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pH-metric studies on formation constant of ternary metal complexes of glutamine and adenine

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ABSTRACT

Investigation of metal complexes with biologically active ligands has significant scientific and practical value. In this study, we focused on examining the formation of binary and ternary complexes involving metal ions such as Cu (II), Ni (II), Co (II) and Zn (II) with two biologically important ligands: glutamine (A) as the primary ligand and adenine (B) as the secondary ligand. To assess the complexation behaviour of these species in aqueous media, a potentiometric technique was employed at a temperature of 37±1°C and an ionic strength of I = 0.1 M $NaNO_3$. The stability constants of the complexes were determined using the method proposed by Irving and Rossetti, and then refined using the SCOGS computer program. The results revealed that the formation of mixed-ligand ternary complexes occurred simultaneously in most cases, typically at higher pH values, leading to a gradual decrease in the concentration of the binary complexes for the respective metal ions. The binary and ternary species examined are shown in the species distribution curve. The protonation constant of the ligands and the stability constant of their complexes with metal ions are shown in the order of MA, MB, and MAB.

KEYWORDS: Chelation, Biomolecules, Potentiometric studies, Transition metal ions, Formation constant, SCOGS.

INTRODUCTION

The chelation of a coordination complex is an important aspect of chemistry. It is an intravenous treatment that was specifically developed to address heavy metal toxicity in the body (M. Singh et al., 2017). The primary objective of chelation therapy is to bind and remove heavy metals from the body. This therapeutic approach involves the use of chelating agents, which are ligands that are capable of coordinating with a single metal ion using two or more donor atoms. When these ligands bind to a metal ion and form a cyclic structure with the metal ion at the centre, they are referred to as chelating ligands. The resulting compound formed from the interaction between the chelating ligand and the metal ion is called a metal chelate (Agents et al., 2014). This study will help change the coordination environment of toxic metal ions and increase their excretion from the organisms (Rulisek & Havlas, 2000).

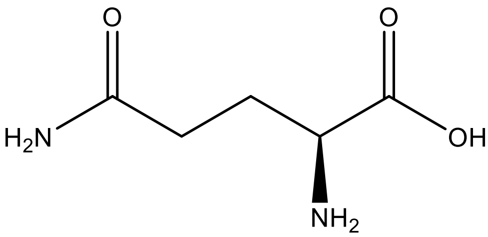
The study of the potentiometric behaviour of coordination complexes has developed interest of researchers toward the speciation and stability constant of mixed ligand complexes, i.e., the ternary form in which the mixed ligands facilitates the discovery of new technique with more sensitivity and selectivity (Bindu & Rao, 2012). The relationship between chelation therapy and potentiometry of ternary chelates is of growing interest because of the common occurrence of mixed chelation in biological fluids. Millions of potential ligands were present, competing for the available metal ions. This competition among ligands for metal ions is a complex process that can significantly affect the equilibrium and behaviour of metal-chelate complexes (Complexes & Trans, 1980).

Essential metal ions such as Cu (II) (D. Singh, Verma, et al., 2016), Ni (II) (D. Singh, Singh, et al., 2016), Co (II) (D. Singh et al., 2014) and Zn (II) (Amin Mir et al., 2021)form metal chelates with amino acids such as, glutamine and adenine and play crucial role in complexation of metal ions within living systems. These metal ions often form complexes with amino acids and peptides, which serve as models for understanding the metal-amino acid equilibria that occur in enzymatic processes (Catania & Doria, 1998). Therefore, it would be interesting to investigate the formation constants of these metal ions with the ligands commonly present in biological fluids.

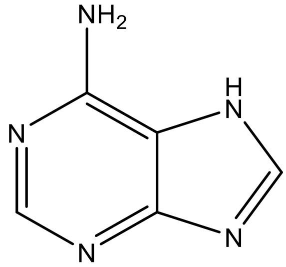
Glutamine Fig. 1(a) (Newsholme et al., 2003)is an amino acid, commonly referred to as L-glutamine, that is classified as a non-essential amino acid. It is one of the 20 amino acids that forms the building blocks of proteins (Sujatha et al., 2017). Glutamine is synthesized in the body from other amino acids, primarily glutamate and ammonia, and is also obtained from dietary sources (Gollapalli Nageswara Rao, 2012). Glutamine plays a critical role in various biological processes, and is involved in several metabolic pathways (Amin Mir et al., 2021). It is particularly abundant in skeletal muscles and is considered an important fuel source for cells that dividing cells, such as immune cells, intestinal cells, and certain cancer cells (Yoo et al., 2020).

