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A study on ternary complexes involving drugs and amino acids of cadmium metal

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ABSTRACT

Equilibrium studies on metal ligand complex system involving cadmium metal with drugs, (2S)-1-(3-mercapto-2-methyl propionyl)-L- proline i.e. captopril and 4-[2-hydroxy- 3(1-methyl ethyl amino) propoxy] benzene acetamide i.e. atenolol with alanine, phenyl alanine and methionine in 50%(v/v) alcohol-water mixture at 30±0.1°C and ionic strength of 0.1M $NaClO_4$ has been made. Formation of complex species have been evaluated by computer program SCOGS and discussed by Irving-Rossoti technique.

Key words: cadmium, amino acids ternary complexes.

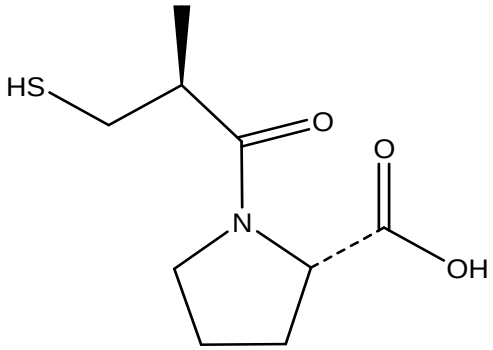
INTRODUCTION

Drugs have special importance in biochemical systems as they are used to cure an ailment caused due to microorganisms. Drugs have N, O, S which can be used to form metal ligand complexes. The affinity of metals towards sulphur containing ligand was attributed towards reduced steric hindrance and increase in polarization of sulphur atom [1]. The metal complexes of Cu (II), Cd (II) and Ni (II) with sulphur containing ligand showed by IR spectra that the co-ordination takes place through both sulphur and oxygen as potential donors [2]. It has been shown that the stability of transition metals decreases as the group changes from –SH to –OH to $–NH_2$ [3]. Captopril is a sulpha drug which is widely used in treatment of arterial hypertension [4]. Atenolol is ß-adrenoceptor blocking agent. Its principle effect is to reduce cardiac activity by diminishing ß-adrenoceptor stimulations. This property is used in treatment of angina. Both these drugs have ability to bind metals by form N, O and S to form metal chelates. Interesting results have been reported earlier on complex formation reactions on oxygen, nitrogen and oxygen-nitrogen mixed donor ligands [5-13]. Expecting some useful information on mixed ligand complexes of such ligands a detailed p^H metric study involving captopril and atenolol with cadmium metal has been made and the results are discussed.

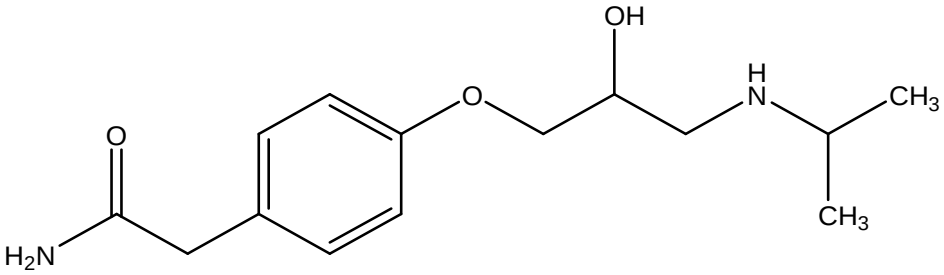
MATERIALS AND METHODS

All the reagents used were of A.R. grade and all the solutions were prepared in doubly distilled water and standardized by usual procedure [14]. The titrations were carried out using a digital pH meter [Elico model LI-120] in conjunction with combined electrode. All titrations were carried out at 30±0.1°C. For the determination of formation constants of ternary complexes following solutions were prepared.0.008M perchloric acid, 0.002M primary ligands (drugs), 0.002M secondary ligands (amino acids), 0.002M metal solutions and an ionic strength of 0.1M sodium perchlorate. The experimental data which were obtained from titration utilized to analyze the proton ligand formation constants of primary and secondary ligand and their metals. Concentration of total metal, total ligands, free metal free ligands and various possible species that are formed during the complexation are calculated

using SCOGS program [15]. Complex formation equilibria were elucidated with the aid of the species distribution curves obtained as computer output [16]·



