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ORIGINAL ARTICLE **OPEN ACCESS**

Mixed ligand stability constant complex equilibrium study of Lamivudine drug with Ca (II), Cu(II) and Cr(II) transition metal ions

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ABSTRACT
Well known method of P^H metrically chemical equilibrium studies of transition metal complexes of Ca(II), Cu(II) and Cr(II) transition metal ions with Lamivudine (3CT) drug (D) and a series of eight amino acids (A) have been investigated at 30^0C temperature and 0.1 Molar ionic strength Sodium perchlorate ($NaClO_4$) in aqueous solution. During reaction formation of various possible complex species had been evaluated and analysed by using the special computer program and discussed in terms of various relative stability parameters. By using Calvin and Bjerrum as Proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of metal complexes were determined the method which was as modified by Irving and Rossetti methods at various temperatures.
***Keywords**: Mixed ligand complex, transition metal ions, amino acids, stability constant and ionic strength and drug Lamivudine (3CT).*

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INTRODUCTION

Drug Lamivudine (also known as 3TC) is phosphorylated by intracellular enzymes to form lamivudine triphosphate, the putative active metabolite. Lamivudine triphosphate is required to prevents HIV replication by competitive inhibition mechanism of enzyme viral reverse transcriptase and terminating proviral DNA chain extension. Its intracellular elimination half-life was between up to 10 to 15.5 hours only in HIV-infected cells [1, 2]. Lamivudine belongs to the nucleoside reverse transcriptase inhibitors class of drugs (NRTIs). It's an antiviral drug that keeps the human immunodeficiency virus (HIV) or hepatitis B from growing in your body. Its structure is shown in following figure as,

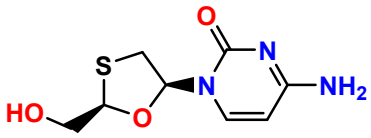

Figure 1 : Structure of Lamivudine Drug Molecule

The formation of metal complexes wasbased on metal ligand selectivity in complex chemical equilibria media [3, 4].The equilibrium constants are useful for measuring metal ligand selectivity in terms of relative strength of metal ligand bonds in medicine [5-7]. The Metals Ca(II), Cu(II) and Cr(II) and its complexes with ligand plays very important pivotal role in living system. As we know very better that the metal complexes with different drugs are important to understand proper dose of drug in human system [8]. It is also known that the complex physiological working function and mode of action of drugs and their impact circulatory systems [9]. It is also found that in literature survey that the metal complexes of drugs are more effective than their respective drugs [10]. It has also been observed that in transportation, metabolism detoxification and catalytic process metal complexes plays a vital role [11-12]. According to the literature survey very limited research work of ternary complexes of transition metals with biologically essential drugs and amino acids has reported in the past few years [13]].Therefore, this research paper deals with the planned and disciplined study of equilibrium constants of ternary complexes of Ca(II), Cu(II) and Cr(II) transition metal ions with tamsulosin drug (D) and different amino acids (A).

MATERIAL AND METHODS

The instrument used for this work is digital Elico pH meter in conjunction with combined electrode which is for the pH measurements and experiments were carried out at 30^0C temperature and inert atmosphere by maintaining 0.1M ionic strength sodium perchlorate ($NaClO_4$) in aqueous solution as which was also used by earlier researchers [14]. By using [21] 4.00 and 9.00 pH standard buffer solutions pH meter was calibrated before the use for every set of titrations for clear cut reading and with this all the necessary safety measures were taken for smooth conduct of electrode [15-18]. All the chemicals in this present research work have been used as A.R. grade. The of borosil glass quality's glassware's used during this research work and they are well standardized as per standard experimental procedure [19]. By using double glass distilled water having 6.80 to 6.90 pH the solutions of reagents were prepared [20] and NaOH solution also prepared using above water and fresh solution was used as a titrant for pH titrations of respective solutions. This NaOH solution is standardized with pure oxalic acid for proper calibration. The maintenance of the 0.1 M ionic strength of the titration solutions by using 1.0 M $NaClO_4$ solutions which has been prepared earlier. The solutions of these Ca(II), Cu(II) and Cr(II) transition metal ions were standardized by usual procedure [21].

