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Research paper

On the Multimetal - Multiligand Complex Formation Equilibria of Adenine and Histidine

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Abstract

Quaternary metal chelates of Cu (II), Co (II), Cd (II), Pb (II), Zn (II) and Ni (II) metal ions with Adenine and L-Histidine have been studied by Potentiometric technique at 0.1 M $NaNO_3$ ionic strength under biologically relevant condition in aqueous medium. Formation of quaternary species along with hydroxyl, protonated, binary and ternary species has been reported. The percentage of species formation of different systems was determined through SCOGS computer program by utilizing titration values of ternary and quaternary systems. The obtained species percentage was shown through graphs plotted between species and solution pH. The distribution of species at different pH was sketched out through ORIGIN 6.1. The order of stability constants of quaternary system has been calculated. Speciation curves of all the quaternary system under studied show that complexation takes place simultaneously.

***Key words**: Adenine, L-Histidine, Multimetal-Multiligand Complexes, SCOGS, Potentiometry*

1. Introduction

Mixed metal – mixed ligand complexes involving more than one metal ions of the same or different type may prove as better models for multimetal-multiligand equilibrium occurring in the biological systems [1]. The study of multimetal-multiligand complexes is of extreme importance because it helps to predict general and probable form of existence of element in solution. This makes possible to understand the mechanism and kinetics in analytical reactions and open new prospects for development of selective and sensitive method for determination and separation. It also has important biological implications because of the enhanced probability of bridging two different ligands, together or of facilitating enzyme-substrate interaction through a linking metal ion. Metal coordination complexes have been extensively used in clinical applications as enzyme inhibitors, anti bacterial, antiviral and anti cancerous. The scope of their application in science, technology, agriculture, pharmacology and medicine is very extensive [2]. Complexation of metal ions of biologically importance with amino acid, small peptides and their derivatives are of great significance [3]. Metal complexes of these types are also having usefulness in study of bio-fluids particularly when hyper accumulated metal ions are present for physiological or pathological nature [4]. Metal ions influenced the transfer of genetic information for the synthesis of specific proteins. It may bind with the enzyme protein, with the nucleotide fragments or with the drug itself. Mixed ligand complexes of transition metals are mediators of bioreactions in living organisms and intermediates of technological processes [5]. Most of the metal complexes of purine bases show prime biological importance through nucleic acids ions interactions. Adenine is one of the most common naturally occurring purine derivatives, found as components of nucleic acids, many antibiotics and various coenzyme systems in almost all living tissues. Adenine shows increased anticancer activity when administered as metal complexes as it have chelating properties [6]. Histidine plays an important role in the binding of metal ions by protein as it is one of the strongest metals coordinating ligands among the amino acids [7]. The involvement of Histidine is found in a large number of biochemical processes such as biosynthesis of histamine, antidiuretic hormone, secretion of prolactin and production of red and white blood cells. It is also used in the treatment of anemia, allergies, rheumatoid arthritis, and other inflammatory reactions [8-10]. Considering the importance of complexes of purine bases and amino acid with metal ions we choose to study the mixed metal-mixed ligand complexes of Adenine and Histidine with bivalent metal ions. In continuation of our work on ternary complexes of Adenine and L-Histidine, we extend the present work to the quaternary complexes of adenine and L-Histidine with bivalent metal ions in solution.

2. Experimental

2.1. Employed chemicals

The ligand adenine and L-Histidine purchased from LOBA Chemie. These ligands were used as such. Carbonate free sodium hydroxide and Nitric acid solution were prepared by standard method. All other solutions were prepared in doubly distilled water. Stock solution (0.01M) of Adenine and L-Histidine were prepared by constant stirring in double distilled water. Metal nitrate solutions were prepared and standardized volumetrically by titration with the disodium salt of EDTA in presence of suitable indicators, as directed by Schwarzenbach [11]. The ionic strength of all mixture solutions was kept 0.1M $NaNO_3$.

