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Analysis and Speciation of Ternary Complexes of Copper Metal Ion with Pharmaceutical Ligand β-Diketone Ligand and Amino Acids

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Abstract

The equilibrium studies of the mixed ligand complexes of copper (II) ion with drug β-diketone as primary ligand and the amino acids viz. Glycine, L-Leucine, Tryptophan, DL-Serine, DL-Valine, DL-Alanine, β-phenyl alanine, DL-methionine as secondary ligand were determined pH metrically at 30°C and ionic strength of 0.1 M $NaClO_4$ in 50% (v/v) THF-water medium. The calculations have been made using the stability constant of generalized species computer programme.

Keywords:* *Equillibrium constant; Amino acids; Mixed ligand complexes

Introduction

β-Dike tones and their metal complexes are associated with various pharmacological and biological properties such as anti-inflammatory [1], heptoprotective [2], antitumor [3], antiviral [4], anticancer activity [3]. They are also used in gastrointestinal and respiratory disorder [5]. Their biological activities as evidenced from their anticancer [6], antitumour, antioxidant [7], anti-inflammatory [8], antiviral [9] and immunodulatory activities [10]. In biological front, many of the β-dike tones were reported to be physiologically active and find applications in the treatment of many diseases. Their biological activity enhances on the formation of metal complexes. Literature survey reveals that there is an enormous growth of the study of metal complexes of β-dike tones in last few decades. A lot of work has been published on the study of β-dike tone complexes in solid as well as in solution. The complete formation of a complex may be predicted on the basis of its stability constants in solution. Glycine is the neutral, aliphatic, optically inactive non-essential, glycogenic amino acid [11-16]. It can be synthesized from CO_2 and NH_3 by glycine synthase or transamination of glyoxylate and in metabolism of serine and choline. It plays an important role in haeme synthesis. Heame is a tetra pyrol ring system with transition metal iron. The nitrogen from each pyrol is denied from glycine. It can form serine, creatine and purine.

Leucine [17] is neutral essential ketogenic amino acid and forms an acetoacetate and acetate. It is branched chain amino acid and taken up by brain and muscle. In leucine metabolism, transamination gives α-keto isocaproic acid, which is converted in to corresponding CoA, this is similar to oxidative decarboxylation of alfaketo glutarate and pyruvate. The enzyme complex is very important in the body of living organism.

Tryptophan is important amino acid. A metabolite of tryptophan 5-hydroxytryptophan (5-HTP), has been suggested as a treatment

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for epilepsy [18] and depression, Since 5-HTP readily crosses the blood brain barrier and in addition israpidly decarboxylated to serotonin (5-hydroxytryptamine or 5-HT) [19]. Clinical trials, however, are regarded as inconclusiveand lacking [20]. Serotonin has a relatively short half-life since it is rapidly metabolized by monoamine oxidase. Due to conversion of 5-HTP into serotonin by the liver, there may be a significant risk of heart valve disease from serotonin's effect on the heart [21,22].

Serine is one of the naturally occurring proteinogenic amino acids. Only the L-stereoisomer appears naturally in proteins. D-serine was only thought to exist in bacteria until relatively recently, it was thesecond D amino acid discovered to naturally exist in humans, present as a signalling molecule in the brain, soon after the discovery of D-aspartate. Had D amino acids been discovered in humans sooner, the glycine site on the NMDA receptor mightinstead be named the D-serine site [23]. D-Serine is being studied in rodents as a potential treatment for schizophrenia and L-serine is in FDA approved human clinical trials as a possible treatment for ALS [24,25]. A 2011 meta-analysis found adjunctive sarcosine to have a medium effect size for negative and total symptoms [26].

Valine is essential amino acid [27] widely distributed but rarely occurs in amount exceeding 10%. It is branched chain amino acid and can be derived from alanine by theintroduction of two methyl group present on α-carbon atom. This is glycogenic. On deamination, it forms methyl malonyl-CoA in place of two H atoms of the methyl group. Alanine is a nonessential amino acid, meaning it can be manufactured by the human body, and does not need to be obtained directly through the diet. Alanine isfound in a wide variety of foods, but is particularly concentrated in meats. Good sources of alanine include:

Animal sources
Meat, Seafood, Caseinate, Dairy products, Eggs, Fish, Gelatin, Lactalbumin

