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New organotin(IV) ascorbates: synthesis, spectral characterization, biological and potentiometric studies

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Abstract

New organotin(IV) ascorbates of the general formulae $R_3Sn(HAsc)$ (where R = Me, *n*-Pr, *n*-Bu and Ph) and $R_2Sn(Asc)$ (where R = *n*-Bu and Ph) have been synthesized by the reaction of R_nSnCl_{4-n} (where $n = 2$ or 3) with monosodium-L-ascorbate. The bonding and coordination behaviour in these complexes are discussed on the basis of UV–Vis, IR, Far-IR, ^1H and ^{13}C NMR, and ^{119}Sn Mössbauer spectroscopic studies. L-Ascorbic acid acts as a monoanionic bidentate ligand in $R_3Sn(HAsc)$ coordinating through O(1) and O(3). The Mössbauer studies together with IR and NMR studies suggest that for these polymeric derivatives, the polyhedron is trigonal bipyramidal around tin with three organic groups in the equatorial positions. In $R_2Sn(Asc)$, L-ascorbic acid acts as dianionic tetradentate ligand and a polymeric structure with octahedral geometry around tin with *trans* organic groups has been tentatively proposed. The complexes have been assayed for their anti-inflammatory and cardiovascular activity. $Ph_2Sn(Asc)$ has been found to show the highest activity among the studied complexes. It is suggested on the basis of potentiometric studies of $Me_2Sn(IV)$ and $Me_3Sn(IV)$ systems with L-ascorbic acid that under physiological conditions (pH = 7.0) $Me_2Sn(HAsc)(OH)$ (∼60%), $Me_2Sn(OH)_2$ (∼40%) and $Me_3Sn(HAsc)$ (∼60%), $Me_3Sn(OH)$ (∼40%), respectively, are existing, which may be responsible for their biological activities.

Keywords: L-Ascorbic acid; Organotin(IV); Potentiometric; Anti-inflammatory agent; Cardiovascular; Mössbauer

1. Introduction

L-Ascorbic acid (vitamin C; H_2Asc), one of the most important biomolecule, acts as an anti-oxidant, pH regulator and a two-electron reductant in vitro and in vivo [1]. It is present in all foods of plant origin and is an essential micronutrient in man due to absence of L-gulonolactine oxidase [2]; its deficiency causes a disease known as scurvy.

L-Ascorbic acid is a weak acid in water and forms mono- and dianionic forms, C(3)–O ($HAsc^-$) and C(2)–O (Asc^{2-}), respectively (Scheme 1). Its activity may be due to the fact that it possesses four tautomeric forms and its metabolites are radicals with two different structures (i.e. open and closed) [3] (Scheme 2).

The interaction between the metal ions and L-ascorbic acid results in simple ascorbate salts and rather weak mono- and bidentate complexes [4–7]. L-Ascorbic acid has been proposed to bind a transition metal at two hydroxy groups at the 2- and 3-positions, but in addition to these it also uses the carbonyl C(1)=O group as well as chain OH groups for coordination [7,8]. It means that it utilizes practically all donor oxygen [C(1)–O to C(6)–O] atoms for coordination [7,8]. In view of this, several studies have been focussed on the interaction of L-ascorbic acid with transition and inner transition elements [9–19] as well as with non-transition metals [7,8,20,21] during the last decade.

Further, metal ascorbates have received considerable attention due to their potential antitumor [22,23], antibacterial [13,20], antifungal [13], antioxidant [24], antihypoxic [24], plant-growth regulatory [25], and catalytic [26] activities. Reduction of water-soluble iproplatin $[PtCl_2(OH)_2(NH_2Pr^i)_2]$, currently used as antitumor drug [10,27], when given orally, in chemotherapy by sodium ascorbate or ascorbic acid and reduction of some platinum(IV) ammine complexes by ascorbic acid, and the antitumor activities of several platinum diammine ascorbates

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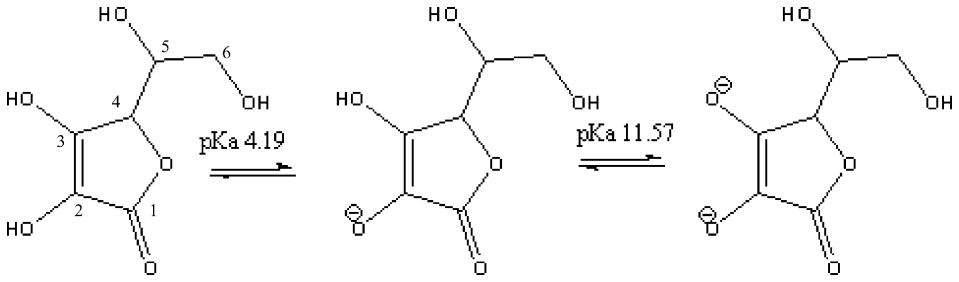

Scheme 1.

$$Na(HAsc) + R_3SnCl \rightarrow R_3Sn(HAsc) + NaCl \quad (1)$$

(Where R = Me, *n*-Pr, *n*-Bu and Ph)

$$2Na(HAsc) + R_2SnCl_2 \rightarrow R_2Sn(Asc) + 2NaCl + H_2Asc \quad (2)$$

(Where R = *n*-Bu and Ph)

Scheme 2.

[28] and some organotitanium and organotin ascorbate complexes [29] have added more attention to the biochemistry of this sugar molecule.

The chemistry of organotins has been a topic of research interest since past few decades, 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, get accumulated in the environment, and finally in biological systems. L-Ascorbic acid is naturally occurring in most of the foods of plant origin and being often added to various food products, beverages, and pharmaceuticals, potentially makes it highly relevant for Sn bio-uptake. Therefore, it becomes indispensable to study the interaction of L-Ascorbic acid with organotins. A few dialkyltin(IV) complexes of L-ascorbic acid have been reported previously [29,30].

