Synthesis, structure and trypanocidal activity of dibutyltin derivatives of 2-mercaptobenzoxazole and 5-chloro-2-mercaptobenzothiazole

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Abstract

Single X-ray crystal structure analysis has been determined for the dibutyltin derivatives of 2-mercaptobenzoxazole **1** and 5-chloro-2-mercaptobenzothiazole **2**. In both cases, the geometry at the tin atom is that of an octahedron, and it is weakly coordinated by N,S chelating ligands. Trypanocidal activity patterns are also presented, showing a large difference in behaviour between **1**, **2** and the related bis (2-mercaptobenzothiazolyl) dibutyltin. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Organotin; X-ray structures; Octahedral environment; Trypanocide

1. Introduction

Apart from those of the platinum group [1,2], a variety of other metal complexes have been shown to be antitumour agents [3], among which several organotin compounds. Many of these organotin compounds have been shown to exhibit in vitro antitumour properties against a wide panel of tumoral cell lines of human origin [4–6]. We have also recently demonstrated the potency of such derivatives against in vitro cultures of trypanosomes [7].

Metallo-complexes of 2-mercaptobenzothiazole (Hmbt) and the related 2-mercaptobenzoxazole (Hmbo) have proved a fertile area for study over a number of years, stimulated both by the diversity of their commercial application and the richness of their structural chemistry. These derivatives (but particularly Hmbt) are parents to a class of organic and metal-organic compounds which have known fungicidal activity, which possibly arises from opening of the thiazole (or oxazole) ring to yield toxic dithiocarbamate [8].

Both mercaptans (Hmbt and Hmbo) may exist in two tautomeric forms (Fig. 1), but crystallographic studies show that the thione form (**a**) is prefered, at least in the solid state. In addition, these molecules have a capacity for binding a great variety of metal ions [9–11].

At least four bonding modes between ligand and tin are conceivable (Fig. 2). Coordination with the exocyclic sulfur (Fig. 2a) can be found in every kind of tetrahedral monomeric structures. Coordination with only the endocyclic nitrogen (Fig. 2b) is not common for tin compounds, but it is often found for zinc derivatives. Chelation by both S and E atoms (Fig. 2c) is to our knowledge unknown, but N, S chelation (Fig. 2d) is commonly observed in dialkyltin compounds [12]. In addition, bridging between different molecules via the heterocycles rather than chelation and/or distortion from regular geometry is possible.

Our interest in the trypanocidal nature of organotin compounds [7] has prompted us to investigate in some detail the synthesis, structure and activity patterns for dibutyltin derivatives of the title heterocycles, which we report herein (compounds **1** and **2**, Fig. 3). Spectroscopy data for $Bu_2Sn(mbt)_2$ have already been reported [13].

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2. Experimental section

Organotin reagents and the title heterocycles were commercialy available, and they were used without further purification. Solvents were dried by conventional methods prior to use. The ^{13}C- and ^{119}Sn-NMR spectra were obtained with a Bruker AC-200 spectrometer operating respectively at 50.32 and 74.54 MHz with tetramethylsilane (for ^{13}C) and tetramethyltin (for ^{119}Sn) as references. Microanalyses (C, H, N) were performed by the 'Service Central de Microanalyses du CNRS (BP 22-69390 Vernaison-France)'.

3. Syntheses

3.1. Preparation of compound 1

A solution of dibutyltin dichloride (1.5 g; 5 mmol) in toluene is added dropwise to a solution of 2-mercaptobenzoxazole (1.5 g; 10 mmol) and triethylamine (1 g; 10 mmol) in the same solvent, at room temperature. The mixture is refluxed for 12 h. The organic layer was then washed twice with brine, dried over sodium sulfate and the solvent was evaporated under reduced pressure to leave a brown solid (m.p. = 98–100°C; yield, 94%). Single crystals of 1 are obtained by slow evaporation of a solution of this solid in a hexane/methylene chloride (8/2) mixture.

Elemental anal. found: C, 48.81; H, 5.04; N, 4.95. $C_{22}H_{26}N_2O_2S_2Sn$ calc.: C, 49.55; H, 4.91; N, 5.25%.

