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Complexation behavior of the antibacterial drugs Oxytetracycline,Cefotaxime and Ceftriaxone along with amino acids towards cobalt(II) in aqueous solution

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Abstract: The stability constant of the mixed ligand complexes of cobalt (II) metal ion withantibacterial drugs Oxytetracycline hydrochloride, Cefotaxime sodiumand Ceftriaxone sodium as primary ligand and the eight amino acidsglycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine as secondary ligands were determined pH metrically in 20%(v/v) ethanol-water medium at 25°C and at an ionic strength of 0.1 M $NaClO_4$. The formation of complex species has been evaluated by SCOGS computer program and discussed in terms of various relative stability parameters.

Keywords: Stability constant, antibacterial drugs, amino acids, pH metry, mixed ligand complexes, ionic strength,SCOGS computer program.

Introduction: Chemistry of drugs attracts many researchers because of its application in medicinal study.The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity.The metal complexes of drugs play an important role in drug action and metabolism. Metal Complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc.Amino acids are the structural unit of proteins. These are essential constituents of all living cells and contain one or more amino and carboxylic groups and have good coordination sites for the metal complexation.

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In continuation of our earlier work with complexation of medicinal drugsand amino acids[1-3], it was thought of interest to study ternary complexes of cobalt metal ion with antibacterial drugs Oxytetracycline hydrochloride(OTC), Cefotaxime sodium(CFO)and Ceftriaxone sodium(CFT)as primary ligand and a series of eight aminoacids viz. glycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine as secondary ligandsin 20% (v/v) ethanol-water medium at 25°C and at an ionic strength of 0.1 M $NaClO_4$.

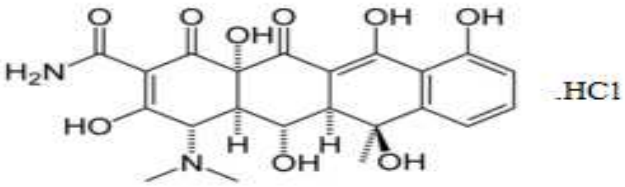


Figure1: Oxytetracycline hydrochloride (molecular formula $C_{22}H_{25}N_2O_9Cl$)

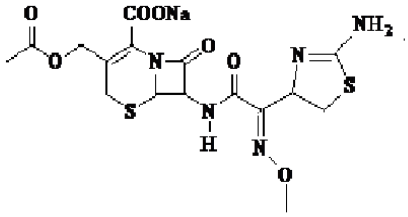


Figure2: Cefotaxime sodium (molecular formula $C_{16}H_{16}N_5O_7NaS_2$)

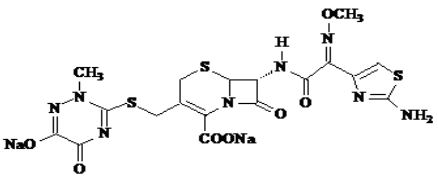


Figure3: Ceftriaxone sodium(molecular formula $C_{18}H_{16}N_8O_7Na_2S_3$)

Experimental:

Materials and Solution: The ligand OTC,CFOandCFTare soluble in 20% (v/v) ethanol-water mixture.NaOH,$NaClO_4$,$HClO_4$ & metal salts were of AR grade.The solutions used in the potentiometric titration were prepared in double distilled water.The NaOH solution was standardized against oxalic acid solution (0.1M)and standard alkali solution was again used for standardization of $HClO_4$.The metal salt solutions were also standardized using EDTA titration[4].All the measurements were made at 25°C in 20% ethanol-water mixture at 0.1M$NaClO_4$ strength. The thermostat model SL-131 was used to maintain the temperature constant.The pH measurement were made using a digital pH meter model Elico L1-120 in Conjunction with a glass and reference Calomel electrode (reading accuracy ±0.01) The pH-meter was adjusted with buffer of pH 4.00,7.00 and 9.18.

