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有机锡 4-(4-吡啶基甲基硫代)苯甲酸酯的合成、结构与生物活性研究

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摘要：通过 4-(4-吡啶基甲基硫代)苯甲酸与三苯基氧化锡以及三环己基氢氧化锡反应,合成了三苯基锡 4-(4-吡啶基甲基硫代)苯甲酸酯(**1**)及三环己基锡 4-(4-吡啶基甲基硫代)苯甲酸酯(**2**)。它们的结构通过红外,核磁以及 X-射线单晶衍射分析得到确证。化合物 **1** 表现为一维链状结构,而化合物 **2** 通过分子间的 O-H…O 和 O-H…N 氢键形成二维网状结构。生物活性测试表明,这 2 个化合物具有较高的抗肿瘤活性。

关键词：有机锡羧酸酯；吡啶基；抗癌活性；晶体结构

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Synthesis, Structure and Biological Activity of Triorganotin 4-(4-Pyridylmethylthio)benzoates

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Abstract: Reaction of 4-(4-pyridylmethylthio)benzoic acid with $(Ph_3Sn)_2O$ and Cy_3SnOH (Cy=cyclohexyl) yielded triphenyltin 4-(4-pyridylmethylthio)benzoate (**1**) and tricyclohexyltin 4-(4-pyridylmethylthio)benzoate (**2**), respectively. Their crystal structures were determined by single-crystal X-ray diffraction analysis. The crystal of **1** belongs to the monoclinic system, space group $P2_1/n$ with a=1.023 1(5) nm, b=1.630 0(8) nm, c=1.5849(8) nm, β=106.417(11)°, V=2.535(2) nm^3, Z=4, D_c=1.557 g·cm^{-3}, μ=1.120 mm^{-1}, F(000)=120 0, R_1=0.065 5 and wR_2=0.142 7. Complex **2** crystallizes with a molecule of water. Its crystal belongs to the monoclinic system, space group $P2_1/c$ with a=1.019 5(2) nm, b=2.112 9(4) nm, c=1.441 1(3) nm, β=103.847(3)°, V=3.014 0(11) nm^3, Z=4, D_c=1.389 g·cm^{-3}, μ=0.948 mm^{-1}, F(000)=1 312, R_1=0.023 7 and wR_2=0.0540. Complex **1** shows a polymeric chain structure, while complex **2** displays an infinite 2D network through intermolecular O-H…O and O-H…N hydrogen bonds. The cytotoxic activity of these two complexes for A549, Bel-7402 and Hela cells in vitro was tested. CCDC: 875206, **1**; 875207, **2**.

Key words: organotin carboxylate; pyridyl; antitumor activity; crystal structure

Organotin carboxylates continue to be an active research area because of their remarkable structural diversity[1] and potential applications in many fields, for example as pesticidal, bactericidal and antitumor agents[2]. It is known that the steric and electronic factors of carboxylic acid ligands significantly affect the coordination geometries of the tin atoms in these complexes as well as their bioactivities. Recently, more and more investigations have focused on the synthesis of organotin carboxylates of functionalized

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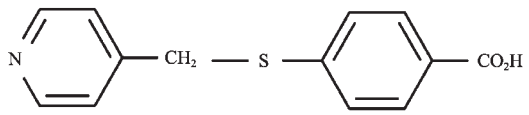
carboxylic acids with additional oxygen [3-6], sulfur [7-8] and nitrogen [9-12] donor atoms. Owing to the introduction of additional coordinating atoms, these organotin carboxylates show various and fascinating structures, such as trinuclear [11], hexanuclear [12] and polynuclear [13] macrocycles as well as a hexanuclear drum[14]. Lately, we are interested in the synthesis and bioactivity of organotin carboxylates with additional nitrogen donor atoms [15-16], which exhibit good antifungal activities and novel cyclotetrameric structures. As an extension of these investigations on biologically active organotin carboxylates, we herein report the synthesis, structure and antitumor activity of triorganotin derivatives of 4-(4-pyridylmethylthio) benzoic acid (Scheme 1).



