Research Article
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Synthesis, characterization and antibacterial activity of cyclohexyltin *N*-(salicylidene)valinates

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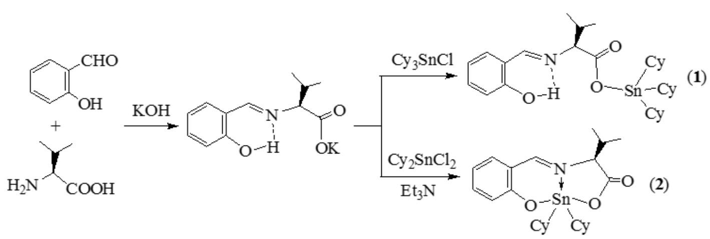
Abstract: Two new cyclohexyltin N-(salicylidene)valinates, [2-$HOC_6H_4CH{=}NCH(CH(CH_3)_2)COO$]$SnCy_3$ (1) and [2-$OC_6H_4CH{=}NCH(CH(CH_3)_2)COO$]$SnCy_2$ (2) (Cy = cyclohexyl), have been synthesized and characterized by elemental analysis, IR, and 1H NMR. The crystal structure of 2 has been determined by X-ray single crystal diffraction. In the complexes, the carboxylate is monodentate. Complex 1 is a four-coordinated tin compound, and 2 has a distorted trigonal bipyramidal geometry with the axial locations occupied by one carboxylate oxygen and a phenolic oxygen of the ligand. Bioassay results show that 1 and 2 have good in vitro antibacterial activity against *Escherichia coli.*

Supporting information: X-Ray (Cif file, Checkcif)

Keywords: *organotin, N-(salicylidene)valine, crystal structure, antibacterial activity*

1. INTRODUCTION

Organotin carboxylates have been received considerable attention due to their structural interest and various applications in the last few decades [1-3]. Some organotin carboxylates possess potent activities against tumours, fungi, bacteria, and other microorganisms [3-6]. Recently, it has been reported that the organotin complexes of Schiff bases have antitumour, antimicrobial, antinematicidal, anti-insecticidal and anti-inflammatory activities [7,8]. N-Salicylidene-a-amino acid derived from salicylaldehyde and a-amino acid is a very versatile ligand having an imine (Schiff base) and a carboxyl group and its organotin complexes have been reported by several groups [9-16]. Structural studies have shown that the diorganotin complexes adopt isolated monomeric structures with the tin atom in a distorted trigonal bipyramid and the dimeric, trimeric and polymeric structures with the tin atom in a distorted octahedron in solid state [9-14], and triorganotin complexes possess [$R_3O_2S_n$] trigonal bipyramidal geometry [15,16]. Bioassay studies showed that the organotin complexes have significant cytotoxic and antibacterial activities [12-16]. In theses investigations [9-17], the more attention was paid to the n-butyl- and phenyltin complexes, and the less to the cyclohexyltin complexes. In order to continue to expand the chemistry and therapeutic potential of the organotin complexes of the ligand, we synthesized two new cyclohexyltin N-(salicylidene)valinates, [2-$HOC_6H_4CH{=}NCH(CH(CH_3)_2)COO$]$SnCy_3$ (1) and [2-$OC_6H_4CH{=}NCH(CH(CH_3)_2)COO$]$SnCy_2$ (2) (Scheme 1), and determined their in vitro antibacterial activity against *Escherichia coli.*



Scheme 1. Synthesis of the complexes.

2. EXPERIMENTAL

2.1 Materials and physical measurements

All chemicals were of reagent grade and were used without further purification (Sinopharm Chemical Reagent Company Limited, Shanghai, China). Carbon, hydrogen and nitrogen 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}. ^1H NMR spectral data were collected using a Bruker Avance DPX300 NMR spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard.

2.2 Synthesis of the ligand

At room temperature, potassium hydroxide (0.224 g, 4 mmol) and L-valine (0.468 g, 4 mmol) were added in methanol (60 mL), and a methanolic solution (20 mL) of salicylaldehyde (0.488 g, 4 mmol) was added dropwise under stirring. The stirring was continued for 0.5 h at 60 °C. The yellow solution obtained was concentrated to about 15 mL under reduced pressure, and then 60 mL anhydrous diethylether was slowly added. The yellow precipitates afforded were filtered out. The yield of product is 0.321 g (62%) after drying for 24 h in vacuum. m.p.: 170-171 °C. Anal. Calcd. for $C_{12}H_{14}KNO_3$: C, 55.57; H, 5.44; N, 5.40%. Found: C, 55.46; H, 5.27; N, 5.32. IR (KBr) cm-1: 3419 (broad, O-H), 1644 [(COO)as], 1612 (C=N), 1395 [(COO)s], 1217 (Ar-O).

