Determination and Comparison of Stability Constant, Enthalpy and Entropy of Formation of Iron(III) Complexes of Gallic Acid and Methyl Ester of Gallic Acid

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Summary: Stability constant of Iron(III) gallic acid complexes had been measured potentiometrically. The experimental results of these potentiometric titrations were treated by well known computer program "Best". The values were further refined till least sigma fit i.e. 0.02. For thermodynamic study the change in log beta values at different temperatures were also examined and entropy and enthalpy of these reactions were determined. Iron(III) complexes of gallic acid methyl ester were prepared in the same way, and the above results were compared with this new complex. The role of carboxylate group on the complex were noted. The β values of these two complexes were then compared with other iron complexes and their biological importance were also discussed.

Introduction

Iron is an essential trace element for all living organisms. It is involved in a number of biological functions, such as transport and storage of oxygen (hemoglobin and myoglobin), electron transfer (cytodchromes and iron sulphur proteins) and a number of oxidase and peroxidase etc. [1].

Iron also becomes toxic when in excess. The toxicity is because of the tendency of this metal to separate in tissues as insoluble hydroxide and phosphate at physiological and higher pH unless bound to iron transfer protein or to iron storage proteins [2].

The iron input (20-25 mg/day) exceeds the capacity of transferrin and ferritin, resulting in separation of insoluble iron in critical tissues, e.g. the heart, liver, pancreas. In principle, this ultimately fatal condition can be treated by administration of an iron chelating agent which would promote remobilization and excretion of the deposited iron [3].

The basic requirement of an iron chelating agent is a high and selective affinity to bind iron avidly under phyhsiological conditions. The tripositive ferric ion is a hard acid and consequently in bound most strongly by hard bases. The most effective of these are oxyanions, such as hydroxide, phenoxide, carboxylate, hydroxamate and phosphonate [4].

The affinity of a ligand for iron(III) may be defined quantitatively in term of the thermodynamic constants of the equilibria involved between the aquo metal ion and ligand L: In some cases H^+ competes for L with the metal [5].

A simple interaction between metal and ligand can be shown by the following equations [6].

$$M + L \overset{K1}{\rightleftharpoons} ML$$

$$ML + L \overset{K2}{\rightleftharpoons} ML_2$$

$$ML_2 + L \overset{K3}{\rightleftharpoons} ML_3$$

$$ML_{n-1} + L \overset{Kn}{\rightleftharpoons} ML_n$$

and

$$H_nL \rightleftharpoons H_{n-1}L + H^+$$

$$H_{n-1}L \rightleftharpoons H_{n-2}L + H^+$$

or

$$HL \rightleftharpoons L + H^+$$

$K = [M]\,[L]^n = K1.K2...Kn$

and $\beta 1 = K1$ $\beta 2 = K1.K2$ $\beta 3 = K1.K2.K3$ and $\beta n = Kf$

Computer program "BEST" is also utilized for potentiometric calculation. The variable measured is $-\log[H^+]$, it is therefore considered logical to carry out the calculations with an algorithm which calculates p[H] directly and minimizes the sum of the weighted squares of $-\log[H^+]$ residuals.

The basic algorithm in BEST can be stated in term of the following equation

$$T_i = \sum_{k=1}^{j=i} e_{ij}\beta_j \pi^i [C_k]^{e_{ij}}$$

which is the statement of the mass balance of the i-th component in term of the j-th species summed over all species present. Each species concentration consists of a product of the over all stability constant and individual component concentration $[C_k]$ raised to the power of the stoichiometric coefficient e_{ij}.

If an ML system is considered consisting of three component L^{4-}, M^{2+} and H^+. The possible species are L^{4-}, HL^{3-}, H_2L^{2-}, H_3L^-, H_4L, ML^{2-}, MHL, H^+ and OH^-

There would be three mass constraints in terms of total ligand, total metal ion and total initial hydrogen concentration: T_L. T_M, T_H, respectively.

