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Electrochemical Study of Zn^{+2}-Theophylline Complex

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Abstract: The interaction between Theophylline and Zn^{2+} was investigated using direct current polarography. The polarographic technique was used to determine the stability constants and thermodynamic parameters such as enthalpy change (ΔH), free energy change (ΔG) and entropy change (ΔS) of Zn^{2+} complexes with Theophylline at pH-5 in 0.1 M acetate buffer. The study was carried out at two different temperatures 25 °C and 35 °C. Zn^{2+} - Theophylline complexes were formed in 1:1 and 1:2 ratios. The electrode processes were reversible and diffusion controlled.

Key words: stability constant, thermodynamic parameters, Zn^{2+}–Theophylline system.

Introduction

A methyl xanthine derivative is diuretic, smooth muscle relaxant, bronchial dilator, cardiac and central nervous system stimulant activities. Theophylline (3,7-dihydro-1,3-dimethyl-1H-purine-2,6- dione) is a methyl xanthine used in the treatment of bronchial asthma.[1] The antibacterial activity of theophylline is well known, especially as this alkaloid is present in tea leaves[2] Theophylline also exerts excitatory influences on the skeletal muscle, gastric secretion, kidneys and fatty acid metabolism in addition to inhibitory effects on smooth muscle. It is well known that excessive administration of Theophylline occasionally produces serious toxicity, including vomiting, tachycardia, and central nervous system excitation including seizures.[3, 4] Theophylline relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels and reduces airway responsiveness to histamine, methacholine, adenosine, and allergen. Theophylline(Fig. 1) has molecular weight 180.1640 g/mol and melting point 272°C.

Zinc is an important trace element and a participant in numerous biochemical processes. It is an integral component of nearly 300 enzymes. Zinc is necessary for the formation of hydrochloric acid in the stomach via its role as the activator of the enzyme carbonic anhydrase. This role of zinc as well as its presence in the metalloenzymes carboxypeptidase A and B makes it especially important to gastrointestinal digestive function. Zinc is also a component in the metalloenzymes superoxide dismutase, alkaline phosphatase, alcohol dehydrogenase, as well as RNA and DNA polymerases.[5] Zinc is one of the most important trace elements. It is essential for all the living systems, even for microorganisms. There are about 300 metalloenzymes, where zinc ion is present in their active site or it plays a structural role.[6, 7] Further zinc is a structural and catalytic co-factor of many metalloproteins, its deficiency causes metabolism defects and growth inhibition in microorganisms.[8] Zinc is one of the most significant biometals. It is an important component of many proteins. Zn^{2+} ion strongly interacts with electronegative sulphur, nitrogen, oxygen. It does not promote the formation of toxic free radicals.[9] Zinc is an essential microelement for all living systems including microorganisms. Zinc is required to maintain normal physiological and biochemical functions in cells. Moreover, zinc is used in prevention and therapy of many illnesses, itself or as a component of drugs (e.g. zinc bacitracin) and biopreparations.[10]

Metal complexes of biologically important ligands are sometimes more effective than the free ligands.[11] Zinc complexes with bioactive ligands catalyze many enzymatic processes in biological systems.[12] Zinc(II) salicylate complex compounds were prepared and their thermal, spectral and biological properties were studied.[13] Some of zinc(II) chelate macrocyclic compounds are very important as lipophilic carriers for anti-HIV substances.[14] The efficacy of a chelating agent in binding a given metal in a biological system depends on the binding constants of the chelator for the particular metal in the system, the concentration of the metal, and the presence and concentrations of other ligands competing for the metal in question. The interaction of the numerous ligands and their concentrations and binding properties based on their environments may alter the clinical outcomes in patients treated with chelation therapy.[15] The interactions of metal ions with purine and pyrimidine nucleobases are of major biological interest, due to their effects on DNA stability, conformation, replication and transcription. The metal complexes with purine and pyrimidine and their derivatives have been widely reported.[16–18]