2.3 Synthesis of the complexes

2. 3.1 Synthesis of complex 1

A methanol solution (20 mL) of potassium N-(salicylidene) valinate (0.518 g, 2 mmol) was added dropwise to a methanol solution (20 mL) of tricyclohexyltin chloride (0.808 g, 2 mmol) under stirring. The reaction mixture was refluxed for 2 h, and then the solvent was removed using a rotary evaporator. The residue was dissolved in dichloromethane and filtered after washed by using hot hexane. The yellow oil was obtained by the removal of solvent under reduced pressure, and washed with cold methanol and dried in vacuum for 24 h. Yield 0.872 g (74%). Anal. Calcd. for $C_{30}H_{47}NO_3Sn$: C, 61.24; H, 8.05; N, 2.38. Found: C, 61.31; H, 7.98; N, 2.41%. IR (KBr) cm-1: 3410 (broad, O-H), 1662 [(COO)as], 1610 (C=N), 1385 [(COO)s], 1285 (Ar-O). 1H NMR ($CDCl_3$) d: 1H NMR 0.97 (d, J = 7.2 Hz, 3H, CH_3), 1.01 (d, J = 7.2 Hz, 3H, CH_3), 1.25～1.95 (m, 33 H, 3Cy), 2.36～2.46 (m, 1H, CH), 3.84 (d, J = 5.2 Hz, 1H, =NCH), 6.58 (t, J = 7.5 Hz, 1H, H-5 of benzene ring) , 6.77 (d, J = 7.5 Hz, 1H, H-3 of benzene ring) , 6.88-7.10 (m, 2H, H-4 and H-6 of benzene ring), 8.16 (s, 1H, CH=N), 14.72 (s, 1H, OH).

2.3.2 Synthesis of complex 2

A methanol solution (20 mL) of dicyclohexyltin dichloride (0.712 g, 2 mmol) was added dropwise to a methanol solution (20 mL) of potassium N-(salicylidene)valinate (0.518 g, 2 mmol) and Et_3N (0.202 g, 2 mmol) under stirring. The reaction mixture was heated under reflux for 2 h, and the solvent was then removed using a rotary evaporator. The residue was dissolved in dichloromethane and filtered after being washed by using hot hexane. The yellow solid was obtained by the removal of solvent under reduced pressure, and recrystallized from methanol and dried in vacuum. Yield 0.842 g (78%), m.p. 196-197° C. Anal. Calcd. for $C_{24}H_{35}NO_3Sn$: C, 57.17; H, 7.00; N, 2.78%. Found: C, 57.09; H, 6.94; N, 2.77. IR (KBr) cm-1: 1672 [(COO) as], 1604 (C=N), 1420 [(COO)s], 1300 (Ar-O). 1H NMR d: 1.04 (d, J = 6.9 Hz, 3H, CH_3), 1.11 (d, J = 6.8 Hz, 3H, CH_3),

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

Empirical formula	$C_{24}H_{35}NO_3Sn$
Formula weight	504.22
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a / Å	9.8298(17)
b / Å	10.4736(19)
c / Å	23.118(4)
Volume / Å ^{3}	2380.1(7)
Z	4
D_c / (g×cm^{-3})	1.407
m / mm^{-1}	1.097
F(000)	1040
q range / (°)	1.76 to 26.00
Crystal size / mm	0.16´0.10´0.09
Reflections collected/unique	18338 / 4679(R_{int}= 0.0582)
Reflections with I>2s(I)	3542
GOF on F^2	1.009
Flack parameter	-0.04(4)
R indices [I>2s(I)]	R=0.045, wR=0.085
R indices (all data)	R=0.065, wR=0.093
Dρ_{min}, Dρ_{max} / (e×nm^{-3})	-0.353, 0.580

2.26～2.30 (m, 1H, CH), 1.27～2.14 (m, 22H, 2Cy), 3.84 (d, J = 5.1 Hz, 3JSn-H = 36.6 Hz, 1H, =NCH), 6.77 (t, J = 7.5 Hz, 1H, H-5 of benzene ring) , 6.84 (d, J = 7.5 Hz, 1H, H-3 of benzene ring) , 7.21 (d, J = 7.5 Hz, 1H, H-6 of benzene ring), 7.45 (t, J = 7.5 Hz, 1H, H-4 of benzene ring), 8.20 (s, 3JSn-H = 40.8 Hz, 1H, CH=N).

