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EQUILIBRIUM STUDIES ON MIXED LIGAND COMPLEX FORMATION OF ANTIPARASITIC DRUG SULPHADOXINE AND SOME AMINO ACIDS WITH CHROMIUM (III).

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ABSTRACT

A solution studies on the complex formation of chromium (III) with drug sulphadoxine and some amino acids pH metrically in 80 % (v/v) ethanol-water medium at fixed ionic strength of $NaClO_4$.

KEYWORD: Complex formation, amino acids, chromium and SCOG.

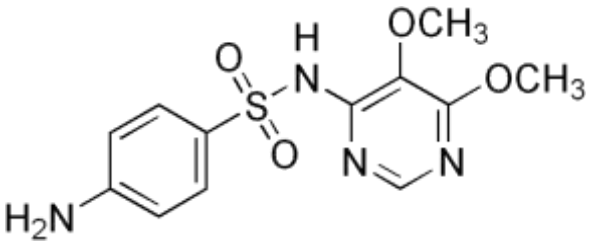
INTRODUCTION:

The metal ions are integral parts of enzymes and play an important role in the biological system, such as to trigger a reaction, control reaction mechanism, stabilize protein structure, maintain structure of cell walls etc. Latest information indicates regulation of metabolism and growth of animal cell is dependent upon the mobilization of divalent and trivalent metal ions. Chromium is a first transition series element. Its abnormal electronic configuration might be play mysterious role in the biological systems. It is widely distributed throughout the body.[1-6] Intake of chromium in minute quantity leads to the glucose tolerance in the body of human being. Infants have a higher chromium concentration than adults. Brewer's yeast is rich in chromium and most grains and cereal products contain significant quantities. Chromium is absorbed poorly in the diet. It is absorbed mainly in the small intestine by pathways. It appears to share with zinc. It is transported to tissues, bound to 'transferrin' and appears in the liver mitochondria, microsomes and cytosol. Chromium is essential ultra trace metal and needed for potentiating of insulin action on carbohydrate and lipids; active as a bioorganic chromium complex. The deficiency of chromium causes insulin resistance. Chromium plays an important role in carbohydrate, lipid and protein metabolism.

It is a true potentiator of insulin and is known as glucose tolerance factor (GTF). Trivalent chromium has been claimed to be a constituent of glucose tolerance factor. Chromium supplementation in deficient diets decreases serum cholesterol levels and prevents atheromatous plaque formation in arota. When given with insulin in chromium deficiency state, it improves amino acid incorporation mainly with α- amino isobutyric acid, glycine, serine and methionine. In protein energy malnutrition (PEM) states, chromium supplementation is beneficial for weight gain. Chromium functions in vivo as an organic chromium complex and biological role to potentiate insulin activity.

Sulphadoxine is an antibacterial, antimalarial drug[7-8] in combination with pyrimethamine. There are several drugs used for the treatment of malaria such as quinine, quinacrine, chloroquine, hydroxychloroquine pamaquine, primaquine, mefloquine, Halofantrine and sulphadoxine in combination with pyrimenthamin.

Pyrimethamine is a potent inhibitor of dihydrofolate redcutase.[9] The drug has been shown to have a significantly higher affinity for binding to the dihydrofolate reductance of plasmodium than host enzyme and as a result has been used selectively to treat plasmodium infections combined with a long chain sulphadoxine which blocks dihydrofolate synthesis, similar to that reported for treatment of bacterial infection.



The present investigation deals with the pH metric studies on chromium (III) metal complexes with sulphadoxine and amino acids in 80% (v/v) ethanol-water medium by SCOG method.

MATERIALS AND METHODS

The nitrates of chromium, of A.R. grade were obtained from B.D.H. (India). Sodium porchlorate (E.Merck) was dissolved in carbon dioxide free distilled water. The solution of sodium hydroxide was also prepared in carbonate free distilled water. The solution was used as titrant for the pH metric titration. As a routine, the solution was standardized at least once

every day by titrating with standard oxalic acid solution. Perchloric acid of Reidal (Germany) was used for the preparation of the stock solution. Its exact normality was obtained by titrating it conductometrically using standard sodium hydroxide solution. Amino acids from Merck (Germany) or Fluka (Germany) were prepared by dissolving A.R. grade sample in 80% (v/v) ethanol – water medium. Drugs such as sulphadoxine were prepared by dissolving as received as sample in 80% (v/v) ethanol-water medium. Drugs samples in pure form were obtained from pharmacy industries.

