New organotin(IV) complexes derived from 1-adamantanethiol: Synthesis, structure, DFT calculation and *in vitro* bioactivities

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1 General information

1.1 Preparation

The reaction reagents of organotin were purchased from Alpha and without purification. The melting points of complexes **1-5** were obtained with Kofler micromelting point apparatus without corrected. Elemental analyses were collected by vario EL cube. NMR data (^{1}H, ^{13}C, and ^{119}Sn NMR) were collected by Bruker AVANCE NEO 500 at frequency 500.0, 125.8 and 186.5 MHz, respectively. Infrared spectra (IR) were recorded with Nicolet-6700 spectrometer (KBr disc method). The single crystal X-Ray diffraction data of complexes **1**, **3-5** were collected with Bruker SMART-1000 CCD diffractometer with graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation at the temperature of 273.15 K, single crystal data of complex **2** were collected with Xcalibur, Eos, Gemini E/xx-9100 diffractometer with graphite-monochromated Cu Kα (λ = 1.54184 Å) radiation at the temperature of 273.15 K. The data of complexes 1-5 were integrated and corrected for Lorentz and polarization effects using SAINT.[1] Absorption corrections were applied with SADABS.[2] The structure of five organotin complexes were refined by direct methods (SHLEX-2018) combined full-matrix least-squares method on F^2 using the SHELXTL and OLEX2 crystallographic software package.[3-5]

The SEM and TEM photographs were collected by FEI Nova Nano 450 (USA) and Hitachi H-7650 (Japan), respectively. The TEM sample of fungal slices were prepared with LEICA EM UC7 ultra-microtome.

1.2 Theoretical calculation methods

In order to give additional theoretical support, a series of DFT (density functional theory) calculations were prepared for complexes **1-5**. ORCA (Release 5.0.2) was used to perform the calculation.[6, 7] For the orbital calculations of complexes **1-5**, the main basis was set in B3LYP/def2-TZVP(-f), the auxiliary basis was set in def2/J.[8, 9] In the calculation, ECPs for Sn (Def2-ECP) and the atom-pairwise dispersion correction (D3BJ) were applied.[10-12] For the geometry analysis, the output files were imported to the Multiwfn to get the orbital energies values and the visible charge density orbitals were rendered by Avogadro.[13, 14]

For the frequency calculations of complexes **1-5**, the main basis was set in B3LYP/def2-TZVP, the auxiliary basis was set in def2/J.[8, 9] In the calculation, ECPs for Sn (Def2-ECP) and the atom-pairwise dispersion correction (D3BJ) were applied. The output files were imported to the Multiwfn to get the values of vibration. In the previous study, selective scaling factors of 0.9961 and 0.9552 were used for B3LYP level at the wavenumbers in the range of 1700-400 cm^{-1} and 4000-1700 cm^{-1}, respectively.[15]

1.3 *In vitro* antitumor effects

Five organotin complexes were valued with HeLa (Cervical carcinoma cell lines) and HepG-2 (Hepatocellular carcinoma cell lines), and MTT assay method to measure the cytostatic activities (IC_{50}) of five complexes **1-5**, respectively. The two cell lines were

