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New trimethyltin(IV) derivatives of dipeptides: synthesis, characteristic spectral studies and biological activity

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New trimethyltin(IV) derivatives with general formulae $Me_3Sn(HL)$, where HL is the monoanion of glycyltyrosine (H_2L-1), glycylisoleucine (H_2L-2), leucylleucine (H_2L-3), leucyltyrosine (H_2L-4), alanylvaline (H_2L-5), and valylvaline (H_2L-6) have been synthesized by the reaction of Me_3SnCl and the sodium salt of the respective dipeptide with filtration of the NaCl formed. The bonding and coordination behaviour in the compounds synthesized are discussed on the basis of IR and ^{119}Sn Mössbauer spectroscopic studies in the solid state and multinuclear ^1H, ^{13}C and ^{117}Sn magnetic resonance in solution. These investigations suggest that, in the solid state, all the ligands in $Me_3Sn(HL)$ act as monoanionic bidentates coordinating through the COO^- and NH_2 groups. The ^{119}Sn Mössbauer studies indicate that, for these polymeric derivatives, the polyhedron around tin in $Me_3Sn(HL)$ is a trigonal-bipyramid with the three methyl groups in the equatorial positions, while the axial positions are occupied by a carboxylic oxygen and the amino nitrogen atom from the adjacent molecule. The NMR data suggest that, in solution, an equilibrium between solvated and intramolecular coordinated monomeric species exists. The anti-inflammatory and cardiovascular activities and toxicity of all these compounds have been determined. All the compounds have also been screened against *Staphylococcus aureus* Mau (29/58), *S. aureus* Mau (78/71), *Bacillus subtilis* (18/64), *Escherichia coli* (326/71), *E. coli, Candida albicans* (Pn-10), *Microsporum gypseum* and *Euglena gracillis*. All the $Me_3Sn(IV)$ compounds exhibit good anti-inflammatory activity. Me_3Sn(Gly–Tyr) and Me_3Sn(Gly–Ile) display a potent cardiovascular activity and Me_3Sn(Ala–Val) exhibits good antibacterial activity against all the strains chosen.

KEYWORDS: trimethyltin(IV); dipeptides; multinuclear magnetic resonance; ^{119}Sn Mössbauer; anti-inflammatory activity; antimicrobial activity

INTRODUCTION

The chemistry of triorganotin derivatives holds considerable importance owing to their potential industrial and biological applications. It has been reported much earlier[1] that mitochondrial oxidative phosphorylation is inhibited for 50%

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in vitro by a low concentration (0.3 μM) of the triethyltin (Et_3Sn) moiety. This indicates that the Et_3Sn moiety may have an affinity for a site or sites in the mitochondrial oxidative-phosphorylation system. Thus, several studies have been carried out to understand how triorganotin(IV) compounds interact with molecules in biological fluids.[1–8] This resulted in concerns about the probable impact of triorganotin derivatives on the environment and prompted researchers to focus attention on the speciation of organotins in biological systems. These studies revealed that the biological activity of these compounds may be due to the presence of easily hydrolysable groups (easily dissociable chelating ligands) yielding intermediates containing formal $R_nSn^{(4-n)+}$ ($n = 2$ or 3) moieties, which may bind with DNA or proteins.[9] Further, Et_3Sn compounds have been proposed as models for the metal–protein interaction, because two Et_3Sn moieties bind to one molecule of the R-quaternary state of cat or rat haemoglobins.[2–4] The binding in the Et_3Sn–haemoglobin complex has been found to depend on the existence of a specific three-dimensional configuration of cysteine and histidine residues.[4] Moreover, from ^{119}Sn Mössbauer data, it was considered that in the binding scheme of triorganotin moieties with protein systems, viz. haemoglobins[10] and the adenosine triphosphate (ATP) systems,[11,12] the tin atom adopts five-coordination in a *cis*-trigonal bipyramidal arrangement.

In this wide context of the chemistry of triorganotin compounds, several studies[6,13–19] addressed the interaction of triorganotin moieties with biomolecules during the last decade. Further, their biological significance widened because they are members of a potential class of biologically active compounds exhibiting antitumour,[7,8,20–25] antimicrobial,[26–32] anti-inflammatory,[33] cardiovascular,[33] and antituberculosis[34] activities.

However, in order to obtain a better insight into the coordination behaviour of triorganotin compounds in biological systems, studies on their binding mode with simple molecules, such as amino acids and peptides, are indispensable. Initial efforts in this field have been made by Ho and Zuckerman[35] in the study of the bonding behaviour of trimethyltin(IV) and tricyclohexyltin(IV) derivatives of glycylglycine and a few amino acids. These findings[35] led to extensive research on triorganotin(IV)–amino acid[6,8,26–29,35] or –terminally protected dipeptide systems.[8] Further, trimethyltin(IV) derivatives of two terminally protected dipeptides, viz. methyl *N*-benzoyl-L-leucyl-L-histidine and methyl *N*-benzoyl-L-histidyl-L-cysteine have been proposed[36] as models for the bonding scheme of trimethyltin moieties with, respectively, the high-affinity site of ATPase (histidine only), and the low-affinity site of ATPase and haemoglobins (histidine and cysteine). Notwithstanding the potential of triorganotin–peptides, only limited studies[25,33,35] have been performed on these systems when compared with studies of diorganotin(IV)–peptide systems.[6,8,25,33,37]

In order to widen the scope of investigations on the coordination behaviour of ligands occurring in biological systems towards triorganotin moieties, we carried out systematic studies of triorganotin(IV) derivatives of biologically relevant ligands, with the final goal to develop new derivatives with potential biological activity. Here, we report the synthesis and structural studies on some trimethyltin(IV) derivatives of dipeptides, viz. glycyltyrosine (Gly–Tyr), glycylisoleucine (Gly–Ile), leucylleucine (Leu–Leu), leucyltyrosine (Leu–Tyr), alanylvaline (Ala–Val) and valylvaline (Val–Val). The structure of the complexes formed is discussed, with special focus on the possible modes of coordination. Also, the cardiovascular, anti-inflammatory and anti-microbial activities of all the complexes are reported.

