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Crystal Structure and *in vitro* Antitumour Activity of Dibutylbis(5-chloro-2-hydroxybenzoato)tin(IV)

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The crystal structure of the title compound, [$nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2$], shows that in the monomeric species the six-coordinate Sn atom exists in a skew trapezoidal bipyramidal geometry in which the four O donor atoms, derived from two asymmetrically chelating carboxylate ligands, define the basal plane and the n-butyl substituents lie over the weaker Sn–O interactions defining a C–Sn–C angle of 147.6(2)°. An unusual feature of the structure is the presence of both intra- and inter-molecular hydrogen bonding contacts which serve to stabilize the structure. The *in vitro* antitumour activity of this compound against mammary and colon carcinoma cell lines is also reported.

Keywords: Diorganotin, carboxylate, crystal structure, antitumour

INTRODUCTION

Interest in the title compound has two, not necessarily unrelated, perspectives. This research is stimulated by a systematic investigation into the potential antitumour activity of organotin compounds[1,2] and also of the structural characteristics of such derivatives.[3] The preparation and spectroscopic characterization of the title compound [$nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2$] has been studied in this context.

EXPERIMENTAL

The [$nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2$] compound was prepared using the literature procedure[4] and crystals for the X-ray study were grown by the slow evaporation of a hexane solution of the compound; m.p. 119–120 °C. The ^1H NMR data (with respect to internal TMS), obtained in $CDCl_3$ solution, showed the following resonances (multiplicity, coupling constant(s) in Hz; assignment): δ 0.92 (t, 7; CH_3), 1.43 (tq, 7, 7; γ-CH_2), 1.75 (tt, 7, 7; β-CH_2), 1.90 (t, 7, unresolved $^2J(^1H-^{119/117}Sn)$ 76; α-CH_2), 6.95 (d, 9; 3-H), 7.43 (dd, 9, 3; 4-H), 7.45 (d, 3; 6-H) and 10.5 ppm (bs; OH). The ^{13}C NMR data were recorded in $CDCl_3$ solution (internal TMS) and were assigned by use of incremental rules for aromatic substitution[5] together with ^{13}C DEPT spectra in which resonances from quaternary C atoms are suppressed; the calculated values of the chemical shifts of C-1 to C-6 are given in parentheses: δ 13.6 (CH_3), 26.5 [unresolved $^3J(^{13}C-^{119/117}Sn) = 96$ Hz; γ-CH_2], 26.7 ($\beta = CH_2$), 26.7 [$^1J(^{13}C-^{119/117}Sn) = 548/525$; α-CH_2], 113.8 (C-1; calcd 117.6), 160.4(C-2; 154.4), 119.2 (C-3; 117.1), 136.3 (C-4; 134.9), 124.4 (C-5; 128.8), 131.0 (C-6; 130.0), 177.3 ppm CO_2. The ^{119}Sn NMR data were measured with respect to external tetramethyltin (coupling constants in Hz): $CDCl_3$, δ −116.4 [$^1J(^{13}C-^{119}Sn) = 548$]; $CDCl_3$ + 1 equiv. DMSO, −153.3 [$^1J(^{13}C-^{119}Sn) = 590$]; $CDCl_3$ + 2 equiv. DMSO, −178.0; DMSO, −280.2 ppm. Mössbauer data (mm s^{-1}): IS 1.52; QS 3.70; Γ_1 0.88 and Γ_2 0.91.

The compound was screened against MCF-7 (mammary tumour) and WiDr (colon carcinoma) cell lines utilizing an automated *in vitro* procedure.[6]

Intensity data for a colourless crystal (0.11 mm × 0.11 mm × 0.42 mm) were measured at room temperature on a Rigaku AFC6R four-circle diffractometer equipped with graphite monochromatized MoKα radiation, λ =

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0.71073 Å (0.071073 nm). A total of 5950 data were measured (ω:2θ scan technique and θ_{max} was 27.5°), of which 5676 were unique and 3621 satisfied the $I \geq 3.0\sigma(I)$ criterion of observability and were used in the subsequent analysis. The data were corrected for Lorentz and polarization effects[7] and for absorption employing the DIFABS program,[8] which resulted in a range of transmission factors of 0.922 to 1.126.