Here, we report the synthesis and spectral characterization of six new complexes of L-ascorbic acid with di- and triorganotin(IV) moieties by using UV–Vis, IR, Far IR, ^{1}H and ^{13}C NMR, and ^{119}Sn Mössbauer spectral studies. The anti-inflammatory and cardiovascular activities of these compounds are also reported. Potentiometric studies relating to the identification of the stability of the species formed in Me_nSn(IV)-L-ascorbic acid (where $n = 2$ or 3) in aqueous solution have also been carried out so that they could be used in modeling studies of the interactions between $R_nSn^{(4-n)+}$ ($n = 2$ or 3) cation and L-ascorbic acid, in vivo.

2. Experimental

2.1. Materials and methods

All the syntheses were carried out under an anhydrous nitrogen atmosphere and precautions to avoid the presence of oxygen were taken at every stage. Solvents were purified, dried, and stored under nitrogen before use. L-Ascorbic acid (Loba Chemie), monosodium-L-ascorbate (Fluka), tri-*n*-butyltin(IV) chloride, trimethyltin(IV) chloride, tri-*n*-propyltin(IV) chloride, and triphenyltin(IV) chloride (Merck-Schudardt) and diphenyltin(IV) dichloride (Sigma-Aldrich) were used as received.

2.2. Synthesis of organotin(IV) ascorbates

2.2.1. Synthesis of triorganotin(IV) ascorbates [$R_3Sn(HAsc)$], where R = n-Bu, n-Pr, and Ph)

To a suspension of monosodium-L-ascorbate (0.59 g; 3.0 mmol) in methanol (25 ml) was added drop wise a methanolic solution of R_3SnCl (where R = *n*-Bu, *n*-Pr, and Ph) (3.0 mmol) with stirring. The resulting solution was stirred at room temperature for 10 min and then refluxed for 6 h. It was filtered and the volatiles were removed in vacuum. The yellow crude product was washed with dichloromethane and dried in vacuum which on recrystallization from methanol afforded yellow powder.

2.2.2. Synthesis of Me_3Sn(IV) and R_2Sn(IV) (where R = n-Bu and Ph) derivatives of L-ascorbic acid

To a suspension of monosodium-L-ascorbate (1.19 g; 6.0 mmol) in methanol (100 ml) was added drop wise a solution of Me_3SnCl (6.0 mmol) or Bu_2SnCl_2 (3.0 mmol) or Ph_2SnCl_2 (3.0 m mol) in 10 ml methanol at 0 °C with constant stirring. After allowing it to warm up to room temperature, the mixture was heated under reflux for 3 h. The resulting solution was filtered and concentrated in vacuum leaving a yellow solid. It was washed with dichloromethane and recrystallized from methanol and collected as yellow powder.

2.2.3. Synthesis of di-n-butyltin(IV) and di-n-octyltin(IV) ascorbate

L-Ascorbic acid (0.59 g; 3.0 mmol) dissolved in 20 ml of methanol was slowly added, with constant stirring, to Oct_2SnO or Bu_2SnO (3.0 mmol) suspended in 40 ml of the same solvent. The mixture was refluxed for 20 h but the unreacted reactants were obtained. Another attempt to synthesize diorganotin(IV)-L-ascorbate by azeotropic removal of water method was made by adding 2,2′-dimethoxypropane

to a mixture of L-ascorbic acid and diorganotin(IV)oxide prior to refluxing, but it also did not result in complexation.

2.3. Measurements and biological studies

The melting points of the synthesized compounds were determined on a Toshniwal capillary melting point apparatus and were uncorrected. Carbon, hydrogen, and tin were determined as reported previously [31]. UV–Vis spectra of the compounds were recorded in methanol on a Shimadzu UV-1601, UV–Vis spectrophotometer. IR and Far-IR spectra of the solid compounds were recorded on the same instrument as reported previously [31]. Conductance measurements were carried out on the same instrument as reported previously [31]. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 (300 MHz FTNMR) spectrometer at the CDRI, Lucknow, India, using DMSO-d_6 or $CDCl_3$ or CD_3OD as solvent and TMS as the internal standard. ^{119}Sn Mössbauer spectra were recorded on Mössbauer spectrometer model MS-900 according to the procedure reported previously [31], at the Department of Chemistry and Physics, University of The District of Columbia, Washington, DC.

2.3.1. Anti-inflammatory activity

A freshly prepared suspension of carrageenan (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. [32]. 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 (p.o.) 30 m before the carrageenan 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 the control group (five rats treated with carrageenan, but not treated with test compounds) and percent anti-inflammatory value was calculated as given below:

$$\text{Percent anti-inflammatory activity} = \left[1 - \left(\frac{\text{DT}}{\text{DC}}\right)\right] \times 100$$

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

2.3.2. 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 (i.v.). 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 and blood-pressure lowering studies were carried out at LLRM Medical College, Meerut, India.

2.4. Potentiometric studies

The protonation and coordination equilibria were investigated by potentiometric titrations in aqueous medium (ionic strength, $I = 0.1$ mol dm^{-3} KNO_3 and $T = 298 \pm 0.1$ K) using an Orion 960 plus autotitroprocessor equipped with Orion Ross flow combined glass electrode. The autotitroprocessor and electrode were calibrated with standard buffer solutions (Merck; pH = 4.0 ± 0.05 and 9.2 ± 0.05). The titrations were carried out in a purified nitrogen atmosphere using a titration vessel. The following mixtures (A−C) were titrated potentiometrically with standardized NaOH solution (0.2 M) in aqueous medium:

(A) 50 ml of a solution containing 0.004 M ascorbic acid and 0.1 M KNO_3.
(B) 50 ml of a solution containing 0.004 M Me_3SnCl/Me_2SnCl_2 and 0.1 M KNO_3.
(C) 50 ml of a solution containing 0.004 M ascorbic acid, 0.004 M Me_3SnCl/Me_2SnCl_2, and 0.1 M KNO_3.

