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Synthesis, characterization and biological activity of a novel binuclear organotin complex, $Ph_3Sn(HL)\cdot Ph_2SnL$ [L = 3,5-Br_2-2-$OC_6H_2CH{=}NCH(i\text{-}Pr)COO$]

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A 1 : 1 reaction of triphenyltin chloride with potassium *N*-[(3,5-dibromo-2-hydroxyphenyl)methylene] valinate in benzene under reflux leads to the formation of a novel mixed organotin binuclear complex, $Ph_3Sn(HL)\cdot Ph_2SnL$ [L = 3,5-Br_2-2-$OC_6H_2CH{=}NCH(i\text{-}Pr)COO$], by means of a facile phenyl–tin bond cleavage process. The X-ray structure reveals that there are two distinct types of carboxylate coordination mode and *trans*-O_2SnC_2N and *trans*-O_2SnC_3 in distorted trigonal bipyramidal geometries. The complex displays good *in vitro* cytotoxicity and antibacterial activities.

KEYWORDS: binuclear tin complex; organotin carboxylate; cytotoxic activity; X-ray structure

INTRODUCTION

In recent years, triorganotin carboxylates (R_3SnO_2CR') have received considerable attention because of their structural diversity[1–3] and biological properties, particularly cytotoxicity/antitumor activity.[4–7] The structural variations are caused by the high coordination ability of tin, more specifically its ability to be involved in either weak or strong intra- and inter-molecular coordination.[3,8] In multifunctional carboxylate ligands, the carboxylate oxygen atoms and the potential donor atoms (nitrogen, oxygen, sulfur, etc.) in the R′ group can be available for coordination to tin atoms. The *N*-[(2-hydroxyaryl)alkylidene]-α-amino acids represent an interesting class of carboxylate ligands. Several triorganotin esters of *N*-[(2-hydroxyaryl)alkylidene]glycine, $R_3Sn(2\text{-}HOArCR'{=}NCH_2COO)$ (R = Me, Bu, Ph; R′ = H, Me) have been prepared.[9] Structural studies have revealed that the complexes adopt a polymeric *trans*-O_2SnR_3 trigonal bipyramidal configuration with the axial locations occupied by a carboxylate oxygen from the ligand and the phenolic oxygen of the ligand on an adjacent complex.[9] However, when triphenyltin chloride reacted with potassium *N*-[(3,5-dibromo-2-hydroxyphenyl)methylene]valinate, 3, 5-Br_2-2-$HOC_6H_2CH{=}NCH(i\text{-}Pr)COOK$ (HLK), in benzene under reflux conditions, a mixed organotin binuclear complex, $Ph_3Sn(HL)\cdot Ph_2SnL$ (**1**), was obtained. This was characterized by elemental analysis, IR and NMR (^1H, ^{13}C and ^{119}Sn) spectra and X-ray diffraction.

RESULTS AND DISCUSSION

Synthesis

The initial aim of our investigation was to synthesize the complex $Ph_3Sn(HL)$ (**2**) by the reaction of triphenyltin chloride with HLK. However, the resulting product was complex **1**, not complex **2**. The possible formation path of **1** is suggested in Scheme 1. The reaction of triphenyltin chloride and the ligand HLK afforded first the triphenyltin ester **2** and KCl, and then the elimination of molecular PhH from **2** by cleavage of the Sn–C bond and H–O bond resulted in the corresponding diphenyltin complex, Ph_2SnL (**3**); finally, the interaction between **3** and **2** gave the novel organotin binuclear complex **1**. In compound **2**, there might be a coordination bond between

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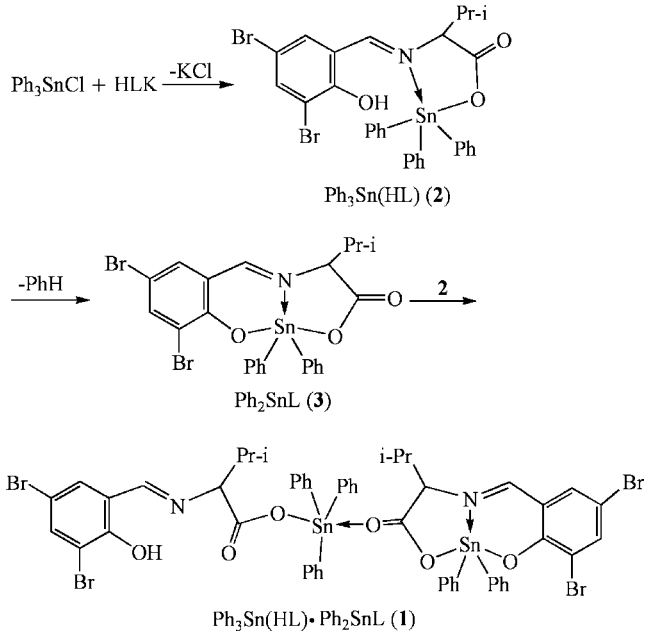

