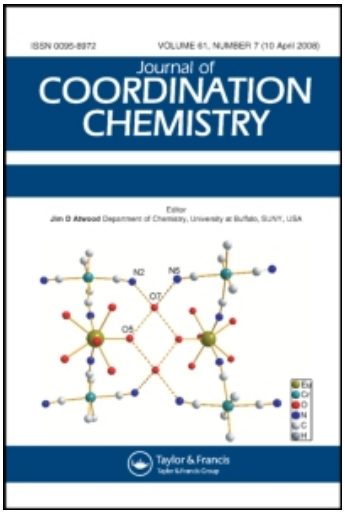

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TRIMETHYLTIN(IV) COMPLEXES WITH SOME SELECTED DNA CONSTITUENTS

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TRIMETHYLTIN(IV) COMPLEXES WITH SOME SELECTED DNA CONSTITUENTS

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The interaction of the trimethyltin(IV) with some selected DNA constituents such as inosine, inosine 5′-monophosphate, adenine, adenosine, adenosine 5′-monophosphate, uracil, thymine, thymidine, cytosine and cytidine were investigated at 25°C and 0.1 M ionic strength in aqueous solutions and dioxane–water mixtures using potentiometry. 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. The effect of dioxane as a solvent on the protonation constants of ligands and the formation constants of trimethyltin(IV) complexes were discussed. The thermodynamic parameters ΔH° and ΔS° calculated from the temperature dependence of the equilibrium constants were investigated.

Keywords: Equilibrium studies; Trimethyltin(IV) complexes; DNA complexes; Stability constants; Speciation

INTRODUCTION

Organotin(IV) compounds are extremely toxic (particularly the trialkyl derivatives) to all animals and humans [1]. The lower trialkyls show the highest toxicity [2, 3], they are powerful neurotoxic agents and may cause paralysis and death. Indeed the toxicity of tetra-alkyltins also appears to be due to trialkyltin(IV) species which are produced as a result of dealkylation

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in vivo [4]. The biological activity of toxic triorganotin(IV) compounds is believed to be due to their ability to bind to certain proteins [5].

We have recently begun a systematic investigation of the complex formation equilibria of organotin(IV) with ligands of biological interest such as amino acids and peptides [6–12]. The main objective of the present study is to establish the stoichiometry and stability constants of trimethyltin(IV) complexes with some selected DNA constituents. The effect of solvent and temperature on the complex formation equilibria were also investigated.

EXPERIMENTAL

Materials and Reagents

Trimethytin(IV) chloride (TMT) was supplied by Merck Chem. Co. DNA constituents studied are inosine (Ino), inosine 5′-monophosphate (IMP), adenine, adenosine, adenosine 5′-monophosphate (AMP), uracil, thymine, thymidine, cytosine and cytidine (structural formulae are shown in Fig. 1). These materials were from Sigma Chem. Co. Dioxane was provided by Aldrich Chem. Co. Sodium hydroxide stock solutions were prepared by diluting the content of BDH concentrated volumetric solution vials. These solutions were systematically checked by titration against potassium hydrogen phthalate. Cytosine, cytidine and inosine 5′-monophosphate and adenine solutions were prepared in the protonated form by dissolution in equimolar solution of nitric acid.

Procedure and Measuring Techniques

The potentiometric titrations were performed using a Metrohm 686 titroprocessor equipped with a 665 dosimat (Switzerland-Herisau). The titroprocessor and electrode were calibrated with standard buffer solutions, prepared according to NBS specifications [13]. The temperature was maintained constant by a colora ultrathermostat. The measurements were carried out in a purified nitrogen atmosphere using a titration vessel described previously [14]. The titrations were performed in different percentage (V/V) dioxane–water mixtures and at different temperatures.

The protonation constants of the ligands and the hydrolysis constants of the trimethyltin(IV) were determined by titrating 40 mL of ligand (1.25×10^{-3} M) or the trimethyltin(IV) (1.25×10^{-3} M) solutions. The stability constants of the trimethyltin(IV) complexes were determined by titrating 40 mL of ligands (1.25×10^{-3} M) and the trimethyltin(IV) with concentrations of 6.25×10^{-4}, 1.25×10^{-3} and 2.5×10^{-3} M. All solutions were

