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A study of dimethyltin(IV)-L-cysteinate in aqueous solution

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The *in vivo* activity of some R_2Sn-L-cysteinate complexes (R = Me, Et, n-Bu) against murine P-388 leukaemia has been tested. Only the Et_2Sn(IV) complex showed a marginal positive effect. Trigonal bipyramidal tin environments with two carbon (R) atoms and the sulfur atom in the equatorial plane and oxygen (carboxylate) and nitrogen (NH_2) in apical positions have been proposed for the solid compexes (R = Me, Et, n-Bu, Ph) on the basis of experimental Mössbauer parameters and infrared (IR) data. Aqueous solutions of the Me_2Sn-L-cysteinate have been studied by IR, ^1H NMR and ^{119}Sn Mössbauer spectroscopy (in frozen solution) at different pH values to identify the Me_2Sn(IV) species present. At pH > 2 the dimethyltin aquocation is complexed by the ionized sulfhydryl group of L-cysteine to form a five-coordinated species. With increasing pH values, NH_3^+ is deprotonated and a chelate is proposed with both the sulfhydryl and the amino group bonded to tin, one water molecule or (at still higher pH values) one hydroxyl ion occupying the fifth coordination site of a trigonal bipyramid around tin. Finally at pH > 10 the NH_2 group is substituted by a hydroxyl ion.

Keywords: organotin, cysteinate, murine P-388 leukaemia, infrared spectra, NMR spectra, Mössbauer spectra, structures

INTRODUCTION

A large quantity of data on the toxicological properties of organotin compounds has accumulated with the increasing application and importance of such compounds,[1a] and further data have been obtained in recent years by studies on the possible antitumor activity of some types of organotin compounds.[1b] Nevertheless, detailed knowledge on the mode of action of organotin species in living organisms is still very scarce, although some remarkable contributions to the understanding of their action have been made by investigating biological systems and model compounds.[1c] A simple relationship between the solid-state structure of an organotin compound and its biological activity cannot be expected, since the composition as well as the structure of the solid compound may drastically change on dissolution and transfer to a biological system.[2] It therefore seemed worthwhile to study the behavior of appropriate organotin compounds in solution, the structure of dissolved species and the existence of equilibria. In a previous paper we reported on studies of solutions of R_2Sn-glycylglycinates (R = alkyl), following the observation that the di-n-butyltin(IV) derivative is active against lymphocytic leukaemia P-388 in mice.[3]

Continuing these investigations, we report in this paper on the results of antitumor tests for members of the series R_2Sn(IV)-L-cysteinate (R = Me, Et, n-Bu, Ph) and also on their experimental Mössbauer parameters. In addition, we have studied the pH dependence of the conductance, infrared, ^{119}Sn Mössbauer and ^1H NMR spectra of aqueous solutions of dimethyltin(IV)-L-cysteinate, the only member of this series which is sufficiently soluble in aqueous media to be suitable for such studies.

EXPERIMENTAL

L-cysteine (L-$HSCH_2CH(NH_2)COOH$) was used as received (from Fluka). The complexes R_2Sn-L-Cy (Cy^{2-} = cysteinate) have been prepared according to

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published procedures.[4] The antitumor tests were carried out at the Institut Mario Megri, Milano, Italy (compound **1**) and at the Institut J. Bordet, Bruxelles, Belgium (compounds **2**–**4**) following the NCI protocols.[5] The conductivity determinations in water were effected by use of LKB conductolyzer 5300B, the cell constant being 4.9 cm^{-1}. The measurements of pH values were performed using a Crison MicropH 2002 equipped with a combined Ingold electrode. The Mössbauer spectra were obtained as previously described[6] using a Laben Master 4000 instrument. All isomer shifts are reported with respect to a $CaSnO_3$ spectrum at room temperature, the solid samples containing about 0.5 mg ^{119}Sn cm^{-2}. The solution samples, in Teflon holders (1.5 cm^3 exposed to the γ-ray beam), were quickly frozen in liquid nitrogen before mounting in the liquid nitrogen cryostat for the γ-resonance measurements; this method of freezing the absorbers possibly yields glassy environments at the tin centres.[7] The ^1H NMR spectra were recorded on a Bruker spectrometer WP80 at 80 MHz at a probe temperature of 31 ± 1 °C. Chemical shifts were measured relative to the methyl resonance of sodium 2,2-dimethyl-2-silapentane-5-sulfonic acid (DSS). Infrared spectra were recorded on a Perkin–Elmer 983G instrument using Nujol mulls between cesium iodide discs for the solids, and 0.05 mm cells with calcium fluoride windows for D_2O solutions. The behavior of Me_2Sn-L-Cy was investigated using solutions of known concentrations, about 10^{-2} mol dm^{-3} in D_2O, containing the appropriate amounts of DCl or NaOD, respectively, to produce the required pH value. About 30 samples of the same concentration, but of different pH, were measured.

