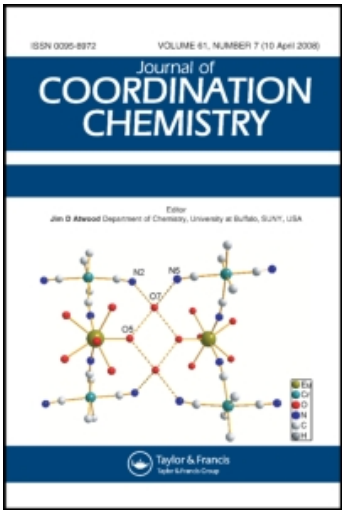

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Interaction of dipropyltin(IV) with amino acids, peptides, dicarboxylic acids and DNA constituents

A. A. Al-Najjar[a]; M. M. A. Mohamed[b]; M. M. Shoukry[c]
[a] Department of Applied Sciences, Faculty of Technological Studies, 70654 Shuwaikh, Kuwait [b] Department of Chemistry, Faculty of Education, Assuit University, New Valley, Egypt [c] Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

To cite this Article Al-Najjar, A. A. , Mohamed, M. M. A. and Shoukry, M. M.(2006) 'Interaction of dipropyltin(IV) with amino acids, peptides, dicarboxylic acids and DNA constituents', Journal of Coordination Chemistry, 59: 2, 193 — 206
To link to this Article: DOI: 10.1080/00958970500270786
URL: http://dx.doi.org/10.1080/00958970500270786

Journal of Coordination Chemistry
Vol. 59, No. 2, January 2006, 193–206

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Interaction of dipropyltin(IV) with amino acids, peptides, dicarboxylic acids and DNA constituents

A. A. AL-NAJJAR†, M. M. A. MOHAMED‡ and M. M. SHOUKRY*§

†Department of Applied Sciences, Faculty of Technological Studies,
PO Box 42325, 70654 Shuwaikh, Kuwait
‡Department of Chemistry, Faculty of Education,
Assuit University, New Valley, Egypt
§Department of Chemistry, Faculty of Science,
Cairo University, Giza, Egypt

(*Received February 2005; accepted 9 March 2005*)

Interaction of dipropyltin(IV) with selected amino acids, peptides, dicarboxylic acids or DNA constituents was investigated using potentiometric techniques. Amino acids form 1 : 1 and 1 : 2 complexes and, in some cases, protonated complexes. The amino acid is bound to dipropyltin(IV) by the amino and carboxylate groups. Serine is complexed to dipropyltin(IV) with ionization of the alcoholic group. A relationship exists between the acid dissociation constant of the amino acids and the formation constants of the corresponding complexes. Dicarboxylic acids form both 1 : 1 and 1 : 2 complexes. Diacids forming five- and six-membered chelate rings are the most stable. Peptides form complexes with stoichiometric coefficients 111(MLH), 110(ML) and 11-1(MLH_{-1})(tin: peptide: H^+). The mode of coordination is discussed based on existing data and previous investigations. DNA constituents inosine, adenosine, uracil, uridine, and thymine form 1 : 1 and 1 : 2 complexes and the binding sites are assigned. Inosine 5′-monophosphate, guanosine 5′-monophosphate, adenosine 5′-monophosphate and adenine form protonated species in addition to 1 : 1 and 1 : 2 complexes. The protonation sites and tin-binding sites were elucidated. Cytosine and cytidine do not form complexes with dipropyltin(IV) due to low basicity of the donor sites. The stepwise formation constants of the complexes formed in solution were calculated using the non-linear least-square program MINIQUAD-75. The concentration distribution of the various complex species was evaluated as a function of pH.

Keywords: Stability constant; Dipropyltin(IV); Amino acids; Peptides; Dicarboxylic acids; DNA constituents

1. Introduction

Cancer chemotherapy based on metal complexes started at the clinical level in the late 1970s with the use of cis-platin [1]. cis-Platin is still in use today in the form of carboplatin or Iproplatin with lower toxicity and higher activity against testicular and

*Corresponding author. Email: Shoukrym@hotmail.com

Journal of Coordination Chemistry
ISSN 0095-8972 print: ISSN 1029-0389 online © 2006 Taylor & Francis
DOI: 10.1080/00958970500270786

bladder tumours, ovarian carcinomas, head and neck cancers, etc. [2]. The mechanism of the antitumour action of cis-platin is believed to be due mainly to the formation of an intrastrand crosslink with DNA [3, 4].

In an attempt to discover more metal based anticancer drugs with higher activity and lower toxicity, several hundred diorganotin(IV) complexes were synthesized and tested [5]. Many showed high antitumour activity in vitro toward a wide variety of human tumours [6].

Equilibrium study of diorganotin(IV) complexes with amino acids, peptides, dicarboxylic acids or DNA constituents may provide further information on their antitumour and cytotoxic activity. In conjunction with our research directed toward solution chemistry of organotin(IV) complexes of ligands of biochemical significance [7–13], the present investigation describes the reaction of dipropyltin(IV)-dichloride with amino acids, peptides, dicarboxylic acids and DNA constituents.

