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# Mixed ligand stability constants of Co (II), Ni (II), Cu (II) and Zn (II) transition metal complexes with chloropheniramine maleate drug and amino acids

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## ABSTRACT

*Chemical equilibrium studies on Co (II), Ni (II), Cu (II) and Zn (II) transition metal complexes with chloropheniramine maleate drug (L) and a series of eight amino acids (R) have been investigated pH metrically at 27$^0$C temperature and 0.1 M ionic strength ($NaClO_4$) in aqueous solution. The formation of various possible complex species has been evaluated by computer program and discussed in terms of various relative stability parameters.*

**Keywords:** Mixed ligand complex, transition metal, drug, amino acids, and ionic strength.

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## INTRODUCTION

The chloropheniramine maleate (L) (IUPAC Name: (Z)-but-2-enedioic acid; 3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-ylpropan-1-amine) drug is an antihistamine drug used to relieves symptoms of allergies [1]. It works by blocking the effect of histamine, a naturally occurring substance that causes swelling, itching, sneezing, watery eyes, hives and other symptoms of allergic reactions. The chloropheniramine maleate is an alkyl amine type drug and structure is shown in Figure 1.

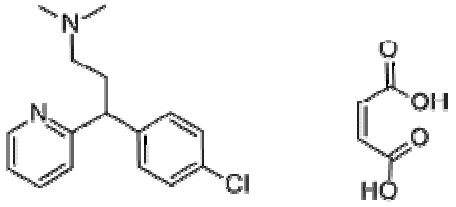



**Figure 1: structure of chloropheniramine maleate drug**

The formation of mixed ligand complexes are the equilibrium process and the studies of complex equilibria of metal ions with drugs are useful in elucidating the mechanism of drugs action [2]. The equilibrium constants have important medicinal implication to measure the metal ligand selectivity in terms of relative strength of metal ligand bonds[3]. The literature survey reveals that very limited work of ternary complexes of transition metals with drugs and amino acids have been reported in the past[4-9]. Hence the present paper deals with the systematic study of equilibrium constants of ternary complexes of Co(II), Ni(II), Cu(II) and Zn(II) transition metal ions with chloropheniramine maleate drug (L) and a series of eight amino acids (R).

## MATERIALS AND METHODS

All the chemicals used in the present study were Analar grade. The glassware's used in the present experiment were borosil glass quality and standardized as per standard procedure [10]. The solutions of reagents were prepared in double glass distilled water having 6.80-6.90 pH. The NaOH solution was prepared in double distilled water and fresh solution was used as a titrant for pH titrations. It is standardized with oxalic acid. The 1.0 M $NaClO_4$ solutions were prepared to maintain the 0.1 M ionic strength of the titration solutions by taking requisite amount of sodium perchlorate. The metal solutions were standardized by usual procedure [11].

### Digital pH meter

The digital pH meter [ Elico model LI 120; inbuilt temperature compensation and 0.0 to 14 pH range with an accuracy of ± 0.01 pH Unit] in conjunction with combined electrode was used for pH measurements and experiments were carried out at $27^0$C temperature and inert atmosphere by maintaining 0.1M ionic strength ($NaClO_4$) in aqueous solution. The pH meter was calibrated before every set of titrations by using 4.00 and 9.00 pH standard buffer solutions. All the necessary precautions were taken for smooth working of electrode[12].

### Titration procedure:

The Calvin Bjerrum pH titration techniques as modified by Irving Rossotti were applied to determine the equilibrium constants of 1:1:1 ternary complexes [13]. Titration procedure involves following steps:

| | |
|---|---|
| 1) Free acid ( $HClO_4$ )+ $NaClO_4$ | (A) |
| 2) Free acid ( $HClO_4$ )+ $NaClO_4$+ primary ligand | (A+L) |
| 3) Free acid ( $HClO_4$ ) + $NaClO_4$+ primary ligand+ metal | (A+L+M) |
| 4) Free acid ( $HClO_4$ ) + $NaClO_4$+ secondary ligand | (A+R) |
| 5) Free acid ( $HClO_4$ )+ $NaClO_4$+ secondary ligand+ metal | (A+R+M) |
| 6) Free acid ( $HClO_4$ )+ $NaClO_4$+ primary ligand + secondary ligand+ metal | (A+L+R+M) |

The above thermostatic mixtures were titrated with standard NaOH solution. The total volume of solution was kept at 50 ml by the adding distilled water.