3.2. Preparation of compound 2

The same procedure is followed with 1.5 g of dibutyltin dichloride (5 mmol), 2 g of 5-chloro-2-mercaptobenzothiazole (10 mmol) and 1 g of triethylamine (10 mmol), to obtain a brown solid (m.p. = 120–122°C; yield, 94%) which was recrystallized from a hexane/methylene chloride (7/3) mixture to obtain single crystals of 2.

Elemental anal. found: C, 41.91; H, 3.80; N, 4.61. $C_{22}H_{24}N_2S_4Cl_2Sn$ calc.: C, 41.66; H, 3.81; N, 4.42%.

4. Crystal structure determination

4.1. Crystal structure determination for 1

Data for a crystal of 1 (approximate size $0.2 \times 0.2 \times 0.4$ mm) were collected on a four-circle X-ray diffractometer. Crystal data and details about data collection and refinement are given in Table 1. The cell parameters were determined by least-squares from setting angles for 25 reflections. In the collection of intensities, the $\theta/2\theta$ scan method was used and 1360 independent reflections were collected in the region $\theta < 25°$.

Correction was made for Lorentz and polarization effects. 1068 reflections with $I > 3\sigma(I)$ were considered observed and were used in the subsequent calculations. A semi-empirical method of absorption correction was applied [14].

The structure was solved by Patterson and Fourier techniques. All the H atoms were located from a difference Fourier map. Diagonal-matrix least-squares refinement of atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms, and isotropic for H atoms, gave a final $R = 0.0457$ ($R_w = 0.0569$ and $S = 0.810$) for 1068 independent significant reflections and 366 parameters. The resulting atomic coordinates are listed in Table 2, selected bond lengths and bond angles in Table 4. The structure of 1, together with the atomic numbering scheme, is depicted in Fig. 4. (there is no atom 7, so that the numbering of the other atoms fits with the one of compound 2).

4.2. Crystal structure determination for 2

Data for a crystal of 2 (approximate size $0.07 \times 0.15 \times 0.25$ mm) were collected on a four-circle X-ray diffractometer. They were corrected for Lorentz and polarization effects. It was considered necessary to correct for absorption [14]. Crystal data and details about data collection and refinement are given in Table 1.
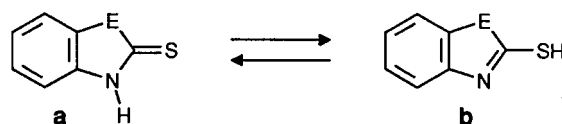

Fig. 1. Thione (a) and thiol (b) tautomeric forms of the title mercaptans, with E = S, O.
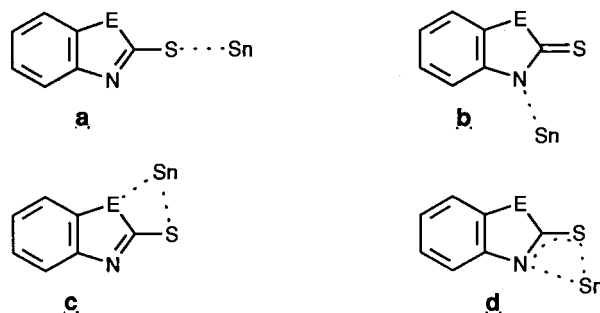

Fig. 2. Possible modes of coordination of the title heterocycles to tin, with E = S (mbt), O (mbo).
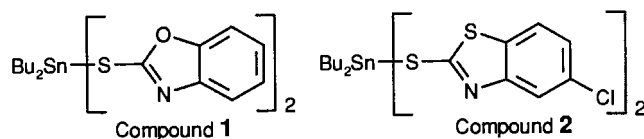

Fig. 3. Structures of the two dibutyl compounds (1 and 2) of the title heterocycles.

