CRYSTALLOGRAPHIC CHARACTERIZATION OF $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$. *IN VITRO* ANTI-TUMOUR ACTIVITY

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Abstract.

The crystal structure of the title compound, $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$, shows that the Sn atom exists in a distorted octahedral geometry with the phenyl substituents in mutually *trans* positions. The Sn-Cl bond distances are 2.493(2) and 2.414(2) Å and Sn-N are 2.448(5) and 2.526(5) Å. The compound displays good cytotoxicity against L1210 mouse leukaemia cells with an ID_{50} score of 0.39 μM.

Introduction.

Adducts of diorganotin dichlorides containing diimine ligands such as 2,2′-bipyridyl and 1,10-phenanthroline are well known and several examples have been characterized by X-ray crystallographic methods as summarized recently [1]. In addition, some of these compounds are known to display *in vitro* anti-tumour activity and a structure/activity relationship has been postulated [2, 3]. Thus, it has been suggested that compounds with Sn-N bond distances > 2.39 Å are active whereas those with shorter Sn-N bond distances are not [2, 3]. In this context, it was thought of interest to explore the coordination chemistry towards diorganotin dihalide systems of other bidentate, non-planar nitrogen-donor ligands. Hence, the adduct of Ph_2SnCl_2 with bis(2,5-dimethylpyrazole)methane,

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hereafter {$Ph_2SnCl_2[(Me_2pz)_2CH_2]$}, has been prepared, characterized spectroscopically and its structure determined by crystallographic methods.

Experimental.

Preparation and spectroscopy. The {$Ph_2SnCl_2[(Me_2pz)_2CH_2]$} compound was prepared by dissolving equimolar amounts of Ph_2SnCl_2 and $[(Me_2pz)_2CH_2]$ in hot benzene (80 cm^3). The suspension that formed was stirred for 1 h and the solution allowed to evaporate to dryness. Crystals were obtained by the slow vapour diffusion of diethyl ether into an acetonitrile solution of the compound; m.pt. 185 °C. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker ACP-300 spectrometer operating at 300.13 and 75.47 MHz, respectively; TMS was the internal reference. ^1H NMR: δ 2.16 s (pz-Me, C1); 2.40 s (pz-Me, C5); 5.78 s (CH_2); 6.03 s (CH); 7.47 - 7.73 ppm (Ph). ^{13}C NMR: δ 11.7 (pz-Me, C1); 13.9 (pz-Me, C5); 106.9 (CH); 140.8 (CN1); 148.9 (CN2); 130.2 - 137.6 (Ph) ppm. The electron impact mass spectrum was measured on a VG ZAB-2HF spectrometer.

Crystallography. Intensity data for a yellow crystal (0.03 x 0.19 x 0.40 mm) were measured at room temperature on a Rigaku AFC6R four-circle diffractometer fitted with graphite-monochromatized MoKα radiation, λ = 0.7173 Å. A total of 5973 data were measured (ω:2θ scan technique and θ_{max} was 55.0°), 5642 were unique and of these 2980 satisfied the $I > 3.0\sigma(I)$ criterion of observability and were used in the subsequent analysis. The data were corrected for Lorentz and polarization effects [4] and for absorption employing the DIFABS program [5] which resulted in a range of transmission coefficients of 0.939 to 1.045.

Crystal data for {$Ph_2SnCl_2[(Me_2pz)_2CH_2]$}: $C_{23}H_{26}Cl_2N_4Sn$, M = 548.1, monoclinic, space group $P2_1/n$, a = 9.335(5), b = 16.422(3), c = 14.984(4) Å, β = 95.96(3)°, V = 2284(1) Å^3, Z = 4 , D_{calcd} = 1.593 g cm^{-3}, $F(000)$ = 1104, μ = 13.69 cm^{-1}.

