APPLIED ORGANOMETALLIC CHEMISTRY, VOL. 9, 227–239 (1995)

Organometallic Complexes with Biological Molecules, IV. Di- and Tri-organotin(IV) Amoxicillin Derivatives: Solid-state and Solution-phase Spectroscopic Investigations

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Novel di- and tri-organotin(IV) derivatives of amoxicillin (amoxicillin$^-$ = Amox$^-$ = 6-[D(−)-β-amino - *p* - hydroxyphenylacetamido]penicillinate) have been prepared. The isolated compounds showed stoichiometries of the type $R_2SnClAmox \cdot 2H_2O$, $R_3SnClAmoxNa \cdot 2H_2O$ and $R_2SnAmox_2 \cdot 2H_2O$ (R = Me, Bu, Ph). The infrared spectra suggest that Amox$^-$, in both $R_2SnClAmox \cdot 2H_2O$ and $R_2SnAmox_2 \cdot 2H_2O$, behaves as a monoanionic bidentate ligand, coordinating the tin(IV) atom through the ester-type carboxylate, as well as through the lactamic carbonyl.

In $R_3SnClAmoxNa \cdot 2H_2O$, Amox$^-$ coordinates the organotin(IV) moieties through the lactamic carbonyl. In all of the compounds, water molecules are not involved in coordination, as inferred by thermogravimetric (TG) investigation. In both $R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$, trigonal bipyramidal configurations are proposed in the solid state, on the basis of infrared (IR) and Mössbauer spectroscopy, while in $R_2SnAmox_2 \cdot 2H_2O$ the coordination geometry at tin could be a skew-trapezoidal bipyramid, with two chelating amoxicillin residues which act as bidentate ligands in the trapezoidal plane, and with the organic groups in axial positions. The C—Sn—C angles calculated from the experimental Mössbauer quadrupole splitting predict a bent skeleton in all the $R_2SnAmox_2 2H_2O$ derivatives.

^1H and ^{13}C NMR measurements showed that both $R_2SnClAmox \cdot 2H_2O$ and $R_2SnAmox_2 \cdot 2H_2O$ are stable in DMSO-d_6 solutions, maintaining their solid-state configuration, while $R_3SnClAmoxNa \cdot 2H_2O$ dissociates.

Coordination hypotheses have been checked through the correlation between the Mössbauer isomer shift (δ) and the partial atomic charge on tin atoms (Q_{Sn}) performed, for all the new organotin(IV) compounds, on the basis of an equalization procedure applied to idealized trigonal bipyramidal structures for $R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$ and octahedral *trans*-R_2 for $R_2SnAmox_2 \cdot 2H_2O$.

Keywords: organotin; antibiotic; amoxicillin; structure; Mössbauer; infrared; ^1H NMR; ^{13}C NMR

INTRODUCTION

Literature reports on semisynthetic penicillins generally deal with their synthesis, their physical properties such as UV, IR, NMR, circular dichroism, Raman and X-ray diffraction spectra, or with pharmacological evidence.[1–8] This aspect of 6 - [D(−) - β - amino - *p* - hydroxyphenylacetamido] - penicillanic acid, denoted briefly as amoxicillin, has been widely investigated.[1,8] On the other hand, generally speaking, little information is available on the interactions of antibiotics and metal ions or organometallic moieties. Copper(II)–ampicillin complexes with 1:1, 1:2 and 1:3 compositions and their stability constants have been determined by Navarro *et al.*,[9] in methanolic media, by spectrophotometry and conductimetry, while the NMR line-broadening technique has been applied to copper(II) and manganese(II) complexes with some antibiotics.[10] Polarographic studies of cobalt(II), copper(II) and zinc(II) complexes with ampicillin and amoxicillin have also been reported recently.[11] Asso *et al.*[12] and Grochowski and Samochocka[13] investigated benzylpencillin complexes with iron(II) and platinum(II). On the basis of IR and NMR spectroscopy Asso hypothesized that penicillin coordinated iron(II) through carboxylate groups and

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CCC 0268–2605/95/030227–13

Received 6 June 1994
Accepted 30 September 1994

Table 1 Analytical data (calculated values in parentheses)

Compound[a]	Elemental analysis (%)					
	C	H	N	Cl	Sn	H_2O[b]
$Me_2SnClAmox \cdot 2H_2O$	38.92	4.38	7.29	6.75	20.91	7.00
	(36.98)	(4.83)	(7.19)	(6.06)	(20.30)	(6.16)
$Bu_2SnClAmox \cdot 2H_2O$	42.47	5.19	7.01	5.53	18.27	5.22
	(43.09)	(5.02)	(6.28)	(5.30)	(17.74)	(5.38)
$Ph_2SnClAmox \cdot 2H_2O$	47.46	4.00	6.28	6.00	16.51	5.20
	(47.45)	(4.55)	(5.93)	(5.00)	(16.75)	(5.08)
$Me_3SnClAmoxNa \cdot 2H_2O$	37.67	5.25	6.18	5.96	19.76	5.96
	(36.65)	(5.02)	(6.75)	(5.69)	(19.06)	(5.78)
$Bu_3SnClAmoxNa \cdot 2H_2O$	44.15	6.42	6.31	4.78	16.43	5.02
	(44.91)	(6.60)	(5.61)	(4.73)	(15.85)	(4.81)
$Ph_3SnClAmoxNa \cdot 2H_2O$	50.96	4.67	5.15	4.10	14.81	4.73
	(50.49)	(4.61)	(5.20)	(4.38)	(14.67)	(4.45)
$Me_2SnAmox_2 \cdot 2H_2O$	44.94	5.32	8.69		12.61	4.05
	(44.69)	(5.07)	(9.19)		(12.99)	(3.90)
$Bu_2SnAmox_2 \cdot 2H_2O$	48.20	6.04	8.05		11.60	3.53
	(48.15)	(5.85)	(8.42)		(11.89)	(3.61)
$Ph_2SnAmox_2 \cdot 2H_2O$	50.23	5.38	7.40		11.18	3.61
	(50.92)	(4.85)	(8.09)		(11.43)	(3.47)

[a] $Amox^-$ = Amoxicillin$^-$. [b] Total water content determined by TG analysis: see Results and discussion section.