Adenine Fig.1(b) is a nucleobase, that is a fundamental component of nucleic acids such as DNA and RNA. It is one of the four nitrogenous bases found in DNA (along with guanine, cytosine, and thymine), and one of the four bases found in RNA (with uracil replacing thymine) (S. Singh et al., 2000). Adenine is found in various coenzymes and other important biological molecules. Structurally, adenine is a purine base characterized by a double-ring structure (Ilavarasi et al., 1997). It consists of a pyrimidine ring fused to an imidazole ring. The chemical formula of is $C_5H_5N_5$ (Ammar et al., 2011).

By understanding the above factors, the present work focusses on the study of the stability constant, formation equilibria, speciation curve and coordination of some ternary chelates involving Glutamine and Adenine with the Cu(II), Ni(II), Co(II) and Zn(II) metal ions under the biologically relevant conditions.



(a)



(b)

Fig.1 Structure of ligands (a) Glutamine, (b) Adenine

MATERIALS AND METHOD

Materials and Reagents - Both glutamine and adenine, the ligands used in the study, were of analytical grade and obtained commercially were used without any further purification steps.

To prepare the solutions, metal nitrates and ligands were dissolved in double-distilled water that had been freed of carbon dioxide. Aqueous solutions of metal nitrates were standardized in the presence of a suitable indicator. Similarly, stock solutions of glutamine and adenine were standardized against a standard oxalic acid solution. This step involved determining the concentrations of the ligand solutions using a known concentration of oxalic acid as a reference (M. Singh et al., 2021).

Potentiometric titrations were carried out at a temperature of 37 ±1ºC, using a glass electrode and an electric digital pH meter from Systronics. The addition of NaOH changed the pH of the solution, and the corresponding electrode potential measurements provide information about the complexation behaviour and stability of the metal-ligand complexes (Shankar et al., 2016). The experiments were conducted in the presence of a sodium nitrate ($NaNO_3$) solution with an ionic strength of 0.1 M. Overall, these standardized solutions, controlled conditions, and potentiometric measurements using a pH meter with a glass electrode contributed to the accurate assessment of the complexation behaviour and stability of the metal-ligand complexes formed between the metal nitrates and glutamine/adenine ligands in the study.

APPARATUS AND MEASURING TECHNIQUES

Potentiometric titrations for both binary and ternary systems were conducted at room temperature using an electric digital pH meter equipped with a glass electrode. The pH meter was operated at 220 V/50 cycles, stabilized by the A.C. mains. The electrode of the pH meter was conditioned monthly using a saturated potassium chloride solution from the BDH to maintain its performance and accuracy, with a reproducibility of ±0.01 pH.

For potentiometric titrations, a standardized NaOH solution with a concentration of 0.01 M was used as the titrant. Solution mixtures, comprising the binary and ternary systems, were titrated with the standardized NaOH solution. The use of a standardized NaOH solution as the titrant allows for the measurement of changes in pH during the titration process. By analysing the pH values at different points of the titration, information about the complexation behaviour and stability of the binary and ternary systems can be obtained (Shalini et al., 2015).

In this study, several solution mixtures were prepared for potentiometric titrations and the potentiometric behaviour of the solutions at different pH values was analysed. The compositions of the solution mixtures are as follows:

1. 5 ml $NaNO_3$ (1.0M) + 5 ml HNO_3 (0.02 M) + H_2O
2. 5 ml $NaNO_3$ (1.0M) + 5 ml HNO_3 (0.02 M) + 5 ml M (0.01) + H_2O
3. 5 ml $NaNO_3$ (1.0M) + 5 ml HNO_3(0.02 M) + 5 ml M (0.01) + 5 ml A (0.01M) + H_2O
4. 5 ml $NaNO_3$ (1.0M) + 5 ml HNO_3 (0.02 M) + 5 ml M (0.01) + 5 ml A (0.01M) + 5 ml B (0.01M) H_2O

In these mixtures, M represents the metal ions Cu(II), Co(II), or Ni(II); A represents glutamine; and B represents adenine. The volume of each component and addition of water were adjusted to achieve the desired concentrations and total volumes 50 ml for the titration experiments (Türkel, 2015). The pH of each solution was measured using a potentiometric method, and the resulting data were used to plot titration curves, which showed the variation in pH as a function of the volume of NaOH added during the titration process. These curves provide information on the potentiometric behaviour of the solutions and the changes in pH upon the addition of NaOH.