Scheme 1. Possible formation path of complex **1**.

the imino nitrogen and tin, and the tin atom would possess a trigonal bipyramidal geometry with one apical and two equatorial phenyl rings. It is well known that apical groups are less covalently linked to the central metal than equatorial groups are,[4] which would be why this phenyl group is then so easily cleaved by an intramolecular SEAr reaction[4,10] to yield **3**. In complex **1**, the three phenyl groups of the **2** moiety are all three equatorial, so that a phenyl group is no longer cleaved here. The nitrogen atom no longer coordinates to tin because the C=O of **3** coordinate.

Crystal structure of 1

The molecular structure of complex **1** is shown in Fig. 1 and selected distances and angles are listed in Table 1. The compound is a binuclear complex formed by a carboxyl group bridging a triphenyltin carboxylate (**2**) and a diphenyltin carboxylate (**3**). Each of the two tin atoms, Sn1 and Sn2, possesses a five-coordination geometry in a distorted

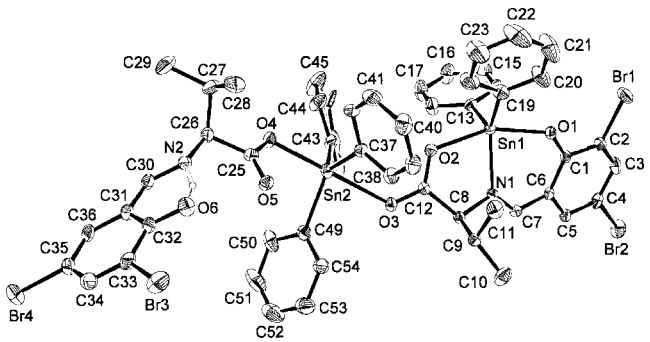

Figure 1. Molecular structure of complex **1**.

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

Sn1–O1	2.069(4)	Sn2–O3	2.435(4)
Sn1–O2	2.150(4)	Sn2–O4	2.165(4)
Sn1–C13	2.107(6)	Sn2–C37	2.119(7)
Sn1–C19	2.110(6)	Sn2–C43	2.139(9)
Sn1–N1	2.152(5)	Sn2–C49	2.122(8)
O2–C12	1.268(7)	O4–C25	1.281(7)
O3–C12	1.237(6)	O5–C25	1.223(7)
N1–C7	1.295(7)	N2–C30	1.302(8)
N1–C8	1.474(7)	N2–C26	1.462(8)
O1–Sn1–C13	97.5(2)	O3–Sn2–C37	86.3(2)
O1–Sn1–C19	92.6(2)	O3–Sn2–C43	83.9(10)
O1–Sn1–O2	156.92(16)	O3–Sn2–O4	178.35(16)
O2–Sn1–C13	96.2(2)	O3–Sn2–C49	82.4(2)
O2–Sn1–C19	95.0(2)	O4–Sn2–C37	94.8(2)
C13–Sn1–C19	123.9(3)	O4–Sn2–C43	94.4(10)
O1–Sn1–N1	82.94(16)	O4–Sn2–C49	98.1(2)
O2–Sn1–N1	75.20(17)	C37–Sn2–C43	124.6(10)
N1–Sn1–C13	107.9(2)	C37–Sn2–C49	120.6(3)
N1–Sn1–C19	128.1(2)	C43–Sn2–C49	111.9(9)

