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Studies of Organotin(IV) Derivatives of DL-Methionine and L-Asparagine

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New organotin(IV) complexes of the general formula R_3SnL [where R = Me, Bu, and Ph], Ph_2SnL_2 and Bu_2SnL_2 [where L = monoanion of DL-methionine (HL-1) and L-asparagine (HL-2)] were synthesized and characterized by elemental analyses as well as molar conductance, electronic, infrared, far-infrared, ^1H and ^{13}C NMR, and ^{119}Sn Mössbauer spectral studies. Probable structures are suggested for the complexes. Thermal studies of a few complexes have been carried out in the temperature range 25—1000 °C using the TG, DTG, and DTA techniques, indicating the formation of SnO as a residue. The complexes were tested in vitro against a wide spectrum of bacteria and fungi and found to be active. Only two complexes, Ph_3SnL-1 and Ph_3SnL-2, have been found to be slightly active in vivo against a multiinfection fungal model in mice.

The chemistry of organotin(IV) compounds with a strongly ligating sulfur and possibly a ligating nitrogen is of interest in view of the biocidal activity of triorgano[R_3SnX] and diorgano[R_2SnX_2] tin compounds.[1,2] In particular, the effective R groups in [R_3SnX] are Me, Et, *n*-Pr, *n*-Bu, and Ph. Remarkably, each is effective against different living species, the toxicity decreasing along with an increase in the alkyl-chain length beyond C_4. Although detailed mechanisms are obscure, [R_3SnX] compounds (which inhibit mitochondrial oxidative phosphorylation) and [R_2SnX_2] compounds (which inhibit α-keto acid oxidation) are known to combine with the thiol and dithiol groups, respectively, in proteins and enzymes. There is also interest in organotin compounds with nitrogen ligands for cancer chemotherapy.[1,2] Some organotin(IV) complexes with sulfur-containing amino acid or other biological ligands have been studied.[3—7]

Trimethyltin glycinate has been shown by X-ray crystallography to be a linear polymer with amino bridged trigonal bipyramidal units having oxygen and nitrogen atoms in apical positions.[8] Coordination occurs through a carboxylate oxygen and an amino nitrogen despite the generally believed greater affinity of tin for oxygen, which would lead to the well-established carboxylate bridged structure.[9,10] The observed stereochemistry presumably reflects the tendency of amino acids to utilize their functional groups as fully as possible in metal coordination.[11] Methionine and asparagine are tridentate ligands, which contain a soft base, like thioether, and a hard base, like the amide group, respectively, in addition to the amino and carboxyl coordinating sites. The differences in the structures of these ligands might be reflected to the biological activities of their corresponding organotin compounds. In view of this, it was considered of interest to synthesize new organotin complexes of methionine and asparagine, and to study their structures and biological activity. The results of these investigations are reported in this paper.

Experimental

Materials: All of the reactions were carried out under an anhydrous and oxygen-free nitrogen atmosphere. The solvents were purified, dried and stored under nitrogen. The di- and triphenyltin(IV) chloride (E. Merck), tributyltin(IV) chloride (E. Merck), trimethyltin(IV) chloride (Aldrich Chemicals), dibutyltin(IV) oxide (Fluka), DL-methionine (Fluka) and L-asparagine (Fluka) were used as received.

Synthesis of Diphenyltin(IV) Complexes of Amino Acids: The amino acid (6.00 mmol) was dissolved in a minimum amount (25 ml) of absolute methanol. To this was added sodium methoxide, prepared by dissolving sodium (7.00 mmol) in absolute methanol (10 ml) under dry nitrogen; the resulting solution was refluxed for 2—3 h with constant stirring. A hot methanolic solution of diphenyltin(IV) chloride (3.00 mmol) in 1 : 2 (organotin : amino acid) molar ratio was added into 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 in order to remove the sodium chloride, and any excess of solvent was removed under reduced pressure. The thus-obtained semisolid product was solidified by trituration with petroleum ether (bp 40—60 °C). The complexes were recrystallized from a methanol and petroleum ether (bp 40—60 °C) mixture.

Synthesis of Triorganotin(IV) Complexes of Amino Acids: The amino acid (4.00 mmol) was dissolved in a minimum amount (25 ml) of absolute methanol. To this was added sodium methoxide, prepared by dissolving sodium (4.00 mmol) in absolute methanol (10 ml) under dry nitrogen; the resulting solution was refluxed for 2—3 h with constant stirring. A hot methanolic solution of trimethyl-/, tributyl-/ or triphenyltin(IV) chloride (4.00 mmol) in ca. 1 : 1 molar ratio was added into 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(IV) Complexes of Amino Acids: The complex was prepared under anhydrous conditions by the 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 in 10—30 min. Refluxing was continued for 9—10 h with an azeotropic removal of water. Any excess of solvent was removed under reduced pressure. The thus-obtained oily product was solidified by trituration with petroleum ether (bp 40—60 °C), and recrystallized from a methanol and petroleum ether (bp 40—60 °C) mixture.

