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Complex Equilibria of Organotin(IV) in Aqueous Solution with Imidazole Derivatives

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Summary. Equilibria studies in aqueous solution containing 25% dioxane (V/V) are reported for dimethyltin(IV) and trimethyltin(IV) (M) complexes with some imidazole derivatives (L). Stoichiometry and stability constants for the complexes formed were determined at 25°C and ionic strength 0.1 M $NaNO_3$. The results of the dimethyltin(IV) complexes showed the best fit of the titration curves when complexes ML, ML_2, ML_2H_{-1}, and ML_2H_{-2} were expected beside the hydrolysis products of the dimethyltin(IV) cation, while the calculations of the trimethyltin(IV) complexes reported the presence of only the complexes ML, MLH_{-1}, and the hydrolysis products of the trimethyltin(IV) cation. The concentration distribution of each species of the complexes in solution was evaluated. The stability of all complexes formed was investigated and discussed in terms of molecular structure of the ligand imidazole and the nature of the alkyltin cation. It is deduced that the stability of the complex formed increases as the basicity of the ligand imidazole is increased. On the other hand, the trimethyltin(IV) cation has a very low ability to form complexes compared to the dimethyltin(IV) cation.

Keywords. Equilibrium studies; Dimethyltin(IV) complexes; Trimethyltin(IV) complexes; Imidazole; Methylimidazole; Dimethylimidazole; Diphenylimidazole.

Introduction

Organotin(IV) compounds attracted considerable attention because of their significant biological activity. It was indicated that the dialkyltin(IV) derivatives exhibit a greater antitumour activity than the corresponding mono-, tri-, and tetraalkyl derivatives [1–8]. This would suggest that the activity of the diorganotin(IV), R_2SnX_2, in general is controlled by the nature of the R_2Sn moiety. On the other hand, imidazole is considered to be an important simple heterocyclic donor ligand for biological media. Accordingly, the study of the organotin(IV) complexes with monodentate nitrogen donor ligands, such as imidazoles would be very useful in the increasing understanding of the mechanism of the biological activity of the

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organotin(IV) species. Moreover, it was indicated that organotin(IV) containing nitrogen ligands are becoming increasingly important as a number of such compounds show antitumour activity [9]. For this purpose several sets of organotin(IV) complexes with imidazoles or pyrazoles were prepared and characterized in solid state and the crystal structures of these compounds were discussed [10–13]. However, measurements of the stability constants of such complexes are not described in the literature. Therefore the work of the present article is devoted to investigate the stability of the different complex species that are liable to exist in such important biological systems. In this work a systematic study for the complex system of the two biologically important organotin(IV) compounds (dimethyltin and trimethyltin chlorides) and imidazole derivatives, (imidazole (*Im*), 2-methylimidazole (*MeIm*), 1,2-dimethylimidazole (Me_2Im), and 4,5-diphenylimidazole (Ph_2Im)) has been carried out. Stoichiometry and stability of the various complex species that may exists in such complex systems at different *pH* values have been investigated by *pH*-metry. The concentration distribution of each species of the complexes in solution was evaluated.

Results and Discussion

Dimethyltin(IV) cation is known [14–18] to form stable and water soluble mono- and polynuclear hydroxo species (*cf.* Table 1A) in the whole *pH*-range studied. Trimethyltin(IV) ion hydrolyzed to form a series of hydroxo species *M*OH, $M(OH)_2$, and $M_2(OH)$ [19]. The stability constants of these species are listed in Tables 1A and 1B. The polymeric species may be a dimeric species bridged by the hydroxide ion. Since the hydroxide ion and the studied ligands are in strong competition for the metal ion, the formed hydroxo species were always taken into consideration in the equilibrium systems.

