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Characteristic Spectral Studies and *in vitro* Antimicrobial and *in vivo* Multi-Infection Antifungal Activities in Mice of New Organotin(IV) Derivatives of Heterocyclic Amino Acids

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The nature of the products obtained on reacting R_3SnCl (R = Me, Bu and Ph), Ph_2SnCl_2 and Bu_2SnO with amino acids having nitrogen-containing heterocyclic rings; i.e. L-histidine and DL-tryptophan, is shown to depend upon the reaction conditions. Ten new organotin(IV) derivatives of these amino acids have been synthesized and characterized by elemental analyses, molar conductance and electronic spectra, and the bonding in these complexes is discussed in terms of their infrared, far-infrared, ^1H and ^{13}C NMR, and ^{119}Sn Mössbauer spectra. The complexes soluble in DMSO have been tested *in vitro* against a wide spectrum of bacteria and fungi and found to be active. Two complexes, Ph_3SnL-1 and Ph_3SnL-2, have been found to be slightly active *in vivo* against a multi-infection fungal model in mice.

Keywords: organotin; amino acids; antimicrobial activity; multi-infection; antifungal activity

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INTRODUCTION

Knowledge of specific or selective bonding of metal and organometal species to donor sites in biological structures and also in simple biologically relevant oligofunctional molecules is still incomplete. Although organotin compounds find many practical applications, their coordination by biological molecules is not well understood.[1] Part of our work in this field concentrates on studies of organo compounds of Group IV elements and amino acids, their derivatives and appropriate model compounds. The effects of organotins in biological systems include inhibition of mitochondrial phosphorylation[1] and the function of the nervous system.[2] Study of triethyltin binding to rat-liver mitochondria has led to the assignment of two binding sites in the membrane: one of high affinity, the other of low affinity.[3] These binding sites are considered to involve histidine and thiol groups, respectively.[3] Triorganotin(IV) derivatives have recently received considerable attention due to their high antifungal activities against *Ceratocystis ulmi*, which causes Dutch elm disease,[4,5] *Phytophthora palmivora* (Butler) isolated from black pepper and coca leaves,[6] *Aspergillus niger* and *Helminthosporium taulosum*[7] and *Candida albicans*, *Cryptococcus neoformans* and *A. fumigatus*.[8] A considerable amount of work on organotin derivatives of amino acids and peptides has been reported.[9–24] Little definite information exists, however, concerning the reactions of organotin compounds with heterocyclic-ring-containing amino acids. Accordingly, we have studied some new organotin derivatives of amino acids having heterocyclic rings such as L-histidine and DL-tryptophan.

EXPERIMENTAL

All the reactions were carried under an anhydrous and oxygen-free nitrogen atmosphere. Solvents

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were purified, dried and stored under nitrogen. The di- and tri-phenyltin chloride (E. Merck), tributyltin chloride (E.Merck), trimethyltin chloride (Aldrich Chemicals), dibutyltin oxide (Fluka), L-histidine and DL-tryptophan (E.Merck) were used as received.

Syntheses

Synthesis of diphenyltin complexes of amino acids

The amino acid (6.00 mmol) was dissolved in the minimum amount (25 ml) of absolute methanol. To this was added sodium methoxide, prepared by dissolving sodium (6.50 mmol) in absolute methanol (10 ml) under dry nitrogen, and the resulting solution was refluxed for 2–3 h with constant stirring. A hot methanolic solution of diphenyltin chloride (3.00 mmol) in 1:2 (organotin/amino acid) molar ratio was added to the solution of the sodium salt of the amino acid. The mixture was again refluxed with constant stirring for 5–6 h. It was centrifuged and filtered to remove the sodium chloride, and any excess of solvent was removed under reduced pressure. The semi-solid product thus obtained was solidified by trituration with petroleum ether (b.p. 40–60 °C). The complexes were recrystallized from a 1:2 (v/v) mixture of methanol and petroleum ether (b.p. 40–60 °C).

Synthesis of triorganotin complexes of amino acids

The amino acid (4.00 mmol) was dissolved in the minimum amount (25 ml) of absolute methanol. To this was added sodium methoxide, prepared by dissolving sodium (4.20 mmol) in absolute methanol (10 ml) under dry nitrogen, and the resulting solution was refluxed for 2–3 h with constant stirring. A hot methanolic solution of trimethyl-, tributyl- or triphenyl-tin chloride (4.00 mmol) in approx 1:1 molar ratio was added to the solution of the sodium salt of the amino acid. It was again refluxed with constant stirring for 5–6 h and crystallization of the complex was carried out as described above.

