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Synthesis, characterization, X-ray crystal structure and *in vitro* antitumour activity of sodium bis(2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylato)triphenylstannate

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Sodium bis[2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylato]triphenylstannate, $[(CH_3OCH_2CH_2OCH_2CH_2OCH_2CH_2)$-1,2-$C_2B_{10}H_{10}$-9-$COO)_2SnPh_3]^-$ Na^+, compound 1, was synthesized by the 1:1 condensation of triphenyltin(IV) hydroxide with 2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid and crystallized in the presence of sodium bicarbonate. Its structure was determined by spectroscopy, elemental analysis and X-ray diffraction. The structure of 1 consists of trigonal bipyramidal $[Sn(Ph)_3(L)_2]^-$ anions and Na^+ cations coordinated by oxygen atoms of polyoxaalkyl chains of different stannate anions, forming cation–anion chains elongated along the *c* axis. Compound 1 is significantly more active *in vitro* against seven tumour cell lines of human origin than 5-fluorouracil, *cis*-platin, carboplatin, and previously reported organotin carboranecarboxylates, but is less active than organotin polyoxaalkylcarboxylates. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: organotin carboranecarboxylate; synthesis; crystal structure; antitumour activity

INTRODUCTION

The *in vitro* antitumour activities of many organotin derivatives against a panel of human cancer cell lines have been determined.[1] Several of these appear to be quite promising active compounds. Additionally, boron derivatives are potentially interesting for boron neutron capture cancer therapy, provided that these compounds exhibit a sufficiently selective affinity towards certain tumour cells. Consequently, several 1,2- or 1,7-dicarba-*closo*-dodecaborane derivatives of tin have been described,[2] and the synthesis, characterization and *in vitro* antitumour screening of several such compounds have been reported. Some of them contain a carborane cage linked to the tin atom via a B–Sn σ-bond.[3] Organotin carboranecarboxylates in which the carborane cage is linked to the carboxylic moiety via a carbon[4,5] or boron[6] atom have been studied. All carborane-based organotin compounds previously tested have revealed *in vitro* antitumour activities that are less than those of the clinically used methotrexate and doxorubicin, but greater than those of 5-fluorouracil, *cis*-platin and carboplatin.[3–6] However, all the compounds mentioned are poorly soluble in water, and water solubility is advisable for antitumour drugs. Therefore, we decided to synthesize an organotin derivative of *o*-carborane containing a polyoxaalkyl substituent that is known to increase the water solubility. The compound we

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planned to synthesize was triphenyltin 2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylate. Instead, we obtained sodium bis[2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylato]triphenylstannate, $[(CH_3OCH_2CH_2OCH_2CH_2OCH_2CH_2)$-1,2-$C_2B_{10}H_{10}$-9-$COO)_2SnPh_3]^-Na^+$ (**1**). Here, we report the synthesis, characterization and *in vitro* antitumour activity of compound **1**, which is water soluble not only because it contains a polyoxaalkyl substituent but also because it is a salt.

RESULTS AND DISCUSSION

Synthesis and characterization

The novel sodium bis[2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylato]triphenylstannate (**1**) was synthesized by the 1:2 (or 1:1) condensation of triphenyltin(IV) hydroxide with 2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid followed by crystallization in the presence of sodium bicarbonate, which permits the isolation of crystals from the mixture (Scheme 1). Its structure was determined by spectroscopy, elemental analysis and X-ray diffraction.

Electrospray mass spectroscopy of a $CHCl_3$ solution revealed a pattern corresponding to $(M - OCOCB_{10}H_{10}CCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_3 + Na)^+$ [mono-isotopic peak (^1H, ^{12}C, ^{11}B, ^{23}Na, ^{120}Sn): 709].

Mössbauer parameters [QS: 3.23 mm^{-1}; IS: 1.27 mm^{-1}; Γ_1: 1.22 mm^{-1}; Γ_2: 1.22 mm^{-1}] have been obtained. The QS values obtained for triphenyltin polyoxacarboxylates (3.60 mm^{-1}, 3.44 mm^{-1})[7,8] are quite similar and typical for a pentacoordinate tin atom.