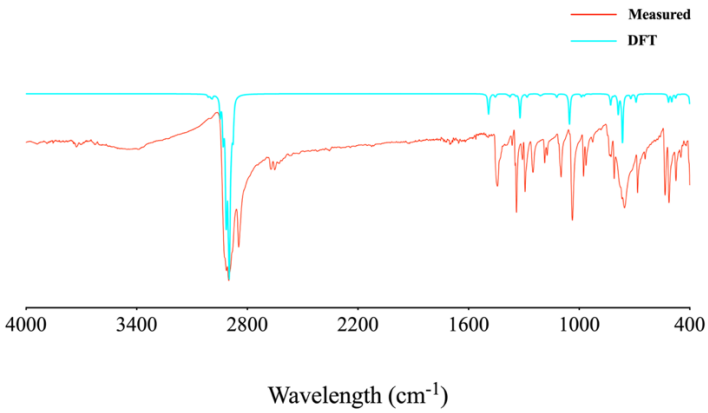
cultured and inherited in DMEM (Gibco) with 10% fetal bovine serum (FBS), 100 kU^{-1} penicillin and streptomycin at 37 ℃ humidified incubator with an atmosphere of 5% CO_2. The three cell lines were then transferred into the 96-well plates, respectively. Per column contains around 10^3 cells $\cdot L^{-1}$. The cell-contained 96-well plates were continued to cultivate for 24 h. After that, complexes **1-5** were dissolved in THF and added to the plates with the concentration of 0.1-100 μmol $\cdot L^{-1}$, respectively. THF shows high solubility of complexes **1-5** and low toxicity.[16] The drug included plates were cultured for 24h. Then 8 μL of MTT (0.5 mg $\cdot L^{-1}$) was added into per well and incubated for 4 h, then 96-well plates were taken out and replaced with 200 μL DMSO while the blue formazan precipitates dissolved into DMSO, shaken for 5 min, then the value of optical density was read by the plate reader (BioTek) at wavelength 490 nm. The IC_{50} value was calculated across the data read from column.

1.4 *In vitro* antifungal effects

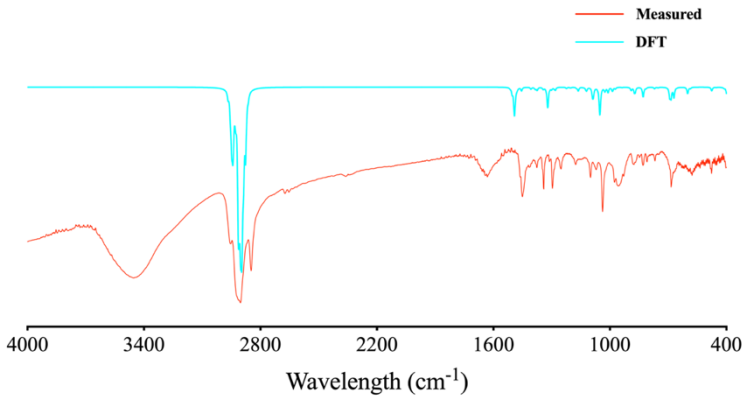
Four types of fungi, *Gibberella zeae* (GZ), *Physalospora piricola* (PP), *Rhizoctonia solani* (RS), *Alternaria kikuchiana Tanaka* (AT), the *in vitro* activities EC_{50} had been tested with the method of fungal growth inhibition.[17-19] All four types of fungi were cultured with potato dextrose agar (PDA). 3 mg of complexes **1-5** were dissolved with 40 μL of THF, respectively. The drug-contained mixtures were mixed in 6 mL sterilized water containing 0.1% Tween-80, the concentration of 500 $\mu g \cdot mL^{-1}$ was obtained. Then using the two-fold dilution method to prepare a range of drug-contained Tween-80 water with a concentration of 250 $\mu g \cdot mL^{-1}$, 125 $\mu g \cdot mL^{-1}$, 62.5 $\mu g \cdot mL^{-1}$, 31.25 $\mu g \cdot mL^{-1}$. These mixtures were mixed with 27 mL PDA medium, respectively. Each petri dish was filled with 10 mL PDA medium with three parallels. After colling down, the 7 mm diameter fungi cakes were inoculated on the dishes, then cultured at 25 ℃ and measured after 72 h. The inhibition rate(I) was calculated by the following equation: I=(C-T)/(C-D) × 100%, where C, T and D mean control radius, treatment group and initial diameter of the fungi cake, respectively.