The acid dissociation constants of ascorbic acid and formation constants of hydroxo organotin species were determined by titrating mixtures (A) and (B), respectively, whereas the formation constants of the trimethyltin- or dimethyltin(IV) ascorbates were determined by titrating mixture (C). The species formed in the systems were characterized by the following general equilibrium:

$$pM + qL + rOH \leftrightarrow M_pL_q(OH)_r$$

where M denotes the dimethyl- or trimethyltin cation and L denotes non-protonated ligand (L-ascorbic acid), r is negative for a protonated species and positive for hydroxo species. Protonation constants of the ligands and formation constants of the complexes were determined by SCOGS program [33]. Tentative values of the constants along with ionic product of water at experimental temperature and activity coefficient of hydrogen ion at experimental ionic strength [34] were supplied as inputs. The constants were refined for several cycles of operations and the values corresponding to the minimum standard deviations were accepted. The complex formation equilibria were elucidated with the help of the speciation curves obtained as outputs.

3. Results and discussion

The reactions of triorganotin(IV) chloride with monosodium-L-ascorbate in a 1:1 molar ratio led to the formation of the compounds according to Eq. (1). Diorganotin(IV) dichloride reacted with monosodium-L-ascorbate in a 1:2 molar, ratio but the product was found to contain only one ascorbate anion as suggested by the elemental analysis of

Table 1
Characteristic properties of organotin(IV) complexes of L-ascorbic acid

Compound number	Complex (empirical formula)	Yield (%)	m.p. (d) (° C)	Analysis percent:found (cal.)		
				Sn	C	H
1	$Me_3Sn(HAsc)[C_9H_{16}O_6Sn]$	20	185–190	36.01 (35.02)	31.18 (31.89)	4.85 (4.76)
2	$Pr_3Sn(HAsc)[C_{15}H_{28}O_6Sn]$	20	165–170	29.63 (28.05)	41.73 (42.58)	6.12 (6.67)
3	$Bu_3Sn(HAsc)[C_{18}H_{34}O_6Sn]$	23	175–180	24.52 (25.52)	45.33 (46.48)	7.06 (7.37)
4	$Ph_3Sn(HAsc)[C_{24}H_{22}O_6Sn]$	47	180–185	23.60 (22.61)	52.72 (54.89)	3.99 (4.22)
5	$Bu_2Sn(Asc)[C_{14}H_{25}O_6Sn]$	20	155–160	30.07 (29.09)	40.15 (41.21)	5.98 (6.18)
6	$Ph_2Sn(Asc)[C_{18}H_{17}O_6Sn]$	50	195–200	25.14 (26.50)	47.19 (48.25)	3.79 (3.82)

the products Eq. (2). Ascorbic acid coordinates as monoanion in triorganotin(IV) ascorbates but as dianion in diorganotin(IV) ascorbates.

The complexes are produced by the nucleophilic substitution at the tin by either C(3) (in triorganotin(IV) ascorbates) or both C(3) and C(2) (in diorganotin(IV) ascorbates) alcoholic groups (or its sodium derivatives) of ascorbic acid. The greater acceptor properties of the tin in the diorganotin(IV) dichlorides presumably favor the coordination at both C(3)–O and C(2)–O positions. The reactions involved in the synthesis of di- and triorganotin(IV) ascorbates were found to be quite feasible and required 3−6 h of reflux. However, even prolonged refluxing of 20 h of a mixture containing dibutyl/dioctyltin(IV) oxide and L-ascorbic acid did not result in complexation.

All the complexes are yellow powders and sparingly soluble in methanol, water, and dimethylsulphoxide and insoluble in chloroform. The yield of the purified organotin ascorbates is low (20−50%), and they are hygroscopic in nature and decompose on exposure in air. They slowly decompose even on standing under dry nitrogen. The analytical data of the complexes are presented in Table 1 and correspond to the proposed stoichiometry. The compounds are non-electrolytes as suggested by their low molar conductance values (0.00–0.40 $\Omega^{-1}\,cm^2\,mol^{-1}$) determined in methanol.

3.1. Electronic spectral studies in solution

The electronic spectral bands (in nm) together with their ε (molar extinction coefficient) values for L-ascorbic acid and its organotin(IV) derivatives recorded in methanol are given in Table 2. The ultraviolet spectrum of L-ascorbic acid exhibits two strong absorption bands at 246 nm (ε 11,000) and 201 nm (ε 1900), which have been assigned to n–π^* and π–π^* transitions of –(C=O) chromophore, respectively. A bathochromic shift of ∼24 nm in the n–π^* transition is observed, indicating extended conjugation upon complexation, as apparent from the proposed structures (Figs. 1 and 3) of the complexes.

Table 2
Electronic spectral bands[a] of L-ascorbic acid and its organotin(IV) derivatives

Compound number	Ligand/complex	n–π^* (C=O)	π–π^* (C=O)
	L-Ascorbic acid	246.0 (11000)	201.0 (1900)
1	$Me_3Sn(HAsc)$	269.0 (8100)	203.0 (1600)
2	$Pr_3Sn(HAsc)$	270.5 (16500)	203.0 (3400)
3	$Bu_3Sn(HAsc)$	269.0 (13800)	203.0 (2800)
4	$Ph_3Sn(HAsc)$	270.5 (15700)	206.0 (10400)
5	$Bu_2Sn(Asc)$	268.5 (8400)	202.5 (2000)
6	$Ph_2Sn(Asc)$	268.5 (11900)	203.5 (5500)

[a] λ_{max} in nm, values of molar extinction coefficient (in $L\,mol^{-1}\,cm^{-1}$) are given in parenthesis.