Furthermore, species distribution curves were obtained using the stability constant of any generalized species (SCOGS) computer program. The program calculated the percentage concentrations of different species formed and were plotted against pH to obtain the species distribution curves, which provided insights into the distribution and relative concentrations of the different species formed in the solution.

RESULT AND DISCUSSION

According to Irving and Rossetti's method, the potentiometric pH titration data are used to calculate the protonation constants of the ligands. The protonation of respective ligand involved in the complex formation due to which the equilibria of the metal-ligand complex formation are regulated by the pH value of the solution. The 1:1:1 ternary complex titration curve overlap with the 1:1 binary titration curve at higher pH. The protonation constant of both ligands and the hydrolytic constant of selected metal ions are shown in Table-1, from the previously reported literature (M. Singh et al., 2021)(Shalini et al., 2015). The ionization equilibria of the ligands viz. Glutamine and Adenine have been studied and the following equilibria were proposed:

$H_2A \leftrightarrow H^+ + HA^-$

$K_1 = [H^+][HA^-]/ [H_2A]$

$HA^- \leftrightarrow H^+ + A^{2-}$

$K_2 = [H^+][A^{2-}]/[HA^-]$

The equilibria of the formation of ternary complex has been shown as follows:

$pM_1 + rA + sB + tOH \leftrightarrow (M_1)_p(A)_r(B)_s(OH)_t$

$ß_{prst} = (M_1)_p(A)_r(B)_s(OH)_t/[M_1]^p[A]^r[B]^s[OH]^t$

where, A stands for the primary ligand i.e., Glutamine and B stands for the secondary ligand i.e., Adenine. The stochiometric numbers p, r, s may be zero or positive integer and t is a negative integer for protonated species,

From the description of species distribution curves obtained through the SCOGS computer program, the following equilibria should be assumed for the ternary system (M. Singh et al., 2010):

$[A]^{--} + [M^{2+}] \leftrightarrow [MA]$

$[AH]^- + M^{2+} \leftrightarrow [MA] + H^+$

$[AH]^- + M^{2+} \leftrightarrow [MAH]^+$

$[BH]^- + M^{2+} \leftrightarrow [MB] + H^+$

$[MA] + [BH]^- \leftrightarrow [MHAB]^-$

$[MAH]^+ + [BH]^- \leftrightarrow [MAB]^{--} + H^+$

The hydrolytic equilibria are as follows:

$M^{2+} + H_2O \leftrightarrow M(OH)^+ + H^+$

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

Table 1 - Proton ligand formation constant of Glutamine as a primary ligand and Adenine as secondary ligand and hydrolytic constant of some essential metal ions:

Species	Protonation constant (Log ß prst)			
	Ligands		Metal Hydrolytic	
	Primary	Secondary	$M(OH)^+$	$M(OH)_2$
H_2A	11.18			
HA	9.01			
H_2B		10.88		
HB		7.02		
Cu(II)			-6.29	-13.10
Ni(II)			-8.10	-16.87
Co(II)			-8.23	-17.83
Zn(II)			-7.89	-14.92

Potentiometric Titration Curves of Complexes

The potentiometric titration curve of the ternary complex (1:1:1) should be plotted against the pH and volume of alkali as shown in Fig. 2, 3, 4, 5. This plot shows the titration curve of acid, ligand, binary and ternary complex. According to potentiometric titration curve, the titration curve 'C' shows the formation of binary complex followed by the formation of titration curve 'B'. Similarly, formation of ternary complex follows the binary complex formation.

