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**NOTE**

# The Reaction of Di-n-butyltin Oxide with Hexafluoro-2,2-bis(4-carboxyphenyl)propane

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**The reaction of hexafluoro-2,2-bis(4-carboxyphenyl)propane with tetrabutyldipropoxydistannoxane, formed *in situ* from dibutyltin oxide and n-propanol in benzene, yields a compound the structure of which is a strained macrocycle with a single dicarboxylate moiety.** 

**Keywords: organotin compounds; macrocycles; ring strain; NMR spectra**

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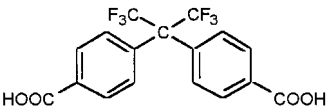
## INTRODUCTION

Several diorganotin fluoro-substituted aromatic carboxylates are very active *in vitro* against human cancer cell lines.[1–5] Di-n-butyltin perfluoroalkanecarboxylates also exhibit significant activities *in vitro* (H. Dalil, M. Biesemans, J. C. Martins, J.-M. Renon, B. Mahieu, D. de Vos, R. Willem and M. Gielen, unpublished results)

When dicarboxylic acids react with a diorganotin oxide, they generally lead to a cyclic structure including one tin atom.[6,7]

In this paper we investigate whether a rather rigid dicarboxylic acid can give rise upon condensation with di-n-butyltin oxide to a strained cyclic diorganotin dicarboxylate. Hexafluoro-2,2-bis(4-carboxyphenyl)propane **1** was found appropriate for this purpose.




**1**

## RESULTS AND DISCUSSION

Di-n-butyltin oxide was converted into tetrabutyldipropoxydistannoxane by reaction with n-propanol in refluxing benzene.[8] Subsequently, hexafluoro-2,2-bis(4-carboxyphenyl)propane was added to the reaction mixture at room temperature. The solid obtained after recrystallization from benzene was not suitable for crystal structure determination by X-ray diffraction. The compound was characterized in solution by NMR.

The NMR data are given in Table 1. The $^{1}H$ spectrum is in agreement with a condensation compound having di-n-butyltin and dicarboxylate units in a molar ratio of 1:1. The $^{13}C$ and $^{19}F$ NMR data are as expected, but uninformative as to the structure. The $CF_3$ $^{13}C$ resonance was identified from the $^{1}J(^{13}C–^{19}F)$ quartet, the C–$CF_3$ one from the $^{2}J(^{13}C–^{19}F)$ coupling pattern. A $^{19}F–^{13}C$ HMQC spectrum confirmed this (see the Experimental section).

The $^{117}Sn$ NMR spectrum exhibits a single resonance at $-142.3$ ppm typical for the usual trapezoidal bipyramid geometry of a diorganotin

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**Table 1** NMR data ($\delta$ ppm) for the condensation compound of di-n-butyltin oxide and hexafluoro-2,2-bis(4-carboxyphenyl)propane[a]

| | $^{1}H$ | $^{13}C$ | |
|---|---|---|---|
| $CH_3$ | 0.89 (t, 7) | 13.5 | |
| $CH_2(\gamma)$ | 1.4–1.8 (m) | 26.4 | $^{3}J(^{13}C–^{119/117}Sn) = 97$ Hz |
| $CH_2(\beta)$ | 1.4–1.8 (m) | 26.7 | $^{2}J(^{13}C–^{119/117}Sn) = 32$ Hz |
| $CH_2(\alpha)$ | 1.4–1.8 (m) | 25.7 | $^{1}J(^{13}C–^{119/117}Sn) = 576/550$ Hz |
| CH(ar1) | 7.5 (d, 7.1) | 130.2 | |
| CH(ar2) | 8.1 (d, 7.8) | 128.2 | |
| $\underline{C}(CF_3)_2$ | — | 64.8 | $^{2}J(^{13}C–^{19}F) = 26$ Hz* |
| $\overline{C}F_3$ | — | 123.9 | $^{1}J(^{13}C–^{19}F) = 288$ Hz(q) |
| | $^{19}F$: −63.8 | $^{117}Sn$: −142.3 | |

[a] Abbreviations: m, complex pattern; d, doublet; t, triplet; q, quartet;
* Noisy multiplet.

dicarboxylate.[9] However, the size of the cyclic structure (Fig. 1) cannot be deduced.