The experimental procedure[10-11], in the study of ternary metal complexes by the pH metric titration technique, involves the titrations of carbonate free solution of against standard sodium hydroxide, where D and R, are the two ligands. The ionic strength of the solutions was maintained constant i.e. 0.1 M by adding appropriate amount of 1M sodium perchlorate solution. The titrations were carried out at 27^0C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO_2.The experimental procedure, in the study of ternary metal complexes by the pH metric titration technique, involves the titration of carbonate free solution of in 80 % (v/v) ethanol-water. The formation constant of ternary complexes were determined by computational programmed SCOGS.

I	Free $HClO_4$ (A)
II	Free $HClO_4$ (A) + Sulphadoxine (D)
III	Free $HClO_4$ (A) + Sulphadoxine (D) + Chromium ion (M)
IV	Free $HClO_4$ (A) + Amino acids (R)
V	Free $HClO_4$ (A) + Amino acids (R) + Chromium ion (M)
VI	Free $HClO_4$ (A) + Sulphadoxine (D) + Amino acids (R)+ Chromium ion (M)

RESULT AND DISCUSSIONS

a. Binary metal complexes

The knowledge of pK of drugs and logK of their binary chelates is necessary for the calculation of the stability constants of ternary chelates. The pK and logK values for most of the amino acid and their chromium complexes are available for aqueous medium in the literature[12-13], however, in the present work these values have been determined in 80% (v/v) ethanol-water medium at 27^0C and μ = 0.1 M ($NaClO_4$), The pK and logK values of drugs and their chromium complexes have been determined under similar conditions. Drugs form mixed ligand complexes with amino acids under consideration. Comparison of binary & ternary constants obtained under identical experimental conditions will lead to precise and

reliable information regarding the extent of stabilisation and destabilisation of the ternary complexes as compared to the corresponding binary complexes. It is therefore necessary to determine binary formation constants for ligands under the same experimental conditions used for the study of ternary complexes.

The proton ligand constant and metal ligand stability constant of drug Sulphadoxine and amino acids with Chromium (III) were determined in 80 % (v/v) ethanol-water mixture at 27°C and ionic strength μ= 0.1 M $NaCl0_4$ and The pK and logK value already published in journal.[14-24] This is here important for the explanation of stability constant of metal drug complexes.

Table No.1

Ligands	PK_1	PK_2	Chromium	
			$Logk_1$	$LogK_2$
Sulphadoxine	7.6012	9.8989	8.1961	-
Glycine	2.7700	9.7400	6.5100	3.9400
Leucine	3.8100	10.3400	7.7078	4.3500
Glutamic acid	3.1360	5.8987	3.5087	3.0419
Glutamine	3.0100	9.2800	7.2486	6.0816
Valine	3.2100	9.8024	5.6122	3.5901
Methionine	3.1200	9.6000	3.1000	-
Phenylalanine	3.1400	9.3000	6.4405	5.3616

b. Ternary Complexes

The complexes, in which the metal ion has two or more types of ligands in its co-ordination sphere, are called as mixed-ligand complexes or ternary complexes. It is generally agreed that the solution containing metal ion & two different ligands (suitable), ternary complexes are formed. The development in the study of mixed- ligand complexes has been very fast in recent years.[25-35] The biochemical reactions taking place in solution involve organic molecules with potential containing sites and also strongly co-ordinating transition metal ions.[36] In living tissues and fluid, the total ligand concentration exceeds the metal concentration, and therefore various complexing species compete for the metal ions present. Under these conditions formation of mixes-ligand complexes is to be expected.[37-39] Ternary complexes [40-45] have been implicated in the storage of metal ions and their transport through membranes in the biological system.[46]