### Calculations

The proton ligand stability constants (pK) and metal ligand stability constants (logK) of binary complexes were determined with the help of computer in Excel MS office by using Irving and Rossotti methods and equilibrium constants of ternary complexes along with various species

formed during complexation were directly obtained as output of 'SCOGS' computer program which employs non linear least square approach [14].

## RESULTS AND DISCUSSION

### Binary complexes

The proton ligand stability constants (pK) and metal ligand stability constants (logK) of binary complexes were determined by using Irving and Rossotti method for the comparison with these of ternary systems.

The formation of binary complex with drug (L) takes places at near 4 pH and remains stable at higher pH. The highest values of $n^{-}A$ and $n^{-}$ are around 2.0, indicates the presence of two pK and two logK values. The order of stability of binary complexes of transition metal ions with drug (L) indicates the least stability of nickel complexes and highest of copper complexes [Cu(II)>Zn(II)>Co(II)>Ni(II)] which has been reported[15].The least stability of nickel and highest stability of copper may be satisfy their less or high occurrence in biological systems.

### Mixed ligand complexes

The formation of 1:1:1 ternary complex (MLR) was inferred qualitatively from pH of precipitations of ML MR and MLR titration curves. The pH of precipitation of MLR systems were found more than that of binary system[16]. It was also confirmed by non super imposable nature of composite curve on mixed ligand titration curves.

### Stability of mixed ligand complexes

The Cu(II) $LR_3$(isoleucine) systems shows higher stability constants values among the present cobalt, nickel, copper and zinc transition metal complexes with drug (L) and eight amino acids whereas Co(II)$LR_7$(methionine) systems shows low value which may be attributed to the bonding interaction of amino acids and metal ions. The equilibrium constants and relative parameters of these ternary complexes are enlisted in Table 1 to 4.

In Co(II)LR systems, the ternary complexes with valine shows high value of stability constant whereas methionine ternary complexes shows low value of stability and isoleucine ternary complexes of Ni(II)LR systems shows high value of stability whereas methionine systems shows low value of stability. Similarly in Cu (II)L R systems isoleucine has high value and glycine low value of stability and in Zn(II)LR systems, glycine shows high value whereas methionine shows low value of stability. These variations may be attributed to steric, inductive effects and the increasing side chain of amino acids results in more strain in bending and leads to the low values of stability. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of $\Delta$LogK, $K_r$, $K_L$ and $K_R$ values which are defined by equations:

$$\Delta \log K = \log\beta_{111} - \log K_{10} - \log K_{01}$$

$$K_r = \beta^2_{111} / \beta_{20} . \beta_{02}$$

$$K_L = \beta_{111} / \log K_{10}$$

$$K_R = \beta_{111} / \log K_{01}$$

And shown in Table 1, 2, 3 and 4 along with stability constants of ternary systems of Co (II), Ni(II), Cu(II) and Zn(II) transition metal ions respectively.

**Table 1 Parameter based on some relationship between formation of mixed ligand complexes of Co(II) with L drug and Amino acids**

| Amino Acids | $\beta_{111}$ | $\beta_{20}$ | $\beta_{02}$ | $K_L$ | $K_R$ | $K_r$ | ΔlogK |
|---|---|---|---|---|---|---|---|
| Alanine | 16.26 | 16.82 | 12.11 | 6.30 | 8.46 | 1.12 | -1.50 |
| Glycine | 16.62 | 16.82 | 13.08 | 6.66 | 8.15 | 1.11 | -1.81 |
| Isoleucine | 17.06 | 16.82 | 12.05 | 7.10 | 9.33 | 1.18 | -0.63 |
| Phenyl alanine | 17.03 | 16.82 | 11.60 | 7.07 | 9.46 | 1.20 | -0.50 |
| Serine | 17.46 | 16.82 | 12.36 | 7.50 | 9.46 | 1.20 | -0.50 |
| Valine | 17.79 | 16.82 | 12.16 | 7.83 | 9.93 | 1.23 | -0.03 |
| Methionine | 12.03 | 16.82 | 4.06 | 2.07 | 7.97 | 1.15 | -1.99 |
| Glutamic acid | 17.31 | 16.82 | 12.42 | 7.35 | 9.46 | 1.18 | -0.50 |