Measurements: The 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.[12,13] Infrared and far-infrared spectra were recorded on a FTIR spectrophotometer (model FTS 165), 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. ^1H and ^{13}C NMR spectra were recorded on a Perkin–Elmer R-32 (90 MHz) and Bruker VM-400 MHz spectrophotometer at the Central Drug Research Institute (CDRI), Lucknow, India, using $CDCl_3$ or DMSO-d_6 as the solvent and tetramethylsilane as the internal standard. The details concerning the ^{119}Sn Mössbauer spectra,[12] thermal measurements and antimicrobial activity[14] of the complexes were similar to those reported previously. A multiinfection fungal (*C. albicans*-vaginal and systemic, *C. neoformans*-lungs and *T. mentagrophytes*-skin infection) model in Balb/c mouse has been developed for a rapid screening of the compounds.[15] The mice were pretreated with estradiol (500 μg/mouse) on day-4, and an evaluation of compound was performed after 5 d of inoculation. The evaluation was based upon a culture, cfu from tissue homogenates-kidney, lung, vagina, and skin.

The analytical data, molar conductance in CH_3OH ($ohm^{-1}\,cm^2\,mol^{-1}$), electronic spectral data in CH_3OH (nm), ^1H and ^{13}C NMR chemical shift (δ/ppm) of the complexes in $CDCl_3$ or DMSO-d_6 are given below:

$CH_3SCH_2CH_2CH(NH_2)COOSn(CH_3)_3$ (Me_3SnL-1) (1): Dark brown; 80% yield; mp 172—175 °C. Found: Sn, 37.99; N, 4.45; S, 10.23%. Calcd for $C_8H_{19}NO_2SSn$: Sn, 38.04; N, 4.49; S, 10.28%. Molar conductance 31.5; UV-vis 213, n–π* (COO); ^1H NMR (90 MHz) δ = 2.82 (H-2, t (5.4, 6.3)), 1.40 (H-3, q), 2.12 (H-4, t (8, 10)), 1.65 (H-5, s), 1.12 (H-α, s), 1.20 (H-α, s); ^{13}C NMR δ = 176.40 (C-1), 54.54 (C-2), 30.10 (C-3), 34.30 (C-4), 14.40 (C-5), 3.91 (C-α).

$H_2NCOCH_2CH(NH_2)COOSn(CH_3)_3$ (Me_3SnL-2) (2): Cream; 41% yield; mp 200—204 °C (decomp). Found: Sn, 40.25; N, 9.60%. Calcd for $C_7H_{16}N_2O_3Sn$: Sn, 40.25; N, 9.50%. Molar conductance 50.10; UV-vis 210, n–π*(COO); ^1H NMR (90 MHz): δ = 3.40 (H-2, t (5,7)), 2.50 (H-3), 2.59 (H-3, d (15)), 7.80 (H-5, d), 1.14 (H-α, s), 1.24 (H-α, s); ^{13}C NMR δ = 172.42 (C-1), 51.55 (C-2), 52.64 (C-3), 175.67 (C-4), 3.95 (C-α).

$CH_3SCH_2CH_2CH(NH_2)COOSn(C_4H_9)_3$ (Bu_3SnL-1) (3): Light yellow; 50% yield; semisolid. Found: Sn, 26.97; N, 3.10; S, 7.30%. Calcd for $C_{17}H_{37}NO_2SSn$: Sn, 27.08; N, 3.20; S, 7.32%. Molar conductance 48.70; UV-vis 226, n–π*(COO).

$H_2NCOCH_2CH(NH_2)COOSn(C_4H_9)_3$ (Bu_3SnL-2) (4): Cream; 45% yield; semisolid. Found: Sn, 28.15; N, 6.65%. Calcd for $C_{16}H_{34}N_2O_3Sn$: Sn, 28.18; N, 6.65%. Molar conductance 70.52; UV-vis 220, n–π*(COO).

$CH_3SCH_2CH_2CH(NH_2)COOSn(C_6H_5)_3$ (Ph_3SnL-1) (5): Cream; 45% yield; mp 115—118 °C. Found: Sn, 23.34; N, 2.78; S, 6.40%. Calcd for $C_{23}H_{25}NO_2SSn$: Sn, 23.82; N, 2.81; S, 6.44%. Molar conductance 39.5; UV-vis 197, 231, π–π* (E_2) benzenoid/n–π*(COO); 252, 258, 264, π–π* (B) benzenoid; ^1H NMR (400 MHz) δ = 3.40 (H-2, t (5.5,6.2)), 3.87 (H-3, q), 2.64 (H-4, t (8,10)), 2.01 (H-5, s), 7.76 (H-6, d), 7.85 (H-β, d (8)), 7.37 (H-γ, dd (8,8)), 7.90 (H-δ, d (2)); ^{13}C NMR δ = 177.26 (C-1), 54.45 (C-2), 30.10 (C-3), 34.88 (C-4), 14.44 (C-5), 136.13 (C-α), 135.93 (C-β), 127.85 (C-γ), 128.43 (C-δ).

