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A new organometallic complex based on the trimethyltin cation and 2,6-pyridinedicarboxylic acid as a potential anticancer agent

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ABSTRACT

The reaction of aqueous/acetonitrile solutions of Me_3SnCl and 2,6-pyridinedicarboxylic acid (2,6-pydcH_2) affords a new organotin complex, [Me_3Sn·(2,6-pydcH)]·H_2O, **1**. The structure of **1** was characterized by IR, UV–Vis, TGA, NMR spectra, cyclic voltammetry and X-ray single crystal analysis. The network structure of **1** is constructed by an infinite number of discrete binuclear molecules forming 1D-chains via H-bonds. The extensive H-bonds and π–π stacking connect the 1D-chains, creating a 2D-array. The 2D-arrays are further connected by H-bonds via the water molecules and methyl groups, forming a 3D-network. The cytotoxic effect of **1** on the viability of MCF-7 cells was also determined by an MTT assay. The organometallic complex **1** has potentially good inhibition activity for MCF-7 cells.

1. Introduction

Recently, coordination complexes have attracted great attention, not only due to their fascinating applications in the areas of magnetism, optics, electronics, catalysis, corrosion inhibitions and antitumor activity [1–10], but also due to their interesting topologies [11]. Among the frameworks reported so far, two types of interactions – coordinate covalent bonds and non-covalent intermolecular forces such as hydrogen bonding and π···π stacking – play major roles in constructing and stabilizing these materials. In this field, it is well known that organotin carboxylates have versatile molecular structures, both in the solid state and in solution, such as monomers, dimers, tetramers, oligomeric ladders, hexameric drums etc [12–13]. These organotin carboxylates have received much attention due to their potential biocidal activities [14–16] and cytotoxicities [17,18] as well as their industrial and agricultural applications [19–24]. Among them, the study of the structural chemistry of triorganotin carboxylates has received considerable attention due to the various structural types that may be adopted in the solid state [25–32]. Organotin(IV) dicarboxylates have been studied in considerable detail, and in general the reported organotin(IV) dicarboxylates exist as binuclear [33] one-dimensional zigzag chain [34] and cyclic structures [35]. Recently, our interest has focused on triorganotin(IV) complexes of nitrogen containing ligands in order to examine their antitumor activity against human breast cancer cell lines [6,8,17,18]. Here, we report the structure and spectral characteristics of the new organotin complex [Me_3Sn·(2,6-pydcH)]·H_2O, **1**, synthesized from an H_2O/CH_3CN solution containing Me_3SnCl and 2,6-pyridinedicarboxylic acid (2,6-pydcH_2), along with a study on the antitumor activity *in vitro* against the human breast cancer cell line MCF-7.

2. Experimental

All chemicals and solvents used in this study were of analytical grade supplied by Aldrich or Merck and used as received. Microanalyses (C, H, N) were carried out with a Perkin Elmer 2400 automatic elemental analyzer. The IR spectra were recorded on a Perkin Elmer 1430 Ratio Recording Infrared spectrophotometer as KBr discs. NMR spectrometry was measured using a 500 MHz AVANCE NMR spectrometer (Model DMX400). The chemical shifts are relative to tetramethylsilane at $\delta = 0$ ppm. Thermogravimetric analysis was carried out on a Shimadzu AT 50 thermal analyzer (under N_2 atmosphere). Electronic absorption spectra as solid matrices were measured on a Shimadzu (UV-310l PC) spectrometer. Fluorescent spectra as solid matrices were measured with a Perkin Elmer (LS 50 B) spectrometer ($\lambda_{ex} = 290$ nm). Voltammetric experiments were performed using the Princeton Applied Research-PAR VersaStat II Evisa's Instrument Database. Measurements were carried out in a DMSO solution containing 0.1 M tertiarybutylammonium perchlorate (TBAP) under a N_2 saturated environment in a conventional three electrode cell with an Ag/AgCl electrode as the reference, a platinum wire with a diameter of 2 mm as the counter electrode and a Platinum Milli-electrode (2 mm) with a surface area of 0.196 cm^2 as the working electrode.

