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Synthesis, characterization and biological activity of diphenyltin(IV) complexes of *N*-(3,5-dibromosalicylidene)-α-amino acid and their diphenyltin dichloride adducts

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Diphenyltin(IV) complexes of *N*-(3,5-dibromosalicylidene)-α-amino acid, Ph_2Sn[3,5-Br_2-2-OC_6H_2CH=NCH(R)COO] (where R = H, Me, *i*-Pr, Bz), and their 1:1 adducts with diphenyltin dichloride, Ph_2Sn[3,5-Br_2-2-OC_6H_2CH=NCH(R)COO]·Ph_2SnCl_2, have been synthesized and characterized by elemental analysis, IR and NMR (^1H, ^{13}C and ^{119}Sn) spectra. The crystal structure of Ph_2Sn[3,5-Br_2-2-OC_6H_2CH=NCH(*i*-Pr)COO] shows a distorted trigonal bipyramidal geometry with the axial locations occupied by a carboxylate–oxygen and a phenolic–oxygen atom of the ligand, and that of Ph_2Sn[3,5-Br_2-2-OC_6H_2CH=NCH(*i*-Pr)COO]·Ph_2SnCl_2 reveals that the two tin atoms are joined via the carbonyl atom of the ligand to form a mixed organotin binuclear complex. Bioassay indicates that the compounds possess better cytotoxic activity against three human tumor cell lines (HeLa, CoLo205 and MCF-7) than *cis*-platin and moderate antibacterial activity against two bacteria (*E. coli* and *S. aureus*).

KEYWORDS: diorganotin complex; biological activity; *N*-(3,5-dibromosalicylidene)-α-amino acid; binuclear adduct; X-ray structure

INTRODUCTION

In recent years, organotin carboxylates have received considerable attention because of their structural diversity[1,2] and biological properties, particularly cytotoxicity/anti-tumor activity.[3–5] In general, both the organotin moiety and the ligand (carboxylic acid) appear to play an important role in cytotoxicity/anti-tumor activity.[3–5] The diorganotin complexes of *N*-(2-hydroxyarylidene)-α-amino acid have been developed by several groups.[6–14] The mode of coordination of such polydentate ligands to diorganotins is known.[6–14] The structural studies have shown that the diorganotin complexes of the ligands have isolated monomeric structures with the tin atom in a distorted trigonal bipyramid,[6,9,11–14] and dimeric,[8] trimeric[8,13] and polymeric[8,13] structures with the tin atom in a distorted octahedron or a distorted pentagonal bipyramid in solid state. In addition, the reaction of diorganotin(IV) complexes of such ligands with R_nSnCl_{4-n} (R = Ph, $n = 3$ and R = *t*-Bu, $n = 2$) forms the dinuclear molecular adducts by the coordination of carbonyl oxygen of the ligand to the tin of R_nSnCl_{4-n}.[6,15] Bioassay showed that the class of diorganotin complexes possesses good cytotoxic activity against some human tumor cell lines.[8,10,16] In order to continue to expand the chemistry and therapeutic potential of the diorganotin(IV) complexes of the ligands, more recently we have reported the synthesis and cytotoxicity of some diorganotin(IV) complexes with *N*-(5-halosalicylidene)-α-amino acid.[17,18] In this paper, we report the synthesis, structure and anti-microbial

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and cytotoxic activity of the diphenyltin(IV) complexes of *N*-(3,5-dibromosalicylidene)-α-amino acid, Ph_2SnL [L = 3, 5-Br_2-2-$OC_6H_2CH{=}NCH(R)COO$, where R = H, Me, *i*-Pr, Bz], and their adducts with diphenyltin dichloride, $Ph_2SnL{\cdot}Ph_2SnCl_2$ (Scheme 1).

EXPERIMENTAL

Materials and physical measurements

3,5-Dibromosalicylaldehyde was prepared according to the method reported in the literature.[19] Diphenyltin dichloride (Aldrich), Glycine, L-Alanine, L-Valine, L-Phenylalanine (Shanghai, China) and other chemicals were of reagent grade and were used 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 NEXUS-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 TMS as internal standard. ^{119}Sn NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Vx300 spectrometer using Me_4Sn internal reference.

Synthesis of diphenyltin complexes

Potassium hydroxide (0.28 g, 5 mmol) and α-amino acid (5 mmol) were added in 80 ml absolute ethanol. The mixed solution was heated with continuous stirring until the solid disappeared, and then an ethanolic solution (20 ml) of 3,5-dibromosalicylaldehyde (1.40 g, 5 mmol) was added dropwise. A deep-yellow color developed almost immediately, and stirring was continued for 1 h at room temperature. A benzene solution (30 ml) of diorganotin dichloride (1.72 g, 5 mmol) and Et_3N (0.51 g, 5 mmol) was added to the yellow mixed solution (30 ml). The reaction mixture was refluxed for 3 h, and then the solvent was removed using a rotary evaporator. The dry mass was washed thoroughly with hot hexane, and then extracted into dichloromethane and filtered. A yellow product was obtained by removal of solvent under reduce pressure, and recrystallized from chloroform–hexane (1 : 1, v/v). Analytical and physical data of these compounds are as follows.

