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A ^{119}Sn Mössbauer spectroscopic study on complexes of di- and tri-organotin(IV) moieties with 2-mercaptoethanesulfonates, in the solid state and in aqueous solution

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The configuration of the bonding environment of tin in the complexes $[R_2Sn(SCH_2CH_2SO_3)_2]^{2-}$ (R = Me,Ph) and $[Me_3Sn(SCH_2CH_2SO_3)]^-$ has been determined to be tetrahedral both in the solid state and in aqueous solution (for the methyl derivatives). The coordination number of tin increases to five in aqueous solutions for the $Me_2Sn(IV)$ complexes in Hepes buffer (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid; at least in fivefold excess, at pH 7.4) due to coordination by the tertiary amino nitrogen atom. No effect is detected due to the surfactant 2-hydroxypropylcellulose concerning both coordination to tin and influence on the Mössbauer parameters. The stoichiometry of mixed complex formation in aqueous solution of $Me_2Sn(IV)$, 2-mercaptoethanesulfonate and Hepes is 1:2:1, according to a procedure of 'Mössbauer titration'. All complexes in aqueous solution undergo slow lysis of the tin–sulfur bonds. Structural assignments have been generally effected on the basis of the magnitude of experimental values of Mössbauer nuclear quadrupole splittings, measured at 77 K for both solid and frozen aqueous absorbers, and comparison with data calculated by the point-charge model approach.

Keywords: Organotin, 2-mercaptoethanesulfonates, solid state, solution, Mössbauer spectra

INTRODUCTION

In the course of our studies on the antitumor activity of organotin(IV) derivatives,[1–3] we recently investigated compounds with tin–sulfur (Sn–S) bonds, and determined that the 2-mercaptoethanesulfonate complex $[Ph_2Sn(SCH_2CH_2SO_3)_2]^{2-}$ exhibited the largest antileukemia P-388 activity in mice.[1] Structural characteristics of these compounds are the availability of additional coordination sites at the tin atom, as well as the occurrence of strong tin–ligand atom bonds which in turn are possibly subjected to hydrolytic decomposition.[1] The activity of the complex mentioned above was attributed to the $Ph_2Sn(IV)$ moiety, while the role of the coordinated ligand was assumed to be concerned with the process of transportation of the drug across the cell membranes, in agreement with the results of previous investigations.[1] In this context, the work reported in the present paper has been carried out with the aim of contributing to an understanding of the structure–activity correlation.

The configuration of diorganotin(IV) bis(2-mercaptoethanesulfonates), $[R_2Sn(SCH_2CH_2SO_3)_2]^{2-}$ (R = Me, Ph) as sodium and guanidinium salts, in the solid state, as well as in aqueous solutions of the $Me_2Sn(IV)$ derivatives, has been studied. The $Me_3Sn(IV)$ complex has been investigated for comparison. The availability of the fifth coordination site at the tin center in $[Me_2Sn(SCH_2CH_2SO_3)_2]^{2-}$ has been studied in aqueous solution. Preliminary information upon the modes of possible lysis of the tin–sulfur bonds has been inferred from the changes occurring in aqueous solutions stored at room temperature. Mössbauer spectroscopy has been employed throughout the present investigation, in order to correlate the results with those concerning diorganotin–hemoglobin systems, where this technique yields excellent structural answers.[4]

EXPERIMENTAL

The organotin compounds were a gift from Schering A G, Bergkamen, FRG, and sodium 2-mercaptoethanesulfonate, $Na(HSCH_2CH_2SO_3)$, from Degussa Pharma Gruppe, Frankfurt, FRG. Hydroxypropylcellulose and Hepes were from Ega-Chemie, Steinheim, FRG and Hoechst Italia, Milan, Italy, respectively. Other reagents and solvents were products of C. Erba, Milan, Italy.