EXPERIMENTAL

All the reactions were carried out under an anhydrous atmosphere. Solvents were purified and dried before use. Trimethyltin(IV) chloride (E. Merck), Gly–Tyr, Gly–lle, Leu–Leu, Leu–Tyr, Ala–Val and Val–Val (racemic, Sigma) were used as received; from NMR data, in solution the trimethyltin complexes of Leu–Leu and Ala–Val appeared to exist in diastereomerically impure forms, i.e. to exist as *RR′*/*SS′* and *RS′*/*SR′* forms.

Synthesis of trimethyltin(IV) derivatives of dipeptides by the NaCl method

The dipeptide (2.5 mmol) was dissolved in a minimum amount (20 ml) of dry methanol. Sodium methoxide, prepared by reacting sodium (1.2 equivalents) in dry methanol (15 ml), was then added. The resulting mixture was first stirred at room temperature for 0.5 h and then refluxed, giving a clear solution of NaHL within 0.5 h. Refluxing was continued for another 8–10 h with constant stirring. A hot methanol solution (20 ml) of trimethyltin(IV) chloride (2.5 mmol) was added to the solution of the preformed dipeptide sodium salt (NaHL), giving a clear solution. The resulting mixture was further refluxed with constant stirring for another 14–16 h, and was then centrifuged and filtered in order to remove the NaCl formed. The excess of solvent was removed under reduced pressure. The oily mass obtained was solidified by trituration with petroleum ether (b.p. 60–80 °C/40–60 °C, E. Merck) and recrystallized from a methanol–petroleum ether (1 : 3 v/v) mixture.

Physical, chemical and biological characterizations

The melting points and carbon, hydrogen and nitrogen analysis of the complexes synthesized were carried out on the same instruments as reported recently.[25,33] The tin content in the complexes synthesized was determined gravimetrically as SnO_2.[25,33,37]

IR and ^{119}Sn Mössbauer spectra were recorded on the same instruments and by the same procedures as reported previously.[25] The NMR spectra were acquired on a Bruker Avance DRX250 instrument equipped with a Quattro probe

tuned to 250.13 MHz, 62.93 MHz and 89.15 MHz for ^{1}H, ^{13}C and ^{117}Sn nuclei respectively, and on a Bruker AMX500 spectrometer (operating at 500.13 MHz and 186.50 MHz for ^{1}H and ^{119}Sn respectively) for ^{1}H–^{119}Sn HMQC spectra, as described previously.[25]

The anti-inflammatory activity (percentage inhibition), LD_{50} (mg kg^{-1}) and cardiovascular activity of all the complexes synthesized were evaluated according to the procedures reported recently.[33,37]

Antimicrobial activity

All the complexes synthesized have been screened *in vitro* for their anti-microbial activity against Gram-positive bacteria: *Staphylococcus aureus* Mau (29/58) and (78/71), and *Bacillus subtilis* (18/64); Gram-negative bacteria: *Escherichia coli* (326/71) and *E. coli*; yeast: *Candida albicans*; and mould: *Microsporum gypseum*. The antimicrobial activity of the complexes synthesized has been carried out by the standard dilution method[38] in sabouraud agar medium (glucose 10 g, peptone 5 g, glycerol 5 g, nutrient broth 25 g, agar 30 g, distilled water to 1000 ml) at 45 °C. The minimum inhibitory concentration (MIC, μg ml^{-1}) of all the compounds was determined. Further, all the complexes synthesized have been tested on the autotrophic form of unicellular flagellate *Euglena gracillis* on growth (toxicity) and on the plastid system (bleaching activity-induction of chloroplast-free mutants). These effects were monitored in a liquid Cramer–Myers medium containing appropriate concentrations (2.0–30.0 μg ml^{-1}) of the synthesized complexes. Fresh solutions of the complexes studied were prepared in dimethylsulfoxide (DMSO). The inoculum *E. gracillis* was taken from the exponential growth phase and cultivation was performed for 96 h under permanent illumination of 26 ± 2 °C. Data were used for the graphical determination of ED_{50} toxicity values (in 10^{-3} mol μl^{-1}) and determination of $\log(1000/ED_{50})$ values (in μmol l^{-1}).

RESULTS AND DISCUSSION

Synthetic aspects

The reaction of Me_3SnCl with the sodium salt, formed according

$$H_2L + NaOMe \longrightarrow NaHL + MeOH \quad (1)$$

of the dipeptides led to the formation of the complex according to

$$Me_3SnCl + NaHL \xrightarrow{1:1} Me_3Sn(HL) + NaCl \quad (2)$$

where H_2L is as given in Scheme 1.

