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Potentiometric determination of stability constants and thermodynamic data for ternary Cd(II) complexes with 2-aminomethyl benzimidazole (AMBI) and other bioactive ligands

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ABSTRACT

The complexing properties of 2-(aminomethyl)-benzimidazole with cadmium(II) were investigated pH-metrically at 25 °C and at ionic strength of 0.1 mol.dm^{-3} ($NaNO_3$). Ternary complex formation equilibria of cadmium(II) complexes involving (AMBI) and some bio-relevant ligands (L = amino acid and peptides) have been investigated. Ternary complexes of amino acids and peptides are formed by a simultaneous mechanism. Amino acids form the complex Cd(AMBI)L, whereas amides form two complex species Cd(AMBI)L and Cd(AMBI)(LH_{-1}). The stability of ternary complexes was quantitatively compared with their corresponding binary complexes in terms of the parameters ΔLog K, Log β_{Stat} and Log X. The effect of the side chains of amino acid ligands (Δ_R) on complex formation was discussed. The values of ΔLog K indicate that the ternary complexes containing aromatic amino acids are significantly more stable than the complexes containing alkyl- and hydroxyalkyl-substituted amino acids. This may be taken as evidence for a stacking interaction between the aromatic moiety of AMBI and the aromatic side chains of the bioactive ligands. The concentration distributions of various species formed in solution were also evaluated as a function of pH. The thermodynamic parameters ΔH^o, ΔG^o and ΔS^o calculated from the temperature dependence of the equilibrium constants were investigated for the interaction of Cd(II)-AMBI with glycine as a representative example of amino acids.

1. Introduction

Ternary complexes formed between metal ions and two different types of bioactive ligands, namely heteroaromatic nitrogen bases and amino acids (or peptides) may be considered as models for substrate-metal ion-enzyme interactions and other metal ion mediated biochemical interactions [1]. Kinetic analysis did show that the ternary complex involving amino acids plays an important role in the exchange and transfer of metal ions between amino acid and albumin [2]. Recently, benzimidazole derived drugs have received much attention owing to the fact that benzimidazole residue is a constituent of vitamin B_{12} [3] which supports their potential use as therapeutics [4]. The great majority of the work of biological chemists is concerned with the coordination chemistry of essential metal ions in living organisms; and the examination of aspects of the interactions of these essential metal ions with the rest of the enzymes of the cells in which they are found. The present study however is concerned with the manipulation of the coordination environment of toxic metal ions in order to accelerate their excretion from the organism. The toxicology of Cd(II) is often governed by its interaction with an abundance of certain potential ligands in biological system [5-7]. In animals, Cd(II) accumulates mainly in the Liver and kidney, where it is largely bound to thionine, a sulfur-rich protein [8]. In red blood cells, Cd(II) is complexed by glutathione and hemoglobin [9]. 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 been long recognized as a key factor in the determination of the chelating agent ability to remove the metal from living organism [10]. Also, chelating agents that bear a charge -2 or more, such as the antidotes EDTA and 2,3-dimercaptopropanol, are not able to pass through cellular membranes to an appreciable extent. With this in mind and in the course of the search for a new antidote for Cd(II), 2-aminomethylbenzimidazole (AMBI) was electrically neutral and found to form extremely stable complex with Cd(II) ion. Also, the choice of 2-aminomethylbenzimidazole was due to the fact that compounds containing this heterocycle have been shown to exhibit a broad spectrum of pharmacological activities [11]. They include a variety of antifungal [12], antibacterial [13,14], antimicrobial [15], antiamobeic [16], antiparasitic [17] and antitumor [18]. Clinical examples include mebendazole and albendazole (antihelmintics) [19]. The antiviral activity of some 2-substituted benzimidazole derivatives considered to be related to their ability to chelate trace metal ions in biological systems [20]. Additionally, AMBI possesses two aromatic rings and one of them contains basic nitrogen (imidazole) and possesses π-accepting properties, which are expected to display a stability-enhancement due to the hydrophobic interaction with the substituted group of the amino acids or involved in the aromatic ring π-π stacking effects with purine and pyrimidine bases. Hence, it seems

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therefore to be of considerable interest to study the formation equilibria of Cd(II)-AMBI complex and to investigate its interaction with other ligands commonly exist in biological fluids (amino acids and peptides). The parameters generally used for indicating the stabilization of the mixed complexes with respect to the binary ones were also discussed.

2. Experimental

2.1. Materials and reagents

2-(Aminomethyl)-benzimidazole.2HCl (AMBI) was obtained from the Aldrich Chem. Co. These ligands: glycine, alanine, valine, β-phenylalanine, threonine, 1,1-cyclobutane dicarboxylic acid, aspartic acid, methionine, histamine.2HCl, histidine.HCl, glycinamide, glycyl-glycine, glutamine together with methylamine hydrochloride were provided by the Sigma Chem. Co. $CdCl_2.2H_2O$ were provided by BDH. Carbonate-free NaOH (titrant) was prepared and standardized against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

2.2. Instrumentations

Potentiometric measurements were made using a Metrohm 686 titroprocessor equipped with a 665 Dosimat (Switzerland-Herisau). A thermostatted glass-cell equipped with a magnetic stirring system, a Metrohm glass electrode, a thermometric probe, a microburet delivery tube and a salt bridge connected with the reference cell filled with 0.1 $mol.dm^{-3}$ KCl solution in which saturated calomel electrode was dipped are used. Temperature was maintained constant inside the cell at 25.0±0.02 °C, by the circulating water by a thermostated bath (precision ± 0.02). The titroprocessor and electrode were calibrated daily with standard buffer solutions, potassium hydrogen phthalate (pH = 4.008) and a mixture of KH_2PO_4 and Na_2HPO_4 (pH = 6.865). All titrations were carried out at 25.0±0.1 °C, in a double-walled glass cell, through the outer jacket of which water was circulated from a constant temperature bath.