The protonation constant values of imidazole derivatives were determined under the same experimental conditions of ionic strength, temperature, and composition of the media (25% dioxane-water (V/V) mixture) for the complex solutions. The values obtained are comparable with those previously reported [20] in pure aqueous media. It is found that $log\,\beta_{011} = 6.80$, 7.66, 7.73, and 5.40 for

Table 1A. Formation constants of $M_pL_qH_r$ species of the dimethyltin(IV) complexes

$Log\,\beta_{pqr}$	H*Im*	*Me*H*Im*	Me_2H*Im*	Ph_2H*Im*
011	6.80(0.01)	7.66(0.01)	7.73(0.01)	5.40(0.01)
110	5.78(0.05)	6.79(0.03)	7.27(0.02)	4.98(0.01)
120	10.15(0.06)	12.03(0.04)	12.83(0.02)	8.66(0.01)
12-1	3.54(0.08)	4.41(0.08)	5.13(0.03)	3.41(0.01)
12-2	−3.44(0.06)	−3.42(0.05)	−2.79(0.03)	−2.53(0.01)
pK^1	6.61	7.62	7.70	5.25
pK^2	6.98	7.83	7.92	5.94

Experimental points ∼200; the hydrolysis constants of the dimethyltin(IV) ion are: $log\,\beta_{10\text{-}1} = -3.13(0.01)$, $log\,\beta_{10\text{-}2} = -8.35(0.01)$, $log\,\beta_{10\text{-}3} = -18.84(0.02)$, $log\,\beta_{10\text{-}4} = -30.17(0.01)$, $log\,\beta_{20\text{-}2} = -3.46(0.01)$, $log\,\beta_{20\text{-}3} = -8.98(0.06)$; standard deviations are given in parentheses

Table 1B. Formation constants of $M_pL_qH_r$ species of the trimethyltin(IV) complexes

$Log\ \beta_{pqr}$	H*Im*	*Me*H*Im*	Me_2H*Im*	Ph_2H*Im*
110	2.36(0.05)	3.38(0.05)	3.99(0.04)	2.55(0.05)
11-1	−4.05(0.01)	−4.13(0.03)	−3.61(0.03)	−4.00(0.05)
pK^1	6.41	7.51	7.60	6.55

Experimental points ~200; the hydrolysis constants of the trimethyltin(IV) ion are: $log\ \beta_{10\text{-}1} = -6.52(0.01)$, $log\ \beta_{10\text{-}2} = -17.39(0.05)$, $log\ \beta_{20\text{-}1} = -4.22(0.06)$; standard deviations are given in parentheses

imidazole, methylimidazole, 1,2-dimethylimidazole, and 4,5-diphenylimidazole, respectively. These values were taken into consideration during the evaluation of the *pH*-metric data. The displayed titration curves for the complex solutions with (1:1) or (2:1) ligand to metal ratio for dimethyltin(IV) and trimethyltin(IV) complexes proved to be different from those representing the hydrolysis of dimethyl- or trimethyltin(IV) (*cf.* Fig. 1). This behaviour reveals the coordination of the imidazole compound to the alkyltin(IV) cation, where different kinds of complexes may

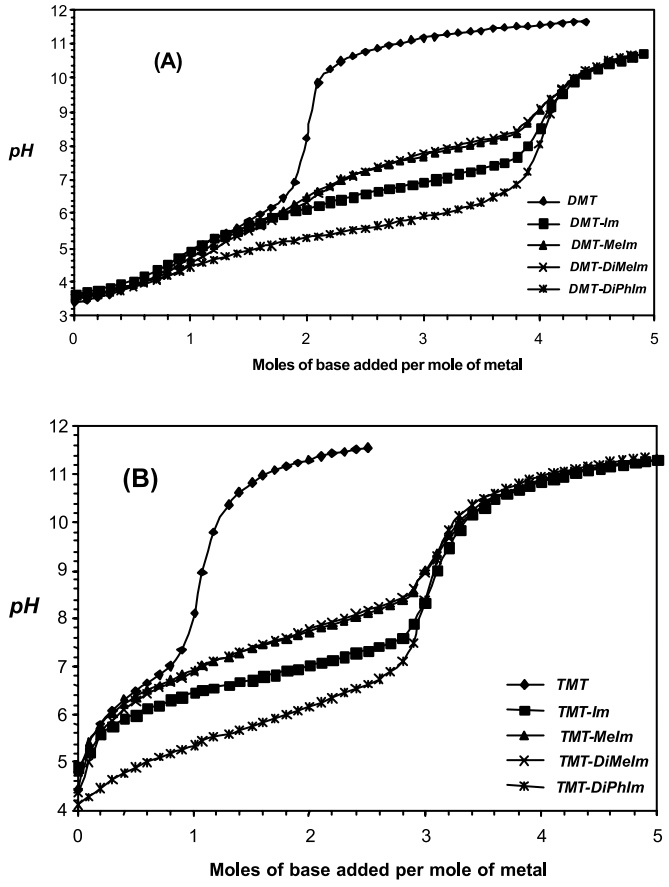

Fig. 1. *pH vs.* H_{-1} curves for the dimethyltin(IV) complexes formed with imidazole derivatives (A) and for the trimethyltin(IV) complexes formed with imidazole derivatives (B)

