Chinese Chemical Letters Vol. 14, No. 8, pp 840 – 843, 2003
http://www.imm.ac.cn/journal/ccl.html

Diorgano, Dichloro-tin (IV) Complexes of 4-X-Benzohydroxamic Acid (X=Cl, OCH_3): Synthesis, Characterization, Antitumor Activity in *Vitro* and the Crystal Structure of *trans*- [$Me_2Sn(L_2)_2$]

Jing Hua ZHAO[1], Tai Gang LIANG[1], Qing Shan LI[1]*, Armando J.L. Pombeiro[2]

[1]School of Pharmaceutical Science, Shanxi Medical University, Taiyuan 030001
[2]Complexo I, Instituto Superior Técnico, Av. Rovisco Pais, 1049-001 Lisbon, Portugal

Abstract: A series of diorganotin (IV) derivatives of R_2SnL_2 (R = Me, Et, *n*-Bu, ph or Cl; L = L_1 or L_2) and their corresponding mixed-ligand complexes $R_2Sn(L_1)(L_2)$ have been prepared and the structure of *trans*-$Me_2Sn(L_2)_2$ was characterized by FT-IR, ^1H, ^{13}C and ^{119}Sn NMR spectroscopies, MS, elemental analysis, melting points and X-ray diffraction. The structure-activity relationships were discussed.

Keywords: Diorganotin, X-ray diffraction, antitumor activity, synthesis.

Diorganotin (IV) complexes constitute a class of potential antitumor agents, which were active against P_{388} lymphocytic leukaemia and MCF-7 mammary tumor[1]. Hydroxamic acids such as arylhydroxamic acid are strong bidentate O-donors with bioactivity[2]. A few years ago, we initiated an investigation on the interactions between diorganotin (IV) acceptors and benzohydroxamic acid and its derivatives[3, 4], hoping that a synergic effect would occur. We found most of this type of diorganotin (IV) derivatives showed promising activity against a series of human tumor cell lines *in vitro*[5]. The results also proved that the diethyltin (IV) and dibutyltin (IV) complexes of benzohydroxamic acid, the simplest ligand in the family of arylhydroxamic acids, are the leading compounds[3, 5]. In this paper we describe the synthesis of two arylhydroxamic acids, HL_1 (X = Cl) and HL_2 (X = OCH_3) (**Figure 1**) and use of them as ligands in tin (IV) complexes.

Experimental

Synthesis of the ligands HL_1 and HL_2

An ice cooled aqueous solution (30 mL) of $NH_2OH{\cdot}HCl$ (1.07 mol/L) was slowly added to an ice cooled aqueous solution (15 mL) of NaOH (4.13 mol/L). Methyl 4-chlorobenzoate (20 mmol) or methyl 4-methoxybenzoate (20 mmol) was then added to the solution under N_2 and the system was stirred at room temperature overnight. Then the pH value of the solution was adjusted to about 7.5 under ice cooling with 5 mol/L

*E-mail: qingshanl@Yahoo.com

HCl. The white precipitate formed was filtered off, recrystallized from methanol-water and dried to constant weight (75.5% yield for HL_1, 83% yield for HL_2, respectively).

*Synthesis of the complexes **1-12***

Dimethyltin (IV) dichloride (1 mmol), diethyltin (IV) dichloride (1 mmol), di-*n*-butyltin (IV) dichloride (1 mmol) or diphenyltin (IV) dichloride (1 mmol) was added to methanol solution (20 mL) of HL_1 or HL_2 and KOH (0.1 mol/L, respectively). The clear solution was stirred at room temperature overnight under N_2, water (20 mL) was then added, leading to form the precipitate, which was filtred off, washed with water and cold methanol, recrystallized from ethanol-chloroform (for complex 1, 4 and 8) or chloroform-light petroleum (for complex 2, 3, 5, 6 and 7) or ethanol-dichloromethane (for complex 9, 10, 11 and 12) and dried to constant weight.

