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Complexing Behaviour of Toxic Thallium (I) With Some Potential Bioligands in Aqueous Phase

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ABSTRACT

Keeping into consideration, the immense role played by various metals and non-metals in their coordinated form, we intended to investigate and report the interacting mode of Toxic Tl (I) ion with some biologically important bioligands by employing Potentiometric techniques. Depending on the Avidity of a Toxic Metal Ion for a particular bioligand or vice versa vis-à-vis the adverse consequences of Toxic Heavy metal Ions on the biological system, the aim of present investigation was to study the complexing behavior of Tl (I) with some selected Bioligands. The Stability Constant (or the strength of bonding) in terms of both the stepwise as well as overall formation constants of the resulting complexes with chelating agent, using Bjerrum's method as modified by Albert in aqueous phase were reported.

Key Words*: *Bioligands, Complexes, Thallium (I), Toxicity, Toxic Metal Ions.

I. INTRODUCTION

Metals play a very important role in maintaining the life of all in the Biosystem. Some of these metal ions are distributed selectively in biological systems and their selective distribution is essential to an understanding of their biological functions. While some metal ions are essential some are potentially toxic. Even essential Metal Ions may become toxic after an optimal concentration. Some of the heavier metal ions, when present in human body, become undesirable, if not very toxic. The principal harm done by these undesirable Toxic metal ions, among others, is that very often they tend to displace some physiologically desirable key metal ions.The scientific and medicinal literature carries negative reports of thallium (I) from mild to highly toxic effects on the biological system. They mainly affect the central nervous system, cause visual disorders, alopecia and even death [1-4]. Thallium, a well-known, colorless, tasteless, and odorless heavy metal, is toxic to all organisms in both monovalent and trivalent form [5]. Tl(l) is even more toxic than Cd (ll), Hg (ll) and Pb (ll) [6]. There are reports that it has caused many accidental, occupational and therapeutic poisoning ever since it was discovered in 1861 by English chemist William Crookes [7]. Due to its high toxicity and longevity in atmosphere, thallium has been considered by the US Environment Protection Agency [8,9] as one of the pollutants to be controlled on priority basis. Short-term exposure to thallium may induce hair loss, skin lesions, and damage to the nervous system [10-14]. It is, therefore, pertinent to ascertain how these metal ions are distributed and concentrated in our bodies and in what forms and concentrations they may be harmful and life threatening. However by complexing with appropriate bioligands (like proteins) these toxic metals can be excreted out of the body which

in turn depend on the stability of these metal protein complexes. The work described in this thesis deals with the interaction of some potential bioligands and their derivatives with Tl (I). The bioligands selected for our investigation are such that in addition to the potential N and O donor sites, some of them have S-atom as an additional donor site. As the chemistry of the metal ions in aqueous phase is actually the chemistry of their aqueous complexes, we thought it proper to investigate their possible role and coordination behavior in aqueous phase, pH metrically. Stability constants of the resulting complexes have been determined using Bjerrum's method in aqueous phase [15].

II.EXPRIMENTAL

2.1 Materials and Methods

The salts of TI(I) used in the investigation was procured from (E.Merck, Germany, AR grade) as $TI(I)(NO_3)_2$. The bioligands employed viz: Barbituric acid, Thiobarbituric acid, Folic acid, Glutathione, Pyruvic Acid, Malonic acid and Methyl malonic acid (AR) grade were purchased from (E. Merck, India) and used as such. Potassium hydroxide of an AR grade was procured from Aldrich. The aqueous solutions of these species were prepared by dissolving the required amounts in doubly distilled water. The required concentration of the metal ion and bioligands solutions were maintained in accordance with the requirements. The volume of the alkali (0.1M KOH) used for each titration was 10 ml. The strength of CO_2 free KOH was checked by titrating it with standard oxalic acid before employing it as the titrant.

The interacting behavior of metal ion and bioligands was studied by carrying out pH-metric titrations in accordance with requirements by Micro-processor controlled pH-Analyzer (7B 454, Lab India Instrument Pvt .Ltd.) in conjunction with Orion Gel-filled combination Electrode (model 9-06). Conductance measurements were carried out with a conductivity meter (EUTECH INSTRUMENT CON 510). The cell was calibrated with desired KCl solution at 25^0C.