(2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid ie.captopril



(RS)-2-{4-[2-Hydroxy-3-(propan-2-ylamino)propoxy]phenyl} acetamide ie. atenolol

RESULTS AND DISCUSSION

Binary complexes

By following Irving Rossoti technique the protonation constants p^{K1} and p^{K2} of drugs (captopril and atenolol), amino acids (alanine, phenyl alanine and methionine) and their stepwise metal ligand formation constants (log $K_1$and log K_2) have been determined (Table1) From the titration, complete formation of MR (charges are omitted for the sake of simplicity) is found to occur at lower pH and they are stable at higher pH.

Table1: Proton -ligand and metal - ligand stability constants

	Ligands	pK_1	pK_2	Log K_1	Log K_2
Drugs	Captopril R_1	3.85	10.68	10.03	7.96
	Atenolol R_2	9.00	-	-	3.10
Amino acids	Alanine L_1	3.23	9.90	5.00	4.01
	Phenylalanine L_2	3.01	9.18	4.06	3.45
	Methionine L_3	3.28	9.30	4.70	3.45

The complexing tendency of cadmium metal is found to be more with captopril than atenolol. In captopril the higher equilibrium constant of metal ligand interaction is because the sulphur containing donor captopril binds the metal through mercapto group. The lower pK of –COOH group than any saturated aliphatic acid is because the amide group present near the carboxylic group is having a tendency of electron withdrawal by mesomeric effect. Slight enhancement in the dissociation constant pK_2 can be justified by partial steric hindrance associated with mercapto group. In atenolol the only one pK observed for atenolol can be attributed to dissociation of conjugated acid formed by interaction of secondary amine and perchloric acid which is used as a medium of titrating mixture. However the observed pK is somehow lower than that of dimethylamine. The lower value of metal ligand interaction is because no inductive or field effect is operative. The hydroxyl group present in the structure is alcoholic and hence the complex formation expected at much higher pH 18.0, which cannot be determined by this technique. Therefore atenolol shows only one pK which is association constant of –NH groups. The amino (NH_2) group present in the structure is so neutral that it cannot dissociate.

Mixed ligand complexes

The stability of mixed ligand complexes is mainly governed by the characteristics of the approaching secondary ligand .The stability therefore depends mainly on the ring size which affects the overall basicity of the secondary ligand .It can inferred that the stability of complex depends more on the length and spatial configuration of the chelate ring than on the acidity of the complexing agent. At the pH of secondary ligand combination, the formation of mixed ligand can be represented by equilibria (1) & (2)

M (aq) + R -------- MR (1)
MR + L ---------MRL (2)

(Charges are omitted for simplicity)

Only 1:1:1 ternary complex have been used in this study to ensure the exclusive formation of the simplest ternary complex MRL. Considering the pK values of the ligands and hydrolytic constants of M^{2+}ions the following species have been considered to exist in the complexation equilibria.

M^{2+}, RH_2, RH, R^{2-}, M $(OH)_2$, MR (OH), MR, L^{2+}, ML (OH), $L^{2-}$and MRL (OH)

The relative stabilities of mixed ligand complexes can be quantitatively expressed in terms of Δ log K, K_r, K_R and K_L values which are defined by equations.

$$\Delta \log K = \log \beta_{111} - \log K_{10} - \log K_{01} \quad (3)$$

$$K_r = \beta_{111}^{\ 2} / \beta_{20}\ \beta_{02} \quad (4)$$

$$K_R = \beta_{111} / \log K_{10} \quad (5)$$

$$K_L = \beta_{111} / \log K_{01} \quad (6)$$

Type I Total number of species -9

$C_1 = H_2R \rightleftharpoons H\ R + H$ (1a)

$C_2 = H\ R \rightleftharpoons H + R$ (1b)

$C_3 = H_2L \rightleftharpoons H\ L + L$ (2a)

$C_4 = H\ L \rightleftharpoons H + L$ (2b)

$C_5 = Cd + R \rightleftharpoons Cd\ R$ (3a)

$C_6 = Cd\ R + R \rightleftharpoons Cd\ R_2$ (3b)

$C_7 = Cd + L \rightleftharpoons Cd\ L$ (4a)

$C_8 = Cd\ L + L \rightleftharpoons Cd\ L_2$ (4b)

$C_9 = Cd + R + L \rightleftharpoons Cd\ RL$ (5a)

(Charges are omitted for brevity)

In Cd L_1R_1(Fig. 1) system the primary ligand captopril (R_1) and secondary ligand alanine (L_1) both form 1:1 and 1:2 complexes with Cd (II). Mixed ligand complex of captopril (R_1) with alanine (L_1) shows following types of equilibria.