2.2. Apparatus and procedures

pH measurements were done by an electric digital pH meter with a glass electrode supplied with the instrument and working on 220 V/50 cycles stabilized by A.C. mains. The pH meter has a reproducibility of 0.01 pH. The electrode of pH meter was conditioned monthly by saturated potassium chloride (BDH) solution. An Ultra Thermostat type U10 (VEB MLW Sitz, Freital, Germany) was used to maintain a constant temperature in all the experiments. The experimental work has carried as described by previous study [12]. The experimental procedure, in the study of quaternary chelates by the potentiometric titration technique, involves the titration of carbonate free following solution mixture:

Set A: 5ml $NaNO_3$ (1.0 M) + 5 ml HNO_3 (0.02M) + H_2O

Set B: 5ml $NaNO_3$ (1.0 M) + 5 ml HNO_3 (0.02M) + 5 ml A (0.01M) +H_2O

Set C: 5ml $NaNO_3$ (1.0 M) + 5 ml HNO_3 (0.02M) + 5 ml A (0.01M) +5 ml M_1(II) (0.01M) + H_2O

Set D: 5ml $NaNO_3$ (1.0 M) + 5 ml HNO_3 (0.02M) + 5 ml A (0.01M) + 5 ml M_1(II) (0.01M) + 5 ml B (0.01M) + H_2O

Set E: 5ml $NaNO_3$ (1.0 M) + 5 ml HNO_3 (0.02M) + 5 ml A (0.01M) + 5 ml M_1(II) (0.01M) + 5 ml B (0.01M) + 5 ml M_2(II) (0.01M) + H_2O

Where, M_1(II) and M_2(II) are Cu/Pb/Cd/Zn/Ni/Co metal ions and A=Adenine, B=L-Histidine.

The potentiometric titrations were performed with carbonate free standard 0.1 M NaOH at fixed temperature 37 ± 1 °C, under ionic strength $I = 0.1$ M $NaNO_3$ keeping the solution volume 50 ml for each set of solution mixture. The pH meter reading with progressive addition of alkali to the titration mixtures were obtained. These pH values were used to plot the titration curves which were obtained by plot of pH vs. volume of NaOH. The titration was discontinued due to appearance of turbidity. In the SCOGS computer program the pH values (which were obtained after titration of solution mixture by NaOH) were used as an input data. After analysis of these data the SCOGS program has produced % concentration of different species at each titration pH values as output data. The curves which is plotted each titration pH vs. % concentration of different species were called the formation curves or species distribution curves Metal-ligand stability constants have been evaluated by SCOGS Computer program [13]. Values of constants were supplied to the computer as input data to obtain distribution curves of the complexes occurring at different pH. Ionic product of water (kw) and activity coefficient of hydrogen ion under the experimental conditions were obtained from literature.

3. Results and discussion

Adenine is chemically 6-amino purine and one of the most common nucleic acid base found in the DNA and RNA, which is prime component for the transfer of the genetic information and for protein synthesis. The heterocyclic molecules generally have a tendency to yield a mixed population of species in equilibrium when the hydrogen atoms attached to nitrogen are able to migrate to other free nitrogen or oxygen within the same molecule (prototropic change) in solution. Adenine shows the amine – imino tautomeric form which is depends on the dielectric constant of the solvent and on the pK value of the heteroatoms.

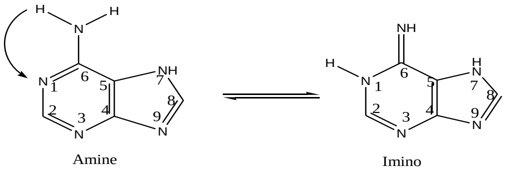

Fig.1 (a): Tautomeric equilibrium of adenine

Although Adenine can undergo a change from an amine to an imino form, the amine form is greatly recommended being more difficult to detect even traces of the imino form in the naturally occurring DNA.

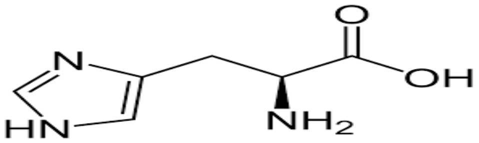

Fig.1 (b): Structure of L-Histidine

L-Histidine is perhaps the most frequently found and most important metal-binding site in biological systems. It is an integral part of many proteins [14]. L-Histidine has three potential donor sites namely amino nitrogen, imidazole nitrogen, and carboxylate oxygen to bind metal ions [15]. The imidazole nitrogen of L-Histidine residues often furnishes the fundamental means by which the metal ions are bound to protein [16].

