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POTENTIOMETRIC STUDIES ON CHROMIUM (III) METAL COMPLEXES WITH ANTIRETROVIRAL DRUG ZIDOVUDINE (AZT) AND BIOLOGICAL IMPORTANT LIGAND IN 80% ETHANOL–WATER MIXTURE

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ABSTRACT

The present study emphasizes on the characterization and Potentiometric evaluation of the Binary copper [Cr^{3+}] – Zidovudine and Ternary complexes Chromium metal ion Zidovudine drug and Some Biological important amino acids as the secondary ligands. The properties of the complexes investigated for determination of the Δ log K values in solution states with the help of Potentiometer in controlled experimental conditions. These metal complexes are evaluated for their formation on the basis of log k values. Metal complexes have shown their significant formation when compared to pure drug. The study of metal complexes is of special interest as per as their enhanced biological activities are concerned. This investigation thus aims at determining the stability constant of ternary metal complexes of chromium (III) ion with Antiretroviral Drug Zidovudine (AZT) and amino acids potentiometricaly in 80% (v/v) ethanol-water mixture at 27°C and fixed ionic strength 0.1M $NaClO_4$.

KEYWORDS

HIV, Zidovudine, Binary Metal Complexes and Ternary complexes.

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INTRODUCTON

The solution study of the metal complexes particularly the stability constant provides the good deal of the ideas about the coordination chemistry of the metal ion and the important organic molecules like the Drugs along with some another ligand such as amino acids which makes our understanding regarding the competition of the ligand for the formation of the coordinated complexes which are the important part of the bioinorganic chemistry and made this research area important in drug designing and the development in

the medicinal field.

The complexion of the metal ions either free or bound in the biological system with the organic ligands like drugs having electron donation capacity may lead to formation of the so called 'metal based drug' or elemental drugs have unique therapeutic applications[1] Human immunodeficiency virus (HIV), the pathogenic retrovirus responsible for the acquired immunodeficiency syndrome (AIDS) causes symptoms and infections ensuing from the specific damage to the immune system[2] for the treatment of treat retroviruses or HIV antiretroviral drugs are used, here In AZT, the azido group is responsible for its antiviral action Zidovudine i.e. azidothymidine (AZT) is the first clinically successful NRTI, which acts as chain terminator of viral DNA but also there is some adverse effects concerned with use AZT such like bone marrow suppression, myalgia, insomnia and haematological toxicity that results in macrocytic anemia[3]. Which leads to appear the idea from the information that if the complexion of the drug and the metal becomes prominent then the metal in combination with this drug in some cases may be the way to tackle the unnecessity of this deadly bunch of the disease worldwide. An extensive literature survey revealed very few studies on the interaction/binding of metal ions with AZT. Complexation of AZT with Fe2+ cation has been studied by polarography and amperometry[4] conductometry, spectrophotometry and mass spectrometric investigation of mg(ii) and ca(ii) complexes with an Antiretroviral drug, zidovudine by Priyanka A. Shaha *et al*[3] has been studied. The present work therefore aims studying the AZT complex with the Chromium metal ion to see whether the complexion is worth considering. The metal ions are essential parts of enzymes and play vital role in the biological system, such as to triggering a reaction, controlling the reaction mechanism, stabilizing the protein structure, maintaining the structure of cell walls, carrying out the specific and absolute reactions etc. Literature available indicates that regulation of metabolism and growth of animal cell is dependent upon the mobilization of divalent and trivalent metal ions. Complex formation of drugs with metal ions is known to influence the bioavailability and other pharmacokinetic properties of drugs. Chromium is a transition metal and its 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. It is widely distributed throughout the body[5]. Infants have a higher chromium concentration than adults. Brewer"s yeast is rich in chromium and most grains and cereal products contain significant quantities. Significant amount of chromium is obtained in the diet by cooking foods in stainless steel cookware. 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, bond to "transferring" and appears in the liver mitochondria, microsomal 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 key role in carbohydrate, lipid and protein metabolism. It is a true potentiator of insulin and is called as glucose tolerance factor (GTF). Trivalent chromium has been known to be a constituent of glucose tolerance factor. Chromium supplementation in deficient diets reduces serum cholesterol levels and controls atheromatous plaque formation in arota. When given with insulin in chromium deficiency state, it improves amino acid incorporation mainly with glycine, serine and methionine. In protein energy malnutrition (PEM) states, chromium supplementation is usefull for weight gain. Chromium functions in vivo as an organic chromium complex and biological role to potentiate insulin. The present investigation deals with the potentiometric studies on chromium (III) metal complexes with high ceiling diuretic drug Zidovudine and amino acids in 80% (v/v) ethanol-water medium.