The formation of ternary complexes also takes place by the reaction

CdR + L → CdRl (6a)
CdL+ R → CdRL (7a)

The other way of the characterizing these ternary complexes in by the disproportion reaction represented by the following equilibria

$CdL_2 + CdR_2 \rightarrow 2\ CdLR$ (8)

This reaction is for the system conaining ligand which form 1:1 and 1:2 complexes individually with the metal ion. The other form of reaction are

$CdR_2 + CdL \rightleftharpoons CdRL + CdR$ (9)

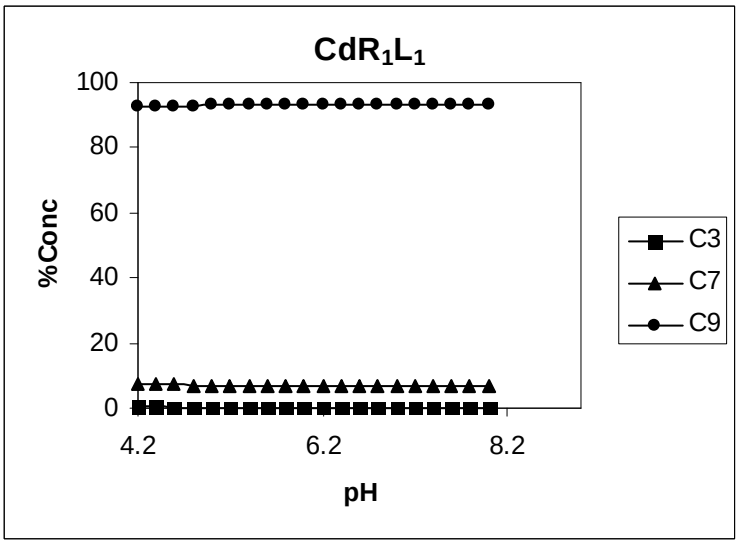
$CdL_2 + CdR \rightleftharpoons CdRL + CdL$ (10)

$CdR + CdL \rightleftharpoons CdRL + Cd$

Therefore reaction (9) and (10) correspond to the systems containing one ligand which forms only 1:1 complex and other forms both 1:1 and 1:2 complexes. The equilibrium reaction (11) represents the system containing the ligand which form 1:1 binary complex with the metal ion.

The species distribution curve points to the fact that formation of ternary complex is about 93% from pH 4.2 and remains constant at pH 8.0. The formation of binary species CdR is 7.3%and remains constant up to pH 8.0.The constant value of the concentration of ternary species during the entire pH range shown by percent distribution curve of ternary species indicates that the formation of complex takes place by reaction (5a).

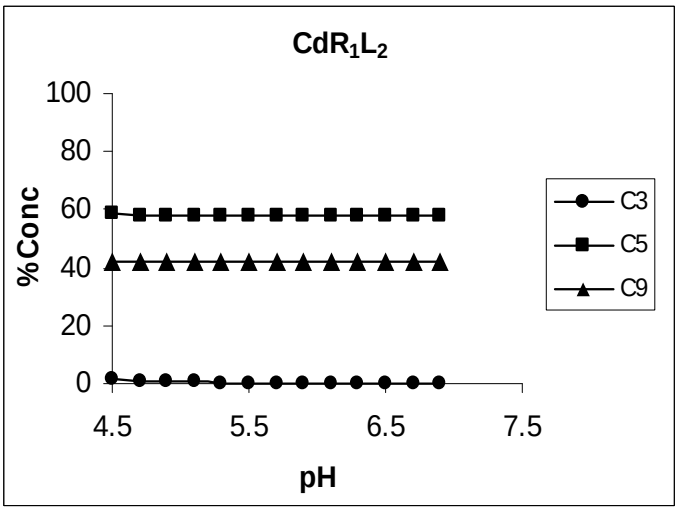
The comparison of $ß_{111}$ values with $ß_{20}$ and $ß_{02}$ of these systems reveals the preferential formation of ternary complexes over binary ones. The low values of K_R and K_L show more stability of ternary complexes with respect to binary complexes of primary and secondary ligands. The positive value of K_r also confirms the stability of mixed ligand complexes. The negative value of Δ log K reveals that the stability of mixed ligand complex is comparable with 1:2 complex of binary species. The 1:2 complexes is less stable than the stability of 1:1 complex. Hence the stability of mixed ligand is less than stability of 1:1 complex. Hence negative values of Δ log K.