Synthesis of dibutyltin complexes of amino acids

The complexes were prepared under anhydrous conditions by dropwise addition of a dry, hot benzene–methanol (3:1 v/v, 100 ml) solution of the dibutyltin(IV) oxide (4.00 mmol) in a 1:2 molar ratio to the amino acid (8.00 mmol) in hot methanol (25 ml). The mixture was refluxed with constant stirring giving a clear solution after 10–30 min. Refluxing was continued for 9–10 h with azeotropic removal of water. Any excess of solvent was removed under reduced pressure. The oily product thus obtained was solidified by trituration with petroleum ether (b.p. 40–60 °C), and recrystallized from a 1:2 (v/v) mixture of methanol and petroleum ether (b.p. 40–60 °C).

Melting points were determined on a Toshniwal capillary melting-point apparatus and were uncorrected. Tin and nitrogen in the complexes were determined by gravimetric and Kjeldahl's methods, respectively.[25,26] Infrared and far-infrared spectra were recorded on an FTIR spectrophotometer model FTS 165, at 4000–400 cm^{-1} in KBr discs and 600–200 cm^{-1} in CsI discs, respectively, at the Institute of Exploration and Petroleum, Dehradun, India. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker VM-400, MHz spectrophotometer at the Central Drug Research Institute (CDRI), Lucknow, India, using DMSO-d_6 as the solvent and tetramethylsilane as the internal standard. Experimental details of the ^{119}Sn Mössbauer spectra[26,27] and antimicrobial activity[27] of the complexes were similar to those reported previously.

Antimicrobial activity

A multi-infection (*Cand. albicans*—vaginal and systemic; *Crypt. neoformans*—lungs; and *Trichophyton mentagrophytes*—skin infection) model in Balb/c mice was used for rapid screening of the compounds.[28] The mice were pretreated with estradiol (500 μg/mouse) on day 4, and the compound was evaluated five after days of inoculation. The evaluation was based upon culture, cfu from tissue homogenates- kidney, lung, vagina and skin.

RESULTS AND DISCUSSION

Reactions of R_3SnCl and Ph_2SnCl_2 with the sodium salt (formed by Eqn [1]) of the amino acids having nitrogen-containing heterocyclic rings; i.e. L-histidine (HL-1) and DL-tryptophan (HL-2), in 1:1 and 1:2 molar ratio, respectively, led to the formation of the complexes according to Eqns [2] and [3]. Reactions of dibutyltin(IV) oxide with the amino acids in a benzene–methanol (3:1, v/v) mixture

afforded the complexes in a 1:2 molar ratio with azeotropic removal of water (Eqn [4]):

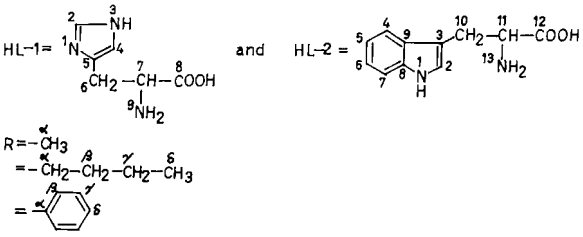
$$\text{HL-1/HL-2} + \text{NaOMe} \rightarrow \text{Na(L-1/L-2)} + \text{MeOH} \quad [1]$$

$$R_3SnCl + \text{Na(L-1/L-2)} \rightarrow R_3Sn\text{(L-1/L-2)} + \text{NaCl} \quad [2]$$

$$Ph_2SnCl_2 + 2\text{Na(L-1/L-2)} \rightarrow Ph_2Sn\text{(L-1/L-2)}_2 + 2\text{NaCl} \quad [3]$$

$$Bu_2SnO + 2\text{(HL-1/HL-2)} \rightarrow Bu_2Sn\text{(L-1/L-2)}_2 + H_2O \quad [4]$$

where



The above reactions were found to be facile and were complete within 9–10 h of refluxing. The resulting complexes were obtained in good yield (45–90%) and were coloured solids, except **3, 5** and **6**, which were viscous semi-solids. They were soluble in methanol and sparingly soluble in chloroform, dimethyl sulphoxide and dimethylformamide. Satisfactory elemental analyses (Table 1) have been obtained for all the complexes, in good agreement with the proposed 1:1 or 1:2 stoichiometry between the organotin moiety and the amino acids. The low values of the molar conductances of 10^{-3} M solutions of the complexes in methanol (37.30–78.01 Ω^{-1} cm^2 mol^{-1}) indicated their non-electrolytic nature (Table 1).

