Potentiometric Studies on Binary and Ternary Complexes of Transition Metal Ions with Some Pharmaceutical Compounds

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To explore the binary and ternary complexation tendencies of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) were studied by the pH-metric technique at the ionic strength 0.1 M (KNO_3) and the temperature 29 ± 0.5°C in aqueous medium. The metal-ligand stability constants of binary complexes were evaluated using Irving-Rossotti titration technique. The metal-ligand stability constants were evaluated using nitrolotriacetic acid (NTA) and iminodiacetic acid (IMDA) as primary ligands and the drugs levodopa (LDP) and methyldopa (MDP) as secondary ligands at the same conditions by the modified form of Irving-Rossotti technique.

INTRODUCTION

In recent years there has been considerable interest in the study of binary, ternary and quaternary complexes by pH-metric method[1–4]. The ligand levodopa (LDP) is well known for its use in neurotransmission process[5] and the treatment of Parkinson disease[6]. The ligand methyldopa (MDP) is an antihypertensive agent which has a depressant action on the central nervous system[7–9].

The mixed ligand complexes of transition metals are comparatively less studied than inner transition elements. Ternary complexes of Ni(II) with glycylglycine and glycinamide as primary ligands and imidazole, histamine and L-histidine as secondary ligands have been investigated by Nair and Neelkantan[10]. Nair *et al.*[11] have studied the ternary complexes of Ni(II) using histamine and L-histidine as primary ligands and some amino acids, diamines and diamino carboxylic acid as secondary ligands pH-metrically. Stability constants of ternary complexes of Zn(II) and Cd(II) containing catechol and amino acids or diperptides have been determined potentiometrically by Bhattacharya *et al*[12]. Nair *et al.*[13] have studied the ternary complexes of Ni(II) and Cu(II) with nicotinic acid as primary ligand and imidazole, benzimidazole, histamine and L-histidine as secondary ligands potentiometrically. The study of stability constants of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) with NTA and IMDA as primary ligands and LDP and MDP as secondary ligands are not reported in literature. It was therefore interesting to study the stability constants of binary and ternary complexes of these metal ions with these medicinal compounds and at 29 ± 0.5°C at

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$\mu = 0.1$ M KNO_3 employing modified form of Irving-Rossotti pH-metric titration technique[14] in aqueous medium.

EXPERIMENTAL

The ligand LDP was obtained from Loba Chemie and the MDP was of Merind Limited. The ligands were used as such. Carbonate-free sodium hydroxide solution was prepared by standard method[15]. All other solutions were prepared in doubly distilled water.

The pH-metric measurements were carried out by using Elico digital pH-meter model L-120 with glass-calomel electrode with an accuracy of ±0.01 of pH unit at 29 ± 0.5°C. The pH-meter was standardized against 0.05 M potassium hydrogen phthalate solution in acid medium and 0.01 M borax solution in alkaline medium.

For the determination of proton-ligand stability constant of the secondary ligands and metal-ligand stability constants of the binary and ternary complexes, the following sets of solutions were prepared and titrated against standard alkali solution.

Binary Systems

(i) 9.4×10^{-3} M HNO_3
(ii) 9.4×10^{-3} M $HNO_3 + 3.0 \times 10^{-3}$ M secondary ligand.
(iii) 9.4×10^{-3} M $HNO_3 + 3.0 \times 10^{-3}$ M secondary ligand + 1.0×10^{-3} M metal ion.

Ternary Systems

(i) 9.4×10^{-3} M HNO_3
(ii) 9.4×10^{-3} M $HNO_3 + 3.0 \times 10^{-3}$ M secondary ligand.
(iii) 9.4×10^{-3} M $HNO_3 + 1.0 \times 10^{-3}$ M primary ligand + 1.0×10^{-3} M metal ion.
(iv) 9.4×10^{-3} M $HNO_3 + 1.0 \times 10^{-3}$ M primary ligand + 1.0×10^{-3} M metal ion + 1.0×10^{-3} M secondary ligand.

The ionic strength was maintained constant (0.1 M) by adding required volume of 1 M KNO_3. The ratio of metal (M) : secondary ligand (L) was maintained at 1 : 3 in each of the binary systems and the ratio of metal (M) : primary ligand (A): secondary ligand (L) was maintained at 1 : 1 : 1 in each of the ternary systems.

RESULTS AND DISCUSSION

Proton-Ligand Stability Constants

The plots of volume of alkali (NaOH) against pH-meter readings were used to evaluate the proton-ligand stability constants of LDP and MDP. The deviation between free acid titration curve and secondary ligand titration curve was used to evaluate the formation functions $\bar{n}_A$. The proton-ligand formation curves were then obtained by plotting the values of $\bar{n}_A$ vs. pH-meter readings. From the graphs

the values of log K_1^H and log K_2^H were evaluated by half integral method (method A) and pointwise calculation method (method B) and presented in Table-1.