III. RESULTS AND DISCUSSIONS

The aim of the present investigation was to study the coordination behavior and avidity of the highly toxic TI (I) metal ion with biologically relevant biomolecules. Our main focus has been to calculate stability constant and examines the formation curves by applying Bjerrum's pH – metric titration method as modified by Albert [15,16]. The computed stability constants values of the resulting complexes are summarized in "Table I". The complexation process is evident from the both pH-metric titration curves and the formation curves "Fig 1-7" of the investigated system.

pH-metric Method

In this electro-analytical method, the pH of the solution is determined in a competitive reaction of the type:

$$M^{m+} + nLH \leftrightarrow ML_n^{(m-n)+} + nH^+$$

Since bioligands are either weak acids or weak bases, there is competition between hydrogen ions and metal ions for grabbing these bioligands, which can be used as a basis for the determination of formation constant. Hence the release of hydrogen ions in this coordination reaction can be correlated with the concentration of

uncomplexed bioligands and thus, the pH measurement, serves as a suitable method for studying the complex formation phenomena.

Appreciable shifts in pH plots indicated stepwise association of ligands with metal ions. Metal - ligand system may be explained by considering the stepwise formation of complex species of different composition in aqueous solution (ML, ML_2, ML_3--------ML_n, where L stands for ligand and M stands for metal ion and n for number of ligands molecules bound by each metal ion).

In general, at equilibrium the concentration of each species is related to that of each of the other complex species by a series of stepwise formation constant expressions such as:

$k_1 = [ML]/ [M][L]$

$k_2= [ML_2]/ [ML][L]$

$k_3= [ML_3]/ [ML_2][L]$

$k_n= [ML_n]/ [ML_{n-1}][L]$

K_s, the overall stability constant is related to the stepwise formation constants $k_1,k_2,$------k_n as: $K_s= k_1k_2k_3$---------k_n

For a divalent metal ion:

$K_s= [ML_2]/ [M^{2+}][L]^2$

and for a monovalent metal ion :

$K_s= [ML]/ [M^+][L]$

Also $\log K_s= \log k_1+\log k_2$

When the complex formation starts, H^+ ions are released and the measurement of the concentration of these ions provides a way to determine the extent of complexation of metal ions with a ligand in aqueous phase. The values of stepwise equilibrium constants are given by the following expression :

$\log k_1=\log \bar{n} - \log (1-\bar{n}) - \log [Sc]$

$\log k_2=\log (\bar{n} -1) - \log (2-\bar{n}) - \log [Sc]$

Here $\bar{n}$ (n bar) is the average number of molecules of complex forming agent attached to one ion of the metal concerned and [Sc] is the concentration of the coordinating species, values of which may be calculated from the equation given below:

$\log [Sc] = (pH-pKa) + \log \{[HSc]^0 - [KOH]\}$

Where $[HSc]^0$ is the concentration of the bioligand before addition of the metal ion and [KOH] is that concentration of alkali (KOH) which would be present if the complex forming agent and the metal ions were both absent i.e.; the initial concentration of KOH. The relationship between n and [KOH] is given by the expression:

$\bar{n} = 2[KOH]/ [HSc]^0$

The values of all these parameters have been computed.

For calculation of $\log k_1$ and $\log k_2$, the most reliable values of [Sc] are found from $\bar{n}$ = 0.10 to 0.70 and from 1.30 to 1.70 respectively as when $\bar{n}$ lies between 0.70 and 1.30, some molecules of $(ML)^+$ start to take on another molecules of (L) before all the ligand molecules have interacted with the metallic ions in 1:1 ratio.

Further where $\bar{n}$ is only a small fraction of (1- $\bar{n}$), knife-edge conditions prevail. Finally when n is approaching 2, the conditions are often such that some of the molecules of the complex ML_2 form a weak association with an extra molecule of the ligand. With the help of following relation which is valid only when $\bar{n}$ =1, the most reliable value of K_s are obtained from the formation curves:

$K_s=1/[Sc]^2$

Or $\log K_s = -2\log [Sc]$

By titrating each ligand in the presence of metallic ion, pH-values were obtained for each addition of alkali. With the help of formation curves, the correct values of [Sc] corresponding to $\bar{n}$ = 1 are also found. Having known the value of [Sc], the standard free energy change of complex formation ΔG^o, may also be calculated with the help of the relation:

$\Delta G^0 = -RT \ln K_s$ or $\Delta G^0 = -2.303\ RT \log K_s$

Where, R =0.008314 and T=297Kelvin

Since $\Delta G^0 = \Delta H - T\Delta S^0$, $2.303\ R \log K_s = (\Delta S^0 - \Delta H^0/T)$