The SEM and TEM scanning images were prepared with *Alternaria kikuchiana* Tanaka with the complex **5**. The fungus was cultivated in the PDB (potato dextrose broth) medium, and then the culture flask was transferred into the vibrating incubator (25 ℃, 150 rpm) for 72 h. After that, the fungus was treated with the concentrate of 100 $\mu g \cdot mL^{-1}$ complex **5** for 24 h. The control group was prepared as the previous method without complex **5**. The hyphae were treated with 2.5% glutaraldehyde at 4 ℃, and then rinsed with 0.1 M phosphate buffer (pH = 7.0), then immobilized with 1% w/v osmium tetroxide solution. The mycelium was dehydrated using a series of ethanol solution concentrations (30%, 50%, 70%, 80%, and 95%), then the sample was treated in the mixture of ethanol and isoamyl acetate (V/V = 1/1) for 0.5 h. The sample was treated further with pure isoamyl acetate for 1 h and left overnight. When the processes of drying at a critical point, mounting, and gold spraying had been completed, the clippings of the mycelium were scanned by the SEM. For the TEM, the sample was sliced with the ultra-microtome, double-stained using uranyl acetate and lead citrate, and then examined the grids.

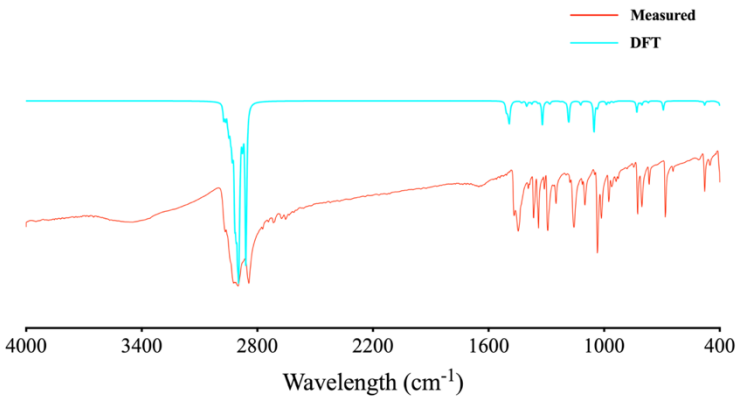
IR spectra of complexes 1-5



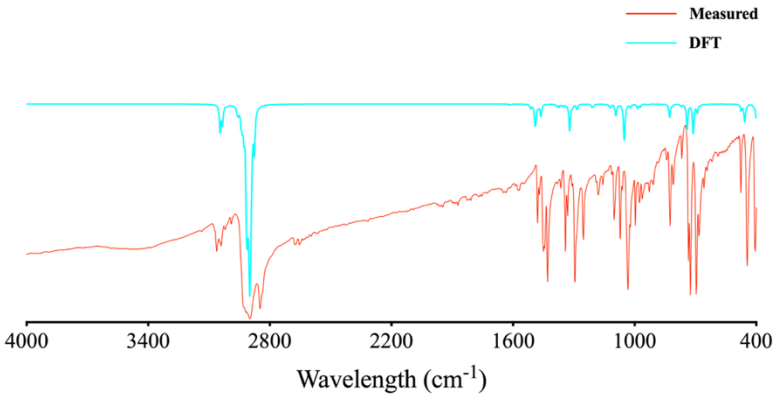
a) IR spectra of complex **1**.



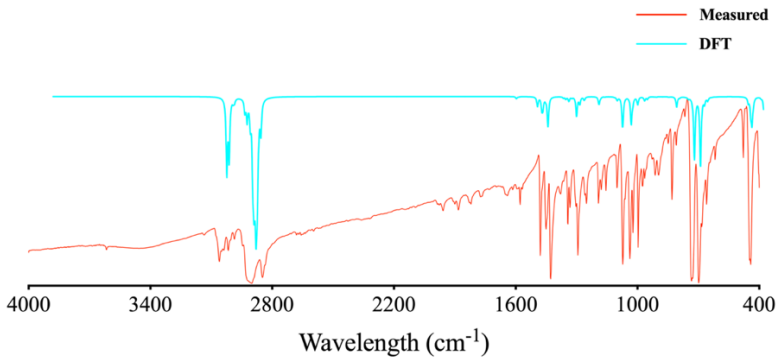
b) IR spectra of complex **2**.



c) IR spectra of complex **3**.