Scheme 1　Structure of 4-(4-pyridylmethylthio) benzoic acid

1　Experimental

1.1　Materials and measurements

NMR spectra were obtained with a Bruker 400 spectrometer, and the chemical shifts were reported in ppm with respect to reference standards (internal $SiMe_4$ for ^1H and ^{13}C NMR spectra, external $SnMe_4$ for ^{119}Sn NMR). IR spectra were obtained from a Shimadzu FTIR 8400S spectrometer as KBr discs. Elemental analyses were carried out on an Elementar Vairo EL analyzer. Melting points were measured with an X-4 digital micro melting-point apparatus and were uncorrected. All the chemicals used are commercially available and used as received without further purification.

1.2　Synthesis of 4-(4-pyridylmethylthio) benzoic acid

To a solution of NaOH (2.64 g, 66 mmol) in a mixed solvent of ethanol (40 mL) and water (10 mL), 4-mercaptobenzoic acid (3.08 g, 20 mmol) and 4-chloromethylpyridine-HCl (3.28 g, 20 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, and then water (100 mL) was added. The aqueous solution was extracted with diethyl ether (3×50 mL), and the organic phase was discarded to remove unreacted starting materials. The aqueous phase was acidified to a pH value of 4 with 2 mol·L^{-1} HCl to give white precipitate, which was filtered, washed with water, and dried in air to give 4-(4-pyridylmethylthio)benzoic acid. This acid could be recrystallized from large amount of ethanol to yield white crystals. Yield 4.0 g (82%); m.p. 252~254 ℃. ^1H NMR (DMSO-d_6): δ 4.39 (s, 2H, CH_2), 7.41 (d, J= 5.6 Hz, 2H), 8.49 (d, J=5.6 Hz, 2H) (C_5H_4N), 7.43 (d, J=8.4 Hz, 2H), 7.82 (d, J=8.4 Hz, 2H) (C_6H_4), 12.96 (s, 1H, CO_2H). ^{13}C NMR (DMSO-d_6): δ 34.0 (CH_2), 123.8, 126.7, 127.8, 129.7, 141.8, 146.3, 149.7 (C_5H_4N and C_6H_4), 166.9 (CO_2H). IR (cm^{-1}): ν(C=O) 1 700. Anal. Calcd. for $C_{13}H_{11}NO_2S\cdot0.5C_2H_5OH$(%): C, 62.67; H, 5.26; N, 5.22. Found (%): C, 63.16; H, 5.17; N, 5.62.

Sodium 4-(4-pyridylmethylthio)benzoate was obtained by the equimolar reaction of 4-(4-pyridylmethylthio)benzoic acid with NaOH in ethanol. Its IR spectroscopic data are as follows: ν_{as}(COO) 1 615, ν_s (COO) 1 399 cm^{-1}.

1.3　Synthesis of triphenyltin 4-(4-pyridylmethylthio)benzoate (1)

The mixture of 4-(4-pyridylmethylthio)benzoic acid (0.25 g, 1 mmol) and $(Ph_3Sn)_2O$ (0.36 g, 0.5 mmol) in toluene (30 mL) was stirred and heated at reflux for 12 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was recrystallized from benzene/hexane to give colorless crystals. Yield 0.52 g (88%); m.p. 177~179 ℃. ^1H NMR ($CDCl_3$): δ 4.01 (s, 2H, CH_2), 7.14 (d, J= 5.0 Hz, 2H), 8.34 (d, J=5.0 Hz, 2H) (C_5H_4N), 7.18 (d, J=8.0 Hz, 2H), 7.97 (d, J=8.0 Hz, 2H) (C_6H_4), 7.42~7.46, 7.71~7.87 (m, m, 9H, 6H, SnC_6H_5). ^{13}C NMR ($CDCl_3$): δ 36.6 (CH_2), 123.8, 127.8, 129.0 ($^3J(^{13}C\text{-}^{119/117}Sn)$=63.6 Hz), 129.1, 130.2, 131.1, 137.0 [$^2J(^{13}C\text{-}^{119/117}Sn)$=47.2 Hz], 138.7, 141.1, 146.4, 149.9 (C_5H_4N, C_6H_4 and SnC_6H_5), 171.8 (C=O). ^{119}Sn NMR ($CDCl_3$): δ −126.8. IR (cm^{-1}): ν_{as} (COO) 1 665, ν_s (COO) 1 368. Anal. Calcd. for $C_{31}H_{25}NO_2SSn$ (%): C, 62.65; H, 4.24; N, 2.36. Found (%): C, 62.36; H, 4.49; N, 2.57.