RESULTS AND DISCUSSION

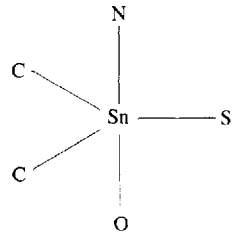
The screening results for the R_2Sn-L-Cy complexes compared with Ph_2Sn-L-Cy (Table 1) reveal that the *in vivo* activity against P-388 lymphocytic leukaemia in mice of Ph_2Sn-L-Cy[8] is remarkable, considering its relatively low toxicity. Activity is not significant for the Me, Et or n-Bu derivatives, the latter being particularly toxic even at low doses.

From infrared data it is concluded that these four compounds possess the same structure in the solid state.

Table 1 Effect of R_2Sn(IV)-L-cysteinate complexes against P-388 leukaemia intraperitoneally implanted in mice[a]

Compound and vehicle[b]		Doses (mg kg per injection)	*T/C*[c] (%)	Ref.
1	Me_2Sn-L-Cy	50	Toxic	This work
	in saline (sol.)	25	110	
		12.5	110	
2	Et_2Sn-L-Cy	60	Toxic	This work
	in Klucel (susp.)	15	125	
		7.5	120	
		3.75	110	
3	n-Bu_2Sn-L-Cy	0.93	Toxic	This work
	in Klucel (susp.)	0.46	103	
		0.23	108	
		0.16	107	
4	Ph_2Sn-L-Cy	100	Toxic	8
	in saline (susp.)	50	181	
		25	156	
		12.5	142	
		6.25	132	

[a] Lymphocytic leukaemia (*ca* 10^6 cells) was implanted i.p. on day 0 in CD_2F_1 mice, and the doses of drugs were administered i.p. on days 1–5. [b] Klucel is a solution of 2-hydroxypropylcellulose (0.3 g) and NaCl (0.9 g) in H_2O (100 cm^3). Saline is NaCl in H_2O (0.9 g in 100 cm^3). [c] *T/C* (%) is the median survival time of test mice divided by that of control mice. A reproducible $T/C > 125$ % is required to demonstrate activity.



In fact the disappearance of ν(SH) at 2550 cm^{-1}, observed in the free ligand, and the presence of bands in the range 315–355 cm^{-1} indicate that the ligand coordinates as the sulphido species. The shifting of $\nu(NH_2)$ to lower frequencies is indicative of tin–nitrogen (Sn–N) coordination[9] and from the position of the antisymmetric and symmetric carboxylate stretching frequencies at 1655–1640 cm^{-1} and at 1385–1395 cm^{-1}, respectively, a unidentate coordination of the carboxylic group[10] is inferred. Finally, bands at 565 cm^{-1} and at 530 cm^{-1}, attributable to antisymmetric and symmetric tin–carbon (Sn–C) stretching frequencies in the dimethyltin derivative, exclude the linearity of the SnC_2 skeleton.[11]

A fingerprint analysis of the Mössbauer data (Table 2) shows that they are typical for compounds containing five-coordinate dialkyltin(IV).[12] Moreover, for the dimethyl derivative, the data are fully consistent with those detected for dimethyltin(IV)-DL-penicillaminate for which, from its lattice dynamics, we proposed a monodimensional polymeric structure.[13] Considering the analogous behavior of Me_2Sn-L-Cy and of the other compounds of the homologous series investigated here, we suggest that in these compounds cysteinate is acting as a tridentate ligand linked to the R_2Sn unit to form a distorted trigonal bipyramid, the two alkyl or phenyl (R) groups and the mercapto group being