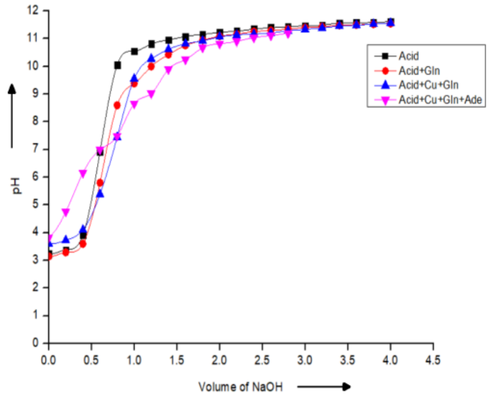


Fig. 2 - Potentiometric Titration Curves of Ternary (1:1:1) Cu(II)- Gln(A)- Ade(B) System

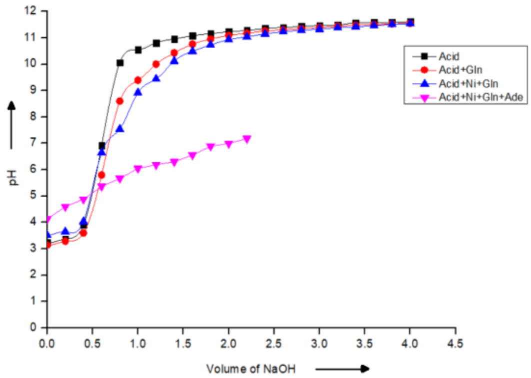


Fig. 3 - Potentiometric Titration Curves of Ternary (1:1:1) Ni(II)- Gln(A)- Ade(B) System

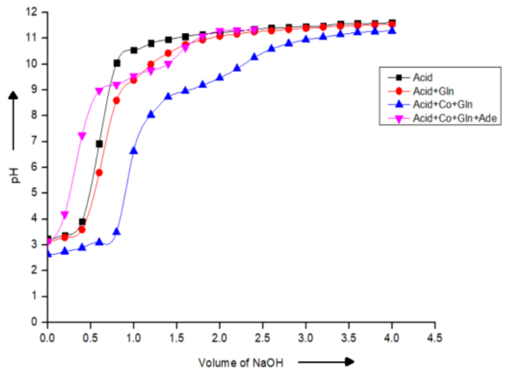


Fig. 4 - Potentiometric Titration Curves of Ternary (1:1:1) Co(II)- Gln(A)- Ade(B) System

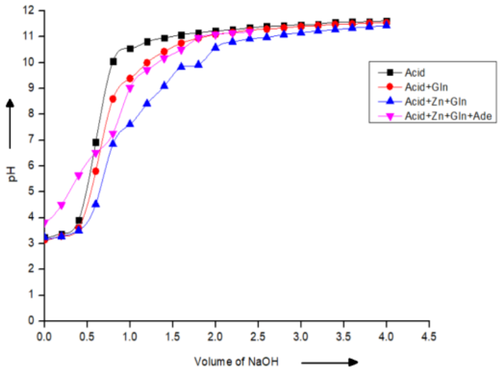


Fig. 5 - Potentiometric Titration Curves of Ternary (1:1:1) Zn(II)- Gln(A)- Ade(B) System

Species Distribution Curves of Complexes

1. Ternary Copper(II) complex formation equilibria involving glutamine and adenine

The species distribution curve of Cu-Gln-Ade system (1:1:1) is shown in Fig. 6 which clearly tells that the formation of ternary complex started at initial pH and attains maximum concentration of about 94% in between pH 9-10. As soon as the reaction starts the concentration of the protonated species of both the ligands viz. H_2A, HA, H_2B and HB decreases due to their involvement in the complexation. The concentration of binary species Cu(II)- A and Cu(II)-B are increases with the pH as the concentration of protonated species declines. Between the pH 5-6 the concentration of Cu(II)-B obtain maximum concentration 80% while the ternary complex formation starts with the decrease in the concentration of Cu(II)-B.

