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EQUILIBRIUM STUDIES ON CALCIUM (II) COMPLEXES WITH DRUG - PHENYLPROPANOLAMINE HYDROCHLORIDE AND AMINO ACIDS - GLUTAMINE AND PHENYLALANINE

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ABSTRACT

Equilibrium studies of the mixed ligands complexes of calcium (II) ion with drug phenylpropanolamine hydrochloride as primary ligand and the amino acids viz. glutamine and phenylalanine as secondary ligand were determined pH metrically at 30°C at ionic strength of 0.1 M $NaClO_4$ in 80% (v/v) ethanol-water medium. Formation of complex species with respect to pH have been discussed by Irving-Rossotti technique and evaluated by SCOGS computer program.

Key words: Equilibrium constant, Δ log K, Mixed ligand complexes, SCOGS.

INTRODUCTION

Phenylpropanolamine hydrochloride[1-4] belongs to the sympathomimetic amine class of drugs. The effects of it are largely the result of alpha adrenergic agonist activity resulting from direct stimulation of adrenergic receptors and release of neuronal norepinephrine. It was widely used as a decongestant and it has been used as an anorectic agent for over 40 years. Glutamine is acidic glycogenic amino acid[5]. Phenylalanine[6] is aromatic essential glucogenic and ketogenic amino acid. In metabolism phenylalanine is converted into tyrosine.

Calcium occurs in the body in large amount than any other mineral elements. The biological functions include its influence on biological calcification, structural role, muscle contraction, nerve impulse, transmission release of hormone, and activation of blood clotting

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enzymes, rhythm of heartbeats and permeability of gap junctions. Literature survey reveals that no work has been reported on complex tendencies of drug phenylpropanolamine hydrochloride with Ca (II) metal ion in ethanol-water solution. Therefore in order to understand the complex formation tendencies of phenylpropanolamine hydrochloride,it was decided to determine the formation constants (1 : 1 : 1 ternary complexes) for phenyl propanol amine hydrochloride with calcium (II) in presence of amino acids in 80% (v/v) ethanol-water medium at 30^{o}C at a fixed ionic strength 0.1 M $NaClO_4$.

EXPERIMENTAL

Drug sample of phenylpropanolamine hydrochloride in pure form were obtained from pharma industries. Ethanol was purified as described in literature[7]. Double distilled water was used for the preparation of ethanol-water mixture and stock solution of phenylpropanolamine hydrochloride. All chemicals used were AR grade. $NaClO_4$ (0.1 M) and NaOH solution was prepared in carbondioxide free double distilled water. Carbonate free NaOH was standardized by titrating with oxalic acid. $HClO_4$ Reidal (Germany) was used for the preparation of the stock solutions of Ca (II) to prevent hydrolysis and standardized by using standard EDTA solution[8]. Experimental procedure by potentiometric titration technique, involves the titration of carbonate free solution of (1) Free $HClO_4$ (A), (2) Free $HClO_4$ + Ligand-Drug, (3) Free $HClO_4$ + Ligand-Drug + Metal ion, (4) Free $HClO_4$ + Ligand-Amino acid, (5) Free $HClO_4$ + Ligand-Amino acid + Metal Ion, (6) Free $HClO_4$ + Ligand-Drug + Ligand-Amino acid + Metal Ion, against standard solution of sodium hydroxide, with drug phenylpropanolamine hydrochloride and amino acids. The ionic strength of solutions was maintained constant i.e. 0.1 M by adding appropriate amount of 1M sodium perchlorate solution. Titrations were carried out at 30^{o}C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO_2. pH meter reading in 80% (v/v) ethanol-water corrected by method of Vanuitert and Hass[9]. Formation constants of ternary complexes were determined by computational programme SCOGS[10].

RESULTS AND DISCUSSION

(a) Binary metal complexes

Proton ligand constant and metal ligand stability constant of phenylpropanolamine hydrochloride and amino acids with Ca (II) determined in 80% (v/v) ethanol-water mixture

at 30°C and ionic strength 0.1 M $NaClO_4$ are given in Table 1.

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

Ligands	K_1^H	K_2^H	Ca^{II} (M) log K
Phenylpropanolamine hydrochloride (L)	3.81	9.60	3.27
Glutamine (R_1)	3.51	9.85	3.17
Phenylalanine (R_2)	3.46	9.29	3.15

(b) Ternary metal complexes

To visualize the nature of the equilibria and to evaluate the calculated stability constants of ternary complexes Ca (II) –phenylpropanolamine hydrochloride – amino acids, species distribution curves have been plotted as a function of pH using SCOGS programme. It can be observed that the concentration of Ca (II) - phenylpropanolamine hydrochloride amino acids such as Glutamine increases from pH 2.9 whereas phenylalanine from pH~ 3.8. The concentration of this species continuously increases; confirm the formation of ternary complexes. From the SCOGS distribution curve it is concluded that the formation of ternary complex started only after the metal primary ligand complex has attained its maximum concentration. This indicates metal primary ligand complex Ca (II)- phenylpropanolamine hydrochloride is formed first then the secondary ligands such as Glutamine & Phenylalanine coordinated to it, resulting the formation of ternary complex. Moreover the maximum percentage of the formation of ternary complexes of phenylpropanolamine hydrochloride is more than that of the Ca (II) amino acids Glutamine and less than of Ca (II) phenylpropanolamine hydrochloride. This indicates that ternary complex is less stable as compare to binary complex. The relative stabilities of the binary and ternary complexes are quantitatively expressed in terms of β_{111}, $\beta_{20,}$ β_{02}, K_L, K_R, K_r and Δ log K value which are represented in Table 2.

Table 2: Stability constants of ternary complexes of Phenylpropanolamine HCl

Metal ion	Amino acid	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	Δ log K
Ca (II)	Glutamine	6.05	3.27	3.17	2.77	2.87	1.87	-0.40
	Phenylalanine	6.23	3.27	3.16	2.95	3.06	1.93	-0.21

The comparison of β_{111} with β_{20} and β_{02} of this system shows that preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The considerably low value of K_L and K_R indicates less stability of ternary complexes with respect to that of primary as well as secondary ligands. The K_r value of this complex is positive but less which indicates lower stability of ternary complexes. Results of the present investigations show that the stability constant of ternary complexes formed are less stable. The negative ΔlogK value of this system indicates that the ternary complex is less stable than binary complex. This is in accordance with statistical considerations. The negative value of ΔlogK is due to the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance[11-14], electronic consideration, difference in bond type, geometrical structure etc. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand phenylpropanolamine hydrochloride coordinates with the metal ion in the lower pH range and form 1 : 1 complex, entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Ca (II)-phenylpropanolamine hydrochloride complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Ca (II) metal ion and thus reduces the stability of ternary complexes.

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