2. Experimental

2.1. *Materials and reagents*

Dipropyltin(IV)-dichloride (Pr_2Sn) was obtained from Merck Chem. Co. Dicarboxylic acids, amino acids, peptides and DNA constituents investigated are: glycine, DL-alanine, DL-proline, L-serine, DL-valine, L-methionine, DL-leucine, L-histidine·HCl, L-histamine·2HCl, L-ornithine-HCl, L-lysine·HCl, L-aspartic acid, L-glutamic acid mercaptoethylamine, mercaptopropionic, 1,1-cyclobutane dicarboxylic acid (CBDCA), oxalic acid, malonic acid, succinic acid, adipic acid, glycinamide, glycylglycine, glycyl-L-alanine, glycyl-L-leucine, glutamine, inosine, inosine 5′-monophosphate, guanosine 5′-monophosphate, adenosine, adenosine 5′-monophosphate, uracil, uridine, thymine, and adenine. These materials were provided by Sigma Chem. Co. 1,4-Dioxane was provided by Aldrich Chem. Co. Sodium hydroxide stock solutions were prepared by diluting BDH concentrated volumetric solution vials. These solutions were systematically checked by titration against potassium hydrogen phthalate.

2.2. *Procedure and measuring techniques*

Potentiometric titrations were performed using a Metrohm 686 titroprocessor equipped with a 665 dosimat (Switzerland–Herisaue). The titroprocessor and electrode were calibrated with standard buffer solutions, prepared according to NBS specifications [14]. The titrations were carried out in a purified nitrogen atmosphere using a titration vessel described previously [15]. The temperature was maintained constant by a colora ultrathermostat.

The protonation constants of the ligands were determined by titrating 40 mL of 2.5×10^{-3} M ligand solution. The hydrolysis constants of dipropyltin(IV) were determined by titrating 40 mL of dipropyltin(IV)-dichloride (2.5×10^{-3} M). The formation constants of organotin(IV) complexes were determined by titrating 40 mL of solution containing the ligand (2.5×10^{-3} M) and dipropyltin(IV) with concentrations 1.0×10^{-2} M, 5.0×10^{-3} M, 1.25×10^{-3} and 6.25×10^{-4} M. Cytosine, cytidine and inosine 5′-monophosphate and adenine solutions were prepared in the protonated form by dissolution in equimolar solution of nitric acid. The titrations were

performed at different temperatures and in dioxane-water solutions of different compositions. The ionic strength was adjusted to 0.1 M by $NaNO_3$. pK_w in dioxane-water solutions was determined as described previously [16]. For this purpose various amounts of standard NaOH solution were added to a solution containing 0.10 M $NaNO_3$. The [OH] was calculated from the amount of base added. The [H] was calculated from pH value. The product of [OH] and [H] obtained in this way for the log concentration product gives $\log K_w = -14.92$ for 50.0% dioxane-water solution.

The equilibrium constants were evaluated from titration data, defined by equation (1) and equation (2).

$$l(M) + p(L) + q(H) \rightleftharpoons (M)_l(L)_p(H)_q \quad (1)$$

$$\beta_{lpq} = \frac{[(M)_l(L)_p(H)_q]}{[M[^l[L]^p[H]^q} \quad (2)$$

where M, L and H represent organotin(IV), ligand and proton, respectively. The calculations were performed using the computer program [17] MINIQUAD-75 by means of an IBM 486 computer. The stoichiometries and stability constants of the complexes formed were determined by trying various possible composition models. The model selected gave the best statistical fit and was chemically consistent with the titration data without giving systematic drifts in the magnitudes of various residuals, as described elsewhere [17]. The fitted model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of acid dissociation constant of the ligand and formation constants of the corresponding complexes. Table 1 lists the formation constants together with their standard deviations and the sum of square of residuals as obtained from the program MINIQUAD-75. The concentration distribution diagrams were obtained using the program SPECIES [18].

3. Results and discussion

The acid-base equilibria of the ligands and their complex formation were investigated in 50% dioxane-water solutions. The pK_a values obtained (table 1) are higher than those reported in water [19], perhaps due to the increased basicity of the ligand donor groups when one goes from pure water to dioxane-water solution mixture.

Hydrolyses of the dimethyl-, diethyl-, dibutyl-, diphenyltin(IV) ions were investigated in a variety of media by several authors [20–24]. Hydrolysis of dipropyltin(IV) was characterized by fitting the potentiometric data to various acid-base models. The fitted model was found to be consistent with the formation of M(OH), $M(OH)_2$, $M(OH)_3$, $M(OH)_4$ and $M_2(OH)_3$ species. This model resembles that obtained in the methyltin(IV) system [24]. Polymeric species such as $[M(OH)]_2$ and $M_2(OH)_4$ reported by Al-Flaijj *et al.* [24] were rejected. The low concentration range of dipropyltin(IV) used may present formation of polymeric species. The concentration distribution diagram for the Pr_2Sn-OH system is shown in figure 1. The concentration of dipropyltin(IV) starts to decrease at pH 1.0, while concentration of the mono-hydroxo species increases with increasing pH attaining a maximum of 84.0% at pH = 4.4. Further increase in pH is accompanied by a decrease in the mono-hydroxo species

Table 1. Formation constants of dipropyltin(IV) complexes in 50% dioxane-water mixture at 25°C and $I = 0.1$ M $NaNO_3$.