thiazolidinic nitrogen.[12] Amidic nitrogen and thioether groups were proposed by Grochowski to bind platinum(II); in the presence of side-products, chelate complexes through the thioether and carboxylic groups were also claimed on the basis of ^1H NMR.[13] On the other hand, Jaworska *et al.*[14] used AM1 and PM3 methods to determine the penicillin complexation sites in the presence of zinc(II) ions. Diorganotin(IV)ClpenG and triorganotin(IV)ClpenGNa (penG = benzylpenicillin G; R = Me, Bu, Ph) derivatives and their *in vivo* cytotoxicity have been the aim of recent investigations in our laboratory.[15–19] IR and Mössbauer spectroscopy studies carried out in the solid state showed a monoanionic bidentate behavior of penG through the ester-type carboxylate and the lactamic C=O in diorganotin(IV)chloropenG derivatives, while in triorganotin(IV)chloropenGNa compounds penG coordinated the tin(IV) atom through the lactamic C=O.[18]

EXPERIMENTAL

$R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$ were synthesized by refluxing methanolic solutions of R_2SnCl_2 and R_3SnCl, respectively (gifts from Witco GmbH, Bergkamen, Germany) with methanolic solutions of the sodium salt of amoxicillin, obtained, in turn, from reaction of amoxicillin trihydrate (US Biochemical Corporation, Cleveland, OH, USA) by the sodium methoxide method,[20] in the molar ratio 1:1.

The $R_2SnAmox_2 \cdot 2H_2O$ derivatives were obtained by reaction of freshly prepared R_2SnO[21] and amoxicillin trihydrate. The solid complexes, recovered by filtration, were recrystallized and analyzed for C, H, N, Sn and Cl content (Table 1). C, H and N analyses were performed at Laboratorio di Chimica Organica (Uaniversità di Milano). Sn and Cl contents were determined in our laboratory according to standard methods.[22,23]

TG measurements were carried out with a mettler TA-3000 system in a pure nitrogen atmosphere. Analyses for SnO_2 and NaCl content of the residual products have been performed according to standard analytical procedures. In particular, a model 372 Perkin–Elmer atomic absorption spectrophotometer equipped with a graphite furnace has been used to assay sodium and tin contents.

IR spectra were recorded, as Nujol and hexachlorobutadiene mulls, on a model 983G Perkin–Elmer grating spectrometer between CsI windows. The spectra were analyzed through a Perkin–Elmer 3600 data station with

Perkin–Elmer PE983 software.

The ^{119}Sn Mössbauer spectra were measured, in duplicate, with a Laben 8001 (Milano) and a model 639 TAKES (Bergamo) multichannel analyzer and an MWE (Munchen) MR250 driving unit, an FG2 digital function generator and an MA250 velocity transducer, moved at linear velocity and constant acceleration in a triangular waveform. A DN700 Oxford cryostat with DTC2 temperature controller was used to maintain the absorber samples (absorber thickness, 0.50–0.60 mg ^{119}Sn cm^{-2}) at the investigated temperature.

^{1}H and ^{13}C NMR spectra of all organotin(IV) derivatives were recorded on a Bruker AC 250E instrument, operating at 63 and 250 MHz respectively, using tetramethylsilane (TMS) as internal standard and DMSO-d_6 as solvent.

RESULTS AND DISCUSSION

IR data

The move relevant bands of the IR spectra of the free amoxicillin trihydrate (Fig. 1) and of its organotin(IV) complexes are reported in Table 2. The coordinating mode of the amoxicillin towards the tin(IV) atom, in the isolated di- and triorganotin(IV) derivatives, can be inferred from the IR spectra of the free and coordinated ligand. In fact, apart from the bands at 3520(s), 3473(s, bd) and 2700–2500 cm^{-1}, attributable to ν(OH) of the water molecules present in the amoxicillin, and to ν(OH) and to $\nu(NH_3^+)$ of the β-amino-p-hydroxyphenyl group, the other characteristic and diagnostic bands resemble those previously reported for the penicillin G ligand.[18]

The bands attributable to ν(NH) (3171(s, bd) cm^{-1}), to lactamic ν(C=O) (1775(s) cm^{-1}), to amidic ν(C=O), (1686(s) cm^{-1}), to ν(CN) (1030(s) cm^{-1}) and finally to ν(CS) (580(s) cm^{-1}) have been all identified in the free amoxicillin.[7] While the lactamic and the amidic ν(C=O) were shifted towards lower wavenumbers, ν(CN) and ν(CS) were found almost in the same position in all of the complexes.

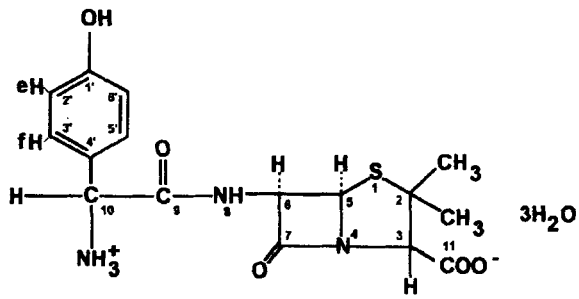

Figure 1 Amoxicillin trihydrate, showing the numbering of the carbon atoms used in the NMR discussion.

According to our previous report on organotin(IV)penG derivatives,[18] the findings described above would suggest an involvement of lactamic C=O in coordinating tin(IV), but would exclude any involvement of lactamic nitrogen and thiazolidinic sulfur in tin(IV) coordination. As far as amidic ν(C=O) shifts are concerned, they might be caused by intermolecular hydrogen bonding.[18]

Furthermore, differences between free and coordinated amoxicillin occurred both in the 4500–3100 and in the 1650–1300 cm^{-1} regions, apart from the presence down to 600 cm^{-1} of the characteristic absorptions of the organotin(IV) moieties.[24–26] In fact, in all the organotin(IV) amoxicillinates, only one strong and broad band due to ν(OH) was present (two in the free amoxicillin), probably due to hydrogen-bonded water molecules, while the broad bands which are present at 2700–2500(bd) cm^{-1} in the free ligand disappeared owing to the deprotonation of NH_3^+. Finally, $\nu_{as}(COO^-)$ and $\nu_{sym}(COO^-)$ in the free ligand are likely to occur at 1582(s, bd) and 1400(s) cm^{-1}, respectively, with $\Delta\nu[=\nu_{as}(COO^-)-\nu_{sym}(COO^-)]=182$ cm^{-1}, following the internal salification of the carboxylic group by the amino group.[27,28]