Theophylline was used to compare the bindings of metal ions at the purine N7 and O6 sites. In Theophylline the N7 site is accessible for metal ion coordination[19] Spectroscopic (IR), thermoanalytical (TG/DTG, DTA) and biological methods were applied to study physicochemical and biological properties of some Zn(II) complex compounds $Zn(HCOO)_2$.tph, $Zn(CH_3COO)_2$.tph, $Zn(CH_3CH_2COO)_2.2H_2O$, where tph = theophylline.[20] Complexes of Theophylline and d^{10} configuration metal ions (Zn^{2+}, Cd^{2+}, and Hg^{2+}) were synthesized and characterized by IR, UV-visible, fluorescence spectrum.[21] $[M(H_2O)_2L_2]$, ($M = Zn^{2+}$, Cd^{2+}; L= 8-methylthiotheophylline) were prepared and characterized by IR and ^1H and ^{13}C NMR spectral studies.[22] $ZnL_2(NH3)_2$, and $CdL_2(NH_3)$.3H2O where L=theophylline, were prepared and characterized by magnetic susceptibility, IR, and ^1H NMR spectral methods.[23] Treatment of theophylline in aq. NH_4OH with aq. NH4OH containing M^{2+} (M = Cd, Cu, Zn) gave the corresponding $ML_2(NH3)_2$.[24] Some new theophylline compounds with transition metal ions were prepared and characterized by FTIR and x-ray powder diffraction.[25]

A large number of pharmaceuticals can be reduced or oxidized in the available potential range and their waves can be used in their determination. It seems that often the therapeutical activity is paralleled by electrochemical reactivity. Some drugs can be determined directly, without separation, by polarography, in some physiological liquids, for example in blood, lymph and saliva. To use polarographic methods for analyses of such simple matrices yields results often much faster, with a better accuracy and without using organic solvents.[26] Numerous examples of such applications have been reported earlier.[27]

In this work, we have demonstrated the binding of Theophylline and Zn^{2+} and the thermodynamics of their interaction. In order to attain these objectives, we have planned to carry out detailed investigation of Theophylline and Zn^{2+} using Direct current Polarography.

Experimental

Procedure

The general procedure for Direct current Polarography is as follows-

A 10 ml of experimental solution was placed in a polarographic cell and deoxygenated with nitrogen for 13 min. The cell was placed in the thermostat and the capillary was inserted in solution. The current and voltage were measured manually. Polarographic experiments were carried out with Elico D.C. recording polarograph CL 357. The current voltage measurements were performed with three electrode assembly, a dropping mercury electrode as working electrode, calomel as reference electrode and platinum electrode as counter electrode. A digital pH meter model 111 E was used for measuring the pH of the analytes. The potential was applied to the working electrode with 150 mV/min span rate and 100 nA/div. sensitivity of current measurement. The dropping mercury electrode had the following characteristics- m = 2.430 mg/sec, t = 3.6 sec, h = 65 cm.

Reagents

All the solutions were prepared from doubly distilled water and analytical reagent grade chemicals (MERCK).

Theophylline {Sidmak Laboratories (India)} solution was prepared freshly every 5 days.

$Zn(CH_3COO)_2.2H_2O$ used was of analytical reagent grade.

0.1 M Acetate buffer (pH-5) has been used as supporting electrolyte. Triton X-100 (0.001%) was used to suppress polarographic maxima.

Table -1: Polarographic data and *Fj (X)* values of Zn^{2+}–Theophylline system.

Cd^{2+} = 1.25 mM, 0.1 M Acetate buffer (pH-5), T = 25 °C

$E_{1/2}(Zn^{2+})$ = – 1.0473 volts vs. S.C.E

[X] mM	i_d ×100 nA	-Ec V	$-\Delta E_{1/2}$ = Ec-Em	FoX	$F_1X\times10^3$	$F_2X\times10^6$
0.12	4.0	1.0482	0.0009	1.126	1.010	7.120
0.25	3.9	1.0483	0.0010	1.164	0.657	2.147
0.38	3.8	1.0496	0.0023	1.322	0.859	1.971
0.50	3.7	1.0512	0.0039	1.538	1.076	1.912
0.62	3.6	1.0532	0.0059	1.850	1.356	1.977

Where ,

i_d = Diffusion current

$\Delta E_{1/2}$ = Difference in $E_{1/2}$ of $Zn^{2+}$and Zn^{2+}-Theophylline complex.