System	l	p	q[a]	log β[b]	S[c]
Pr_2Sn	1	0	−1	−3.27(0.01)	4.5E–8
	1	0	−2	−9.20(0.02)	
	1	0	−3	−21.45(0.05)	
	1	0	−4	−33.34(0.03)	
	2	0	−3	−9.43(0.08)	
Glycine	0	1	1	9.82(0.01)	4.2E–8
	1	1	0	10.56(0.06)	4.8E–8
	1	2	0	16.84(0.07)	
	1	1	1	13.92(0.06)	
Alanine	0	1	1	9.78(0.01)	1.6E–7
	1	1	0	12.16(0.04)	2.3E–9
	1	2	0	19.54(0.05)	
	1	1	1	15.98(0.04)	
Valine	0	1	1	9.66(0.01)	6.5E–7
	1	1	0	11.68(0.04)	7.3E–9
	1	2	0	18.63(0.04)	
	1	1	1	15.96(0.04)	
Leucine	0	1	1	9.89(0.01)	1.7E–7
	1	1	0	11.68(0.06)	8.6E–9
	1	2	0	18.45(0.06)	
	1	1	1	16.23(0.06)	
Proline	0	1	1	10.71(0.01)	4.7E–8
	1	1	0	12.07(0.06)	8.6E–8
	1	2	0	20.20(0.05)	
	1	1	1	16.36(0.06)	
Serine	0	1	1	9.34(0.01)	4.3E–8
	1	1	0	9.35(0.06)	7.8E–9
	1	2	0	14.80(0.08)	
	1	1	1	13.78(0.04)	
	1	1	−1	2.83(0.08)	
Methionine	0	1	1	9.39(0.01)	9.9E–8
	1	1	0	10.18(0.07)	1.0E–7
	1	2	0	15.00(0.06)	
	1	1	1	13.61(0.05)	
Lysine	0	1	1	10.79(0.01)	1.5E–7
	0	1	2	20.02(0.01)	
	1	1	0	14.040.05)	4.0E–9
	1	2	0	19.75(0.05)	
	1	1	1	20.42(0.04)	
	1	1	2	24.58(0.05)	
Ornithine	0	1	1	10.76(0.01)	2.4E–7
	0	1	2	19.58(0.01)	
	1	1	0	13.17(0.05)	2.9E–9
	1	2	0	19.31(0.04)	
	1	1	1	19.34(0.04)	
	1	1	2	23.32(0.03)	
Histidine	0	1	1	9.66(0.02)	5.2E–7
	0	1	2	15.54(0.04)	
	1	1	0	10.42(0.05)	1.9E–8
	1	2	0	16.74(0.06)	
	1	1	1	15.87(0.08)	
	1	1	2	21.24(0.10)	
Histamine	0	1	1	9.40(0.01)	1.0E–7
	0	1	2	14.94(0.01)	
	1	1	0	18.59(0.02)	3.2E–9
	1	2	0	24.85(0.03)	
	1	1	1	24.19(0.02)	

(*Continued*)

Table 1. Continued.

System	l	p	q[a]	log β[b]	S[c]
Aspartic acid	0	1	1	10.13(0.01)	1.8E–7
	0	1	2	14.82(0.02)	
	1	1	0	10.45(0.03)	4.9E–9
	1	2	0	18.25(0.09)	
	1	1	1	15.19(0.04)	
	1	1	2	18.93(0.06)	
Glutamic acid	0	1	1	10.02(0.01)	5.8E–8
	0	1	2	15.25(0.01)	
	1	1	0	10.41(0.05)	5.3E–9
	1	2	0	18.95(0.04)	
	1	1	1	14.86(0.04)	
	1	1	2	18.51(0.07)	
Mercaptoethylamine	0	1	1	11.98(0.01)	2.4E–7
	0	1	2	20.52(0.01)	
	1	1	0	17.21(0.04)	8.3E–9
	1	2	0	25.04(0.05)	
	1	1	1	21.69(0.03)	
Mercaptopropionic acid	0	1	1	11.78(0.01)	2.4E–7
	0	1	2	18.47(0.01)	
	1	1	0	14.97(0.06)	3.2E–8
	1	2	0	25.54(0.09)	
Glycinamide	0	1	1	7.58(0.01)	7.0E–8
	1	1	0	8.19(0.02)	
	1	1	1	12.40(0.02)	1.5E–9
	1	1	−1	1.58(0.04)	
Glycylglycine	0	1	1	8.00(0.01)	1.2E–7
	0	1	2	11.11(0.01)	
	1	1	0	7.92(0.07)	4.2E–8
	1	1	1	12.35(0.06)	
	1	1	−1	1.59(0.10)	
Glycylalanine	0	1	1	7.94(0.01)	3.4E–8
	0	1	2	12.33(0.02)	
	1	1	0	8.03(0.09)	6.0E–9
	1	1	1	13.02(0.06)	
	1	1	−1	1.22(0.10)	
Glycylleucine	0	1	1	7.86(0.01)	5.8E–8
	0	1	2	12.40(0.03)	
	1	1	0	8.08(0.06)	1.5E–9
	1	1	1	12.91(0.06)	
	1	1	−1	1.60(0.10)	
Glutamine	0	1	1	9.26(0.01)	5.8E–8
	1	1	0	10.34(0.05)	
	1	1	1	15.25(0.04)	7.7E–9
	1	1	−1	3.31(0.08)	
Inosine	0	1	1	9.14(0.01)	1.6E–8
	1	1	0	8.25(0.03)	2.1E–9
	1	2	0	14.45(0.06)	
Inosine 5′-monophosphate	0	1	1	9.35(0.01)	5.0E–9
	0	1	2	16.63(0.01)	
	1	1	0	11.70(0.02)	1.5E–9
	1	2	0	17.14(0.04)	
	1	1	1	15.87(0.09)	
Guanosine 5′-monophosphate	0	1	1	9.94(0.01)	3.0E–8
	0	1	2	16.57(0.021)	
	1	1	0	11.98(0.05)	7.1E–8
	1	2	0	17.52(0.04)	
	1	1	1	18.94(0.02)	