*Ph_2SnL^1 (R = H, **1**)*

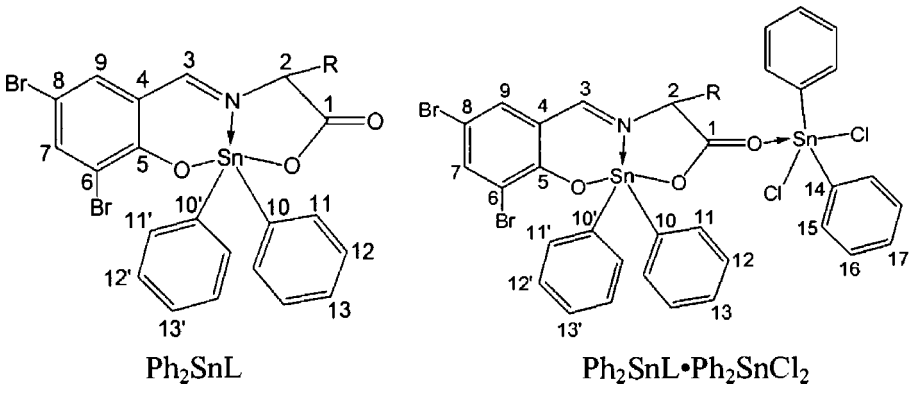
Yield 70%, m.p.: 146–147 °C. Anal. found: C, 41.57; H, 2.35; N, 2.33. Calcd for $C_{21}H_{15}Br_2NO_3Sn$: C, 41.49; H, 2.49; N, 2.30%. IR (cm^{-1}): 1635 [$\nu_{as}(CO_2)$], 1600 [ν(C=N)], 1335 [$\nu_s(CO_2)$], 552 [ν(Sn–O)]. ^1H NMR δ: 4.46 [s, $^3J(^{119}Sn-^1H) = 21$ Hz, 2H, H-2], 7.29 (d, $J = 2.4$ Hz, 1H, H-9), 7.45–7.49 (m, 6H, H-12 + H-13), 7.91–93 (m, 4H, $^3J(^{119}Sn-^1H) = 84$ Hz, H-11), 7.95 (d, $J = 2.4$ Hz, 1H, H-7), 8.35 [s, $^3J(^{119}Sn-^1H) = 54$ Hz, 1H, H-3]. ^{13}C NMR δ: 172.05 (C-1), 170.18 (C-3), 163.50 (C-5), 142.59 (C-7), 136.89 (C-10), 136.62 [$^2J(^{119}Sn-^{13}C) = 58$ Hz, C-11], 136.50 (C-9), 131.45 [$^4J(^{119}Sn-^{13}C) = 17$ Hz, C-13], 129.49 [$^3J(^{119}Sn-^{13}C) = 90$ Hz, C-12], 118.76 (C-4), 118.48(C-6), 108.47 (C-8), 57.64 (C-2).^{119}Sn NMR δ: −332.3.

*Ph_2SnL^2 (R = CH_3, **2**)*

Yield 67%, m.p.: 122–123 °C. Anal. found: C, 42.40; H, 2.58; N, 2.26. Calcd. for $C_{22}H_{17}Br_2NO_3Sn$: C, 42.49; H, 2.76; N, 2.25%. IR (cm^{-1}): 1643 [$\nu_{as}(CO_2)$], 1608 [ν(C=N)], 1383 [$\nu_s(CO_2)$], 559 [ν(Sn–O)]. ^1H NMR δ: 1.55 (d, $J = 7.2$ Hz, 3H, CH_3), 4.31 (q, $J = 7.2$ Hz, 1H, H-2), 7.31 (d, $J = 2.3$ Hz, 1H, H-9), 7.36–7.41 (m, 3H, H-12 + H-13), 7.46–7.50 (m, 3H, H-12′ + H-13′), 7.83–7.85 [m, 2H, $^3J(^{119}Sn-^1H) = 86$ Hz, H-11], 7.93 (d, $J = 2.3$ Hz, 1H, H-7), 7.98–8.00 [m, 2H, $^3J(^{119}Sn-^1H) = 85$ Hz, H-11′], 8.33 [s, $J(^{119}Sn-^1H) = 56$ Hz, 1H, H-3]. ^{13}C NMR 173.79 (C-1), 171.12 (C-2), 163.58 (C-5), 142.57 (C-7), 137.16 (C-10), 137.01 (C-10′), 136.58 [$^2J(^{119}Sn-^{13}C) = 56$ Hz, C-11], 136.35 [$^2J(^{119}Sn-^{13}C) = 56$ Hz, C-11′], 136.19 (C-9), 131.30 (C-13), 131.17 (C-13′), 129.26 ($^3J(^{119}Sn-^{13}C) = 89$ Hz, C-12), 129.09 [$^3J(^{119}Sn-^{13}C) = 90$ Hz, C-12′], 118.62 (C-4), 117.44 (C-6), 107.23 (C-8), 64.59 (C-2), 22.58 (CH_3).^{119}Sn NMR δ: −337.5.

*Ph_2SnL^3 (R = $CH(CH_3)_2$, **3**)*

Yield 60%, m.p.: 219–220 °C. Anal. found: C, 44.23; H, 3.19; N, 2.17. Calcd. for $C_{24}H_{21}Br_2NO_3Sn$: C, 44.35; H, 3.26; N, 2.16%. IR (cm^{-1}): 1675 [$\nu_{as}(CO_2)$], 1609 [ν(C=N)], 1431[$\nu_s(CO_2)$], 580



Ph_2SnL $Ph_2SnL{\bullet}Ph_2SnCl_2$

Scheme 1. The structures of Ph_2SnL and $Ph_2SnL{\cdot}Ph_2SnCl_2$ (R = H, L = L^1; R = Me, L = L^2; R = *i*-Pr, L = L^3; R = Bz, L = L^4).