Table 1
Experimental data for the crystal structure determination of **1** and **2**

	1	**2**
Crystal data		
Formula	$C_{22}H_{26}N_2O_2S_2Sn$	$C_{22}H_{24}N_2S_4Cl_2Sn$
Formula weight	533.3 g mol^{-1}	634.3 g mol^{-1}
Absorption coefficient	$\mu = 1.252$ mm^{-1}	$\mu = 1.483$ mm^{-1}
Crystal system	Monoclinic	Monoclinic
Space group	$P\,c$, $Z = 2$	$P2_1/c$, $Z = 4$
Lattice constants	$a = 7.676$ Å	$a = 10.680(1)$ Å
(Mo–K$_\alpha$)	$b = 7.296$ Å	$b = 31.222(3)$ Å
	$c = 21.851$ Å	$c = 8.084(1)$ Å
	$\beta = 99.72°$	$\beta = 100.16(1)°$
Temperature	293 K	293 K
Density	$D_m = 1.468$ g cm^{-3}	$D_m = 1.588$ g cm^{-3}
Data collection		
Diffractometer	Four circle CAD4 (Enraf–Nonius)	
Radiation	Mo–Kα; graphite monochromator	
Scan type	ω scans	
Scan width	$(2.00 + 0.35 \tan \theta)°$	$(1.80 + 0.35 \tan \theta)°$
Measuring angles		
θ	2–25°	2–25°
h, k, l	h, 0 → 9; k, 0 → 8; l, −26 → 26	h, 0 → 9; k, 0 → 37; l, −12 → 12
Reflections	2503 total	2986 total
	1360 independent	2673 independent
	1068 with $I > 3\sigma(I)$	1560 with $I > 3\sigma(I)$
Computing		
Programs	MITHRYL [15]	
Atomic scattering factors for neutral atoms	$\Delta f'$, $\Delta f''$ [16]	
Refinement	Diagonal matrix least-squares on F	
Residuals	$R_w = 0.0569$	$R_w = 0.0979$
	$R = 0.0457$	$R = 0.0704$
Goodness of fit	$S = 0.810$	$S = 2.236$
Number of parameters refined	366	376

Table 2
Fractional coordinates and equivalent isotropic temperature factors for **1**

Atom	x	y	z	B_{eq}
C(1)	0.7918(25)	0.8138(24)	0.6456(8)	5.2(8)
C(2)	0.8481(26)	0.6966(24)	0.6082(7)	5.4(8)
C(3)	0.8461(23)	0.5139(30)	0.6256(7)	4.9(7)
C(4)	0.7893(21)	0.4657(24)	0.6796(7)	4.6(7)
C(5)	0.7312(17)	0.5821(16)	0.7213(5)	2.5(5)
C(6)	0.7415(25)	0.7875(23)	0.6994(8)	5.3(8)
O(8)	0.7810(16)	0.2897(16)	0.7085(5)	5.0(5)
C(9)	0.7199(18)	0.3384(20)	0.7613(6)	3.2(6)
N(10)	0.6947(16)	0.5176(19)	0.7687(5)	3.9(5)
S(11)	0.6886(7)	0.1686(7)	0.8135(2)	5.8(2)
Sn(12)	0.5831(5)	0.4113(1)	0.8799(2)	4.5(0)
C(13)	0.8220(18)	0.5305(22)	0.9218(6)	3.3(6)
C(14)	0.8203(26)	0.7383(27)	0.9317(9)	6.2(10)
C(15)	0.9925(32)	0.8006(32)	0.9702(11)	7.5(12)
C(16)	0.9941(32)	0.9856(46)	0.9906(12)	9.1(14)
C(17)	0.3299(27)	0.5229(38)	0.8341(11)	7.6(12)
C(18)	0.3312(22)	0.7205(30)	0.8290(9)	6.3(10)
C(19)	0.1655(23)	0.8065(26)	0.7954(8)	5.4(8)
C(20)	0.1572(27)	1.0085(40)	0.7921(9)	7.3(10)
S(21)	0.5081(7)	0.1639(7)	0.9505(2)	5.9(2)
C(22)	0.4642(29)	0.3396(32)	0.9969(9)	6.9(10)
O(23)	0.3880(15)	0.2962(15)	1.0496(5)	4.9(5)
C(24)	0.3683(22)	0.4527(25)	1.0760(7)	5.1(8)
C(25)	0.4246(21)	0.6172(30)	1.0459(7)	6.1(9)
N(26)	0.4898(22)	0.5030(27)	0.9887(6)	6.1(7)
C(27)	0.4425(27)	0.7695(28)	1.0616(8)	6.3(10)
C(28)	0.3746(33)	0.8121(39)	1.1185(9)	8.8(14)
C(29)	0.3157(29)	0.6482(28)	1.1506(7)	6.2(9)
C(30)	0.3085(26)	0.4697(32)	1.1327(8)	6.0(9)

