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Synthesis, characterization, and cytotoxic activity of tricyclohexyltin(IV) carboxylates derived from cyclic dicarboxylic anhydrides

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Some tricyclohexyltin(IV) carboxylates, HOOC–R–COOSn(c-C_6H_{11})$_3$ (**1**) and (c-C_6H_{11})$_3$SnOOC–R–COOSn(c-C_6H_{11})$_3$ (**2**) [R = 1,2-C_6H_4 (**a**), 1,2-C_6F_4 (**b**), (Z)-CH=CH (**c**), CH_2CH_2 (**d**)], have been synthesized from reaction of tricyclohexyltin hydroxide with cyclic dicarboxylic anhydrides under microwave irradiation in 1 : 1 and 2 : 1 M ratio, respectively, and characterized by elemental analysis, IR and NMR (^{1}H, ^{13}C, and ^{119}Sn) spectra. Crystal structures of **1a–1c** and **2d** are determined by X-ray single crystal diffraction. The carboxylate in each compound is monodentate to tin. Compounds **1a** and **1c** possess a *trans*-C_3SnO_2 trigonal bipyramidal geometry with axial positions occupied by carboxylate and carbonyl oxygen of carboxylate of an adjacent molecule forming a one-dimensional chain. Compound **1b** is tetrahedral and forms $R_2^2(8)$ hydrogen-bonded dimers by pairs of intermolecular O–H···O hydrogen bonds between two carboxylic acid groups. Compound **2d** is dinuclear with tin possessing distorted tetrahedral geometry; a trimer supramolecular structure is formed by weak intermolecular Sn···O interactions. The compounds have potent *in vitro* cytotoxic activity against two human tumor cell lines, A549 and HeLa.

Keywords: Organotin complex; Tricyclohexyltin(IV) carboxylate; Cytotoxic activity; Crystal structure

1. Introduction

Organotin carboxylates receive attention for varied applications [1–3], as catalysts, PVC stabilizers, biocides, antifouling agents, and as wood preservatives [3–5]. Investigations have been carried out to test their antitumor activity and some organotin species show potential as antineoplastic agents [5–8]. In general, the organotin moiety, the ligand (carboxylic acid), and the coordination number of tin play important roles in determining their cytotoxicity activity [5–9]. Aminobenzoic acids, pyridinedicarboxylic acid, 4-ketopimelic acid, and cyclohexanedicarboxylic acid have been used for design and synthesis of organotin carboxylates [9–12].

Microwave irradiation reduces reaction times from many hours to a few minutes [13]. Triorganotin carboxylates are usually synthesized by reaction of triorganotin hydroxide and

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a carboxylic acid in benzene or toluene with azeotropic removal of water. The reactions often take 8–10 h [14]. In order to continue to expand the structural chemistry and therapeutic potential of triorganotin carboxylates, we synthesize tricyclohexyltin carboxylates with a carboxylic acid group by reaction of tricyclohexyltin hydroxide with cyclic dicarboxylic anhydrides under microwave irradiation and determined their cytotoxic activity against two human tumor cell lines, A549 and HeLa.

2. Experimental

2.1. *Materials and physical measurements*

Tricyclohexyltin hydroxide (Merck Chemicals) and other chemicals (Shanghai Chemicals, China) were of reagent grade and used without purification. Microwave synthesis was carried out on an XH-100A microwave synthesis apparatus (made by Beijing Xiang Hu Science and Technology Development Co. Ltd.). Carbon, hydrogen, and nitrogen analyses were obtained using a Perkin Elmer 2400 Series II elemental analyzer. The melting points were measured on a WRS-1A digital melting point apparatus. IR spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs from 4000 to 400 cm^{-1}. ^{1}H and ^{13}C NMR spectral data were collected using a Bruker Avance 300 FT-NMR spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. ^{119}Sn NMR spectra were recorded in $CDCl_3$ on a Varian Mercury V×300 spectrometer using Me_4Sn external reference.

2.2. *Synthesis of the complexes*

2.2.1. Synthesis of 2-$HOOCC_6H_4COOSn(c\text{-}C_6H_{11})_3$ (1a). A mixture of tricyclohexyltin hydroxide (0.77 g, 2 mmol) and phthalic anhydride (0.30 g, 2 mmol) in dry 1,4-dioxane (50 mL) was heated on reflux for 20 min in a XH-100A microwave reactor (400 W) and then allowed to cool to room temperature. The solution was filtered and the solvent was removed under reduced pressure. The white solid obtained was recrystallized from ethanol to afford colorless crystals of **1a** (0.85 g, 80%), m.p. 170–171 °C. Anal. Calcd for $C_{26}H_{38}O_4Sn$ (%): C, 58.56; H, 7.18. Found: C, 58.44; H, 7.09. IR (KBr): 3454 [broad, ν(OH)], 1672 [ν(C=O)], 1627 [$\nu(COO^-)_{as}$)], 1365 [($\nu(COO^-)_s$)], 496 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 12.07 (s, OH), 7.20–7.98 (4H, m, Ar–H), 1.95–1.26 (33H, m, Sn(c-$C_6H_{11})_3$). ^{13}C NMR ($CDCl_3$) δ: 171.86 (COOSn), 169.47 (COOH), 132.93, 132.62, 131.23, 131.05, 128.87, 128.36 (Ar–C), 33.84 ($^{1}J(^{119}Sn\text{-}^{13}C) = 338$ Hz, C-α), 31.14 ($^{2}J(^{119}Sn\text{-}^{13}C) = 15$ Hz, C-β), 29.06 ($^{3}J(^{119}Sn\text{-}^{13}C) = 62$ Hz, C-γ), 27.03 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 16.05.

2.2.2. Synthesis of 2-$HOOCC_6F_4COOSn(c\text{-}C_6H_{11})_3$ (1b). Complex **1b** was prepared by the same procedure as **1a** by reaction of tricyclohexyltin hydroxide (0.77 g, 2 mmol) with tetrafluorophthalic anhydride (0.44 g, 2 mmol). Yield 1.02 g (85%), m.p. 166–167 °C. Anal. Calcd for $C_{26}H_{34}F_4O_4Sn$ (%): C, 51.59; H, 5.66. Found: C, 51.54; H, 5.49. IR (KBr): 3387 [broad, ν(OH)], 1688 [ν(C=O)], 1629 [$\nu(COO^-)_{as}$)], 1387 [($\nu(COO^-)_s$)], 500 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 12.39 (s, OH), 1.92–1.30 (33H, m, Sn(c-$C_6H_{11})_3$). ^{13}C NMR ($CDCl_3$) δ: 172.76 (COOSn), 169.96 (COOH), 165.13–114.17 (complex C–F

coulping, Ar–C), 33.98 ($^1J(^{119}Sn\text{-}^{13}C) = 332$ Hz, C-α), 30.91 ($^2J(^{119}Sn\text{-}^{13}C) = 14$ Hz, C-β), 28.75 ($^3J(^{119}Sn\text{-}^{13}C) = 65$ Hz, C-γ), 26.72 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 15.26.