*Synthesis of the complexes **13-14***

Tin tetrachloride (1 mmol) was added to a dichloromethane solution (25 mL) of HL_1 (0.08 mol/L). The reaction mixture was refluxed overnight, the hot solution was then filtered and the white crystals were formed slowly from the filtrate at room temperature. The physical data of complexes**1-14** are presented in **Table 1**.

Antitumor Activity in vitro

The antitumor activity against tumor cell lines was assayed by the MTT method. The result is presented in **Table 2**.

Results and Discussion

All the complexes except **13** and **14** are stable in air, insoluble in water and soluble in chloroform, acetone, DMSO and dilute alcohol. Complexes **13** and **14** are not stable to moisture. The complexes **9-12** in polar solvents gradually decompose to their corresponding single-ligand complexes R_2SnL_2 as inferred from IR and NMR spectra.

By comparing the IR spectra of the free ligands with those of the complexes, the strong broad band (O-H…O stretch) centered at *ca.* 2700 cm^{-1} of the free ligands was disappeared in the latter. The $\nu_{C=O}$ at *ca.* 1680 cm^{-1} shifted to *ca.* 1600 cm^{-1} in the complexes indicated a coordination of the ligand in the monomeric form through the carbonyl oxygen. The IR spectra indicated the coordination of the ligand *via* both oxygen atoms of the CO-NH-O^- group. The ^1H NMR spectra provided further evidence for the mononuclear nature of the diorganotin (IV) derivatives. The ^{13}C NMR spectra indicated that the carbon atom of the carbonyl was deshielded by *ca*. 1-2 ppm upon coordination. Deshielding was also observed for C (7) and C (4), but the resonances of the C (1), C (3) and -OCH_3 underwent an upfield shift upon coordination. The ^{119}Sn NMR data showed the products were the typical hexacoordinated tin (IV) derivatives.

Table 1 The physical data for the diorgano, dichloro-tin (IV) complexes

No.	Compound	Color	mp (ºC)	Yield (%)	Elemental Analysis: Found (calc.) (%)		
					C	H	N
1	$Me_2Sn(L_1)_2$	white	205-206	45	38.93 (39.22)	3.32 (3.27)	5.14 (5.72)
2	$Et_2Sn(L_1)_2$	white	>300	47	41.56 (41.73)	3.88 (3.90)	5.29 (5.41)
3	$Bu^n{}_2Sn(L_1)_2$	white	189-191	65	46.83 (46.02)	4.95 (4.92)	4.79 (4.88)
4	$Ph_2Sn(L_1)_2$	white	235-237	48	50.65 (50.85)	3.51 (3.29)	4.38 (4.55)
5	$Me_2Sn(L_2)_2$	white	219-223 (dec)	42	44.80 (44.93)	4.86 (4.62)	5.72 (5.82)
6	$Et_2Sn(L_2)_2$	white	188-190	62	47.27 (47.17)	5.30 (5.16)	5.67 (5.50)
7	$Bu^n{}_2Sn(L_2)_2$	white	110-113	40	51.22 (50.99)	6.24 (6.07)	4.78 (4.96)
8	$Ph_2Sn(L_2)_2$	white	209-212 (dec)	39	55.86 (55.56)	4.56 (4.34)	4.59 (4.63)
9	$Me_2Sn(L_1)(L_2)$	white	195-197	55	42.38 (42.05)	4.02 (3.95)	5.51 (5.77)
10	$Et_2Sn(L_1)(L_2)$	white	253-255	65	44.31 (44.43)	4.69 (4.52)	5.47 (5.46)
11	$Bu^n{}_2Sn(L_1)(L_2)$	Light yellow	196-200 (dec)	48	48.13 (48.49)	5.48 (5.44)	4.76 (4.92)
12	$Ph_2Sn(L_1)(L_2)$	white	155-158	70	54.01 (53.20)	3.90 (3.81)	5.42 (4.60)
13	$(L_1)_2SnCl_2$	white	246(dec)	60	31.75 (31.68)	1.85 (1.90)	5.10 (5.28)
14	$(L_2)_2SnCl_2$	white	210(dec)	50	36.96 (36.84)	3.15 (3.10)	5.28 (5.37)