The $\Delta\nu$ values are increased by over 200 cm^{-1}, in both the $R_2SnClAmox \cdot 2H_2O$ and $R_2SnAmox_2 \cdot 2H_2O$ (210 cm^{-1} in $Me_2SnClAmox \cdot 2H_2O$; up to 235 cm^{-1} in $Ph_2SnAmox_2 \cdot 2H_2O$, suggesting a monodentate ester-type coordination[27,28] of the carboxylate group towards the tin(IV) atom, while in $R_3SnClAmoxNa \cdot 2H_2O$ $\Delta\nu$ ranged between 160 cm^{-1} in $Bu_3SnClAmoxNa \cdot 2H_2O$ and 184 cm^{-1} in $Me_3SnClAmoxNa \cdot 2H_2O$ derivatives, in which the carboxylate group seems not to be involved in coordination. In conclusion, IR evidence showed that tin(IV) achieved five-coordination in both $R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$. As far as $R_2SnAmox_2 \cdot 2H_2O$ derivatives are concerned, exacoordination of the tin(IV) atom would be reached through the involvement, for each amoxicillin molecule, both of lactamic C=O and of the ester-type carboxylic group.

TG measurements performed from room tem-

Table 2 Assignment of relevant absorption bands of amoxycillin · $3H_2O$, $R_2Sn(IV)ClAmox \cdot 2H_2O$, $R_2Sn(IV)Amox_2 \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$ derivatives in the 4000–250 cm^{-1} region[a, b]

Assignment	Amox · $3H_2O$	I	II	III	IV	V	VI	VII	VIII	IX
ν(OH)	3552s 3457s,bd	3450s	3453s,bd	3453s,bd	3462s,bd	3450s,bd	3458s,bd	3450s,bd	3450s,bd	3470s,bd
ν(NH) $\nu(NH_3^+)$	3161s 2700–2500s,bd	3287s,bd	3292s,bd	3303s,bd	3333s,bd	3296s,bd	3311s,bd	3354s	3309,s	3302s,bd
ν(C=O) (β-lactam)	1775s	1735s	1739s	1735s	1737s	1742s	1737s	1735s	1739s	1730s
νC=O (amide)	1686s	1660s	1665s	1665s	1665	1660s	1660s	1671s, bd	1670s,bd	1665s,bd
$\nu_{as}(COO)^+$	1582s,bd	1590s,bd	1590s,bd	1590s,bd	1580s,bd	1600s,bd	1598s,bd	1590s,bd	1590s,bd	1592s,bd
Amide II (amide)	1560s	1566s	1560s	1563s	1563s	1560s	1563s	1566s	1561s	1565s
$\nu_{sym}(COO^-)$	1400s	1384s	1376s	1370s	1396s	1440s	1429s	1360s	1366s	1367s
ν(CN)	1021m	1020w	1014w	1022m	1020m	1019m	1022m	1020w	1022m	1024m
ν(CS)	582m	580m	578m	580m	580w	580w	582w	580w	578m	585m
$\nu_{as}(SnC_2)$	—	558s	560s	—	550s	525s	—	563m	565m	—
$\nu_{sym}(SnC_2)$	—	527w	—	—	—	—	—	526w	—	—
Y – Ph	—	—	—	450s	—	—	450s	—	—	450s
ν(SnCl)	—	278w	260w	276w	282w	247m	272m	—	—	—
$\Delta\nu(cm^{-1})$	182	210	214	220	184	160	169	230	234	235

[a] Nujol and hexachlorobutadiene mulls; s = strong; m = medium; w = weak; bd = broad.

[b] Compounds are designed by **I–IX** as follows:

I = $Me_2SnClAmox \cdot 2H_2O$ **II** = $Bu_2SnClAmox \cdot 2H_2O$ **III** = $Ph_2SnClAmox \cdot 2H_2O$

IV = $Me_3SnClAmoxNa \cdot 2H_2O$ **V** = $Bu_3SnClAmoxNa \cdot 2H_2O$ **VI** = $Ph_3SnClAmoxNa \cdot 2H_2O$

VII = $Me_2SnAmox_2 \cdot 2H_2O$ **VIII** = $Bu_2SnAmox_2 \cdot 2H_2O$ **IX** = $Ph_2SnAmox_2 \cdot 2H_2O$

perature up to 600 °C showed, for all the derivatives, a one-step water loss pattern below 120 °C (43–118 °C), [two water molecules per mole, Table 1; amoxicillin trihydrate lost its three water molecules, with the same one-step pattern, at 104 °C (calculated 12.87%, found 13.61%)]. The experimental evidence described above rules out coordination of water molecules to tin in all these organotin(IV) compounds, but H_2O may be involved in hydrogen bonding analogous to that occurring in the free amoxicillin trihydrate.[5] The residual product at 600 °C is SnO_2 in the case of diorganotin(IV)amoxicillin derivatives, and an SnO_2 + NaCl mixture in the case of triorganotin(VI) chloroamoxicillin Na.

Mössbauer data

The values of the Mössbauer parameters, isomer shift (δ) and nuclear quadrupole splitting (ΔE, mm s^{-1}) are characteristic or organotin(IV) derivatives[29–31] (Table 3).

In particular, δ increased within the diorganotin(IV) series from diphenyl- to dibutyl-tin(IV) compounds, and from triphenyl- to tributyltin(IV) for the triorganotin(IV) derivatives.[29–31] The small differences found cannot be interpreted in chemically meaningful terms. Nevertheless, simple and qualitative structural information can be extracted by comparing congeneric and isostructural derivatives.[32–39] Consequently, partial atomic charges on the tin(IV) atom (Q_{Sn}) and on the atoms directly bonded to the tin (Q) have been calculated by the program CHELEQ,[32–34] which was written on the basis of an orbital electronegativity equalization procedure described in detail by Jolly and Perry.[32–34]

Calculations have been performed by assuming idealized trigonal bipyramidal (tbp) valence bond structures and appropriate bond orders and formal charges (used as input data in the CHELEQ program), which for $R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$ derivatives are reported in Figs 2(a) and 2(b), respectively. In Table 4 are summarized the partial charges of the tin(IV) and of the atoms directly bonded to tin, obtained as output of the above-mentioned CHELEQ program.