1.4 Synthesis of tricyclohexyltin 4-(4-pyridylmethylthio)benzoate (2)

This complex was obtained similarly using tricyclohexyltin hydroxide instead of $(Ph_3Sn)_2O$ as described above for **1**, but in a 1∶1 molar ratio. Yield 69%; m.p. 67~69 ℃. ^{1}H NMR ($CDCl_3$): δ 1.31~1.40, 1.64~1.76, 1.89~2.01 (m, m, m, 9H, 14H, 10H, C_6H_{11}), 4.13 (CH_2), 7.25~7.27 (m, 4H) (C_5H_4N and C_6H_4), 7.94 (d, J=8.3 Hz, 2H) (C_6H_4), 8.52 (d, J=5.9 Hz, 2H, C_5H_4N). ^{13}C NMR ($CDCl_3$): δ 26.9, 28.9 (^3J (^{13}C-$^{119/117}$Sn)=64.3 Hz), 31.1[^2J(^{13}C-$^{119/117}$Sn)= 14.4 Hz], 33.9 (^1J (^{13}C-$^{119/117}$Sn)=338.8, 321.6 Hz), 36.8 (CH_2), 123.7, 127.9, 130.4, 130.7, 140.2, 146.2, 150.0 (C_5H_4N and C_6H_4), 170.6 (C=O). ^{119}Sn NMR ($CDCl_3$): δ 19.2. IR (cm^{-1}): ν_{as} (COO) 1 644, ν_s (COO) 1 374. Anal. Calcd. for $C_{31}H_{43}NO_2SSn\cdot H_2O$ (%): C, 59.06; H, 7.19; N, 2.22. Found (%): C, 59.27; H, 6.79; N, 1.82.

1.5 Crystal structure determination

Crystals of **1** and **2** suitable for X-ray analysis were obtained by slowly cooling their hot benzene/hexane solutions. All intensity data were collected with a Rigaku Saturn724 CCD diffractometer, using graphite monochromated Mo $K\alpha$ radiation (λ = 0.071 073 nm) at 113(2) K. Semi-empirical absorption corrections were applied and all calculations were performed using the Crystalclear program [17]. The structures were solved by direct methods and difference Fourier map using SHELXS of the SHELXTL package and refined with SHELXL [18] by full-matrix least-squares on F^2. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms attached on the carbon atoms were added geometrically and refined with riding model position parameters, and those on water molecule were obtained from difference Fourier maps. A summary of the fundamental crystal data for **1** and **2** is listed in Table 1.

CCDC: 875206, **1**; 875207, **2**.