Of the 2986 reflections measured ($\theta_{max} = 25°$), 2673 were independent, of which 1560 had $I > 3\sigma(I)$. The positions of the non-hydrogen atoms were found from the three-dimensional Patterson and Fourier synthesis. Block-diagonal least-squares refinement with isotropic temperature factors for hydrogen atoms, and non isotropic for the other atoms, gave a final $R = 0.0704$ ($R_w = 0.0979$, $S = 2.2236$). Final atomic coordinates are listed in Table 3, selected bond lengths and bond angles in Table 4. The structure of **2**, together with the atomic numbering scheme, is depicted in Fig. 5.

5. Results and discussion

5.1. Description of the solid state crystal structures

Both compounds contain a six-coordinate tin atom. In each case, two carbons and two sulfur atoms are covalently linked to the metal. The valence extension is performed via the nitrogen atoms, N10 and N26, of the benzoxazole or the benzothiazole ring for **1** and **2** respectively. The two chelating nitrogens occupy *cis* positions, as it is the case for the sulfur bonding. The strongly distorted square bipyramid presents apical organic groups bound to tin and equatorial bidentate groups with unequal sulfur-tin and nitrogen-tin bonds.

The Sn–S, Sn–N and Sn–C bond distances of the distorted octahedral geometry of **1** and **2** are presented
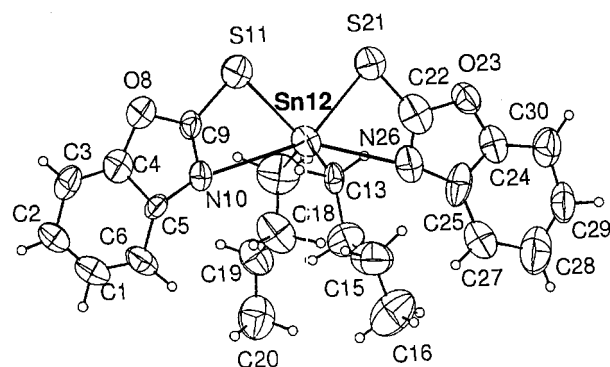

Fig. 4. Structure and atomic numbering scheme for compound **1**.

Table 3
Fractional coordinates and equivalent isotropic temperature factors
for **2**

Atom	x	y	z	B_{eq}
C(1)	0.2259(38)	0.0377(10)	0.1426(44)	6.8(19)
C(2)	0.1250(34)	0.0491(13)	0.2146(45)	6.9(20)
C(3)	0.1066(35)	0.0906(11)	0.2511(57)	7.4(20)
C(4)	0.1982(28)	0.1208(14)	0.2332(44)	6.6(19)
C(5)	0.3056(26)	0.1079(9)	0.1609(37)	4.2(13)
C(6)	0.3207(31)	0.0660(11)	0.1111(39)	5.4(16)
Cl(7)	0.2476(14)	−0.0158(3)	0.0866(16)	10.2(7)
S(8)	0.2087(8)	0.1755(3)	0.2692(12)	5.3(4)
C(9)	0.3421(24)	0.1774(9)	0.1831(30)	3.5(12)
N(10)	0.3824(23)	0.1426(6)	0.1246(32)	4.4(11)
S(11)	0.4195(7)	0.2261(3)	0.1647(12)	5.3(4)
Sn(12)	0.5950(2)	0.1867(1)	0.0560(3)	3.4(1)
C(13)	0.5236(25)	0.1682(7)	−0.1935(34)	3.1(11)
C(14)	0.5194(31)	0.1194(8)	−0.2217(37)	4.6(14)
C(15)	0.4634(38)	0.1032(10)	−0.3960(49)	6.8(20)
C(16)	0.4630(39)	0.0558(14)	−0.4100(45)	7.8(23)
C(17)	0.6969(26)	0.1542(8)	0.2647(35)	3.6(12)
C(18)	0.7039(38)	0.1028(9)	0.2390(42)	6.1(17)
C(19)	0.7783(35)	0.0840(13)	0.4037(44)	6.7(20)
C(20)	0.7923(39)	0.0357(13)	0.3876(59)	8.3(23)
S(21)	0.7161(6)	0.2545(2)	0.0448(9)	3.6(3)
C(22)	0.8373(25)	0.2253(7)	−0.0255(33)	3.1(11)
S(23)	0.9690(7)	0.2501(3)	−0.0756(10)	4.3(3)
C(24)	1.0208(27)	0.2026(8)	−0.1406(37)	3.7(12)
C(25)	0.9304(23)	0.1688(7)	−0.1169(37)	3.4(12)
N(26)	0.8215(19)	0.1847(7)	−0.0482(31)	4.3(10)
C(27)	0.9456(23)	0.1263(9)	−0.1602(32)	3.2(12)
C(28)	1.0539(29)	0.1181(10)	−0.2228(36)	4.7(15)
C(29)	1.1469(33)	0.1487(14)	−0.2452(44)	7.0(20)
C(30)	1.1293(24)	0.1919(13)	−0.1988(35)	5.5(16)
Cl(31)	1.0829(9)	0.0655(3)	−0.2800(12)	6.6(5)