Structural proposals are based on vibrational data, which are collected in Table 2; additional information came from Mössbauer measurements of the complexes. Infrared NH_2 stretching frequencies were used to distinguish coordinated from free amino groups. The amino acids themselves exist in a zwitterionic form RCH $(NH_3^+)COO^-$, in the solid state. Free NH_2 groups are found in the amino-acid salts and matrix isolated species. Comparison of the $\nu(NH)_{amino}$ of the sodium salts (3200 and 3228 cm^{-1} for NaL-1 and NaL-2, respectively) or of matrix isolated amino acids (HGly: 3414 cm^{-1}) with those of the solid compounds **1–10** (2861–2969 cm^{-1}; Table 2) shows a shift to lower frequencies for the latter compounds, indicating coordination of the amino group to the central tin atom.[10] Similar results have been reported for R_3SnAA (AA = amino acid)[10] and R_2SnL (H_2L = dipeptide).[23,24] The zwitterionic forms of the amino acids in the solid state have symmetric anionic carboxylate groups, as do their salts. The ν_{as} (COO) and ν_s (COO) in the compounds **1–10** were observed at 1660 ± 16 and 1412 ± 24 cm^{-1}, respectively, indicating that ν_{as} (COO) moved to higher frequencies and ν_s (COO) to lower frequencies than in the amino acids themselves. Strong interactions between the carboxylate carbonyl and the tin atom were ruled out on this basis.[10] The band positions and also $\Delta\nu$ values [ν_{as}(COO) – ν_s(COO)] were in the range 235–260 cm^{-1} (Table 2) and were comparable with those obtained for R_3SnAA[10] and R_3Sn(AcGlyO), R_3Sn(AcAlaO) and R_3Sn(AcMetO),[13] indicating that the carboxylate groups act as monodentate; ionic as well as bridging or chelated (COO) groups, which would give $\Delta\nu < 200$ cm^{-1}, were excluded.[13] The conclusions drawn above were further supported by the presence of new bands in the far-IR spectra of all the complexes, at *ca* 447 ± 27 and

Table 1 Analytical and physical data of organotin(IV) complexes of amino acids

	Complex (empirical formula)	Yield (%)	Colour	M.p. (°C)	Analysis (%): Found (Calcd) Sn	N	Molar conductance (Ω^{-1} cm^2 mol^{-1})
1	Ph_3SnL-1 ($C_{24}H_{23}N_3O_2Sn$)	67	Cream	248–249 (d)	23.08(23.54)	8.00(8.33)	38.02
2	Ph_3SnL-2 ($C_{29}H_{26}N_2O_2Sn$)	87	Light brown	212–215 (d)	21.25(21.45)	5.01(5.06)	70.43
3	Me_3SnL-1 ($C_9H_{17}N_3O_2Sn$)	45	Cream	Semi-solid	36.98(37.33)	13.18(13.22)	37.30
4	Me_3SnL-2 ($C_{14}H_{20}N_2O_2Sn$)	71	Brown	207–210 (d)	32.08(32.34)	7.50(7.63)	50.02
5	Bu_3SnL-1 ($C_{18}H_{35}N_3O_2Sn$)	50	Cream	Semi-solid	26.61(26.72)	9.32(9.46)	47.50
6	Bu_3SnL-2 ($C_{23}H_{38}N_2O_2Sn$)	75	Dark brown	Semi-solid	23.98(24.06)	5.61(5.67)	60.57
7	$Ph_2Sn(L\text{-}1)_2$ ($C_{24}H_{26}N_6O_4Sn$)	60	Light yellow	235–236 (d)	20.12(20.42)	14.35(14.46)	40.05
8	$Ph_2Sn(L\text{-}2)_2$ ($C_{34}H_{32}N_4O_4Sn$)	76	Light grey	219–222	17.02(17.47)	8.13(8.25)	78.01
9	$Bu_2Sn(L\text{-}1)_2$ ($C_{20}H_{34}N_6O_4Sn$)	69	Light brown	209–210 (d)	20.98(21.93)	15.49(15.53)	53.02
10	$Bu_2Sn(L\text{-}2)_2$ ($C_{30}H_{40}N_4O_4Sn$)	90	Dark brown	180–183 (d)	18.21(18.56)	8.72(8.76)	60.00

Table 2 Characteristic infrared frequencies (cm^{-1}) of organotin(IV) complexes of amino acids

