Research Article

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Synthesis, crystal structure and biological activity of triphenyltin 4-acetylphenolate

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Abstract: Triphenyltin 4-acetylphenolate, 4-$CH_3COC_6H_4OSnPh_3$ (1), has been synthesized and characterized by elemental analysis, IR, NMR (^1H, ^{13}C and ^{119}Sn) spectra, and X-ray single crystal diffraction. Compound **1** possesses a *trans*-C_3SnO_2 trigonal bipyramidal geometry with the axial positions occupied by the phenolate oxygen and carbonyl oxygen of an adjacent molecule and form an one-dimensional infinite chain. Bioassay results have shown that the compound has good in vitro anti-bacterial and anti-tumor activities.

Supporting information: X-Ray (CIF file)

Keywords: *organotin, 4-acetylphenol, crystal structure, biological activity*

1. INTRODUCTION

Organotin compounds have found wide agricultural and industrial applications [1]. Recent studies have shown their relatively high *in vitro* anti-tumor activity [1-3]. The organotin moiety and the ligand appear to play an important role in determining their anti-tumor activity [2]. Some carboxylato (RCOO-) ligands with different structural features such as aminobenzoic acids [4], pyridinedicarboxylic acid [5], 4-ketopimelic acid [6], cyclohexanedicarboxylic acid [7], and ferrocenecarboxylic acid [3] have been widely used for the design and synthesis of the organotin carboxylates. However, few attentions were paid to the phenolato (ArO-) ligands in the study on the synthesis and biological activity of organotin compounds [2,8]. In this paper, we have synthesized a new organotin phenolate, triphenyltin 4-acetylphenolate, 4-$CH_3COC_6H_4OSnPh_3$ (**1**), and determined its *in vitro* anti-bacterial and anti-tumor activities.

2. EXPERIMENTAL

All chemicals were of reagent grade and were used without further purification. Carbon and hydrogen analyses were determined using a Perkin Elmer 2400 Series II elemental analyzer. IR spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs in the range 4000-400 cm^{-1}. NMR spectral data were collected using a Bruker Avance DPX300 NMR spectrometer with $CDCl_3$ as solvent and TMS as internal standard for ^1H and ^{13}C and $SnMe_4$ as external standard for ^{119}Sn.

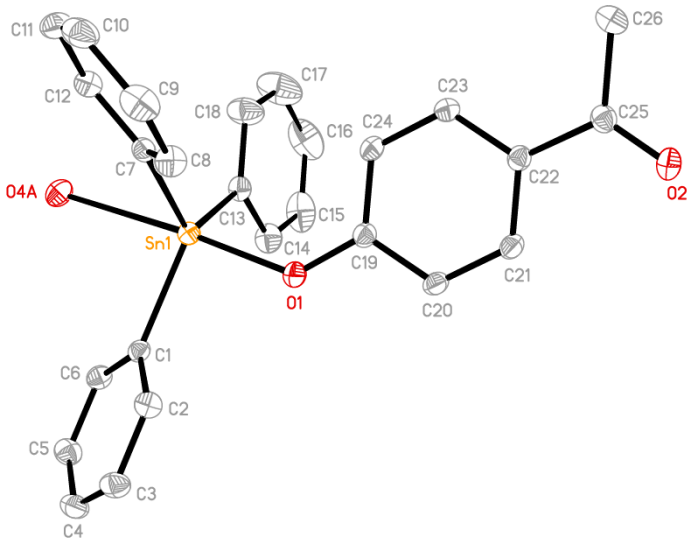

Figure 1. The coordination geometry of the tin atom; symmetry code A: *x*+1, *y*, *z*+1; all hydrogen atoms are omitted for clarity.

2.1 Synthesis of 4-$CH_3COC_6H_4OSnPh_3$ (1)

To a suspension of triphenyltin hydroxide (1.10 g, 3 mmol) in 50 ml of toluene was added 4-acetylphenol (0.41 g, 3 mmol). Under electromagnetic stirring, the reaction mixtures were refluxed for 5 h with a Dean–Stark separator, and then allowed to cool to room temperature. The solution was filtered and the solvent was removed under reduced pressure by a rotary evaporator. The resulting white solid was recrystallized from chloroform-hexane (1:2). Yield 1.25 g (86%), m.p. 133.2-134.4°C. Anal. Found: C, 64.26; H, 4.38. Calcd for $C_{26}H_{22}O_2Sn$: C,

