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Determination of Stability Constants of Mixed Ligand Complexes of Tricine and Amino Acids with Cd(II) by Potentiometric Titration Method

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A potentiometric titration technique has been used to determine the stability constants for the various complexes of Cd(II) with tricine (T) as primary ligand and amino acids (L) as secondary ligand in aqueous solution at 25 °C and ionic strength of I = 0.1 M ($NaNO_3$). The relative stabilities of the ternary complexes are compared with those of the corresponding binary complexes and explained in view of their Δ log K values. Finally, species distributions in solution for all complexes were also evaluated.

Keywords: Tricine, Amino acids, Potentiometric studies, Stability constants.

INTRODUCTION

In view of the fact that ternary metal complexes play a pivotal role in various fields such as biological systems, chemotherapy and as catalysis, the formation, stabilities and reactivities of these complexes have been an active field of research [1-4]. Tricine compound is an interesting chelating agent due to their flexibility to bind with metal ions forming unidentate, bidentate and tridentate structures [5]. Metal complexes involving such compounds are of immense biological interest because of their role in the exchange and transport mechanism of trace metal ions in the biological systems [6].

The toxicology of cadmium(II) is often governed by its interaction with an abundance of certain potential ligands in biological systems [7-10]. In animals, Cd(II) accumulates mainly in the liver and kidney, where it is largely bound to thionein, a sulphur-rich protein [11-13]. In red blood cells, Cd(II) has been shown to become complexed by glutathione (GSH) and haemoglobin [14]. The goal of chelating agents treatment of metal intoxication is to transform a toxic metal bound to a constituent (usually a protein) of a living organism into a less toxic metal chelate which is readily excreted. In discussing chelating agent design it was reported that stability constant has long been recognized as a key factor in the determination of the ability of the chelating agent to remove the metal from living organism [15,16]. In the course of the search for a new antidote for cadmium, tricine, Fig. 1 was found to form extremely stable complex with Cd(II) ion. Hence, it seems interesting to study the formation equilibrium of Cd(II)-tricine (T) complex and to investigate its interaction with other ligands

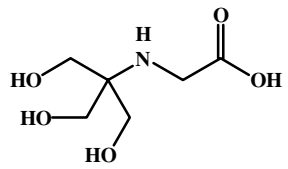

Fig. 1. Chemical structure of tricine

commonly exist in biological fluids. In continuation of our studies on the binary and ternary complexes of biological significance [17,18], we report here the stoichiometry and stability constants of tricine complexes with some selected amino acids by potentiometric titration method.

EXPERIMENTAL

Tricine was obtained from Aldrich. The amino acids and related compounds, glycine, β-phenylalanine, valine, serine, methylamine, methionine, S-methylcysteine, histidine, histamine, lysine, ornithine, aspartic acid and mercaptoethylamine were provided by Sigma. All these chemicals were used as received without any further purification, their purities ranged from 99 to 99.9 %. Carbonate-free NaOH (titrant) was prepared and standardized against potassium hydrogen phthalate solution. Cadmium(II) nitrate was provided by Aldrich. The cadmium content of solution was estimated complexometrically [19].

Potentiometric titrations were followed with a Metrohm 686 titroprocessor equipped with a 665 dosimat (Switzerland). The titroprocessor and the combined glass electrode were calibrated with standard buffer solutions, KH phthalate, pH = 4.008

and a mixture of KH_2PO_4 and Na_2HPO_4, pH = 6.865 under the same experimental conditions.The temperature was maintained constant (± 0.1) by a Coloraultra thermostat.

Procedure: The experimental procedure, in the study of ternary chelated by the potentiometric titration technique, involves the titration of carbonate free solutions. The acid dissociation constants of the ligands were determined potentiometrically by titrating the ligand (40 mL) solution (1.25×10^{-3} M) of constant ionic strength 0.1 M, adjusted with $NaNO_3$. The stability constants of the binary complexes were determined by titrating 40 mL of a solution mixture of Cd(II) (1.25×10^{-3} M), the ligand (2.5×10^{-3} M) and 0.1 M $NaNO_3$. The stability constants of mixed ligand complexes were determined by titrating 40 mL of solution containing Cd(II), tricine (T) and amino acids, all of concentration (1.25×10^{-3} M) and 0.1 M $NaNO_3$.

The above solutions were virtually titrated against 0.1 mol/L NaOH in an atmosphere of pure N_2 gas. For all the titrations, HNO_3 solution was added, so that they were fully protonated at the beginning of the titrations.