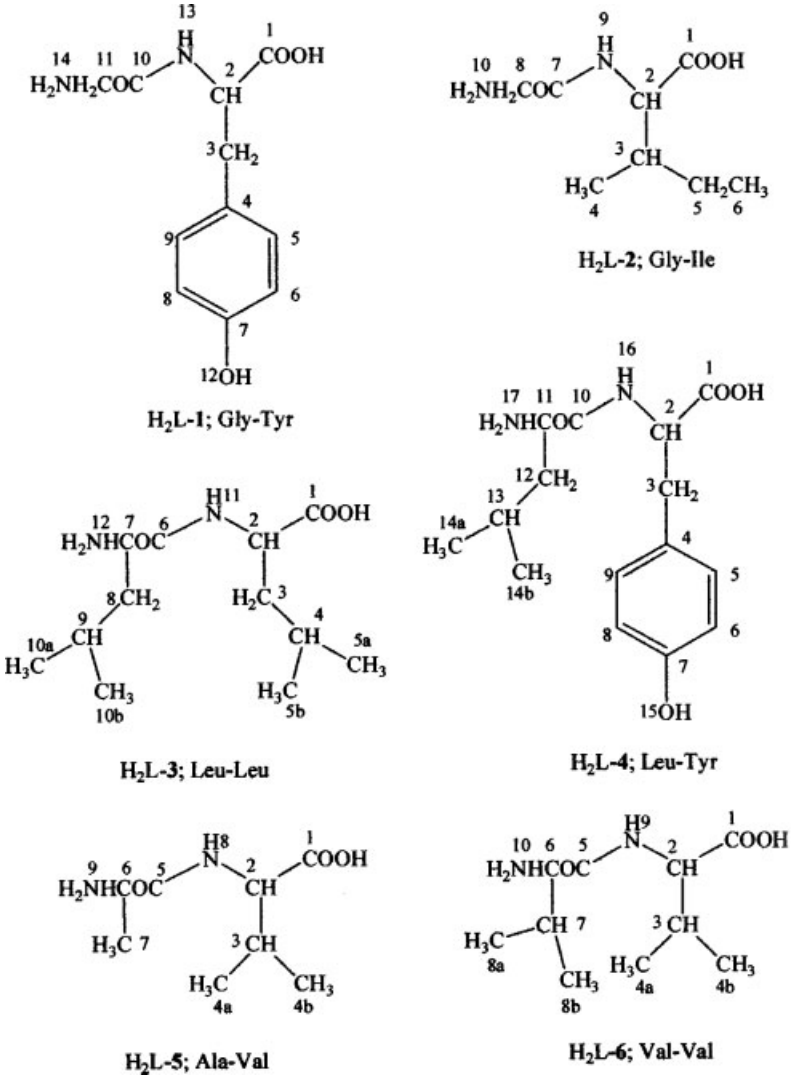
The reactions in Eqns (1) and (2) required 18–20 h of reflux. The resulting solids were obtained in good yields. The complexes are stable towards air and moisture, soluble in methanol and DMSO, but sparingly soluble in chloroform and other usual organic solvents. The analytical data of the complexes are presented in Table 1. From the data it can be inferred that the resulting complexes crystallized with 1:1 stoichiometry regardless of the proportions of the trimethyltin(IV) moiety and dipeptide used.

IR spectral studies

Characteristic IR frequencies (cm^{-1}) and their assignments for the dipeptides and their trimethyltin(IV) derivatives are presented in Table 2. In all the trimethyltin(IV) derivatives of the dipeptides studied, very intense absorption bands in the range 3430–2925 cm^{-1} due to the $\nu(N–H)_{amino}$ undergo a substantial lowering in comparison with the dipeptides (3465–2955 cm^{-1}), indicating coordination by the amino group to the central tin atom. Similar results have been reported for R_3SnAA (AAH = amino acid)[8,26–29,35] and $R_3Sn–L$ (H_2L = dipeptide).[25,33,35] Further, for all these derivatives broadening occurs in the region 3500–3000 cm^{-1}, which indicates either overlapping of ν(OH) and ν(NH) vibrations, especially in the derivatives of H_2L-1 and H_2L-4, or the presence of inter- and/or intra-molecular hydrogen bonding.[8,35] The appearance of a new band of medium intensity in the region 410–465 cm^{-1} in all the trimethyltin(IV) derivatives, which may be assigned to $\nu(Sn\leftarrow N)$, further confirms the coordination of the amino nitrogen to the trimethyltin(IV) group.[8,25–29,33,35]

The IR absorption spectra indicate that ν_{as}(O–C=O) absorption frequencies shown by these amino-coordinated derivatives get shifted to higher frequencies (1645–1615 cm^{-1}) in comparison with the dipeptides (1615–1550 cm^{-1}), whereas the corresponding ν_s(O–C=O) absorption frequencies (1405–1390 cm^{-1}) shift slightly to higher frequencies (5–15 cm^{-1}), except in Me_3Sn(HL-3) and Me_3Sn(HL-5), when compared with the dipeptides (1400–1385 cm^{-1}). The magnitude of the $(\nu_{as} - \nu_s)$(O–C=O)/$(\Delta\nu)$ separation, which has been shown to be useful in identifying structural features,[8] is larger in the amino-coordinated trimethyltin(IV) derivatives ($\Delta\nu$ = 220–250 cm^{-1}) than in the dipeptides ($\Delta\nu$ = 150–215 cm^{-1}). Further, the magnitude of $\Delta\nu$ for all these derivatives has been found to be comparable to that obtained for R_3SnAA (AAH = amino acid)[8,26–29,35] and R_3SnHL (H_2L = dipeptide),[25,33,35] indicating that the carboxylate group acts as a monodentate ligand, and hence the possibility of ionic bonding and also bridging or chelation (which would give $\Delta\nu < 200$ cm^{-1}) can be excluded.[8,26–29,35] Furthermore, the disappearance of a broad band in the spectra of the complexes in the region 2750–2600 cm^{-1}, which was present in all the dipeptides as a weak intensity band (due to $\nu(O–H)_{carboxyl}$), suggests the deprotonation of the COOH group upon complexation.[8] The appearance of a new band of medium intensity in the IR spectra of all the derivatives in the region 545–580 cm^{-1}, which may be assigned to ν(Sn–O), further supports the bonding of the (O–C=O) group to the tin atom.[8,25–29,33,35]

In all the trimethyltin(IV) derivatives studied, an intense band of the amide I (essentially ν(C=O)) at 1650–1675 cm^{-1} in the dipeptides either remains unaffected or shifts slightly by



Scheme 1.

Table 1. Characteristic properties of trimethyltin(IV) derivatives of dipeptides

Complex no.	Complex [empirical formula]	Yield (%)	M.p. (°C)	Colour and physical state	Analysis (%): Found (Calc.)			
					Sn	N	C	H
1	$Me_3Sn(HL\text{-}1)$ $[C_{14}H_{22}N_2O_4Sn]$	77	120–122	Cream solid	29.29 (29.60)	6.79 (6.98)	41.59 (41.94)	5.47 (5.52)
2	$Me_3Sn(HL\text{-}2)$ $[C_{11}H_{24}N_2O_3Sn]$	81	128–131	White solid	33.48 (33.82)	7.56 (7.98)	37.17 (37.65)	6.42 (6.88)
3	$Me_3Sn(HL\text{-}3)$ $[C_{15}H_{32}N_2O_3Sn]$	78	90–92	White solid	28.94 (29.16)	6.58 (6.88)	43.92 (44.26)	7.55 (7.92)
4	$Me_3Sn(HL\text{-}4)$ $[C_{18}H_{30}N_2O_4Sn]$	74	90–93	Cream solid	25.49 (25.97)	6.08 (6.13)	46.87 (47.30)	6.50 (6.60)
5	$Me_3Sn(HL\text{-}5)$ $[C_{11}H_{24}N_2O_3Sn]$	74	164–167	White solid	33.42 (33.82)	7.51 (7.98)	37.22 (37.65)	6.44 (6.88)
6	$Me_3Sn(HL\text{-}6)$ $[C_{13}H_{28}N_2O_3Sn]$	80	117–120	White solid	30.92 (31.32)	6.93 (7.39)	40.88 (41.19)	6.98 (7.44)