MATERIAL AND METHODS

The nitrates of chromium, of A.R. grade were obtained from Doodle (India). Metal ion were used as perchlorates to avoid the possibility of complex formation with anions, which was prepared of the corresponding nitrates[6]. The concentration of metal ions was estimated by the standard procedures[7]. Sodium porchlorate (E.Merck) was dissolved in carbon dioxide free distilled water.

The solution of sodium hydroxide was allowed to stand for a long time till any carbonate if present precipitated and this carbonate free solution was used as titrant for the potentiometric titration. As a routine, the solution was standardized at least once every day by titrating with standard oxalic acid solution. Perchloric acid of A.R. grade from SD fine 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 SD fine (India) were prepared by dissolving A.R. grade sample in 80% (v/v) ethanol – water medium. Drugs such as Zidovudine were prepared by dissolving a recrystallized sample in 80% (v/v) ethanol-water medium. The pure grade AZT drug was received as a gift sample from *Wockhardt* Ltd. Pharmaceutical Industrial Company and further used by recrystallization. The experimental procedure, in the study of ternary metal complexes by the potentiometric 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 2 M 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 this study by the potentiometric titration technique, involves the titration of carbonate free solution of in 80% (v/v) ethanol-water, were corrected by method of Vansittart and Hass. The Stability constant of ternary complexes were determined by computational programmed SCOGS to minimize the standard derivation.

RESULTS AND DISCUSSION

Binary metal complexes

The proton ligand constant and metal ligand stability constant of drug Zidovudine and amino acids with chromium (III) determined in 80 % (v/v) ethanol-water mixture at 27°C and ionic strength μ= 0.1 M $NaCl0_4$ are given in Table No.1.

Ternary metal complexes

The potentiometric titration, ternary systems of glycine shows that the mixed ligand curve coincide with A+D complex curve up to the pH ~ 2.9 and after this pH, it deviates. Theoretical composite curve remains toward left of the mixed ligand complex curve. After pH ~ 2.9, 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 curves, the formation of 1:1:1 complex by involving stepwise equilibrium.

The primary ligand drug Zidovudine form 1:1 and secondary ligand i.e. all the amino-acid form 1:1 and 1:2 complexes while only Arginine and methionine forms 1:1 complexes with Cr (III). It is evident from the figure of percentage concentration species of Cr (III) -Zidovudine –Amino acids - system that the percentage distribution curves of free metal decreases sharply with increase in the pH this indicates involvement of metal ion in the complex formation process.

Species distribution studies

To explain the equilibrium and evaluate the calculated stability constant of ternary complexes Cr (III) -Zidovudine -glycine, species distribution curves have been plotted as a function of pH at temperature 27^0C and μ = 0.1 M $NaClO_4$ by using SCOG programme.

Figure Distribution curve of ternary complex between Chromium metal Drug Zidovudine and Glycine

It can be seen that, the concentration of Cr (III) – Zidovudine –glycine (C8) increases from pH~2.7, whereas the concentration for the formation of D (Zidovudine) and HR (Glycine) (C2) show continuous decrease with increasing pH which indicates the formation of Cr (III)- Zidovudine - glycine. The concentration of this species

continuously increases; confirm the formation of ternary complexes.

It can be observed that the concentration of Cr (IlI) - Zidovudine amino acids such as glycine increases from pH 2.7 whereas Lucien, Glutamine, Valine, Methionine, Phenyl alanine, Glutamic acid Alanine, Arginine and tryptophan concentration increases from 2.1, 2.2, 1.9, 1.3, 2.3, 1.4, 1.8, 1.3, and 1.5 respectively. The concentration for the formation of D (drug Zidovudine) and HR (glycine amino acid) represented by C_1 and C_2 show continuous decrease with increasing pH which indicates the formation of Cr (III) - drug (D)- amino acid (R) such as glycine, tryptophan, leucine and glutamic acid. The curve represented by C_8 concentration continuously increases; confirm the formation of ternary complexes. Cr (III) - drug (D) – amino acid (R). From the SCOG 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 indicate that metal primary ligand complex Cr (III)- Zidovudine is formed first then the secondary ligands such as glycine, arginine, tryptophan, leucine and glutamic acid coordinated to it, resulting the formation of ternary complex.

