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Multinuclear NMR and crystallographic studies of triorganotin valproates and their *in vitro* antifungal activities

Bárbara P. de Morais [a], Geraldo M. de Lima [a,*], Carlos B. Pinheiro [b], Rosane A.S. San Gil [c], Jacqueline A. Takahashi [a], Daniele C. Menezes [d], José D. Ardisson [e]

[a] Departamento de Química, Universidade Federal de Minas Gerais, UFMG, Avenida Antônio Carlos 6627, Belo Horizonte, MG CEP 31270-901, Brazil
[b] Departamento de Física, Universidade Federal de Minas Gerais, UFMG, Avenida Antônio Carlos 6627, Belo Horizonte, MG CEP 31270-901, Brazil
[c] Instituto de Química, Universidade Federal do Rio de Janeiro, UFRJ, Avenida Athos da Silveira Ramos, 149, Cidade Univesitária, RJ CEP 21941-909, Brazil
[d] Departamento de Química, Universidade Federal de Viçosa, UFV, Avenida Peter Henry Rolfs s/n, Viçosa, MG CEP 36570-001, Brazil
[e] Centro de Desenvolvimento em Tecnologia Nuclear, CDTN/CNEN, Avenida Antônio Carlos 6627, Belo Horizonte, MG CEP 31270-901, Brazil

HIGHLIGHTS

- Complexes $[\{SnR_3(OVp)\}_n]$, R = Me **(1)**, Bu **(2)** and Ph **(3)** have been prepared.
- Complexes **(1)** and **(3)** have been structurally authenticated.
- Complexes **(1)**–**(3)** have been studied by solution- and solid-state ^{119}Sn NMR.
- The biocide activity of **(1)**–**(3)** have been screened.

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ABSTRACT

The reactions of triorganotin chlorides and sodium valproate, Na(OVp), yielded three triorganotin valproates $[\{SnMe_3(OVp)\}_n]$ **(1)**, $[\{SnBu_3(OVp)\}_n]$ **(2)** and $[SnPh_3(OVp)]$ **(3)**. All complexes have been authenticated in terms of infrared, ^{1}H and ^{13}C NMR, and solution- and solid-state ^{119}Sn NMR, ^{119}Sn Mössbauer and X-ray crystallography. The ^{119}Sn NMR experiments provided important informations concerning the structures of **(1)**–**(3)** in solution and in the solid state. The X-ray experiments revealed the double-polymeric chain of complex **(1)**, in which the geometry at the Sn(IV) is trigonal bipyramidal with intermolecular valproate bridges. The structure of complex **(3)** was re-determined and the new data show the tin cation at the centre of a distorted trigonal bipyramid, and not coordinated by four electron donating groups. The biological activity of all derivatives has been screened in terms of IC_{50} ($\mu mol\ L^{-1}$) against *C. albicans* (ATCC 18804), *C. tropicalis* (ATCC 750), *C. glabrata* (ATCC 90030), *C. parapsilosis* (ATCC 22019), *C. lusitaniae* (CBS 6936) and *C. dubliniensis* (clinical isolate 28). Complex **(3)** exhibited the best biocide activity.

Introduction

Tributyltin oxide (TBTO) was one of the first organotin compounds to be used as a biocide agent [1] in anti-fouling paints for ships [2,3]. However, important environmental problems led some nations to ban its use [4–7]. In spite of these drawbacks, organotins are among the most widely used organometallic compounds [8], and other potential applications have been discovered. In the 1970s the growth of malignant tumours was retarded by organotin carboxylates and aminoacids [9–14]. The antitumour activity of organotin complexes is still under investigation. In the last decades different biological applications of organotin complexes have been discovered. For example, Bu_2SnCl_2 or Ph_3SnCl can inhibit oedema in mice as effective as hydrocortisones [15,16]. Complexes with ligands derived from aminoquinolines have schizonticidal properties as antimalarial activities [17]. Those derivatives with some Schiff bases have potential use as amebicidal agents [18]. Some 2-alkylindole derivatives have been tested against *B. subtilis*, *B. pumilus*, *S.aureus* and *M. luteus* [19]. Activity against leshmaniasis in mice and helminthes in cats has been found for dioctyltin maleate [20,21]. Their complexes with 2,9-dimethyl-1,10-phenanthroline (Neocuproine) or with 3- and 4-aminobenzoic acids were tested towards human cervix

* Corresponding author. Tel.: +55 31 3409 5744; fax: +55 31 3409 5720.
E-mail address: gmlima@ufmg.br (G.M. de Lima).

