Research Article

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Synthesis, structural characterization and antibacterial activity of bis(triorganotin) 2-butynedioates

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Abstract: Two new bis(triorganotin) 2-butynedioates, $R_3SnOOCC{\equiv}CCOOSnR_3$ (where R = *c*-C_6H_{11}, **1**; $CH_2C(CH_3)_2C_6H_5$, **2**), have been synthesized and characterized by means of elemental analysis, IR, and NMR (^1H, ^{13}C and ^{119}Sn) spectra. The crystal structure of complex **2** is determined by X-ray single crystal diffraction. In the complexes, the carboxylate is monodentate and tin atom is four-coordinate in solid and non-coordinating solvent. Complex **2** is a centrosymmetric dinuclear tin complex in which tin atom adopts a distorted tetrahedral geometry. Bioassay results have shown that the complexes have good *in vitro* antibacterial activity against *Escherichia coli*.

Supporting information: X-Ray (Cif file, Checkcif), *μ-C* curve diagram.

Keywords: *organotin, 2-butynedioic acid, organotin carboxylate, crystal structure, antibacterial activity*.

1. INTRODUCTION

In recent years, organotin carboxylates have been receiving considerable attention due to their structural interest and various applications [1-3]. Many researchers have described the preparation and characterization of organotin carboxylates and their activity against tumours, fungi, bacteria, and other microorganisms [3-6]. It has been observed that some di- and triorganotin carboxylates show potential as antineoplastic agents [7-9]. The number and nature of the organic groups bonded to the tin centre and the carboxylate ligand appear to play an important role in determining their biological activity [3,7,9]. To design and synthesize new organotin carboxylates by selecting ligands and organotin substrates has been encouraged in order to achieve efficacy.

2-Butynedioic acid is a linear dicarboxylic acid with a shorter bridge (-C≡C-), and used to construct metal polycarboxylate coordination polymers [10,11]. Crystal structures of some transition metal and lanthanide complexes of the ligand have been published in the literature [10-13]. However, up to now, only one structure of 2-butynedioate organotin complex, $(n\text{-Bu})_3SnOOCC{\equiv}CCOOSn(Bu\text{-}n)_3$, was reported [14]. In order to continue to expand the chemistry and therapeutic potential of the organotin complexes of 2-butynedioic acid, we synthesized two new bis(triorganotin) 2-butynedioates, $R_3SnOOCC{\equiv}CCOOSnR_3$ (where R = *c*-C_6H_{11}, **1**; $CH_2C(CH_3)_2C_6H_5$, **2**), and determined their *in vitro* antibacterial activity.

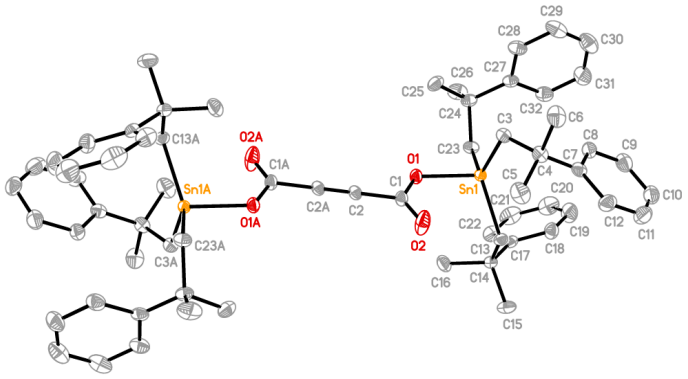


Figure 1. The molecular structure of **2**. Hydrogen atoms are omitted for clarity.

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 tetramethylsilane (TMS) as internal standard. ^{119}Sn NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Vx300 spectrometer using Me_4Sn external reference.

2.1 Synthesis of the complexes

Bis(tricyclohexyltin) 2-butynedioate (1)

To a suspension of tricyclohexyltin hydroxide (0.770 g, 2 mmol) in 50 mL of benzene was added 2-butynedioic acid (0.114 g, 1 mmol). Under electromagnetic stirring, 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 by a rotary evaporator. The resulting white solid was re-crystallized from methanol and dried in a vacuum dryer for 24 h to afford colorless crystal of **1** (0.611 g, 72%), m.p. 120-121°C. Anal. calcd. for $C_{40}H_{66}O_4Sn_2$ (%): C, 56.63; H, 7.84. Found: C, 56.34; H, 7.57. IR (KBr): 1676 [$\nu_{as}(COO^-)$], 1365 [$\nu_s(COO^-)$] cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.21-1.89 (m, 66H, *c*-C_6H_{11}) ppm. ^{13}C NMR ($CDCl_3$) *d*: 26.89 (C-δ), 28.77 [$^3J(^{119}Sn\text{-}^{13}C)$ = 62 Hz, C-γ], 31.04 [$^2J(^{119}Sn\text{-}^{13}C)$ = 18 Hz, C-β], 34.22 [$^1J(^{119}Sn\text{-}^{13}C)$ = 336 Hz, C-α], 76.04 (C≡C), 156.06 (COOSn) ppm. ^{119}Sn NMR ($CDCl_3$) δ: 11.98 ppm.

