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Comparative study of structure–activity relationship of di- and tri-organotin(IV) derivatives of amino acid and peptides

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Abstract

Novel non-electrolytic di- and tri-organotin(IV) derivatives of the general formula $R_2Sn(L/HL')$ and $Ph_3Sn(HL/H_2L')$, where R is *n*-Bu and Ph, and L/HL is dianion/monoanion of D-penicillamine (H_2L-1) and L-carnosine (H_2L-2), and HL'/H_2L' is dianion/monoanion of triglycine (H_3L-3) have been synthesized in 1:1 molar ratio either at pH 7.0 or pH < 2.0. All *n*-$Bu_2Sn(IV)$ derivatives have been synthesized by the reaction of Bu_2SnO with amino acid/peptides under azeotropic removal of water. $Ph_2Sn(IV)/Ph_3Sn(IV)$ derivatives have been synthesized by either sodium chloride method or alkoxide method. The dibutyltin(IV) complexes synthesized at pH < 2.0 possess chlorine in the coordination sphere (as revealed from molar conductance measurement in methanol) and a molecule of water in the crystal lattice. The structures of the complexes are discussed on the basis of IR, far-IR, multinuclear (^{1}H-, ^{13}C- and ^{119}Sn-) NMR and ^{119}Sn-Mössbauer spectroscopic studies. All the diorganotin(IV) derivatives possess a distorted trigonal bipyramidal structure in which D-penicillamine/peptides are tridentate coordinating through N_{amino}, $C(O)O_{carboxyl}$ and $S_{thiol}/N_{peptide}$. The NH_2 group bridging/hydrogen bonding may lead to the associated structure. Whereas a linear polymeric structure with a distorted trigonal bipyramidal environment around tin has been tentatively proposed for $Ph_3Sn(IV)$ derivatives in which the ligands may act as bidentate coordinating through N_{amino} and $C(O)O_{carboxyl}$. *n*-$Bu_2SnCl(HL\text{-}1)\cdot H_2O$, synthesized at low pH, is dimeric. The anti-inflammatory activity, ALD_{50} and blood pressure lowering activity of the synthesized derivatives are reported. Some complexes exhibit good anti-inflammatory activities comparable to that of phenylbutazone (a comparative analysis is presented through plots). The triorganotin(IV) derivatives exhibit significantly better activities than the diorganotin(IV) derivatives.

Keywords: Organotin(IV); Amino acid; Peptide; Multi-nuclear NMR; ^{119}Sn-Mössbauer; Structure–activity relationship

1. Introduction

The chemistry of organotins has witnessed quantum leap during the last fifty years, owing to their potential biological and industrial applications. Inorganic tin has been evaluated as the third most important pollutant in the ecosystem, which has raised the concern that tin may enter into the human food chain [1], get accumulated in the environment, and finally in the biological systems. However, the organotin(IV) compounds, which were modeled on the original active platinum compound, *cis*-platin [2], have also found their place among a class of non-platinum chemotherapeutic metallopharmaceuticals exhibiting good anti-tumor activity [3a–e]. Further, the biological activity of the organotin compounds may be due to the presence of easily hydrolysable groups (easily dissociable chelating ligands) yielding the intermediates, such as $R_nSn^{(4-n)+}$ ($n = 2$ or 3) moieties, which may bind with DNA [4a] or high-affinity site of ATPase (histidine only) and low-affinity site of ATPase, and haemoglobins (histidine and cystine) [4b–e]. Therefore, considerable efforts have been made to characterize model organotin compounds of the ligands having hetero donor atoms (O, N and/or S) [5a–g], and simultaneously several studies have been focused on structure–activity correlations [6a–c] during the last two

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decades. In order to get a better insight in how the metallic species behave inside the biological systems, it is necessary to study their coordination behavior with biomolecules, and hence to formulate structure–activity correlations to devise novel derivatives with potential anti-tumor activity. Because of this, attention has shifted towards metal derivatives of amino acids and peptides. The organotin-amino acid systems [3e] have been extensively studied, whereas only limited studies have been carried out on the interaction of organotins with peptides [3e,7–16].

In order to widen the scope of investigations on the coordination behavior of the ligands occurring in the biological systems towards organotins, we carried out systematic studies of organotin(IV) derivatives of biologically relevant ligands such as amino acids and dipeptides [3e,17–20]. Recently, the diorganotin(IV) compounds of some dipeptides have been reported to exhibit significant biological [15] and anti-tumor activities [16]. In the present communication, we report the synthesis, structural studies and biological activity of the diorganotin(IV) {R_2Sn(IV), R = *n*-Bu and Ph} and triorganotin(IV) {R_3Sn(IV), R = Ph} derivatives of D-penicillamine {a thiol containing amino acid}, L-carnosine {(β-alanyl-L-histidine), a dipeptide} and triglycine {a tripeptide}. An attempt is being made to formulate a correlation between structure and activities of these organotin(IV) derivatives of the S, N and O donor ligands. However, penicillamine derivatives, viz. R_2Sn(DL-Pen), R_2Sn(DL-PenH)$_2$ (where R = Me and Ph), Me_3Sn(DL-PenH), Ph_3Sn(DL-Pen)$SnPh_3$, Me_2Sn-(D-Pen), -(L-Pen), -(D-PenH)$_2$, -(L-PenH)$_2$ [21a], and *n*-Bu_2Sn(DL-Pen) [21b] and Me_2SnCl(DL-PenH), *n*-Bu_2SnCl(DL-PenH)·H_2O [21c], have already been synthesized and their structures have been described with the help of variable temperature Mössbauer spectral studies [22a–d]. The anti-tumor activity and the structure–activity (P-388 lukaemic) relationship of these diorganotin(IV)– penicillaminates have also been reported [21b,22b].

2. Experimental

2.1. Materials

All the reactions were carried out under an anhydrous nitrogen atmosphere. Solvents were purified and dried before use. di-*n*-Butyltin(IV)oxide, triphenyltin(IV)-chloride (E. Merck), diphenyltin(IV)dichloride (Aldrich), D-penicillamine, L-carnosine and triglycine (Sigma) were used as received.

2.1.1. Synthesis of di-n-butyltin(IV)-D-penicillaminate, -L-carnosinate and -triglycinate at pH 7.0

The complexes were prepared under anhydrous conditions by dropwise addition of a dry, hot methanol solution of di-*n*-butyltin(IV) oxide (2.49 g; 0.01 mol) to a hot methanol solution of the amino acid/peptide (0.01 mol). The mixture obtained was refluxed with constant stirring giving a turbid solution. Refluxing was continued for at least 14–16 h with azeotropic removal of water. The solution was filtered, and the excess of solvent was removed under reduced pressure. The oily product obtained was solidified, purified, and crystallized by trituration with hexane (b.p. 60–80 °C fraction from petroleum (E. Merck)). It was recrystallized from methanol-hexane mixture.

2.1.2. Synthesis of di-n-butyltinchloro-D-penicillaminate monohydrate and -triglycinate monohydrate at low pH ~ 2.0

HCl (12 N) was added to the methanolic solution of D-penicillamine (or triglycine) (0.01 mol) to adjust the pH to 2.0. di-*n*-Butyltin(IV) oxide (2.49 g; 0.01 mol) was dissolved in methanol (20 ml) and added to the amino acid/peptide solution with stirring and the pH of the resulting solution being maintained at ≤ 2.0 with dil. HCl. The rest of the procedure is same as mentioned in Section 2.1.1.

2.1.3. Synthesis of di- and tri-phenyltin(IV) complexes

Di- and tri-phenyltin(IV) complexes of D-penicillamine, L-carnosine and triglycine have been synthesized by using following two methods.

2.1.3.1. Synthesis by sodium chloride method. The ligand (amino acid/peptide, 0.01 mol) was dissolved in minimum amount (20 ml) of dry methanol. Sodium methoxide, prepared by dissolving sodium (0.012 mol for Ph_3Sn(IV) complexes; 0.024 mol for Ph_2Sn(IV) complexes) in dry methanol (15ml), was then added. The resulting mixture was refluxed with constant stirring giving a clear solution of NaHL or Na_2L within half an hour. Refluxing was continued for 3–4 h with constant stirring. A hot methanolic solution (20 ml) of di- or triphenyltin(IV) chloride (0.01 mol) was added to the solution of the preformed sodium salt of ligand (Na_2L or NaHL) giving a clear solution (except triphenyltin(IV) complexes of H_2L-2 and H_3L-3). The resulting mixture was further refluxed with constant stirring for another 6–7 h, and was then centrifuged and filtered to remove sodium chloride formed. The excess of the solvent was removed under reduced pressure. The semi-solid mass obtained was solidified by trituration with either hexane (b.p. 60–80 °C) or petroleum ether (b.p. 60–80 °C, E. Merck), and recrystallized from either methanol–hexane or methanol–petroleum ether mixture.

2.1.3.2. Synthesis of triphenyltin(IV)–D-penicillaminate monohydrate and –triglycinate monohydrate by alkoxide method at low pH ~2.0. Triphenyltin(IV) chloride (1.49 g, 0.01 mol) was dissolved in the minimum amount of dry methanol (~40 ml). Sodium methoxide, prepared by dissolving sodium (0.60 g, 0.026 mol) in dry methanol (~15 ml), was then added. The resulting mixture was refluxed with constant stirring for at least 6 h to give a solution of triphenyltin(IV) methoxide. A hot methanolic solution of ligand (0.01 mol) adjusted to pH ≤ 2.0 by adding dil. HCl, was added to the preformed hot methanolic solution of triphenyltin(IV) methoxide with constant stirring. The resulting solution was then refluxed for at least 14 h. The rest of the procedure is same as mentioned in Section 2.1.3.1.