[ν(Sn–O)]. ^{1}H NMR δ: 0.88 (d, $J = 6.8$ Hz, 3H, CH_3), 0.98 (d, $J = 6.8$ Hz, 3H, CH_3), 2.29–2.33 (m, 1H, CH), 3.99 [d, $J = 4.6$ Hz, $^3J(^{119}Sn-^1H) = 37$ Hz, 1H, H-2], 7.32 (d, $J = 2.1$ Hz, 1H, H-9), 7.35–7.37 (m, 3H, H-12 + H-13), 7.48–7.51 (m, 3H, H-12′ + H-13′), 7.69–7.71 [m, 2H, $^3J(^{119}Sn-^1H) = 84$ Hz, H-11], 7.95 (d, $J = 2.1$ Hz, 1H, H-7), 8.07–8.09 [m, 2H, $^3J(^{119}Sn-^1H) = 85$ Hz, H-11′], 8.20 [s, $^3J(^{119}Sn-^1H) = 55$ Hz, 1H, H-3]. ^{13}C NMR δ: 172.73 (C-1), 171.59 (C-3), 163.67 (C-5), 142.36 (C-7), 136.96 (C-10), 136.79 (C-10′), 136.68 (C-11), 136.60 (C-11′), 136.36 (C-9), 131.37 (C-13), 131.23 (C-13′), 129.38 [$^3J(^{119}Sn-^{13}C) = 89$ Hz, C-12], 129.03 [$^3J(^{119}Sn-^{13}C) = 89$ Hz, C-12′], 118.90 (C-4), 118.67 (C-6), 108.61 (C-8), 74.88 (C-2), 35.17 (CH), 19.20(CH_3), 18.68 (CH_3). ^{119}Sn NMR δ: −333.2.

*Ph_2SnL^4 ($R = CH_2C_6H_5$, **4**)*

Yield 75%, m.p.: 119–120 °C. Anal. found: C, 48.31; H, 3.00; N, 2.03. Calcd for $C_{28}H_{21}Br_2NO_3Sn$: C, 48.18; H, 3.03; N, 2.01%. IR (cm^{-1}): 1677 [$\nu_{as}(CO_2)$], 1621 [ν(C═N)], 1433 [$\nu_s(CO_2)$], 550 [ν(Sn–O)]. ^{1}H NMR δ: 2.69 (dd, $J = 10.8$, 13.9 Hz, 1H, C*H*H), 3.55 (dd, $J = 3.2$, 13.9 Hz, 1H, CH*H*), 4.20 [dd, $J = 3.2$, 10.8 Hz, $^3J(^{119}Sn-^1H) = 46$ Hz, 1H, H-2], 6.77 (d, $J = 2.4$ Hz, 1H, H-9), 6.87–6.99 (m, 2H, H-*o* of C_6H_5), 7.09 [s, $^3J(^{119}Sn-^1H) = 56$ Hz, 1H, H-3], 7.16–7.17 [m, 3H, (H-*m* + H-*p*) of C_6H_5], 7.38–7.40 (m, 3H, H-12 + H-13), 7.52–7.53 (m, 3H, H-12′ + H-13′), 7.82–7.83 [m, 2H, $^3J(^{119}Sn-^1H) = 84$ Hz, H-11], 7.89 (d, $J = 2.4$ Hz, 1H, H-7), 8.02–8.04 [m, 2H, $^3J(^{119}Sn-^1H) = 84$ Hz, H-11′]. ^{13}C NMR δ: 172.88 (C-1), 171.35 (C-3), 163.76 (C-5), 141.98 (C-7), 137.32 (C-10), 137.03 (C-10′), 136.80 [$^2J(^{119}Sn-^{13}C) = 58$ Hz, C-11], 136.69 [$^2J(^{119}Sn-^{13}C) = 56$ Hz, C-11′], 136.09 (C-9), 134.98(C-*i* of C_6H_5), 131.53 [$^4J(^{119}Sn-^{13}C) = 16$ Hz, C-13], 131.44 [$^4J(^{119}Sn-^{13}C) = 16$ Hz, C-13′], 130.34 (C-*m* of C_6H_5), 129.46 [$^3J(^{119}Sn-^{13}C) = 90$ Hz, C-12], 129.33 (C-*o* of C_6H_5), 129.22 [$^3J(^{119}Sn-^{13}C) = 89$ Hz, C-12′], 127.96 (C-*p* of C_6H_5), 118.30 (C-4), 118.14 (C-6), 107.41 (C-8), 70.46 (C-2), 42.02 (CH_2). ^{119}Sn NMR δ: −336.9.

Synthesis of 1 : 1 adducts with diphenyltin dichloride

To Ph_2Sn[3, 5-Br_2-2-OC_6H_2CH═NCH(R)COO] (1.0 mmol) in benzene (20 ml) was added dropwise diphenyltin dichloride (0.34 g, 1.0 mmol) in benzene (20 ml) under stirring. The reaction mixture was refluxed for 2 h, and excess solvent was removed using a rotary evaporator. The yellow solid thus obtained was recrystallized from chloroform-hexane solution (3 : 1, v/v). Analytical and physical data of these compounds are as follows.

*$Ph_2SnL^1 \cdot Ph_2SnCl_2$ (**5**)*

Yield 50%, m.p.: 178–179 °C. Anal. found: C, 41.50; H, 2.54; N, 1.36. Calcd for $C_{33}H_{25}Br_2Cl_2NO_3Sn_2$: C, 41.65; H, 2.65; N, 1.47%. IR (cm^{-1}): 1618 [$\nu_{as}(CO_2) + \nu$(C═N), an unresolved broad band], 1436 [$\nu_s(CO_2)$], 550 [ν(Sn–O)]. ^{1}H NMR δ: 4.26 [s, $^3J(^{119}Sn-^1H) = 21$ Hz, 2H, H-2], 7.30 (d, $J = 2.1$ Hz, 1H, H-9), 7.35–7.53 (m, 12H, H-12 + H-13 + H-16 + H-17), 7.72–7.85 (m, 8H, H-11 + H-15), 7.93 (d, $J = 2.1$ Hz, 1H, H-7), 8.25 [s, $^3J(^{119}Sn-^1H) = 51$ Hz, 1H, H-3]. ^{119}Sn NMR δ: −46.1, −332.5.

