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Synthesis, crystal structures, electrochemical studies and anti-tumor activities of three polynuclear organotin(IV) carboxylates containing ferrocenyl moiety

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ABSTRACT

A novel ferrocene-containing ligand 3-trifluoromethyl-5-ferrocenyl -pyrazol-1-yl-acetic acid (**LCOOH**) and three organotin(IV) carboxylate derivatives $[Ph_4Sn_2O(OCH_3)(OOCL)]_2$ **(1)**, $[BuSnO(OOCL)]_6$ **(2)** and $[Bu_4Sn_2O(OOCL_2)_2]$ **(3)** have been synthesized and structurally characterized by means of FT-IR, elemental analysis, ^1H NMR, ^{119}Sn NMR, X-ray crystallography and cyclic voltammetry. Both complexes **1** and **3** are centrosymmetric with ladder framework. Complex **2** is a hexanuclear one with drum structure. Furthermore, their anti-tumor activities were also evaluated, using HepG2 human hepatocellular liver carcinoma cells, A549 human lung carcinoma cells and B16-F10 melanoma cells. Complex **1** displayed the best cytotoxicity and can be pointed out as a promising substrate to be subject of further investigations.

1. Introduction

Metallocenes are known to exhibit a wide range of biological activity [1]. Among them, ferrocene has attracted special attention since it is neutral, chemically stable, non-toxic, anomalous metabolism and membrane-permeation properties [2,3]. Many ferrocenyl compounds display interesting cytotoxic, anti-tumor, anti-malarial, antifungal and DNA-cleaving activity [4–7]. Recent studies have suggested that combination of a ferrocenyl moiety with heterocyclic structures may increase their biological activities or create new medicinal properties [8,9]. Accordingly, using ferrocenyl moiety derivatives as drugs has long been recognized as an attractive way, such as anti-malarial drugs chloroquine (termed ferroquine) [10], quinine, mefloquine, and artemisinin and the anti-cancer drug tamixofen to give ferrocifen [11].

On the other hand, organotin carboxylates have emerged as potential biologically active metallopharmaceuticals owing to their practical applications as fungicides, bactericides, biocides, pesticides [12–15]. Recently, this kind of compounds had been found to be active toward a number of tumor cells [16–18]. The results of such testings showed that these oxygen containing organotin compounds are even more effective than cisplatin [19]. With these in mind we are now interested in obtaining organotin complexes with carboxylic ligands that containing ferrocenyl moiety as a strategy of preparation of new drug candidates in which the metal and the ligand could act synergistically. Herein, we reported the synthesis, structures, electrochemical studies and antiproliferative activities of three novel organotin(IV) carboxylates of the formulas $[Ph_4Sn_2O(OCH_3)(OOCL)]_2$ (**1**), $[BuSnO(OOCL)]_6$ (**2**) and $[Bu_4Sn_2O(OOCL)_2]_2$ (**3**) in order to investigate their preliminary structure–reactivity relationships.

2. Experimental

2.1. Materials and physical measurements

The reagents employed in the present study were purchased from commercial sources and used without further purification. Carbon, hydrogen and nitrogen assays were carried out with a CHN–O-Rapid instrument and were within ±0.4% of the theoretical values. IR spectra were record on a Nicolet 470 FT-IR spectrophotometer using KBr discs in the range 4000–400 cm^{-1} ^1H and

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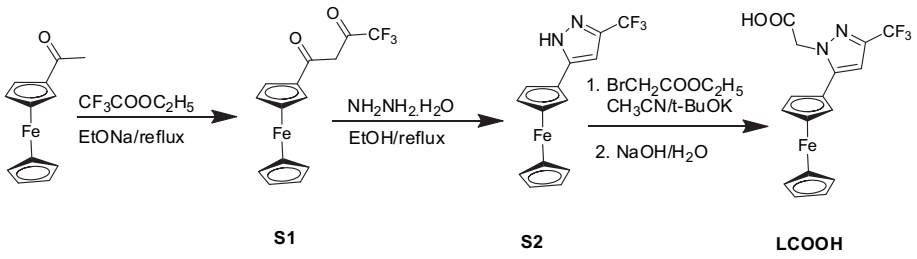


Scheme 1. Synthesis of **LCOOH**.