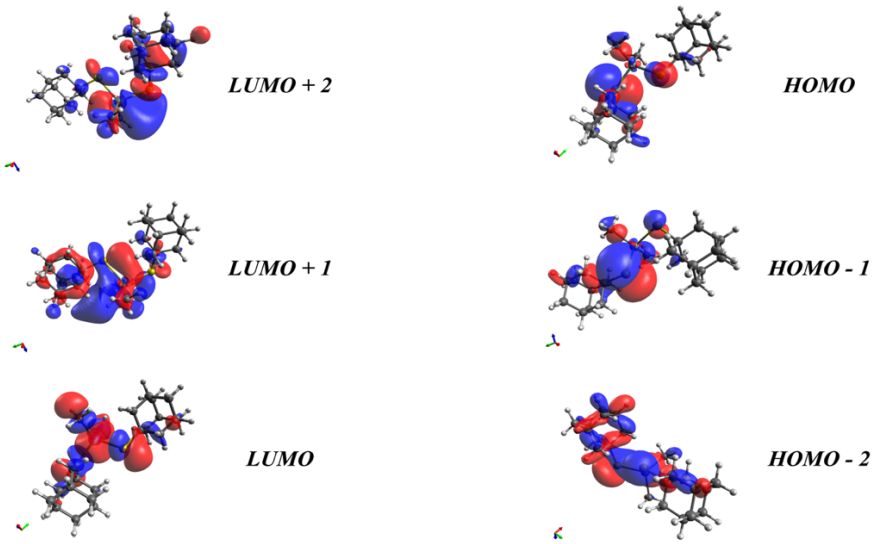
d) IR spectra of complex **4**.



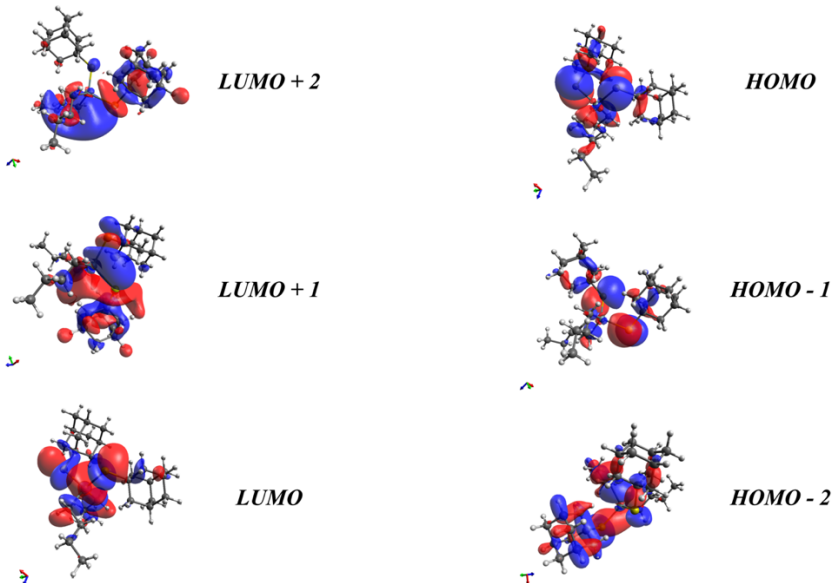
e) IR spectra of complex **5**.

Fig. S1. Measured and calculated IR spectra of complexes **1-5**.