The structure was solved by direct methods [6] and refined by a full-matrix least-squares procedure based on F [4]. The non-H atoms were refined with anisotropic thermal parameters and the H atoms were included in the model at their calculated positions (C-H 0.97 Å). At convergence R = 0.041 and R_w = 0.038 (sigma weights [4]).* The final fractional atomic coordinates are listed in Table 1 and the

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* where $R = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma wF_o^2]^{1/2}$

crystallographic numbering scheme used is shown in Figure 1, which was drawn with ORTEP [7] at 30% probability ellipsoids. Data manipulation was performed with the teXsan package [4] installed on an Iris Indigo workstation.

Table 1. Fractional atomic coordinates for $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$

Atom	x	y	z
Sn	0.09174(5)	0.78640(3)	0.68260(3)
Cl(1)	0.0679(2)	0.8362(1)	0.8375(1)
Cl(2)	0.2494(2)	0.8958(1)	0.6477(1)
N(11a)	0.0948(6)	0.7245(3)	0.5342(3)
N(12a)	-0.0131(6)	0.6740(3)	0.4989(3)
N(21a)	-0.0712(5)	0.6637(3)	0.6840(3)
N(22a)	-0.1654(6)	0.6427(3)	0.6120(3)
C(1)	-0.1012(7)	0.8460(4)	0.6372(4)
C(1a)	-0.1545(7)	0.6830(4)	0.5272(4)
C(2)	-0.1101(9)	0.8972(4)	0.5639(5)
C(3)	-0.2421(11)	0.9319(5)	0.5314(5)
C(4)	-0.3602(10)	0.9160(5)	0.5724(6)
C(5)	-0.3544(8)	0.8681(5)	0.6451(6)
C(6)	-0.2250(8)	0.8325(4)	0.6768(4)
C(7)	0.2553(7)	0.7026(4)	0.7262(4)
C(8)	0.3609(8)	0.7264(4)	0.7897(4)
C(9)	0.4643(9)	0.6717(5)	0.8235(5)
C(10)	0.4595(9)	0.5929(5)	0.7958(5)
C(11a)	0.3493(8)	0.7425(5)	0.5129(5)
C(11)	0.3553(8)	0.5691(4)	0.7313(5)
C(12a)	0.2084(8)	0.7039(4)	0.4917(4)
C(12)	0.2543(8)	0.6235(4)	0.6974(4)
C(13a)	0.1709(9)	0.6423(4)	0.4309(4)
C(14a)	0.0300(8)	0.6240(4)	0.4381(4)
C(15a)	-0.0642(9)	0.5617(4)	0.3914(5)
C(21a)	-0.0141(9)	0.6128(5)	0.8379(4)
C(22a)	-0.0986(7)	0.6122(4)	0.7481(4)
C(23a)	-0.2114(8)	0.5613(4)	0.7165(5)
C(24a)	-0.2511(7)	0.5812(4)	0.6307(5)
C(25a)	-0.3672(8)	0.5488(5)	0.5655(5)

In vitro anti-tumour testing. L1210 mouse leukaemia cells were grown as suspension cultures in MEM (Eagle's Minimum Essential Medium) plus 1% glutamine and 10% foetal calf serum (Flow Laboratories). The compound was dissolved in DMSO at 10 concentrations over a 3-log range, with a final maximum DMSO concentration in the medium of 0.5%. Growth inhibition was tested by incubation of log-phase cells at 37°C in a humidified incubator gassed with 10% CO_2/90% air for 48 h in the presence of the compound. Cells were then counted using a Coulter counter, and the ID_{50} in µmol dm^{-3}, or dose causing 50% inhibition of cell growth, was determined from the curve of percentage growth versus dose. All assays were performed in duplicate. Control cultures exposed only to the vehicle were included with each test.

Results and Discussion.