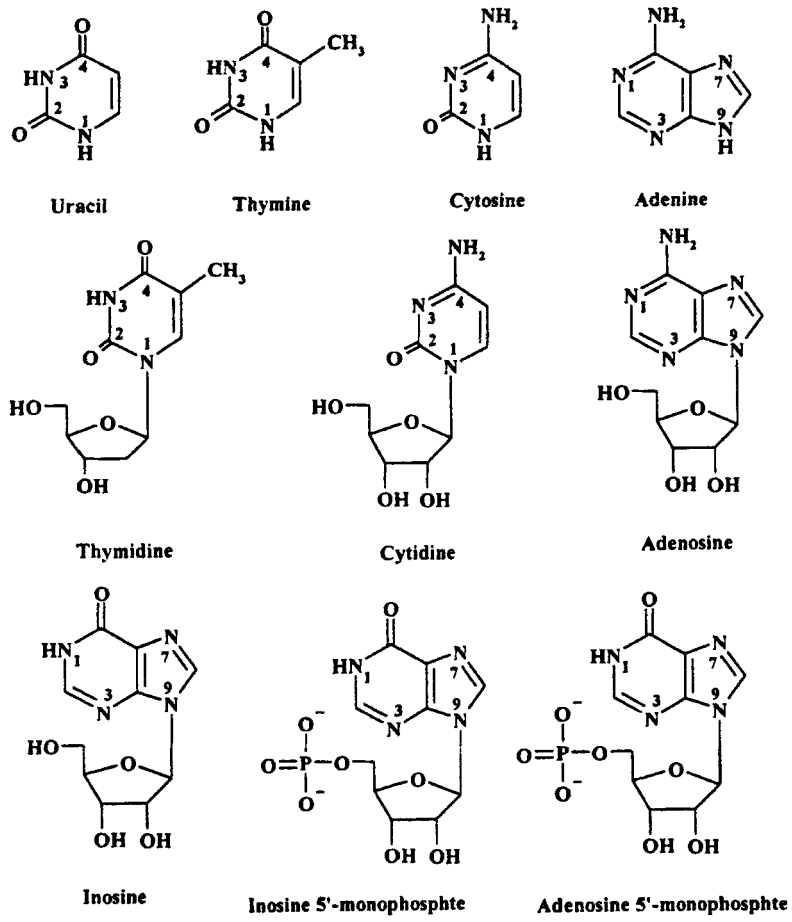

FIGURE 1 Structural formulae of some DNA units.

adjusted to 0.1 M ionic strength by addition of $NaNO_3$ and were titrated against standard 0.05 M NaOH solution.

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

$$l(\mathrm{M}) + p(\mathrm{L}) + q(\mathrm{H}) \rightleftharpoons (\mathrm{M})_l(\mathrm{L})_p(\mathrm{H})_q \tag{1}$$

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

where M, L and H represent organotin(IV), ligand and proton respectively. The calculations were performed using the computer program [14] 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 any systematic drift in the magnitudes of various residuals, as described elsewhere [14]. The fitted model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of acid dissociation constants of the ligand and formation constants of the corresponding complexes. Tables I and II list 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 [15].

TABLE I Formation constants of trimethyltin(IV) complexes in water at different temperatures

System	*Temp* (°C)	*l*	*p*	*q*[a]	*log β*[b]	*S*[c]
TMT	15	0	0	−1	−14.25(0.05)	
		1	0	−1	−6.14(0.01)	3.3E−8
		1	0	−2	−16.84(0.04)	
		2	0	−1	−2.74(0.02)	
		2	0	−2	−9.07(0.01)	
		2	0	−3	−19.40(0.04)	
Inosine		0	1	1	8.77(0.01)	2.2E−8
		1	1	0	5.26(0.05)	5.3E−8
		1	1	−1	−2.96(0.04)	
Inosine		0	1	1	9.33(0.02)	3.2E−7
5′-monophosphate		0	1	2	15.28(0.04)	
		1	1	0	6.33(0.07)	9.7E−8
		1	1	1	12.91(0.06)	
		1	1	−1	−1.99(0.06)	
TMT	20	0	0	−1	−14.07(.05)	
		1	0	−1	−6.01(0.01)	3.2E−8
		1	0	−2	−16.61(0.04)	
		2	0	−1	−2.62(0.02)	
		2	0	−2	−8.83(0.01)	
		2	0	−3	−19.04(0.04)	
Inosine		0	1	1	8.67(0.01)	2.4E−8
		1	1	0	5.35(0.05)	7.4E−8
		1	1	−1	−2.69(0.04)	
Inosine		0	1	1	9.17(0.02)	3.2E−7
5′-monophosphate		0	1	2	15.17(0.03)	
		1	1	0	6.43(0.08)	1.1E−7
		1	1	1	12.97(0.07)	
		1	1	−1	−1.88(0.06)	
TMT	25	0	0	−1	−13.89(0.05)	
		1	0	−1	−5.90(0.02)	3.8E−8
		1	0	−2	−16.40(0.03)	
		2	0	−1	−2.44(0.02)	

TABLE I (Continued)

System	Temp (°C)	l	p	q[a]	log β[b]	S[c]
		2	0	−2	−8.56(0.04)	
		2	0	−3	−18.70(0.05)	
Inosine		0	1	1	8.55(0.01)	5.2E−8
		1	1	0	5.49(0.05)	8.7E−8
		1	1	−1	−2.42(0.04)	
Inosine		0	1	1	9.09(0.02)	3.5E−7
5′-monophosphate		0	1	2	15.07(0.03)	
		1	1	0	6.55(0.08)	1.1E−7
		1	1	1	13.04(0.07)	
		1	1	−1	−1.76(0.06)	
Adenine		0	1	1	9.65(0.00)	1.6E−8
		0	1	2	13.85(0.01)	
		1	1	0	7.33(0.01)	7.9E−9
		1	1	1	12.79(0.02)	
		1	1	−1	0.01(0.04)	
Adenosine		0	1	1	3.49(0.01)	5.4E−8
		1	1	0	2.52(0.01)	1.4E−8
		1	1	−1	−3.60(0.04)	
Adenosine		0	1	1	6.04(0.01)	2.6E−8
5′-monophosphate		0	1	2	9.32(0.02)	
		1	1	0	4.41(0.03)	1.5E−8
		1	1	1	9.16(0.04)	
		1	1	−1	−2.20(0.06)	
Urcil		0	1	1	9.15(0.00)	6.9E−8
		1	1	0	6.39(0.05)	1.0E−7
		1	1	−1	−0.96(0.07)	
Thymine		0	1	1	9.58(0.00)	3.4E−8
		1	1	0	6.74(0.05)	7.2E−8
		1	1	−1	−0.36(0.07)	
Thymidine		0	1	1	9.50(0.00)	2.9E−8
		1	1	0	6.67(0.05)	7.4E−8
		1	1	−1	−0.41(0.07)	
Cytosine		0	1	1	4.53(0.00)	2.5E−8
		1	1	0	2.96(0.03)	5.1E−8
		1	1	−1	−2.95(0.07)	
Cytidine		0	1	1	4.10(0.00)	2.1E−8
		1	1	0	2.90(0.01)	5.4E−9
		1	1	−1	−2.42(0.01)	
TMT	30	0	0	−1	−13.74(0.05)	
		1	0	−1	−5.78(0.02)	7.7E−8
		1	0	−2	−16.22(0.04)	
		2	0	−1	−2.27(0.03)	
		2	0	−2	−8.28(0.02)	
		2	0	−3	−18.37(0.08)	
Inosine		0	1	1	8.44(0.00)	6.2E−8
		1	1	0	5.59(0.06)	1.2E−7
		1	1	−1	−2.14(0.05)	
Inosine		0	1	1	8.95(0.01)	2.4E−7
5′-monophosphate		0	1	2	14.99(0.03)	
		1	1	0	6.63(0.09)	1.2E−7
		1	1	1	13.09(0.07)	
		1	1	−1	−1.66(0.07)	