2.2. Measurements

The melting points of the synthesized complexes were determined on a Toshniwal capillary melting point apparatus and were uncorrected. Carbon, hydrogen and nitrogen analysis of the di-*n*-butyl- and di-phenyltin(IV) complexes were carried out on a Perkin–Elmer, CHN-rapid elemental analyzer at the Indian Institute of Technology, Delhi, India, those of the triphenyltin(IV) complexes, on a CHN analyzer Carlo Erba 1108, Heraeus, at the Central Drug Research Institute (CDRI), Lucknow, India. The tin content in the synthesized complexes was determined gravimetrically as SnO_2 [20]. Molar conductance measurements were carried out on the same instrument as reported previously [20]. Infrared and far-infrared spectra of the solid complexes were recorded on a Perkin–Elmer 1600 series FTIR spectrophotometer in the range 4000–400 cm^{-1} from KBr discs and 600–200 cm^{-1} from CsI discs, respectively, whereas infrared spectra of the semi-solid complexes were recorded on the same spectrophotometer, in the range 4000–400 cm^{-1} from Nujol mull (loaded over NaCl pellets), at the Department of Chemistry, Indian Institute of Technology, Roorkee, India. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR) spectrometer at the CDRI, Lucknow, India, using DMSO-d_6 or $CDCl_3$ as solvent and TMS as the internal standard. ^{119}Sn-NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR) spectrometer at the Indian Institute of Technology, Delhi, India, using DMSO-d_6 as solvent and tetramethyltin as the internal standard. ^{119}Sn-Mössbauer spectra were recorded on Mössbauer spectrometer model MS-900 according to the procedure reported previously [20], at the Department of Chemistry and Physics, University of The District of Columbia, Washington, DC.

2.2.1. Anti-inflammatory activity

A freshly prepared suspension of carrageenin (0.2 ml, 1.0% in 0.9% saline) was injected subcutaneously into the plantar aponeurosis of the hind paw of the rats of both sexes (body weight 120–160 g) by the method of Winter et al. [23]. One group of five rats was kept as a control and the animals of the other group of five; each was pretreated with the test drugs given orally 30 min before the carrageenin injection. The paw volume was measured by a water plethysmometer socrel at the time of treatment and then at an interval of 1 h for 4 h. The mean increase of paw volume at each time interval was compared with that of control group (five rats treated with carrageenin, but not treated with test compounds) and per cent anti-inflammatory value was calculated as given below:

$$\%\ \text{anti-inflammatory} = \left(1 - \frac{DT}{DC}\right) \times 100$$

where, DT and DC are the volumes of paw edema in drug treated and control groups, respectively.

2.2.2. Acute toxicity study

ALD_{50} (average lethal dose at 50% survival) of the compounds was determined in albino mice. The mice of either sex (body weight 20–25 g) were used. The test compound was injected intraperitoneally at different dose levels in groups of 10 animals and percent mortality in each group was observed after 24 h of drug administration. The ALD_{50} value (mg kg^{-1}) was calculated from the data obtained by the method of Smith [24].

2.2.3. Blood pressure lowering activity

The study was carried out on either adult mongrel dogs (body weight 10–20 kg) or on cats (body weight 3–4 kg) of either sex. The animals were anesthetized with chloralose (80 mg kg^{-1}) injected intravenously. The right femoral vein was cannulated in each case with an indwelling polythene tube. All the animals were maintained on artificial positive pressure ventilation by cannulation of the trachea in order to avoid reflex changes in respiration. The blood pressure was recorded from the left common carotid artery by means of a mercury manometer on smoked kymograph paper. Anti-inflammatory, ALD_{50} and blood pressure lowering activities were carried out at LLRM Medical College, Meerut, India.

3. Results and discussion

Di-*n*-butyltin(IV) oxide reacts with the amino acid/peptides in equimolar ratio in dry methanol (at pH ~ 7.0) to give the complexes of type Bu_2SnL/Bu_2SnHL-3

under azeotropic removal of water (Eq. (1a)). The reactions of di-*n*-butyltin(IV) oxide with H_2L-1/H_3L-3 at pH $\leq$ 2.0 afforded the complexes according to Eq. (1b). The reactions of Ph_2SnCl_2 and Ph_3SnCl with the sodium salt of amino acid/peptide (formed according to Eqs. (2a) and (2b)) in a 1:1 molar ratio led to the formation of the complexes according to Eqs. (3a) and (3b), respectively. The reactions of H_2L-1/H_3L-3 with triphenyltin methoxide (formed according to Eq. (4)) in equimolar ratio at pH $\sim$2.0 afforded the complexes according to Eq. (5).

$$n\text{-}Bu_2SnO + H_2L/H_3L\text{-}3 \xrightarrow{1:1,\ pH\ \sim 7.0} n\text{-}Bu_2SnL/Bu_2Sn(HL\text{-}3) + H_2O \quad (1a)$$

$$n\text{-}Bu_2SnO + H_2L\text{-}1/H_3L\text{-}3 \xrightarrow{1:1,\ pH < 2.0\ by\ HCl} n\text{-}Bu_2SnCl(HL\text{-}1/H_2L\text{-}3)\cdot H_2O \quad (1b)$$

$$H_2L/H_3L\text{-}3 + 2NaOMe \rightarrow Na_2L/Na_2HL\text{-}3 + 2MeOH \quad (2a)$$

$$H_2L + NaOMe \rightarrow Na(HL) + MeOH \quad (2b)$$

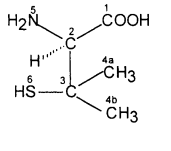
$$Ph_2SnCl_2 + Na_2L/Na_2HL\text{-}3 \xrightarrow{1:1} Ph_2SnL/Ph_2Sn(HL\text{-}3) + 2NaCl \quad (3a)$$

$$Ph_3SnCl + Na(HL) \xrightarrow{1:1} Ph_3Sn(HL) + NaCl \quad (3b)$$

$$Ph_3SnCl + NaOMe \rightarrow Ph_3Sn(OMe) + NaCl \quad (4)$$

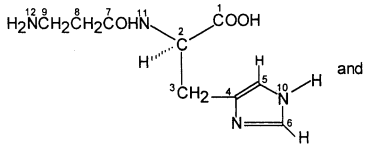
$$Ph_3Sn(OMe) + H_2L\text{-}1/H_3L\text{-}3 \xrightarrow{1:1} Ph_3Sn(HL\text{-}1/H_2L\text{-}3) + MeOH \quad (5)$$

where, H_2L =



(H2L-1; D(-) Pen; D(-) Penicillamine)

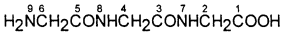
,



and

(H2L-2; β-Ala-His; L-Carnosine)

H_3L =



(H3L-3; GlyGlyGly; Triglycine)

The reactions for the synthesis of *n*-Bu_2Sn(IV) and Ph_2Sn(IV) derivatives were found to be quite feasible and were complete within 14–16 and 6-7 h of refluxing, respectively. Whereas, the reactions involving the synthesis of Ph_3Sn(IV) derivatives of H_2L-2 and H_3L-3 yielded a turbid solution after a prolonged heating, and the complex was obtained from the filtrate after filtering the unreacted peptide/organotin chloride. Most of the complexes were colored solids (except *n*-Bu_2-Sn(IV) complexes synthesized at low pH, which were semi-solids) and obtained in good yields (except $Ph_3Sn(H_2L\text{-}3).H_2O$). All of the complexes are found to be stable towards air and moisture. Most of the complexes of H_2L-1 and H_3L-3 are adequately soluble in dimethylsulfoxide and methanol upon heating and they show very low solubility in chloroform and other organic solvents. The complexes of H_2L-2 show extre-

Table 1
Characteristic properties of di- and tri-organotin(IV) complexes of amino acid and peptides