Em = Half wave potential of Zn^{2+} ion.

Ec = Half wave potential of Zn^{2+}-Theophylline complex

Table -2: Polarographic data and *Fj (X)* values of Zn^{2+}–Theophylline system.

Zn^{2+} = 1.25 mM , 0.1 M Acetate buffer(pH-5), T = 35 °C

$E_{1/2}(Zn^{2+})$ = 1.0359 volts vs. S.C.E

[X] mM	Id×100 nA	$-E_{1/2}c$ V	$-\Delta E_{1/2}$ = Ec-Em	FoX	$F_1X\times10^3$	$F_2X\times10^6$
0.12	5.0	1.0370	0.0011	1.108	0.865	1.1470
0.25	4.9	1.0383	0.0024	1.250	0.988	1.0670
0.38	4.8	1.0396	0.0037	1.404	1.078	0.9490
0.50	4.7	1.0410	0.0051	1.594	1.187	0.9309
0.62	4.6	1.0426	0.0067	1.837	1.339	0.9877
0.75	4.5	1.0443	0.0084	2.134	1.513	1.0540

Table -3: Stability constant of Zn^{2+}–Theophylline system.

System	**Ratio**	**T = 25 °C**		**T = 35 °C**	
		B	log β	β	log β
$Zn(THP)^{+2}$	1:1	β1 = 120	2.079	β1 = 772	2.888
$Zn(THP)_2^{+2}$	1:2	β2 =1.98 ×10^6	6.297	β2 =0.97×10^6	5.987

Table -4: Thermodynamic parameters of Zn^{2+}–Theophylline system at 25 °C and 35 °C.

System	**Ratio**	**Thermodynamic parameters**		
		ΔG	ΔH	ΔS
$Zn(THP)^{+2}$	1:1	-11863.5	142074.7	516.571
$Zn(THP)_2^{+2}$	1:2	-35927.8	-54460.7	-62.1909

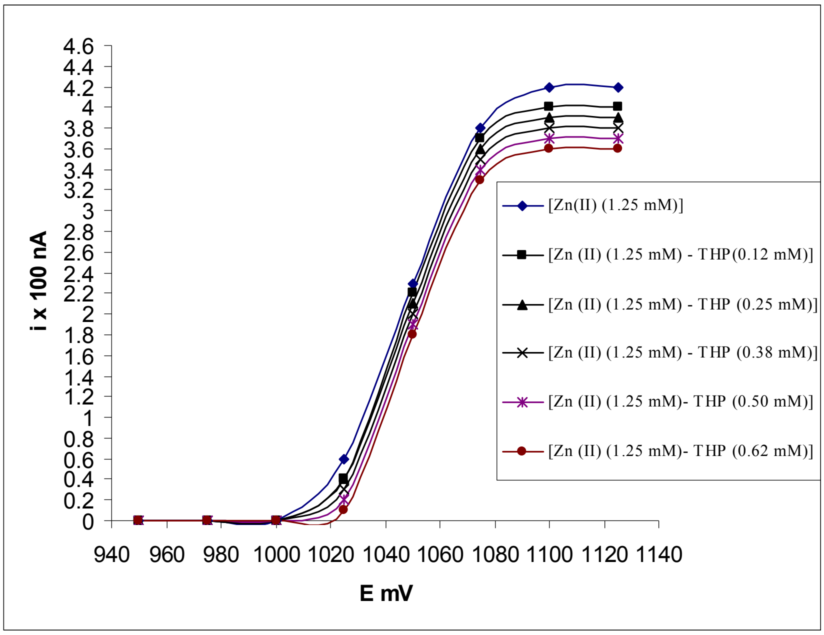

Fig. 2. Polarograms of Zn^{2+} - Theophylline system at 25 °C.