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Electrochemical measurements were carried out at room temperature (25 ± 0.5 °C).

2.1. Synthesis of $[Me_3Sn{\cdot}(2,6\text{-}pydcH)]{\cdot}H_2O$, **1**

At ambient temperature, a solution of 99 mg (0.5 mmol) of Me_3SnCl in 20 mL H_2O was added, under gentle stirring, to a solution of 83.6 mg (0.5 mmol) of 2,6-pyridinedicarboxylic acid (2,6-pydcH_2) in 20 mL acetonitrile. After three days, colorless prismatic crystals started growing from the initially clear solution. On filtration, washing with a small cold quantity of H_2O and acetonitrile and overnight drying, about 73 mg (42% referred to 2,6-pyridinedicarboxylic) of colorless prismatic crystals were obtained. *Anal.* Calc. for **1** ($C_{10}H_{15}NO_5Sn$): C, 34.52; H, 4.35; N, 4.03. Found: C, 34.61; H, 4.23; N, 4.05%. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm; s = singlet, b = broad m = complex pattern): 13.5 (s, 1H; COOH), 8.0–8.6 (m, 3H, 2,6-pydcH moiety), 3.5 (b, 2H, H_2O), 0.7 (s, 9H, $(Me)_3Sn$, $^2J_{(^1H\text{-}^{117}Sn)}$ = 70.0 Hz and $^2J_{(^1H\text{-}^{119}Sn)}$ = 75.0 Hz). ^{13}C NMR (500 MHz, DMSO-d_6, δ, ppm): 166.0 (s, 1C, COOH), 128.5, 140.0, 148.5 (s, 5C, 2,6-pydcH moiety) (vide infra), 0.9 (s, 3C, $(Me)_3Sn$, J = 510.0 Hz).

2.2. Single crystal structure determination

Structural measurements for **1** were performed on a Kappa CCD Enraf Nonius FR 90 four circle goniometer with graphite monochromatic Mo Kα radiation {[λMo Kα] = 0.71073 Å} at 25 ± 2 °C. The structure was solved using direct-methods and all of the non-hydrogen atoms were located from the initial solution or from subsequent electron density difference maps during the initial stages of the refinement. After locating all of the non-hydrogen atoms in each structure, the models were refined against F^2, first using isotropic and finally using anisotropic thermal displacement parameters. The positions of the hydrogen atoms were then calculated and refined isotropically, and the final cycle of refinements was performed. Crystallographic data for **1** are summarized in Table 1. Selected bond distances and bond angles are given in Table 2.

2.3. In vitro antitumor activity

The cytotoxic activity of the organotin complex **1** was determined using an MTT assay. Human cancer cells of the cell line MCF-7 were obtained from the American Type Culture Collection (Manassas, VA) ATCC. Cells were cultured in the medium RPMI 1640 supplemented with 10% FBS (fetal bovine serum) under a humidified atmosphere of 5% CO_2 at 37 °C. Compound **1** was initially dissolved in DMSO then diluted to the desired concentration by adding cell culture medium. Samples (100 μL) of **1** with different concentrations were added to the wells on 96-well plates. Cells were detached with trypsin and EDTA and seeded in each well with 5×10^5 cells per well. After incubation for 48 h, a MTT solution (20 μL, 4 mg mL^{-1}) of phosphate buffer saline (8 g NaCl, 0.2 g KCl, 1.44 g Na_2HPO_4 and 0.24 g KH_2PO_4/L) was added into each well. The cells were further incubated for 4 h and a purple formazan precipitate was formed, which was separated by centrifugation. DMSO (100 μL) was added to each well to dissolve the precipitate. The optical density of the solution was determined by a plate reader (TECAN) at 540 nm. The inhibition ratio was calculated on the basis of the optical densities obtained from three replicate tests. The 50% inhibition concentration (IC50) was determined by curve fitting.

Table 1
Crystal data for the organotin complex **1**.

