

Metal Complexes in Biology and Medicine: The System Cadmium ((II))/ Iron ((II))/ Zinc ((II)) - α - Aminobutenoic Acid

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Abstract

Metal ions play an important role in biological system. The importance of metal ions to essential functions of living systems and for wellbeing of living organisms is well known. Metal ions are fundamental elements for the maintenance of life spans of the human, animals, and plants. Recent advances in inorganic chemistry have made possible formation of number of transition metal complexes with organic ligand of interest, which can be used as therapeutic agent. In coordination compounds studies, knowledge of the stability constants of complexes is necessary for preliminary quantitative treatment. The present technique involving the use of paper electrophoresis is described for the study of equilibria in binary complex systems in solution. The method is based on the movement of a spot of a metal ion in an electric field at various pH's of background electrolyte. A graph of pH versus mobility was used to obtain information in the binary complexes and to calculate its stability constants. Using this method, the stability constants of binary complexes metal (II) – α – aminobutenoic acid have been determined to be (3.78 ± 0.01 , 2.48 ± 0.03); (3.27 ± 0.04 , 2.33 ± 0.07); and (4.45 ± 0.02 , 2.66 ± 0.05); (logarithm stability constant values) for cadmium (II), iron (II) and zinc (II) complexes, respectively, at ionic strength 0.01 Mol / L and a temperature of 35° C.

Keywords: Paper electrophoresis; Overall mobility; Metal complexes; Stability constants.

Introduction

For a mononuclear binary complex, if a central atom (central group) M (the 'metal') and a ligand L have been defined then in the following expression K, is the stepwise formation constant, and β_n is the cumulative formation constant for the complex ML_n . They can both referred to as stability constants (stepwise and cumulative) (McNaught & Wilkinson, 1997).

$$K_n = K (M L_{n-1} + L = M L_n)$$

$$\beta_n = K (M + nL = M L_n)$$

Metal complexes play an important role in various biological systems, hence the formation, stability and reactivity of these complexes have been an active field research (Sherman & Lippard, 1978). Cadmium is hazardous both by inhalation and ingestion and can cause acute and chronic intoxications. Cadmium persist in soils and sediments for decades. It is taken by plants and accumulated in the body of people eating contaminated foods. Cd is highly taking metal and disrupts a number of biological systems usually at doses that are much lower than most toxic metals (Bernard, 2008). Cadmium causes genotoxicity, teratogeny and cancer in some tissues

and non-malignant chronic toxicity in others (e.g. Cancer of lungs, nephrotoxicity of kidney) (De Falco et al., 2010). Testis is known to serve as one of the important target organs for cadmium. Cadmium induces testicular damage in animals such as mice, hamster, rabbits, dogs and guinea pigs. Cadmium expose associated with elevated lipid peroxidation in brain, kidney, liver, erythrocytes and testis. Cadmium induces DNA single strand breaks in Leydig cells in vitro (Kini et al., 2009). Iron is an essential constituent of a number of proteins involved in oxygen transport of metabolism. It must also be transported around the body, stored, and made available for synthesis of iron protein. Iron undergoes cyclic redox process and produce free radicals and other strongly oxidizing species causing injury to biological organs, which occur through a variety of mechanism (Winterbourn, 1995). Iron is vital for almost all living organisms by participating in a wide variety of metabolic processes, including oxygen transport, DNA synthesis and electron transport (Lieu et al., 2001). The metals Mn, Fe, Cu, Zn, and non-metal Se are considered "trace elements" because of their essentiality and very limited quantity in human. The biological activities of Cu, Fe, Mn