Vegetarian sources
Beans, nuts, seeds, soy,whey, brewer's yeast, brown rice, bran, corn,legumes, whole grains. Alanine plays a key role in glucose–alanine cycle between tissues and liver. In muscle and other tissues that degrade amino acids for fuel, amino groups are collected in the form of glutamate by transamination.Glutamate can then transfer its amino groupthrough the action of alanine aminotransferase to pyruvate, a product of muscle glycolysis, forming alanine and α-ketoglutarate. The alanine formed is passed into the blood and transported to the liver. A reverse of the alanine aminotransferase reaction takes place in liver. Pyruvate regenerated forms glucosethrough gluconeogenesis, which returns to muscle through the circulation system. Glutamate in the liver enters mitochondria and degrades into ammonium ion through the action of glutamate dehydrogenase, which in turn participate in the urea cycle to form urea [28].

Phenylalanine is aromatic essential glucogenic and ketogenic amino acid. In metabolism phenylalanine is converted in to tyrosine. In metabolism homogenstic acid is formed which undergoes cleavage and form fumarate and acetoacetate. The hormones such as adrenaline, noradrenaline, tyrosine and melanin pigment formed from tyroxine.Several abnormalities observed inphenyl nine metabolisms such as phenylketonuria and alkaptonaria.

Methionine [29] is essential glycogenic amino acid. It is the only common amino acidpossessing an ether linkage. Cereals have sufficient quantity of mehionine whereas pulses lack in it. It is methylation product of homocysteine. Apart from its role as a protein constituent and as an essentialamino acid, methionine is particularly important as a donor of active methyl groups.

Copper is a transition metal ion and is used by various enzymes in the body in different biochemical reactions. These reactions may be creating, decreasing the body's inflammatory blood clotting [30] etc. Copperis absorbed by the body at two main sites such as small intestine and stomach. Copperdoes not float through the blood stream as copper ion but is carried by proteins. Two main carrier proteins especially for copper are ceruloplasmin [31] and albumin; thesecan carry many things including copper. Copper is stored in proteins called metallothione [32-34].

Survey of literature reveals that no work hasbeen reported on complex tendencies ofdrug 1-[3,4,5-triethoxyphenyl-3(2-Hydroxyphenyl) propane 1, 3 dione with transition metal ion copper (II) in THF water solution. Therefore in order to understandthe complex formation tendencies of 1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione it was though worthwhileto determine the formation constant 1:1:1ternary complexes of 1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione with copper (II) in thepresence of amino acids in 50%(v/v) THF-water medium at 30°C at a fixed ionicstrength 0.1 M $NaClO_4$.

Materials and Methods

Experimental

Micro analysis of the ligand is performed at the Central Drug Research Institute (CDRI). The H^1 NMR spectra of ligand were recorded on EM-360 spectrophotometer at RSIC, Punjab University, Chandigarh (India) [35]. IR spectra of ligand were recorded in KBr pelleton a FTIR-4100 Jasco in the region 4000 cm^{-1}-400 cm^{-1}.

Reagents and chemicals

The glass distilled water was collected in a Stoppard bottle and always used fresh. Its pH was about 6.60 to 6.80. THF: HPLC grade THF was freshly distilled and used. Commercial THF was purified by standard method described by Vogel [34]. All other chemicals like perchloric acid, sodium perchlorate and sodium hydroxide were of AR grade, obtained either from B.D.H. (London) or E. Merck, Reidal (Germany). The solutions of above reagents were prepared in CO_2 free glass distilled water by taking precautions to avoid errors in their concentrations. Exact normalities were obtained by standard methods.

Instruments

An Elico model LI-120 digital *p*H meters in conjunction with an Elico combined electrode consisting of glass and reference electrodes in a single entity of the type CL-51 was used for the *p*H measurements. Synthesis and characterization of 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 dione [35].

Series of amino acids were of Anal R quality, obtained from Fluka (Germany) and were used as secondary ligands. These were recrystallized and their purity was checked by their M.P. Fresh solution of β-dike tone in freshly distilled THF and acid solutions in glass distilled water were prepared before performing the titrations. The potentiometric titration technique for the study of the mixed ligand complexes includes the titration of free $HClO_4$ (A).
Free $HClO_4$+Ligand 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 dione Drug (A+L).
Free $HClO_4$+Ligand 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 dione+Metal ion (A+L+M) Free $HClO_4$+Ligand Amino acids (A+R).
Free $HClO_4$+Ligand Amino acids+Metal ion(A+R+M).
Free $HClO_4$+Ligand Amino acids+Ligand 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 dione+Metal ion (A+R+L+M).

