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Spectroscopic Studies of Biologically Active Organotin(IV) Derivatives of 2-[N-(2,4,6- Tribromophenylamido]propanoic Acid

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Herein we describe the synthesis and characterization of compounds having the formulae R_2SnL_2 and R_3SnL , where $R = Me$, *n*-Bu, Ph and *n*-Oct and $L = 2-[N-(2,4,6-tribromophenylamido]propanoic acid. All the complexes have been characterized by$ various spectroscopic methods (IR and ${}^{1}H$, ${}^{13}C$, ${}^{119}Sn$ NMR), elemental analysis, mass spectrometry and physical data. These compounds were also screened for their biological activity and found some encouraging results.

Keywords: Organotin(IV) carboxylates, NMR, IR, Mass, Biological activity

INTRODUCTION

 Tin played a full part in the great increase of activity in organometallic chemistry, which started in about 1949 and this was stimulated by the discovery of variety of applications [1]. The considerable development over recent decades in the use of organotin compounds as reagents or intermediate in inorganic synthesis has promoted the preparation of many new organotin compounds and the developments of new, rapid and convenient synthetic procedures [2,3].

 The most significant recent developments in organotin carboxylates is because of biological activity associated with these compounds; thus, there has been a large increase in reports on their synthesis, structure elucidation and biological activity-structure relationships [4-6].

 Recently, considerable attention has been paid to triorganotin(IV) derivatives having high *in vitro* antifungal activities against some medically important fungi. The low aqueous solubility of organotin compounds is a limiting factor

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^{<i>h*}Department of Chemistry, in further research of their use in medicine [7]. On the basis of the known electron-acceptor properties of these compounds, it can be proposed that their toxicity is related to their interaction with electron donor groups in biologically important molecules. Refering to various applications of organotin carboxylates and continuation of our studies of biologically active organotin(IV) derivatives of substituted anilines [8,9], here we synthesized some organotin(IV) derivatives of 2-[N- (2,4,6-tribromophenylamido]propanoic acid (Fig. 1). These complexes were characterized by elemental analysis, infrared, multinuclear NMR (${}^{1}H$, ${}^{13}C$, ${}^{119}Sn$) and mass spectrometry. Their biological activity data has also been reported.

Fig. 1. Chemical structure of 2-[N-(2,4,6-tribromophenyl amido]propanoic acid.

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Complexes

EXPERIMENTAL

Material and Methods

 All the chemicals were of analytical grade and used without further purification. Melting points were determined in capillary tubes using a MP-D Mitamura Riken Kogyo (Japan) electrothermal melting point apparatus and are uncorrected. Infrared absorption spectra were recorded as KBr (4000-400 cm*-*¹) pellets on Bio-Rad FT-IR spectrometer.

The ${}^{1}H$, ${}^{13}C$ and ${}^{119}Sn$ NMR spectra were recorded on a Bruker AM 250 spectrometer (Germany), using $CDCl₃$ as an internal reference [δ of ¹H(CDCl₃) = 7.25 and δ of ¹³C(CDCl₃) $= 77.0$]. ¹¹⁹Sn NMR spectra were obtained using Me₄Sn as external reference [δ of ¹¹⁹Sn = 37.290665]. Mass spectral data were measured on a MAT 8500 Finnigan 70 eV mass spectrometer (Germany).

General Procedure for Synthesis of 2-[N-(2,4,6- Tribromophenylamido]propanoic Acid

 A solution of succinic anhydride (5 mmol) in HOAc (300 ml) was added to a solution of 2,4,6-tribromoaniline (5 mmol) in HOAc (150 ml) and the mixture was stirred overnight at room temperature. The pale yellow precipitates were filtered,

 2-[N-(2,4,6-Tribromophenylamido)]propanoic acid (1 mmol) was suspended in dry toluene (100 ml) and treated with Et₃N (0.29 ml, 1 mmol). The mixture was refluxed for 2-3 h. To this stirring solution, diorganotin dichloride (0.5 mmol) or

washed with cold distilled $H₂O$ (200 ml) and air dried.

General Procedure for Synthesis of Organotin(IV)

triorganotin chloride (1 mmol) was added as solid and the reaction mixture was refluxed for 8-10 h. The reaction mixture contained Et₃NHCl was filtered off. The solvent was removed through rotary apparatus. The mass left behind was recrystallized from CHCl₃ and *n*-hexane (1:1). In case of $Oct₂SnL₂, 2-[N-(2,4,6-tribromophenylamido)]propanoic acid$ (1 mmol) was refluxed with Oct₂SnO (0.5 mmol) in toluene (100 ml) using Dean and Stark apparatus for removal of H_2O formed during the reaction. The remaining procedure was followed as for others.