3.2. IR spectral studies

The IR spectral data of L-ascorbic acid, its sodium salts, and organotin(IV) derivatives together with the assignments made following references [7,15,29,30] are presented in Table 3. Six sharp bands in the region 3000−3526 cm^{-1} obtained in the spectra of ascorbic acid and sodium ascorbate are assigned to the –OH stretching vibrations [30]. In the spectra of the complexes, it is difficult to assign the exact position of each hydroxyl group; however, all the complexes show a shift in the position of these bands, and few peaks are shifted to higher wave numbers while some to lower. A shift of –OH stretching vibration to higher wave number may be due to breaking down of extensive H-bonding present in the crystal structure of L-ascorbic acid upon complexation, while a shift to lower wave number indicates participation of –OH group in coordination.

The carbonyl C(1)=O stretching vibration in L-ascorbic acid appears as a medium intensity band at 1753 cm^{-1}. Upon complexation, this band is bathochromically shifted by 31−46 cm^{-1} in compounds **1**–**5** and by 15 cm^{-1} in compound **6**, indicating the participation of carbonyl (C(1)=O) group in coordination [7,8,15,29,30]. In the triorganotin(IV) ascorbates, as observed in sodium ascorbate [7,8], there is a

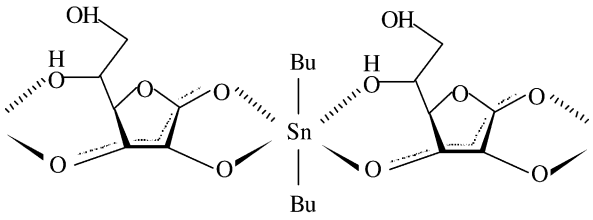

Fig. 1. Octahedral polymeric structure of $Bu_2Sn(Asc)$.

Table 3
Characterstic IR frequencies[a] (in cm^{-1}) of L-ascorbic acid, sodium-L-ascorbate, and its organotin(IV) derivatives[b]

H_2(Asc)[c]	Na(HAsc)[c]	**1**	**2**	**3**	**4**	**5**	**6**	Assignments
3526s	3437sh	3495s	3482s	3540sh	3484vs	3460m	3470m	ν(OH)
3410s	3360sh	3452s	3441m	3450m	3411vs	3367m	3400s	
3316s	3312vs	3379m	3369m	3386w	3228m	3279m	3370m	
3217s	3260vs	3280s	3326m	3275s	3028m	3224m	3260m	
3030s	3187sh	3065m	3246m	3201m		3073m		
3000sh			3162m	3137s				
			3002m					
1753m	1703s	1722s	1707m	1718m	1716m	1720m	1738s	ν(C=O)
	1632s							
1672s,b	1599s	1596vs	1602vs	1596vs	1601vs	1650sh	1632vs	ν(C=O) +
						1627vs		δ(C=C)
1363w	1360m	1419vs	1412m	1422m	1412s	1422sh	1422w	ν(C–O) +
1321s	1308vs	1321sh	1314m	1314m	1314w	1337m	1380vs	δ(C–OH) +
1275m	1280sh	1270sh	1275sh	1260sh	1275 w			δ(C–H)
1221m	1233m							
1199m	1157m						1150m	ν(C–O) +
1140vs	1128s	1130s	1128m	1128s	1126m	1130m	1126sh	ν(C–C)
1119vs	1076s	1075m	1074m	1072m	1070w		1062m	
1076m	1051m							
–	–	601s	603w	596m	590w	610w	579m	ν(Sn–O)+
–	–	579m	587m		550w	560w	502vw	νSn ← O
		505m	500m	494m	281m	506m	280m	ν(Sn−C)
					217s		220m	

[a] vs, very strong; s, strong; m, medium; w, weak; sh, shoulder.
[b] Complex numbers as indicated in Table 1.
[c] [30].

larger shift than in the diorganotin(IV)ascorbates, which may be due to the intramolecular hydrogen [C(1)O···H–C(2)O] bonding [15].

The combination band due to ν(C=O) + δ(C=C), which appear at 1672 cm^{-1} as a strong broad band in L-ascorbic acid, is also shifted towards lower frequency (1596−1632 cm^{-1}) upon complexation [15,29,30]. This may be due to the delocalization of electronic charge among C–1, C–2, and C–3 atoms as indicated in Figs. 1 and 3. Further, the lowering of ν(C=O) + δ(C=C) in the triorganotin ascorbates **1**–**4** (1596−1602 cm^{-1}) is much larger than in **5** and **6** (1627−1632 cm^{-1}) and in fact it is close to that of monosodium ascorbate (1599 cm^{-1}), where a monoanionic ligand is present.

In the region 1500−1200 cm^{-1}, there are several bands which are assigned to strongly coupled C–O–C, CH_2, and OH bending modes [15]. They are overlapped by the very strong, broad C(3)–O stretching vibrations which appear at 1417 ± 5 cm^{-1} in the complexes studied. A considerable shift (49−59 cm^{-1}) of C(3)–O to higher wave numbers in the complexes, as compared to the free ligand, indicates participation of C(3)–O in coordination. Disappearance of δ[O(3)–H] in all of the complexes, which appears at 1221 cm^{-1} in free ascorbic acid, also confirms the replacement of O(3)–H proton by the organotin moiety in all the di- and triorganotin(IV) ascorbates. δ[O(2)–H] occurring at 1321 cm^{-1} in the ascorbic acid is absent in the diorganotin(IV) ascorbates, suggesting deprotonation of O(2)–H also.

