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Synthesis, characterization and cytotoxic activity of complexes of diorganotin(IV) dihalides with mepirizole

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Reaction of mepirizole (M) with diorganotin(IV) dihalides yielded compounds of type $[SnR_2X_2(M)]$ (R, X = Et, Cl; Et, Br; Bu, Cl; Bu, Br; Ph, Cl). The structure of dichlorodiphenyl (mepirizole)tin(IV) was determined by X-ray diffractometry. The crystal consists of discrete $[SnPh_2Cl_2(M)]$ units in which an *N*,*N*′-bidentate mepirizole, the *trans* phenyl rings and the *cis* chlorine atoms define a pseudo-octahedral coordination polyhedron around the tin atom. Mössbauer and vibrational spectroscopic data suggest similar structures for the other compounds prepared. The ^1H NMR spectra show that the mepirizole ligand is largely dissociated in $CDCl_3$. The most active compounds against the human carcinoma cell line KB were the butyl derivatives. Copyright © 2001 John Wiley & Sons, Ltd.

Keywords: tin; mepirizole; NMR; Mössbauer; IR, Raman; crystal structure

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INTRODUCTION

Attempts to obtain compounds with greater antitumour activity and lower toxicity than platinum complexes have involved the synthesis and characterization of a considerable number of metal-based compounds, including many organotin derivatives.[1] Among diorganotin complexes of type $[SnR_2X_2(LL)]$, where LL is an *N*,*N*′-bidentate ligand, anti-tumour activity is influenced by Sn—N distance, the average Sn—N bond length being >2.39 Å among active complexes and <2.39 Å among inactive ones.[2] This suggests that an important step in the mechanism of action of these compounds is cleavage of the Sn—(LL) bond.[2]

Guided by the results of early studies,[3] in previous work[4] we obtained Sn—N distances >2.39 Å by using a semi-rigid ligand, bis(1-methyl-2-imidazolylthio)methane (bmimt), which by forming an eight-membered $CS_2C_2N_2Sn$ ring led to long Sn—N bond distances. We have now selected a ligand in which steric hindrance by substituents close to the donor atoms prevents tight binding to metals, namely mepirizole [4-methoxy-2-(5-methoxy-3-methyl-pyrazol-1-yl)-6-methyl-pyrimidine, hereinafter M], a biologically active compound used as an anti-inflammatory agent.[5]

In this paper we report the synthesis of the compounds $[SnR_2X_2(M)]$ (R, X = Et, Cl; Et, Br; Bu, Cl; Bu, Br; Ph, Cl), their characterization by vibrational, NMR and Mössbauer spectroscopy, the crystal structure of $[SnPh_2Cl_2(M)]$ as determined by X-ray diffractometry, and *in vitro* cytostatic activities against the human carcinoma cell line KB.

EXPERIMENTAL SECTION

Materials

Diethyltindichloride, diethyltindibromide, dibutyltindichloride, dibutyltindibromide, diphenyl-

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tindichloride (all from Ventron) and mepirizole (from ICN Biomedicals Inc.) were used as supplied. Solvents were purified by the usual methods.

Preparation of compounds

General procedure: a solution of SnR_2X_2 in 10 ml of CH_2Cl_2 was added dropwise to a solution of mepirizole in 10 ml of the same solvent. After refluxing and stirring, the solution was refrigerated. The solid formed was filtered out and dried *in vacuo*.

[$SnEt_2Cl_2$(M)]. As above, from 0.247 g (1 mmol) of $SnEt_2Cl_2$ and 0.234 g (1 mmol) of mepirizole. Anal. found: C, 37.8; H, 5.3; N, 11.6%. Calc. for $C_{15}H_{24}Cl_2N_4O_2Sn$: C, 37.8; H, 5.0; N, 11.6%. M.p. 119 °C. Mössbauer: δ 1.81, ΔE_Q 3.95, Γ 0.81, $A_{2/1}$ 1.06. Λ_M 2.17 S cm^2 mol^{-1}. IR and Raman (in parentheses), cm^{-1}: 1607vs, ν(C=N); 1000m, ν(ring); 541m (545w), ν_{as}(Sn—C); 491m (488s), ν_{sym}(Sn—C); 268s, 255s (273m), ν(Sn—Cl).