Against standard solution of sodium hydroxide, were drug 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 dione and amino acid are two ligands. The ionic strength of solution was maintained constant i.e. 0.1 M by the addition of appropriate amount of sodium perchlorate solution. All the titrations are carried out at 30°C in an inert atmosphere by bubbling oxygen free nitrogen gas through the assembly containing the electrodes to keep out CO_2. The formation constant of ternary complexes were determined by computational programme SCOGS [36] to minimize the standard derivation.

Result and Discussion

Binary metal complexes

The proton ligand constant and metal ligand stability constant of 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 dione (L) and amino acids with Copper (II) determined in 50% (v/v) THF-Water mixture at 30°C and ionic strength μ=0.1 M $NaClO_4$ are given in Table 1.

TABLE 1. **The proton ligand constant and metal ligand stability constant of 1-[3,4,5-triethoxy phenyl Propane 1,3 dione and amino acids with copper (II) determined in 50% (v/v) THF-water mixture at 30°C and ionic strength μ=0.1 M $NaClO_4$.**

Ligands	**PK_1**	**PK_2**	**Copper**	
			$Logk_1$	**$Logk_2$**
1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione				
Glycine	3.13	10.81	10.35	8.99
Leucine	3.88	11.21	10.74	8.14

Tryptophan	3.74	10.58	10.92	9.12
Serine	3.4	10.43	9.92	8.41
Valine	3.08	10.76	9.91	8.67
Alanine	3.61	11.48	9.79	7.97
Phenylalanine	3.55	10.34	8.37	8.07
Methionine	3.71	10.39	10.13	7.78

Ternary metal complexes

In the ternary systems, the mixed ligand titration curve coincides with acid+drug complex curve up to pH 2.8 and deviates afterwards. Theoretical composite curve remains towards left of the experimental mixed ligand curve, which is the indicative of mixed ligand complex formation. Since the mixed ligand curve do not coincides witheither of the individual metal ligand binary complex curves, the formations of 1:1:1 complex by simultaneous equilibria wasinferred.

The primary ligand 1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione (L_1) form 1:1 and secondary ligand amino acids such as Glycine, Tryptophan, Serine, Valine, Alanine, Phenylalanine and Methionine form 1:1 and 1:2 complexes with Cu (II). It is evident from the figure of the percentage concentration species Cu (II)-1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione (L)-amino acids system,that the percentage distribution curve offree metal decreases sharply with increasing pH.

Species distribution studies

To visualize the nature of the equilibria andto evaluate the calculated stability constantof ternary complexes Cu (II)-1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione (L_1)-glycine, speciesdistribution curves have been plotted as afunction of pH at temperature 30°C and ionicstrength μ=0.1 M $NaClO_4$ using SCOGprogram. From the SCOG distribution curve it is concluded that the formation of ternary complex started only after the metal-primary complex has attained its maximum concentration. This indicates that the metal-primary ligand complex Cu (II)-1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione (L_1) is formed first and the secondary ligand Cu (II)-glycine coordinated to it, resulting the formation of ternary complex.

According to this method in this system ternary complex of 1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione (L_1) with glycine, leucine, tryptophan, serine, valine, alanine, phenylalanine, and methionine show the following types of the concentration species distribution.

$C_1=H_2L_1 \rightleftharpoons HL_1+H$
$C_2=HL_1 \rightleftharpoons H+L_1$
$C_3=H_2R \rightleftharpoons HR+R$
$C_4=HR \rightleftharpoons H+R$
$C_5=M+L_1 \rightleftharpoons ML_1$
$C_6=ML_1+L_1 \rightleftharpoons ML_2$
$C_7=M+R \rightleftharpoons MR$
$C_8=MR+R \rightleftharpoons MR_2$
$C_9=M+L+R \rightleftharpoons MLR$