Complex number	Complex (empirical formula)	Method of preparation	Yield (%)	M.p. (°C)	Colour and physical state	Analysis (%) found (calculated)			
						Sn	N	C	H
1	$Bu_2Sn(L\text{-}1)[C_{13}H_{27}NO_2SSn]$	Section 2.1.1	70	213–216	Yellowish-Brown solid	30.94 (31.23)	3.27 (3.68)	41.29 (41.08)	7.60 (7.16)
2	$Ph_2Sn(L\text{-}1)[C_{17}H_{19}NO_2SSn]$	Section 2.1.3.1	80	210–213	Brownish-yellow solid	27.90 (28.26)	2.86 (3.33)	48.17 (48.60)	4.30 (4.56)
3	$Ph_3Sn(HL\text{-}1)[C_{23}H_{25}NO_2SSn]$	Section 2.1.3.1	74	94–97	Cream solid	23.54 (23.83)	2.31 (2.81)	55.06 (55.45)	4.71 (5.06)
4	$Bu_2SnCl(HL\text{-}1)\cdot H_2O[C_{13}H_{30}NO_3SSnCl]$	Section 2.1.2	70	Semi-solid	Brown semi-solid	26.97 (27.34)	2.98 (3.22)	35.56 (36.00)	5.97 (6.27)
5	$Ph_3Sn(HL\text{-}1)\cdot H_2O[C_{23}H_{27}NO_3SSn]$	Section 2.1.3.2	64	96–99	Cream solid	22.57 (22.99)	2.60 (2.71)	53.08 (53.52)	4.91 (5.27)
6	$Bu_2Sn(L\text{-}2)[C_{17}H_{30}N_4O_3Sn]$	Section 2.1.1	79	243–246	White solid	25.64 (25.97)	11.94 (12.25)	44.20 (44.66)	6.42 (6.61)
7	$Ph_2Sn(L\text{-}2)[C_{21}H_{22}N_4O_3Sn]$	Section 2.1.3.1	81	132–135	Light cream solid	23.38 (23.88)	10.87 (11.27)	50.40 (50.74)	4.17 (4.46)
8	$Ph_3Sn(HL\text{-}2)[C_{27}H_{28}N_4O_3Sn]$	Section 2.1.3.1	66	101–104	Pink solid	20.21 (20.63)	9.49 (9.74)	56.07 (56.38)	4.78 (4.91)
9	$Bu_2Sn(HL\text{-}3)[C_{14}H_{27}N_3O_4Sn]$	Section 2.1.1	75	164–167	Brownish-yellow solid	27.78 (28.26)	9.52 (10.00)	39.69 (40.03)	6.06 (6.48)
10	$Ph_2Sn(HL\text{-}3)\cdot MeOH[C_{19}H_{23}N_3O_5Sn]$	Section 2.1.3.1	80	218–221	White solid	23.71 (24.12)	8.19 (8.54)	45.95 (46.37)	3.35 (4.71)
11	$Bu_2SnCl(H_2L\text{-}3)\cdot H_2O[C_{14}H_{30}N_3O_5SnCl]$	Section 2.1.2	65	Semi-solid	Brown semi-solid	24.81 (25.02)	8.46 (8.86)	35.07 (35.44)	5.95 (6.37)
12	$Ph_3Sn(H_2L\text{-}3)\cdot H_2O[C_{24}H_{27}N_3O_5Sn]$	Section 2.1.3.2	41	109–112	Creamish-yellow solid	20.94 (21.34)	7.16 (7.55)	51.42 (51.83)	4.41 (4.89)

mely low solubility in common organic solvents. The analytical data of the complexes, as presented in Table 1, suggest that in every instance the resulting complexes crystallized with 1:1 stoichiometry regardless of the proportions of the organotin moiety and amino acid/peptide used. The molar conductance of 10^{-3} M solution of the complexes in methanol lie in the range (0.0–0.1 Ω^{-1} cm^2 mol^{-1}), indicating their non-electrolytic nature.

3.1. Infrared spectral studies

The characteristic infrared absorption frequencies (in cm^{-1}) and their assignments for the ligands and their organotin(IV) complexes are presented in Table 2.

3.1.1. Coordination by amino group

Infrared NH_2 stretching frequencies were used to distinguish coordinated from non-coordinated amino groups. The position and intensity of ν(N–H) bands are influenced by hydrogen bonding, and by coordination of the nitrogen to tin [3e,7]. In all the organotin(IV) derivatives of amino acid/peptides, very intense absorption bands in the range 3266–2958 cm^{-1} due to the $\nu(N–H)_{amino}$ undergo a substantial lowering in comparison to the non-coordinated amino acid/peptides (3288–3017 cm^{-1}), indicating coordination by the amino group to the tin atom. Similar results have been reported for R_3SnAA (AA = amino acid anion) [3e,7,18,19] and R_2SnL (H_2L = dipeptide) [10,11,20]. Further, the $\nu(NH_2)$ absorption bands are broad, suggesting the presence of inter- and/or intra-molecular hydrogen bonding [3e,7]. However the $\nu(N–H)_{amino}$ absorption bands are of weak intensity in n-Bu_2Sn(IV) complexes of H_2L-1 and H_3L-3, synthesized at low pH, indicating weak interactions of the NH_2 group with tin in these complexes.

3.1.2. Coordination by carboxylate group

Infrared O–C=O stretching frequencies have been utilized to distinguish coordinated from non-coordinated carboxyl groups, and also, to identify the nature of bonding of carboxylic group, viz., monodentate or bridging. The carboxylate groups in the organotin(IV) derivatives generally adopt a bridged structure in the solid state unless the organic substituents at tin are bulky or unless the carboxylate group is branched at the α-carbon [10]. The infrared absorption spectra indicate that ν_{as}(O–C=O) values shown by these amino-coordinated complexes get shifted to higher frequencies (1671–1621 cm^{-1}) in comparison to those of H_2L-1 (1590 cm^{-1}), H_2L-2 (1582 cm^{-1}) and H_3L-3 (1648 cm^{-1}). Whereas, the corresponding ν_s(O–C=O) absorption frequencies (1408–1322 cm^{-1}) either remain at the same value or move to lower frequencies (except Ph_2Sn(L-1), Ph_3Sn(HL-1) and Ph_2Sn(L-2)) than in the amino acid/peptides themselves (1400–1386 cm^{-1}). The magnitude of the (ν_{as}–ν_s)(O–C=O) ($\Delta\nu$) separation, which has been found to be useful in identifying structural features, is larger in the amino coordinated organotin(IV) derivatives of H_2L-1 and H_3L-3 ($\Delta\nu$ = 287 ± 53 cm^{-1}) than in H_2L-1 (207 cm^{-1}) and H_3L-3 (248 cm^{-1}) (Table 2). Further, the values of $\Delta\nu$ (> 230 cm^{-1}) for all the derivatives have been found comparable with those obtained for R_3SnAA (AA = amino acid anion) [3e,7,18,19] and R_2SnL (H_2L = dipeptide) [20], indicating that the carboxylate group acts as a monodentate ligand [3e,7,18–20]. However, in n-Bu_2SnCl(D-HPen)·H_2O, the ν_{as}(O–C=O) band is observed at lower frequency (1617 cm^{-1}) as a medium intensity band than in all other complexes of D-$PenH_2$ (1635 ± 1 cm^{-1}), indicating the non-involvement of the (O–C=O) group in coordination with tin, and this shift is due to the hydrogen bonding between the (O–C=O) group and water molecule. The magnitude of the (ν_{as}–ν_s) (O–C=O) ($\Delta\nu$) separation in the organotin(IV) derivatives of L-carnosine is < 200 cm^{-1}, indicating that the carboxylate group is bidentate and bridging. Similar results are also reported for $R_2SnGlyGly$ (R = Me and n-Bu), n-$Bu_2SnGlyGly.H_2O$ and $Me_2SnGlyAla$ [11]. Furthermore, the disappearance of a broad band in the spectra of all the complexes except n-Bu_2SnCl(D-HPen)·H_2O in the region 2355–2265 cm^{-1}, which was present in all the ligands as a medium/weak intensity band (due to ν(O–H) carboxyl), suggests the deprotonation of COOH group upon complexation [3e]. The appearance of a new band in the IR spectra of all the synthesized complexes except n-Bu_2SnCl(D-HPen)·H_2O in the region 572–528 cm^{-1}, which may be assigned to ν(Sn–O), further supports the bonding of (O–C=O) group to the tin atom [3e,18-21].

3.1.3. Coordination by thiol/peptide group

In the derivatives studied, apart from the carboxylic oxygen and amino nitrogen as potential coordinating sites to the tin atom, the amide group (in the organotin(IV) derivatives of H_2L-2 and H_3L-3) and thiol group (in the organotin(IV) derivatives of H_2L-1) also exhibit strong tendency to coordinate with the organotin(IV) moiety. Two characteristic bands, viz. amide I [essentially ν(C=O)] and amide II [δ(N–H) coupled with ν(C–N)], give the crucial information on the occurrence of metal coordination by the basic atoms of the amide group [25,26]. The intense bands of the amide I observed at 1651 cm^{-1} and 1671 cm^{-1}, 1648 cm^{-1} in H_2L-2 and H_3L-3, respectively, undergo a shift by ~5–10 cm^{-1} to a lower frequency (1665–1642 cm^{-1}) in the IR spectra of the diorganotin(IV) derivatives of H_2L-2 and H_3L-3 (except n-$Bu_2SnCl(H_2L\text{-}3).H_2O$) upon complexation. This is probably due to the involvement of the peptide nitrogen in bonding with tin, which lowers the

Table 2
Characteristic IR frequencies [a] (in cm^{-1}) of amino acid/peptides and their di- and tri-organotin(IV) complexes

