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Metal Complexes in Biology and Medicine the System Cadmium (II) / Iron (II) /Zinc (II) - Proline

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ABSTRACT

Metal ions are fundamental elements for the maintenance of the life span' s of the humans, animals and plants. In coordination compound studies, a knowledge of the magnitude of the stability constants of complexes is necessary for preliminary quantitative treatment. Present work described method that involves the use of paper electrophoretic technique for the study of the equilibria in binary complex systems in solution. This method is based on the movement of a spot of metal ion in an electric field at various pHs of the background electrolyte. A plot of overall mobility of metal / complex ion versus pH was used to obtain information on the formation of binary complexes and to calculate their stability constants. The stability constant of the ML and ML_2 complexes of cadmium (II) – proline,iron(II) – proline and zinc(II) – proline, have been found to be (4.61 ± 0.01; 3.04 ± 0.03), (4.21 ± 0.01; 2.89 ± 0.09) and (4.98 ± 0.02; 2.44 ± 0.05) (logarithm constant values), respectively at 35 °C and ionic strength 0.1 mol L^{-1}. The first and second stability constants follow the order zinc (II) >cadmium (II) > iron (II). Metal complexes can offer their action such as anti-inflammatory, antidiabetic, antimicrobial, anticancer and ant thyroid compounds. Metal based drugs bioactivity can be increase by metal chelation, which in turn increase their absorbance and stability.

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Introduction

Quantitative indication of the process of forming a complex comes from the evaluation of the stability constants, which characterize the equilibria corresponding to the successive addition of ligands. That is, we can consider the steps

$$M + L \overset{K_1}{\leftrightarrows} ML$$

$$ML + L \overset{K_2}{\leftrightarrows} ML_2$$

$$\vdots$$

$$ML_{n-1} + L \overset{K_n}{\leftrightarrows} ML_n$$

These are characterized by equilibrium constants K_1, K_2 …, K_n such that

$$K_1 = [ML]/[M][L]$$
$$K_2 = [ML_2]/[ML][L] \text{ and}$$
$$K_n = [ML_n]/[ML_{n-1}][L]$$

These constants K, are termed as stepwise formation constants. An alternative formulation is to consider the overall formation reaction

$$M + n\,L \leftrightarrows ML_n$$

Characterized by the n^{th} over all formation constant β

$\beta_n = [ML_n]/[M][L]^n = K_1 . K_2 . K_n$.

The inverse of formation constant, the dissociation constant kd is also sometime useful

$$ML \overset{Kd}{\leftrightarrows} M + L \quad kd = \frac{[M][L]}{[ML]}$$

K_d has the same form as Ka for acids, which facilities comparison between metal complexes and Bronsted acids. The complexation data involving biologically active metal ions and bioactive ligand proline give insight into many physiochemical processes. The

knowledge of the stabilities of metal complexes are known to play an important role in many metabolic and toxicological functions [1]. Cadmium is naturally present in the environment; it is present in soil and sediments at concentrations which are generally more than 1.0 mg kg^{-1} and its total concentrations in unpolluted seawater, where it exists mainly as chlorocomplexes is generally <1.0 µg kg^{-1} [2]. Cadmium is considered to be toxic, heavy metal that causes nephrotoxicity in humans. More evidence demonstrates the role of high-serum uric acid levels in Cd - induced overproduction of endogenous reactive oxygen species, which subsequently leads to renal injury and lipid metabolism disorder [3].

Iron is necessary for neuronal function but excess generates neurodegeration. Iron is a pro-oxidant that in the reductive intracellular environment catalyzes hydroxyl radical formation through the Fenton reaction. [4]. Disorders of iron metabolism are among the most common disease of humans and encompass a broad spectrum of disease with diverse clinical manifestations, ranging from anemia to iron overload and, possibly to neurodegenerative disease [5]. Zinc is a trace element bound in biological system with protein B, forming metalloprotein and useful in maintaining human health [6]. Cadmium (II), iron (II) and zinc (II) are well known for its biomedical applications and toxicity [7-15]. It seems to be very interesting to study the feasibility of controlling their level by complexation.

