International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.2, pp 1036-1041, April-June 2010

Mixed-ligand complex formation of copper (II) with some aminoacids and Drug Dapsone

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Abstract : The stability constant of the mixed ligand complexes of copper (II) ion with drug dapsone as primary ligand and the aminoacids viz. glycine, leucine, glutamic acids, glutamine, valine, methionine and phenyl alanine as secondary ligand were determined pH metrically at 27^0C and an ionic strength of 0.1 M $NaClO_4$ in 80% (v/v) ethanol-water medium. The calculations have been made using the stability constant of generalized species computer programme.
Key word : Stability constant, ΔlogK and mixed ligand complexes.

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 occurance of gastrointestinal irritation. Despite the lack of solubility, the drug is efficiently absorbed from the gastrointestinal tract. Although, dapsone is bound to plasma protein, it is distributed through the body. Dapsone have significant anti-inflamatory action which may or may not play a role in the antimicrobial action. The anti-inflamatory action may come about by inhibition of myelopeperoxidase catalysed reaction[5]. Several derivatives of dapsone have been prepared in an attempt to increase the activity of dapsone. The chemical modification of dapsone derivatives continue to be pursued with the intention of finding newer agents useful for the treatment of resist strain of Leprae[6]. In addition to the treatment of leprae, dapsone include the treatment of dermatitis herpetiformis, brown recluse spider bites, inflammatory bowel disorder, leishmaniasis, malaria prophylaxis, relapsing polychondritis, rheumatic and connective tissue disorders and prophylaxis of pnemocystis carinii in HIV patients and organ transplant patients. Survey of literature reveals that no work has been reported on complex tendencies of drug dapsone with transition metal ion copper (II) in ethanol-water solution. 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 copper (II) in the presence of aminoacids in 80%(v/v) ethanol-water medium at 27^0C at a fixed ionic strength 0.1 M $NaClO_4$

Experimental

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. $NaClO_4$ (0.1M) 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 copper (II) to

prevent hydrolysis and standardized by using standard EDTA solution[8].

The experimental procedure, in the study of ternary chelated by the potentiometric titration technique, involves the titration of carbonate free solution of

1) Free $HClO_4$(A)
2) Free $HClO_4$ + Ligand Dapsone
3) Free $HClO_4$ + Ligand Dapsone + Metal ion
4) Free $HClO_4$ + Ligand Aminoacids
5) Free $HClO_4$ + Ligand Aminoacids + Metal Ion
6) Free $HClO_4$ + Ligand Drug + Ligand Aminoacids + Metal Ion

Against standard solution of sodium hydroxide, were drug dapsone and aminoacid are two ligands. The ionic strength of the solutions was maintained constant i.e. 0.1M by adding appropriate amount of 1M sodium perchlorate solution. The titration 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. 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 programme SCOGS[10] to minimize the standard derivation.

Results and Discussion

a. Binary metal complexes

The proton ligand constant and metal ligand stability constant of dapsone and amino acids with copper (II) determined in 80%(v/v) ethanol-water mixture at 27^0C and ionic strength μ = 0.1M $NaClO_4$ aregiven in Table 1[11]

The basicities of the ligand dapsone have been measured in term of their proton-ligand stability constant. The determination of proton ligand stability constant of the ligand dapsone is a prerequisite for the evaluation of metal-ligand stability constant. Hence proton-ligand stability constant of the ligand have been detrmined by Irving-Rossotti's pH metric titration techniques[12]. The titration curve for dapsone show buffer region in pH<3. The release of proton in the lower buffer region indicate the dissociation of proton from protonated nitrogen atom. From the acid and ligand curve the value of nA have been calculated using Irving Rossotti method[13] & further by computational programme.

The $\bar{n}A$ values range between 0.1 and 1 for dapsone indicating the liberation of one proton. The pK value for dapsone was determined pH metrically. The pK value of dapsone is found to be lower, the reason is more electrogenative oxygen atom of SO_2 attached to ring having a loan pair of electrons, increases the electron density of $-NH_2$, which affect the deprotonation of NH_2 group, therefore dapsone is weak basic[14]. pH decreases, if a neutral metal ion solution is added to ligand solution. The metal ligand titration curve lie below the pure ligand titration curve. The pH of complex formation is much below than the pH of metal ion hydrolysis. These features of the pH metric studied confirm the formation of complexes by metal ion with drug.