$$T_L = [L^{4-}]+[HL^{3-}]+[H_2L^{2-}]+[H_3L^-]+[H_4L]+[ML^{2-}]+[MHL^-]$$

$$T_M = [M^{2+}] + [ML^{2-}] + [MHL^-]$$

$$T_H = [HL^{3-}]+2[H_2L^{2-}]+3[H_3L^-]+4[H_4L]+[MHL^-]+[H^+]+[OH^-]+[BASE]$$

T_H respresents the amount of H initially present and [base]that which has been removed by the added titrant. The internal computer representation is set up in terms of β'-s, and the concentrations of the inidividual species, an expressed by

$$T_M = [M^{2+}] + \beta_{ML}[M^{2+}][L^{4-}] + \beta_{MHL}[M^{2+}][H^+][L^{4-}]$$

$$T_L = [L^{4-}] + \beta_{HL}[H^+][L^{4-}] + \beta_{H2L}[H^+]^2[L^{4-}] + \beta_{H3L}[H^+]^3[L^{4-}] + \beta_{H4L}[H^+]^4[L^{4-}] + \beta_{ML}[M^{2+}][L^{4-}] + \beta_{MHL}[M^{2+}][H^+][L^{4-}]$$

$$T_H = \beta_{HL}[H^+][L^{4-}] + 2\beta_{H2L}[H^+]^2[L^{4-}] + 3\beta_{H3L}[H^+]^3[L^{4-}] + 4\beta_{H4L}[H^+]^4[L^{-4}] + \beta_{MHL}[M^{2+}][H^+][L^{4-}] + [H^+] - \beta_{OH}[H^+]^{-1}$$

This set of simultaneous equations is solved for each component $[C_k]$. In any calculation based on p[H] profile, there will be some know, previously calculated, β values as well as the unknown values to be determined. Thus the use of the algorithm for computing equilibrium constants in "BEST" involves the following sequence:

1. Start with a set of known and estimated over all stability constants and compute [H] at all equilibrium points.

2. Compute the weighted sum of the squares of the deviations in p[H] as in

$$U = w(p[H]obs - p[H]calcd)^2$$

where w = 2, as weighted factor which serve to lesson the influence of the less accurate p[H] profile on the calculation.

3. Adjust the unknown stability constants and repeat the calculation until no further minimization of U is obtained.

The standard deviation in p[H] unit is obtained by the use of equation [9].

$$fit = (U/N)^{1/2} \text{ where } N = w$$

The data file for this program requires the knowledge about

i) total volume of the solution
ii) molarity of the base used for pH titration
iii) change in pH after each step
iv) number of millimoles of metal ions present in the solution
v) number of millimoles of ligand present in the solution

Finally the expected β values for each species present in the solution are given. The program calculates the fit and auto refines it, till the minimum fit value is obtained. The corresponding β values at minimum fit is noted. The goodness of fit reflects on the accuracy of K values [10,11].

Results and Discussion

A number of titrations at different temperature, between gallic acid complex and NaOH and similarly iron gallic acid ester complex with NaOH. An input data file "FOR004. DAT" was written for each titration with approximate log beta values of different species. Sigma fit was calculated. After refining and minimizing sigma fit values up to

Table-1Logß values calculated by "best" at different temperature iron gallic acid complex

Complex	25°	30 C°	32°C	35°C	40°C	45°C	50°C
Logß 10-1	-12.83	-12.95	-13.04	-13.13	-13.25	-13.44	-13.62
Logß 101	11.392	11.145	11.045	10.913	10.760	10.676	10.550
Logß 102	19.81	19.670	19.570	19.472	19.100	19.100	19.02
Logß 103	24.26	24.090	24.033	23.927	23.870	23.700	23.480
Logß 01-1	-3.05	-2.983	-2.950	-2.920	-2.873	-2.800	-2.780
Logß 111	------	17.600	18,600	18.92	20.650	22.640	23.060
Logß 110	------	13.320	13.800	14.30	15.600	17.630	18.100
logß 22-2	------	10.380	10.540	10.77	11.500	11.672	11.600
Logß 210	------	20.200	20.700	21.10	23.300	24.000	24.55
Logß 310	------	25.600	25.800	25.90	26.200	26.700	27.10
Iron gallic acid merthyl ester							
Logß 110	------	12.400	--------	12.99	13.900	14.600	16.980
Logß 210	------	24.100	--------	25.70	26.600	28.040	30.433
Logß 310	------	34.030	--------	35.05	36.500	37.540	39.900

0.02396 the log beta values obtained were as follows:

Fe(HGA)(H) = 17.6 for Fe(HGA) = 13.32 for Fe(HGA)2 = 20.2 and for Fe(HGA)3 = 25.6 at 30°C.

Species distribution for different pH determined from this program for iron-gallic acid complex at 30°C (Fig. 1). Log beta values were calculated at different temperatures (Table 1) and used to calculate entropy and enthalpy values (Table 2. Fig. 2.3).