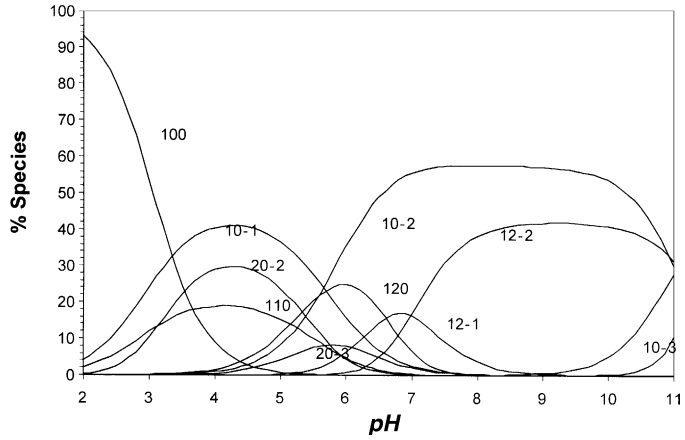

Fig. 2. Species distribution curves in the dimethyltin(IV)-diphenylimidazole system; $[M] = 6.25 \times 10^{-1}$ mM, $[L] = 1.25$ mM; the notation of the different species corresponds to the pqr values of the corresponding complex $M_pL_qH_r$

form. Furthermore, careful examination of the different titration curves suggests that coordination of the imidazole compound to the $(CH_3)_2Sn^{2+}$ or $(CH_3)_3Sn^{+}$ cations starts at *pH* values largely dependent on the nature of the ligand imidazole. Generally the *pH* at which coordination of the ligand compound to the cation starts is increased along the sequence: $(Ph)_2Im < Im < MeIm < Me_2Im$ (Fig. 1). This is in line with the decrease of deprotonation constants (pk_a increases) of the imidazole compounds in the same direction. The best fit of the titration curves of dimethyltin(IV) cation-imidazole solutions was obtained when complexes ML, ML_2, ML_2H_{-1} and ML_2H_{-2} were expected beside the hydrolysis products of the dimethyltin(IV) cation. On the other hand, the model which filled the titration curves of trimethyltin(IV) cation-imidazole solutions best suggested the presence of complexes ML and MLH_{-1} beside the hydrolysis products of the trimethyltin(IV) cation. The results obtained are listed in Tables 1A and 1B.

The obtained concentration distribution diagrams of dimethyltin(IV)-*Im*, *MeIm*, *and* Me_2Im solution systems (Fig. 2) are typical where these diagrams demonstrate that in the $pH = 3$–6 region MH_{-1} and M_2H_{-2} species are predominant over the ML and ML_2 complexes. On the other hand, the corresponding diagrams in the case of the dimethyltin(IV)-Ph_2Im solution system reveal that the complexes ML and ML_2 are predominant over the MH_{-1} and MH_{-2} in the same *pH* range. This behaviour could be attributed appreciably to the high deprotonation constant of Ph_2HIm ($pK_a = 5.40$) compared to corresponding values of the the other imidazoles (pK_a of H*Im*, *Me*H*Im* and Me_2HIm is 6.80, 7.66, and 7.73, respectively; *cf.* Table 1A). Therefore, coordination of Ph_2Im to the dimethyltin(IV) cation occurs only at lower *pH* values ($pH \leq 4.0$, *cf.* Fig. 1A). Thus, one should expect that in the low *pH* range ($pH = 3$–6), the free $(Ph)_2Im$ will highly compete with OH^- towards coordination to the alkyltin(IV) cation, *i.e.*, the formation of $M(Ph_2Im)$ and $M(Ph_2Im)_2$ complexes will predominate over the MH_{-1} and M_2H_{-2} hydroxo species in this *pH* range.