(*Continued*)

Table 1. Continued.

System	l	p	q[a]	log β[b]	S[c]
Adenine	0	1	1	10.19(0.01)	2.2E–8
	0	1	2	14.03(0.01)	
	1	1	0	10.26(0.04)	2.9E–9
	1	2	0	17.49(0.08)	
	1	1	1	13.69(0.09)	
Adenosine 5′-monophosphate	0	1	1	7.17(0.02)	6.0E–8
	0	1	2	10.28(0.03)	
	1	1	0	8.17(0.05)	2.2E–7
	1	2	0	11.42(0.07)	
	1	1	1	12.84(0.04)	
Adenosine	0	1	1	2.73(0.01)	1.0E–8
	1	1	0	3.01(0.06)	2.7E–9
	1	2	0	5.71(0.08)	
Uridine	0	1	1	10.33(0.01)	8.7E–8
	1	1	0	9.23(0.08)	4.3E–9
	1	2	0	17.18(0.09)	
Uracil	0	1	1	10.18(0.01)	4.3E–8
	1	1	0	9.92(0.03)	8.6E–8
	1	2	0	17.58(0.07)	
Thymine	0	1	1	10.51(0.01)	2.9E–8
	1	1	0	9.14(0.05)	2.7E–8
	1	2	0	17.10(0.06)	
Oxalic acid	0	1	1	5.71(0.02)	1.1E–7
	0	1	2	8.64(0.05)	
	1	1	0	11.06(0.06)	1.7E–7
Cyclobutane dicarboxylic acid	0	1	1	7.44(0.01)	8.5E–9
	0	1	2	12.00(0.01)	
	1	1	0	8.20(0.02)	3.0E–8
	1	2	0	12.85(0.01)	
Malonic acid	0	1	1	7.18(0.01)	8.6E–9
	0	1	2	11.08(0.01)	
	1	1	0	7.98(0.01)	2.7E–9
	1	2	0	12.70(0.03)	
Succinic acid	0	1	1	6.93(0.01)	8.0E–9
	0	1	2	12.46(0.01)	
	1	1	0	7.69(0.02)	4.3E–9
	1	2	0	12.67(0.02)	
Adipic acid	0	1	1	6.75(0.01)	1.6E–8
	0	1	2	12.75(0.01)	
	1	1	0	7.43(0.05)	1.3E–8
	1	2	0	12.08(0.04)	

[a]l, p and q are the stoichiometric coefficient corresponding to dipropyltin(IV), amino acid, peptide, dicarboxylic acid, DNA units and H^+, respectively; [b]standard deviations are given in parentheses; [c]sum of square of residuals. The ionic strength was adjusted to 0.1 M by $NaNO_3$.

and an increase in the dihydroxo species reaching maximum concentration of 99.0% in the pH range 8.4–10.0. The tri-hydroxo species starts to form at pH = 10.0 and attains a maximum concentration of 24.0% at pH 12.0. The tetra-hydroxo species is formed at pH = 10.0 and attains a maximum concentration of 99.0% at pH ~ 14.0. The dimeric species $M_2(OH)_3$ occurs with a maximum formation of 30% at pH = 6.0. Under physiological conditions, $M(OH)_2$, M(OH) and $M_2(OH)_3$ predominate.

3.1. *Complex formation equilibria involving amino acids*

The potentiometric titration curve of dipropyltin(IV) complex is lowered from the corresponding amino acid curve (figure 2), corresponding to formation of a complex

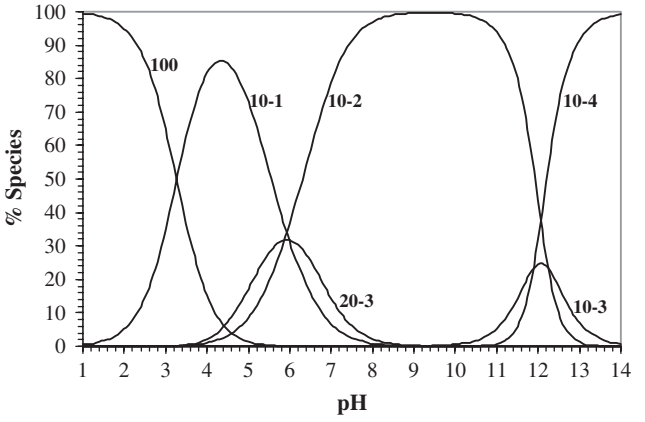


Figure 1. Concentration distribution of various species as a function of pH in the Pr_2Sn-OH system (at concentration of 1.25 mmol/L for Pr_2Sn).