RESULTS AND DISCUSSION

 All the complexes are soluble in most of organic solvents. The synthetic pathway to the target compounds (**1**)-(**6**) are

Spectroscopic Studies of Biologically Active Organotin(IV)

$$
R_2SnCl_2 + 2Et_3NHL \longrightarrow R_2SnL_2 + 2Et_3NHCI
$$
 (1)

$$
R = Me (1), n-Bu (2)
$$

 $R_3SnCl + Et_3NHL \longrightarrow R_3SnL + Et_3NHCl$ (2) R = Me (**4**), *n*-Bu (**5**), Ph (**6**)

 $R_2SnO + 2HL$ \longrightarrow $R_2SnL_2 + H_2O$ (3) $R = n$ -Oct (3)

Scheme 1

outlined in Scheme 1. The physical data for the complexes are reported in Table 1.

Infrared Spectroscopy

 The infrared spectra of di- and triorganotin complexes were recorded in the range of $4000-400$ cm⁻¹ as KBr disc. The IR absorption bands for structural assignment are given in Table 2. The complexation of tin with ligand is confirmed by the presence of Sn-O band in range of $427-408$ cm⁻¹ which was absent in the ligand. Bands in the range of 536-528 cm⁻¹ indicate the presence of Sn-C in these compounds. The bands for -NH and -OH are observed almost in the same range but these are distinguished by broad band for -OH and sharp band for -NH group in the ligand [10]. The difference between $v_{\text{asym}}COO - v_{\text{sym}}COO = \Delta v$ is very important in prediction of nature of ligand. In all complexes the difference Δν is less than 200 cm⁻¹ which indicates the bidentate nature of the ligand in all complexes [11,12].

 Referring to the literature [13], the geometry of tin atom in the diorganotin(IV) carboxylates is based on skew-trapezoidal

bipyramidal geometry shown in Figs. 2a and 2b. The triorganotin(IV) carboxylates are known to adopt a variety of motifs in the solid state, Figs. 2c-2e [13,14]. However, it is likely that the triorganotin(IV) species are linear polymers

Compound	vNH	$vC=O$	$vCOO$ (asym)	$vCOO$ (sym)	Δv	$vSn-C$	$vSn-O$
HL	3329	1765	1590	1346	244	-	
(1)	3332	1760	1590	1432	158	533	411
(2)	3326	1764	1570	1410	160	528	422
(3)	3331	1769	1580	1416	164	531	408
$\left(4\right)$	3325	1766	1596	1411	185	530	416
(5)	3321	1770	1570	1431	139	536	427
(6)	3323	1772	1580	1432	148	-	418

Table 2. IR Spectral Data for R_2SnL_2 and R_3SnL (cm⁻¹)

(Fig. 2e) as commonly found for triorganotin(IV) carboxylates with bidentate ligands leading to *trans*-R₃SnO₂ geometry for tin [13]. In conclusion, the infrared data (Δv) suggest a bidentate coordination of COO group to tin atom for carboxylate ligands in the solid state.

Mass Spectrometry

peaks were not observed. It appears that
 be calculated by using the Lockhart

energies are relatively low so to tatt they
 APC are relatively low so that they

dimary fragmentation. In diorganotin(IV)
 $\theta = 0.0161\left[\$ Molecular ion peaks were not observed. It appears that bond dissociation energies are relatively low so that they suffer considerable fragmentation. In diorganotin(IV) derivatives, the primary fragmentation is due to the loss of ligand, R″COO. While the secondary fragmentation occurs through elimination of hydrogen (H) or $CO₂$ or simply involves loss of ligand ($R^{\prime\prime}COO$) where $R^{\prime\prime} = C_9H_7Br_3NO$. Tertiary fragmentation occurs *via* cleavage of ligand or the ligand moiety R' and gives the fragments $[RSnR'']^+$ and $[R_2Sn]^+$, respectively, and is followed by elimination of R or $R^{\prime\prime}$ and ending at $[Sn]^+(m/z = 120)$.