TABLE-1
PROTON-LIGAND STABILITY CONSTANTS

Ligands	log K_1^H Method		log K_2^H Method		log β^H Method	
	A	B	A	B	A	B
LDP	9.940	9.942	8.770	8.773	18.710	18.715
MDP	10.825	10.820	9.250	9.210	20.075	20.035

Metal-Ligand Stability Constants of Binary Complexes

The metal-ligand stability constants of binary complexes were evaluated assuming that the formation of hydrolysed products, polynuclear complexes, hydrogen and hydroxyl bearing complexes were absent. An examination of titration curves indicates that complex formation has taken place in solution on the following grounds:

1. The metal titration curves showed displacement with respect to the ligand titration curves along the volume axis. This indicates the affinity of ligand with metal ions which release protons and produce the volume difference $(V_3 - V_2)$.
2. The colour change of the ligand in presence of metal ions appeared showing the formation of new species.
3. The hydrolysis of the metal ions was suppressed due to complex formation and precipitation did not appear during the titrations.

From the ligand and metal titration curves the values of $\bar{n}$ and from that the values of pL were evaluated. The formation curves obtained were used to evaluate the metal-ligand stability constants by methods (A) and (B) and presented in Table-2.

TABLE-2
METAL-LIGAND STABILITY CONSTANTS OF BINARY COMPLEXES

Systems	log K_1		log K_2		log β	
	Method A	Method B	Method A	Method B	Method A	Method B
[Mn(II)-LDP]	5.48	5.50	3.74	3.73	9.22	9.23
[Co(II)-LDP]	6.13	6.16	3.86	3.87	9.99	10.03
[Ni(II)-LDP]	6.85	6.86	4.25	4.26	11.10	11.12
[Cu(II)-LDP]	7.16	7.11	5.03	5.10	12.19	12.21
[Zn(II)-LDP]	6.51	6.54	4.39	4.40	10.90	10.94
[Mn(II)-MDP]	8.58	8.61	5.90	5.94	14.48	14.55
[Co(II)-MDP]	9.38	9.39	5.80	5.82	15.18	15.21
[Ni(II)-MDP]	9.42	9.45	5.86	5.87	15.28	15.31
[Cu(II)-MDP]	9.78	9.80	6.20	6.22	15.98	16.02
[Zn(II)-MDP]	9.54	9.50	5.94	5.94	15.48	15.44

The variation of $\bar{\eta}$ was found to be 0 to 2 which indicates that the composition of complexes was 1 : 2 in solution. From Table-2, it is obvious that the metal-ligand stability constants of MDP were greater than those of LDP in every metal.

The Irving-Williams order[16, 17] of stability constants was followed by both ligands.

Metal-Ligand Stability Constants of Ternary Complexes

The metal-ligand stability constants of the ternary complexes were evaluated assuming that the formation of hydroxy products, polynuclear complexes, hydrogen and hydrogen bearing complexes was absent. An examination of the titration curves indicated that ternary complex formation has taken place in solution on the following grounds.

1. The ternary complex titration curves show displacement with primary complex titration curves. The horizontal distance measured between acid curves and secondary ligand curves ($V_2 - V_1$) and subtracted through the horizontal distance between ternary complex curves and primary complex titration curves ($V_4 - V_3$) show the positive difference which proves the earlier release of protons in the formation of ternary complexes.
2. The hydrolysis of metal ions was suppressed and precipitation did not result.

The values of $\bar{\eta}$ varies from 0 to 1, thus confirming the formation of 1 : 1 : 1 mixed ligand complexes. The values of $\log_{MAL}^{NTA}$ and $\log_{MAL}^{IMDA}$ have been evaluated from the formation curves ($\bar{\eta}$ *vs.* pL). At $\bar{\eta} = 0.5$, in the formation curve, pL = log K. The log K values were also evaluated by pointwise calculation method (B). The metal-ligand stability constants of LDP and MDP as secondary ligands and NTA and IMDA as primary ligands are presented in Table-3.

TABLE-3
METAL-LIGAND STABILITY CONSTANTS OF TERNARY COMPLEXES

Systems	Constants (log K)									
	Mn(II)		Co(II)		Ni(II)		Cu(II)		Zn(II)	
	A	B	A	B	A	B	A	B	A	B
[M(II)-NTA-LDP]	4.17	4.18	4.47	4.49	4.69	4.71	5.70	5.69	4.27	4.27
[M(II)-IMDA-LDP]	4.22	4.24	4.29	4.31	4.35	4.38	5.50	5.51	4.30	4.31
[M(II)-NTA-MDP]	5.99	6.01	6.23	6.28	7.25	7.27	7.93	7.94	7.71	7.72
[M(II)-IMDA-MDP]	7.06	7.05	7.37	7.38	7.57	7.60	9.32	9.40	7.55	7.58

The values for metal-ligand stability constants $\log_{MAL}^{NTA}$ and $\log_{MAL}^{IMDA}$ are found to be less than for binary complexes. This is because of in the formation of ternary complexes lesser number of sites are available for incoming ligand groups as compared to binary complexes. Hence the affection of metal for the ternary complexes is less for most of the cases.

The Irving-Willams natural order[16, 17] was observed in case of binary as well as ternary complexes which is

$$Mn(II) < Co(II) < Ni(II) < Cu(II) > Zn(II).$$

The aim of the study was to know whether the effect of binary and ternary complexes as compared to plain drug is different or the same. This part of the application is in progress as it is time consuming.

ACKNOWLEDGEMENTS

The authors are thankful to Principal, Govt. V.M.V., Amravati and Principal, P.N. College, Pusad for providing necessary facilities.

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(*Received:* 28 May 2001; *Accepted:* 30 August 2001) AJC-2411