trigonal bipyramidal arrangement. The Sn1 atom forms a five-membered and a six-membered chelating ring with the ligand. The two phenyl groups and the imino N1 atom occupy the equatorial positions of the trigonal bipyramid, and the axial positions are taken up by a phenoxide-O1 and a carboxylate-O2 atom. The O1–Sn1–O2 bond angle is 156.92(16)°, which is comparable to that observed in each of $Ph_2Sn(OC_6H_4C(CH_3)=NCH_2COO)$ (158.6(2)°),[11] $Bu_2Sn(OC_6H_4CH=NCH(i\text{-}Pr)COO)$ (155.07(18)°)[12] and $Ph_2Sn(OC_6H_4CH=NCH(i\text{-}Pr)COO)$ (159.39(17)°).[13] Distortions from the ideal geometry may be rationalized partly by the restricted bite angles of the tridentate ligand. The trigonal plane of the Sn2 atom is defined by the three phenyl groups, and the C–Sn–C angles are in the range 111.9(9)–124.6(10)°. The axial position is occupied by the carbonyl-O3 atom of the bridging carboxylate group and the carboxylate-O4 atom of the other ligand. The O3–Sn2–O4 angle is 178.35(16)° and is greater than those (170–175°) found in the single-strand $[R_3Sn(O_2CR')]_n$ chain polymers.[1–3] The difference between two Sn–O bonds, Sn2–O3 and Sn2–O4 is 0.270 Å, which is similar to that of the aforementioned $[R_3Sn(O_2CR')]_n$ polymers.[1–3] The Sn2–O4 distance (2.165(4) Å) is the nearly same as that (2.164(2) Å) of $Ph_3Sn(2\text{-}HOC_6H_4CH=NCH_2COO)$ [9] and is well within the range of Sn–O bond distances usually observed for triorganotin carboxylates.[1–3] The Sn2···O5 separation of 3.0155(2) Å is shorter than the sum of van der Waals radii of tin and oxygen (3.73 Å),[14] indicating that there is weak interaction between the Sn2 and O5 atoms, which contributed to the distortion of the geometry at the tin atom. The two coordination modes for the carboxylate group in **1**, i.e. monodentate and bidentate bridging, are also reflected in the disparity in the respective carboxylate C–O

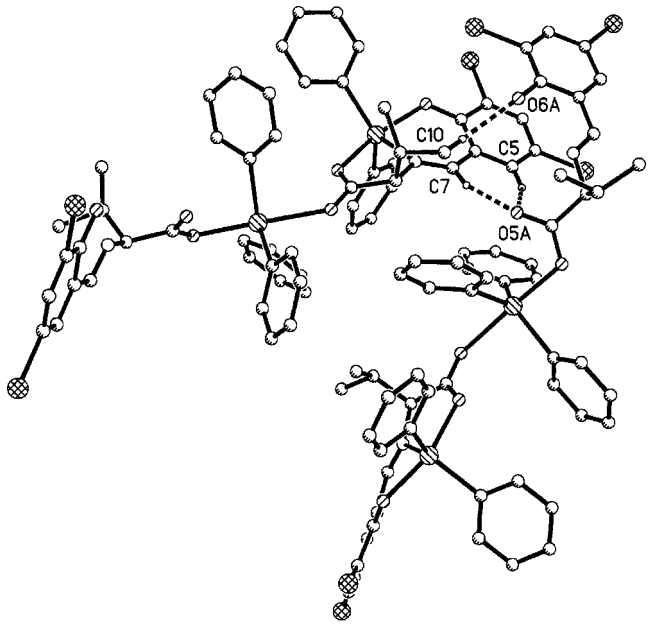

Figure 2. Intermolecular non-classical hydrogen bonds in **1**.

bonds: the difference (0.058(0) Å) between the O4–C25 and O5–C25 is clearly greater than that (0.031(1) Å) between the O2–C12 and O3–C12. An analysis of the crystal structure of **1** reveals the presence of several intra- and intermolecular interactions. Thus, an intramolecular O–H···N hydrogen bond is found between the uncoordinated imino N2 and the phenolic hydroxy group (O6–H6 0.82 Å, O6···N2 2.54(1) Å, H6···N2 1.82 Å, O6–H6···N2 145.5(1)°) (Fig. 1). Three intermolecular non-classical hydrogen bonds are found to be of the type C–H···O[a] (symmetry code a: $1/2+x$, $1/2-y$, $-z$), C7–H7···O5[a] (C7···O5[a] 3.07(1) Å, H7···O5[a] 2.18 Å, C7–H7···O5[a] 159.4(1)°), C5–H5···O5[a] (C5···O5[a] 3.33(1) Å, H5···O5[a] 2.59 Å, C5–H5···O5[a] 136.9(1)°) and C10–H10A···O6[a] (C10···O6[a] 3.37(1) Å, H10A···O6[a] 2.18 Å, C10–H10A···O6[a] 159.4(1)°), which are responsible for the stability of the crystal lattice (Fig. 2)

The presence of bidentate bridging carboxylate residues in organotin carboxylate structures has been well established.[1–3] However, a diorganotin carboxylate and a triorganotin carboxylate linked via a bridging carboxyl group to produce a binuclear tin complex is rare.

