

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°C and an ionic strength of 0.1 M NaClO₄ 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, $\Delta\log K$ 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 occurrence 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-inflammatory action which may or may not play a role in the antimicrobial action. The anti-inflammatory action may come about by inhibition of myeloperoxidase catalysed reaction⁵. 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 Leptrae⁶. In addition to the treatment of lepra, 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 pneumocystis 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 thought 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°C at a fixed ionic strength 0.1 M NaClO₄

Experimental

Drug sample of dapsone in pure form were obtained from pharma industries and used as received. Ethanol was purified as described in literature⁷. Double distilled water was used for the preparation of ethanol-water mixture and stock solution of dapsone.

All chemicals used were AnalaR grade. NaClO₄ (0.1M) and NaOH solution was prepared in carbondioxide free double distilled water. Carbonate free NaOH was standardized by titrating with oxalic acid. HClO₄ Reidal (Germany) was used for the preparation of the stock solutions of copper (II) to

prevent hydrolysis and standardized by using standard EDTA solution⁸.

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

- 1) Free $\text{HClO}_4(\text{A})$
- 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°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 were corrected by method of Vanuitert and Hass⁹. The formation constant of ternary complexes were determined by computational programme SCOGS¹⁰ 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°C and ionic strength $\mu = 0.1\text{M}$ NaClO_4 are given in Table 1¹¹

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 determined by Irving-Rossotti's pH metric titration techniques¹². The titration curve for dapsone show buffer region in $\text{pH} < 3$. 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 n_A have been calculated using Irving Rossotti method¹³ & further by computational programme.

The 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 lone pair of electrons, increases the electron density of $-\text{NH}_2$, which affect the deprotonation of NH_2 group, therefore dapsone is weak

basic¹⁴. 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 complexes¹⁵ with drug dapsone in solution. The $\log K$ 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 equation¹⁶.

$$\log K = a\text{pK} + b$$

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 constant¹⁶. The comparison between the stability constant of $\text{Cu}(\text{II})$ with ligand indicate that the weakly basic copper¹⁷ 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 filled 'd' electrons are involved in metallic bonding. This factor contributes to much more noble character of copper to make compound more covalent¹⁸. Copper has greater lattice and solvation energies, hence stability constant for complexes of $\text{Cu}(\text{II})$ 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 $\text{pH} \sim 2.9$ and after this pH, it deviates. Theoretical composition curve remains toward left to the mixed ligand titration complex curve. After $\text{pH} \sim 3.0$, 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.

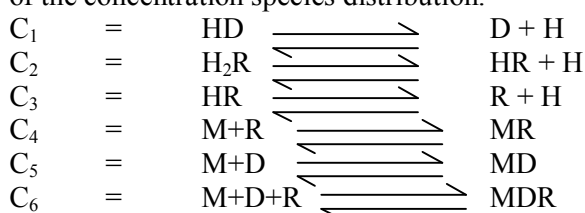
The Primary ligand dapsone form 1:1 and secondary ligand amino acids such as Glycine, leucine, glutamic acid, glutamine, valine, methionine & phenylalanine form 1:1 and 1:2 complex with Cu(II). It is evident from the figure of the percentage concentration species Cu(II)- dapsone amino acids system, that 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.

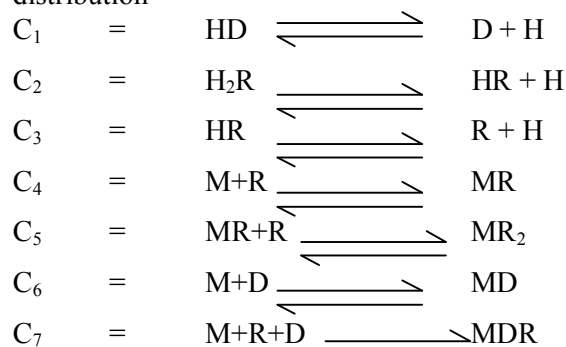
To visualize the nature of the equilibria and to evaluate the calculated stability constant of ternary complexes Cu(II) - dapsone- aminoacids, species distribution curves have been plotted as a function of pH at temperature 27°C & $\mu = 0.1$ M NaClO₄ using SCOG programme.

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 C₁ and C₂ 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 C₆. 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.



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

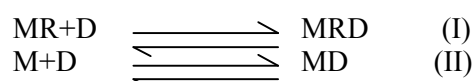


Where M = Metal, R = Aminoacids & D = drug capsone.

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

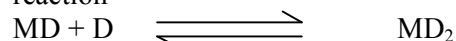
The stability constant of ternary complexes

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 $\Delta \log K$ 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 $\Delta \log K$ and second disproportion constant.



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

The first equation mentioned above is similar to the reaction

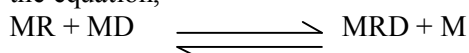


With respect to the availability of coordination sites for ligand D in MR or MD. Generally $K_{ML1} > K_{ML2}$ because more coordination positions are normally available for bonding first ligand to a metal ion than the second ligand. Evidently $K_{ML1} > K_{ML2}$ or $\Delta \log K$ is negative. $\Delta \log K$ can be calculated by the expression.

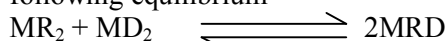
$$\Delta \log K \longrightarrow \log \beta_{MRL} - (\log K_{MR1} + \log K_{MD1})$$

The negative $\Delta \log K$ 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

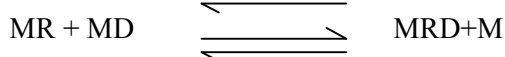
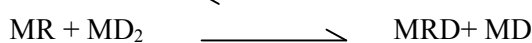
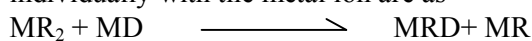
difference, $\Delta \log K$ results from the subtraction of two constants and therefore, a constant which corresponds the equation,



The positive value of $\Delta \log K$ indicates the equilibrium is more on its right side. The other characterization is based on the disproportion reaction represented by the following equilibrium

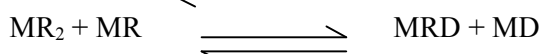


The disproportion reactions for the system containing the ligands which form 1:1 and 1:2 complexes individually with the metal ion are as



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. $\Delta \log K$ value can be calculated by using first or second approach. The calculated $\Delta \log K$ 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.



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 $\Delta \log K$ 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 $\Delta \log K$ 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 hindrance¹⁹⁻²², electronic consideration²³⁻²⁴, 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 $\Delta \log K = -0.4, -0.6$ & -0.9 for square planer & distorted octahedral complexes. Hence the experimentally determined value $\Delta \log K < -0.6$ indicate less stabilization in ternary complexes.

The $\Delta \log K$ value of this system 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 $\Delta \log K$ value is less negative.

Thompson & Lorass pointed out that more negative $\Delta \log K$ 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 sphere 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 to 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°C and ionic strength $\mu = 0.1\text{M NaClO}_4$ are given in Table 1¹¹

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°C I = 0.1 M NaClO₄ Medium = 80% (V/V) Ethanol-Water

AMINOACIDS	β_{11}	β_{02}	β_{20}	K _D	K _R	K _f	$\Delta\log K$
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
Phenyl Alanine	14.2041	16.66	5.2139	8.9902	5.2141	1.2987	0.0002

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