[$SnEt_2Br_2$(M)]. As above, from 0.336 g (1 mmol) of $SnEt_2Br_2$ and 0.234 g (1 mmol) of mepirizole. Anal. found: C, 32.3; H, 4.2; N, 10.3%. Calc. for $C_{15}H_{24}Br_2N_4O_2Sn$: C, 31.6; H, 4.2; N, 9.8%. M.p. 116 °C. Mössbauer: δ 1.86, ΔE_Q 3.93, Γ 1.32, $A_{2/1}$ 0.97. Λ_M 3.83 S cm^2 mol^{-1}. IR and Raman (in parentheses), cm^{-1}: 1607s, ν(C=N); 999m, ν(ring); 542m (545w), ν_{as}(Sn—C); 478m (477s), ν_{sym}(Sn—C); 180s,br (184m), ν(Sn—Br).

[$SnBu_2Cl_2$(M)]. As above, from 0.303 g (1 mmol) of $SnBu_2Cl_2$ and 0.234 g (1 mmol) of mepirizole. Anal. found: C, 42.4; H, 6.0; N, 10.7%. Calc. for $C_{19}H_{32}Cl_2N_4O_2Sn$: C, 42.4; H, 5.9; N, 10.4%. M.p. 77 °C. Mössbauer: δ 1.76, ΔE_Q 3.84, Γ 0.81, $A_{2/1}$ 0.90. Λ_M 2.71 S cm^2 mol^{-1}. IR and Raman (in parentheses), cm^{-1}: 1608s, ν(C=N); 1005m, ν(ring); 624m (620w), ν_{as}(Sn—C); 592w (588s), ν_{sym}(Sn—C); 270sh, 255s,b (268m), ν(Sn—Cl).

[$SnBu_2Br_2$(M)]. As above, from 0.392 g (1 mmol) of $SnBu_2Br_2$ and 0.234 g (1 mmol) of mepirizole. Anal. found: C, 36.6; H, 5.1; N, 9.1%. Calc. for $C_{19}H_{32}Br_2N_4O_2Sn$: C, 36.4; H, 5.1; N, 8.9%. M.p. 72 °C. Mössbauer: δ 1.87, ΔE_Q 3.85, Γ 0.87, $A_{2/1}$ 0.99. Λ_M 3.09 S cm^2 mol^{-1}. IR and Raman (in parentheses), cm^{-1}: 1608s, ν(C=N); 1005m, ν(ring); 617w (615w), ν_{as}(Sn—C); 586w (586s), ν_{sym}(Sn—C); 223m,b, (213m), ν(Sn—Br).

[$SnPh_2Cl_2$(M)]. As above, from 0.343 g (1 mmol) of $SnPh_2Cl_2$ and 0.234 g (1 mmol) of mepirizole. Anal. found: C, 46.8; H, 4.1; N, 9.4%. Calc. for $C_{23}H_{24}Cl_2N_4O_2Sn$: C, 47.8; H, 4.2; N, 9.7%. M.p. 182 °C. Mössbauer: δ 1.49, ΔE_Q 3.55, Γ 0.81, $A_{2/1}$ 0.99. Λ_M 10.84 S cm^2 mol^{-1}. IR and Raman (in parentheses), cm^{-1}: 1612s, ν(C=N); 1001m, ν(ring); 287s (288m), ν(Sn—C); 264s, 230s (263m, 230m), ν(Sn—Cl).