TABLE I (Continued)

System	Temp (°C)	l	p	q[a]	log β[b]	S[c]
TMT	35	0	0	−1	−13.69(0.05)	
		1	0	−1	−5.64(0.02)	8.4E−8
		1	0	−2	−16.06(0.03)	
		2	0	−1	−2.09(0.04)	
		2	0	−2	−8.01(0.02)	
		2	0	−3	−18.05(0.05)	
Inosine		0	1	1	8.37(0.01)	1.2E−8
		1	1	0	5.68(0.06)	1.0E−7
		1	1	−1	−1.81(0.04)	
Inosine		0	1	1	8.89(0.00)	2.5E−8
5′-monophosphate		0	1	2	15.17(0.01)	
		1	1	0	6.76(0.07)	1.2E−7
		1	1	1	13.04(0.08)	
		1	1	−1	−1.53(0.09)	

[a] *l*, *p* and *q* are the stoichiometric coefficient corresponding to trimethyltin(IV), DNA units and H^+ respectively.
[b] Standard deviations are given in parentheses.
[c] Sum of square of residuals.

TABLE II Formation constants of trimethyltin(IV) complexes at 25°C in dioxane–water solutions of different compositions

System	Dioxane %	l	p	q[a]	log β[b]	S[c]
TMT	25	0	0	−1	−14.23(0.07)	4.4E−8
		1	0	−1	−6.21(0.02)	
		1	0	−2	−16.96(0.05)	
		2	0	−1	−2.73(0.02)	
		2	0	−2	−9.29(0.01)	
		2	0	−3	−19.94(0.03)	
Inosine		0	1	1	8.85(0.00)	5.3E−9
		1	1	0	5.74(0.06)	1.2E−7
		1	1	−1	−1.52(0.03)	
Inosine		0	1	1	9.12(0.00)	2.6E−9
5′-monophosphate		0	1	2	15.83(0.01)	
		1	1	0	6.17(0.06)	7.5E−8
		1	1	1	13.02(0.07)	
		1	1	−1	−2.22(0.05)	
TMT	37.5	0	0	−1	−14.50(0.07)	6.1E−8
		1	0	−1	−6.39(0.02)	
		1	0	−2	−17.29(0.06)	
		2	0	−1	−2.86(0.03)	
		2	0	−2	−9.62(0.02)	
		2	0	−3	−20.39(0.08)	
Inosine		0	1	1	9.04(0.00)	2.7E−9
		1	1	0	5.61(0.06)	1.1E−7
		1	1	−1	−1.92(0.03)	
Inosine		0	1	1	9.24(0.00)	9.3E−10
5′-monophosphate		0	1	2	16.28(0.00)	
		1	1	0	6.09(0.06)	6.5E−8
		1	1	1	13.25(0.07)	
		1	1	−1	−2.50(0.05)	

TABLE II (Continued)

System	Dioxane %	l	p	q[a]	log β[b]	S[c]
TMT	50	0	0	−1	−14.92(0.07)	3.8E−8
		1	0	−1	−6.54(0.03)	
		1	0	−2	−17.60(0.05)	
		2	0	−1	−2.98(0.02)	
		2	0	−2	−9.90(0.01)	
		2	0	−3	−20.83(0.05)	
Inosine		0	1	1	9.14(0.01)	1.6E−8
		1	1	0	5.52(0.06)	8.2E−8
		1	1	−1	−2.22(0.03)	
Inoside		0	1	1	9.35(0.00)	5.0E−9
5′-monophosphate		0	1	2	16.63(0.01)	6.1E−8
		1	1	0	5.92(0.07)	
		1	1	1	13.41(0.07)	
		1	1	−1	−2.76(0.05)	
TMT	62.5	0	0	−1	−15.12(0.07)	1.7E−7
		1	0	−1	−6.70(0.02)	
		1	0	−2	−17.87(0.07)	
		2	0	−1	−3.11(0.05)	
		2	0	−2	−10.15(0.04)	
		2	0	−3	−21.28(0.09)	
Inosine		0	1	1	9.36(0.00)	5.1E−9
		1	1	0	5.37(0.08)	5.9E−8
		1	1	−1	−2.49(0.03)	
Inosien		0	1	1	9.39(0.00)	9.9E−10
5′-monophosphate		0	1	2	16.72(0.00)	
		1	1	0	5.68(0.10)	6.0E−8
		1	1	1	13.54(0.07)	
		1	1	−1	−2.89(0.06)	
TMT	75	0	0	−1	−15.63(.10)	9.9E−8
		1	0	−1	−6.84(0.02)	
		1	0	−2	−18.15(0.08)	
		2	0	−1	−3.22(0.04)	
		2	0	−2	−10.51(0.03)	
		2	0	−3	−22.00(0.07)	
Inosine		0	1	1	9.48(0.00)	6.9E−9
		1	1	0	5.27(0.09)	7.9E−8
		1	1	−1	−2.78(0.03)	

[a] *l*, *p* and *q* are the stoichiometric coefficient corresponding to trimethyltin(IV), DNA units and H^+ respectively.
[b] Standard deviations are given in parentheses.
[c] Sum of square of residuals.