Bis[tris(2-methyl-2-phenylpropyl)tin] 2-butynedioate (2)

This complex was prepared in the same way as **1** by the reaction of tris(2-methyl-2-phenylpropyl)tin hydroxide (1.071 g, 2 mmol) with 2-butynedioic acid (0.114 g, 1 mmol). Yield 0.804 g (70%), m.p. 101-102°C. Anal calcd for $C_{64}H_{78}O_4Sn_2$: C, 66.92; H, 6.84. Found: C, 66.99; H, 6.78. IR (KBr): 1670 [$\nu_{as}(COO^-)$], 1346 [$\nu_s(COO^-)$] cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.25 (s, 36H, CH_3), 1.36 (s, $J(^{119}Sn\text{-}^1H)$ = 49 Hz, 12H, CH_2Sn), 7.16-7.29 (m, 30H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 33.06 [$^3J(^{119}Sn\text{-}^{13}C)$ = 42 Hz, CH_3], 37.76 [$^1J(^{119}Sn\text{-}^{13}C)$ = 344 Hz, CH_2Sn], 38.50 [$^2J(^{119}Sn\text{-}^{13}C)$ = 19 Hz, CCH_2], 75.96 (C≡C), 125.70, 125.79, 128.41, 150.84 (C_6H_5), 155.89 (COOSn) ppm. ^{119}Sn NMR ($CDCl_3$) δ: 94.74 ppm.

X-ray crystallography

The colorless single crystal of **2** was obtained from methanol-trichloromethane (2:1, 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 *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 [15]. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions in the riding model approximation. Crystal data, collection procedures and refinement results are shown in Table 1. The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1420784.

Table 1. Crystallographic and refinement data of **2**

Empirical formula	$C_{64}H_{78}O_4Sn_2$
Formula weight	1148.64
Crystal system	monoclinic
Space group	$P2_1/c$
a /Å	17.4022(12)
b /Å	13.2379(10)
c /Å	12.8626(9)
α/(°)	90
β/(°)	92.1080(1)
γ/(°)	90
Volume /Å^3	2961.1(4)
Z	2
D_c / (g×cm^{-3})	1.288
μ / mm^{-1}	0.887
F(000)	1188
Crystal size / mm	0.10 ´ 0.30 ´ 0.40
θ range /(°)	1.17 to 25.50
Total reflections	21686
Unique reflections	5505 (R_{int} = 0.0242)
Reflections with $I>2\sigma(I)$	4633
Goodness of fit on F^2	1.033
R indices [$I>2\sigma(I)$]	R = 0.0278, wR = 0.0700
R indices (all data)	R = 0.0343, wR = 0.0739
$\Delta\rho_{min}$, $\Delta\rho_{max}$/(e· Å^{-3})	-0.267, 0.400

Table 2. Growth rate constants (μ) at different concentrations (*C*) of **1** and **2.**

1							
C (μg/ml)	1.24	2.48	3.72	4.96	6.20	7.44	8.68
μ (min^{-1})	0.031014	0.026512	0.023891	0.015262	0.012288	0.007779	0.003290
2							
C (μg/ml)	1.158	2.316	3.475	4.633	5.791	6.949	8.107
μ (min^{-1})	0.036392	0.031418	0.027571	0.023751	0.019028	0.016309	0.013289

Antibacterial activity

The antibacterial activity of the complexes against *Escherichia coli* was determined by microcalorimetric method according to the literature [16]. A 2277 Thermal Activity Monitor (Thermometric AB, Sweden) was used to determine the power-time curves of bacterial growth at 310*K*. After a stable baseline was obtained, the bacterial sample, a beef extract soluble medium (pH = 7.2-7.4) containing NaCl (1 g), peptone (2 g), beef extract (1 g) and different concentration of organotin drug in each 200 mL were pumped into the flow cell system and the monitor began to record the power-time curves of continuous growth for bacteria. When the recording pen returned to the baseline the process of bacterial growth was completed. Based on the data of power-time curves and theoretical model, the growth rate constants (μ) were calculated (the μ value was given by the data processing software Digitam 4.1) [16]. The growth rate constants (μ) at different concentrations (C) of organotin drug **1** and **2** are listed in Table 2. The relationship between the growth rate constants (μ) and concentration (C) of organotin drug was fitted by using computer, μ = -0.00381C+0.03604 for **1** and μ = -0.00333C+0.03940 for **2** (see Figures S1 and S2). When the growth rate constant is 0, the minimum inhibitory concentration (MIC) was confirmed.