The study of ternary complexes in solution provides simpler models for the more complicated biochemical reactions.[47-58] The synthetic ternary complexes with metal atom bound to two

different ligands mimic the metalloenzymes with the metal ion bridging the carrier ligand and substrate.[59-67]

Mixed Coordination by protein and related substances has been a subject of investigation of many researchers.[68-75] The mixed ligand complexes of the transition metal ions and uranyl ion have been reported in the literature.[76-79] The theoretical principle and the essential mathematics involved in the ternary complex equilibria are reviewed by Marcus and Eliezer[80] and also by beck.[81]

The co-ordination sphere of the central ion arising out of the difference in nature of the donor atoms, leads to the formation of two types of mixed complexes, "mixed donor complexes" and mixed ligand complexes.[82] In the former, donor atoms belong to the same ligand, while in the latter the donor atoms are from different ligands.

The formation of mixed-ligand complexes in solution is a rule rather than an exception. Even if there are apparently only two components in the solution, it can not be called as single ligand complex, since in most cases complexes contains solvent molecules as well as hydroxyl ions as a result of central ion hydrolysis.

Ternary or mixed two ligands complexes are made up of a central ion and two different ligand molecules in addition of solvent molecules required to make up the co-ordination sphere.

The stability of the mixed-ligand complex is measured by the overall formation constant β i.e. according to the equilibrium

$$M + iL + jB \rightleftarrows Ml_i B_j$$

Where M is the metal ion, L and B being either neutral or anionic or cationic ligands. If n= i +j $\leq$ N where n cannot exceed the co-ordination number N, a total of N-n co-ordination sites will be occupied by solvent molecules and 'n' is the level coordination number when ligands are monodentate.

The stepwise and simultaneous mixed-ligand complex formation has been investigated by Sharma and Tandon[83-84] and Ramamoorthy and Santappa[85-86] respectively.

The effect of ionic strength and the dielectric constants has also been reported.[87-90]

In pH metric titration for Cr (III) – Sulphadoxine – Glycine System, mixed ligand curve coincide with sulphadoxine complex curve up to the pH~3.0 and after this pH, it deviates. Theoretical composite curve remains toward left of the mixed ligand complex curve. After pH~3.0, the mixed ligand curve drifts towards X-axis, indicating the formation of hydroxide species. Since the mixed ligand curve coincide with individual metal complex titration curve, the formation of 1:1:1 complex by involving stepwise equilibrium.

The primary ligand drug sulphadoxine forms 1:1 and secondary ligand amino acid glycine form 1:1 and 1:2 complexes with Cr (III). It is evident from the of percentage concentration species of Cr (III) -sulphadoxine and glycine system, that the percentage distribution curve of free metal decreases sharply with increasing pH.

This indicates involvement of metal ion in the complex formation process. Percentage concentration of free ligand FD and FR increases and practically negligible as compared with that of free metal. This increase in percentage concentration may be due to the dissociation of excess ligand present in the system.

To visualize the nature of the equilibrium and to evaluate the calculated stability constant of ternary complexes Cr (III) -sulphadoxine and glycine, species distribution curves have been plotted as a function of pH at temperature 27^0C and μ = 0.1 M $NaClO_4$ using SCOG program. It can be seen from the figure that, the concentration of Cr (III) -D-R increases whereas the concentration for the formation of D and HR continuous decrease with increasing pH which indicates the formation of Cr-D-R. The concentration of this species continuously increases; confirm the formation of ternary complexes.

Species distribution curve of ternary system Cr (III) -sulphadoxine and glycine showed that the formation of ternary complex started at pH ~ 2.8 when Cr (III) at pH ~ 6. Ternary complexes attain their maximum concentration in the pH ~6. From the species 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 that the metal-primary ligand complex Cr (III) -sulphadoxine is formed first and then the secondary ligand glycine get coordinated to it, resulting the formation of ternary complex..

The concentration of species distribution in ternary complexes of sulphadoxin with glutamic acid and methionine show the following types.