Table 1 ^{119}Sn Mössbauer parameters at 77.3 K of di- and tri-organotin(IV) 2-mercaptoethanesulfonates in the solid state and in aqueous frozen solutions

No.	Compound	δ[b] (mm s^{-1})	ΔE[c] (mm s^{-1})	Γ_1[d] (mm s^{-1})	Γ_2[d] (mm s^{-1})
(A) Solid state[a]					
1	$Na_2[Me_2Sn(SCH_2CH_2SO_3)_2].2H_2O$	1.36	1.68	0.96	0.97
2	$[C(NH_2)_3]_2$[e]$[Me_2Sn(SCH_2CH_2SO_3)_2]$	1.38	1.66	0.85	0.83
3	$Na_2[Ph_2Sn(SCH_2CH_2SO_3)_2].2H_2O$	1.35	1.44	0.86	0.84
4	$[C(NH_2)_3]_2$[e]$[Ph_2Sn(SCH_2CH_2SO_3)_2]$	1.38	1.67	0.88	0.88
5	$Na[Me_3Sn(SCH_2CH_2SO_3)].H_2O$	1.29	1.40	0.93	0.93
(B) Aqueous solutions, frozen[f]					
6	$[C(NH_2)_3]_2$[e]$[Me_2Sn(SCH_2CH_2SO_3)_2]$[g]	1.37	1.67	0.79	0.78
7	$Na_2[Me_2Sn(SCH_2CH_2SO_3)_2]$[g]	1.39	1.84	0.83	0.71
7′	Stored 72 days at R.T.	1.15	2.14	0.64	1.42
7″	Stored 6 months at R.T.	1.07	2.79	0.69	0.59
8	$Na[Me_3Sn(SCH_2CH_2SO_3)]$[h]	1.30	1.42	0.77	0.78
8′	Stored 18 days at R.T.	1.23	2.66	0.79	0.88
(C) Aqueous solutions in presence of Hepes, frozen[f,i]					
9	$Na_2[Me_2Sn(SCH_2CH_2SO_3)_2]$: Hepes, 1:1	1.36	1.97	0.82	0.74
10	$Na_2[Me_2Sn(SCH_2CH_2SO_3)_2]$: Hepes, 1:5	1.40	2.16	0.64	0.89
11	$Na_2[Me_2Sn(SCH_2CH_2SO_3)_2]$: Hepes, 1:20 (Hepes 0.2 mol dm^{-3})[j]	1.39	2.19	0.81	0.82
11′	Stored 7 months at R.T.	1.07	3.05	0.93	0.95
12	$[C(NH_2)_3]_2[Me_2Sn(SCH_2CH_2SO_3)_2]$ in Hepes (0.2 mol dm^{-3})	1.43	2.16	0.65	0.93
12′	Stored 2–5 months at 4–20 °C	1.16	3.02	1.01	0.98
13	Me_2SnCl_2: $HSCH_2CH_2SO_3Na$ in Hepes (0.2 mol dm^{-3})	1.27	2.63	0.92	1.12
14	Me_2SnCl_2: $3HSCH_2CH_2SO_3Na$ in Hepes (0.2 mol dm^{-3})	1.36	2.16	0.91	0.83
15	Me_2SnCl_2: $4HSCH_2CH_2SO_3Na$ in Hepes (0.2 mol dm^{-3})	1.36	2.22	0.87	0.94

[a] Absorber thickness was 0.46–0.52 mg ^{119}Sn cm^{-1}. [b] Isomer shift with respect to $Ca^{119}SnO_3$ at room temperature. [c] Nuclear quadrupole splitting (± 0.02 mm s^{-1})[4]. [d] Full width at half height of the resonant peaks. [e] Guanidinium, $C(NH_2)_3^+$. [f] Data for undashed system numbers refer to samples of solutions in redistilled water immediately frozen after preparation by immersion in liquid nitrogen; data with dashed code numbers concern solutions which were stored at room temperature for the given time, under normal laboratory conditions, before freezing and submitting a suitable sample for Mössbauer spectroscopy. [g] Concentrations were 10–30 mmol dm^{-3}, pH 6.6–7.4; some samples contained 0.3% (w/v) of 2-hydroxypropylcellulose. [h] Concentrations were 10–35 mmol dm^{-3}, pH 7.4; some samples contained 0.3% (w/v) of 2-hydroxypropylcellulose. [i] Hepes = *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid. In systems 9–15 the concentration of the organometal moiety was constantly 10 mmol dm^{-3}, pH 7.40–7.47. For 9–11, solutions of Me_2SnCl_2 (10 mmol dm^{-3}) + $HSCH_2CH_2SO_3Na$ (20 mmol dm^{-3}) + Hepes were also used in the correct proportion, eventually adjusting the pH to 7.40. [j] Some samples were added with 0.3% (w/v) of 2-hydroxypropylcellulose.