Potentiometric procedure: For evaluating the protonation constant of the ligand & the formation constant of the complexes in 20%ethanol-water mixture with different metal ions, we prepared the following six sets of solutions.

(i) $HClO_4$ (A)

(ii) $HClO_4$+Drug (A+ L)

(iii) $HClO_4$+Drug+ Metal (A+ L+ M)

(iv)$HClO_4$+Amino acid (A+ R)

(v) $HClO_4$+Amino acid + Metal (A+ R+ M)

(vi) $HClO_4$+Drug +Amino acid + Metal (A+L+R+ M)

The above mentioned sets prepared by keeping M:L: Rratio, the concentration of perchloric acid & sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was

made upto 50ml with double distilled water. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded until stable values, within ± 0.002 pH units were obtained.Graphs were obtained by plotting pH vs volume of NaOH added.These data were used to determine the pKa of ligands and logK values of metal complexes of primary and secondary ligands. The equilibrium constants of ternary complexes were calculated by using SCOGS program.The total concentrations of metal ions, free metals, free ligands and various possible species that are formed during complexation were obtained as computer output of program.

Table 1: Proton-ligand stability constant and metal-ligandstability constantof antibacterial drugs and amino acids with Co (II) at 0.1M ionic strength in 20% (v/v)ethanol-water medium

Ligands	Proton-ligand stability constant PK_1 PK_2	Metal-ligandstability constant $logK_1$ $logK_2$
Oxytetracycline	--- 4.316	3.7723.019
Cefotaxime	3.15610.764	5.5234.889
Ceftriaxone	4.093 10.741	4.7084.129
Glycine	2.4729.582	5.0343.786
DL -Alanine	2.3649.658	3.7532.999
Glutamic acid	2.5014.416	2.8592.697
DL -Isoleucine	2.6549.624	4.4063.158
DL -Methionine	2.3039.079	4.7983.395
DL-β-Phenyl alanine	2.2559.174	4.4413.408
DL -Serine	2.3448.983	4.1732.942
DL -Valine	2.4889.501	4.5783.368

Table 2: Parameters based on some relationship between formations of mixed ligand complexes of Co (II) with OTC (L_1)drug and amino acids

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	Δlogk
Glycine	8.8014	6.7906	8.8197	5.0298	3.7679	1.1276	-0.004
DL -Alanine	6.0239	6.7906	6.7515	2.2523	2.2711	0.8897	-1.501
Glutamic acid	6.3050	6.7906	5.5557	2.5334	3.4458	1.0214	-0.326
DL -Isoleucine	6.9289	6.7906	7.5639	3.1573	2.5227	0.9654	-1.249
DL -Methionine	8.5690	6.7906	8.1934	4.7974	3.771	1.1438	-0.0006
DL-β-Phenyl alanine	7.2138	6.7906	7.8488	3.4422	2.7729	0.9855	-0.999
DL -Serine	6.6930	6.7906	7.1152	2.9214	2.5196	0.9626	-1.252
DL -Valine	8.0994	6.7906	7.9456	4.3278	3.5214	1.0993	-0.250

Table 3: Parameters based on some relationship between formations of mixed ligand complexes of Co (II) with CFO (L_2)drug and amino acids.

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	Δlogk
Glycine	9.0519	10.4115	8.8197	3.5289	4.0184	0.9414	-1.5046
DL -Alanine	8.0306	10.4115	6.7515	2.5076	4.2778	0.9358	-1.2452
Glutamic acid	8.1299	10.4115	5.5557	2.6069	5.2707	1.0183	-0.2523
DL -Isoleucine	9.6731	10.4115	7.5639	4.1501	5.2669	1.0763	-0.2561
DL -Methionine	10.3206	10.4115	8.1934	4.7976	5.5226	1.1094	-0.0004
DL-β-Phenyl alanine	8.9632	10.4115	7.8488	3.4402	4.5223	0.9817	-1.0007
DL -Serine	8.6949	10.4115	7.1152	3.1719	4.5215	0.9922	-1.0015
DL -Valine	9.6030	10.4115	7.9456	4.0800	5.025	1.0462	-0.4980

Table 4: Parameters based on some relationship between formations of mixed ligand complexes of Co (II) with CFT (L_3)drug and amino acids.

