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Synthesis, crystal structure and biological activity of thiophene-2-carboxaldehyde thiosemicarbazone and its tin complexes

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Abstract

Thiophene-2-carboxaldehyde thiosemicarbazone, $C_4H_3S–CH=N–NH–C(S)NH_2$ (tctscH) obtained by the condensation reaction of thiophene-2-carboxaldehyde with thiosemicarbazide forms $SnPh_2Cl$(tctsc), **1** and $SnCl_2$(tctsc)$_2$, **2** with $SnPh_2Cl_2$ and $SnPhCl_3$ in 1:1 and 1:2 tin:ligand molar ratios, respectively. The crystal structure determination shows that in both **1** and **2**, tctscH is deprotonated and functions as an anionic bidentate ligand, co-ordinating to the tin atom through its azomethine-*N* and thiol-*S* atoms. The geometry about the tin atom for complex **1** is distorted trigonal bipyramidal whereas for complex **2** is distorted octahedral. Note that dephenylation occurs during the formation of complex **2**. Fungitoxicity and cytotoxicity of the two tin complexes and tctscH have been evaluated and the biological activity is more remarkable in complex **1** in comparison to the other.

Keywords: Tin; Thiosemicarbazone; Fungitoxicity; Cyotoxity

1. Introduction

Relationships between the structure and biological activity of α-(*N*)-heterocyclic carboxaldehyde thiosemicarbazones for instance, pyridine and isoquinoline carboxaldehyde thiosemicarbazones have been extensively investigated [1,2]. However, thiosemicarbazones of other heterocyclic ring systems have not been explored to any extent. Besides, little is known about the complexing behaviour of non-transition metals with these ligands, [3–5] although the co-ordination of these ligands with several transition metals has been studied [6–9].

In view of the need to obtain more data on the structure–activity relationships, thiophene-2-carboxaldehyde thiosemicarbazone, $C_4H_3S–CH=N–NH–C(S)NH_2$ (tctscH) which is an α-(*S*)-heterocyclic carboxaldehyde thiosemicarbazone has been prepared and reacted with diphenyltin(IV) dichloride and phenyltin(IV) trichloride. The crystal structure of tctscH has been determined by Mathew and Palenik (1971) [10]. Here, we report the synthesis and biological activity of tctscH and its corresponding tin complexes, $SnPh_2Cl$(tctsc) and $SnCl_2$(tctsc)$_2$. X-ray crystal structure determination of these two title complexes are also reported.

2. Experimental

2.1. General and instrumental

Thiosemicarbazide and thiophene-2-carboxaldehyde were purchased from Fluka Chemie AG. Diphenyltin dichloride and phenyltin trichloride were used as obtained from Aldrich and the solvents used were reagent grade.

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Table 1
Crystal data and structure refinement details

Compound	$SnPh_2Cl(tctsc)$ (**1**)	$SnCl_2(tctsc)_2$ (**2**)
Formula	$C_{18}H_{16}ClN_3S_2Sn$	$C_{12}H_{12}Cl_2N_6S_4Sn$
Formula weight	492.6	558.1
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$C2/c$
a (Å)	13.7150(10)	15.5430(10)
b (Å)	16.3700(10)	9.8850(10)
c (Å)	17.4420(10)	13.4360(10)
β (°)	94.790(10)	106.900(1)
U (Å^3)	3902.3(4)	1975.2(3)
Z	4	4
$D_{calc.}$ (Mg m^{-3})	1.677	1.877
μ (mm^{-1})	1.666	1.996
$F(000)$	1952	1096
h, k, l ranges	−1 to 17, −1 to 21, −22 to 22	−1 to 20, −1 to 12, −17 to 16
Reflections collected	10673	2797
Independent reflections	8892	2258
R_{int}	0.0185	0.0147
Observed reflections [$F>4.0\sigma(F)$]	6437	2060
No. parameters refined	451	140
R	0.0344	0.0249
R_w	0.0369	0.0331
w	$[\sigma^2(F)+0.0003F^2]^{-1}$	$[\sigma^2(F)+0.0058F^2]^{-1}$
Largest diff. peak and hole (e Å^{-3})	1.23 and −0.93	0.31 and −0.53

Microanalyses were carried out on a Control Equipment Corporation 240XA elemental analyser at the School of Chemical Sciences, Universiti Sains Malaysia, Penang, Malaysia. The tin analysis was performed using an Instrumental Laboratory aa/ae 357 atomic spectrophotometer. The IR spectra were recorded for KBr dies on a Mattson 1000 FTIR spectrophotometer in the frequency range of 4000–200 cm^{-1}. The ^{1}H-NMR spectra were recorded on a Bruker AC-P 300 MHz NMR spectrometer in $(CD_3)_2SO$ solution.