Moreover the maximum percentage of the formation of ternary complexes is more than that of the Cr (III) amino acids and Cr (III) Zidovudine binary complex, this indicates that the stabilization of ternary complex.

The stability constant of ternary complexes

The relative stabilities of the binary and ternary complexes are quantitatively expressed in tern of β_{11}, β_{02}, β_{02}, K_D, K_R, K_r and Δ logK value which are represented in table II.

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 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 the binary 1:1 metal-Zidovudine and metal-amino acids complex. This is in accordance with statistical considerations. The negative value of ΔlogK does not mean that the complex is not formed. The negative value may be due to reduced number of coordination sites, Electronic consideration[9,10] difference in bond type, geometrical structure etc.

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

Table No.1: The values of Pka's of amino acids are already published[8]

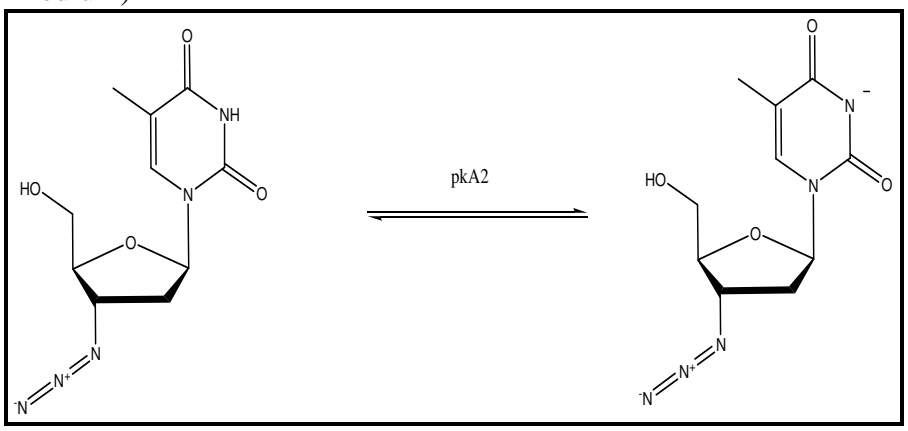
Ligands	PK_1	PK_2	Chromium	
			$Logk_1$	$LogK_2$
AZT	2.64563	6.731383	4.74736	-
Glycine	2.7700	9.7400	6.5100	3.9398
Leucine	3.8100	10.3400	7.7079	4.3502
Glutamine	3.0100	9.2800	7.2510	6.0821
Arginine	4.2659	12.200	8.5166	---
Tryptophan	3.8000	10.3900	8.4701	6.4134
Valine	3.2100	9.8084	5.6119	3.600
Methionine	3.1200	9.600	3.0998	---
Alanine	3.6989	10.179	10.701	8.7198
Phenyl alanine	3.1400	9.300	6.4405	5.3615
Glutamic acid	3.1360	5.8987	3.5087	3.0419

Table No.2: Parameters based on some relationship between the formation of ternary complexes of chromium (III) metal ion with Zidovudine in the presence of amino acids (1:1:1) system at temp = 27^0C and μ = 0.1 M $NaClO_4$ Medium = 80% (V/V) Ethanol-Water are given

S.No	amino acid	B11	β20	β02	KD	KR	Kr	Δlog K
1	GLYCINE	11.0875	4.7313	10.45	6.3562	4.5775	2.486397	-0.1538
2	Leucine	15.0005	4.7473	12.0578	10.2532	7.2927	3.930943	2.5454
3	Glutamine	11.4949	4.7473	13.3297	6.7476	4.2463	2.088062	-0.501
4	Valine	9.8593	4.7473	9.2029	5.112	4.2469	2.224953	-0.5004
5	Metheonine	11.3404	4.7473	3.1	6.5931	8.2404	8.738731	3.4931
6	Phenyl alanine	12.9401	4.7473	15.769	8.1928	4.84	2.236786	0.0927
7	Glutamic acid	7.0059	4.7473	6.5506	2.2586	3.4972	1.578338	-1.2501
8	Alanine	9.9373	4.7473	11.8021	5.19	3.4968	1.762507	-1.2505
9	Arginine	13.2625	4.7473	8.5166	8.5152	4.7459	4.350487	-0.0014
10	Tryptophan	12.7168	4.7473	14.8835	7.9695	4.2467	2.288779	-0.5006