Table 2 Experimental Mössbauer parameters of R_2Sn(IV)-L-cysteinates

Compound	δ^a (mm s^{-1})	ΔE^b (mm s^{-1})	$\Gamma_{av}{}^c$ (mm s^{-1})
Me_2Sn-L-Cy	1.25	2.75	0.93
Et_2Sn-L-Cy	1.37	2.85	0.90
n-Bu_2Sn-L-Cy	1.33	2.73	0.92
Ph_2Sn-L-Cy	1.26	2.75	0.88

[a]Isomer shift with respect to room temperature $Ca^{119}SnO_3$. [b]Nuclear quadrupole splitting. [c]Full width at half height of the resonant peaks, average.

ranged equatorially, while oxygen (unidentate carboxylate) and amine (NH_2) occupy the apical positions. The proposed structure corresponds to that of Me_2Pb-L-Cy.H_2O determined by an X-ray study.[14]

In solutions of Me_2Sn-L-Cy in water, monomolecular species are present. This follows from the experimental molecular weight data and from the very low molar conductivity of the aqueous solution compared with that of Me_2SnCl_2 in water (Table 3), where dissociation into ions is known to occur.[15] Moreover, the time independence of the conductivities at different pH values supports the hypothesis that the species are relatively stable in solution.

The spectra of the carboxylate absorption in D_2O solutions at different pH values (Table 4) allow a number of interesting conclusions. When the pH value is increased, the absorption at 1728 cm^{-1}, characteristic of an uncoordinated carbonyl group, shifts to the range expected for uncoordinated carboxylate ($-CO_2^-$), intermediate between the values characterizing the zwitterionic and anionic forms of the free acid (Table 4).

According to Shindo and Brown[16] an increase of the carboxylate frequency of cysteinate results from

Table 3 Molar conductivity, Λ_M, pH values and molecular weight of Me_2Sn-L-cysteinate in H_2O solution[a]

Compound	Molar concn. $\times 10^3$	Λ_M (Ω^{-1} cm^2 mol^{-1})	pH	Mol.weight:[d] found(calcd)
$Me_2S^bCl_2$	3.8	338.4		
H_2Cy	10.0		5.8	
Me_2Sn-L-Cy	5.0	4.62[b]	6.1[b]	244 (267.9)
	5.0	4.08[c]	6.1[c]	
	10.0	5.20[b]	5.9[b]	
	10.0	5.57[c]	5.9[c]	

[a]Solutions of Me_2SnCl_2 and H_2Cy (L-cysteine) in H_2O have been studied for reasons of comparison. The temperature was kept between 25 and 26 °C. [b]Data for a freshly prepared solution. [c]Data after 30 days from solubilization. [d]Determined osmometrically in H_2O at 37 °C.

Table 4 Infrared data (cm^{-1})[a] of Me_2Sn-L-cysteinate and L-cysteine in D_2O at different pH values

Compound	pH	νCOOH	$\nu_{as}COO^-$	$\nu_{sym}COO^-$
Me_2Sn-L-Cy	0.90	1728 s		
	1.65	1728 m	1623 m	1395 w
	2.24	1730 w	1624 m	1400 m
	4.60		1606 s	1397 m
	5.45		1605 s	1397 m
	6.10		1605 s	1400 m
	7.90		1595 s	1400 m
	10.20		1593 s	1400 m
	11.62		1591 s	1400 m
	12.50		1591 s	1400 m
L-cysteine	1.00	1729 s		
	6.00		1620 s	1400 m
	13.00		1569 s	1412 m

[a]Abbreviations: m=medium; s=strong; w=weak.

the appearance of a positive charge at the amino nitrogen. Thus if it is assumed that the dimethyltin(IV) moiety can bind to the sulfhydryl group of L-cysteine at low pH (about 3), analogous to trimethyllead, $Me_3Pb(IV)$,[17] then one can attribute the shift of $\nu_{as}(CO_2)$ of the complex to intra- or inter-molecular interactions involving the amino group.

