

RETRACTED: Synthesis, Structure and Antitumor Activity of Dibutyltin Oxide Complexes with 5-Fluorouracil Derivatives. Crystal Structure of [(5-Fluorouracil)-1-CH₂CH₂COOSn(*n*-Bu)₂]₄O₂

Dai-shu Zuo ¹, Tao Jiang ^{1,*}, Hua-shi Guan ¹, Kui-qi Wang ¹, Xin Qi ¹ and Zhan Shi ²

¹ Marine Drug and Food Institute, Ocean University of Qingdao, Qingdao, China 266003

² Key Laboratory of Inorganic Synthesis and Preparative Chemistry, Jilin University, Changchun, China, 130022

* Author to whom correspondence should be addressed; Tel.: (+86) 0532-2032712; Fax: (+86) 0532-2033054; E-mail: jiangt@public.qd.sd.cn.

Received: 19 March 2001; in revised form 20 March 2001 / Accepted: 2 May 2001 / Published: 31 July 2001

Abstract: Dibutyltin (IV) oxide complex reacts with the fluorouracil compounds 5-fluorouracil-1-propanonic or 5-fluorouracil-1-acetic acid (Fu) to give the complexes [(5-Fu)-1-(CH₂)_nCOOSn(*n*-Bu)₂]₄O₂ (**I**, *n*=2; **II**, *n*=1) which were characterized by IR and ¹H-NMR. The crystal structure of complex **I** shows that the molecular is a dimer, in which two [(5-Fu)-1-CH₂CH₂COOSn(*n*-Bu)₂]₂O units are linked by a bridging oxygen atom, and the tin atoms adopt distorted trigonal bipyramids via two carbons from a dibutyl moiety and three oxygen atoms from 5-Fu and bridging oxygen. These complexes have potential anti-tumour activity: *in vitro* tests showed that complexes **I** and **II** exhibit high cytotoxicity against OVCAR-3 and PC-14.

Keywords: Organotin complex, 5-Fu, synthesis, crystal structure, antitumor activity.