Since stabilities of the metal complexes cannot be accounted by a single factor, each metal ion-bioligand system is considered separately which reveals that the stability constants show a large variation in values as shown in "Table I". In fact stability constants of metal complexes in solution phase are generally considered as being stable or unstable, depending on the strength of bond between metal ion and the bioligands. Stability of complex is very often expressed in terms of stability constant, which is used to describe the equilibrium behavior of metal complexes. As a general rule the greater is stability of the resulting complexes, the higher will be the value of equilibrium constants. In principle, stability constants are determined by studying the concentrations of the various species present in a wide range of equilibrium mixture containing the metal ion and the bioligands in different proportions. The disappearance of usual chemical properties of the metal ion in a complex is an important parameter for establishing the possibility and extent of formation of a metal-bioligand complex. If a metal-bioligand system does not show the usual chemical properties of the metal ion, it is authentic evidence that the free metal ion is present in an extremely low concentration and most of it has complexed with the bioligands. A distinctly direct dependence of the stability constants of metal-bioligand complexes upon the pK_a values of bioligands is the most convincing correlation; more the pK_a of the concerned bioligands, greater will be the stability of the resulting complexes. The difference in the avidities of various bioligands for TI (I) ion may be due to several factors, such as replacement or substitution of a group, nature of donor atoms, orientation of $-NH_2$, -COOH and R groups, length of carbon chain, involvement of additional coordinating sites/centers, aromatic substitution, acetylation thereby play an important role in deciding the extent and mode of complexation of bioligands. In some cases effect of one factor may be counterbalanced or diminished by the effect of some other factors.

The high thermodynamic stability of Complexes with Sulfur containing Bioligands confirms the participation of highly polarisable sulphur atom in the complex formation on the basis of soft-soft interaction. The oxygen of an amide group is less electronegative than oxygen of a carbonyl group resulting in the less involvement of amide nitrogen in the bonding as its basicity decreases due to the resonance with carbonyl group.

Dicarboxylic acid (Malonic acid) used in our studies is a strong chelating agents for metals like Fe(III), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II) and Pb(II) using both the carboxylate anions (0 ,0) for binding the metal ions. However, the stability data reveals that Tl (I) metal ion has a slightly less preference. In case of 'R'substitution of dicarboxylic acids, the stability decreases to some extent due to inductive effect of the R (methyl) group. Hence the stability of methyl malonic acid is lower than that of malonic acid, because the inductive effect destabilizes the carboxylate anion and lowers its tendency to lose proton, resulting in the formation of weak chelate. The same is true for the ketoacid (pyruvic acid). But the stability of metal-pyruvate systems is lower because the oxygen of keto group in pyruvic acid is less electronegative, since it is influenced by the inductive effect of carboxylic group in close vicinity and hence shows reluctance in sharing electrons.

The structure of folic acid reveals that it can be used as a bidentate, tridentate or else as a polydentate ligand. However, the stability data shows that the resulting metal complex is not as stable as expected which may probably, be due to the bulkier nature and low solubility (in aqueous solution) of the bioligand. Also folic acid is similar to dipeptides and like metal-glycylglycine completes, its stability is lower than that of the simple amino acid complexes.

As the name reveals, pyrimidines act as bases, forming very stable coordination complexes. Hence, the bioligands containing pyrimidine bases in their structure can provide a means for coordinating with metals (especially the toxic ones), thereby resulting in their detoxification. In this regard, barbituric acid and its

derivative (thiobarbituric acid) can serve the purpose. The stability data shows that these bases, like the pyrimidine bases, form very stable metal chelates. However, the stability of thiobarbituric acid (4,6-dihydroxy-2-mercaptopyrimidine) with Tl (I) is much greater than the stability of corresponding

Tl (I) barbituric acid (2,4,6-trihydroxy pyrimidine) complex in view of the fact that basicity for a particular donor set of chelating agents decreases in the order:

SNN ~ SNO > SO > OO > NO ~ NN

Among all chelating agents, used in our experiments, the coordination potential of the bioligands decreased in the same order.This trend agrees well with the theoretical consideration that sulfur atom being a soft

base has more avidity for soft acids, the heavy metals according to the Pearson's HSAB rule of thumb.Thus thiol containing chelating agents like thiobarbituric acid, glutathione, etc. used in our experiments have high stability with the heavy metal ions.Glutathione plays an important role in cell antioxidant defence mechanism, composed of three amino acid residues having four protons that can dissociate as the titration proceeds from acidic to basic region, from pH < 2 to pH=10 regions and at a pH 3 zwitterions species of glutathione exists. From the investigation, it evident that glutathionine have high avidity with thallium metal ion and hence form stable complex. Since glutathione-metal complexes, clearly reveal soft-soft interaction and act as bidentate ligand coordinating through thiol and amide or thiol and carboxylic group, glutathione can be used as an antidote in metal toxicity detoxification. A distinctly direct dependence of the stability constant of metal-bioligand complexes upon the pK_a values of bioligands is the most convincing correlation;more the pKa of the concerned bioligand, greater will be the stability of the resulting complex as is evident from "Table 1".