$H_2NCOCH_2CH(NH_2)COOSn(C_6H_5)_3$ (Ph_3SnL-2) (6): Cream; 85% yield; mp 212—215 °C (decomp). Found: Sn, 23.98; N, 5.80%. Calcd for $C_{22}H_{22}N_2O_3Sn$: Sn, 24.67; N, 5.82%. Molar conductance 22.7; UV-vis 197, 224, π–π*(E_2) benzenoid/n–π*(COO); 251, 258, 264, π–π*(B) benzenoid; ^1H NMR (90 MHz) δ = 3.20 (H-2, t (5,7)), 2.62 (H-3), 2.81 (H-3, d (16)), 7.79 (H-5, d), 7.83 (H-β, d (8)), 7.34 (H-γ, dd (7,7)), 7.92 (H-δ, d (2)); ^{13}C NMR δ = 172.20 (C-1), 51.65 (C-2), 52.44 (C-3), 175.54 (C-4), 138.85 (C-α), 135.90 (C-β), 127.40 (C-γ), 128.01 (C-δ).

$[CH_3SCH_2CH_2CH(NH_2)COO]_2Sn(C_4H_9)_2$ (Bu_2Sn(L-1)$_2$) (7): Light yellow; 47% yield; mp 146—150 °C. Found: Sn, 22.10; N, 5.23; S, 12.08%. Calcd for $C_{18}H_{38}N_2O_4S_2Sn$: Sn, 22.42; N, 5.29, S, 12.12%. Molar conductance 54.1; UV-vis 211, n–π*(COO).

$[H_2NCOCH_2CH(NH_2)COO]_2Sn(C_4H_9)_2$ (Bu_2Sn(L-2)$_2$) (8): Light cream; 90% yield; mp 196—200 °C (decomp). Found: Sn, 23.54, N, 11.10%. Calcd for $C_{16}H_{32}N_4O_6Sn$: Sn, 23.97; N, 11.32%. Molar conductance 49.6; UV-vis 208, n–π*(COO); ^1H NMR (90 MHz) δ = 3.02 (H-2, t (5,7)), 2.51 (H-3), 2.61 (H-3, d (15)), 7.65 (H-5, d), 1.25—1.32 (H-α and H-β, m), 0.90 (H-γ, tq (7,7)), 0.65 (H-δ, t (7)); ^{13}C NMR δ = 174.96 (C-1), 54.16 (C-2), 53.44 (C-3), 177.91 (C-4), 29.07 (C-α), 32.58 (C-β), 29.72 (C-γ), 14.22 (C-δ).

$[CH_3SCH_2CH_2CH(NH_2)COO]_2Sn(C_6H_5)_2$ (Ph_2Sn(L-1)$_2$) (9): Cream; 80% yield; mp 148—149 °C (decomp). Found: Sn, 20.52; N, 4.50; S, 11.02%. Calcd for $C_{22}H_{30}N_2O_4S_2Sn$: Sn, 20.85; N, 4.92; S, 11.26%. Molar conductance 57.0; UV-vis 197, 228, π–π*(E_2) benzenoid/n–π*(COO); 250, 256, 264, π–π*(B) benzenoid; ^1H NMR (400 MHz) δ = 3.26 (H-2, t (5,6)), 3.90 (H-3, q), 2.51 (H-4, t (8,10)), 1.97 (H-5, s), 7.79 (H-6, d), 7.87 (H-β, d (8)), 7.36 (H-γ, dd (8,8)), 7.92 (H-δ, d (2)); ^{13}C NMR δ = 176.52 (C-1), 54.50 (C-2), 31.01 (C-3), 34.28 (C-4), 14.34 (C-5), 140.01 (C-α), 136.05 (C-β), 127.98 (C-γ), 128.01 (C-δ).

$[H_2NCOCH_2CH(NH_2)COO]_2Sn(C_6H_5)_2$ (Ph_2Sn(L-2)$_2$) (10): Cream; 78% yield; mp 118—120 °C. Found: Sn, 21.98; N, 10.42%. Calcd for $C_{20}H_{24}N_4O_6Sn$: Sn, 22.18; N, 10.47%. Molar conductance 54.1; UV-vis 197, 233, π–π*(E_2) benzenoid/n–π*(COO); 253, 258, 264, π–π*(B) benzenoid.

Results and Discussion

Reactions of R_3SnCl or Ph_2SnCl_2 with the sodium salt of the amino acids viz. DL-methionine (HL-1) and L-asparagine (HL-2) in 1 : 1 and 1 : 2 molar ratios, respectively, led to the formation of the complexes according to the Eqs. 2 and 3. The 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 an azeotropical removal of water [Eq. 4].