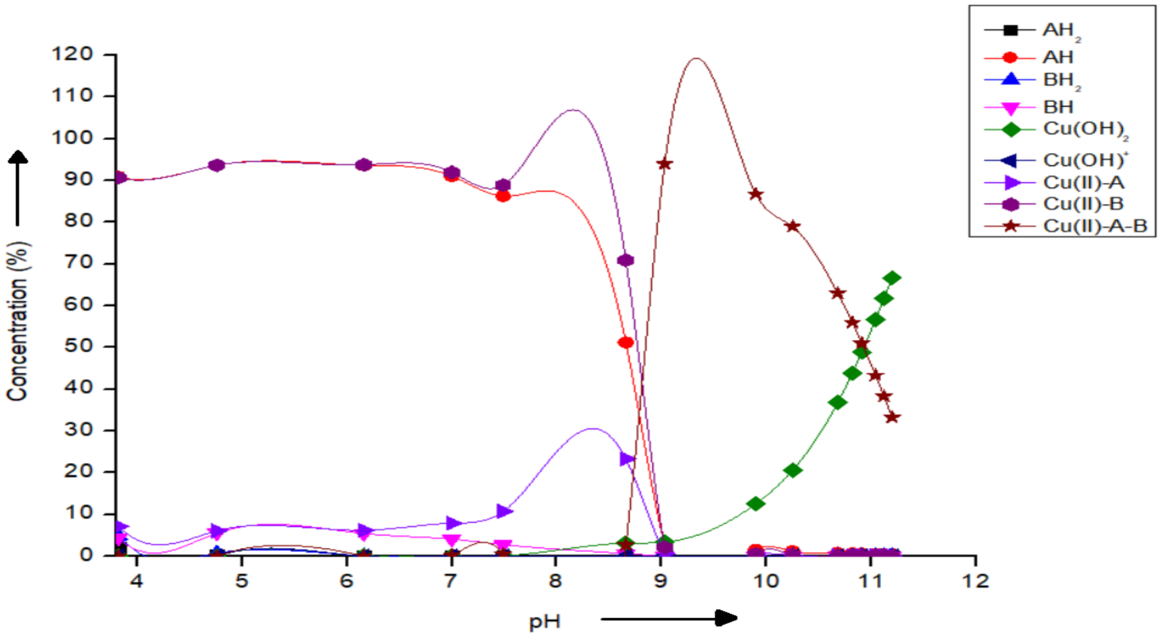


Fig. 6 – Species distribution curve of Cu (II) – Glutamine (A) – Adenine (B) system (1:1:1)

2. **Ternary Nickel(II) complex formation equilibria involving glutamine and adenine**
The species distribution curve of Ni-Gln-Ade system (1:1:1) is shown in Fig.7 which reveals the formation of various species depends on the change of pH with the increase in the volume of alkali. The formation of ternary complex started at initial pH and attains maximum concentration of approximately 38% at pH 7. The occurrence of reaction depicts the decline in the concentration of the protonated species of both the ligands viz. H_2A, HA, H_2B and HB due to their involvement in the complexation. The concentration of binary species Ni(II)- A and Ni(II)-B are increases with the pH as the concentration of protonated species decreases. At pH 6 the concentration of Ni(II)-B obtain maximum concentration 81% while the concentration of ternary species increases with the decrease in the concentration of Ni(II)-B.

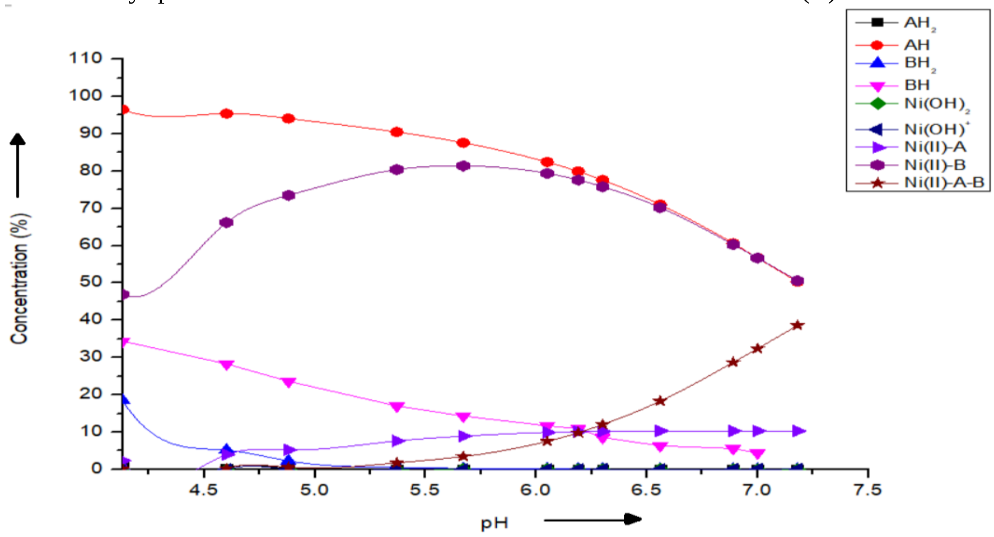


Fig. 7 – Species distribution curve of Ni (II) – Glutamine (A)– Adenine (B) system (1:1:1)