In order to clarify this aspect, we monitored the ^1H NMR chemical shift of the protons of the methyl groups at tin, and of the protons of the —CH group in Cy^{2-}, as a function of pH for solutions of Me_2Sn-L-Cy in D_2O to get more information on the species present in solution. In Figs 1 and 2, ^1H NMR spectra are reported for a 10^{-2} mol dm^{-3} solution of Me_2Sn-L-Cy in D_2O, in the pH range 0.90–13.40, while in Fig. 3 the pH dependences of the shifts of the methyl ($\delta CH_3/pH$) and —CH protons ($\delta CH/pH(1-3)$)

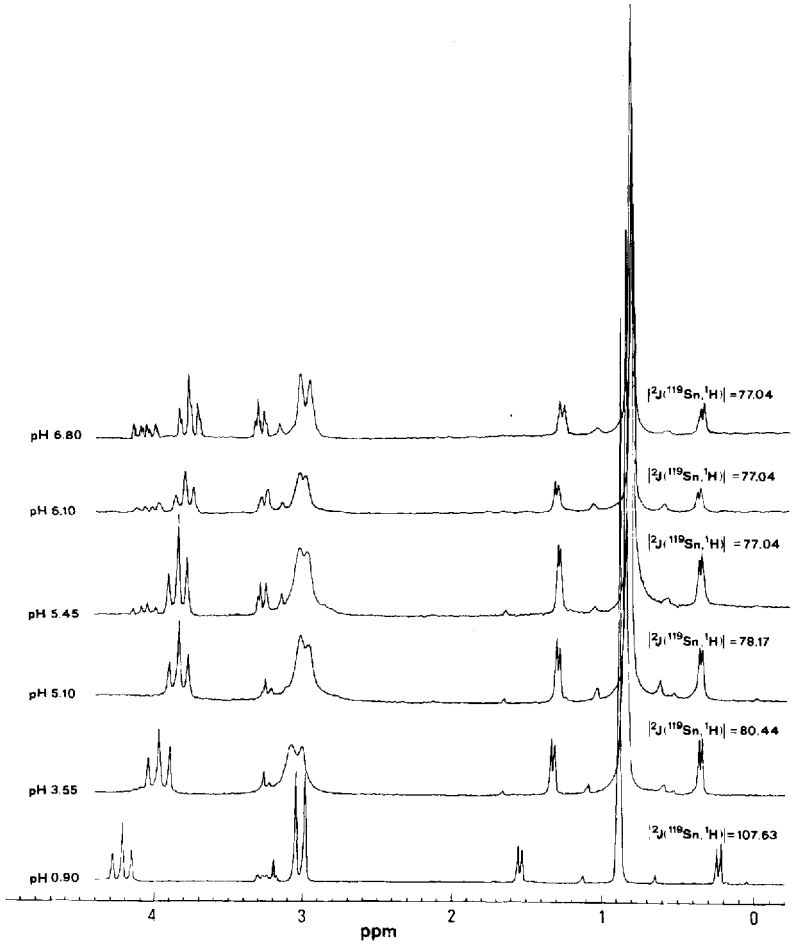


Figure 1 ^1H NMR spectra of solutions containing 10^{-2} mol dm^{-3} of Me_2Sn-L-cysteinate in the pH range 1–7. Values of pH are uncorrected for D_2O.

for the same solution and for a L-cysteine solution (δCH/pH) are shown.

L-Cysteine has, in acid solution, the structure HS—CH_2—CH(COOH)NH_3^+. The plot of the —CH shift against pH (Fig. 3) shows three steps, corresponding to the three dissociation constants. The first ionization is attributed to the carboxylic group.[18]

A qualitative comparison of δCH/pH(1) and δCH/pH in the pH range 1.0–2.0 (Fig. 3) suggests the presence of the same species in the equilibria in both solutions, i.e. the protonated amino-acid. In addition, the value of the angle C—Sn—C of 177.8° determined from the coupling constant $^2J(^{119}Sn-^1H)$[19] indicates a linear C—Sn—C skeleton. Therefore, the aquodimethyltin(IV)