There is a reduction in the number of bands in the sugar ring C–O and C–C stretching vibration region (1200−900 cm^{-1}) followed by accompanying shift upon complexation [15]. The skeletal deformations of C–O–C and C–C–C bands in this region are also reduced in intensity upon complexation [15]. The ionization of the C(3)O–H and C(2)O–H groups will drastically alter the electron distribution within the lactone ring. New peaks in the region 610−217 cm^{-1} are assigned to ν(Sn–O) and ν(Sn–C) (Table 3), which also confirm coordination. The ν_s(Sn–C_2) in R_2Sn(Asc) and ν_{as}(Sn–C_3) in R_3Sn(HAsc) could not be identified with reasonable certainty, which indicates the presence of *trans* organic groups in the proposed octahedral geometry (Fig. 1) and equatorial organic groups in the proposed trigonal bipyramidal geometry (Fig. 3), respectively.

These spectral investigations reveal that complexation occurs through O(1) and O(3) atoms in the triorganotin(IV) ascorbates, whereas through O(1), O(2), O(3), and some contribution of O(5) in the diorganotin(IV) ascorbates.

3.3. ^1H and ^{13}C NMR solution spectral studies

^{1}H and ^{13}C NMR spectral data of L-ascorbic acid [29,35] and its organotin(IV) derivatives are presented in Tables 4 and 5, respectively.

Table 4
^{1}H NMR spectral data of L-ascorbic acid and its organotin(IV) derivatives

Compound number	Ligand/complex (solvent)	δ[a] (ppm)
	L-Ascorbic acid[b] [CD_3OD]	4.80 (d, 1H, H-4); 3.90 (m, 1H, H-5); 3.69 (m, 2H, H-6).
	L-Ascorbic acid[c] [$CDCl_3$ + DMSO-d_6]	4.75 (s, 1H, H-4); 3.82 (t, 1H, H-5); 3.55 (m, 2H, H-6); 8.01 (s, 1H, O(2)-H).
1	Me_3Sn(Hasc) [DMSO-d_6]	4.14 (s, 1H, H-4); 3.80 (mbr, 1H, H-5); 3.43 (m, 2H, H-6); 0.45 (s, 6H, H-α); [83.0 Hz][d]; 8.40 (s, 1H, O(2)-H).
2	Pr_3Sn(HAsc) [DMSO-d_6]	4.06 (s, 1H, H-4); 3.81 (mbr, 1H, H-5); 3.43 (m, 2H, H-6); 1.59 (t, 6H, H-α); 1.24–1.18 (mbr, 6H, H-β); 0.90 (tbr, 9H, H-γ); 8.40 (s, 1H, O(2)-H).
3	Bu_3Sn(HAsc) [CD_3OD]	4.06 (s, 1H, H-4); 3.77 (m, 1H, H-5); 3.65 (m, 2H, H-6); 1.21 (t, 6H, 8.4 Hz, H-α); 1.66 (m, 6H, H-β); 1.37 (m, 6H, H-γ); 0.93 (t, 9H, 7.5 Hz, H-δ); 8.40 (s, 1H, O(2)-H).
4	Ph_3Sn(HAsc) [CD_3OD]	4.50 (d, 1H, 2.4 Hz, H-4); 3.85 (td, 1H, 6.5 Hz, 2.4 Hz, H-5); 3.65 (d, 2H, 6.6 Hz, H-6); 7.82 (d, 6H, 6.3 Hz, H-β) [70.0/58.5 Hz][d]; 7.42 (m, 9H, H-γ and H-δ); 8.40 (s, 1H, O(2)-H).
5	Bu_2Sn(Asc) [CD_3OD]	4.78 (d, 1H, 1.5 Hz, H-4); 3.92 (td, 1H, 5.1 Hz, 1.5 Hz, H-5), 3.68 (d, 2H, 7.0 Hz, H-6); 1.60 (br, 4H, H-β); 1.48 (br, 4H, H-α); 1.28 (br, 4H, H-γ); 0.88 (tbr, 6H, H-δ).
6	Ph_2Sn(Asc) [DMSO-d_6]	4.61 (d, 1H, 2.4 Hz, H-4); 3.75 (t, 1H, 6.0 Hz, H-5); 3.50 (m, 2H, 7.0 Hz, H-6); 7.90 (d, 4H, 6.3 Hz, H-β) [73.2/58.2 Hz][d]; 7.38 (mbr, 6H, H-γ and H-δ).

[a] s, singlet; d: doublet; t: triplet; q: quartet; dd: doublet doublet; sbr: singlet broad: dbr, doublet broad; tbr: triplet broad; m: multiplet; mbr: multiplet broad; td: triplet doublet.
[b] [29].
[c] [35].
[d] ^{2}J ($^{1}H-^{119/117}Sn$) ( ; $Sn-\overset{\alpha}{C}H_3$; $Sn-\overset{\alpha}{C}H_2-\overset{\beta}{C}H_2-\overset{\gamma}{C}H_3$; $Sn-\overset{\alpha}{C}H_2-\overset{\beta}{C}H_2-\overset{\gamma}{C}H_2-\overset{\delta}{C}H_3$).

Table 5
^{13}C NMR spectral data of L-ascorbic acid and its organotin(IV) derivatives

