Organotin Compound Derived from 3-Hydroxy-2-formylpyridine Semicarbazone: Synthesis, Crystal Structure, and Antiproliferative Activity

Joanna Wiecek, 1 Dimitra Kovala-Demertzí, 1 Zbigniew Ciunik, 2 Joanna Wietrzyk, 3 Maria Zervou, 4 and Mavroudis A. Demertzí 1

1 Inorganic and Analytical Chemistry, Department of Chemistry, University of Ioannina, 45110 Ioannina, Greece
2 Faculty of Chemistry, University of Wrocław, 14 F. Joliot-Curie St., 50-383 Wrocław, Poland
3 Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 12 R Weigl St, 53-114 Wrocław, Poland
4 Laboratory of Molecular Analysis, Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, 48, Vas. Constantinou Ave, 11635 Athens, Greece

Correspondence should be addressed to Dimitra Kovala-Demertzí, dkovala@cc.uoi.gr

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The novel diphenyltin(IV) compound [Ph2(HyFoSc)Sn] (2), where H2HyFoSc (1) is 3-hydroxy-2-formylpyridine semicarbazone, was prepared and characterized by vibrational and NMR (1H, 13C) spectroscopy. The structure of [Ph2(HyFoSc)Sn] was confirmed by single-crystal X-ray crystallography. The doubly deprotonated ligand is coordinated to the tin atom through the enolic-oxygen, the azomethine-nitrogen, and phenolic-oxygen, and so acts as an anionic tridentate ligand with the ONO donors. Two carbon atoms complete the fivefold coordination at the tin(IV) center. Intermolecular hydrogen bonding, C-H → π, and π → π interactions combine to stabilize the crystal structure. Compounds 1 and 2 have been evaluated for antiproliferative activity in vitro against the cells of three human tumor cell lines: MCF-7 (human breast cancer cell line), T24 (bladder cancer cell line), A549 (nonsmall cell lung carcinoma), and a mouse fibroblast L-929 cancer cell line.

1. Introduction

Organotin compounds are of interest in view of their considerable structural diversity [1]. Increasing interest in organotin(IV) chemistry has arisen in the last few decades and is attributed to their significantly important biological properties. Several di- and tri-organotin species have shown potential as antineoplastic and antituberculosis agents [2–5]. The binding ability of organotin compounds towards DNA depends on the coordination number and nature of groups bonded to the central tin atom. The phosphate group of DNA-sugar backbones usually acts as an anchoring site and DNA base-nitrogen binding is extremely effective and this often results in the stabilization of the octahedrally coordinated tin center. Recent studies have shown that low doses of organotins can exhibit antitumoral activity and have suggested a mode of action via a gene-mediated pathway in the cancer cells, opening a new research subarea on organotin compounds [6].

Thio- and semicarbazones (TSC) possess a wide range of bioactivities, and their chemistry and pharmacological applications have been extensively investigated. The more significant bioactivities of a variety of semicarbazones (antiprotozoa, anticonvulsant) and thiosemicarbazones (antibacterial, antifungal, antitumoral, antiviral) and their metal complexes have been reviewed together with proposed mechanisms of action and structure-activity relationships [7, 8]. Casas et al. [9] have surveyed structural aspects of main group metal complexes of semicarbazones and thiosemicarbazones. The survey shows that heterocyclic and nonheterocyclic TSC’s are very versatile coordination agents with these elements [9].

Following our interest in the chemistry and pharmacological properties of thiosemicarbazones [10–17] and towards organotins [18–21], herein, the preparation and
spectroscopic characterization of a novel semicarbazone and a novel diphenyl organotin compound derived from the reaction of SnPh2O with 3-hydroxy-2-formylpyridine semicarbazone H2HyFoSc (1) are described with the final goal of developing new biologically active pharmaceuticals. The results of the cytotoxic activity of 1, SnPh2O, and of the organotin compound (2) against the cells of three human cancer cell lines: MCF-7 (human breast cancer cell line), T24 (bladder cancer cell line), A549 (non-small cell lung carcinoma), and a mouse fibroblast L-929 cancer cell line are also reported. To our knowledge, this is the first report of synthesis of 1 and 2.