The compound $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$ has been been prepared from the stoichiometric mixing (1:1) of Ph_2SnCl_2 and $(Me_2pz)_2CH_2$ in benzene solution. The ^1H NMR spectrum recorded in $CDCl_3$ solution showed the expected peaks and integration; the expected peaks were also found in the ^{13}C NMR spectrum recorded in the same solvent (see Experimental). The major ion in the electron impact mass spectrum of the compound was $[(Me_2pz)_2CH_2]^+$ at m/z 205. The parent ion was not observed, however, ions due to fragments were present: $[Ph_2SnCl(Me_2pz)_2CH_2]^+$ (m/z 513, rel. int. 40%); $[SnCl(Me_2pz)_2CH_2]^+$ (359, 22) and $[PhSnCl]^+$ (233, 8); all other fragments had relative intensity < 2%. Unambiguous structure determination has been afforded by crystallographic methods.

The molecular structure of $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$ is shown in Figure 1 and selected interatomic parameters are collected in Table 2. The Sn atom exists in a distorted octahedral geometry defined by the two N atoms of the bidentate ligand, two Cl atoms and two C atoms derived from the phenyl groups. The phenyl groups occupy mutually *trans* positions and are virtually orthogonal to each other as seen in the dihedral angle between the two rings of 97.9°. The maximum distortion from the ideal octahedral geometry is seen in the chelate angle of 75.0(2)° which reflects the restricted bite angle of the ligand. The two Sn-Cl bond distances are experimentally different from each other, i.e. Sn-Cl(1) is 2.493(2) Å and Sn-Cl(2) is 2.414(2) Å. The reason for the disparity is not obvious. There are no significant intermolecular interactions in the lattice that may explain this variation; the closest non-H contact of 3.41(1) Å occurs between C(25a) and C(25a)' (symmetry operation: -1-*x*, 1-*y*, 1-*z*). The most likely explanation for the disparity in the Sn-Cl bond distances may lie in the asymmetric mode of coordination of the bidentate ligand which most likely occurs owing to the restricted bite angle of the ligand. Thus, the Sn-N bond lengths are different from each other with the shorter Sn-N(11a) bond distance of 2.448(5) Å being *trans* to the longer of the Sn-Cl bonds; the Sn-N(21a) bond distance is 2.526(5) Å. The Sn-N bond distances fall between 2.27 to 2.58 Å, i.e. in the range of Sn-N distances found for related systems as determined by a search of the Cambridge Crystallographic Data Base [8]. The six-membered chelate ring adopts a boat conformation and the dihedral angle between the two pyrazole rings (including the methyl groups) is 69.7°. The Sn atom geometry reported here, i.e. *trans* organo substituents and *cis* chlorides, is in essential agreement with those found in related diimine adducts of R_2SnCl_2 [1].