RESULTS AND DISCUSSION

The acid dissociation constants of the DNA units in aqueous solution have been reported [16]. We redetermined them under the experimental conditions used for determining the stability constants of the organotin(IV)

complexes, *i.e.*, in dioxane–water solution of various proportions and at different temperatures. The pKa values of the ligands in dioxane–water solutions are higher than those reported in water. This may be due the increased basicity of the ligand donor groups as one goes from water to dioxane solutions.

The hydrolysis of trimethyltin(IV) ion was previously investigated [17, 18] and the results were contradictory. The acid–base chemistry of trimethyltin(IV) has also been investigated. The fitted model according to the aforementioned method of calculation was found to be consistent with the following acid–base equilibria (Fig. 2). The hydrolysed species 10-1, 10-2 and 20-1 were consistent with the model proposed by Takahashi *et al.* [18]. Considering the species 20-2 and 20-3 (Fig. 2) improved the data fitting. The formation of dimeric species through OH^- was previously established by Extended X-ray Absorption Fine Structure (EXAFS) [18]. However, the dimerizing ability of the aquahydroxo complexes by the general equilibrium:

$$TMT(H_2O)_2^+ + TMT(H_2O)OH \rightleftharpoons (TMT)_2(H_2O)_2OH^+ + H_2O$$

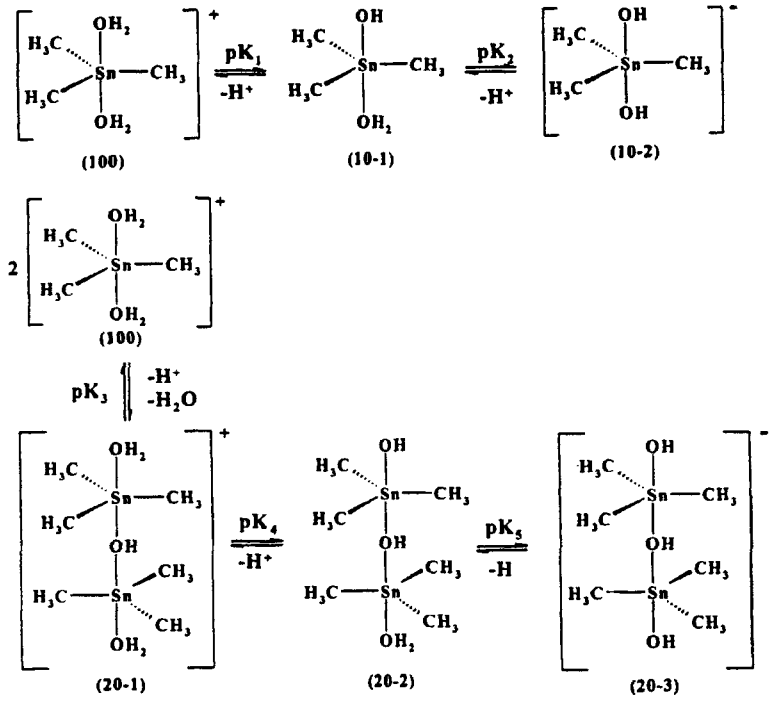

FIGURE 2 The acid base equilibria of trimethyltin(IV) species.

can be determined by calculating the dimerization constants $\log K_D = \log \beta_{20\text{-}1} - \log \beta_{10\text{-}1} = -2.44 - (-5.90) = 3.46$ at 25°C.

The potentiometric titration curves of the DNA units in the presence and absence of trimethyltin(IV) are compared. The complex titration curve is significantly lower than the ligand titration curve (Fig. 3). This corresponds to the formation of a complex species through release of a hydrogen ion. The pH titration data were fitted with the model composed of the 110 and 11-1 species. However the results of inosine-5′-monophosphate, adenine and adenosine-5′-monophosphate showed the formation of the protonated species 111 in addition to the 110 and 11-1 species. The pKa of the protonated complex is given by the relation [1]:

$$pK^{H}_{M(L)(H)} = \log K^{M}_{M(L)(H)} - \log K^{M}_{M(L)} \quad (4)$$

Earlier structural studies by means of X-ray, neutron and electron diffraction [20] and Mossbouer spectroscopy [21] revealed that the trimethyltin(IV) complexes have a trigonal bipyramidal configuration with three methyl groups in equatorial and two water molecules in axial

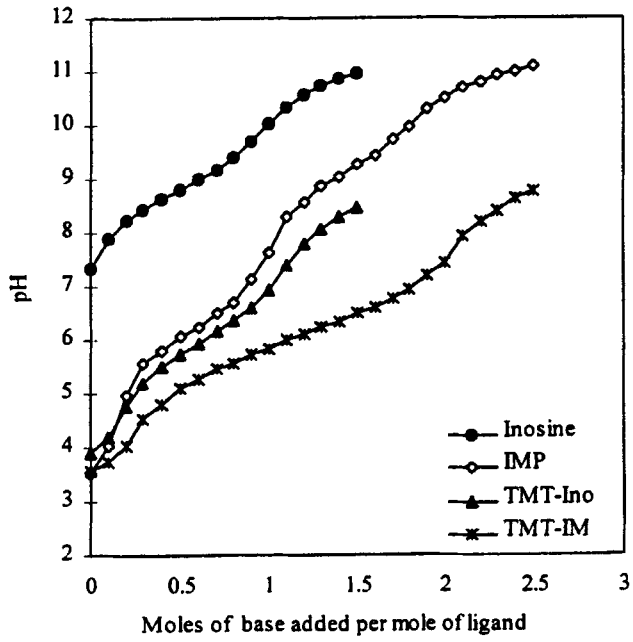

FIGURE 3 Potentiometric titration curves of trimethyltin(IV) with inosine and inosine 5′-monophosphate system.