and Se are strongly associated with the presence of unpaired electrons that allow their participation in redox reactions (Frago, 2005). The interactions of transition metals have partial covalent character and involve the d – orbitals of divalent and the p – orbitals of nitrogen, sulfur and oxygen ligands from the protein. The formation of a coordinate bond in complexes of transition metals can be consider as transfer of a lone electron pair from the coordinated group or ligand to the metal ions. Zinc prefers tetrahedral binding sites in proteins. Zinc always occurring as a divalent cation in biological systems, is the second most abundant transition metal following iron. In an adult human body there are 2 – 3 g of zinc total, while the content of copper is only 250 mg. The large amount of Zn (II) is likely to concentrate in nerve tissue (0.1 – 0.5 m M for brain tissue) (Zaid et al., 2012). The Cd^{2+} , Zn^{2+} and Fe^{2+} metal ions have significant biomedical applications but are toxic at higher concentration (Knote – Smith et al., 2003; Schubert & Derr, 1978; Peralta – Vide, et al., 2009; Bahanin et al., 2010; Sigel, 1978; Speeckaert et al., 2010; Jobe et al., 2011; Henryk et al., 2009; Sigel, 1983). α – Aminobutenoic acid or 2-amino-3-butenoic acid is a naturally occurring amino acids which do not occur in proteins. It has molecular formula of $C_4H_7NO_2$ with molecular weight 101.1. Kiso (1972) has done a comprehensive study on paper electrophoretic migration of metal complexes. The present modified method is almost free from numbers of defects of common electrophoresis technique such as temperature during electrophoresis, capillary flow on paper, electroosmosis and adsorption. The technique is convenient in use. It gives results in fair agreements with the accepted literature values.

Publications (Tewari, 1998; Tewari, 2008; Tewari, 2002; Tewari, 1994; Tewari, 2010; Tewari, 2002) from our laboratory described a new method for the study of metal complexes. A search of literature indicated few reports on Cd (II) / Fe (II) / Zn (II) – α – aminobutenoic acid complex formation. In addition, present paper describes a paper electrophoretic method for the determination of stability constants of Cd (II) / Fe (II) / Zn (II) – α – aminobutenoic acid binary complexes.

Experimental Section

Instrument

Systronics paper electrophoresis equipment horizontal cum-vertical type No 604 (India) has been used. The apparatus consisted of a PVC molded double tank vessel. In our laboratories a significant change in the instrument has been made. Two hollow rectangular plates were covered with thin polythene sheets have been used through which thermostated water is run for controlling the temperature. The tank is closed with a transparent PVC molded lid. The whole assembly is tight which prevents moisture changes, which may upset the equilibria in a paper strip. The assembly design thus keeps to a minimized the disturbing effects of evaporation from the unwanted liquid flow in the paper strips. Each electrolyte tank contains a separate electrode chamber in which the anode and cathode are placed, respectively. The auxiliary unit is especially designed to operate upon either voltage mode or on current mode. The voltage can be changed through three

ranges, viz., 0 - 100, 100 - 200, 200 – 300 Volts. Whatman No 1 filter paper for chromatography was used for the purpose of electrophoresis. Electrophoresis cell showing sandwiched paper strips is shown in Figure 1.

Elico (Hyderabad, India) Model L_{1-10} pH meter having glass and calomel electrode assembly and working on 220 volts/50 cycles established A. C. mains were employed for pH measurements

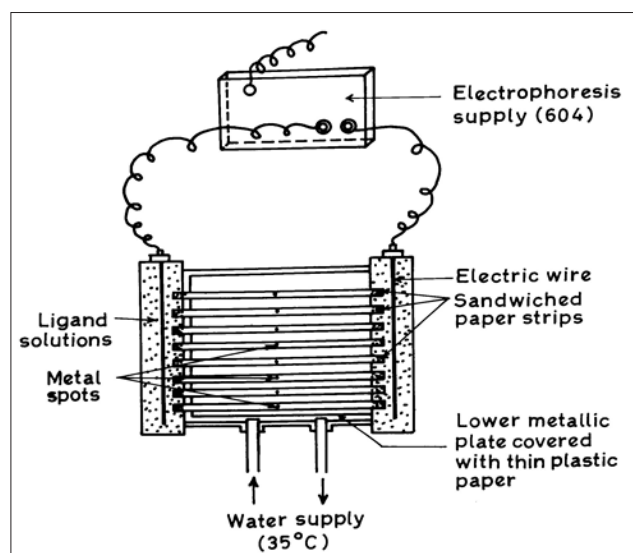


Figure 1: Electrophoresis cell showing sandwiched paper strips

Chemicals

Water: Distilled water was redistilled over alkaline potassium permanganates. The resulting distillate cooled in well stoppered pyrex flask. This was used for preparing solutions and for dilution throughout their studies.