PROCEDURE OF TITRATION

The Calvin Bjerrum pH metric titration techniques which was modified by Irving Rossotti were applied for the determination of the equilibrium constants of 1:1:1 ternary complexes [22, 23]. Titration procedure involves following steps:

a) Free $HClO_4$ + $NaClO_4$ (A)
b) Free $HClO_4$ + $NaClO_4$+ primary ligand (A+L)
c) Free $HClO_4$ + $NaClO_4$+ primary ligand+ metal (A+L+M)
d) Free $HClO_4$ + $NaClO_4$+ secondary ligand (A+D)
e) Free $HClO_4$ + $NaClO_4$+ secondary ligand+ metal (A+D+M)
f) Free$HClO_4$ + $NaClO_4$+ primary ligand + secondary ligand+ metal (A+L+D+M)

Standard NaOH solution was used to titrate the above Mixtures. By adding distilled water, the total volume of the solution was maintained at 50 ml.

OBSERVATIONS AND CALCULATIONS

With the help of computer in Microsoft Excel Irving and Rossotti methods were used to determine the proton ligand stability constants (pK) and metal ligand stability constants (logK) of binary complexes and The output of a specific computer programme that uses a non-linear least square technique yielded the equilibrium constants of ternary complexes as well as different species formed during complexation.[29-30].

RESULTS AND DISCUSSION

For comparison with ternary systems, the proton ligand stability constants (pK) and metal ligand stability constants (logK) of binary complexes were measured using the Irving and Rossotti method. From this Ca(II) < Cu(II) < Cr(II)order of stability of binary complexes of transition metal ions with drug lamivudine (D) indicates the less stability of calcium complexes than that of highest of copper complexes, from this highest stability of copper information over the calcium, it's clear that their occurrence in biological systems is more than other [24, 25]. The chelating tendency of the copper has been reveled in many inorganic metal complexes due to its biological importance and it is found true in case of the Lamivudine copper binary system, but in the present study it is found that the chelation tendency of Cr(II) ion is more compared to that of the Cu (II) ion. The ternary complex formed between Ca(II) metal ion, lamivudine and Leucine and Phenyl Alanine were found their ΔlogK values negative shows the less stability of the ternary complex but in other drugs binary complexes does not appear. Comparing the correlation of copper and chromium ternary complexes it is found that they are not in accordance may be due to variation in their valances. The formation of the binary complex with drug (D) occurs at pH 4 and is stable at higher pH. The presence of two pK and two logK values is indicated by the greatest values of nA and n being around 2.0.The formation of the 1:1:1 ternary complex (MDR) was qualitatively understood based on the pH of precipitations of the ML MR and MDR titration curves. The pH of precipitation in MDR systems was found to be higher than in binary systems [27]. It was also validated by the composite curve's non-superimposable nature on mixed ligand titration curves. The equilibrium constants and relative properties of these ternary complexes are listed in Tables 1-3.

These changes can be related to steric and inductive effects, as well as the increased amino acids side chain, which causes more strain in bending and resulting in poor stability values. The relative stabilities of mixed ligand complexes were expressed quantitatively in terms of ΔLogK, Kr, K_L and K_R values, which are described by formulae employed by previous researchers [28-30].

$\Delta logK = log\beta_{111} - logK_{10} - logK_{01}$

$Kr = \beta^2_{111} / \beta_{20} . \beta_{02}$

$K_L = \beta_{111}/logK_{10}$

$K_R = \beta_{111}/logK_{01}$

The relative stabilities and stability constants of ternary systems of Ca(II) < Cu(II) < Cr(II) metal ions are shown in tables 1, 2, and 3, respectively.

Amino acids	β_{11}	β_{20}	β_{02}	K_D	K_R	K_r	Δlog K
Leucine	14.5751	7.4544	7.247	7.1107	7.3342	3.972720	-0.1432
Phenyl alanine	10.1344	7.4578	3152	2.6787	6.9745	4.333455	-0.5014

Table 1 : The parameter is based on a correlation between the formation of mixed ligand Ca(II) complexes with Lamivudine drug and amino acids.