in Table 5, parallel to those of bis (5-nitro-2-mercap-topyridinyl) dibutyltin [17].

Sn–C bond lengths are quite close to the ones previously described in the litterature.

The same can be noted for the Sn–N bond distances, which are totally in agreement with the valence extension of the metal atom [18,19]. These Sn–N distances are between 2.68 and 2.82 Å, values which lie within the sum of their respective Van der Waals' radii (3.67 Å).

Concerning the Sn–S bond lengths, we may note that they are a little longer than the sum of the atomic radii (2.43 Å). Besides, on each side of the tin atom, the S and N equatorial ligating atoms belong to the same moiety, so their positions are fixed and the S–Sn–N angles (Table 4) can only admit very little deformation. Accession to a six-coordinate state requires a little stretching of the Sn–S bonds so that the nitrogen atoms can be close enough to perform valence extension.

In such structures, the sum of angles between the tin atom and the equatorial ligating atoms (i.e. two N and two S in each case) is 359.7° for **1** and 360.6° for **2**,

compared to the ideal octahedral value of 360°. This indicates that these four atoms are in the same plane.

The distribution of these 360°, which should normally be of 90° for each angle, is totally unequal (from 60 to 149°). This difference in angle is another consequence of the very distorted octahedron structure observed.

5.2. Characteristics in solution

Compounds **1** and **2** were characterized in $CDCl_3$ solutions by ^{13}C- and ^{119}Sn-NMR spectroscopy [20,21]. The chemical shifts, together with the $J(^{13}C-^{119}Sn)$ coupling values, are reported in Table 6. The aromatic carbon resonances were assigned by comparison of experimental chemical shifts with those calculated with increments from literature data [22,23]. NMR data for $Bu_2Sn(mbt)_2$ have already been reported in the literature, and they are also listed in Table 6 for comparison [13].

In these solutions, the structural choice lies between a tetrahedral, penta- or hexa-coordinate geometry around tin.

The ^{119}Sn-NMR spectra display a singlet in each case, at -112.6 ppm for compound **1** and -89.05 ppm for **2**. These chemical shifts are not informative enough, as they can belong to penta- or weakly hexa-coordinate species in solution [24,25]. Complementary information is given by the values of the coupling constant.

