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Mixed ligand complexes of zinc metal ion with antibacterial drug Oxytetracycline hydrochloride and amino acids in aqueous media

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Abstract:

The stability constant of the mixed ligand complexes of zinc(II) ion withantibacterial drugOxytetracycline hydrochloride as primary ligand and eightaminoacidsglycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-â-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 bySCOGS computer program and discussed in terms of various relative stability parameters.

Keywords : Stability constant, antibacterial drug, amino acids, mixed ligand complexes.

Introduction :

Metal complexes of drugs are found to

be more potent than parent drugs.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.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.In continuation of earlier work with complexation of antibacterial drug[1-7], we study ternary complexes of zinc metal ion with antibacterial drug Oxytetracycline hydrochloride (OCT)as primary ligand and eight amino acidsas secondary ligands in 20% (v/v) ethanol-water medium at 25 °C and at an ionic strength of 0.1 M $NaClO_4$.

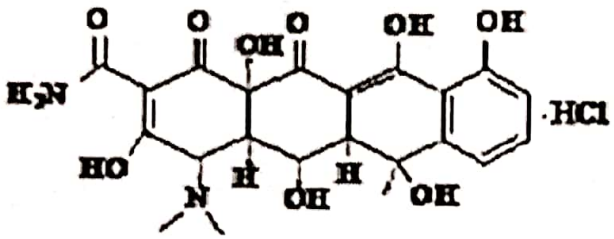


Figure1: Oxytetracyclinehydrochloride (molecular formula $C_{22}H_{25}N_2O_9Cl$)

Experimental:Materials and Solution:

The ligand OCT is soluble in ethanol. 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.All the measurements were made at 25°C in 20% ethanol-water mixture at 0.1M$NaClO_4$ strength. The thermostat 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. The pH-meter was adjusted with buffer of pH 4.00,7.00 and 9.18.

pHmetric 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.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 drug OCT and amino acids with zinc(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 $logK_1$ $logK_2$
Oxytetracyclinehydrochloride	--- 4.316	3.909 3.107
Glycine	2.4729 582	5.5254 239
DL -Alanine	2.3649 658	4.4923 561
Glutamic acid	2.5014 416	2.9212 744
DL -Isoleucine	2.6549 624	6.9605 071
DL -Methionine	2.3039 079	4.8833 655
DL-β Phenyl alanine	2.2559 174	4.8634 056
DL -Serine	2.3448 983	4.6443 476
DL -Valine	2.4889 501	5.1494 175

Table 2: Parameters based on some relationship between formations of mixed ligand complexes of Zn (II) with OCTdrug and amino acids

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	?logk
Glycine	8.0239	7.1058	9.7634	4.0246	2.4992	0.9513	-1.5001
DL -Alanine	6.9912	7.1058	8.0529	2.9919	2.4992	0.9224	-1.5001
Glutamic acid	5.6699	7.1058	5.6647	1.6706	2.7489	0.888	-1.2504
DL -Isoleucine	9.7089	7.1058	12.029	5.7096	2.7492	1.0148	-1.2501
DL -Methionine	8.6319	7.1058	8.538	4.6326	3.7488	1.1036	-0.2505
DL-β-Phenyl alanine	8.8605	7.1058	8.918	4.8612	3.998	1.1059	-0.0013
DL -Serine	7.1424	7.1058	8.1205	3.1431	2.4981	0.9382	-1.5012
DL -Valine	8.6485	7.1058	9.3243	4.6492	3.4991	1.0528	-0.5002

Result and Discussion:*Binary complex*:

Theproton ligand stability constants (pKa) of drug and amino acids were calculated by point wise and half integral method.The metal ligand stability constant logK of Zn(II) transition metal complexes with antibacterial drugs were calculated by using Calvin Bjerrum titration techniques as adopted by Irving and Rossotti. 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 4-6.The mean value the average number of protons associated with the ligand . $\bar{n}_A$ different pH values were calculated.The pKa values were determined from $\bar{n}_A$ Similarly . $\bar{n}$ .e metal ligand formation number,which can be defined as average number of ligand molecules co-ordinated to the metal $\bar{n}_A$ ions, were also obtained using Irving &Rossotti method. T- he 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 constantspKaand metal ligand stability constant logKare 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 $\log K_1 > \log K_2$ 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.The standard deviation for various metal ligand system is 0.036. Irving and Rossotti have proposed a relation between the stability of the complexes and basicity of the ligand by equation

$$\text{Log } K = apk + b$$

The relation graph shows a straight line and the value of slope should be unity for a series of closely related ligand.

***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:

$$\Delta\log K=\log B_{111}-(\log K_{10}+\log K_{01}) \quad (1)$$

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

$$K_L = \frac{\beta_{111}}{log\, K_{10}} \quad (3)$$

$$K_R = \frac{\beta_{111}}{log\, K_{01}} \quad (4)$$

Where β_{111} is the equilibrium constant of ternary system.

β_{20} is the overall stability constant of primary complexs.

β_{02} is the overall stability constant of secondary complexs.

The equilibrium constants β_{111} of ternary systems of Zn(II) transition metal ion and relative stability parameters are shows in **Table 2**.The ternary complexes of zinc metal ions with DL-isoleucine shows higher values of stability whereas glutamic acid ternary 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 constants β_{111} of ternary systems of Zn(II) transition metal ion with respect of secondary ligand is

OCT: isoleucine >β-phenyl alanine >valine >methionine >glycine >serine >alanine >glut.acid

The comparison of β_{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 Krvalue ispositive but less,whichindicates lower stability of ternary complexes.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 groups of ligands.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.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.

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 Zn(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 Zn(II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Zn(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:

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

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

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

$$C_4 = M + L \rightleftharpoons ML \quad (3a)$$

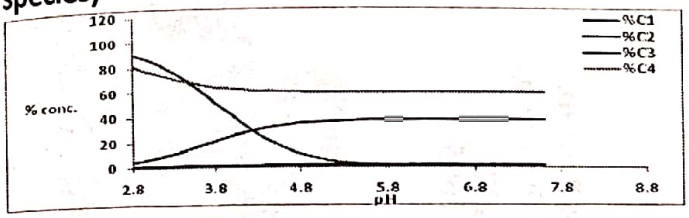
$$C_5 = M + R \rightleftharpoons MR \quad (4a)$$

$$C_6 = M + L + R \rightleftharpoons MLR \quad (5)$$

The species distribution curves of Zn(II)LR systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH

of solution as shown in **figure 2**.In Zn(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 ofZn(II)LR system shows the formation of mixed ligand complexes.The concentration for the formation of drug (L) and HR represented by C_1 and C_2show continuous decrease with increasing pH. The concentration of C_6species continuously increases, confirm the formation of ternary complexesZn (II)LR.

Figure 2: Species distribution curve of Zn (II) LR_4 system(pH versus % conc.of various possible species)



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