Compound number	Ligand/complex (solvent)	δ (ppm)
	L-Ascorbic acid[a][$CDCl_3$ + DMSO-d_6]	C-1: 170.67; C-2: 118.31; C-3: 152.47; C-4: 75.03; C-5: 68.90; C-6: 62.37.
1	Me_3Sn(HAsc) [DMSO-d_6]	C-1: 173.00; C-2: 114.00; C-3: 154.00; C-4: 78.40; C-5: 71.30; C-6: 63.40; C-α: 11.00.
2	Pr_3Sn(HAsc) [DMSO-d_6]	C-1: 173.20; C-2: 113.50; C-3: 152.00; C-4: 79.00; C-5: 71.80; C-6: 63.60; C-α: 22.00; C-β: 29.00; C-γ: 18.10.
3	Bu_3Sn(HAsc) [$CDCl_3$]	C-1: 169.00; C-2: 119.00; C-3: 153.00; C-4: 74.30; C-5: 71.44; C-6: 64.50; C-α: 19.49; C-β: 29.13 [30.2 Hz][b]; C-γ: 27.99 [75.0 Hz][c]; C-δ: 14.00.
4	Ph_3Sn(Hasc) [CD_3OD]	C-1: 171.00; C-2: 118.00; C-3: 151.20; C-4: 78.90; C-5: 71.50; C-6: 64.00; C-α: 140.01; C-β: 137.4 [37.8 Hz][b]; C-γ: 129.60 [75.5 Hz][c]; C-δ: 130.50.
5	Bu_2Sn(Asc) [$CDCl_3$]	C-1: 173.90; C-2: 119.50; C-3: 156.30; C-4: 77.20; C-5: 70.70; C-6: 63.60; C-α: 20.04; C-β: 28.00; C-γ: 27.00; C-δ: 13.00.
6	Ph_2Sn(Asc) [$CDCl_3$]	C-1: 171.90; C-2: 117.60; C-3: 164.4; C-4: 76.00; C-5: 69.50; C-6: 62.70; C-α: 140.01; C-β: 136.70 [36.0 Hz][b]; C-γ: 128.70 [75.5 Hz][c]; C-δ: 129.30.

[a] [35].
[b] ^{2}J ($^{1}H-^{119/117}Sn$).
[c] ^{3}J ($^{1}H-^{119/117}Sn$) ( ; $Sn-\overset{\alpha}{C}H_3$; $Sn-\overset{\alpha}{C}H_2-\overset{\beta}{C}H_2-\overset{\gamma}{C}H_3$; $Sn-\overset{\alpha}{C}H_2-\overset{\beta}{C}H_2-\overset{\gamma}{C}H_2-\overset{\delta}{C}H_3$).

In the ^{1}H NMR spectrum of L-ascorbic acid O(2)–H and O(3)–H signals appear at δ 8.01 ppm and δ 11.3 ppm, respectively, in DMSO-d_6 [30]. In all the studied triorganotin(IV) ascorbates the signal due to O(3)–H disappears and a weak signal of O(2)–H appears at δ 8.4 ppm, suggesting deprotonation of O(3)–H and participation of O(2)–H in hydrogen bonding in these complexes, whereas in the diorganotin(IV) complexes, both the signals are absent suggesting deprotonation of both the hydroxyl groups of the lactone ring. The ascorbic acid spectrum consists essentially of three groups of resonances assigned to the protons on C(4), C(5), and C(6), respectively, in order of increasing field [29]. Greater change is expected in C(4)–H signals [29] when complex formation is achieved either through C(3)–O– in the triorganotin(IV) ascorbates or both C(3)–O and C(2)–O– in the diorganotin(IV) ascorbates. This is reflected by the fact that C(4)–H signals for all the complexes have a significant shift in comparison to the C(5)–H and C(6)–H_2 signals. Further, the resonances of the organotin(IV) moieties have also been assigned in the spectra of the complexes.

All the ^{13}C resonances of the ascorbate anion are slightly shifted towards higher δ values upon complexation. The characteristic signals for alkyl- or aryl-carbons of the organotin moieties have also been assigned which are in good agreement with the reported values [31].

Due to insufficient solubility of the organotin(IV) ascorbates their ^{119}Sn NMR spectra could not be recorded. Ready oxidation of the complexes prevents collection of crystals, suitable for single crystal X-ray study. All other studies of these ascorbates were done within minimum possible time after their synthesis and isolation. There still remains controversy about the structures of metal ascorbates both in solution and the solid state. The metal ascorbates are weaker than those with other chelating ligands [36] and moreover, isolation of the analytically pure compounds from solution is difficult due to the instability of the ascorbate anion to oxidation. Only a few of such compounds have been analyzed by X-ray crystallography [9–12].

3.4. ^{119}Sn Mössbauer spectral studies

The spectra of Bu_2Sn(Asc) and Bu_3Sn(HAsc) could be taken as representative in assignment of the structure of the studied ascorbates on the basis of ^{119}Sn Mössbauer spectra. The spectra of rest of the compounds could not be recorded due to their ready decomposition.

The di-*n*-butyltin(IV) and tri-*n*-butyltin(IV) ascorbates show Q.S. value of 2.83 mm s^{-1} and 3.25 mm s^{-1}, respectively, indicating that the electric field gradient around the tin nucleus is produced by the inequalities in the tin−oxygen σ bonds and is also due to geometric distortions. The ρ (QS/IS) values [Bu_2Sn(Asc) = 2.42; Bu_3Sn(HAsc) = 2.62] in these compounds indicate a coordination number greater than four with either 5- or 6-coordinated tin.

Octahedral, cationic [37], neutral [37,38], and anionic [39] tin complexes containing two organic residues and four electronegative ligands possess a mutually *trans* geometry for the tin−carbon bonds (with a few exceptions). In this context, the magnitude of the ^{119}Sn Mössbauer Q.S. is a useful parameter. Point change calculations [40] for octahedral diorganotin(IV) derivatives with two organic groups predict that the Q.S. for the *trans* isomer will be twice (∼4.0 mm s^{-1}) than that of the *cis* isomer (∼2.0 mm s^{-1}). However, the dibutyltin(IV) ascorbate exhibits I.S. value of 1.17 mm s^{-1} and Q.S. value of 2.83 mm s^{-1}. The data can not be directly interpreted in terms of the structure, since other diorganotin(IV) complexes with similar parameters have been assigned as 5-coordinate with monodentate carboxyl in R_2SnL (L = dianion of tridentate dipeptides) [41,42] or *cis* octahedral structures [43–45]. Indeed, where the other ligands have high electronegativity, the Q.S. is governed mainly by C–Sn–C bond angle [44,45] and distortion from regular 6-coordination can give values similar to those for 5-coordination [46]. Further, it has been reported [47] that I.S. values for *cis*-$[R_2SnX_4]^{2-}$ are less than 1.0 mm s^{-1} while *trans* compounds have I.S. values approximately 1.2−1.3 mm s^{-1}. For dibutyltin(IV) ascorbate, the Mössbauer parameters are best interpreted in terms of distorted *trans* octahedral configuration in which dibutyltin(IV) complex has ascorbate-bridged linear polymeric structure and O(1), O(2), O(3) as well as O(5) take part in coordination (Fig. 1). This proposed structure also explains very low solubility of the complex and is also consistent with the Goldanskii–Karyagin effect [48] observed in its Mössbauer spectrum. Similar structure can also be proposed for Ph_2Sn analogue.