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carcinoma and leukemia K562. In the case of the former complexes they exhibited higher activities than cisplatin [22,23]. Therefore, it is quite significant that there is a wide range of applications and potential uses of organotin derivatives among other metal-derivatives, in fields such as agriculture, biology, catalysis, or organic synthesis [24]. Many works have described the preparation and characterization of organotin carboxylates [25–27] and their action against tumours, fungi, bacteria, and other microorganisms [1,28–31]. The number and nature of the organic groups bonded to the tin centre influence the toxicity towards microorganisms, which, in general, decreases in the order $R_3SnX > R_2SnX_2 > RSnX_3$. However, the order of toxicity depends on the microorganism, and varies from strain to strain [32]. It has been proposed that toxicity in the R_3Sn series correlates with total molecule surface (TSA) and hence *n*-propyl-, *n*-butyl-, *n*-pentyl-, phenyl-, and cyclohexyl-substituted tin should be more toxic than the ethyl- and methyl-containing derivatives. Moreover, the literature shows a correlation between toxicity and lipophilicity since the toxic effects of organotin complexes are intra-cellular as a consequence of the transport through the cell membrane [33]. Besides preparing new organotin-dithiocarbamates, investigating their potential applications [34] and screening their activity in the presence of some parasites [35] we have been interested in the mechanism of action of such complexes in biological media [36,37]. The effects of organotin dithiocarbamate or carboxylates on the cellular activity of some variety of *C. albicans* revealed no changes in DNA integrity or in the mitochondria function. However, all complexes reduced the ergosterol biosynthesis. Special techniques used for morphological investigations such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM) suggested that the organotin complexes act on the cell membrane, in view of the observed cytoplasm leakage and strong deterioration of the cellular membrane [36,37]. Complexes **(1)**–**(3)** have been prepared earlier [38]. In the present work we have performed a deeper NMR study, in solution and in the solid state, correlating the results with those obtained from other spectroscopic techniques. In addition we have carried out the structural authentication of complexes **(1)**, and the chemical structure of **(3)** has been reviewed. The antifungal activity of the complexes has been screened in the presence of *C. albicans* (ATCC 18804), *C. tropicalis* (ATCC 750), *C. glabrata* (ATCC 90030), *C. parapsilosis* (ATCC 22019), *C. lusitaniae* (CBS 6936) and *C. dubliniensis* (Clinic isolate 28).

Experimental

Chemistry

Materials and instruments

All starting materials were purchased from Aldrich, Alfa Aesar, Fluka, Merck, Vetec or Synth and used as received. NMR spectra in solution were recorded at 200 MHz using a Bruker DPX-200 spectrometer equipped with an 89 mm wide-bore magnet. NMR spectra in solid state were recorded at 400 MHz using a Bruker Advance III DPX-400 spectrometer equipped with an 89 mm wide-bore magnet.^{1}H and ^{13}C{^{1}H} shifts are reported relative to $SiMe_4$ and ^{119}Sn{^{1}H} shifts relative to $SnMe_4$. The infrared spectra were recorded with samples pressed as KBr pellets on a Perkin–Elmer 238 FT-IR spectrometer in the range of 4000–400 cm^{-1}. Carbon and hydrogen analyses were performed on a Perkin–Elmer PE-2400 CHN equipment using tin sample-tubes. Tin analyses were performed on a Hitachi Z-8200 spectrometer. ^{119}Sn Mössbauer spectra were obtained in standard equipment at liquid nitrogen temperature using a $BaSnO_3$ source kept at room temperature. Intensity data for the X-ray study were collected on a Xcalibur, Atlas, Gemini, Kα/Mo (λ = 0.7107 Å). Data collection, reduction and cell refinement were performed using the CrysAlis RED program [39]. The structures were solved and refined employing the SHELXS-97 [40]. Further details are given in Table 3. All non-H atoms were refined anisotropically. The H atoms were refined with fixed individual displacement parameters [Uiso (H)Z1.2 Ueq (C)] using the SHELXL riding model. The ORTEP-3 program for windows [41] was used in the preparation of Figs. 4 and 5, sketched employing the Mercury program [42].