The synthesis of the solid complexes listed in Table 1 was effected by literature procedures.[1,5]

The Mössbauer spectra were measured at 77.3 K with the usual apparatus and data reduction techniques.[4] The sources (e.g. $Ca^{119}SnO_3$, 1–10 mCi, Radiochemical Centre, Amersham, UK) were moving at room temperature with linear velocity, constant acceleration, in a triangular waveform. The absorber samples from aqueous solutions consisted of about 2 cm^3 of solution in a polythene holder, quickly prefrozen by immersion in liquid nitrogen before insertion into the cryostat.[4] The related Mössbauer parameters were reproducible and considered to reflect reasonably the structural characteristics of the organotin compounds in the solutions at room temperature.[4] The results obtained are reported in Table 1.

The point-charge model calculations of Mössbauer nuclear quadrupole splitting, reported in Fig. 1 and related to possible structural arrangements of our organotin compounds in the solid state and in solution, have been effected by the principles and procedures described in a previous paper[4] according to relevant literature,[4,7] and employed tabulated values of partial nuclear quadrupole splitting parameters[4,6,8–10] (the value for $\{NR_3\}$ in Fig. 1 being that of piperidine[10]). A computer program supplied by T.C. Gibb (Leeds, UK) was employed for the calculations.

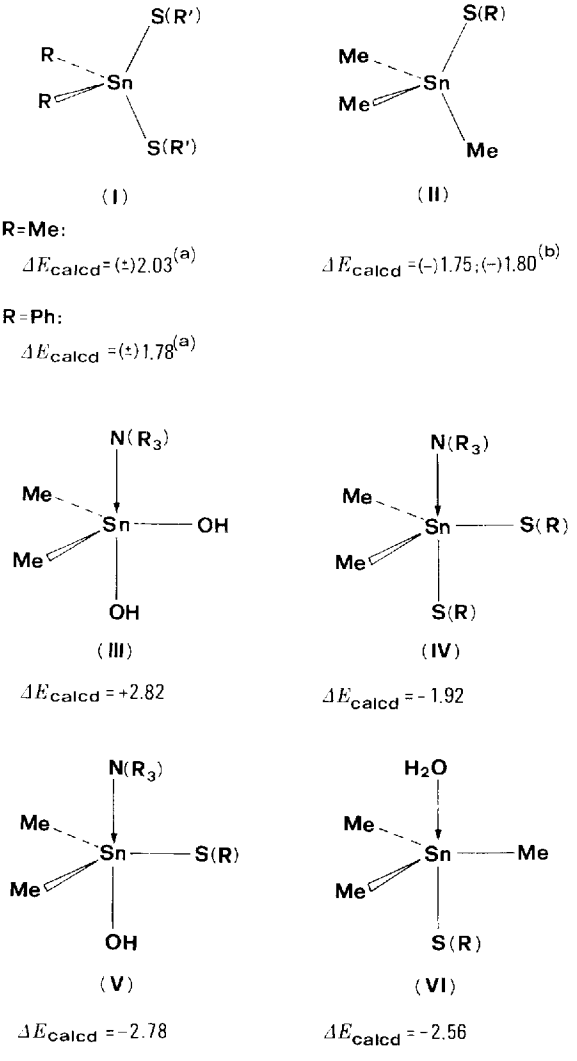

Figure 1 Possible regular structures (idealized) for the complexes discussed in the text, and related point-charge model estimates of Mössbauer nuclear quadrupple splittings ΔE (see text).
(a)Sign undetermined, the asymmetry parameter $\eta = (\gamma_{xx} - \gamma_{yy})/(V_{zz}$ being unity. (b) Experimental value, used as estimator of the partial nuclear quadrupole splitting ([S thiol]—[hal]), tetrahedral.[9]

DISCUSSION

The magnitudes of the Mössbauer parameter isomer shift, δ, listed in Table 1 for systems 1–15, are consistent with established values of $Me_2Sn(IV)$, $Ph_2Sn(IV)$ and $Me_3Sn(IV)$ derivatives.[6,7,9] In solution phases, δ-values constantly decrease as a function of the time of storage at room temperature (systems 7′, 7″, 8′, 11′, 12′; Table 1), which suggests that the respective steady diminution of the *s*-electron density at the tin nuclei originates from the replacement of sulfur by more electronegative atoms or groups.