2.3. Procedure and measurements

The following mixtures were prepared and titrated potentiometrically with 0.05 M NaOH solution at constant ionic strength of 0.1 $mol.dm^{-3}$ $NaNO_3$.

a) 40 mL of solution containing $1.25x10^{-3}$ $mol.dm^{-3}$ Cd(II) ion;
b) 40 mL of solution containing $1.25x10^{-3}$ $mol.dm^{-3}$ ligand (AMBI, amino acid and peptide);
c) 40 mL of solution containing $1.25x10^{-3}$ $mol.dm^{-3}$ Cd(II) ion, $1.25x10^{-3}$ $mol.dm^{-3}$ and ligand (AMBI);
d) 40 mL of solution containing $1.25x10^{-3}$ $mol.dm^{-3}$ Cd(II) ion, $2.5x10^{-3}$ $mol.dm^{-3}$ ligand (amino acid and peptide);
e) 40 mL of solution containing $1.25x10^{-3}$ $mol.dm^{-3}$ Cd(II) ion, $1.25x10^{-3}$ $mol.dm^{-3}$ AMBI, $1.25x10^{-3}$ $mol.dm^{-3}$ and ligand (amino acid or peptide).

The hydrolysis constants of Cd^{II} were determined by titrating mixture (A). The proton association constants of the ligands were determined potentiometrically by titrating mixture (B). The stability constants of the binary Cd(II)-AMBI complexes were determined by titrating mixture (C). The formation constants of Cd(II)-L (L = amino acid and peptide) were determined by titrating mixture (D). The stability constants of the mixed-ligand complexes of amino acids and peptides were determined using potentiometric data obtained from mixture (E). Furthermore, the stability constants of the ternary complexes involving amino acids were determined using potentiometric data obtained from mixtures of Cd^{II} ($1.25x10^{-3}$ M), AMBI and the amino acid solutions in a concentration ratio of 1:1:1, 1:2:1 and 1:1:2. All titrations were performed in a purified N_2 atmosphere, using aqueous 0.05 M NaOH as titrant.

The pH meter readings were converted into hydrogen ion concentration by titrating a standard acid solution (0.05 $mol.dm^{-3}$) with standard base solution (0.05 $mol.dm^{-3}$) at 25 °C and I = 0.1 $mol.dm^{-3}$ $NaNO_3$. The pH is plotted against p[H]. The relationship pH - p[H] = 0.05 was observed. $[OH^-]$ value was calculated using a pK_w value of 13.921 [21].

The general four component equilibrium can be written as follows (charges are omitted for simplicity).

$$l(Cd) + p(AMBI) + q(L) + r(H) \rightleftharpoons (Cd)l(AMBI)p(L)q(H)r \quad (1)$$

$$\beta_{lpqr} = \frac{[(Cd)_l(AMBI)_p(L)_q(H)_r]}{[Cd]^l[AMBI]^p[L]^q[H]^r} \quad (2)$$

2.4. Data processing

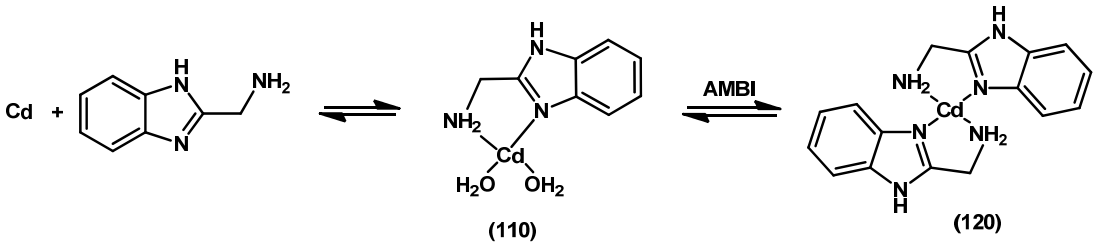
The calculations were obtained from ca. 100 data points in each titration using the computer program MINIQUAD-75 [22]. The stoichiometry and stability constants of the complexes formed were determined by trying various possible composition models. The model selected gave the best statistical fit and was chemically consistent with the titration data without giving any systematic drifts in the magnitudes of various residuals, as described elsewhere [22]. The fitted model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of the acid dissociation constant of the ligand and the formation constants of the corresponding complexes. The MINIQUAD-75 program actually computes the overall stability constants. The stepwise constants were then obtained accordingly. The species distribution diagrams were obtained using the program SPECIES [23] under the experimental condition employed.

3. Results and discussion

3.1. Protonation equilibria of AMBI and its binary complex formation equilibria

AMBI was titrated in the presence and absence of Cd(II) ion. The titration curve (Figure 1) of the Cd(II) complex was lowered from that of AMBI curve. This indicates a complex formation associated with release of hydrogen ions. The titration data as calculated for Cd(II) ions and AMBI, taking into consideration all feasible theoretical models were compared with those experimentally obtained. The equilibrium patterns were chosen so as to lie between the observed and the calculated data applying accurate statistical analysis involving the sum of squares of residuals. At this point, all protonation constants were kept constant, and the computer program MINIQUAD was applied for a second stage of refinement. The whole titration data obtained fitted with different composition models and the selected model with best statistical fit was found to consist of 1:1 and 1:2 complexes as shown in Scheme 1.

This model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of acid dissociation constants of AMBI and formation constants of the Cd^{2+} complex. The good fit is an indication of the validity of the complex. The corresponding stability constants are Log K_1 = 4.56 and Log K_2 = 3.98 i.e. the successive stability constants of the binary complexes decrease in accordance with statistical expectation. The (Log_{10} K_1-Log_{10} K_2) value is usually positive, since the coordination sites of the metal ions are more freely available for binding of the first molecule than the second one.



Scheme 1

The formation constants of M(II)-complexes of bivalent 3d transition metal ions with AMBI are in the order: Cd^{2+} (Log $K_{[Cd(AMBI)(Gly)]}$ = 9.20) < Zn^{2+} (Log $K_{[Zn(AMBI)(Gly)]}$ = 13.50) [24] < Cu^{2+} (Log $K_{[Cu(AMBI)(Gly)]}$ = 16.67) [25]. Thus, the Irving-Williams'order [26] of complexation which is related to the ligand-field stabilization energy is full field. In general, it is noted that the stability constant of the Cu^{2+} complex is quite large compared to the other metals. The ligand field will give Cu^{2+} some extra stabilization due to tetragonal distortion of the octahedral symmetry [27].