Calculations: The stoichiometries and stability constants of the complex species formed in solution were determined by examining various possible composition models for the systems studied. About 110 to 150 experimental data points were available for evaluation in each run. All the dissociation and the complex formation constants were determined using the HYPERQUAD program [20] and the speciation as a function of pH using the HYSS program [21].

RESULTS AND DISCUSSION

The stability of binary and ternary complexes may be evaluated by the following equilibria (charges were omitted for simplicity):

$$lM + pT(\text{or } L) + rH \rightleftharpoons MLT_pH_r \text{ (or L)} \quad (1)$$

$$lM + pT + qL + rH \rightleftharpoons MLT_pL_qH_r \quad (2)$$

where M, T, L and H denote Cd(II), tricine, amino acids and proton, respectively.

The stability constant of the binary and ternary complexes may be represented by:

$$\log\beta_{l\,pr} = \frac{[M_lT_pH_r]_l}{[M]^l[T]^p[H]^r} \quad (3)$$

$$\log\beta_{l\,pqr} = \frac{[M_lT_pL_qH_r]}{[M]^l[T]^p[L]^q[H]^r} \quad (4)$$

It is also possible to define the stability constants of ternary complexes in relation to their corresponding binary ones, represented by the equilibria (eqns. 5 and 6):

$$M + T \rightleftharpoons MA,\ K^M_{MA} = [MT]/[M][T] \quad (5)$$

$$MT + L \rightleftharpoons MTL,\ K^M_{MA} = [MTL]/[MT][L] \quad (6)$$

Acid-base equilibria of the free ligands

Tricine: Tricine (T) exists in solution as zwitterionic amino acid. In acid medium both the carboxylate and imino groups are protonated. The calculated acid dissociation constants, expressed as pK_a values, are in good agreement with reported values [5,6] amounting to 7.70 and 2.63. The highest pKa value was due to the protonated imino group while the other value was due to the carboxylic proton. When the proton dissociation constant value of tricine ($10^{-7.70}$) is compared with that of glycine ($10^{-9.45}$), the higher value of the former may be due to the inductive electron attraction by the hydroxyl oxygen.

Amino acids (L): The results indicate that all the amino acids have undergone two reversible proton dissociation steps identified by fairly well-separated pH ranges. They can be represented by:

$$\overset{+}{N}H_3{-}CH(R)COOH \underset{-H^+}{\overset{\text{pH 2-3}}{\rightleftharpoons}} \overset{+}{N}H_3CH(R)COO^- \underset{-H^+}{\overset{\text{pH 8-10}}{\rightleftharpoons}} NH_2CH(R)COO^-$$

Beside the above two functional groups, most of the amino acids usually contain an additional acidic proton in the side chain (R). The occurrence of such protonated side-chain groups has been shown to play an important role in biological processes exhibited by peptides and proteins and other charged biomolecules. The deprotonation of these functional groups and the respective pH ranges have been extensively investigated [22]. The acid-dissociation constants of the ammonium radical $(NH_3)^+$ and of each of the side chains (R) were redetermined under the experimental conditions used for determining the stability constants of the respective binary and ternary complexes.

Binary Cd(II) complex formation equilibria with tricine (T): Potentiometric titration curves of (tricine) in presence and absence of Cd(II) ion are shown in Fig. 2. In the metal complex curve, there is a significant lowering from that of the free tricine, indicating formation of metal complexes by release of protons. Equilibrium models have been tried to fit the experimental potentiometric data for the Cd-(tricine). The selected model with the best statistical fit was found to consist of 110, 120 and 11-1 complexes. The stability constants of their complexes are given in Table-1. It was reported [23] that the chelating ligand in the 110 complex has a tendency to undergo deprotonation from one of the ($-CH_2OH$) group, affording the 11-1 complex and tricine acts as an NOO tridentate ligand, where it chelates to the metal ion through the carboxylic oxygen and imino nitrogen in addition to one of the ($-CH_2OH$) alcoholic oxygen atoms after deprotonation. The concentration distribution diagram of various species as a function of pH is depicted in Fig. 3.