*$Ph_2SnL^2 \cdot Ph_2SnCl_2$ (**6**)*

Yield 46%, m.p.: 165–166 °C. Anal. found: C, 41.93; H, 2.79; N, 1.31. Calcd for $C_{34}H_{27}Br_2Cl_2NO_3Sn_2$: C, 42.29; H, 2.82; N, 1.45%. IR (cm^{-1}): 1612 [$\nu_{as}(CO_2) + \nu$(C═N), an unresolved broad band], 1431 [$\nu_s(CO_2)$], 564 [ν(Sn–O)]. ^{1}H NMR δ: 1.55 (d, $J = 7.3$ Hz, 3H, CH_3), 4.31 [q, $J = 7.2$ Hz, $^3J(^{119}Sn-^1H) = 40$ Hz, 1H, H-2], 7.31 (d, $J = 2.4$ Hz, 1H, H-9), 7.37–7.42 (m, 3H, H-12 + H-13), 7.48–7.50 (m, 3H, H-12′ + H-13′), 7.53–7.57 (m, 6H, H-16 + H-17), 7.72–7.74 [m, 4H, $^3J(^{119}Sn-^1H) = 85$ Hz, H-15], 7.80–7.83 [m, 2H, $^3J(^{119}Sn-^1H) = 85$ Hz, H-11], 7.95 (d, $J = 2.4$ Hz, 1H, H-7), 7.97–7.99 [m, 2H, $^3J(^{119}Sn-^1H) = 85$ Hz, H-11′], 8.28 [s, $^3J(^{119}Sn-^1H) = 55$ Hz, 1H, H-3]. ^{13}C NMR δ: 173.84 (C-1), 171.08 (C-3), 163.54 (C-5), 142.61 (C-7), 137.09 (C-10), 136.93 (C-10′), 136.83 (C-14), 136.69 [$^2J(^{119}Sn-^{13}C) = 58$ Hz, C-11], 136.58 [$^2J(^{119}Sn-^{13}C) = 56$ Hz, C-11′], 136.51(C-9), 135.36 [$^2J(^{119}Sn-^{13}C) = 62$ Hz, C-15], 132.04 [$^4J(^{119}Sn-^{13}C) = 17$ Hz, C-17], 131.53 [$^4J(^{119}Sn-^{13}C) = 18$ Hz, C-13], 131.43 [$^4J(^{119}Sn-^{13}C) = 18$ Hz, C-13′], 129.96 [$^3J(^{119}Sn-^{13}C) = 84$ Hz, C-16], 129.60 [$^3J(^{119}Sn-^{13}C) = 91$ Hz, C-12], 129.50 [$^3J(^{119}Sn-^{13}C) = 94$ Hz, C-12′], 118.87(C-4), 118.77(C-6), 108.54 (C-8), 64.67 (C-2), 22.54 (CH_3). ^{119}Sn NMR δ: −45.6, −338.2.

*$Ph_2SnL^3 \cdot Ph_2SnCl_2$ (**7**)*

Yield 48%, m.p.: 193–194 °C. Anal. found: C, 43.35; H, 3.08; N, 1.16. Calcd for $C_{36}H_{31}Br_2Cl_2NO_3Sn_2$: C, 43.51; H, 3.14; N, 1.41%. IR (cm^{-1}): 1605 [$\nu_{as}(CO_2) + \nu$(C═N), an unresolved broad band], 1432 [$\nu_s(CO_2)$], 570 [ν(Sn–O)]. ^{1}H NMR δ: 0.87 (d, $J = 6.9$ Hz, 3H, CH_3), 0.97 (d, $J = 6.8$ Hz, 3H, CH_3), 2.27–2.34 (m, 1H, CH), 3.99 (d, $J = 4.5$ Hz, $^3J(^{119}Sn-^1H) = 38$ Hz, 1H, H-2), 7.32 (d, $J = 2.3$ Hz, 1H, H-9), 7.34–7.39 (m, 3H, H-12 + H-13), 7.48–7.50 (m, 3H, H-12′ + H-13′), 7.53–7.56 (m, 6H, H-16 + H-17), 7.66–7.68 [m, $^3J(^{119}Sn-^1H) = 81$ Hz, 4H, H-15], 7.72–7.74 [m, 2H, $^3J(^{119}Sn-^1H) = 85$ Hz, H-11], 7.95 (d, $J = 2.3$ Hz, 1H, H-7), 8.04–8.06 (m, 2H, $^3J(^{119}Sn-^1H) = 86$ Hz, H-11′), 8.19 [s, $^3J(^{119}Sn-^1H) = 56$ Hz, 1H, H-3]. ^{13}C NMR δ: 173.21 (C-1), 171.59 (C-3), 163.70 (C-5), 142.48 (C-7), 136.52 (C-9), 118.94 (C-4), 118.66 (C-6), 108.72 (C-8), 137.03(C-10), 136.87(C-10′), 136.70 (C-11), 136.37 [$^2J(^{119}Sn-^{13}C) = 58$ Hz, C-11′], 131.43 [$^4J(^{119}Sn-^{13}C) = 18$ Hz, C-13], 131.30 [$^4J(^{119}Sn-^{13}C) = 18$ Hz, C-13′], 129.44 [$^3J(^{119}Sn-^{13}C) = 92.0$ Hz, C-12 + C-12′], 136.80 (C-14), 135.36 [$^2J(^{119}Sn-^{13}C) = 63$ Hz, C-15], 131.88 [$^4J(^{119}Sn-^{13}C) = 18$ Hz, C-17], 129.86 [$^3J(^{119}Sn-^{13}C) = 85$ Hz, C-16], 74.87 (C-2), 35.21 (CH), 19.22 (CH_3), 18.66 (CH_3). ^{119}Sn NMR δ: −46.4, −333.4.