2. Experimental

2.1. General and Instrumental. The reagents (Aldrich, Merck, Sigma) were used as supplied while the solvents were purified according to standard procedures. Melting points were determined in open capillaries and are uncorrected. Infrared and far-infrared spectra were recorded on a Perkin–Elmer Spectrum GX FT IR System spectrophotometer using KBr pellets (4000–400 cm⁻¹) and nujol mulls dispersed between polyethylene disks (400–40 cm⁻¹). The 1H, 13C NMR spectra were recorded on a Bruker AC-300 MHz spectrometer and on a Varian 600 MHz spectrometer. The spectra were acquired at room temperature (298 K). The chemical shifts are reported in ppm with respect to the references (external tetramethylsilane (TMS) for 1H and 13C NMR). Elemental analyses were carried out by the microanalytical service of the University of Ioannina, Greece.

2.2. Synthesis

2.2.1. 3-Hydroxypyridine-2-carbaldehyde Semicarbazone (1). Commercially available 3-hydroxy-(2-hydroxymethyl) pyridine hydrochloride was oxidized with MnO2, prepared by heating MnCO3 for 12 h at 300°C, according to [22, 23] to afford 3-hydroxypyridine-2-carbaldehyde as a yellow powder, yield 62%, and m.p. 77°C. The aldehyde (2 mmol) in EtOH (6 mL) was then reacted with a solution of bazeone (0.360 g, 2.0 mmol) and 3-hydroxypyridine-2-carbaldehyde semicarbazone (0.360 g, 2.0 mmol) in benzene (100 mL) were refluxed for 24 h under azotropic removal of H2O (Dean-Stark trap). The resulting clear solution was concentrated in vacuo to a small volume. The oily product was chilled and triturated with distilled diethyl ether (Et2O) to give a yellow solid. The yellow powder was recrystallized from distilled ether and was dried in vacuo over silica gel. Yield 24%; m.p. 209°C. UV-Vis for 1 (DMF) λ/μm (logε): 388 br (3.87); 331 sh (4.15); 320 (4.18). IR cm⁻¹: 3144 s, 3065 m, (ν(NH2)); 1664 (ν(C=O)), 1542 s (ν(C=N)); 1283 (ν(C=O)); 997 s (ν(NN)) 339 sh, 321 ms (ν(SnC)); 446 sh (ν(SnNC)); 284 mw (ν(SnO2–)); 248 mw (ν(SnO)). 1H-NMR (DMSO-d6): δ 7.30 (d, H4), 7.36 (t, H5), 8.15 (d, H6), 8.20 (s, H7), 6.74 (br, NH2), 7.95 (s, Ho), 7.45, 7.57 (m, Hmp), 13C-NMR: δ 137.5 (C2), 153.2 (C3), 128.0 (C4), 128.2 (C5), 138.0 (C6), 139.5 (C7), 155.8 (C8=O), 134.7 (Co), 127.7 (Cm), 127.2 (Cp). Anal. calc. for C19H16N4O2Sn (451.0 g mol⁻¹) C, 50.6; H, 3.6; N, 12.4; Found: C, 50.4; H, 3.7; N, 12.3%. Crystals suitable for X-ray analysis were obtained by slow evaporation of a freshly distilled diethyl ether solution of 1.

2.3. X-Ray Crystallography. Crystal data are given in Table 1, together with refinement details. All measurements were performed on a Kuma KM4 CCD kappa-axis diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The data were corrected for Lorentz and polarization effects. An analytical absorption correction was applied to the data using a multifaceted crystal model [24]. Data reduction and analysis were carried out with the Kuma Diffraction (Wroclaw) programs. The structure was solved by direct-methods and refined by a full-matrix least-squares method on all F² data using the SHELXL97 [25]. Nonhydrogen atoms were refined with anisotropic displacement parameters; all hydrogen atoms were placed in calculated positions and allowed to ride on their parent atoms with a common isotropic displacement parameter. Molecular graphics were performed with PLATON 2004 [26].

Crystallographic data for 2 have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 634269 for compound 2. Copies of this information may be obtained free of charge from The Director, CCDC, 12, Union Road, Cambridge CB2 1EZ [FAX ++44(1223)336-033] or e-mail deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

2.4. Antiproliferative Assay In Vitro

Compounds. Test solutions of the tested compounds (1 mg/mL) were prepared by dissolving the substance in 100 μL of DMSO completed with 900 μL of tissue culture medium. Afterwards, the tested compounds were diluted in culture medium to reach the final concentrations of 100, 50, 10, 1, and 0.1 ng/μL. The solvent (DMSO) in the highest concentration used in the test did not reveal any cytotoxic activity.