Amino-acid complex	ν(N-H) of heterocyclic ring/of amino group	ν_{as}(COO)	ν_s(COO)	$\Delta\nu$	ν_{as}(Sn–C)	ν_s(Sn–C)	ν(Sn–O)	ν(Sn⟶N)
HL-1	3494s 3379s 2883w	1633w	1450m	183	—	—	—	—
HL-2	3567vw 3397vs 3301w 3038vs	1662vs	1453s	209	—	—	—	—
NaL-1	3500s 3382m 3200m	1580s	1453s	127	—	—	—	—
NaL-2	3563w 3422vs 3287s 3228w	1661sh 1583s	1468m	115	—	—	—	—
Ph_3SnL-1	3485s 3412s 3257m 2967w	1647vs	1407vs	240	266s	245m	555m	467w
Ph_3SnL-2	3472w 3424vs 3072vs 2880w	1676vs	1420s	256	267s	238s	540s	431s
Me_3SnL-1	3456w 3070s 2912s	1644m	1388vs	256	544vs	525w	—[a]	420w
Me_3SnL-2	3404vs 3329m 3042m 2861m	1664vs	1418vs	246	540s	529s	583vs	426vs
Bu_3SnL-1	3467sh 3408s 3328s 2954s	1644vs	1407w	237	572m	516w	545w	456w
Bu_3SnL-2	3421brm 2954w 2923vs	1670m	1435m	235	575m	520w	556w	473w
$Ph_2Sn(L\text{-}1)_2$	3366m 3074w 2950m	1645m	1402vs	243	274m	246brs	538w	420w
$Ph_2Sn(L\text{-}2)_2$	3470m 3425s 3250m 2969w	1670m	1410s	260	270m	240m	550m	424m
$Bu_2Sn(L\text{-}1)_2$	3448s 3410m 3010m 2925m	1653m	1394m	259	580m	516s	540w	420w
$Bu_2Sn(L\text{-}2)_2$	3407m 3063w 2955s 2930s	1648vs	1403vs	245	602w	520w	569w	422w

Abbreviations: vs, very strong; s, strong; m, medium; w, weak; sh, shoulder; br, broad.
[a] Merge with ν_{as} (Sn–C).

$554 \pm 16\ cm^{-1}$, which may be assigned to (Sn⟶N) and ν(Sn-O), respectively.[26,27] The presence of both stretching vibrations, ν_{as} (Sn-C) and ν_s (Sn-C), in the IR spectra of the triorganotin(IV) compounds in the solid state (Table 2) ruled out an exactly planar arrangement of the three Sn-C bonds (i.e. an exactly symmetrical trigonal-bipyramidal arrangement around the central tin

Table 3 ^{1}H NMR data of organotin(IV) derivatives of amino acids

Complex[a]	δ (ppm)[b]
1	8.01, s, 1H (H-3); 7.05–7.90, m, 17H (15H of 3(-C_6H_5) of tin + H-2, H-4); 3.15, d, 2H (H-6); 3.30, m, 1H (H-7); 6.85, m, 2H (H-9)[c]
2	7.90, s, 1H (H-1); 7.10–7.85, 2m centred at 7.28, 7.70, 20H [15H of 3(-C_6H_5) of tin + H-2, H-4, H-5, H-6, H-7]; 3.50, d, 2H (H-10); 3.60, m, 1H (H-11); 6.95, brm, 2H (H-13)[c]
4	7.89, s, 1H (H-1); 7.30, m, 2H (H-2, H-5); 7.50–7.70, m, 3H (H-4, H-6, H-7); 3.25, d, 2H (H-10); 3.70, m, 1H (H-11); 6.75, brm, 2H (H-13)[c]; 0.50, t, 9H [3(-CH_3)of tin]
10	8.05, s, 2H [2(H-1)]; 7.05, m, 4H [2(H-2,H-5)]; 7.35–7.80, m, 6H [2(H-4, H-6, H-7)]; 3.25, d, 4H [2(H-10)]; 3.75, m, 2H [2(H-11)]; 6.80, brm, 4H [2(H-13)]; 1.25–1.85, brm, 12H [2(-$CH_2CH_2CH_2$) of tin]; 0.65, t, 6H [2(-CH_3) of butyl of tin]

[a] As indicated in Table 1.
[b] Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.
[c] δ(NH), concentration-dependent.