The metal ligand formation curve data for dapsone with copper (II) indicate that the n value range between 0.2. to 0.8. This suggest that metal ions form 1:1 complexes[15] with drug dapsone in solution. The logK value is evaluated by the computational techniques are in good agreement. The binary formation constants so obtained are presented in Table 1. The order of $\log K_1 > K_2$ is commonly observed. The reason is statistical effect, statistically coordination of a second molecule is difficult when compare to the first due to availability of less number of coordinating sites on the metal ion for the second ligand. The standard deviation for various metal ligand system is 0.036. The ligand dapsone contain different coordinating sites. Irving and Rossotti have proposed a relation between the stability of the complexes and basicity of the ligand by equation[16].

$$\text{LogK} = \text{apK} + \text{b}$$

The relation graph shows a straight line and the value of slope should be unity for a series of closely related ligand. In the present study such relationship do not exists since the drug used are of diverse in nature. The stability constant of metal-ligand such as dapsone show the good agreement with Irving-William order of stability constant[16]. The comparison between the stability constant of Cu(II) with ligand indicate that the weekly basic copper[17] from strong complex it suggest that strength of bonding in these complexes depends on the ability of the metal to form homopolar bond between the metal and ligand. The another reason for the higher stability constant of copper is that, copper has single 'S' electron outside the filled third shell. The filed 'd' electrons are involved in metallic bonding. This factor contributes to much more noble character of copper to make compound more covalent[18]. Copper has greater lattice and solvation energies, hence stability constant for complexes of Cu(II) ion is observed.

b. 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 equilibria.

The Primary ligand dapsone form 1:1 and secondary ligand amino acids such as Glycine, leucine, glutamic acid, glutamine, valine, methionine & phenylalanine form 1:1 and 1:2 complexex with Cu(II). It is evident from the figure of the percentage concentration species Cu(II)- dapsone amino acids system, that the percentage distribution curve of free metal decreases sharply with increasing pH. This indicate involvement of metal ion in the complex formation process. Percentage concentration of free ligand dapsone and aminoacids 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 equilibria and to evaluate the calculated stability constant of ternary complexes Cu(II) - dapsone- aminoacids, species distribution curves have been plotted as a function of pH at temperature 27^0C & μ = 0.1 M $NaClO_4$ using SCOG programme.

It can be observed that the concentration of Cu (II)-dapsone aminoacids such as glycine increases from pH 3.6 where as lucine, glutamic acid, glutamine, Valine, methionine & pheny lalanine from pH~ 2.7. The concentration for the formation of D(drug) and HR (aminoacid) represented by C_1 and C_2 show continuous decrease with increasing pH which indicates the formation of Cu (II) – drug (D)-aminoacid(R) and represented by C7. The concentration of this species continuously increases, confirm the formation of ternary complexes. Cu(II) – drug (D) – aminoacid(R) leucine represented by C_6. The concentration of this species continuously increases, confirm the formation of ternary complexes. 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 Cu(II)- dapsone is formed first then the secondary ligands such as glycine, lucine, glutamic acid, glutamine, Valine, methionine & Phenylalanine coordinated to it, resulting the formation of ternary complex.

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

C_1 = HD $\rightleftharpoons$ D + H

C_2 = H_2R $\rightleftharpoons$ HR + H

C_3 = HR $\rightleftharpoons$ R + H

C_4 = M+R $\rightleftharpoons$ MR

C_5 = M+D $\rightleftharpoons$ MD

C_6 = M+D+R $\rightleftharpoons$ MDR

Ternary complexes with glycine, glutamic acid, glutamine, valine, methionine & Phenylalanine show the following types of the concentration species distribution

C_1 = HD $\rightleftharpoons$ D + H

C_2 = H_2R $\rightleftharpoons$ HR + H

C_3 = HR $\rightleftharpoons$ R + H

C_4 = M+R $\rightleftharpoons$ MR

C_5 = MR+R $\rightleftharpoons$ MR_2

C_6 = M+D $\rightleftharpoons$ MD

C_7 = M+R+D $\rightleftharpoons$ MDR

Where M = Metal, R= Aminoacids & D = drug capsone.