positions. Complex formation would then involve ligand substitution of one water molecule [18]. The location of the two *trans* water molecules prevents the chelation of the ligands. The pKa_1 and pKa_2 values of water molecules coordinated to $(CH_3)_3Sn(H_2O)_2^{2+}$ are 5.81 and 10.35, respectively. The first coordinated water molecule is more acidic than the second water molecule, located *trans*. This may be explained on the premise that the water molecule is attracted to the tin(IV) center by the ion–dipole interaction. The bond length between Sn(IV) and H_2O to OH^- should be elongated because of the significant increase of the electron density on the central Sn(IV) atom. The pKa values of the coordinated water molecule in $(CH_3)_3Sn(DNA)(H_2O)$ ($pKa = \log\beta_{110} - \log\beta_{11\text{-}1}$) are lower than the pKa_2 of $(CH_3)_3Sn(H_2O)_2^{2+}$. This reflects the elongation of the Sn(IV)—H_2O bond caused by the coordination of OH^-.

The formation constant β_{110} of the inosine complex is in good agreement with that of inosine 5′-monophosphate. This reveals that both ligands are coordinating in the same way, probably *via* N_1. Binding through N_1 in transition metal complexes was extensively documented by NMR [22] and ESR [23] spectroscopic measurements. The pK^H of protonated IMP complex is calculated as 6.49. This value is in fair agreement with that of the phosphate group in IMP, indicating that the extra proton in the protonated complex of IMP is located on the phosphate group and binding occurs through N_1.

Uracil, thymine and thymidine have a dissociable proton at N_3. The acid dissociation constants obtained from this study were compared with that of the N_1 proton of inosine. The purinic derivative (inosine) is slightly more acidic than the pyrimidinic ones (uracil, thymine and thymidine), a property which can be related to the existence of a higher number of resonance forms in the inosine anion because of the presence of two condensed rings in this ligand. Based on the existing data, the pyrimidinic ones are ligating as a mono-anion, probably through N_3. The thymine complex is more stable than that of uracil. This may be due to the presence of an extra electron donating methyl group in thymine, which increases the basicity of the donor atom, N_3.

Protonated adenine undergoes proton dissociation from N_1 and N_9 sites. Hodgson [24] and Marzilli [25] have discussed complex formation both in solution and solid state. Evidence has been provided for the point of attachment of adenine to a metal center; it has been frequently reported that N_9 is the coordination site in the trimethyltin(IV) complex. The pKa of protonated adenosine is for the N_1H site. This value is lower than that of the N_1 site of adenine. This may be due to the electron withdrawing sugar

moiety of adenosine. The trimethyltin(IV) complex of adenosine is less stable than that of adenine, probably owing to the availability of binding site *viz.* N_9 in adenine. AMP has two protonation sites, corresponding to the phosphate group (pKa = 6.04) and the N_1H site (pKa = 3.28). The phosphate group does not markedly affect the basicity of the base, indicating that the intramolecular interaction between the base and phosphate moieties do not play an important role in solution. The trimethyltin(IV) complex of AMP is considerably more stable than that of adenosine. Accordingly, the phosphate group may participate in the binding process.

Both cytosine and cytidine undergo N_3 protonation under mildly acidic conditions as previously reported by UV [26] and ^{1}H [27],^{13}C [28] and ^{15}N [29] NMR spectroscopy. The assignment of N_3 as the preferential site of protonation also receives support from *ab initio* SCF calculations [30]. The values obtained for the protonation constants are 4.53 and 4.10 for cytosine and cytidine, respectively. The lower basicity of the nucleoside probably results from the electron withdrawing effect of the ribofuranosyl group which reduces the electron density in the cytosine ring. The stability constants for their organotin(IV) complexes reflects the difference of the basicity of the donor site.

Estimation of the concentration distribution of various species in solution provides a useful picture of trimethyltin(IV) binding in the biological system. The concentration distribution diagram for the hydrolysis of trimethyltin(IV) is shown in Figure 4. The main species under physiological

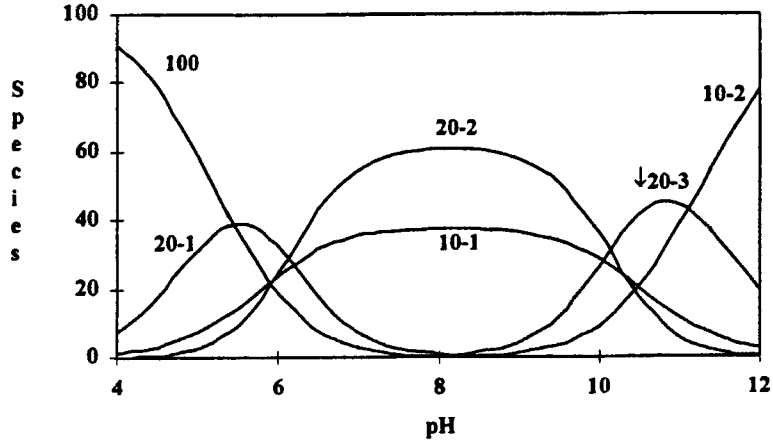

FIGURE 4 Concentration distribution of various species as a function of pH in the TMT-OH system (at concentration of 1.25 mmol/liter for TMT).

conditions (pH 6–8) are 10-1 and 20-2. The 20-2 species could be viewed as dimerization of two 10-1 species. Distribution curves of inosine and inosine 5′-monophosphate complexes with trimethyltin(IV) are given in Figures 5 and 6. The concentration of the formed complex increases with increasing pH, thus making complex formation more favorable in the physiological pH

