Research Article

EQUILIBRIUM STUDIES ON MIXED LIGAND COMPLEXES OF DRUG INDAPAMIDE WITH CHROMIUM AND COBALT METAL IONS

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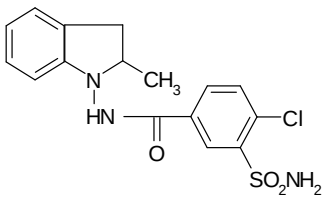
ABSTRACT

Equilibrium studies on metal-ligand complex equilibria involving Chromium and Cobalt metal ions with drug, Indapamide with Amino acids Glycine and Glutamic acid in 80% (v/v) ethanol-water mixture at 30°C ± 0.1°C and ionic strength of 0.1M ($NaClO_4$) has been studied. Formation of complex species with respect to pH have been discussed by Irving-Rossotti technique and evaluated by SCOGS computer program.

Keywords: Equilibrium constant, Ionic strength, pH, ΔlogK, SCOGS.

INTRODUCTION

Drugs have various functional groups present in its structure, which can bind to metal ions present in human body[1]. Metal complexes of drugs are found to be more potent than parent drugs[2]. Chemistry of drugs attracts many researchers because of its applications in medicinal study. Interesting results have been reported earlier on complex formation reactions of drug-amino acid-metal ion mixed ligand complexes[3-7]. Expecting some useful information on mixed ligand complexes a detailed pH metric study involving drug Indapamide with Chromium and Cobalt metal ions has been carried out and discussed with results.



Indapamide

MATERIALS AND METHODS

All the reagents used were of A.R. grade and all the solutions were prepared in 80 %(v/v) ethanol-water mixture and standardized by known procedures[8]. Titrations were carried out using a digital pH meter (Elico model LI-127) in conjunction with combined electrode. All titrations were carried out at 30°C ± 0.1°C temp. All sets of solutions were titrated against 0.4N sodium hydroxide solution. The titration curves were plotted by using the experimental data. On the basis of these plots, proton-ligand and metal-ligand formation constants were calculated. Concentrations of total metal, total ligands, free metal, free ligands and various possible species that are formed during the complexation are calculated by using SCOGS computer program[9, 10].

RESULTS AND DISCUSSION

Binary Complexes

Indapamide[11-16] is a mild diuretic and antihypertensive agent. It is the lipid soluble moiety, which distinguishes the activity of Indapamide from other diuretics. It has been shown to be a potent long acting antihypertensive agent when used along- with other therapeutic agents. The accepted chemical name for Indapamide is 3-(Aminosulfonyl)-4-chloro-N-(2, 3-dihydro-2-methyl-1H-indol-1-y1) benzamide.

The protonation constants K_1^H and K_2^H of drug Indapamide, amino acids Glycine and Glutamic acid and their metal-ligand formation constants (K^H_{ML} and K^{ML}_{ML2}) have been determined (Table 1).

Table 1: Proton-ligand and metal-ligand stability constants in binary system

Ligands	K_1^H	K_2^H	$Cr^{III}(M_1)$		$Co^{II}(M_2)$	
			log K_1	log K_2	log K_1	log K_2
Indapamide (L)	3.23	9.97	7.28	3.49	7.09	3.59
Glycine (R_1)	2.78	9.89	9.95	3.91	8.85	4.91
Glutamic acid (R_2)	4.75	9.82	12.52	--	9.18	7.38

Indapamide drug molecule contains three different nitrogens. The calculated pK 3.23 can be assigned to amino nitrogen which readily undergoes the protonation in presence of acidic condition and subsequently deprotonates. The pK 9.97 can be assigned to amido group which undergoes self-deprotonation since it is connected to carbonyl group on one side and protonated nitrogen on other side, which stabilizes the corresponding nitrogen anion produced due to self-deprotonation.

Alongwith $K_1^H$and K_2^H values, also the stepwise metal-ligand formation constants of the ligands were determined for comparison with ternary systems. The complexing tendency of Cr^{III} metal is found to be more than Co^{II}. It shows that Cr^{III} forms more stable five

membered chelate ring[17] with drugs used than other metal ions, it is due to higher charge on metal ion and smaller size[18, 19].