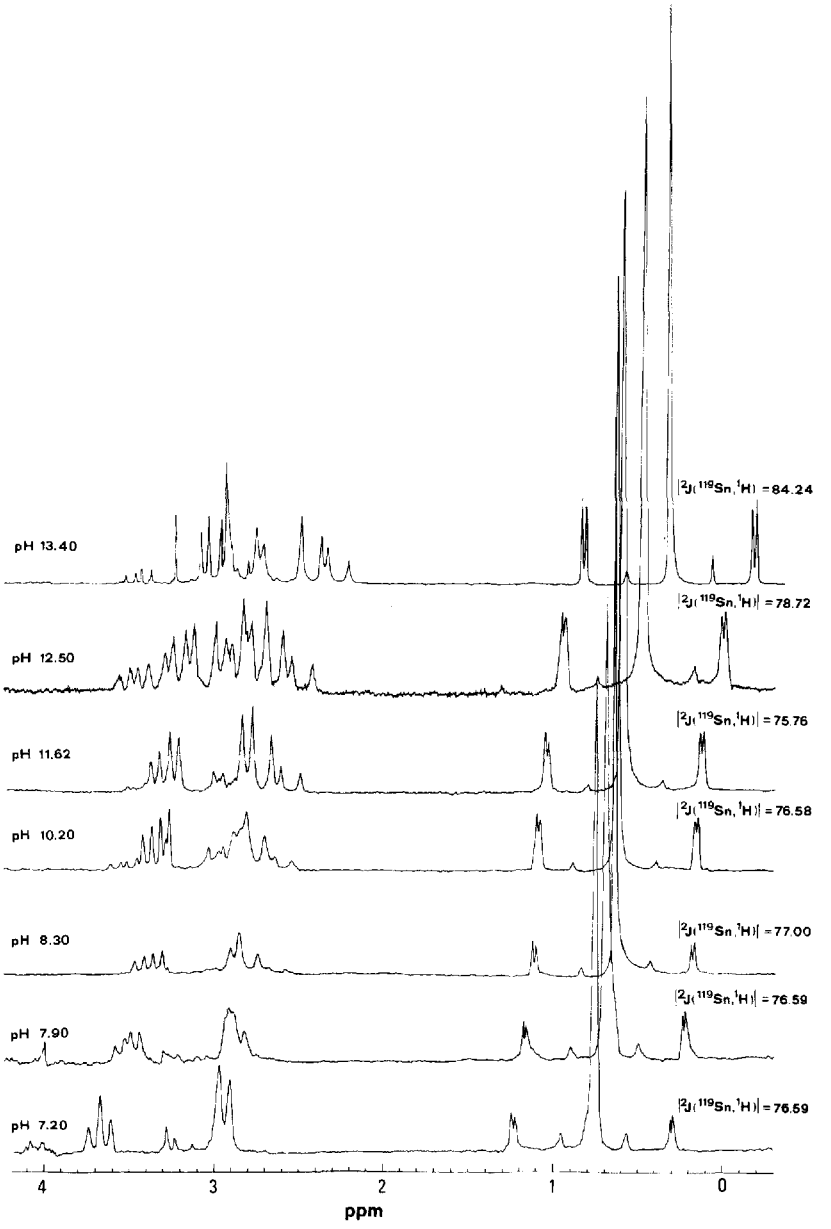


Figure 2 ^1H NMR spectra of solutions containing 10^{-2} mol dm^{-3} of Me_2Sn-L-cysteinate in the pH range 7–13. Values of pH are uncorrected for D_2O.