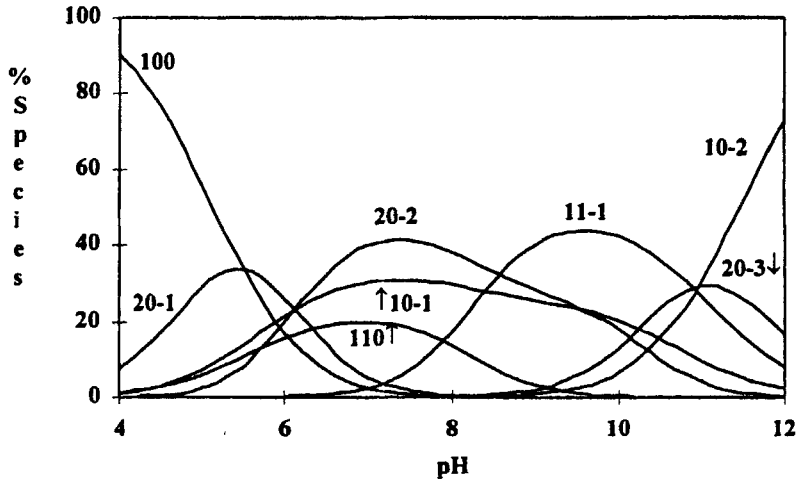

FIGURE 5 Concentration distribution of various species as a function of pH in the TMT-Inosine system (at concentration of 1.25 mmol/liter for TMT and 1.25 mmol/liter for Inosine).

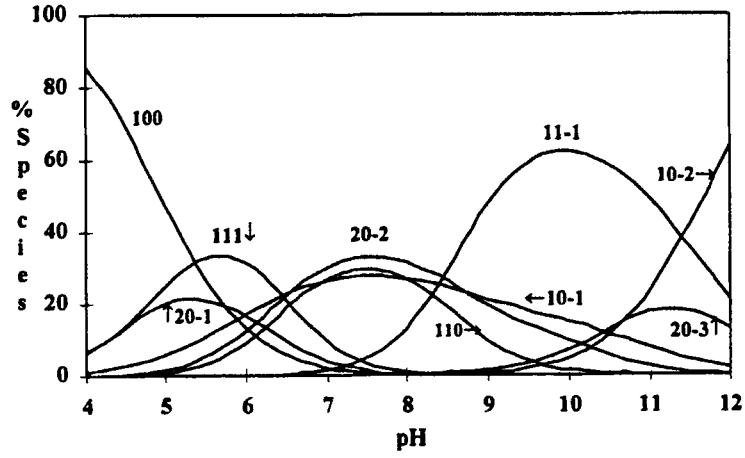

FIGURE 6 Concentration distribution of various species as a function of pH in the TMT-IMP system (at concentration of 1.25 mmol/liter for TMT and 1.25 mmol/liter for IMP).

range. The $(CH_3)_3Sn(Ino)(H_2O)$ complex (110) reaches the maximum concentration of 19.8% at pH = 7.0 and the $(CH_3)_3Sn(IMP)(H_2O)$ complex (110) reaches the maximum concentration of 29.5% at pH = 7.4. However, the $(CH_3)_3Sn(Ino)(OH)^-$ species predominates with a maximum concentration of 44% at pH 9.6, $(CH_3)_3Sn(IMP)(OH)^{3-}$ reaches the maximum concentration of 62% at pH 10 and $(CH_3)_3Sn(IMP)(H)^-$ has a maximum concentration of 33.6% at pH 5.6.

Effect of Temperature

The values obtained for the thermodynamic parameters ΔH°, ΔS° and ΔG° associated with the protonation of ionsine and inosine 5'-monophosphate and their complex formation with the organotin(IV) species were calculated from the temperature dependence of the data in Table I.

ΔH° and ΔS° were obtained by linear least square fit of $\ln K$ *vs.* $1/T$ ($\ln K = -\Delta H^\circ/RT \pm \Delta S^\circ/R$) leading to an intercept $\Delta S^\circ/R$ and a slope $-\Delta H^\circ/R$, where K is the equilibrium constant. The data in Table I can be employed to extrapolate the equilibrium constants to other temperatures. The main conclusions from the data can be summarized as follows:

(1) The formation constant for the hydrolyzed species of trimethyltin(IV) β_{OH} can be calculated for the species 10-1, taken as an example, as:

$$\log \beta_{OH} = pKw + \log \beta_{10-1}$$

The hydrolysis reactions (**1–5** in Tab. III) are exothermic, *i.e.* the hydrolyses are favored. However, ΔH° values can be considered as the net summation of two opposing effects, namely the exothermic hydrolysis reaction and the endothermic liberation of ordered water of hydration. Although Reaction (**3**) in Table III is endothermic, it has the largest change in entropy ($\Delta S^\circ = 242.3\,JK^{-1}\,mol^{-1}$) due to the release of two ordered water molecules of hydration. This makes more negative the free energy change $\Delta G^\circ = -65.6\,kJmol^{-1}$. Reaction (**3**), the formation of species 20-1, can be considered as a summation of reaction (**1**), the formation of species 10-1 and the dimerization reaction (**6**). Although the dimerization reaction (**6**) has a positive ΔH°, it is has a large entropy change $114.0\,JK^{-1}\,mol^{-1}$ due to loss of ordered water of hydration, so the net contribution to ΔG° is negative ($\Delta G^\circ = -19.8\,kJmol^{-1}$). The formation of 10-2, reaction (**2**), and 20-3, reaction (**5**), both have comparable values of ΔH°, ΔS° and ΔG°. Although they have more negative ΔH° values, they are the least favored

TABLE III Thermodynamic parameters for the equilibria of trimethyltin(IV) complexes[a]