3. **Ternary Cobalt(II) complex formation equilibria involving glutamine and adenine**
The species distribution curve of Co-Gln-Ade system (1:1:1) are presented in Fig.8 which clearly reveals the formation of ternary complex started at pH 8.9 and attains maximum concentration of about 89% at pH 10. With the initiation of reaction, the concentration of the protonated species of both the ligands viz. H_2A, HA, H_2B and HB declines due to their involvement in the complex formation. Their should be rise in the concentration of binary species Co(II)- A and Co(II)-B following with the decline in the concentration of protonated species. The ternary complex formation obtains maximum concentration at pH 10 while the concentration of binary complex Co(II)-B started decreasing.

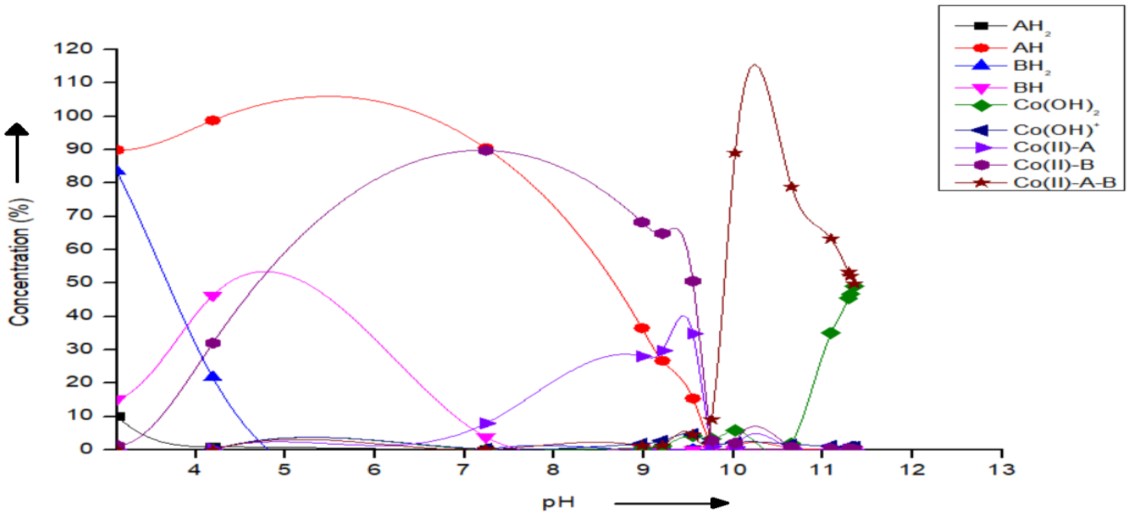


Fig. 8 – Species distribution curve of Co (II) – Glutamine (A) – Adenine (B) system (1:1:1)

4. **Ternary Zinc(II) complex formation equilibria involving glutamine and adenine**
The species distribution curve of Zn-Gln-Ade system (1:1:1) is shown in Fig.9 which represented the formation of ternary complex attains maximum concentration of about 96% at pH 10. Along with the initiation of reaction the concentration of the protonated species of both the ligands viz. H_2A, HA, H_2B and HB found to be decreases due to their involvement in the formation of complex. The concentration of binary species i.e., Zn(II)- A and Zn(II)-B are increases with increase in the pH and the concentration of protonated species decreases simultaneously. The maximum concentration of Zn(II)-B species at pH 5.6 started decreasing with the formation of ternary species.