The experimental isomer shifts δ have been plotted as a function of the partial atomic charges on tin, Q_{Sn} (Table 5 and Fig. 3). For comparison, in Fig. 3 are reported also the analogous diorganotin(IV)chloro and triorganotin(IV)chloropen G derivatives.[18] The dependence of δ on Q_{Sn} is linear, in agreement with results obtained for a number of homologous tin(IV) and organotin(IV) compounds.[35–39]

ΔE values of diorganotin(IV)chloro and triorganotin(IV)chloroamoxicillin derivatives have been rationalized according to the point charge model formalism[29,40,41] applied to the idealized trigonal bipyramidal structures of Figs 2(a) and 2(b), where, *inter alia*, are reported the directions of the diagonalized electric gradient

Table 3 Experimental Mössbauer parameters,[a] isomer shift (δ; mm s^{-1}) and nuclear quadrupole splitting (ΔE_{exp}, mm s^{-1}) measured at liquid N_2 temperature, and calculated nuclear quadrupole splittings according to the point charge formalism applied to the idealized structures of Figs 2(a) and (b)

Compound	δ	ΔE_{exp}	Γ_1	Γ_2	C–Sn–C angle ± 13°	ΔE_{calcd}	Figure
$Me_2SnClAmox \cdot 2H_2O$	1.21	2.99	0.84	0.86	120	3.17	2(a)
$Bu_2SnClAmox \cdot 2H_2O$	1.27	2.86	1.02	1.04	117	3.17	2(a)
$Ph_2SnClAmox \cdot 2H_2O$	0.98	2.69	1.00	1.01	123	2.78	2(a)
$Me_3SnClAmoxNa \cdot 2H_2O$	1.31	3.52	1.07	1.06	b	−3.77	2(b)
$Bu_3SnClAmoxNa \cdot 2H_2O$	1.43	3.33	1.01	1.02	b	−3.77	2(b)
$Ph_3SnClAmoxNa \cdot 2H_2O$	1.16	2.87	1.00	0.98	b	−3.26	2(b)
$Me_2SnAmox_2 \cdot 2H_2O$	1.24	3.10	0.88	0.92	130	b	
$Bu_2SnAmox_2 \cdot 2H_2O$	1.37	3.14	0.85	0.92	132	b	
$Ph_2SnAmox_2 \cdot 2H_2O$	1.14	2.65	0.92	1.00	124	b	

[a] Sample thickness ranged between 0.50 and 0.60 mg $^{119}Sn\ cm^{-2}$; isomer shift, $\delta \pm 0.03$, mm s^{-1} with respect to $BaSnO_3$; Γ_1 and Γ_2 values are the full width at half height of the resonant peaks, respectively at greater and lower velocity, with respect to the centroid of the Mössbauer spectra; nuclear quadrupole splitting, $\Delta E_{exp} \pm 0.02$ mm s^{-1}.

[b] Not calculated.

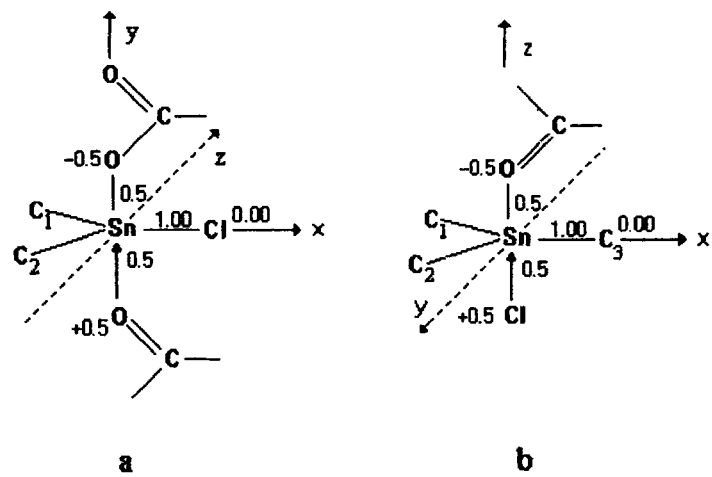

Figure 2 Regular tbp structures of tin assumed to estimate the nuclear quadrupole splittings according to the point charge model, for $R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$ derivatives. In (a) and (b) are also shown the principal components of the diagonalized electric gradient tensor. The partial quadrupole splittings used in the calcualtions are: $\{Alk\}^{tbe} = -1.13$; $\{Ph\}^{tbe} = -0.98$; $\{Cl\}^{tbe} = 0.20$; $\{COO^-\}^{tba}_{unid} = -0.10$; $\{CO\}^{tba}_{lact} = \{CO\}^{tba}_{DMA} = 0.16$ (see Refs 41 and 60). The reported bond orders and formal charges are assumed as input in the calculation of partial atomic charge on the tin atom (Q_{Sn}) (see text).

tensors as obtained as output from the computing software.

The calculated ΔE values agree with the experimental data (Table 3) within less than $\pm 0.4\ mm\ s^{-1}$, the maximum difference allowed between experimental and calculated ΔE in order to accept the predicted geometry.[42]

Furthermore, C–Sn–C angles have been calculated for the diorganotin(IV)chloroamoxicillin derivatives from the experimental ΔE by applying the Sham and Bancroft model,[43] and are reported in Table 3.

The C–Sn–C angles, as calculated (Table 3), are in good agreement with those expected for

Table 4 Calculated Q(CHELEQ)[32–34] values for the atoms bonded to the tin(IV) atoms, according to structures, bond orders and charges of Figs 2(a) and (b)

	Partial atomic charge, Q, on the atom						
Compound[a]	Sn	C1	C2	C3	Chloro	−O—C=O	C=O (β-lactamic)
$Me_2SnClAmox \cdot 2H_2O$	0.268	−0.025	−0.025	—	−0.093	−0.516	−0.040
$Bu_2SnClAmox \cdot 2H_2O$	0.271	−0.011	−0.011	—	−0.093	−0.516	−0.040
$Ph_2SnClAmox \cdot 2H_2O$	0.317	−0.042	−0.042	—	−0.091	−0.515	−0.051
$Me_3SnClAmoxNa \cdot 2H_2O$	0.150	−0.028	−0.028	−0.018	−0.507	—	−0.042
$Bu_3SnClAmoxNa \cdot 2H_2O$	0.105	−0.017	−0.017	−0.464	−0.509	—	−0.042
$Ph_3SnClAmoxNa \cdot 2H_2O$	0.208	−0.009	−0.009	−0.110	−0.506	—	−0.042
$Me_2SnAmox_2 \cdot 2H_2O$	0.443	−0.164	−0.164	—	—	−0.396	0.011
						−0.396	0.011
$Bu_2SnAmox_2 \cdot 2H_2O$	0.445	−0.148	−0.148	—	—	−0.396	0.011
						−0.396	0.011
$Ph_2SnAmox_2 \cdot 2H_2O$	0.481	−0.140	−0.140	—	—	−0.395	0.012
						−0.395	0.012

[a] $Amox^- = Amoxicillin^-$.