atom.[10]) Since the ν_{as} (Sn-C) bands were not split, a T-shaped geometry could be ruled out as well.[10] The presence of both ν (Sn-C) stretching vibrations in the diorganotin(IV) derivatives excluded the presence of a linear C–Sn–C bond in the octahedral diorganotin derivatives with two *trans–axial* organic groups. One Sn-C band only in the 500–610 cm^{-1} region has been reported in the dialkyltin(IV) complexes of *N*-acetylamino acids indicating two alkyl groups in *trans–axial* positions.[29]

The chemical shifts (δ ppm) of the various protons in the organotin compounds which are sufficiently soluble in DMSO-d_6 are given in Table 3. ^{1}H NMR spectra of all other complexes could not be recorded due to their low solubility in $CDCl_3$ and DMSO-d_6. The absence of a signal due to the -OH proton at δ = 12.00–13.00 ppm suggests deprotonation of the carboxylic oxygen atom of the amino acids on complexation.[30] The NH signal of the amino group is shifted to higher field, $\delta = 6.85 \pm 0.1$ ppm, indicating the coordination of the NH_2 group to tin. Similarly the -NCH< signal is shifted upfield (δ = 3.30 ppm for compound **1** and $= 3.70 \pm 0.1$ ppm for compounds **2, 4** and **10**) on complexation in comparison with the free zwitterionic form (-NCH< at δ = 3.97 ppm for HL-1 and at δ = 4.04 ppm for HL-2 in D_2O).[31] The ^{13}C chemical shifts of the various carbon atoms in the compounds **1, 2, 4** and **10** in DMSO-d_6 are given in Table 4. The resonances of COO for the amino acids are observed at larger δ on complexation as compared with those of free amino acids; HL-1 shows COO at δ = 173.7 ppm and HL-2 shows COO at δ = 174.7 ppm.[31] The shifts observed in C^{α} (C-7 for compound **1** and C-11 for compounds **2, 4** and **10**) and C^{β} (C-6 for compound **1** and C-10 for compounds **2, 4** and **10**) resonances of amino acids in the organotin derivatives are due to the coordination of the amino acids through the NH_2 and COO groups to tin. The ^{13}C chemical shifts of phenyl, butyl and methyl groups attached to tin are observed at positions comparable with other, similar compounds.[32–34] Due to insufficient solubility of the organotin complexes in $CDCl_3$ and DMSO-d_6, their ^{119}Sn NMR spectra could not be recorded.

Whether the coordination of the amino-group nitrogen atom tends to lead to chelation or polymerization can be discussed with reference to the ^{119}Sn Mössbauer data listed in Table 5. The chemical shift (C.S.) values indicate the presence of tin in the +IV oxidation state and quadrupole splitting (Q.S.) shows that the electric field gradient around the tin nucleus is produced by the inequalities in the tin–amino acids σ-bonds. The ρ(Q.S./C.S.) values (>2.1 in all the complexes) indicate a coordination number greater than four. A possible geometry around the tin in R_3SnL (where R = Me, Bu, Ph and L = anion of HL-1 and HL-2) is a distorted trigonal bipyramid in which the amino-acid anion is monofunctional and bidentate coordinating through an ON donor set derived from the carboxylic oxygen and amino nitrogen atoms (as revealed from infrared spectra). All the

Table 4 ^{13}C NMR data of organotin(IV) derivatives of amino acids

Complex[a]	δ(ppm)
1	C-2, 135.95; C-4, 127.57; C-5, 103.94; C-6, 28.82; C-7, 53.05; C-8, 175.35; C-α, 137.20; C-β, 134.10; C-γ, 128.71; C-δ, 129.95
2	C-2, 123.50; C-3, 96.38; C-4, 121.25; C-5, 118.45; C-6, 111.20; C-7, 128.05; C-8, 136.35; C-9, 120.00; C-10, 29.85; C-11, 55.10; C-12, 176.10; C-α, 136.80; C-β, 134.21; C-γ, 128.50; C-δ, 129.80
4	C-2, 123.46; C-3, 95.34; C-4, 120.60; C-5, 118.00; C-6, 111.15; C-7, 127.55; C-8, 136.19; C-9, 118.38; C-10, 29.97; C-11, 55.34; C-12, 176.21; C-α, 1.54
10	C-2, 123.52; C-3, 96.20; C-4, 120.75; C-5, 118.02; C-6, 111.25; C-7, 127.57; C-8, 136.20; C-9, 118.45; C-10, 29.95; C-11, 55.41; C-12, 176.34; C-α, 21.67; C-β, 26.82; C-γ, 26.51; C-δ, 13.62

[a] As indicated in Table 1.