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	Δlogk
Glycine	9.4887	8.835	8.8197	4.7812	4.4552	1.0749	-0.2523
DL -Alanine	8.4598	8.835	6.7515	3.7523	4.707	1.0855	-0.0005
Glutamic acid	6.8152	8.835	5.5557	2.1077	3.956	0.9472	-0.7515
DL -Isoleucine	8.9220	8.835	7.5639	4.2145	4.5158	1.0881	-0.1917
DL -Methionine	7.7554	8.835	8.1934	3.0479	2.9574	0.9109	-1.7501
DL-β-Phenyl alanine	9.1479	8.835	7.8488	4.4404	4.7070	1.0966	-0.0005
DL -Serine	8.3805	8.835	7.1152	3.673	4.2071	1.0508	-0.5004
DL -Valine	8.0354	8.835	7.9456	3.3279	3.4574	0.9577	-1.2501

Result and Discussion:

Binary complex:Theproton ligand stability constants (pKa) of drugs and amino acids were calculated by point wise and half integral method.The metal ligand stability constant (logK) of Co(II) transition metal complexes with antibacterial drugs were calculated by using Calvin Bjerrum titration techniques as adopted by Irving and Rossotti[5]. Titration curves were obtained for different sets.During titration no precipate was formed indicating that there is no tendency to form hydroxo complexes.The stability constants of the formed complexes were investigated in the pH range of 3-6.The mean value the average number of protons associated with the ligand $\bar{n}_A$, at different pH values were calculated.The pKa values were determined from $\bar{n}_A$. Similarly $\bar{n}$ i.e metal ligand formation number,which can be defined as average number of ligand molecules co-ordinated to the metal ions,were also obtained using Irving & Rossotti method. The $\bar{n}$ values obtained between 0.2 to 0.8 indicates 1:1 complexation and when $\bar{n}$ lies in between 1.2 to 1.8 indicate 1:2 complexation.The values of proton ligand stability constants(pKa) and metal ligand stability constant (logK) are represented in **Table 1**. Since we got $\bar{n}_A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formation.The order of $logK_1 > logK_2$ is commonly observed.The reason is statistical effect,statistically coordination of a second molecule is difficult when compare to the first due to availability of less number of coordinating sites on the metal ion for the second ligand.Irving and Rossotti have proposed a relation between the stability of the complexes and basicity of the ligand by equation

$$logK = apK + b$$

The relation graph shows a straight line and the value of slope should be unity for a series of closely related ligand.In the present study such relationship do not exists since the antibacterial drugs (ligand) OTC,CFO andCFT used are of diverse in nature.

Mixed ligand complexes:The formation of 1:1:1 mixed ligand complex were identified by the pH of precipitation of ML, MR and MLR titration curves.These curves indicate the higher value of pH of precipitation of ternary system than corresponding binary systems.The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of ΔlogK, Kr, K_L, and K_R values which are defined by equations:

$$\Delta logK = log\beta_{111} - (logK_{10} + logK_{01}) \qquad (1)$$

$$K_r = \frac{\beta_{111}^2}{(\beta_{20}\beta_{02})} \qquad (2)$$

$$K_L = \frac{\beta_{111}}{logK_{10}} \qquad (3)$$

$$K_R = \frac{\beta_{111}}{logK_{01}} \qquad (4)$$

Where

β_{111} - Equilibrium constant of ternary system.

β_{20}- Overall stability constant of primary complexs.

β_{02} - Overall stability constant of secondary complexs.