5–10 cm^{-1} in the IR spectra of the trimethyltin(IV) derivatives upon complexation. Further, the amide II band [ν(CN) + δ(NH) as well as ν(NH)] observed at 1505–1565 cm^{-1} in the dipeptides remains unaffected upon complexation. These observations indicate that the C═$O_{(amide)}$ and $NH_{(peptide)}$ groups are not involved in the coordination to the Me_3Sn(IV) moiety; instead, they may probably be involved in the intermolecular hydrogen bonding, as reported previously for R_3SnL (H_2L = dipeptide) derivatives.[25,33,35] The ν_{as}(Sn–C) and ν_s(Sn–C) bands in all the trimethyltin(IV) derivatives

Table 2. Characteristic IR frequency (cm^{-1}) of dipeptides and their trimethyltin(IV) derivatives[a]

Complex	Ligand/complex	$\nu(NH)_{amino}$/ $\nu(NH)_{peptide}$	$\nu(CO)_{amide}$ Amide I	$\nu_{as}(OCO)$	$\nu_s(OCO)$	$\Delta\nu$	ν(Sn–O)	ν(Sn←N)	ν_{as}(Sn–C) ν_s(Sn–C)
	H_2L-1	3500[b] s 3417 s 3233 s 3167 s	1668 vs	1559 s	1388 vs	171	—	—	— —
1	Me_3Sn(HL-1)	3406[b] s 3333 s 3271 s 3023 s	1668 s	1615 vsbr	1391 s	224	547 m	420 w	660 m 509 w
	H_2L-2	3442 m 3252 vs 3061 s 2964 s	1667 s	1617 sh	1401 vs	216	—	—	— —
2	Me_3Sn(HL-2)	3299 vs 3260 m 3178 m 2923 vs	1659 vs	1630 vs	1404 s	226	554 vs	449 m	667 m 511 w
	H_2L-3	3255 m 3096 m 2955 m	1650 sh	1589 s	1393 s	196	—	—	— —
3	Me_3Sn(HL-3)	3299 s 3099 m 2960 s	1642 sh	1633 vs	1390 s	243	551 m	426 w	658 w 586 w
	H_2L-4	3433[b] m 3250 s 3108 s 2958 s	1675 m	1596 s 1642 wsh	1394 s	202	—	—	— —
4	Me_3Sn(HL-4)	3424[b] m 3300 s 3203 s 3075 s 2950 s	1682 w	1645 vs 1650 wsh	1396 s	249	551 m	412 m	667 w 617 w
	H_2L-5	3317 s 3042 s 2975 s	1667 s	1550 s	1400 s	150	—	—	—
5	Me_3Sn(HL-5)	3272 vs 3218 sh 3087 m 2933 m	1664 vs	1618 vs	1391 vs	227	579 m	442 w	669 m 549 m
	H_2L-6	3467 m 3167 s 3083 s 2971 s	1659 m	1583 vs	1387 vs	196	—	—	— —
6	Me_3Sn(HL-6)	3432 s 3286 s 3104 m 2965 s 2935 sh	1651 w	1620 vs	1400 s	220	547 w	465 m	638 m 530 w

[a] Intensity of characteristic bands as: vs, very strong; s, strong; m, medium; w, weak; sh, shoulder; br, broad.
[b] ν(OH).

were observed[8,25–29,33,35] at 635–665 cm^{-1} and 510–615 cm^{-1} respectively.

^{119}Sn Mössbauer spectral studies

Whether coordination of the amino group nitrogen atom and bonding of the carboxylic oxygen to tin lead to chelation or polymerization is discussed with reference to the ^{119}Sn Mössbauer spectral data presented in Table 3.

A possible geometry around the tin atom in $Me_3Sn(HL)$ may be a distorted trigonal-bipyramidal one in which the dipeptide anion is bidentate coordinating through a nitrogen–oxygen chelating donor associated with the carboxylic oxygen and amino nitrogen atoms (as revealed from IR).

The Mössbauer spectra of all the $Me_3Sn(IV)$ derivatives exhibit a doublet centred in the isomer shift (IS) value range 1.21–1.32 mm s^{-1} and the quadrupole splitting (QS) values in the range 3.13–3.46 mm s^{-1} show that the electric field gradient around the tin nucleus is generated by the unequal electron densities in the tin–peptide σ bonds[25,28,29,33] and is also due to the geometric distortions. The ρ (QS/IS) values (>2.0 in all the $Me_3Sn(IV)$ derivatives) suggest a tin coordination number superior to four. It has been reported[39,40] that the three conceivable (Fig. 1) five-coordinate isomers of $R_3Sn(OX)$ (where X═O/N; OX are the donor sites of the ligands), have different QS values ranges: 1.7–2.3 mm s^{-1} for isomer (a), 3.0–3.9 mm s^{-1} for (b), and 3.5–4.1 mm s^{-1} for (c).