2.4 X-ray crystallography

The yellow single crystal of 2 was obtained from dichloromethane/n-hexane (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-Ka 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 F2 using SHELXL-97 [18]. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions in the riding model approximation. In 2, a cyclohexyl (C(7)-C(12)) was disordered over two conformations, the site occupancies were refined to 0.55(4):0.45(4). 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 1473499.

3. RESULTS AND DISCUSSION

Complexes 1 and 2 were synthesized by the reaction of tricyclohexyltin chloride or dicyclohexyltin dichloride with potassium N-(salicylidene)valinate derived from the condensation of salicylaldehyde and L-valine in the presence of KOH in 1:1 molar ratio (Scheme 1). The complexes are yellow oil or solids that are soluble in common organic solvents such as benzene, chloroform, methanol, acetone and tetrahydrofuran.

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

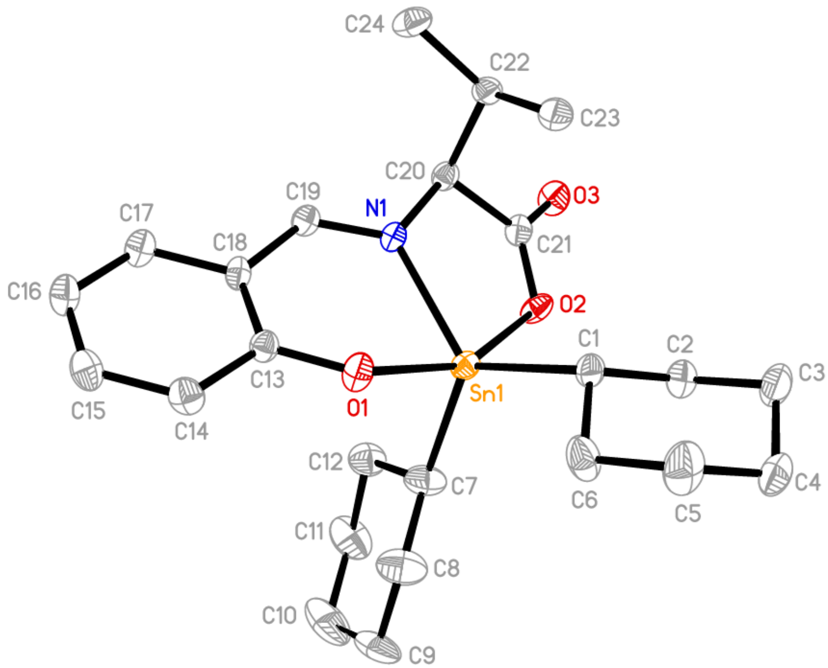
1							
C (µg/ml)	1.28	2.56	3.84	5.12	6.40	7.68	8.96
μ (min^{-1})	0.02302	0.02112	0.02087	0.01904	0.01691	0.01668	0.01481
2							
C (µg/ml)	1.05	2.10	3.15	4.20	5.25	6.30	7.35
μ (min^{-1})	0.03087	0.03004	0.02632	0.02372	0.02112	0.01960	0.0159

The ligand and complex 1 both show a strong band at ~3400 cm -1 assigned to v(O–H×××N) (Scheme1). In 2 this band disappears, indicting the deprotonation of phenolic oxygen of the ligand upon complexation with the tin atom. In 1 and 2, the bands appearing at 1662, 1672 cm-1 and 1385, 1420 cm^{-1} are assigned to ν_{as}(COO) and ν_s(COO), respectively. The difference between ν_{as}(COO) and ν_s(COO) bands, Δν(COO), is indicative of the coordination mode of the carboxylate to tin [20]. The Δν (COO) value is 277 cm^{-1} for 1 and 252 cm^{-1} for 2, which is larger than 200 cm-1, suggesting that the carboxylate is coordinated to tin in a monodentate mode [20]. In the ligand, and 1 and 2, the v(C=N) band appears as a single sharp band at ~1610 cm^{-1} due to the O–H×××N=C intramolecular hydrogen bond and C=N → Sn coordination [9, 15].