At higher *pH* values, further deprotonation was observed leading to species MH_{-2}, ML_2H_{-1}, and ML_2H_{-2}. The relative amount of the complex hydroxo

species ML_2H_{-1} reaches ~18% at $pH \sim 7.0$ in the case of ligand *Im*, *MeIm*, Me_2Im and ~32% at $pH = 5.5$ in the case of the ligand Ph_2Im (*cf.* Fig. 2). Species ML_2H_{-2} and the hydrolysis product of the dimethyltin(IV) cation (MH_{-2}) are present in the solution above *pH ca.* 7.0 and both become predominant at basic *pH* range (*cf.* Fig. 2).

The pK^1 values for the first deprotonation process $ML_2 \rightleftharpoons ML_2H_{-1} + H$ as calculated from the relationship $pK^1 = log\,\beta_{120} - log\,\beta_{12\text{-}1}$ amount to 6.61, 7.62, 7.70, and 5.25 for the ligands imidazole, methylimidazole, dimethylimidazole, and diphenylimidazole, respectively (Table 1A).

The second deprotonation process ($ML_2H_{-1} \rightleftharpoons ML_2H_{-2} + H$) occurs in the case of all studied imidazoles above pH ~ 7.0. The pK^2 values corresponding to this process as calculated from the relationship ($log\,\beta_{12\text{-}1} - log\,\beta_{12\text{-}2}$) amount to 6.98, 7.83, 7.92, and 5.94 in the case of imidazole, methylimidazole, dimethylimidazole, and diphenylimidazole, respectively (Table 1A).

Examination of the formation constant values listed in Table 1A reveals that the stability of the complexes formed, *ML* or ML_2, and of hydroxo complex species ML_2OH, $ML_2(OH)_2$ ($M + 2L + OH \rightleftharpoons ML_2OH$; $M + 2L + 2OH \rightleftharpoons ML_2(OH)_2$) as well as pK^1 and pK^2 values increase as the basicity of the imidazole nitrogen is increased ($Ph_2Im \rightarrow Im \rightarrow MeIm \rightarrow Me_2Im$). This could be explained on the principle of the expected increase in M–N bond strength along the same direction, *i.e.*, higher stability of the complex species formed.

It is worthy mentioning that the trimethyltin(IV) cation has a very low tendency to form complexes with all imidazoles under investigation (*cf.* Fig. 3 and Table 1B) and only *ML* and MLH_{-1} complex species are formed. The *ML* complex species in the case of *Im*, *MeIm*, and Me_2Im exist in very low proportion (~5.0%) at $pH \sim 6.5$, while the $M(Ph_2Im)$ complex exists in amounts of ~27% at $pH \sim 5.70$. This behaviour is similar to that observed in the case of dimethyltin complexes and therefore could be interpreted as a result of the same principle. On the other hand, in the

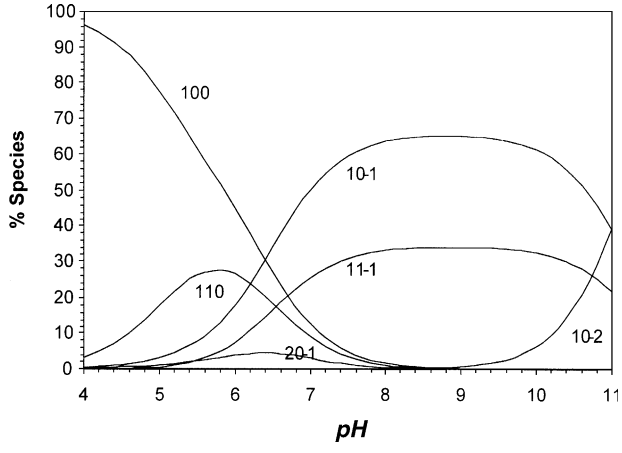

Fig. 3. Species distribution curves in the trimethyltin(IV)-imidazole system; $[M] = 6.25 \times 10^{-1}$ m*M*, $[L] = 1.25$ m*M*; the notation of the different species corresponds to the pqr values of the corresponding complex $M_pL_qH_r$