Proline or pyrrolidine-2-carboxylic acid is an amino acid found in protein. Proline properties includes molecular formula: $C_5 H_9 NO_2$; molar mass: 115.13g mol^{-1}; appearance colorless crystals, hygroscopic; m. p. 205°C decompose; water Soluble. Proline has several applications in biological systems [16-18]. The present modified method is almost free from number of defects of common electrophoretic technique such as temperature during electrophoresis, capillary flow on paper, electro osmosis and adsorption. The technique is very convenient in use. It gives results in fair agreement with accepted literature values. Publications [19-21] from our laboratory have described a new method for the study of metal complexes. A search of literature indicated coordination of amino acids. with metal ions [22,23] but few reports available on binary complexes of cadmium (II), iron (II) and zinc (II) with proline. In view of this, an attempt was made to establish the optimum conditions for metal (II) - proline complex formation. In addition, the present paper describes a paper electrophoretic method for the determination of the stability constant of cadmium (II)/ iron (II)/ zinc (II) - proline binary complexes

Experimental

Apparatus

A Systronic (Naroda, India) Model 604, electrophoresis was used. The apparatus consisted of a Poly (vinyl chloride) PVC moulded double tank vessel. In our laboratory significant change in the instrument has been made. Two hollow rectangular iron plates each weighing one kg, and covered with thin polythene sheets have been used through which thermostated water circulated for controlling the temperature. The tanks are closed with a transparent PVC moulded lid. The whole assembly is tight to prevent moisture changes, which might upset the equilibria in the paper strip. This assembly design thus keeps to a minimum the disturbing effect of evaporation from the unwanted liquid flow in the paper strips. Each electrolyte tank contains a separate electrode chamber in which Pt-wire anode and cathode are placed, respectively. Applied voltage was from a stabilized source.

Whatman No. 1 filter papers for chromatography were used for the purpose of electrophoresis. Elico (Hyderabad, India,) Model L_{1-10} pH meter using a glass and calomel electrodes assembly working on 220 V/50 Hz established a. c. mains, was used for the pH measurements. pH meter was calibrated with buffer solution of pH 7.0. Electrophoresis cell showing sandwiched paper strips is shown in Figure 1.

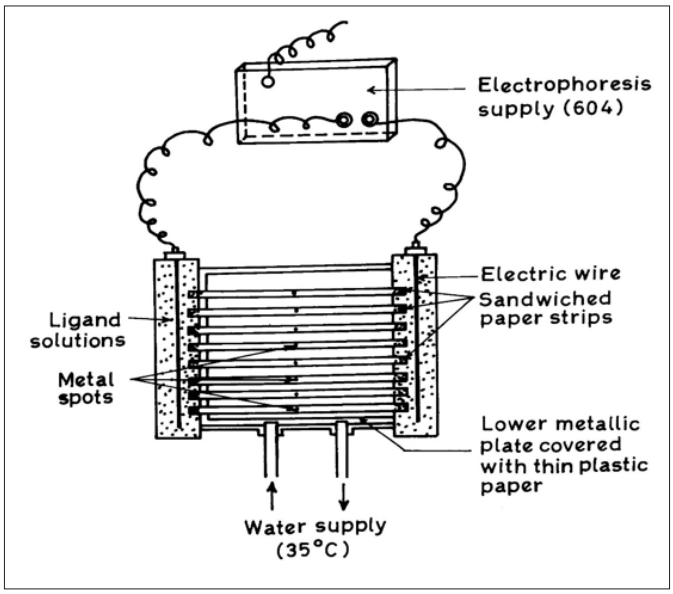


Figure 1: Electrophoresis Cell Showing Sandwiched Paper Strips

Chemicals

Preparation of Metal Solutions

Cadmium (II), iron (II) and zinc (II) metal perchlorate solutions were prepared by the precipitation of metal carbonates from a 0.1 Mol L^{-1} solution of beryllium(II) and cobalt(II) nitrates with the solution of sodium carbonate (chemically pure grade, BDH, Poole, UK). The precipitates were washed with boiling water and treated with calculated amounts of 1% perchloric acid. They were heated and filtered. The metal contents of the filtrates were determined and final concentration was kept 0.005 Mol L^{-1} [24].

Sodium Hydroxide Solution

Carbon dioxide free sodium hydroxide solution was prepared by dissolving 500 grams of sodium hydroxide in 500 mL of water in a flask. The flask was left overnight. The clear supernatant liquid was filtered rapidly using a high vacuum pump. A suitable volume of the filtrate was diluted and the concentration determined by titrating against a standard oxalic acid solution. A solution (2.0 Mol L^{-1}) was obtained by suitable dilution. The concentration of stock solution was checked from time to time.

Detecting Reagents for Metal Ions and Glucose

Metal spots were detected on the paper using dithizone in carbon tetrachloride for Zn(II). A solution of 1-(2-pyridylazo - 2-naphthol (PAN) (E. Merck, Darmstadt, Germany), in ethanol was used for detecting cadmium (II) and iron (II) metal ions. 0.005 Mol L^{-1} glucose (BDH, Analytical Reagent grade) solutions was 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 20mL. Glucose was detected by spraying with this silver nitrate solution then with 2% ethanoic sodium hydroxide, when a black spot was formed.