2.2.3. Synthesis of (*Z*)-HOOCCH=CHCOOSn(*c*-C_6H_{11})$_3$ (1c). Complex **1c** was prepared by the same procedure as **1a** by reaction of tricyclohexyltin hydroxide (0.77 g, 2 mmol) with maleic anhydride (0.20 g, 2 mmol). Yield 0.78 g (80%), m.p. 151–152 °C. Anal. Calcd for $C_{22}H_{36}O_4Sn$ (%): C, 54.68; H, 7.51. Found: C, 54.66; H, 7.39. IR (KBr): 3450 [broad, ν(OH)], 1667 [ν(C=O)], 1613 [$\nu(COO^-)_{as}$)], 1338 [($\nu(COO^-)_s$)], 490 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 11.96 (s, OH), 6.34 (1H, d, $J = 12.5$ Hz, CH), 6.25 (1H, d, $J = 12.5$ Hz, CH), 1.94–1.28 (33H, m, Sn(*c*-C_6H_{11})$_3$). ^{13}C NMR ($CDCl_3$) δ: 172.16 (COOSn), 167.22 (COOH), 131.35, 130.09 (CH=CH), 34.08 ($^1J(^{119}Sn\text{-}^{13}C) = 339$ Hz), 31.26 ($^2J(^{119}Sn\text{-}^{13}C) = 17$ Hz), 29.14 ($^3J(^{119}Sn\text{-}^{13}C) = 66$ Hz), 27.14 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 13.56.

2.2.4. Synthesis of HOOCCH$_2$CH$_2$COOSn(*c*-C_6H_{11})$_3$ (1d). Complex **1d** was synthesized by the same procedure as **1a** from tricyclohexyltin hydroxide (0.77 g, 2 mmol) with succinic anhydride (0.20 g, 2 mmol). Yield 0.82 g (85%), m.p. 142–144 °C. Anal. Calcd for $C_{22}H_{38}O_4Sn$ (%): C, 54.45; H, 7.89. Found: C, 54.32; H, 7.66. IR (KBr): 3448 [broad, ν(OH)], 1683 [ν(C=O)], 1634 [$\nu(COO^-)_{as}$)], 1378 [($\nu(COO^-)_s$)], 487 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 11.46 (s, OH), 2.62–2.55 (4H, m, CH_2CH_2), 2.01–1.31 (33H, m, Sn(*c*-C_6H_{11})$_3$). ^{13}C NMR ($CDCl_3$) δ: 175.67 (COOSn), 172.07 (COOH), 33.96 ($^1J(^{119}Sn\text{-}^{13}C) = 346$ Hz), 31.34 ($^2J(^{119}Sn\text{-}^{13}C) = 13$ Hz), 30.48, 29.92 (CH_2CH_2), 29.21 ($^3J(^{119}Sn\text{-}^{13}C) = 65$ Hz), 27.09 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 12.89.

2.2.5. Synthesis of 1,2-C_6H_4[COOSn(*c*-C_6H_{11})$_3$]$_2$ (2a). Complex **2a** was prepared by the same procedure as **1a** by reaction of tricyclohexyltin hydroxide (1.54 g, 4 mmol) with phthalic anhydride (0.30 g, 2 mmol). Yield 1.56 g (87%), m.p. 159–160 °C. Anal. Calcd for $C_{44}H_{70}O_4Sn_2$ (%): C, 58.69; H, 7.84. Found: C, 58.36; H, 7.60. IR (KBr): 1636 [$\nu(COO^-)_{as}$)], 1328 [($\nu(COO^-)_s$)], 494 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.76 (2H, dd, $J = 7.8$, 1.6 Hz, Ar–H), 7.58 (2H, dd, $J = 7.8$, 1.6 Hz, Ar–H), 2.12–1.20 (66H, m, 2[Sn(*c*-C_6H_{11})$_3$]). ^{13}C NMR ($CDCl_3$) δ: 172.04 (COOSn), 133.02, 131.96, 129.87 (Ar–C), 33.84 ($^1J(^{119}Sn\text{-}^{13}C) = 336$ Hz, C-α), 31.08 ($^2J(^{119}Sn\text{-}^{13}C) = 16$ Hz, C-β), 28.98 ($^3J(^{119}Sn\text{-}^{13}C) = 64$ Hz, C-γ), 26.93 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 16.75.

2.2.6. Synthesis of 1,2-C_6F_4[COOSn(*c*-C_6H_{11})$_3$]$_2$ (2b). Complex **2b** was prepared by the same procedure as **1a** by reaction of tricyclohexyltin hydroxide (1.54 g, 4 mmol) with tetrafluorophthalic anhydride (0.44 g, 2 mmol). Yield 1.59 g (82%), m.p. 178–179 °C. Anal. Calcd for $C_{44}H_{66}F_4O_4Sn_2$ (%): C, 54.35; H, 6.84. Found: C, 54.49; H, 6.76. IR (KBr): 1646 [$\nu(COO^-)_{as}$)], 1334 [($\nu(COO^-)_s$)], 486 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.12–1.16 (66H, m, 2[Sn(*c*-C_6H_{11})$_3$]). ^{13}C NMR ($CDCl_3$) δ: 171.34 (COOSn), 165.68–115.06 (complex C–F coulping, Ar–C), 33.96 ($^1J(^{119}Sn\text{-}^{13}C) = 339$ Hz, C-α), 31.23 ($^2J(^{119}Sn\text{-}^{13}C) = 15$ Hz, C-β), 29.04 ($^3J(^{119}Sn\text{-}^{13}C) = 64$ Hz, C-γ), 27.03 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 17.82.