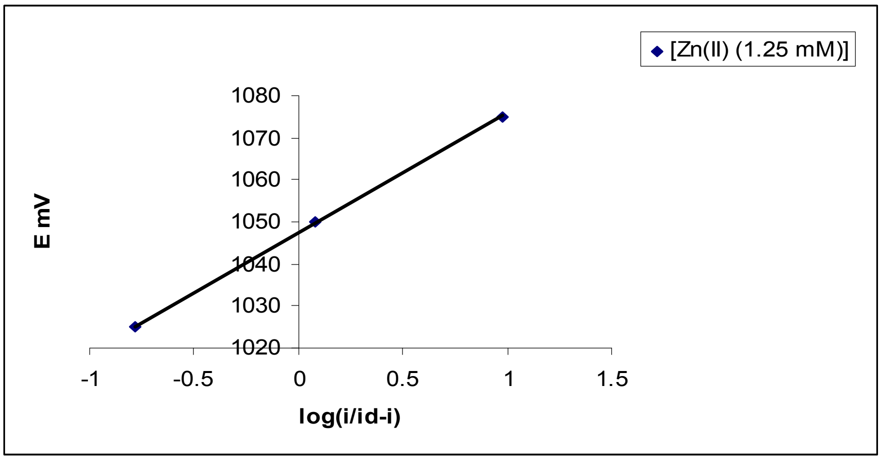

Fig. 3.A

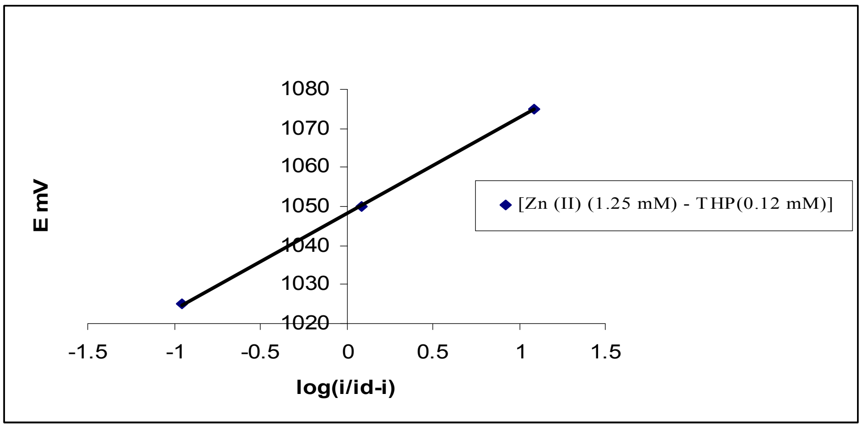

Fig. 3.B

Fig. (3.A & 3.B) plot E vs. log(i/i$_d$-i) at 25 °C

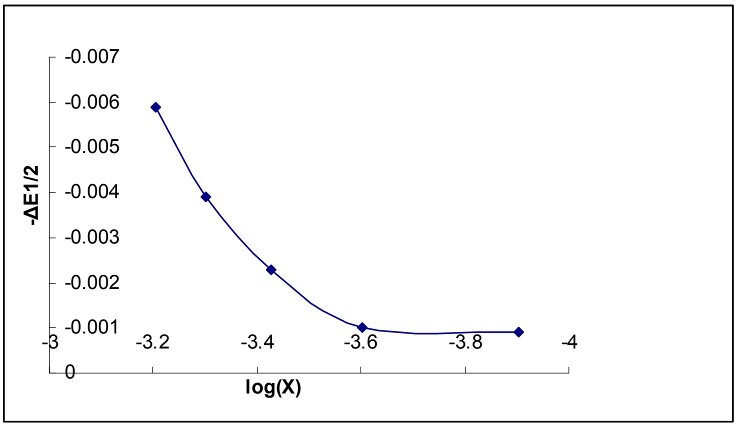

Fig 4. plot -$\Delta E_{1/2}$ vs. log[concentration] at 25^0C.

