Turk J Chem
29 (2005) , 273 – 287.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) as Donor Ligands in Organotin(IV) Derivatives: Synthesis, Spectroscopic Characterization and Biological Applications

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Received 11.03.2004

Some new di- and tri-organotin(IV) derivatives of 4 different non-steroidal anti-inflammatory drugs (NSAIDs) with the general formulae R_2SnL_2 and R_3SnL (where R = n-C_8H_{17} and $C_6H_5CH_2$) and L = 2-[(2,3-dimethylphenyl)amino]benzoic acid, 2-(2-fluoro-4-biphenyl)propionic acid, 2-(4-isobutylphenyl) propionic acid and 2-(3-benzoylphenyl)-propionic acid were synthesized. These compounds were structurally characterized by infrared and multinuclear NMR (^1H, ^{13}C, ^{119}Sn) spectroscopies and mass spectrometry. The isotopic effect of tin was studied by comparison of experimental data with the simulated isotopic pattern using the Chemtool software package. These compounds were also screened against different animal and plant pathogens to study their biological activity. LD_{50} data show that the reported compounds have significant toxicity.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are utilized primarily as analgesics, anti-inflammatories and anti-pyretics. Their main known mode of action is through inhibition of the cyclo-oxygenase-mediated production of prostaglandins, but this is not deemed to be sufficient to explain their wide variety of actions [1,2]. Although there are many differences in the kinetics of NSAIDs, they have some general properties in common. Most of these drugs are well absorbed, and food does not substantially change their bioavailability. All NSAIDs are highly protein-bound ($\geq$ 98%), usually to albumin. Thus, they are most frequently used as medicinal drugs. Some NSAIDs (e.g., ibuprofen) are racemic mixtures, while others (e.g., naproxen) are provided as a single enantiomer and a few have no chiral centre (e.g., diclofenac) [3]. Organotin compounds have gained an edge over other organometallics owing to their bioavailability in the ecosystem and entrance

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into the food chain, the fact they are less hazardous to the environment and their pharmaceutical applications, including antitumor and anticancer uses [4].

In view of the diverse fields of application of organotin compounds, we synthesized and characterized a number of organotin compounds with different NSAIDs, based on the fact that newly synthesized compounds are supposed to be more biologically active against different animal and plant pathogens. Qualitative structural characterization of these compounds is based on infrared, NMR and mass spectral data. Biological screening results of these compounds show significant activity against various bacteria and fungi. The cytotoxicity data show positive lethality.

Experimental

All the chemicals were of analytical grade and were used without further purification. All the reactions were carried out in dried solvents, which were dried by the reported methods [5]. Di- and tri-benzyltinchloride were prepared by reported method [6]. Most organotin halides and their carboxylate derivatives are air and moisture sensitive; hence all glassware was completely dried at 140 ^{o}C. Infrared spectra were obtained using Bio-Rad FTIR spectrophotometer in the 4000-400 cm^{-1}range with the samples as KBr discs.

The ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a Bruker AM 250 spectrometer (Germany) using $CDCl_3$ as an internal reference [δ^{1}H ($CDCl_3$) = 7.25 and δ^{13}C ($CDCl_3$) = 77.0]. ^{119}Sn NMR spectra were obtained with Me_4Sn as an external reference [Ξ (Sn) = 37.290665]. The EI mass spectra were recorded on a MAT 8500 Finnigan 70 eV mass spectrometer (Germany). The measurements were obtained in solution or by a direct analysis system in solid state. The simulated isotopic distribution was computed with the CHEMTOOL software package [7a]. Melting points were recorded on a MP-D Mitamura Riken Kogyo (Japan) electrothermal melting point apparatus and were uncorrected.