2.2.7. Synthesis of (*Z*)-(*c*-C_6H_{11})$_3$SnOOCCH=CHCOOSn(*c*-C_6H_{11})$_3$ (2c). Complex **2c** was prepared by the same procedure as **1a** from tricyclohexyltin hydroxide (1.54 g, 4 mmol) with maleic anhydride (0.20 g, 2 mmol). Yield 1.53 g (90%, Ref. [15]: 38%), m.p. 151–152 °C (Ref. [15]: 149–151 °C). Anal. Calcd for $C_{40}H_{68}O_4Sn_2$ (%): C, 56.50; H, 8.06. Found: C, 56.21; H, 7.89. IR (KBr): 1654 [$\nu(COO^-)_{as}$)], 1368 [($\nu(COO^-)_s$)], 492 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 6.24 (2H, s, CH=CH), 2.14–1.18 (66H, m, 2[Sn(*c*-$C_6H_{11})_3$]). ^{13}C NMR ($CDCl_3$) δ: 173.86 (COOSn), 133.42 (CH=CH), 33.68 ($^1J(^{119}Sn\text{-}^{13}C) = 342$ Hz), 31.14 ($^2J(^{119}Sn\text{-}^{13}C) = 15$ Hz), 28.94 ($^3J(^{119}Sn\text{-}^{13}C) = 66$ Hz), 27.02 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 10.96.

2.2.8. Synthesis of (*c*-C_6H_{11})$_3$SnOOCCH$_2$CH$_2$COOSn(*c*-C_6H_{11})$_3$ (2d). Complex **2d** was synthesized by the same procedure as **1a** by reaction of tricyclohexyltin hydroxide (1.54 g, 2 mmol) with succinic anhydride (0.20 g, 2 mmol). Yield 1.58 g (93%, Ref. [15]: 78%), m.p. 186–188 °C (Ref. [15]: 186–191 °C). Anal. Calcd for $C_{40}H_{70}O_4Sn_2$ (%): C, 56.36; H, 8.28. Found: C, 56.18; H, 7.97. IR (KBr): 1648 [$\nu(COO^-)_{as}$)], 1387 [($\nu(COO^-)_s$)], 496 (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.54 (4H, s, CH_2CH_2), 2.07–1.21 (66H, m, 2[Sn(*c*-$C_6H_{11})_3$]$_2$). ^{13}C NMR ($CDCl_3$) δ: 176.17 (COOSn), 33.47 ($^1J(^{119}Sn\text{-}^{13}C) = 340$ Hz), 30.96 ($^2J(^{119}Sn\text{-}^{13}C) = 15$ Hz), 31.17 (CH_2CH_2), 29.05 ($^3J(^{119}Sn\text{-}^{13}C) = 63$ Hz), 27.01 (C-δ). ^{119}Sn NMR ($CDCl_3$) δ: 9.87.

2.3. *X-ray crystallography*

Colorless single crystals of **1a–1c** and **2d** were obtained from slow evaporation of methanol solution. Intensity data for the crystals were measured at 295(2) K on a Bruker Smart Apex area-detector diffractometer with graphite monochromated Mo-*K*α radiation (0.71073 Å) using the φ and ω scan technique. The structures were solved by direct methods and refined by a full-matrix least squares based on F^2 using SHELX-97 [16]. Nonhydrogen atoms were refined anisotropically and hydrogens were placed at calculated positions in the riding model approximation. In refinements, the C–C bonds and 1,3-distances of the disordered cyclohexyl groups were restrained to 1.52(1) and 2.50(2) Å, respectively. Several carbons are refined using the pseudo-isotropic 'ISOR' restraint as the free refinement gave unrealistic anisotropic displacement parameters. Crystallographic parameters and refinements of **1a–1c** and **2d** are listed in table 1.

2.4. *In vitro cytotoxicity*

Cytotoxic activities were assayed against two human tumor cell lines, A549 (lung tumor cell) and HeLa (cervix tumor cell). The samples were prepared by dissolving the test compounds in dimethyl sulfoxide (DMSO) and by diluting the resultant solutions with water. In the assays, the final concentration of DMSO was less than 0.1% (concentration used was found to be noncytotoxic against tumor cells). *In vitro* cytotoxic activities of the compounds were measured by the MTT assay according to the literature [17]. All cells were cultured in Dulbecco's Modified Eagle Medium supplemented with 10% heat-inactivated new-born calf serum at 37 °C in a humidified 5% CO_2 incubator and were seeded into each well of a 96-well plate and fixed for 24 h. The following day, different concentrations of the test compounds were added. After incubation with various concentrations of test

Table 1. Crystallographic data and structure refinements for **1a–1c** and **2d**.

Compound	**1a**	**1b**	**1c**	**2d**
Empirical formula	$C_{26}H_{38}O_4Sn$	$C_{26}H_{34}F_4O_4Sn$	$C_{44}H_{72}O_8Sn_2$	$C_{40}H_{70}O_4Sn_2$
Formula weight	533.27	605.22	966.40	852.34
Crystal system	Monoclinic	Triclinic	Orthorhombic	Triclinic
Space group	*C*2/c	*P*-1	*P*bcn	*P*-1
a/Å	19.5284(14)	9.962(3)	22.32(2)	9.829(4)
b/Å	15.2127(11)	10.645(3)	12.476(11)	15.304(6)
c/Å	17.8738 (13)	12.920(4)	34.09(3)	21.190(8)
α (°)	90	85.734(3)	90	78.521(4)
β (°)	107.141(1)	76.633(3)	90	82.361(4)
γ (°)	90	85.047(3)	90	83.747(4)
Volume/Å^3	5074.1(6)	1325.9(7)	9493(15)	3085(2)
Z	8	2	8	3
D_c/(g cm^{-3})	1.396	1.516	1.352	1.376
μ (mm^{-1})	1.035	1.021	1.098	1.250
F(000)	2208	616	4000	1326
θ range	1.73–26.00	1.62–25.10	1.19–25.30	1.36–25.02
Crystal size/mm	0.19 × 0.10 × 0.10	0.22 × 0.13 × 0.12	0.18 × 0.13 × 0.09	0.33 × 0.08 × 0.03
Uniq. reflections	4984	4638	8217	10,620
Reflections [$I>2\sigma$ (I)]	4194	3304	4137	5259
Goodness of fit on F^2	1.038	1.002	0.961	0.979
R indices [$I>2\sigma$ (I)]	$R=0.039$, $wR=0.101$	$R=0.063$, $wR=0.148$	$R=0.091$, $wR=0.160$	$R=0.074$, $wR=0.149$
R indices (all data)	$R=0.046$, $wR=0.107$	$R=0.088$, $wR=0.164$	$R=0.176$, $wR=0.193$	$R=0.157$, $wR=0.181$
$\Delta\rho_{max}$, $\Delta\rho_{min}$/(e Å^{-3})	0.661, −0.390	1.629, −0.657	0.731, −0.545	0.821, −1.131

compounds for 72 h, inhibition of cell proliferation was measured. The experiments were repeated three times for each test. The dose causing 50% inhibition of cell growth (IC_{50}) was calculated by NDST software as previously described [18].