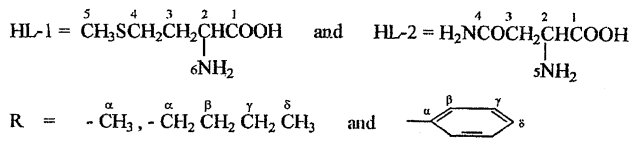
$$\text{HL-1/HL-2} + \text{NaOMe} \rightarrow \text{Na(L-1/L-2)} + \text{MeOH} \quad (1)$$

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

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

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

where,



The above reactions were found to be quite facile and were completed within 9—10 h of refluxing. All of the newly synthesized complexes are colored, crystalline solids, except for **3** and **4**, which are viscous semisolids. Although the complexes were stable towards air and soluble in methanol, some of them were sparingly soluble in chloroform, dimethyl sulfoxide, and dimethylformamide. The analytical data of the complexes given in experimental show that the metal-to-ligand ratio in triorgano- and diorganotin complexes is 1 : 1 and 1 : 2. The molar-conductance values of the complexes of 10^{-3} M (1 M = 1 mol dm^{-3}) solutions were in the range 22.70—70.52 ohm^{-1} cm^2 mol^{-1}, suggesting a non-electrolytic nature of the complexes.

The electronic spectra of DL-methionine and L-asparagine exhibit a very intense band at 204 and 201 nm, respectively, which may be due to the n–π^* transition of the (COO) chromophore. The corresponding absorption band in the spectra of the organotin(IV) complexes has been observed at 220±12 nm. In the spectra of Ph_3SnL and Ph_2SnL_2 complexes, additional bands at 197 and 257±7 nm are observed which may be assigned to the π–π^* (E_2) and π–π^* (B) bands of phenyl groups attached to the tin.

The characteristic infrared frequencies of the complexes are listed in Table 1. The choices of the coordination number and geometry are known to be sensitive to the size of the substituent groups at tin[9] and on the degree of branching in the ligand.[16] The infrared NH_2 stretching frequencies can help to distinguish coordinated groups from free amino groups. The amino acids, themselves, exist in a zwitterionic form in the solid state, $RCH(NH_3^+)COO^-$, in which there are NH_3^+ groups. The free NH_2 groups are found in the amino acid salts. The ν_{NH} of the amino group is observed at 2909 and 2877 cm^{-1} in HL-1 and HL-2, respectively, whereas their sodium salts show the corresponding absorption at 3000 and 3053 cm^{-1}, respectively. There is thus a substantial lowering on protonation. Coordination to metal centres also gives rise to a substantial shift. In the IR spectra of organotin(IV) complexes this band has undergone a substantial lowering (2736—3065 cm^{-1}) from the values for the sodium salts of HL-1 and HL-2, indicating the coordination of the amino acids through the amino group to tin. Similar results have also been reported for R_3SnAA (R = Me or cyclohexyl, AA = anion of amino acid).[17] A band at 3418±18 cm^{-1} in the IR spectra of HL-2 and its sodium salts has been assigned to the stretching mode of the amido ($-CONH_2$) group which remains unaltered in the organotin(IV) complexes, indicating its non-involvement in coordination. Therefore, we interpret the observed shifts to lower energy and accompanying intensity enhancement as arising from amino-group coordination to tin, because coordination increases the electron demand at nitrogen and the polarity of the N–H bond. Apparently the change in this dipole during a stretching vibration is also increased, since an increase in the total absorption intensity generally accompanies coordination of the amino group.[17] As previously reported[17] the intense NH_2 absorption observed here is relatively narrow, suggesting that hydrogen bonding, usually prominent in amino acids and their derivatives, is not pronounced in tin compounds. The zwitterionic forms of the amino acids in the solid state have symmetric anionic carboxylate groups, as do their salts. The sodium salts of HL-1 and HL-2, and the zwitterionic solids, HL-1 and HL-2, have ν_{as} carboxyl absorptions at 1630 and 1595, and 1623 and 1594 cm^{-1}, respectively. The ν_{as}(COO) and ν_s(COO) in the organotin derivatives of HL-1 and HL-2 are observed at 1651±21 and 1428±23 cm^{-1}, respectively, indicating that the ν_{as}(COO) moves to higher frequencies than in the amino acids, themselves. The band positions as well as $\Delta\nu$ (ν_{as}(COO) − ν_s(COO) = 235±33 cm^{-1}) are comparable to those reported for R_3SnAA[17] and R_3Sn(AcglyO) as well as R_3Sn(AcAlaO) and R_3Sn(AcMetO).[18] Ionic bonding as well as bridging or chelation can therefore be excluded, and carboxylic groups bonding tin unidentately must be assumed.[17,18] It has further been confirmed based on the appearance of a sharp band at 563±33 cm^{-1}, assignable to the Sn–O stretching vibration.[12,14] The conclusions drawn above are further supported by the presence of a new band in the far-IR spectra of all complexes, at ca. 432±25 cm^{-1}, which may be assigned to the ν(Sn←N).[12] The ν_{as}(Sn–C) and ν_s(Sn–C) in the tri- and diphenyltin derivatives are observed at 275±5 and 240±5 cm^{-1}, respectively, whereas, the corresponding vibrations in tri- and dialkyltin compounds are observed at 627±59 and 549±84 cm^{-1}, respectively. This clearly indicates the existence of *cis*-organic groups in all of the organotin complexes.[12,14]