*$Ph_2SnL^4 \cdot Ph_2SnCl_2$ (**8**)*

Yield 66%, m.p.: 165–166 °C. Anal. found: C, 46.22; H, 2.85; N, 1.29. Calcd for $C_{40}H_{31}Br_2Cl_2NO_3Sn_2$: C, 46.11; H, 3.00; N, 1.34%. IR (cm^{-1}): 1610 [$\nu_{as}(CO_2) + \nu$(C═N), an unresolved broad band], 1431 [$\nu_s(CO_2)$], 575 [ν(Sn–O)]. ^{1}H NMR δ: 2.67 (dd, $J = 10.9$, 13.9 Hz, 1H, C*H*H), 3.53 (dd, $J = 3.2$, 13.9 Hz, 1H, CH*H*), 4.18 [dd, $J = 3.2$, 13.9 Hz, $^3J(^{119}Sn-^1H) = 48$ Hz, 1H, H-2], 6.75 (d, $J = 2.4$ Hz, 1H, H-9), 6.86–6.87 (m, 2H, H-*o* of C_6H_5), 7.07 [s, $^3J(^{119}Sn-^1H) = 56$ Hz, 1H, H-3],

7.14–7.16 [m, 3H, (H-*m* + H-*p*) of C_6H_5], 7.37–7.38 (m, 3H, H-12 + H-13), 7.50–7.54 (m, 9H, 12′ + H-13′ + H-16 + H-17), 7.69–7.71 (m, $^3J(^{119}Sn-^1H) = 82$ Hz, 4H, H-15), 7.79–7.81 (m, 2H, H-11), 7.87 (d, $J = 2.4$ Hz, 1H, H-7), 7.99–8.01 (m, 2H, $^3J(^{119}Sn-^1H) = 83$ Hz, H-11′). ^{119}Sn NMR δ: −45.7, −337.6.

X-ray crystallography

The yellow single crystals of compounds **3** (0.04 × 0.09 × 0.20 mm) and **7** (0.12 × 0.15 × 0.25 mm) were obtained from dichloromethane-petroleum ether (60–90 °C; 2 : 1, v/v) solutions of **3** and **7** by slow evaporation at room temperature. The intensity data for crystals of the complexes were measured at 295(2) K on a Bruker Smart Apex area-detector fitted with graphite monochromatized Mo *Kα* radiation (0.71073 Å) using the omega scan technique. Empirical corrections were made by using the SADABS program.[20] The structures were solved by direct-methods[21] and refined by a full-matrix least-squares procedure based on F^2 using the SHELXL-97.[22] The non-H atoms were refined with anisotropic displacement parameters, and H atoms were included in their calculated positions. Disorder was noted in the refinement of each of **3** and **7** so that the C19-phenyl for **3** and C13-methyl for **7** were disposed over two positions each; from refinement, these had 50% site occupancies. The crystallographic parameters and refinements are summarized in Table 1.

Determination of antibacterial activity

The antibacterial activity of the compounds against *E. coli* and *S. aureus* was determined by microcalorimetric method according to the literature.[23] A 2277 Thermal Activity Monitor (Thermometric AB, Sweden) was used to determine the power–time curves of bacterial growth at 310 K. 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 a different concentration of organotin complexes 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. Based on the data of power–time curves and theoretical model,[23] the growth rate constants were calculated. The relationship between the growth rate constants and concentration of organotin medicine was fitted by using computer. When the growth rate constant was 0, the minimum inhibitory concentration (MIC) was confirmed. The experiments were repeated in triplicate for each tested Sn compound concentration.

In vitro cytotoxicity screening

The samples were prepared by dissolving compounds in ethanol, and by diluting the solution obtained with water. In the assays, the concentration of the solvent (ethanol) was less than 0.1%. *Cis*-platin was purchased from Mayne Pharma Pty Ltd (Australia). Three human tumor cell lines, HeLa (cervix tumor cell), CoLo 205 (colon carcinoma cell) and MCF-7 (mammary tumor cell), were obtained from the Tumor Institute of Zhejiang University. *In vitro* cytotoxic activities of the compounds were measured by the MTT assay according to the literature.[18,24] The experiments were repeated three

Table 1. Crystallographic data and structure refinements for **3** and **7**

	3	**7**
Empirical formula	$C_{24}H_{21}Br_2NO_3Sn{\cdot}0.5CH_2Cl_2$	$C_{36}H_{31}Br_2Cl_2NO_3Sn_2$
Formula weight	692.39	993.72
Crystal system	Monoclinic	Triclinic
Space group	*C*2/*c*	*P*-1
a (Å)	29.930(2)	12.0476(5)
b (Å)	9.4742(6)	12.3358(4)
c (Å)	18.4570(16)	14.1244(5)
α (deg)	90	79.597(2)
β (deg)	101.046(10)	79.604(2)
γ (deg)	90	64.512(2)
Volume (Å^3)	5136.8(7)	1851.16(12)
Z	8	2
D_c (g/cm^3)	1.791	1.783
μ (mm^{-1})	4.236	3.687
Reflections collected	28 865	16 691
Independent reflections	5886 ($R_{int} = 0.039$)	7598 ($R_{int} = 0.021$)
Data with $I > 2\sigma(I)$	4318	6158
Goodness-of-fit on F^2	1.03	1.18
Final *R* indices [$I > 2\sigma(I)$]	$R = 0.036$, $Rw = 0.083$	$R = 0.032$, $Rw = 0.078$
R indices (all data)	$R = 0.057$, $Rw = 0.092$	$R = 0.047$, $Rw = 0.093$
CCDC deposition no.	260 174	252 450

times for each test. The dose causing 50% inhibition of cell growth (IC_{50}) was calculated by NDST software.[25]