Crystal data for [$nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2$]: $C_{22}H_{26}Cl_2O_6Sn$, $\underline{M} = 576.0$, triclinic, space group $\underline{P}\bar{1}$, $\underline{a} = 11.797(3)$, $\underline{b} = 12.109(3)$, $\underline{c} = 9.564(2)$ Å, $\alpha = 112.84(2)$, $\beta = 97.29(2)$, $\gamma = 103.32(2)°$, $\underline{V} = 1189.1(6)$ Å^3, $\underline{Z} = 2$, $\underline{D}_{calcd} = 1.609$ g cm^{-3}, $\underline{F}(000) = 580$, $\mu = 13.33$ cm^{-1}.

The structure was solved by direct methods[9] and refined by a full-matrix least-squares procedure based on $\underline{F}$.[7] Non-H atoms were refined with anisotropic thermal parameters and H-atoms were included in the model at their calculated positions (C–H 0.97 Å), except for the O$\underline{H}$ atoms which were located but not refined. At convergence $\underline{R} = 0.036$ and $\underline{R}_w = 0.036$ (sigma weights[7]). The analysis of variance showed no special features and the maximum residual in the final difference map was 0.56 e Å^{-3}. The final fractional atomic coordinates are listed in Table 1 and the crystallographic numbering scheme used is shown in Fig. 1, which was drawn with ORTEP[10] at 30% probability ellipsoids. Data manipulation was performed with the teXsan package[7] installed on an Iris Indigo workstation. Other crystallographic details, comprising thermal parameters, H-atom parameters, all bond distances and angles, and tables of observed and calculated structure factors, are available on request from ERTT.

Table 1 Fractional atomic coordinates for [$nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2$]

Atom	*x*	*y*	*z*
Sn	0.83742(3)	0.16955(3)	0.23678(4)
Cl(13)	1.2070(1)	0.3744(2)	0.2237(2)
Cl(23)	0.7186(1)	−0.4194(1)	−0.4554(2)
O(1)	0.9369(3)	0.2359(3)	0.1049(3)
O(2)	0.9585(3)	0.3985(3)	0.3224(4)
O(3)	0.7930(3)	−0.0019(3)	0.0396(3)
O(4)	0.7043(3)	−0.0442(3)	0.2058(4)
O(16)	1.1022(3)	0.6161(3)	0.3788(4)
O(26)	0.5467(3)	−0.2636(3)	0.1104(4)
C(1)	0.9832(4)	0.3525(4)	0.1942(5)
C(2)	0.7270(4)	−0.0802(4)	0.0755(6)
C(11)	1.0672(4)	0.4294(4)	0.1428(5)
C(12)	1.0941(4)	0.3740(4)	0.0002(5)
C(13)	1.1739(4)	0.4449(5)	−0.0460(6)
C(14)	1.2289(4)	0.5700(5)	0.0478(7)
C(15)	1.2034(4)	0.6254(4)	0.1870(7)
C(16)	1.1222(4)	0.5562(4)	0.2374(6)
C(21)	0.6779(4)	−0.2114(4)	−0.0402(5)
C(22)	0.7164(4)	−0.2504(4)	−0.1760(5)
C(23)	0.6691(4)	−0.3708(4)	−0.2865(5)
C(24)	0.5797(5)	−0.4546(4)	−0.2661(6)
C(25)	0.5412(4)	−0.4174(4)	−0.1335(7)
C(26)	0.5894(4)	−0.2962(4)	−0.0175(6)
C(31)	0.9737(5)	0.1559(4)	0.3837(5)
C(32)	1.0230(4)	0.0499(4)	0.3024(5)
C(33)	1.1336(5)	0.0542(5)	0.4013(6)
C(34)	1.1804(5)	−0.0540(5)	0.3253(7)
C(41)	0.6843(5)	0.2274(5)	0.2145(7)
C(42)	0.5819(7)	0.1794(9)	0.2657(12)
C(43)	0.5957(8)	0.1861(9)	0.4127(10)
C(44)	0.4955(7)	0.1618(9)	0.4833(12)

DISCUSSION

The expected integration (^{1}H) and multiplicities were observed (^{1}H and ^{13}C) in the NMR spectra of [$nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2$]. The chemical shifts in the ^{119}Sn NMR spectra, when recorded in DMSO solution (a strongly nucleophilic solvent) and in $CDCl_3$ solution, were characteristic for hexacoordinate and pentacoordinate species, respectively.[11] Unambiguous structure determination was afforded, however, by a single-crystal structure analysis.