64.37; H, 4.57%. Selected IR (KBr) cm^{-1}: 1638 (C=O), 1296 (C-O), 538 (Sn-O). ^{1}H NMR δ: 7.96 (d, 2H, J = 8.0 Hz, H-3 of C_6H_4), 7.68-7.64 (m, 6H, $^3J(^{119}Sn\text{-}H)$ = 54.0 Hz, *o*-H of Ph), 7.24-7.48 (m, 9H, *m*- and *p*-H of Ph), 6.92 (d, 2H, J = 8.0 Hz, H -2 of C_6H_4), 2.56 (s, 3H, CH_3). ^{13}C NMR δ: 200.01 (C=O), 162.63(C-1), 137.68 ($^1J(^{119}Sn\text{-}^{13}C)$ = 642 Hz, C-*i* of PhSn), 136.96 ($^2J(^{119}Sn\text{-}^{13}C)$ = 48 Hz, C-*o* of PhSn), 131.93(C-3), 130.41 ($^4J(^{119}Sn\text{-}^{13}C)$ = 14 Hz, C-*p* of PhSn), 129.99 (C-4), 129.01($^3J(^{119}Sn\text{-}^{13}C)$ = 64 Hz, C-*m* of PhSn), 114.88 (C-2), 26.37(CH_3). ^{119}Sn NMR δ: −105.9.

2.2 X-ray crystallography

The colorless single crystal of **1** was obtained from chloroform-hexane (1:1, V/V) by slow evaporation at room temperature. Diffractions measurements were performed on a Bruker Smart Apex imaging-plate area detector fitted with graphite monochromatized Mo-Ka radiation (0.71073 Å) using the *j* and *w* scan technique. The structures were solved by direct-methods and refined by a full-matrix least squares procedure based on F^2 using SHELXL-97 [9]. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions. In **1**, the C atoms of a phenyl group (C39-C44) are disordered over two positions, and their site occupancies were refined to 0.542(4):0.458(4). Crystal data, collection procedures and refinement results are summarized in Table 1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 993922.

Table 1. Crystallographic and refinement data of **1**

Empirical formula	$C_{26}H_{22}O_2Sn$
Formula weight	485.13
Crystal system	triclinic
Space group	*P*-1
a /Å	9.7515(7)
b /Å	14.1678(10)
c /Å	16.1833(11)
α/(°)	86.723(1)
β/(°)	87.660(1)
γ/(°)	80.874(2)
Volume /Å^3	2202.8(3)
Z	4
D_c / (g×cm^{-3})	1.463
μ / mm^{-1}	1.178
(000)	976
Crystal size / mm	0.15 ´ 0.32 ´ 0.44
θ range /(°)	1.26 to 26.00
Tot. reflections	17161
Uniq. reflections	8535 (R_{int} = 0.0199)
Reflections with $I>2\sigma(I)$	7331
GOF on F^2	1.027
R indices [$I>2\sigma(I)$]	*R*=0.0276, *wR*=0.0721
R indices (all data)	*R*=0.0332, *wR*=0.0756
$\Delta\rho_{min}$, $\Delta\rho_{max}$/(e· Å^{-3})	-0.410, 0.442

2.3 Anti-bacterial activity

The anti-bacterial activity of **1** against *Escherichia coli* and *Staphylococcus aureus* was determined by microcalorimetric method [10]. A 2277 Thermal Activity Monitor (Thermometric AB, Sweden) was used to determine the power-time curves of bacterial growth at 310K. Based on the data of power-time curves, the growth rate constants were calculated [10]. The relationship between the growth rate constants and concentration of organotin medicine was fitted. When the growth rate constant is 0, the minimum inhibitory concentration (MIC) was confirmed.

2.4 *In vitro* anti-tumor activity

Anti-tumor activity was assayed against two human tumor cell lines, MCF-7 (mammary tumor cell) and CoLo 205 (colon carcinoma cell). The sample was prepared by dissolving compound **1** in DMSO and by diluting the solution obtained with water. In the assays, the final concentration of DMSO was less than 0.1% (this concentration was found to be non-cytotoxic against tumor cells.). *In vitro* cytotoxicity of **1** was measured by the MTT assay according to the literature [11]. The dose causing 50% inhibition of cell growth (IC_{50}) was calculated as previously described [12].