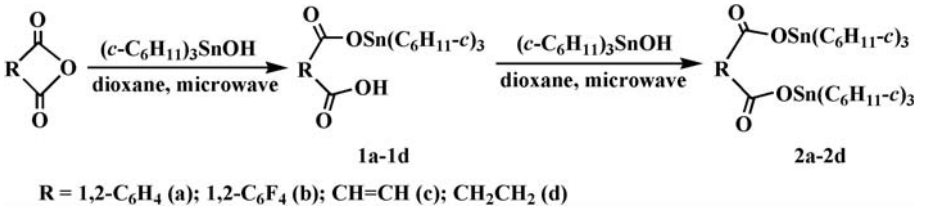
3. Results and discussion

3.1. *Synthesis*

Under microwave irradiation at 400 W, the cyclic dicarboxylic anhydrides reacted with tricyclohexyltin hydroxide in 1 : 1 M ratio in 1,4-dioxane for 20 min to form tricyclohexyltin carboxylates with a carboxylic acid group **1a–1d**, while in 2 : 1 M ratio to obtain dinuclear **2a–2d** in good yields (Scheme 1). The reaction provided a convenient method for preparing triorganotin carboxylates with a carboxylic acid group and dinuclear bistriorganotin carboxylates. These compounds are white crystals, air stable, and soluble in solvents such as benzene, trichloromethane, acetone, and methanol.

3.2. *IR Spectra*

Compounds **1a–1d** show broad ν(OH) at ~3400 cm^{-1} and strong ν(C=O) at 1667–1688 cm^{-1} and do not show the double bands of cyclic dicarboxylic anhydrides at ~1850



Scheme 1. Synthetic route.

and 1790 cm^{-1}, indicating that the reaction of dicarboxylic anhydride with tricyclohexyltin hydroxide has formed the products (**1a–1d**) with the carboxylic acid group. This is further supported by the appearance of a sharp band at ~490 cm^{-1}, assignable to Sn–O stretch [19]. Compared with ν(C=O) of the corresponding carboxylic acid, benzoic acid (1689 cm^{-1}), 2,3,4,5-tetrafluorobenzoic acid (1690 cm^{-1}), 2-butenoic acid (1703 cm^{-1}), and butanoic acid (1708 cm^{-1}), ν(C=O) of the carboxylic acid of **1a**, **1c**, and **1d** shift to low frequencies while that of **1b** has little change. This indicates that C=O of the carboxylic acid in **1a**, **1c**, and **1d** is coordinated to tin while in **1b** it is not consistent with their X-ray diffraction results. In **2a–2d**, ν(OH) and ν(C=O) disappear, indicating this carboxylic acid group further reacts with the second tricyclohexyltin hydroxide. In all compounds (**1** and **2**), strong bands at 1613–1654 and 1328–1387 cm^{-1} are assigned to the asymmetrical stretch [$\nu_{as}(CO_2^-)$] and symmetrical stretch [$\nu_s(CO_2^-)$] of carboxylates, respectively. In organotin carboxylates, IR spectroscopy provides useful information concerning the coordination of carboxylate. Generally, the difference between the $\nu_{as}(CO_2^-)$ and $\nu_s(CO_2^-)$ bands, $\Delta\nu(CO_2^-)$, of bidentate carboxylate is smaller than 200 cm^{-1}, while unidentate carboxylate is larger than 200 cm^{-1} [20,21]. The magnitudes (242–312 cm^{-1}) of $\Delta\nu(CO_2^-)$ in **1** and **2** indicate that carboxylate is monodentate in the solid state, in agreement with X-ray diffraction analyses of **1a–1c** and **2d**.

3.3. *NMR spectra*

^{1}H NMR spectra of the compounds show broad single resonances at ~12 ppm, further, confirming the presence of the carboxylic acid group in **1a**–**1d**. All compounds show multiplet at 1.16–2.14 ppm due to cyclohexyl protons. The ^{13}C chemical shifts of the carboxyl carbon are 167–176 ppm. Resonances of cyclohexyl carbons are at *ca*. 34, 31, 29, and 27 ppm, respectively, and the spin–spin coupling constants $^1J(^{119}Sn\text{-}^{13}C)$, $^2J(^{119}Sn\text{-}^{13}C)$, and $^3J(^{119}Sn\text{-}^{13}C)$ are *ca*. 340, 15, and 65 Hz, respectively. The coordination number of tin in organotin compounds has been related to $^1J(^{119}Sn\text{-}^{13}C)$ coupling constants [22]. The $^1J(^{119}Sn\text{-}^{13}C)$ value of the compounds is close to that of corresponding four-coordinate tricyclohexyltin carboxylates, such as 2-$HOC_6H_4N{=}NC_6H_4COOSn(c\text{-}C_6H_{11})_3$ ($^1J(^{119}Sn\text{-}^{13}C)$ = 335 Hz) [23] and $(c\text{-}C_6H_{11})_3SnO_2CCH_2CH_2COCH_2CH_2CO_2Sn(c\text{-}C_6H_{11})_3$ ($^1J(^{119}Sn\text{-}^{13}C)$ = 325 Hz) [11], suggesting that tin in these compounds is four coordinate in $CDCl_3$ solution.

The ^{119}Sn chemical shifts primarily depend on coordination number and the nature of the donor directly bonded to tin [24]. The ^{119}Sn chemical shifts of **1** and **2** (10–18 ppm) are in accord with values found for four-coordinate tin in solution of noncoordinating solvent [11,25,26], which confirms that there is not C=O→Sn coordination in solution.

3.4. *X-ray structures of complexes 1a-1c and 2d*

The structures of **1a–1c** and **2d** are shown in figures 1–8 and selected geometric parameters are given in table 2.