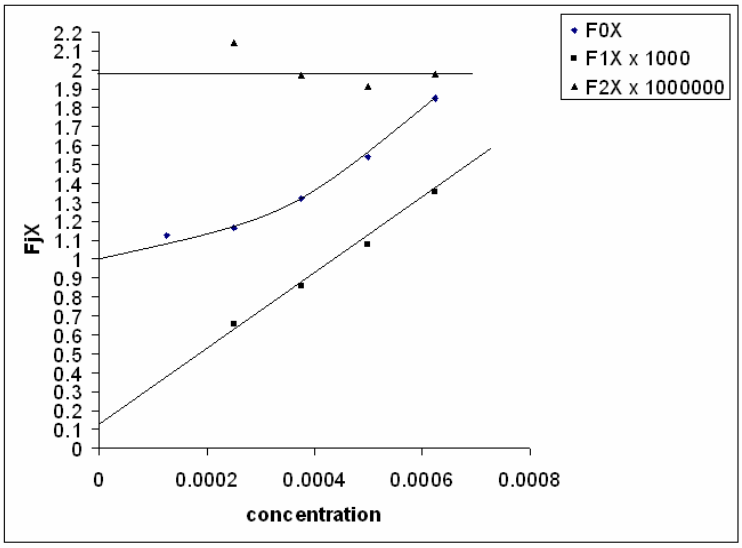

Fig. 5 Fj (X) values of Zn^{2+}–Theophylline system at T = 25 °C

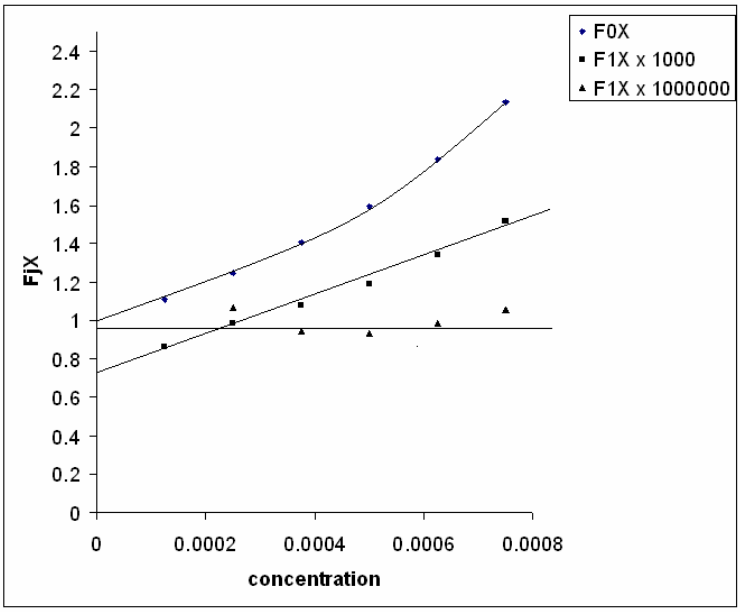

Fig. 6 Fj (X) values of Zn^{2+}–Theophylline system at T = 35 °C

Results and Discussion

A well-defined two-electron reversible reduction and diffusion controlled wave of Zn^{2+} was observed in 0.1 M Acetate buffer at pH-5. The value of $E_{1/2}$ reversible for Zn^{2+} was –1.040 mV vs. SCE. The nature of the Current-Voltage curve of Zn^{2+} complexes with Theophylline was also reversible and diffusion-controlled.