The equilibrium constantsβ_{111} of ternary systems of Co(II) transition metal ion and relative stability parameters are shows in **Table 2-4**.The ternary complexes of cobalt metal ions

with CFO-DL-methionineshows higher values of stability whereasOTC-DL-alanineternary complexesshows low values of stability.This may be attributed to the aliphatic nature of secondary ligand, steric effect and chelation formation.The order of stability of equilibrium constantsβ_{111} of ternary systems of Co(II) transition metal ion with respect of secondary ligand is as

OTC:gly > methio > val > β-phenyl ala > isoleu >serine>glut acid >alanine.

CFO: methio>isoleu > valine > gly > β-phenyl ala > serine> glut acid> alanine.

CFT:gly > β-phenyl ala >isoleu > alanine >serine > valine > methio > glut acid.

The comparison of $\beta_{111}$with β_{20} and β_{02} of these systems reveals the preferential formation of ternary complexes over binary complexes. The low positive values of K_L and K_R indicatesless stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands.The Krvalues arepositive but less,whichindicates lower stability of ternary complexes[6].This 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 noncoordinated charge group of ligands[6].The negative values of ΔlogK have been found in all systems, which show the formation of ternary complex but less stable and destabilized nature of complexes which has been reported in N and O coordination of amino acids[7]. The higher negative values than statistical values (-0.4) found in some system indicates relatively less stable complexes with square planar geometry of

ternary complexes.The negative value of ΔlogK does not mean that the complex is not formed.The negative value may be due to the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance,electronic consideration,difference in bond type, geometrical structure etc.

Sigel concluded that the experimentally determined valueΔlogK < -0.6 indicate less stabilitization in ternary complexes. The ΔlogK value of some system is higher than the statistically expected value, showing the stabilized nature of the ternary complex.Thompson and Lorass pointed out that more negative ΔlogK value of ternary complexes is due to the electrostatic repulsion between the negative charge on the ligand and amino acids. steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand coordinates with the metal ion in the lower pH range and form 1:1 and 1:2 complex.In solution,ternary complex forms as the titration curve run below the Co (II)-drug titration curve. So, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Co(II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Co(II) metal ion and thus reduces the stability of ternary complexes.

Species distribution curves:Accordingto the result given by SCOGS computer programme, the concentration of different species distributed are as follows:

$$C_1 = HL \rightleftharpoons H + L \qquad (1a)$$

$$C_2 = H_2R \rightleftharpoons HR + H \qquad (2a)$$

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

$$C_4 = Co + L \rightleftharpoons CoL \qquad (3a)$$

$$C_5 = CoL + L \rightleftharpoons CoL_2 \qquad (3b)$$

$$C_6 = Co + R \rightleftharpoons CoR \qquad (4a)$$

$$C_7 = CoR + R \rightleftharpoons CoR_2 \qquad (4b)$$

$$C_8 = Co + L + R \rightleftharpoons CoLR \qquad (5)$$

The species distribution curves of Co(II)LR systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH of solution as shown in figure(4).In all Co(II)LR ternary systems, primary as well as secondary ligands forms 1:1 and 1:2 binary complexes.The species distribution curves of free metal(M),free ligands L and R indicates that there is a slowly decrease in concentration of free metal ions with increase in pH whereas increase in concentration of ligands with pH and indicates higher percentage concentration of FL than FR.The species distribution diagram of various possible species ofCo(II)LR system shows the formation of mixed ligand complexes. The concentration for the formation of drug (L) and HR continuous decrease with increasing pH. The concentration of MLRspecies continuously increases, confirm the formation of ternary complexesCo(II)LR.

