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Synthesis and Characterization of Tripositive Metal Ions Catechol Siderophore Complexes

M. IBRAHIM[1], T. FAROOQ[1], M. IMRAN[2], F.S. REHMANI[2,*], T. GULZAR[1], A.A. SHAFIQUE[3], A. SHAFIQUE[3] and M. ASLAM[2]

[1]Department of Applied Chemistry, Government College University Faisalabad, Faisalabad, Pakistan
[2]Department of Chemistry, University of Karachi, Karachi, Pakistan
[3]Liaquat College of Medicine and Dentistry and Dar-ul-Sehat Hospital, Karachi, Pakistan

*Corresponding author: E-mail: fsrehmani@uok.edu.pk

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Over the past few years, siderophore desferrioxamine mesylate has been used for the treatment of iron overload. It is a linear trihydroxamate, a natural siderophore produced by streptomyces and employed to remove the extra iron contents from human body. In deed, catechol is a simple model of catechol type siderophore. So, taking it as an advantage, catechol was used for complexation with tripositive metal ions like Al(III), Cr(III) and Fe(III) with emphasis on their availability in biological environments/systems. Further, these catechol complexes were studied by potentiometric titrations and thermodynamic stability and stability constants were calculated by using BEST® software. Moreover, competitive reactions were performed to evaluate the ability of tripositive metal ions to replace Fe(III) which is widely found in biological system.

Key Words: Siderophore, Catechol, Potentiometric titrations, Thalasemia.

INTRODUCTION

Patients of thalasemia and sickle cell anemia need repeated blood transfusions which cause an excessive accumulation of iron in the body. This condition is known as iron overload and commonly affects liver, heart and endocrine glands[1]. There are many natural mechanisms for iron removal, the micro organism utilizes a well define iron acquisition strategy[2,3] which includes the production of low molecular weight chelating agents called siderophores or microbial iron chelators to solubilize and transport ferric ions in aqueous medium. These siderophores have high affinity for Fe(III) and are better chelators for Fe(III) than Fe(II)[4,5]. Mainly, there are three tripositive ions such as Fe(III), Al(III) and Cr(III) which found in the biological system[6,7]. As their ionic radii are very close to each other so they are involved in competition reactions[8]. Consequently, the iron requirement of biological system may be influenced by the presence of Al(III)[6,9]. It binds more strongly to the iron binding sites in the vital systems. Metal ions play indispensable roles in cell growth, maintenance of normal metabolic functions at molecular level, as catalysts or co-factors in a range of highly specific associations. In such associations, metals bind potentially to the protein in a certain stoichiometry. In fact, Al(III) is not implicated in any known biological or metabolic function. Its accumulation in tissues impairs their functions. Further, its toxic effect has been rapidly identified by pathological symptoms mainly anemia, encephlopaty and renal failure[10].

Chromium(III) possesses very strong reducing power, so as a matter of fact, its compounds are unlikely to occur in biological systems. It is capable to fabricate very stable octahedral complexes with oxygen and nitrogen containing ligands. Biologically active, low molecular weight chromium binding protein was isolated from bovine colostrums. Chromium forms essential part of the glucose tolerance factor (GTF) which together with insulin is responsible for controlling the clearance of glucose from the blood stream. Cr(VI) compounds are hepatotoxic, neurotoxic, nephrotoxic, mutagenic and has carcinogenic effects[11]. When the concentration of metal ions increases toxicity results significant metal sequestration to occur, the affinity of the metal for the chelator must be greater than its affinity for endogenous ligands, the chelator must be exchanged faster than the rate of elimination of the chelator. If a chelator eliminates more rapidly than the dissociation of the metal endogenous ligand complex, it may not be present in sufficient concentration for effective competition with the metal endogenous binding sites[12].

In the present study, initially, we focused the synthesis of Al(III), Cr(III) and Fe(III) catechol complexes. Further, they were studied by potentiometric titrations and their thermodynamic stability and stability constants were calculated by using BEST® software. Moreover, competitive reactions were

conducted to assess the ability of tripositive metal ions to replace Fe(III) which is generally found in biological system.