In ^{1}H NMR spectra of 1, the single resonance of phenolic O–H is observed at 14.72 ppm because the action of intramolecular O–H×××N=C hydrogen bond makes H shift to N atom, while the signal of OH does not appear in 2, which indicates the replacement of OH proton by the cyclohexyltin moiety on complex formation. In 1 and 2, the signal assigned to azomethine proton (CH=N) and methine proton (=N–CH) appears at ~8.20 and ~3.84 ppm, respectively. The spin-spin coupling of the CH=N proton with tin nucleus (^3J, 40.8 Hz) and =N–CH proton with tin nucleus (^3J, 36.6 Hz) are observed in 2, and are not in 1, which proves that there is CH=N→Sn coordination in 2, and is not in 1.

The molecular structure of 2 is shown in Figure 1, and selected geometric parameters are given in Table 2. Complex 2 crystallizes in chiral space group $P2_12_12_1$, and the coordination geometry of the tin atom is a distorted trigonal bipyramid with two carbons (C(1) and C(7)) of cyclohexyl groups and a N(1) atom from the ligand defining the trigonal plane and a phenolic O(1) and a carboxylic O(2) atom occupying the axial positions. The tin atom forms a five- and a six-membered chelate rings with the ONO tridentate ligand. The two chelate rings both are not planar as seen in the following torsion angles Sn(1)-N(1)-C(20) -C(21) (20.02(2)°) and Sn(1)-O(1)-C(13)-C(18) (-31.31(2)°). The five-membered ring formed by the N(1)-C(20)-C(21)-O(2)-Sn(1) fragment has the C(20) atoms out of the mean planes by 0.121(4) Å. With respect to the six-membered ring defined by the O(1)-C(13)-C(18)-C(19)-N(1)-Sn(1) fragment, the maximum deviation from the mean plane at O(1) atom is 0.263(5) Å. The bond distance of Sn(1)-O(2) is longer than that of Sn(1)-O (1). The bond angle of the axial positions, O(1)-Sn(1)-O(2) (156.54(15)°), is similar to those of the reported analogues such as $Ph_2Sn(3,5-Br_2-2-OC_6H_2CH=NCH(i-Pr)COO)$ (158.03(10)°) [13] and

$Bu_2Sn(3,5-Br_2-2-OC_6H_2CH=NCH(i-Pr)COO)$ (155.1(3)°) [21]. Three angles in the NC2 equatorial plane are in the range of 115.5(3)-122.2(2)°. The tin atom is 0.090(2) Å out of the NC2 trigonal plane in the direction of the more tightly held O(1) atom. Distortions from the ideal geometry may be rationalized partly by the restricted bite angles (O(1)-Sn(1)-N(1), 82.17(16)° and O(2)-Sn(1)-N(1), 74.41(16)°) of the tridentate ligand. The monodentate mode of coordination of carboxylate is also reflected in the disparate C(21)-O(2) and C(21)-O(3) bond



lengths of 1.287(7) and 1.206(7) Å, respectively.

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

Sn(1)-O(1)	2.104(4)	Sn(1)-C(1)	2.139(5)
Sn(1)-O(2)	2.151(4)	Sn(1)-C(7)	2.119(7)
Sn(1)-N(1)	2.169(4)		
O(1)-Sn(1)-C(1)	95.2(2)	C(7)-Sn(1)-O(2)	91.9(2)
O(1)-Sn(1)-C(7)	99.5(3)	O(1)-Sn(1)-N(1)	82.17(16)
C(1)-Sn(1)-C(7)	121.7(3)	C(1)-Sn(1)-N(1)	122.2(2)
O(1)-Sn(1)-O(2)	156.54(15)	C(7)-Sn(1)-N(1)	115.5(3)
C(1)-Sn(1)-O(2)	96.1(2)	O(2)-Sn(1)-N(1)	74.41(16)

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* are active and comparable with the reported tricyclohexyltin 2-phenyl-1,2,3-triazole-4-carboxylates (MIC 13.50 μg/mL) [22] , and dicyclohexyltin N-(3,5-dibromosalicylidene)valinate (MIC 38.63 μg/mL) [21]. The activity of 1 is stronger than that of 2, which may be due to the existence of triorganotin moiety in 1. 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 drugs.

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

Complex	**1**	**2**	Penicillin sodium	cefazolin sodium
Escherichia coli	14.84	23.11	8.03	2.01

[a] MIC = minimum inhibitory concentration.

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References

[1] Tiekink, E. R. T. *Appl. Organomet. Chem*. **1991**, 5, 1-23. DOI: 10.1002/aoc.590050102

[2] Tiekink, E. R. T. *Trends Organomet. Chem*. **1994**, 1, 71-116.