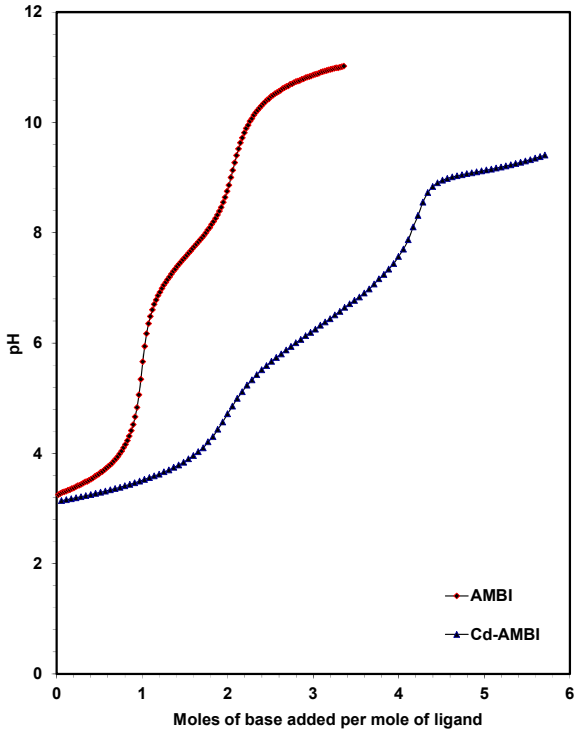


Figure 1. Potentiometric titration curve of Cd-AMBI system.

3.2. Ternary complex formation equilibria

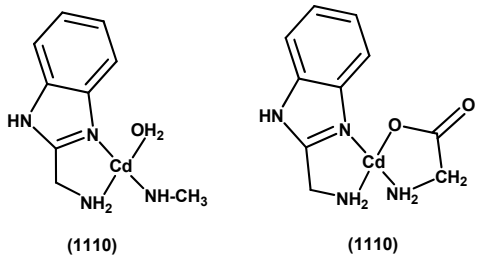
Depending on the chelating ability of the two ligands AMBI and the other ligand (L), the ternary complex formation may proceeds through either a step-wise or simultaneous mechanism. The formation constants of the binary Cd(II)-L complexes are given in Table 1. The formation constants of the binary cadmium(II) complexes with AMBI and the other selected bio-ligands were found to be of the same order. Consequently, the ligation of AMBI and the other ligands mentioned will occur simultaneously according to the following equilibrium (3), charges are omitted for simplicity.

$$Cd + AMBI + L \rightleftharpoons Cd(AMBI)L \quad (3)$$

The overall formation constants values expressed as Log β_{1110} given in Table 1 were calculated considering the acid dissociation constants of the ligands and formation constants of the binary complexes as known quantities.

3.2.1. Ternary complex formation equilibria involving amino acids

The titration data of the ternary complexes with amino acids and AMBI fit satisfactorily with formation of the species: Cd(AMBI), $Cd(AMBI)_2$, Cd(L), $Cd(L)_2$ and Cd(AMBI)(L). The stability constant of Cd(AMBI)-amino acid systems is larger than those for the corresponding monodentate methylamine complexes. This indicates that the amino acids are coordinating as bidentate ligands through the amino and carboxylate groups (Scheme 2).



Scheme 2

Evidence for formation of mixed ligand complex by simultaneous mechanism was further verified by the good agreement observed between the observed and the calculated data.

Threonine has an extra binding centre on the β-alcoholate group. This group was reported [28,29] to participate in transition metal ion complex-formation reactions. The titration curve for the threonine complex is much lower than the curves for the other amino acid complexes in the region followed by the complete formation of the (1110) complex. Also, the potentiometric data are fitted much better when the formation of the complex species with stoichiometric coefficients 1110 and 111-1 is assumed. Therefore, threonine forms, in addition to the previously mentioned complexes the Cd(AMBI)(LH_{-1}) species. The latter complex is formed through induced ionization of the β-alcoholato group, as mentioned in the literature [28,29].

Aspartic acid has one amino and two carboxylic groups as potential chelating centers. It may coordinate either via the two carboxylate groups or by the amino and one carboxylate group. The stability constant of the aspartic acid complex is in the range of those for amino acids.

Table 1. Stability constants of binary and ternary species in the Cd(II)-AMBI-amino acid systems 25 °C and 0.1 mol.dm^{-3} ionic strength using $NaNO_3$.