General Procedure for Synthesis

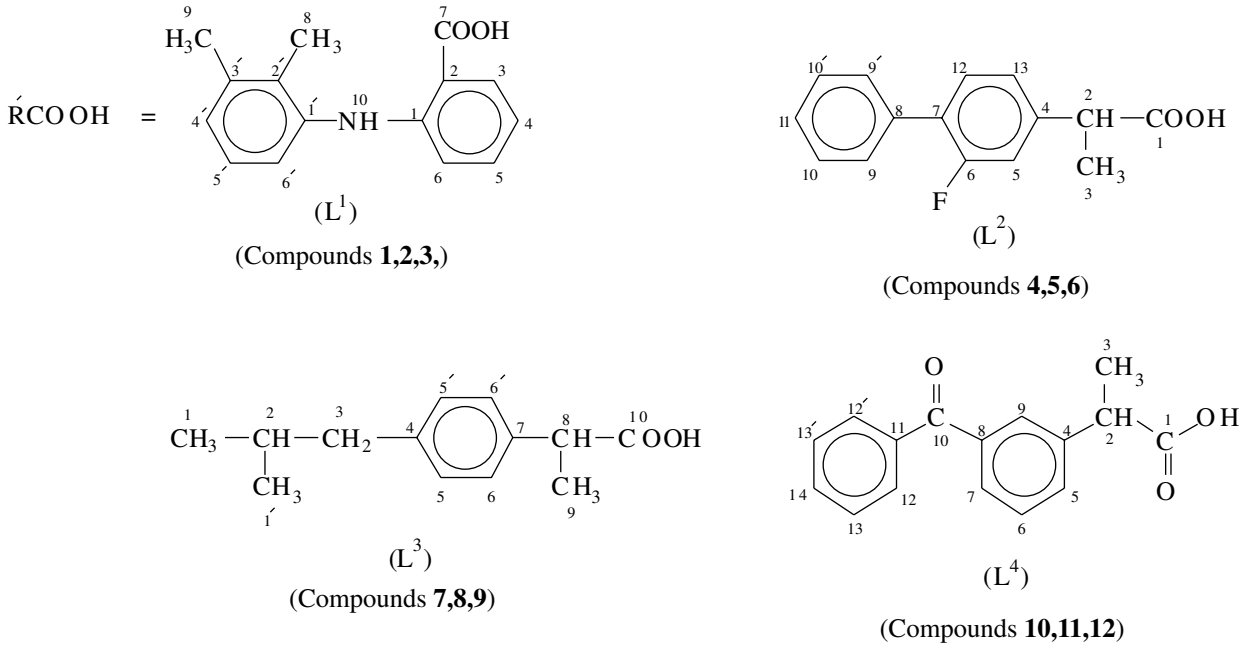
a) Stoichiometric amounts of ligand acid (1 mmol) and dioctyltin oxide (5 mmol) were refluxed in toluene (100 mL) for 3-4 h. The water formed was removed via a Dean and Stark apparatus. Toluene was evaporated under reduced pressure in a high vacuum. The solid was recrystallized from $CHCl_3$/n-hexane (1:1).

a) To a sodium salt of ligand acid in dry toluene (100 mL) were added tribenzyltin chloride (1 mmol) or dibenzyltin dichloride (5 mmol) with constant stirring. The mixture was refluxed for 3-4 h, and allowed to stand overnight at room temperature. The sodium chloride formed was filtered and toluene was evaporated under reduced pressure and the solid formed was recrystallized from $CHCl_3$/n-hexane (1:1).

$$(\text{n-}C_8H_{17})_2SnO + 2R'COOH \xrightarrow[\substack{Reflux\\3-4h}]{Toluene} (\text{n-}C_8H_{17})_2\ Sn(OCOR')_2 + 2H_2O$$

$$(C_7H_7)_3SnCl + R'COONa \xrightarrow[\substack{Reflux\\3-4h}]{Toluene} (C_7H_7)_3SnOCOR' + NaCl$$

$$(C_7H_7)_2SnCl_2 + 2R'COONa \xrightarrow[\substack{Reflux\\3-4h}]{Toluene} (C_7H_7)_2Sn(OCOR')_2 + 2NaCl$$



Scheme 1

Results and Discussion

All the compounds are colorless solids and have sharp melting points. Their physical data along with their m.p., mol. wt. and % yield are reported in Table 1. All drugs have anti-inflammatory and analgesic properties [7b].

Table 1. Physical data for octyltin and benzyltin carboxylates.

Comp. No.	Compound	Molecular Formula	M.W.	M.P. (^{o}C)	Yield (%)
(**1**)	$Oct_2SnL^1_2$	$C_{46}H_{60}NO_4Sn$	809	132	59
(**2**)	$Bz_2SnL^1_2$	$C_{44}H_{42}NO_4Sn$	767	65	75
(**3**)	Bz_3SnL^1	$C_{36}H_{35}NO_2Sn$	632	120	66
(**4**)	$Oct_2SnL^2_2$	$C_{46}H_{56}F_2O_4Sn$	827	60-5	82
(**5**)	$Bz_2SnL^2_2$	$C_{44}H_{38}F_2O_4Sn$	785	122-5	90
(**6**)	Bz_3SnL^2	$C_{39}H_{36}FO_2Sn$	673	110-1	52
(**7**)	$Oct_2SnL^3_2$	$C_{42}H_{66}O_4Sn$	753	128	48
(**8**)	$Bz_2SnL^3_2$	$C_{40}H_{48}O_4Sn$	711	105	79
(**9**)	Bz_3SnL^3	$C_{34}H_{38}O_2Sn$	597	120	55
(**10**)	$Oct_2SnL^4_2$	$C_{48}H_{58}O_6Sn$	849	99	45
(**11**)	$Bz_2SnL^4_2$	$C_{46}H_{40}O_6Sn$	807	116	53
(**12**)	Bz_3SnL^4	$C_{37}H_{34}O_3Sn$	645	152	60