 In triorganotin(IV) carboxylates, the primary fragmentation is due to the loss of R″COO group, followed by successive cleavage of R groups and ends at $[Sn]^+$. A second fragmentation pathway is characterized by the loss of R group in primary fragmentation followed by liberation of $CO₂$. The secondary and tertiary fragmentations involve the loss of R or R' and end at $[Sn]^+$ [15,16]. This rout is the most probable than the first one. The most common fragments together with their m/z ratios and relative abundances is given in Table 3.

NMR Spectroscopy

The ¹H NMR chemical shifts and coupling constants for reported compounds (**1**)-(**6**) are given in Table 4. The -NH resonance appears at 4.59 ppm for all the complexes. The aromatic protons give signals in the range of 7.28-7.69 ppm. The different R groups attached to tin atom give signals at expected range thus confirming the complexation. The values of coupling constant 50 and 75 Hz for di- and triorgantoin derivative, respectively, provides information regarding coordination number [17] and organotin(IV) structure.

The 13 C NMR data also reveals expected signals with specified range. The presence of -CO and -COO was confirmed by the signals in the range of 164.2-159.9 and 177- 179 ppm, respectively. The R groups attached to tin are in expected range which are reported in Table 5. The value of

Sn-C coupling ${}^{n}J$ [119 Sn- 13 C] describes a tetrahedral geometry around the tin atom. The magnitudes for ${}^{n}J$ ^{[119}Sn,¹³C] coupling are also observed and are given in Table 6. The coupling constants, ^{n}J [^{119}Sn ,¹³C] are important parameters for the determination of C-Sn-C bond angles and structure characterization of organotin(IV) compounds. Coupling parameter (*J*) can easily be measured in solution, while θ can be calculated by using the Lockhart's equation (4) [18].

$$
\theta = 0.0161 \, [^2 \text{J}]^2 - 1.32 \, [^2 \text{J}] + 133.4 \tag{4}
$$

This equation is used for non-coordinating solvents. Similarly on substituting value of θ in the Lockhart's equation (5) [18], 1 *J*¹¹⁹Sn, ¹³C] can be calculated.

$$
{}^{1}J_{\left[\right]}^{119}\text{Sn}, {}^{13}\text{C} = 11.4 \theta - 875
$$
 (5)

 In order to gain the further information about the possible coordination geometries in solution, a close examination of the ${}^{17}J$ [¹¹⁹Sn-¹³C] and ² J [¹¹⁹Sn-¹H] coupling constants were undertaken, as structural details, such as the determination of C-Sn-C bond angles, can be enumerated by use of the literature methods [18,19]. For triorganotin compounds the magnitudes of ${}^{1}J$ ^{[119}Sn,¹³C] coupling suggest the typical tetrahedral geometry around the tin atom in solution [20], while diorganotin dicarboxylates in non-coordinating solvents may acquire penta-coordinated geometry around the tin atom [20].

The chemical shifts of 119 Sn are found in the range of -108.7 to 154.3 ppm for all complexes. For diorganotin dicarboxylates, it suggests a coordination number of tin greater than five due to increased polarization of phenyl groups. The 119 Sn chemical shifts move to higher field [21] as the electron releasing power of the alkyl group increases the tin atom becomes progressively more shielded and ^{119}Sn chemical shifts value moves to higher field. The ^{119}Sn chemical shifts for compound (**4**) and (**5**) are 101.2 and 154.3, respectively [22-25].

The ¹¹⁹Sn chemical shifts for triorganotin carboxylates also support the geometry on the basis of ${}^{1}H$ and ${}^{13}C$ NMR data as reported in Table 7. The ¹¹⁹Sn chemical shift values obtained for the triorganotin(IV) derivatives lie in the range expected for a tetrahedral geometry whereas the diorganotin(IV)

Fragment ion	$\bf(1)$	(2)	(3)	$\left(4\right)$	(5)	(6)
$[R_3Sn]^+$	-			165(16)	291(11)	351(16)
$[R_2Sn]^+$	150(12)	234(15)	346(8)	150(9)	234(4)	274(10)
$[BrC7H5OSn]+$	304(10)	304(3)	304(4)	304(6)	304(10)	304(5)
$[BrC_6H_5]^+$	155(6)	155(12)	155(7)	155(4)	155(9)	155(100)
$[Br_3C_6H_5N]^+$	328(100)	328(100)	328(100)	328(100)	328(100)	328(92)
$[C_7H_7]^+$						
$[C_6H_5]^+$	77(18)	77(16)	77(57)	77(18)	77(1)	77(18)
$[Sn]^+$	120(5)	120(6)	120(3)	120(2)	120(7)	120(6)