RESULTS AND DISCUSSION

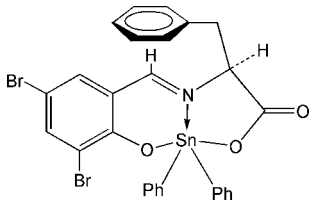
The reaction of diphenyltin dichloride with *in situ* formed potassium salt of *N*-(3,5-dibromosalicylidene)-α-amino acid by condensation of 3,5-dibromosalicylaldehyde and α-amino acid in 1:1 molar ratio in the presence of KOH, affording compounds **1**–**4**. The diphenyltin complex reacted with Ph_2SnCl_2 in refluxing benzene to give the organotin dinuclear adducts **5**–**8**. All complexes were yellow crystalline solids that were soluble in benzene and in polar organic solvents such as chloroform, dichloromethane, ethanol and acetone, but insoluble in water and in saturated aliphatic hydrocarbons.

IR spectra

None of these complexes showed a strong band at ~3400 cm^{-1} assigned to ν(OH), indicting the deprotonation of the phenolic oxygen of the ligand upon complexation with tin atom.[10,14] This was further confirmed by the appearance of a sharp band at ~560 cm^{-1} assignable to the Sn–O stretching vibration[10,26]. In complexes **1**–**4**, the bands appearing in the range 1635–1677 and 1335–1433 cm^{-1} were assigned to $\nu_{as}(CO_2)$ and $\nu_s(CO_2)$, respectively. The difference between the $\nu_{as}(CO_2)$ and $\nu_s(CO_2)$ bands, $\Delta\nu(CO_2)$, is indicative of the coordination number around tin.[27] The difference (from 244 to 300 cm^{-1}) between the $\nu_{as}(CO_2)$ and $\nu_s(CO_2)$ bands is indicative of the unidentate bonding through the carboxylate moiety.[10,27,28] The ν (C=N) band appeared as a single sharp band at ~1610 cm^{-1} and was assigned as being due to C=N → Sn coordination in the solid state.[6] Thus, it may be suggested that compounds **1**–**4** are five-coordinated to tin in the solid. In adducts **5**–**8**, the $\nu_{as}(CO_2)$ appeared at ~1610 cm^{-1} and overlapped the ν(C=N) band. Compared with that of the complexes **1**–**4**, the shift of the band at ~50 cm^{-1} to lower wave-numbers confirmed the interaction of the carbonyl oxygen atom of complexes **1**–**4** with Ph_2SnCl_2.[6] The $\Delta\nu(CO_2)$ value for **5**–**8** (from 173 to 186 cm^{-1}) further indicated that the carboxylate group bridged two tin atoms[29] to form mixed organotin dinuclear compounds.

NMR spectra

The ^1H and ^{13}C chemical shift assignments of the compounds are straightforward from the multiplicity patterns and/or resonance intensities of the signals and also the related literature.[13,30] The ^1H NMR spectra of the complexes show that the signal assigned to azomethine proton N=CH (H-3) appears in the range 8.19–8.35 ppm for compounds **1**–**3** and **5**–**7**, while this signal shifts to lower frequencies and appears at 7.09 and 7.07 ppm in **4** and **8**, respectively, due to the shielding effect of CH_2–phenyl group on H-3 (Scheme 2). The signal in the range of 3.99–4.46 ppm was assigned to CH_2–N=/CH–N= proton (H-2). The appearances of



Scheme 2. Shielding of $-CH_2C_6H_5$ on H-3 in **4** and **8**.

spin–spin coupling of the –N=CH– proton (H-3) with tin nucleus (^3J, from 51 to 56 Hz) and the CH_2–N=/CH–N= proton (H-2) with tin nucleus (^3J, from 21 to 46 Hz) further confirmed the presence of nitrogen–tin coordination in all complexes. In all cases, the $^3J(^{119}Sn-^1H)$ coupling constants for H-3 were larger than those for H-2. The signals of the carboxyl carbon (C-1) and imine carbon (C-3) appeared in the range 172.05–173.84 ppm and 170.18–171.59 ppm, respectively. The signal of N-C (C-2) appeared in the range 57.64–74.88 ppm, depending on the nature of the substituent R. The $^1J(^{119}Sn-^{13}C)$ couplings in these compounds were not observed. With the exception of **1** and **5**, the other complexes showed two resonances for the protons (H-11–H-13 and H-11′–H-13′) and carbon atoms (C-10–C-13 and C-10′–C-13′) of two phenyl groups bonded to tin, which may be due to the presence of the chiral center (C-2) in these complexes.[31] The ^{119}Sn chemical shifts depend on the number and nature of alkyl or aryl groups coordinated with tin central atom.[32] In $CDCl_3$, complexes **1**–**4** showed a resonance between −332.3 and −337.5 ppm, characteristic of pentacoordinated tin atoms in non-coordinating solvents[6,13]. Adducts **5**–**8** give two ^{119}Sn NMR resonances in the range of −45.6 to −46.4 ppm and −332.5 to −338.2 ppm, respectively, which were assigned to the Ph_2SnCl_2 moiety and Ph_2SnL core, respectively. This indicates that these adducts dissociate into four-coordinate Ph_2SnCl_2 and five-coordinate Ph_2SnL in solution at room temperature.[6]