Infrared spectroscopy

The infrared spectra of the reported compounds were recorded in the range 4000-400 cm^{-1}. Tentative assignments were made on the basis of earlier publications [8,9] and the important data are listed in Table 2. The IR spectra of all organotin(IV) compounds do not show a strong band in the 2900-2600 cm^{-1} region, due to ν(OH), indicating deprotonation and coordination of the carboxylate group with tin metal

as expected. The vacant 5d orbital on tin tends to give higher coordination with ligands having a lone pair of electrons, and the IR stretching vibration frequencies of carboxyl groups in organotin carboxylates are important for determining their structures. When there are interactions between the carboxyl oxygen atoms of carboxylates groups and the tin atom, the asymmetric absorption vibration frequencies ν_{asym}(COO) of the carboxylate groups decrease and the symmetric absorption frequencies ν_{sym}(COO) increase. In the IR spectra of title compounds the carboxylate bands are observed in the characteristic region for ν_{asym}(COO) between 1591 and 1507 cm and for ν_{sym}(COO) between 1458 and 1325 cm^{-1}. In all compounds $\Delta\nu$ is less than 200 cm^{-1}, which indicates that the carboxylate groups are chelated and bonded to the metal bidentately [10-13]. In addition, the frequencies ν(Sn-O) appear between 490 and 426 cm^{-1}. This is consistent with the literature values (520-425 cm^{-1}).

Table 2. Characteristic infrared frequencies (cm^{-1}) for octyltin and benzyltin carboxylates.

Comp. No.	$\nu_{C=O}$	ν_{COO} (sym)	ν_{COO} (asym)	$\Delta\nu$	ν_{Sn-C}	ν_{Sn-O}
(**1**)	–	1325	1507	182	525	429
(**2**)	–	1390	1585	197	542	430
(**3**)	–	1385	1575	190	535	426
(**4**)	–	1394	1583	189	529	453
(**5**)	–	1451	1591	140	570	436
(**6**)	–	1411	1544	133	530	441
(**7**)	–	1422	1578	156	519	429
(**8**)	–	1393	1576	183	511	452
(**9**)	–	1411	1558	147	551	436
(**10**)	1752	1458	1592	134	542	490
(**11**)	1760	1410	1578	168	526	446
(**12**)	1707	1409	1560	151	562	449

Mass spectrometry

The mass fragmentation patterns of di- and triorganotin(IV) complexes are given in Schemes 2 and 3. The main ion fragments observed for all the complexes are given in Table 3 along with their m/z values and relative abundance. A molecular ion peak of very low intensity is observed for all triorganotin(IV) carboxylates, while it is absent for all diorganotin(IV) carboxylates [14]. In triorganotin(IV) carboxylates the primary fragmentation is due to the loss of the R group and the same is true for diorganotin(IV) derivatives. However, the secondary and tertiary decomposition is also followed by loss of the R group and the same is true for diorganotin(IV) derivatives. However, the secondary and tertiary decomposition is also followed by loss of the R group in triorganotin(IV) derivatives, while diorganotin(IV) derivatives manifest slightly different patterns of fragmentation. Isotopic patterns of the complexes were studied as given in the Experimental and some representative spectra are given in Figure, which shows the isotopic effect on M^+ ions in compounds (**3**), (**5**) and (**7**). As Sn has 10 naturally occurring isotopes, the effect is very pronounced from the mass spectra presented (Figure).