Physical measurements

Elemental analyses were performed with a Carlo-Erba 1108 apparatus. Melting points were measured on a Gallenkamp apparatus. IR spectra were recorded in Nujol mulls, and Raman spectra in capillary tubes, on a Bruker IFS-66V FT-IR apparatus equipped with an FRA-106 Raman module. Conductivities (10^{-3} M, CH_3CN) were measured in a CRISON micro CM 2200 conductimeter. Mössbauer spectra were determined at 80.0 K in a constant acceleration apparatus with a $Ca^{119m}SnO_3$ source, with δ referred to SnO_2. ^{1}H NMR spectra at 250.13 MHz were recorded in $CDCl_3$ at room temperature on a Brucker WM-250 spectrometer, and were referred to TMS.

Determination of the structure of [$SnPh_2Cl_2$(M)]

Well-formed crystals obtained by slow concentration of a solution of [$SnPh_2Cl_2$(M)] in CH_2Cl_2 were selected and used for X-ray analysis. Data were collected at 293 K on an Enraf–Nonius CAD-4 four-circle diffractometer using Mo $K\alpha$ radiation. Unit cell dimensions were determined and refined by least squares using the setting angles of 25 automatically centred reflections ($2.4<\theta<26.3°$), and are listed in Table 1. The intensities of two standard reflections were essentially constant throughout the experiments.

The structures were solved by the standard heavy atom Patterson method followed by normal difference Fourier techniques. Full matrix least squares anisotropic refinement was performed for all non-hydrogen atoms, the positional parameters and equivalent isotropic temperature factors of which are listed in Table 2. Mepirizole hydrogen atoms were included as fixed contributors at positions calculated on stereochemical grounds and were treated using an overall isotropic temperature factor that refined to 0.073(12) Å^2. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ with the weighting scheme $w = 1/[\sigma^2(F_o)^2 + (0.0218P)^2 + 5.99P]$; $P = (F_o^2 + 2F_c^2)/3$ The programs used were SHELX76,[6] SHELXL93,[7] and ORTEP.[8]

In vitro cytostatic activity

Cytostatic activity was assayed against the estab-

Table 1 Crystal data and structure refinement for $[SnPh_2Cl_2(M)]$

Empirical formula	$C_{23}H_{24}Cl_2N_4O_2Sn$
Formula weight	578.05
Temperature (K)	293(2)
Wavelength (Å)	$\lambda = 0.710\ 73$
Crystal system	monoclinic
Space group	$P2_1/n$
Cell constants	
a (Å)	11.5843(10)
b (Å)	15.6967(10)
c (Å)	14.4207(10)
β (deg)	104.650(10)
Volume (Å^3)	$V = 2536.9(3)$
Molecules per cell	$Z = 4$
Density (calcd.) (g cm^{-3})	$D_c = 1.513$
Absorption coeff. (mm^{-1})	$\mu = 1.244$
$F(000)$	1160
Theta range (deg)	2.40 to 26.30
Index ranges	$-14 \leq h \leq 13$, $-19 \leq k \leq 0$, $0 \leq l \leq 17$
Reflections collected	5350
Independent reflections	5143
Absorption correction	Psi-scans
Max./min. transmission factors	0.881/0.725
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	5143/0/269
Goodness of fit on F^2	1.076
Final R indices $[I>2\sigma(I)]$	$R_1 = 0.0343$, $wR_2 = 0.0689$
R indices (all data)	$R_1 = 0.0812$, $wR_2 = 0.1003$
Largest diff. peak and hole (e Å^{-3})	0.675 and -0.478

lished cell line KB, which derives from a human oral epidermoid carcinoma. Stock cultures were grown in 25 cm^3 flasks containing 10 ml of buffered Eagle's Minimum Essential Medium (MEM) supplemented with glutamine, non-essential aminoacids (1%) and newborn calf serum (10%), as previously described.[9] The cell population doubling time was *ca* 24 h. The cells were dissociated with 0.05% trypsin solution, plated at a density of 5×10^5 cells per well in 24-well cell culture clusters (Costar) containing 1.0 ml of MEM per well, and preincubated for 24 h to allow adhesion to the substrate.