3. RESULTS AND DISCUSSION

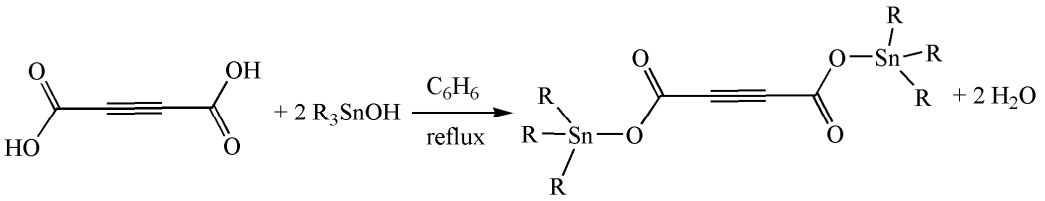
Complexes **1** and **2** were synthesized by azeotropic removal of water from the reaction between tricyclohexyltin hydroxide (or tris(2-methyl-2-phenylpropyl)tin hydroxide) and 2-butynedioic acid in the molar ratio 2:1 in anhydrous benzene (Scheme 1). The complexes are white solids and soluble in benzene and in common polar organic solvents such as methanol, trichloromethane, acetone, and *N*,*N*-dimethylformamide.

In complexes **1** and **2**, the bonds of 3500 and 1725 cm^{-1} assigned to ν (O-H) and ν (C=O), respectively, of free 2-butynedioic acid do not appear, and the new strong bands appeared at ~1670 cm^{-1} and ~1360 cm^{-1} are assigned to the asymmetrical stretching vibration, $\nu_{as}(COO^-)$, and symmetrical stretching vibration, $\nu_s(COO^-)$, of the 2-butynedioate, respectively. In organotin complexes of the carboxylate ligand, IR spectroscopy can provide useful information concerning the coordination mode of the carboxylate group [17,18]. The difference between the $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ bands, $\Delta\nu(COO^-)$, is 311 cm^{-1} for **1** and 324 cm^{-1} for **2**, respectively, which is larger than 200 cm^{-1}, indicating that the carboxylate group is coordinated to tin in monodentate mode [17,18].

In ^{1}H NMR spectra of **1** and **2**, the single resonance of COOH in the spectra of the free ligand is not observed at ~12 ppm, which further confirms the replacement of the carboxylic acid protons by the triorganotin moiety on complex formation. The cyclohexyl protons of complex **1** show the multiplet in the range 1.21-1.89 ppm, and the resonances of methyl and methylene protons of **2** appear at 1.25 and 1.36 ppm, respectively.

The ^{13}C chemical shifts of the carboxyl and acetylene carbons of **1** and **2** appear at ~156 and ~76 ppm, respectively. The resonance signals of cyclohexyl carbons of **1** appear at 26.89, 28.77, 31.04, and 34.22 ppm, respectively, and the spin-spin coupling constants $^1J(^{119}Sn\text{-}^{13}C)$, $^2J(^{119}Sn\text{-}^{13}C)$ and $^3J(^{119}Sn\text{-}^{13}C)$ is 336, 18 and 62 Hz, respectively. In **2**, the resonances appeared at 33.06, 37.76, and 38.50 ppm are assigned to methyl, methylene, and quaternary carbons, and the $^1J(^{119}Sn\text{-}^{13}C)$, $^2J(^{119}Sn\text{-}^{13}C)$ and $^3J(^{119}Sn\text{-}^{13}C)$ is 344, 19 and 42 Hz, respectively. The coordination number of the tin atom in organotin complexes has been related to the $^1J(^{119}Sn\text{-}^{13}C)$ coupling constants [3,19]. Nadvornik *et al*. [19,20] reported that the $^1J(^{119}Sn\text{-}^{13}C)$ coupling constant can be a function of the coordination number of triorganotin complexes, ranging between 327 and 387 Hz for four-coordinated complexes, and between 442 and 509 Hz for five-coordinated ones. Thus, it is suggested that the tin atom in **1** and **2** is four-coordinated in $CDCl_3$ solution. The $^1J(^{119}Sn\text{-}^{13}C)$ value of **1** and **2** is also close to that of the corresponding four-coordinate tricyclohexyltin and tris(2-methyl-2-phenylpropyl) tin carboxylates, such as 2-$HOC_6H_4N{=}NC_6H_4COOSn(c\text{-}C_6H_{11})_3$ (335 Hz) [21], $(c\text{-}C_6H_{11})_3SnOOCCH_2CH_2COCH_2CH_2COOSn(c\text{-}C_6H_{11})_3$ (325 Hz) [22], $(2\text{-}C_6H_5C_2HN_3)COOSn[CH_2C(CH_3)_2C_6H_5]_3$ (354 Hz) [23], and $Ph_3GeCH(o\text{-}C_6H_4Cl)CH_2COOSn[CH_2C(CH_3)_2C_6H_5]_3$ (352 Hz) [24].