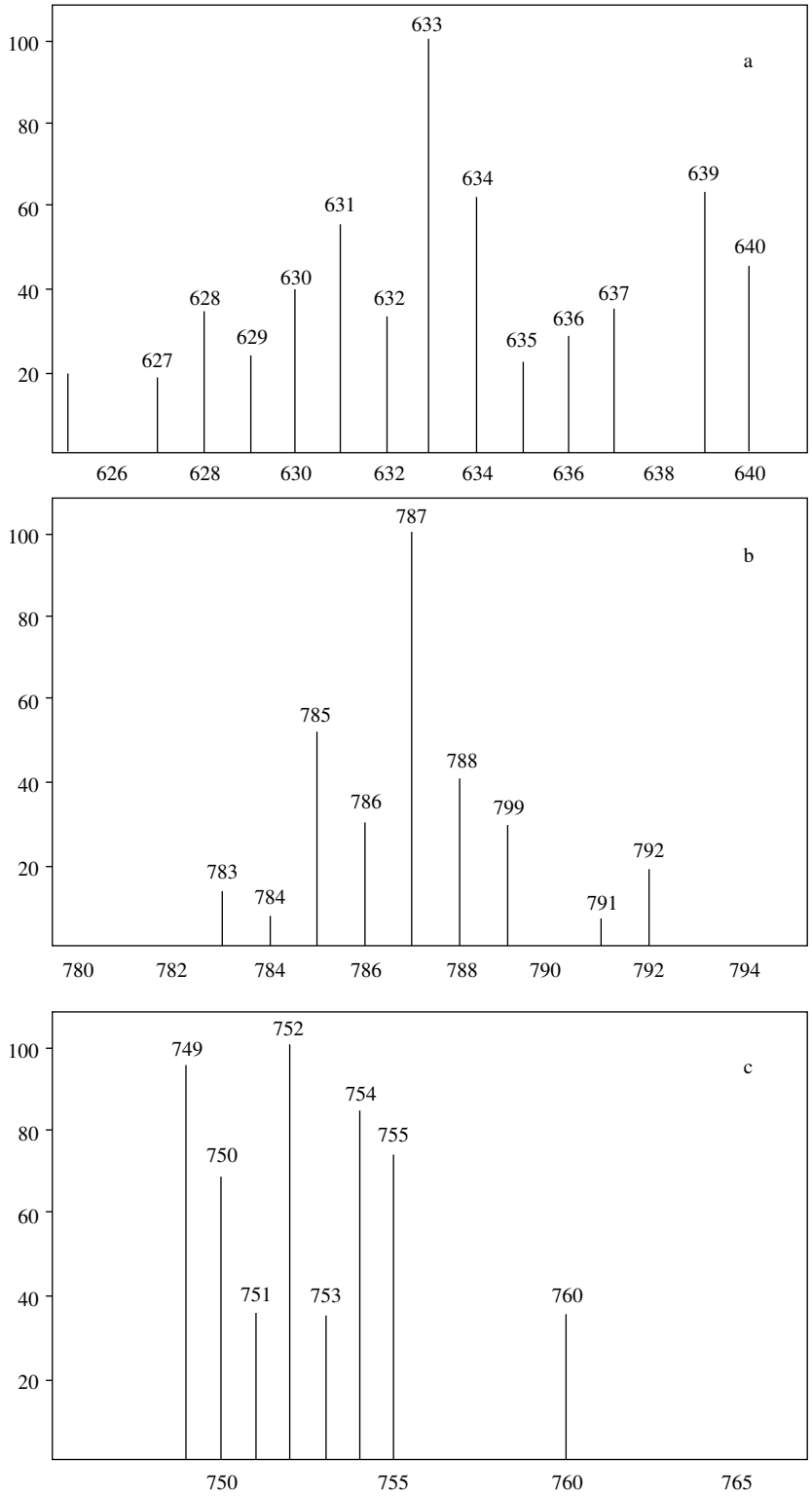
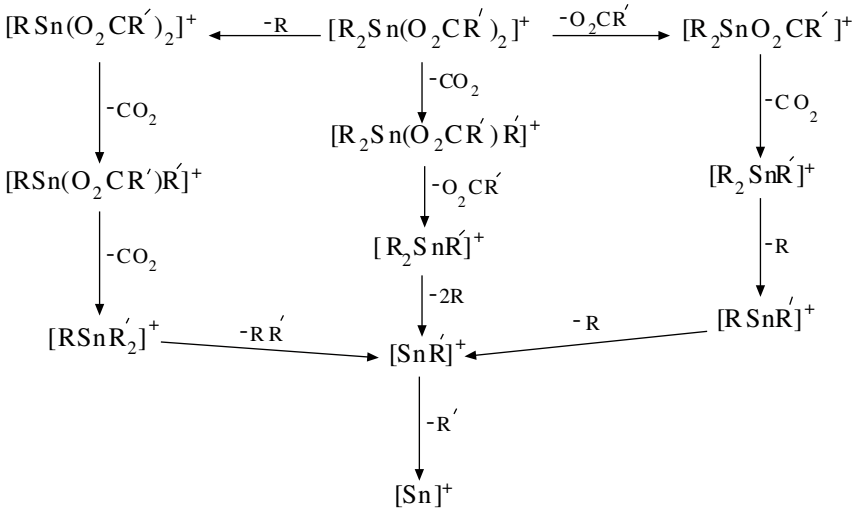
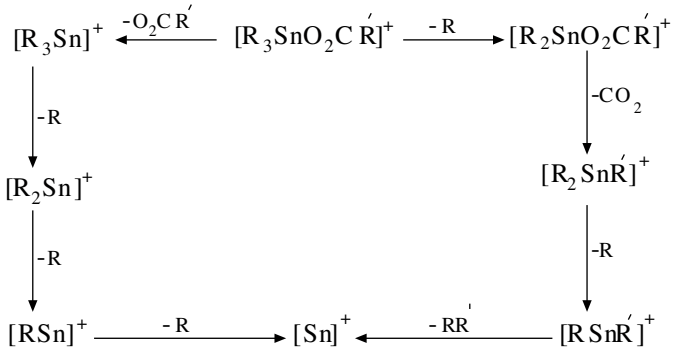


Figure. Isotopic pattern of M^+ ions for the (a) compound 3 (b) compound 5 and (c) compound 7.



Scheme 2. Fragmentation pattern of R_2 SnL_2.



Scheme 3. Fragmentation pattern of R_3 SnL.

NMR spectroscopy

^{1}H NMR spectroscopy

The ^{1}H NMR spectra of compounds (**1**)-(**12**) were recorded in deuterichloroform and are given in Table 4. The number of protons calculated from the integration curves is equal to that calculated from the molecular formula of each compound. Thus, the compounds studied were fully identified by analysis of ^{1}H NMR spectra. The absence of a carboxylic proton signal confirms the deprotonation of the ligand and hence coordination to the tin atom through the COO^- group. The R groups bonded to tin are assigned in their characteristic range.

^{13}C NMR spectroscopy

In recording the NMR spectra of organotin complexes in solution, non-coordinating solvents are preferred over coordinating solvents to preclude possible changes in the coordination number of the tin atom. Thus, deuterichloroform was used to record the ^{13}C NMR spectra of the title compounds (**1**)-(**12**) and the data are given in Table 5. The number of signals found corresponds with the presence of magnetically nonequivalent carbon atoms, which were assigned by comparison with other related organic analogues as model compounds

Table 3. Mass spectral data for octyltin and benzyltin carboxylates.