basic *pH* range the hydroxo complex species *ML*OH along with the hydrolysed species of the trimethyltin(IV) cation, *M*(OH), are predominant up to pH = 10, where the hydrolysed species $M(OH)_2$ starts to form. This behaviour can be explained on the principle of the coordination geometry around tin in the trimethyltin(IV) cation in aqueous solution which is believed to be trigonal bipyramidal in which the three methyl groups are situated in the equatorial plane. Complex formation would then involve imidazole ring binding in the apical site [19]. Dimethyltin(IV) cation, on the other hand, is able to form octahedral complexes with the two methyl groups being probably colinear and placed vertically [14, 15]. This means that the dimethyltin(IV) cation is more favoured towards complex formation than its trimethyltin(IV) cation homologue, which suffers from steric crowding between the three methyl groups and imidazole derivatives. This behaviour can be supported by the observed appreciably lower stability of the complex formed from the reaction of trimethyltin(IV) cation with imidazole compound compared to that of the complex formed from the reaction of dimethyltin(IV) cation with the same imidazole derivative (*cf.* Tables 1A and 1B). However, the dependence of the formation constant values of the complex species *ML* and *ML*OH as well as the pK^1 values $= log\,\beta_{110} - log\,\beta_{11\text{-}1}$ corresponding to the deprotonation process ($ML \rightleftharpoons ML\text{H}_{-1} + \text{H}$) for the trimethyltin-imidazole solution systems on the nature of the imidazole ligand (*cf.* Table 1B) follows the same sequence observed in the case of the dimethyltin-imidazole complexes.

Experimental

Materials and Reagents

Dimethyltin(IV) dichloride and trimethyltin(IV) chloride were received from Aldrich Chemicals Co. The ligands, imidazole derivatives, were supplied from Fluka Chem. Co. 1,4-Dioxane was provided by Fluka Chem. Co. All ligands were dissolved in equal amounts of nitric acid (one equivalent of ligand to one equivalent of nitric acid). Carbonate-free sodium hydroxide stock solutions were prepared by diluting the contents of *BDH* (*British Drug House*) concentrated volumetric solution vials. These solutions were systematically checked by titration against potassium hydrogen phthalate. All solutions were prepared in deionized water.

Apparatus

pH Titrations were performed on a Metrohm 751 GPD titrino. The titroprocessor was calibrated with standard buffer solutions prepared according to NBS specification [21].

The *pH* meter readings were converted into hydrogen ion concentration by titrating a standard acid solution (0.01 *M*), and the ionic strength was adjusted to 0.1 *M* $NaNO_3$ with standard base (0.1 *M*) at 25°C. The *p*(*H*) was plotted against *p*[*H*] and a relationship *p*(*H*)–*p*[*H*] = 0.05 was observed. The pK_w was calculated as described previously [22].

Procedure and Measuring Techniques

The protonation constants of the ligands were determined by titrating 40 ml of ligand solution (1.25 m*M*). The hydrolysis constants of dimethyltin(IV) and trimethyltin(IV) were determined by titrating 40 ml of 1.25 m*M* dimethyltin(IV) or trimethyltin(IV) solutions. The formation constants of dimethyltin(IV)- or trimethyltin(IV)-imidazole complexes were determined by titrating 40 ml of

solutions containing the ligand (1.25 mM) and dimethyltin(IV) or trimethyltin(IV) (1.25 mM and 6.25×10^{-1} mM). For all systems 25% dioxane-water (V/V) mixtures were used as solvent. The ionic strength was adjusted to 0.1 M by $NaNO_3$. The titrations were carried out at 25°C by circulating thermostat water into the appropriate reaction cell and a slow and constant stream of N_2 passed over the tested solutions.

The formed species in the studied systems were characterized by the general equilibrium processes (1), while the formation constants for these generalized species are given by Eq. (2).

$$pM + qL + rH \rightleftharpoons [M_pL_qH_r] \tag{1}$$

$$\beta_{pqr} = \frac{[M_pL_qH_r]}{[M]^p[L]^q[H]^r} \tag{2}$$

The calculations were performed using the computer program [23] MINIQUAD-75 loaded on a Pentium II-233 computer. The stoichiometries and stability constants of the complexes formed were determined by trying various possible composition models for the system studied. The model selected gave the best statistical fit and was chemically consistent with the titration data without giving any systematic drifts in the magnitudes of various residuals, as described elsewhere [23]. The concentration distribution diagrams were obtained using the program SPECIES [24].

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