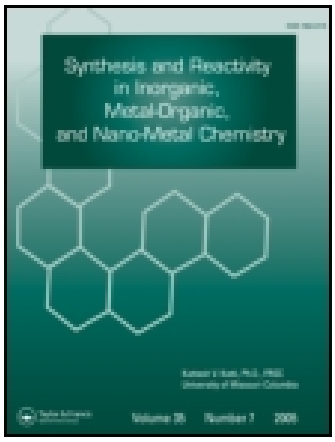

Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

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Synthesis, Characterization, and In Vitro Cytotoxicity of Triorganotin 3,5-Di-tert-butyl-4-hydroxybenzoates

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Synthesis, Characterization, and *In Vitro* Cytotoxicity of Triorganotin 3,5-Di-*tert*-butyl-4-hydroxybenzoates

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The triorganotin 3,5-di-*tert*-butyl-4-hydroxybenzoates, 3,5-(*t*-Bu)$_2$-4-HO-C$_6$H$_2$COOSnR$_3$ (R = *c*-C$_6$H$_{11}$, 1; C$_6$H$_5$, 2; C$_6$H$_5$CH$_2$, 3; C$_6$H$_5$C(CH$_3$)$_2$CH$_2$, 4), have been synthesized and characterized by elemental analysis, IR, and ^{1}H and ^{13}C NMR spectra. The crystal structures of 1 and 4 have been determined by X-ray single crystal diffraction and show that the tin atom possesses a distorted tetrahedral geometry. Intermolecular O−H···O hydrogen bond in 1 connects neighboring molecules into a cyclic tetramer. The *in vitro* cytotoxicity of the compounds against the human tumor cell lines A549 was found to be higher than that of *cis*-platin used clinically.

Keywords crystal structure, cytotoxicity, organotin carboxylate, 3, 5-di-*tert*-butyl-4-hydroxybenzoic acid

INTRODUCTION

Organotin carboxylates have been receiving increasing attention, not only because of their structural interest but also because of their varied applications.[1] Some examples find wide use as catalysts and stabilizers, and certain derivatives are used as biocides, antifouling agents, and wood preservatives.[2,3] In recent years, investigations have been carried out to test their antitumor activity and it has been observed that several triorganotin species show potential as antineoplastic agents.[4,5] In general, the organotin moiety, ligand (carboxylic acid), and coordination number of the tin atom appear to play an important role in anti-tumor activity.[5] To synthesize new organotin esters of carboxylic acid having biological activity is a optimized strategy to find the organotin anti-tumor agents. 3,5-di-*tert*-butyl-4-hydroxybenzoic acid is an important pharmaceutical intermediate,[6,7] and its organotin esters are not reported in the literature, to our knowledge. In order to explore the chemistry and cytotoxicity of triorganotin esters of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid, we have synthesized and characterized some triorganotin 3,5-di-*tert*-butyl-4-hydroxybenzoates (Scheme 1).

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EXPERIMENTAL

Materials and Physical Measurements

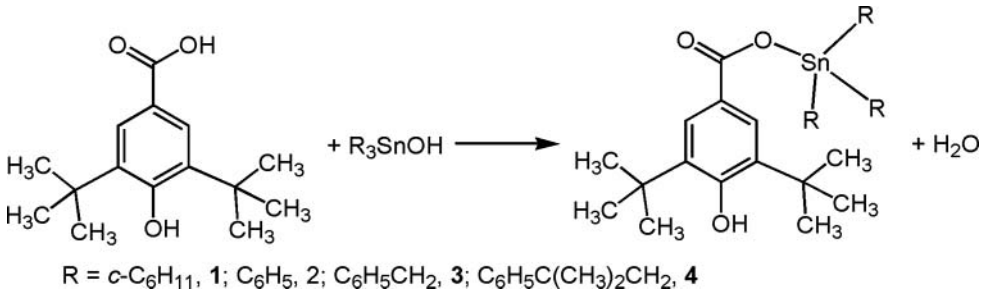
All chemicals were of reagent grade and were used without further purification. Carbon and hydrogen analyses were determined using a Perkin-Elmer 2400 Series II elemental analyzer. Melting points were measured on a WRS-1A digital melting point. IR spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs in the range 4000–400 cm^{-1}. ^{1}H and ^{13}C NMR spectral data were collected using a Bruker Avance DMX500 NMR spectrometer with $CDCl_3$ as solvent and TMS as internal standard.