System	l	p	q	r [a]	Log β	S [b]
$Cd(H_2O)_6^{2+}$	1	0	0	-1	-9.11±0.07	3.6 x 10^{-6}
	1	0	0	-2	-18.57±0.06	
AMBI	0	1	0	1	7.86±0.04	4.8 x 10^{-7}
	0	1	0	2	11.11±0.05	
	1	1	0	0	4.56±0.07	1.6 x 10^{-7}
	1	2	0	0	8.54±0.06	
Glycine	0	0	1	1	9.71±0.02	3.1 x 10^{-7}
	0	0	1	2	11.99±0.03	
	1	0	1	0	4.38±0.01	2.2 x 10^{-8}
	1	0	2	0	8.02±0.02	
	1	1	1	0	9.20±0.09	2.1 x 10^{-7}
Alanine	0	0	1	1	9.69±0.01	9.2 x 10^{-8}
	0	0	1	2	11.88±0.02	
	1	0	1	0	4.19±0.03	4.6 x 10^{-9}
	1	0	2	0	7.62±0.01	
	1	1	1	0	9.01±0.08	1.0 x 10^{-6}
Phenylalanine	0	0	1	1	9.12±0.01	8.0 x 10^{-8}
	0	0	1	2	11.01±0.03	
	1	0	1	0	3.98±0.03	7.3 x 10^{-7}
	1	0	2	0	7.01±0.04	
	1	1	1	0	9.56±0.09	2.8 x 10^{-6}
Valine	0	0	1	1	9.57±0.01	9.9 x 10^{-8}
	0	0	1	2	11.70±0.03	
	1	0	1	0	3.95±0.05	2.3 x 10^{-7}
	1	0	2	0	7.05±0.04	
	1	1	1	0	9.11±0.06	1.5 x 10^{-6}
Threonine	0	0	1	1	9.06±0.01	7.9 x 10^{-8}
	0	0	1	2	11.03±0.02	
	1	0	1	0	4.02±0.04	1.3 x 10^{-9}
	1	0	2	0	7.29±0.05	
	1	1	1	0	8.52±0.08	3.1 x 10^{-7}
	1	1	1	-1	3.29±0.1	
Histamine	0	0	1	1	9.88±0.01	2.4 x 10^{-8}
	0	0	1	2	15.97±0.03	
	1	0	1	0	4.75±0.06	3.9 x 10^{-7}
	1	0	2	0	7.91±0.07	
	1	1	1	0	10.15±0.05	
	1	1	1	1	17.89±0.03	4.5 x 10^{-7}
Histidine	0	0	1	1	9.53±0.01	1.8 x 10^{-7}
	0	0	1	2	15.81±0.03	
	1	0	1	0	5.81±0.08	1.9 x 10^{-8}
	1	0	2	0	10.12±0.09	
	1	1	1	0	10.01±0.1	
	1	1	1	1	17.66±0.09	3.2 x 10^{-7}
Aspartic	0	0	1	1	9.68±0.01	3.9 x 10^{-8}
	0	0	1	2	13.35±0.01	
	1	0	1	0	4.63±0.04	2.9 x 10^{-8}
	1	0	2	0	7.75±0.07	
	1	1	1	0	9.12±0.07	2.3 x 10^{-7}
Methionine	0	0	1	1	9.10±0.01	8.9 x 10^{-8}
	0	0	1	2	11.08±0.03	
	1	0	1	0	3.82±0.01	3.8 x 10^{-9}
	1	0	2	0	7.22±0.07	
	1	1	2	0	8.09±0.08	3.1 x 10^{-7}
CBDCA	0	0	1	1	5.68±0.004	1.3 x 10^{-7}
	0	0	1	2	8.80±0.006	
	1	0	1	0	2.68±0.05	2.9 x 10^{-7}
	1	0	2	0	3.98±0.07	
	1	1	1	0	7.87±0.08	5.6 x 10^{-7}
Methylamine	0	0	1	1	10.55±0.004	8.9 x 10^{-9}
	1	0	1	0	3.59±0.04	3.9 x 10^{-6}
	1	0	2	0	6.82±0.09	
	1	1	1	0	7.48±0.07	3.8 x 10^{-7}
	1	1	2	0	13.80±0.08	

[a] l, p, q and r are stoichiometric coefficients corresponding to Cd(II), AMBI, amino acid and H^+ respectively.
[b] Sum of square of residuals.

This may reveal that aspartic acid coordinates via the amino and one carboxylate group.

Histamine has two binding sites via imidazole and amino group. Histamine has been shown to form protonated complex species (1111). The acid dissociation constants of the protonated species is given by the equation (4) [30].

$$pK^{H}_{Cd(AMBI)L} = \log K^{Cd(AMBI)}_{Cd(AMBI)(L)(H)} - \log K^{Cd(AMBI)}_{Cd(AMBI)(L)} \qquad (4)$$

The pK_a value for the histamine complex is (pK_a = 7.74), being lower than that of the protonated amino group (NH_3^+) in histamine ligand (pK_a = 9.85) considering the increase in acidity due to complex formation. This reveals that the proton in the protonated complex would be located mainly on the amino group.

Evaluation of the concentration distribution of various complex species as a function of pH provides a useful description of metal ion binding in the biological system. In all species distribution curves the concentration of the formed complex increases with increasing pH; thus making the complex formation more favored in the physiological pH range, whereas at higher value than the physiological pH, hydroxo species predominates.

Table 2. Stability constants of binary and ternary species in the Cd(II)-AMBI- peptide systems 25 °C and 0.1 mol.dm^{-3} ionic strength using $NaNO_3$.

System	l	p	q	r[a]	Log β	S[b]
Glycinamide	0	0	1	1	7.60±0.01	8.5 x 10^{-8}
	1	0	1	0	2.65±0.07	1.4 x 10^{-7}
	1	0	2	0	4.88±0.05	
	1	1	1	0	8.88±0.09	2.8 x 10^{-6}
	1	1	1	-1	0.24±0.09	
Glycylglycine	0	0	1	1	7.99±0.006	4.5 x 10^{-8}
	0	0	1	2	11.27±0.01	
	1	0	1	0	2.89±0.02	1.7 x 10^{-8}
	1	0	2	0	5.36 ±0.05	
	1	1	1	0	9.07±0.08	5.3 x 10^{-7}
	1	1	1	-1	0.19±0.09	
Glutamine	0	0	1	1	8.95±0.008	4.5 x 10^{-8}
	1	0	1	0	3.47±0.06	3.4 x 10^{-7}
	1	0	2	0	6.51±0.04	
	1	1	1	0	9.36±0.06	1.2 x 10^{-6}
	1	1	1	-1	0.21±0.01	

[a] l, p, q and r are stoichiometric coefficients corresponding to Cd(II), AMBI, peptide ligand and H^+, respectively.
[b] Sum of square of residuals.

The concentration distribution diagram of Cd-AMBI-alanine taken as a representative example of amino acids, is shown in Figure 2, the binary complexes Cd(AMBI) and $Cd(AMBI)_2$ are formed with maximum percent of 45% and 20% at pH = 7 and 7.6 respectively. The mixed ligand species [Cd(AMBI)Ala] (1110) starts to form at pH ~7.0 and with increasing of pH, its concentration increases reaching the maximum of 60 % at pH = 10.