(Species C_1, C_2, C_4, C_6, C_7, C_8, have very low concentration so the curves of these species are approx. on x axis)

Fig. 1

In the Cd R_1L_2 (Fig 2) system, it is observed that the primary ligand $R_1$and secondary ligand L_2 form both 1:1 and 1: 2 complexes with Cd (II). The positive values of K_R, K_L and Kr confirm the stability of ternary complexes The low values of K_r also indicate low stability of ternary complexes. The negative value of Δ log K of these complexes is compared with the 1:2 complexes which is less stable than 1:1 complex in binary species.

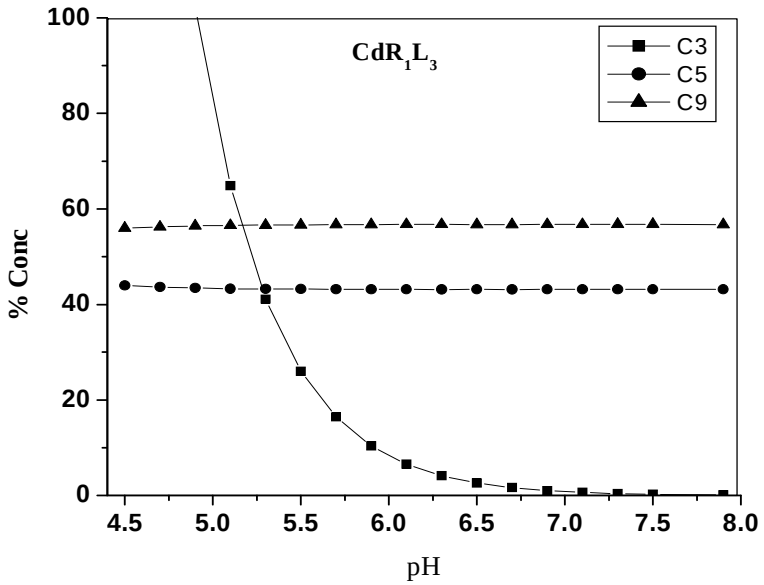


(Species C_1, C_2, C_4, C_6, C_7, C_8, have very low concentration so the curves of these species are approx. on x axis)

Fig. 2

The species distribution curve of to CdR_1L_2 system. Shows that the per ml concentration of HL is negligible ie. ≈ 2 at pH 4.5 and reduces to zero at pH 5. The concentration of CdR is 59% at pH 4.5 and remains constant at pH 6.9 which is shown by parallel straight line to the x-axis. The percent formation of the ternary complex remains constant ≈ 42% at pH 4.5 to 6.9 which is shown by straight parallel line to the x-axis. The constant value of the ternary complex in the complete pH range indicates its formation by reaction (5a) at the initial stage of the reaction, comparatively higher concentration of C_5 (CdR) species prove its higher stability than the ternary species. Similarly its constant concentration indicates its non involvement in the formation reaction of ternary complex. All other species are meagre in amount which cannot take part in the formation reaction.

It is observed from Fig. 3 that the ternary complexes for Cd R_1L_3 system are formed at relatively higher pH regions. The primary R_1 and secondary ligand L_3 both form 1:1 and 1:2 complexes with Cd (II). The species distribution diagram for CdR_1L_3 system points to the fact that the concentration of binary species is 44% at initial pH 4.5 and remains constant throughout till 7.9 which is shown by straight parallel line to x-axis. The mixed ligand formation takes place upto 56% and remains constant throughout the pH range. The ternary complex formation may take place by the reaction involving Cd, R and L species by reaction (5).