Table 5 ^{119}Sn Mössbauer spectroscopic data of organotin(IV) derivatives of amino acids

Complex	Q.S. (mm s^{-1})	C.S. (mm s^{-1})	ρ	τ_1	τ_2
Ph_3SnL-1	2.74 ± 0.03	1.18 ± 0.01	2.32	1.21	1.18
Ph_3SnL-2	2.52 ± 0.03	1.15 ± 0.01	2.19	0.72	0.88
Me_3SnL-2	3.06 ± 0.02	1.27 ± 0.01	2.41	0.58	0.63
$Ph_2Sn(L\text{-}1)_2$	2.35 ± 0.03	1.07 ± 0.01	2.20	0.89	1.06
$Ph_2Sn(L\text{-}2)_2$	2.40 ± 0.02	1.02 ± 0.00	2.35	0.88	1.05
$Bu_2Sn(L\text{-}2)_2$	2.46 ± 0.02	1.15 ± 0.01	2.14	0.84	0.95

triorganotin derivatives exhibit C.S. and Mössbauer Q.S. values in the range 1.15–1.27 and 2.54–3.02 mm s^{-1}, respectively, and pronounced line-intensity asymmetry (the Goldanskii–Karyagin effect), suggesting an intermolecularly associated lattice.[10] Each of the three isomers (Fig. 1) of R_3SnL has been reported[35,36] to have different Q.S. values: Q.S. for isomer (a) 1.7–2.3 mm s^{-1}; for (b) 3.0–3.9 mm s^{-1}; and for (c) 3.5–4.1 mm s^{-1}. The observed values of the chemical shifts in Ph_3SnL-1, Ph_3SnL-2 and Me_3SnL-2 lie in the range typical of triorganotin(IV) carboxylates, whereas quadrupole splitting values are slightly lower than those typical for *trans* trigonal-bipyramidal coordination of tin in R_3SnO_2 fragments (3.00–4.00 mm s^{-1}), but substantially higher than that for *cis* trigonal-bipyramidal (1.70–2.40 mm s^{-1}) and pseudotetrahedral (1.00–2.40 mm s^{-1}) arrangements.[37] Q.S. values in the region of 2.8–3.0 mm s^{-1} were also found in triorganotin derivatives of amino acids with *trans* trigonal-bipyramidal geometry around the tin atom with an amino-bridged intermolecular interaction,[10] and for other triorganotin carboxylates with an O·Sn(R_3)O intermolecular interaction.[38] The observed Q.S. values of R_3SnL support structure (b) with an oxygen and a nitrogen atom from an

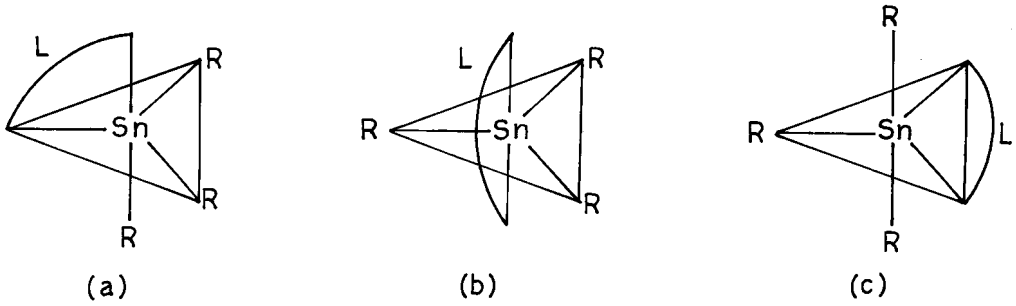


Figure 1 Structure of R_3 SnL.

Table 6 Antimicrobial activity of organotin(IV) derivatives of amino acids

	Minimum inhibitory concentration (MIC)[a] in (μg ml^{-1}) against									
	Bacteria[b]					Fungi[b]				
Complex[a]	1	2	3	4	5	6	7	8	9	10
Ph_3SnL-1	< 12.5	25	< 12.5	25	< 12.5	< 12.5	< 12.5	25	12.5	25
Ph_3SnL-2	< 12.5	25	25	25	< 12.5	< 12.5	< 12.5	25	25	< 12.5
Me_3SnL-2	25	50	I	I	I	I	50	50	50	50
$Bu_2Sn(L\text{-}2)_2$	25	< 12.5	25	12.5	25	12.5	12.5	25	25	50
Ph_3SnCl	I	I	12.5	I	6.25	12.5	1.56	6.25	3.125	3.125
Bu_2SnO	50	I	I	I	I	I	50	50	I	50
Amphotericin B	—	—	—	—	—	0.20	0.39	1.00	0.42	0.76
Flucytosine	—	—	—	—	—	1.20	0.59	I	0.39	I
Sofaclonzo	—	—	—	—	—	I	I	I	I	0.78
Norfloxacin	I	12.5	6.2	12.5	3.0	—	—	—	—	—
Cap.flox	1.5	3.1	1.5	0.78	0.78	—	—	—	—	—

