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Studies of Mixed-Ligand Complex Formation of Drug Dapsone and Amino Acids with Chromium (III).

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ABSTRACT

The stability constant of the mixed ligands complexes of chromium (III) ion with drug dapsone as primary Ligands and the amino acids were determined in 80 % (v/v) ethanol-water medium at 27°C at a fixed ionic strength 0.1M $NaClO_4$ by computational programmed SCOGS.

Keyword: Stability constant, ΔlogK and mixed ligand complexes.

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INTRODUCTION

Dapsone is antileprotic drug [1-4], nearly water insoluble and very weakly basic drug. The lack of solubility may account in part for the occurrence of gastrointestinal irritation. Therefore in order to understand the complex formation tendencies of dapsone it was though worthwhile to determine the formation constant 1: 1: 1 ternary complexes of dapsone with chromium (III) in the presence of amino acids in 80 %(v/v) ethanol-water medium at 27°C at a fixed ionic strength 0.1M NaCLO4

MATERIALS AND METHODS

Drug sample of dapsone in pure form were obtained from pharma industries and used as received. Ethanol was purified as described in literature [7]. Double distilled water was used for the preparation of ethanol-water mixture and stock solution of dapsone.

All chemicals used were AnalaR grade. The experimental procedure, in the study of ternary chelated by the potentiometric titration technique, involves the titration of carbonate free solution of pH meter reading in 80%(v/v) ethanol-water were corrected by method of Vanuitert and Hass [9]. The formation constant of ternary complexes were determined by computational programmed SCOGS [10] to minimize the standard derivation.

RESULTS AND DISCUSSION

Binary metal complexes

The proton ligand constant and metal ligand stability constant of dapsone 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 I , already published in research journal [11]. These values are important for the determination of stability constant of mixed ligand complexes therefore mentioned here.

Ternary metal complexes

In the ternary systems, the mixed ligand titration curve coincide with acid +drug complex curve up to the pH ~ 2.9 and after this pH, it deviates. Theoretical composition curve remains toward left to the mixed ligand titration complex curve. After pH~ 3.0, the mixed ligand curve drift 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 dapsone form 1: 1 and secondary ligand amino acids such as glycine, arginine, tryptophan, leucine, glutamic acid, glutamine, valine, methionine, phenylalanine & alanine form 1: 1 and 1:2 complexes with Cr(III). It is evident from the figure of the percentage concentration species Cr(III)- dapsone amino acids 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 dapsone and amino acids increases and this increase may be due to the dissociation of ligand present in the system, as a function of pH.

Species distribution studies.

To visualize the nature of the equilibrium and to evaluate the calculated stability constant of ternary complexes Cr(III) - dapsone- amino acids, species distribution curves have been plotted as a function of pH at temperature 27°C & μ = 0.1M $NaCl0_4$ using SCOG programmed.

It can be observed that the concentration of Cr (III)-dapsone amino acids such as glycine increases from pH 3.5 where as lucine, glutamic acid, glutamine, valine, methionine & phenylalanine from pH- 2.7. The concentration for the formation of D(drug) and HR (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, leucine, glutamic acid, glutamine, valine, phenylalanine, alanine represented by C_7. The concentration

continuously increases; confirm the formation of ternary complexes. Cr (III) - drug (D) – amino acid (R) such as arginine and methionine represented by C_6. The concentration continuously increases; confirm the formation of ternary complexes. Cr (III) - drug (D)- amino acid (R) such as tryptophan represented by C_8. 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)- dapsone is formed first then the secondary ligands such as glycine, arginine, tryptophan, leucine, glutamic acid, glutamine, valine, methionine, phenylalanine & alanine coordinated to it, resulting the formation of ternary complex.

According to this method in this system ternary complex with arginine & methionine show the following types of the concentration species distribution.

C_1 = HD ⇌ D + H

C_2 = H_2R ⇌ HR + H

C_3 = HR ⇌ R + H

C_4 = M+R ⇌ MR

C_5 = M+D ⇌ MD

C_6 = M+D+R ⇌ MDR

Ternary complexes with glycine, leucine, glutamic acid, glutamine, valine, phenylalanine & alanine show the following types of the concentration species distribution.

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

Ternary complexes with tryptophan show the following types of the concentration species distribution.

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+D ⇌ MD_2

C_8 = M+D+R ⇌ MDR

Where M = Metal, R = Amino acids & D = drug daspsone

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

Table I: The proton ligand constant and metal ligand stability constant of dapsone and amino acids with chromium (III) determined in 80 %(v/v) ethanol-water mixture at 27^{0}C and ionic strength μ=0.1M $NaClO_4$ are given in Table 1[11]

Ligand	pK			
	pK_1	pK_2		
Dapsone	3.1237	--	$LogK_1$	5.9640
			$LogK_2$	--
			Logβ	5.9640
Glycine	2.7700	9.7400	Log K_1	6.5100
			Log K_2	3.9400
Leucine	3.8100	10.3400	Log K_1	7.7078
			Log K_2	4.3500
Glutamic acid	3.1360	5.8987	Log K_1	3.5087
			Log K_2	3.0419
Glutamine	3.0100	9.2800	Log K_1	7.2486
			Log K_2	6.0816
Valine	3.2100	9.8024	Log K_1	5.6122
			Log K_2	3.5901
Methionine	3.1200	9.6000	Log K_1	3.1000
			Log K_2	--
Phenylalanine	3.1400	9.3000	Log K_1	6.4405
			Log K_2	5.3616
Arginine	4.2659	12.2000	Log K_1	8.5166
			Log K_2	--
Tryptophan	3.8000	10.390	Log K_1	8.4701
			Log K_2	6.9137
Alanine	3.7000	10.180	Log K_1	10.699
			Log K_2	8.7200

The stability constant of ternary complexes.