Table 4
Selected bond lengths (Å) and angles (°) for **1** and **2**

	1		**2**
Bond lengths			
S(21)–C(22)	1.70(3)	S(21)–C(22)	1.75(3)
C(22)–O(23)	1.41(3)	C(22)–S(23)	1.72(3)
C(22)–N(26)	1.24(3)	C(22)–N(26)	1.29(4)
O(8)–C(9)	1.36(2)	S(8)–C(9)	1.69(3)
C(9)–N(10)	1.28(2)	C(9)–N(10)	1.29(4)
C(9)–S(11)	1.73(2)	C(9)–S(11)	1.75(3)
S(11)–Sn(12)	2.509(7)	S(11)–Sn(12)	2.527(9)
Sn(12)–C(13)	2.09(2)	Sn(12)–C(13)	2.11(3)
Sn(12)–C(17)	2.19(3)	Sn(12)–C(17)	2.10(3)
Sn(12)–S(21)	2.505(7)	Sn(12)–S(21)	2.490(8)
Sn(12)–N(10)	2.81(1)	Sn(12)–N(10)	2.82(4)
Sn(12)–N(26)	2.68(2)	Sn(12)–N(26)	2.69(2)
Interatomic angles			
S(11)–Sn(12)–C(13)	101.5(5)	S(11)–Sn(12)–C(13)	107.7(8)
S(11)–Sn(12)–C(17)	110.3(7)	S(11)–Sn(12)–C(17)	105.4(8)
S(11)–Sn(12)–N(10)	60.1(6)	S(11)–Sn(12)–N(10)	59.8(8)
N(10)–Sn(12)–N(26)	151(1)	N(10)–Sn(12)–N(26)	149.0(1)
S(11)–Sn(12)–S(21)	88.8(2)	S(11)–Sn(12)–S(21)	91.2(3)
C(13)–Sn(12)–C(17)	133.7(9)	C(13)–Sn(12)–C(17)	133.0(1)
C(13)–Sn(12)–S(21)	107.7(5)	C(13)–Sn(12)–S(21)	107.4(7)
C(17)–Sn(12)–S(21)	105.8(7)	C(17)–Sn(12)–S(21)	103.9(8)
N(26)–Sn(12)–S(21)	60.8(4)	N(26)–Sn(12)–S(21)	60.6(5)
N(26)–Sn(12)–S(11)	148.3(4)	N(26)–Sn(12)–S(11)	151.8(6)
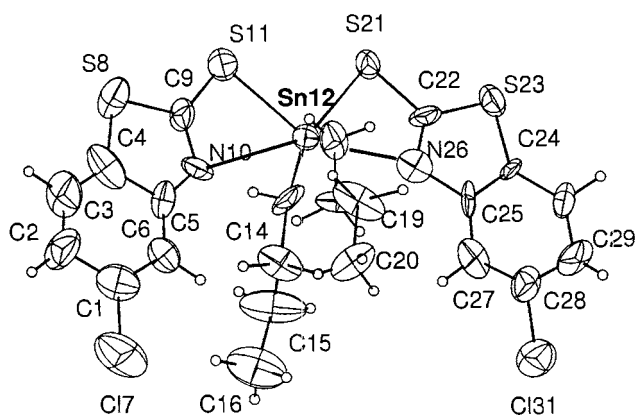
Fig. 5. Structure and atomic numbering scheme for compound **2**.

The $^1J(^{13}C-^{119}Sn)$ values (506.1 and 501.4 Hz for **1** and **2** respectively) are strongly in keeping with the ones usually found for weakly six-coordinate dibutyltin compounds, which are in the range of 580–640 Hz [26]. But these coupling constant values are totally in agreement with the ones of penta-coordinate dibutyltin compounds, which are in the range of 480–540 Hz [24].

So, it can reasonably be assumed that the distorted octahedral structure observed in the solid state is not retained upon dissolution in CDCl$_3$.

It is replaced by a penta-coordinate structure. In this case, the fifth interaction with the metal could occur via either the nitrogen (Fig. 6a) or the heteroatom E (sulfur or oxygen) (Fig. 6b) of the heterocyclic moiety.
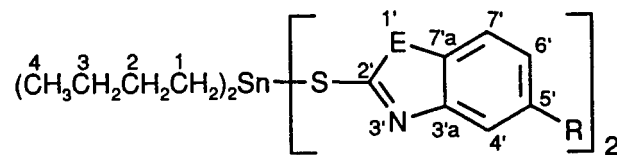
Although such structures may be written, their strict existences in solution make the two heterocycles linked to tin become unequivalent. But the NMR measurements show equivalent carbon shifts, thus suggesting for their real behaviour a rapid bidentate-unidentate interchange of the coordinating groups.