Table 5 Experimental Mössbauer parameters: isomer shift (δ mm s^{-1}), and calculated partial atomic charge on the tin atoms (QA_{Sn}) (CHELEQ)[32-34] for homologues series of penta-coordinated tri- and di-organotin(IV) derivatives

Compound[a]	δ[b]	Q_{Sn}[b]	Point[c]	Ref. for δ and Q_{Sn}[c]
$Alk_2SnClAmox \cdot 2H_2O$	1.24	0.270	1	This work
$Ph_2SnClAmox \cdot 2H_2O$	1.20	0.317	2	This work
$Alk_3SnClAmoxNa \cdot 2H_2O$	1.36	0.128	3	This work
$Ph_3SnClAmoxNae \cdot 2H_2O$	1.26	0.208	4	This work
$Alk_2SnClpenG$	1.28	0.270	5	18
$Ph_2SnClpenG$	1.21	0.317	6	18
$Alk_3SnClpenGNa$	1.40	0.128	7	18
$Ph_3SnClpenGNa$	1.30	0.208	8	18

[a] Amox$^-$ = Amoxicillin$^-$; penG$^-$ = penicillin G$^-$.
[b] Average of the δ and Q_{Sn} (CHELEQ) values reported in the quoted references.
[c] Identification numbers of the points reported in Fig. 3.

cis-R_2 trigonal bipyramidal structures around the tin(IV) atom.

ΔE values of diorganotin(IV)$Amox_2$ compounds are *ca* 3 mm s^{-1}. These data are consistent with a tetrahedral environment around the tin(IV) atoms, highly distorted towards an octahedral *trans*-R_2SnO_4 configuration, in agreement with IR data, but with anisobidentate amoxicillin moieties coordinating through ester-type carboxylate and β-lactamic carbonyl oxygens and with the C–Sn–C angle $\ll 180°$ (Fig. 4). The approximate measure of the distortions has been calculated according to Ref. 43, by ignoring the contribution of the atoms other than the carbon of the organic groups, bonded to the tin atom. In fact, ΔE values in organotin compounds are pre-eminently determined by the C–Sn–C angles.[43]

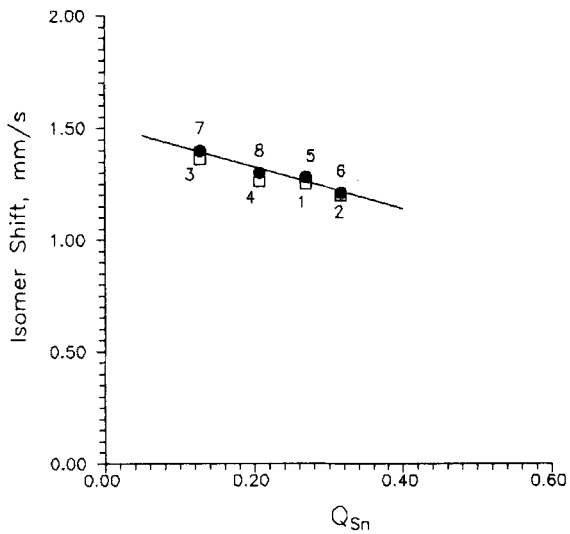

Figure 3 Isomer shifts (δ) versus partial atomic charge (Q_{Sn}) for $R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$ and penG derivatives (Table 5). The full line is the least-squares fit of the data points. The related equations are: $\delta = 1.48 - 0.87Q_{Sn}$; $r = 0.957$.

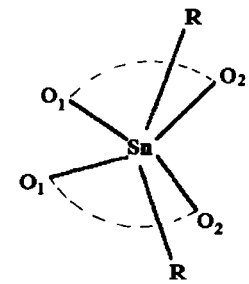

Figure 4 Skew trapezoidal-bipyramidal configuration proposed for the $R_2SnAmox_2 \cdot 2H_2O$ derivatives. O_1 and O_2 represents the oxygen donor atoms for each amoxicillin moiety.

Under these conditions, C–Sn–C angles may be calculated as $(180° - 2\theta)$ (Table 6), where θ may be extracted by solving Eqn [1]:

$$\Delta E = 4\{R\}[1 - 3\cos^2\theta \sin^2\theta]^{1/2} \quad [1]$$

where $\{R\}$ = the partial quadrupole splitting of the hydrocarbon groups in an idealized octahedral configuration ($\{Alkyl\} = -1.03$ and $\{Phenyl\} = -0.98$, according to Refs 29 and 41).

Some examples of diorganotin(IV) complexes with chelating ligands (SS, NS, SO or ON donor atoms) are also reported for comparison in Table 6, together with C–Sn–C angles determined by X-ray and also calculated according to the Sham and Bancroft model[43] from the experimental ΔE. For the majority of these complexes, whose formula may be represented as $R_2Sn(L^1—L^2)$, $L^1—L^2$ being a uninegative bidentate chelating ligand, a skew-trapezoidal structure (STB) has been proposed, this geometry often being advanced for diorganotin chelates in cases of C–Sn–C angles ranging between 122 and 157°.[44] C–Sn–C angles calculated for the diorganotin(IV) bis(amoxicillinate)s, $R_2SnAmox_2 \cdot 2H_2O$ (Table 6) are in the range of the reported values for STB configurations, so that we may conclude that in our derivatives also such an environment around the tin atom is highly probable (Fig. 4).