Table 2
Selected bond lengths (Å) with estimated S.D. in parentheses

Compound	$SnPh_2Cl(tctsc)$	$SnCl_2(tctsc)_2$
C(1)–N(1)	1.317(6)	1.351(4)
C(1)–N(2)	1.335(6)	1.293(3)
C(l)–S(1)	1.757(4)	1.765(2)
C(2)–N(3)	1.325(6)	1.301(3)
N(2)–N(3)	1.348(5)	1.372(3)
C(2)–C(3)	1.445(6)	1.430(3)
Sn(1)–Cl(1)	2.481(1)	2.420(1)
Sn(1)–S(1)	2.434(1)	2.455(1)
Sn(1)–N(3)	2.370(3)	2.258(2)
Sn(1)–C(7)	2.139(4)	
Sn(1)–C(13)	2.141(4)	

Table 3
Selected angles (°) with estimated S.D. in parentheses for $SnPh_2Cl(tctsc)$

C(7)–Sn(1)–Cl(1)	96.0(1)	C(7)–Sn(1)–N(3)	97.5(1)
C(13)–Sn(1)–Cl(1)	95.0(1)	C(13)–Sn(1)–N(3)	88.4(1)
N(3)–Sn(1)–S(1)	76.4(1)	C(7)–Sn(1)–C(13)	124.2(2)
S(1)–Sn(1)–Cl(1)	85.7(1)	C(13)–Sn(1)–S(1)	118.4(1)
N(3)–Sn(1)–Cl(1)	161.1(1)	C(7)Sn(1)–S(1)	116.9(1)

*2.2. Preparation of chlorodiphenyl(thiophene-2-carboxaldehydethiosemicarbazonato-N,S)tin(IV), $SnPh_2Cl(tctsc)$, **1***

Thiophene-2-carboxaldehyde thiosemicarbazone (3 mmol) which was prepared by the reported method [3], was dissolved in hot ethanol (20 cm^3) and then added to a solution of $SnPh_2Cl_2$ (3 mmol) in ethanol (20 cm^3). The mixture was heated and stirred for 30 min. The mixture was cooled and slow evaporation at room temperature (r.t.) gave yellow crystals which were then filtered and washed with ethanol. Yield 73%, m.p. 170–171°C (Found: C, 43.5; H, 2.8; N, 8.4; Sn, 24.3. Calc. for $C_{18}H_{16}ClN_3S_2Sn$: C, 43.9; H, 3.3; N, 8.5; Sn, 24.1%). IR (KBr, cm^{-1}): 1604 (C=N), 1058 (N–N), 726(C–S). ^{1}H-NMR [$(CD_3)_2SO$]: δ 8.27 (s, 1H, CH=N), 8.21 (s, 1H, NH_2), 7.55 (s, 1H, NH_2).

*2.3. Preparation of bis(thiophene-2-carboxaldehydethiosemicarbazonato-N,S)dichlorotin(IV), $SnCl_2(tctsc)_2$, **2***

This compound was prepared using the same method as **1** from $SnPhCl_3$ (2 mmol) and thiophene-2-carboxaldehydethiosemicarbazone (4 mmol) in ethanol (50 cm^3). Yellow crystals which were formed by slow evaporation at r.t. were filtered. Yield 73.5% (based on $SnPhCl_3$), m.p. 230°C (dec.) (Found: C, 25.9; H, 1.7; N, 15.0; Sn, 20.5. Calc. for $C_{12}H_{12}Cl_2N_6S_4Sn$: C, 25.8; H, 2.2; N, 15.1; Sn, 21.3%) IR (KBr, cm^{-1}): 1596 (C=N), 1060 (N–H), 730 (C–S). ^{1}H-NMR [$(CD_3)_2SO$]: δ 8.26 (s, 1H, CH=N), 8.20 (s, 1H, NH_2), 7.55 (s, 1H, NH_2).