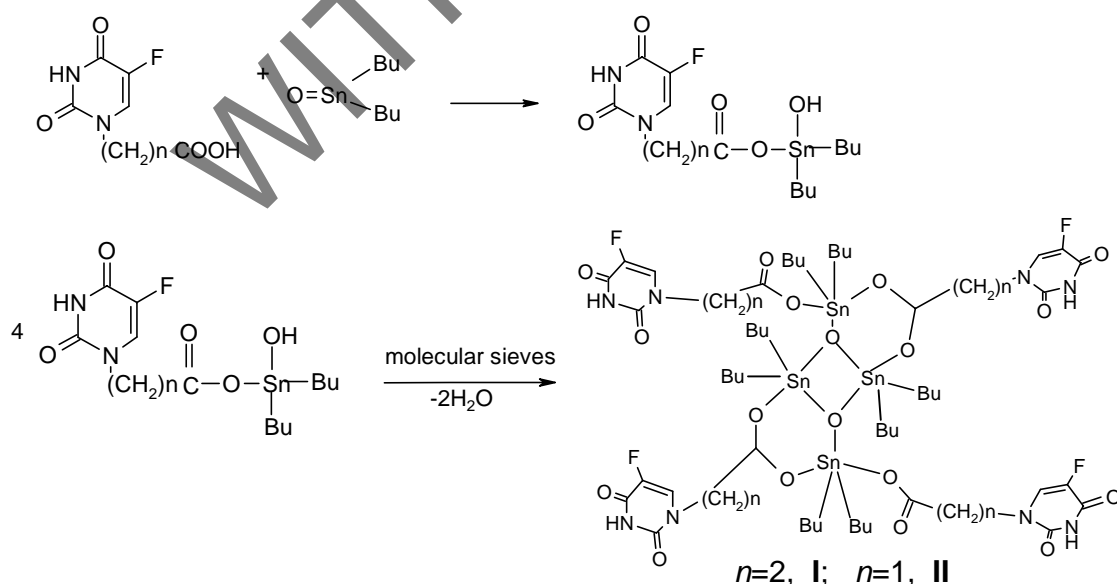
Introduction

Many groups have reported the chemotherapeutic properties of tin compounds possessing anti-tumor activity [1-5]. Since then intense interest has developed in this field and a large number of organotin compounds have been synthesized and tested [6-7]. Among these compounds dibutyltin derivatives have displayed both higher activity and relatively low toxicity [8]. On the other hand, the cycle-specific schedule dependent antimetabolite 5-fluorouracil (5-Fu) has been in clinical use for 40 years and has evolved as an important agent in the treatment of a large spectrum of tumors, including all gastrointestinal cancers and breast cancer. While attempting to study organotin (IV) complexes as possible candidates for anti-tumor agents and the structure-activity relationships of these complexes, we successfully prepared two kinds of new 5-Fu dibutylorganotin (IV) derivatives and determined the X-ray crystal structure of one of them. At the same time, their anticancer activity was also tested. We report these results herein.

Results and Discussion

Synthesis

The [(5-fluorouracil)-1-(CH₂)_nCOOSn(*n*-Bu)₂]₄O₂ compounds **I** (*n*=2) and **II** (*n*=1) were synthesized by the reaction of (Bu)₂SnO with (5-fluorouracil)-1-(CH₂)_nCOOH (*n* = 2,1) in the appropriate molar ratio of 1:1. A possible mechanism for the formation of compounds **I** and **II** is shown in Scheme 1



Scheme 1. The synthesis of [(5-Fu)-1-(CH₂)₂COOSn(*n*-Bu)₂]₄O₂

The (5-fluorouracil)-1-(CH₂)_nCOOH (*n* = 2, 1) starting materials were obtained by the reaction of 5-fluorouracil with CH₂=CHCN (*n* = 2) or ClCH₂COOH (*n* = 1) in NaOH solution. 4Å molecular sieves were used as the catalyst for the dehydration reaction. If the reaction temperature were raised to 80°C, the 2:1 molar ratio (5-Fu:Sn) complexes would be formed. The resulting complexes **I** and **II** are stable in the air and are difficult to dissolve in aromatic or ether solvents, but can be easily dissolved in methanol or H₂O when heated.

Molecular structure

The IR and ¹H-NMR spectroscopic spectra supported the fact that the complexes **I** and **II** contain the expected 5-Fu and butyl moieties. In order to confirm their molecular structure, the X-ray crystal structure of **I** was also determined. Its molecular structure and the unit cell are shown in Figures 1 and 2, and selected interatomic bond distances (Å) and angles (°) are listed in Table 1.

Figure 1. Molecular structure and atomic numbering system for [5-fluorouracil-1-(CH₂)₂COOSn(*n*-Bu)₂]₄O₂