The relative stabilities of the binary and ternary complexes are quantatively expressed in tern of β_{11}, β_{02}, β_{02}, K_D, K_R, K_r and ΔlogK value which are represented in table II. The stability constants of ternary systems are represented in table II. The stability of ternary complexes is conveniently characterizes by two ways, one based on difference of stability constant Δlog K and second disproportion constant.

Table II: Parameters based on some relationship between the formation of ternary complexes of chromium (III) metal ion with dapsone in the presence of aminoacids (1:1:1) system.

Temp = 27^{0}C I=0.1 M $NaClO_4$ Medium = 80% (V/V) Ethanol-water

AMINOACIDS	β_{11}	β_{02}	β_{20}	K_D	K_R	K_r	ΔlogK
Glycine	11.1881	10.45	5.9640	5.2241	4.6781	1.3632	-1.2859
Arginine	13.9787	8.5166	5.9640	8.0147	5.4621	1.9306	-0.5019
Tryptophan	15.8392	14.8835	5.9640	9.8752	7.3691	1.5195	1.4051
Leucine	13.6712	12.0578	5.9640	7.7072	5.9634	1.51718	-0.0006
Glutamic acid	8.4727	6.5506	5.9640	2.5087	4.9640	1.3540	-1.0000
Glutamine	12.7123	13.1302	5.9640	6.7483	5.4637	1.3177	-0.5003
Valine	10.5765	9.2023	5.9640	4.6125	4.9643	1.3946	-0.9997
Methionine	8.8128	3.1000	5.9640	2.8488	5.7128	1.9445	-0.2512
Phenylalanine	10.9045	11.8021	5.9640	4.9405	4.4640	1.2275	-1.5000
Alanine	16.0132	19.4190	5.9640	10.0492	5.3142	1.2617	-0.6504

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$$MR + D \rightleftharpoons MRD \quad (I)$$

$$M+D \rightleftharpoons MD \quad (II)$$

$$\Delta \log K \longrightarrow \log K_{ML2} - \log K_{ML1}$$

The first equation mentioned above is similar to the reaction

$$MD+D \rightleftharpoons MD_2$$

With respect to the availability of coordination sites for ligand D in MR or MD. Generally $K_{MLI} > K_{ML2}$ because more coordination positions are normally available for bonding first ligand to a metal ion than the second ligand. Evidently $K_{MLI} > K_{ML2}$ or ΔlogK is negative. ΔlogK can be calculated by the expression.

$$\Delta \log K \longrightarrow \log_{\beta MRL} - (\log K_{MR1} + \log K_{MD1})$$

The negative ΔlogK for ternary systems indicates that the primary ligand anion and secondary ligand anions preferentially form ternary complexes to their binary ones. It follows from above expression that the difference, ΔlogK results from the subs traction of two constants and therefore, a constant which corresponds the equation,

$$MR+MD \rightleftharpoons MRD + M$$

The positive value of ΔlogK indicates the equilibrium is more on its right side. The other characterization is based on the disproportion reaction represented by the following equilibrium

$$MR_2 + MD_2 \rightleftharpoons 2MRD$$

The disproportion reactions for the system containing the ligands which form 1: 1 and 1:2 complexes individually with the metal ion are as

$$MR_2 + MD \rightleftharpoons MRD + MR$$

$$MR + MD_2 \rightleftharpoons MRD + MD$$

$$MR + MD \rightleftharpoons MRD + M$$

Above two reactions are for the system containing one ligand which form only 1: 1 and other form both 1: 1 and 1:2 binary complexes. The last reaction is for the system containing ligands which form only 1: 1 binary complexes. The magnitude of the constant is the measure of stability of mixed ligand complexes. Watter and Kida calculated statistically expected value 0.6 log units by considering with probabilities for a variety of reason discussed by Sigel. ΔlogK value can be calculated by using first or second approach. The calculated ΔlogK values for all systems are given in table II.

In Cr (II) - dapsone-aminoacids, Primary ligand dapsone form only 1: 1 and secondary ligand form both 1: 1 and 1:2 binary complexes. Therefore this system favour the following disproportion reactions.

$$MR_2 + MD \rightleftharpoons MRD + MD$$

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$MR_2 + MR \rightleftharpoons MRD + MD$

The Comparison of β11 with β20 and β02 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 KD & KR indicates less stability of ternary complexes with respect to that of primary as well as secondary ligands. The Kr 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-dapsone & 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 the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance [12-15], electronic consideration[16-17] difference in bond type, geometrical structure etc. Sigel concluded that in the case of bidentate ligand dapsone & amino acid, there are twelve edges of a regular octahedron available to the first entering ligand. But only five for the second. Then the statistical factor would be 5/12 and accordingly ΔlogK = -0.4, -0.6 &-0.9 for square planer & distorted octahedral complexes. Hence the experimentally determined value ΔlogK < -0.6 indicate less stabilization in ternary complexes. Parameters based on some relationship between the formation of ternary complexes of chromium (III) metal ion with dapsone in the presence of aminoacids (1:1:1) system are given in table No.II.

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 dapsone having smaller size. Therefore its ΔlogK value is less negative.

Thompson & Lorass pointed out that more negative Δ1ogK value of ternary complexes is due to the electrostatic repulsion between the negative charges on dapsone & amino acids. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand dapsone coordinates with the metal ion in the lower pH range and form 1: 1 complex. In solution, ternary complex forms as the titration curve run below the Cr (III)-dapsone 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 (III)-dapsone complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Cr (III) metal ion & thus reduces the stability of ternary complexes. The order of stability of ternary complexes of Cr (III) with respect of secondary ligand for respective primary ligands is Dapsone = Trypto > leu> methio > glu > argi > ala> val> = gluta > gly > phenylala.

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