[a] The samples were not screened below 12.5 μg ml^{-1}; I, inactive; solvent used, DMSO.
[b] Key: 1, *Streptococcus faecalis*; 2, *Klebsiella pneumoniae*; 3, *Escherichia coli*; 4, *Pseudomonas aeruginosa*; 5, *Staphylococcus aureus* [penicillin resistance (2500 units)]; 6, *Candida albicans*; 7, *Cryptococcus neoformans*; 8, *Sporotrichum schenckii*; 9, *Trichophyton mentagrophytes*; 10, *Aspergillus fumigatus*.

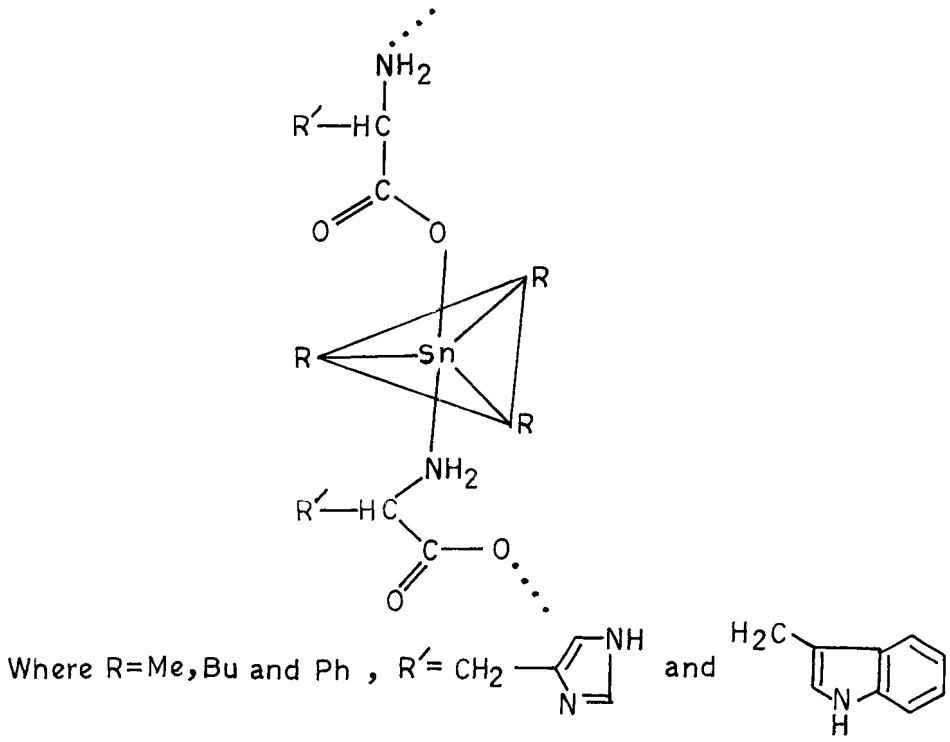


Figure 2 Structure of trioganotin (IV) complexes.

adjacent molecule occupying axial positions (Fig. 2). This arrangement is the conventional, one (ie. the most electronegative axial structure) found in organotin chemistry. Hence all the trioganotin derivatives have been proposed to have amino-bridged linear polymeric structures, similar to that reported for Me_3SnGly[10], and this is also consistent with their low solubility. There is the possibility of hydrogen bonding between carbonyl oxygen and amino N–H moieties, along and between the chains.[10]