Syntheses

*Synthesis of [{$Me_3Sn(OVp)$}$_n$] **(1)***: To a round bottom flask (250 mL) charged with Na(OVap) (1.00 g, 6.02 mmol) in EtOH (100 mL) was added $SnMe_3Cl$ (1.24 g, 6.02 mmol) dissolved in 20 mL of EtOH. After 5 h of stir and reflux, the reaction vessel was left to settle down, and NaCl was separated by filtration. The solvent was removed in vacuum and the remaining white solid was recrystallized in a mixture of CH_2Cl_2/MeOH/H_2O (10:10:1) yielding X-ray quality crystals of **(1)**. Yield 62%. Mp 114.8–117.3 °C. IR (cm^{-1}): 1556 (ν_{as} CO_2^-), 1409 (ν_s CO_2^-), 477 (ν Sn—O). ^{1}H NMR (δ, $CDCl_3$): 2.32 {$O_2CC\underline{H}(CH_2CH_2CH_3)_2$}, 1.63–1.17 {$O_2CCH(C\underline{H}_2C\underline{H}_2CH_3)_2$}, 0.87{$^3J_{^1H4-^1H5}$ = 7.0 Hz} {$O_2CCH(CH_2CH_2C\underline{H}_3)_2$}, 0.50 $\left\{^2J_{(^{119}Sn-^1H)} = 57.3\ Hz\right\}$ {$Sn(C\underline{H}_3)_3$}; ^{13}C NMR (δ, $CDCl_3$): 182.5 {$O_2\underline{C}CH(CH_2CH_2CH_3)_2$}, 46.0 {$O_2C\underline{C}H(CH_2CH_2CH_3)_2$}, 35.4 {$O_2CCH(\underline{C}H_2CH_2CH_3)_2$}, 21.0 {$O_2CCH(CH_2\underline{C}H_2CH_3)_2$}, 14.3 {$O_2CCH(CH_2CH_2\underline{C}H_3)_2$}, −2.3 $\left\{^1J_{(^{119}Sn-^{13}C)} = 401\ Hz\right\}$ and $\left\{^1J_{(^{117}Sn-^{13}C)} = 383\ Hz\right\}$ {$Sn(\underline{C}H_3)_2$}.^{119}Sn NMR (δ, $CDCl_3$) 123.6 (weak) and −128.3 (strong). ^{119}Sn MAS NMR (δ_{iso}, 13 kHz): −34.9. ^{119}Sn Mössbauer, δ (mm s^{-1}) 1.29; Δ (mm s^{-1}) 3.47. Elemental analysis for $C_{11}H_{24}O_2Sn$ (MW 307.02 g mol^{-1}) found(calc): C 43.08 (43.03); H 7.90 (7.88); Sn 37.96 (38.67).