When aqueous solution of Theophylline(THP) was added, half wave potential was shifted towards more negative direction i.e. towards more cathodic value of the system, the difference being related to the free energy of dissociation of complex[28] and The diffusion currents were found to decrease with increase of ligand concentration, which suggests complex formation.(Fig. 2) The complex ion formed is of much larger size as compared to the aqua metal ion hence there is the low value of diffusion currents with the increase of ligand concentration.[29]

The slope values of the plots of $\log(i/i_d\text{-}i)$ vs. E (mV) are found in the range 26±2 mV suggesting the reversible nature of electrode reaction.(Fig. 3.A & 3B)

The plot of $\Delta E_{1/2}$ against log [X] consists of a smooth curve which is convex with respect to the abscissa axis, with increase of the activity of the ligand, complexes with a larger coordination number are formed and the slope of the plot increases.[30] (Fig. 4)

The Deford and Hume method[31] confirmed the formation of 1:1 and 1:2 complexes of Zn^{2+} with Theophylline. Complexation has been carried out at two (25°C and 35°C) temperatures. At 25°C more shift in half wave potential was observed. The temperature coefficient of the half wave potential is between -1.00 to -1.12 mV/degree so the system is reversible.[32] The plots of *Fj (X)* vs. X (where X is the concentration of Theophylline in mole/liter) are given in Fig. 5 & 6 and results are summarized in tables 1 & 2 at 25°C & 35°C respectively.

Fig. 5 & 6 illustrates plots of the functions *Fj (X)* for the Zn^{2+}-Theophylline system. Evidently two complexes are formed in this system: $Zn(THP)^{+2}$ and $Zn(THP)_2^{+2}$. From the plots of *Fj (X)* vs. X values of β_1 and β_2 have been evaluated. Value of intercept gives the value of β, whereas value of logβ represents the stability constant. More will be the value of stability constant more will be stability.

As shown in Table 3 stability constant values increases with increases in coordination number suggesting more stability of Zn^{2+}-Theophylline complexes in 1:2 ratio. The stability constant values suggest that 1:2 complex is more stable at 25^0C than at 35^0C.

Thermodynamic parameters

The thermodynamic parameters[33-34] such as free energy change (ΔG), enthalpy change (ΔH), and entropy change (ΔS) of interaction are important to interpret the binding mode of metal-ligand complex.[35] The kind of complex species that can be measured with a dropping mercury electrode depends on thermodynamic aspect.[36] Experiments were carried out at 25 °C and 35 °C, since Theophylline does not undergo any gross structural change in this temperature range. The values of thermodynamic parameters of the complexes are given in Table 4.

In Table 4, the negative value for ΔG indicates the spontaneity of the binding of Theophylline with Zn^{2+}. The more negative value for ΔG in case of 1:2 complexes shows that deriving tendency of complexation reaction increases from left to right and reaction tend to proceed more spontaneously.[37] The value of ΔH suggests that Zn^{2+}–Theophylline system in ratio 1:1 is endothermic i.e. in stepwise replacement of solvent molecule by ligand, heat is involved in first step while ratio 1:2 is exothermic in nature.[38] It means greater the amount of heat released in reaction, more stable are the reaction products. The negative value of ΔS in 1:2 ratio corresponds to a more ordered activated complex and this implies a small value of the steric factor. Positive value of entropy in ratio 1:1 reveals the formation of comparatively disordered complex.[39]

Conclusion

It is clear from the study that the shift of $E_{1/2}$ becomes more negative on increasing the concentration of Theophylline to Zn^{2+}, which confirms complex formation. Zn^{2+} formed 1:1 and 1: 2 complexes. The values of their stability constants varied from 2.1 to 6.7. The stability constants (log β) and thermodynamic parameters, such as free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS) of Zn^{2+} complexes with Theophylline were determined by employing the polarographic technique in (0.1M) Acetate buffer at pH- 5 at 25 °C and 35 °C.

