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Synthesis, X-ray Structure, and Bioassay of Newly Synthesized Trimethyltin(IV) 2,3-Methylenedioxy Benzoate

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Trimethyltin(IV) complex containing the carboxylate ligand 2,3-methylenedioxybenzoic acid (**HL**) have been synthesized and characterized in solution state by multinuclear NMR (^{1}H, ^{13}C and ^{119}Sn) using the noncoordinating solvent and also in solid sate by FTIR, mass spectrometry, and X-ray crystallography. Spectroscopic data have shown that methylenedioxy moiety has not coordinated with tin atom; instead, the coordination site is a -COO group, which is proved by spectral and XRD data. The solid state structure shows the trigonal bipyramidal geometry with a space group $P2_1/c$. This compound was tested for its in vitro antitumor activity.

Key Words: 2,3-methylenedioxybenzoic acid, spectroscopy, X-ray structure, antitumor activity

Introduction

During the last 50 years, the organotin compounds have witnessed a quantum leap due to their new structural diversity and broad therapeutic activity.[1] Due to their structural behavior, organotin carboxylates are playing very important role in industry and agriculture.[2−6] In organotin compounds, the easily dissociable chelating ligand cause the preparation of intermediates such as $R_nS_n^{+(4-n)}$(n = 2 or 3) moieties. The biological activities of these compounds may be due to these moieties, which may bind to the DNA[7] or high affinity site ATPase (histidine) or low affinity site ATPase and hemoglobin (cystine).[8,9] The study of coordination behavior of these compounds makes more easy to get a better insight that how the metallic

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species behave inside the biological system and also help to formulate structure-activity correlations to devise novel derivatives with potential antitumor and other biocidal activities. The mode of coordination of the donor atoms to tin centers depends upon several factors including reaction medium, pH, conformational equilibrium occurring in solution state and also the nature of moieties attached to the main ring. The increasing interest in the chemistry of organotin(IV) compounds has led to the extended studies on their reactions with different biomolecules, e.g., carbohydrates,[10] nucleic acid derivatives,[11] amino acids[12] and peptides.[13]

Keeping in view these applications and our interest in the synthesis, characterization and biological studies of organotin(IV) carboxylates,[14,15] we have synthesized trimethyltin(IV) derivative of 2,3-methylenedioxybenzoic acid (Figure 1) and characterized by multinuclear NMR (^{1}H, ^{13}C, and ^{119}Sn), FT-IR, mass spectrometry, and X-ray crystallography. This compound was tested for its in vitro antitumor activity.

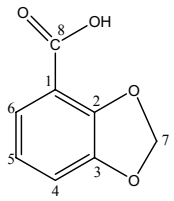

Figure 1. The structure and numbering scheme of 2,3-methylenedioxybenzoic acid.

Experimental

Materials and Instrumentation

Melting point was determined in a capillary tube using an MPD Mitamura Riken Kogyo (Japan) electrothermal melting point apparatus. The infrared spectra were recorded as KBr pellets on a Bio-Rad Excalibur FT-IR, model FTS 300 MX spectrophotometer (USA), in the frequency range of 4000-400 cm^{-1}. Multinuclear NMR (^{1}H, ^{13}C, ^{119}Sn) spectra were recorded on a Bruker ARX 300 MHz, FT-NMR spectrometer using $CDCl_3$ as an internal reference for [δ^1H ($CDCl_3$) = 7.25 and δ^{13}C ($CDCl_3$) = 77.0]. Elemental analyses were carried out with a Perkin-Elmer 2400 Series II instrument. Mass spectral datum was taken on a MAT-312 Mass spectrometer. X-ray single crystal analysis was made on a Nonius Kappa CCD diffractometer with graphite monochromated MoK_α radiation. The reaction was carried out under an anhydrous atmosphere. Solvents were purified and dried before use.[16] All the chemicals, purchased from Aldrich, were of analytical grade and used without further purification.