Synthesis of the Title Complexes 1–4

To a suspension of triorganotin hydroxide (2 mmol) in 50 ml of toluene was added 3,5-di-*tert*-butyl-4-hydroxybenzolic acid (0.50 g, 2 mmol). The reaction mixtures were heated under reflux 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. The resulting white solid was recrystallized from ethanol. The yield, m.p., and spectral data for compounds **1–4** are as follows.

3,5-(*t*-Bu)$_2$-4-HO-C$_6$H$_2$COOSnCy$_3$ (**1**)
Yield 82%, m.p. 131–132°C. Anal. Found: C, 66.06; H, 7.43. Calcd. for C$_{33}$H$_{54}$O$_3$Sn: C, 66.33; H, 7.65%. IR (KBr) cm^{-1}: 3600, 3367 (O-H), 3050 (Ar-H), 2921, 2848 (C-H), 1620 [ν(COO$^-$)$_{as}$)], 1598, 1565, 1445, 1422 (Ar), 1332 (vs) (ν(COO$^-$)$_s$), 1257, 1230 (C-O). ^{1}H NMR ($CDCl_3$) δ: 7.96 (2H, s, Ar-H), 5.56 (1H, s, OH), 1.46 (18H, s, 6CH$_3$), 1.98–1.96 (9H, m), 1.75–1.63 (15H, m), 1.37–1.32 (9H, m) (Cy). ^{13}C NMR ($CDCl_3$) δ: 172.12 (C = O), 157.64, 135.84, 127.60, 124.22 (Ar), 34.66 (***C***(CH$_3$)$_3$), 33.89 (^1J(^{13}C-^{119}Sn) = 336 Hz, C-α), 31.18 (^2J(^{13}C-^{119}Sn) = 15 Hz, C-β), 30.48 (C(***C***H$_3$)$_3$), 29.02 (^3J(^{13}C-^{119}Sn) = 64 Hz, C-γ), 27.04 (C-δ).

3,5-(*t*-Bu)$_2$-4-HO-C$_6$H$_2$COOSnPh$_3$ (**2**)



SCH. 1. Preparation of triorganotin 3,5-di-*tert*-butyl-4-hydroxybenzoates **1**–**4.**

Yield 78%, m.p. 178–179°C. Anal. Found: C, 65.86; H, 5.89. Calcd. for $C_{33}H_{36}O_3Sn$: C, 66.13; H, 6.05%. IR (KBr) cm^{-1}: 3598 (O-H), 3067, 3056 (Ar-H), 2958, 2872 (C-H), 1614 ($\nu(COO^-)_{as}$), 1595, 1565, 1480, 1430 (Ar), 1337 ($\nu(COO^-)_s$), 1262, 1239(C-O). ^{1}H NMR ($CDCl_3$) δ: 8.00 (2H, s, Ar-H), 7.79 (6H, dd, J = 2.4, 7.4 Hz, $J(^{119}Sn\text{-}H)$ = 65.5 Hz, H-2 in Ph), 7.47–7.44 (9H, m, H-3 and H-4 in Ph), 5.63 (1H, s, OH), 1.45 (18H, s, $6CH_3$). ^{13}C NMR ($CDCl_3$) δ: 171.56 (C = O), 157.58, 135.87, 127.61, 124.34 (Ar), 137.84 ($^2J(^{13}C\text{-}^{119}Sn)$ = 47 Hz, *o*-C in Ph), 137.17 ($^1J(^{13}C\text{-}^{119}Sn)$ = 632 Hz, *i*-C in Ph), 130.55 ($^4J(^{13}C\text{-}^{119}Sn)$ = 12 Hz, *p*-C in Ph), 128.86 ($^3J(^{13}C\text{-}^{119}Sn)$ = 62 Hz, *m*-C in Ph), 34.72 ($\boldsymbol{C}(CH_3)_3$), 30.48 ($C(\boldsymbol{C}H_3)_3$).