Fragment Ion	(**1**) m/z(%)	(**2**) m/z(%)	(**3**) m/z(%)	(**4**) m/z(%)	(**5**) m/z(%)	(**6**) m/z(%)	(**7**) m/z(%)	(**8**) m/z(%)	(**9**) m/z(%)	(**10**) m/z(%)	(**11**) m/z(%)	(**12**) m/z(%)
$R_3SnOOCR'$	–	–	632(2)	–	–	673(n.o)	–	–	597(6)	–	–	645(3)
$R_2SnOOCR'$	809(n.o)	767(n.o)	541(n.o)	827(n.o)	785(n.o)	544(n.o)	753(2)	711(3)	506(10)	849(n.o)	807(30)	554(22)
$RSnOOCR'$	472(n.o)	450(18)	450(4)	475(2)	453(58)	453(34)	437(n.o)	415(14)	415(18)	485(2)	463(n.o)	463(16)
$SnOOCR'$	359(12)	359(6)	359(1)	362(6)	362(10)	362(31)	324(12)	324(51)	324(36)	372(36)	372(8)	372(18)
$OOCR'$	241(58)	241(100)	241(100)	244(14)	244(24)	244(53)	206(10)	206(44)	206(16)	253(10)	253(4)	253(n.o)
R'	194(59)	194(57)	194(18)	199(18)	199(100)	199(100)	161(24)	161(100)	161(56)	209(36)	209(57)	209(38)
Sn^+	120(4)	120(n.o)	120(9)	120(5)	120(12)	120(3)	120(9)	120(n.o)	120(3)	120(8)	120(7)	120(n.o)
$C_6H_5^+$	77(9)	77(3)	77(5)	77(n.o)	77(4)	77(4)	77(n.o)	77(3)	77(1)	77(n.o)	77(9)	77(4)
$C_4H_9^+$	57(100)	57(2)	57(63)	57(100)	57(82)	57(28)	57(100)	57(13)	57(n.o)	57(100)	57(100)	57(n.o)
R_3Sn^+	–	–	392(8)	–	–	392(n.o)	–	–	392(n.o)	–	–	392(n.o)
R_2Sn^+	346(4)	301(n.o)	301(4)	346(3)	301(16)	301(12)	346(2)	301(n.o)	301(8)	346(4)	301(2)	301(26)
RSn^+	233(2)	210(9)	210(10)	233(4)	210(7)	210(5)	233(4)	210(n.o)	210(n.o)	233(18)	210(36)	210(6)
$C_7H_7^+$	–	91(86)	91(92)	–	91(96)	91(78)	–	91(68)	91(100)	–	91(44)	91(100)

Table 4. ^{1}H NMR data (δ, ppm)^{a,b} for octyltin and benzyltin carboxylates.

Proton No.	(**1**)	(**2**)	(**3**)	Proton No.	(**4**)	(**5**)	(**6**)	Proton No.	(**7**)	(**8**)	(**9**)	Proton No.	(**10**)	(**11**)	(**12**)
3	6.8 d (7.5)	6.83 d (7.5)	6.84 d (7.5)	2	3.79 m	3.77 m	3.78 m	1,1′	0.89 d (7.5)	0.88 d (7.5)	0.91 d (7.5)	2	3.84 m	3.66 m	3.78 m
4	7.3 t (7.53)	7.23 t (7.53)	7.28 t (7.53)	3	1.56 d (5.0)	1.53 d (5.0)	1.55 d (5.0)	2	1.47 m	1.48 m	1.51 m	3	1.49 d (5.0)	1.48 d (5.0)	1.45 d (5.0)
5	6.6 t (7.63)	6.4 t (7.63)	6.72 t (7.63)	5	7.23 d (7.5)	7.22 d (7.5)	7.23 d (7.5)	3	2.41 d (7.5)	2.42 d (7.5)	2.45 d (7.5)	5 5	7.44 t (7.65)	7.47 t (7.66)	7.41 t (7.66)
6	8.2 d (8.0)	8.15 d (8.0)	8.16 d (8.0)	9,9′	7.52 m	7.55 m	7.53 m	5,5′	7.07 d (7.5)	7.03 d (7.5)	1.09 d (7.5)	6	7.36 t (7.54)	7.37 t (7.54)	7.38 t (7.55)
8	2.2 s	2.3 s	2.3 s	10,10′	7.44 m	7.45 m	7.49 m	6,6′	7.21 d (7.5)	7.23 d (7.5)	7.26 d (7.5)	7	7.60 t (7.71)	7.59 t (7.70)	7.58 t (7.70)
9	2.35 s	2.34 s	2.33 s	11	7.44 m	7.45 m	7.49 m	8	7.21 m	3.47 m	3.45 m	9	7.74 s	7.78 s	7.77 s
10	9.24 s	9.48 s	9.4 s	12	7.40 m	7.43 m	7.42 m	9	1.50 d (5.0)	1.51 d (5.0)	1.57 d (5.1)	12,12′	7.74 d (7.5)	7.78 d (7.5)	7.77 d (7.5)
4′	7.12d (7.5)	7.24 d (7.5)	6.81 d (7.5)	13	7.18 m	7.16 m	7.17 m	R	0.85-1.85 m	2.92 s	2.97 s, 6.35-7.48 m	13,13′	7.59 d (7.5)	7.58 d (7.5)	7.58 d (7.5)
5′	7.20 t (7.51)	7.13 t (7.52)	7.10 t (7.50)	R	0.82-1.82 m	2.63 s, 6.94-7.56 m	2.60 s, 6.72-7.39 m	–	–	6.87-7.60 m	–	14	7.68d (7.5)	7.65 d (7.5)	7.69 d (7.5)
6′	7.26 t (7.52)	7.24 t (7.53)	7.26 t (7.52)	–	–	–	–	–	–	–	–	R	0.85-1.91 m	2.91 s, 6.80-7.90 m	2.96 s, 7.00-7.71 m
R	0.89-1.92 m	2.41 s, 7.2-7.93 m	2.75 s, 7.3-7.78 m	–	–	–	–	–	–	–	–	–	–	–	–