**Table 2 Parameter based on some relationship between formation of mixed ligand complexes of Ni(II) with L drug and Amino acids**

| Amino Acids | $\beta_{111}$ | $\beta_{20}$ | $\beta_{02}$ | $K_L$ | $K_R$ | $K_r$ | ΔlogK |
|---|---|---|---|---|---|---|---|
| Alanine | 18.49 | 15.40 | 15.27 | 9.32 | 8.63 | 1.21 | -0.54 |
| Glycine | 18.24 | 15.40 | 16.36 | 9.07 | 7.67 | 1.15 | -1.50 |
| Isoleucine | 18.89 | 15.40 | 15.12 | 9.72 | 9.17 | 1.24 | 0.00 |
| Phenyl alanine | 17.21 | 15.40 | 14.73 | 8.04 | 7.63 | 1.14 | -1.54 |
| Serine | 17.84 | 15.40 | 15.40 | 8.67 | 7.88 | 1.16 | -1.29 |
| Valine | 16.90 | 15.40 | 15.15 | 7.73 | 7.19 | 1.11 | -1.98 |
| Methionine | 13.17 | 15.40 | 5.49 | 4.00 | 7.68 | 1.26 | -1.49 |
| Glutamic acid | 18.42 | 15.40 | 15.35 | 9.25 | 8.67 | 1.20 | -0.50 |

**Table 3Parameter based on some relationship between formation of mixed ligand complexes of Cu(II) with L drug and Amino acids**

| Amino Acids | $\beta_{111}$ | $\beta_{20}$ | $\beta_{02}$ | $K_L$ | $K_R$ | $K_r$ | ΔlogK |
|---|---|---|---|---|---|---|---|
| Alanine | 18.07 | 19.06 | 8.11 | 7.31 | 9.96 | 1.33 | -0.80 |
| Glycine | 17.30 | 19.06 | 8.16 | 6.54 | 9.14 | 1.27 | -1.62 |
| Isoleucine | 19.99 | 19.06 | 8.41 | 9.23 | 11.58 | 1.46 | 0.82 |
| Phenyl alanine | 18.59 | 19.06 | 7.87 | 7.83 | 10.72 | 1.38 | -0.04 |
| Serine | 16.87 | 19.06 | 7.88 | 6.11 | 8.99 | 1.25 | -1.77 |
| Valine | 17.86 | 19.06 | 8.12 | 7.10 | 9.74 | 1.31 | -1.02 |
| Methionine | 19.08 | 19.06 | 8.31 | 8.32 | 10.77 | 1.39 | 0.01 |
| Glutamic acid | 17.57 | 19.06 | 7.87 | 6.81 | 9.70 | 1.30 | -1.06 |

**Table 4 Parameter based on some relationship between formation of mixed ligand complexes of Zn(II) with L drug and Amino acids**

| Amino Acids | $\beta_{111}$ | $\beta_{20}$ | $\beta_{02}$ | $K_L$ | $K_R$ | $K_r$ | ΔlogK |
|---|---|---|---|---|---|---|---|
| Alanine | 17.08 | 16.84 | 13.18 | 7.60 | 8.49 | 1.14 | -0.99 |
| Glycine | 18.04 | 16.84 | 14.13 | 8.56 | 8.87 | 1.16 | -0.61 |
| Isoleucine | 16.83 | 16.84 | 12.95 | 7.35 | 8.35 | 1.13 | -1.13 |
| Phenyl alanine | 17.31 | 16.84 | 12.61 | 7.83 | 8.97 | 1.18 | -0.51 |
| Serine | 17.42 | 16.84 | 13.34 | 7.94 | 8.74 | 1.15 | -0.74 |
| Valine | 15.62 | 16.84 | 12.67 | 6.14 | 7.39 | 1.06 | -2.09 |
| Methionine | 12.29 | 16.84 | 4.63 | 2.81 | 7.66 | 1.14 | -1.82 |
| Glutamic acid | 15.97 | 16.84 | 12.81 | 6.49 | 7.74 | 1.08 | -1.74 |

The comparison of $\beta_{111}$ with $\beta_{20}$ and $\beta_{02}$ of these systems reveals the preferential formation of ternary complexes over binary systems[17]. The low values of $K_L$ and $K_R$ indicates the stability of ternary complexes are more with respect to binary complexes of ligands. The positive values of Kr also supports the extra stability of mixed ligand complexes which may be attributed to the interactions outside the coordinated sphere such as formation of hydrogen bonding between coordinated ligands, charge neutralization, chelate effect and electrostatic interactions between non coordinated charge group of ligands[18].The negative values of ΔlogK suggests the formation of ternary complexes and destabilized nature of complexes which has been reported in N and O coordination of amino acids[19].The positive value of ΔlogK in some cases is attributed to the extra stability of ternary complexes.