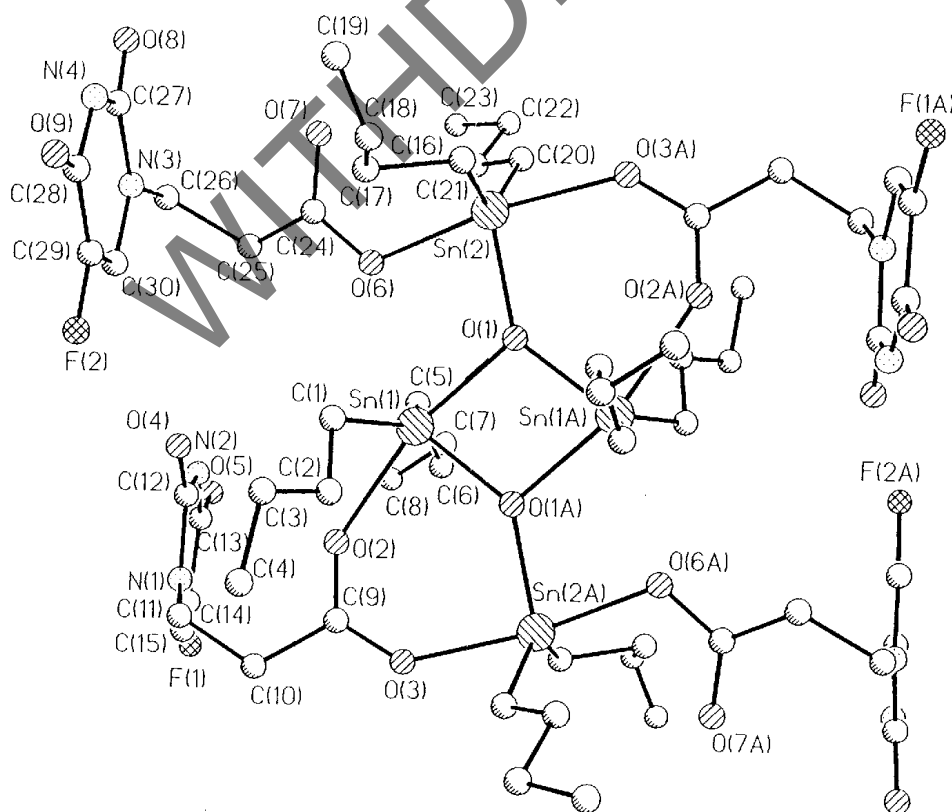
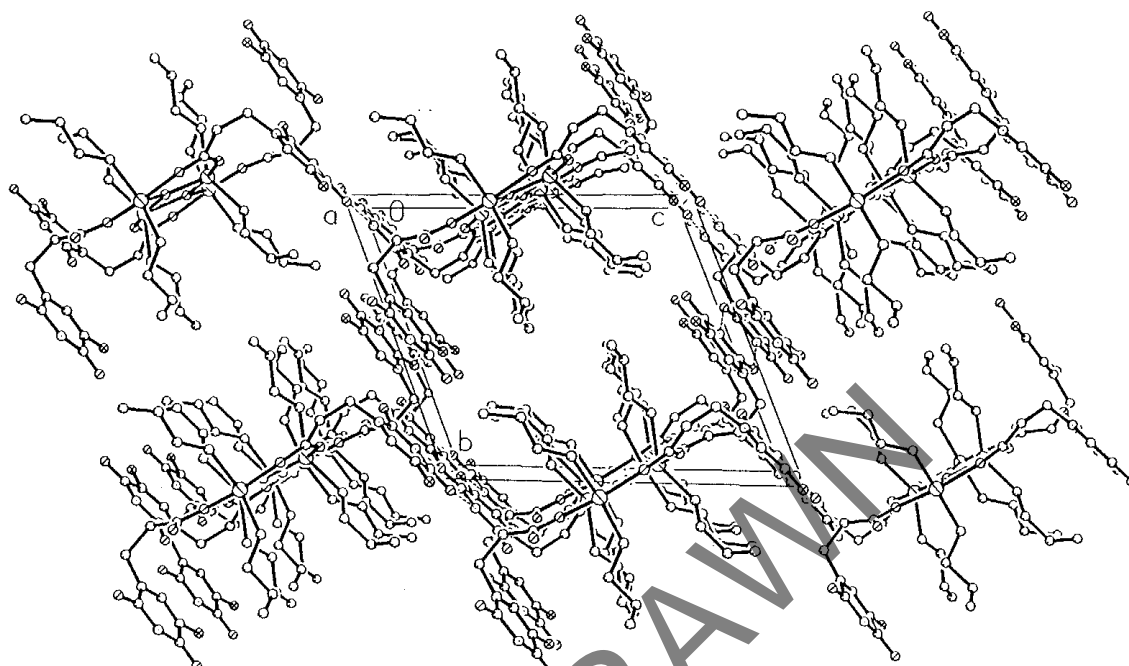


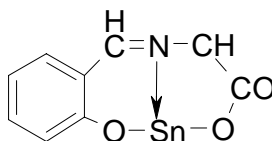
Figure 2. Unit cell of [5-fluorouracil-1-(CH₂)₂COOSn(*n*-Bu)₂]₄O₂**Table 1.** Selected Bond lengths [Å] and angles [°] for (I)