[a]Downfield from $CDCl_3$ set at 7.25 ppm, [b]Numbering of hydrogens as shown in scheme 1.

Table 5. ^{13}C NMR data (δ, ppm)^{a,b} for octyltin and benzyltin carboxylates.

C No.	(**1**)	(**2**)	(**3**)	C No.	(**4**)	(**5**)	(**6**)	C No.	(**7**)	(**8**)	(**9**)	C No.	(**10**)	(**11**)	(**12**)
1	114.6	114.3	114.1	1	184.0	183.1	183.6	1,1′	22.6	22.3	22.7	1	174.7	175.2	175.8
2	149.3	151.3	151.6	2	46.2	46.4	46.3	2	45.0	45.0	45.0	2	25.5	25.7	25.9
3	113.2	113.4	113.6	3	18.7	18.5	18.6	3	30.1	30.1	30.1	3	18.9	18.6	18.4
4	134.8 134.8	136.2 136.2	135.6 135.6	4	142.0, 141.9 (7.9)	142.6, 141.8	142.5, 141.6	4	137.9	137.7	137.6	4	132.6	132.3	132.2
5	115.8	116.2	117.2	5	115.3 115.3 (23.8)	115.2, 115.6 (23.4)	115.4, 115.7	5,5′	127.1	127.9	127.8	5	131.6	131.6	131.7
6	133.4	133.6	133.8	6	158.6, 160.6 (248.3)	157.6, 161.5 (248.3)	158.2, 161.4	6,6′	129.2	129.7	129.1	6	128.4	128.4	128.5
7	177.3	177.8	178.9	7	127.6, 127.8 (13.4)	127.0,	127.0,	7	140.3	140.3	140.8	7	128.6	128.6	128.6
8	13.7	13.4	13.6	8	135.4	135.5	135.2	8	45.8	45.8	45.6	8	141.0	141.4	141.3
9	20.6	20.9	21.3	9,9′	129.4	129.7	129.0	9	20.5	20.6	20.8	9	130.2	130.6	130.7
1′	139.2	139.8	140.3	10,10′	128.8	128.9	128.4	10	184.9	182.4	182.4	10	196.5	196.3	196.7
2′	131.6	132.4	132.6	11	127.7	127.5	127.6	11	33.1	29.6	29.7	11	137.9	137.5	137.3
3′	138.5	139.8	139.5	12	130.7	130.6	130.8	12	31.8	132.4	132.6	12,12′	129.4	129.5	129.9
4′	122.3	122.6	121.9	13	123.5	123.7	123.8	13	29.7	128.9	128.5	13,13′	128.6	128.2	128.2
5′	125.6	125.7	125.8	14	33.1	29.7	29.7	14	29.1	128.5	128.4	14	131.8	131.7	131.6
6′	127.4	126.9	126.7	15	31.9	132.5	132.8	15	25.2	124.4	124.6	15	33.2	29.5	29.5
10	33.3	26.8	22.4	16	29.6	128.5	128.9	16	24.3	–	–	16	31.9	132.8	132.6
11	31.6	134.8	139.2	17	29.3	128.4	128.5	17	22.3	–	–	17	29.8	128.8	128.4
12	29.8	129.6	129.4	18	25.3	124.6	124.7	18	14.1	–	–	18	29.5	128.1	128.1
13	29.2	129.0	128.7	19	24.4	–	–	–	–	–	–	19	26.2	126.8	126.7
14	26.5	127.6	126.5	20	22.6	–	–	–	–	–	–	20	24.5	124.4	124.6
15	24.3	–	–	21	14.0	–	–	–	–	–	–	21	22.7	–	–
16	22.8	–	–	–	–	–	–	–	–	–	–	22	14.2	–	–
17	14.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–

[a]Downfield from $CDCl_3$ set at 77.0 ppm, [b]Numbering of carbons as shown in scheme 1.

