability constants and  $\Delta \log K$  values for Cu(II) ternary complexes containing ethylenediaminediacetic acid, ethylenediamine monoacetic acid\* and ethylenediamine as primary ligands with various secondary ligands.

Temperature 35°C;  $\mu = 0.2 \text{ M (KNO}_3\text{)}$

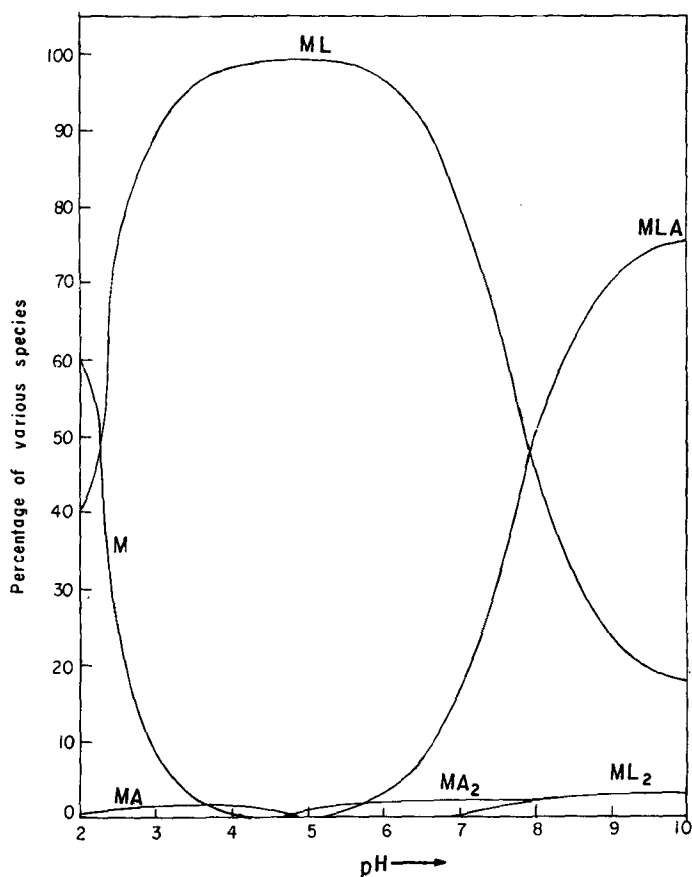
Ligand (A)	EDDA		EDMA		EN	
	$\log K_{MLA}^{ML}$	$\Delta \log K$	$\log K_{MLA}^{ML}$	$\Delta \log K$	$\log K_{MLA}^{ML}$	$\Delta \log K$
Gly	4.56	-3.44	5.39	-2.25		
Ala	4.17	-3.77	5.43	-2.71	9.70	-0.62
Leu	4.39	-3.69			8.56	-0.76
Ser	4.13	-3.72			9.45	-0.87
Thr	4.14	-3.78			9.16	-1.16
Met	4.10	-3.60				
Pro	4.63	-3.97				
Phe	3.92	-3.72	5.37	-2.49	9.83	-0.49
Trp	4.09	-3.87	5.98	-2.16	9.77	-0.55
His	4.99	-4.77			8.87	-1.45
Asp	4.44	-3.94			9.33	-0.99
EN	6.47	-3.85				
Hin	5.17	-3.85				
2,2'-Bipy	10.78	-3.72				
1,10-Phen	10.74	-3.76				
Im	3.36	-0.75				
(Im) <sub>2</sub>	0.95	-2.38				
Pyr	9.01	-4.63				
4-NPyr	6.97	-4.21				

$\Delta \log K$  values calculated according to (12) and (13).

\*Data taken from Leporati (1986).

in the range of  $-0.49$  to  $-0.87$  (table 2). In contrast, the  $\Delta \log K$  values for ternary Cu(II) complexes containing EDDA (L) and the above amino acids (A) are quite negative (table 2, about  $-3.70$ ) due to the fact that the above amino acids may occupy two equatorial sites of Cu(II) displacing the carboxylate oxygens of EDDA from the equatorial sites to the two weak axial sites. Electrostatic repulsion between the negative charge(s) on ligand L and A can also contribute to the lower stability. The decrease in stability of the ternary complex is almost equivalent to the stabilization resulting from the formation of two chelate rings in the binary Cu(II)-EDDA complex.