Preliminary assessments of binary and ternary constants obtained by least-square method [17] were further refined by SCOGS computer program [18] in our previous work [19]. These values are listed in Table 1, which are in good agreement with those reported in the literature [20-23]. For evaluation of stability constants by the SCOGS computer program in a system of the two different metal ions M_1 and M_2 and two different ligands A and B in aqueous solution complex formation may be described as equilibiria (1):

$$pM_1 + qM_2 + rL_1 + sL_2 + t(OH) \leftrightarrow (M_1)p(M_2)q(L_1)r(L_2)s(OH)t \quad (1)$$

The overall stability constant (βpqrst) defined may be used to calculate the species distribution curves that provides the clues for the formation equilibiria of the complexes. Where the stoichiometric numbers p,q,r,s are either 0 or positive integers and t is a negative integer for a protonated species , positive for a hydroxo or a deprotonated species and zero for a neutral species. The overall stability constant (βpqrst) defined as equilibiria (2):

$$\beta_{pqrst} = \frac{[(M_1)_p(M_2)q(L_1)_r(L_2)_s(OH)_t]}{[M_1]^p[M_2]^q[L_1]^r[L_2]^s[OH]^t} \quad (2)$$

Multinuclear complex species, protonated ligand species, binary and ternary complex species viz. $[M_1(II)\text{-}A\text{-}BH]^-$ and $[M_2(II)\text{-}A\text{-}BH]^-$ were present in quaternary system under studied.

On the basis of the description of speciation curves obtained through SCOGS, following equilibiria have been described :

$$A^{2-} + M^{2+} \leftrightarrow MA \quad (3)$$
$$(AH)^- + M^{2+} \leftrightarrow MA + H^+ \quad (4)$$
$$(AH)^- + M^{2+} \leftrightarrow (MHA)^+ \quad (5)$$
$$(BH)^- + M^{2+} \leftrightarrow MB + H^+ \quad (6)$$

The simultaneous formation of ternary complex may be explained as per the following equilibiria:

$$(AH)^- + M_1^{2+} + (BH)^- \leftrightarrow (M_1ABH)^- + H^+ \quad (7)$$

$$(AH)^- + M_2^{2+} + (BH)^- \leftrightarrow (M_2ABH)^- + H^+ \quad (8)$$

The alternative method for the formation of ternary complex is expressed by the following equilibiria (9, 10):

$$MA + (BH)^- \leftrightarrow (MHAB)^- \quad (9)$$
$$(MHA)^+ + (BH)^- \leftrightarrow (MAB)^{2-} + H^+ \quad (10)$$

The simultaneous formation of quaternary complex may be expressed as equilibiria (11):

$$(AH)^- + M_1^{2+} + (BH)^- + M_2^{2+} \leftrightarrow M_1M_2AB + 2H^+ \quad (11)$$

Another form of equilibiria may be represented as equilibiria (12, 13):

$$(M_1ABH)^- + M_2^{2+} \leftrightarrow M_1M_2AB + H^+ \qquad (12)$$
$$(M_2ABH)^- + M_1^{2+} \leftrightarrow M_1M_2AB + H^+ \qquad (13)$$

Dissociation of the quaternary complex and appearance of hydroxo species at higher pH region may be expressed as equilibiria (14, 15):

$$M^{2+} + H_2O \leftrightarrow M(OH)^+ + H^+ \qquad (14)$$
$$M^{2+} + 2H_2O \leftrightarrow M(OH)_2 + 2H^+ \qquad (15)$$

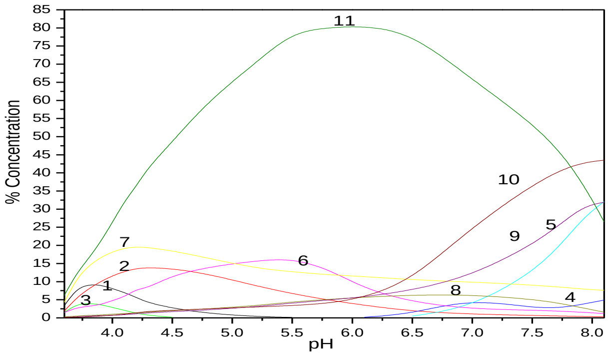

Fig.2: Distribution curves of (1:1:1:1) Cu(II)-Cd(II)-Ade-His system; (1) AH_2 (2) AH (3) BH_3 (4) $M_1(OH)_2$ (5) $M_2(OH)_2$ (6) M_1L_1 (7) M_1L_2 (8) M_2L_1 (9) $M_1L_1L_2$ (10) $M_2L_1L_2$ (11) $M_1M_2L_1L_2$