The ^{119}Sn chemical shifts primarily depend on the coordination number and the nature of the donor atom directly bonded to the central tin atom [25]. The ^{119}Sn chemical shifts of **1** and **2** (11.98 and 94.74 ppm) are in accord with the values found for four-coordinated tin in solution of non-coordinating solvent [21-24].



R = *c*-C_6H_{11}, **1**; $CH_2C(CH_3)_2C_6H_5$, **2**

Scheme 1. Synthesis of the complexes.

Table 3. Selected bond lengths (Å) and angles (°) for **2**

Sn(1)-C(3)	2.140(2)	Sn(1)-O(1)	2.0788(17)
Sn(1)-C(13)	2.147(2)	C(1)-O(1)	1.280(3)
Sn(1)-C(23)	2.145(2)	C(1)-O(2)	1.196(4)
O(1)-Sn(1)-C(3)	99.80(8)	O(1)-Sn(1)-C(13)	106.54(8)
O(1)-Sn(1)-C(23)	93.96(9)	C(3)-Sn(1)-C(13)	118.00(9)
C(3)-Sn(1)-C(23)	118.60(10)	C(23)-Sn(1)-C(13)	114.32(9)

The molecular structure of **2** is shown in Figure 1, and the selected bond lengths and bond angles are listed in Table 3. Complex **2** crystallizes in monoclinic space group $P2_1/c$, and is a centrosymmetric di-nuclear tin complex in which the tin atom adopts a distorted tetrahedral geometry. The four coordination atoms of tin atom come from three carbon atoms of 2-methyl-2-phenylpropyl groups and a carboxylate oxygen atom which is mono-dentate to tin, respectively. The mean Sn-C distance of 2.144(2) Å is similar to that found in other reported tris(2-methyl-2-phenylpropyl)tin carboxylates, such as (2-$C_6H_5C_2HN_3$)$COOSn[CH_2C(CH_3)_2C_6H_5]_3$ (2.149(3) Å) [23], and $Ph_3GeCH(o\text{-}C_6H_4Cl)CH_2COOSn[CH_2C(CH_3)_2C_6H_5]_3$ (2.149(4) Å) [24] and $CH_3COOSn[CH_2C(CH_3)_2C_6H_5]_3$ (2.148(6) Å) [26]. The bond length of Sn(1)-O(1) in **2** is 2.0788(17) Å, which lies in the range of the Sn-O covalent bond length (2.038~2.115 Å) [27] and is consistent with that reported in related complexes [23,24,26]. The Sn(1)···O(2) separation of 3.120(2) Å for **2** 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(3)-Sn(1)-C(13) angle to 118.00(9)° and reducing the O(1)-Sn(1)-C(23) angle to 93.96 (9)°. The monodentate mode of coordination of the ligand is also reflected in the disparate two C-O bond lengths of carboxylate (C(1)-O(1) 1.280(3) Å and C(1)-O(2) 1.196(4) Å). In molecule of **2**, the distance between two tin atoms, Sn(1) and Sn(2), is 9.690(2) Å.

Table 4. Antibacterial activity (MIC, μg/mL) of the complexes[a]

Complex	**1**	**2**	Penicillin sodium	cefazolin sodium
Escherichia coli	9.46	11.83	8.03	2.01

[a] MIC = minimum inhibitory concentration.

The antibacterial activity of the complexes and the reference drug (penicillin sodium and cefazolin sodium) was listed in Table 4. The results showed that the complexes against *Escherichia coli* is active, and are more active than the reported tricyclohexyltin and tris(2-methyl-2-phenylpropyl)tin 2-phenyl-1,2,3-triazole-4-carboxylates (MIC 13.50 and 16.34 μg/mL) [23], ferrocenecarboxylates (MIC 23.98 and 31.26 μg/mL) [28], and triphenyltin tryptophanate (MIC 25 μg/mL) [29]. This may be due to the existence of two triorganotin units in the complexes. They can be considered as anti-bacterial compounds to further study and modified although the activity of the complexes is lower than that of the reference drug.

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