The narrowness of the linewidths, Γ, Table 1, is indicative of the general occurrence of single tin sites in each system; if desulfuration reactions take place (*vide infra*), Γ-values are consistent with the presence of at least two distinct metal sites (see for example system 7′).

Turning to the possible determination of the configuration of the environment of tin in the species investigated here, the experimental parameters ΔE of systems 1 to 8, Table 1, undoubtedly indicate the occurrence of tetrahedral configurations of types **I** and **II** (Fig. 1), in both solid state and aqueous solution, according to fingerprint criteria[9,11] as well as to the agreement of experimental and calculated ΔE data (Table 1 and Fig. 1; differences lie within the maximum accepted range[8] of ± 0.4 mm s^{-1}). Coordina-

tion to tin by sulfonate oxygen atoms is ruled out, since it would imply $\Delta E_{exp} = 4.17-5.54$ mm s^{-1} for di- and tri-organotin(IV) derivatives in the solid state;[12,13] moreover sulfate oxygen does not bind to organotins in aqueous solution.[4] As far as systems in aqueous solution are concerned, it may be recalled that $Me_2Sn(OH)_2$ has been assumed as a tetrahedral species,[14] in excellent agreement with Mössbauer spectroscopic data.[4] The reluctance of tin in $Me_2Sn(OH)_2$ solution to accept coordination by solvent H_2O may be ascribed to the effect of the large electron density donated to the metal by hydroxyls,[15] and an analogous reason could be invoked for our compounds in aqueous solution, systems 6 and 7 of Table 1. Moreover, Alk_3SnOH (Alk = Me, Et) in aqueous solution at pH = 7.40 appears to be a severely distorted trigonal bipyramidal species with an axial water molecule quite loosely bound;[16] the strictly tetrahedral tin environment in the aqueous solution of the $Me_3Sn(IV)$ complex No 8, Table 1, could then be rationalized in terms of the larger electron donation to tin by thiol sulfur with respect to hydroxyl oxygen.

The lack of oxygen coordination to tin in our $Me_2Sn(IV)$ and $Me_3Sn(IV)$ compounds is also shown by the Mössbauer parameters of the aqueous systems containing 2-hydroxypropylcellulose, systems 6, 7 and 8, Table 1 (and related footnotes), where no influence due to the surfactant is detected. The latter has been considered in the present context since it is employed in antitumor testing as a dispersive agent ('Klucel', with 0.9% NaCl, w/v) for the injection of drugs in suspension;[1,2] its eventual interaction with the compounds studied here has been taken into account in view of the facile reactivity of carbohydrates with organotins, such as that detected for ribose moieties in $Me_2Sn(IV)$–nucleoside systems.[17]

The data for systems 6–8 reveal also a physical implication, in the sense that formation of gel, rather than crystalline solid (ice), takes place upon rapidly freezing (to liquid nitrogen temperature) the solutions containing the surfactant. This further demonstrates the reliability of Mössbauer data measured for crystalline absorbers, in the hypothesis for the formation of glassy zones in the neighborhood of the metal centres.[18]

The formation of complexes between $[Me_2Sn(SCH_2CH_2SO_3)_2]^{2-}$ and Hepes buffer, through coordination to the tin center by the tertiary amino nitrogen of the buffer (which may mimic the bonding assumed to occur in organotin–protein systems, involving thiol sulfur and imidazole nitrogen[19,20]) is evidenced by the ΔE values for the aqueous systems with mole ratios 1:5 and 1:20, systems 10, 11 and 12 of Table 1. These results are perfectly equivalent to those concerning the complexation of $Me_2Sn(OH)_2$ by Hepes, where the formation of the trigonal bipyramidal species **III** (Fig. 1) has been assumed.[4] The analogous complex **IV** (Fig. 1) is advanced here in line with the agreement between the related ΔE_{exp} and ΔE_{calcd} data. It is worth noting that these mixed complexes involve large stability constants for the bonding of thiol sulfur to tin, and consistently lesser tendencies for complexation by a nitrogen donor, which is in line with findings concerning analogous $Me_3Sn(IV)$ complex systems.[21]