Table 5
Comparison of some bond distances of compounds **1** and **2**, and the related bis (5-nitro-2-mercaptopyridinyl) dibutyltin [17]

1 Bu$_2$Sn(mbo)$_2$	**2** Bu$_2$Sn(5-Clmbt)$_2$	Bu$_2$Sn(S–C$_5$H$_3$N-2-NO$_2$-5)$_2$
Sn–C		
2.09(2)	2.11(3)	2.162
2.19(3)	2.10(3)	
Sn–S		
2.509(7)	2.527(9)	2.477
2.507(7)	2.490(8)	
Sn–N		
2.81(1)	2.82(4)	2.77
2.68(2)	2.69(2)	

Table 6
^{13}C and ^{119}Sn NMR characteristics of **1** and **2** in CDCl$_3$ solutions, related to the ones of Bu$_2$Sn (mbt)$_2$

$(CH_3CH_2CH_2CH_2)_2Sn$ ...

	E = O, R = H, compound **1**	E = S, R = Cl, compound **2**	E = S, R = H
δ C-1	29.2	28.7	28.9
δ C-2	27.9	28.0	28.2
δ C-3	26.1	26.2	26.3
δ C-4	13.5	13.5	13.7
δ C2′	173.1	172.1	172.4
δ C3′a	139.3	139.2	134.5
δ C4′	110.0	124.2	124.0
δ C5′	115.3	152.3	126.6
δ C6′	123.5	119.2	126.1
δ C7′	124.4	121.8	122.6
δ C7′a	152.0	135.4	154.2
$^1J(^{13}C-^{119}Sn)$	506.1	501.4	505
$^2J(^{13}C-^{119}Sn)$	35.6	36.6	36.6
$^3J(^{13}C-^{119}Sn)$	103.6	98.7	100.7
δ ^{119}Sn	−112.6	−89.05	

^{13}C chemical shifts are expressed in ppm (reference = TMS). ^{119}Sn chemical shifts are expressed in ppm with tetramethyltin as reference. The $^nJ(^{13}C-^{119}Sn)$ coupling constants are expressed in Hz. Concentrations: ca 50 mg/0.5 ml.

5.3. Trypanocidal activities

Trypanosome is the causative agent of sleeping sickness. Organoarsenic compounds are still the most common drugs used for treatment.

Bloodstream forms of parasites were first purified and then cultivated in vitro according to Baltz et al. [27]. Both compounds **1** and **2**, together with Bu$_2$Sn(mbt)$_2$, were tested as trypanocidal agents [7]. The activity tests were carried out on cultures of *Trypanosoma equiperdum*. Values indicated for these activities correspond to the minimum amount required to

Table 7
MEC values for compounds **1** and **2**, and the related Bu$_2$Sn(mbt)$_2$

Compound	MEC (nM)
1	0.7
2	49
Bu$_2$Sn(mbt)$_2$	0.7

MEC is the minimal efficient concentration which allows complete depletion of trypanosoma population. The tests were carried out three times for each sample and the average value was tabulated.
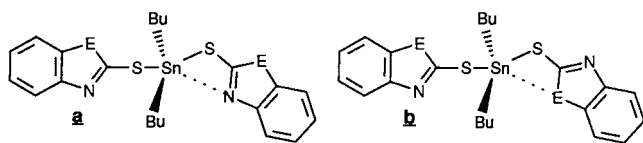
Fig. 6. Possible ways of coordination leading to five-coordinate states in solution with E = S, O.

cause death of all parasites within 24 h (Table 7). As reference, we can take the MEC values of the two most used organoarsenicals, Arsobal and Cymelarsan, which are 5 and 0.6 nM respectively.

We may note that compound **2** is 70 fold less active than **1** or the related $Bu_2Sn(mbt)_2$. We have shown in this work that these three compounds adopt the same configuration in solution. So, such a difference in activity may be due to the presence of the chlorine atom on the heterocyclic moiety of **2**. Thus, it can reasonably be infered that the trypanocidal activity of these tin compounds depends on an enzymatic targetting, the recognition of the heterocyclic moiety being probably strongly disturbed by the presence of the chlorine atom.

Acknowledgements

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