Table 2 The data of the antitumor activity of the complexes *in vitro*

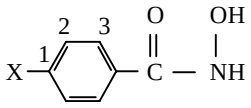
Compound	HL-60	KB	Bel-7402	Hela	B	T
1 $Me_2Sn(L_1)_2$	+	—	—	—	—	+
2 $Et_2Sn(L_1)_2$	++	++	++	++	++	++
3 $Bu^n{}_2Sn(L_1)_2$	+++	+++	++	++	++	++
4 $Ph_2Sn(L_1)_2$	+	+	—	—	++	—
6 $Et_2Sn(L_2)_2$	++	++	—	—	++	—
7 $Bu^n{}_2Sn(L_2)_2$	++	++	++	++	+	—
8 $Ph_2Sn(L_2)_2$	++	++	++	++	++	—
Cisplatin	++	++	++	++	++	+

" – " means $IC_{50} > 1\times10^{-4}$ mol/ L; " + " means $IC_{50} \leq 1\times 10^{-4}$ mol/ L; " ++ " means $IC_{50} \leq 1\times 10^{-5}$ mol/ L; " +++ " means $IC_{50} \leq 1\times 10^{-6}$ mol/ L.

The antitumor activity *in vitro* showed some structure-activity-relationships. The R group of the diorganotin (IV) complexes played an important role in the antitumor activity. The electronic influence of the X substituent of the hydroxamate ligands also affected the antitumor activity of the complexes. Hence, the antitumor activity is determined by a delicate balance of electronic effects of the ligands and the best

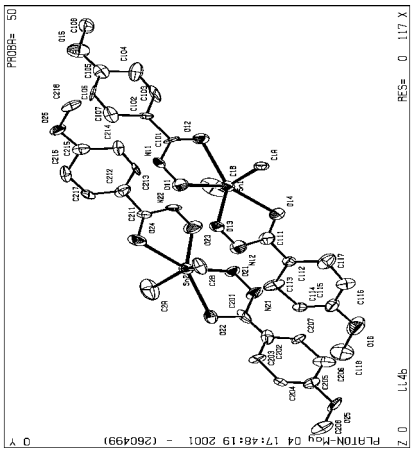
combination of dibutyltin (IV) (R = Bu^n) complexes with the chloro-substituted (X= Cl) hydroxamate ligand. The molecular structure of the complex $Me_2Sn\ (L_2)_2$ is authenticated by single-crystal X-ray diffraction analysis in our laboratory. Its structure is presented in **Figure 2**.

Figure 1 Structure of the ligand



HL_1: X=Cl; HL_2: X=OCH_3

Figure 2 The crystal structure of *trans*- $[Me_2Sn(L_2)_2]$



Acknowledgment

The financial supports from the National Natural Science Foundation of China (No.39900185) , from the State Commission of Science and Technology of China (NO. 96-901-06-38) and from TRAPOYT are gratefully acknowledged.

References and Note

1. Crowe, P. J. Smith, G. Atassi, Chem. *Biol. Interact*., **1980,** *436*, 171.
2. A. Dobosz, N. Dudarenko, Z. O. Friksky, H. Kozlowski, *J. Chem. Soc. Dalton Trans*., 1999, 743
3. P. Yang, Q.S. Li, *Chinese J. Structure. Chem.*, **1996,** *15*, 163.
4. Q.S. Li, P. Yang, *Syn. React. Inorg-Organomet.* Chem., **1996**, *26*, 561.
5. Q.S. Li, *PhD. Thesis*, Nanjing University, Sep., **1996**.
6. The crystallographic parameters have been deposited in the editorial office of CCL.

Received 2 September, 2002