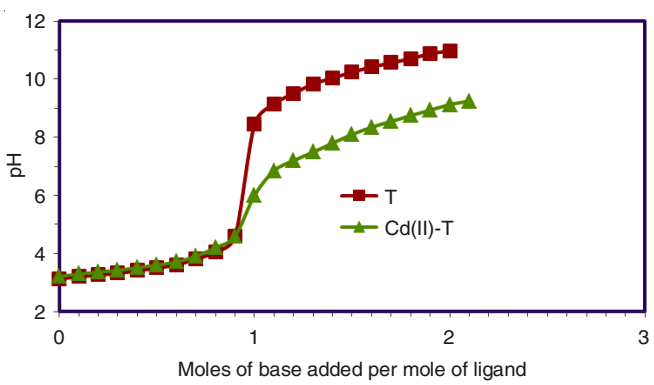

Fig. 2. Potentiometric titration curves of free tricine and Cd(II)-tricine obtained from aqueous solution

TABLE-1
FORMATION CONSTANTS OF THE BINARY COMPLEXES IN Cd(II)-TRICINE OR AMINO ACIDS SYSTEMS AT 25 °C AND 0.1 M IONIC STRENGTH

System	l	P	q*	log β**	S***
Tricine (T)	0	1	1	7.70 (0.02)	2.3×10^{-7}
	0	1	2	10.33 (0.03)	
	1	1	0	4.23 (0.01)	2.6×10^{-8}
	1	2	0	8.89 (0.03)	
	1	1	-1	-3.22 (0.04)	
Glycine	0	1	1	9.45 (0.00)	1.3×10^{-9}
	1	1	0	5.33 (0.01)	4.4×10^{-8}
	1	2	0	9.77 (0.02)	
	1	3	0	12.34 (0.01)	
β-Phenylalanine	0	1	1	9.12 (0.01)	8.0×10^{-8}
	0	1	2	11.01 (0.03)	
	1	1	0	4.13 (0.02)	6.9×10^{-9}
	1	2	0	7.55 (0.02)	
	1	3	0	11.76 (0.01)	
Valine	0	1	1	9.57 (0.01)	9.9×10^{-9}
	0	1	2	11.70 (0.03)	
	1	1	0	4.56 (0.01)	1.2×10^{-9}
	1	2	0	9.23 (0.01)	
	1	3	0	11.99 (0.05)	
Serine	0	1	1	9.14 (0.05)	1.7×10^{-8}
	0	1	2	11.40 (0.01)	
	1	1	0	5.12 (0.01)	2.8×10^{-8}
	1	2	0	9.86 (0.02)	
	1	3	0	12.46 (0.01)	
Methylamine	0	1	1	10.43 (0.01)	8.9×10^{-8}
	1	1	0	4.00 (0.01)	6.9×10^{-8}
	1	2	0	8.15 (0.03)	
	1	3	0	10.89 (0.05)	
Methionine	0	1	1	9.100 (0.00)	8.0×10^{-8}
	0	1	2	11.08 (0.03)	
	1	1	0	5.12 (0.03)	6.0×10^{-8}
	1	2	0	9.01 (0.03)	
	1	3	0	12.45 (0.01)	
S-Methylcysteine	0	1	1	8.43 (0.01)	1.6×10^{-8}
	1	1	0	5.12 (0.01)	2.6×10^{-8}
	1	2	0	10.65 (0.02)	
	1	3	0	11.25 (0.03)	
Histidine	0	1	1	9.53 (0.01)	1.8×10^{-7}
	0	1	2	15.81 (0.03)	
	0	1	3	17.81 (0.06)	
	1	1	0	7.12 (0.06)	6.4×10^{-9}
	1	2	0	13.78 (0.04)	
Histamine	0	1	1	9.85 (0.01)	1.2×10^{-7}
	0	1	2	16.07 (0.01)	
	1	1	0	6.23 (0.01)	6.9×10^{-8}
	1	2	0	10.41 (0.03)	
	1	3	1	13.01 (0.03)	
Aspartic acid	0	1	1	9.68 (0.01)	3.8×10^{-8}
	0	1	2	13.35 (0.01)	
	1	1	0	6.76 (0.01)	5.1×10^{-8}
	1	2	0	11.87 (0.01)	
Lysine	0	1	1	10.60 (0.00)	1.3×10^{-8}
	0	1	2	19.85 (0.00)	
	1	1	0	6.92 (0.04)	6.9×10^{-8}
	1	2	0	11.87 (0.06)	
Ornithine	0	1	1	10.58 (0.00)	1.0×10^{-8}
	0	1	2	19.44 (0.01)	
	0	1	3	21.39 (0.02)	
	1	1	0	7.19 (0.05)	1.8×10^{-8}
	1	2	0	10.78 (0.02)	
	1	3	1	15.77 (0.04)	
Mercaptoethylamine	0	1	1	10.37 (0.01)	3.7×10^{-8}
	0	1	2	18.64 (0.02)	4.9×10^{-7}
	1	1	0	10.06 (0.03)	
	1	2	0	17.98 (0.05)	

*l, p and q are the stoichiometric coefficient corresponding to Cd(II), T or amino acids and H^+, respectively.
**Standard deviations are given in parentheses; ***Sum of square of residuals.