Subsequently the agents to be tested were added. The compounds were dissolved immediately before use in dimethylsulfoxide, and these solutions were diluted with the growth medium to the desired concentrations. At least five concentrations of each compound were used, with eight cell culture wells for each concentration. Each agent was assayed on at least three separate occasions. Each assay included a blank containing complete medium without cells.

The cells were incubated with the compounds being tested at 37 °C in an atmosphere that was 5% CO_2 and had a relative humidity of 100%. The incubation time was 72 h, during which period the control cells showed exponential growth.

Cell growth was terminated by *in situ* fixation and followed by staining with the protein-binding dye sulforhodamine B (SRB).[10] Specifically, adherent cell cultures were fixed *in situ* by addition of 250 µl of cold 50% (w/v) trichloroacetic acid (TCA) and were kept for 60 min at 4 °C. The supernatant was then discarded and the plates were washed three times with deionized water and dried. SRB solution (500 µl, 0.4% w/v in 1% acetic acid) was added to each well, and the cells were allowed to stain for 20–30 min at room temperature. Unbound SRB was removed by washing three times with 1% acetic acid, the plates were air-dried, bound stain was solubilized with unbuffered Tris base [tris(hydroxymethyl)aminomethane], and optical densities at 565 nm were read on a Perkin-Elmer 550 SE spectrophotometer.

The SRB assay was also used to measure the cell population density at time zero (the time at which the test compounds were added).

Cytostatic activity was evaluated from the

Table 2 Atomic coordinates ($Å \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for [$SnPh_2Cl_2$(M)]. $U_{(eq)}$ is defined as one-third of the trace of the orthogonalized U_{ij} tensor

Atom	*x*	*y*	*z*	$U_{(eq)}$
Sn	246(1)	1640(1)	2352(1)	37(1)
Cl(1)	1823(1)	2211(1)	3654(1)	58(1)
Cl(2)	1294(1)	1878(1)	1070(1)	60(1)
O(1)	−5347(3)	1122(3)	79(3)	67(1)
O(2)	−4173(3)	1708(3)	3175(3)	69(1)
N(1)	−1829(3)	1103(2)	1418(3)	36(1)
N(2)	−3863(4)	1324(3)	1445(3)	44(1)
N(3)	−2343(3)	1460(3)	2827(3)	40(1)
N(4)	−1153(3)	1337(3)	3312(3)	39(1)
C(1)	−2198(4)	899(3)	476(3)	40(1)
C(2)	−1273(5)	643(4)	−24(4)	64(2)
C(3)	−3376(4)	900(3)	7(4)	48(1)
C(4)	−4185(4)	1125(3)	525(4)	47(1)
C(5)	−6187(5)	1351(5)	620(5)	75(2)
C(6)	−2697(4)	1301(3)	1843(3)	36(1)
C(7)	−3013(5)	1592(4)	3478(4)	51(1)
C(8)	−4810(6)	1733(6)	3917(6)	110(3)
C(9)	−2246(5)	1553(4)	4372(4)	59(2)
C(10)	−1117(5)	1394(3)	4231(4)	49(1)
C(11)	25(6)	1276(5)	4982(4)	68(2)
C(21)	807(3)	336(2)	2533(3)	46(1)
C(22)	−5(3)	−330(2)	2448(3)	65(2)
C(23)	399(5)	−1167(2)	2559(3)	86(2)
C(24)	1614(5)	−1338(2)	2754(3)	94(3)
C(25)	2425(3)	−673(3)	2839(3)	94(3)
C(26)	2022(3)	164(3)	2729(3)	74(2)
C(31)	−706(3)	2814(2)	2051(2)	40(1)
C(32)	−1130(3)	3101(2)	1115(2)	54(1)
C(33)	−1762(4)	3861(2)	935(2)	71(2)
C(34)	−1970(4)	4335(2)	1691(3)	82(2)
C(35)	−1545(4)	4048(2)	2627(3)	76(2)
C(36)	−913(3)	3288(2)	2807(2)	57(1)

inhibition of cell growth in the treated cultures with respect to the controls. IC_{50}, the concentration of test compound at which cell proliferation was 50% of that observed in control cultures, was determined by linear regression analysis. The statistical significance of these results was estimated by means of Student's *t* test ($P<0.01$).