In the IR spectrum, the band corresponding to the asymmetric C═O stretching, observed at 1664 cm^{-1} (KBr), allows one to exclude a polymeric structure sometimes observed for triphenyltin polyoxacarboxylates.[7,8]

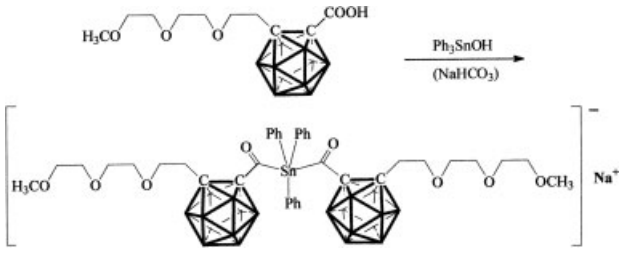
The ^{117}Sn NMR chemical shift in $CDCl_3$ (−88.9 ppm) is quite similar to those obtained for triphenyltin polyoxaalkylcarboxylates (−100 ppm).

The crystal structure was determined by X-ray diffraction. In the structure of **1** (Fig. 1) the six-coordinate Na^+ cations serve to link neighbouring anions via Na···O contacts so that a zig-zag chain is formed aligned along the *c*-axis, as shown in Fig. 2.

The coordination polyhedron of tin is a trigonal bipyramid with oxygen atoms in axial positions. The Sn–C bond lengths (average 2.138(4) Å) have standard values. The Sn–O bond distances are significantly different (Sn–O1 and Sn–O1′: 2.274(2) Å and 2.206(2) Å respectively).

The bond lengths and angles in the carborane fragments and in the terminal trioxadecyl substituents are standard.

The sodium ions are bonded to carbonyl oxygen O2 and to five oxygen atoms of trioxadecyl substituents. It should be



Scheme 1.

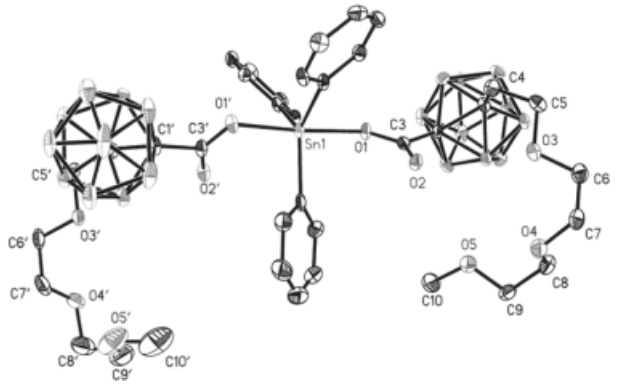


Figure 1. Structure of the stannate anion **1**; hydrogen atoms have been omitted for clarity. Key geometric parameters: Sn–C(Ph) 2.133(4), 2.140(4); 2.151(4); Sn–O1 2.274(2); Sn–O1′ 2.206(2) Å; O1–Sn–O1′ 175.85(9); O1–Sn–C11 92.9(1); O1′–Sn–C11 91.2(1)°.

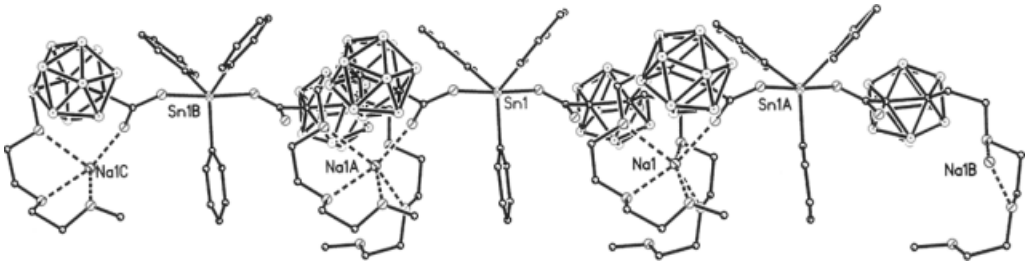


Figure 2. Coordination of the oxygen atoms of the stannate ion **1** with sodium ions in the crystal; hydrogen atoms have been omitted for clarity. Key geometric parameters: Na–O 2.386(3), 2.494(3), 2.300(3), 2.347(3), 2.449(3), 2.539(3) Å (symmetry transformation $x, y, z + 1$).

noted that sodium forms stronger bonds with one trioxadecyl moiety (Sn–O3, O4, O5 is 2.347(3) Å, 2.449(3) Å and 2.539(3) Å respectively) than with the other (O3′ and O4′ of 2.386(3) Å and 2.494(3) Å respectively). Sodium does not form bonds with the methoxy O5′ of the second trioxadecyl substituent (the Na···O5′ distance is more than 4 Å). Sodium ions form the shortest bond with the carbonyl O2 (2.300(3) Å).

The coordination polyhedron of sodium is a distorted octahedron with the O2 and O4 atoms in apical positions.