Table 6 Experimental nuclear quadrupole splittings (ΔE_{exp}, mm s^{-1}) measured at liquid N_2 temperature, and C–Sn–C angles for diorganotin(IV) chelates assuming skew-trapezoidal bipyramidal structure

Compound[a]	Donor atoms L_1—L_2	ΔE (mm s^{-1})	C–Sn–C angle (±13°) calculated according to Ref. 43	C–Sn–C angles measured by X-ray	References
$Me_2SnAmox_2 \cdot 2H_2O$	$(O—O)_2$	3.10	130	—	This work
$Bu_2SnAmox_2 \cdot 2H_2O$	$(O—O)_2$	3.14	132	—	This work
$Ph_2SnAmox_2 \cdot 2H_2O$	$(O—O)_2$	2.66	124	—	This work
$Bu_2Sn[ON(Me)C(O)C_6H_4$-*p*-Br$]$	$(O—O)_2$	3.27	135	145.1	49
$Bu_2Sn[ON(Ph)C(O)Ph]_2$	$(O—O)_2$	3.10	130	133.9	49
$Me_2Sn[S_2CN(CH_2)_4]_2$	$(S—S)_2$	2.85	123	137.3	48, 50
$Me_2Sn[S_2CNMe_2]_2$	$(S—S)_2$	3.14	132	136.0	51
$Me_2Sn[S_2CNEt_2]_2$	$(S—S)_2$	3.14	132	135.6	50, 52
$Me_2Sn[S_2CN(CH_2)_4]$	$(S—S)_2$	2.85	123	129.7	53
$Cyhex_2Sn(2\text{-}Py)_2$	$(S—N)_2$	2.84	123	126.9	54
$Ph_2Sn(2\text{-}Spy)_2$	$(S—N)_2$	2.30	113	125.5	54, 55
$Me_2Sn(2\text{-}SPyO)_2$	$(S—O)_2$	3.29	136	138.9	44
$[CH_3OC(O)(CH_2)_2]_2SnClOx$	(ClO_2N)	3.09	130	135.4	56, 57

[a] $Amox^-$ = Amoxicillin$^-$; [ON(Ph)C(O)Ph] = (*N*-phenyl-*N*-benzoylhydroxylaminate); [ON(Me)C(O)C_6H_4-Br] = (*N*-methyl-*N*-*p*-bromo-benzoylhydroxylaminate); $S_2CNR_2^-$ = dialkyl and diphenyl dithiocarbamate; $2\text{-}SPy^-$ = 2-pyridinethiolato; $2\text{-}SPyO^-$ = 2-pyridinethiolato-*N*-oxide; Ox^- = quinolin-8-olato.

Isomer shifts (δ) for the diorganotin(IV)bis-(amoxicillinate)s and for the other complexes reported in Table 6 have been plotted as a function of the partial atomic charge on the tin atom (Q_{Sn}) calculated using the CHELEQ program, the bond orders and formal charges of the *trans*-R_2 octahedral configuration of Fig. 5 being input of the program. Table 7 summarizes the partial electric charges both on the tin atom (Q_{Sn}) and on the atoms bonded to the tin, obtained as output. Figure 6 shows the reasonably good linear trend of the data within the represented homologous series, which qualitatively led us to assume that all of the analyzed six-coordinated derivatives must be congeneric and isostructural.

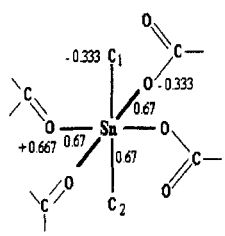

Figure 5 Regular octahedral structure of tin assumed to calculate the partial atomic charge on the tin atom, Q_{Sn}, for the derivatives of Table 7. Bond orders and formal charges assumed as input in the calculation are also reported (see text).

Molecular dynamics of $R_2SnClAmox \cdot 2H_2O$, $R_3SnClAmoxNa \cdot 2H_2O$ and $R_2SnAmox_2 \cdot 2H_2O$ have been investigated by variable-temperature ^{119}Sn Mössbauer spectroscopy. Preliminary results show that the absolute recoil free-fractions, for all the derivatives, is characteristic of Debye solids, while the calculated mean square displacements of the tin nucleus suggest the occurrence of molecular association.[45]

Investigations by X-ray difrraction of powdered compounds are in progress and preliminary data show that while $R_2SnAmox_2 \cdot 2H_2O$ compounds are amorphous, $R_2SnClAmox \cdot 2H_2O$ and $R_3SnClAmoxNa \cdot 2H_2O$ are mixtures of crystalline and amorphous phases.[46] A detailed analysis of the amorphous part of the scattering curve, obtained at small angles, is being performed in order to obtain the pair-correlation function $g(r)$ versus the intra- and inter-particle distances. This function would be strictly related to the probability of finding distances which are typical of a certain atomic arrangement.[47]

Organotin(IV) amoxicillin derivatives in solution

^1H and ^{13}C NMR spectra for organotin(IV) amoxicillinates were measured in dimethyl sulfoxide (DMSO-d_6) to probe the stability of the complexes and to gain an insight of their structures in solution. ^1H and ^{13}C NMR spectra for β-lactam

Table 7 Experimental Mössbauer parameter, isomer shift (δ, mm s^{-1}) and calculated partial atomic charge on tin atoms (Q_{Sn}) (CHELEQ)[32-34] for homologous series of skew-trapezoidal bipyramidal diorganotin(IV) derivatives

Compound[a]	δ[b]	Q_{Sn}	Point[c]	Refs for δ and Q_{Sn}
$Alk_2SnAmox_2 \cdot 2H_2O$	1.30	0.443	9	This work
$Ph_2SnAmox_2 \cdot 2H_2O$	1.14	0.481	10	This work
$Bu_2Sn(hydroxamate)_2$	1.28	0.443	11	49
$Alk_2Sn[S_2CNR_2]_2$	1.59	0.227	12	50, 58
$Alk_2Snpdtc$	1.54	0.227	13	59
$Alk_2Snbis(2\text{-}SPy)$	1.56	0.178	14	54
$Me_2Sn(2\text{-}SPyO)_2$	1.30	0.330	15	44

[a] $Amox^-$ = Amoxicillin$^-$; hydroxamate = (*N*-phenyl-*N*-benzoylhydroxylaminate) or (*N*-methyl-*N*-*p*-bromobenzoylhydroxylaminate); $S_2CNR_2^-$ = dialkyl and diphenyl dithiocarbamate; $pdtc^-$ = piperazinebis(dithiocarbamate); $2\text{-}SPy^-$ = 2-pyridinethiolato; $2\text{-}SPyO^-$ = 2-pyridinethiolato-*N*-oxide; Ox^- = quinolin-8-olato.

[b] Identification numbers of the points reported in Fig. 6.

[c] Average of the δ and Q_{Sn} (CHELEQ) values reported in the quoted references.

antibiotics and for a few complexes with metal ions such as platinum(II), copper(II) and manganese(II) have been reported.[6-8, 10, 13] Shifts in the ^1H and ^{13}C NMR resonances observed upon metallation of the free ligand give an indication as to which binding sites are involved in the complex molecule. Of course, ^1H and ^{13}C resonances of a molecule not only reflect the electronic environment at the nucleus, but also depend on steric and conformational effects.