(Species C_1, C_2, C_4, C_7, C_8, have very low concentration so the curves of these species are approx. on x axis)

Fig. 3

The K_R and K_L species show positive values which reveal the preferential formation of ternary complexes over binary ones. The negative Δ log K values reveal the stability of mixed ligand with 1:2 complexes of binary species.

The stability of mixed ligand is less than the stability of complex. Hence the Δ log K has negative value.

Mixed ligand complex of atenolol (R_2) with alanine (L_1) shows following types of equilibria.

Type II Total number of species -7

$C_1 = HR \rightleftharpoons H + R$ (1a)

$C_2 = HL \rightleftharpoons H\,L + H$ (2a)

$C_3 = HR \rightleftharpoons H + R$ (2b)

$C_4 = Cd + R \rightleftharpoons Cd\,R$ (3a)

$C_5 = Cd + L \rightleftharpoons Cd\,L$ (4a)

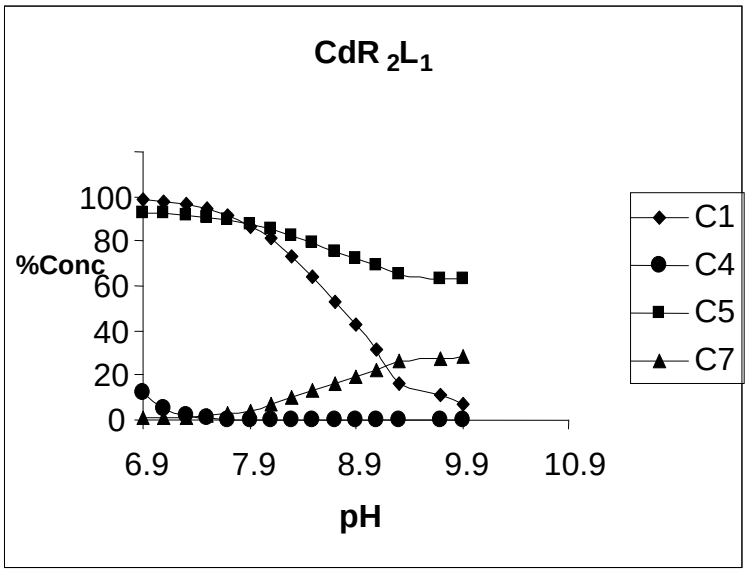
$C_6 = Cd\,L + L \rightleftharpoons Cd\,L_2$ (4b)

$C_7 = Cd + R + L \rightleftharpoons Cd\,R\,L$ (5a)

(Charges are omitted for brevity)

In CdR_2L_1 (Fig. 4) system, the primary ligand forms 1:1 complexes and the secondary ligand forms 1:1 and 1:2 complexes with Cd(II).It has been observed that the stability of mixed ligand complexes of captopril are found to be higher than the mixed ligand complexes of atenolol which is shown in Table2. The positive values of K_R, $K_L$and K_r show the stable nature of mixed ligand complexes but these complexes are less stable than the 1:1 complexes of binary ones hence we get negative values of Δ log K.

The species distribution diagram reveals the preferential formation of ternary species over binary species of primary and secondary ligands. The species R, which is 100% initially, goes on sharply decreasing to about 10% at pH 9.9. The concentration of CdR increases to 4.5 % at pH 9.9 and also the concentration of binary species CdL which is 96% at pH 6.3 slowly decreases to 84%. From these observations it is clear that R is used in the formation of CdRL with increasing pH.