Amino acids	β_{11}	β_{20}	β_{02}	K_D	K_R	K_r	Δlog K
Glycine	13.1988	4.8578	18.60	8.22	3.3477	1.88977	-1.7
Leucine	15.0045	4.8455	8.1072	10.1757	6.9324	5.77877	2.03147
Glutamine	13.8857	4.8722	17.295	9.04001	4.4891	2.301547	-0.42201
Valine	14.4555	4.4777	18.50	9.5001	4.3210	2.29457	-0.5614
Methionine	14.5477	4.8455	18.35	9.6244	4.8399	2.378655	-0.0102
Phenyl alanine	12.9340	4.8455	16.77	8.1021	3.9602	2.077653	-0.8998
Glutamic acid	14.8798	4.8778	19.66	9.9898	3.8387	2.312980	-1.01002

Table 2 **:** The parameter is based on a correlation between the formation of Cu(II) mixed ligand complexes with Lamivudine drug and amino acids.

AMINO acids	β_{11}	β_{20}	β_{02}	K_D	K_R	K_r	Δlog K
Glycine	11.2577	4.7577	10.4588	6.34877	4.56877	2.415777	-0.17188
Leucine	12.2147	4.7544	12.0678	7.514	4.4500	2.610444	-0.26004
Glutamine	11.5014	4.74511	13.3400	6.75477	4.25444	2.087544	-0.51444
Valine	9.8687	4.7455	9.2011	5.1244	4.24155	2.23455	-0.51111
Methionine	11.3144	4.7547	3.9987	6.6001	8.2502	8.74002	3.45042
Phenyl alanine	12.9500	4.7547	11.8140	8.2001	6.5007	2.989977	1.7688
Glutamic acid	7.0057	4.7547	6.5671	2.2601	3.5014	1.56777	-1.2516
Alanine	9.9325	4.7547	19.4122	5.1985	-0.7745	1.08001	-5.50059

Table 3 : The parameter is based on a correlation between the formation of mixed ligand Cr(II) complexes with Lamivudine drug and amino acids.

The comparison of β_{111} with β_{20} and β_{02} of these systems indicates that ternary complexes form preferentially over binary systems [31]. Very low K_L and K_R values show ternary complexes are more stable than binary ligand complexes. Interactions outside the coordinated sphere, such as hydrogen bonding between coordinated ligands, charge neutralisation, the chelate effect, and electrostatic interactions between non coordinated charge groups of ligands, may also be contributing to the extra stability of mixed ligand complexes [32]. Negative ΔlogK values suggest ternary complex formation and destabilised complexes, as found in N and O coordination of amino acids [33].The increased stability of ternary complexes is sometimes attributed to a positive logK. Primary ligands produce 1:1 and 1:2 binary complexes with copper in the Cu(II)LD 8 (glutamic acid) ternary system, whereas secondary ligands form only 1:1 binary complex with copper.

CONCLUSION

Lamivudine interact with metal ions Cu(II) and Cr(III) to form normal (ML) and bis binary(ML_2) complex and form stable complexes with Cu (II) and Cr (III) due to the formation of more stable five membered chelate ring, but it is also observed that Cr (III) form more stable five membered ring with these ligands than Cu (II), because of higher charge on metal ion and small size. These results shows that because of calcium (Ca^{+2}) is a strongly basic metal, it forms the weakest chelates, it forms complexes with

Lamivudine but less compared to other metal ions. This demonstrates that the strength of bonding in these chelates is dependent on the metal's tendency to form homopolar bonds with the ligand. The ternary complexes shows that the copper complex is the most stable. It's also clear that ternary complexes formation has been confirmed from above data.