Metal Solution: Solutions of Cd^{2+} , Fe^{2+} and Zn^{2+} metal perchlorate was prepared by preliminary precipitation of metal carbonates from 0.1 Mol L^{-1} solution of sodium carbonate, which were washed with boiling water and treated with calculated amounts of 1% per chloric acid. These were heated and filtered. The metal contents of the filtrates were detected on paper using dithizone in carbon tetrachloride for Zn (II). A 0.1% solution of 1- (2 - pyridylazo) – 2 – naphthol (PAN) (E. Merc, Darmstadt Germany) in ethanol was used for detecting the Cd (II) and Zn (II) metal ions. A 0.005 M glucose (BDH, AnalaR) solution were prepared in water and used as an electro – osmotic indicator for the correction due to electro – osmosis. A saturated aqueous solution (0.9 mL) of silver nitrate was diluted with acetone to 20 mL. Glucose, as the black spot, was detected by spraying with this solution and then with 2% ethanolic solution of solution of sodium hydroxide. Paper strips showing position of metal ion spots after electrophoresis is shown in Figure 2.

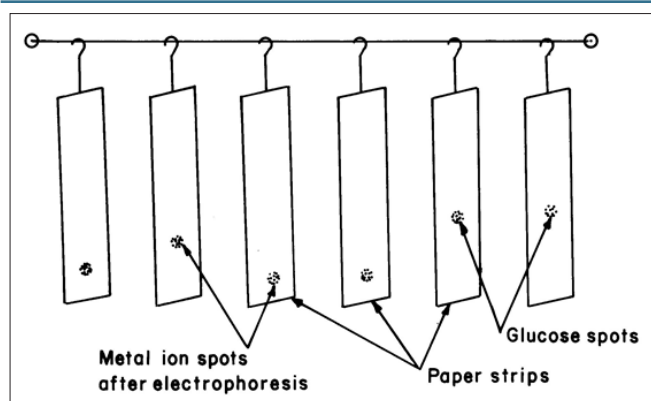


Figure 2: Paper strips showing position of metal ion spots after electrophoresis

Background electrolyte (BGE): The background electrolyte used in the study of binary complexes were 0.1 Mol L⁻¹ perchloric acid and 0.001 Mol L⁻¹ α -aminobutenoic acid. The variation in the pH was made by addition of sodium hydroxide. Stock solutions of 5.0 Mol L⁻¹ perchloric acid (SDC, AnalaR). 2.0 Mol L⁻¹ sodium hydroxide (AnalaR grade). 0.5 Mol L⁻¹ α -aminobutenoic acid (BDH, Poole, UK) were prepared.

Procedure: For recording observation of particular metal ion, two paper strips were spotted with the metal ion solution along with additional two spotted with glucose using 0.1 μ L pipette and then mounted on the insulated plate. The hollow base plate in the instrument was made horizontal using a spirit level and 150 mL volume of BGE containing 0.1 Mol L⁻¹ perchloric acid and 0.01 Mol L⁻¹ α -aminobutenoic acid was placed in each of the two tanks of the electrophoretic apparatus. The paper became moistened with the BGE solution due to diffusion. The second insulated plate was placed on paper strips and then thermostated water (35°C) was circulated in the plates to keep the temperature constant. The lid was then placed on the instrument to make it airtight. It was left for 15 minutes to ensure wetting of the strips. Subsequently, 200 V potential difference was then applied between the tank solutions to initiate electrophoresis. The electrophoresis was carried out for 60 minutes after which, the paper strips were taken out by means of glass rod, dried on a horizontal platform and the spot detected. The observations were repeated for different pH values of BGE (variation in pH was made by addition of sodium hydroxide solution). The differences in the distances recorded in the duplicates were within \pm 5% and the average distances in the duplicates were noted for the calculation. The distance travelled toward the anode was assumed to be negative and that toward cathode positive. The actual distance of the sample spot was measured after taking into account the distance travelled by the reference glucose spot.

Ionophoretic observation at metal ions were recorded at various pH values of the BGE, the ionic strength being maintained at 0.1 Mol L⁻¹. The observed mobility of migrant was calculated by using the formula

$$U = \frac{d}{x \cdot t}$$

After applying the correction factor the observed mobility is given as:

$$U = \frac{d \pm d_G}{x \cdot t}$$

Where U = mobility of metal ion / complex ion; d = mean of duplicate distance travelled by metal ion / complex ion; d_G = mean of duplicate distance travelled by glucose spot; x = field strength; t = time for electrophoresis. The mobility of metal/complex ions spots on the paper strips were thus calculated and are reported with different pH values (Figure 3).