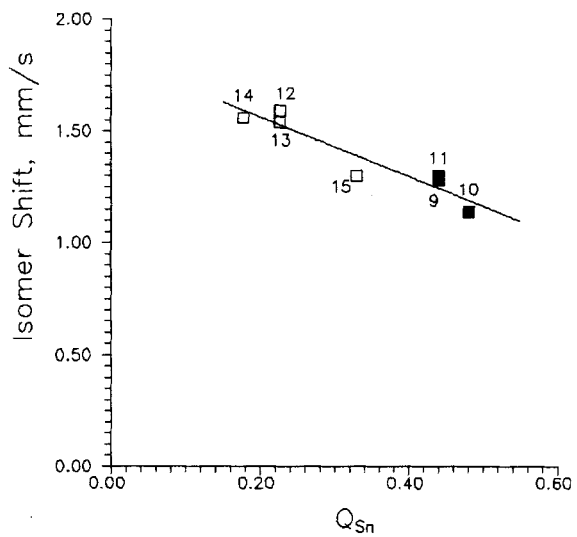

Figure 6 Isomer shifts (δ) versus partial atomic charge (Q_{Sn}) for $R_2SnAmox_2 \cdot 2H_2O$ and related derivatives of Table 7. The full line is the least-squares fit of the data points. The related equations are: $\delta = 1.83 = 1.35Q_{Sn}$; $r = 0.947$.

Amoxicillin. (6-[D(−)-β-amino-*p*-hydroxyphenylacetamido]penicillanic acid) does not appear to be present in the form of the various conformers of the thiazolidine five-membered ring, and evidence based on ^1H NMR data has been presented for a conformation similar to that of natural penicillin in the case of platinum–penicillin derivatives.[13]

Concentration effects should always be taken into account when comparing the spectra of β-lactam molecules, especially when polar solvents are employed.[7]

The main evidence which the NMR spectra provide concerning the stability of the compounds reported in this work, is mainly related to the adducts $R_3SnClAmoxNa \cdot 2H_2O$: in a polar and donor solvent such as dimethyl sulfoxide, they all appear to be completely dissociated, as indicated by the appearance of the virtually unshifted resonances of the amoxicillin ligand.

In contrast, both $R_2SnClAmox \cdot 2H_2O$ and $R_2SnAmox_2 \cdot 2H_2O$ appear to be reasonably stable, the presence of very small amounts of chemical species different from the reported complexes probably being due to the donor ability of the DMSO solvent.

^{13}C NMR spectra

^{13}C NMR spectra of diorganotin(IV)chloro-Amox $\cdot 2H_2O$ and diorganotin(IV)$Amox_2 \cdot 2H_2O$ show resonances which are shifted with respect to the free ligand, the major shifts occurring for the C11, C3, C7 and C10 signals (Table 8 and Fig. 1).

For C3 (Fig. 1), which is adjacent to the carboxylate group, the shift relative to the free ligand is found to be upfield (*ca* 2 ppm) in $Me_2SnClAmox \cdot 2H_2O$, while for $Bu_2SnClAmox \cdot 2H_2O$ and $Ph_2SnClAmox \cdot 2H_2O$ it is downfield by nearly the same amount (*ca* 3 ppm). The geminal 2α- and 2β-methyl carbons (Table 8) are also somewhat sensitive to the bulkiness of the organometallic moiety; C2α moves upfield and C2β downfield, relative to amoxicillin, in $Me_2SnClAmox \cdot 2H_2O$ while the opposite is true for both $Bu_2SnClAmox \cdot 2H_2O$ and $Ph_2SnClAmox \cdot 2H_2O$. These differences may illustrate the existence of steric and electronic

interactions between the C2α and C2β of methyl groups of amoxicillin and aliphatic and/or aromatic groups of the organometallic moieties without proving a change in the conformation of the antibiotic. The occurrence of doubled sets of resonances for the ligand carbon atoms in the case of $R_2SnAmox_2 \cdot 2H_2O$ complexes is indicative of ligand–ligand interactions, which may responsible for the magnetic non-equivalence of signals.

^{1}H NMR spectra

The existence of ligand–ligand interactions is expected on the basis of hydrogen bonding and self-association ^{1}H NMR studies of penicillins.[6] In this work, the occurrence of similar interactions in the $R_2SnAmox_2 \cdot 2H_2O$ derivatives is presented, viz. interactions between the two amoxillin moieties in the complexes, where a skew-trapezoidal bipyramidal structure is advanced in the solid state of the basis of Mössbauer data and is though to be responsible for the non-equivalence of the resonances associated with the amoxicillin ligand as found in $R_2SnAmox_2 \cdot 2H_2O$ complexes (Table 9).

Several proton resonances in these complexes appear to be doubled. These findings may be attributed to differences in the local electronic environment of the antibiotic molecules caused by inter- and/or intra-molecular interactions between the ligands.

Of particular diagnostic value appear to be the relative shifts of both 2α-CH_3 and 2β-CH_3 signals. Different conformations of the thiazolidine five-membered ring are present in natural penicillins, where the β-lactam ring and the axial methyl groups are *syn*, and in penicillin sulfoxide, where they are *anti*. The ^{1}H NMR resonance of 2α-CH_3 is shifted by small amounts downfield and that of 2β-CH_3 upfield by changing from one conformation to the other.[13] In platinum(II) complexes of penicillins, where the metal is proposed to be *S*,*N*-bonded to the ligand, downfield shifts were recorded for both methyl groups and the original conformation is thought to be maintained. In all the complexes presented in this work, 2α-CH_3 protons appear to be shifted upfield by as much as 0.3 ppm, while 2β-CH_3 protons appear to be shifted downfield by a lesser amount, except for $Me_2SnClAmox \cdot 2H_2O$ and $Me_2SnAmox_2 \cdot 2H_2O$

Table 8 ^{13}C NMR data for organotin(IV) amoxicillin derivatives[a,b]