Empirical Formula	$C_{10}H_{15}NO_5Sn$
Formula weight (g mol^{-1})	347.92
T (K)	298
Crystal system	monoclinic
Space group	P_12_1/c
a (Å)	11.6031 (4)
b (Å)	13.2562 (4)
c (Å)	7.7670 (2)
α (°)	90.00
β (°)	93.068 (2)
γ (°)	90.00
V (Å^3)	1192.95 (6)
Z	4
μ (Mo Kα) (mm^{-1})	2.15
D_{calc} (g cm^{-3})	1.937
Goodness-of-fit (GOF) on F^2	1.046
F(000)	688
R indices [$I > 3\sigma(I)$]R_1/wR_2]	0.099/0.139
R indices(all data)	0.083/0.199
R_{int}	0.0710
Data/restraints/parameters	2163/0/190

Table 2
Bond lengths (Å) and bond angles (deg.) of the organotin complex **1**.

Sn1–O2	2.468(4)	O2–Sn1–O2^i	66.29(14)
Sn1–O2^i	2.582(4)	O2–Sn1–C5	147.24(14)
Sn1–C5	2.309(4)	O2–Sn1–N6	66.98(13)
Sn1–N6	2.293(5)	O2–Sn1–C7	88.2(2)
Sn1–C7	2.076(7)	O2–Sn1–O12	137.62(14)
Sn1–C17	2.100(7)	O2–Sn1–C17	87.6(2)
Sn1–O12	2.208(4)	O2^i–Sn1–C5	80.95(14)
O2–O2^i	2.762(7)	O2^i–Sn1–N6	133.26(13)
Sn1–Sn1^i	4.228(4)		

Symmetry codes: (i) 1 − ×, −y, 1 − z.

3. Results and discussion

3.1. Crystal structure of $[Me_3Sn{\cdot}(2,6\text{-}pydcH)]{\cdot}H_2O$, **1**

2,6-Pyridinedicarboxylic acid is a versatile multi-dentate N- and O-donor ligand which can be considered a crucial factor for the construction of the metal-organic architecture of **1**. Complex **1** was obtained at ambient temperature by treating Me_3SnCl and 2,6-pydcH_2 in H_2O/acetonitrile solution, Scheme 1. X-ray crystal analysis reveals that **1** adopts a H-bonded structure with the space group P_12_1/c, and the asymmetric unit comprises one Me_3Sn cation, one 2,6-pydcH ligand and one H_2O molecule, Fig 1a. Two asymmetric units form repeat units containing two of each of the Me_3Sn cation and 2,6-pydcH ligand in addition to one H_2O molecule, Fig 1b. The charge neutrality is achieved by one deprotonated carboxylate group of the 2,6-pydcH ligand.

In the extended structure of **1**, there are two crystallographically identical tin atoms. Each tin atom is coordinated by seven atoms, with the ligand 2,6-pydcH providing four of these atoms. Here, two basal coordination sites are occupied by one nitrogen and one of the oxygen atoms of a 2,6-pydcH ligand (Sn1–O12 = 2.208(4) Å and Sn1–N6 = 2.293(5) Å), and other two basal coordination sites are occupied by two μ_2-oxygen atoms (O2) from two 2,6-pydcH ligands (Sn1–O2 = 2.468(4) Å and Sn1–O2^i = 2.582(4) Å). The fifth basal coordination site is occupied by one of the methyl groups (Sn1–C5 = 2.309(4) Å). The two apical coordination sites are occupied by the other two methyl groups, Table 2. Thus, the seven-coordinated Sn(IV) exhibits an unusual distorted pentagonal pyramidal geometry. The basal angles of the pentagon are within the range 100.68–112.86°, whereas the apical angles are 87.22 and 89.63°, Table 2. In **1**, one of the carboxylate groups functions as a bridging ligand connecting two adjacent Sn(IV) centers, resulting in the formation of a mini cyclic motif, Sn_2O_2, with the Sn–Sn distance equal to 4.223 Å. Each tin site contains two five member chelate rings. The tin sites and the two 2,6-pydcH ligands are in the same plane, forming a discrete sheet. The