3. RESULTS AND DISCUSSION

Compound **1** was prepared by azeotropic removal of water from the reaction between triphenyltin hydroxide and 4-acetylphenol in the molar ratio 1:1 in toluene. The compound is white crystals and soluble in benzene and in common polar organic solvents such as CH_3OH, $CH_3CO\,CH_3$, $CHCl_3$, $CH_3COOCH_2CH_3$.

The infrared spectra of **1** do not show a strong band at ~3200 cm^{-1} assigned to n(OH), indicting the deprotonation of the phenolic oxygen of 4-acetylphenol upon complexation with tin atom [13]. It has further been confirmed by the appearance of a sharp band at 538 cm^{-1} assignable to the Sn-O stretching vibration [13,14]. The stretching vibrations of phenolic C-O and C=O appear at 1296 and 1638 cm^{-1}, respectively. Compared with 4-acetylphenol (1658 cm^{-1}), the n(C=O) band undergoes a shift to lower frequency by 20 cm^{-1}. This indicates that there is carbonyl oxygen atom coordination to tin atom in **1** [15]. The C=O→Sn coordination decreases the double bond characteristic and vibration frequency of C=O. Thus, it may be suggested that the tin atom in **1** is five-coordinated in the solid.

The ^{1}H NMR spectra of **1** show the expected resonances and integration. The signals of phenyl ring (C_6H_4) protons appear as doublets at 7.96 and 6.92 ppm, respectively, and the singlet assigned to CH_3 protons appear at 2.56 ppm. The ^{13}C chemical shift of the carbonyl carbon is 200 ppm. In **1**, the coupling between tin nuclear and carbon can be observed, and the $^1J(^{119}Sn\text{-}^{13}C)$ is 642 Hz. The ^{119}Sn NMR chemical shift and $^1J(^{119}Sn\text{-}^{13}C)$ values may be used to give tentative indications of the environ-

ment around tin atoms [16]. The ^{119}Sn NMR and $^{1}J(^{119}Sn-^{13}C)$ values of **1** indicate that the tin atom is four-coordinated and carbonyl does not coordinate to tin in $CDCl_3$ solution.

The coordination environment of tin atom in the crystal of **1** is shown in Figure 1. The selected bond lengths and bond angles are listed in Table 2. The compound crystallizes with two molecules in the crystallographic asymmetric unit that do not differ from each other significantly, and is a chain polymer associating *via* phenolate oxygen atoms [O(1) and O(3)] and carbonyl oxygen atoms [O(2) and O(4)] in the ligand (Figure 2). The tin atoms in this polymeric structure exist in distorted *trans*-C_3SnO_2 trigonal bipyramidal environment with trigonal plane defined by the three carbon atoms [C(1), C(7), C(13) and C(27), C(33), C (39)] of phenyl groups. The C-Sn-C angles are in the range 115.62(10)-121.27(10)°. The axial positions are occupied by the phenolate O(1), O(3) and carbonyl O(4A) (Symmetry code A: x+1, y, z+1), O(2) of the ligand of an adjacent molecule with the angles O(1)-Sn(1)-O(4A) [175.21(7)°] and O(3)-Sn(2)-O(2) [172.08(7)°]. The bond lengths of the coordinated Sn(1)-O(4A) [2.703(2) Å] and Sn(2)-O(2) [2.651(2) Å] are significantly longer than those of the covalent Sn(1)-O(1) (2.0573(17) Å) and Sn(2)-O(3) [2.0622(19) Å], so that the Sn(1) and Sn(2) atoms are displaced out of the C_3 trigonal plane of the *trans*-C_3SnO_2 trigonal bipyramidal polyhedron in the direction of O(1) and O (3) by 0.229(2) and 0.300(2) Å, respectively. There are few examples of triorganotin systems having $ArC(CH_3)=O\rightarrow Sn$, and a