^{1}H NMR data of the complexes, except for complexes of Sl. Nos. **3**, **4**, **7** and **10**, because of their insufficient solubility in $CDCl_3$ and DMSO-d_6, have been recorded and are given in Experimental. The absence of a signal due to the –OH proton at δ = 12.00—13.00 suggests deprotonation of the carboxylic oxygen atom of the amino acids upon complexation.[19] The NH signal of the amino group is shifted to lower δ values, δ = 7.73±0.08, (if not obscured by superposition by phenyl protons in DMSO-d_6 solutions of $SnPh_3$ and $SnPh_2$ compounds), indicating the coordination of the NH_2 group to tin. Similarly, –NCH< signal is shifted to lower δ (δ = 3.11±0.29 for compounds **1**, **5**, and **9** and δ = 3.21±0.19 for compounds **2**, **6**, and **8**) upon complexation, compared to the free zwitterionic form (–NCH< at δ = 3.80 for HL-1 and δ = 4.00 for HL-2 in D_2O).[20] The butyl protons attached to the tin in compound **8** appear at appropriate positions in accordance to the previously reported values.[21] The signals for the phenyl groups attached to tin are observed in the range δ = 7.92—7.34 in compounds **5**, **6**, and **9**. Two singlets due to $SnMe_3$ protons of compounds **1** and **2** have been assigned at δ = 1.13±0.01 and 1.22±0.02, respectively, indicating the presence of methyl groups in two different environments. The number of protons of the various groups, calculated from the integration curves, and those calculated for the expected molecular formula agree with each other.

Table 1. Infrared Frequencies (in cm^{-1}) of the Amino Acids and their Complexes

HL/NaL/ Complexes	νCH/νNH	ν_{as}(COO)	ν_{s}(COO)	$\Delta\nu$	ν_{as}(Sn–C)	ν_{s}(Sn–C)	ν(Sn–O)	ν(Sn←N)
HL-1	3075w 3036w 2940m 2909m	1623s	1410s	—	—	—	—	—
HL-2	3436m (amide) 3099m 2923m 2877m	1594s	1439s	—	—	—	—	—
NaL-1	3086m 3000m 2970m 2949m	1630s	1414s	—	—	—	—	—
NaL-2	3400m (amide) 3053m 2968m 2840m	1595s	1432s	—	—	—	—	—
Me_3SnL-1	2964m 2920m	1660m	1415s	245	685m	595m	554m	440s
Me_3SnL-2	3405w (amide) 3364w 3067w	1672s	1405s	267	681m	633s	543s	456s
Bu_3SnL-1	2955s 2905s	1670m	1405m	265	570m	465s	530w	407m
Bu_3SnL-2	3402m (amide) 2934w	1660m	1450w	210	568m	464m	535s	410s
Ph_3SnL-1	3100brw 3000w	1630w	1428s	202	270s	240s	554w	446s
Ph_3SnL-2	3405brs (amide) 3065m	1671s	1413m	258	272m	245s	540s	448s
$Bu_2Sn(L\text{-}1)_2$	3000m 2920m	1652m	1415s	237	685s	554vs	596s	440s
$Bu_2Sn(L\text{-}2)_2$	3405m (amide) 2736m	1660s	1436s	224	658m	488m	536s	428m
$Ph_2Sn(L\text{-}1)_2$	3005w 2900w	1670m	1416s	254	280m	236s	565m	434s
$Ph_2Sn(L\text{-}2)_2$	3403w (amide) 2976m	1653s	1430s	223	276w	244m	545m	428s

m, medium; s, strong; w, weak; brs, broad strong; brw, broad weak.

The ^{13}C chemical shifts of various carbon atoms in compounds **1**, **2**, **5**, **6**, **8**, and **9** in DMSO-d_6 are given in Experimental. The signals of the carboxyl carbon of the amino acids are observed at lower δ upon complexation, compared to those of free amino acids; HL-1 shows a carboxyl carbon at δ=182.7 and HL-2 shows a carboxyl carbon at δ=174.1.[20] The shifting observed in the C-2 and C-3 resonances of the amino acids in the organotin derivatives is due to coordination of the amino acids through the $-NH_2$ and –COO groups to tin. The ^{13}C chemical shifts of methyl, butyl and phenyl groups attached to tin are observed at positions comparable with other, similar compounds.[22—24] Due to an insufficient solubility of the organotin complexes in $CDCl_3$, their ^{119}Sn NMR spectra could not be recorded.