Thus, the coordination of $SnPh_3$ with two carboxylic ligands L in **1** is characterized by significantly different Sn–O bond lengths and Sn–O–C angles. To determine whether the bond lengths and angles are specific for compound **1** or comparable to other related compounds, we searched these geometric parameters for similar complexes $[Sn(R^1)_3(OCOR^2)_2]^-$. There are 15 similar structures described in the Cambridge Structural Database,[9] of which 10 have isolated complex anions similar to **1**, nine structures have $[Sn(R^1)_3(OCOR^2)_2]^-$ anions ($R^1 = CF_3$, $C(CS_2NMe_2)_2$, CH_2NHMe, $CH_2CS_2N(Me)Ph$ and coumarin-3-yl), and one contains the $[Sn(C_6H_{11})_3(OCOCF_3)_2]^-$ anion. Three structures with dicarboxylate ligands (1,3-$Py(COO)_2$, $OCOCH_2COO$ and $OCOCH_2CH_2COO$) have polymeric structures due to coordination of COO groups with $Sn(Bu)_3$. They could be considered to be structures with an isolated fragment $\{Sn(Bu)_3(OCOR)_2\}$. In addition, the two structures $Sn(Ph)_3(OCOCH_2SC(S)CN(Ph)Me)_2$ and $Sn(Me)_3(OCOCH_2SC(S)NMe_2)_2$ are polymeric, due to the coordination of both carboxylic oxygen atoms. The structures of the $\{SnC_3O_2\}$ fragment of all the compounds described and **1** are identical.

The Sn–O and O–C bonds lengths and the Sn–O–C angles of these anions vary over wide intervals (Sn–O 2.19–2.31 Å, O–C 1.22–1.32 Å, Sn–O–C 119–140°), and systematic variations are not obvious. Therefore, we can suppose that these geometric parameters are not characteristic for these types of molecule and depend on global crystal packing considerations.

Compound **1** was screened *in vitro* against seven tumour cell lines of human origin. The ID_{50} values obtained are given in Table 1. Compound **1** is significantly more active than 5-fluorouracil, *cis*-platin and carboplatin, and is comparable with methotrexate and doxorubicin. It is more active than the previously reported organotin carboranecarboxylates[4–6] (1,2-$C_2B_{10}H_{11}$-9-$COO)_2SnBu_2$ (**2**), $\{[(1,7\text{-}C_2B_{10}H_{11}\text{-}1\text{-}COO)_2Bu_2Sn]_2\}_2$ (**3**), $\{[(2\text{-}Ph\text{-}1,2\text{-}C_2B_{10}H_{10}\text{-}1\text{-}COO)_2Bu_2Sn]_2\}_2$ (**4**), $\{[(2\text{-}Me\text{-}1,2\text{-}C_2B_{10}H_{10}\text{-}1\text{-}CH_2COO)_2Bu_2Sn]_2\}_2$ (**5**). Its activity is lower than observed for organotin polyoxaalkylcarboxylates[7,8] and is comparable to other organotin stannates.[10–13]

EXPERIMENTAL

2-(3′,6′,9′-Trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid was prepared as described previously.[14]

^1H and ^{13}C NMR spectra were obtained on a Bruker AMX-400 spectrometer at 400.13 MHz and 100.61 MHz respectively. ^{117}Sn NMR spectra were acquired on a Bruker Avance 250 instrument equipped with a Quattro probe tuned to 89.15 MHz for ^{117}Sn. The ^{117}Sn reference frequency was calculated from the absolute references $\Xi(^{117}Sn) = 35.632\,295$ MHz.[15]

IR data were recorded in the range 400–4000 cm^{-1} using a Perkin–Elmer System 2000 FT-IR spectrometer and a Mid-IR beam. Samples were prepared as KBr pellets with about 3 mg of product and 200 mg of dry KBr.

Mössbauer spectra were obtained as described previously.[16]

Boron, tin and sodium elemental analyses were performed by the express-gravimetry method of Pregl–Korshun.[17]

An analytical sample was burned in an oxygen flow at 950 °C in a platinum boat in the presence of quartz and PbO. The boron, tin and sodium contents were calculated on the basis of the ash composition $20B_2O_3 \cdot 2SnO_2 \cdot Na_2O$. The boron and sodium contents were also independently determined

Table 1. *In vitro* antitumour activities (ID_{50}) of **1** against MCF-7 and EVSA-T (two breast cancers), WiDr (a colon carcinoma), IGROV (an ovarian cancer), M19 MEL (a melanoma), A498 (a renal cancer) and H226 (a non-small-cell lung cancer), together with those of some reference compounds used clinically and of some carborane-based organotin compounds described previously

	ID_{50} (ng ml^{-1})						
Compound	MCF-7	EVSA-T	WiDr	IGROV	M19 MEL	A498	H226
1	44	38	37	39	39	45	41
2	146	142	439	139	174	195	291
3	45	38	290	110	110	140	
4	138	164	514	169	220	301	338
5	74	140	283	102	172	182	246
5-Fluorouracil	350	720	440	850	310	340	5300
Methotrexate	15	26	7	20	18	16	70
Doxorubicin	25	13	18	150	21	55	180

by spectrophotometry and atomic emission spectroscopy respectively.