Where M=Metal; L=β-diketone; R=Amino acid

The stability constant of ternary complexes. The relative stabilities of the binary and ternary complexes are quantitatively expressed in terms of β_{111}, β_{20}, β_{02}, K_L, K_R, K_r and log K values which are presented in Table 1. The values of β_{111}, β_{20} and β_{02}, reveals the preferentialformation of ternary complexes over bothbinary complexes of 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 Dione and Glycine ligands. Theconsiderably high positive values of K_L and K_R indicate that the ternary complex ishighly stable as compared to the metalcomplex of primary and secondary ligands. Inaddition to this, the positive values of K_r support the higher stability of ternarycomplexes than the binary complexes. Theobserved slight negative values of log K is in accordance with HSAB principle [Greaser R and Singh H, inorg. Chem. 9(1970) 1238] which states that the log K value is less negative when the secondary ligand coordinates through an oxygen and a nitrogen atom viz. amino

acids. In order to demonstrate the mechanism of the formation of ternary complex, various equilibria involved in the process are taken into consideration. In addition to equilibrium reaction 5, the following reaction equilibria are also possible for the formation of ternarycomplex.

$$ML+R \rightarrow MLR \quad (6)$$
$$MR+L \rightarrow MLR \quad (7)$$

The other way of characterizing the ternary complexes is by disproportionate reaction.

$$ML_2+MR_2 \rightarrow 2MLR \quad (8)$$

This reaction is possible only if both the ligands form 1:1 and 1:2 complexes

$$ML_2+MR \rightarrow MLR+ML \quad (4)$$
$$MR_2+ML \rightarrow MLR+MR \quad (5)$$
$$ML+MR \rightarrow MLR+M \quad (6)$$

The reactions (4) and (5) correspondsto the systems containing one ligand which forms only 1:1 complex and the other formsboth 1:1 and 1:2 complexes. The equilibriumreaction (6) represents the system containing the ligands which forms 1:1 complexes with the metal ion. This reactionis possible only if the sufficient concentration of ML and MR are available. The stability of ternary complexes in terms of secondary ligands is also examined in the present study. The observed order of stability of Cu (II) complexes is as follows.

For Cu 1-[3,4,5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1,3 dione Amino acid Leucine R_2>Glycine R_1>Valine R_5>Tryptophan R_3>Methionine R_8>Serine R_4>Alanine R_6>Phenylalanine R_7 Among these, K_r is a statistical relationship and gives the relative stability of mixed ligand chelate with the overall stabilities of binary chelates. It can be seen from Table 2 that the K_r values are positive for all the ternary chelates investigated in the presentwork which shows that $\beta_{111}>\beta_{20}>\beta_{02}$. The magnitudes of K_r are almost same in therange of 0.99 to 1.4 for all the systems, suggesting that the ternary chelate in every case is more stable than binary ones. In addition to K_r, two more constants K_R and K_L are calculated and used to discuss the relative stability of mixed ligand and binary complexes.

TABLE 2. **Parameters based on some relationship between the formation of ternary complexes ofCopper (II) metal ion with 1-[3, 4, 5-triethoxyphenyl-3(2-hydroxyphenyl) propane 1, 3 dione (L) in the presence of amino acids (1:1:1) system. [Temp=30°C; Ionic strength=0.1 M $NaClO_4$; Medium=50% (V/V) THF-Water].**

Amino Acids	β11	β 20	β02	K_L	K_R	K_r	Δ log K
Glycine	19.43	18.14	19.35	9.5	9.08	1.14	-0.84
Leucine	19.9	18.14	18.88	9.97	9.16	1.15	-0.76
Tryptophan	19.19	18.144	20.04	9.27	8.27	1.01	-1.64
Serine	18.32	18.14	18.33	8.4	8.4	1	-1.51
Valine	19.29	18.14	18.39	9.36	9.37	1.11	-0.55
Alanine	18.07	18.14	17.76	8.14	8.28	1.01	-1.69
Phenylalanine	17.25	18.14	16.44	7.32	8.88	0.99	-1.04
Methionine	18.75	18.4	17.91	8.83	8.62	1.08	-1.29

Conclusion

In all the systems studies, the value of K_L is greater than K_{20}. Same trend isseen from all the systems. Similarly the value of K_R for all the system with some exceptions is greater than K_{02}. These higher values of K_L and K_R indicate that the formation of ternary complexes is favorable than the formation of 1:2 binarycomplexes of both the ligands. The positive values of Kr in all the systems also confirm that the ternary complexes are more stable than their corresponding binarycomplexes. A simpler way of this comparison is to obtain Δ log K values. In thepresent work Δ log K values are calculated for all the systems by using relationship. $\Delta \log K=\log \beta_{MLR}-(\log_{KML}+\log_{KMR})$. It is observed from theTable that Δ log K values of all the ternary systems

are negative values which indicatethe extra stabilization of ternary complexes.

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The Authors Declared that the research Work was carried out on their Own.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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