Two structures may reasonably be considered, one with a single tin atom and characterized by some ring strain (Fig. 1a), and a cyclodimeric one generating a macrocyclic structure released from any such potential ring strain (Fig. 1b).

The cationic-mode electrospray mass spectrum of the compound shows fragments corresponding to $(M + H^+ + CH_3CN)$ (72%) and to $(M + H^+)$ (100%), favouring the ring structure with a single tin atom because no heavier fragment is observed. The other fragment observed, $Bu_2SnOH^+$ ($m/z$ = 251, 41%), is unindicative.

The molar mass of 632 found by cryoscopy in camphor[10] establishes undoubtedly the structure to be the smallest possible ring structure, thus indicating no major influence of the ring strain on the overall stability. This structure excludes any weak contact from the carbonyl oxygen atoms to tin, showing that such contacts have little influence on the $^{117}Sn$ chemical shift whenever they are present.

The antitumour activity *in vitro* of the di-n-butyltin dicarboxylate derived from hexafluoro-2,2-bis(4-carboxyphenyl)propane was determined against seven tumour cell lines of human origin: two mammary cancers (MCF-7, EVSA-T), a colon carcinoma (WiDr), an ovarian cancer (IGROV), a melanoma (M19 MEL), a renal cancer (A 498) and a lung cancer (H226).[11] This compound is completely inactive, exhibiting high inhibition doses $ID_{50}$ (3114, 981, 9593, 5397, 3298, 9428 and 12391 ng ml$^{-1}$, respectively), much higher than those found for reference compounds such as cisplatin or other cytostatics used clinically.[12]

## EXPERIMENTAL

### Synthesis

Di-n-butyltin oxide (1.27 g, 5.10 mmol) reacted with an excess (4 ml) of propanol in 150 ml of benzene. After 3 h of reflux with elimination (Dean–Stark) of the ternary azeotrope benzene/water/propanol, the reaction mixture was allowed to cool to room temperature; 2 g (2.55 mmol) of hexafluoro-2,2-bis(4-carboxyphenyl)propane in 20 ml of benzene/methanol (1:1, v/v) was subsequently added and the mixture was further stirred for one night. The solvent was evaporated. Purification was achieved by crystallization from benzene and yielded 0.90 g (1.07 mmol) of the condensation product (Fig. 1a), m.p. 212–215 °C. Analysis: calcd for $C_{25}H_{26}O_4F_6Sn$: C 4.21, H 48.18; found: C 4.25, H 48.15%; yield 55%. Molar mass[10] (50 mg in 550 mg of camphor): calcd for $C_{25}H_{26}O_4F_6Sn$ (Fig. 1a): 623.18; found: $632 \pm 7$ (SD; $n = 5$).

### NMR measurements

All 2D NMR spectra and some of the 1D spectra were recorded on a Bruker AMX500 spectrometer interfaced with a X32 computer and operating at 500.13, 125.77 and 186.50 MHz for the $^{1}H$, $^{13}C$, and $^{119}Sn$ nuclei, respectively. The $^{19}F$ NMR spectra as well as other spectra were acquired on a Bruker AC250 instrument equipped with a Quattro probe tuned to 250.13, 62.93, 89.15 and 235.19 MHz for $^{1}H$, $^{13}C$, $^{117}Sn$ and $^{19}F$ nuclei, respectively. $^{1}H$ and $^{13}C$ chemical shifts were referenced to the standard $Me_4Si$ scale from

 