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REFERENCES

1. Cattaneo, D.; Capetti, A.; Rizzardini, G. (2019). Drug–Drug Interactions of a Two-Drug Regimen of Dolutegravir and Lamivudine for HIV Treatment. *Expert Opin. Drug Metab. Toxicol.*, *15* (3), 245–252.
2. Kewn, S.; Veal, G. J.; Hoggard, P. G.; Barry, M. G.; Back, D. J. (1997). Lamivudine (3TC) Phosphorylation and Drug Interactions in Vitro. *Biochem. Pharmacol.*, *54* (5), 589–595.
3. Singh, J.; Srivastav, A. N.; Singh, N.; Singh, A. (2019). Stability Constants of Metal Complexes in Solution. *Stab. Appl. Coord. Compd.*. http://dx.doi.org/10.5772/intechopen.90183
4. Gyurcsik, B.; Nagy, L. (2000). Carbohydrates as Ligands: Coordination Equilibria and Structure of the Metal Complexes. *Coord. Chem. Rev 203* (1), 81–149.
5. Alam, M. J.; Ullah, M. R.; Akther, M. (2018). Stability of Ternary Complexes of Cu (II) Metal Ion with 2, 2'-Bipyridyl and Oxalic Acid, Tyrosin, Ethylenediamine, Glycine, α-Alaline, Phenylalanine, Tryptophan. IOSR Journal of Applied Chemistry (IOSR-JAC). Volume 11, Issue 1 Ver. I (, PP 01-04
6. Pawar, R. P.; Raut, V. M.; Bhise, M. P.; Murhekar, G. H.; Wadekar, M. P.; Banewar, V. W.; Gulwade, D. P. (2009). Metal Ion Complexes of Sr (Ll), Cd (Ll), Pb (Ll), Zn (Ll) with Substituted Pyrazoles, Isoxazoles and Their Antimicrobial Activities. *Orient. J. Chem.*, *25* (4), 1117.
7. MAGARE^1, B.; Farooqui, M. N.; Shelke, R. S.; Ubale, M. B.(2009). Interaction of Some Anti Tuberculosis Drugs with Transition Metal Ions. *Orient. J. Chem. 25* (2), 387–390.
8. Magare, B. K.; Magar, B. K.; Ubale, M. B. (2019).Effect of Temperature on Stability Constants of Transition Metal Complexes with Ethambutol Hydrochloride Drug in Aqueous Medium. International Research Journal of Engineering and Technology. 6[8]:904-908
9. Gouda, G. A. H.; Ali, G. A. M. (2017). Potentiometric Study of Rhenium (V) Complex Formation with Azathioprine and Ceftriaxone. *Malays. J Analy Sci*, *21*, 1266–1275.
10. Rena, G.; Hardie, D. G.; Pearson, E. R. (2017).The Mechanisms of Action of Metformin. *Diabetologia*, *60* (9), 1577–1585.
11. Guzy, R. D.; Schumacker, P. T. (2006). Oxygen Sensing by Mitochondria at Complex III: The Paradox of Increased Reactive Oxygen Species during Hypoxia. *Exp. Physiol*, *91* (5), 807–819.
12. Pandey, A. K.; Gautam, A.; Dubey, R. S.(2019). Transport and Detoxification of Metalloids in Plants in Relation to Plant-Metalloid Tolerance. *Plant Gene*, *17*, 100171.
13. Andresen, E.; Peiter, E.; Küpper, H. (2018). Trace Metal Metabolism in Plants. *J. Exp. Bot. 69* (5), 909–954.
14. Ducic, T.; Polle, A. (2005). Transport and Detoxification of Manganese and Copper in Plants. *Braz. J. Plant Physiol.*, *17*, 103–112.
15. Koch, K. A.; Peña, M. M. O.; Thiele, D. J. (1997). Copper-Binding Motifs in Catalysis, Transport, Detoxification and Signaling. *Chem. Biol.*, *4* (8), 549–560.
16. Agrawal, B. R.; Magare, B. K.; Farooqui, M. N.; Janrao, D. M.; Ubale, M. B. (2009). Stability Constants Of Cu (Ii) Ni (Ii) And Mn (Ii) Metal Complexes With Cetrizine And Benzoic Acid. *Int J Chem Sc*, *7* (3), 2169–2172.
17. Thomas, A. B.; Patil, S. D. (2011). Simultaneous Spectrophotometric Estimations of Nateglinide and Metformin Hydrochloride in Pharmaceutical Formulation. *Pharm Chem*, *3*, 271–276.
18. Kayande, D. D.; Jadhav, S.; Farooqui, M.; Rai, M. PH-Metric Study of Stability Constant of Ternary Complexes Involving Transition Metals, Nicotinamide and Penicillamine. To Chemistry Journal, 2 , 512-516.
19. Magarea, B. K.; Ubaleb, M. B. (2009). Mixed Ligand Stability Constants of Co (II), Ni (II), Cu (II) and Zn (II) Transition Metal Complexes with Chloropheniramine Maleate Drug and Amino Acids. Der Pharma Chemica 3(4):323-329
20. Magarea B K.; Farooqui, M. N.; Shelke, R. S.; Ubale, M. B. (2009). Interaction of Some Anti Tuberculosis Drugs with Transition Metal Ions. *Orient. J. Chem.*, *25* (2), 387–390.
21. Bates, R. G.; Vijh, A. K. (1973). Determination of PH: Theory and Practice. *J. Electrochem. Soc. 120* (8), 263C.
22. Federman Neto, A.; Borges, A. D. L.; Lavrador, M. A. S. (2006).A Simple Protocol for the Routine Calibration of PH Meters. *Rev Ciênc Farm Básica Apl*, 63–72.
23. NETO, A. F.; Borges, A. D. L.; Lavrador, M. A. S. (2006). A Simple Protocol for the Routine Calibration of PH Meters. *Rev. Ciênc. Farm. Básica E Apl.*, *27* (1).
24. A Guide To Ph Measurement (2009). The theory and practice of laboratory pH applications.pp52.
25. A. L.Vogel, (1975). A Text Book of Quantitative Inorganic Analysis', Pergamon Green and Co. Ltd. London, 539.
26. G.Schwarzenbach, (1957). Complexometric Titration, Mentthuen and Co. Ltd.London,69,79,82.
27. Irving, H. M.; Rossotti, H. S. (1954). The Calculation of Formation Curves of Metal Complexes from PH Titration Curves in Mixed Solvents. *J. Chem. Soc. Resumed*, 2904–2910.