2 Results and discussion

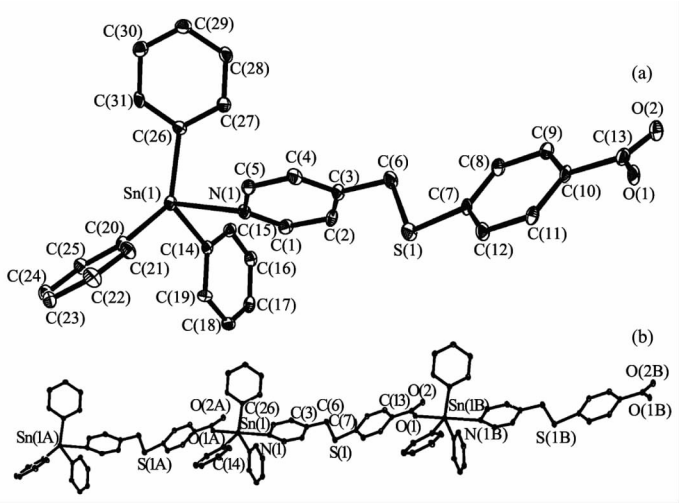
2.1 Synthesis and characterization

4-(4-Pyridylmethylthio)benzoic acid was readily

Table 1 Crystal data and experimental details for 1 and 2

Complex	**1**	**2**
Formula	$C_{31}H_{25}NO_2SSn$	$C_{31}H_{45}NO_3SSn$
Formula weight	594.27	630.43
Crystal size / mm	0.20×0.18×0.10	0.22×0.20×0.10
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
a / nm	1.023 1(5)	1.019 5(2)
b / nm	1.630 0(8)	2.112 9(4)
c / nm	1.584 9(8)	1.441 1(3)
β / (°)	106.417(11)	103.847(3)
Volume / nm^3	2.535(2)	3.014 0(11)
Z	4	4
D_c / (g·cm^{-3})	1.557	1.389
F(000)	1 200	1 312
Absorption coefficient / mm^{-1}	1.120	0.948
2θ range for data collection / (°)	3.66~55.70	3.50~55.74
Reflections collected	25 486	27 685
Independent reflections	5 969 (R_{int}=0.101 4)	7 184 (R_{int}=0.039 5)
Observed reflections (I>2σ(I))	4 564	6 275
Parameters	325	342
Goodness-of-fit on F^2	1.068	1.012
Final R indices (I>2σ(I))	R_1=0.065 5, wR_2=0.142 7	R_1=0.023 7, wR_2=0.054 0

obtained by the reaction of 4-mercaptobenzoic acid with 4-chloromethylpyridine. Treatment of this acid with $(Ph_3Sn)_2O$ or Cy_3SnOH (Cy=cyclohexyl) yielded triphenyltin 4-(4-pyridylmethylthio)benzoate (**1**) and tricyclohexyltin 4-(4-pyridylmethylthio)benzoate (**2**), respectively. These two complexes have been characterized by IR and NMR spectra. It is known that the difference between the asymmetric and symmetric carboxylate stretching vibrations is correlated with the coordination mode of the carboxylate group in the solid state. Generally, when the difference is larger than the corresponding value in ionic compounds, a monodentate coordination mode is suggested [19]. The absorption frequency of the carbonyl group markedly decreases in **1** and **2**, compared with that in the free acid. In addition, the differences between asymmetric and symmetric stretching vibrations of the carboxylate group are 297 cm^{-1} for **1** and 270 cm^{-1} for **2**, respectively, remarkably larger than that observed in sodium 4-(4-pyridylmethylthio)benzoates (219 cm^{-1}), suggesting that the carboxylate group in these two complexes possibly acts as a monodentate ligand. Their ^1H NMR spectra exhibit the expected integration values and peak multiplicities. The ^{119}Sn NMR signals appeared in −126.8 for **1** and 19.2 for **2**, compared to those values reported in the corresponding four-coordinated triaryltin and tricyclohexyltin carboxylates[1], indicating that these two complexes exist in monomeric structure in solution. The chain structure as shown in Fig.1 should lose in solution.



Symmetry code: A x, y+1, z; B x, y−1, z

Fig.1　(a) The asymmetric unit showing 30% probability displacement ellipsoids and (b) polymeric chain structure of **1**