In the context of a previous study on the interaction of $Me_2Sn(IV)$ compounds with hemoglobin, we investigated the stoichiometry of the reaction of $Me_2Sn(IV)$ with cysteine in model aqueous systems containing organotin–Hepes complexes.[4] A 'Mössbauer titration' procedure [ΔE versus the molar ratio cysteine:$Me_2Sn(IV)$ in Hepes] established that not more than two molecules of cysteine bind to a $Me_2Sn(IV)$ moiety yielding the saturated complex $Me_2Sn(SR)_2$. (Hepes[4], **IV** of Fig. 1 of the present paper). A perfectly analogous result has been obtained in the present work for the bonding of 2-mercaptoethanesulfonate to $Me_2Sn(IV)$ acceptors: in fact the ΔE values of the solutions 11–15 of Table 1, which refer to systems with composition 2-mercaptoethanesulfonate:$Me_2Sn(IV)$ ranging from 1:1 to 4:1, reproduce exactly the 'titration' graph for cysteine referred to above, involving sequentially the species **III**, **V** and **IV** (Fig. 1). The formation of the saturated complex $Me_2Sn(SR)_2$, Hepes, **IV**, is clearly shown by the constancy of the ΔE values for the solutions 11–12, 14 and 15 (Table 1). An analogous behavior has been found in the aqueous systems $Alk_3Sn(IV)$–cysteine–Hepes (Alk = Me, Et) where 1:1:1 complexes are ultimately formed, as indicated by 'Mössbauer titrations'.[16] It is accordingly concluded that the reaction of thiol sulfur with organotin(IV) moieties in aqueous solution at pH 7.40 very probably proceeds generally through acid–base reactions between R–SH and $R_nSn(OH)_{4-n}$ (n = 2,3), there being no possibility of further sulfur–tin bonding. These assumptions seem to be essential for the correct interpretation of the interaction of organotins with proteins,[19,20] also being in accordance with the results of a recent potentiometric study on $Me_3Sn(IV)$–thiol ligand complexes.[21]

The last part of the present paper concerns the study

of the possible lysis of tin–sulfur bonds in aqueous solution of these compounds at physiological pH, which has been undertaken to obtain evidence for the reliability of the hypothesis that the antileukemia P-388 activity of these compounds in mice can be attributed to diorganotin(IV) moieties which are produced by the dissociation of ligands and which are then released into cells.[1] Lysis indeed may occur, based on data for long-term storage conditions of the compounds studied here in aqueous systems. In fact, the Mössbauer nuclear quadrupole splitting parameters of $Me_2Sn(IV)$ and $Me_3Sn(IV)$ complexes exhibit large increases (systems 7′, 7″, 8′, 11′, 12′, Table 1) with respect to data for the tetrahedral configurations **I** and **II** (Fig. 1) (inherent in the initial conditions). Formation of disulfide groups by free ligand oxidation (for example of 2,2-dimercaptodiethanesulfonate[22], in agreement with *in vivo* findings on the nature of coenzyme-M[23]) may take place, with consequent steady dissociation of the related $Me_2Sn(IV)$ complexes. Speculating on the nature of the products of the lysis process, the sulfur-free complex **III**, formed from **IV** via the partially hydrolyzed species **V** (Fig. 1), could be the species present in the samples 11′, 12′ (Table 1), considering the agreement between ΔE_{exp} and ΔE_{calcd} values. The role of the water solvent could consist of a gradual aquation process such as that sketched for **VI** (Fig. 1[16]), where ΔE_{calcd} particularly agrees with ΔE_{exp} system B′ (Table 1).

In conclusion, the present investigation suggests the following.

(1) $[R_2Sn(SCH_2CH_2SO_3)_2]^{2-}$ (R = Me, Ph) and $[Me_2Sn(SCH_2CH_2SO_3)]^-$ exhibit tetrahedral tin sites C_2SnS_2 and C_3SnS in both the solid state and aqueous solutions (the latter concerning the methyl derivatives).
(2) Further coordination to the tin center in C_2SnS_2 groups may take place.
(3) Lysis of tin–sulfur bonds may occur (very slowly) in aqueous solution.

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