[3] Davies, A. G.; Gielen, M.; Pannell, K. H. and Tiekink, E. R. T. Tin Chemistry: *Fundamentals, Frontiers, and Applications. John Wiley & Sons, Chichester*, U.K., **2008**. DOI: 10.1002/9780470758090

[4] Amir, M. K.; Khan, S.; Rehman, Z.; Shah, A; Butler, I. S. Anticancer activity of organotin carboxylates, *Inorg. Chim. Acta* **2014**, 423, 14-25. DOI：10.1002/9780470758090

[5] Hadjikakou, S. K.; Hadjiliadis, N. *Coord. Chem. Rev*. **2009**,

253, 235-249. DOI: 10.1016/j.ccr.2007.12.026

[6] Wang, W.; Shi, X.; Liu, Q.; Liu, X.; Tian, L. *Commun. Inorg. Synth*. **2015**, 3, 47-51. DOI : 10.21060/cis.2015.333

[7] Nath, M.; Saini, P. K. *Dalton Trans*. **2011**, 40, 7077–7121. DOI: 10.1039/C0DT01426E

[8] Zamudio-Rivera, L. S.; George-Tellez, R.; Lopez-Mendoza, G.; Morales-Pacheco, A.; Flores, E.; Hopfl, H.; Barba, V.; Fernandez, F. J.; Cabirol, N.; Beltran, H. I. *Inorg. Chem*. **2005**, 44, 5370-5378. DOI: 10.1021/ic048628o

[9] Dakternieks, D.; Basu Baul, T. S.; Dutta, S.; Tiekink, E. R. T. *Organometallics* **1998**, 17, 3058-3062. DOI:10.1021/om9800290

[10] Beltran, H. I.; Zamudio-Rivera, L. S.; Mancilla, T.; Santillan, R.; Farfan, N. *Chem. Eur. J.* **2003**, 9, 2291-2306. DOI: 10.1002/chem.200204260

[11] Rivera, J. M.; Reyes, H.; Cortes, A.; Santillan, R. *Chem. Mater*. **2006**, 18, 1174-1183. DOI: 10.1021/cm051589+

[12] Kehie, P.; Chanu, O. B.; Duthie, A.; Hopfl, H. J. *Organomet. Chem.* **2013**, 733, 36-43. DOI:10.1016/j.jorganchem.2013.02.021

[13] Tian, L.; Shang, Z.; Zheng, X.; Sun, Y.; Yu, Y.; Qian, B.; Liu, X. *Appl. Organometal. Chem*. **2006**, 20, 74-80. DOI:10.1002/aoc.1005

[14] Tian, L.; Liu, X.; Zheng, X.; Sun, Y.; Yan, D.; Tu, L. *Appl. Organometal. Chem.* **2011**, 25, 298-304. DOI: 10.1002/aoc.1758

[15] Basu Baul, T. S.; Masharing, C.; Ruisi, G.; Jirasko, R.; Holcapek, M.; Vos, D.; Wolstenholme, D.; Linden, A. J. *Organomet. Chem.* **2007**, 692, 4849-4862. DOI:10.1016/j.jorganchem.2007.06.061

[16] Basu Baul, T. S.; Basu, S.; Vos, D.; Linden, A. Invest. *New Drugs* **2009**, 27, 419-431. DOI: 10.1007/s10637-008-9189-1

[17] Tian, L.; Liu, X.; Mao, W.; Sun, Y.; Liu, X.; Zhou, Z. *Chinese J. Org. Chem.* **2007**, 27, 1258-1263. http://sioc-journal.cn/Jwk_yjhx/CN/Y2007/V27/I10/1258

[18] Sheldrick, G. M. *Acta Crystallogr.* **2008**, A64, 112-122. DOI: 10.1107/S0108767307043930

[19] Zhang, H.; Yu, X.; Li, X. and Pan, X. *Thermochim. Acta* **2004**, 416, 71-74. DOI:10.1016/j.tca.2003.11.033

[20] Deacon, G. B. and Phillips R. J. *Coord. Chem. Rev*. **1980**, 33, 227-250. DOI: 10.1016/S0010-8545(00)80455-5

[21] Tian, L.; Sun, Y.; Zheng, X.; Liu, X.; Yu, Y.; Liu, X; Qian, B. *Chin. J. Chem*. **2007**, 25, 312-318. DOI: 10.1002/cjoc.200790061

[22] Tian, L.; Sun, Y.; Li, H.; Zheng, X.; Cheng, Y.; Liu, X.; Qian, B. *J. Inorg. Biochem*. **2005**, 99, 1646-1652. DOI:10.1016/j.jinorgbio.2005.05.006