Background Electrolyte

The background electrolytes used in the study of binary complexes were 0.1 Mol L^{-1} perchloric acid and 0.01 Mol L^{-1} proline. The system was maintained at various pH by the addition of sodium hydroxide. Stock solution of 5.0 Mol L^{-1} perchloric acid (SDS, Analytical Reagent grade), 2.0 Mol L^{-1} sodium hydroxide (Analytical Reagent grade) and 0.5 Mol L^{-1} proline were prepared. Each solution was standardized using the appropriate method. Paper strips showing the position of metal ion spots after electrophoresis is shown in Figure 2.

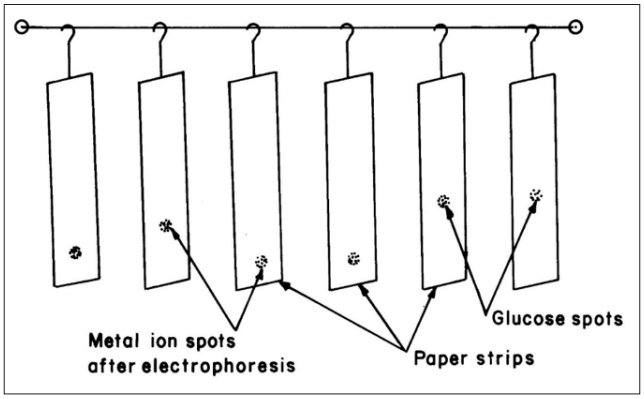


Figure 2: Paper Strips Showing Position of Metal Ion Spots After Electrophoresis

Procedure

Whatman No 1 filter paper for chromatography was used for the purpose of electrophoresis. For recording observation of particular metal ion, two strips were spotted with the metal ion solution along with additional two spotted with glucose using 1.0 µL pipette and then mounted on the insulated plate. Each of the two electrolyte vessel was filled with 150 mL of background electrolyte containing 0.1 Mol L^{-1} perchloric acid and 0.01 Mol L^{-1} proline. The paper became moistened with the background electrolyte solutions 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 10 minutes to insure wetting of strips. Subsequently a direct 200 Volts potential was applied between the electrodes. Electrophoresis was carried for 60 minutes after which these strips were removed from the tank and dried. The metal ion and glucose spots were detected by specific reagents. The leading and tailing edge were measured from the marked center point and the mean were taken. The distance moved by glucose was subtracted (in case of migration toward anode) to obtain correct path length. Migration towards anode and cathode were designated by negative and positive signs respectively.

Electrophoretic observations on metal ions were recorded at various pH values of the background electrolyte obtained by adding sodium hydroxide solution. The ionic strength being maintained at 0.1 Mol L^{-1}. The observed mobility of migrant was calculated by using the formula.

$$U = \frac{d}{x \, . \, t}$$

after applying the correction factor the observed mobility is given as

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

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 ion spots on the paper strips were thus calculated and are reported with different pH values (Figure 3)

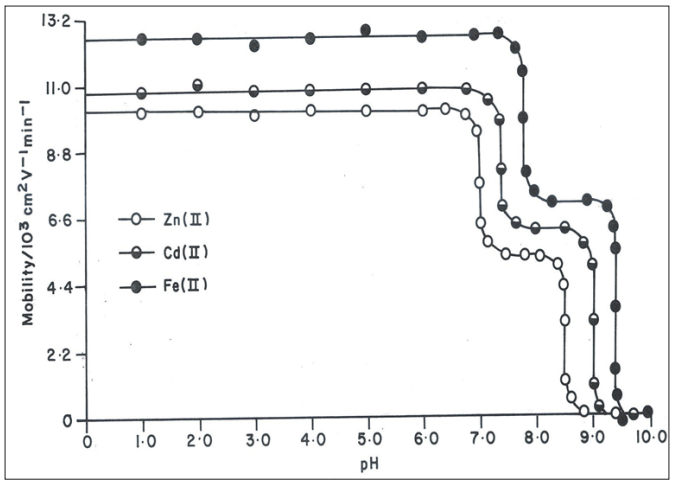


Figure 3: Mobility Curve for The Metal (II) - Proline Systems. Background Electrolytes: 0.1M Perchloric Acid and 0.01M Proline. PH's were Maintained by Addition of Sodium Hydroxide. The Paper Strips were Spotted with 0.1 ML of Sample Solutions and Glucose (for Making Osmotic Corrections).