Spectral properties

The very broad IR absorption band in the region 3100–3600 cm^{-1} was assigned to the stretching vibration of hydroxyl group. The ν(C=N) and $\nu_{as}(CO_2)$ appeared as an unresolved broad band at 1609 cm^{-1} and $\nu_s(CO_2)$ as a broad band was observed at 1400 cm^{-1}. The ^1H and ^{13}C NMR spectra of **1** showed the expected resonances and integration. The signal at 8.11 ppm was assigned to the non-coordinated azomethine (CH=N) proton and the coordinated azomethine proton appeared at 8.20 ppm with spin–spin coupling of 55.8 Hz between the azomethine proton and the tin nucleus. Two sets of resonances for the protons and carbon atoms of the phenyl groups in the Ph_2SnL core were detected, which may be due to the presence of the chiral center and rigid chelating rings.[15] The $^1J(^{119}Sn-^{13}C)$ coupling was not detected. The complex displayed two ^{119}Sn resonances, at −96.1 and −333.4 ppm, in $CDCl_3$ solution. These fall well within the range of four-coordinate and five-coordinate tin centers respectively,[11,16] indicating the dissociation of compound **1** into $Ph_3Sn(HL)$ and Ph_2SnL at room temperature. The signal at −96.1 ppm was assigned to the four-coordinate $Ph_3Sn(HL)$,[9,16] and the resonance at −333.4 ppm was assigned to the five-coordinate tin center in the Ph_2SnL.[11]

Biological activity

The results of *in vitro* cytotoxicity of **1** and the reference drug (*cis*-platin) against three human tumor cell lines, i.e. HeLa (cervix tumour cell), CoLo 205 (colon carcinoma cell) and MCF-7 (mammary tumour cell), are shown in Table 2. The compound belonged to the very efficient cytostatic agents and its *in vitro* antitumor activities were more active than that of the clinically used *cis*-platin.

The antibacterial activities of **1** and a reference drug (penicillin G sodium) are listed in Table 3. The results show that **1** is active against the two bacteria *Staphylococcus aureus* and *Escherichia coli* and that its activity against *S. aureus* is better than against *E. coli*. Compound **1** is more active than the reference against *E. coli*, but less than the reference against *S. aureus*.

EXPERIMENTAL

Materials and physical measurements

LHK was prepared according to the reported method,[11] and other chemicals were of reagent grade and were used

Table 2. *In vitro* cytotoxicity activity of the title complex

	IC_{50} (μmol l^{-1})		
Compound	HeLa	CoLo 205	MCF-7
1	0.096 ± 0.035	0.29 ± 0.03	0.21 ± 0.07
cis-Platin	4.81 ± 1.10	13.94 ± 0.47	18.73 ± 0.60

Table 3. Antibacterial activity of the compounds

	MIC[a] (μg ml^{-1})	
Compound	*E. coli*	*S. aureus*
1	9.37 ± 0.37	2.16 ± 0.10
Penicillin G sodium	15.11 ± 0.63	1.79 ± 0.06

[a] MIC: minimum inhibitory concentration.

without further purification. Carbon, hydrogen and nitrogen analyses were obtained using a Perkin Elmer 2400 Series II elemental analyzer. Melting points were measured on an X-4 microscopic melting point apparatus. IR spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs in the range 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectral data were collected using a Bruker Avance DMX500 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 Vx300 spectrometer using Me_4Sn as internal reference.