3,5-(*t*-Bu)$_2$-4-HO-$C_6H_2COOSn(CH_2Ph)_3$ (**3**)

Yield 72%, m.p. 104–105°C. Anal. Found: C, 67.56; H, 6.48. Calcd. for $C_{36}H_{42}O_3Sn$: C, 67.41; H, 6.60%. IR (KBr) cm^{-1} 3607 (O-H), 3057 (Ar-H), 2957, 2872 (C-H), 1624 ($\nu(COO^-)_{as}$), 1596, 1492, 1452 (Ar), 1323 ($\nu(COO^-)_s$), 1259, 1237(C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.92 (2H, s, Ar-H), 7.15 (6H, t, J = 7.6 Hz, H-3 in Ph), 7.04 (3H, t, J = 7.3 Hz, H-4 in Ph), 6.82 (6H, d, J = 7.3 Hz, H-2 in Ph), 5.66 (1H, s, OH), 2.68 (6H, s, $J(^{119}Sn\text{-}H)$ = 71.0 Hz, CH_2Sn) 1.49 (18H, s, $6CH_3$). ^{13}C NMR ($CDCl_3$) δ: 171.96 (C = O), 157.88, 135.92, 127.66, 124.34 (Ar), 138.36, 129.32, 128.94, 124.88 (Ph), 34.74 ($\boldsymbol{C}(CH_3)_3$), 30.46 ($C(\boldsymbol{C}H_3)_3$), 24.49 ($^1J(^{13}C\text{-}^{119}Sn)$ = 366 Hz, CH_2Sn).

3,5-(*t*-Bu)$_2$-4-HO-$C_6H_2COOSn(CH_2C(CH_3)_2Ph)_3$ (**4**)

Yield 83%, m.p. 122–123°C. Anal. Found: C, 70.66; H, 7.89. Calcd. for $C_{45}H_{60}O_3Sn$: C, 70.41; H, 7.88%. IR (KBr) cm^{-1}: 3623 (O-H), 3052 (Ar-H), 2959, 2926, 2873 (C-H), 1642 ($\nu(COO^-)_{as}$), 1599, 1497, 1443 (Ar), 1328 ($\nu(COO^-)_s$), 1261, 1235(C-O). ^{1}H NMR ($CDCl_3$) δ: 7.98 (2H, s, Ar-H), 7.30 (6H, t, J = 7.4 Hz, H-3 in Ph), 7.22 (3H, t, J = 7.3 Hz, H-4 in Ph), 7.17 (6H, d, J = 7.4 Hz, H-2 in Ph), 5.61 (1H, s, OH), 1.51 (18H, s, $6CH_3$), 1.28 (18H, s, $6CH_3$), 1.27 (6H, s, $J(^{119}Sn\text{-}H)$ = 50.8 Hz, $(CH_2)_3Sn$).^{13}C NMR ($CDCl_3$) δ: 171.25 (C = O), 157.52, 135.46, 127.80, 124.24 (Ar), 151.27, 128.57, 126.02, 125.54 (Ph), 38.00 ($^2J(^{119}Sn\text{-}^{13}C)$ = 20 Hz, Ph-***C***), 37.53 ($^1J(^{119}Sn\text{-}^{13}C)$ = 352 Hz, CH_2Sn), 34.61 ($\boldsymbol{C}(CH_3)_3$), 32.87 ($^3J(^{119}Sn\text{-}^{13}C)$ = 42 Hz, CH_3), 30.49 ($C(\boldsymbol{C}H_3)_3$).