Table 3. Mass Spectral Data for R₂SnL₂ and R₃SnL

Table 4. ¹H NMR Data^a (ppm) for R_2SnL_2 and R_3SnL

$ DI_3C_6H_5N $	320(IUU)	320(TUU)	320(TUU)	340(TUU)	J ₂₀ (100)	320(YZ)
$[C_7H_7]^+$						
$[C_6H_5]^+$	77(18)	77(16)	77(57)	77(18)	77(1)	77(18)
$[Sn]^{+}$	120(5)	120(6)	120(3)	120(2)	120(7)	120(6)
Table 4. ¹ H NMR Data ^a (ppm) for R_2SnL_2 and R_3SnL						
Compound	$Br_3-C_6H_2$	$-NH$	$-CH_2-CH_2$ -		${\bf R}$	
HL	7.52s	4.59s	$8.02 - 8.08d(9.1)$			
			$8.42 - 8.51d(9.1)$			
(1)	7.28s	4.59s	$8.12 - 8.16d(9.1)$		$1.28s$ [74]	
			$8.39 - 8.43d(9.1)$			
(2)	7.53s	4.59s	$8.1\overline{1} - 8.18d(9.1)$		0.96t, 1.25-1.33m	
			$8.36 - 8.40d(9.1)$			
(3)	7.53s	4.59s	$8.09 - 8.14d(9.1)$		0.89t [50], 1.68-1.75m	
			8.34-8.49d (9.1)			
(4)	7.55s	4.59s	$8.05 - 8.20d(9.1)$		$0.73s$ [58]	
			$8.31 - 8.45d(9.1)$			
(5)	7.49s	4.59s	$8.08 - 8.19d(9.1)$		0.94t [75], 1.15-1.69m	
			8.34-8.46d (9.1)			
(6)	7.69s	4.59s	$8.02 - 8.18d(9.1)$		7.48-7.84m	
			8.37-8.48d (9.1)			
^a Chemical shifts (δ) in ppm. ² J[¹¹⁹ Sn, ¹ H] and ³ J(¹ H, ¹ H) in Hz are listed in square brackets and parenthesis,						
respectively. Multiplicity is given as: $s = singlet$, $d = doublet$, $t = triplet$, $m = multiplet$.						
indicate higher coordination, number [21].					some toxicity. The toxicity of organotin compoun	

^aChemical shifts (δ) in ppm. ² $J[$ ¹¹⁹Sn, ¹H] and ³ $J($ ¹H, ¹H) in Hz are listed in square brackets and parenthesis, respectively. Multiplicity is given as: $s =$ singlet, $d =$ doublet, $t =$ triplet, $m =$ multiplet.

compounds indicate higher coordination, number [21].

Biological Activity

 Bioactive compounds are often toxic to Shrimp larvae and *in vivo* lethality to these species can be used as a rapid and simple preliminary monitor for bioactive compounds during the isolation of natural products. Brine Shrimp's method [26] has been used for the determination of toxicity of the organotin carboxylates. The results are reported in Table 8. As it is seen, compound (4) shows the highest toxicity with LD_{50} value 10.99 μ g ml⁻¹, while the other compounds also show

some toxicity. The toxicity of organotin compounds depends upon the nature of organic group as earlier reports manifested [27].

 All synthesized compounds were also screened for their antibacterial activity by agar well diffusion method [28]. The results have been reported in Table 9. All compounds show significant antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Stephlococcus aureus*, *Pseudomonoas aeruginosa*, *Salmonella typhi* and *Shigella flexenari*.

 Antifungal activity data is given in Table 10 and the tube diffusion method [28] is used. Earlier reports show that higher

Chemical shifts (δ) in ppm. ^{n}J [$^{117/119}Sn$,¹³C]; ^{n}J [^{119}Sn ,¹³C] in Hz are listed in parenthesis.

