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Thermodynamic Study of Trace Metal Complexes with Hydroxamate Drug of Iron overload.

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bstract.

e potentiometer data at different tempratures for hydroxamate drug and its trace metal complexes such as Al(III), Cr(III), (III), Mn (II), Ca(II), Zn(II), Cd(II), Cu(II), Mg(II), Ni(II) and Co(II) were analysed by computer program "BEST". The β values these complexes at different tempratures were used to calculate the entropy and enthalpy values of complexes. The lues of result showed that tripositive ions such as Fe(III), Al(III) and Cr(III) have high thermodynamic stability. Among positive ions Cu(II), have high values which are close to Fe(III), hence this drug has potential to disturb the equilibrium of (II) as well.

troduction

alassaemia is the condition appear commonly in people om countries in a broad tropical belt extending from editerranean basin through the middle east and for east. alaseamia is not a single disease entity but a group of sorder resulting from an inherited defective rate of oduction of one of the types of polypeptide chain volved in hemoglobin structure. The B chain of normal emoglobin has glutamic acid at 6th amino acid sequence, sickle cell anemia this glutamic acid is replaced by line amino acid. It has hydrophobic character instead of rmal hydrophilic group of glutamic acid. So the molecule ssesses reduced solubility and high concentration of the emoglobin induce aggregation. As a result of termoleculer interactions double-stranded polymer is rmed. Its further aggregation occurs in form of sickle haped RBCs. Severe anemia occurs. These RBCs have horter life span than normal cells and are more easily sed. In the alpha thalassaemia, the alpha type chains are nder produced. Each of these main type of thalasseamia onsists of several genetically distinct disorders which can e distingvished by the electrophoretic pattern of the emoglobin and by the associated haematological findings. alasseamia major is the severest form. It usually seen in ildren when both of the parent are suffering from minor rm of this disease (Lehninger, 1975). The patients who e suffering from theses diseases need blood transfusion ver a long period of time, results an excess amount of on is deposited in the organ of body which damages the ssues. This condition is known as iron overload Britenham, 1991; Katzung, 1995). There are many natural echanism for solubilization or removal of iron, for xample, the micro-organism utilize a well define iron cquisition strategy which includes the production of low olecular weight chelating agents called siderophores or icrobial iron chelators to solubilize and transport ferric ions aqueous medium. These siderophores have high affinity or Fe(III) and they are better chelators for Fe(III) than Fe(II) Raymond 1987). Desferrioxamine mesylate a linear trihydroxamic acid natural siderophore produced by streptomyces have been used for the treatment of iron over load. It chelate out the excess burden of iron. The efficiency of the chelator is partly determined by the number of ligands available for metal binding. The greater the number of these ligands, the more stable the metal chelator complex. The relative efficacy of various chelators in facilitating excretion of metal from the body is also determined in part by the pharmacokinetics of the chelator. For any significant metal sequestration to occur, the affinity of the metal for the chelator must be greater than its affinity for endogenous ligands, and the relative rate of exchange of the metal between the endogenous ligands and the chelator must be faster than the rate of elimination of the chelator. If a chelator is eliminated more rapidly than the dissociation of the metal endogenous ligand complex, it may not be present in sufficient concentrations for effective competition with the metal-endogenous binding sites (Katzung 1995).

Materials and Methods

All reagents used were of AR 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 deionized water was used in preparation of all solutions of reagents. The salts of metals (E. Merck) taken were aluminium chloride, cadmium chloride, calcium chloride, cobalt chloride, copper chloride chromium chloride, magnesium chloride, manganese chloride, nickle chloride and zinc chloride. All these metal solutions were standardized by standard method. The hydroxamate was obtained from E.Merck and was used with any further purification. NaOH solution was standardized by standard HCl solution. For all pH measurements in potentiometric titrations,Orion pH meter model SA 720, was used. A 0.05M solution of potassium hydrogen pthalate, which has

Table 1: Enthapy and Entropy values of metal salicylhydroxamic acid complexes.