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References

1. Nunes, C., Mahendrasingam, A., and Uryanarayanan, R., Investigation of the Multi-Step Dehydration Reaction of Theophylline Monohydrate Using 2-Dimensional Powder X-ray Diffractometry. *Pharm. Res.*, 2006, 23(10) 2393-2404.
2. Dreosti, I. E., Bioactive ingredients: antioxidants and polyphenols in tea. *Nutr. Rev.*, 1996, 54, s51-s58.
3. Auritt, W.A., MeGeady, S.J., and Mansmann, H.C., The relationship of cerebrospinal fluid and plasma theophylline concentrations in children adolescents taking Theophylline. *J. Allergy Clin. Immunol.* 1985, 75, 731–735.
4. Hirose, M., Yokoyama, H., and Iinuma, K., Theophylline impairs memory/learning in developing mice. *Brain Dev.*, 2004, 26, 448–452.
5. Waters, R. S., Bryden, N. A., Patterson, K. Y., Veillon, C., and Anderson, R. A., EDTA Chelation Effects on Urinary Losses of Cadmium, Calcium, Chromium, Cobalt, Copper, Lead, Magnesium, and Zinc. *Biol. Trace Elem. Res.*, 2001, 83, 207-221.
6. Fridovich, I., The biology of oxygen radicals. *Science*, 1978, 10, 875-880.
7. Magonet, E., Hayen, P., Delface, D., Delaive, E., and Remacle, J., *Biochem. J.*, 1992, 287, 361.
8. Sigel, H., Zinc and its Role in Biology and Nutrition Metal Ions in Biological Systems, 15, *Marcel Dekker, New York*, 1983, pp.1–493.
9. Berg, J. M., and Shi, Y., The galvanization of biology: a growing appreciation for the roles of zinc. *Science*. 1996, 271, 1081-1085.
10. Stefanitsi, D., and Garel, J. R., A zinc-dependent proteinase from the cell wall of Lactobacillus delbrueckii subsp. Bulgaricus. *Lett. Appl. Microbiol.*, 1997, 24, 180-184.
11. Brewer, JG. In: Sigel H., editor. Metal ions in biological systems. *New York: Marcel Dekker*; 1982, 14, pp.57.
12. Ko¨ro¨s E. Bioinorganic chemistry. *Budapest: Gondolat*, 1992.
13. Zuzana Bujdosˇova´ Æ Katarı´na Gy}oryova´ Æ Jana Kova´rˇova´ Æ Daniela Hudecova´ Æ Ladislav Hala´s, Synthesis, biological and physicochemical properties of Zinc(II) salicylate and 5-chlorosalicylate complexes with theophylline and urea. *J Therm Anal Calorim*, 2009, 98, 151-159.
14. Koteswara, N. S., and Raene, R. M., *Biol. Met.*, 1990, 3, 19.
15. Bryden, Patterson, K. Y., Veillon, C., and Anderson, R. A., EDTA Chelation Effects on Urinary Losses of Cadmium, Calcium, Chromium, Cobalt, Copper, Lead, Magnesium, and Zinc. *Biol. Trace Elem. Res.*, 2001, 83,207-221.
16. Ahmad, R., Arakawa, H., and Tajmir-Riahi, H.A., A comparative study of DNA binding to Mg(II) and Ca(II) in aqueous solution: Major and minor grooves bindings. *Biophys. J.*, 2003, 84, 2460–2466.
17. Korn, S., and Sheldrick, W.S., Oligomeric (η6-arene) ruthenium(II) complexes of adenine and adenosine with N6, N7 coordination. *Inorganica Chimica Acta*, 1997,254, 85-91.
18. Boghai, D., and Nafisi, S., The effect of Ti(I) cation on the structure of Na~2-AMP and Na~2-GMP: Determination of possible binding sites and nucleotide conformation. *Iran J. Chem. Eng.*, 1996, 15, 98-107.
19. Tu, A.T., and Reinosa, J.A., the interaction of silver ion with guanosine and related compounds. *Biochemisty*, 1966, 5, 3375-3383.
20. Szunyogova, E., Mudronova, D., Gyoeryova, K., Nemcova, R., Kovarova, J., Piknova-Findorakova, L., The physicochemical and biological properties of zinc(II) complexes. Journal of Thermal Analysis and Calorimetry. *J. Therm. Anal. Calorim.*, 2007, 88(2), 355-361.
21. Chao, J., Chen, L., Wang, J., Li, J., Wang, P., and Feng, Y., Study on synthesis and properties of Zn(II), Cd(II), Hg(II) complexes of 1,3-dimethylxanthine. *Shanxi Daxue Xuebao, Ziran Kexueban,* 1997, 20(3), 306-309.
22. Skipworth, M. H., Taylor, M. R., Avila-Roson, J. C., Hidalgo, M. A., Suarez-Varela, J., and Colacio, R. E., Metal ion-purine base interactions. Zinc(II) and cadmium(II) complexes of 8-methylthiotheophylline. X-ray crystal structure and solution structure of bis(8-methylthiotheophyllinato)diaquazinc(II). *J. Inorg. Biochem.*, 1993, 49(4), 245-253.
23. Salas, P. J. M., Colacio, R. E., Moreno, C. M., and Lopez, G. J. de D. Fac. Cienc., Xanthine and its methylated derivatives as ligands. I. Synthesis and characterization of various theophylline complexes of cobalt(II), copper(II), silver(I), zinc(II) and cadmium(II). *Quimica Analitica*, 1984, 80(2), 167-171.