In all the trimethyltin(IV) derivatives studied, the observed values of IS (1.21–1.32 mm s^{-1}) lie in the range typical of the triorganotin(IV) carboxylates, whereas the QS values (3.13–3.46 mm s^{-1}) are comparable to the typical value of *trans*-trigonal-bipyramidal coordination (Fig. 1b) of tin in R_3SnO_2 fragments (3.00–3.90 mm s^{-1}).[8,41] The QS values in the range 3.0–3.1 mm s^{-1} were also found in the trimethyltin(IV) derivatives of amino acids with *trans*-trigonal-bipyramidal geometry around the tin atom with amino-bridged intermolecular interactions.[29,35] Thus, the tin atom configuration as shown in Fig. 2, in which three methyl groups are in equatorial positions, and the carboxylic oxygen and the amino nitrogen atom from an adjacent molecule are axial, can again be proposed for the $Me_3Sn(HL)$ derivatives. This arrangement with the most electronegative ligands in axial positions of a trigonal bipyramidal structure is quite conventional in organotin(IV) chemistry.[29,35] Further, the possibility of the inter-/intramolecular hydrogen bonding, which is consistent with low solubility of all the trimethyltin(IV) derivatives, as well as with the IR data, cannot be ruled out.

Table 3. ^{119}Sn Mössbauer data (80 K) of the trimethyltin(IV) dipeptido derivatives[a]

Complex	QS (mm s^{-1})	IS (mm s^{-1})	ρ (QS/IS)	τ_1(L)	τ_2(R)
1	3.37	1.30	2.59	0.94	1.10
2	3.13	1.21	2.59	0.93	0.97
3	3.29	1.32	2.49	0.91	0.98
4	3.28	1.27	2.58	1.00	1.24
5	3.17	1.23	2.58	0.94	1.01
6	3.46	1.29	2.68	0.91	1.00

[a] QS: quadrupole splitting; IS: isomeric shift relative to $BaSnO_3$ (splitting: 2.52 mm s^{-1}); τ_1(L): half line-width, left doublet component; τ_2(R): half line-width, right doublet component (mm s^{-1}).

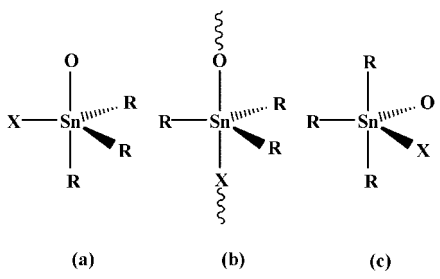


Figure 1. Structure of possible isomers for $R_3Sn(OX)$ (OX = donor sites of the ligand).

Solution NMR spectral studies

^{1}H, ^{13}C and ^{117}Sn NMR chemical shifts and coupling constants obtained from methanol-d_4 solutions of compounds **1**–**6** are summarized in Tables 4 and 5. Compounds **3** and **5** show two pairs of resonances in both ^{1}H and ^{13}C spectra due to diastereomerism (*RR′*/*SS′* and *RS′*/*SR′*). All compounds exhibit a broadened, somewhat concentration-dependent, ^{117}Sn chemical shift in the region 25–35 ppm. Although triorganotin carboxylates in the solid state often adopt the polymeric motif described above, with a five-coordinated tin atom, these compounds are mostly four coordinate in solution.[42] The ^{117}Sn chemical shift for four-coordinate trimethyltin carboxylates in non-coordinating solvents is reported in the region 140–150 ppm,[43] suggesting that the compounds under investigation, with chemical shift 25–35 ppm, exhibit additional coordination, originating from inter- or intra-molecular association and/or from complexation with the solvent.[43] The broadness (±400 Hz) of the ^{117}Sn resonance at room temperature suggests the existence of an equilibrium reaction between different species. Spectra of compounds **3, 4** and **6** recorded at lower temperature all show an extreme broadening (±4000 Hz) of the resonance between −25 and −50 °C. This sharpens up into two resonances at −90 °C with chemical shifts in the region of 21–23 ppm and 5 to −7 ppm respectively, in approximate intensity ratio of 80/20. This observation is attributed to the slowing down of an equilibrium reaction between a (methanol) solvated species (the major one) and an associated species (the minor one), both chemical shifts being in accordance with five-coordination at tin. The rather small chemical shift dependence on temperature is in favour of an intramolecular association. However, this could

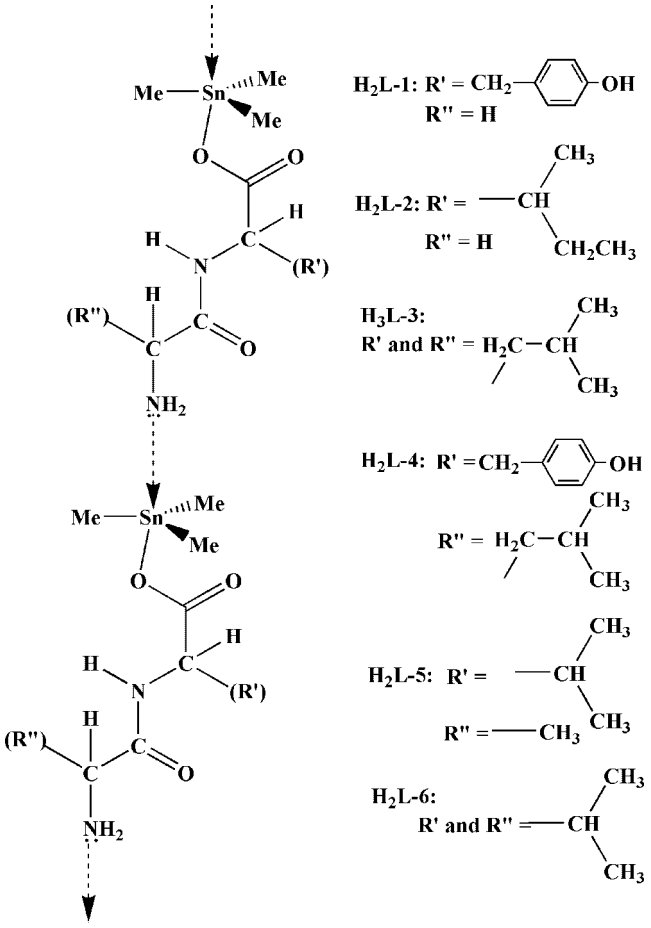


Figure 2. Proposed coordination structure of the trimethyltin(IV) derivatives of dipeptides.

not be confirmed unequivocally by $^{1}H-^{117}Sn$ correlation experiments (see later), due to the residual broadness (±500 Hz) of the tin resonance and, consequently, the very short relaxation time, which prevents the development of long-range coupling correlations.