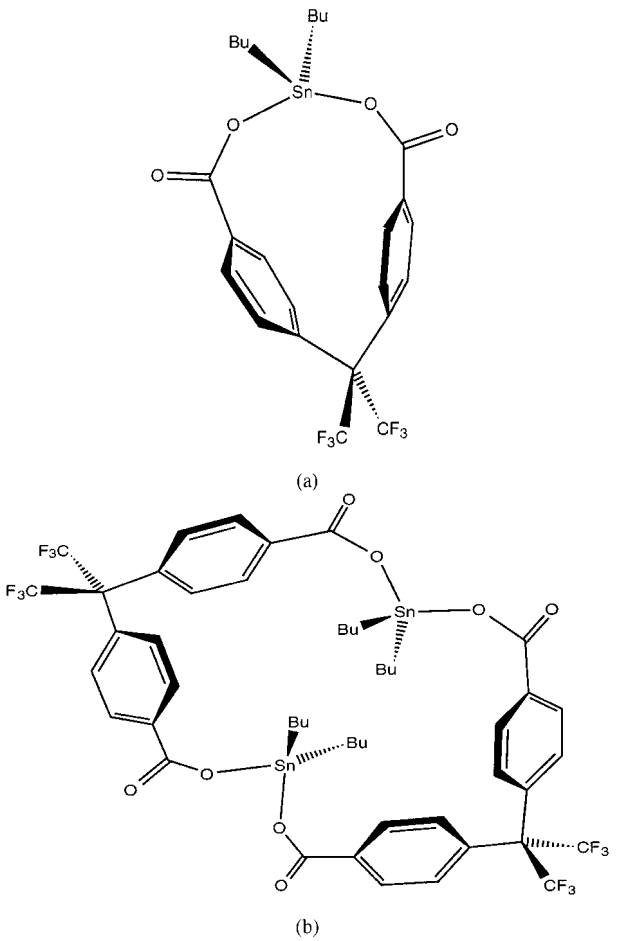


**Figure 1** Possible structures for the di-n-butyltin dicarboxylate derived from hexafluoro-2,2-bis(4-carboxyphenyl)propane.

respectively residual $^{1}H$ and $^{13}C$–$^{2}H$ solvent resonances of chloroform ($CHCl_3$, 7.23 and $CDCl_3$, 77.0 ppm for $^{1}H$ and $^{13}C$ nuclei, respectively). The $^{119}Sn$, $^{117}Sn$ and $^{19}F$ resonance frequencies were set from the absolute references $\Xi(^{119}Sn) = 37.290665$ MHz, $\Xi(^{117}Sn) = 35.632295$ MHz[13,14] and $\Xi(^{19}F) = 94.094003$ MHz.[13] $^{13}C$ and $^{119}Sn$ BB proton-decoupled 1D spectra and $^{13}C$ DEPT spectra, as well as the 1D and 2D $^{1}H$-$^{13}C$ HMQC[15] and HMBC[16] correlation spectra, were acquired using the pulse sequences of the Bruker program library, adapted to include gradient pulses,[17–20] as described recently[21]. The $^{19}F$ detected 2D $^{19}F$–$^{13}C$ HMQC correlation spectrum was acquired without $^{13}C$ decoupling using the resources of two NMR spectrometers, in a 'master–slave' relationship, according to Berger.[22,23] $^{19}F$ acquisition was performed on the AC250 instrument with the $^{1}H$ coil of the QNP probe tuned to the $^{19}F$ resonance frequency. $^{13}C$ pulses were generated on the AMX500 instrument under direct control of the AC250 spectrometer and sent to the X-coil of the QNP probe. The $^{19}F$–$^{13}C$ HMQC spectra were acquired in the phase-sensitive mode using TPPI,[24] and processed as described elsewhere.[25]

## Mass spectrometry

The electrospray mass spectra were recorded in the cationic mode on a Micromass Quattro II instrument coupled with a Masslynx system (ionization in an electric field of 3.5 kV; source temperature 80 °C; source pressure 1 atm; analyser pressure $10^{-5}$ mbar).[26,27]

 

## Antitumour screening

The protocol followed for the antitumour screenings has already been reported.[28,29]

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