2.2　Crystal structures of 1 and 2

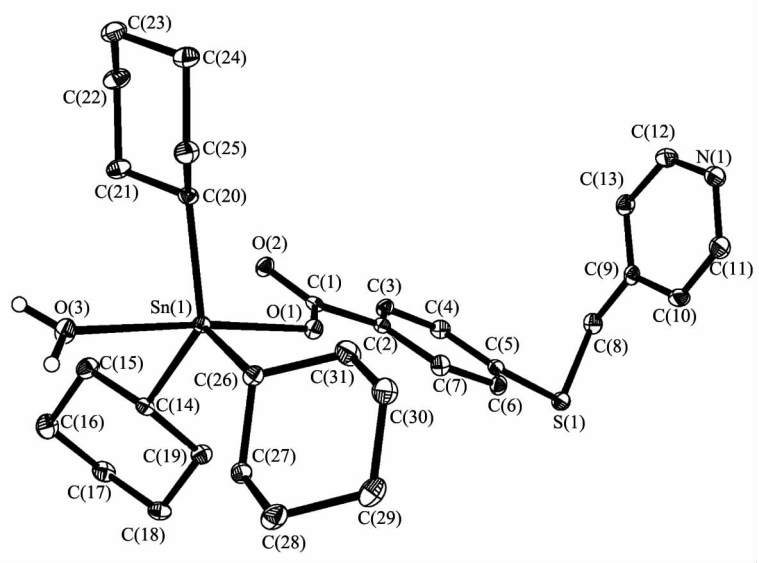
The molecular structure of **1** is determined by X-ray crystallography, and presented in Fig.1. Selected bond distances and angles are listed in Table 2. 4-(4-Pyridylmethylthio)benzoate acts as a bridging bidentate ligand by the carboxylate oxygen and the pyridyl nitrogen atoms to yield a linkage coordination polymer. The carboxylate group coordinates to the tin atom in a monodentate manner, as mentioned by IR spectra. The tin atom adopts a five-coordinate distorted trigonal bipyramidal geometry with the electronegative nitrogen and oxygen atoms occupying the axial positions with an axial angle N(1)-Sn(1)-O(1A) of 178.8(1)°. The Sn(1)-N(1) bond distance is 0.2545(4) nm, longer than that in triphenyltin 2-(1*H*-imidazol-1-yl)acetate (0.235 3 (2) nm)[16], but similar with those in other reported polymeric triphenyltin derivatives with pyridyl carboxylate ligands, such as triphenyltin 2-(4-pyridylmethylthio)benzoate (0.252 4(2) nm)[20], 4-$PyCO_2SnPh_3$ (0.251 2(6) nm)[21]. These results reflect the stronger donor ability of the imidazolyl nitrogen atom compared to the corresponding pyridyl nitrogen atom [22-23]. The non-bond Sn (1) ⋯O (2A) distance is 0.333 5 (4) nm, shorter than the sum of the van der Waals radii for the Sn and O atoms[24], suggesting some weak interactions between these two atoms.

Table 2 Selected bond distances (nm) and bond angles (°) for 1 and 2

			1[a]		
Sn(1)-N(1)	0.254 5(4)	Sn(1)-O(1A)	0.213 5(4)	Sn(1)···O(2A)	0.333 5(4)
Sn(1)-C(26)	0.213 3(5)	C(13)-O(1)	0.131 1(6)	C(13)-O(2)	0.122 5(6)
N(1)-Sn(1)-O(1A)	178.8(1)	C(14)-Sn(1)-C(26)	129.4(2)	C(26)-Sn(1)-N(1)	84.2(2)
O(1)-C(13)-O(2)	125.5(5)	C(6)-S(1-C(7)	103.6(3)	C(14)-Sn(1)-O(1A)	93.4(2)
C(3)-C(6)-S(1)	106.3(4)				
			2		
Sn(1)-O(1)	0.216 4(1)	Sn(1)-O(3)	0.245 8(1)	Sn(1)···O(2)	0.317 7(1)
Sn(1)-C(26)	0.215 9(2)	C(1)-O(1)	0.124 2(2)	C(1)-O(2)	0.181 3(2)
O(1)-Sn(1)-O(3)	175.46(4)	C(14)-Sn(1)-C(20)	126.71(6)	C(20)-Sn(1)-O(1)	97.12(5)
C(14)-Sn(1)-O(3)	82.15(5)	O(1)-C(1)-O(2)	124.7(1)	C(9)-C(8)-S(1)	115.2(1)
C(5)-S(1)-C(8)	100.86(8)				