RESULTS AND DISCUSSION

Description of the structure of [$SnPh_2Cl_2$(M)]

Figure 1 shows an ORTEP view of the structure of the compound, with the numbering scheme used, and Table 3 lists selected distances and angles.

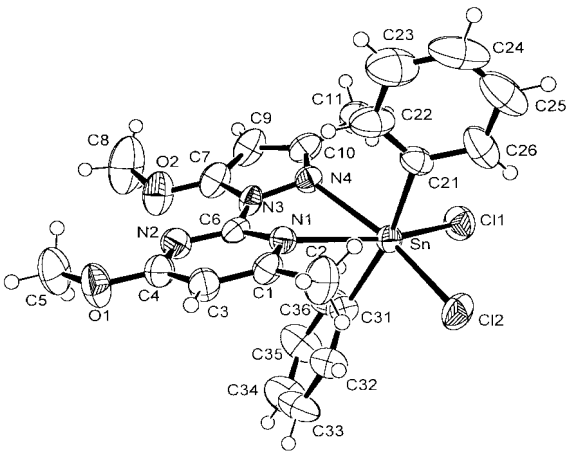

Figure 1 The molecular structure of [$SnPh_2Cl_2$(M)], showing the numbering scheme.

The crystal consists of discrete units in which the metal is coordinated to two chlorine atoms (Sn—Cl = 2.4359(14), 2.4829(13) Å), two phenyl groups (Sn—C = 2.135(2), 2.144(3) Å) and two mepirizole nitrogen atoms (Sn—N = 2.581(4), 2.430(4) Å) in a pseudo-octahedral configuration. The Sn—C and Sn—Cl bond lengths are in the ranges found for other diphenyltindichloride complexes with bidentate *N*,*N*′-donor ligands,[11] but one of the Sn—N distances, 2.581(4) Å, is outside the corresponding range, being the longest Sn—N distance found in this type of compound. The N—Sn—N angle, 64.28(12)°, is narrower than in these other complexes or complexes of mepirizole with other metals.[12–20] The mepirizole ligand, in its usual A form,[21] is bidentate, coordinating through its pyrimidine N(1) and pyrazole N(4) atoms. The pyrimidine and pyrazole rings are essentially planar and make an angle of 12.46° with each other. Coordination does not significantly change the ring parameters from the values found for the free ligand,[22] even around the donor atom (for instance, C(6)—N(1) = 1.320(5), 1.339(5) Å; N(1)—C(1) = 1.346(6), 1.356(6) Å; N(3)—N(4) = 1.376(4), 1.392(5) Å; C(6)—N(3) = 1.405(5), 1.396(6) Å; C(6)—N(1)—C(1) = 115.9(4), 115.5(4)°; N(3)—N(4)—C(10) = 105.6(3), 105.8(4)° for the free ligand and the complex respectively).

Comparison of this structure with those of the similarly octahedral complexes of dichlorodiphenyltin(IV) with bipyridyl[23,24] and 2,2′,6,6′-

Table 3 Selected bond lengths (Å) and angles (deg) in [$SnPh_2Cl_2$(M)] with esds in parentheses