					VII		VIII		IX	
Assignment	$Amox \cdot 3H_2O$	I	II	III	$Amox_1$	$Amox_2$	$Amox_1$	$Amox_2$	$Amox_1$	$Amox_2$
C2	64.44	65.60	c	64.28	65.72	65.79	65.75	c	65.77	c
C2α	27.42	27.17	26.44	26.98	26.66	27.18	26.46	26.83	26.09	27.11
C2β	31.00	32.42	27.67	27.66	28.94	32.24	27.65	28.02	29.24	32.36
C3	73.23	71.43	76.39	76.37	71.73	75.71	74.48	75.41	72.40	74.60
C5	66.89	65.77	68.28	68.28	65.76	65.90	65.75	c	67.22	c
C6	57.74	57.96	58.31	58.39	57.63	59.40	57.64	58.35	58.31	59.32
C7	169.59	166.13	167.08	167.16	165.98	166.81	165.99	167.63	165.98	167.89
C9	170.34	171.58	167.82	170.97	170.51	171.24	170.37	170.53	169.42	170.48
C10	55.45	52.57	50.69	52.01	56.21	56.37	56.19	56.17	52.29	56.10
C11	173.14	171.85	172.62	172.29	171.51	172.34	170.83	171.52	171.14	171.79
C_3', C_5'	115.55	115.25	115.08	115.10	115.35		115.30	115.43	115.41	115.52
C_1'	125.72	128.33	128.20	127.81	128.96		128.38	128.98	128.08	128.14
C_2', C_6'	129.17	128.58	128.74	128.50	129.02		129.18	129.41	129.07	129.58
C_4	158.23	156.99	157.60	156.87	157.72		157.71	157.88	157.37	157.41
Organotin		5.33	13.84	128.15	5.05		13.91		128.57	128.88
carbons			26.93	136.28			19.05		135.92	136.01
				136.77			23.75		136.14	136.22
							27.12			

[a] Solvent DMSO-d_6. Abbreviations: s, singlet; d, doublet; m, multiplet; b, broad.

[b] **I** = $Me_2SnClAmox \cdot 2H_2O$ **II** = $Bu_2SnClAmox \cdot 2H_2O$ **III** = $Ph_2SnClAmox \cdot 2H_2O$
VII = $Me_2SnAmox_2 \cdot 2H_2O$ **VIII** = $Bu_2SnAmox_2 \cdot 2H_2O$ **IX** = $Ph_2SnAmox_2 \cdot 2H_2O$

[c] Not observed.

Table 9 ^{1}H NMR data of organotin(IV) amoxicillin derivatives[a, b]

					VII			VIII			IX		
Assignment	Amox	I	II	III	$Amox_1$		$Amox_2$	$Amox_1$		$Amox_2$	$Amox_1$		$Amox_2$
2α-CH_3	1.38s	1.15s	1.17s	1.13s	1.08s		1.17s	1.08s		1.17s	1.17s		1.28s
2β-CH_3	1.49s	1.23s	157s	1.54s		1.26s		1.52s		1.59s	1.51s		1.54s
H3	3.98s	3.54s	3.64s	3.59s	3.51s		3.53s		3.52s			3.49s	
H10	4.87s	4.40s	4.84s	4.83s		4.35s			4.33m			4.38m	
H5	5.32d	d	5.00m	4.97m		4.76s			4.77s			4.88m	
H6	5.32d	d	5.00m	4.97m		4.93s			4.94d			4.88m	
NH_3^+	5.42s,bd												
NH_2		3.55s	3.61	3.51s		3.65s			3.63bd		3.62s		3.64s
NH	8.68d	8.29s	8.92bd	8.31s	9.04s,bd		8.67d		8.66d			8.77d	
OH	9.05d	8.52bd	9.47bd	8.48bd		9.49vbd			9.05bd			9.04bd	
e[c]	6.78d	6.71d	6.74d	6.70d	6.77d		6.72d		6.72d			6.75d	
f[c]	7.24d	7.22d	7.24d	7.26s	7.31d		7.26d		7.24d			7.08d	
R		0.61s	0.86s	7.35–7.89m		0.65			0.81–0.89m			7.11–7.82m	
			1.28d						1.20–1.35m			7.11–7.82m	
J_{HH}[c]	8.3	8.6	10	8.5	8.6		8.6		8.2			7.9	
$^2J(^1H-^{119}Sn)$		61.7				80.5							
C–Sn–C angle		114°				131.°							

[a] Solvent DMSO-d_6. Abbreviations: s, singlet; d, doublet; m, multiplet; bd, broad; v, very.

[b] **I** = $Me_2SnClAmox \cdot 2H_2O$ **II** = $Bu_2SnClAmox \cdot 2H_2O$ **III** = $Ph_2SnClAmox \cdot 2H_2O$
VII = $Me_2SnAmox_2 \cdot 2H_2O$ **VIII** = $Bu_2SnAmox_2 \cdot 2H_2O$ **IX** = $Ph_2SnAmox_2 \cdot 2H_2O$

[c] H atoms as indicated by e and f in Fig. 1.

[d] Broad band overlapped by DMSO.

where upfield shifts are recorded. While the organic groups R (=Me, Bu, Ph) attached to tin apparently exert a strong stereochemical influence on the geometry of the complexes, a change of conformation cannot be ruled out since one of them (*anti*) could accommodate more easily the bulkiest organometallic moieties.

For $Me_2SnAmox_2 \cdot 2H_2O$, where $|^2J(^1H-^{119}Sn)|$ could be detected, the C–Sn–C angle could be evaluated by means of the Lockhart relationship.[48] The value of 131° for the organometallic moieties in solution is in very good agreement with that of the species in the solid phase (130 ± 13°) (Table 6). As for $R_2SnClAmox \cdot 2H_2O$ complexes, the limited solubility of these compounds in most solvents prevented the evaluation of ^2J coupling constants, except for the case of $Me_2SnClAmox \cdot 2H_2O$. The value of 70 Hz for $|^2J(^1H-^{119}Sn)|$ gives a C–Sn–C angle of 114°, which is reasonably near to the 120° found for the solid state on the basis of Mössbauer data (Table 3). The calculated C–Sn–C angles support the conclusion that the same structure is maintained both in the solid and in solution phase.

CONCLUSION

Numerous new diorgano and triorganotin derivatives of amoxicillin have been prepared and their stoichiometries demonstrated.

Finally, work is in progress in order to investigate the *in vivo* cytotoxicity of the complexes. In particular there is preliminary evidence for damage towards mitotic chromosomes of *Rutilus rubilio* (Bp.) (pisces, cyprinidae) in solutions of organotin(IV)chloroamoxicillin derivatives.

Acknowledgements Financial support by the Ministero per l'Università e la Ricerca Scientifica e Tecnologica, Roma, is gratefully acknowledged.

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