Syntheses

Synthesis of 2,3-methylenedioxybenzoic acid (HL)

Finely powdered *o*-piperonal (5.0 g, 3.3 mmol) was added to water (300 mL) and the mixture was heated to 40-50 °C and stirred mechanically in a round bottom flask (500 mL). To this, potassium permanganate solution (12.5 g, 10%) run slowly until the odor of piperonal is no longer perceptible. Excess of the latter was destroyed by the addition of a little alcohol, the mixture was filtered hot, and the filtrate was acidified with dilute hydrochloric acid (5 mL, 15%). The piperonylic acid, which was separated as solution when

cooled, was practically pure. After the preparation of acid, it was converted to its sodium salt by dissolving the acid (3.5 g, 2.1 mmol) in absolute ethanol (10 mL) and treating it with sodium bicarbonate (1.77 g, 2.1 mmol). After 1 h of stirring, the mixture of water and ethanol was evaporated by rotary evaporator. The solid product, which was dried over CaO/P_2O_5, was obtained. Yield (4.5 g, 95%), mp 300 °C. Analysis: Calculated for $C_8H_5O_4Na$: C, 51.06; H, 2.65. Found: C, 51.12; H, 2.70. ^{1}H–NMR ($CDCl_3$, ppm), $^nJ(^1H, ^1H)$, 6.20 (H-4, t, (7.8)), 7.23 (H-5, dd, (1.2, 7.8)), 7.34 (H-6, dd, (1.2, 7.8)), 6.01 (H-7, s). ^{13}C–NMR ($CDCl_3$, ppm), 112.79 (C-1), 148.72 (C-2), 149.11 (C-3), 112.32 (C-4), 121.14 (C-5), 123.85 (C-6), 102.04 (C-7), 173.72 (C-8). IR (KBr, cm^{-1}), 1679 (υ_{asym} COO), 1400 (υ_{sym} COO), 279 ($\Delta\upsilon$).

Synthesis of $Me_3Sn[C_8H_5O_4]$ (1)

$C_8H_5O_4Na$ (1.0 g, 5.31 mmol) and Me_3SnCl (1.06 g, 5.31 mmol) were added to 100 cm^3 of dry toluene in 1:1 ratio in a round-bottom 2-necked flask (250 mL). The mixture was refluxed for 5-6 h. After cooling, sodium chloride was filtered off and filtrate was evaporated by rotary evaporator under reduced pressure. The solid product obtained was recrystallized from chloroform and *n*-hexane (4:1). Yield (1.1 g, 75%), mp 150-151 °C. Analysis: Calculated for $C_{11}H_{14}O_4Sn$: C, 40.12; H, 4.25. Found: C, 40.26; H, 4.32. ^{1}H–NMR ($CDCl_3$, ppm), $^nJ(^1H, ^1H)$, $^nJ[^{119}Sn, ^1H]$), 6.83 (H-4, t (8.0)), 7.33 (H-5, dd (1.3, 7.9)), 7.62 (H-6, dd (1.3, 7.9)), 6.01 (H-7, s), 0.65 [58.0] (s, Sn-CH_3). ^{13}C–NMR ($CDCl_3$, ppm), 114.47 (C-1), 148.47 (C-2), 148.51 (C-3), 111.71 (C-4), 120.83 (C-5), 123.72 (C-6), 101.67 (C-7), 178.93 (C-8), 14.02 [394.8] (Sn-CH_3). IR (KBr, cm^{-1}), 1567 (υ_{asym}COO), 1396 (υ_{sym}COO), 171 ($\Delta\upsilon$), 552 (υSn-C), 430 (υSn-O).

EIMS major positive ions m/z, $[(CH_3)_3Sn(C_7H_5O_2COO)]^{+\cdot}$ 330(7.69), $[(CH_3)_3Sn(C_5H_3COO)]^{+\cdot}$ 272(100), $[Sn(C_6H_5COO)]^+$ 241(69.85), $[(CH_3)_3Sn]^+$165(42.98), $[(CH_3)_2Sn]^{+\cdot}$ 150(39.88), $[CH_3Sn]^+$ 135(5.30), $[Sn]^+$ 120(10.55), $[SnH]^+$ 121(9.20). δ (^{119}Sn) NMR ($CDCl_3$, ppm), +155.37.

X-Ray Crystallography

X-ray crystallographic data were collected on a Nonius Kappa CCD diffractometer. Correction for semiempirical from equivalents was applied, and the structure was solved by direct methods and refined by a full-matrix least squares procedure based on F^2 using the SHELX97 Program System.[17] All data were collected with graphite-monochromated M_oK_α radiation (λ = 0.71073 Å) at 173 K. An ORTEP drawing [18] showing the atom-labeling scheme is presented in Figure 2. The structure was solved by the direct method and expanded using Fourier-techniques. Methyl H atoms were included in calculated positions using the riding method, with C-H distances of 0.95 Å and torsion angles optimized to give the best fit to the electron density.