Tin environment			
Sn—C(31)	2.135(2)	Sn—C(21)	2.144(3)
Sn—N(4)	2.430(4)	Sn—N(1)	2.581(4)
Sn—Cl(1)	2.4359(14)	Sn—Cl(2)	2.4829(13)
Cl(1)—Sn—N(1)	160.06(9)	Cl(2)—Sn—N(1)	103.11(9)
C(31)—Sn—N(4)	84.28(13)	C(21)—Sn—N(4)	88.20(14)
C(31)—Sn—Cl(1)	94.98(10)	C(21)—Sn—Cl(1)	96.44(11)
N(4) —Sn—Cl(1)	96.35(10)	C(31)—Sn—Cl(2)	92.51(10)
C(21)—Sn—Cl(2)	92.54(10)	N(4)—Sn—Cl(2)	167.36(10)
Cl(1)—Sn—Cl(2)	96.11(5)	C(31)—Sn—N(1)	79.12(13)
C(21)—Sn—N(1)	88.02(13)	N(4)—Sn—N(1)	64.28(12)
N(3)—N(4)—Sn	113.8(3)	C(22)—C(21)—Sn	122.0(2)
C(6)—N(1)—Sn	113.2(3)	C(26)—C(21)—Sn	118.0(2)
C(1)—N(1)—Sn	128.0(3)	C(10)—N(4)—Sn	134.7(3)
C(32)—C(31)—Sn	121.0(2)	C(36)—C(31)—Sn	119.0(2)
C(31)—Sn—C(21)	166.95(14)		
Mepirizole ligand			
N(3)—C(6)	1.396(6)	N(3)—N(4)	1.392(5)
N(4)—C(10)	1.318(6)	O(2)—C(7)	1.317(6)
O(1)—C(4)	1.337(6)	O(1)—C(5)	1.438(6)
N(1)—C(6)	1.339(5)	C(7)—C(9)	1.370(8)
C(1)—C(3)	1.362(7)	C(3)—C(4)	1.384(7)
N(1)—C(1)	1.356(6)	C(9)—C(10)	1.396(7)
N(2)—C(4)	1.322(6)	C(10)—C(11)	1.495(8)
N(2)—C(6)	1.328(6)	N(3)—C(7)	1.377(6)
O(2)—C(8)	1.445(7)	C(1)—C(2)	1.489(6)
C(7)—O(2)—C(8)	115.4(5)	C(4)—N(2)—C(6)	115.2(4)
C(7)—N(3)—C(6)	130.4(4)	C(7)—N(3)—N(4)	109.6(4)
C(6)—N(3)—N(4)	119.1(4)	C(10)—N(4)—N(3)	105.8(4)
O(2)—C(7)—C(9)	133.0(5)	C(4)—O(1)—C(5)	118.4(5)
O(2)—C(7)—N(3)	120.0(5)	N(1)—C(1)—C(3)	121.3(4)
C(9)—C(7)—N(3)	107.0(5)	N(1)—C(1)—C(2)	117.8(4)
N(4)—C(10)—C(9)	111.5(5)	C(3)—C(1)—C(2)	120.9(5)
N(4)—C(10)—C(11)	121.1(5)	C(1)—C(3)—C(4)	117.6(5)
C(9)—C(10)—C(11)	127.4(5)	N(2)—C(4)—O(1)	118.5(4)
C(6)—N(1)—C(1)	115.5(4)	N(1)—C(6)—N(3)	116.4(4)
N(2)—C(4)—C(3)	123.0(5)	O(1)—C(4)—C(3)	118.5(5)
N(2)—C(6)—N(1)	127.4(4)	N(2)—C(6)—N(3)	116.1(4)
C(7)—C(9)—C(10)	106.2(4)		

bipyrimidine[25] shows differences that, although possibly due in part to the crystal packing,[26] seem to be mainly attributable to the asymmetry of mepirizole. The difference between the two donor atoms leads to significant differences between both the two Sn—N distances and the two Sn—Cl distances (and to smaller differences between the two Sn—C distances). However, both the Sn—N distances (2.581(4) and 2.430(4) Å) are longer than in, for example, [$SnPh_2Cl_2$(bipy)] (monoclinic form, 2.344(6) and 2.375(6) Å;[23] tetragonal form, 2.325 and 2.333 Å)[24] and, in accordance with a trend previously discussed in detail,[25] the C—Sn—C angle is narrower (166.95(14)° as against 173.5(3)° in [$SnPh_2Cl_2$(bipy)]). The small Cl—Sn—Cl angle (96.11(5)°) is probably due to both the long Sn—N distance and the influence of the methyl groups, in particular the C(2) methyl: the angle N(1)—Sn—Cl(2) (103.11(9)°) is wider than N(4)—Sn—Cl(1) (96.35(10)°) even though the Sn—N(1) distance is longer than Sn—N(4), presumably because of differences between the relevant N—C—C angles (N(4)—C(10)—C(11) = 121.1(5)°, N(1)—C(1)—C(2) = 117.8(4)°) and the different orientations of the pyrimidine and pyrazole rings.