Compound **1a** (figure 1) crystallizes in monoclinic space group *C*2/c and is a chain polymer associating *via* unidentate carboxylate O(2) and carbonyl oxygen O(4) of the carboxylic acid group with distance of 9.138(3) Å between two tins (figure 2). Sn in this polymeric structure is distorted *trans*-O_2SnC_3 trigonal bipyramid with trigonal plane defined by three cyclohexyl groups. The C–Sn–C angles are 115.41(18)–127.46(18)°. The axial positions are occupied by carboxylate O(2) and O(4)$^{\#1}$ (symmetry code #1: x,−y+1, z+1/2) of the carboxylic acid of an adjacent molecule with the 171.55(11)° O(2)–Sn(1)–O(4)$^{\#1}$ angle. The Sn–C lengths from 2.123(4) to 2.156(4) Å are similar to those found in other five-coordinate tricyclohexyltin carboxylates, such as 3-$C_5H_4NCO_2Sn$(*c*-$C_6H_{11})_3(H_2O)$ [27] and (4-$MeC_6H_4)_3GeCH(C_6H_4OMe$-4)$CH_2CO_2Sn$(*c*-$C_6H_{11})_3(H_2O)$ [28]. The covalent Sn(1)–O(2) (2.247(3) Å) and coordinate Sn(1)–O(4) (2.434(3) Å) bond distances are consistent with those reported. There is an intramolecular hydrogen bond O(3)–H(3)···O(1) between carboxylic acid O–H and carbonyl O(1) of carboxylate (table 3).

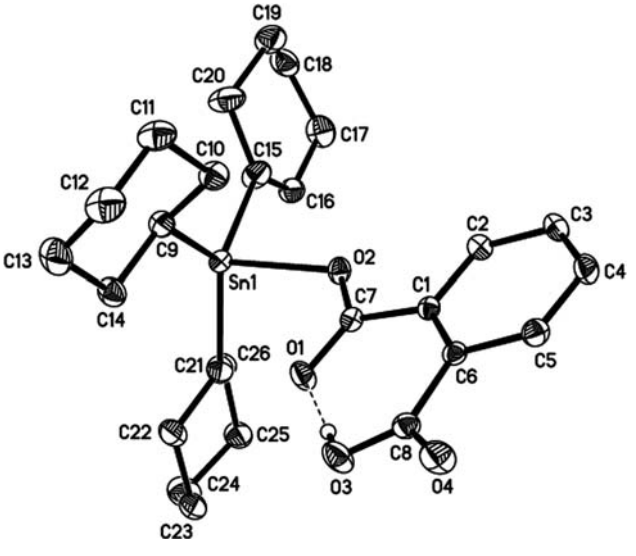


Figure 1. The asymmetric unit of **1a**. Hydrogens except H3 are omitted for clarity.

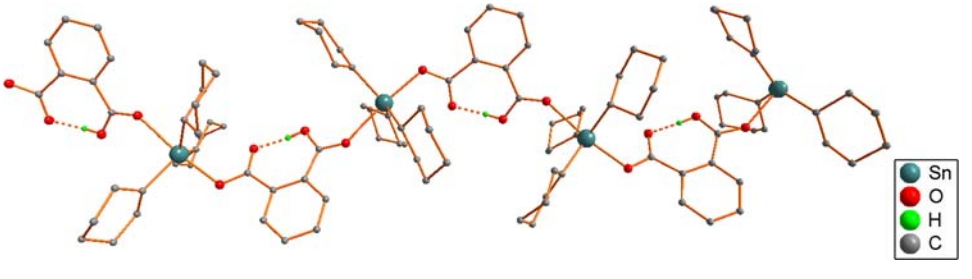


Figure 2. The polymeric structure of **1a**.

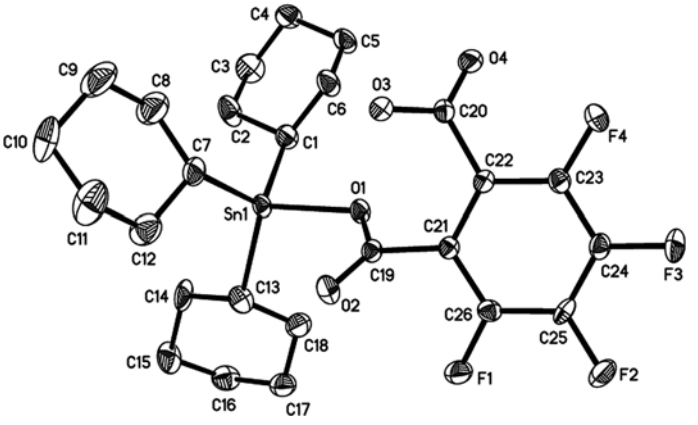


Figure 3. The molecular structure of **1b**. Hydrogens are omitted for clarity.

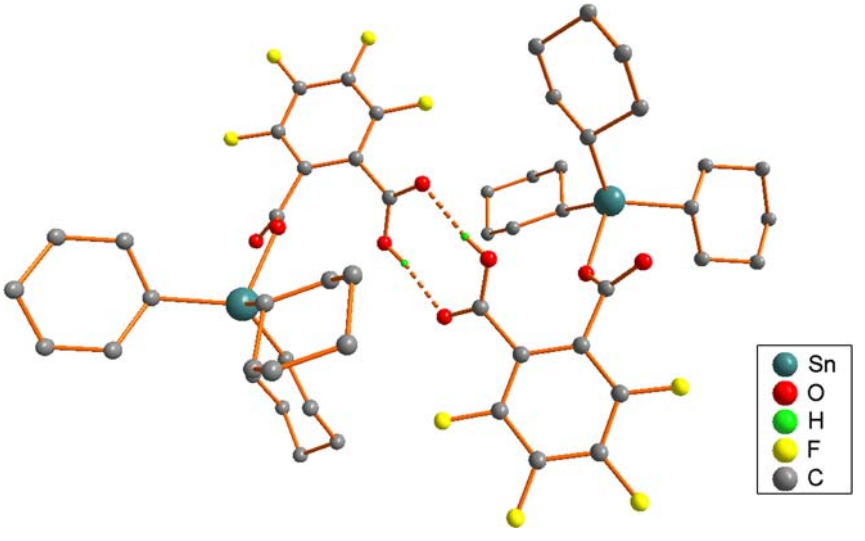


Figure 4. The dimeric structure of **1b** formed by intermolecular hydrogen bonds.

Compound **1b** (figure 3) crystallizes in triclinic space group *P*-1. Tin is four coordinate and possesses a distorted SnC_3O tetrahedral geometry. Bond distances around tin (Sn–C bond length of 2.125(9)–2.152(8) Å and Sn(1)–O(1) bond length of 2.069(4) Å) are in agreement with those found in reported tricyclohexyltin carboxylates such as tricyclohexyltin 3-indoleacetate [29]. The distance (3.018(5) Å) between Sn(1) and O(2) is considerably longer than a normal OSn coordination bond (~2.40 Å), but much shorter than the sum of the van der Waals radii of these atoms (3.77 Å) [30]. This indicates weak interactions which distort the tetrahedral geometry. The O(1)–Sn(1)–C(1) and C(7)–Sn(1)–C(1) angles are 93.9(2) and 117.0(3)°, respectively. Monodentate coordination of benzoate is reflected in the disparate C–O bond lengths of carboxylate (C(19)–O(1) 1.284(8) Å and C(19)–O(2) 1.200(8) Å). In the crystal structure of **1b**, neighboring molecules are linked into $R_2^2(8)$ hydrogen-bonded dimers by a pair of hydrogen bonds [O(3)–H(3)···O(4)$^{\#2}$ and O(3)$^{\#2}$–H(3)$^{\#2}$···O(4)] between free carboxylic acid groups (figure 4 and table 3).