Results and Discussion

Synthesis

The organotin(IV) derivative was obtained by heating at reflux, the stoichiometric amount of sodium salt of 2,3-methylenedioxybenzoic acid with the corresponding trimethyltin(IV) chloride in anhydrous toluene [Eq. (**1**)].

$$Me_3SnCl + NaL \longrightarrow Me_3SnL + NaCl \quad (1)$$

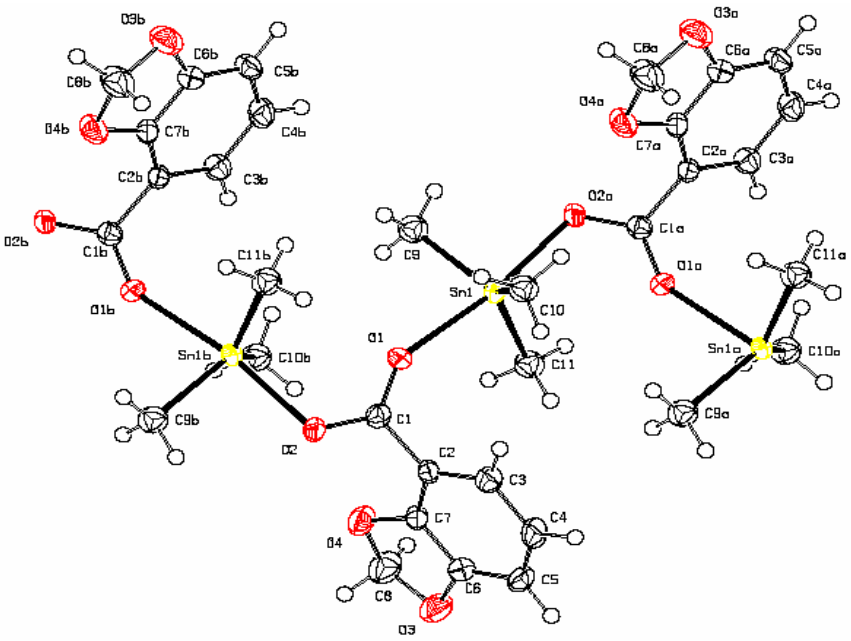

Figure 2. An ORTEP [18] drawing of complex **1**. Displacement ellipsoids are drawn at 50% probability level.

IR spectra

The infrared spectra of the compound have been recorded in the range of 4000-400 cm^{-1} using KBr optics. Tentative assignment has been made on the basis of earlier work and important data are listed in the Experimental section. The absorption of interest is those of carbonyl υ(C=O), υ(Sn-C), and υ(Sn-O). In the spectrum of the complex, medium to weak band in the region 430 cm^{-1} is assigned to Sn-O [19]and that in the region of 552 cm^{-1} is assigned to Sn-C bond [20].

As we know that the vacant 5d orbitals on tin tends to give higher coordination with ligands having a lone pair of electrons, the IR stretching vibration frequencies of carbonyl group in organotin carboxylates are important for determining their structures. When the structure changes from 4 to 5 to 6 coordinated symmetry, the asymmetric absorption vibration (υ_{asym}) of the carbonyl groups decreases and the symmetric absorption vibration frequencies (υ_{sym}) increases so that the difference $\Delta\upsilon$ decreases.

In organotin compound, the $\Delta\upsilon$ is less than 200 cm^{-1}, which indicates a bidentate coordination mode for the carboxylate ligand. These results suggest that the tin atom in triorganotin specie approaches 5 coordination.

NMR spectroscopy

^{1}H–NMR

^{1}H–NMR data of the sodium salt of ligand acid and its organotin derivative in $CDCl_3$ solution are given in the Experimental section. The methyl protons of **1** appear as sharp singlet at 0.65 ppm with $^nJ[^{119}Sn\text{-}^1H]$ coupling of [58.0]. The proton H-4 give triplet at 6.83 with $^3J(^1H,^1H)$ 8.0, H-5 and H-6 give the doublet of doublet at 7.33 and 7.62 ppm with $^3J(^1H,^1H)$ (1.3, 7.9). While the proton H-7 gives the singlet at 6.01 ppm.

