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Mixed Ligand Complexes of Cadmium Metal Ion with Diphenhydramine and Amino Acids in Aqueous Media

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Abstract:

In the present study the stability constant of the mixed ligand complexes of Cd (II) ion with drug Diphenhydramine as primary ligand and eight amino acids glycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine as secondary ligands were determined potentiometric technique in 20% (v/v) ethanol-water medium at 27 °C and at an ionic strength of 0.1 M NaClO4. The formation of complex species has been evaluated by SCOGS computer program and discussed in terms of various relative stability parameters.

Keywords: stability constant, Diphenhydramine drug, amino acids, mixed ligand complexes.

Introduction:

Diphenhydramine is first generation antihistamines mainly used to treat allergies. It has a powerful hypnotic effect and often it is used as a nonprescription sleep aid and a mild anxiolytic and antipsychotics. It is also used to treat motion sickness, insomnia, cough, nausea and phenothiazine drug induced abnormal muscle movement. The physical properties of medicinal drug Diphenhydramine are shown below:

Sr.No.	Physical property	Value
1	Molecular weight	291.855 g/mol
2	Phase	Solid (at STP)
3	Melting point	188 ºC
4	Boiling Point	343.7 ºC
5	Density	1.024 g/cm3
6	Colour	White
7	Solubility	Soluble in water [3.06 mg/ml (at 27 °C)

In continuation of earlier work with complexation of medicinal drug[1-30], we study ternary complexes of Cd metal ion with medicinal drug Diphenhydramine {2-(diphenylmethoxy)-*N,N*-dimethyl ethanamine hydrochloride}as primary ligand and eight amino acids as secondary ligands in ethanol-water media at 27 °C and at 0.1M $NaClO_4$ ionic strength.

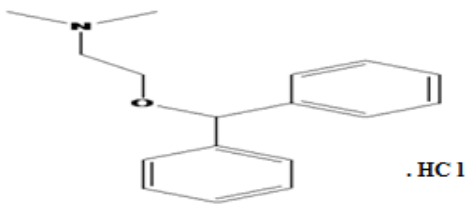

Figure 1: Diphenhydramine hydrochloride (molecular formula $C_{17}H_{22}ClNO$)

Experimental: Materials and Solution:

The ligand Diphenhydramine (DPH) is soluble in water. NaOH, $NaClO_4$, $HClO_4$ & metal salts were of AR grade. The solutions used in the pH metric 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 27 $^{\circ}$C in 20% ethanol-water mixture at 0.1M $NaClO_4$ strength. The thermostat was used to maintain the temperature constant. The pH measurements 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.

pH metric 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: R ratio, the concentration of perchloric acid & sodium perchlorate were kept constant for all sets. The volume of every mixture was made upto 50 ml with double distilled water. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded. 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.

Table 1: Proton-ligand stability constant and metal-ligand stability constant of drug DPH and amino acids with Cd (II) at 0.1M ionic strength in ethanol-water media.

Ligands	Proton-ligand stability constant		Metal-ligand stability constant		
	pK_1	**pK_2**	**$logK_1$**	**$logK_2$**	***logβ***
Diphenhydramine	…….	9.3814	3.5699	3.5476	7.1175
DL-Alanine	2.5336	9.8082	4.2567	3.0844	7.3411
Glycine	2.5660	9.7850	4.5527	3.0878	7.6405
Glutamic acid	2.2732	4.4116	2.8519	2.8266	5.6785
DL-Isoleucine	2.5141	9.7599	4.3226	3.2796	7.6022
DL-Methionine	2.0793	9.3410	3.8005	3.0706	6.8711
β-Phenyl alanine	2.2552	9.0546	4.0265	3.3512	7.3777
DL-Serine	2.1152	9.1066	4.4659	3.6178	8.0837
DL-Valine	2.5923	9.6759	4.1585	3.2113	7.3698

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

Amino Acid	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	**ΔlogK**
DL-Alanine	7.5684	7.1175	7.3411	3.9985	3.3117	1.0469	-0.2582
Glycine	6.8599	7.1175	7.6405	3.29	2.3072	0.9296	-1.2627

Glutamic acid	6.4183	7.1175	5.6785	2.8484	3.5664	1.0031	-0.0035
DL-Isoleucine	6.6379	7.1175	7.6022	3.068	2.3153	0.9019	-1.2546
DL-Methionine	5.6142	7.1175	6.8711	2.0443	1.8137	0.8026	-1.7562
β-Phenyl alanine	6.3414	7.1175	7.3777	2.7715	2.3149	0.8749	-1.255
DL-Serine	6.7832	7.1175	8.0837	3.2133	2.3173	0.8924	-1.2526
DL-Valine	6.4732	7.1175	7.3698	2.9033	2.3147	0.8936	-1.2552

Result and Discussion:

I. Binary complex: The proton 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 Cd(II) transition metal complexes with Diphenhydramine drug 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 $\bar{n}_A$, 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 $\bar{n}_M$ values obtained between 0.2 to 0.8 indicates 1:1 complexation and when $\bar{n}_M$ 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 $\log K_1 > \log K_2$ 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.

II. 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. The equilibrium constants of ternary systems of Cd (II) transition metal ion and relative stability parameters are shows in **Table 2**. The ternary complex of cadmium metal ions with alanine (7.5684) shows higher values of stability whereas methionine (5.6142) ternary complexes show 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 of ternary systems of Cd(II) transition metal ion with respect of secondary ligand is
DPH: alanine> gly.> serine > isoleucine > valine > glut. acid> β-phenyl alanine > methionine

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 indicates less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The Kr value is positive but less, which indicates 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 non coordinated 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 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 Cd (II)-drug titration curve, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Cd (II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Cd (II) metal ion and thus reduces the stability of ternary complexes.