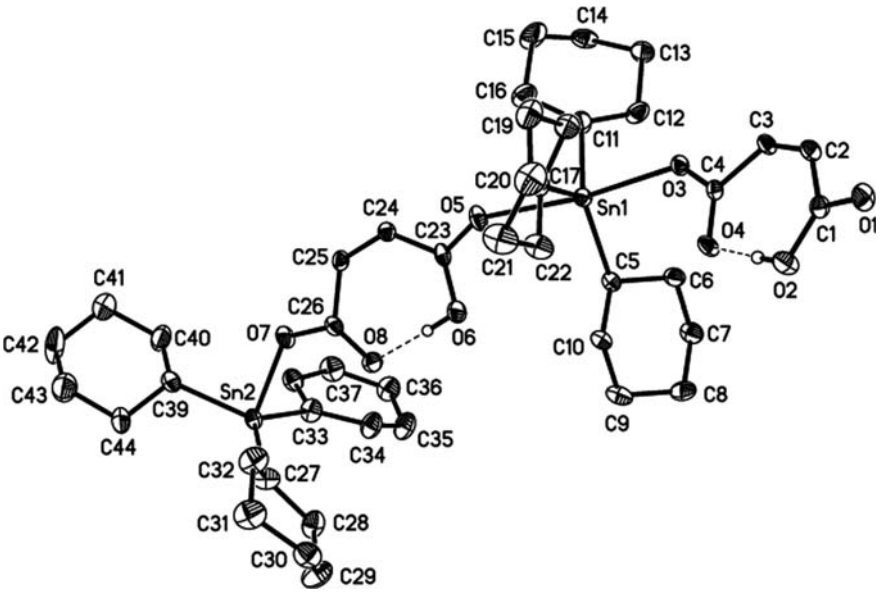


Figure 5. The asymmetric unit of **1c**. Hydrogens except H2 and H6 are omitted for clarity.

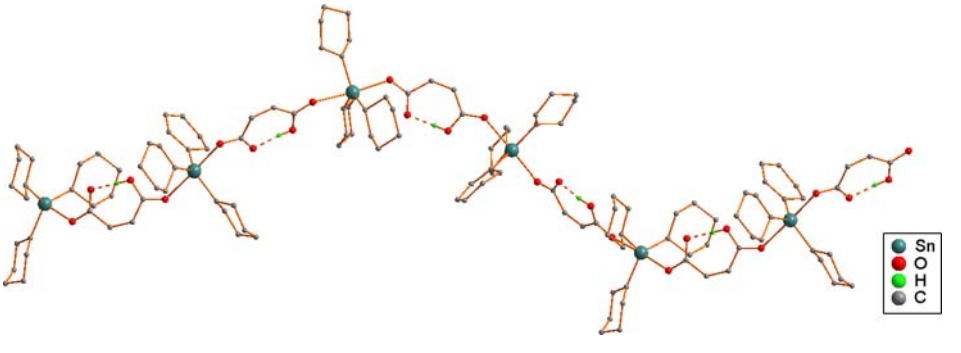


Figure 6. The polymeric structure of **1c**.

Compound **1c** (figure 5) crystallizes in orthorhombic space group *P*bcn. The asymmetric unit contains two (*Z*)-$HO_2CCH{=}CHCO_2Sn(c\text{-}C_6H_{11})_3$ which do not differ from each other significantly. Molecules of **1c** are connected into an infinite S-shape-like chain (figure 6) by coordination of carbonyl oxygen of carboxylic acid to another tin (Sn(1)–O(5) 2.431(7) Å and Sn(2)–$O(1)^{\#3}$ 2.386(8) Å) (symmetry code #3: $-x+1/2,-y+3/2,z+1/2$). Each tin is five-coordinate and possesses a distorted trigonal bipyramidal geometry with axial positions being occupied by the O(3) and O(7) of unidentate carboxylate and O(5) and $O(1)^{\#3}$ of carboxylic acid of an adjacent molecule at the other end (O(3)–Sn(1)–O(5) 173.2(3)° and O(7)–Sn(2)–$O(1)^{\#3}$ 176.1(3)°). The C–O bond distances in the carboxylate are readily distinguishable: C(4)–O(3) 1.276(10) and C(4)=O(4) 1.233(10) Å, C(26)–O(7) 1.277(12) and C(26)=O(8) 1.233(12) Å. In contrast, in carboxylate-bridged tricyclohexyltin carboxylates, such as $CH_3CH_2CH_2CO_2Sn(c\text{-}C_6H_{11})_3$, carboxylate C–O bond lengths are nearly equal, at 1.268(2) and 1.254(2) Å [29]. The Sn(1) and Sn(2) are 0.117(1) and 0.091(1) Å

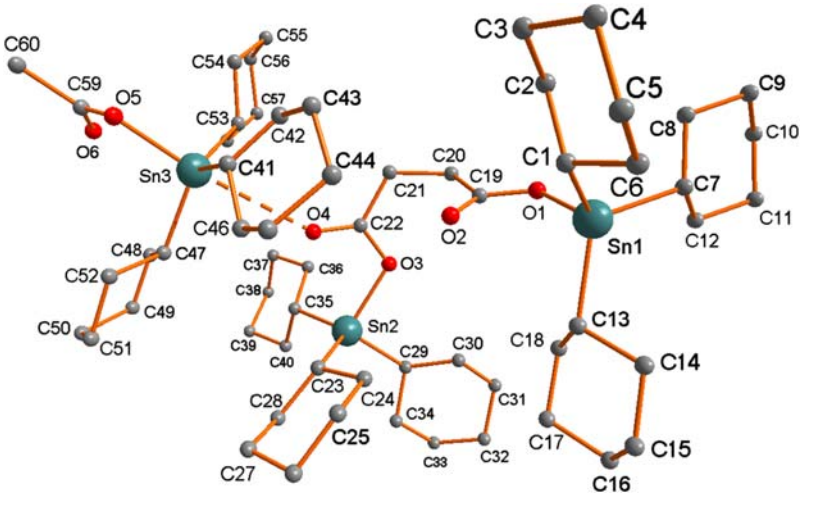


Figure 7. The asymmetric unit of **2d**. Hydrogens are omitted for clarity.