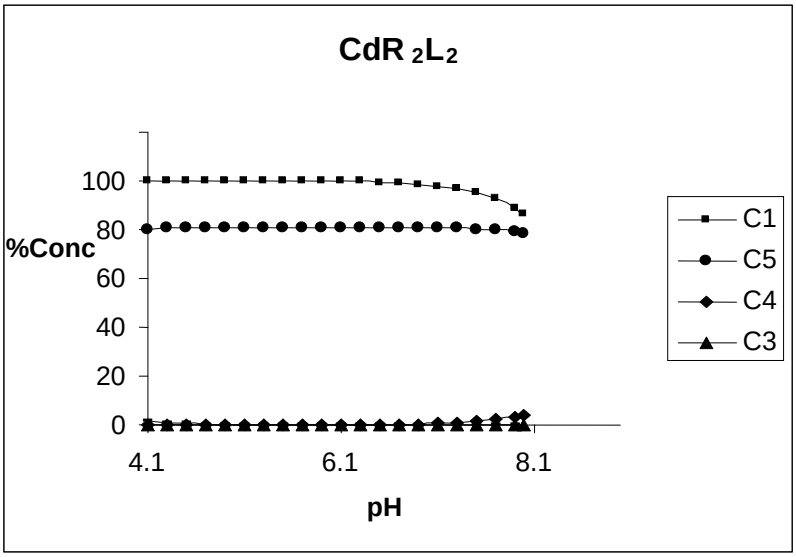


(Species C_2, C_3, C_6, have very low concentration so the curves of these species are approx. on x axis)

Fig. 4

The percentage formation of mixed ligand complex is very less i.e. 9%. The decrease in R to such a large extent may be due to its use in formation of CdR, which also increases with pH and some other species, which cannot be detected by this method.

In Cd R_2L_2(Fig. 5) system, the primary ligand R_2 form 1:1 complex and secondary ligand forms 1:1 and 1:2 complexes with Cd (II). The stability of mixed ligand complexes of phenyl alanine as secondary ligand is less as compared to CdR_1L_2 system. The negative values of Δ log K indicate stability of binary complex over as over ternary ones. For the system formation of ternary complex does not take place. The binary complex formation of primary ligand is preferred over ternary complex. The initial concentration of R is 100% which is decrease very slowly to 87% and CdL. The conc. Of HR at pH 4.1 which is ≈2% remaince in same and at pH 8.0 the concentration of CdR, which is ≈2% at pH 4.1 reduces to zero which is 80% initially also decreases very slowly to 78%.



(Species C_6, C_7, have very low concentration so the curves of these species are approx. on x axis)

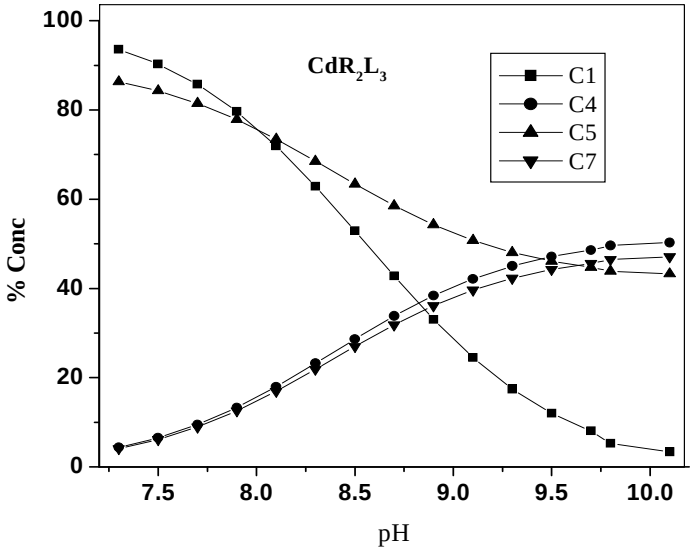
Fig. 5

In CdR_2L_3 (Fig. 6) system the primary ligand forms 1:1 and secondary ligand forms 1:1 and 1:2 complexes with cadmium. The percentage distribution curve shows similar nature as earlier systems

In the species distribution diagram the concentration of R which is 94% initially decreases rapidly to 34% and the concentration of CdL which is 86% decreases slowly to 43% at pH 10.10. The concentration of CdR_2L_3 complexes is 4 at pH 7.30 increases upto 47% at pH 10. Considering decrease in R and CdL species it can be seen that the formation of CdRL is increasing during the same pH range in such a way so as to compensate for the decreasing amounts of R and CdL. From the above discussion it is clear that the formation of CdRL is favoured by the reaction involving CdL and R species and to some extent by disproportionation reaction (11). Similarly decrease (7a) in concentration of R and increase in of CdR species indicate the involvement of R to some extent in formation of CdR.