Synthesis of complex 1

A benzene solution (30 ml) of triphenyltin chloride (0.58 g, 1.5 mmol) was added dropwise with continuous stirring to a suspension of LHK (0.63 g, 1.5 mmol) in benzene (30 ml). The reaction mixture was refluxed for 3 h and then filtered to remove KCl. The yellow filtrate was evaporated under reduce pressure. The yellow solid obtained was washed with petroleum ether and then recrystallized from chloroform/hexane (1 : 1, v/v) and dried *in vacuo*. Yield 63%, m.p. 172–173 °C, $[\alpha]_D^{20}$ (EtOH) = −311.8°. Anal. Found: C, 47.12; H, 3.44; N 2.01. Calc. for $C_{54}H_{48}Br_4N_2O_6Sn_2$: C, 47.07; H, 3.51; N, 2.03%. IR (KBr, cm^{-1}): 1609 (s, broad, $\nu_{as}(CO_2) + \nu(C{=}N)$), 1400 (s, broad, $\nu_s(CO_2)$). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 0.88 (d, $J = 6.8$ Hz, 3H, CH_3), 0.90 (d, $J = 6.8$ Hz, 3H, CH_3), 0.90 (d, $J = 6.8$ Hz, 3H, CH_3), 0.98 (d, $J = 6.8$ Hz, 3H, CH_3), 2.27–2.34 (m, 1H, CH), 2.38–2.45 (m, 1H, CH), 3.93 (d, $J = 5.0$ Hz, 1H, CHN), 3.98 (d, $J = 4.7$ Hz, 1H, CHN), 7.27 (d, $J = 2.1$ Hz, 1H, H-2 in $Br_2C_6H_2$), 7.30 (d, $J = 2.1$ Hz, 1H, H-2 in $Br_2C_6H_2$), 7.35–7.50 (m, 15H, *m*-H + *p*-H in C_6H_5), 7.69 (d, $J = 2.1$ Hz, 1H, H-4 in $Br_2C_6H_2$), 7.70–7.75 (m, 8H, *o*-H in C_6H_5), 7.94 (d, $J = 2.1$ Hz, 1H, H-4 in $Br_2C_6H_2$), 8.07–8.09 (m, 2H, $J(^{119}Sn{-}H) = 85.0$ Hz, *o*-H in C_6H_5), 8.11 (s, 1H, N=CH), 8.20 (s, $J(^{119}Sn{-}H) = 55.8$ Hz, 1H, N=CH), 14.63 (s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 175.78, 172.52 (C=O), 171.25, 164.04 (CH=N), 163.39, 158.66, 142.08, 137.79, 137.50, 137.18, 137.06, 136.82, 136.54, 136.38, 136.11, 132.90, 131.11($J(^{119}Sn{-}C) = 18$ Hz), 130.96 ($J(^{119}Sn{-}C) = 16$ Hz), 130.34, 129.13 ($J(^{119}Sn{-}C) = 90$ Hz), 128.97 ($J(^{119}Sn{-}C) = 62$ Hz), 119.64, 118.65, 112.61, 118.37, 109.02, 108.33 (Ar ring), 76.18, 74.62 (=NCH), 34.91, 32.22 (CH), 19.50, 18.96 18.40, 17.72 (CH_3). ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ ppm: −96.1, −333.4.

Crystal structure determination of complex 1

A yellow, plate-like crystal of **1** with approximate dimensions of $0.04 \times 0.12 \times 0.36$ mm^3 was mounted on a glass fiber. The intensity data were measured at 295 K on a Bruker Smart Apex area-detector with graphite monochromatized Mo Kα radiation (0.710 73 Å) using the ω scan technique so that $\theta_{max} = 27.5°$. Of the 47 865 reflections that were collected, 12 621 were unique ($R_{int} = 0.088$). An empirical absorption correction was made by using the SADABS program.[17] Crystal data: $C_{54}H_{48}Br_4N_2O_6Sn_2$, $M = 1377.96$, orthorhombic, space group $P2_12_12_1$, $a = 11.7776(9)$, $b = 18.0548(14)$, $c = 26.039(2)$ Å, $V = 5537.0(7)$ $Å^3$, $Z = 4$, $D_c = 1.653$ g cm^{-3}, $\mu = 3.836$ mm^{-1}, $F(000) = 2696$. The structure was solved by direct-methods[18] and refined by a full-matrix least-squares procedure based on F^2 using SHELXL-97.[19] The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions in the riding model approximation. The refinement converged to final $R = 0.052$ (for 8096 reflections with $I > 2\sigma(I)$). $wR = 0.094$ (all 12 621 data). One phenyl group (C43–C48) was found to be disordered and, from refinement, the two components were refined with 50% site occupancy factors. The absolute configuration was determined from the analysis; the Flack parameter was 0.001(8).[20] CCDC deposition no. 260447.

Determination of biological activity

In vitro cytotoxicity screening of compound **1** against three human tumor cell lines HeLa, CoLo 205 and MCF-7 was performed according to a published method.[21] The sample was prepared by dissolving compound **1** in ethanol, and by diluting the solution obtained with water. In the assays, the concentration of ethanol was less than 0.1%. The antibacterial activity against *E. coli* and *S. aureus* was determined by a microcalorimetric method according to the literature.[22] A 2277 Thermal Activity Monitor (Thermometric AB, Sweden) was used to determine the power–time curves of bacterial growth at 310 K.

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