The $^{1}J(^{13}C-^{117/119}Sn)$ coupling constants of about 500 Hz are consistent with five-coordination, since values in the range 325–390 Hz are reported for four-coordinate tri-*n*-butyltin(IV) compounds, whereas five-coordinated ones exhibit coupling constants in the range 440–540 Hz.[44,45] A similar $^{1}J(^{13}C-^{117/119}Sn)$ coupling constant of about 500 Hz was observed in CD_3OD solutions of the trimethyltin derivative of *N*-benzoylglycylglycine,[46] where a five-coordinated trialkyltin moiety in a trigonal plane is proposed as structural motif.

In all solutions at room temperature, apart from the main broad resonance at 25–35 ppm, a sharp ^{117}Sn resonance is observed in the range −95 to −115 ppm (two resonances for compounds **3** and **5**), together with a signal around 0 ppm. The 2D $^{1}H-^{119}Sn$ HMQC spectra of these solutions display merely $^{2}J(^{1}H-^{119}Sn)$ coupling correlations between proton methyl resonances and ^{119}Sn resonances at 0 ppm, identified to raise from $(CH_3)_4Sn$, on the one hand, and at 25–30 ppm, raising from $(CH_3)_3Sn(HL)$, on the other hand (with $^{2}J(^{1}H-^{119}Sn)$ coupling constants of respectively 54 Hz and 69 Hz). By contrast, the (small) sharp tin resonances in the region −95 to −115 ppm not only correlate with two diastereotopic methyl resonances ($^{2}J(^{1}H-^{119}Sn) = 80$ Hz), but also with the α-proton H-2 of the amino-acid ($^{3,4}J(^{1}H-^{119}Sn) = 40$ Hz (see below)). In some favourable cases, even a correlation with the α-proton of the second amino acid is observed. The absence of long-range couplings for the main resonance at 25–30 ppm is to be ascribed to its broadness, preventing the development of such correlations.

The presence of the additional ^{117}Sn resonances can be explained by a decomposition reaction of the triorganotin-carboxylates, as given in Equation (3), a process which is favoured by the nucleophilic complexation by the methanol molecule from the solvent, which weakens one of the $Sn-CH_3$ bonds that becomes prone to methyl group redistribution:

$$2(CH_3)_3Sn(HL) \longrightarrow (CH_3)_4Sn + (CH_3)_2SnL + H_2L \quad (3)$$

In the dimethyltin compound $(CH_3)_2SnL$, the dipeptide acts as a dianion, the peptide N–H proton being transferred to liberate H_2L, as evidenced by the NMR data. Indeed, both the

Table 4. Characteristic ^{1}H, ^{13}C and ^{117}Sn NMR data of trimethyltin(IV) derivatives **1**–**3** in CD_3OD at 303 K. $^{1}J(^{13}C–^{117/119}Sn)$ coupling constants and $^{2}J(^{1}H–^{117/119}Sn)$ coupling constants for the methyl groups are given between square brackets; homonuclear proton–proton coupling multiplet abbreviations given in parentheses: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet

	1		**2**		**3**	
Atom	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	177.8		177.8		179.8; 179.6[b]	
2	56.9	4.47 (dd: 5.0, 7.7)	60.0	4.17 (d: 5.0)	54.6; 54.5[b,c]	4.28; 4.32[b] (dd)
3	38.4	3.06 (dd: 5.0, 14.0); 2.86 (dd: 7.7, 14.0)	39.0	1.79 (m)	45.2; 43.3[b,c]	1.9–1.3 (m)[d]
4	129.7		16.3	0.83 (d)[e]	26.4; 26.3[b,c]	1.9–1.3 (m)[d]
5	131.4	7.00 (d: 8.5)	26.2	1.42 (m); 1.10 (m)	23.8, 23.7; 23.6, 23.2[b,c]	1.0–0.9 (d)[e]
6	116.4	6.67 (d: 8.5)	12.1	0.83 (dd)[e]	176.5; 175.7	
7	157.4		173.1		54.5; 54.4[b,c]	3.46; 3.48[b] (dd)
8	116.4	6.67 (d: 8.5)	44.4	3.40 (s)	43.2; 42.9[b,c]	1.9–1.3 (m)[d]
9	131.4	7.00 (d: 8.5)			26.0; 25.8[b,c]	1.9–1.3 (m)[d]
10	172.5				22.9; 22.5, 22.4; 22.0[b,c]	1.0–0.9 (d)[e]
11	44.2	3.33 (s)				
Methyl α	−2.0 [480/502]	0.47 [65/68]	−1.9 [484/507]	0.39 [65/68]	−2.1 [480/502]	0.46 [65/67]
^{117}Sn	+36 (−93)[a]		+27 (−99)[a]		+31 (−105; −112)[a]	

[a] Resonances in the region −90 to −115 ppm integrate for 5–10%.
[b] Resonances are in approximate ratio of 45/55 due to diastereomerism; ^{1}H coupling constants cannot be determined due to overlap.
[c] Assignment of 2 and 7, 3 and 8, 4 and 9, 5 and 10 may be interchanged.
[d] Strongly overlapping multiplets.
[e] Strongly overlapping doublets; coupling constants ±7 Hz.

^{117}Sn chemical shifts and the $^{1}H–^{119}Sn$ correlations mentioned are in agreement with a distorted trigonal bipyramidal geometry, similar to the one observed for dibutyltin dipeptide derivatives,[25] where R_2SnL acts as a dianionic tridentate coordinating through the COO^-, NH_2 and $N_{peptide}$ groups. This coordination motif creates two pathways from tin to α H-2, explaining the rather large $^{3,4}J(^{1}H–^{119}Sn)$ coupling constant of 40 Hz.

Anti-inflammatory activity

The anti-inflammatory activity (percentage inhibition) of compounds **1**–**6** was conducted against carrageenan-induced oedema. The results are presented in Table 6. The activity of the standard drugs, phenylbutazone and indomethacin, are also added for comparison.