Moreover the maximum percentage of the formation of ternary complexes is more than that of the Cu(II) aminoacids and Cu(II) dapsone 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 term of β_{11}, β_{20}, β_{02}, K_D, K_R, K_r and ΔlogK value which are represented in table 2. The stability constants of ternary systems are represented in table 2. The stability of ternary complexes is conveniently characterizes by two ways, one based on difference of stability constant Δlog K and second disproportion constant.

MR+D $\rightleftharpoons$ MRD (I)

M+D $\rightleftharpoons$ MD (II)

Δlogk $\longrightarrow$ $\log K_{ML2} - \log K_{ML1}$

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 $K_{ML1} > K_{ML2}$ because more coordination positions are normally available for bonding first ligand to a metal ion than the second ligand. Evidently $K_{ML1} > K_{ML2}$ or Δ log K is negative. Δ log K can be calculated by the expression.

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

The negative Δ log K 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, Δ logK results from the substraction of two constants and therefore, a constant which corresponds the equation,

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

The positive value of Δ logK 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 unit by considering with probabilities for a variety of reason discussed by Sigel. Δ logK value can be calculated by using first or second approach. The calculated Δ logK values for all systems are given in table 2

In Cu (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.

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

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

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 & K_R indicate 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 Δ logK value of this system indicates that the ternary complex is less stable than the binary 1:1 metal –dapsone & metal – aminoacids complex. This is in accordance with statistical considerations. The negative value of Δ logK 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[19-22], electronic consideration[23-24], difference in bond type, geometrical structure etc.

Sigel concluded that in the case of bidentate ligand dapsone & aminoacid, 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 Δ logK= -0.4, -0.6 & -0.9 for square planer & distorted octahedral complexes. Hence the experimentally determined value Δ logK < -0.6 indicate less stabilization in ternary complexes.

The Δ logK value of this syste is higher than the statistically expected value except leucine & phenylalanine, showing the stabilized nature of the ternary complex. The primary ligand dapsone having smaller size. Therefore its Δ logK value is less negative.

Thompson & Lorass pointed out that more negative Δ logK 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 Cu (II) – 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 Cu(II) dapsone complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination spehere of the Cu (II) metal ion & thus reduces the stability of ternary complexes. The order of stability of ternary complexes of Cu(II) with respect of secondary ligand for respective primary ligands is

Dapsone = Phenylala < Gluta < gly < Val < Methio < glutamic < Leu

Table 1

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

Ligand	pK			
	pK_1	pK_2		
Dapsone	3.1237	--	$LogK_1$	5.2139
			Log K_2	--
			Log β	5.2139
Glycine	2.7700	9.7400	$LogK_1$	9.6900
			Log K_2	8.9800
Leucine	3.8100	10.3400	$LogK_1$	8.0703
			Log K_2	--
Glutamic acid	3.1360	5.8987	$LogK_1$	10.9800
			Log K_2	8.6400
Glutamine	3.0100	9.2800	$LogK_1$	9.5400
			Log K_2	7.8900
Valine	3.2100	9.8024	$LogK_1$	10.0100
			Log K_2	8.4800
Methionine	3.1200	9.6000	$LogK_1$	9.6400
			Log K_2	8.6700
Phenylalanine	3.1400	9.3000	$LogK_1$	8.9900
			Log K_2	7.6700

Table 2

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

Temp = 27^0C 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	14.8514	18.67	5.2139	9.6375	5.1614	1.2436	-0.0525
Leucine	11.7853	8.07	5.2139	6.5696	3.7132	1.7740	-1.5007
Glutamic Acid	14.9438	19.62	5.2139	9.7299	3.9638	1.2035	-1.2500
Glutamine	14.7520	17.43	5.2139	9.5381	5.2120	1.3029	-0.0019
Valine	14.7161	18.49	5.2139	9.5022	4.7061	1.24166	-0.5078
Methionine	13.8538	18.31	5.2139	8.6399	4.2138	1.1778	-1.0001
Phelyl Alanine	14.2041	16.66	5.2139	8.9902	5.2141	1.2987	0.0002

Acknowledgement

The authors very much thankful to the principal Dr. P.L. More, The Head, Department of Chemistry and Dean of the Faculty Dr. W.N. Jadhav, Dr. C.H. Gill for providing necessary facilities & UGC (W.R.) for financial assets under minor research project.

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