In the earlier studies on EDMA-Cu(II)-Gly/Ala/Norval ternary complexes (Leporati 1986) the decrease in stability was found to be about  $-2.7 \log$  units. This is consistent with the carboxylate group of EDMA being displaced from a strong equatorial site to a weak axial site by the bidentate amino acids. The greater stability of ternary complexes containing EDMA-Cu(II) and Phe or Trp was attributed to the aromatic side chains of the amino acid being located at an axial site of Cu(II), causing the metal ion to become more electronegative and thereby facilitating stronger interaction with the two ligands in the coordination sphere of the metal ion. However in the present investigation enhanced stability for ternary systems containing Phe or Trp was not observed and the stability is of the same order as that found for amino acids without an aromatic side chain (Gly, Ala, etc). The difference in behaviour of tridentate EDMA and tetradentate EDDA containing Cu(II) ternary complexes may be due to the fact that in the EDDA-containing complexes the axial sites are occupied by

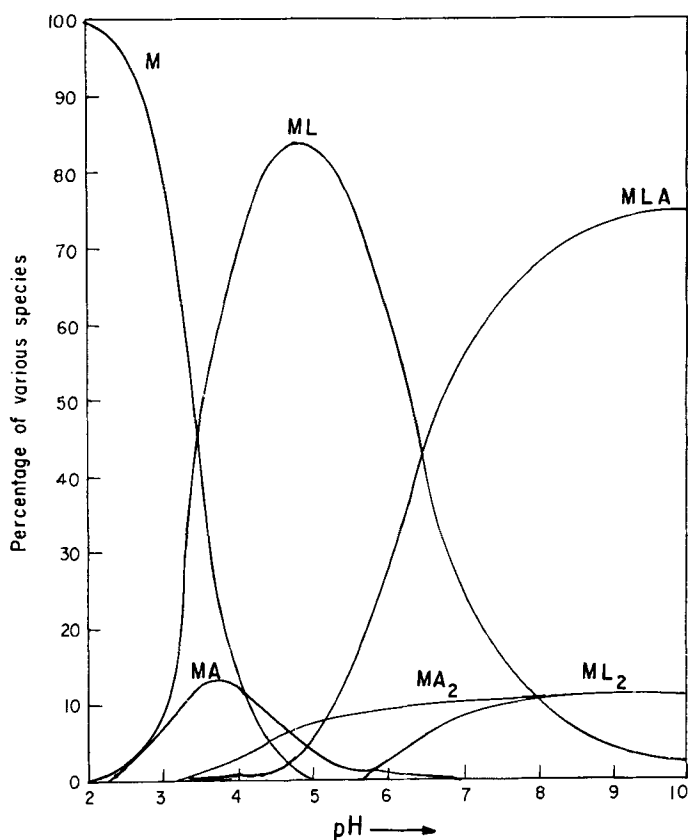


**Figure 1.** pH-Species distribution profiles for ternary EDDA-Cu(II)-Trp system. Ordinate represents the percentage of various uncomplexed and complexed metal species as a function of pH.  $T = 35^{\circ}\text{C}$  and  $\mu = 0.2 \text{ M (KNO}_3\text{)}$ .  $\text{EDDA} = \text{Cu(II)} = \text{Trp} = 2 \times 10^{-3} \text{ M}$ .

carboxylate oxygens which prevent the aromatic rings of Phe or Trp from occupying the axial sites of metal ions.

#### 4.3 EDDA-Cu(II)-Ox/Mal/Pyr/NPyr ternary complexes

It was observed that ternary complex formation does not take place in systems containing EDDA-Cu(II)-Ox or Mal taken in a 1:1:1 molar ratio. The electrostatic repulsion between the two negative charges on each of the two ligands as well as the low basicity of oxalic acid and malonic acid hamper the formation of these ternary complexes. However, in the case of dinegative ligands Pyr/NPyr the basicity of these ligands is much higher and hence formation constants for ternary complexes can be computed. However the ternary complexes containing these bidentate anionic oxygen donors are destabilized to a greater extent relative to the amino acids ( $-\text{N}-\text{O}^-$  donors). In these complexes the equatorial plane of the tetragonally distorted Cu(II) may be occupied by two nitrogens of EDDA and two oxygens of Pyr/NPyr with the two axial sites being occupied by the carboxylate oxygens of EDDA. The two negative charges



**Figure 2.** pH-Species distribution profile for ternary EDMA-Cu(II)-Trp system. Ordinate represents the percentage of various uncomplexed and complexed metal species as a function of pH.  $T = 25^{\circ}\text{C}$  and  $\mu = 0.5 \text{ M}$  (KCl).  $\text{EDMA} = \text{Cu(II)} = \text{Trp} = 2 \times 10^{-3} \text{ M}$ .

each on Pyr/NPyr and EDDA could lead to greater electrostatic repulsion and hence lower stability.