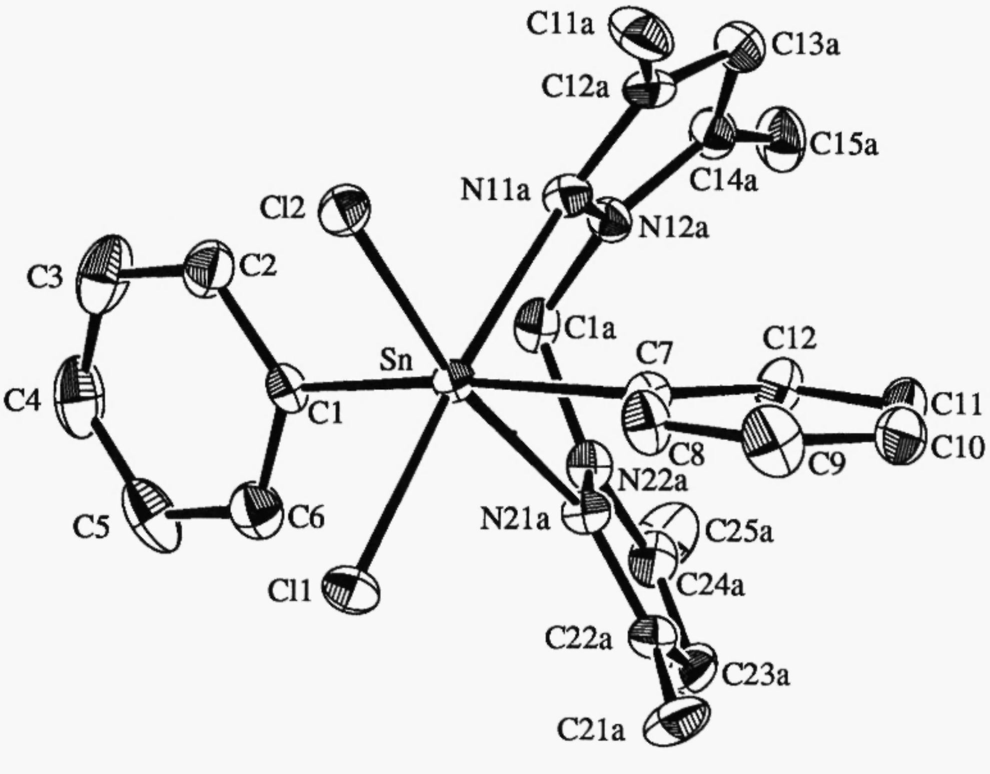

Figure 1. Molecular structure and crystallographic numbering scheme for $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$.

The *in vitro* cytotoxic activity of $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$ has been investigated against L1210 mouse leukaemia cells. The ID_{50} value for this compound (i.e. the dose of compound causing 50% growth inhibition) was 0.39 µM. On the basis of this result, this compound is more active than cisplatin, with an ID_{50} value of 0.6 µM, and lends support to the hypothesis that organotin compounds with Sn-N bond distances > 2.39 Å show good activity [2, 3].

Table 2. Selected bond distances (Å) and angles (°) for $\{Ph_2SnCl_2[(Me_2pz)_2CH_2]\}$

Sn-Cl(1)	2.493(2)	Sn-Cl(2)	2.414(2)
Sn-N(11a)	2.448(5)	Sn-N(21a)	2.526(5)
Sn-C(1)	2.100(6)	Sn-C(7)	2.108(6)
N(11a)-N(12a)	1.368(7)	N(21a)-N(22a)	1.364(6)
N(11a)-C(12a)	1.336(8)	N(21a)-C(22a)	1.324(6)
N(12a)-C(1a)	1.436(8)	N(22a)-C(1a)	1.445(8)
N(12a)-C(14a)	1.320(8)	N(22a)-C(24a)	1.336(8)
Cl(1)-Sn-Cl(2)	94.20(6)	Cl(1)-Sn-N(11a)	173.1(1)
Cl(1)-Sn-N(21a)	98.2(1)	Cl(1)-Sn-C(1)	89.5(2)
Cl(1)-Sn-C(7)	93.3(2)	Cl(2)-Sn-N(11a)	92.7(1)
Cl(2)-Sn-N(21a)	167.6(1)	Cl(2)-Sn-C(1)	96.0(2)
Cl(2)-Sn-C(2)	96.6(2)	N(11a)-Sn-N(21a)	75.0(2)
N(11a)-Sn-C(1)	89.4(2)	N(11a)-Sn-C(7)	86.2(2)
N(21a)-Sn-C(1)	83.0(2)	N(21a)-Sn-C(7)	83.9(2)
C(1)-Sn-C(7)	166.8(2)	Sn-N(11a)-N(12a)	121.7(4)
Sn-N(11a)-C(12a)	128.5(4)	Sn-N(21a)-N(22a)	122.3(4)
Sn-N(21a)-C(22a)	132.6(4)	N(12a)-N(11a)-C(12a)	104.5(5)
N(11a)-N(12a)-C(1a)	119.1(5)	N(11a)-N(12a)-C(14a)	112.3(6)
C(1a)-N(12a)-C(14a)	128.6(6)	N(22a)-N(21a)-C(22a)	104.8(5)
N(21a)-N(22a)-C(1a)	118.7(5)	N(21a)-N(22a)-C(24a)	112.1(5)
C(1a)-N(22a)-C(24a)	128.9(5)	N(12a)-C(1a)-N(22a)	111.4(5)

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