Molecular weights of chelating agents have been noted as yet another factor affecting the stability of Tl(I)-complexes. The aliphatic thiol-containing chelating agents like cysteine of low molecular weight, form more

stable Tl (I)-complexes than the ligands having higher molecule weights such as glutathione. On the basis of stability constant data, it can be said that bioligands containing –SH and -NH_2, or –SH and –COOH group of low molecular weight form more stable complexes. Therefore, thallium (I) can defang the function of the bioligand, which it has to play in the biological system, causing immense toxic effect. TI (I) metal ion is of toxicological concerns, especially as environment pollutants, as it is able to inactivate thiol containing enzymes even in low concentration, and thus interfere with cellular metabolisms and functions. Therefore, it can be proposed that these bioligands can serve as antidotes in case of metal poisoning by heavy metals. In fact whole complexation process is pH dependent, which increases with increasing the pH of the solution but decrease near pH 8.3, with the optimal pH region being nearer to physiological pH value.

IV.CONCLUSIONS

The interaction of thallium ion with bioligands was studied pH-metrically. In all the cases, the presence of metal ion and the bioligand together in the solution causes shift in the titration curves (in comparison to individual titration curves) which indicates that complexes are formed. All the bioligands used are of immense importance biologically. Complexation of Bioligands HX with Thallium (I) Plays major role in drug metabolism, calcium metabolism, the gamma glutamyl cycle, blood platelet and membrane functions. Further these biomolecules can reduce thallium burden

significantly from the tissues and can overcome the toxic effect of the metal in the biological systems.

The Formation plots clearly show that the values of n increase with the increase in the pH value, showing thereby, participation of the anionic from of bioligand in the complex formation. The shape of formation curves,in some metal-bioligand systems, is quite deviated from the expected sigmoidal shape, which may be due to the formation of hydroxo and protonated species in the aqueous medium and/or complications posed by the concerned bioligands. However, in other cases, there is a good resemblance between the statistical and the graphical log K_s values. Further, the involvement of kinetic factor cannot be ruled out. The metal bioligand interaction is rapid and no time lag exists at attaining equilibrium, as indicated by a sudden change in pH on the addition of alkali-metal hydroxide solution to the solution of Tl (I) salt, the bioligands and the mixture of Tl (I) and bioligand. Whereas the available information in the chemical literature on the nature of complexes of metal ions and ligands of biological importance and interests and

their avidity for each other are sufficient to throw light on metal-bioligand chelates,our studies, observation, elucidation and inferences are not less than sufficient to eliminate the various aspects of the topic. Nevertheless, the real mode of binding and the actual nature of resulting complexes demand further investigations for the quittance to be reached at, instead of relying on the fragrances attached with.

V.FIGURES AND TABLES

TABLE I: Computed values of log K_s at 25^0C for TI (I) - Bioligand complexes.

S.No	Bioligands	pka	logk1	logk2	logKs (C*)	logKs (G*)
1	Thiobarbituric Acid	12.81	8.90	4.75	13.65	13.20

2	Barbituric acid	12.5	8.88	5.00	13.88	13.53
3	Folic Acid	8.26	3.62	0.53	4.15	3.64
4	Malonic Acid	6.10	4.30	1.55	5.85	5.59
5	Pyruvic Acid	2.50	0.82	0.00	0.82	0.47
6	MethylMalonic Acid	5.87	3.90	2.06	5.96	5.99
7	Glutathione	9.65	6.66	2.31	8.97	8.77

C*=Calculated values, G*=Graphical values

Fig. 1-7

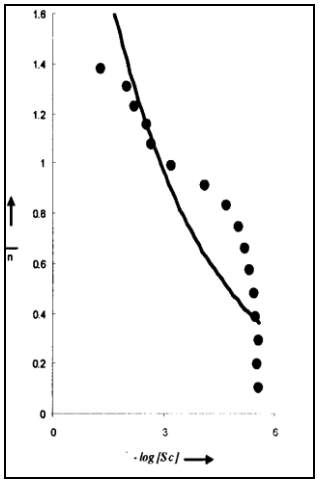
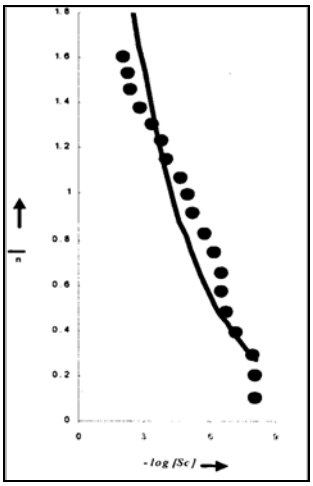