Figure 4: Species distribution curve of Co (II) LR_1 system (pH versus % conc.of various possible species)

Fig 4a: Co (II)-OCT- glycine

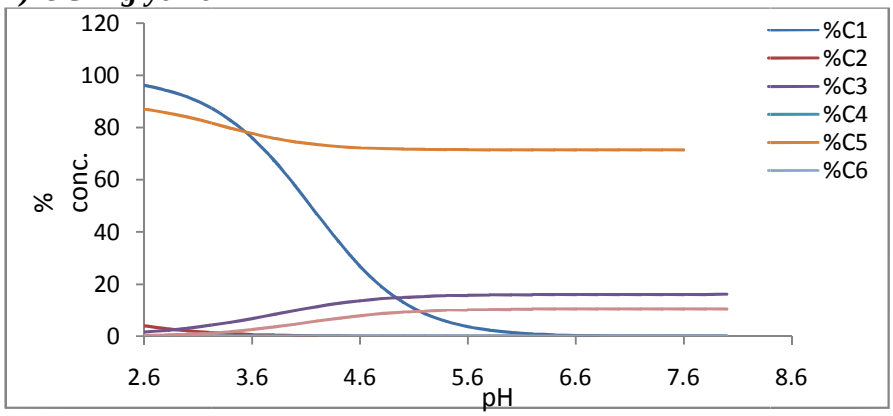


Fig 4b: Co (II)-CFO-glycine

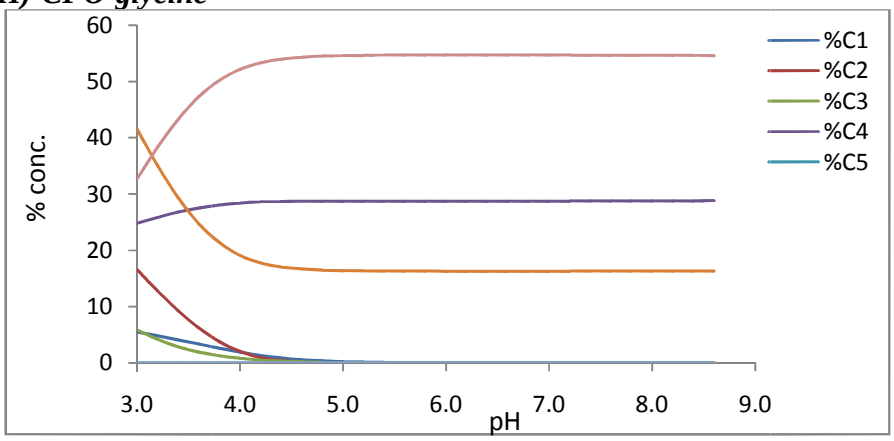
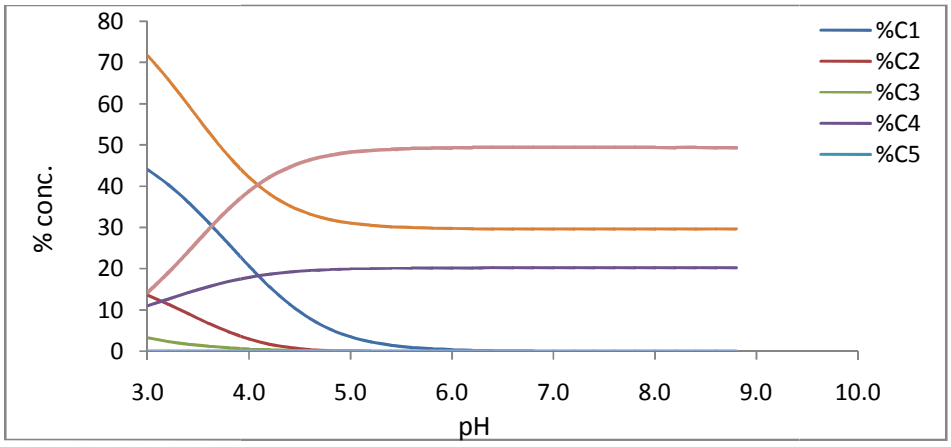


Fig 4c: Co (II)-CFT-glycine



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