Table 4
Selected angles (°) with estimated S.D. in parentheses for $SnCl_2(tctsc)_2$

N(3)–Sn(1)–N(3a)	83.4(1)	Cl(1)–Sn(1)–Cl(1a)	95.3(1)
N(3)–Sn(1)–Cl(1a)	167.0(1)	N(3a)–Sn(1)–Cl(1)	167.0(1)
N(3)–Sn(1)–Cl(1)	91.8(1)	N(3a)–Sn(l)—Cl(1a)	91.8(1)
N(3)–Sn(1)–S(1)	78.8(1)	N(3a)–Sn(1)–S(1a)	78.8(1)
N(3a)–Sn(1)–S(1)	95.4(1)	N(3)–Sn(1)–S(1a)	95.4(1)
Cl(1)–Sn(1)–S(1)	95.5(1)	Cl(1a)–Sn(1)–S(1a)	95.5(1)
Cl(1a)–Sn(1)–S(1)	89.7(1)	Cl(1)–Sn(1)–S(1a)	89.7(1)
S(1)–Sn(1)–S(1a)	172.3(1)		

Table 5
Antifungal activity

	ED_{50} (μg cm^{-3})			
Compound	*Curvularia* sp.	*Drechsiera* sp.	*Rhizoctonia* sp.	*Alternaria* sp.
tctscH	52	24	123	68
$SnPh_2Cl$(tctsc)	1.4	2.4	48	2.95
$SnCl_2$(tctsc)$_2$	>100	55	48	>100

2.4. Crystallography

Intensity data for complexes **1** and **2** were measured at 298 K on a Siemens P4 diffractometer fitted with graphite-monochromated Mo–K_α radiation, $\lambda = 0.71073$ Å. The $\theta - 2\theta$ scan technique was employed to measure data up to a maximum Bragg angle of 27.5°. The data were corrected for Lorentz and polarization effects but not for absorption. The structures were each solved by direct methods using Siemens SHELXTL (PC version) [11], and refined by a full-matrix least-squares procedure based on *F*. All non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were included in their idealised positions (C–H 0.96 Å, N–H 0.90 Å) and refined isotropically except for complex **2** whereby hydrogen atoms were located from difference maps and refined with isotropic thermal parameters. The crystal data and structure refinement details for complexes **1** and **2** are given in Table 1. Selected bond distances are listed in Table 2 and selected bond angles in Table 3 and 4, respectively. Additional data, including fractional atomic co-ordinates and their equivalent isotropic displacement parameters, hydrogen atom co-ordinates, anisotropic temperature factors, and a list of observed and calculated structure factors for complexes **1** and **2** have been deposited as supplementary material with the editor from whom copies are available on request.

Table 6
Cytotoxic activity

	IC_{50} (μg cm^{-3})			
Compound	COLO-205[a]	HA226/VGH	SKBR-3	MOLT-4
tctscH	29.98	>100	9.30	24.70
$SnPh_2Cl$(tctsc)	2.19	1.97	0.53	0.43
$SnCl_2$(tctsc)$_2$	>100	>100	7.33	>100
Adriamycin[b]	0.470	0.300	0.053	<0.001

[a] COLO-205, human colon adenocarcinoma; HA22T/VGH, human hepatocellular carcinoma; SKBR-3, human breast adenocarcinoma; MOLT-4, human acute lymphoblastic leukemia.

[b] Adriamycin: a reference.

2.5. Fungitoxicity and cytotoxicity tests

The biological activity of both compounds was evaluated using previously reported procedures [12].

Antifungal activity was tested against four plant pathogens: *Curvularia* sp., *Drechsiera* sp, *Rhizoctonia* sp. and *Alternaria* sp. Cytotoxic activity was evaluated against human colon adenocarcinoma, breast adenocarcinoma, hepatocellular carcinoma and acute lymphoblastic leukaemia.

The antifungal activity and cytotoxic activity of tctscH and its tin complexes **1** and **2** are summarized in Table 5 and 6, respectively.