Bond lengths			
Sn(1)-O(1A)	2.037(8)	Sn(2)-C(20)	2.143(2)
Sn(1)-C(1)	2.083(17)	Sn(2)-O(6)	2.151(9)
Sn(1)-C(5)	2.086(15)	Sn(2)-O(3A)	2.251(10)
Sn(1)-O(1)	2.183(8)	O(1)-Sn(1A)	2.037(8)
Sn(1)-O(2)	2.269(8)	O(2)-C(9)	1.258(14)
Sn(2)-O(1)	2.043(7)	O(3)-C(9)	1.261(14)
Sn(2)-C(16)	2.119(19)	O(3)-Sn(2A)	2.251(10)
Bond angles			
O(1A)-Sn(1)-C(1)	106.6(5)	C(5)-Sn(1)-O(2)	87.0(4)
O(1A)-Sn(1)-C(5)	110.6(4)	O(1)-Sn(1)-O(2)	165.6(3)
C(1)-Sn(1)-C(5)	141.4(6)	O(1)-Sn(2)-C(16)	109.0(5)
O(1A)-Sn(1)-O(1)	76.4(3)	O(1)-Sn(2)-C(20)	113.1(6)
C(1)-Sn(1)-O(1)	100.0(5)	C(16)-Sn(2)-C(20)	136.4(7)
C(5)-Sn(1)-O(1)	98.2(4)	O(1)-Sn(2)-O(6)	79.6(3)
O(1A)-Sn(1)-O(2)	89.2(3)	C(16)-Sn(2)-O(6)	102.5(6)

C(1)-Sn(1)-O(2)	83.7(5)	C(20)-Sn(2)-O(6)	95.8(6)
O(1)-Sn(2)-O(3A)	91.9(4)	Sn(1A)-O(1)-Sn(1)	103.6(3)
C(16)-Sn(2)-O(3A)	84.6(6)	Sn(2)-O(1)-Sn(1)	118.9(4)
C(20)-Sn(2)-O(3A)	83.1(6)	C(9)-O(2)-Sn(1)	138.2(8)
O(6)-Sn(2)-O(3A)	170.4(3)	C(9)-O(3)-Sn(2A)	135.4(9)
Sn(1A)-O(1)-Sn(2)	137.4(4)	C(24)-O(6)-Sn(2)	118.5(8)
O(2)-C(9)-O(3)	123.1(12)		

This complex is a dimeric compound in which the $[(5\text{-Fu})\text{-}1\text{-CH}_2\text{CH}_2\text{COOSn}(n\text{-Bu})_2]_2\text{O}$ units are linked by bridging oxygen atoms thus increasing coordinative saturation. The tin atom is pentacoordinated. The geometry about the four tin atoms are based on the trigonal bipyramids with the trigonal planes defined by the C (1), C(5), O(1A) atoms for Sn (1); C(16), C(20), O(1) for Sn(2); C(1A), C(5A), O(1) for Sn(1A) and C(16), C (20A), O(1A) for Sn(2A), while the O(1) and O(2), O(3A) and O(6), O(2A) and O(1A), O(6A) and O(3) are in the axial position for Sn(1), Sn(2), Sn(1A) and Sn(2A) respectively. The bonding of the bridging ligands is asymmetric with a Sn(1)-O(1A) bond length of 2.037(8) Å and a Sn(1)-O(1) contact of 2.183 (8)Å, which forms a parallelogram. The complex also contains two five-member chelate rings, formed via carbonyl oxygen to tin coordination. The bond distances Sn(1)-O(2) (2.269(8)Å), Sn(2A)-O(3) (2.251 (10)Å) are longer than the bond distance of Sn(2)-O(6) or Sn(2A)-O(6A) (2.151(9)Å) , and the bond distances of C(9)-O(2) (1.258(14)Å), C(9)-O(3) (1.261(14)Å) are almost equal and both are between the length of C=O double bond (1.212Å) and C-O single bond (1.291Å) in the model complex shown in Figure 3 below [12]. This indicates that the coordination of two of the circular-linked 5-Fu ligand oxygen atoms to tin atoms is weaker than that of the other oxygen atom of the linearly-linked 5-Fu ligand.