Table 2 Stability constants of ternary complexes

R	L	$ß_{111}$	$ß_{20}$	$ß_{02}$	K_R	K_L	K_r	ΔlogK
Captopril (R_1)	Alanine (L_1)	15.02	17.99	9.01	4.99	10.02	1.11	-0.65
	Phenyl alanine (L_2)	12.84	17.99	7.51	2.81	8.78	1.14	-1.89
	Methionine (L_3)	13.23	17.99	8.15	3.20	8.53	1.10	-2.14
Atenolol (R_2)	Alanine (L_1)	7.60	3.10	9.01	4.50	2.60	1.25	-0.50
	Phenylalanine (L_2)	5.85	3.10	7.51	2.75	1.79	1.10	-1.31
	Methionine (L_3)	7.80	3.10	8.15	4.70	3.10	1.38	0.00



(SpeciesC_2, C_3, C_6, have very low concentration so the curves of these species are approx. on x axis)

Fig. 6

CONCLUSION

The stability of mixed ligand complex with respect to secondary ligands in captopril complexes $L_1>L_3>L_2$ and in atenolol complexes is $L_3>L_1>L_2$. The stability of ternary complexes is mainly governed by the characteristics of the approaching secondary ligand. The stability therefore depends on the ring size which is offsets the overall basicity of the secondary ligand. It can therefore be inferred that the stability of ternary complexes depend much more on the length and spatial configuration of the chelate ring flow on the acidity of the complexing agent. The stability constants of ternary complexes were found to be greater in R_1 than in R_2.The higher stability of R_1 complex may be due to the extra stabilization of five membered ring and also because it is a sulpha drug. The low stabilization of R_2 complexes may be due to its only one dissociation constant. The Δ log K values were less negative or positive. This may be attributed to the Π-acidic character of drugs and O-N coordination of amino acids.

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REFERENCES

[01] O. Prochazkova, J. Podlahova and J. Podlaha Colin, *Czech Chem. Comm*., **1973**, 38, 1120.
[02] P. Petras, J. Podlahova and J. Podlaha Colin, *Czech chem. Comm*., **1973**, 38, 3321;
[03] S. E. Livingston, *Quart.Rev*. **1965**, 19, 388.
[04] C. Nachev, *Intern. Medicine Bulgaria*, 1985, 24, 1.
[05] D. D Perrin,Stability Constants of Metal Ion Complexes,"Pergamon, New York.**1979**.
[06] J. Springborg and I. Stofte, *Acta, Chem. Scand.*, **1997**, 51, 357.
[07] K. Varnagy, J. Szabo, I. Sovago, G. Malandrinos, N. Hadjiliadisi, Sanna and G. Micera, *J. Chem. Soc. Dalton* Trans., **2000**;467,
[08] S. Brooker, T. C. Davidson, S. J. Hay, R. J. Kelley, D. K. Kennepohl., P.G Plieger, B. Mubaraki, K. S. Murray, E. Bill and E. Bothe, *Coord. Chem. Rev*, **2001**, 3, 216;
[09] K. Oaz, K. Varnagy, J. Sovago, L. Lennert, H. Suli, Varga,D. Sanna and Micera, *New J, Chem*., **2001**,25,7001;
[10] D. Sanna, C, G.Agoston, I. Sovago and G.Micera *Polyhedron*, **2001**, 20,937;
[11] M. Singh and R. Nayan, *Asian J. Chem*., **1996**, 8, 470,.
[12] A. Kumar, S. Jain and S.K. Tiwari, *J. Inorg. Nucl. Chem*., **1975**, 37, 2439.
[13] C. Furlani, M. L. Luciani and R. Chanderi, *J. Inorg. Chem*., **1968,** 30, 3121.
[14] G.A. Nelson, M. P. Crawford and B. J. Geddes, *Inorg. Chem*., **1970**, 9, 1123.
[15] I.G. Sayce, *Talanta*, **1988**, 15, 1397.
[16] R. Nayan and A. K. Dey, *Ind. J. Chem. Sec*. A., **1976**, 14, 892.