C_1 = HD ⇌ D + H

C_2 = H_2R ⇌ HR + H

C_3 = HR ⇌ R + H

C_4 = M+R ⇌ MR

C_5 = MR+R ⇌ MR_2

C_6 = M+D ⇌ MD

C_7 = M+D+R ⇌ MDR

(Where M = Chromium, R = Amino acids & D = drug sulphadoxine.)

The concentration of species distribution in ternary complexes of sulphadoxine with glycine, leucine, glutamine, valine and phenyl alanine show the following types

C_1 = HD ⇌ D + H

C_2 = H_2R ⇌ HR + H

C_3 = HR ⇌ R + H

C_4 = M+R ⇌ MR

C_5 = MR+R ⇌ MR_2

C_6 = M+D ⇌ MD

C_7 = MD + D ⇌ MD_2

C_8 = M+D+R ⇌ MDR

Moreover, the maximum percentage of the formation of ternary complexes is less than that of the Cr (III) -glycine binary complex; and more than Cr (III) -sulphadoxine binary complex, this indicates that the ternary complex is less stable as compare to Cr (III) -R1 binary complex and more stable than Cr (III) -sulphadoxine binary complex.

The relative stabilities of the binary and ternary complexes are quantitatively expressed in term of β_{11}, β_{20}, β_{02}, K_D, K_R, K_r and Δ logK values which are presented in Table.2.

In Cr (III) -D-R system, primary ligand D form only 1:1 and secondary ligand form both 1:1 and 1:2 binary complexes. Therefore this system favors the following disproportion reactions

$MR_2 + MD \rightleftarrows MRD + MR$

$MD_2 + MR \rightleftarrows MRD + MD$

The comparison of β_{11} with β_{20} and β_{02} of this system show that preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The

considerably low positive value of K_D and K_R indicate less stability of ternary complexes with respect to that of primary as well as secondary ligands. The K_r values of this complex are positive but less which indicates lower stability of ternary complexes.

Results of the present investigation show that the ternary complexes formed are less stable. The negative ΔlogK value of this system is due to statistical consideration, stability of binary complexes, reduced number of coordination sites, steric hindrance, electrostatic consideration, difference in bond type and geometrical structure etc. Similarly the amino acids such as leucine, glutamic acid, glutamine , valine, methionine and phenyl alanine are studied.

Parameters based on some relationship between the formation of ternary complexes of Cr (III) metal ion with sulphadoxine in the presence of amino acids (1:1:1) system Temp = 27^0C I = 0.1 M $NaClO_4$ Medium = 80% (V/V) Ethanol-Water.

Table2.

AMINOACIDS	β_{11}	β_{02}	β_{20}	K_D	K_R	K_r	ΔlogK
Glycine	12.9214	10.4500	8.1961	4.7253	6.4114	1.3859	-1.7847
Leucine	13.8976	12.0578	8.1961	5.7015	6.1898	1.3723	-2.0063
Glutamic acid	11.2029	6.5506	8.1961	3.0068	7.6942	1.5193	-0.5019
Glutamine	14.9452	13.3302	8.1961	6.7491	7.6966	1.3885	-0.4995
Valine	13.8094	9.2023	8.1961	5.6133	8.1972	1.5874	0.0011
Methionine	11.2932	3.1000	8.1961	3.0971	8.1932	1.9994	-0.0029
Phenyl alanine	14.1216	11.8021	8.1961	5.9255	7.6811	1.4122	-0.5150

CONCLUSIION

The conclusion drawn from the value of Kr (Statistical relationship) is presented in table 2, which indicates the measure of relative stability of a mixed-ligand complex with respect over all stabilities of binary complexes. From Table 2, it is observed the negative ΔlogK values for ternary systems indicate less stability of complexes.

The orders of stability of ternary complexes of Cr (III) with respect to secondary ligand Glycine Leucine, Glutamic acid, Glutamine, Valine , Methionine and Phenyl alanine for respective primary ligand are, Sulphadoxine = Val> Methi>Gluta >Gluta. acid > Phenyl.ana.>Gly.>Leu.

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