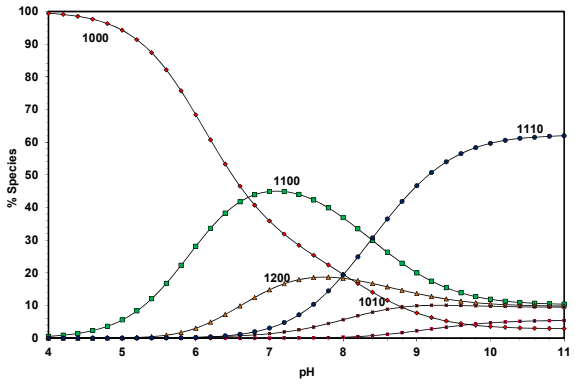


Figure 2. Concentration distribution of various species as a function of pH in the Cd-AMBI-Alanine system at concentration of 1.25x10^{-3} mol.dm^{-3} for Cd(II), AMBI and alanine, I = 0.1 mol.dm^{-3} ($NaNO_3$) and T = 25 ± 0.1 °C).

3.2.2. Ternary complex formation equilibria involving amides

Ternary complex formation of amides proceeds also through simultaneous mechanism. Cd(AMBI)(L) and Cd(AMBI)(LH_{-1}) species detected and their formation constants are given in Table 2. The amide may form the Cd(AMBI)(L) complex by coordination through the amine and carbonyl groups. On increasing the pH, the coordination sites should switch from carbonyl oxygen to amide nitrogen. Such changes in coordination centers are now well documented [31]. The amide groups undergo deprotonation and the Cd(AMBI)(LH_{-1}) complexes are formed. The pK^H values are calculated by the equation (5) [30].

$$pK^H = \text{Log } \beta_{1110} - \text{Log } \beta_{111\text{-}1} \quad (5)$$

The pK^H values of the amide complexes are 8.64, 8.88 and 9.12 for glycinamide, glycylglycine and glutamine respectively. It is noteworthy that the pK^H for the glycinamide complex is lower than the pK^Hs of other amides, this signifies that the more bulky substituent group on the amides may serve to hinder the structural change in going from protonated to deprotonated complexes. The pK^H of the glutamine complex, on the other hand is exceptionally relatively higher than the others. This is due to the formation of a seven membered chelate ring, which would be more strained and less favored. Therefore, under physiological conditions (pH = ~7.4), glutamine would coordinate in its protonated form, whereas glycinamide would preferably coordinate in the deprotonated form. The speciation diagram of glycinamide complex is given in Figure 3. The mixed ligand species [Cd(AMBI)L] (1110) starts to form at pH = ~5.2 and with increasing pH, its concentration increases reaching the maximum of 62% at pH = 7.6. Further increase of pH is accompanied by a decrease in [Cd(AMBI)L] (1110) complex concentration and an increase of [Cd(AMBI)LH_{-1}] (111-1) complex concentration reaching a maximum of 98% at pH = 10.8.

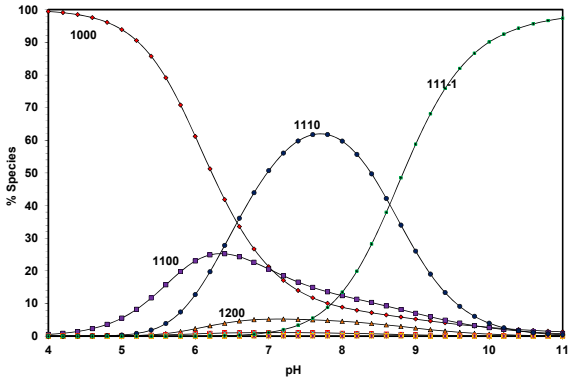


Figure 3. Concentration distribution of various species as a function of pH in the Cd-AMBI-Glycinamide system at concentration of 1.25x10^{-3} mol.dm^{-3} for Cd(II), AMBI and glycinamide, I = 0.1 mol.dm^{-3} ($NaNO_3$) and T = 25 ± 0.1 °C).

3.3. Comparison of the stability constant of the ternary complexes with those of the binary complexes

The relative stabilities of the species and the magnitudes of interactions involved can be understood by comparing the stepwise formation constants. The formation constants of Cd-AMBI and Cd-L (L = Glycine as a representative example of amino acids) are used for comparison as shown in Scheme 3.

Hence, it seems therefore to be of considerable interest to discuss the parameters generally used for indicating the stabilization of the mixed complexes with respect to the binary ones namely:

Table 3. Evaluated values of Log β; ΔLog K, ΔLog β; Log X for the formation of the ternary complexes [Cd(AMBI)(L)] and Δ_R for the side chains of amino acid ligands at 25 °C and 0.1 mol.dm^{-3} ionic strength using $NaNO_3$.

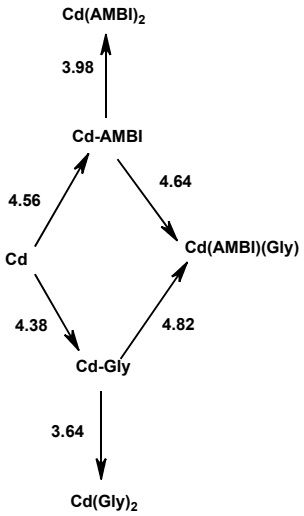
Ligand	Log β_{1110} (Exp.)	Log $\beta_{Stat.}$ [a] (Calcd.)	Δ Log β [b]	Δ Log K [c]	Log X [d]	Δ_R
Glycine	9.20	8.58	0.62	0.24	1.85	-
Alanine	9.01	8.38	0.63	0.26	1.86	0.02
Phenylalanine	9.56	8.08	1.48	1.02	3.57	0.78
Valine	9.11	8.10	1.01	0.60	2.63	0.36
Threonine	8.52	8.22	0.30	-0.06	1.21	-0.30
Histidine	10.01	9.63	0.38	-0.36	1.36	-0.60
Aspartic	9.12	8.45	0.67	-0.07	1.95	-0.31
Histamine	10.15	8.53	1.62	0.84	3.85	0.60

[a] Log β_{stat} = Log 2 +1/2 Log β_{1020} + 1/2 Log β_{1200}
[b] Δ Log β = Log β_{1110} - Log β_{stat}
[c] Δ Log K = Log β_{1110} - Log β_{1100} - Log β_{1010}
[d] Log X = 2 Log β_{1110} - Log β_{1020} - Log β_{1200}

Table 4. Evaluated values of Log β; ΔLog K, ΔLog β; Log X for the formation of the ternary complexes [Cd(AMBI)(L)] at 25 °C and 0.1 mol.dm^{-3} ionic strength using $NaNO_3$.