Equilibrium[b]	ΔH° $kJmol^{-1}$	ΔS° $JK^{-1}mol^{-1}$	ΔG° [c] $KJmol^{-1}$
Trimethyltin(IV)			
(1) $M(H_2O)_2^+ + OH^- \rightleftharpoons M(H_2O)(OH) + H_2O$	−7.63(0.12)	128.3(1.1)	−45.9(1.2)
(2) $M(H_2O)(OH) + OH^- \rightleftharpoons M(OH)_2^- + H_2O$	−24.8(0.3)	−18.2(0.4)	−19.4(0.5)
(3) $2M(H_2O)_2^+ + OH^- \rightleftharpoons M_2(H_2O)_2(OH)^+ + 2H_2O$	6.60(0.13)	242.3(1.2)	−65.6(1.4)
(4) $M_2(H_2O)_2(OH)^+ + OH^- \rightleftharpoons M_2(H_2O)(OH)_2 + H_2O$	−14.7(0.2)	100.2(1.0)	−44.6(0.9)
(5) $M_2(H_2O)(OH)_2 + OH^- \rightleftharpoons M_2(OH)_3^- + H_2O$	−25.5(0.4)	−13.5(0.5)	−21.5(0.7)
(6) $M(H_2O)_2^+ + M(H_2O)(OH) \rightleftharpoons M_2(H_2O)_2(OH)^+ + H_2O$ (Reaction **3 − 1**)	14.2(0.2)	114.0(1.2)	−19.8(0.4)
Inosine			
(7) $L^- + H^+ \rightleftharpoons LH$	−35.0(0.5)	46.3(0.6)	−48.8(0.7)
(8) $M(H_2O)_2^+ + L^- \rightleftharpoons M(H_2O)L + H_2O$	36.7(0.5)	228.0(1.5)	−31.3(0.6)
(9) $M(H_2O)L + OH^- \rightleftharpoons ML(OH)^- + H_2O$	17.5(0.2)	174.4(1.2)	−34.4(0.5)
inosine 5′-monophosphate			
(10) $L^{3-} + H^+ \rightleftharpoons LH^{2-}$	−33.0(0.4)	64.6(0.8)	−52.2(0.9)
(11) $LH^{2-} + H^+ \rightleftharpoons LH_2^-$	0.32(0.01)	114.6(1.2)	−33.8(1.2)
(12) $M(H_2O)_2^+ + L^{3-} \rightleftharpoons M(H_2O)L^{2-} + H_2O$	36.0(0.5)	246.1(1.6)	−37.3(0.6)
(13) $M(H_2O)L^{2-} + H^+ \rightleftharpoons M(H_2O)LH^-$	−22.9(0.4)	46.8(0.6)	−36.9(0.6)
(14) $M(H_2O)L^{2-} + OH^- \rightleftharpoons ML(OH)^{3-} + H_2O$	−39.8(0.6)	−26.1(0.7)	−32.0(0.8)

[a] M denote trimethyltin(IV), Standard deviations are given in parentheses.
[b] Stepwise formation constants.
[c] Obtained from $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$, at 25°C.

species $\Delta G^\circ \sim -20\,kJmol^{-1}$. This can be due to the longer bond length[18] of the water molecules in the species 10-1 and 20-2. So, the loss of water molecules is not accompanied with a large degree of disorder and the formation of species 10-2 and 20-3 have net negative ΔS° of −18.2 and $-13.5\,JK^{-1}mol^{-1}$, respectively.

(2) The protonation reactions (**7**) and (**10**) of the N_1 site of ionsine and inosine 5′-monophosphate are exothermic and of comparable ΔH°, ΔS° and ΔG° values. Three factors affect the protonation reactions (7), (10) and (11):

(i) The neutralization reaction, which is an exothermic process.
(ii) Desolvation of ions, which is an endothermic process.
(iii) The change of the configuration and the arrangements of the hydrogen bonds around the free and the protonated ligands.

The phosphate ion in IMP is more solvated than its protonated form. Consequently it contributes more to the endothermic process upon protonation and the net ΔH° is only $0.32\,kJmol^{-1}$. Also, the phosphate ions

form ordered hydrogen bonds with water molecules, which is confirmed by the large entropy change $\Delta S^\circ = 114.6\,JK^{-1}mol^{-1}$. This contributes to a negative free energy change $\Delta G^\circ = -33.8\,kJmol^{-1}$. The positive entropies due to the release of ordered water molecules and the breaking of hydrogen bonds was found by Kramer *et al.* [30] to give positive ΔH°, large ΔS° and net negative ΔG° for the protonation and complexation reactions of organic monophosphates and copper ions.

(3) Complexation reactions (**8**) and (**12**) between trimethyltin(IV) and inosine and IMP are surprisingly endothermic with ΔH values of 36.7 and $36.0\,kJmol^{-1}$, respectively. This is similar to that found by Kamer [30] and can be interpreted as above by assuming that the enthalpy change is a net summation of two opposing effects, namely the exothermic complexation and the endothermic liberation of ordered water of hydration. This is confirmed by large ΔS° of 228.0 and $246.1\,JK^{-1}mol^{-1}$ for reactions (**8**) and (**12**), respectively. This contributes to negative $\Delta G^\circ - 31.3$ and $-37.3\,kJmol^{-1}$ for inosine and IMP complexes with trimethyltin(IV), respectively.