Mössbauer spectrum of Bu_3Sn(HAsc) exhibits Q.S. at 3.25 mm s^{-1} and I.S. at 1.24 mm s^{-1} and pronounced line-intensity asymmetry (the Goldanskii–Karyagin effect), suggesting an intermolecularly associated lattice [48]. Each of the three isomer (Fig. 2) of R_3SnL has been reported [49,50] to have different Q.S. values: Q.S for isomer (a) 1.7−2.3 mm s^{-1}; for (b) 3.0−3.9 m ms^{-1}; and for (c) 3.5−4.1 mm s^{-1}.

The observed value of Q.S. of Bu_3Sn(HAsc) lies in the range of *trans* trigonal bipyramidal structure ((b) of Fig. 2). A possible geometry around the tin in Bu_3Sn(HAsc) is a distorted trigonal bipyramid in which ascorbate anion is monofunctional and bidentate coordinating through O(1)

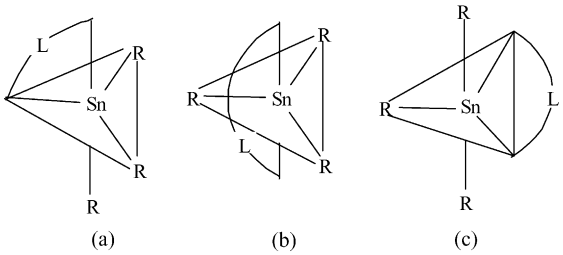

Fig. 2. Structures of different isomers of R_3SnL.

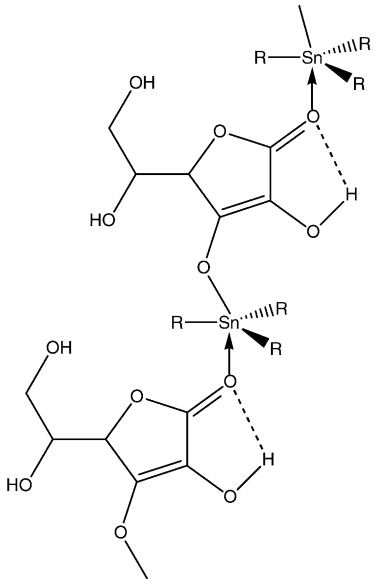

Fig. 3. Trigonal bipyramidal polymeric structure of R_3Sn(HAsc), where R = Me, *n*-Pr, *n*-Bu, and Ph.

and O(3). The structure as shown in Fig. 3 is proposed for Bu_3Sn(HAsc). Intramolecular hydrogen bonding between O(1) and H(2) is also supported by IR spectra. This arrangement is the conventional one (i.e. the most electronegative axial structure) found in organotin chemistry similar to that reported for Me_3Sn(Gly) [48] and R_3SnL [51]. Therefore, the other triorganotin ascorbates have also been proposed to have the same ascorbate bridged linear polymeric structure.

3.5. Anti-inflammatory activity

The anti-inflammatory activity (percent inhibition) of the complexes was conducted on adult albino rats (body weight 120−160 g) of Froster Charles species against carageenan induced edema in the doses of 50 mg kg^{-1} given orally. The anti-inflammatory activities of the complexes are reported in Table 6.

The test compounds showed mild anti-inflammatory activity (15.2−31.0% inhibition). Among the studied ascorbates, the Ph_2Sn(Asc) showed good activity (31.0% inhibition), but lower than that of the standard drug phenylbutazone (38.4% inhibition). A number of studies [52,53] of the triorganotin compounds, R_3SnX, and diorganotin compounds, R_2SnXY, indicated that the marked biological activity of the organotins may be due to the transport of either more active species ($R_nSn^{(4-n)+}$, where $n = 2$ or 3) or the molecule as a whole across the cellular membrane, and X or XY group influences only the readiness of delivery of the active part R_3Sn^+/R_2Sn^{++} into the cell [52]. Further, the studies on structure–activity correlation of organotin(IV) compounds reveal that the biologically active compounds should have available coordination positions at tin and relatively stable ligand–Sn bonds viz., Sn–N [54] (bond length > 2.39 Å) and Sn–S bonds. These bonds should have low hydrolytic decomposition. Thus, it can be proposed that the same mechanism may be involved in the observed activity of the studied organotin(IV) derivatives. The analysis of data in Table 6 indicates that the anti-inflammatory activity of the studied compounds is influenced by the nature of ligand environment and organic groups attached to tin. Diorganotin(IV) derivatives have been found to show better activity than the triorganotin(IV) derivatives.

3.6. Cardiovascular activity

The cardiovascular (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 compounds exhibited mild hypotensive activity which lasted for 3−5 min at a dose of 5.0 mg kg^{-1} i.v., without affecting the carotid occlusion and noradrenaline response. Such a profile of pharmacological effect is indicative of direct vasodilator action of these compounds. The results are presented in Table 6.