[15,16]. In the ^{13}C NMR spectra, the ligand's COO values were found to be shifted considerably downfield in the case of all organotin complexes. This shift may be attributed to COO→Sn coordination [17]. The R groups attached to the tin atom have their signals in various ranges according to the nature of the R group.

^{119}Sn NMR spectroscopy

^{119}Sn NMR spectra of all organotin(IV) complexes were recorded in order to obtain information regarding their structures. According to the data given in Table 6, all compounds show tetrahedral geometry around tin atom in solution. These values are strongly dependent upon the nature and orientation of the organic groups attached to tin. The shifts observed in the above cases can be explained qualitatively in terms of an increase in electron density on the tin atom as the coordination number increases [18].

Table 6. ^{119}Sn NMR data for octyltin and benzyltin carboxylates in $CDCl_3$.

Compound No.	$\delta(^{119}Sn)$ ppm
(**1**)	-201.46
(**2**)	-200.00
(**3**)	-37.93
(**4**)	-196.32
(**5**)	+239.66
(**6**)	-69.14
(**7**)	-201.71
(**8**)	+235.08
(**9**)	–
(**10**)	-197.26
(**11**)	-36.51
(**12**)	-36.21

Biological Activity

All the reported compounds were screened against different fungal strains using tube diffusion [19]. The results of the antifungal assay are given in Table 7. It has been reported that, within a given series, triorganotin(IV) derivatives are more active against fungi [20]. Our screening tests are consistent with early reports except that compound (**9**) was found to be inactive against fungi [9].

Diorganotin(IV) carboxylates show high activity against *Trichophyton longifusum*. Compounds (**4**), (**5**), (**7**), (**8**) and (**11**) do not show any activity at all. All the synthesized compounds were also tested for their antibacterial activity by using 6 different bacteria. These compounds were tested at a concentration of 100 mg/mL in DMSO solution, the susceptibility zones being measured in millimeters and presented in Table 8. All the compounds show significant antibacterial activity against the tested bacteria. The brine shrimps (*Artemia salina*), a tiny crustacean, was used for the determination of the toxicity of the organotin(IV) carboxylates. The results are reported in Table 9.

Previous reports [21,22] show that the toxicity of organotin compounds depends upon the nature of the organic group. The highest toxicity was shown by compound (**4**) and the least by compound (**11**), while compounds (**1**)-(**3**), (**5-10**) and (**12**) did not show any toxicity.

Table 7. Antifungal activity[a] for octyltin and benzyltin carboxylates.

Name of Fungi	Percent inhibition												Reference
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**	**(8)**	**(9)**	**(10)**	**(11)**	**(12)**	Drug
Trichophyton longfusum	57.8	42.1	89.4	0	0	71.5	0	0	0	63.1	0	66.6	Miconazole Ketoconazole
Candida albicans	0	0	0	0	0	0	0	0	0	0	0	0	Miconazole Ketoconazole
Aspergillus flavus	0	0	0	0	0	0	0	0	0	0	0	0	Amphotericin B Flucytosine
Microsporum canis	0	0	60	0	0	74	0	0	0	30	0	0	Miconazole Ketoconazole
Fusarium solani	0	0	0	0	0	0	0	0	0	0	0	0	Miconazole
Candida glabrata	0	0	0	0	0	0	0	0	0	0	0	0	Miconazole

[a] Concentration: 200 (μg/mL).

Table 8. Antibacterial activity[a] for octyltin and benzyltin carboxylates.

Name of Bacteria	Zone of inhibition (mm)											
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**	**(8)**	**(9)**	**(10)**	**(11)**	**(12)**
Escherichia coli	10	10	10	–	–	10	14	–	–	–	–	–
Bacillus subtilis	–	10	17	16	16	12	–	–	–	–	17	13
Shigella flexneri	–	10	10	–	10	10	–	–	–	–	–	9
Staphlyococcus aureus	10	10	12	–	–	10	7	–	–	10	10	–
Pseudomonas aeruginosa	11	12	11	11	–	11	19	15	11	12	13	9
Salmonella typhi	–	–	–	13	–	–	–	–	–	–	12	–

[a] Reference drugs: Ampicillin $(H_2O)_3$ and Cephalexin Na.

Table 9. Brine shrimp (*Artemia salina*) lethality bioassay[a] for octyltin and benzyltin carboxylates.