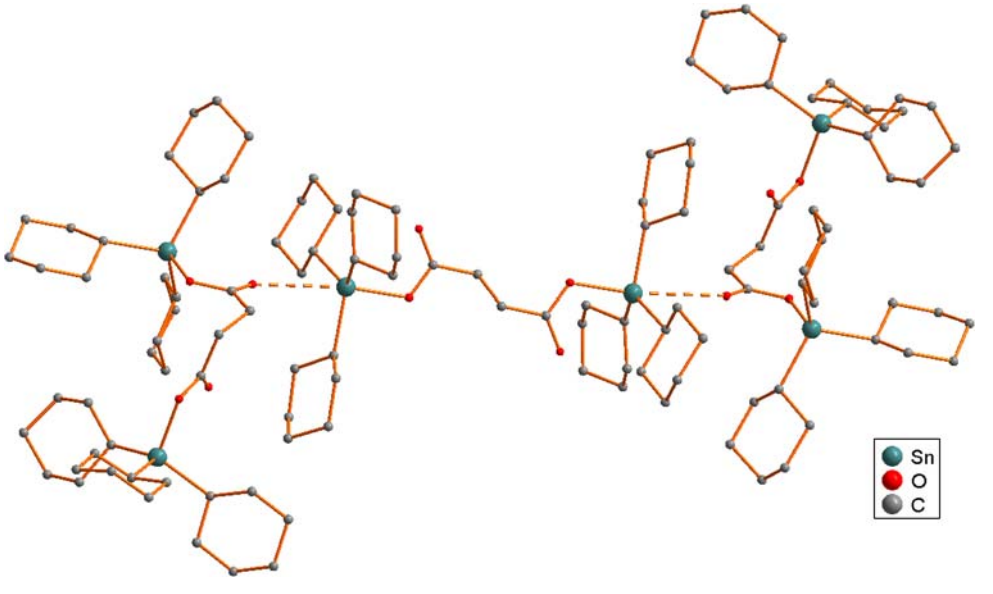


Figure 8. Sn···O weak interactions in **2d** between carbonyl oxygen and tin.

out of the C_3 trigonal plane in the direction of the more tightly held O(3) and O(7), respectively. The dihedral angle between two C_3 trigonal planes is 44.01°. The distance between Sn(1) and Sn(2) is 9.863(3) Å. The tin-oxygen distances are Sn(1)–O(3) 2.245(6), Sn(1)–O(5) 2.430(6), Sn(2)–O(7) 2.251(7), and Sn(2)–$O(1)^{\#3}$ 2.386(7) Å, well within the range usually observed for tricyclotin carboxylates such as 3-$C_5H_4NCO_2Sn$(*c*-$C_6H_{11})_3(H_2O)$ [27] and $CH_3CH_2CH_2CO_2Sn$(*c*-$C_6H_{11})_3$ [31].

Compound **2d** (figure 7) crystallizes in triclinic space group *P*-1 and an asymmetric unit contains one and a half molecules. Compound **2d** is dinuclear in which each tin possesses distorted tetrahedral geometry. The four coordination of tin comes from three cyclohexyl

Table 2. Selected bond lengths (Å) and angles (°) for **1a**–**1c** and **2d**.

1a					
Sn(1)–C(9)	2.156(4)	Sn(1)–C(21)	2.128(4)	Sn(1)–O(4)$^{\#1}$	2.434(3)
Sn(1)–C(15)	2.123(4)	Sn(1)–O(2)	2.247(3)		
C(9)–Sn(1)–C(15)	115.41(18)	C(21)–Sn(1)–O(2)	96.62(16)	C(21)–Sn(1)–O(4)$^{\#1}$	88.06(17)
C(9)–Sn(1)–C(21)	127.46(18)	C(9)–Sn(1)–O(2)	93.97(14)	C(9)–Sn(1)–O(4)$^{\#1}$	77.61(15)
C(15)–Sn(1)–C(21)	115.6(2)	C(15)–Sn(1)–O(4)$^{\#1}$	93.02(19)	O(2)–Sn(1)–O(4)$^{\#1}$	171.55(11)
C(15)–Sn(1)–O(2)	91.30(18)				
1b					
Sn(1)–O(1)	2.069(4)	Sn(1)–C(7)	2.125(9)	Sn(1)–C(13)	2.140(8)
Sn(1)–C(1)	2.152(8)				
O(1)–Sn(1)–C(7)	107.1(3)	O(1)–Sn(1)–C(1)	93.9(2)	C(7)–Sn(1)–C(1)	117.0(3)
O(1)–Sn(1)–C(13)	107.1(2)	C(7)–Sn(1)–C(13)	116.9(3)	C(13)–Sn(1)–C(1)	111.7(3)
1c					
Sn(1)–C(5)	2.162(9)	Sn(1)–O(5)	2.431(7)	Sn(2)–C(39)	2.112(11)
Sn(1)–C(11)	2.119(8)	Sn(2)–C(27)	2.099(9)	Sn(2)–O(7)	2.248(7)
Sn(1)–C(17)	2.145(9)	Sn(2)–C(33)	2.084(9)	Sn(2)–O(1)$^{\#3}$	2.386(7)
Sn(1)–O(3)	2.244(6)				
C(11)–Sn(1)–C(17)	117.7(4)	C(17)–Sn(1)–O(5)	86.0(3)	C(27)–Sn(2)–O(7)	99.0(4)
C(11)–Sn(1)–C(5)	113.7(4)	C(5)–Sn(1)–O(5)	88.5(3)	C(39)–Sn(2)–O(7)	86.7(4)
C(17)–Sn(1)–C(5)	127.7(3)	O(3)–Sn(1)–O(5)	173.3(2)	C(33)–Sn(2)–O(1)$^{\#3}$	89.4(5)
C(11)–Sn(1)–O(3)	88.2(4)	C(33)–Sn(2)–C(27)	122.2(5)	C(27)–Sn(2)–O(1)$^{\#3}$	83.1(4)
C(17)–Sn(1)–O(3)	92.5(3)	C(33)–Sn(2)–C(39)	124.7(5)	C(39)–Sn(2)–O(1)$^{\#3}$	89.5(4)
C(5)–Sn(1)–O(3)	97.6(3)	C(27)–Sn(2)–C(39)	112.5(5)	O(7)–Sn(2)–O(1)$^{\#3}$	176.1(3)
C(11)–Sn(1)–O(5)	86.7(4)	C(33)–Sn(2)–O(7)	92.2(4)		
2d					
Sn(1)–C(1)	2.159(11)	Sn(2)–C(23)	2.155(12)	Sn(3)–C(41)	2.144(10)
Sn(1)–C(7)	2.126(12)	Sn(2)–C(29)	2.127(12)	Sn(3)–C(47)	2.143(10)
Sn(1)–C(13)	2.172(11)	Sn(2)–C(35)	2.130(10)	Sn(3)–C(53)	2.133(12)
Sn(1)–O(1)	2.040(7)	Sn(2)–O(3)	2.057(6)	Sn(3)–O(5)	2.079(10)
O(1)–Sn(1)–C(7)	94.5(4)	O(3)–Sn(2)–C(29)	95.8(3)	O(5)–Sn(3)–C(53)	104.2(5)
O(1)–Sn(1)–C(1)	111.0(4)	O(3)–Sn(2)–C(35)	105.8(3)	O(5)–Sn(3)–C(47)	106.0(4)
C(7)–Sn(1)–C(1)	114.4(4)	C(29)–Sn(2)–C(35)	108.8(5)	C(53)–Sn(3)–C(47)	119.8(4)
O(1)–Sn(1)–C(13)	108.6(4)	O(3)–Sn(2)–C(23)	107.0(4)	O(5)–Sn(3)–C(41)	91.0(4)
C(7)–Sn(1)–C(13)	117.0(5)	C(29)–Sn(2)–C(23)	117.5(5)	C(53)–Sn(3)–C(41)	116.4(5)
C(1)–Sn(1)–C(13)	110.2(5)	C(23)–Sn(2)–C(35)	118.7(4)	C(47)–Sn(3)–C(41)	113.7(4)