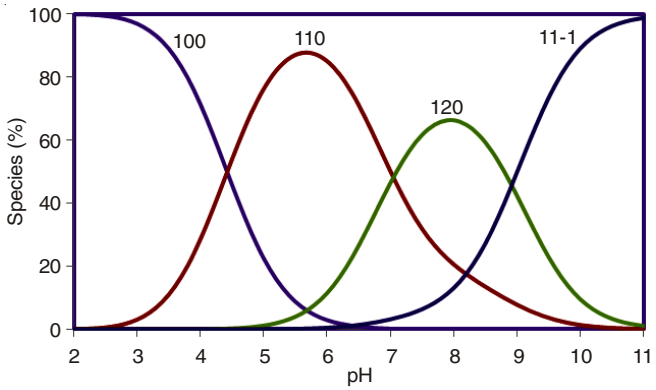

Fig. 3. Concentration distribution of various species as a function of pH in the Cd(II)–tricine system.

Ternary Cd(II) complex formation equilibria involving tricine and amino acids: The ternary complex formation may proceed either through a stepwise or simultaneous mechanism depending on the chelating potentiality of tricine and other ligands. The formation constants of 1:1 Cd(II) complexes with tricine or amino acids are of the same order of magnitude (Table-1). Consequently the ligation of tricine and amino acid will proceed simultaneously. The stability constants of their complexes are given in Table-2. The titration data of the ternary complexes with amino acids (HL) and tricine (HT) fit satisfactory with formation of the species Cd(T), Cd(L), $Cd(L)_2$ and Cd(T)(L). The formation of mixed-ligand complex by simultaneous mechanisms may be confirmed by comparing the theoretical curve, conducted based on the calculated formation constants and the experimental titration data points, glycine complex, taken as a representative, is given in Fig. 4. The good fit obtained is indicative of the validity of the complex formation model. Thus, the formation of ternary complexes can be described by following equilibria:

$$HT \rightleftharpoons H + T$$

$$HL \rightleftharpoons H + L$$

$$Cd + L \rightleftharpoons CdL$$

$$Cd + 2L \rightleftharpoons CdL_2$$

$$Cd + T \rightleftharpoons CdT$$

$$Cd + T + L \rightleftharpoons Cd\,(T)\,(L)$$

(Charges are omitted for simplicity)

It has to be mentioned that the acid dissociation constants of the carboxylic groups of tricine and amino acid are not considered as the stability constants of their complexes are determined in the pH range where this group is completely dissociated. Amino acids form 1110 complexes but methylamine forms 1110 and 1120 complexes as seen in Table-2. The methylamine complex (1110) is less stable than those of amino acids. This indicates that amino acids function as bidentate ligands coordinating through the amino and carboxylate groups.

Histidine is a tridentate ligand and may coordinate in a glycine-like or histamine-like way. The stability constant value of the histidine complex is higher than that of α-amino acids and close to that of histamine. This indicates that histidine is coordinating in the histamine - like way.

The stability constant values of methionine and S-methylcysteine complexes are in fair agreement with those of α-amino acids and lower than that of mercaptoethylamine (N,S-donor set). This may be taken to indicate that methionine and S-methylcysteine chelate through the α-amino and carboxylate groups.

Ornithine was found to form more stable complex than α-amino acids. The stability constant of its complex is higher than those of α-amino acids, by about four logarithmic units.

TABLE-2
FORMATION CONSTANTS OF THE TERNARY COMPLEXES IN Cd(II)-TRICINE-AMINO ACIDS SYSTEMS AT 25 °C AND 0.1 M IONIC STRENGTH