Compound No.	Dose (μg/mL)	No. of Shrimps	No. of Survivors	LD_{50} (μg/mL)
(**1**)	100	30	10	–
	10	30	10	
	1	30	10	
(**2**)	100	30	10	–
	10	30	10	
	1	30	10	
(**2**)	100	30	10	–
	10	30	10	
	1	30	10	
(**4**)	100	30	7	25.8344
	10	30	20	
	1	30	30	
(**5**)	100	30	10	–
	10	30	10	
	1	30	10	
(**6**)	100	30	10	–
	10	30	10	
	1	30	10	
(**7**)	100	30	30	–
	10	30	30	
	1	30	30	
(**8**)	100	30	30	–
	10	30	30	
	1	30	30	
(**9**)	100	30	10	–
	10	30	10	
	1	30	10	
(**10**)	100	30	10	–
	10	30	10	
	1	30	10	
(**11**)	100	30	22	387.6887
	10	30	30	
	1	30	30	
(**12**)	100	30	30	–
	10	30	30	
	1	30	30	

[a] LD_{50} value of standard drug (Etoposide) = 7.4625 (μg/mL)

Conclusions

Carboxylate groups in solid state act bidentately, having 6 coordination around tin, while multinuclear NMR data show that in solution the bidentate carboxylate group is cleaved and the resulting monomer contains 4 coordinated tin with a distorted tetrahedral arrangement. Mass spectral data reveal that primary fragmentation is due to successive loss of the alkyl group followed by the elimination of CO_2 and the remaining part of the ligand, which leaves Sn^+ as the end product. Biological screening results show that all of the compounds exhibit significant activity against different animal and plant pathogens.

Acknowledgments

SA is grateful to the Alexander von Humboldt Foundation for a George Forster Research Fellowship and to Prof. Dr. B. Wrackmeyer, University of Bayreuth, Germany, for providing spectroscopy facilities. Financial support from the University Research Fund (URF) of Quaid-i-Azam University is gratefully acknowledged. The pharmaceutical companies Wilson, Ferozsons Laboratories, and Upjohn are also acknowledged for providing the pure drugs.

References

1. P.A. Insel, in Goodman and Gilman's **"The Pharmacological Basis of Therapeutics",** Chapter 27, McGraw-Hill, New York, 1996.
2. J. Reynolds, K. Parfitt, A.V. Parsons and S.C. Sweetman, **Martindale**: **The Extra Pharmacopoeia,** 15, 23, 30^{th} edn., London, 1993.
3. B.G. Katzung, **Basic and Clinical Pharmacology,** 585, 7^{th} edn., USA, 1998.
4. M. Mazhar, M.A. Choudhary, S. Ali, Q.L. Xie and X.Q. Song, **J. Chem. Soc. Pak., 23**, 103 (2001).
5. D.D. Perrin and W.L.F. Armengo, **Purification of Laboratory Chemicals,** 3^{rd} eds., Pergamon., Oxford, 1988.
6. K. Sisido, Y. Yakeda and Z. Kingawa, **J. Am. Chem. Soc., 83,** 538-541 (1961).
7. (a) S. Frank, **Chem Tool Prog**., 1990 (b) **The Merck Index,** 11^{th} edn. Merck and Co. Inc. Rahway, NJ, USA, 1989.
8. S. Shahzadi, M.H. Bhatti, K. Shahid, S. Ali, S.R. Tariq, M. Mazhar and K.M. Khan, **Monatsh. Chem., 133**, 1089 (2002).
9. S. Ahmad, S. Ali, F. Ahmad, M.H. Bhatti, A. Badshah, M. Mazhar and K.M. Khan, **Synth. React. Inorg. Met.-Org. Chem., 32,** 1521 (2002).
10. K.C. Molloy, K. Quill and I.W. Nowell, **J. Chem. Soc., Dalton Trans.,** 101-106 (1987).
11. R.R. Homes, **Acc. Chem. Res., 22,** 190-197 (1989).
12. M. Nath, C.L. Sharma and N. Sharma, **Synth. React. Inorg. Met.-Org. Chem., 21,** 807-824 (1991).
13. A. Sexena, J.P. Tandon, K.C. Molloy and J.J. Zuckerman, **Inorg. Chim Acta, 63,** 71-74 (1982).
14. M. Gielen, E. Joosen, T. Mancilla, K. Jurkschat, R. Willem, C. Roobol, J. Bernheim, G. Atassi, F. Huber, E. Hoffmann, H. Prent and B. Mahieu, **Metal Chem., 10,** 147-167 (1987).
15. G.C. Levy, R.L. Lichter and G.L. Nelson, **Carbon-13 Nuclear Magnetic Resonance Spectroscopy,** Wiley; New York, 1980.
16. J. Holecek, H. Handlir, A. Lycka, T.K. Chattopadhyay, B. Majee and A.K. Kumar, **Collect. Czech. Chem. Commun. 15,** 1100-1111 (1986).
17. J. Holecek and A. Lycka, **Inorg. Chim. Acta. 118,** L15-L16 (1986).
18. A. Adhikari, D.L. Greenslade and A.K. Ghosh, **Indian J. Chem., 32A**, 454-456 (1993).
19. (a) H. Blank and G. Rewbell, **Arch. Derm., 92,** 319-322 (1965). (b) S.S. Shaukat, N.A. Khan and F. Ahmed, **Pakistan J. Bot., 12,** 97-106 (1980).

20. K.C. Molloy, **Bioorganotin Compounds, In the Chemistry of the Metal-Carbon Bond;** ed. F.R. Hartley, Wiley, New York and London, 1989.

21. M.R. Krigman and A.P. Silverman, **Neurotoxicology, 5,** 129-139 (1984).

22. J.M. Barnes and H.B. Stoner, **Brit. J. Ind. Med., 15,** 15-22 (1958).