Effect of Solvent

It is well established that the "effective" or "equivalent solution" dielectric constants in protein [31, 32] or active site cavities of enzymes [33] are small compared to that in bulk water. Estimates for the dielectric constants in such locations range from 30 to 70 [31–34]. Hence by using aqueous solutions containing $\approx 10-50\%$ dioxane, one may expect to simulate to

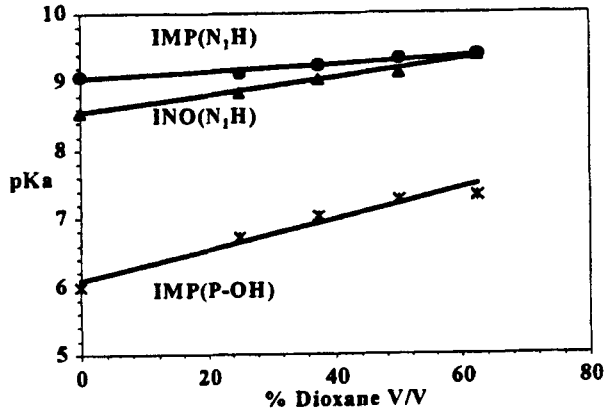

FIGURE 7 Effect of dioxane on the pKa of inosine and IMP.

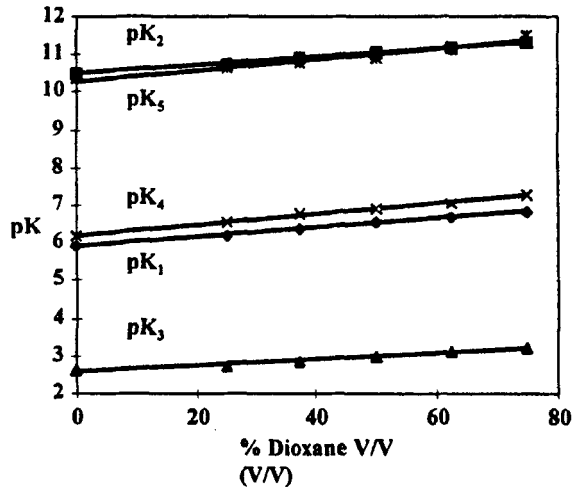

FIGURE 8 Effect of dioxane on the pKa TMT-H_2O system.

some degree the situation in active site cavities [35], hence to extrapolate the data to physiological conditions. Careful examination of media effects on the equilibrium constants reveals the following features:

(1) pKa (N_1H) of inosine increases linearly with increasing percentage of organic solvent in the medium, Figure 7. This may be correlated with the ability of a solvent of relatively low dielectric constant to increase the electrostatic forces between the proton and the ligand anion and consequently the pKa value increases. The same trend was observed for the pKa's of (N_1H) and phosphoric acid (P—OH) groups of IMP, Figure 7. The pKa of the phosphate group in IMP is more affected by replacement of water molecules with dioxane. This is in agreement with the above finding, namely the existence of hydrogen bonds between water molecules and phosphate ions. Thus, the phosphate ions are easily protonated in going from water to dioxane.

(2) The hydrated trimethyltin(IV) is subjected to hydrolysis by deprotonation as shown in Figure 2. The deprotonation constants are decreased with increasing dioxane proportion of the solvent (Fig. 8). This can be explained as discussed above for the acid–base equilibria of the ligands in dioxane–water solution.

(3) The formation constants for trimethyltin(IV) complexes with inosine and inosine-5′-monophosphate (Fig. 9) decrease upon addition of dioxane to an aqueous solution of the corresponding species. This can be explained by better solvation of hydrophobic species

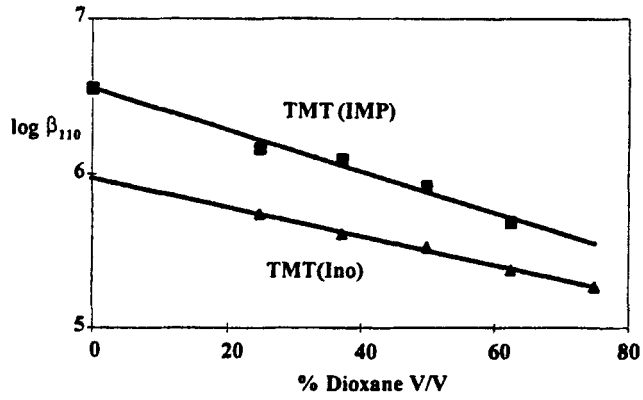

FIGURE 9 Effect of dioxane on the formation constants of the TMT with inosine and IMP.

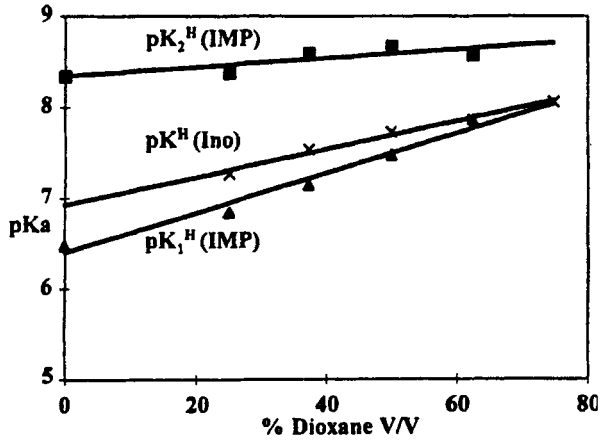

FIGURE 10 Effect of dioxane on the deprotonation constants of the TMT with inosine and IMP.

CH_3Sn^+/CH_3SnCl by dioxane resulting in lowering complex stability. This behavior is in agreement with that proposed for alkyltin(IV) complexes with *D*-glucosamine [36].

(4) The deprotonation constants of trimethyltin(IV) complexes with inosine ($pK^H = \log\beta_{110} - \log\beta_{11\text{-}1}$), and inosine-5′-monophosphate ($pK_1^H = \log\beta_{111} - \log\beta_{110}$) and ($pK_2^H = \log\beta_{110} - \log\beta_{11-1}$), Figure 10, are increased with increasing dioxane proportion. This change may be related to the decrease of the dielectric constant of the medium and an increase of the electrostatic forces between the released proton and trimethyltin(IV) complexes.

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