Ligand (L)	Log β_{1110} (Exp.)	Log $\beta_{Stat.}$ [a] (Calcd.)	Δ Log β [b]	Δ Log K [c]	Log X [d]
Glycinamide	8.88	7.01	1.87	1.67	4.34
Glycylglycine	9.07	7.25	1.82	1.62	4.24
Glutamine	9.36	7.83	1.53	1.33	3.67

[a] Log β_{stat} = Log 2 +1/2 Log β_{1020} + 1/2 Log β_{1200}
[b] Δ Log β = Log β_{1110} - Log β_{stat}
[c] Δ Log K = Log β_{1110} - Log β_{1100} - Log β_{1010}
[d] Log X = 2 Log β_{1110} - Log β_{1020} - Log β_{1200}



Scheme 3

(1) ΔLog K, the difference between the stabilities of the binary and mixed complexes. One expects to obtain negative values for ΔLog_{10} K (Tables 3 and 4), since more coordination positions are available for the bonding of ligand (L) in the binary than in the ternary complexes. According to Sigel [32], the relative stability of a ternary complex Cd(AMBI)L (1110) compared to its binary complex Cd(AMBI) (1100) or Cd(L) (1010) can be expressed quantitatively by equations (7) and (8).

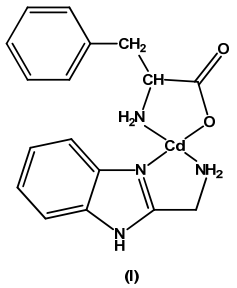
$$Cd(AMBI) + Cd(L) \rightleftharpoons Cd(AMBI)(L) + Cd \quad (6)$$

$$\Delta \text{ Log K}_{Cd(AMBI)L} = \text{Log } \beta_{Cd(AMBI)(L)} - (\text{Log } \beta_{Cd(AMBI)} + \text{Log } \beta_{Cd(L)}) \quad (7)$$

The Δ Log K value for protonated ternary complex is given by equation (8).

$$\Delta \text{ Log K} = \text{Log } \beta_{1111} - \text{Log } \beta_{1100} - \text{Log } \beta_{1011} \quad (8)$$

The Δ Log K values for ternary complex of phenylalanine is more positive than that of alanine. This may be explained on the premise that the noncoordinating aromatic side groups of pheylalanine can approach the aromatic moiety of AMBI and exert a stacking interaction as shown in structure (I) of [Cd(AMBI)Phe] complex, since the presence of an aromatic ring above the Cd(II) coordination plane is probably essential for preferential formation of ternary complexes (Scheme 4).



(I)

Scheme 4

(2) Log X, the quantitative stabilization of ternary complexes can be expressed in terms of their disproportionation constant X. The values of Log X (Tables 3 and 4) can be calculated by equations (9-11) for Cd(AMBI)L complexes.

$$Cd(AMBI)_2 + Cd(L)_2 \rightleftharpoons 2\ Cd(AMBI)(L) \quad (9)$$

$$X_{Cd(AMBI)(L)} = \frac{[Cd(AMBI)(L)]^2}{[Cd(AMBI)_2][Cd(L)_2]} \quad (10)$$

$$\text{Log X}_{Cd(AMBI)(L)} = 2 \text{ Log } \beta_{Cd(AMBI)(L)} - (\text{Log } \beta_{Cd(AMBI)2} + \text{Log } \beta_{Cd(L)2}) \quad (11)$$

The value for Log X expected from statistical reasons is +0.6 [33] for all geometries. The values of Log X in Table 3 are >> 0.6, indicating marked stabilities of the ternary complexes. A heteroaromatic N base is essential for the high stability of a ternary complex [33,34]. This was attributed to π back-bonding from the metal ion to the aromatic ligand [34-37]. The same finding was obtained for the ternary complexes formed by Cu(Pyrocatecholate) with 2-picolylamine, bipyridyl and 2-aminomethylbenzimidazole [38].

Table 5. Effect of temperature on the formation constants of Cd(AMBI)-Glycine complex at I = 0.1 mol.dm^{-3} $NaNO_3$.

System	T (°C)	l	p	q	r [a]	Log β	S [b]
Cd-AMBI-Glycine	20	0	1	0	1	7.95±0.01	2.1 x 10^{-7}
		0	1	0	2	11.23±0.02	
		0	0	1	1	9.86±0.03	3.2 x 10^{-8}
		0	0	1	2	12.17±0.05	
		1	1	0	0	4.61±0.03	5.7 x 10^{-7}
		1	2	0	0	8.64±0.06	
		1	0	1	0	4.44±0.03	3.5 x 10^{-8}
		1	0	2	0	8.14±0.07	5.9 x 10^{-7}
		1	1	1	0	9.34 ±0.08	
Cd-AMBI-Glycine	25	0	1	0	1	7.86±0.04	4.8 x 10^{-7}
		0	1	0	2	11.11±0.05	
		0	0	1	1	9.71±0.02	3.1 x 10^{-7}
		0	0	1	2	11.99±0.03	
		1	1	0	0	4.56±0.07	1.6 x 10^{-7}
		1	2	0	0	8.54±0.06	
		1	0	1	0	4.38±0.01	2.2 x 10^{-8}
		1	0	2	0	8.02±0.02	
		1	1	1	0	9.20±0.09	2.1 x 10^{-6}
Cd-AMBI-Glycine	30	0	1	0	1	7.78±0.06	1.8 x 10^{-7}
		0	1	0	2	11.01±0.08	
		0	0	1	1	9.58±0.03	5.1 x 10^{-7}
		0	0	1	2	11.83±0.05	
		1	1	0	0	4.50±0.05	3.6 x 10^{-7}
		1	2	0	0	8.43±0.08	
		1	0	1	0	4.31±0.04	4.9 x 10^{-7}
		1	0	2	0	7.90±0.06	
		1	1	1	0	9.07±0.07	8.1 x 10^{-7}
Cd-AMBI-Glycine	35	0	1	0	1	7.70±0.03	3.5 x 10^{-7}
		0	1	0	2	10.90±0.05	
		0	0	1	1	9.43±0.03	7.1 x 10^{-8}
		0	0	1	2	11.65±0.04	
		1	1	0	0	4.44±0.05	3.6 x 10^{-7}
		1	2	0	0	8.32±0.05	
		1	0	1	0	4.25±0.03	2.2 x 10^{-7}
		1	0	2	0	7.78±0.04	
		1	1	1	0	8.94±0.08	9.2 x 10^{-7}

[a] l, p, q and r are stoichiometric coefficients corresponding to Cd(II), AMBI, Glycine and H^+, respectively.
[b] Sum of square of residuals.