Crystal Structure Determination of 1 and 4

The colorless single crystals of **1** and **4** were obtained from dichloromethane-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-Kα radiation (0.71073 Å) using the φ and ω scan technique. The data reductions were performed using SAINT program and empirical corrections for absorption effects were made using the SADABS program.[8] The structures were solved by direct methods and refined by a full-matrix least squares procedure based on F^2 using SHELXL-97.[8] The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions in the riding model approximation, with C−H = 0.93 Å for aromatic H atoms, C−H = 0.96 Å for methyl H atoms, C−H = 0.97 Å for methylene H atoms, C−H = 0.98 Å for methine H atoms, and O−H = 0.82 Å for hydroxy H atoms. Crystallographic parameters and refinements were listed in Table 1.

In Vitro Cytotoxicity

Cytotoxic activity was assayed against the human tumor cell lines (lung tumor cell). The samples were prepared by dissolving compounds in C_2H_5OH and by diluting the solution obtained with water. In the assays, the final concentration of C_2H_5OH was less than 0.1% (the concentration used was found to be non-cytotoxic against the tumor cell.). *In vitro* cytotoxicities of the compounds were measured by the MTT assay according to the literature.[9] The experiments were repeated three times for each test. The dose causing 50% inhibition of cell growth (IC_{50}) was calculated by NDST software.[10]

RESULTS AND DISCUSSION

Four organotin compounds **1–4** were prepared by azeotropic removal of water from the reaction between the triorganotin hydroxide and 3,5-di-*tert*-butyl-4-hydroxybenzoic acid in the molar ratio 1:1 in toluene (Scheme 1). The compounds are white crystals, air stable and soluble in common organic solvents such as benzene, trichloromethane, acetone, and methanol.

TABLE 1
Crystal data and structure refinement for **1** and **4**

Compound	**1**	**4**
Formula	$C_{33}H_{54}O_3Sn$	$C_{45}H_{60}O_3Sn$
Formula weight	617.45	767.62
Crystal system	Tetragonal	Monoclinic
Space group	$I4_1/a$	$P2_1/c$
a/Å	20.053(2)	14.920(3)
b/Å	20.053(2)	27.862(6)
c/Å	33.815(5)	19.950(4)
β/°	90	90.90(3)
V/Å^{-3}	13598(3)	8292(3)
Z	16	8
Temperature/K	295(2)	295(2)
Crystal size /mm	0.38 × 0.24 × 0.22	0.23 × 0.12 × 0.10
D_c/g·cm^{-3}	1.206	1.230
μ/mm^{-1}	0.779	0.652
$F(000)$	5216	3232
θ_{max}	25.5	25.5
Reflns meas.	36988	60936
Reflns unique, R_{int}	6346, 0.074	14992, 0.048
Reflns with $I>2\sigma(I)$	3094	12232
Weighting scheme	$[\sigma^2(F^2) + (0.0948P)^2]^{-1}$	$[\sigma^2(F^2) + (0.0420P)^2 + 3.4338P]^{-1}$
R indices $[I>2\sigma(I)]$	$R = 0.058$, $wR = 0.151$	$R = 0.045$, $wR = 0.095$
R indices (all data)	$R = 0.129$, $wR = 0.183$	$R = 0.059$, $wR = 0.100$
$\Delta\rho_{min}$, $\Delta\rho_{max}$/e Å^{-3}	–0.470, 0.405	–0.528, 0.546

Crystal Structure of Compounds 1 and 4

The molecular structures of **1** and **4** are shown in Figures 1 and 2, respectively. The selected bond lengths and bond angles are listed in Tables 2 and 3. Compounds **1** and **4** crystallize in tetragonal space group $I4_1/a$ and monoclinic space group $P2_1/c$, respectively. In **4**, the asymmetric unit contains two independent molecules which are labeled as molecules **4A** and **4B**, respectively, and do not differ from each other significantly.