Crystal structures of 3 and 7

The molecular structures and the atom numbering schemes for compounds **3** and **7** are respectively shown in Figs 1, and 2, and selected geometric parameters are given in the respective figure captions. Compound **3** crystallizes with half a dichloromethane molecule in the crystallographic asymmetric unit. The Sn atom is in a distorted trigonal bipyramid with two phenyl groups and the imino-N1 atom occupying the equatorial positions and the axial positions being occupied by a phenoxide–O1 and a unidentate carboxylate–O3 atom. The bond length of Sn–O3 was longer than that of Sn–O1 and the bond angle O1–Sn–O3 was 158.03(10)°; these were comparable to that observed in $Ph_2Sn(2\text{-}OC_6H_4CH{=}NCHRCOO)$ (R = H, Me, Et, *i*-Pr),[11,13] $Ph_2Sn(2\text{-}OC_6H_4C(CH_3){=}NCH_2COO)$,[6] $Ph_2Sn(3\text{-}CH_3\text{-}2\text{-}OC_6H_3C(CH_3){=}NCH_2COO)$,[8] $Ph_2Sn(5\text{-}CH_3\text{-}2\text{-}OC_6H_3C(CH_3){=}NCH_2COO)$[9] and $Ph_2Sn(2\text{-}OC_{10}H_6$

Table 2. Structure data for some diphenyltin complexes of *N*-(2-hydroxyarylidine)-α-amino acid, Ph_2SnL

Compound (L)	Sn–N1 (Å)	Sn–O1 (Å)	Sn–O3 (Å)	O1–Sn–O3 (°)	Reference
2-$OC_6H_4CH{=}NCH_2COO$	2.155(3)	2.071(2)	2.117(3)	160.03(13)	11
2-$OC_6H_4CH{=}NCH(Me)COO$	2.148(3)	2.073(2)	2.140(2)	156.90(9)	13
2-$OC_6H_4CH{=}NCH(Et)COO$	2.148(2)	2.083(2)	2.151(2)	158.02(8)	13
2-$OC_6H_4CH{=}NCH(i\text{-}Pr)COO$	2.165(5)	2.075(4)	2.134(4)	159.39(17)	13
2-$OC_6H_4C(CH_3){=}NCH_2COO$	2.190(5)	2.064(4)	2.127(4)	160.3(2)	6
3-CH_3-2-$OC_6H_3C(CH_3){=}NCH_2COO$	2.151(2)	2.049(2)	2.116(2)	161.21(8)	8
5-CH_3-2-$OC_6H_3C(CH_3){=}NCH_2COO$	2.185(3)	2.055(4)	2.122(3)	157.7(1)	9
2-$OC_{10}H_6CH{=}NCH_2COO$	2.142(5)	2.092(4)	2.124(4)	157.24(15)	33
3,5-Br_2-2-$OC_6H_2CH{=}NCH(i\text{-}Pr)COO$	2.170(3)	2.084(3)	2.125(2)	158.03(10)	This work

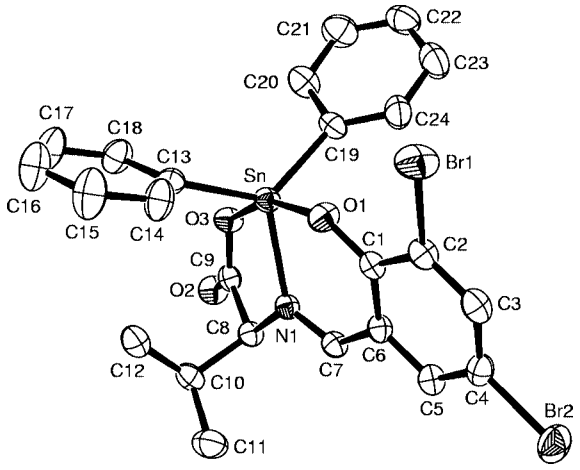


Figure 1. The molecular structure of **3**; H atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Sn–O1 2.084(3), Sn–O3 2.125(2), Sn–N1 2.170(3), Sn–C13 2.109(4), Sn–C19 2.113(3), C9–O2 1.213(4), C9–O3 1.297(4); O1–Sn–O3 158.03(10), O1–Sn–N1 82.74(10), O1–Sn–C13 94.41(13), O1–Sn–C19 95.13(12), O3–Sn–N1 75.61(10), O3–Sn–C13 97.30(12), O3–Sn–C19 93.01(12), N1–Sn–C13 112.72(12), N1–Sn–C19 121.42(13), C13–Sn–C19 125.76(15).