The results obtained indicate the order of the anti-inflammatory activity of Me_3Sn(IV) derivatives as: Me_3Sn(HL-3) > Me_3Sn(HL-4) > Me_3Sn(HL-1) > Me_3Sn(HL-6) > Me_3Sn(HL-5) > Me_3Sn(HL-2). The analysis of the results obtained indicates that the anti-inflammatory activity is influenced by the nature of the ligand environment of the metal. Furthermore, among the trimethyltin(IV) derivatives studied, compounds **3** and **4** exhibited good anti-inflammatory activity (percentage inhibition 34.3 and 33.3 respectively), slightly lower than that of phenylbutazone (percentage inhibition 38.4), and comparable to that of Ph_3Sn(L-carnosinate) (percentage inhibition 31.2), as reported recently.[33]

The structure–activity correlation of the trimethyltin(IV) derivatives studied reveals that the presence of the substituents in the side chain at the methylene carbon (adjacent to either the O–C=O or NH_2 group), the steric factor, the conformation that the peptidic anion (attached to the Me_3Sn(IV) moiety) may adopt in the cellular fluid, and the stability of Sn–O/N bond may all play an important role in the transport of the Me_3Sn^+ moiety across the cellular membrane, either as a single entity or as a dipeptide derivative as a whole, in order to show any activity.

Toxicity study (LD_{50})

The trimethyltin(IV) derivatives of dipeptides studied were further evaluated for their average LD_{50} (mg kg^{-1}) on albino mice (body weight 20–25 g) of either gender. It has previously been proposed that the triorganotin compounds $R_3Sn(XY)$ act by inhibiting mitochondrial oxidative phosphorylation, probably by binding with amino acids at certain active sites, most likely the imidazole N–H of a histidine residue and/or an S–H group.[9] The LD_{50} values, as presented in Table 6, indicate that these derivatives have a wider safety margin (LD_{50} > 1000 mg kg^{-1}, the maximum dose tested). The observed LD_{50} values of these trimethyltin(IV) derivatives of dipeptides are found to be greater than their triphenyltin(IV) analogues, as reported recently.[33]

Table 5. Characteristic ^{1}H, ^{13}C and ^{117}Sn NMR data of trimethyltin(IV) derivatives **4–6** in CD_3OD at 303 K. $^{1}J(^{13}C–^{117/119}Sn)$ coupling constants and $^{2}J(^{1}H–^{117/119}Sn)$ coupling constants for the methyl groups are given between square brackets; homonuclear proton–proton coupling multiplet abbreviations given in parentheses: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet

	4		**5**		**6**	
Atom	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	178.2		177.9; 178.0[b]		177.8	
2	57.1	4.45 (dd: 5.1, 7.7)	60.8; 60.7[b]	4.17 (d: 5.0); 4.20 (d: 4.7)[b]	61.2	4.18 (d: 5.2)
3	38.6	2.89 (dd: 7.7, 13.8); 3.09 (dd: 5.1, 13.8)	32.4	2.16 (m)[d]	32.9	2.01–2.20 (m)[d]
4	130.1		20.9; 20.8; 20.0; 20.1[b]	0.92, 0.94 (d); 0.91, 0.93 (d)[c]	19.9; 18.5	1.01 (d); 0.94 (d)[c,e]
5	131.6	7.03 (d: 8.5)	176.4; 176.1[b]		175.3	
6	116.2	6.66 (d: 8.5)	51.5; 51.3[b]	3.65 (q: 6.8); 3.69(q: 6.8)	60.7	3.32
7	157.2		18.5; 18.4[b]	1.35 (d), 1.36 (d)[c]	32.3	2.01–2.20 (m)[d]
8	116.2	6.66 (d: 8.5)			19.7; 17.6	0.96 (d); 0.92 (d)[c,e]
9	131.6	7.03 (d: 8.5)				
10	176.6					
11	54.8	3.33 (dd: 5.9, 8.4)				
12	45.0	1.63; 1.32 (m)				
13	25.8	1.47 (m)				
14	23.6; 22.4	0.91 (d: 6.5); 0.89 (d: 6.5)				
Methyl α	−2.1 [n.o.]	0.46 (s) [65/67]	−1.6 [484/507]	0.48 (s) [65/68]	−1.8[484/505]	0.48 (s) [65/68]
^{117}Sn	+36 (−102)[a]		+27 (−104; −115)[a]		+29 (−108)[a]	

[a] Resonances in the region −90 to −115 ppm integrate for 5–10%.
[b] Resonances are in approximate ratio of 45/55 due to diastereomerism.
[c] Overlapping doublets; coupling constants ±7 Hz.
[d] Strongly overlapping multiplets.
[e] Resonances 4 and 8 may be interchanged.

Cardiovascular activity

The cardiovascular activity of the compounds **1–6** was studied on either adult mongrel dogs (body weight 10–20 kg) or on cats (body weight 3–4 kg) of either gender. The results are presented in Table 6. The data for the standard drug Captopril at the same dose level are also included in Table 6. All the trimethyltin(IV) derivatives studied are much less active than Captopril. All the trimethyltin(IV) derivatives studied exhibited mild and delayed hypotensive activity of varying degree and duration (Table 6) without affecting the carotid occlusion and noradrenaline response, which suggests that these compounds may act as direct vasodilator on the smooth muscles of blood vessels. Moreover, none of the compounds studied has shown bradycardia, and hence no change in the resting heart rate. Furthermore, among the trimethyltin(IV) derivatives studied, compound **1** is found to be the most effective, and compounds **2** and **4** have comparable activity. Furthermore, compound **3** has shown a mild activity (fall of 11 mmHg) of shorter duration (9 min). However, the behaviour of compounds **5** and **6** is different, as they had shown immediate fall in blood pressure (8–10 mmHg at a dose of 2.5 mg kg^{-1} (i.v.)) followed by mild and gradual fall in blood pressure (9–11 mmHg) compared with the control value, which lasted for 9 min (compound **5**) and for 29 min (compound **6**). These observations indicate that the hypotensive activity is influenced by the structural features of the side chain at the methylene carbon atom adjacent to either O–C═O and/or amino group in the dipeptide anion coordinated to the trimethyltin(IV) moiety.