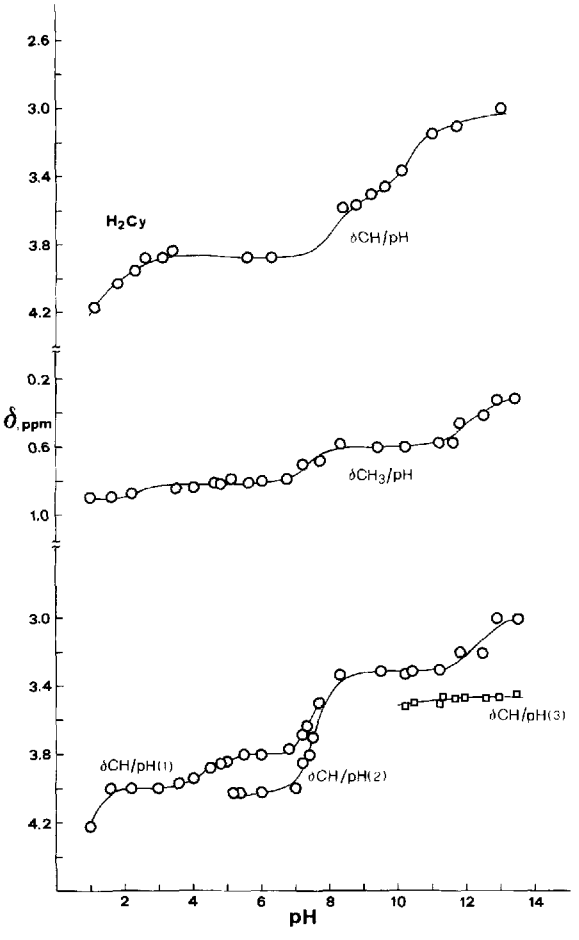
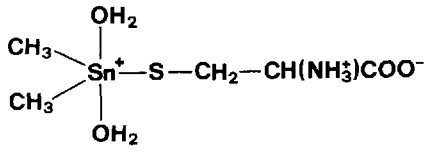


Figure 3 pH dependence of the chemical shifts of the —CH [δCH/pH(1–3)] and —CH_3 (δCH_3/pH) protons of solutions containing 10^{-2} mol dm^{-3} of Me_2Sn-L-cysteinate, and of the —CH proton (δCH/pH) of solutions containing 10^{-2} mol dm^{-3} of L-cysteine (H_2Cy). Values of pH are uncorrected for D_2O.

ion[20] is probably present in the solution of Me_2Sn-L-Cy. According to the plateau in the line δCH_3/pH no variation of the Me_2Sn moiety occurs in the same pH range.

On the basis of these considerations one can infer that the tin-sulfur bond is broken when the pH value is lowered to about 2. In the pH range from 2.0 to 3.5, δCH/pH(1) shows a plateau; however, δCH_3/pH changes slightly and the coupling constant $2J(^{119}Sn-^{1}H)$ decreases to values consistent with a C—Sn—C angle of 131.4°. These observations suggest that bonding of the diorganotin(IV) moiety to the mercapto group and the formation of species **I** occurs.



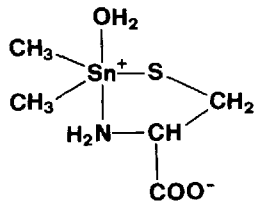
(I)

Up to a pH value of about 6.0, δCH_3/pH does not change and $2J(^{119}Sn-^{1}H)$ (indicating a C—Sn—C angle of 127.3°) remains nearly constant. It therefore can be assumed that the environment of the tin atom is practically unchanged. However, it is important to note in the spectrum recorded at pH 5.45 a double doublet centered at 4.05 ppm. Considering that in this pH range the deprotonation of the ammonium group in the amino-acid residue has to be expected, and attributing this new signal to the —CH proton forming a system of the type ABX with the —CH_2 group, we can propose the existence of a species **II**, arising from the displacement of a water molecule by the amino group. Considering also the possibility of a polymeric nature for this species it should be remembered that, from NMR spectroscopic studies of diorganochlorotin(IV) cysteamine complexes,[21] it appears that in contrast to their polymeric solid-state structures[22] they are monomeric in solution, the aminothiolate ligand chelating the $(CH_3)_2SnCl$ moiety. Similar chelation is observed in the $(CH_3)_2SnCl$ complex of ethyl-L-cysteinate.[23]

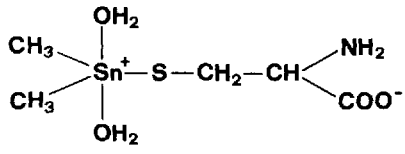
Inspecting Fig. 3 at still higher pH values, the three lines δCH_3/pH, δCH/pH(1) and δCH/pH(2) have to be taken into account. Apparently the concentration of the species giving rise to the line δCH/pH(2) is negligible up to pH values of about 5, i.e. as long as the species giving rise to the line δCH/pH(1) are prevailing.