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

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

$C_2 = HR \rightleftharpoons H + R$ (2)

$C_3 = M + L \rightleftharpoons ML$ (3)

$C_4 = M + R \rightleftharpoons MR$ (4)

$C_5 = M + L + R \rightleftharpoons MLR$ (5)

The species distribution curves of Cd(II)LR systems were obtained by plotting percentage concentration of various possible species formed during complexation vs pH of solution as shown in **figure 2**. In Cd(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 Cd (II)LR system shows the formation of mixed ligand complexes. The concentration for the formation of drug (L) and HR represented by C_1, C_2 and C_4 show continuous decrease with increasing pH. The concentration of C_5 species continuously increases, confirm the formation of ternary complexes Cd (II)LR as shown in **figure 3**.

Conclusion:

The *KL, KR* and *Kr* values are positive, which indicates lower stability of ternary complexes. The negative values of *ΔlogK have* been found in all systems, which show the formation of ternary complex but less stable. The negative value of *ΔlogK* 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.

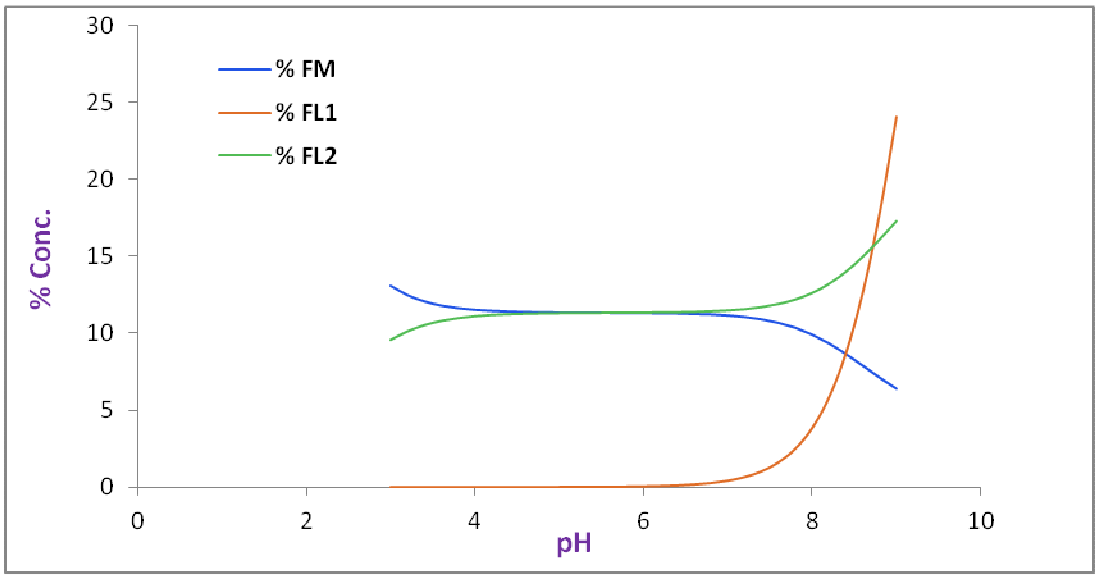

***Figure 2*: Species distribution curve of [Cd (II) L_1R_2] system (pH versus % conc. of free metal free ligand)**

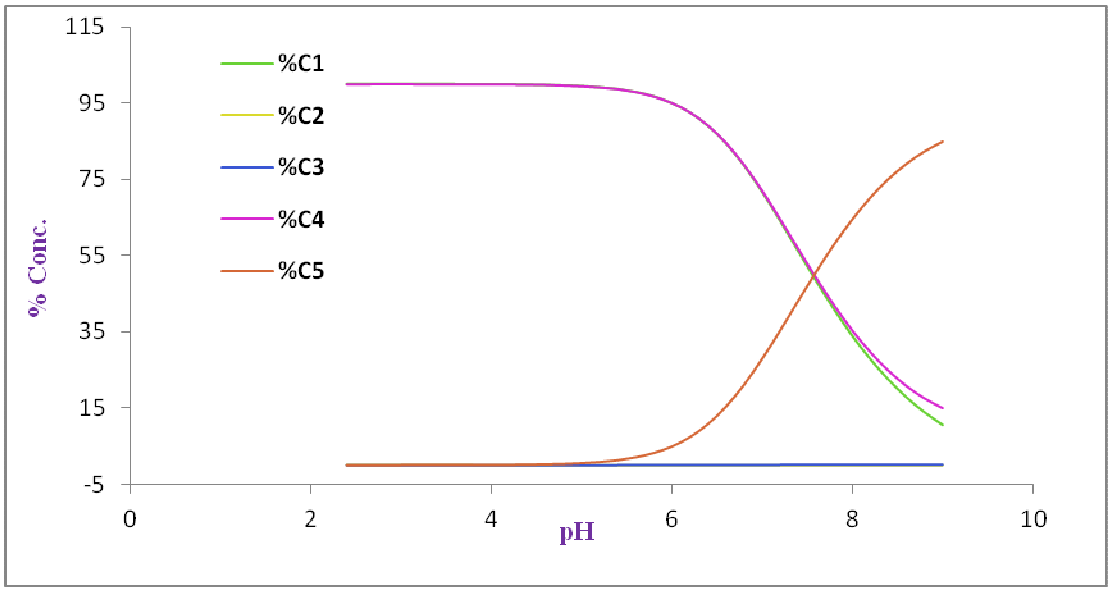

***Figure 3*: Species distribution curve of [Cd (II) L_1R_2] system (pH versus % conc. of various possible species)**

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