System	l	p	q	r*	log β**	S***	Δ log K
Glycine	1	1	1	0	9.23 (0.01)	1.2×10^{-9}	-0.33
β-Phenylalanine	1	1	1	0	8.99 (0.02)	2.9×10^{-8}	0.63
Valine	1	1	1	0	8.77 (0.01)	8.3×10^{-8}	-0.02
Serine	1	1	1	0	9.12 (0.01)	7.0×10^{-8}	-0.23
Methylamine	1	1	1	0	5.64 (0.01)	6.2×10^{-8}	-2.59
	1	1	2	0	8.00 (0.02)		
Methionine	1	1	1	0	9.12 (0.01)	7.4×10^{-9}	-0.14
S-methylcysteine	1	1	1	0	9.32 (0.01)	1.1×10^{-9}	-0.03
Histidine	1	1	1	0	10.98 (0.01)	8.2×10^{-9}	-0.44
	1	1	1	1	13.31 (0.01)		
Histamine	1	1	1	0	10.35 (0.01)	3.4×10^{-9}	-0.11
	1	1	1	1	14.68 (0.03)		
Aspartic acid	1	1	1	0	10.45 (0.01)	5.0×10^{-9}	-0.54
Lysine	1	1	1	0	9.85 (0.01)	2.4×10^{-9}	-1.48
	1	1	1	1	16.93 (0.01)		
Ornithine	1	1	1	0	11.38 (0.04)	5.6×10^{-9}	-0.06
	1	1	1	1	20.75 (0.06)		
Mercaptoethylamine	1	1	1	0	13.74 (0.06)	7.1×10^{-9}	-0.55
	1	1	1	1	18.02 (0.01)		

*l,p,q and r are the stoichiometric coefficient corresponding to Cd(II), tricine, (amino acids) and H^+, respectively.
**Standard deviations are given in parentheses. ***Sum of square of residuals.

This may be taken to indicate that ornithine most likely chelates through the two amino groups.

Unlike ornithine, the stability constant of the complex, Cd(T)-lysine, is in fair agreement with those of α-amino acids. This may be taken to indicate that lysine most likely chelates through the α-amino and carboxylate groups, because chelates formed through binding with the two amino groups will form strained eight-membered rings.

The parameter Δ log K values are generally used to indicate the relative stability of the ternary complexes as compared to the binary ones as in equations:

$$Cd(T) + Cd(L) \rightleftharpoons Cd(T)(L) + Cd$$

$$\Delta \log K = \log K^{(T)}_{Cd(T)L} - (\log K^{Cd}_{Cd(T)} + \log K^{Cd}_{Cd(L)})$$

It is worthy to mention that positive Δ log K values (Table-2) for the mixed-ligand complexes indicate that the ternary complexes are more stable than the corresponding binary complexes and this may be attributed to inter ligand interactions [24] occur in the ternary complexes. On the other hand, negative Δ log K values for the mixed-ligand complexes imply that the ternary complexes are less stable than the corresponding binary ones and therefore can be used to indicate that no interaction occurs between the ligands in the ternary complexes. However, this does not mean that the negative value Δ log K precludes the formation of ternary complexes in solution [25,26]. In this regards, the negative value may be interpreted in terms of higher stability of the binary complexes and/or reduced number of coordination sites in the ligand. Other electronic and structural factors [27,28], bond type and geometrical configuration are also expected to have an effect on Δ log K values.

Estimation of the concentration distribution of various complex species in solution provides a useful elucidation of the concentration of the complexes as a function of pH. In all the investigated systems, the concentration of the ternary complex increases with increasing pH. The concentration of Cd-tricine-amino acids ranges from about 25 to 68 % in the pH range 7.8-9.7 with different amino acids investigated. Protonated ternary complex species has been found to be most favoured at lower pH values.

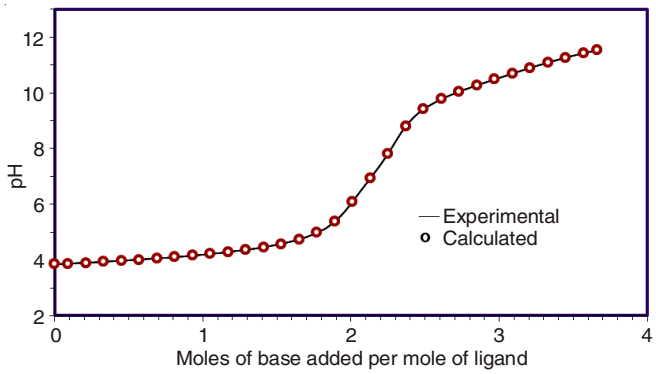

Fig. 4. Potentiometric titration curve of the Cd(II)-T-glycine system

Conclusion

The present investigation describes potentiometric study the formation constants of binary and ternary tricine (T) complexes involving Cd(II) and some amino acids in water solutions at 25 °C and ionic strength 0.1 mol/L $NaNO_3$ by HYPERQUAD program. Beside, the relative stabilities of each ternary complexes are compared with those of the corresponding binary complexes. Additionally, the concentration distribution curves of the various complex species existing in solution were evaluated.

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