**Figure: 2 Species distribution curve of Cu (II) LR8**
**(pH versus % conc. of free metal and free ligands)**

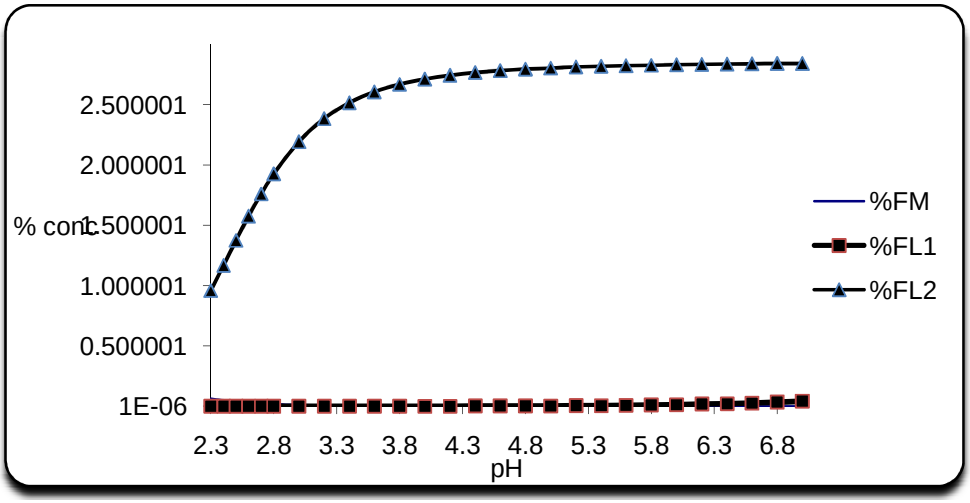
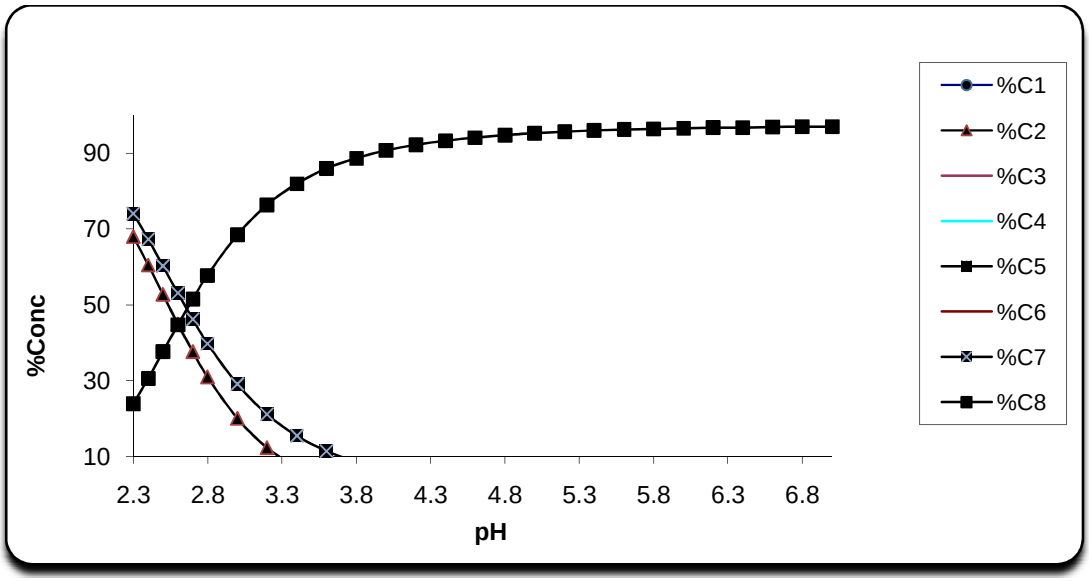



**Figure : 3.00 Species distribution curve of Cu(II)$LR_8$ system (pH versus % conc. of various possible species )**



**Species distribution curves**

The concentration of various species formed in the complex formation process was directly obtained as a computer outputs. The species distribution curves of Cu(II)$LR_8$($R_8$=Glutamic Acid) systems were obtained by plotting percentage concentration of various possible species versus pH of solution as shown in Figure 2 and 3 as representative graphs.