Figure 3



Biological activity

The MTT method was used for a preliminary estimation of the *in vitro* tumor-inhibiting activity of complexes **I** and **II**. The data summarized in Table 2 shows that complexes **I** and **II** possess rather high cytotoxicity towards tumor cells of OVCAR-3 and PC-14 and the dibutyltin 5-fluorouracil-1-propanonic acid derivative is more active than the dibutyltin 5-fluorouracil-1-propanonic acid derivative.

Table 2. Inhibitory effect of the complexes on tumor cells of OVCAR-3 and PC-14 (MTT)

Tumor cell	Complex	Concentration of complex ($\mu\text{g/mL}$)	Inhibitory Rate (%)
OVCAR-3	I	1	-
		10	72.99
		100	97.8
	II	1	-
		10	20.51
		100	95.30
PC-14	I	1	-
		10	64.93
		100	98.1
	II	1	-
		10	31.98
		100	92.71

Acknowledgements

This project was supported by the Foundation for University Key Teachers of the Chinese Ministry of Education and the Foundation of the Key Laboratory of Inorganic Synthesis and Preparative Chemistry, Chinese Ministry of Education.

Experimental:

General Methods

IR spectra were recorded using KBr pellets on a Nicolet NEXUS 470 FT-IR. ^1H -NMR spectra were recorded at 298K for CDCl_3 solutions with TMS as the internal reference using a Unity-400MHz-NMR spectrometer. The elemental analyses were determined on a GmhH Varin EL analyzer. Tin was determined using complexometric titration with EDTA and lead nitrate as the volumetric solution. Toluene was dried over Na and distilled prior to use under N_2 . Dibutyltin oxide was synthesized following the literature method [9]. 5-Fluorouracil-1-acetic acid and 5-fluorouracil-1-propanoic acids were prepared according to the literature methods [10-11]. 5-Fluorouracil was a gift from Rudong Pharmaceutical Factory of Jiangsu.

The tumor inhibiting effect of complex 1 and 2 was tested *in vitro* using the human ovarian carcinoma cell line OVCAR-3 and lung carcinoma cell line PC-14 by the MTT method.

General preparation of the complexes of dibutyltin oxide and 5-fluorouracil -1-propanonic acids

Both complexes were prepared in a similar fashion and therefore, only the synthesis of one of them, namely [(5-fluorouracil)-1-CH₂CH₂COOSn(*n*-Bu)₂]₄O₂ (**I**) is described in detail herein. 5-Fluorouracil-1-propanonic acid (0.404g, 2mmol) was added to the solution of dibutyltin oxide (0.498g, 2mmol) in toluene (15mL) containing a few 4Å molecular sieves. The mixture was stirred under N₂ for 8 hours at a temperature of 50°C. After cooling down and filtration, the residue was extracted three times with methanol. Concentration of the resulting solution gave colorless needle-shaped crystals of [(5-fluorouracil)-1-CH₂CH₂COOSn(*n*-Bu)₂]₄O₂ (**I**). Yield: 0.5613g (62%); m.p. 168-170°C (from methanol); ¹H-NMR: δ: 0.908 (6H, t, J₁=5.6Hz, J₂=4.8Hz, CH₃), 1.243-1.370 (8H, m, CH₂CH₂), 1.642 (2H, m, Sn-CH₂), 2.799 (2H, t, J₁=6.0Hz, J₂=5.6Hz, CH₂CH₂CO), 3.963 (2H, t, J₁=6.0Hz, J₂=5.6Hz, N-CH₂-CH₂), 7.527 (1H, d, J=5.6Hz, =CH), 8.210 (b, NH); IR (cm⁻¹): ν(N-H) 3412, ν(C-H) 3168, ν(CH₃) 3064, 2929, ν(CH₂) 2959, 2868, ν(C=O) 1770 (-O-C=O), ν(C=O) 1693(-N-C=O), ν(C=C) 1576, ν(CH) 1339, ν(C-C) 1238, ν(Sn-O) 682, 543; Anal Calcd for C₃₀H₄₆F₂N₄O₉Sn₂: C 40.81, H 7.66, N 6.45, Sn 26.91; Found C 40.56, H 7.97, N 6.28, Sn 26.91.