Vibrational spectra

The mepirizole ν(C=N) and ν(pyrimidine ring) bands, located at 1603 and 980 cm^{-1} in the spectrum of the free ligand, shift to slightly higher wavenumbers in those of all the complexes (see Experimental Section). These shifts and other minor changes in the vibrations of the pyrazole and pyrimidine rings are similar for all the complexes, and are in keeping with the *N*,*N*′-bidentate coordination shown for $[SnPh_2Cl_2(M)]$ by X-ray diffractometry.

The two Sn—C bands are close to those found in the spectra of other complexes of *N*,*N*′-bidentate ligands with *trans* C—Sn—C structures.[4] Both appear in both the IR and Raman spectra, which, like the Mössbauer data, suggests that the C—Sn—C fragment is bent. The ν(Sn—X) bands are close to their positions in the spectra of similar compounds,[4] but, as in the case of some of the latter, only one of the two stretching bands expected for a non-linear X—Sn—X fragment can confidently be identified.

Mössbauer spectra

With the exception of $[SnEt_2Br_2(M)]$, all the compounds have a Mössbauer spectrum showing a single quadrupole split doublet with a narrow linewidth (0.81–0.87 mm s^{-1}) suggesting the presence of a single tin site. For $[SnEt_2Br_2(M)]$ a value of 1.32 mm s^{-1} was found and the high degree of symmetry between the two peaks suggested the possible presence of two doublets in 1:1 area ratio, but since all attempts to fit the spectrum with such a model failed, the anomalous Γ value can only be ascribed to structural disorder. The hyperfine parameters (isomer shift and quadrupole splitting) are in all cases typical of diorganotin(IV) derivatives. The isomer shifts differ as expected given the electronegativities of the ligands (presence of Cl or Br, alkyl or aryl groups) and their inductive effects (in the case of the ethyl and butyl derivatives).[4] Quadrupole splitting reflects the field gradient generated around the tin nucleus by the σ and π bonds formed with the six donor atoms. The observed values are very similar to each other and typical of octahedral coordination, although slight deviations from theoretical values indicate small distortions from ideal geometry; for the phenyl derivative these discrepancies are in full agreement with the results of the X-ray study. Since the deviations from ideal geometry are small, the point charge model can be used. Using the angles observed by X-ray diffractometry, the partial quadrupole splitting for the nitrogen donor atoms in $[SnPh_2Cl_2(M)]$ was optimized to make the calculated and observed ΔE_Q values equal. The resulting value (-0.07 mm s^{-1}, similar to the

Table 4 ^{1}H NMR parameters (δ in ppm)