^{13}C–NMR

^{13}C–NMR spectral data in $CDCl_3$ solution of the sodium salt of ligand acid and its trimethyltin(IV) derivative are given in the Experimental section. The number of signals found corresponds with the presence of magnetically nonequivalent carbon atoms, which were assigned analogues as model compounds.[21] The position of carboxylate carbon moves to lower field in the complex as compared with the ligand acid, indicating the participation of the carboxylic group in coordination to tin(IV).[22] The C-7 of methylene group does not show any shift in the complex, which means that this site is not involved in bonding to tin rather the bonding is through –COO group.

The identification of alkyl carbons in the complex confirms complexation, and the complete assignment of the signals confirms the identity of the compound. The coupling constant $^{n}J[^{119}\text{Sn},^{13}\text{C}]$ and the value of C-Sn-C bond angle are the most important indicators for the structural elucidation of organotin (IV) carboxylates.[23] In order to gain further information about the possible coordination geometries in solution, a close examination of the $^{1}J[^{119}\text{Sn}\text{-}^{13}\text{C}]$ and $^{2}J[^{119}\text{Sn}\text{-}^{1}\text{H}]$ 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.[24] Data are summarized in Table 1. As indicated by Nadvornik et al.,[24] $^{1}J[^{119}\text{Sn}\text{-}^{13}\text{C}]$ coupling constant is quite amenable for making predictions about the geometry around the tin atom. For the trimethyltin(IV) derivative, with the $^{1}J[^{119}\text{Sn}\text{-}^{13}\text{C}]$ value being 394.8 Hz and by the use of the Holecek and Lycka equation,[22] a C-Sn-C value of 111.4° was calculated, which corresponds to a quasi-tetrahedral geometry in $CDCl_3$ solution. The geometric data calculated, as just described, are consistent with tetrahedral geometry for the triorganotin(IV) species, i.e. monomer in solution.

Table 1. C-Sn-C angles (°) calculated from NMR.

Compound No.	$^{1}J[^{119}\text{Sn}\text{-}^{13}\text{C}]$ (Hz)	$^{2}J[^{119}\text{Sn}\text{-}^{1}\text{H}]$ (Hz)	C-Sn-C angles (°) Calculated from	
			^{1}J	^{2}J
(**1**)	394.8	58.0	111.4	111.0

^{119}Sn–NMR

^{119}Sn–NMR spectra were recorded and the chemical shift for the trimethyltin(IV) derivative lies in the range of tetrahedral geometry. Data are given in the Experimental section. This value strongly dependent upon the nature and the orientation of organic groups bonded to tin. The shift observed in the above case can be explained quantitatively in terms of an increase in electron density on the tin atom as the coordination number increases.[25]

Mass spectrometry

The 70 eV mass spectral data for the reported compound are given in Experimental section. The molecular ion peak is not observed in the orgnotin(IV) carboxylate. The fragment ions are in good agreement with the expected structures of the compound. The base peak for compounds (**1**) is due to $[(CH_3)_3SnC_5H_3COO]^+$ fragment. Other fragments observed are quite intense as given in the Experimental section.

Crystal structure

Figure 2 shows the molecular structure and atom numbering scheme of complex (**1**). The crystal data and intermolecular bond distances and angles are given in Tables 2 and 3, respectively.

Table 2. Crystal data and structure refinement parameters for complex **1**.

Empirical formula	$C_{11}H_{14}O_4Sn$
Formula weight	328.91
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimension	
a (Å)	10.7071(7)
b (Å)	9.9808(10)
c (Å)	12.4504(8)
α (^{o})	90
β (^{o})	111.976(7)
γ (^{o})	90
V (Å^3)	1233.84(17)
Z	4
Dc (gcm^{-3})	1.771
Crystal size (mm)	0.50 x 0.30 x 0.10
F(000)	648
Total reflections	2235
Independent reflections	1876
All indices (all data)	$R_1 = 0.0465$, $WR_2 = 0.1105$
Final R indices [I>2σ(I)]	$R_1 = 0.0378$, $WR_2 = 0.0945$
Goodness of fit	1.096
θ Range for data collection (^{o})	2.00-25.85
Date/restrains/parameters	2235/0/136