Octahedral, cationic,[39] neutral[39,40] and anionic[41] tin complexes containing two organic residues and four electronegative ligands possess a mutually *trans* geometry for the tin–carbon bonds (with a few exceptions). In this context, the magnitude of the ^{119}Sn Mössbauer Q.S. is a useful parameter. Point-charge calculations[42] for octahedral diorganotin(IV) derivatives with two organic groups predict that the Q.S. for the *trans* isomer will be twice ($\sim$4 mm s^{-1}) that of the *cis* isomer ($\sim$2 mm s^{-1}). However, the organotin(IV) derivatives reported herein have observed C.S. values of *ca* 1.11 ± 0.04 mm s^{-1} and a Q.S. of *ca* 2.41 ± 0.06 mm s^{-1}. These data cannot be directly interpreted in terms of the structure, since other diorganotin(IV) complexes with similar parameters have been assigned as five-coordinate with monodentate carboxyl in R_2SnL (L = dianion of tridentate dipeptides)[23,24] or *cis* octahedral structures.[43–45] Indeed where the other ligands have high electronegativity, the Q.S. is governed mainly by the C–Sn–C bond angle[44,45] and distortion from regular six-coordination can give values similar to those for five-coordination,[46] the values observed here correspond to bond angles of 99.5–104.4 °. The C.S. values are also somewhat lower than *trans* analogues (C.S. = 1.35–1.50 mm s^{-1})[29,44,45] due to a decrease in the 5*s* character of the Sn–C bonds. However, in the light of the other data, the Mössbauer parameters are best interpreted in terms of distorted *cis* octahedral configurations (Fig. 3). Intermolecular hydrogen bonds between the carbonyl oxygen of one molecule and the amino group of another cannot be ignored, however.

Antimicrobial activity

In vitro antimicrobial results (minimum inhibitory concentration, MIC, in μg ml^{-1}) against a wide

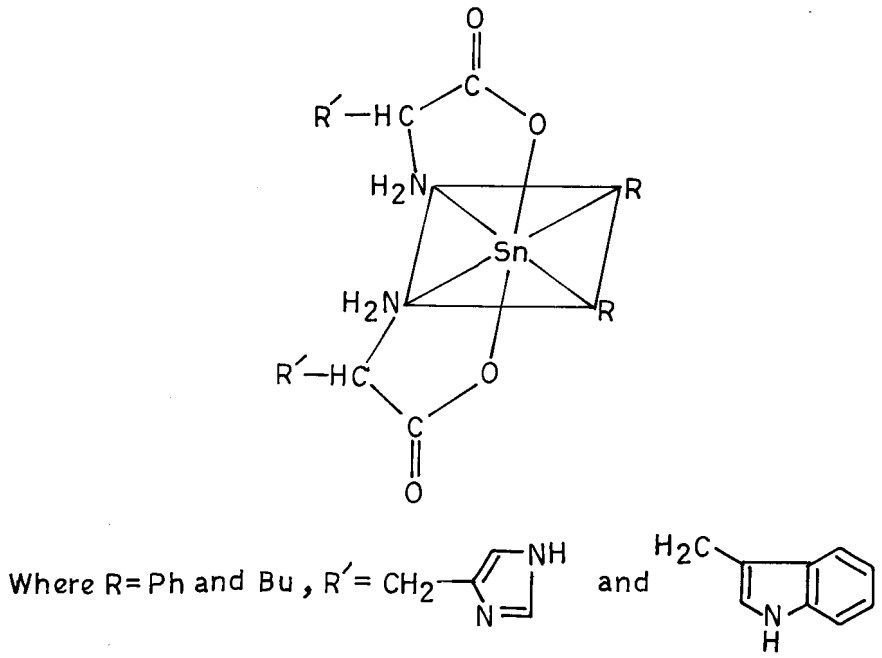


Figure 3 Structure of diorganotin (IV) complexes.

spectrum of bacteria and fungi are presented in Table 6 for compounds **1, 2, 4** and **10**, which are soluble in DMSO, as well as the MIC values of Ph_3SnCl, Bu_2SnO and some reference compounds. Due to their insufficient solubility in DMSO, none of the other compound could be screened. In comparison with the parent tin compounds i.e, Ph_3SnCl and Bu_2SnO, all the four organotin(IV) amino-acid derivatives exhibited good activities. Further, as is evident from the data shown in Table 6, fungicidal and bactericidal activities of the organotin complexes under experimental conditions decreased in the order: triphenyltin > dibutyltin > trimethyltin.

Because of the high antifungal activities of Ph_3SnL-1 and Ph_3SnL-2, they have been screened *in vivo* against a multi-infection model in mice. The compounds were tested at 100 and 50 mg kg^{-1}, p.o., for four days for antifungal efficacy. However, at 100 mg kg^{-1} the compounds were toxic as most of the animals died during the experimental period and they did not show promising activity. Both of the compounds were found to be active at a dose of 50 mg kg^{-1}, but they were not found active as compared (cfu) with the controls.

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