In these new species the rotation around the C—C bond apparently is not hindered as the —CH and —CH_2 protons of the cysteinato complex display a simple AX_2 pattern. Therefore, and considering the conductivity and infrared data (*vide supra*), we attribute the plateaus of δCH/pH(1) and δCH/pH(2) in the range 5.0–6.5 to species **II** and **III** being in equilibrium.

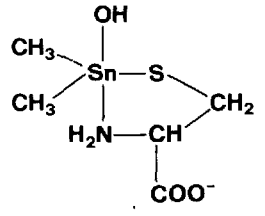
At pH > 6.5 the slopes of the lines δCH/pH(2) and δCH/pH(1) indicate the development of a new equilibrium related, probably, to the loss of a proton from a water molecule coordinated to the tin atom.



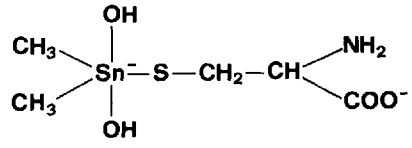
(II)



(III)



(IV)



(V)

At about pH 8, the lines δCH/pH(1) and δCH/pH(2) coincide due to the disappearance of species which are free to rotate. The sequence of experimental points is similar to that of the line δCH_3/pH. The plateau present in the pH range 8.5–11.5 is, then, attributable to a species **IV**.

At a pH value of about 10, the ^1H NMR spectrum is characterized by the presence at 3.50 ppm of a new double doublet at low intensity (δCH/pH(3), Fig. 3). We suppose that this originates from a new species, in which the amino group at tin is replaced by hydroxyl, in accordance with Domazetis *et al.*,[24] resulting in a species **V**.

At pH > 11.5, according to line δCH_3/pH, a considerable change occurs in the tin environment. A similar trend is observed in the line δCH/pH(2). From the data available it is difficult to make a reasonable proposal for the structure of the species present in the solution. The C—Sn—C bond angle is 136.4° as calculated from $^2J(^{119}Sn-^1H)$ = 84.24 Hz. A species could be envisaged which is a result of tin–sulfur bond breakage and in which the tin environment is distorted.

In order to obtain additional information on the tin environment in the Me_2Sn-L-cysteinate solution, a Mössbauer investigation of frozen solutions containing 10^{-1} mol dm^{-3} of Me_2SnCl_2 and 10^{-2} mol dm^{-3} of L-cysteine has been carried out at different pH values.

In Fig. 4 we report the details of nuclear quadrupole splitting parameter ΔE versus pH. From a qualitative analysis of this line, it is possible to infer that: (i) at pH < 2.0, the Mössbauer parameter value (ΔE = 4.10 mm s^{-1}) agrees with literature data assigned to the hydrated dimethyltin ion $[Me_2Sn(H_2O)_n]^{2+}$;[3,25] (ii) according to the slope variation with increasing pH, complexation occurs, being complete at pH values greater than 3.0; (iii) from pH = 3.0 onwards, the ΔE values agree with the presence of species containing five-coordinated tin in the solutions.

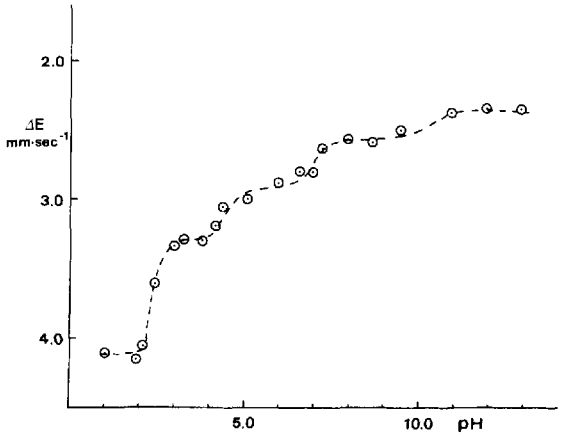


Figure 4 pH dependence of the Mössbauer parameter nuclear quadrupole splitting, ΔE, for aqueous solutions containing 10^{-2} mol dm^{-3} of Me_2SnCl_2 and 10^{-2} mol dm^{-3} of L-cysteine.