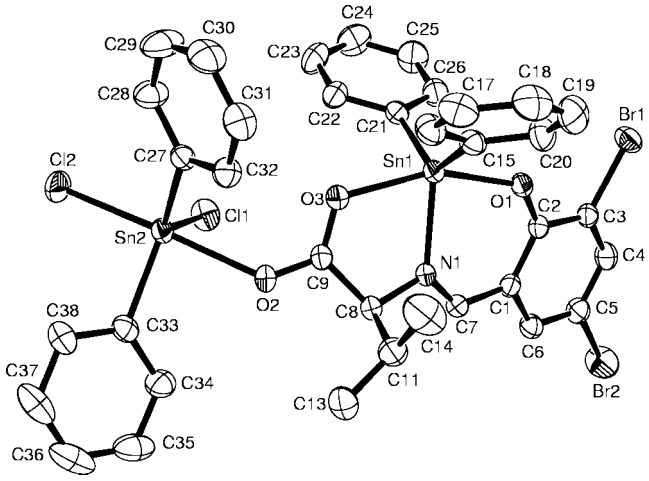


Figure 2. The molecular structure of **7**; H atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Sn1–O1 2.087(3), Sn1–O3 2.171(3), Sn1–N1 2.180(3), Sn1–C15 2.116(4), Sn1–C21 2.117(4), Sn2–Cl1 2.355(1), Sn2–Cl2 2.440(1), Sn2–O2 2.315(3), Sn2–C27 2.120(4), Sn2–C33 2.126(4), C9–O2 1.254(4), C9–O3 1.263(5); O1–Sn1–O3 157.40(11), O1–Sn1–N1 83.07(11), O1–Sn1–C15 95.52(14), O1–Sn1–C21 96.50(14), O3–Sn1–N1 74.37(11), O3–Sn1–C15 94.90(14), O3–Sn1–C21 93.05(13), N1–Sn1–C15 113.94(14), N1–Sn1–C21 118.41(14), C21–Sn1–C15 127.25(16), Cl1–Sn2–Cl2 90.49(5), Cl1–Sn2–O2 81.70(9), Cl2–Sn2–O2 171.07(9), C1l–Sn2–C27 118.63(11), Cl1–Sn2–C33 114.02(12), Cl2–Sn2–C27 97.52(11), Cl2–Sn2–C33 94.91(12), C27–Sn2–C33 125.54(16), C27–Sn2–O2 90.06 (13), C33–Sn2–O2 84.42(14).

$CH{=}NCH_2COO$)[33] (Table 2). Distortions from the ideal geometry may be rationalized partly by the restricted bite angles of the tridentate ligand. Neither of the five or six-membered rings formed upon chelation are planar, as seen in the following torsion angles: Sn–O1–C1–C6 −20.4(5)°, Sn–N1–C7–C6 11.8(5)°, Sn–O3–C9–C8 6.8(4)° and Sn–N1–C8–C9 20.0(3)°).

The compound **7** is a binuclear adduct by carboxyl group bridging two different organotins [Sn1–O3 2.171(3) Å and Sn2–O2 2.316(3) Å]. The geometric parameters around the Sn1 atom in **7** were almost identical to those around the Sn atom in **3**. The Sn1–O3 bond was slightly longer in **7** due to the withdrawal of electron density from O2 and donation to the Sn2 atom via the carboxylate group to form the O2 → Sn2 interaction. This was further confirmed by the apparent lengthening of the C9–O2 bond [1.254(5) Å] and shortening of the C9–O3 bond [1.262(5) Å] in **7** compared with the distances [C9–O2 1.213(4) Å, and C9–O3 1.297(4) Å] in **3**. Thus, the Sn2 atom was five-coordinate with Cl2 and O2 along the axial direction [Cl2–Sn2–O2, 171.08(9)°] and Cl1 and two C atoms, C27 and C33, of the two phenyls forming the equatorial plane. The apical Sn2–Cl2 bond distance [2.440(1) Å] was longer than the equatorial Sn2–Cl1 distance [2.355(2) Å]. The

Table 3. Antibacterial activity of some compounds

Compound	MIC[a] (μg ml^{-1})	
	E. coli	*S. aureus*
1	21.56	2.36
2	17.03	2.73
3	19.12	2.79
7	24.21	3.53
Ph_2SnCl_2[34]	25	12.5
Ph_2SnL[34,b]	<12.5	<12.5
penicillin G sodium	15.11	1.79

[a] MIC = minimum inhibitory concentration.
[b] L = 2-$OC_{10}H_6CH{=}NCHRCOO$ (R = Me, Et, *i*-Pr).

Table 4. Cytotoxic results against HeLa, CoLo205 and MCF-7of **1**, **3** and **7**

Compound	IC_{50} (μmol l^{-1})		
	HeLa	CoLo205	MCF-7
1	1.96	1.99	2.14
3	3.31	11.60	5.74
7	0.16	1.10	0.28
cis-Platin	4.81	13.94	18.73

structural characteristic of compound **7** is similar to that found in the reported binuclear adducts with triphenyltin chloride, $Ph_2Sn(2\text{-}OC_6H_4C(CH_3){=}NCH_2COO)\cdot SnPh_3Cl$[6] and $Ph_2Sn(OC(CH_3){=}CHC(CH_3){=}NCH_2COO)\cdot SnPh_3Cl$.[15]

Biological activity

The antibacterial activities of several compounds and the reference drug (penicillin G sodium) are listed in Table 3. The results show that the complexes are more active against the two bacteria than the parent organotin, Ph_2SnCl_2[34], and the activity against *S. aureus* is better than against *E coli*. However, their activity is lower than the reference drug. As seen from Table 3, the results are comparable with those of $Ph_2Sn(2\text{-}OC_{10}H_6CH{=}NCHRCOO)$ (R = Me, Et, *i*-Pr). Thus, the complexes possess moderate bactericidal activity.[34]

The results of cytotoxic assay of **1, 3** and **7** against HeLa, CoLo205 and MCF-7 are shown in Table 4. The three compounds belong to the efficient cytostatic agents and their cytotoxic activities were higher than those of the clinically widely used *cis*-platin. The data from Table 4 also reveal that the binuclear adduct **7** is the more active against the three cell lines than the mononuclear complexes **1** and **3**. In comparison with the reported diphenyltin analogs, compounds **1** and **3** were less active than $Ph_2Sn(2\text{-}OC_{10}H_6CH{=}NCH_2COO)$[10] (the IC_{50} against MCF-7 is 170 ng ml^{-1}, i.e. 0.34 μmol l^{-1}) against MCF-7, and the cytotoxicity of compound **7** against MCF-7 was similar to that of $Ph_2Sn(2\text{-}OC_{10}H_6CH{=}NCH_2COO)$.

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