Table 2. Selected bond lengths (Å) and angles (°) of **1**

Sn(1)-C(1)	2.125(2)	Sn(2)-C(27)	2.115(2)
Sn(1)-C(7)	2.139(2)	Sn(2)-C(33)	2.118(3)
Sn(1)-C(13)	2.1185(15)	Sn(2)-C(39)	2.121(3)
Sn(1)-O(1)	2.0573(17)	Sn(2)-O(2)	2.651(2)
Sn(1)-O(4A)	2.703(2)	Sn(2)-O(3)	2.0622(19)
O(1)-Sn(1)-C(13)	98.24(8)	O(3)-Sn(2)-C(27)	105.78(8)
O(1)-Sn(1)-C(1)	91.58(8)	O(3)-Sn(2)-C(33)	93.63(10)
C(13)-Sn(1)-C(1)	120.14(8)	C(27)-Sn(2)-C(33)	117.17(10)
O(1)-Sn(1)-C(7)	98.60(9)	O(3)-Sn(2)-C(39)	95.35(10)
C(13)-Sn(1)-C(7)	120.19(8)	C(27)-Sn(2)-C(39)	115.62(10)
C(1)-Sn(1)-C(7)	116.24(9)	C(33)-Sn(2)-C(39)	121.27(10)
O(1)-Sn(1)-O(4A)	175.21(7)	O(3)-Sn(2)-O(2)	172.08(7)
C(13)-Sn(1)-O(4A)	80.74(8)	C(27)-Sn(2)-O(2)	81.53(8)
C(1)-Sn(1)-O(4A)	84.94(8)	C(33)-Sn(2)-O(2)	80.09(9)
C(7)-Sn(1)-O(4A)	85.91(8)	C(39)-Sn(2)-O(2)	83.95(9)

Symmetry code A: x+1, y, z+1.

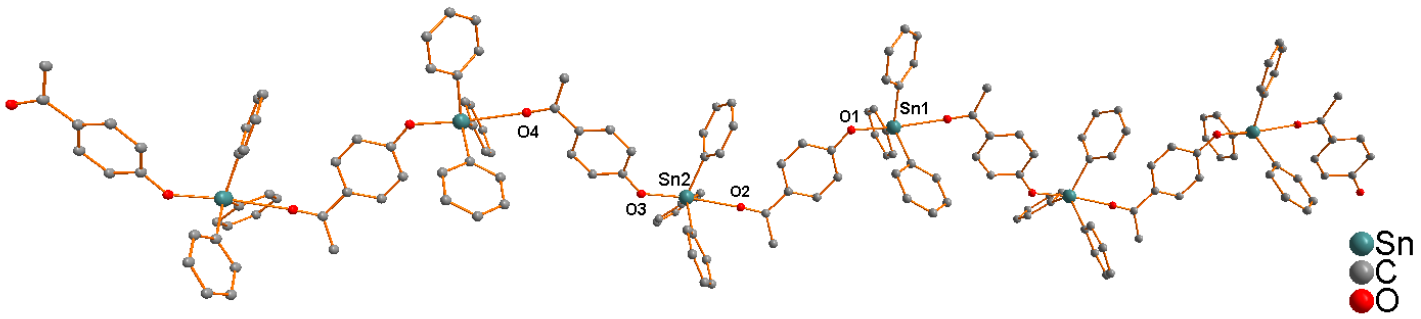

Figure 2. The 1D zigzag chain formed in **1**; all hydrogen atoms have been omitted for clarity.

similar example is (2,6-dimethoxyflavone)triphenyltin chloride which features the long O→Sn bond (2.485(5) Å) [17]. The O→Sn bond length in **1** is longer than that in the above-mention the compound, which may be due to the difference from phenolato and chlorine bonded on the tin. In the one-dimensional zigzag chain, the distance of between two tin atoms is Sn(1)···Sn(2) 10.132(2) Å and Sn(1)···Sn(2A) 10.389(2) Å, respectively (Figure 2). The Sn–C lengths from 2.115(2) to 2.139(2) Å are similar to those found in the five-coordinated chain triphenyltin compounds such as $Ph_3SnOC_6H_4CHO$-2 [15], and Ph_3SnO-$COCCH_3$ [18].

The anti-bacterial activity of **1** and the reference drug (sodium penicillin G) was shown in Table 3. The results indicated that the compound possesses considerable anti-bactericidal activities and the activity against *S. aureus* is better than against *E. coli*. The results of *in vitro* anti-tumor assay against MCF-7 and CoLo205 were shown in Table 4.

Compound **1** displayed the high *in vitro* anti-tumor activities, which were more active than clinically widely used *cis*-platin did. Although these results are preliminary, the compound as the efficient cytostatic agents is worth further studying.

Table 3. Antibacterial activity (MIC, mg/ml) of **1**

Compound	*E. coli*	*S. aureus*
1	9. 58±0.44	0.23±0.02
Sodium penicillin G	15.11±0.63	1.79±0.06

Table 4. *In vitro* antitumor results (IC_{50}, mg/ml) of **1**

Compound	MCF-7	CoLo205
1	0.44±0.06	0.73±0.09
cis-platin	5.46±0.35	4.61±0.86

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