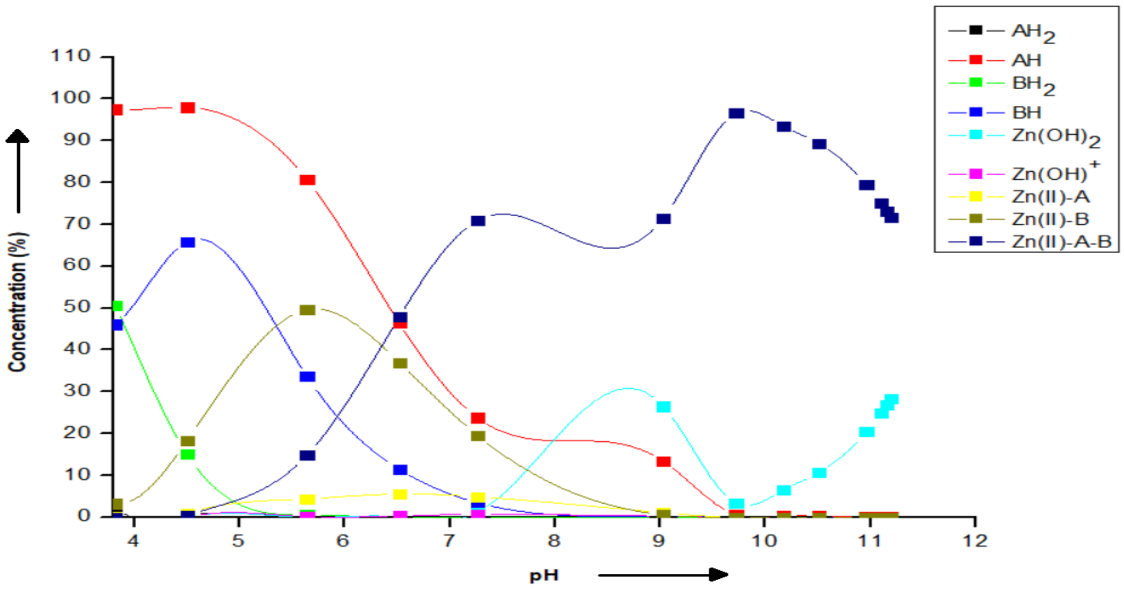


Fig. 9 – Species distribution curve of Zn (II) – Glutamine (A) – Adenine (B) system (1:1:1)

From the structural point of view, the solution structure for the mixed ligand ternary complex of 1:1:1 Copper(II)-Glutamine-Adenine are as follows:

(i) (ii)

Fig. 10 Schematic representation of (i) binary complex and (ii) ternary complex

In the binary system Fig. 10(i), the two protonated species released from the binding site of glutamine and participate in the process of complex formation. Adenine has three binding site which can take part in complexation. In ternary system Fig. 10(ii), glutamine bonded to metal ion through the nitrogen and oxygen, while adenine bonded via 5- membered nitrogen ring to metal ion to form square planar complex.

CONCLUSION

From the above study, it should be concluded that the ternary complex should be formed at higher pH in each of the system. With the increase of pH, it was observed that the ternary complex titration curves (1:1:1) overlap with the binary complex curve (1:1) due to its dissociation and involvement in the formation of ternary complex. The stability constants of binary and ternary species of metal ions with Glutamine (A) And Adenine (B) are shown in Table-2 (Shalini et al., 2015)and Table-3. The formation of ternary complex also depends on the nature of both the ligands. The percentage of formation of ternary species based on the method suggested by the Irving-Rossetti should be 94% for Cu(II)-Gln-Ade at pH 9.03, 38% for Ni(II)-Gln-Ade at pH 7.18, 90% for Co(II)-Gln-Ade at pH 9.76 and 96.6% for Zn(II)-Gln-Ade at pH 9.72. According to method, the overall stability constant of mixed ligand ternary system of Glutamine (A) and Adenine (B) are obtained in the following order – A-Cu(II)-B > A-

Ni(II)-B > A-Co(II)-B > A-Zn(II)-B. The high stability of Cu(II) ion complex is due to its odd arrangement, which allows for extra stabilisation through Jahn-Teller distortion. This study provides insight on metal availability and transit in biofluids. Because of their increased stability, ternary complexes are better suitable for "metal transport". This work also contributes to a better understanding of metal chelation behaviour as a model for metal detoxification in biological systems and heavy metal remediation from contaminated sites.

Table 2 - Stability constant of the binary species of some essential metal complexes with Glutamine as a primary ligand and Adenine as secondary ligand:

S.No.	Metal ions	Ligands	
		Glutamine (A)	Adenine (B)
1.	Cu(II)	7.75	8.18
2.	Ni(II)	5.56	5.32
3.	Co(II)	4.40	4.84
4.	Zn(II)	4.62	4.06

Table 3 - Stability constant ternary species of some essential metal complexes with Glutamine as a primary ligand and Adenine as secondary ligand:

S.No.	Ternary Metal Complex	
	Complexes	Stability Constants
1.	Cu-A-B	11.40
2.	Ni-A-B	11.35
3.	Co-A-B	7.52
4.	Zn-A-B	11.00

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