Mixed ligand complexes

Complexes in which metal ion has two or more types of ligands in its coordinating sphere are called as mixed ligand complexes. The study of ternary complexes in solution provides simpler models for more complicated biochemical reactions[20-23]. Only 1:1:1 ternary complex have been used in this study to ensure the exclusive formation of the simplest ternary complex MLR. By considering the proton-ligand and metal-ligand constants of ligands, the species that exist in complexation equilibria have been plotted as a function of pH.

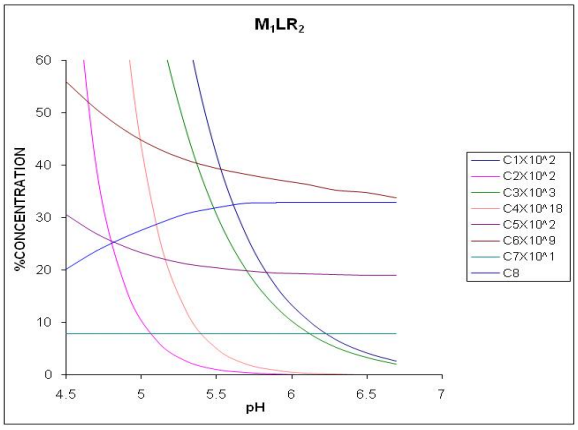


Figure 1: Species distribution curve for M_1LR_2 system

It can be observed from Fig. 1 that mixed ligand curve of $Cr(III)LR_2$ increases in the pH range of 4.5 to 5.9 with increase of pH. Whereas, the concentration for the formation of C_1 and C_3 shows continuous decrease with increasing pH which indicate the formation of $Cr(III)L_4R_1$ complex and represented by C_8. Moreover, the maximum percentage of the formation of ternary complex is less than that of $Cr(III)R_2$ binary complex and more than Cr(III)L binary complex, this indicates that the ternary complex is less stable as compared to $Cr(III)R_2$ binary complex and more stable than Cr(III)L binary complex.

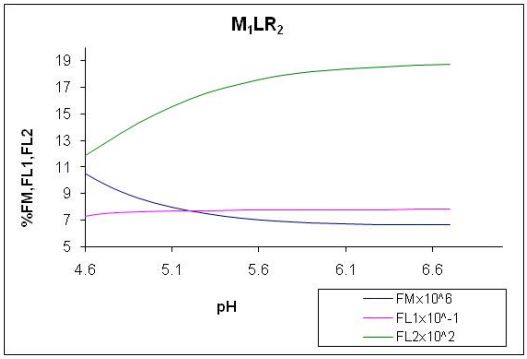


Figure 2: Percentage distribution curve for M_1LR_2system

Fig.2 shows that percentage distribution curve of free metal decreases with increase of pH, which indicates the involvement of metal ion in the complex formation process. Percentage concentration of free ligands FL_1 and FL_2 increases with increase of pH and this increase may be due to dissociation of ligand present in the system.

CONCLUSION

The relative stabilities of the binary and ternary complexes are quantitatively expressed in terms of β_{111},β_{20},β_{02}, K_L, K_R, K_r and ΔlogK values which are presented in Table No.2. The comparison of $\beta_{111}$with β_{20} and β_{02} of this system shows preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The considerably low positive value of K_L and K_R indicate less stability of ternary complex with respect to that of primary and secondary ligands. The Kr value of this complex is positive but less which indicate lower stability of ternary complex. The ΔlogK value of this system indicates less stability of ternary complex.

Table 2: Stability constants of ternary complexes of Drug Indapamide

Metal ion	Amino Acid	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	ΔlogK
Cr(III)	Glycine	14.48	10.77	13.86	7.20	4.53	1.17	-2.75
	Glutamic acid	15.81	10.77	12.52	8.52	3.28	1.36	-4.01
Co(II)	Glycine	13.14	10.68	13.77	6.04	4.27	1.07	-2.81
	Glutamic acid	17.13	10.68	16.56	10.04	7.94	1.25	0.86

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