Cells. The cell lines are maintained in the Cell Culture Collection of the University of Ioannina. Twenty-four hours before addition of the tested agents, the cells were plated in 96-well plates at a density of 10⁴ cells per well. The
Table 1: X-ray crystal data and structure refinement for 2.

| Property                              | Value                   |
|---------------------------------------|-------------------------|
| Empirical formula                     | C_{10}H_{18}N_{4}O_{2}Sn |
| Formula weight                        | 451.05                  |
| Temperature (K)                       | 100(2)                  |
| Crystal system                        | Monoclinic              |
| Space group                           | P2_1/n                  |
| Crystal size (mm)                     | 0.17 × 0.20 × 0.23      |
| a (Å)                                 | 10.5498(6)              |
| b (Å)                                 | 12.5794(7)              |
| c (Å)                                 | 13.9477(8)              |
| β (°)                                 | 103.594(5)              |
| Volume (Å^3)                          | 1799.2(2)               |
| Z                                      | 4                       |
| D_{calc} (g cm^{-3})                  | 1.665                   |
| Absorption coefficient (mm^{-1})      | 1.441                   |
| θ range for data collection (°)       | 3.0–36.6                |
| Reflections collected                 | 29597                   |
| Independent reflections (R_{int})     | 8324 (0.056)            |
| Data/parameters                       | 8324/243                |
| Goodness-of-Fit (F^2)                 | 0.857                   |
| Final R indices (I > 2σ(I))           | 0.037                   |
| wR                                    | 0.062                   |
| Maximum and minimum residuals (e Å^{-3}) | 1.03/−0.74          |

MCF-7 cells were cultured in the D-MEM (Modified Eagle's Medium) medium supplemented with 1% antibiotic and 10% fetal calf serum. L-929 cells were grown in Heps-buffered RPMI 1640 medium supplemented with 10% fetal calf serum, penicillin (50 U/mL), and streptomycin (50 mg/mL). A-549 cells were grown in F-12K Ham’s medium supplemented with 1% glutamine, 1% antibiotic/antimycotic, 2% NaHCO_3, and 10% fetal calf serum. The cell cultures were maintained at 37°C in a humid atmosphere saturated with 5% CO_2. Cell numbers were counted by the Trypan blue dye exclusion method. MCF-7, L-929, and A-549 cells were determined by the sulfonhodamine B assay [27], while T24 cells by the MTT assay [28]. The in vitro tests were performed as described previously [29].

3. Results and Discussion

3.1. Synthesis. Compound 1 was synthesized by means of the Heinert–Martell reaction (Scheme 1) [22]. The corresponding diorganotin compound 2 was prepared by reacting diorganotin(IV) oxide with the semicarbazone in benzene solution in a 1:1 molar ratio.

3.2. Crystal Structure of 2. A perspective view of 2, together with the atom-labeling scheme, is given in Figure 1 and selected bond lengths and angles are given in Table 2.

The doubly deprotonated ligand is coordinated to the tin atom through the enolic-oxygen, azomethine-nitrogen, and phenolic-oxygen atoms. Two carbon atoms complete the fivefold coordination at the diorganotin(IV) fragment. Analysis of the shape determining angles using the approach of Addison et al. [30] yields τ = 0.54 (τ = 0.0 and 1.0 for SPY and TBPY geometries, resp.). The metal coordination geometry is therefore described as distorted trigonal bipyramidal with the O(2) and O(1) atoms occupying the apical positions around the tin atom.

The dianionic, tridentate ONO ligand has a ZEZ configuration, Figure 1. The coordinated part of the ligand is made of three rings, two chelates Sn(1)O(2)N(1)N(2)C(4) (I) and Sn(1)O(1)N(1)C(1)C(2)C(3) (II) and one heterocyclic ring (III). The dihedral angles between the planes of the rings 1 and II, I and III are 7.17(7) and 10.32(9), respectively, indicating that the ligand as a whole deviates from planarity. The C(3)–N(1) bond length is 1.298(3) Å and is close to the distance of a double bond (1.28 Å). The deprotonation of the N(2)H group produces a negative charge, which is delocalized in the C(3)–N(1)–N(2)–C(4) moiety. The distortion from the ideal trigonal-bipyramidal configuration is shown by the O(1)–Sn(1)–O(2) angle of 156.78(6)°, which deviates from the ideal value of 180°, due in part to the ligand constraint. All the metal–donor bond distances, Table 2, are similar to other organotin complexes presented in the literature [18–21].

The polar hydrogen atoms on N(3) participate in two intermolecular hydrogen bonds. The monomers of 2 are connected into dimers by a pair of cooperative hydrogen bonds [see Table 3 for geometric parameters describing these interactions]. Further, adjacent dimers are connected by C–H···N contacts, as illustrated in Figure 2. The presence of additional C–H···π and π–π contacts further stabilizes the crystal structure.