The sections of the curve could, in principle, be related to structural modifications of the tin environment but, except for the transition which occurs between pH 2 and 4, this is difficult to rationalize. In addition it has to be emphasized that for all solutions with pH values varying between 4.5 and 13, the resonant peaks are narrow (the average value of the full width at half-height, Γ_{av}, is about 0.84 mm s^{-1}) preventing us from obtaining a deconvolution of the Mössbauer signal into contributions eventually due to the presence of more than one species. On the other hand, a constant value of Γ_{av} might also be a consequence of the fact that, due to the low concentration of our solution, the changes in the tin environment are not sufficiently pronounced to be detected.

However, in the vicinity of pH=6 the slope of ΔE versus pH seems to flatten out. We made an attempt to rationalize, by means of a point charge formalism, the ΔE data for species in the pH ranges where the line flattens out, and in the pH range > 10. The results are shown in Fig. 5.

It appears that a good agreement between experimental and calculated parameters exists. In fact ΔE_{exp} differs from ΔE_{calcd} by less than the limiting value of 0.4 mm s^{-1}.[26]

Then, the actual configuration of the environment of tin would be of the type proposed, and the probability of structures advanced on the basis of ^{1}H NMR studies of solutions of Me_2Sn-L-cysteinate (*vide supra*) gains weight.

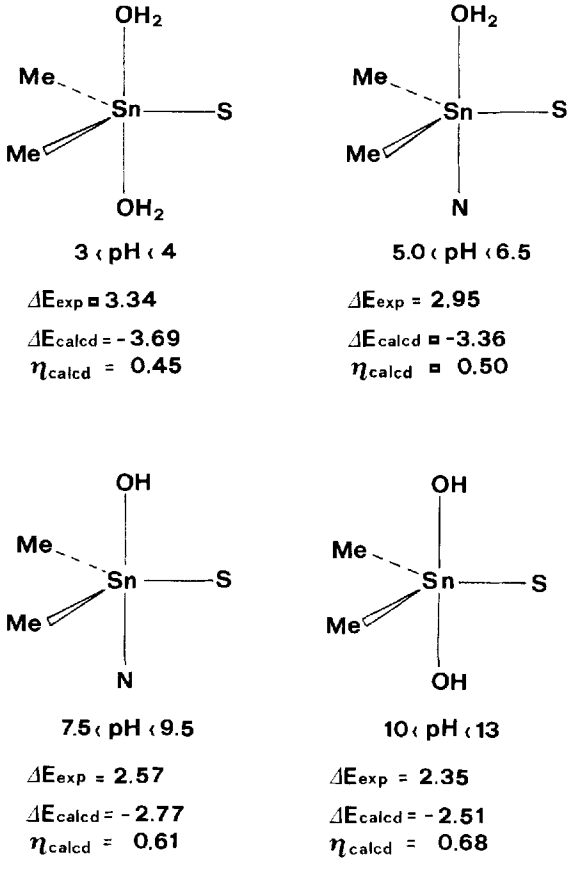


Figure 5 Mössbauer parameters (mm s^{-1}), experimental[a] (77 K) and calculated by point-charge model formalism,[b] for tin environments in solutions containing 10^{-2} mol dm^{-3} of Me_2SnCl_2 and 10^{-2} mol dm^{-3} of L-cysteine.

[a]Standard error ±0.02 mm s^{-1}. The ΔE_{exp} values are the average of the values relative to the pH range. [b]Regular trigonal bipyramidal structures are considered in the different pH ranges. The partial quadrupole splitting values, p q s (mm s^{-1}) employed in the calculations are: $[Alk]^{tbe} = -1.13$; $[S]^{tbe} = -0.60$; $[H_2O]^{tba} = +0.18$; $[NH_2]^{tba} = +0.01$; $[OH^-]^{tba} = -0.13$; η is the asymmetry parameter.

CONCLUSIONS

In aqueous solutions, at pH > 2, L-cysteine readily complexes $[Me_2Sn(H_2O)_n]^{2+}$. The complexation occurs by the ionized sulfhydryl group of the ligand, rendering a species containing five-coordinate tin; two molecules of water occupy the apical positions of the trigonal bipyramidal environment of tin. At physiological pH values, the amino group displaces one molecule of water; the other water molecule or one hydroxyl ion occupies the fifth position of the bipyramid. At pH > 10 a hydroxyl ion displaces the amino group.

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