Metal	ΔH kJ mole^{-1}	ΔS JK^{-1} mole^{-1}	ΔH_2 kJ mole^{-1}	ΔS_2 JK^{-1}mole^{-1}	ΔH_3 kJ mole	ΔS_3 JK^{-1}mole^{-1}
Al(III)	12.5	459	8.25	310	-	-
Mg(II)	8.40	290	5.00	200	-	-
Ca(II)	7.45	250	4.20	180	-	-
Cr(III)	11.35	410	8.50	300	5.10	100
Mn(II)	8.35	325	5.20	225	3.00	80
Fe(III)	11.75	480	8.45	325	5.5	115
Co(II)	9.00	335	7.13	255	4.5	95
Ni(II)	9.50	360	7.9	265	-	-
Cu(II)	10.35	395	8.90	280	-	-
Zn(II)	9.35	345	7.4	203	-	-
Cd(II)	8.50	270	5.5	190	-	-

Table 2: Ionic Radii of dipositive and tripositive metal Ions in pM

Metal	Ionic	Metal Radii	Ionic	Metal Radii	Ionic Radii
Mn(II)	58	Mg(II)	72	Al (III)	53
Co(II)	54.5	Ca(II)	100	Cr (III)	61
Ni(II)	56	Zn(II)	74	Fe (III)	55
Cu(II)	54	Cd(II)	95		

pH value 4.01 at room temperature, 25°C was used to calibrate the pH meter. The titration were carried out in double walled glass cell, fitted with an air tight cork, having three holes. One for the nitrogen purging other for base added and third one for the electrode to be dipped in the solution. The temperature of the cell was kept constant through out the experiment by thermostat. The capacity of the cell was about 75 ml. The solution used for the titration were prepared in double deionized and decarbonized water, pH was measured with a combination glass electrode 0.001 pH unit. All the titrations were performed at 30, 35, 40, 45, and 50 °C, 20ml of 0.01 M of hydroxamate 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. Equilibrium conditions, determined by a constant meter reading falling with an interval of less than 0.002 pH unit was obtained for each experimental point before proceeding with the next step. The solution was stirrered with magnetic stirrer constantly. For each metal hydroxamate solution these titrations were performed twice to minimize the probable errors (Bessette, 1979).

Determination of Log B Values and Thermodynamic Values Through Pot Entiometric Method by Computerprogram Best: The data obtained from pH titrations were utilized for the calculations of log β values. For this purpose computer program BEST was used. Data files FOR004.DAT was prepared for each titration. Calculated β values was refined several times, till the sigmafit values reduced upto 0.04. The date file of this program was required the following informations:-

1. Total volume of the solution.
2. Molarity of the base used for pH titration.
3. Change in pH after each step.
4. No of millimole of metal ions present in the solution
5. No. of millimole of ligand present in the solution.

The whole calculations in this program were based upon th expected β values for each species present in the solutio by refining these values to get sigmafit values, th goodness of sigmafit was reflected on accuracy of values. The K values of the complexes at differen temperature was used to calculate the thermodynamic values of complexes.

$$G = -Rt \text{ in } \beta$$

$$\Delta G = H - T\ \Delta S$$

$$\text{In } B = H/T + \Delta S/R$$

A plot in β vs 1/T, slope = $-\Delta H/R$, intercept = $\Delta S/R$ [Martell *et.al* 1988].

Results and Discussion.

The potentiometric data at different tempratures hydroxamate drug and its trace matel complexes such Al(III), Cr(III), Fe(III), Mn(II), Ca(II), Zn(II), Cd(II), Cu(Mg(II),Ni(II) and Co(II) were analyzed by computer progra "BEST". The β values of these complexes at differe temperatures were used to calculate the entropy a enthalpy values of complexes (Martell, *et.al.*, 1988). wh are shown in Table 1. From this table conclude that positive ions have high thermodynamic stability as compa to di-positive ions. Both ΔH and ΔS are effected by io radii and follow the Irrving William order of stability (Irvi *et al.*, 1953). The effect of ionic radii on transition met ion are greater than in non-transition metals ions. Among positive ions Cu(II) has the highest values which is nea close to Fe(III). This expected because both have ne same ionic radii (Greenwood *et al.*, 1984) (Table Interestingly, biochemistry of Fe(III) is very much similar that of Cu(II), both having involved in biological oxidat reduction (Huges *et.al.*, 1989). As the Table 1 shows enthalpy and entropy values of Mg(II) and Ca(II) comparable with Zn(II) and Cd(II). These are relatively lo than transition metal ions because they have larger i

Table 3: Enthapy and Entropy values of different metal ions.