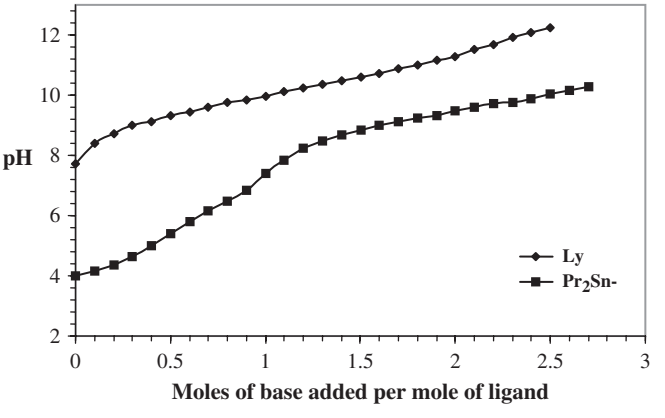


Figure 2. Potentiometric titration curves of Pr_2Sn-Lysine system.

species through release of hydrogen ion. The potentiometric data of the amino acid complexes were fitted with a model composed of the species ML, ML_2 and MLH. Histidine, ornithine, lysine, aspartic acid and glutamic acid form in addition to MLH_2. The formation of ML_2 complexes is supported by previous investigations on dimethyltin(IV) complexes with amino acids [10].

The acid dissociation constants of the protonated complexes are calculated using equation (3):

$$\begin{aligned} pK_1^H &= \log \beta_{MLH} - \log \beta_{ML} \\ pK_2^H &= \log \beta_{MLH_2} - \log \beta_{MLH} \end{aligned} \tag{3}$$

Values for the α-amino acids are in the range 3.28–6.38. This reveals that the amino acids coordinate by the carboxylic oxygen leaving amino group susceptible for protonation.

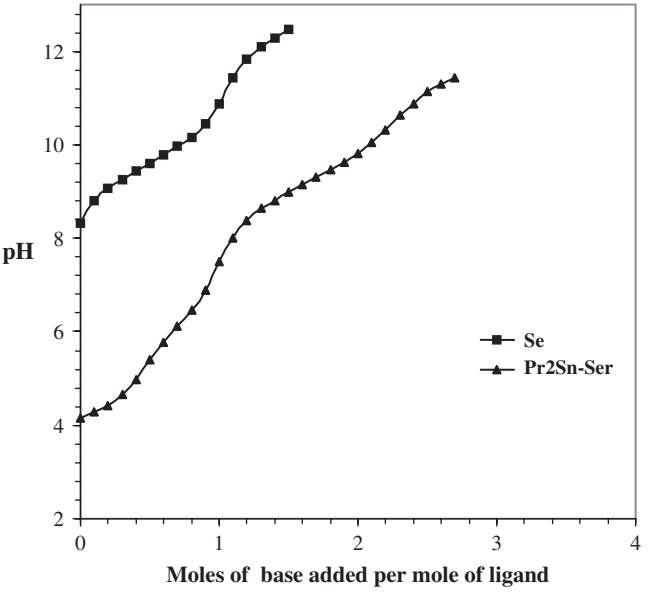


Figure 3. Potentiometric titration curves of Pr_2Sn-Serine system.

Serine has an extra binding centre on the β-alcoholato group. This group was reported [25] to participate in transition metal ion complex formation. The titration curve of serine complex is lower than the curves of the other amino acid complexes in the region $2 \leq a \leq 3$, corresponding to complete formation of its complex (figure 3), perhaps revealing that the β-alcoholato group participates in complex formation. The potentiometric data are much better fit assuming formation of ML, MLH, ML_2 and MLH_{-1}. The pK_a value of the β-alcoholato group incorporated in the Pr_2Sn complex ($\log \beta_{ML} - \log \beta_{MLH_{-1}}$) is 6.52, supporting the observation that in basic solutions Cu(II) promotes ionization of the alcoholato group of threonine with a pK_a value of 10.3 [26]. Participation of the thioether group [27] in coordination of methionine with Pr_2Sn(IV) seems to be unfavoured, because the stability constants of their complexes are in fair agreement with those of α-amino acids.

It is known that a relationship exists between the dissociation constant of a series of structurally related ligands and the stability constants of their 1 : 1 complexes with a given metal ion. Such a relationship can be used to estimate the stability constants of metal complexes of closely related substances if their pKa and any K_{ML} values are known. Figure 4 demonstrates such a relationship for the dipropyltin(IV) complexes of simple amino acids having no extra functional group.

The species distribution for the lysine complex, taken as a representative example, is given in figure 5. The protonated species MLH dominates (74.4%) at pH ca. 5.2; the deprotonated ML complex predominates (67.4%) at pH ca. 7.6; the hydroxo complex $[Pr_2Sn(H_2O)(OH)]^+$ plays a minor role in that region. In the physiological pH range the OH^- ion does not compete with amino acid in reaction with the dipropyltin(IV) complex.