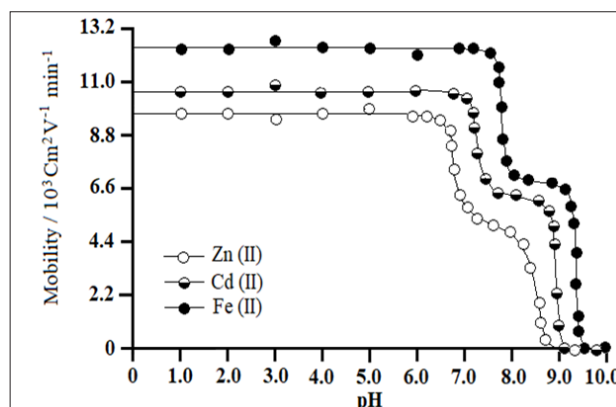


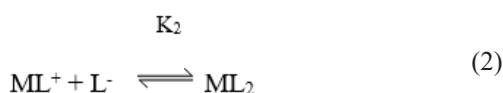
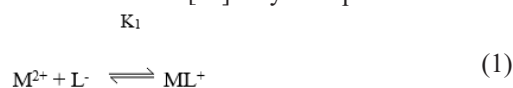
Figure 2: Mobility curves for the metal (II) - α -aminobutenoic acid. Background electrolytes = 0.1 Mol L⁻¹ perchloric acid and 0.01 Mol L⁻¹ α -aminobutenoic acid concentration of Cd (II), Fe (II) and Fe (II) = 0.005 Mol L⁻¹. Variation in the pH was made by the addition of sodium hydroxide.

Results and Discussion

The plot of overall electrophoretic mobility of metal spot against pH is shown in Figure 3. The first plateau in the beginning corresponds to a region in which metal ions are uncomplexed. It is obvious that protonated ionic species of α -aminobutenoic acid, which exist in low pH ranges are non-complexing [CH₂ = CH - CH (NH₃⁺) COOH]. Figure 3 reveals that second plateau lies in positive region indicating cationic nature of 1:1 metal complex. Cadmium (II), iron (II), and zinc (II) metal ions form their first complex movements towards negative electrode. Hence, one α -aminobutenoic anionic species [CH₂ = CH - CH (NH₂) COO⁻] must have combined with cadmium (II), iron (II) and zinc (II) to give 1:1, [Cd {CH₂ = CH - CH (NH₂) COO}]⁺; [Fe {CH₂ = CH - CH (NH₂) COO}]⁺ and [Zn {CH₂ = CH - CH (NH₂) COO}]⁺ complex cations, respectively. The third plateau in each case is in zero region of mobility curve showing neutral nature of metal ligand complex. Hence, two anionic species of one α -aminobutenoic acid [CH₂ = CH - CH (NH₂) COO⁻] must have combined with metal ions to give [Cd {CH₂ = CH - CH (NH₂) COO}]₂⁻; [Fe {CH₂ = CH - CH (NH₂) COO}]₂⁻ and [Zn {CH₂ = CH - CH (NH₂) COO}]₂⁻ complexes, respectively. Further increase of pH has no effect on the mobility of metal ions, which indicates no further interaction between metal ions and ligands.

Chemical literature also assigns prominent chelating properties of the unprotonated anionic species of α – aminobutenoic acid ruling out any such property to zwitterions (Blackburn & Jones, 1973).

In general, the complexation of metal ions with α – aminobutenoic acid anion [L⁻] may be represented as



Wherein M^{2+} is Cd^{2+} , Fe^{2+} and Zn^{2+} metal ions; [L⁻] is the ligand α – aminobutenoic acid anion; K_1 and K_2 are first and second stability constants, respectively. ML^+ and ML_2 are 1:1 and 1:2 metal complexes, respectively.