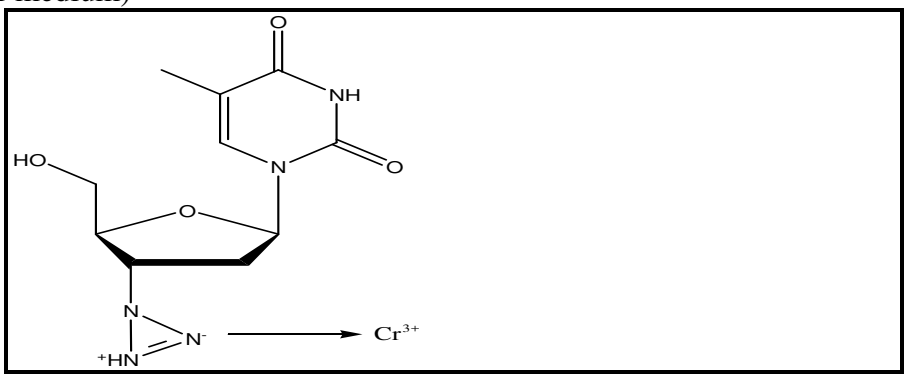
PROTON DISSOCIATION SCHEME FOR FREE LIGAND ZIDOVUDINE

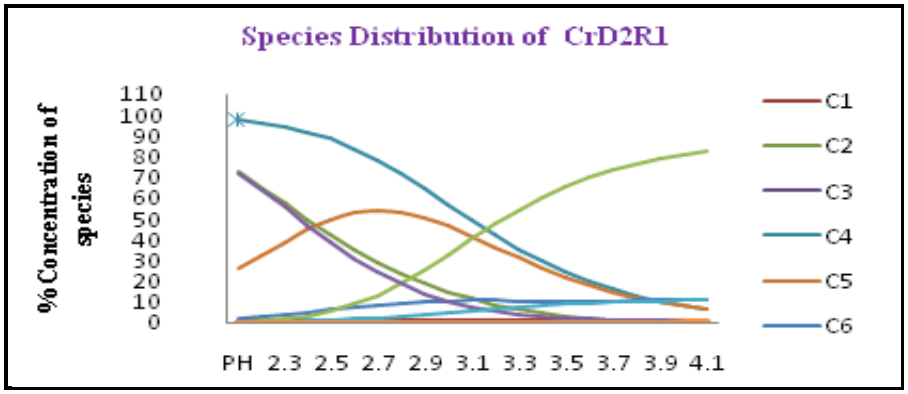
(80% Ethanol- Water medium)



COMPLEX FORMATIOON OF LIGAND ZIDOVUDINE AND METAL CHROMIUM

(80% Ethanol- Water medium)





CONCLUSION

The ΔlogK value of this system is higher than the statistically expected value showing the stabilized nature of the ternary complex. The primary ligand Zidovudine having smaller size. Therefore its ΔlogK value is less negative. Thompson and Lorass pointed out that more negative 1ogK value of ternary complexes is due to the electrostatic repulsion between the negative charges on Zidovudine and amino acids. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand Zidovudine coordinates with the metal ion in the lower pH range and form 1: 1 complex. In soluteon, ternary complex forms as the titration curve run below the Cr (III) - Zidovudine titration curve. So, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Cr (Ill) - Zidovudine complex as compared to aqua ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Cr (Ill) metal ion and thus reduces the stability of ternary complexes. The order of stability of ternary complexes of Cr (lll) with respect of secondary ligand for respective primary ligands is Zidovudine =Methionine> Leucine > Phenyl alanine > Arginine > Glycine >Valine > Tryptophan > Glutamine > Glutamic acid > Alanine.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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