Note: Symmetry codes: #1 $x,-y+1,z+1/2$; #3 $-x+1/2,-y+3/2,z+1/2$.

Table 3. Hydrogen bonds in **1a**–**1c**.

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
1a				
O(3)–H(3)···O(1)	0.82	1.573(3)	2.386(5)	171.1(3)
1b				
O(3)–H(3)···O(4)$^{\#2}$	0.82	1.840(5)	2.655(7)	172.7(3)
1c				
O(2)–H(2)···O(4)	0.82	1.620(3)	2.438(5)	175.7(3)
O(6)–H(6)···O(8)	0.82	1.632(3)	2.443(5)	171.4(3)

Note: Symmetry code: #2 $-x,-y,-z+2$.

groups and a carboxylate oxygen which is monodentate. The parameters around the three tins in the asymmetric unit do not differ significantly; the range of Sn(1)–C, Sn(2)–C, and Sn(3)–C bond distances is 2.126(12)–2.172(11), 2.130(10)–2.155(12), and 2.133(12)–2.144

Table 4. Cytotoxicities [IC_{50} ($\mu mol\,L^{-1}$)] of the compounds.

Compound	A549	Hela
1a	0.8 ± 0.1	0.16 ± 0.01
1b	0.68 ± 0.08	0.133 ± 0.004
1c	1.0 ± 0.1	0.39 ± 0.04
1d	1.6 ± 0.1	0.57 ± 0.01
2a	0.25 ± 0.04	0.062 ± 0.006
2b	0.13 ± 0.01	0.074 ± 0.004
2c	0.63 ± 0.02	0.104 ± 0.006
2d	0.83 ± 0.01	0.116 ± 0.006
cis-platin	9.5 ± 0.4	5 ± 1

(10) Å, respectively, similar to that found in 4-$O_2NC_6H_4OCH_2CO_2Sn(C_6H_{11}$-*c*$)_3$) [32]. The distance between carbonyl oxygen O(4) and Sn(3) of an adjacent molecule is 3.176(3) Å, much larger than the distance (~2.4 Å) of Sn–O coordination bond but smaller than the sum (3.77 Å) of the van der Waals radii of tin and oxygen [30]. By weak intermolecular Sn···O interactions, the distorted trigonal bipyramidal units are linked into a trimer supramolecular structure (figure 8) in which the distances between Sn(1) and Sn(2), Sn(2) and Sn (3), and Sn(3) and $Sn(3)^{\#4}$ (symmetry code #4: $-x,1-y,-z$) are 7.150(6), 5.666(5), and 9.063(6) Å, respectively.

3.5. *In vitro cytotoxicity*

To evaluate the cytotoxicities of the tricyclohexyltin carboxylates, we test the activities against two human tumor cell lines, A549 and HeLa. The results of the cytotoxic assays are shown in table 4. These compounds are active and their cytotoxic activities are higher than those of *cis*-platin, an anticancer drug. The data from table 4 also reveal that dinuclear **2** are more active against the cell lines than the mononuclear **1**. The activities of all compounds against A549 are similar to that of reported analogs, 3,4-$(H_2N)_2C_6H_3COOSnPh_3$ (IC_{50} 0.30 $\mu mol\,L^{-1}$) and 3,4-$(H_2N)_2C_6H_3COOSn(C_4H_9$-*n*$)_3$ (IC_{50} 0.57 $\mu mol\,L^{-1}$) [33]. The activity against the HeLa is comparable with the result of our previously reported tricyclohexyltin 2-phenyl-1,2,3-triazole-4-carboxylate (IC_{50} 0.1867 $\mu g\,mL^{-1}$) [25]. However, their activities are lower than those of the recently reported triorganotin selenites [34]. As these results are preliminary, further study on the antitumor effects of these compounds is highly recommended.

4. Conclusion

We have developed a convenient synthetic procedure for triorganotin carboxylates by using the reaction of triorganotin hydroxide with cyclic dicarboxylic anhydrides under microwave irradiation. In the solid state, **1a** and **1c** possess a *trans*-C_3SnO_2 trigonal bipyramidal geometry and form an infinite chain by coordination of carbonyl oxygen of carboxylic acid to tin of an adjacent molecule. Compound **1b** shows a tetrahedral geometry and forms $R_2^2(8)$ hydrogen-bonded dimers. Compound **2d** is dinuclear in which tin possesses a distorted tetrahedral geometry and forms a trimer supramolecular structure by weak Sn···O interactions. In noncoordinating solvents, these compounds are monomers. The compounds have potent *in vitro* cytotoxicities against A549 and HeLa, and can be considered as excellent antitumor compounds for further study.

Supplementary material

Crystallographic data for **1a**–**1c** and **2d** have been deposited with the Cambridge Crystallographic Data Center, CCDC Nos. 837934, 837935, 837936, and 867158. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk/data_request/cif.

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