The protonation constants of pure proline were determined by the same paper electrophoresis technique. The two paper strips were spotted with pure proline along with two glucose using 0.1 Mol L^{-1} perchloric acid only in a background electrolyte. The electrophoresis was carried for 60 minutes as for metal ions. The electrophoretic speed was calculated. The speed of the metal ion/ proline spots are reported with pH values. The individual speeds of the duplicate spots were found to be fairly equal.

Results and Discussion

Chemical literature [25, 26] confirms that anionic species of amino acids are the sole ligating species for metal ions. The plot of overall electrophoretic mobility of the metal spot against pH is shown in Figure 3. The first plateau in beginning corresponds to a region in which metal ions are uncomplexed. It is obvious that protonated ionic species of proline, which exists in low pH ranges, are non-complexing. Figure 3 reveals that cadmium (II), iron (II) and zinc (II) ions form their first complex movement toward negative electrode. Hence, one proline anionic species must have combined with cadmium (II), iron (II) and zinc (II) to give 1:1 $[Cd\ L]^+$, $Fe\ L]^+$ and $[Zn\ L]^+$ complex cations, respectively. The third plateau in each case is in zero region showing neutral nature of metal - ligand complex. Hence, two anionic species of proline must have combined with metal ions to give 1:2, $[Cd\ L_2]$, $[Fe\ L_2]$ and $[Zn\ L_2]$ 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. In view of above observations, the complexation of metal ions of with proline anion [L-] may be represented as

$$M^{2} + L^{-} \underset{}{\overset{K_1}{\leftrightarrows}} ML^{+} \quad (1)$$

$$ML^{+} + L^{-} \underset{K_2}{\leftrightarrows} ML_2 \quad (2)$$

Where M^{2+}= Cd^{2+}, Fe^{2+} and Zn^{2+} cations; [L^-] = proline ligand; ML^+ and ML^{2+} are the 1:1 and 1:2 metal complexes: K_1 and K_2 are the first and second stability constants, respectively. The metal spot on the paper is thus a combination of uncomplexed metal ions; 1:1 complex and 1:2 complex. The spot is moving under the influence of electric field; the overall mobility is given by well-known equation of Jokl [27].

$$U = \frac{u_o + u_1 K_1[L^-] + u_2 K_1 K_2 [L^-]^2}{1 + K_1[L^-] + K_1 K_2 [L^-]^2} \quad (3)$$

Where u_0, u_1 and u_2 are the mobility's of metal ions, 1: I and 1:2 metal complexes, respectively. Equation (3) was used for the determination of the stability constants of metal ions with proline. The protonation constants of pure proline [pka_1 = 1.90; pka_2 =10.03] were determined by the same paper electrophoretic technique. The mode of deprotonation of pure proline can be represented as:

$$[CH_3\ CH_2\ CH_2\ CH\ (NH_2^+)\ COOH]$$
$$-H^+ \quad \Updownarrow\ pka_1$$
$$[CH_3\ CH_2\ CH_2\ CH\ (NH_2^+)\ COO^-]$$
$$-H+ \quad \Updownarrow\ pka_2$$
$$[CH_3\ CH_2\ CH_2\ CH\ (NH)\ COO\text{-}]$$

using protonation constant of proline, the concentration of pure proline anion [L^-] is determined for the pH values of interest from which K_1 can be calculated. The concentration of complexing proline anion [L^-] is calculated with the help of equation.

$$[L^-] = \frac{[L_T]}{1 + [H]/\ pka_1 + [H]^2/\ pka_1 \cdot pka_2} \quad (4)$$

Wherein [L_t] is the total concentration of proline (0.01 mole L^{-1}); $Þka_1$ and $Þka_2$ are the first and second protonation constants of pure proline, respectively.

For calculating first stability constant, K_1, the region between first and second plateau is pertinent. The overall mobility will be equal to the arithmetic mean of the mobility of uncomplexed metal ion, uo, and that of first complex, u_1 at a pH where K_1 = 1/[L^-]. The second stability constant, K_2, of 1:2 complex can be calculated by taking into consideration, the region between second and third plateau of the mobility curve. These calculated values of K_1 and K_2 are given in Table 1. It is clear from the Table 1 that first and second stability constants values follow the order Zinc (II) > Cadmium (II) Iron (II).