Compound	$\delta(SnR_2)$	δ(Ligand)[a]
Mepirizole	—	2.30 (CH_3 3,s) 2.51 (CH_3 6′,s) 3.94 (CH_3O 5,s) 4.01 (CH_3O 4′,s) 5.51 (H 4,s) 6.42 (H 5′,s)
$[SnEt_2Cl_2(M)]$	1.42(CH_3,t) 1.75 (CH_2,q)	2.34 (CH_3 3,s) 2.54(CH_3 6′,s) 3.95 (CH_3O 5,s) 4.01 (CH_3O 4′,s) 5.53 (H 4,s) 6.43 (H 5′,s)
$[SnEt_2Br_2(M)]$	1.39(CH_3,t) 1.83(CH_2,q)	2.31 (CH_3 3,s) 2.52 (CH_3 6′,s) 3.94 (CH_3O 5,s) 4.00 (CH_3O 4′,s) 5.51 (H 4,s) 6.42 (H 5′,s)
$[SnBu_2Cl_2(M)]$	0.90(CH_3,t) 1.37(CH_2,q) 1.77(CH_2,m) 1.80(Sn—CH_2,m)	2.31(CH_3 3,s) 2.51(CH_3 6′,s) 3.93(CH_3O 5,s) 3.98(CH_3O 4′,s) 5.51(H 4,s) 6.40(H 5′,s)
$[SnBu_2Br_2(M)]$	0.93(CH_3,t) 1.39(CH_2,q) 1.75(CH_2,m) 1.86(Sn—CH_2,m)	2.29(CH_3 3,s) 2.49(CH_3 6′,s) 3.93(CH_3O 5,s) 4.00(CH_3O 4′,s) 5.50(H 4,s) 6.41(H 5′,s)
$[SnPh_2Cl_2(M)]$	7.50(3,4,5,m) 7.70(2,6,m)	2.32(CH_3 3,s) 2.52(CH_3 6′,s) 3.95(CH_3O 5,s) 4.01(CH_3O 4′,s) 5.53 (H 4,s) 6.43(H 5′,s)

s = singlet; t = triplet; q = quadruplet; m = multiplet.
[a] Numbering scheme:

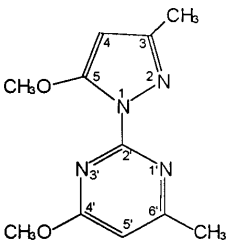

Table 5 Results of *in vitro* cytostatic assays against cell line KB

Compound	IC_{50} (μg/ml medium)	IC_{50} (μM)
$[SnEt_2Cl_2(M)]$	1.01	2.09
$[SnEt_2Br_2(M)]$	1.62	2.84
$[SnBu_2Cl_2(M)]$	0.09	0.17
$[SnBu_2Br_2(M)]$	0.06	0.10
$[SnPh_2Cl_2(M)]$	0.33	0.57
cis-$[PtCl_2(NH_3)_2]$	0.11	0.37

$-0.04\ mm\ s^{-1}$ reported for phenanthroline in the same structural situation) implies C—Sn—C bond angles of 170° and 163° for the ethyl and butyl derivatives respectively.

Solution studies

The molar conductivities are in all cases lower than for 1:1 electrolytes in acetonitrile[27] (120–160 $S\ cm^2\ mol^{-1}$), showing the essentially non-conducting behaviour of the compounds in solution. In the ^1H NMR spectra of the complexes the mepirizole signals are either unaltered or shifted slightly downfield from their positions in the spectrum of the free ligand,[20] even the methyl signals, the groups closest to the nitrogen atoms coordinating to the metal (Table 4). The smallness of the shifts and the fact that the SnR_2 signals are very close to those of free SnR_2X_2 in this solvent (e.g. $SnEt_2Cl_2$, 1.43(t), 1.79(q); $SnEt_2Br_2$, 1.40(t), 1.85(q))[28] suggest that the complexes are largely dissociated, even though $CDCl_3$ is a poorly coordinating solvent. Unfortunately, the poor solubility of the complexes prevented determination of the value of the coupling constant, which is useful for deciding on the persistence of the Sn—N bond in solution in similar systems.[4]

In vitro cytostatic activity

Table 5 lists the IC_{50} values of the compounds, together with that of *cis*-$[PtCl_2(NH_3)_2]$ for comparison. The butyl derivatives were the most active, even more than *cis*-$[PtCl_2(NH_3)_2]$, and the ethyl derivatives the least. This behaviour parallels that found previously in complexes of type $[SnR_2X_2(LL)]$ where LL is 2,2′-bisimidazole[3] or *N*-methyl-2,2′-bisimidazole.[29] However, the nature of the halogen bound to the metal atom does not seem to have much influence on activity, whereas $[SnBu_2Cl_2(LL)]$ is significantly more active than $[SnBu_2Br_2(LL)]$ when LL is *N*-methyl-2,2′-bisimidazole.

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