Tin-119 Mössbauer spectroscopy has been employed to obtain additional structural information; also, the results obtained for organotin(IV) complexes of amino acids are reported in Table 2. The C.S. values indicate the presence of tin in the +IV oxidation state, and the quadrupole splitting shows that the electric field gradient around the tin nucleus is produced due to inequalities in the tin-amino acids σ bonds. The ρ (Q.S./C.S.) values of >2.1 in these complexes indicate a coordination number greater than four. The monomeric six-coordinate structures seem to be the most

Table 2. ^{119}Sn Mössbauer Spectroscopic Data of the Complexes

Complexes	Q. S. ($mm\,s^{-1}$)	C. S. ($mm\,s^{-1}$)	ρ
Me_3SnL-1	3.06±0.02	1.27±0.01	2.41
Me_3SnL-2	3.05±0.01	1.26±0.01	2.42
Ph_3SnL-1	2.40±0.02	1.13±0.01	2.12
Ph_3SnL-2	2.45±0.03	1.09±0.00	2.25
$Bu_2Sn(L\text{-}1)_2$	2.49±0.02	1.14±0.01	2.18
$Bu_2Sn(L\text{-}2)_2$	2.35±0.03	1.06±0.01	2.22
$Ph_2Sn(L\text{-}1)_2$	2.42±0.03	1.03±0.01	2.35
$Ph_2Sn(L\text{-}2)_2$	2.40±0.02	1.08±0.01	2.22

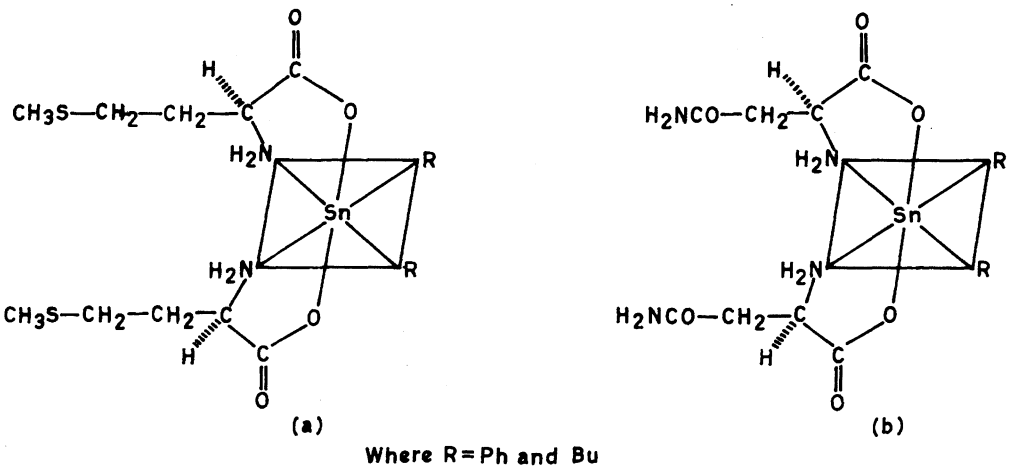


Fig. 1. Structures of diphenyl- or dibutyltin complexes of (a) DL-methionine and (b) L-asparagine.

probable for dibutyl- and diphenyltin complexes of HL-1 and HL-2, as the C.S. and Q.S. values are well within the range (1.14±0.01—1.03±0.01 and 2.49±0.02—2.35±0.03 mm s^{-1}, respectively) presented for the octahedral geometries with *cis*-R groups [Fig. 1. (a) and (b)]. The point-charge calculations predict that octahedral organotin(IV) compounds with two organic groups have a Q.S. value of 2.00 mm s^{-1} for the *cis* isomer and 4.00 mm s^{-1} for the *trans* isomer.[25—27] The *cis* configuration is also consistent with the observed multiple Sn–C vibrational modes in the infrared spectra. The possible geometry around the tin in R_3SnL (where R = Me, Bu, Ph, and L = anion of HL-1 and HL-2) is distorted trigonal bipyramidal, in which the amino acid anion is monofunctional bidentate coordinating through an ON donor set derived from the carboxylic oxygen and the amino nitrogen atoms. Each of the three isomers (Fig. 2) of R_3SnL (L = bidentate ligand) has been reported[21] to have a different Q.S. value, viz. Q.S. for an isomer (c) 1.7—2.3 mm s^{-1}; for (d) 3.0—3.9 mm s^{-1}; and for (e) 3.5—4.1 mm s^{-1}. The observed Q.S. values of Me_3SnL-1, Ph_3SnL-2 (3.06—2.40 mm s^{-1}) support structure (c), which is in agreement with the observed multiple Sn–C vibration in the IR spectra. The structures of R_3SnL are shown in Fig. 3 (a) and (b), which are further supported by the occurrence of two methyl signals in the ^1H NMR spectra of Me_3SnL-1