The molecular structure of [$nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2$] is shown in Fig. 1, and selected interatomic parameters are listed in Table 2. The tin atom exists in a skew-trapezoidal bipyramidal geometry with the basal plane defined by the four oxygen donor atoms; the tin atom lies 0.0076(4) Å out of the basal plane in the direction of the C(31) atom. Each of the carboxylate ligands chelates the tin atom, forming disparate Sn–O bond distances of approximately 2.1 and 2.6 Å. The disparity in the Sn–O bond distances is reflected in the associated C–O bond distances (see Table 2) with the longer C–O bond distances being associated with the stronger of the Sn–O bonds and *vice versa*. However, the differences in the C–O bond distances are not as great as expected owing to the presence of intramolecular O···H interactions (see below) which elongate the C=O bond distances, compared with related structures,[3] for the O-atoms involved in the weak interactions to the tin atom. The n-butyl substi-

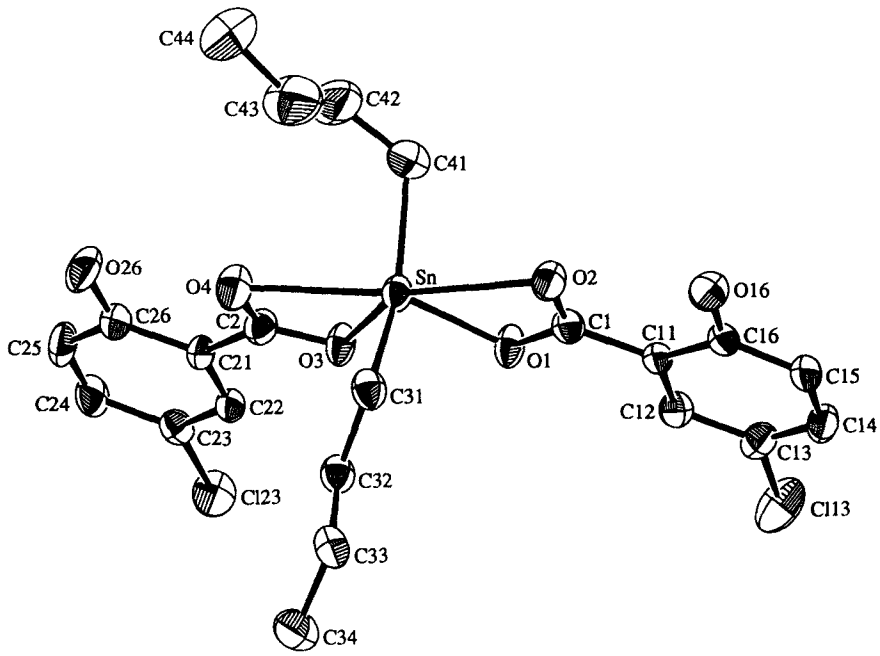

Figure 1 Molecular structure and crystallographic numbering scheme for $[nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2]$.

tuents are orientated so as to lie over the weaker Sn–O(2) and Sn–O(4) interactions and define a C–Sn–C angle of 147.6(2)°. To a first approximation, the environment about the tin atom reported here for $[nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2]$ resembles closely those found in other $[R_2Sn(O_2CR)_2]$ derivatives.[3] A difference between this structure and those of related

Table 2 Selected bond distances and angles for $[nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2]$

Atoms	Distance (Å)	Atoms	Distance (Å)
Sn–O(1)	2.083(3)	Sn–O(2)	2.552(3)
Sn–O(3)	2.086(3)	Sn–O(4)	2.582(3)
Sn–C(31)	2.078(5)	Sn–C(41)	2.098(6)
O(1)–C(1)	1.269(5)	O(2)–C(1)	1.238(5)
O(3)–C(2)	1.266(5)	O(4)–C(2)	1.237(5)
C(1)–C(11)	1.465(6)	C(2)–C(21)	1.460(6)
Atoms	**Angle (deg)**	**Atoms**	**Angle (deg)**
O(1)–Sn–O(2)	54.8(1)	O(1)–Sn–O(3)	83.1(1)
O(1)–Sn–O(4)	137.1(1)	O(1)–Sn–C(31)	99.9(2)
O(1)–Sn–C(41)	103.1(2)	O(2)–Sn–O(3)	137.9(1)
O(2)–Sn–O(4)	168.1(1)	O(2)–Sn–C(31)	88.5(1)
O(2)–Sn–C(41)	86.3(2)	O(3)–Sn–O(4)	54.0(1)
O(3)–Sn–C(31)	102.1(2)	O(3)–Sn–C(41)	103.1(2)
O(4)–Sn–C(31)	88.7(2)	O(4)–Sn–C(41)	89.8(2)
C(31)–Sn–C(41)	147.6(2)	Sn–O(1)–C(1)	103.1(3)
Sn–O(2)–C(1)	81.8(2)	Sn–O(3)–C(2)	104.5(3)
Sn–O(4)–C(2)	81.7(3)	O(1)–C(1)–O(2)	120.2(4)
O(3)–C(2)–O(4)	119.8(4)		