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(Sn←N)	ν_{as}(Sn–C); ν_{s}(Sn–C)	Others	[δ(NH)+ν(CN)] ⟨amide II⟩
H_2L-1	3250s; 3017vs	–	1590vs	1386s	204	–	–	–	ν(SH): 2595m; ν(COOH): 2065m	–
Bu_2Sn(L-1)	3239s; 2958vs	–	1636vs	1389s	247	572m	477m	622m; 530w	ν(Sn–S): 370m	–
Ph_2Sn(L-1)	3223s; 3120sbr	–	1636vs	1397s	239	568m	448m	283vs; 222m	ν(Sn–S): 355m	–
Ph_3Sn(HL-1)	3223s; 3058m	–	1634s	1399s	235	529w	451m	285vs; 220m	ν(SH): 2604m; ν(COOH): absent	–
Bu_2SnCl(HL-1)·H_2O [b]	3174w; 2967vsbr	–	1617m	1375s	242	–	423m	598m; 532vs	ν(Sn–S): 369m; ν(COOH): 1952w; ν(Sn–Cl): 251m	–
Ph_3Sn(HL-1)·H_2O [c]	3220w; 3117s; 3066s	–	1636s	1352m	284	545w	444vs	284vs; 221m	ν(SH): 2620m; ν(COOH): absent	–
H_2L-2	3399w [d]; 3243s; 3089m	1651s	1582vs	1400s	182	–	–	–	ν(COOH): 2355m	1513m
Bu_2Sn(L-2)	3377s [d]; 3227s; –	1647s	1578s	1399s	179	569m	419s	667w; 592m	ν(COOH): absent	Absent
Ph_2Sn(L-2)	3381s [d]; 3135s; –	1642s	1592s	1408s	184	528m	447m	280s; 221s	ν(COOH): absent	Absent
Ph_3Sn(HL-2)	3383s [d]; 3200s; 3100s	1642s	1588s	1399s	189	570m	458w	281s; 223s	ν(COOH): absent	1509s
H_3L-3	3288vs; 3094s; 3050sh	1671sh	1648vs [e]	1400s	248	–	–	–	ν(COOH): 2349w	1550s
Bu_2Sn(HL-3)	3208vs; 3150m; 3010sh	1665s	1623s	1331s	292	561vs	447s	630s; 511m	ν(COOH): absent	1568s
Ph_2Sn(HL-3)·MeOH [f]	3247s; 3105sh; 3047s	1662s	1662s [e]; 1621sh	1322s	299	556s	486s; 461w	284m; 220vs	ν(COOH): absent	1582s
Bu_2SnCl(H_2L-3)·H_2O [g]	3266w; 3174w	1708w	1635m [e]	1376m	259	556w	421w	666w; 526m	ν(COOH): absent; ν(Sn–Cl): 255m	1555s
Ph_3Sn(H_2L-3)·H_2O [h]	3219s; 3102s	1697sh	1659s [e]	1373s	286	563m	462m	285m; 223m	ν(COOH): absent	1556s

[a] vs, very strong; s, strong; m, medium; w, weak; sh, shoulder; br, broad.
[b] Medium intensity bands at 3495 and 3433 cm^{-1} due to ν(O–H).
[c] Strong band at 3404 cm^{-1} with a shoulder at 3410 cm^{-1}due to ν(O–H).
[d] ν(N–H) of histidine ring.
[e] Merged with CO_{amide}.
[f] Medium intensity band at 3483 cm^{-1} due to ν(O–H).
[g] Weak bands at 3401 and 3314 cm^{-1} due to ν(O–H).
[h] Strong bands at 3334 and 3295 cm^{-1} due to ν(O–H).

bond order of the C=O (amide) group due to the resonance stabilization. The possibility of the involvement of the C=O (amide) group in the intermolecular hydrogen bonding can not be excluded. Further, in *n*-$Bu_2SnCl(H_2L\text{-}3).H_2O$, the amide I band is observed at 1708 cm^{-1} due to the involvement of the $(C{=}O)_{amide}$ in the hydrogen bonding. Apart from this, a medium intensity band of the amide II observed at 1513 cm^{-1} in H_2L-2 is absent in the IR spectra of *n*-Bu_2Sn(L-2) and Ph_2Sn(L-2) due to the bonding of the $N_{peptide}$ to tin after deprotonation of the amide nitrogen. Whereas a band in the range 1582–1555 cm^{-1} has been observed in the diorganotin(IV) derivatives of H_3L-3 due to the non-participation of the second CONH group of triglycine. It has been reported that the σ-donor power of the peptide nitrogen is large than that of the amino nitrogen in $Ph_2Sn(^{-}OOCCH_2N^{-}COCH_2NH_2)$ for which a valence bond structure is considered with resonance in peptide bonds only [27]. This is also in agreement with the crystallographic data of the coordinated glycylglycine in Ph_2Sn(Gly–Gly) with formal charges being QN_{Pept}–$QO_{Pept} = -0.50$ and bond orders 1.50 for $(C{-}N)_{pept}$ and $(C{-}O)_{pept}$ [28]. The ($\nu(C{=}O)_{peptide}$) and the ν_{as}(O–C=O) merged into a broad band in the organotin(IV) derivatives of H_3L-3. In Ph_3Sn(HL-2) both amide I and amide II bands get shifted to lower frequencies (1642 and 1509 cm^{-1}), whereas in $Ph_3Sn(H_2L\text{-}3).H_2O$ to higher wave numbers (1697 and 1556 cm^{-1}) than in the free peptides, suggesting that the peptide nitrogen is not involved in bonding with tin. The appearance of a pair of bands of medium intensity in the region 486–419 cm^{-1} in the diorganotin(IV) derivatives is assigned to ν(Sn–N) and ν(Sn←N). This further confirms the coordination of the amino nitrogen as well as the peptide nitrogen to the diorganotin(IV) moiety, whereas the ν(Sn←N) at 447 cm^{-1} and 453 ± 9 cm^{-1} are observed in *n*-$Bu_2SnCl(H_2L\text{-}3)\cdot H_2O$ and Ph_3Sn(IV) derivatives, respectively [3e,19,20].

In the diorganotin(IV) derivatives of H_2L-1, instead of a broad band of medium intensity (2600–2400 cm^{-1}) due to ν(S–H), a medium intensity band due to ν(Sn–S) in the range 370–355 cm^{-1} is observed. This suggests that the thiol group (S_{thiol}) is involved in bonding with tin [21a,21c,22a]. Whereas the ν(Sn–H) at 2620 cm^{-1} is observed in $Ph_3Sn(HL\text{-}1)\cdot H_2O$ indicating the non-involvement of the thiol group in bonding. In *n*-$Bu_2SnCl(HL\text{-}1)\cdot H_2O$ and *n*-$Bu_2SnCl(H_2L\text{-}3)\cdot H_2O$, the ν(Sn–Cl) has also been assigned at 251 and 255 cm^{-1}, respectively [29].

The ν_{as}(Sn–C) and ν_s(Sn–C) bands in all the di-*n*-butyltin(IV) derivatives are observed at 630 ± 42 and 550 ± 42 cm^{-1}, respectively, suggesting the existence of a bent C–Sn–C moiety [19,20], whereas in the diphenyltin(IV) and triphenyltin(IV) derivatives, the corresponding ν_{as}(Sn–C) and ν_s(Sn–C) are observed at 283 ± 2 and 222 ± 2 cm^{-1}, respectively [19,20].

3.2. NMR spectral studies

3.2.1. ^{1}H-NMR spectral analysis

The characteristic resonance peaks in the ^{1}H-NMR spectra of the complexes, recorded in deuterodimethylsulfoxide, are presented in Table 3. The ^{1}H-NMR spectral data of H_2L-1, H_2L-2 and H_3L-3 [30–32], are also included in Table 3 for comparison. In the ^{1}H-NMR spectra of all the complexes studied, the CO(OH) resonance of the ligands (δ 12.0–13.0 ppm) is absent which suggests the replacement of the carboxylic proton by the organotin(IV) moiety. In all the diorganotin(IV) and triphenyltin(IV) complexes, the $-NH_{amino}$ resonances observed either as a broad weak signal or in conjugation with $NH_{peptide}$/phenyl protons attached to the tin atom, are shifted towards low field in the ranges δ 6.57–8.63 ppm and δ 7.73–8.85 ppm, respectively, when compared to those of the ligands (δ 5.0–8.0 ppm) [30]. This is probably due to the coordination of the amino group to the organotin(IV) moiety. In the diorganotin(IV) derivatives of H_2L-1, the –SH resonance in the region δ 1.0–2.0 ppm is not observed which suggests the replacement of the thiolic proton by the organotin(IV) moiety, whereas in compound **5** a singlet at δ 1.63 ppm is observed, indicating the non-involvement of the thiol group. In the diphenyltin(IV) derivative of H_2L-2 (compound **7**), a singlet due to $NH_{histidine}$ appears at δ 8.33 ppm. As reported previously [3e,17–20], the magnetically non-equivalent alkyl protons of the ligands undergo the diamagnetic shielding upon complexation. This is probably due to the conformation which the ligand molecule may adopt upon complexation. The resonances due to the tin-alkyl protons in the di-*n*-butyltin(IV) and tin-phenyl protons in the di- and tri-phenyltin(IV) derivatives are observed in the regions δ 0.81–1.54 ppm and δ 7.30–8.26 ppm, respectively [17–20]. All the protons in the complexes have been identified and the total number of protons calculated from the integration curve are in agreement with those calculated from the proposed molecular formula.

3.2.2. ^{13}C-NMR spectral analysis

The characteristic resonance peaks in the ^{13}C-NMR spectra of the complexes, recorded in deuterodimethylsulfoxide/deuterochloroform, are presented in Table 4. The ^{13}C-NMR data of H_2L-1 and H_3L-3 [32] are also included in Table 4. The ^{13}C-NMR spectra of the di- and tri-organotin(IV) complexes of H_2L-2 could not be recorded because of their extremely low solubility in DMSO-d_6/$CDCl_3$/CD_3OD.