Table 1: Stability Constants of the Binary Bomplexes of Cadmium (ii), Iron (ii) and Zinc (ii)- Proline

Metal Ions	Complexes	Stability Constants	Logarithm Stability Constant Values *
Cadmium (II)	ML^+	K_1	4.61±0.01 (4.40) [38]
	ML_2	K_2	3.04±0.03
Iron(II)	ML^+	K_1	4.21±0.01 (4.07) [38] (4.07) [40]
	ML_2	K_2	2.89 ± 0.09 (4. 23) [40]
Zinc (II)	ML^+	K_1	4.98 ± 0.02 (5.15) [38] (5.13 ± 0.01) [39]
	ML^2	K_2	2.44±0.05 4.56±0.01[39]

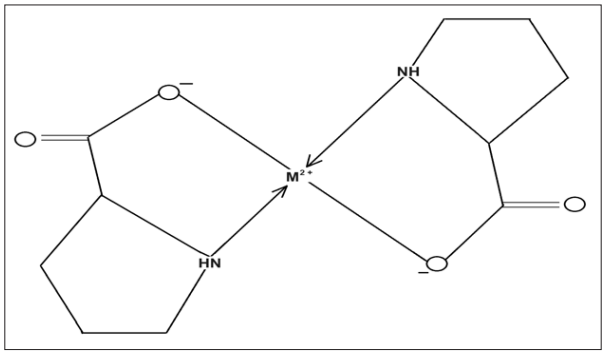
Ionic strength = 0.1 Mole L^{-1}; temperature = 35°C; M = metal cations (Cd^{2+}, Fe^{2+} and Zn^{2+}); L= ligand (proline); proline anion = [$CH_3\ CH_2\ CH_2\ CH\ (NH)\ COO^-$].
*Literature values are given in the bracket.

The values of second stability constants are found to be lower in comparison to first stability constant in each case this may be due to the decrease in coordinating tendency of ligand 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. This conclusion is of universal validity as evident in chemical literature [28]. According to standard deviation (statistics) the precision of the method is limited to that of paper electrophoresis, and uncertainty in the result is ± 5 %. Hence, it cannot immediately replace the most methods, even though it is new approach deserving further development.

The parallel studies on the metal complexes in biology and medicine and stability constants determination are reported in chemical literature. The summary of proper treatment of Cd poisoning, based on the use of selected Cd destroying agents and chelators and the potential preventive approached to counteract its chronic exposure [29]. Recio et al. [30] has investigated zinc cluster transcription factors frequently activate target genes using a non – canonical half- site binding mode, which bind to DNA to regulate gene expression. Management of redox nature of iron to crucial biochemical processes and to preserving health has been described by Silvestri et al. [31]. Applications of hybrid inorganic metal magnesium tartarate complexes as cancer therapeutic agents has been studies by Betalla et al. [32] in vitro. Bortolamial et al. [33] has discussed biomolecules conjugated transition metal complexes for cancer therapy. A review on the applications of Zn (II) carboxylate – based coordination polymers, such as sensors, catalysts, species with potential in infections and cancers treatment is reported by Scalteunu et al. [34]. Gurung et al. [35] has investigated therapeutic applications of proline isomerization in regulating multiple biological pathways. Detachment induced accumulation and secretion of proline may contribute to tumor progression by supporting increased production of extracellular matrix and providing proline to surrounding stromal cells is studied by Pilley et al. [36]. Synthesis of Cd complexes using N (4) – phenyl -2- formylpiridine thiosemicarbazone (L_1) and

5-aminotetrazole (L_2) as organic ligands and evolution of their anti-cancer and nephrotoxic potential in vitro is reported by Abyar et al. [37].

The proposed structure for M (II) – proline, ML_2 binary complexes may be given as follow:



Proposed structure of ML_2 metal - proline complex

Concluding Remarks

Following conclusion can be shown from the present study Cadmium (II) iron (II) and zinc (II) are significant for biological systems but as such, they are toxic, the proline used may be used to reduce the level of these metal ions in biological systems. Zinc (II) - proline and iron (II)-proline complexes are found to have highest and lowest values of stability constant respectively.

ML_2 complexes are found to have low stability constant value and less stable in comparison to ML complexes.

The present paper electrophoretic technique is very helpful in finding that complex system is formed or not, if formed its stability constants can also be determined.

Stability constants of metal Complexes can be very easily calculated by this technique, so the present paper electrophoretic technique has significant advantages over the other Physiochemical methods reported in chemical literature for the determination of stability constants of metal complexes.

Future work is to prepare Cd (II), Fe (II) and Zn (II) binary complexes with proline at a optimum conditions mentioned in this paper, characterize them and study their possible medical potential as antibiotic, anti-inflammatory and anti – cancer agents.

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