#### 4.4 EDDA-Cu(II)-EN/Hin/Bipy/Phen and His ternary complexes

The four N-N donor ligands investigated, namely Bipy, Phen, EN and Hin form ternary complexes with negative  $\Delta \log K$  values around 3-80. The coordination sphere of the metal ion may involve the four nitrogens of the two ligands in the equatorial plane and the two carboxylate oxygens of EDDA at the axial sites. Due to the absence of electrostatic repulsion between the donor atoms of the two ligands, ternary complexes involving the N-N donor ligands are destabilized to a lesser extent than the corresponding complexes containing dinegative oxygen donor ligands. The  $\Delta \log K$  values show that ternary complexes involving histidine are more unstable than the corresponding complexes containing histamine. The decreased stability is attributable to the electrostatic repulsion arising from the negatively charged histidine anion and its decrease in denticity from tridentate in the binary (Martin 1979) to bidentate in the ternary complexes. On the other hand, histamine is neutral and bidentate in both binary and ternary systems.

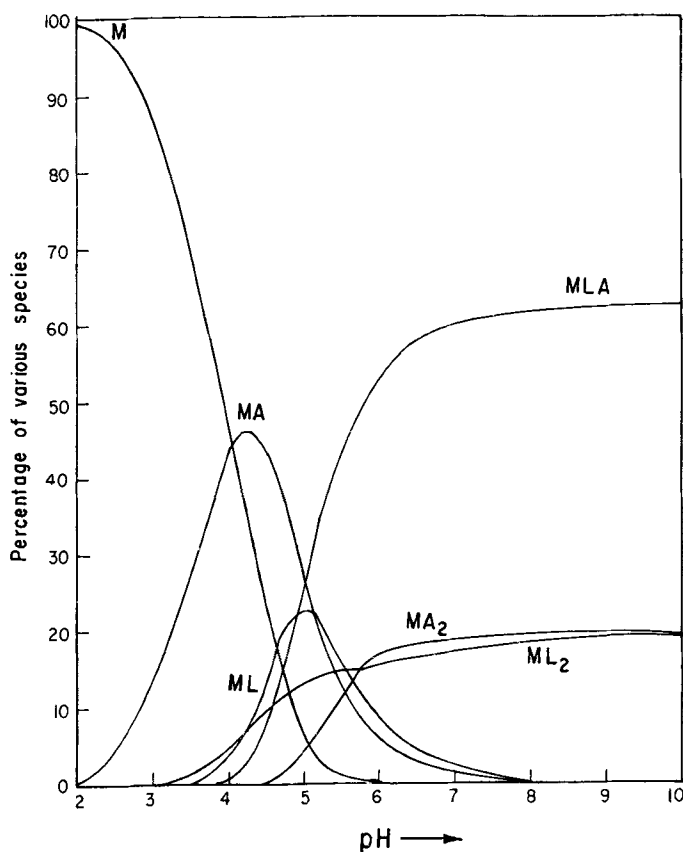


Figure 3. pH-Species distribution profile for ternary EN-Cu(II)-Trp system. Ordinate represents the various uncomplexed and complexed metal species as a function of pH.  $T = 35^{\circ}\text{C}$  and  $\mu = 0.2\text{ M}$  ( $\text{KNO}_3$ ).  $\text{EN} = \text{Cu(II)} = \text{Trp} = 2 \times 10^{-3}\text{ M}$ .

#### 4.5 EDDA-Cu(II)-Im (MLA and MLA<sub>2</sub>) ternary complexes

The  $\Delta \log K$  values for EDDA-Cu(II)-imidazole ternary complexes namely MLA and MLA<sub>2</sub> are  $-0.75$  and  $-2.33$ , respectively. Due to its  $\sigma$ -donor and  $\pi$ -acceptor capability an imidazole moiety binds strongly to an equatorial site of Cu(II) (Prasad *et al* 1988). Hence in the MLA complex one of the carboxylate oxygens of EDDA may be displaced from an equatorial site. However in the 1:1:2 complex the second imidazole may prefer to bind to an axial site instead of a *cis*-equatorial site due to steric hindrance between the two *cis*-coordinated imidazoles (Freeman 1973). Therefore the ternary complex (MLA<sub>2</sub>) containing two imidazoles is of lower stability than the MLA complex containing one  $\pi$ -acceptor imidazole in the equatorial plane. This promotes the binding of anionic oxygen donor carboxylate moieties in the MLA complex.

A critical analysis of the  $\Delta \log K$  values for all the ternary systems investigated (table 2) shows that with respect to the ligand L, the stability decreases in the order  $\text{EN} > \text{EDMA} > \text{EDDA}$ . This order corresponds to the increase in the number of carboxylate groups on ligand L.



**Acknowledgement**

Two of the authors (DSY and GNK) are thankful to the Council of Scientific and Industrial Research, New Delhi, for providing financial assistance in the form of fellowships.

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