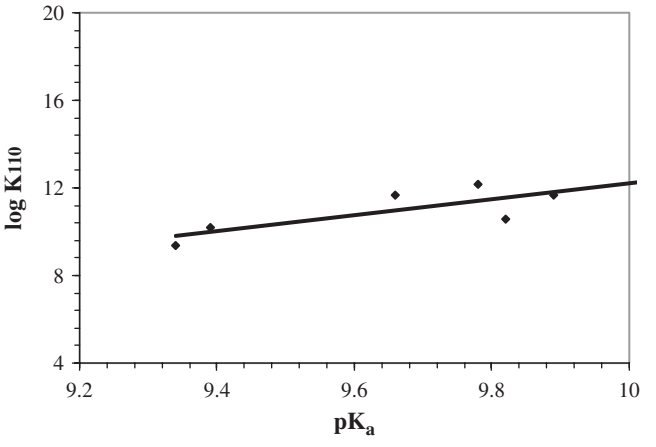


Figure 4. Correlation of formation constant of dipropyltin(IV)-amino acid complexes with acid dissociation constant of the α-amino acids.

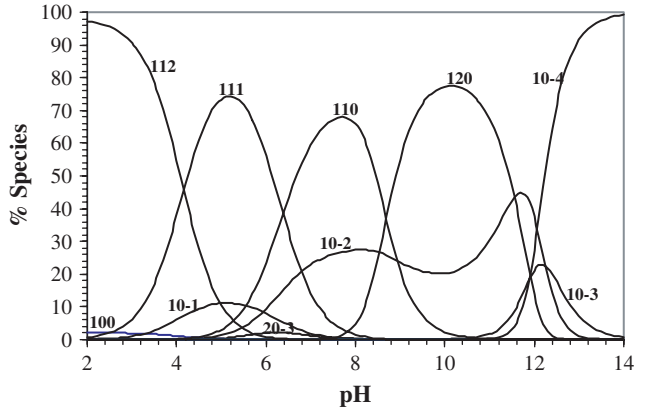


Figure 5. Species distribution of various species as a function of pH in the Pr_2Sn-lysine system (at concentration of 1.25 and 2.5 mmol/L, respectively).

3.2. *Complex formation equilibria involving dicarboxylic acids*

In the Pr_2Sn-dicarboxylic acid system computer analysis of the pH titration data showed the presence of ML and ML_2. Table 1 shows that the formation constant of the ML complex involving formation of a five-membered chelate ring as in oxalic acid is the highest. The formation constants of the ML complexes involving six-membered chelate rings as in cyclobutane dicarboxylic acid and malonic acid are higher than those of seven-membered chelated rings as in succinic acid, and eight-membered chelated rings as in adipic acid. Five- and six-membered rings are favoured energetically over seven- and eight-membered rings. Cyclobutane dicarboxylic acid has a higher stability constant than malonic acid. This may be due to hydrophobic contact between the cyclobutane ring of CBDCA and the propyl group of Pr_2Sn. This was supported on the basis of molecular models. A similar observation was found in the reaction of carboplatin and guanosine-5′-monophosphate [27].

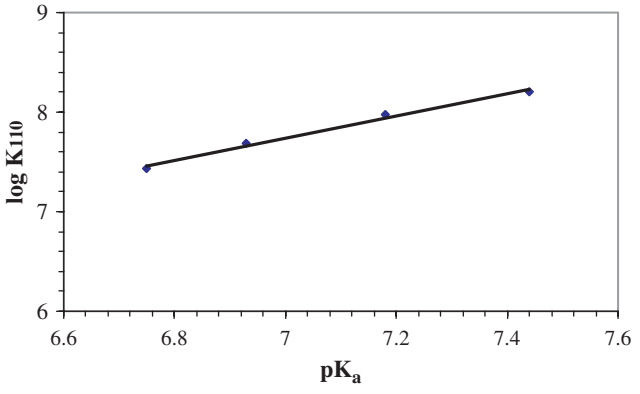


Figure 6. Correlation of formation constant of dipropyltin(IV)-dicarboxylic acid complexes with acid dissociation constant of the dicarboxylic acids.

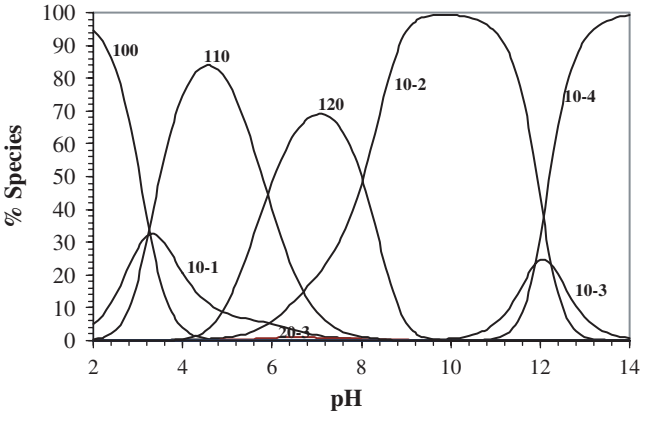


Figure 7. Species distribution of various species as a function of pH in the Pr_2Sn-CBDCA system (at concentration of 1.25 and 2.5 mmol/L, respectively).