The tin atoms in **1** and **4** are both four-coordinate and possess a distorted SnC_3O tetrahedral geometry. The Sn–C distances (the mean of 2.142(8) Å for **1** and 2.150(4) Å for **4**) are similar to those found in other reported tricyclohexyltin and tris(2-methyl-2-phenylpropyl)tin carboxylates, such as tricyclohexyltin 3-indoleacetate[11] and tris(2-methyl-2-phenylpropyl)tin acetate.[12] The bond length of Sn(1)–O(1) in **1** and **4** is 2.051(4) and 2.054(2), 2.074(2)Å, respectively, which lies in the range of the Sn–O covalent bond length (2.038−2.115 Å)[13] and is consistent with that reported in related compounds.[11,12] The Sn(1)···O(2) separation of 2.963(4) Å for **1** and 3.014(2), 3.002(2) Å for **4** is not indicative of a significant interaction between these atoms. The major stereochemical role of atom O(2) is to distort the tetrahedral geometry by opening up the C(7)–Sn(1)–C(13) angle to 118.7(3)° and reducing the O(1)–Sn(1)–C(1) angle to 97.9(3)° for **1,** and opening up the C(1)–Sn(1)–C(11) angle to 117.19(14) and 117.91(18)° and reducing the O(1)–Sn(1)–C(1) angle to 100.76(11) and 100.02(13)° for **4**. The monodentate mode of coordination of 3,5-di-*tert*-butyl-4-hydroxybenzoate is reflected in the disparate two C–O bond lengths of carboxylate (C(19)–O(1) 1.310(6) Å

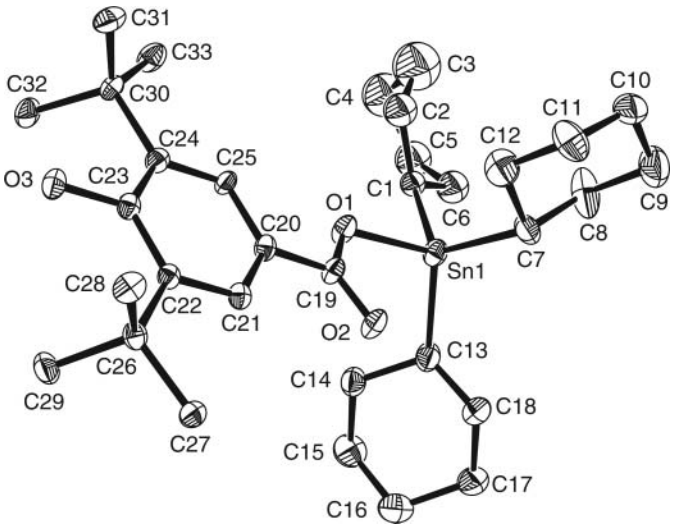


FIG. 1. Molecular structure of **1**; hydrogen atoms are omitted for clarity.

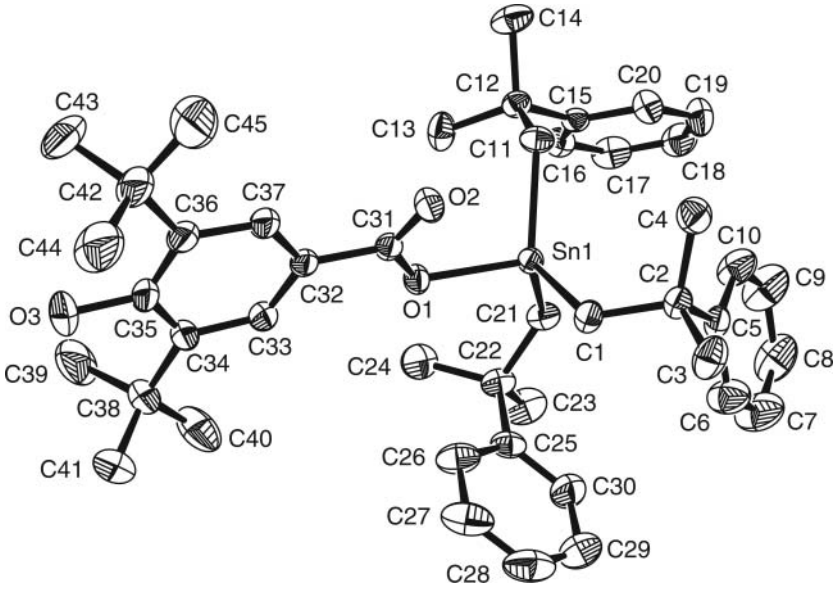


FIG. 2. Molecular structure of **4**; hydrogen atoms are omitted for clarity.

and C(19)–O(2) 1.220(6) Å for **1**, and the mean C(31)–O(1) 1.310(4) Å and C(31)–O(2) 1.219(4) Å for **4**.