Table-2 Enthalpy and entropy values for iron gallic acid and iron gallic acid methyl ester complex

	Iron gallic acid complex		iron gallic methyl ester	
	$\Delta H_{Kcal.}$ $K^{-1}M^{-1}$	$\Delta S_{cal.}$ $K^{-1}M^{-1}$	ΔH_{Kcal} $K^{-1}M^{-1}$	$\Delta S_{cal.}$ $K^{-1}M^{-1}$
ß111	2.4	142	----	-----
ß110	2.9	150	3.3	160
ß210	1.8	122	2.1	132
ß310	0.5	81	1.4	111

Stability constant K1, K2, and K3 of gallic acid showed a distinct change e.g. K1/K2 = 10^6 and K2/K3 = 10^4. In case of complex with methyl ester of gallic acid these values are not distinctly different from each other e.g. K1 = 10^{12}, K2 = $10^{11.5}$ and K3 = 10^{10}. When these values were compared with literature values (Table 3) [13], it was found that ligand having three negative charges

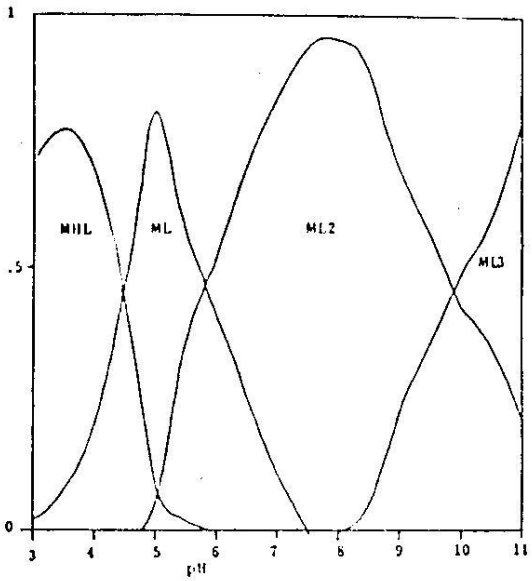

Fig. 1: Species distribution at different pH by computer program BEST.

$[L]^{3-}$, like meconic acid or 4-nitroso-5,6-dihydroxy benzene-1,3-disulphonic acid are comparable to gallic acid [13], while ligands having two negative charges $[L]^{2-}$, such as salicylic acid and tropolon 5 sulphonic acid, resemble gallic acid methyl ester. Tropolon ought to be a most promising class of compounds for study. The pKa of the pseudo-phenolic group is about 7 and consequently, there is virtually no proton interference, greater negative charge on ligand shows competition between metal and ligand.

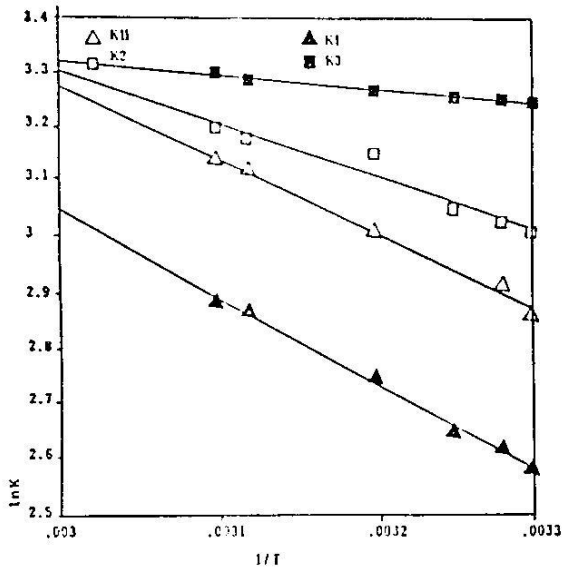

Fig. 2: Graph for the heat energies of iron gallic acid.