(3) Δ Log β, the stabilization constant which results from the difference of the stability constant measured for the mixed complex and that calculated from statistical grounds. The stability of the ternary complexes investigated can also be calculated using a statistical method [39] according to the equation (12).

$$\text{Log } \beta_{stat} = \text{Log } 2 + 1/2 \text{ Log } \beta_{1020} + 1/2 \text{ Log } \beta_{1200} \quad (12)$$

The values of Log β_{stat} for the mixed ligand complexes detected in this study are shown in Tables 3 and 4. The large differences of Δ Log β values (Log β_{1110} - Log β_{stat}) indicate that the Cd(AMBI)L system is more stable than both $Cd(AMBI)_2$ and $Cd(L)_2$.

3.4. Δ_R of amino acids

In order to evaluate the effect of the side chains of the amino acid ligands on their ability to coordinate with the binary Cd-AMBI, the parameter Δ_R, defined by equation (13), is reasonably considered [40],

$$\Delta_R = \text{Log } K_{Cd(AMBI)(L)} - \text{Log } K_{Cd(AMBI)(gly)} = (\text{Log } \beta_{1110(L)} - \text{Log } \beta_{1110(gly)}) - (\text{Log } \beta_{1010(L)} - \text{Log } \beta_{1010(gly)}) \quad (13)$$

Using Δ_R only the effect of the side chains can be extracted, referring to the hydrogen of glycine. The parameter Δ_R represents the Logarithm of the equilibrium constant of the apparent ligand exchange reactions shown by equation (14),

$$Cd(AMBI)(gly) + Cd(L) \rightleftharpoons Cd(AMBI)(L) + Cd(gly) \quad (14)$$

By viewing the values of Δ_R listed in Table 3, it is quite evident that the aromatic side chains have a large stability-enhancing effect compared with the hydrogen of glycine, also the C-alkyl side chains show a stability-enhancing effect. This fact indicates that

a) A ring stacking interaction with the aromatic side chains.
b) A sort of hydrophobic intramolecular interaction operating between the hydrophobic moiety of AMBI and the alkyl groups in aqueous solutions. Such a hydrophobic interaction has been reported for the ternary complexes including phen or Bipy and C-alkyl substituted amino acids [41,42]. Since the hydrophobicity of the aromatic amino acids is large compared with that of the alkyl side groups [42,43]. This probably the reason why the ternary complexes containing AMBI and the aromatic amino acids show high stabilities.
c) The extent of intramolecular ligand-ligand interaction decreases in the series aromatic-aromatic > aromatic-aliphatic > aliphatic-aliphatic.
d) Hydrophobic interactions are very important in amino acid complexes [21].

3.5. Effect of temperature

The values obtained for the thermodynamic parameters ΔH^o, ΔS^o and ΔG^o, associated with the protonation of AMBI, Gly and its complex formation with Cd(II) species were calculated from the temperature dependence of the data in Table 5. ΔH^o and ΔS^o were obtained by linear least square fit of ln K versus 1/T ($\ln K = -\Delta H^o/RT + \Delta S^o/R$) leading to an intercept $\Delta S^o/R$ and a slope $-\Delta H^o/R$, where K is the equilibrium constant.

Table 6. Thermodynamic parameters for protonation and complex formation equilibria of [Cd(AMBI)(Gly)] system in aqueous solution at I = 0.1 mol.dm^{-3} $NaNO_3$*.

T (°C)	Log K_1	ΔG_1^o	ΔH^o	ΔS_1^o	Log K_2	ΔG_2^o	ΔH^o	ΔS_2^o
AMBI								
20	7.95	-44.83	-28.68	54.19	3.28	-18.73	-12.44	20.68
25	7.86				3.25			
30	7.78				3.23			
35	7.70				3.20			
Cd-AMBI								
T (°C)	**Log K_1**	**Log K_2**	**Log K_1 – Log K_2**	**ΔG_1^o**	**ΔH_1^o**	**ΔG_2^o**	**ΔH_2^o**	**ΔS_1^o**	**ΔS_2^o**
20	4.61	4.03	0.58	-26.10	-19.66	-20.47	-17.28	21.62	10.72
25	4.56	3.98	0.58						
25	4.50	3.93	0.57						
35	4.44	3.88	0.56						
Gly								
T (°C)	**Log K_1**	**ΔG_1^o**	**ΔH_1^o**	**ΔS_1^o**	**Log K_2**	**ΔG_2^o**	**ΔH_2^o**	**ΔS_2^o**
20	9.86	-55.40	-49.07	21.25	2.31	-13.00	-10.36	8.85
25	9.71				2.28			
25	9.58				2.25			
35	9.43				2.22			
Cd-Gly								
T (°C)	**Log K_1**	**Log K_2**	**Log K_1 – Log K_2**	**ΔG_1^o**	**ΔH_1^o**	**ΔG_2^o**	**ΔH_2^o**	**ΔS_1^o**	**ΔS_2^o**
20	4.44	3.70	0.79	-25.02	-22.12	-20.81	-19.35	9.57	4.80
25	4.38	3.64	0.74						
30	4.31	3.59	0.68						
35	4.25	3.53	0.63						
Cd-AMBI-Gly								
T (°C)	**Log K**	**ΔG^o**	**ΔH^o**	**ΔS^o**				
20	9.34	-52.47	-45.97	21.83				
25	9.20							
30	9.07							
35	8.94							

* ΔG^o, kJ/mol; ΔH^o, kJ/mol and ΔS^o, J.K/mol.