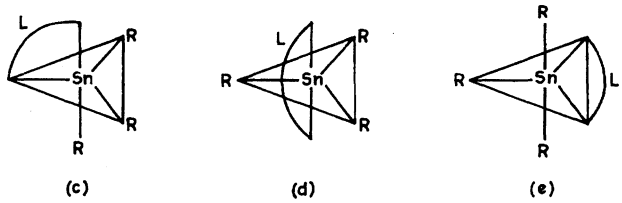


Fig. 2. The possible isomers of R_3SnL.

and Me_3SnL-2. All of the organotin(IV) complexes of the amino acids have a monomeric structure with chelated amino acids. It was previously reported[17] that substituents on the carbon next to the amino group (the α carbon) will not hinder any intramolecular association (chelation), since they can be directed away from the organic groups attached to tin, whereas in intermolecular association (polymerization) the substituents on the adjacent carbon are brought into close contact with the organic groups. Thus, bulky substituents on the α carbon would be expected to disrupt polymerization, but not chelation, and only pointed ligand groups, such as CH_2NH_2, can achieve intermolecular coordination with the organic groups.[8,17] Therefore, the bulky groups, such as ($-CH_2CH_2SCH_3$) in methionine and ($-CH_2CONH_2$) in asparagine, can disrupt polymerization, but not chelation. Hence, monomeric six-coordinate and five-coordinate structures with chelated amino acid anion for R_2SnL and R_3SnL,

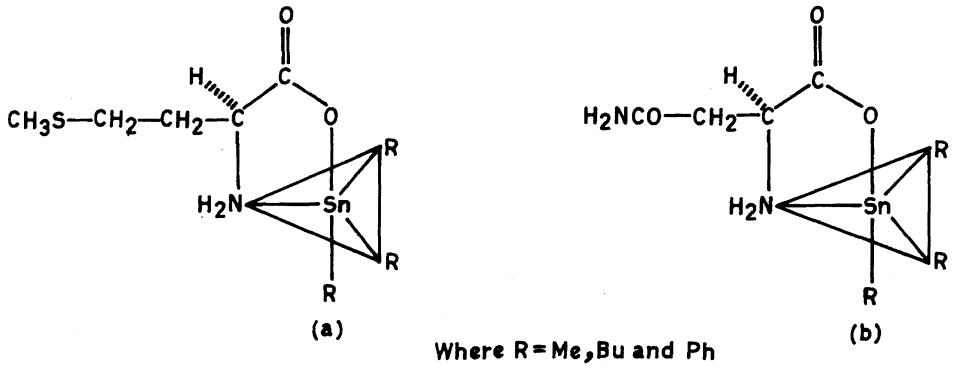


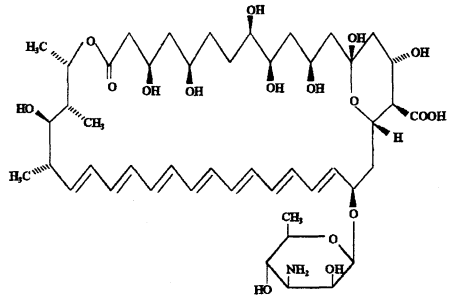
Fig. 3. Structures of triorganotin complexes of (a) DL-methionine and (b) L-asparagine.

Table 3. Results of Antimicrobial Activity of Organotin(IV) Complexes of Amino Acids

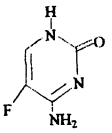
Complexes	Minimum inhibitory concentration (MIC)[a] in $\mu g\,ml^{-1}$ against									
	Bacteria					Fungi				
	1	2	3	4	5	6	7	8	9	10
Me_3SnL-1	I	I	I	I	50	50	50	I	50	I
Me_3SnL-2	I	I	I	I	I	50	I	50	50	50
Ph_3SnL-1	25	<12.5	50	<12.5	50	<12.5	<12.5	I	<12.5	<12.5
Ph_3SnL-2	25	50	<12.5	I	50	<12.5	I	<12.5	<12.5	<12.5
$Bu_2Sn(L\text{-}2)_2$	50	I	I	I	I	50	I	50	50	I
$Ph_2Sn(L\text{-}1)_2$	25	50	I	25	50	25	12.5	I	25	<12.5
Ph_3SnCl	I	I	12.5	I	6.25	12.5	1.56	6.25	3.925	3.125
Ph_2SnCl_2	25	I	25	I	12.5	I	25	I	25	I
Bu_2SnO	50	I	I	I	I	I	50	50	I	50
Amphotericin-B[b]	—	—	—	—	—	0.20	0.39	1.00	0.42	0.76
5,Flucytosine[c]	—	—	—	—	—	1.20	0.59	—	0.39	—
Norflox[d]	—	12.5	6.2	12.5	3.0	—	—	—	—	—
Cap. flox[e]	1.5	3.1	1.5	0.78	0.78	—	—	—	—	—