^{13}C NMR were recorded at Bruker AV 400 spectrometer at 25 °C with TMS and solvent signals allotted as internal standards. ^{119}Sn NMR spectra (proton-decoupled) were recorded on a Bruker AV 400 spectrometer operating at 150 MHz; resonances are referenced to tetramethyltin (external standard, ^{119}Sn). Electrochemical measurements were conducted on an electrochemical analyzer CHI630C potentiostat/galvanostat in a three-electrode cell. A platinum disk (2 mm diameter) was used as the working electrode, an Ag wire quasi-reference electrode and a platinum wire counter electrode. Cyclic voltammograms were recorded at the scan rate of 50 mV s^{-1} in dichloromethane solutions (sample concentrations 1.00 mM) containing 0.1 M tetrabutylammonium perchlorate (TBAP) as supporting electrolyte.

2.2. Synthesis of trifluoromethyl-5-ferrocenyl-pyrazol-1-yl-acetic acid (*LCOOH*) (Scheme 1)

The intermediates 4,4,4-trifluoro-1-ferrocenylbutane-1,3-dione (**S1**) and 3-ferrocenyl-5-(trifluoromethyl)-1H-pyrazole (**S2**) were synthesized according to established methods [20]. Then, **S2** (3.20 g, 0.01 mol) and *t*-BuOK (1.68 g, 0.015 mol) was added to CH_3CN (15 mL), and Ethyl bromoacetate (3.34 g, 0.02 mol) was added. The mixture was stirred and refluxed for 6 h (monitored by TLC). Then, the solvent was removed under reduced pressure and the oily product was hydrolyzed in 5% NaOH at 100 °C. After cooling to room temperature, the solution was acidified, extracted and the yellow oily product was purified by flash column chromatography using silica gel and elution with Ethyl acetate-petroleum ether (1:6, v/v) (Rf 0.20). Yield: 47%. M. p. 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.32$ (s, 5H, C_5H_5), 4.51 (s, 4H, C_5H_4), 5.11 (s, 2H, NCH_2), 6.53 (s, 1H, NH). IR (KBr, cm^{-1}): 2928(s), 2742, 2549, 1744(s), 1574, 1513, 1407, 1335, 1245, 1223(s), 1165, 1130, 1105, 1079, 1030, 987, 886, 808 (s), 745, 658 (s), 511, 484. Anal. Calcd. for $C_{16}H_{13}O_2N_2F_3Fe$ (378.13): C, 50.82; H, 3.47; N, 7.41%. Found: C, 51.02; H, 3.46; N, 7.39%. MS (EI): $m/z = 378.02$ [M^+]. Anal. Calc for $C_{16}H_{13}O_2N_2F_3Fe$: C, 47.70, H, 3.39, N, 7.38%; Found: C, 47.62; H, 3.44; N, 7.41%.