Antimicrobial activity

The *in vitro* anti-microbial activity data (MIC, μg ml^{-1}) of compounds **1–6**, screened against the chosen strains, are presented in Table 7.

The results indicate that all the trimethyltin(IV) derivatives (except compound **6**) show a mild activity against the chosen strains, whereas compound **6** has exhibited potent antibacterial activity. The activity of compound **6** is comparable to that of Norflox against *S. aureus* (29/58 and 78/71) and slightly better against *E. coli*. Furthermore, the nature of the ligand environment has little influence on

Table 6. LD_{50} (mg kg^{-1}), anti-inflammatory and cardiovascular activities of trimethyltin(IV) derivatives of dipeptides

Complex[a] / standard	LD_{50} (50 mg kg^{-1} p.o.)	Anti-inflammatory activity (% inhibition) (50 mg kg^{-1} p.o.)	Change in mean blood pressure[b,c] (mmHg)				
			Dose (mg kg^{-1} i.v.)	Control Mean ± SE	Immediate Mean ± SE	Delayed Mean ± SE	Duration (min) Mean ± SE
1	>1000	30.55	2.5	131.2 ± 10.25	—	71.0 ± 11.18[d]	39.6 ± 2.19
2	>1000	26.98	2.5	132.0 ± 7.07	—	92.8 ± 6.41[d]	41.4 ± 2.60
3	>1000	34.28	2.5	131.6 ± 6.69	—	120.4 ± 7.02[e]	9.2 ± 2.28
4	>1000	33.33	2.5	133.2 ± 6.45	—	84.0 ± 4.52[e]	20.0 ± 1.41
5	>1000	27.77	2.5	132.2 ± 8.13	122.0 ± 8.68[d]	113.0 ± 6.32[f]	9.2 ± 2.28
6	>1000	29.79	2.5	137.6 ± 7.66	129.0 ± 6.55[d]	118.2 ± 6.18[f]	29.2 ± 2.28
Phenylbutazone	—	38.90[g]	—	—	—	—	—
Indomethacin[h]	—	—	—	—	—	—	—
Captopril	—	—	2.5	160.0 ± 9.45	150.0 ± 6.95[f]	100.0 ± 10.45[f]	1440.0 ± 30.0

p.o.: pretreated orally; i.v.: intravenously.
[a] Complex number as mentioned in Table 1.
[b] No change in the resting HR (bpm) has been observed in all the derivatives studied.
[c] No effect on carotid occlusion (CO) and noradrenaline (NA) responses by all the derivatives studied.
[d] $p < 0.05$.
[e] $p < 0.01$.
[f] $p < 0.001$.
[g] 65.20% inhibition at 100 mg kg^{-1} p.o.
[h] 52.2% and 93.2% inhibition at 5.0 mg kg^{-1} and 10.0 mg kg^{-1} p.o. respectively.

Table 7. Antimicrobial activity of trimethyltin(IV) derivatives of dipeptides

Complex[a]	MIC (μg ml^{-1}) against							Toxicity value log(1000/ED_{50}) (μmol l^{-1})
	Bacteria[b]					Fungi[b]		
	1	2	3	4	5	6	7	8
1	>25.0	>25.0	>25.0	>25.0	>25.0	>25.0	>30.0	3.60
2	>25.0	>25.0	>25.0	>25.0	>25.0	>25.0	>30.0	3.75
3	>25.0	>25.0	>25.0	>25.0	>25.0	>25.0	>30.0	4.11
4	>25.0	>25.0	>25.0	>25.0	>25.0	>25.0	>30.0	3.31
5	>25.0	>25.0	>25.0	>25.0	>25.0	>25.0	>30.0	3.75
6	2.0	2.0	10.0	10.0	2.0	50.0	18.0	4.62
Norflox	3.0	3.0	—	—	6.2	—	—	—
Cap. Flox	0.78	0.78	—	—	1.5	—	—	—
Amphotericin-B	—	—	—	—	—	0.20	—	—
5-Flucytosine	—	—	—	—	—	1.20	—	—

[a] Complex number as mentioned in Table 1.
[b] Key: 1, *S. aureus* Mau (29/58); 2, *S. aureus* Mau (78/71); 3, *B. subtilis* (18/64); 4, *E. coli* (326/71); 5, *E. coli*; 6, *C. albicans* (Pn-10); 7, *M. gypseum*; 8, *E. gracillis*.

the activity (except for compound **6**). The log(1000/ED_{50}) value (μmol l^{-1}), as determined for the measurement of toxicity value (ED_{50} in 10^{-3} mol μl^{-1}) of these trimethyltin(IV) derivatives against *E. gracillis*, is found to lie in the range 3.31–4.62, the highest being for compound **6**.

An attempt is being made to correlate the toxicity, anti-inflammatory activity, cardiovascular activity and antimicrobial activity of the derivatives studied. The concomitant use of several drugs to treat inflammatory conditions that might be associated with some microbial infections may cause health problems, especially in patients with impaired liver or kidney functions. Thus, from the pharmacological point of view, an anti-inflammatory/antimicrobial agent with minimum adverse side effects and high safety margin is highly desirable. Therefore, it can be proposed on the basis of the results obtained that compounds **1** and **4** can act

as effective anti-inflammatory agents (percentage inhibition ~30 and 33 respectively) because these compounds possess mild antimicrobial activity (MIC 25 μg ml^{-1}), and low toxicity (LD_{50} > 1000 mg kg^{-1}) in spite of the observation that they simultaneously exhibit potent hypotensive activity (~60 mmHg that lasted for 40 min for compound **1** and ~50 mmHg that lasted for 20 min for compound **4**). Furthermore, Me_3Sn(HL-6) can also act as an effective antimicrobial agent because it is less toxic (LD_{50} > 1000 mg kg^{-1}) and exhibits mild hypotensive activity (~20 mmHg that lasted for 30 min, though an immediate fall of ~8 mmHg in blood pressure has been observed).

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