In Cu(II)$LR_8$ (glutamic acid) ternary system, primary ligand forms 1:1 and 1:2 binary complexes whereas secondary ligands forms only 1:1 binary complexes with copper. The species distribution diagram of free metal (FM), free ligands (FL,FR) shows the slow decrease in percentage concentration of free metal ions with increase in pH, which indicates complex formation. There is increase in percentage concentration of ligands with pH of solution. The percentage formation of FR is high than FL as shown in Figure 2.

The species distribution curve of various possible species of Cu(II)$LR_8$ system(Figure:3) clearly indicates the formation of ternary complexes(CuLR) and is which is 97% at pH 7.0($C_8$). The percentage of CuL binary species (2.84% at 7.0 pH) is low which favored the formation of ternary complexes. It also suggests that the concentration of $CuR_2$ ($C_7$) and HL ($C_2$) decreases with increase in concentration of the ternary complexes as pH increases. The possible equilibria in the formation of ternary complex are as follows:

$$CuL_2+CuR \leftrightarrow CuLR + CuL$$
$$CuR_2+CuL \leftrightarrow CuLR + CuR$$
$$Cu+L+R \leftrightarrow CuLR$$

## CONCLUSION

The formation of binary complexes with transition metal ions indicates the low stability of nickel complexes which may be one of the reasons to fewer occurrences of nickel complexes in the biological systems. The ternary complexes indicate the most stability of copper complex and low stability of cobalt complex which is commonly true in 3d series of present transition metal ions. The species distribution curve shows the formation of ternary complexes.

## REFERENCES

[1] M. Index, Merck and Co. INC. Whitehouse station, 14$^{th}$Edn, NJ USA P-180,**2006**.
[2] C.D Coryell, “Special Problems in the Formation of Metal Complexes in Chemical Specificity in Biological Interaction”, Academic Press, New York, 90. **1954.**
[3] G.Thomas, Medicinal Chemistry, John Wiley and Son Co. Ltd. London. P-1. **2002.**
[4] A.B.Thomas, S.D.Patil, *Der Pharma Chemica*,**2011**,3(3): 271-276
[5] B. R. Agrawal, B.K. Magare, M.N. Farooqui, D. M. Janrao, M.B. Ubale, *Int. J. Chem. Sci.* **2009,** 7(3), 2169-2172.
[6] G. N. Mukherji, T. K.,Ghosh *J. Indian Chem. Soc.* **1991**., 68,194-196.
[7] L.Gandhi , B. S.Sekhon, *J. Indian Chem. Soc.,* **2006.** 83,868-870.
[8] B.K.Magare, M. N. Farooqui, R.S. Shelke, M.B.Ubale,*Orient. J.Chem.*,**2009,**25(2),387- 390.
[9] A.A.Zaid,M.Mohsin,M.FarooquiD.M.Janrao,.*JournalofSaudiChemicalSociety,***2011**,doi:10.1016 / j.jscs.2011.02.020(Article in press).

[10] A. L.Vogel, 'A Text Book of Quantitative Inorganic Analysis', Pergamon Green and Co. Ltd. London, 539. **1975**
[11] G.Schwarzenbach, Complexometric Titration, Mentthuen and Co. Ltd.London,69,79,82. **1957.**
[12] R. G.Bates, Determination of pH Theory and Practice, A Wiley Interscience Publication New York . **1973.**
[13] H.M. Irving, H. S.Rossotti, *J. Chem. Soc.*, **1953.** 3397.
[14] I.G. Sayce ,*Talanta*, **1988,**15,1397.
[15] P.B.Chakrawarti, M.Chakrawarti, P.Maini, *J. Indian Chem. Soc.* **2000.** Vol. 77,P-85-87.
[16] V. M. Rao, M.P.Latha, T. S. Rao, G.N. Rao, *J. Indian Chem. Soc*., **2006.** 83, 925-927.
[17] A.S.Rajbhoj , S.T. Gaikwad , T. K.Chondhekar, *J. Indian Chem. Soc.* **2007.**, 84,987-990.
[18] T.Sakurai, O.Yamauchi, A.Nakahara, *Bull. Chem. Soc. Japan*, **1977.**50,1776.
[19] R. Griesser, H.Sigel, *Helv. Chim. Acta*., **1967.**50,1842.