3. Results and discussion

Figs. 1 and 2 show the molecular structures of complex **1**, $SnPh_2Cl$(tctsc) and complex **2**, $SnCl_2$(tctsc)$_2$. In both complexes, the tctsc ligand functions as a bidentate anion, co-ordinates to the central Sn atom through the thiol-*S* atom and the azomethine-*N* atom, yielding a five-membered chelate ring after the enolization and deprotonation of the thiol proton. The occurrence of the enolization process is supported by the shortening of the C(1)–N(2) bond (increase in bond order). Dur-

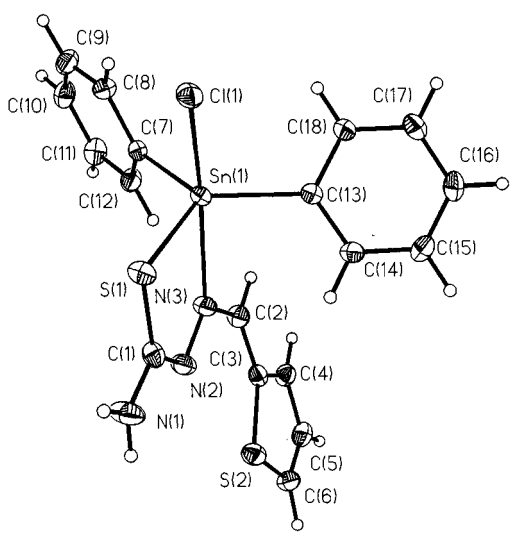

Fig. 1. Molecular structure with atom labelling for complex **1**, $SnPh_2Cl$(tctsc).

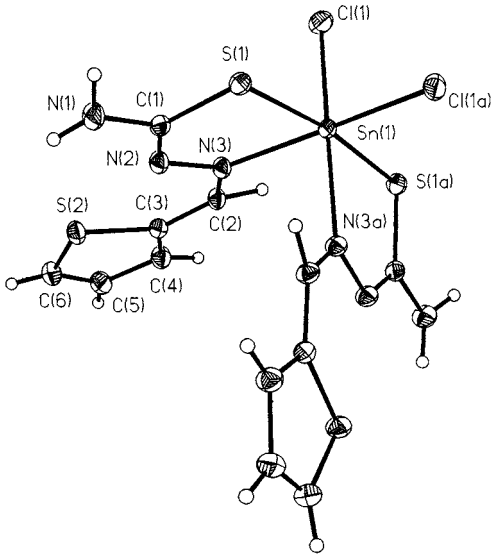

Fig. 2. Molecular structure with atom labelling for complex **2**, $SnCl_2(tctsc)_2$.

ing the formation of these complexes, a conformational change of the ligand from *trans* to *cis* configuration (refer to S(1) and N(3) atoms) occurs so as to enable it to co-ordinate in a bidentate manner [10,13].

Structurally there are few significant differences between the protonated and coordinated tctsc ligand. The C(1)–S(1) bond length has been increased from 1.695(3) Å in the protonated ligand [10] to 1.757(4) Å in complex **1** or 1.765(2) Å in complex **2**. Hence, the previous conclusion by Nardelli and co-workers that co-ordination causes an increase of the single-bond character for C–S bond seems to remain valid [14]. The C(2)–N(3) distance is lengthened (0.02–0.04 Å) whilst the N(2)–N(3) distance is shortened (0.01–0.03 Å) in the title complexes compared with the corresponding bond distances in the protonated ligand [10], indicating the involvement of N(3) in the co-ordination to tin atom by lone pair electron donation.

The Sn–S lengths (2.434(1) Å in complex **1** and 2.455(1) Å in complex **2**) are close to the sum of the covalent radii of Sn and S (2.44 Å) [15] and are comparable to those observed for organotin compounds with sulphur containing ligands [16–19].

As shown in Fig. 1, complex **1** exists in a distorted trigonal bipyramidal geometry about the tin atom, where the Cl and azomethine-*N* atoms which are most electronegative occupy the axial position. The deviation of the complex from the trigonal bipyramidal geometry is indicated by the bond angles, C(7)–Sn(1)–C(13) [124.2(2)°], C(13)–Sn(1)–S(1) [118.4(1)°] and C(7)–Sn(1)–S(1) [116.9(1)°] which deviate from the ideal angle, 120°.

In the formation of complex **2**, dephenylation has taken place where the phenyl group is released from the co-ordination to the tin atom, so as to achieve the idealized geometry in the product. Complex **2** exists in a distorted octahedral geometry. This is shown by the bond angles' deviation from linearity for the atoms which are *trans* to each other, namely N(3a)–Sn(1)–Cl(1) [167.0(1)°], N(3)–Sn(1)–Cl(1a) [167.0(1)°], S(1)Sn(1)–S(1a) [172.3(1)°] and from 90° for the 12 angles subtended at the tin atom by adjacent donor atoms ranging from 78.8(1) to 95.5(1)°.