Table 6. (C-Sn-C) angles (^o) Based on NMR Parameters of Organotin(IV) Derivatives for R₂SnL₂ R₃SnL

Compound No.	Compound	^{1}J [^{119}Sn , ^{13}C] (Hz)	^{2}J [¹¹⁹ Sn, ¹ H] (Hz)	Angle $(°)$		
$\bf{(1)}$	Me ₂ SnL ₂	536	74	123.8	124.0	
(3)	n -Oct ₂ SnL ₂	476		122.4	$\overline{}$	
$\bf(4)$	Me ₃ SnL	394	58	111.4	111.3	
(5)	n -Bu ₃ SnL	365		111.3	-	

Table 7. ¹¹⁹Sn NMR Data (ppm) for R_2SnL_2 and R_3SnL

Table 8. Cytotoxicity Data for R₂SnL₂ and R₃SnL

Compound No.	LD_{50}
(1)	16.19
(2)	7.88
(3)	8.88
(4)	10.99
(5)	8.99
ϵ	9.9

antifungal activity is associated with tributyltin and triphenyltin compounds [29]. Tributyltin carboxylate shows highest activity against *Trichophyton longiusus*, *Aspergillus flavis*, *Microsporum canis*, *Fusarium solani* and *Candia glaberata,* while dibutyltin and trimethyltin carboxylates do not show any activity.

 The insecticidal activity data of the compounds are given in Table 11 and the data were collected by contact toxicity

9.9								in Table 11 and the data were collected by con			
Table 9. Antibacterial Activity for R_2SnL_2 and R_3SnL											
Name of bacteria			Zone of inhibition (mm)								
			(1)	(2)	(3)	$\overline{4}$	(5)	(6)			
Escherichia coli			12		14	15		14			
Bacillus subtilis			14		14	10		15			
Shigella flexenari			16		18	8		15			
Staphylococcus aureus			16		8	8	5	15			
Pseudomonas aeruginosa			16		12	12		10			
Salmonella typhi			10		14	18		16			
Standard drug = Ampicilline (H ₂ O) ₃ , Cephalexin Na. Concentration of standard drug = 3 mg ml ⁻¹ .											
Table 10. Antifungal Activity for R_2SnL_2 and R_3SnL											
				Compound No.							
Fungi	HL	(1)	(2)	(3)	(4)	(5)	(6)	Standard drug			
Trichophyton longiusus	89.4	88.8		100		100	55	Miconazole Ketoconazole			
Candida albicans				100		100		Miconazole Ketoconazole			
Aspergillus flavis				100		100		Amphotericin-B Flucytosine			
<i>Microsporum</i> canis				100		100		Miconazole Ketoconazole			
Fusarium solani				100		100		Miconazole			
Candida glaberata				100		100		Miconazole			

Table 10. Antifungal Activity for R_2SnL_2 and R_3SnL

Table 11. Insecticidal Data for R_2SnL_2 and R_3SnL

Insects	Compounds						
			3		\mathbf{z}		
Tribolium continuum							
Sitophilius orgyzae			25				
Rhyzopertha domininca	25		25		25		
Callosbruchus analis			25				

Standard drug = Permethrin. Concentration of standard drug = $235.55 \mu g \text{ cm}^{-2}$.

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Table 12. Antileishmanial Activity for R_2SnL_2 and R_3SnL

Compound No.	IC_{50}
(1)	61.00
(2)	65.15
(3)	62.50
(4)	62.00
(5)	61.00
(6)	58.00

 Standard drug = Amphotericin. Concentration of standard drug = 0.19μ g ml⁻¹.

method [28]. It shows that compound (**1**) is found to be inactive against the tested insects while the compounds (**3**), (**5**) and (**6**) show the activity.

61.00 [1] A.G. Davis, P.G. Smith,

58.00 [1] A.G. Davis, P.G. Smith,

1982

1983

1993

1994

1993

1994

1983

1994

1 Leishmaniasis is caused by a protozoa species of the genus leishmania. The organotin derivatives were tested for antileishmanial activity and was found to be significantly more active in reducing the parasite load at much lower concentration (Table 12). The results suggest that the compounds could be exploited as an antileishmanial drug and have potential to be used as a new agent for leishmaniasis.

 Thus the presence of an organic group directly attached to tin is an important factor which is responsible for enhanced activity of organotin(IV) complexes. This indicates that the alkyl group directly appended to the central tin atom is important contributor to the activity.

CONCLUSIONS

 It is observed that the multinuclear NMR data for all complexes found were in agreement with reported values. IR spectroscopy proved the bidentate nature of the carboxylic groups and suggests the penta and hexa coordinated geometry in solid state for tri- and diorganotin derivatives, respectively. Mass spectral data are also in agreement with the proposed molecular formulae of all the synthesized compounds.

 A particular feature of these complexes is that the properties of central metal atom may be tuned by introducing different substituents particularly in regard to their biological activity.

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