Stability constants of ML complexes with dicarboxylic acids show a linear relationship with the pK_a of the dicarboxylic acid (figure 6). Such a relationship can be used to estimate the stability constants of metal complexes of closely related substances if their pK_as are known.

A representative species distribution diagram of the CBDCA complex given in figure 7 shows that the ML complex prevails with formation degree (84%) at pH = 4.4. The ML_2 complex predominates at pH = 7.0 with formation degree 68%. In the physiological pH range the ML_2 species contributes significantly as the hydrolyzed species of dipropyltin(IV) are not formed in that pH range. This reveals that hydroxyl ion is not competing with CBDCA in the reaction with dipropyltin(IV).

3.3. *Complex formation equilibria involving peptides*

The potentiometric data of Pr_2Sn-peptide (L) were fitted to various models. The most acceptable model was consistent with formation of complexes MLH,

ML and MLH_{-1}. Consequently the complex formation may be explained by the following equilibria.

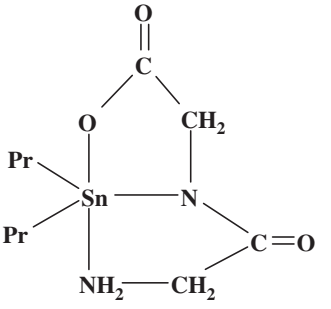
$$Pr_2Sn^{2+} + L^- \overset{K_1}{\rightleftharpoons} (Pr_2Sn)L^+$$
$$(Pr_2Sn)L^+ \rightleftharpoons [(Pr_2Sn)LH_{-1}] + H^+ \quad (4)$$

The pK_a of the ionized amide group is calculated by equation (5):

$$pK_a = \log \beta_{ML} - \log \beta_{MLH_{-1}} \quad (5)$$

The acid dissociation constants of the protonated complexes with peptides (MLH) compare favourably with the acid dissociation constant of the protonated complexes of α-amino acids indicating peptides bind to $Pr_2Sn(IV)$ by a carboxylato group at low pH, while the amino group remains free. On increasing the pH, the amino and the amide groups undergo deprotonation and the complexes $[Pr_2Sn(L)]$ (110) and $[Pr_2Sn(LH_{-1})]$ (11-1) are formed. The binding in the $[Pr_2Sn(LH_{-1})]$ complex involves the amino group, deprotonated amide-N atom and the carboxylate oxygen atom. The pK_a values of the amide group, incorporated in the dipropyltin(IV) complexes, are in the range of 6.28 to 7.83.

Based on previous investigation of dipeptide-diorganotin(IV) complexes [13], complex formation between dipropyltin(IV) and glycylglycine results in a chelate involving the terminal amino moiety, carboxylate oxygen and the amide nitrogen atoms.



$(Pr_2Sn)LH_{-1}$

A linear relationship holds between the stability constant of the complex and acid dissociation constant of the ligand (figure 8).

Estimation of the concentration distribution of various species in solution provides a useful picture of organotin(IV) binding in biological systems. Distribution curves of glycylglycine complexes with dipropyltin(IV) are given in figure 9. The concentration of the formed complex increases with increasing pH making complex formation more favourable in the physiological pH range. The protonated species Pr_2SnLH (MLH) reaches maximum concentration of 86% at pH = 3.0. However, the Pr_2SnL species dominates with a formation degree of 57% at pH 5.0. The deprotonated form Pr_2SnLH_{-1} reaches maximum concentration of 45% at pH 7.4, revealing that induced ionization of peptide hydrogen is feasible in the physiological pH range.

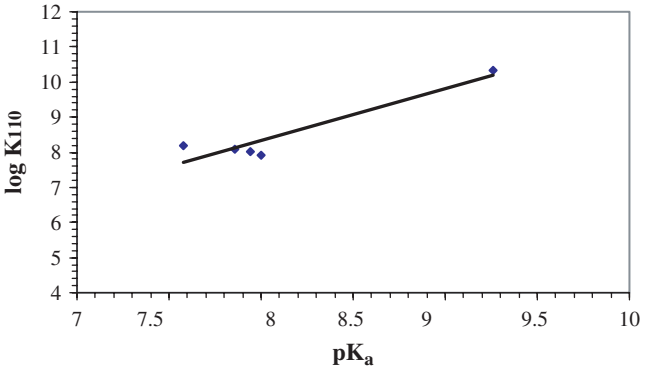


Figure 8. Correlation of formation constant of dipropyltin(IV)-peptide complexes with acid dissociation constant of the peptides.

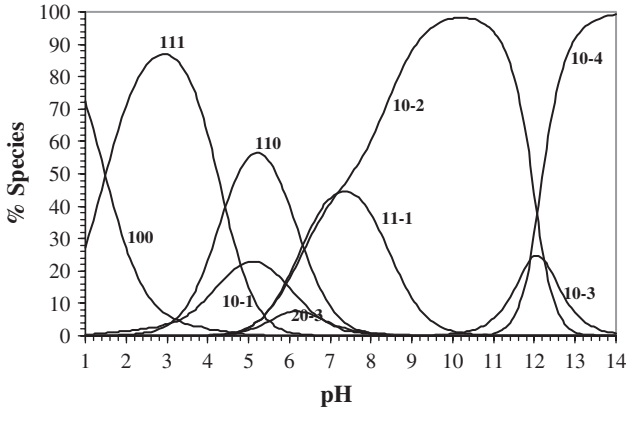


Figure 9. Species distribution of various species as a function of pH in the Pr_2Sn-glycylglycine system (at concentration of 1.25 and 1.25 mmol/L, respectively).