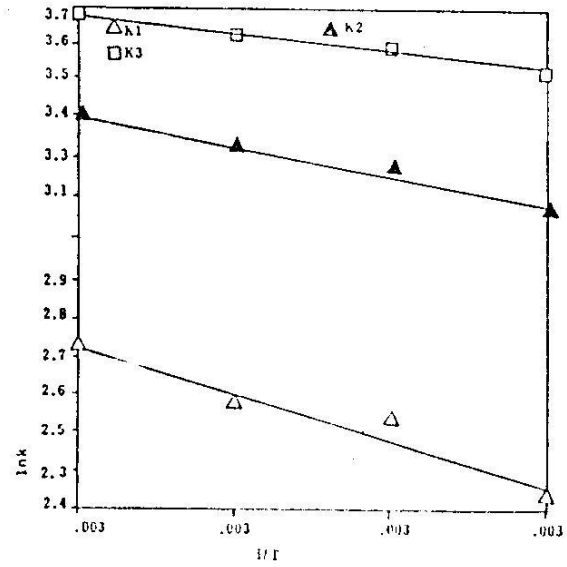

Fig. 3: Graph for the heat energies of iron gallic acid methyl ester.

The entropy and enthalpy values of Fe(III) complex with methyl ester of gallic acid is compared with the Fe(III) gallic acid complex and observed that there is not much difference between the enthalpy and entropy values of both the complexes. It is found that both show very large entropy values. When these values were compared with

Table-3: Stability constants of different iron chelators

LIGAND	Logß1	Logß2	Logß3
Salicylic Acid	16.355	27.450	36.560
ß Reorcylic Acid	15.055	---------	---------
5 Bromo Salicylic Acid	16.762----	----	
5 Chloro Salicylic Acid	16.842----------		
Dipicoloric Acid	----	16.740	-----
3-Nitro Salicylic Acid	14.193	-----	-----
5-Nitro Salicylic Acid	14.339	---	------
Aminopyridin 2,6 Dicarboxylic Acid	13.150	22.890	----
Tropolon 5 Sulphonic Acid	8.700	16.133	23.720
5 Sulpho Salicylic Acid	2.540	----	----
Benzohydroximic Acid	12.180	----	----
Salicylic Aldoxim	3.890	-----	----
Amino Topolon	12.580	---	----
ß Resorcylamide	3.580	-----	-----
Meconic Acid	15.00	25.300	30.900
4-Nitroso 5,6 Dihydroxy Benzene 1,3 Disulphonic Acid	16.42	29.050	35.540

other complexes from literature (Table 4,5), following points are noteworthy.

i) monodentate ligands do not show any drastic entropy change with trivalent metals as compared to divalent metals e.g. isobutyric acid.

ii) polydentate ligands show very high entropy values with tripositive metals as compared to dipositive metals e.g. CDTA and DTFA resembling gallic acid and methyl ester of gallic acid. (Table 4.5) [13].

iii) non transition metals show low entropy values with chelating agents as compared to transition metals.

Experimental

All reagents used were of AR equivalent grade. Distilled water was redistilled and subsequently passed through a column of cation exchanger (Amberlite resin IRA-401 from BDH chemicals).

For pH titration CO_2 free water was required which was prepared by boiling redistilled and deionized water for 10 minutes and then cooling it in an air tight flask. For all pH measurement Orion Research analog pH-meter, model 301, was used. For more accurate potentiometric titrations. Orion pH-meter, model SA 720, was used. A 0.05M solution of potassium hydrogen pthalate, which has pH

Table-4: Enthalpy and entropy values of different metal complexes

Metal	Ligand	Δ_{H1} Kcal.M^{-1}	Δ_{S1} cal.M^{-1}	Δ_{H2} Kcal.m^{-1}	Δ_{S2} cal.m^{-1}
Mn^{2+}	malonoc acid	3.7+ .1	27.4	-----	------
Zn^{2+}	"	3.0+ .1	27.4	-----	-----
Co^{2+}	succinic acid	3.2+ .2	21	----	-----
Cu^{2+}	"	4.5+ .07	30.1	-------	-------
Mn^{2+}	"	3.0+.2	220.5	----	----
Ni^{2+}	"	2.5 +.1	26.0	----	-----
Zn^{2+}	"	4.4 +.1	26.0	-----	---
Co^{2+}	thiocarbaside 1,1 diacetic acid	2.6	33.0	---	----
Mn^{2+}	"	7.2	33.0	---	----
Zn^{2+}	"	3.1	37.0	---	--
Be^{2+}	salicyclic	1.2	6.00	----	----
Cu^{2+}	"	4.4	26.0	----	-----
Ca^{2+}	"	3.7	9.00	-----	----
Co^{2+}	thiosalicylic acid	7.3	52.0	5.00	40.0
Fe^{2+}	"	5.1	42.0	3.10	31.0
Mn^{2+}	"	4.1	38.0	5.70	37.0
Ni^{2+}	"	11.5	70.0	8.00	47.0
Zn^{2+}	"	6.50	60.0	9.10	58.0
Co^{2+}	pthalic acid	1.87	19.2	---	---
Mn^{2+}	"	2.20	19.9	---	---
Ni^{2+}	"	1.77	19.4	---	---
Zn^{2+}	"	3.20	23.0	----	----
Al^{3+}	CDTA	11.0	122	---	---
Mg^{2+}	"	1.60	52	---	-----
Al^{3+}	DTPA	8.00	113	---	----
Mg^{2+}	"	3.00	52.4	----	----