(1:1:1:1) species distribution curve of Cu(II)-Cd(II) system is represented by Fig.2 which reveals that formation of mixed metal-mixed ligand quaternary complex is simultaneous. The concentration of ternary species Cd(II)AB > Cu(II)AB at higher pH where as Cd-B binary species does not formed. The maximum concentration of quaternary species is approximately 80% in the pH range 5.5-6.5. The dissociation of the quaternary complex may also be associated to the formation of hydroxo species i.e. $Cu(OH)_2$ and $Cd(OH)_2$.

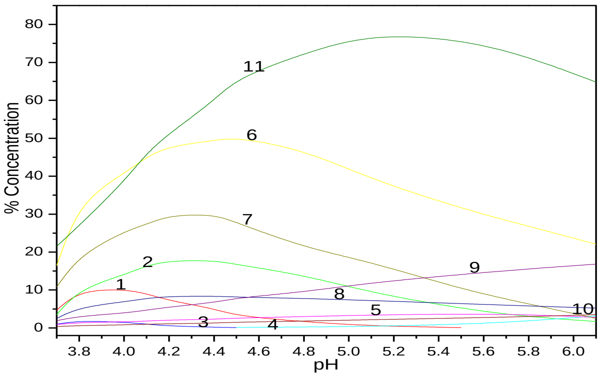

Fig.3: Distribution curves of (1:1:1:1) Cu(II)-Co(II)-Ade-His system; (1) AH_2 (2) AH (3) BH_3 (4) $M_1(OH)_2$ (5) M_1L_1 (6) M_1L_2 (7) M_2L_1 (8) M_2L_2 (9) $M_1L_1L_2$ (10) $M_2L_1L_2$ (11) $M_1M_2L_1L_2$

Speciation curve for Cu(II)-Co(II)-A-B (1:1:1:1) system is represented by Fig.3 which clearly reveals the formation of all the binary, ternary and quaternary species. This curve also shows that quaternary species is dominated among all the species formed whose concentration increases with increasing pH and attain a maximum concentration approximately 76 % at pH range 4.8 to 5.2. Only the $Cu(OH)_2$ hydroxo species is formed.

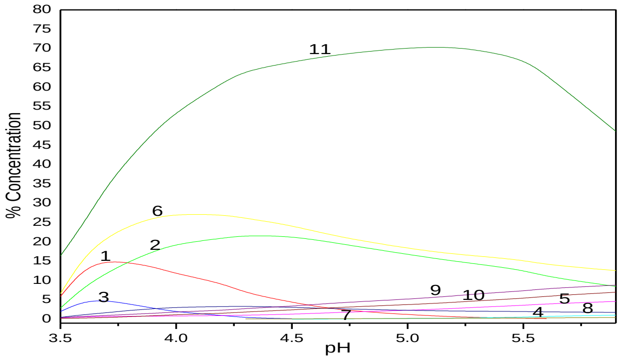

Fig.4: Distribution curves of (1:1:1:1) Cu(II)-Ni(II)-Ade-His system; (1) AH_2 (2) AH (3) BH_3 (4) $M_1(OH)_2$ (5) M_1L_1 (6) M_1L_2 (7) M_2L_1 (8) M_2L_2 (9) $M_1L_1L_2$ (10) $M_2L_1L_2$ (11) $M_1M_2L_1L_2$

Fig.4 shows the speciation curve of Cu(II)-Ni(II)-A-B (1:1:1:1) quaternary complex which reveals the formation of all protonated, binary, ternary and quaternary species. Concentration of protonated species is high in lower pH range which gets inclined with increasing pH as the concentration of binary and ternary species is increased. Quaternary species is dominated among all the species formed and attain a maximum concentration 70% at pH range 4.7 to 5.5