[a] Symmetry code: A: x, y+1, z

The molecular structure of **2** is shown in Fig.2. One water molecule coordinates to the tin atom, leading to the tin atom to adopt a five-coordinate distorted trigonal bipyramidal geometry with two oxygen atoms occupying the apical positions with an axial angle O(1)-Sn(1)-O(3) of 175.46(4)°, which is similar with that in $(PHPCO_2)SnEt_3$ [10]. 4-(4-Pyridylmethylthio)benzoate adopts a monodentate coordination mode by the carboxylate oxygen atom, different from that in **1**. The pyridyl nitrogen atom does not take part in the coordination to the tin atom. Two asymmetric Sn-O bonds are observed. The Sn(1)-O(1) bond (0.216 4(1) nm) is significantly shorter than the Sn(1)-O(3) (0.245 7(1) nm) bond. In addition, the non-bond Sn (1) ···O (2) distance is 0.317 7 (1) nm, markedly longer than the covalent Sn-O bond distances, but slightly shorter than the corresponding bond distance in **1** and the sum of the van der Waals radii for the Sn and O atoms, suggesting that the weak interactions between these two atoms still exist.



Hydrogen atoms except for O-H are omitted for clarity

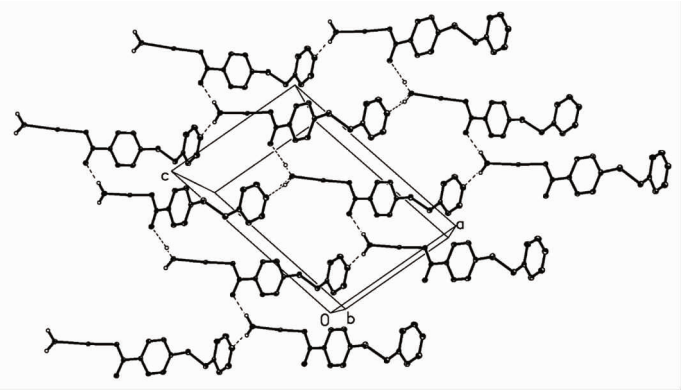
Fig.2 Structure of **2**

Although the pyridyl nitrogen atom does not directly take part in the coordination to the tin atom in **2**, it plays important roles in constructing the integral multidimensional structure. This complex forms an interesting infinite 2D network through the strong intermolecular O (3)-H···O (2)^{i} (H···O/O···O distances: 0.183 9(19)/0.2743 7(18) nm; symmetric operation: ^{i} x, $-y+1.5$, $z-0.5$) and O(3)-H ··· N(1)^{ii} hydrogen bonds (H···N/O···N distances: 0.195 3(19)/0.280 51(18) nm; symmetric operation: ^{ii} $x+1$, $-y+1.5$, $z-0.5$) (Fig.3).

2.3 *In vitro* cytostatic activity

The cytotoxic activity of complexes **1** and **2** for A549, Bel-7402 and Hela cells *in vitro* was assayed by the CCK-8 method according to the manufactures instructions. The activities of compounds were evaluated in terms of their IC_{50} values obtained by linear regression analysis. 4-(4-Pyridylmethylthio) benzoic acid has scarcely activity against these tested cells, but its triorganotin derivatives **1** and **2** display good cytotoxicities. The IC_{50} values of **1** for A549 and Hela cells in vitro are 0.34 and 0.42 μmol·L^{-1}, respectively, which are similar to these values of **2** for A549 (0.31 μmol·L^{-1}) and Hela (0.53 μmol·L^{-1}) cells. The cytotoxic activity of these two complexes for Hela cell is compared to that of organotin bis(pyrazol-1-yl) acetate [25]. In addition, complex **2** shows good cytotoxicity for Bel-7402 cell, and its IC_{50} value is 0.24 μmol·L^{-1}, relatively higher cytotoxic activity than complex **1** (IC_{50} value of 0.50 μmol·L^{-1}).

In conclusion, two triorganotin 4-(4-pyridylmethylthio)benzoates have been synthesized by the reactions of 4-(4-pyridylmethylthio)benzoic acid with triphenyltin oxide and tricyclohexyltin hydroxide. These two complexes exhibit good cytotoxicities for A549, Hela and Bel-7402 cells *in vitro*.



The cyclohexyl groups on the tin atom have been omitted for clarity

Fig.3　Infinite 2D network of **2** through hydrogen bonds

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