Complex **II** was similarly prepared. Yield: 63.7%; m.p 176-178°C (from methanol); ¹H-NMR: δ: 0.881 (6H, t, J₁=5.6Hz, J₂=4.8Hz, CH₃), 1.254-1.341 (8H, m, CH₂CH₂), 1.647 (2H, m, Sn-CH₂), 4.448 (2H, s, N-CH₂-CO), 7.521 (1H, s, =CH), 8.184 (b, NH); IR (cm⁻¹): ν(N-H) 3420, ν(C-H) 3187, ν(CH₃) 3071, 2929, ν(CH₂) 2956, 2866, ν(C=O) 1693(-O-C=O), ν(C=O) 1680(-N-C=O), ν(C=C) 1599, ν(CH) 1465, ν(CH) 1321, ν(C-C) 1241, ν(Sn-O) 685, 588. Anal Calcd for C₂₆H₃₈F₂N₄O₉Sn₂: C 39.52, H 5.26, N 6.34, Sn 27.98; Found: C 39.28, H 5.18, N 6.54, Sn 27.73..

Crystal structure determination of I

A single crystal of 0.34x0.20x0.04mm was placed in a Siemens SMART CCT four-circle diffractometer with MoK_α (λ=0.71073Å) and a scan range 1.83 ≤ θ ≤ 23.28 at room temperature. Of the 9452 reflections collected, 5491 reflections with I > 2 σ(I) were considered to have been observed. The structure was solved by the heavy-atom method and refined by Full-matrix least-squares on F² by the use of SHELXL Version 5.1 program. The final agreement factor was R=0.0693. Crystal data: C₃₀H₄₆F₂N₄O₉Sn₂, Fw=882.09, Triclinic, P1, a=11.423(3)Å, b=12.843(3)Å, c=14.770(4)Å, α=66.711(6)deg, β=79.319(6)deg, γ=78.172(7)deg, V=1935.0(8)Å³, Z=2, F(000)=888, D_c=1.514 mg/m³.

References

1. Crown, A. J. *Drugs of the Future* **1987**, *12*, 40.
2. Biddle, B.N.; Grey, J. S. *Appl. Organomet. Chem.* **1991**, *5*, 43
3. B.H. Keppler, *Metal Complexes in Cancer Chemotherapy*, VCH Publishers: Weinheim, **1993**.

4. (a) Guli, G.; Gennaro, G.; Pellerito, L.; Stocco, G. C. *Appl. Organomet. Chem.* **1993**, *7*, 407.
(b) Huber, F.; Vornefeld, M.; Preut, H.; Angerer, E.; Ruisi, G. *Appl. Organomet. Chem.* **1992**, *6*, 597.
5. Wang, J. T. *Progress in Natural Science* **1998**, *8*, 180
6. Li, Z. F.; Fu, F. X.; Pan, H. D. Xing, Y.; Lin, Y. H. *Acta Chimica Sinica* **1999**, *57*, 820
7. Tian, L. J.; Zhou, Z. Y.; Zhao, B.; Yu, W. T. *Polyhedron* **1998**, *17*, 1275
8. Pettina, C.; Pellei, M.; Marchetti, F.; Santini, C.; Miliani, M. *Polyhedron* **1998**, *17*, 561
9. Hu, C.; Wang, S.; Zhao, S. *Chin. J. Med. Chem.* **1994**, *4*, 32 (in Chinese)
10. Masao, T. *Bullet. Chem. Soc. Jap.* **1975**, *48*, 3427
11. Zhou, R. X.; Fan, C. L.; Zhao R. L. *Chem. J. Chinese Univ.* **1986**, *7*, 508
12. Wang, J. T.; Zhang, Y. W.; Xu, Y. M.; Yang, Z. W. *Youji Huaxue (Chinese J. Org. Chem.)* **1993**, *13*, 289

Sample Availability: Available from the authors.

© 2001 by MDPI (<http://www.mdpi.org>). Reproduction is permitted for noncommercial purposes.