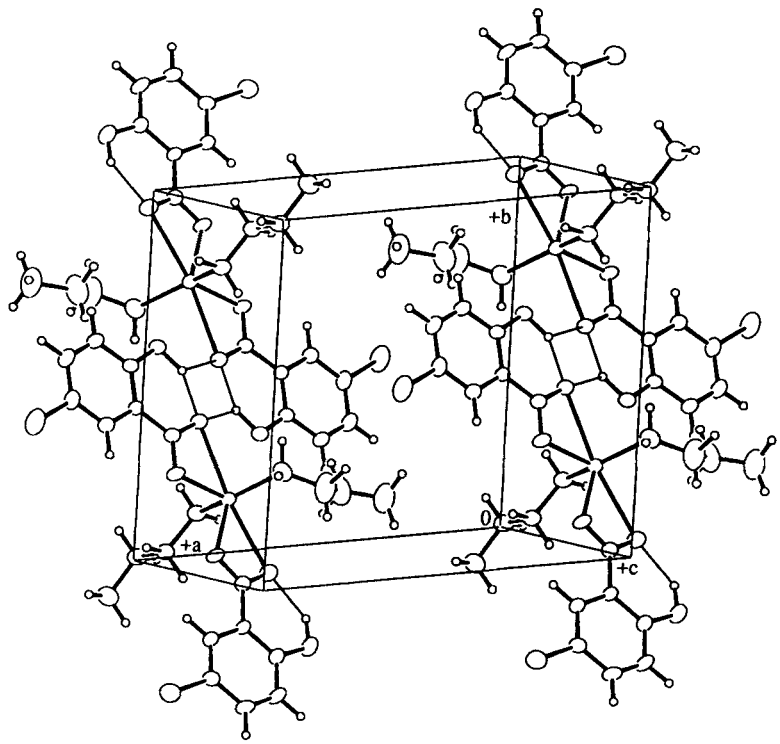

Figure 2 Unit cell contents for $[nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2]$.

species is found in the nature of hydrogen bonding contacts that stabilize both the molecular and crystal structures.

The structure features both intra- and intermolecular hydrogen bonding contacts. Within the molecule there are intramolecular contacts between the hydroxyl-bound hydrogen atoms and the weakly coordinated oxygen atoms derived from the carboxylate ligands. The O(2)···HO(16) and O(4)···HO(26) separations are 1.63 and 1.81 Å, respectively. The carboxylate residues are coplanar with the disubstituted phenyl groups, presumably to maximize these contacts; the values for the C(1)/C(11)/C(16)/O(16) and C(2)/C(21)/C(26)/O(26) torsion angles are −0.4(7) and −1.3(7)°, respectively. It was mentioned above that the molecular geometry about the tin atom is as found for related derivatives and hence it can be concluded that the presence of the intramolecular contacts does not have a significant effect on the overall structure.

In addition to the intramolecular contacts described above, there are intermolecular hydrogen bonding contacts in the lattice, albeit weaker, involving the O(2) atom and a centrosymmetrically related HO(16) atom; the O(2)···H(16)′ separation is 2.72 Å (symmetry operation: $2-x$, $1-y$, $1-z$). This has the result that the lattice comprises loosely associated dimers linked by hydroxyl hydrogen atoms. A view of the unit cell contents of $[nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2]$ is shown in Fig. 2, which highlights the intra- and inter-molecular hydrogen bonding contacts. The formation of such dimeric units places the symmetry-related O(16) atom in close proximity with the tin atom; however, the Sn···O(16)′ separation of 3.441(3) Å is not considered a significant bonding interaction.

The *in vitro* antitumor trials on $[nBu_2Sn(5\text{-Cl-2-OH-}C_6H_3CO_2)_2]$ against MCF-7 (mammary tumour) and WiDr (colon carcinoma) cell lines revealed values for ID_{50} of 89 and 319, respectively. These compare well with values of 850 and 624, respectively, for cisplatin and 63 and 31, respectively, for doxorubucin, and are comparable with the activities found for related organotin compounds.[1,2]

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