3.3. Spectroscopic Studies. In the IR spectrum of H_2HyFoSc (1), the strong bands at 3147 and 3088 cm^{-1} are assigned to the asymmetric and symmetric modes of terminal NH_2, respectively. The ν(NH) band appears at 2920 cm^{-1}. The strong broad band at ca. 2650 cm^{-1} is assigned to the ν(NH···O) and ν(OH···O) mode due to strong intramolecular hydrogen bonding. The absence of the ν(NH) stretching motion at 2 is indicative of deprotonation of the amide proton. The strong broad band at ca. 2650 cm^{-1} at 2 is probably due to the ν(NH···N) intermolecular hydrogen bonds as confirmed by X-ray crystallography. The coordination of the azomethine-N atom to the tin center was suggested in the IR spectrum by a shift of the ν(C=N) band to a lower frequency, along with the occurrence of a ν(N–N) band to higher frequency [12, 13, 16]. An IR band at 1322 cm^{-1} for 1 was assigned to ν(C=O). This band was found to be shifted to 1283–1289 cm^{-1}, in the spectrum of 2, which indicates the coordination of this O atom. The low energy of the τ(C=O) vibration in the spectra of 1, that is, 1664 cm^{-1}, is indicative that the carbonyl O-atom is involved in hydrogen bonding. The replacement of the hydrogen by the metal atom does not shift this band to lower frequency. Coordination of the imine nitrogen is also consistent with the presence of a band at 446 cm^{-1}, assignable to ν(Sn–N). Bands at 284 and 248 cm^{-1} are assigned to ν(Sn–O_{c–o}) and ν(Sn–O_{c–o}), respectively [18–21].
**Scheme 1:** The reaction scheme for synthesis of 1 and 2.

**Table 2:** Selected bond lengths (Å) and angles (°) for complex 2.

| Bond/Angle | Distance/Value |
|------------|----------------|
| Sn(1)–O(1) | 2.073 (2)      |
| Sn(1)–O(2) | 2.152 (2)      |
| Sn(1)–N(1) | 2.166 (2)      |
| Sn(1)–C(8) | 2.115 (2)      |
| Sn(1)–C(14) | 2.121 (2)    |
| O(1)–Sn(1)–O(2) | 156.78 (6) |
| O(1)–Sn(1)–N(1) | 84.71 (6) |
| O(1)–Sn(1)–C(8) | 98.51 (7)  |
| O(1)–Sn(1)–C(14) | 95.64 (7)  |
| O(1)–Sn(1)–N(1) | 73.14 (6)  |
| O(1)–Sn(1)–C(8) | 95.84 (7)  |
| O(1)–Sn(1)–C(14) | 90.80 (7)  |
| O(1)–Sn(1)–N(1) | 123.88 (7) |
| O(1)–Sn(1)–C(8) | 124.44 (8) |

**Table 3:** Geometric parameters for hydrogen bonds and for C–H–π and π···π interactions in 2.

| Bond/Distance | Value 1 | Value 2 | Value 3 |
|---------------|---------|---------|---------|
| N(3)–H(3A)···N(4)(i) | 2.29(2) | 3.070(3) | 175(3) |
| N(3)–H(3B)···O(2)(ii) | 2.07(3) | 2.925(2) | 183(4) |
| C(3)–H(3)···N(2)(i)  | 2.34(2) | 3.280(3) | 170(3) |
| C(7)–H(7)···Cg(5)(iii) | 2.76 | 3.619(2) | 151 |
| C(12)–H(12)···Cg(5)(iv) | 2.86 | 3.722(3) | 152 |

- Where Cg(3), Cg(4), and Cg(5) are referred to the centroids N(4)–C(1)–C(2)–C(5)–C(6)–C(7), C(8)–C(14), and C(14)–C(19); Cg–Cg is the distance between ring centroids; symmetry transformations: (i) 2–x, 1–y, –z; (ii) 1–x, 1–y, –z; (iii) 1+x, y, z; (iv) –1/2+x, 1/2–y, –1/2+z; (v) 1/2+x, 1/2–y, 1/2+z.
- Where β is the angle Cg(I)–Cg(J) or Cg(i)–Me vector and normal to plane I (°); Cg–Perp is the perpendicular distance of Cg(I) on ring I; Cg–Perp is the perpendicular distance of Cg(I) on ring I.