The spectra of the organotin(IV) derivatives of H_2L-1 are consistent with the following observations:

Table 3
^{1}H-NMR spectral data of the di- and tri-organotin(IV) complexes of amino acid and peptides

Complex number [a]	Solvent	δ (ppm) [b]
DL-H_2L-1 [32]	D_2O + DCl	4.20 (s, 1H, H-2); 1.60 (s, 3H, H-4a); 1.52 (s, 3H, H-4b); 6.10 (s, 1H, H-5).
2	DMSO-d_6	3.41 (s, 1H, H-2); 0.95-1.50 (mbr, 6H, H-4a and H-4b); 7.70 (dbr, 2H, H-5); 7.52 (d, 4H, 3 Hz, H-β); 7.30 -7.43 (m, 8H, H-γ and H-δ).
5	DMSO-d_6	3.83 (s, 1H, H-2); 1.34-1.51 (mbr, 6H, H-4a and H-4b); 8.15 (s, 2H, H-5); 1.63 (s, 1H, H-6); 8.03 (d, 6H, 7 Hz, H-β); 7.33 (dd, 6H, 7, 6 Hz, H-γ); 7.91 (d, 3H, 7 Hz, H-δ).
H_2L-2 [31]	D_2O	4.46 (dd, 1H, H-2); 3.06 (dd, 2H, H-3); 6.95 (s, 1H, H-5); 7.71 (s, 1H, H-6); 2.65 (t, 2H, H-8); 3.22 (t, 2H, H-9).
7	DMSO-d_6	2.95 (dd, 1H, H-2); 2.50 (t, 2H, H-3); 2.12 (dd, 2H, H-8); 2.68 (t, 2H, 6 Hz, H-9); 8.33 (s, 1H, H-10 histidine ring); 6.57 (s, 2H, H-12); 7.87 (d, 2H, H-β); 7.40 (m, 8H, H-γ, H-δ, H-5 and H-6).
8	DMSO-d_6	3.36 (s, 1H, H-2); 2.63 (d, 2H, 6 Hz, H-3); 7.40 (s, 1H, H-5); 7.64 (s, 1H, H-6); 2.08 (t, 2H, H-8); 2.91 (dd, 2H, 18 Hz [c], H-9); 7.73 (sbr, 4H, H-10, H-11 and H-12); 7.55 (dbr, 6H, 6 Hz, H-β); 7.32 (dd, 6H, 6, 7 Hz, H-γ); 7.46 (dd, 3H, 7 Hz, H-δ).
H_3L-3 [32]	D_2O	4.01 (s, 2H, H-2); 3.91 (s, 2H, H-4); 3.80 (s, 2H, H-6).
10	DMSO-d_6	3.70 (s, 2H, H-2); 2.50 (s, 2H, H-4); 3.30 (s, 2H, H-6, merged with CH_3OH protons); 8.31 (s, 3H, H-8 and H-9); 7.56 (dbr, 4H, H-β); 7.32 (dd, 4H, 7, 8 Hz, H-γ); 7.43 (ddbr, 2H, H-δ).
11	DMSO-d_6	3.57 (sbr, 4H, H-2 and H-6); 2.51 (s, 2H, H-4); 8.63 (sbr, 4H, H-7, H-8 and H-9); 1.24-1.54 (m, 12H, H-α, H-β and H-γ); 0.81 (t, 4H, H-δ).
12	DMSO-d_6	3.84 (s, 2H, H-2); 3.50 (s, 2H, H-4); 3.62 (s, 2H, H-6); 8.58 (s, 2H, H-7 and H-8); 8.85 (s, 2H, H-9); 8.26 (dbr, 6H, H-β); 7.31 (dd, 6H, H-γ); 7.91 (dbr, 3H, H-δ).

[a] Complex number as mentioned in Table 1.
[b] s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet doublet; sbr, singlet broad; dbr, doublet broad; m, multiplet; mbr, multiplet broad.
[c] Geminal coupling.

- The resonances of the carboxylic carbon (i.e, C-1) in compounds **1**, **2** and **3** are observed at larger δ (δ 175.00–174.01 ppm) than in the ligand (δ 169.60 ppm) [32], suggesting the coordination of the ligand, through the carboxylic oxygen, to the organotin(IV) moiety [21c].
- Various carbons of the ligand; especially C-2, undergo a shift upon complexation. C-2 resonances at low field (δ 77.95–80.05 ppm) in compounds **1** and **2**, indicating the strong interactions of the O–C=O with tin, whereas in compounds **3**, **4** and **5** it resonances at high field (δ 61.24–58.71 ppm), indicating either the weak interactions/or the non-involvement of the O–C=O group in the coordination with tin.
- The carbons of phenyl (δ 127.00-147.10 ppm) and alkyl (δ 11.25–26.61 ppm) groups attached to tin are observed at positions comparable with other, similar compounds [3e,17–20,21c].

Table 4
^{13}C-NMR spectral data of the di- and tri-organotin(IV) complexes of amino acid and peptides

Complex number [a]	Solvent	δ (ppm)
DL-H_2L-1 [32]	D_2O + DCl	C-1: 169.60; C-2: 63.30 (63.20); C-3: 44.30; C-4a: 30.70 (30.68); C-4b: 28.32.
1	DMSO-d_6	C-1: 175.00; C-2: 80.05; C-3: 45.01; C-4a and C-4b: 13.75; C-α: 23.75; C-β: 26.15; C-γ: 25.00; C-δ: 11.25.
2	DMSO-d_6	C-1: 174.01; C-2: 77.95; C-3: 32.96 (32.41); C-4a: 28.81 (28.24); C-4b: 19.41 (19.93, 18.82); C-α: 140.02; C-β: 136.22 (135.36); C-γ: 128.35 (127.61); C-δ: 129.14.
3	$CDCl_3$	C-1: 174.80; C-2: 61.24 (59.07); C-3: 37.49; C-4a: 25.89 (26.16); C-4b: 17.75 (16.84), 18.73 (19.21); C-α: 139.01; C-β: 136.70 (136.50); C-γ: 128.82 (128.50, 129.31); C-δ: 130.11.
4	DMSO-d_6	C-1: 167.40; C-2: 58.71; C-3: 48.52; C-4a: 25.67; C-4b: 24.71; C-α: 23.84; C-β: 26.61 (26.90, 26.32); C-γ: 24.62; C-δ: 12.83.
5	DMSO-d_6	C-1: 168.52 (168.30); C-2: 59.53; C-3: 49.46; C-4a: 25.53; C-4b: 24.85; C-α: 147.10; C-β: 136.50 (136.10); C-γ: 127.50 (127.00); C-δ: 128.00.
H_3L-3 [32]	D_2O	C-1: 179.20; C-2: 46.08; C-3: 174.22; C-4: 45.45; C-5: 170.28; C-6: 43.43.
9	DMSO-d_6	C-1: 172.60 (172.20, 173.00); C-2: 48.86; C-3: 168.02; C-4: 47.39 (47.76); C-5: 166.21; C-6: 44.33; C-α: 25.99 (25.91); C-β: 27.37; C-γ: 26.93 (27.10); C-δ: 13.76 (13.50).
12	DMSO-d_6	C-1: 169.91 (169.72); C-2: 52.51; C-3: 168.81; C-4: 51.72; C-5: 166.22; C-6: 41.63; C-α: 147.21; C-β: 136.40 (136.70, 136.05), 134.70 (135.20, 134.20); C-γ: 127.31 (127.11), 126.60 (126.90); C-δ: 127.81.

[a] Complex number as mentioned in Table 1. Non-prominent or weak signals are in parentheses.

However, in compounds **4** and **5** (synthesized at pH ~2.0), the δ(C(O)OH) is slightly shifted upfield as compared to compounds **1**, **2** and **3** (prepared at neutral pH). This is probably due to the coordination of the C(O)OH group with tin as well as its involvement in the hydrogen bonding with H_2O molecule in n-Bu_2SnCl(D-HPen)·H_2O, and due to the weak interactions of the C(O)O group with tin in Ph_3Sn(HPen).

In n-Bu_2Sn(IV) and Ph_3Sn(IV) complexes of H_3L-3, the C(O)O resonances are observed at lower δ (δ 172.60 and 169.91 ppm, respectively) as compared with that of the ligand (δ 179.20 ppm), suggesting the coordination of the C(O)O to tin. The resonances of the $CO_{peptide}$ also get substantial upfield shift (δ 168.43 ± 0.41 and 166.21 ± 0.01 ppm) in comparison to the ligand (δ 174.22 and 170.28 ppm) [32] due to the presence of the inter-/intra-molecular hydrogen bonding to the some extent. The observed downfield shifts in the magnetically non-equivalent alkyl carbons of the ligand upon complexation are due to: (i) the coordination of the COO^-, N_{amino} and $N^-_{peptide}$ to the di-n-butyltin(IV) or COO^- and N_{amino} to the triphenyltin(IV) moiety; (ii) the resonance in the –CONH– group; and (iii) the inter-/intra-molecular hydrogen bonding. The above observations are consistent with the infrared and ^{1}H-NMR spectral data. Moreover, in some complexes, doublets of some signals have been observed due to the presence of stereoisomers.

3.2.3. ^{119}Sn-NMR spectral analysis

The ^{119}Sn chemical shifts of n-$Bu_2SnCl(H_2L\text{-}3)\cdot H_2O$, Ph_3Sn(HL-1), Ph_3Sn(HL-1)·H_2O and Ph_3Sn(HL-3)·H_2O are observed at −200.25, −237.34, −238.41 and −248.43 ppm, respectively, which are characteristic of the five-coordinated dibutyl- and triphenyl-tin derivatives [3e,17,20]. Further, ^{119}Sn-NMR spectra of Ph_3Sn(HL-1), Ph_3Sn(HL-1)·H_2O and $Ph_3Sn(H_2L\text{-}3)\cdot H_2O$ gave additional peaks at −247.60; −279.35(br), −248.10(br); and −391.38 ppm, respectively, indicating the presence of stereoisomers.