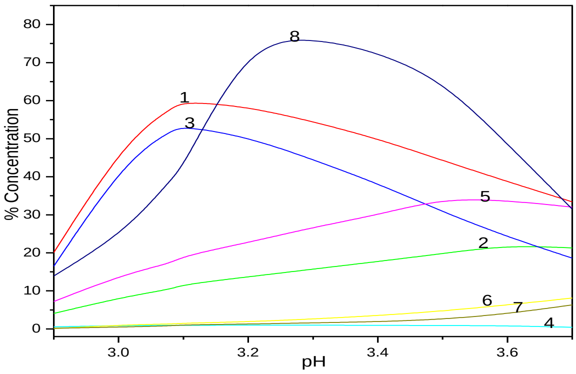

Fig.5 Distribution curves of (1:1:1:1) Cu(II)-Pb(II)-Ade-His system; (1) AH_2 (2) AH (3) BH_3 (4) M_1L_1 (5) M_1L_2 (6) $M_1L_1L_2$ (7) $M_2L_1L_2$ (8) $M_1M_2L_1L_2$

Species distribution curve of (1:1:1:1) Cu(II)-Pb(II)-A-B system is represented by Fig.5. This curve reveals that complex species formation occurs in lower pH range. Concentration of HA>H_3B at lower pH, which decreases with increasing pH as the concentration of binary and ternary species is increased. In this system binary species of Pb(II) metal ion with both the ligand does not formed. Quaternary species is dominated among all the species formed which attain maximum concentration of approximately 76% at pH 3.4.

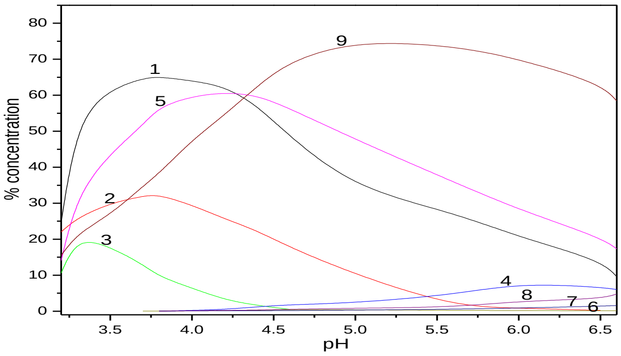

Fig.6: Distribution curves of Cu(II)-Zn(II)-Ade-His system; (1) AH_2 (2) AH (3) BH_3 (4) $M_1(OH)_2$ (5) M_1L_2 (6) M_2L_2 (7) $M_1L_1L_2$ (8) $M_2L_1L_2$ (9) $M_1M_2L_1L_2$

Fig.6 shows the speciation curve Cu(II)-Zn(II)-Ade-His (1:1:1:1) quaternary complex. This curve also reveal that protonated species HA>H_2A>H_3B at lower pH. The curve shows that formation of ternary species is dominated over the binary species. Concentration of quaternary species is high at higher pH range and attains a maximum concentration of approximately 75% at pH range 5-6.

4. Conclusion

The quaternary metal complexes species detected are (M_1M_2AB) for all the metal ions under study. The stability constants of complexes in solution have been calculated and their concentration distributions are evaluated. The overall stability constant of mixed-metal-mixed ligand (M_1M_2AB) quaternary system have been found to pursue following order:

Cu – Zn > Cu – Cd > Cu – Pb > Cu – Ni > Cu – Co.

The considerable stabilization of the quaternary relative to binary and ternary complexes is emulated in the species distribution plots (figure 2 - 6) i.e., the quaternary complexes occur in higher concentration than the ternary and binary complexes at higher pH in each the system studied. The interaction outside the coordination sphere enhanced the stability of ternary complexes. This may frequently be due to the charge neutralization, chelates effect, formation of hydrogen bonds between the coordinated ligands, strong interaction and a similar stabilizing effect may also be strived by the electrostatic interactions between non-coordinated, charged groups of the ligands. The speciation curves also reveal that formation of ternary and quaternary complex species take place simultaneously. A perception into the metal availability/metal transport in biofluids is also given by this study.

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