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

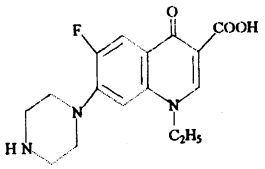
Chemical names: b)



c) 5, Fluorocytocine



d) Norfloxacin



e) Ciprofloxacin

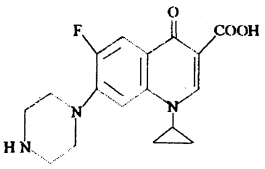


Table 4. In Vivo Evaluation of the Selected Organotin(IV) Complexes of Amino Acids Against Multiinfection Fungal Model

Complexes	No. of animal used/survival	Dose ($mg\,kg^{-1}$)	A.V. cfu/gram tissue		Vaginal culture cfu	Skin culture positive/ Total No. animals
			Kidney	Lungs		
Ph_3SnL-1	5/0	100	—	—	—	—
	5/2	50	0.1	0.0	2.4×10^4	1/1
Ph_3SnL-2	5/0	100	—	—	—	—
	5/1	50	0.0	0.0	2.0×10^4	1/1
Control	5/5	(PEG)	6×10^4	2×10^7	3.5×10^4	3/5

respectively, have been proposed.

In vitro antimicrobial results (MIC in $\mu g\,ml^{-1}$) against a wide spectrum of bacteria and fungi of complexes Me_3SnL-1, Me_3SnL-2, Ph_3SnL-1, Ph_3SnL-2, $Bu_2Sn(L\text{-}2)_2$, and $Ph_2Sn(L\text{-}1)_2$, which are soluble in DMSO, as well as the MIC values of Ph_3SnCl, Ph_2SnCl_2, Bu_2SnO, and of some reference compounds are presented in Table 3. Due to insufficient solubility of compounds **3**, **4**, **7**, and **10** in DMSO, they could not be screened. In comparison to the parent tin compounds, viz. Ph_3SnCl, Ph_2SnCl_2, and Bu_2SnO, all six organotin(IV) derivatives of the amino acids exhibit considerable activity. Further, as is evident from the data collected in Table 3, the fungicidal and bactericidal activities of the organotin compounds under the experimental conditions decreased in the following order: triphenyl- > diphenyl- > dibutyl- > trimethyltin complex. Because of the high antifungal activities of Ph_3SnL-1 and Ph_3SnL-2, they have been screened in vivo against a multiinfection fungal model in mice. The

Table 5. Thermal Analysis Data of the Complexes

Complexes	Temp range (°C) from TG	Peak temp in DTG (°C)	Peak temp in DTA (°C) [Nature of peak]	Loss of weight % from TG obsd (calcd)	Total %wt loss obsd (calcd)
Ph_3SnL-1	80—512 with inflection at 310	310	120 (endothermic)[a] followed by broad exotherm in the range 170—510	—	73.91 (72.96)
Ph_3SnL-2	80—310	305	123 (exothermic)	47.91 (48.08)	72.91 (72.00)
	310—503	350	279 (broad exotherm)	25.00 (23.92)	
Me_3SnL-1	80—160	94	107 (exothermic)	14.72 (14.46)	56.35 (56.83)
	160—424	192	198 (exothermic)	41.63 (42.36)	
$Bu_2Sn(L\text{-}2)_2$	85—210	181	181 (endothermic)	23.00 (23.07)	72.92 (72.80)
	210—500	284	280 (broad exotherm)	49.92 (49.73)	

a) mp of the complex.

compounds were tested at 100 and 50 mg kg^{-1}, P.O., for 4 d concerning antifungal efficacy. The results (Table 4) indicate that the compounds at 100 mg kg^{-1} were toxic, since most of the animals died during the experimental period, and did not show promising activity. Both compounds were found to be active at a dose of 50 mg kg^{-1}, but were not found to be active as compared (cfu) to the controls. Although the ligands, methionine and asparagine have different structures containing a soft-base thioether and a hard-base amide group, respectively, the observed antimicrobial activities of their organotin(IV) compounds are more or less the same. It seems that the activities of the organotin(IV) compounds are apparently due to the organic groups attached to tin, and the amino acid anion has little influence on their biological behavior.

Thermal Studies: The thermal decomposition of some complexes, viz. Me_3SnL-1, Ph_3SnL-1, Ph_3SnL-2, and $Bu_2Sn(L\text{-}2)_2$, has been studied using TG, DTG, and DTA techniques. All of the complexes gradually decomposed along with the formation of SnO under a dry nitrogen atmosphere above 424 °C. As is evident from the data compiled in Table 5, all of the complexes, except for Ph_3SnL-1, decomposed in two steps, corresponding to the loss of organic groups attached to tin in the first step, followed by the loss of an amino acid anion, giving SnO as a residue. The observed percent weight loss in each step is in close agreement with the calculated value for all complexes. The corresponding DTG and DTA peak temperatures are also given in Table 5. The Ph_3SnL-1 complex decomposes in a single step in the range 80—512 °C, giving SnO as a residue. The residues in all cases have been characterized by X-ray analyses and tin determinations. All of the '*d*' values observed in the residues were in good agreement with the reported '*d*' values for SnO.[28]

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