The thermodynamic parameters ΔH^o, ΔS^o and ΔG^o were given in Table 6 and the linear relation for Cd(AMBI)-Gly complex between Log K and 1/T is given in Figure 4. The main conclusions from the data can be summarized as follows.

(1) The protonation reactions of AMBI can be represented by equations (15) and (16):

$$L + H^+ \rightleftharpoons HL^+ \qquad K_1 = [HL^+]/[L][H^+] \qquad (15)$$

$$HL^+ + H^+ \rightleftharpoons H_2L^{2+} \qquad K_2 = [H_2L^{2+}]/[HL^+][H^+] \qquad (16)$$

(2) The protonation reactions of glycine can be represented by equations (17) and (18):

$$L^- + H^+ \rightleftharpoons HL \; K_1 = [HL^+]/[L][H^+] \qquad (17)$$

$$HL + H^+ \rightleftharpoons H_2L^+ \; K_2 = [H_2L^{2+}]/[HL^+][H^+] \qquad (18)$$

The thermodynamic processes accompanying the protonation reactions are:

a) the neutralization reaction, which is an exothermic process;
b) desolvation of ions, which is an endothermic process;
c) the change in the configuration and the arrangements of the hydrogen bonds around the free and protonated ligands.

(3) The Log K^H values for the protonation reaction of AMBI and glycine as given in equations 15-18 decrease with increasing temperature. This means that, the dissociation constants increase with the increase of the temperature revealing that their acidity increase with increasing temperature [44]

(4) A negative value of ΔH^o for the protonation process of both ligands indicates that their association process is accompanied by a release of heat and the process is exothermic.

(5) The protonation reaction of the ligands has positive entropy; this may be due to increased disorder as a result of desolvation processes and the breaking of hydrogen bonds. Moreover, the second protonation processes are accompanied by less positive entropy than the first one.

The stepwise stability constants of the Cd-AMBI and Cd-Gly complexes formed at different temperatures were calculated and the average values are included in Table 6. These values decrease with increasing temperature (Figure 4), confirming that the complexation process is more favorable at lower temperatures. From these results the following conclusions can be made.

1. All values of ΔG^o for complexation are negative, indicating that the chelation process proceeds spontaneously.
2. The negative values of ΔH^o show that the chelation process is exothermic, indicating that the complexation reactions are favored at low temperatures. Furthermore, when a coordinate bond between the ligand and the metal ion is formed, the electron density on the metal ion generally increases. Consequently, its affinity for a subsequent ligand decreases, leading to an increase in ΔG^o and ΔH^o of complexation.
3. It is generally noted that $-\Delta G_1^o > -\Delta G_2^o$ and $-\Delta H_1^o > -\Delta H_2^o$. This may be attributed to the steric hinderance produced by the entrance of a second ligand.
4. The ΔS^o values for all investigated complexes are positive, indicating that the increase in entropy by the release of bound solvent molecules on chelation is greater than the decrease resulting from the chelation process itself. It occurs because the solvent molecules arranged in an orderly fashion around the ligand and the metal ion has acquired a more random configuration on chelation.

4. Conclusions

The present investigation describes the formation equilibria of Cd(II) complexes involving 2-(aminomethyl)-benzimidazole and some ligands of biological significance. In combination of stability constants data of such Cd(II) complexes with amino acids and peptides, it would be possible

to calculate the equilibrium distribution of the metal species in biological fluids where most types of ligands are present simultaneously. This would form a clear basis for understanding the mode of action of such metal species under physiological conditions. From the above results it may be concluded that ternary complex formation proceeds through simultaneous mechanism. Amino acids form highly stable complexes; the substituent on the α-carbon atom has a significant effect on the stability of the formed complex. The β-alcoholate group in the side chain of the amino acid threonine has been found to play an essential role in the functionating of a number of proteolytic enzymes, e.g. chymotrypsin and subtilisin [Cd(AMBI)LH_{-1}] is formed through induced ionization of the alcohol group of threonine under complex formation as reported in the literature [18,21,23]. The present study shows clearly that the deprotonation of the peptide bond was promoted under complex formation. Also, the slight difference in the side chain of the peptides seems to produce dramatic differences in their behavior on complexation process. The more positive Log X and less negative ΔLog K is attributed to the extra stability of the ternary complexes. From the values of the thermodynamic parameters, the following points could be abstracted:

a) Acidity of AMBI increases with increasing temperature.
b) The values of Log K_1-Log K_2 are positive, indicating that the coordination of the first ligand molecule to the metal ion is more favorable than the bonding to the second one.
c) The negative free energy and enthalpy changes of all the complexes indicated a spontaneous and exothermic nature of complexation reactions.

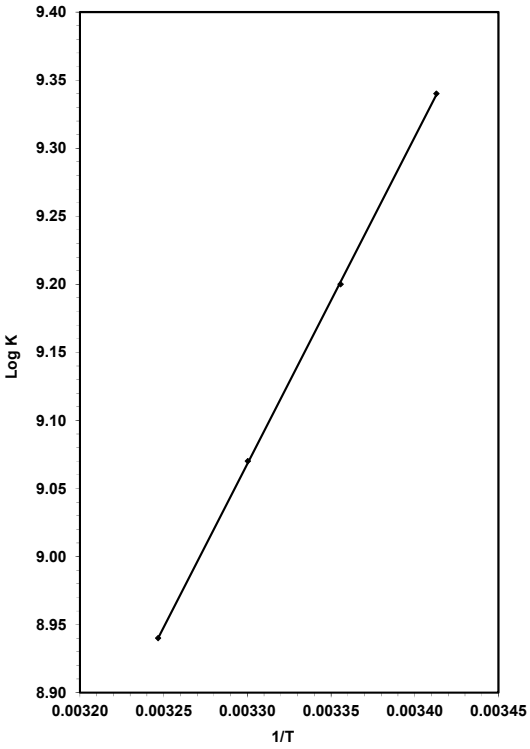


Figure 4. Van·t Hoff plot for [Cd(AMBI)(Gly)] complex.

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