EXPERIMENTAL

All reagents used were of AnalaR or equivalent grade and were used without further purification. Distilled water was re-distilled and subsequently passed through a column of cation exchanger (Amberlite resin IRA-401 from BDH chemicals) in order to make it free of cations. This doubly distilled and deionzed water was utilized to prepare solutions of reagents. The chlorides of almunium, chromium and iron of E. Merck® were selected. Further, metal salt solutions were standardized by standard method. The catechol of E.Merck® was used without any further purification. Sodium hydroxide salution was standardized by standard HCl solution. For pH measurments in potentiometric titrations (Orion pH meter model SA 720), a 0.05 M solution of potassium hydrogen pthalate of pH 4.01 at room temperature was used to calibrate the pH meter. The titrations were carried out in double wall glass cell, fitted with an air tight cork with three holes. One for nitrogen purge, other for base addition and third for the electrode to be dipped in the solution. The temperature of the cell with 75 mL capacity was kept constant throughout the experiment by thermostat. The solutions used for the titration were prepared in double deionized and decarbonized water. All the titrations were performed from 30 to 50 ºC with interval of 5 ºC. Further, 20 mL of 0.01 M of catechol were mixed with 20 mL of 0.01 mL of metal ions solution and were titrated with 0.1 M NaOH solution. The change in pH was noted with the small increment (0.05 mL) of base. For each experiment, equilibrium condition was determined by a constant meter reading with an interval of less than 0.002 pH unit variations before proceeding for the next step. Constantly, the solution was stirred. For each metal catechol solution, titrations were performed twice to minimize the probable errors[13].

Determination of competetion of metal ions with iron catechol complexes: For competition reaction study, two sets of experiments were performed selecting metals with stability constants close to iron siderophore complexes. Seven volumetric flasks of 10 mL were selected. These flasks were filled in the following manner.

	Iron catehol complex	Metal ions solution	Buffer pH 5
1	5 mL	X	5 mL
2	5 mL	1 mL	4 mL
3	5 mL	2 mL	3 mL
4	5 mL	3 mL	2 mL
5	5 mL	4 mL	1 mL
6	5 mL	5 mL	–
7	X	5 mL	5 mL

Second set was made as under,

	Metal catechol complex	Fe(III) solution	Buffer pH 5
1	5 mL	X	5 mL
2	5 mL	1 mL	4 mL
3	5 mL	2 mL	3 mL
4	5 mL	3 mL	2 mL
5	5 mL	4 mL	1 mL
6	5 mL	5 mL	–
7	X	5 mL	5 mL

The absorption of these solutions was recorded at room temperature after 0.5 h and 24 h.

RESULTS AND DISCUSSION

The potentiometric data at different tempratures for catechol siderophore and its tripositive metal ions complexes such as Al(III), Cr(III), Fe(III), was analyzed by BEST® computer software. Table-1 shows the stability constant values of these complexes at different temperatures. Further, these values were used to calculate the entropy and enthalpy values of these complexes[13]. It revealed that Fe(III) form most stable complexes with catechol type siderophore having one metal, one ligand and one proton which can be expressed as 110 at pH 3, with one metal two ligand no proton 210 at pH 7. Al(III) and Cr(III) also form two types of complexes 1:1 or 110 at pH 3 and 2:1 or 210 at pH 4. In fact, Al(III) has higher stability than Cr(III). The stability constant values depend upon charge to radius ratio, hard-soft character of metal ions and the ligand involved. The cation with high polarizing power would have high stability constant values for complex formation with ligands whose donor groups also have high polarizing power. Tripositive cations are classified as hard acids and form strong complexes with oxygen donor groups[14]. Table-2 shows the competition of Al(III) ions with iron catechol siderophore complexes while Table-3 shows absorbance of aluminium catechol siderophore in the presence of Fe(III) ions. However, the competition of Cr(III) ions with iron catechol siderophore complexes are shown in Table-4. Table-5 shows the absorbance of chromium catechol siderophore in the presence of Fe(III) ions. The results of Table-2 indicates the decrease in absorbance by increasing concentration of Fe(III) ions, which suggests that Fe(III) ions do not replace Al(III) ions from aluminum catechol complexes. Table-3 also justify the results framed in Table-2. According to Table-4, the concentration of Fe(III) catechol were kept constant while the concentration of Cr(III) ions were increased however the absorbance almost remained constant in each case. It was observed that Cr(III) ions were not replaceing Fe(III) ions. The result shown in Table-5 also justifies the results of Table-4.

TABLE-1
STABILITY CONSTANT (log β) VALUES OF TRIPOSITIVE METAL CATECHOL COMPLEXES AT DIFFERENT TEMPERATURES WERE CALCULATED BY BEST® SOFTWARE PROGRAM

Complex	30 ºC	35 ºC	40 ºC	45 ºC	50 ºC
			Al(III)		
log β 110	12.00	12.85	13.00	12.85	13.88
log β 210	22.00	23.53	22.89	23.50	23.90
log β 310	–	–	–	–	–
			Cr(III)		
log β 110	9.50	9.82	9.95	10.10	10.20
log β 210	18.50	18.72	18.95	19.29	19.00
log β 310	22.30	22.77	22.98	22.75	22.50
			Fe(III)		
log β 110	13.32	14.30	15.60	17.60	18.10
log β 210	20.20	21.10	23.30	24.00	24.50
log β 310	25.60	25.90	26.20	26.70	27.10