In the crystal structure of **1**, neighboring molecules are linked into a cyclic tetramer that is saddle-shaped supramolecular structure by the hydrogen bond between phenolic hydroxyl and adjacent carbonyl oxygen of carboxylate, O(3)−H(3)···O(2)$^{\#1}$ [O(3)−H(3) 0.82 Å, H(3)···O(2)$^{\#1}$ 2.02 Å, O(3)···O(2)$^{\#1}$ 2.740(5) Å, O(3)−H(3)···O(2)$^{\#1}$ 146.6°, symmetry code #1: $-x+5/4$, $y+3/4$, $-z+5/4$] (Figure 3). However, the intermolecular hydrogen bond is not found in **4**, which is caused by the bulky 2-methyl-2-phenylpropyl on the tin.

Spectroscopic Analysis

The compounds **1–4** do not show the broad ν (OH) band at 3600 ∼ 2500 cm^{-1} and the ν (C = O) strong band at 1690 cm^{-1}, indicating the deprotonations of the carboxylic group of the ligand due to the formation of the oxygen-tin bond. The existence of stretching vibration absorption of the phenolic hydroxyl group at ∼3600 cm^{-1} proves that the phenolic hydroxyl groups remain intact in **1–4**. In organotin carboxylates, IR spectroscopy can provide useful information concerning the coordination mode of the carboxylate group. Generally, the difference between the $\nu_{as}(CO_2)$ and $\nu_s(CO_2)$ bands, $\Delta\nu(CO_2)$, of bidentate carboxylate group is below 200 cm^{-1}, while unidentate carboxylate is above 200 cm^{-1}.[14,15] The magnitudes (277–314 cm^{-1}) of $\Delta\nu(CO_2)$ in **1**−**4** indicate that the carboxylate group is monodentate coordination to tin in the solid state, which is agreement with the previous X-ray structures of **1** and **4**.

The ^{1}H NMR spectra of the compounds show the expected integration and peak multiplicities. The singlet appeared at ∼7.95, 5.60, and 1.50 ppm is assigned to proton resonance of phenyl ring, hydroxyl group and *tert*-butyl of 3,5-di-*tert*-butyl-4-hydroxybenzoate ligand, respectively. The ^{13}C resonances of the phenyl of ligand lie in the range of 157.64–124.22 ppm. The ^{13}C chemical shift the carboxyl carbon is at *ca*. 172 ppm. The coordination number of the tin atom in organotins has been related to the $^1J(^{119}\text{Sn-}^{13}\text{C})$ coupling constants.[16,17] The $^1J(^{119}\text{Sn-}^{13}\text{C})$ of the compounds **1–4** is 336, 632, 366, and 350 Hz, respectively, which is close to that of the corresponding four-coordinate triorganotin carboxylates,[16,17] such as 2-$HOC_6H_4N = NC_6H_4COOSnCy_3$,[18] $Ph_3GeCH(o\text{-}C_6H_4Cl)CH_2COOSn(CH_2C(CH_3)_2Ph)_3$,[19] and $C_6H_5C_6H_4COOSnPh_3$,[20] suggesting that the tin atom in **1–4** is four-coordinated in $CDCl_3$ solution.