Fig.1: Tl(l) – Malonic Acid



F ig.2: Tl(l) - Glutathione

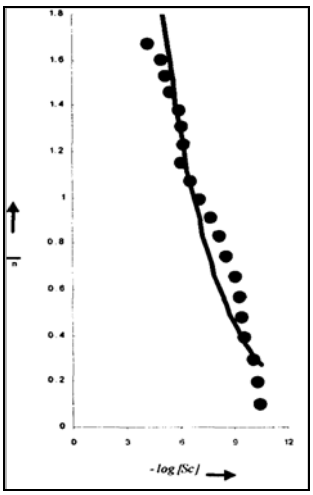


Fig.3: Tl(l) - Barbituric Acid

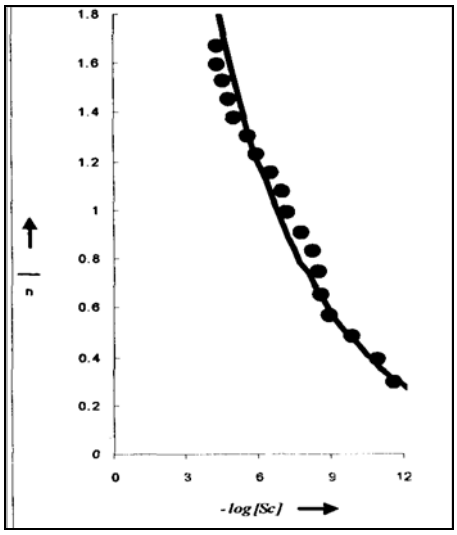


Fig.4:Tl(l)-Thiobarbituric Acid

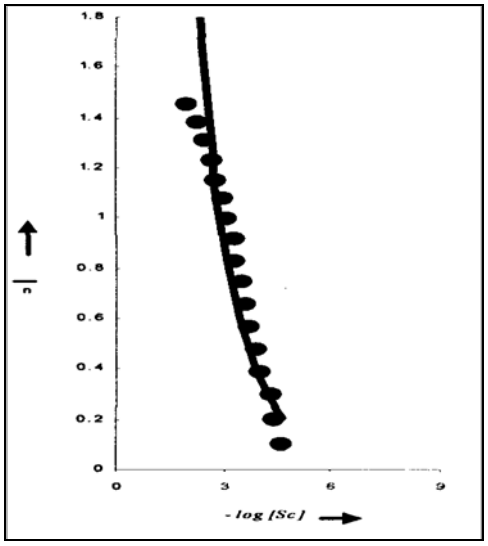
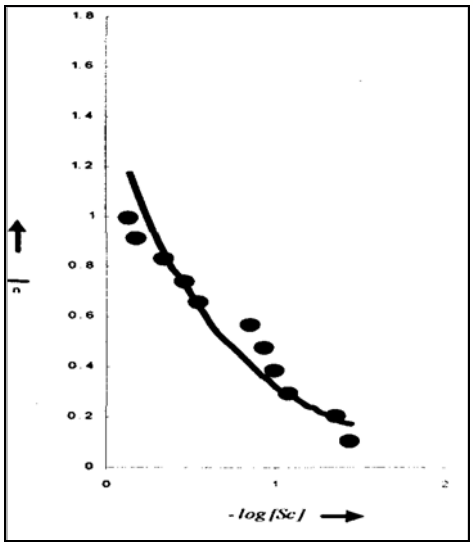


Fig.5: Tl(l) – Methyl Malonic Acid



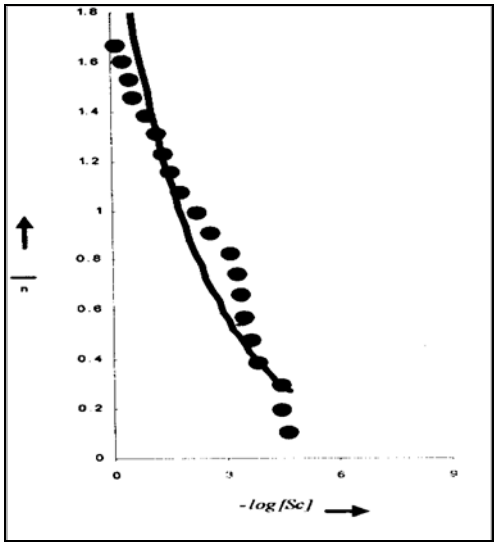


Fig.6 : TI(I)-Pyruvic Acid

Fig.7: TI(I)-Folic acid

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