3.7. Potentiometric studies

Di- and trimethyltin(IV) cations are known to form stable and water-soluble mono- and polynuclear hydroxo complexes [55] in the whole pH range studied. Since the hydroxide ion and ascorbate anion are in strong competition

Table 6
Biological activity of the organotin(IV) complexes of L-ascorbic acid

Compound number[a]	Percent decrease in paw edema (percent inhibition) (50 mg kg^{-1}, p.o.)	Cardiovascular activity (5 mg kg^{-1} i.v.)	
		Fall in b.p. (mm Hg)	Duration (min)
1	21.0	−10	3
2	15.3	−6	4
3	25.4	−7	5
4	23.3	−10	5
5	25.7	−10	3
6	31.0	−8	5
Phenylbutazone	38.4	–	–

[a] Complex number as mentioned in Table 1.

Table 7
Proton (log K) and organotin(IV) complex formation constants (log β) of L-ascorbic acid at 298 ± 0.1 K, I = 0.1 M KNO_3, $\beta_{pqr} = M_pL_qH_r/[M]^p[L]^q[H]^r$

log β_{pqr}	Me_2Sn(IV)	Me_3Sn(IV)
111	16.084	14.282
110	11.876	8.347
11-1	6.135	–
10-1	3.25	6.18
10-2	8.48	17.80
10-3	19.52	–

pK_1 and pK_2 for L-ascorbic acid are 3.96 (reported 4.04 [15]) and 11.52 (reported 11.34 [15]), respectively.

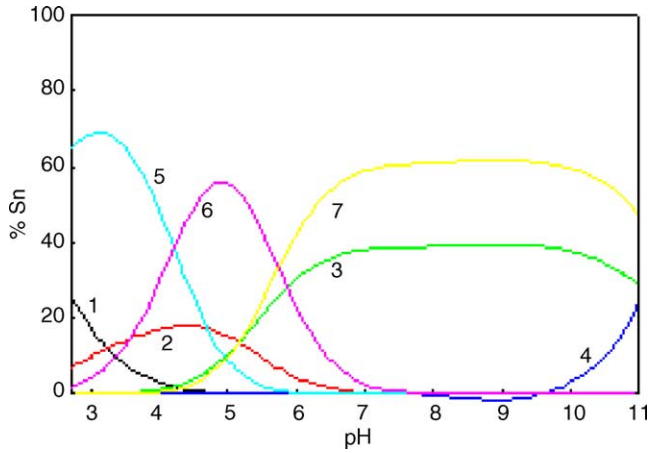

Fig. 4. Speciation curves for 1:1 Me_2Sn(IV)–ascorbic acid system: (1) M, (2) M(OH), (3) $M(OH)_2$, (4) $M(OH)_3$, (5) M(LH), (6) ML, (7) ML(OH).

for the metal ion, these hydroxo compounds were always taken into consideration in the equilibrium systems. Protonation constants of ascorbic acid and stability constants of the complexes formed with dimethyl- and trimethyltin(IV) are summarized in the Table 7. The speciation curves (Figs. 4 and 5) indicate that the monoprotonated complex, Me_2Sn(HAsc), is the predominant species for dimethyltin

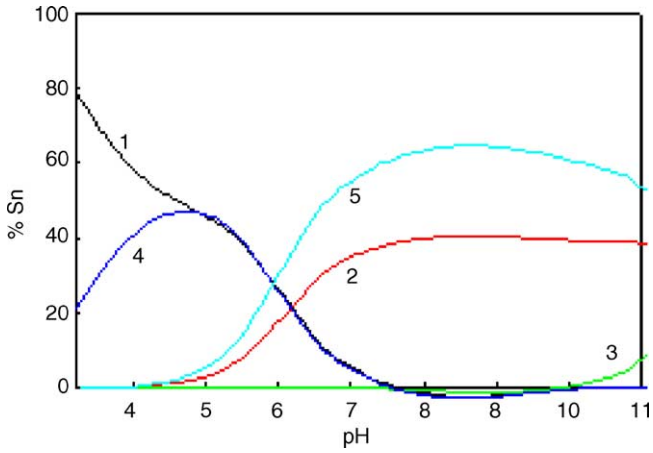

Fig. 5. Speciation curves for 1:1 Me_3Sn(IV)–ascorbic acid system: (1) M, (2) M(OH), (3) $M(OH)_3$, (4) M(LH), (5) ML.

system, while the analogous complex, Me_3Sn(HAsc), is formed in case of the trimethyltin system below pH 5.0. In both the cases the ascorbate anion coordinates the metal through one of the enol oxygens, probably C(3)–O. Deprotonation of the other enolic hydrogen of Me_nSn(HAsc) (where n = 2 or 3) complexes starts from as early as pH 3.0 for dimethyltin system and from pH 4.5 for the trimethyltin system. The speciation curves show two additional equilibria for the dimethyltin system, where the Me_2Sn(HAsc) and Me_2Sn(OH) take up more OH to give rise to Me_2Sn(HAsc)(OH) and $Me_2Sn(OH)_2$ in the pH region 5.0−9.5.

The species distribution curves for Me_2Sn(IV) system indicate that the major species at physiological pH, in aqueous medium, is Me_2Sn(HAsc)(OH) (∼60%) along with some $Me_2Sn(OH)_2$ (∼40%). Whereas, for Me_3Sn(IV)–ascorbic acid system, the major species is Me_3Sn(HAsc) (∼60%) along with some Me_3Sn(OH) (∼40%) under same conditions.

It can be concluded from the potentiometric studies that Me_2Sn(Asc), which was isolated in solid state, when administered in vivo, hydrolyses at physiological pH to form hydroxo-mixed ascorbic acid complex, Me_2Sn(HAsc)(OH). Whereas, Me_3Sn(HAsc) does not form the hydroxo-mixed ligand complex under similar conditions. The better activity (Table 6) of diorganotins may be attributed to the hydroxo-mixed ligand complex formation. The OH group is labile and provide more coordinating ability to the complex with cellular constituents, thereby showing greater activity.

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