3.4. *Complex formation equilibria involving DNA units*

The potentiometric titration curves of DNA units in the presence and absence of dipropyltin(IV) are compared. The complex titration curve is significantly lower than the ligand titration curve, indicating formation of a complex through release of a hydrogen ion. The formation equilibria were characterized by fitting their potentiometric data to various models. The best model was found to be consistent with formation of complexes ML and ML_2. 5′-IMP, 5′-GMP, AMP and adenine titration data were found to be consistent with formation of ML, MLH and ML_2.

The purines inosine and inosine 5′-monophosphate may undergo protonation at N_7. In the present study, the pK_a of N_1H was determined. The pK_a of N_7H is too low to determine by potentiometry. It has been reported that in the acidic range N_1 remains protonated, while the organotin(IV) ion coordinates to N_7. In the neutral and alkaline pH range organotin(IV) ion is coordinated to N_1. In the potentiometric titration of the complexes described in this investigation the pH was varied from 3.0 to 9.0. Therefore we assume that N_1 plays a role during complex formation, in agreement

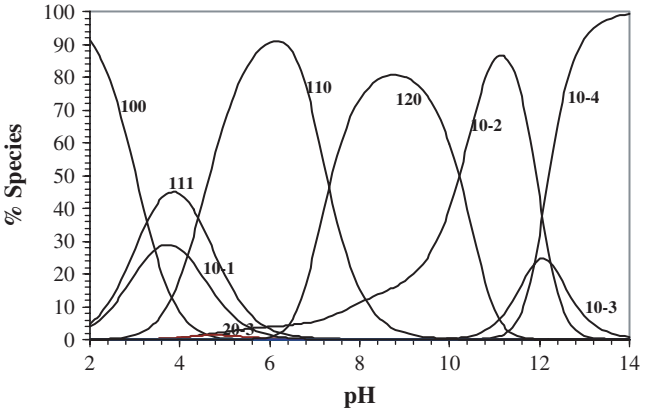


Figure 10. Concentration distribution of various species as a function of pH in the Pr_2Sn-IMP system (at concentration of 1.25 mmol/L for Pr_2Sn and 2.50 mmol/L for IMP).

with Martin *et al*. [28]. Also, if the purines interact with Pr_2Sn by the N_7 site, leaving N_1 non-coordinating, the N_1 site will be protonated. However, the fitted model consists of the deprotonated complex only revealing that the N_1 site is not free and is involved in complex formation with Pr_2Sn(IV). The dipropyltin(IV) complex of IMP is considerably more stable than that of inosine; consequently, the phosphate group may participate in the binding process.

The pyrimidines uracil, thymine and uridine have only one basic nitrogen atom in the measurable pH range (N_3). Consequently, the pyrimidines ligate in the deprotonated form through N_3.

Both cytosine and cytidine undergo N_3 protonation under mildly acidic conditions as shown by NMR spectroscopy in solution and by X-ray crystallography in the solid state [29–33]. The pK_a values of the N_3 mono-cations of cytosine and cytidine are 4.53 and 4.10, respectively. The lower basicity of the nucleoside results from the electron-withdrawing effect of the ribofuranosyl group reducing the electron density in the cytosine ring. The formation of the complexes is, however, not detected.

Protonated adenine undergoes proton dissociation from N_1 and N_9. Hodgson [34] and Marzilli [35] have discussed complex formation in solution and solid state. Evidence has been provided that N_9 is the coordination site in the dipropyltin(IV) complex. The pK_a of protonated adenosine refers to the N_1H site. This value is lower than that of N_1 site of adenine, due to the electron-withdrawing sugar moiety of adenosine. The dipropyltin(IV) complex of adenosine is less stable than that of adenine, probably due to availability of binding site *viz* N_9 in adenine. AMP has two protonation sites, corresponding to phosphate group ($pK_a = 7.17$) and N_1H site ($pK_a = 3.11$). The phosphate group does not markedly affect the basicity, indicating that the intramolecular interaction between the base and phosphate moieties does not play an important role in solution. The dipropyltin(IV) complex of AMP is considerably more stable than that of adenosine. Accordingly, the phosphate group may participate in binding.

Distribution curves of inosine 5′-monophosphate complexes with dipropyltin(IV) are given in figure 10. The concentration of the 1 : 1 complex (ML) reaches the maximum of 93% at pH 4.4. The 1 : 2 complex (ML_2) predominates and reaches the

maximum concentration of 95% at physiological pH. The hydrolyzed dipropyltin(IV) species have minor contribution compared to the complexes. This reveals that the hydroxyl ion is not competing with the DNA constituents in the reaction with dipropyltin(IV) ions.

Acknowledgements

The project team is grateful for the financial support from the Kuwait Foundation for the Advancement of Sciences.

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