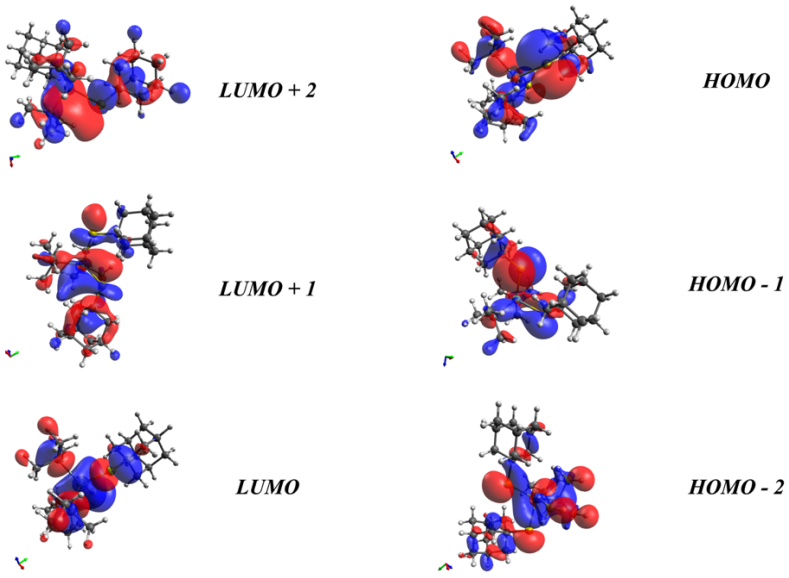
HOMO and LUMO orbitals of complexes 1-5



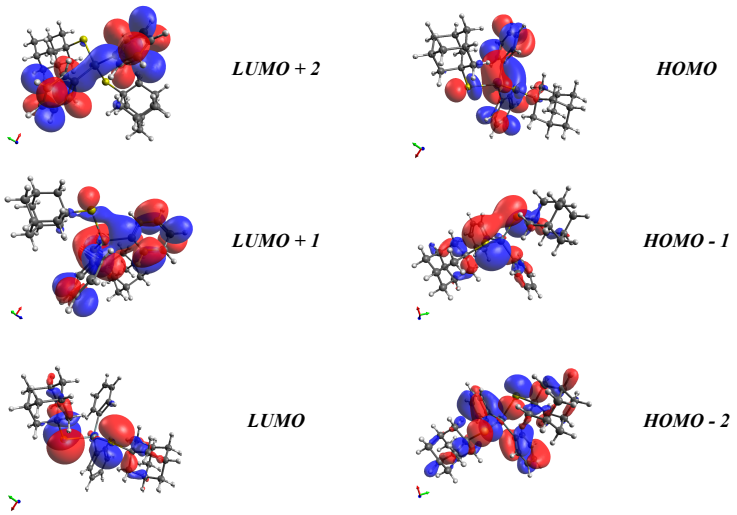
a) HOMO and LUMO orbitals of complex **1**.



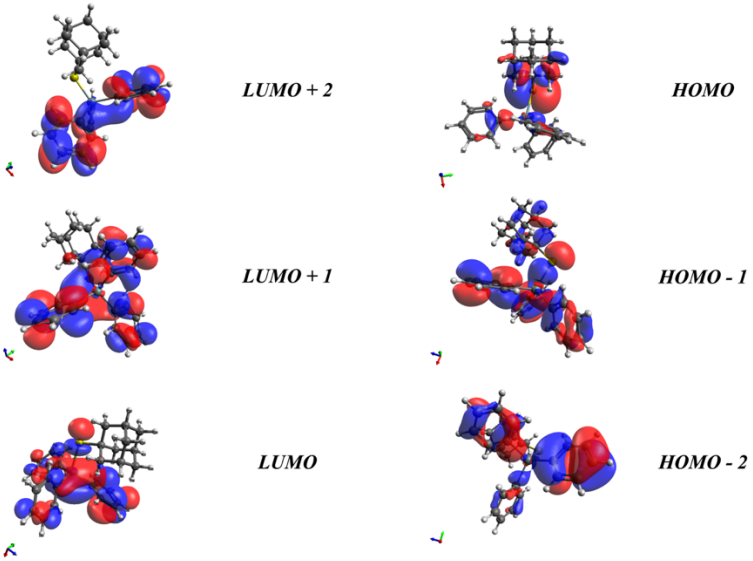
b) HOMO and LUMO orbitals of complex **2**.



c) HOMO and LUMO orbitals of complex **3**.



d) HOMO and LUMO orbitals of complex **4**.



e) HOMO and LUMO orbitals of complex **5**.

Fig. S2. HOMO and LUMO orbitals of complexes **1-5**.

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