The protocol followed for the antitumour screenings has been reported elsewhere.[18,19]

Synthesis

Sodium bis(-2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylato)triphenylstannate (**1**) was synthesized in benzene (150 ml) from 2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid (0.42 g, 1.25 mmol) and triphenyltin(IV) hydroxide (0.46 g, 1.25 mmol). After 30 min of reflux, a clear solution was obtained; this was then refluxed for a further 5 h. The binary azeotrope water–benzene was distilled off using a Dean–Stark funnel. The benzene solution obtained was evaporated *in vacuo*. A cloudy oil was obtained; this was dissolved in 50 ml of diethyl ether to which 50 ml of a saturated solution of $NaHCO_3$ in water was added. The resulting mixture was extracted twice with 40 ml of diethyl ether. The ether solution was evaporated *in vacuo*. The solid obtained was purified by recrystallization from methylene chloride–*n*-heptane to give 1.3 g (67%) of colourless crystals. Anal. Found: C, 44.25; H, 6.64; B, 19.52 (19.44, spectrophotometry); Na, 2.09 (2.61, atom emission spectroscopy); Sn, 10.81. Calc. for $C_{38}H_{65}B_{20}O_{10}NaSn$: C, 43.89; H, 6.30; B, 20.79; Na, 2.21; Sn, 11.41.

^{1}H NMR ($CDCl_3$): CH_{2carb} 2.56 (broad s); CH_3 3.35 (s); OCH_2 3.49–3.6 (m); *p*-Ph 7.25 (s); *m*-Ph 7.48 (s); *o*-Ph 7.68 (s, ^3J ^{1}H–$^{119/117}$Sn = 28.8 Hz). ^{13}C NMR ($CDCl_3$): C_{carb} 35.11 (s); OCH_3 58.96 (s); CH_2 69.45, 69.77, 69.85, 71.23 (m); *m*-Ph 129.15 (s, ^2J ^{13}C–$^{119/117}$Sn = 31.4 Hz); *p*-Ph 130.68 (s); *o*-Ph 136.56 (s, ^2J ^{13}C–$^{119/117}$Sn = 23.8 Hz); C=O 162.09. ^{117}Sn NMR ($CDCl_3$): −88.9 (s). IR ν(CO) = 1664 cm^{-1}. Mössbauer parameters: QS: 3.23 mm^{-1}; IS: 1.27 mm^{-1}; Γ_1: 1.22 mm^{-1}; Γ_2: 1.22 mm^{-1}.

Crystal structure determination

Crystal data **I**: $C_{38}H_{65}B_{20}NaO_{10}Sn$, $M = 1039.78$, monoclinic, space group $P2_1/c$, $a = 12.286(2)$ Å, $b = 39.527(7)$ Å, $c = 11.909(2)$ Å, $\beta = 116.007(5)°$, $V = 5198(2)$Å^3, $Z = 4$, $D_{calc} = 1.329$ g cm^{-3}, μ(Mo − Kα) = 0.551 mm^{-1}, crystal size 0.10 × 0.20 × 0.50 mm^3. Intensity data were measured at 110 K on a Bruker SMART 1000 CCD area detector so that $2\theta < 60°$. Final $R_1 = 0.052$ (from 5859 unique reflections with $I > 2\sigma(I)$) and $wR_2 = 0.109$ (all 15 037 data) for 851 parameters, ρ_{max} 1.21 e$^-$ Å^{-3} – CCDC deposition number: 225304. Reflection intensities were integrated using the SAINT software[20] and correction for the effects of absorption was made with SADABS.[21] The structure was solved by direct methods and refined on F^2 (anisotropic displacement parameters for non-hydrogen atoms and isotropic displacement parameters for hydrogen atoms) using SHELXTL.[22] All hydrogen atoms were located from the difference Fourier syntheses; the hydrogen atoms of CH_2CH_2OMe groups were calculated geometrically and included in the final refinement using the 'riding' model with the U_{iso}(H) parameters equal to $1.5U_{eq}(C_i)$, where U(C_i) are the equivalent thermal parameters of the carbon atoms to which corresponding hydrogen atoms are bonded.

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