The crystal structure of compound **1** shows that the tin atom is coordinated with 2 oxygen atoms of 2,3-methylenedioxy benzoate ligand via carboxylate moieties and acquires a polymeric chain structure. The Sn1-O1 2.376(3) Å bond is significantly different from Sn1-O2 2.217(3) Å bond indicating that the former is a covalent bond and the latter is acting as a weak coordinate covalent bond corresponding to an anisobidentate ligand. The Sn-C distances (Table 3) lie in the range reported earlier for the related compounds.[26] The angles C10-Sn1-C9 [118.6(2)^o], C11-Sn1-C9 [116.0(2)^o], and C10-Sn1-C11 [124.5(2)^o] slightly deviate from the ideal value of 120^o. The 5 coordination around Sn1 can be described as a trigonal pyramid. Further information can be obtained by estimating the structural index τ,[27] which represent the relative amount of trigonality (square pyramid, $\tau = 0$; trigonal pyramid $\tau = 1$; $\tau = (\beta - \alpha)/60^o$, where α and β being the 2 largest angles [β (C10-Sn1-C11) = 124.5(2)^o and α (C10-Sn1-C9 = 118.6(2)^o] around the central atom. The value of τ is 0.098(1). The coordination geometry of Sn1 is, therefore, best described as a trigonal pyramid and the total puckering amplitude Q_T is 0.49(1) Å.[28]

Table 3. Selected bond lengths (Å) and bond angles (^{o}) for complex **1**.

C1-O1	1.256(6)
C1-O2	1.264(6)
C1-C2	1.496(6)
C2-C7	1.373(7)
Sn1-O1	2.376(3)
C3-C4	1.403(8)
C11-Sn1	2.122(5)
C10-Sn1	2.122(6)
C9-Sn1	2.128(5)
Sn1-O2	2.217(3)
C10-Sn1-C11	124.5(2)
C10-Sn1-C9	118.6(2)
C11-Sn1)-C9	116.0(2)
C10-Sn1-O2	89.02(18)
C11-Sn1-O2	100.21(17)
C9-Sn1-O2	89.92(18)
C10-Sn1-O1	84.84(17)
C11-Sn1-O1	91.34(17)
C9-Sn1-O1	84.45(18)
O2-Sn1-O1	168.43(12)
C1-O1-Sn1	145.0(3)

All this description suggests the trigonal bipyramidal geometry with O1 and O2 in the apical positions and the 3 methyl groups in the equatorial positions. The sum of the equatorial angles is 359.1^o and the tin atom lies 0.9 (e.s.d) Å out of equatorial plane towards the more strongly bonded O1 atom. This shows the slightly distorted bipyramidal geometry, which is compatible with the earlier reports.[29,30] The central trimethyltin group bridges 2 neighboring 2,3-methylenedioxy benzoate ligands via the carboxylate moieties to form a 1-dimensional polymeric structure.

Microbial Assay

Antitumor potato disc assay

Organotin(IV) complex (**1**) was screened against the bacterial strain At10 with the concentration of 1000 ppm for the incubation period of 21 days to check the antitumor potato disc activity[31] by using the following formula:

% inhibition of tumors = 100-ns/nc × 100

ns = Average number of tumors in sample

nc = Average number of tumors in control

Fifteen replicates were used to study this activity. The reported complex shows the significant antitumor activity. The data are given in Table 4.

Table 4. Antitumor activity for complex **1.**

Comp. No.	Average number of tumors +SE	% inhibition of tumors
(**1**)	0.0±0.00	100
-ve Control	7.6±0.68	

Conclusions

Organotin(IV) complex of 2,3-methylenedioxybenzoic acid has been synthesized in anhydrous toluene and characterized by various analytical and spectroscopic techniques. Detailed studies of the reported complex in solution state indicate that the structure is tetrahedral for triorganotin(IV) complex. In the solid state, triorganotin(IV) complex shows the distorted trigonal bipyramidal geometry. Antitumor activity data have shown that the reported complex has a significant antitumor activity against the tested bacterial strain At10.

Supplementary Material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 623840. Copies of these information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CBZ 1EZ, UK (Fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk).

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