3.3. ^{119}Sn-Mössbauer spectral studies

The ^{119}Sn-Mössbauer parameters have been utilized as a diagnostic tool for proposing the structure that a particular complex can adopt in the solid state. Whether, the coordination of the amino group nitrogen atom, bonding of the $N_{peptide}$/S_{thiol} (excluding Ph_3Sn(IV) complexes) and the carboxylic oxygen to tin lead to chelation or polymerization is discussed with reference to the ^{119}Sn Mössbauer spectral data presented in Table 5.

The narrowness of the linewidths, τ, except the diphenyltin(IV) derivatives, implies the general occurrence of single tin sites in each compound, as well as of multiple coordination sites with corresponding environment [11]. The experimental nuclear quadrupole splitting (Q.S.) values of the solid state R_2Sn(IV) complexes (R = n-Bu and Ph), presented in Table 5, describe two classes of compounds:

i) those having a doublet centered in the region 0.72–1.01 mm s^{-1}; quadrupole splitting (Q.S.) in the region 1.74–2.04 mm s^{-1} for Ph_2Sn(L-1), R_2Sn(L-2) (R = n-Bu and Ph) and Ph_2Sn(HL-3)·MeOH.
ii) those having a doublet centered in the region 1.28–1.35 mm s^{-1}; quadrupole splitting (Q.S.) in the region 2.74–2.95 mm s^{-1} for Bu_2Sn(L-1) and Bu_2Sn(HL-3).

These observations indicate that on going from class (i) to class (ii) complexes, both I.S. (isomer shift) and Q.S. (quadrupole splitting) values increase due to an increase in s-electron density as well as the large asymmetry of the electron distribution around the tin atom [10,11]. This is probably due to stronger bonding of the ligand to the n-dibutyltin(IV) than to the diphenyltin(IV) moiety, and partly due to the strain developed in the ligand. It has been reported that the replacement of an alkyl group by a phenyl group lowers the isomer shift in the organotin(IV) derivatives of the dipeptides/amino acids [11,19,20,29,33]. Similar trend is

Table 5
^{119}Sn-Mössbauer data (80 K) of the di- and tri-organotin(IV) complexes of amino acid and peptides

Complex number [a]	Complex	(Q.S.) (mm s^{-1})	(I.S.) (mm s^{-1})	ρ (Q.S/I.S.)	τ_1 (L)	τ_2 (R)
1	Bu_2Sn(L-1)	2.74	1.35	2.03	0.50	0.52
–	Bu_2Sn(DL-Pen) [22b]	2.69	1.29	2.09	0.89	0.91
2	Ph_2Sn(L-1)	1.74	0.72	2.42	1.58	2.06
3	Ph_3Sn(HL-1)	2.57	1.17	2.19	1.47	1.69
6	Bu_2Sn(L-2)	2.04	1.01	2.02	0.44	0.45
7	Ph_2Sn(L-2)	1.74	0.88	1.98	1.02	4.40
8	Ph_3Sn(HL-2)	2.81	1.16	2.42	0.94	1.02
9	Bu_2Sn(HL-3)	2.95	1.28	2.30	0.42	0.59
10	Ph_2Sn(HL-3)·MeOH	1.76	0.84	2.10	1.00	1.90
12	$Ph_3Sn(H_2L\text{-}3)\cdot H_2O$	2.78	1.16	2.39	1.05	1.10

[a] Complex number as mentioned in Table 1.

also observed in I.S. values of the diphenyltin(IV) complexes studied (Table 5).

I.S. and Q.S. values observed in $R_2Sn(IV)$ complexes of the peptides are slightly lower than those of previously reported complexes [11,20,33]. The spectroscopic and crystallographic studies indicated a distorted trigonal bipyramidal configuration for $R_2Sn(L)$ (where H_2L = dipeptide), where the organic groups of the organotin(IV) moiety and peptide nitrogen are lying in equatorial position, and the amino nitrogen and carboxylic oxygen atoms are axial [3e,11,20,27,33]. Thus, the tin atom configuration as shown in Fig. 1a and b can be proposed for R_2SnL, which would then be [L-carnosinato/triglycinato-*O*,*N*,*N*-(2-)diorganotin(IV)], mainly on the basis of the above mentioned similarity between the observed and reported Q.S. values [3e,11,20,27,33], taking also into account the symmetry of the coordinated ligand [34].

But in triglycinatodiorganotin(IV), the NH_2 group in axial position may involve in bridging with other molecule and in L-carnosinatodiorganotin(IV), the O–C=O group is bidentate and bridging (as indicated by IR) leading to the associated structure.

Further, it has been reported that in $R_2Sn(Gly–Gly)$ [28,33] the equatorial nitrogen would release more negative charge into the neighborhood of tin than the apical nitrogen atom. The bond length $Sn–N_{pept}$ is quite short [28], which is indicative of a consistent s-character in that bond as well as its involvement into the π-delocalization of the peptide group [28]. The latter feature would concentrate negative charge in the trigonal plane in the proximity of the tin nucleus, so that $\{N\}^{tbe}$ would be not very much different from $\{R\}^{tbe}$ [28,33]. The slightly lower values of I.S. and Q.S. in all the diorganotin(IV) derivatives of di- and tri-peptide may be due to the almost symmetrical distribution of charge in the plane containing O,N,N donor atoms, even though considerable s-character in the $Sn–N_{peptide}$ bond makes $N_{peptide}$ similar to $\{R\}^{tbe}$, R = *n*-Bu and Ph. This suggests that considerable electron withdrawal from equatorial plane occurs due to the involvement of axial groups in bonding with neighboring molecules, thereby, giving a polymeric structure (as evident from low solubility of the complexes in common organic solvents, and from IR and NMR data). Further, the Mössbauer data (Table 5) indicate a pronounced line intensity asymmetry (the Goldanskii–Karyagin effect), in all $Ph_2Sn(IV)$ derivatives, which reflects a lattice dynamic anisotropy in the recoil-free fraction arising in the organotin(IV) complexes possessing intermolecular association along particular axes in the solid state [7]. Further, the intermolecular hydrogen bonding between the amino nitrogen and carbonyl oxygen taking place in $Ph_2Sn(Gly–Gly)$ [28,33] is also present to the some extent in the complexes studied, which is responsible for the low solubility of the compounds, particularly the diphenyltin(IV) derivatives, in common organic solvents.

I.S. and Q.S. values (Table 5) of di-*n*-butyltin-D-penicillaminate are in close agreement with those of *n*-Bu_2Sn(DL-Pen) [21b]. Taking into account the reported structures for R_2Sn(DL-Pen) (R = Me, *n*-Bu and Ph) [22a,22b,28] having a distorted trigonal bipyramidal configuration around tin, the compounds Bu_2Sn(D-Pen) and Ph_2Sn(D-Pen) are also one-dimensional polymeric in the solid state where the organic groups and thiol sulfur, bound to tin, lie in the equatorial plane, being axially bridged by amino nitrogen and monodentate carboxyl oxygen (according to IR and Mössbauer studies) (Fig. 2). In solution, the polymeric structure would be destroyed, and molecular species

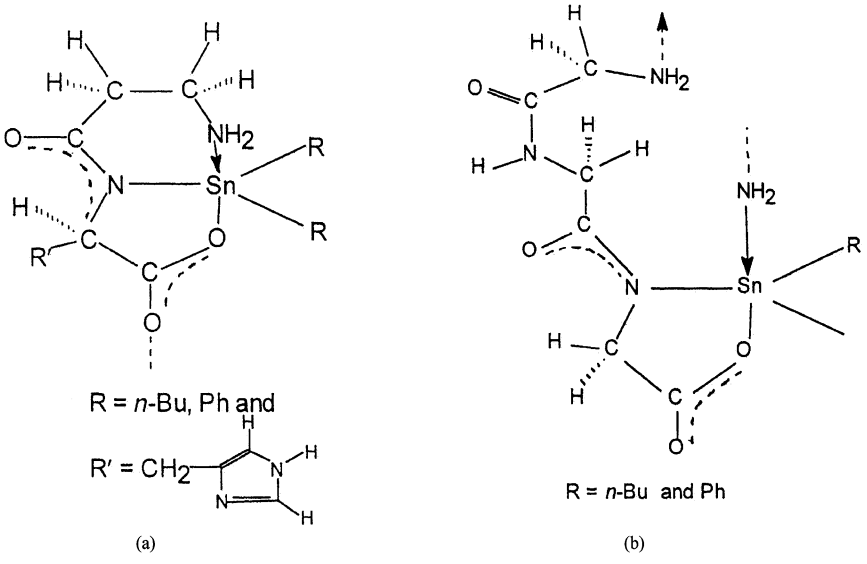


Fig. 1. Structures of diorganotin(IV) complexes of: (a) L-carnosine; (b) triglycine.

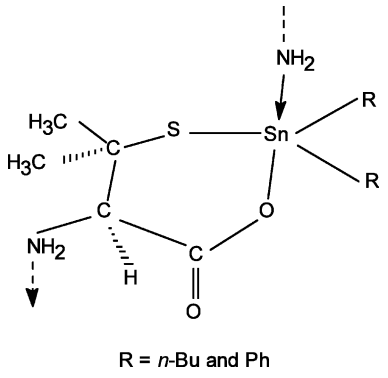


Fig. 2. Structure of diorganotin(IV) complexes of D-penicillamine.

are expected to occur [21b] and it is also supported by the NMR data. It may be reasonably assumed that the D-penicillamine acts as tridentate (SNO) donor or bidentate (S, and O or N) donor in organic solutions of the complexes [21b].