*Synthesis of [{$Bu_3Sn(OVp)$}$_n$] **(2)***: Prepared in a similar manner using Na(OVp), (1.00 g 6.02 mmol) and $SnBu_3Cl$ (2.04 g, 6.02 mmol). Yield 58%. Mp 51.2–53.4 °C. IR (cm^{-1}): 1574 m (ν_{as} CO_2^-), 1401 m (ν_s CO_2^-), 408 (ν Sn–O). ^{1}H NMR (δ, $CDCl_3$): 2.33 {$O_2CC\underline{H}(CH_2CH_2CH_3)_2$}, 1.78–1.02 {$O_2CCH(C\underline{H}_2C\underline{H}_2CH_3)_2$}, 0.85 {$O_2CCH(CH_2CH_2C\underline{H}_3)_2$}, 1.78–1.02 {$Sn(C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3)_3$}, 0.87 {$Sn(CH_2CH_2CH_2C\underline{H}_3)_3$}; ^{13}C NMR ($\delta$, $CDCl_3$): 182.2 {$O_2\underline{C}CH(CH_2CH_2CH_3)_2$}, 46.0 {$O_2C\underline{C}H(CH_2CH_2CH_3)_2$}, 35.4 {$O_2CCH(\underline{C}H_2CH_2CH_3)_2$}, 21.0 {$O_2CCH(CH_2\underline{C}H_2CH_3)_2$}, 14.2 {$O_2CCH(CH_2CH_2\underline{C}H_3)_2$}, 16.5 {$^1J_{(^{119}Sn-^{13}C)}$ = 361 Hz and $^1J_{(^{117}Sn-^{13}C))}$ = 345 Hz}, {$Sn(\underline{C}H_2CH_2CH_2CH_3)_3$}, 28.0 $\left\{^2J_{(^{119}Sn-^{13}C)} = 21.1\ Hz\right\}$ {$Sn(CH_2\underline{C}H_2CH_2CH_3)_3$}, 27.1 $\left\{^3J_{(^{119}Sn-^{13}C)} = 63.2\ Hz\right\}$ {$Sn(CH_2CH_2\underline{C}H_2CH_3)_3$}, 13.8 {$Sn(CH_2CH_2CH_2\underline{C}H_3)_3$}. ^{119}Sn NMR ($\delta$, $CDCl_3$) 100.2 (weak) and −153.4 (strong). ^{119}Sn MAS NMR (δ_{iso}, 13 kHz): −27.6. ^{119}Sn Mössbauer δ (mm s^{-1}) 1.41, Δ (mm s^{-1}) 3.52. Elemental analysis for $C_{20}H_{42}O_2Sn$ (MW 433.26 g mol^{-1}) found (calc) C 55.85 (55.44); H 9.80 (9.77); Sn 26.77 (27.40).

*Synthesis of [$Ph_3Sn(OVp)$] **(3)***: Similarly prepared using $SnPh_3Cl$ (2.44 g, 6.02 mmol) and sodium valproate, [Na(OVp)] (1.00 g, 6.02 mmol). Yield 67%. Mp 90.3–91.9 °C. IR (cm^{-1}): 1634 (ν_{as} CO_2^-); 1429 (ν_s CO_2^-); 444 (ν Sn–O). ^{1}H NMR (δ, $CDCl_3$): 7.96–7.48 {$Sn(C_6\underline{H}_5)_3$}; 2.60 {$O_2CC\underline{H}(CH_2CH_2CH_3)_2$}, 1.79–1.21 {$O_2CCH(C\underline{H}_2C\underline{H}_2CH_3)_2$}, 0.90 $\left\{^3J_{(^1H4-^1H5} = 7.1\ Hz\right\}$ {12H, $O_2CCH(CH_2CH_2C\underline{H}_3)_2$}; ^{13}C NMR ($\delta$, $CDCl_3$): 183.8 {$O_2\underline{C}CH(CH_2CH_2CH_3)_2$} 45.3 {$O_2C\underline{C}H(CH_2CH_2CH_3)_2$}; 35.2 {$O_2CCH(\underline{C}H_2CH_2CH_3)_2$}; 20.8 {$O_2CCH(CH_2\underline{C}H_2CH_3)_2$}; 14.2 {$O_2CCH(CH_2CH_2\underline{C}H_3)_2$}; 138.8 {$^1J_{(^{119}Sn-^{13}C)}$ = 648 Hz and $^1J_{(^{117}Sn-^{13}C)}$ = 619 Hz} {$Sn(\underline{C}_6H_5)_3$};137.0 $\left\{^2J_{(^{119}Sn-^{13}C)} = 48.1\ Hz\right\}$ {$Sn(\underline{C}_6H_5)_3$}; 129 $\left\{^3J_{(^{119}Sn-^{13}C)} = 63.1\ Hz\right\}$ {$Sn(\underline{C}_6H_5)_3$}; 130.2 {$Sn(\underline{C}_6H_5)_3$}. ^{119}Sn NMR (δ, $CDCl_3$): −116.9.