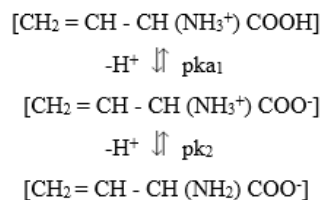
The overall mobility U of uncomplexed and complexed metal ions spot moving under the influence of electric field is given by equation (Jokl, 1964).

$$U = \frac{U_{0.0} \beta_{0.0} + U_{1.0} \beta_{1.0} [L] + U_{2.0} \beta_{2.0} [L]^2 + \dots + U_{1.1} \beta_{1.1} [HL] + U_{2.1} \beta_{2.1} [HL]^2 + \dots + U_{2.1} \beta_{2.1} [H_2L] + U_{2.2} \beta_{2.3} [H_2L]^2 + \dots}{\beta_{0.0} + \beta_{1.0} [L] + \beta_{2.0} [L]^2 + \beta_{1.1} [HL] + \beta_{2.1} [HL]^2 + \beta_{1.2} [H_2L] + \beta_{2.2} [H_2L]^2 + \dots} \quad (3)$$

Whereas $U_{0.0}$ is the speed of uncompleted metal ions, $U_{1.0}$ is the speed of complex formed by the combination of one protonated anionic ligand with metal ion and $U_{x.p}$, is the speed of complex formed by the combination of x anions containing p protons each. β 's are the overall stability constant of the different metal complexes formed in the interaction. On taking into consideration different equilibrium above equation transformed into following useful form.

$$U = \frac{u_0 + u_1 K_1 [L^-] + u_2 K_1 K_2 [L^-]^2}{1 + K_1 [L^-] + K_1 K_2 [L^-]^2} \quad (4)$$

Wherein u_0 , u_1 and u_2 are mobilities of uncomplexed metal ion, 1:1 metal complex and 1:2 metal complex, respectively. Equation (4) has been used for calculating stability constants of the complex of metal ions with α – aminobutenoic acid ($pka_1 = 2.45$; $pka_2 = 9.25$) was obtained by same paper electrophoretic technique. The mode of dissociation of pure α – aminobutenoic acid represented as:



For calculating first stability constant K_1 , the region between the first and second plateau is pertinent. The overall mobility U will be equal to the arithmetic mean of mobility of the uncomplexed metal ion u_0 and that of first complex u_1 at a pH where

$$K_1 = 1 / [CH_2 = CH - CH(NH_2) COO^-]$$

First stability constant K_1 can be calculated with the help of concentration of α – aminobutenoic acid anion and protonation constant of pure α – aminobutenoic acid. The concentration of chelating amino acid (α – aminobutenoic acid) species [L⁻] is calculated with the help of following equation.

$$[L^-] = \frac{[L_T]}{1 + [H] / Ka_2 + [H]^2 / Ka_1 \cdot Ka_2} \quad (5)$$

Wherein $[L_T]$ is the total concentration of ligand (α – aminobutenoic acid) 0.01 / Mol L⁻¹. The second stability constant K_2 of 1:2 complex can be calculated by taking into consideration the region between the second and third plateau of the mobility curve. The calculated values of first and second stability constants are given in Table 1.

Metal ions	Complexes	Stability constants	Logarithm stability calculated	Constant values literature
Cadmium (II)	ML ⁺	K_1	3.78 ± 0.01	3.84 [37]
	ML ₂	K_2	2.48 ± 0.03	-
Iron (II)	ML ⁺	K_1	3.27 ± 0.04	3.73 [37]
	ML ₂	K_2	2.33 ± 0.07	-
Zinc (II)	ML ⁺	K_1	4.45 ± 0.02	4.63 [37]
	ML ₂	K_2	2.66 ± 0.05	3.73 (37)

Iron strength = 0.1 Mol L⁻¹; temperature 35° C; α – Aminobutenoic acid anion: $[CH_2 = CH - CH(NH_2) COO^-]$; M = metal cations $[Cd^{2+}, Fe^{2+}, Zn^{2+}]$; L = Ligand (α – aminobutenoic acid)

Table 1: Stability constants of binary complexes of cadmium (II) iron (II) and zinc (II) with α – aminobutenoic acid

It is clear from Table 1 that order of stability constant zinc (II) > cadmium (II) > iron (II) is same for ML and ML₂ binary complexes.