A possible geometry around the tin atom in Ph_3Sn(HL-1), Ph_3Sn(HL-2) and $Ph_3Sn(H_2L\text{-}3)\cdot H_2O$ is a distorted trigonal bipyramidal in which the ligand anions are bidentate coordinating through an ON donor set derived from the carboxylic oxygen and amino nitrogen atoms (as revealed from IR spectra). All the triphenyltin(IV) derivatives studied exhibit a doublet centered in the range 1.16–1.17 mm s^{-1} and Q.S. in the range 2.57–2.78 mm s^{-1}. The ρ(Q.S./I.S.) of these complexes suggests coordination number of tin greater than four, and significant line intensity asymmetry (the Goldanskii–Karyagin effect), suggesting an intermolecularly associated lattice [3e,7]. The three possible isomers (Fig. 3) of R_3SnL (where, L = bidentate ligand) have been reported [35] 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}.

In the triphenyltin(IV) derivatives studied the observed values of I.S. (1.16–1.17 mm s^{-1}) lie in the range typical of triorganotin(IV) carboxylates, whereas the Q.S. values (2.57–2.81 mm s^{-1}) are slightly lower than those typical for *trans* trigonal bipyramidal coordination (Fig. 3b) of tin in R_3SnO_2 fragments (3.00–4.00 mm s^{-1}), but substantially higher than those for *cis* trigonal bipyramidal (1.70–2.40 mm s^{-1}) (Fig. 3a) and pseudo-tetrahedral (1.00–2.40 mm s^{-1}) arrangements [36]. The Q.S. values in the range of 2.8–3.0 mm s^{-1} were also found in the triorganotin(IV) derivatives of amino acids

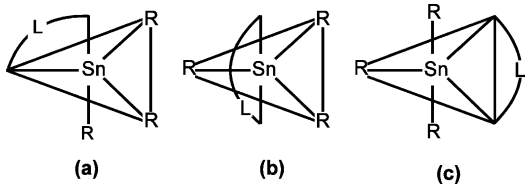


Fig. 3. Structures of different isomers of R_3SnL.

with *trans* trigonal bipyramidal geometry around the tin atom with an amino-bridged intermolecular interactions [7,19], and for other triorganotin(IV) carboxylates with an O–Sn(R_3)O intermolecular interactions [37]. Therefore, the observed Q.S. values of Ph_3Sn(HL-1/HL-2/H_2L-3) support the structure **b** of Fig. 3, with a carboxylic oxygen and a nitrogen atom from an adjacent molecule occupying the axial positions (as shown in Fig. 4). This arrangement is the conventional one (i.e. the most electronegative axial structure), found in the organotin chemistry. Hence, all the triphenyltin(IV) derivatives have been proposed to have amino-bridged linear polymeric structure. The charge around the tin atom is thus concentrated in the axial plane leading to the intermolecular interactions, and thereby, giving rise to line intensity asymmetry as well as the imbalance in the p-orbital population. Further, there is the possibility of the intra-/inter-molecular hydrogen bonding which is consistent with low solubility of all the triphenyltin(IV) complexes.

Mössbauer spectral data of n-Bu_2SnCl(D-HPen)$\cdot H_2O$ could not be obtained because it is semi-solid. On the basis of observed infrared and NMR spectral data, a five coordinate structure (Fig. 5) has been tentatively proposed for n-Bu_2SnCl(D-HPen)$\cdot H_2O$ which is in close agreement with previously reported structure of n-Bu_2SnCl(DL-HPen)$\cdot H_2O$ [21c], but whether the coordination is via carboxylate or amino group is not clear. It has been reported [22c] that Me_2SnCl(DL-HPen)$\cdot H_2O$ exists in a lattice made up of dimeric or small oligomeric units associated by hydrogen bonds, and the hydrogen bonding involved both water of hydration and carboxylate group [22c]. Therefore, the structure as shown in Fig. 5 has been proposed for n-Bu_2SnCl(D-HPen)$\cdot H_2O$.

3.4. Biological studies

3.4.1. Anti-inflammatory activity

The anti-inflammatory activity (% inhibition) of the synthesized complexes was conducted on adult albino rats (body weight 120–160 g) of Froster Charles species against carrageenin induced edema in the doses of 50 mg kg^{-1} given orally and the acute toxicity (ALD_{50}) was studied on albino mice (body weight 20–25 g) of either sex. The results are presented in Table 6 and Fig. 6. The activity of the standard drug, phenyl butazone, is used for the comparison.

The studies on structure–activity correlation of organotin(IV) compounds reveal that the active compounds are characterized by the following structural features [3e]:

i) the availability of coordination positions at tin,
ii) the occurrence of relatively stable ligand–Sn bonds viz., Sn–N and Sn–S bonds, and
iii) low hydrolytic decomposition of these bonds.

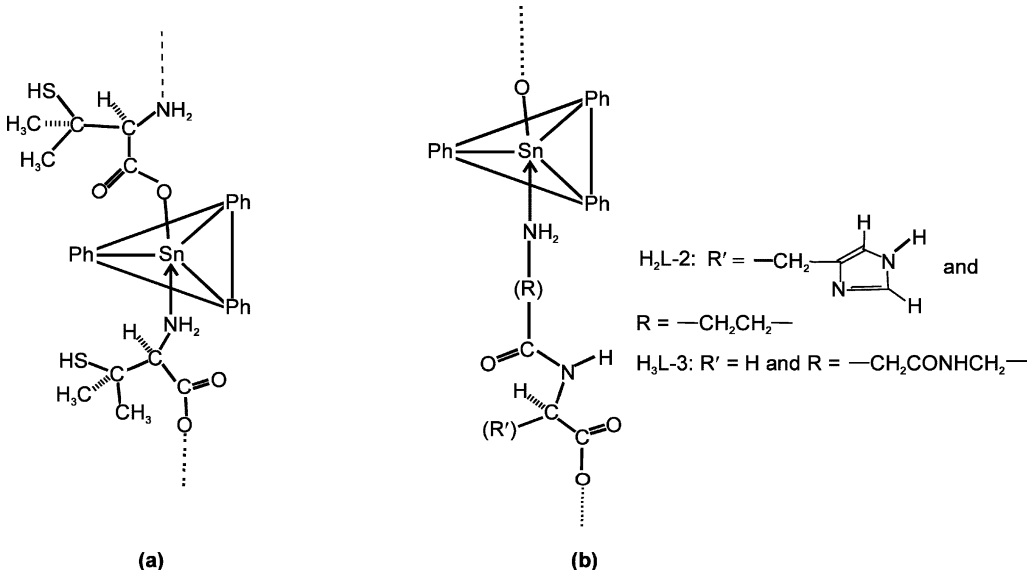


Fig. 4. Structures of Ph_3Sn(IV) derivatives of: (a) H_2L-1; and (b) H_2L-2/H_3L-3.

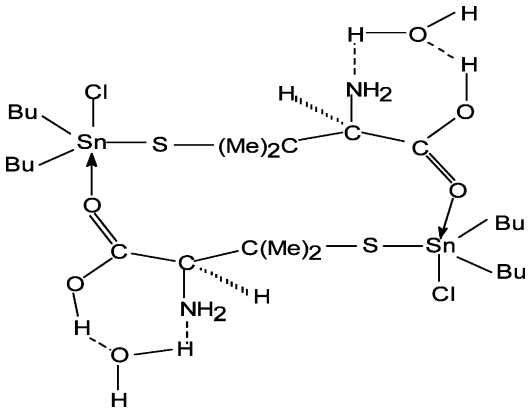


Fig. 5. Structure of n-Bu_2SnCl(D-HPen)·H_2O.

Further, it has been stated that the inactive species are associated with stable complexes having Sn–N bond lengths of <2.39 Å [38], and the activity is due to dissociation of the nitrogen containing ligand as part of the mechanism for inhibition [4e]. Furthermore, it has been proposed for R_2Sn(IV)–glycylglycinates (R = Me, n-Bu, n-Oct and Ph) on the basis of solution studies using several spectroscopic techniques [8,11], that solvated species in aqueous solution or a mixture of H_2O and organic solvent and unsolvated species (mainly organic solvent) are present in equilibrium and contribute to the passage of the alkyltin complexes across the cell membrane [8,11]. A quantitative structure–activity relationship (QSAR) for a series of the triaryltin chloride derivatives and diorganotin(IV) compounds R_2SnXY [4a,39] indicated that R_3Sn^+ and R_2Sn^{2+} are the causative agents and the XY group influences only the readiness of delivery of the active part R_3Sn^+/R_2Sn^{2+} into the cell [4a]. Thus, an attempt is being made to formulate the structure–activity correlation of the synthesized di- and tri-organotin(IV) derivatives. Among the diorganotin(IV) complexes, as revealed from the data presented in Table 6, the diphenyltin(IV) derivatives are found to be more active than the dibutyltin(IV) complexes. The anti-inflammatory activities of the studied diorganotin complexes decrease on increasing the amino acid residue (i.e., on going from H_2L-1 to H_3L-3, except n-Bu_2Sn(L-2)). Although all the three bio-ligands, i.e. D-penicillamine (amino acid, H_2L-1), L-carnosine (dipeptide, H_2L-2) and GlyGlyGly (tripeptide, H_3L-3) used in the present study do not contain same parent amino acid residue, the proper comparison should have been made with the ligands of increasing amino acid residue of the same type, i.e. Gly, Gly–Gly and Gly–Gly–Gly. But, here we have chosen D-penicillamine (the S-containing amino acid, having side chain), L-carnosine (a dipeptide, having heterocyclic ring in the side chain) and Gly–Gly–Gly (a tripeptide, having no side chain) in order to see the effect of the thiol group and side chain on the activities.