Metal	Ligand	ΔH kJ mole^{-1}	ΔS JK^{-1} mole^{-1}	ΔH_2 kJ mole^{-1}	ΔS_2 JK^{-1}mole^{-1}
Mn^{2+}	Malonic acid	57.27	114.64	-	-
Zn^{2+}	""	12.55	112.96	-	-
Co^{2+}	Succinic acid	13.50	87.86	-	-
Cu^{2+}	""	18.8	125.93	-	-
Mn^{2+}	""	12.55	85.77	-	-
Ni^{2+}	""	10.46	79.50	-	-
Zn^{2+}	""	18.50	108.78	-	-
Co^{2+}	Thiocarbazide				
	1,1 diacetic acid	10.70	138.00	-	-
Mn^{2+}	""	30.12	138.00	-	-
Zn^{2+}	""	13.20	184.80	-	-
Be^{2+}	Salicylic acid	5.02	25.10	-	-
Cu^{2+}	""	18.50	108.78	-	-
Ca^{2+}	""	57.27	37.65	-	-
Co^{2+}	Thiosalicylic acid	30.54	217.56	20.92	167.36
Fe^{2+}	""	21.33	175.73	13.20	129.70
Mn^{2+}	""	17.15	158.99	23.84	184.80
Ni^{2+}	""	48.11	293	33.47	196.64
Zn^{2+}	""	27.19	251	38.07	242.67
Co^{2+}	Pthalic acid	7.60	80.33	-	-
Mn^{2+}	""	8.95	83.26	-	-
Ni^{2+}	""	7.40	81.16	-	-
Zn^{2+}	""	13.50	99.57	-	-
Al^{3+}	CDTA	45.00	510.44	-	-
Mg^{2+}	""	7.12	217.56	-	-
Al^{3+}	DTPA	33.44	262.80	-	-
Mg^{2+}	""	37.00	259.40	-	-

radii (Table 2). The stability of tripositive ions and some dipositive ions of hydroxamte complexes are largely determined by large +ve entropy change (Table 1). This can be explained by assuming that the hydration sphere of a metal is largely lost on combination with ligand molecules. It is this loss of hydration, or increased random motion of water molecules, which is the main factor in the entropy changes (Ganther 1975). A chelating drug may be effective in removing toxic metal from the body, it must satisfy the second law of therdynamics i.e. the free energy change for the transfer of the metal ions from the binding sites in vivo to the chelating drug must be negative. To achieve this requirement, conditional stability constant between the toxic metal and the chelating drug must be greater than that of the competing ligands with the metal concerned (Rehmani *et.al.*, 1997). When we compare these thermodynamic values of trace metal ions with other ligands as shown in table 3, it was observed that hydroxamate complexes do show the significant enhancement in values over those for the typical aminocarboxylate ligand. From the above performed experiment it can be suggested that hydroxamate drugs are responsable to chelate out the excess amount of iron from iron overload patients. It may also be useful in treatment of aluminum toxicity and wilsons disease in which copper is accumulated in tissues which leads to disorder of liver and central nervous system (Rehmani 1998). For the treatment of iron overload the hydroxamate appears to be more selective as its stability constant and thermodynamic values for Fe(III) complex is several order of magnitude greater than those for other useful metal ions complexes. Its calculated dose chelate out the excess burden of ferric ions without depleting the other essential metal ions of living system. If larger excess of a hydroxamate based drug is administered, it might form a neutral Al(III) complex at physiological pH. The electroneutrality of this complex may enable to cross blood brain barrier and thus causes neurotoxicity. When a host is challenged by iron chelator either as a drug for iron overload or as a result of microbial invasion, balance of metal other than iron may be disturbed. Although microbial iron chelators are highly specific for Fe(III) with a very high degree of stability constants values as compared to dipositive ions persent, they can also form complexes with other trace metals such as Al(III), Cr(III) and Cu(II). Hence this lingand has the potential for disturbing the equilibrium of other metal ions in the living system.

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