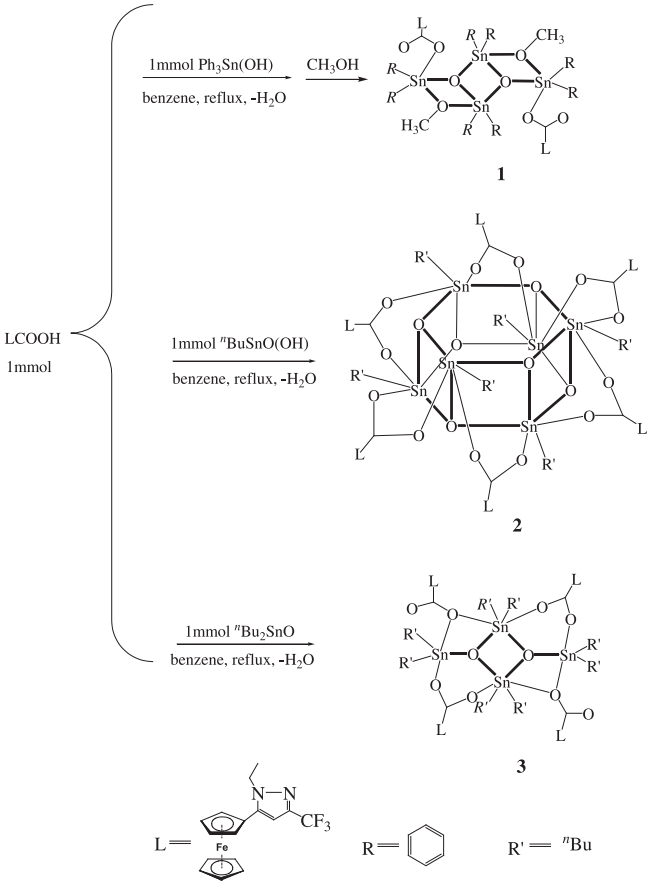
2.3. Synthesis of the organotin(IV) complexes (Scheme 2)

2.3.1. Synthesis of $[Ph_4Sn_2O(OCH_3)(OOCL)]_2$ (*1*)

To a benzene solution (30 mL) of **LCOOH** (0.378 g, 1 mmol), $Ph_3Sn(OH)$ was added (0.37 g, 1 mmol) under a nitrogen atmosphere. A clear solution formed which was refluxed overnight by using a Dean–Stark apparatus. Then, the solvent was removed under reduced pressure to afford the orange powder. Yield: 89%. Single crystals of complex **1** were obtained by evaporating slowly in methanol/dichloromethane (1:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.06$ (s, 10H), 4.14 (s, 4H), 4.21 (s, 4H), 5.05 (s, 4H), 6.56 (s, 2H), 7.36–7.77 (m, 40H). ^{13}C NMR ($CDCl_3$): $\delta = 50.7$ (CH_3), 52.7 (CH_2), 66.8, 68.6, 69.4, 69.6 (C_5H_5), 73.3 (C_5H_4), 104.2 (CH), 120.1, 122.7 (CF_3), 128.8, 129.1, 129.4, 130.5, 136.6, 136.9, 137.2 (C_6H_5), 141.7, 142.1 (CN), 143.99 (CCF_3), 172.5 (COOH). ^{119}Sn NMR ($CDCl_3$): $\delta = -88.2$ ppm. Anal. Calcd. for $C_{82}H_{70}N_4O_8F_6Fe_2Sn_4$: C, 50.77; H, 3.64; N, 2.89%; Found: C, 50.62; H, 3.65; N, 2.90%. IR (KBr, cm^{-1}): 3421, 3408, 2924, 1678, 1617, 1511, 1479, 1430, 1370, 1323, 1274, 1245, 1226, 1197, 1153, 1128, 1073, 1044, 998, 975, 923, 886, 808, 730 (s), 699, 661, 621, 589, 534, 491.

2.3.2. Synthesis of $[^nBuSnO(OOCL)]_6$ (*2*)

This compound was obtained by the same method used for **1**, using **LCOOH** (0.378 g, 1 mmol) and ^{n}BuSnO(OH) (0.210 g, 1 mmol). Yield: 91%. Yellow, block crystals of **2** suitable for single-crystal X-ray diffraction analysis were obtained by evaporating slowly in acetonitrile solution. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (s, 18H), 1.05–1.08 (m, 12H), 1.09–1.23 (m, 12H), 1.26 (t, 12H), 4.17 (s, 30H), 4.36 (s, 12H), 4.48 (s, 12H), 4.85 (s, 12H), 6.56 (s, 6H). ^{13}C NMR ($CDCl_3$): $\delta = 13.3$, 26.0, 26.6, 27.4 ($CH_3CH_2CH_2CH_2$), 53.7 (CH_2), 67.8,



Scheme 2. Synthesis of the organotin complexes **1**–**3**.