The first and second stability constants for ML and ML₂ complexes, respectively follow the order

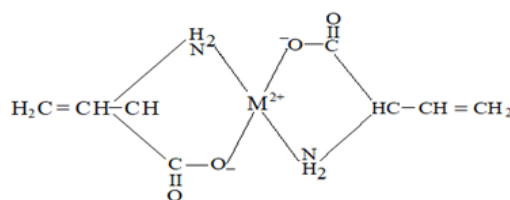
$$\text{Log } K_1 > \text{Log } K_2$$

The corresponding second stability constant values are found to be lower for the binary complexes. It is therefore inferred that coordinating tendency of a ligand decreases with higher state of aggregation. In other words, the metal progressively lessens its tendency of linkage with a ligand on progressive filling of vacant orbitals (Joshi, 1983). High stability constant values of zinc (II) and α – aminobutenoic acid complex indicate strong bonding between zinc (II) and α – aminobutenoic acid, while low stability constant value of iron (II) - α – aminobutenoic acid complex indication weak bonding between iron (II) cation and α – aminobutenoic acid anion. The difference in stability constants values in complexes may be due to difference in electronic configuration of central metal because ligand is common in all metal complexes. The stability constants of metal complexes can be very easily calculated by this technique, therefore present method has significant advantages over other method (viz: polarography, potentiometry, solubility etc.) reported in chemical literature for the determination of stability constants of metal complexes.

According to standard deviation (statistics) the precision of the method is limited to that of paper electrophoresis, and uncertainty in the result is $\pm 5\%$. Hence, it cannot immediately replace the most reliable methods, even though it is a new approach deserving further development.

The parallel studies on the metal complexes in biology and medicine and their stability constants determination are reported in chemical literature. A complex of zinc and carnosine called zinc – L – carnosine (Zn C) has been extensively used in tumor adjuvant therapy (Tang et al., 2022). A vitro antibacterial and antitumor potential of iron based on Schiff base is described by Aly et al. (2023), Ajayi et al. (2024) has address the therapeutic relevance of transferrin, stressing its function as a marker for diagnosing iron deficiency well as its implications in health conditions such as hemochromatosis and atransferrinemia. Application of ferroptosis in systemic chemotherapy, radiotherapy, immunotherapy, nanomedicine and its potential in the treatment of tumors, has been described by Nie et al. (2022), Tiang et al. (2019) has reported the use of zinc (II) complexes in bioimaging, molecular, protein recognition and photodynamic therapy. A novel artemisinin/ quercetin/zinc mixed ligand complex was synthesized, tested for its antiviral activity against coronavirus (SARS – COV – 2), and investigated for its effect against toxicity and oxidative stress induced by acrylamide by El – Megharbel et al. (2024). Pavlova et al. (2024) has studied the biological effect of the L – cysteine in case of combined chronic cadmium and lead poisoning of white rats in laboratory conditions. A total of 12 cancer types associated with specific genes coding for the Cd – metalloproteome were identified by Peana et al. (2022).

The proposed structure for metal (II) - α – aminobutenoic acid ML₂ binary complexes may be given as follow:



Concluding Remarks

The following conclusions can be drawn from the present study.

1. Cadmium (II), iron (II) and zinc (II) metal ions are significant for biological systems as such they are toxic, the - α – aminobutenoic acid may be used to reduce to reduce the level of these metal ions in the biological systems.
2. The present paper electrophoretic technique is very helpful in finding whether complex systems are formed or not, if formed its stability constant can also be determined.
3. The stability constants of metal (II) complexes with - α – aminobutenoic acid follows the order zinc (II) > cadmium (II) > iron (II).
4. The higher stability of zinc (II) - α – aminobutenoic acid complexes may be due to its greater affinity with oxygen donor ligand.
5. Stability constants of metal complexes can be very easily calculated by this technique, therefore present paper electrophoretic technique have significant advantages over other method (viz Polarography, potentiometric, solubility etc.) reported in chemical literature for the determination of stability constants of metal complexes.
6. Future work is to prepare cadmium (II), iron (II) and Zinc (II) binary complexes with proline at an optimum condition mentioned in this paper, characterize them and study their possible medical potential as anti-biotic, anti-inflammatory, and anti-cancer agent.

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