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(a) Where Cg(3), Cg(4), and Cg(5) are referred to the centroids N(4)–C(1)–C(2)–C(5)–C(6)–C(7), C(8)–C(14), and C(14)–C(19); Cg–Cg is the distance between ring centroids; symmetry transformations: (i) 2–x, 1–y, –z; (ii) 1–x, 1–y, –z; (iii) 1+x, y, z; (iv) –1/2+x, 1/2–y, –1/2+z; (v) 1/2+x, 1/2–y, 1/2+z.
(b) Where β is the angle Cg(I)–Cg(J) or Cg(i)–Me vector and normal to plane I (°); Cg–Perp is the perpendicular distance of Cg(I) on ring I; Cg–Perp is the perpendicular distance of Cg(I) on ring I.
Table 4: The antiproliferative activity in vitro of H₂HyFoSc and its organotin complex 2 (expressed as ID₅₀ (μM)) against MCF-7, T-24, A-549, and L-929 cancer cell lines.

| Compounds               | L-929 | A-549 | T-24 | MCF-7 |
|-------------------------|-------|-------|------|-------|
| [H₂HyFoSc] (1)          | n.a   | 175.0 | n.a. | 164.0 |
| [Ph₂(HyFoSc)Sn] (2)     | 1.19  | 0.086 | n.a. | 8.65  |
| [Ph₂SnO]                | 10.73 | 47.10 | n.a. | 3.46  |
| Cisplatin               | 0.69  | 1.53  | 41.7 | 8.00  |

1H- and 13C-NMR Spectra. In the 1H-NMR spectrum of 1, the N(3)-H resonance at δ 12.30 and C–OH at δ 11.23 ppm indicates that these H atoms are involved in hydrogen bonding, Figure 3. In the 1H-NMR spectrum of 2, the formyl H-atom H–C(7) was shifted downfield upon coordination, which indicates variations in the electron density at position 7. Deshielding of carbons C₄, C₅, and C₇ is observed in complexes, which is related to the electrophilicity of the tin atom. A σ-charge donation from the C–O and N donors to the tin center removes electron density from the ligand and produces this deshielding which will attenuate at positions remote from the tin center, Figure 4.

3.4. Pharmacology. Antiproliferative Activity In Vitro. Pd(II) and Pt(II) complexes of 2-carbaldheyde thiosemicarbazone, HFOtsc, were found to be active in vivo against leukemia P388 cells and Pt(II) complexes of N₄-ethyl 2-formyl and 2-acetylpuridine thiosemicarbazones showed cytotoxicity and were found to be able to overcome the cisplatin-resistance of A2780/Cp8 cells [10–16]. Also, Zn(II) complexes of 2-carbaldheyde thiosemicarbazone, HFOtsc, and 2-acetylpuridinide thiocemicarbazone, HAcTsc, were found active against the MCF-7 (human breast cancer cell line), T24 (bladder cancer cell line), and a mouse L-929 (a fibroblast-like cell line cloned from strain L) [29]. Compounds 1 and 2 and the organotin oxide precursor of 2 were tested for their anti-proliferative activity in vitro against the cells of three human cancer cell lines: MCF-7 (human breast cancer cell line), T24 (bladder cancer cell line), A549 (non-small cell lung carcinoma), and a mouse fibroblast L-929 cell line [see Table 4 for a summary of the cytotoxicity data].

The IC₅₀ values for H₂HyFoSc (1) against the MCF-7 and A-549 cell lines are 164 and 175 μM, respectively, while
against the L-929 and T-24 cell lines IC$_{50}$ are $>555 \mu$M. Thus, 1 is considered as nonactive against these tested cell lines. Compound 2 is also considered nonactive against T24 cell line. The IC$_{50}$ values for 2 against the L-929 and MCF-7 cell lines are 1.19 and 8.65 $\mu$M, respectively. These values are in the same range as observed for cisplatin and Ph$_2$SnO, indicating that the observed cytotoxicity is probably due to the cytotoxicity of Ph$_2$SnO. Compound 2 may then be considered as a vehicle for activation of the Ph$_2$SnO as the cytotoxic agent. The IC$_{50}$ value for 2 against A549 is 0.086 $\mu$M and therefore 2 is significantly more active compared to Ph$_2$SnO (47.1 $\mu$M) and cisplatin (1.53 $\mu$M), respectively. Compound 2 is thus 547.7 and 17.8 times more cytotoxic than the Ph$_2$SnO and cisplatin, respectively, against this cell line. Thus, 2 exhibits selectivity and is considered as an agent with potential antitumor activity against A-549 tumor cell line and can therefore be a candidate for further stages of screening in vitro and/or in vivo.

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