Table 5:Enthalpy and entropy values of iso-butyric acid with diff. matals

Metals	Δ_{H1} Kcal.M^{-1}	Δ_{S1} cal.M^{-1}	Δ_{H2} Kcal.M^{-1}	Δ_{S2} cal.M^{-1}
Ce^{3+}	3.33	18.6	2.6	13.6
Dy^{3+}	5.00	25.0	3.4	16.6
Er^{3+}	5.50	25.8	3.4	16.6
Eu^{3+}	2.90	18.8	1.9	12.2
Gd^{3+}	3.45	20.1	1.7	11.7
Ho^{3+}	5.30	25.3	2.6	14.1
La^{3+}	3.47	18.8	2.5	12.5
Lu^{3+}	5.40	25.5	3.7	17.4
Nd^{3+}	2.84	18.3	2.4	13.3
Pr^{3+}	3.04	18.4	2.5	13.5
Sm^{3+}	2.66	18.1	2.1	12.7
Tb^{3+}	4.40	22.6	1.5	11.3
Tm^{3+}	5.40	25.5	4.1	18.6
Y^{3+}	5.40	25.5	3.2	16.0
Yb^{3+}	5.40	25.4	4.0	18.1

value 4.010 at room temperature (25°C) was used to calibrate the pH meter along with buffer tablet solution (BDH Chemicals) [12].

Experimental procedure for potentiometric titrations

The titration was carried out in a double walled glass cell. The temperature was controlled by circulating thermostated water through the jacket. The solution was completely sealed from the atmosphere.

(a) pH titration of iron gallic acid complex

50 ml of deionized and CO_2 free water was taken in the above mentioned cell 0.200 m moles of gallic acid and 0.0500 m moles of ferric nitrate water dissolved in this water. Purified nitrogen gas was purged through the solution for half an hour. The temperature was controlled at 30°C by means by circulating water from the water bath. The solution was stirred on a magnetic stirrer (IKAMAG R.C.T.).

1M sodium hydroxide solution was prepared and standardized by 1M standards HCl solution. To the gently stirred acid solution of the ligand prepared as described above, standard base was added in sufficiently small increments (.05 ml) to provide 50 or more experimental points for each run. Equilibrium conditions, determined by a constant meter reading failing within an interval of less than ±0.002 pH unit was obtained for each experimental point before proceeding with the next step.

For most system protonation and deprotonation of ligand and complexation is rapid and complete in the time required for mixing.

The same titration was repeated at 32°C, 35°C, 40°C, 45°C and 50°C. Each time fresh reaction mixture was prepared and base was standardized with standard solution of HCl.

(b) pH titration of gallic acid

A similar titration was done at 30°C with gallic acid only. The ferric ion was replaced by another tripositive metal (Bi) which is inert towards gallic acid.

(c) pH titration of iron and gallic acid methyl ester complex

In this 50 ml reaction mixture 0.060 m moles of iron was mixed with 0.260 m. moles of gallic acid methyl ester. The rest of procedure was same as mentioned above. The experimental runs were taken at 30°C, 35°C, 40°C, 45°C and 50°C.

Conclusion

The comparison of gallic acid iron complex with gallic acid methyl ester iron complex showed that log K1 values (formation constant of ML) are very similar for two complexes. K2 values on other hand for ester complex is higher and close to K1 value (K2/K1 = 10^{-0}. This indicates that ML_2 formation starts at low pH in ester complex while a higher pH is needed for ML_2 of the gallic acid complex.

K3/K2 values for both ligands are similar and high (K3 in gallic acid complex is = 10^5 and in gallic acid methyl ester complex it is 10^{10}). The K2 and K3 are much higher in case of methyl ester complex than in gallic acid complex (10^5 times).

Both complexes showed positive ΔH and ΔS values with more or less same magnitude.

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