110 = ML, 210 = ML_2, 310 = ML_3

TABLE-2
ABSORBANCE OF IRON CATECHOL SIDEROPHORE COMPLEX (5×10^{-4} M) IN THE PRESENCE OF Al(III) IONS

Fe catechol complex solution	Al(III) ion solution	Buffer pH 5	$A\lambda_{500}$
5 mL	–	5 mL	0.51
5 mL	1 mL	4 mL	0.50
5 mL	2 mL	3 mL	0.48
5 mL	3 mL	2 mL	0.49
5 mL	4 mL	1 mL	0.48
–	5 mL	5 mL	–

TABLE-3
ABSORBANCE OF Al(III) CATECHOL SIDEROPHORE COMPLEX (5×10^{-4} M) IN THE PRESENCE OF Fe(III) IONS

Al catechol complex solution	Fe(III) ion solution	Buffer pH 5	$A\lambda_{500}$
5 mL	–	5 mL	–
5 mL	1 mL	4 mL	0.40
5 mL	2 mL	3 mL	0.45
5 mL	3 mL	2 mL	0.47
5 mL	4 mL	1 mL	0.52
X	5 mL	5 mL	–

TABLE-4
ABSORBANCE OF IRON CATECHOL SIDEROPHORE COMPLEX (5×10^{-4} M) IN THE PRESENCE OF Cr(III) IONS

Fe catechol complex solution	Cr(III) ion solution	Buffer pH 5	$A\lambda_{500}$
5 mL	–	5 mL	0.40
5 mL	1 mL	4 mL	0.42
5 mL	2 mL	3 mL	0.43
5 mL	3 mL	2 mL	0.45
5 mL	4 mL	1 mL	0.48
–	5 mL	5 mL	–

TABLE-5
ABSORBANCE OF Cr(III) CATECHOL COMPLEX (5×10^{-4} M) IN THE PRESENCE OF Fe(III) IONS

Cr catechol complex solution	Fe(III) ion solution	Buffer pH 5	$A\lambda_{500}$
5 mL	–	5 mL	–
5 mL	1 mL	4 mL	0.20
5 mL	2 mL	3 mL	0.25
5 mL	3 mL	2 mL	0.30
5 mL	4 mL	1 mL	0.42
–	5 mL	5 mL	–

In living systems, metal ions toxicity can be cured by using chelating drug. Chelating drug may be effective in removing toxic metals from the body, it must satisfy the second law of thermodynamics, the free energy change for the transfer of the metal ions from the binding sites to the chelating drug must be negative, to achieve this requirement, stability constant between the toxic metal and the chelating drug must be greater than that of the competing ligands with the metal concerned. From the comparison of thermodynamic values of tripositive ions, it was observed that catechol siderophore complexes do show the significant enhancement in values over those for the typical aminocarboxylate ligand. The above performed experiments suggested that catechol complexes are responsible to chelate out the excess amount of iron from iron overloaded patients which otherwise increase the risk of cancer by increasing the production of free oxygen radical[15]. This drug may also be useful in treatment of aluminum toxicity and Wilson's disease in which copper is accumulated in tissues leading to the disorder of liver and central nervous system. In the treatment of iron overload, the catechol type siderophore appears to be more selective as its stability constant and thermodynamic values for Fe(III) complex is greater in several order of magnitude than those for other useful metal ions complexes. Its calculated dose chelate out the excess burden of ferric ions without depleting other essential metal ions of living system.

The results of competition reactions of metal ions are based upon the stability constants and thermodynamic stability of metal ions. These reactions are of major nutritional and toxicological importance. Similarities in these values are believed to underlie many of similar biological reactions like competition for binding sites on metallo enzyme, transport of storage proteins[16]. Our results showed, among tripositive ions Al(III) has high stability constant and thermodynamic stability values therefore it preferred to occupy binding sites of the ligands used in the present study. However, the other cations will only be able to win the competition if the concentration of Al(III) is reduced and Fe(III) will be the second in the competition.

Conclusion

The present study clearly indicate that for the treatment of iron overload, the catechol siderophore appears to be more selective as its stability constant for Fe(III) complex is greater in several orders of magnitude than those for other useful metal ion complexes. The success of this drug probably lies in the selectivity of catechol siderophore for Fe(III). A careful administration chelates out the excess burden of ferric ions without depleting the body of other essential metal ions. While the metal ions other than Fe(III) whose stability constants although smaller than Fe(III) will be still in excess. Thus if a larger excess of a catechol siderophore based drug is administered, there may be depletion of other essential nutrients occur. Another complication might arise with respect to Al(III), which also forms rather strong 1:3 complex at neutral pH and the charge of such a complex is expected to be zero. The electroneutrality of the complex may enable Al(III) to cross the blood-brain barrier and thus a trishydroxamate based drug might be good for Fe(III) detoxification but might confer neurotoxicity upon Al^{3+} as a result of formation of the neutral complex.

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