The results of the in vitro antifungal activity given in Table 5 show that complex **1** exhibited a greater fungitoxicity in comparison to complex **2** and tctscH. The increased fungitoxicity of complex **1** as compared to the tctscH may be ascribed to the polarity of the compounds. On co-ordination, the charge of the Sn ion is greatly reduced due to the sharing of its positive charge with the donor atoms and consequent π-electron delocalization over the entire chelate ring manifold. Thus, the lipophilic character of complex **1** increases and promotes its permeation through lipoid layers of the fungus membranes [20]. However, complex **2**, an inorganic tin complex is less reactive than the protonated ligand in fungal growth inhibition due to the greater polarity of the complex. The absence of the organo group in complex **2** makes it more polar than complex **1**; moreover, its structure is more bulky than the ligand and hence complex **2** is difficult to permeate through the fungus membranes compared to complex **1** and tctscH. The antifungal activity of the thiosemicarbazone ligand can be ascribed to its ability to chelate the necessary metals that the fungus requires in its metabolism [21].

The anticancer screening data presented in Table 6 also indicate that **1** is the only effective complex against the cell tested; remarkable activities were found against human breast adenocarcinoma and human acute lymphoblastic leukaemia since an IC_{50} value of less than 4 $\mu g\ cm^{-3}$ is normally considered to be active [12]. Once again, complex **2** exhibited less cytotoxicity in comparison to tctscH except for breast adenocarcinoma. Therefore, the presence of the organo (phenyl) group in the tin compound has been considered to play an important role in biological activity.

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References

[1] P. Umapathy, A.P. Budhkar, C.S. Dorai, J. Indian Chem. Soc. 63 (1986) 714.
[2] F.A. French, E.J. Blanz, J. Med. Chem. 9 (1966) 585.
[3] K. Singh, R.V. Singh, J.P. Tandon, Synth. React. Inorg. Met.-Org. Chem. 16 (1986) 1341.
[4] M. Nath, N. Sharma, C.L. Sharma, Synth. React. Inorg. Met.-Org. Chem. 19 (1989) 339.
[5] V.K. Arora, K.B. Pandeya, R.P. Singh, J. Indian Chem. Soc. 56 (1979) 656.
[6] B. Singh, H. Misra, J. Indian Chem. Soc. 63 (1986) 692.
[7] N. Kanoongo, R.V. Singh, J.P. Tandon, J. Prakt. Chem. 330 (1988) 479.
[8] P.S.N. Reddy, B.V. Agarwala, Synth. React. Inorg. Met.-Org. Chem. 17 (1987) 584.
[9] P. ChatterJee, H.K. Duggel, B.V. Agarwala, A.K. Dey, J. Indian Chem. Soc. 66 (1989) 550.
[10] M. Mathew, G.J. Palenik, Acta Crystallogr. Sect. B 27 (1971) 59.
[11] G.M. Sheldrick, SHELXTL PC™, Release 4.1, Siemens Crystallographic Research Systems, Madison, USA, 1990.
[12] S.G. Teoh, S.H. Ang, S.B. Teo, H.K. Fun, K.L. Khew, C.W. Ong, J. Chem. Soc. Dalton Trans. (1997) 465.
[13] M.J.M. Campbell, Coord. Chem. Rev. 15 (1975) 279.
[14] M. Mathew, G.J. Palenik, J. Am. Chem. Soc. 91 (1969) 6310.
[15] L. Pauling, The Nature of the Chemical Bond, 3rd edn., Cornell University Press, Ithaca, 1960, p. 64.
[16] S.W. Ng, V.G.K. Das, B.W. Skelton, A.H. White, J. Organomet. Chem. 377 (1989) 211.
[17] J.S. Casas, A. Sanchez, J. Sordo, A. Vazquez-Lopez, E.E. Castellano, J. Zukerman-Schpector, M.C. Rodriguez-Arguelles, U. Russo, Inorg. Chim. Acta 216 (1994) 169.
[18] S.B. Teo, S.G. Teoh, R.C. Okechukwu, C. Wei, J. Coord. Chem. 28 (1993) 81.
[19] V.G.K. Das, C. Wei, E. Sinn, J. Organomet. Chem. 290 (1985) 291.
[20] T.T. Bamgboye, O.A. Bamgboye, Inorg. Chim. Acta 133 (1987) 247.
[21] A. Albert, R.J. Goldere, Nature (Lond.) 161 (1948) 95.