Lower activities of n-Bu_2Sn(IV) complexes than Ph_2Sn(IV) complexes are probably due to butyl groups, which would increase the electron density around tin forming relatively more stable Sn–N/O/S bonds upon complexation, thereby, diminishing the easy delivery of Bu_2Sn^{2+} moiety. Further, the formation of amino acid/peptide anion is favored by the presence of electron-withdrawing substituents in the ligand molecule, thereby, reducing the stability of the tin-ligand bond. For dibutyltin(IV) complexes, n-Bu_2Sn(L-2) shows maximum per cent inhibition (24.6%) followed by n-Bu_2Sn(L-1) (19.7%) and n-Bu_2Sn(HL-3) (16.8%). The highest activity of n-Bu_2Sn(L-2) is due to the presence of an imidazole ring in the side chain at the C-2 carbon, a

Table 6
ALD_{50} (in mg kg^{-1}), anti-inflammatory activity and blood pressure lowering activity of di- and tri-organotin(IV) complexes of amino acid and peptides

Complex number [a]	Complex	ALD_{50} (mg kg^{-1})	Anti-inflammatory activity (% inhibition) 50 mg/kg p.o.	Blood pressure lowering activity			
				Dose (mg/kg) i.v.	Change in blood pressure (mm Hg)		Duration (min)
					Immediate	Delayed	
–	Phenyl butazone	–	38.4	–	–	–	–
1	Bu_2Sn(L-1)	> 500	19.7	2	–	−40	20
2	Ph_2Sn(L-1)	> 500	30.2	2	–	−50	45
3	Ph_3Sn(HL-1)	> 500	34.3	1	–	−10	5
6	Bu_2Sn(L-2)	> 500	24.6	2	–	−20	10
7	Ph_2Sn(L-2)	> 500	29.3	2	–	−30	10
8	Ph_3Sn(HL-2)	> 400	31.2	1	–	−35	40
9	Bu_2Sn(HL-3)	> 500	16.8	2	–	−15	5
10	Ph_2Sn(HL-3)·MeOH	> 500	27.4	2	–	−40	20
12	$Ph_3Sn(H_2L\text{-}3)\cdot H_2O$	> 400	42.0	1	–	−20	20

[a] Complex number as mentioned in Table 1.

methylene group close to NH_2 group and a peptide group together with the steric factor. The slightly greater activity of *n*-Bu_2Sn(L-1) than *n*-Bu_2Sn(HL-3) may probably be due to the presence of $-C(SH)(CH_3)_2$ as a side chain at C-2 carbon which creates a steric hindrance. But, there is very little difference in the activities of Ph_2Sn(L-1) (30% inhibition), Ph_2Sn(L-2) (29.3% inhibition) and Ph_2Sn(HL-3)·MeOH (27.4% inhibition), which can be explained on the basis of the above mentioned reasons.

Among the triphenyltin(IV) derivatives studied, the anti-inflammatory activity decreases in the order; $Ph_3Sn(H_2L\text{-}3)\cdot H_2O > Ph_3Sn$(HL-1) > Ph_3Sn(HL-2). This order is probably due to the weakest interaction of Ph_3Sn(IV) with triglycine anion (as evident from IR spectroscopy), and due to the absence of the Sn–S bond in Ph_3Sn(HL-1). Apart from that, Ph_3Sn(IV) derivatives show higher activities (> 30% inhibition) than Ph_2Sn(IV) derivatives (ca. ≤ 30% inhibition) for a particular ligand. This is probably due to an extra phenyl group around tin in the equatorial plane, and less number of coordinating sites/bonds which facilitate the easier formation of Ph_3Sn^+(IV) moiety as a part of inhibition. Furthermore, di-*n*-butyltin(IV) and diphenyltin(IV) derivatives show lower and higher activities, respectively, than the diorganotin(IV) derivatives of dipeptides as reported earlier [20]. It may be due to stronger interactions in *n*-Bu_2Sn(IV) and weaker interactions in Ph_2Sn(IV) of the ligand with tin, thereby, regulating the formation of R_2Sn^{2+}(IV) moiety.

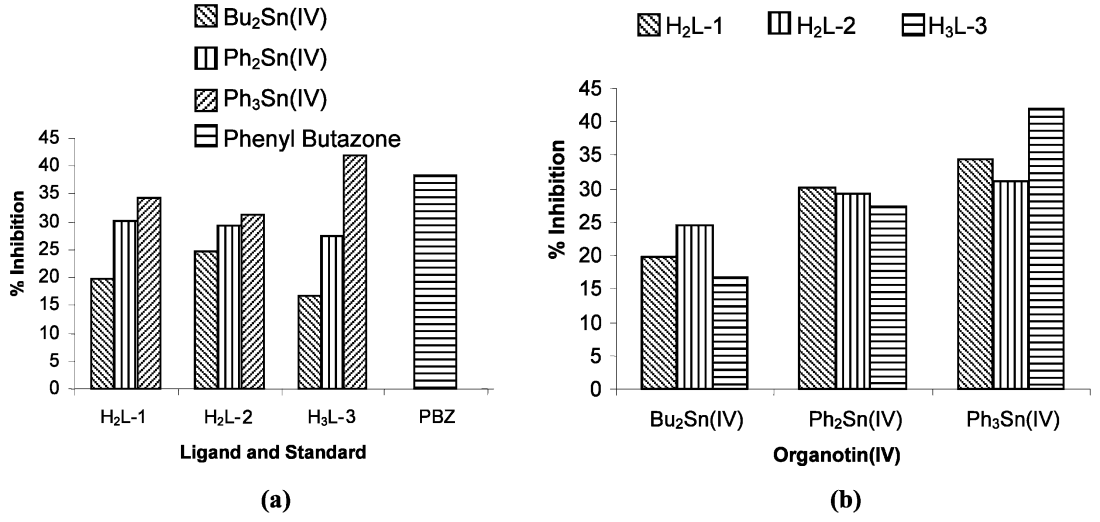


Fig. 6. (a) Comparison of anti-inflammatory activity of different organotin(IV) derivatives for a particular ligand. (b) Comparison of anti-inflammatory activity of organotin(IV) derivatives for different ligands.

3.4.2. Acute toxicity studies

The ALD_{50} values of the studied diorganotin(IV) derivatives were found to be more than 500 mg kg^{-1} (the maximum dose tested), whereas those of the triphenyltin(IV) derivatives were >400 mg kg^{-1}, suggesting the safety margin of these derivatives. Further, it has been observed that the toxicities of these di- and triorganotin(IV) peptides are comparable (>500 mg kg^{-1}) with those reported earlier [20], and much lower than those of the di- and tri-organotin(IV) derivatives of the simple α-amino acids (<50 mg kg^{-1}) [19], indicating that the bigger biomolecules lower the toxicities but enhance the activities of the resulting organotin(IV) derivatives.

3.4.3. Blood-pressure lowering (cardiovascular) activity

The blood pressure lowering activity of the synthesized complexes was carried out on either adult mongrel dogs (body weight 10–20 kg) or on cats (body weight 3–4 kg) of either sex. The results are presented in Table 6. It is an established fact that, when a drug is administered there is a change in blood pressure with the passage of time. Thus, a drug, which lowers the blood pressure in longer duration, is considered to be more effective than the one by which the lowering occurs in shorter duration. An attempt is being made in the present study to formulate the structure–activity relationship of the synthesized complexes. Among the diorganotin(IV) derivatives, Ph_2Sn(IV) derivatives are more active than n-Bu_2Sn(IV) derivatives, irrespective of the structure of the ligand. This is consistent with the trend observed in the anti-inflammatory activities of the diorganotin(IV) derivatives. Also, among the di-n-butyltin(IV) complexes, n-Bu_2Sn(L-1) is found to be the most active followed by n-Bu_2Sn(L-2) and n-Bu_2Sn(HL-3). The order of decreasing activity for diphenyltin(IV) derivatives is: Ph_2Sn(L-1) > Ph_2Sn(HL-3).MeOH > Ph_2Sn(L-2) and for triphenyltin(IV) derivatives is: Ph_3Sn(HL-2) > $Ph_3Sn(H_2L\text{-}3)\cdot H_2O$ > Ph_3Sn(HL-1), and these are inconsistent with the observed trends in the anti-inflammatory activities.

As it is evident from Table 6 that for a given ligand, Ph_2Sn(IV) derivative is found to lower blood pressure far more effectively than n-Bu_2Sn(IV) derivative, which is consistent with the anti-inflammatory activities of the diorganotin(IV) derivatives. However, on going from Ph_2Sn(IV) to Ph_3Sn(IV) derivatives, the rate of blood pressure lowering decreases, except the derivatives of L-carnosine.

From the above discussion it can be concluded that a derivative, which contains easily dissociable groups, will release the cationic organotin(IV) moiety readily, and that its efficacy can be attributed in terms of its lifetime in solution.

Acknowledgements

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