24. Zitzman, M. S., and Krebs, R. R., Divalent metal complexes of purines. Preparation of copper(II), zinc(II) and cadmium(II) complexes of theophylline in ammonia and methylamine. *J. Inorg. Nucl. Chem.*, 1978, 40(3), 571-572.
25. Marian, E., Jurca, T., Kacso, I., Borodi, G., and Bratu, I., Structure investigations of some complexes of theophylline with transitional metals. *Revista de Chimie (Bucharest, Romania)*, 2009, 60(6), 599-608.
26. Zuman, P., What Can DC Polarography Offer Today. *Review Acta Chim. Slov.* 2009, 56, 18–29.
27. Brˇezina, M., Zuman, P., Polarography in Medicine, Biochemistry and Pharmacy, *Interscience Publ., New York*, 1958; also German, 1956 and Czech, 1952 editions.
28. Meites, L., Polarographic techniques. *Brooklyn, New York*, 1964, 290.
29. Karadia, C., and Gupta, O.D., Polarograhic studies on the complexes of ga(iii), in(iii) and tl(i) with histidine. *Rasayan J. Chem.*, 2009, 2, 18-22.
30. Mambetkaziev, E.A., Zhdanov, S.I., Polarographic Study of Complex Formation Equilibria in Solutions. *Russ. Chem. Rev.*, 1980, 49(4), Translated from Uspekhi Khimii, 1980, 49, 588-617.
31. Deford, D., and Hume, D. N., *J. Am. Chem. Soc.*, 1951, 73, 5321.
32. Meites, L., “Polarographic techniques”, *Brooklyn, New York*, 1964, 288.
33. Khan, F., and Tantuvay, l., Thermodynamicsin [Mn(II)-antibiotics-bacitracin] Mixed System: A Polarographic Approach. *J. Pharm. Biomed.* Anal., 2002, 27, 933-944.
34. Chadar, S. N., Khan, F., and Sharma, S., Electrochemical study and thermodynamic parameters of Cd^{2+} complexes with some antibiotics and vitamin BX system. *chemija*, 2008, 19, 1–6.
35. Ross, P.D., and Subramanian, S., Thermodynamics of Protein Association Reactions: Forces Contributing to Stability. *Biochemistry*, 1981, 20, 3096–3102.
36. Martell, A. E., Calvin, M., Chemistry of Metal Chelate Compounds. *Prentice-Hall Inc., New York*, 1952, 155.
37. Saini, K., and Pandey R. S., Electrochemical Study of Complexes of Cu(II) at d.m.e.. *J. Electrochem. Soc.*, India, 2003, 52-2, 56-58.
38. Pandey, R. S., and Dugar, S., Thermodynamics Studies of Zinc Ethylenediamine Complexes in Aqueous-Non-Aqueous Media by polarography. *Asian J. Exp. Sci.*, 2001, 15, 49-62.
39. Saini, K., Gupta, H.P., and Pandey, R.S., Electrochemical study of complexes of Cd (II) with antibiotic drug at d.m.e. in 20% methanol-water and ethanol-water mixtures. *J. Indian Chem. Soc.* 2006, 83, 495-496.

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