28. Kurzak, B.; Kroczewska, D.; Jezierska, J.; Huza-Koralewicz, M. (1988). Stability and Structure of Copper (II)-L-Histidinehydroxamic Acid Complexes. *Transit. Met. Chem.*, *13* (4), 297–302.
29. May, P. M.; Murray, K.; Williams, D. R. (1988). The Use of Glass Electrodes for the Determination of Formation Constants—III Optimization of Titration Data: The Esta Library of Computer Programs. *Talanta*, *35* (11), 825–830.
30. Landner, L.; Reuther, R. (2004). Metals in Society and in the Environment: A Critical Review of Current Knowledge on Fluxes, Speciation, Bioavailability and Risk for Adverse Effects of Copper, Chromium, Nickel and Zinc. DOI:10.1007/1-4020-2742-7. ISBN: 978-1-4020-2740-6
31. Bal, W.; Jeżowska-Bojczuk, M.; Kasprzak, K. S. (1997). Binding of Nickel (II) and Copper (II) to the N-Terminal Sequence of Human Protamine HP2. *Chem. Res. Toxicol. 10* (8), 906–914.
32. V. M. Rao, M.P.Latha, T. S. Rao, G.N. Rao, J.(2006). Indian Chem. Soc., 83, 925-927.
33. Ubale, M. Mixed Ligand Stability Constants of Co (II), Ni (II), Cu (II) and Zn (II) Transition Metal Complexes with Chloropheneriamine Maleate Drug and Amino Acids. *Pharma Chem.***2011**, *3*, 323–329.
34. Sakurai, T.; Yamauchi, O.; Nakahara, A. (1977). Stereoselectivity in Mixed Ligand Copper (II) Complexes with Electrostatic Ligand-Ligand Interactions. Applications to Optical Resolution of a-Amino Acids with a Charged Side Chain. *Bull Chem Soc Jpn. 50*, 1776–1779.
35. Yamauchi, O.; Sakurai, T.; Nakahara, A. (1977). Stereoselectivity in Mixed Ligand Copper (II) Complexes with Electrostatic Ligand-Ligand Interactions. Application to Optical Resolution of α-Amino Acids with a Charged Side Chain. *Bull. Chem. Soc. Jpn. 50* (7), 1776–1779.

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