TABLE 2
Selected bond lengths (Å) and angles (°) for **1**

Sn(1)-O(1)	2.051(4)	Sn(1)-C(7)	2.170(8)	C(19)-O(1)	1.310(6)
Sn(1)-C(1)	2.114(8)	Sn(1)-C(13)	2.132(7)	C(19)-O(2)	1.220(6)
O(1)-Sn(1)-C(1)	97.9(3)	O(1)-Sn(1)-C(7)	102.6(2)	C(1)-Sn(1)-C(7)	114.9(4)
O(1)-Sn(1)-C(13)	109.9(2)	C(1)-Sn(1)-C(13)	110.3(5)	C(13)-Sn(1)-C(7)	118.7(3)

TABLE 3
Selected bond lengths (Å) and angles (°) for **4**

	4A	**4B**		**4A**	**4B**
Sn(1)-O(1)	2.074(2)	2.054(2)	Sn(1)-C(21)	2.157(4)	2.151(4)
Sn(1)-C(1)	2.158(3)	2.151(4)	C(31)-O(1)	1.311(4)	1.309(4)
Sn(1)-C(11)	2.142(3)	2.142(4)	C(31)-O(2)	1.220(4)	1.218(4)
O(1)-Sn(1)-C(11)	102.63(12)	102.06(12)	O(1)-Sn(1)-C(1)	100.76(11)	100.02(13)
O(1)-Sn(1)-C(21)	103.58(12)	104.18(13)	C(1)-Sn(1)-C(11)	117.19(14)	117.91(18)
C(11)-Sn(1)-C(21)	114.76(14)	113.71(18)	C(1)-Sn(1)-C(21)	114.78(14)	115.54(14)

In Vitro Cytotoxicity

In order to evaluate the cytotoxicity of the synthesized organotin carboxylates, we test their activity against a human tumor cell lines A549. The IC_{50} of compounds **1**-**4** against A549 is 0.22 ± 0.03, 0.08 ± 0.01, 0.46± 0.03, and 3.24 ± 0.12 $\mu mol \cdot l^{-1}$, respectively, indicating that they are active against this tumor cell, and their activity are higher than that of the reference drug *cis*-platin (IC_{50} 9.46 ± 0.43 $\mu mol \cdot l^{-1}$). The activity of the compounds decreased in the order **2**>**1**>**3**>**4**. The activity of compounds **1–4** against the A549 is similar to that of the reported analogues, 3,4-$(H_2N)_2C_6H_3COOSnPh_3$ (IC_{50} 0.30 $\mu mol \cdot l^{-1}$) and 3,4-$(H_2N)_2C_6H_3COOSn(C_4H_9\text{-}n)_3$ (IC_{50} 0.57 $\mu mol \cdot l^{-1}$).[21] As these results are preliminary, further study on the anti-tumor effects of these compounds is highly recommended.

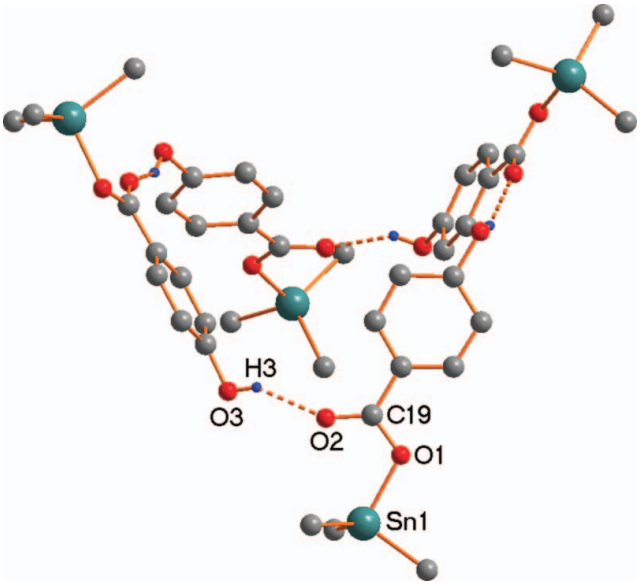


FIG. 3. The supramolecular structure of **1** formed by intermolecular hydrogen bond. Cyclohexyl, *tert*-butyl, and H atoms except H3 are omitted for clarity (color figure available online).

SUPPLEMENTARY MATERIAL

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC Nos. 822995 and 822996. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: 44–1223-336–033; email: deposit@ccdc.cam. ac.uk or www: http://www.ccdc.cam.ac.uk).

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