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Organotin mefenamic complexes—preparations, spectroscopic studies and crystal structure of a triphenyltin ester of mefenamic acid: novel anti-tuberculosis agents

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The triphenyltin adduct of mefenamic acid, $[SnPh_3L]$ (1), the monophenyltin complex $[PhSnOL]_n$ (2), and the dibutyltin complex $[SnBu_2L_2]$ (3), where HL is 2-[bis(2,3-dimethylphenyl)amino]benzoic acid (mefenamic acid), have been prepared and structurally characterized by means of vibrational, ^1H and ^{13}C NMR spectroscopies. The crystal structure of 1 has been determined by X-ray crystallography. X-ray analysis revealed a pseudo-pentacoordinated structure containing Ph_3Sn coordinated to the carboxylato group. The structural distortion is a displacement from the tetrahedron toward the trigonal bipyramid. Significant C—H–π interactions and intramolecular hydrogen bonds stabilize the structure 1. The polar imino hydrogen atom participates in intramolecular hydrogen bonds. Complex 1 is self-assembled *via* C—H–π and stacking interactions. Vibrational and NMR data are discussed in terms of the crystal structure and the proposed structures for 1–3. Compounds 1 and 3 were tested for antimycobacterial activity against *Mycobacterium tuberculosis H37Rv*. **Copyright © 2002 John Wiley & Sons, Ltd.**

KEYWORDS: anti-inflammatory drugs; mefenamic acid; organotin; structure; anti-tuberculosis agents

INTRODUCTION

2-[Bis(3-methyl-2-methylphenyl)amino]benzoic acid or *N*-(2,3-xylyl)anthranilic acid (mefenamic acid), Scheme 1, belongs to a family of non-steroidal anti-inflammatory drugs (NSAIDs) that are derivatives of *N*-phenylanthranilic acid. NSAIDs are among the most frequently used medicinal drugs. They are utilized primarily as analgesics, anti-inflammatories and anti-pyretics and their side effects have been well studied. Their main known mode of action is through inhibition of the cyclo-oxygenase-mediated production of prostaglandins, but this is not thought to be sufficient to explain their wide variety of actions.[1,2] Several NSAIDs, such as mefenamic acid, sulindac or indomethacin, have been used in combination with a number of cytotoxic drugs, e.g. cyclophosphamide, melphalanor and carmustine.[3] The effect on cytotoxicity of clinically important NSAIDs with a variety of chemotherapeutics was studied in different human cancer cells. A specific group of NSAIDs indomethacin, sulindac, tolmetin, acemetacin, zomepirac and mefenamic, all at non-toxic levels, significantly increased the cytotoxicity of the anthracyclines, doxorubicin, daunorubicin and epirubicin, as well as teniposide, VP-16 and vincristine.[4] Mefenamic acid chemically resembles tolfenamic and flufenamic acids and other fenamates in clinical use. Crystal structures of dimeric tetraorganodistannoxane adducts of tolfenamic and mefenamic acids have been reported by our group.[5–7] Complexes of mefenamic acid with iron(III),[8] sodium(I) and calcium(II)[9] have been reported. Characterization of the complexes based on spectroscopic results was performed and possible structures were proposed.[8,9] The crystal structures of mefenamic acid and a copper(II) complex have been solved.[10,11]

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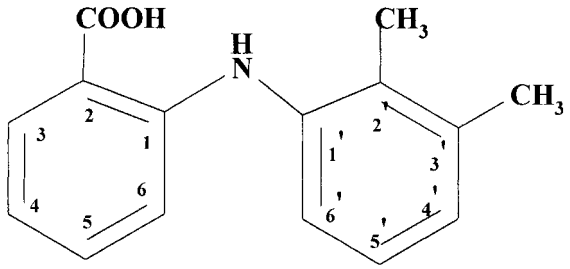

Scheme 1

Organotin(IV) carboxylates form an important class of compounds and have been receiving increasing attention in recent years, not only because of their intrinsic interest but owing to their varied applications. Some examples find wide use as catalysts and stabilizers, and certain derivatives are used as biocides, as antifouling agents and as wood preservatives.[12,13] Information on the structures of organotin carboxylates continues to accumulate, and at the same time new applications of such compounds are being discovered in industry, ecology and medicine. In recent years, investigations have been carried out to test their anti-tumor activity and it has indeed been observed that several diorganotin species, as well as triorganotin species, show potential as anti-neoplastic agents. In general, triorganotin compounds display a higher biological activity than their di- and monoorganotin analogues. This has been attributed to their ability to bind to proteins.[14,15] Triorganotin compounds were found to have a highly specific action on mitochondrial oxidative phosphorylation.[16]

Given the pharmacological importance of mefenamic acid and the potential biological activity of organotin carboxylates, it was thought to be of some interest to explore the chemistry of organotin/mefenamic acid compounds, as a continuation of our studies of biological organotin chemistry[17–22] and on the coordination chemistry and anti-inflammatory properties of NSAIDs, such as diclofenac and tolfenamic acids.[5–7,22–28] The complexes $[SnPh_3L]$ (**1**), the monophenyl adduct $[PhSnOL]_n$ (**2**) and the dibutyl adduct $[SnBu_2L_2]$ (**3**) have been structurally characterized by means of vibrational, ^1H and ^{13}C NMR spectroscopic studies, and the crystal and molecular structure of **1** is described. $[PhSnOL]_n$ (**2**) was prepared by a facile dearylation of diphenyltin(IV) oxide. Such dearylations have previously been reported for phenyltin trichloroacetate complexes.[29]

EXPERIMENTAL

The reagents (Aldrich, Merck) were used as supplied, and the solvents were purified according to standard procedures. Mefenamic acid was a gift from VIANNEX. A.E. carbon, hydrogen and nitrogen analyses were carried out by the microanalytical service of the University of Ioannina. Melting points were determined in open capillaries and are uncorrected. Infrared IR and far-IR spectra were recorded on a Nicolet 55XC Fourier transform spectrophotometer using KBr pellets (4000–400 cm^{-1}) and Nujol mulls dispersed between polyethylene disks (400–40 cm^{-1}). The ^1H (250.13 MHz) and ^{13}C (62.90 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer. Samples were dissolved in $CDCl_3$ or DMSO-d_6 and spectra were obtained at room temperature with the signal of the free DMSO or $CHCl_3$ (at 2.49 ppm and 7.24 ppm respectively) as a reference. Cross-peaking of heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) gradient-assisted spectra of mefenamic acid were performed.

Synthesis

*[SnPh$_3$L] (**1**)*

To a solution of triphenyltin(IV) hydroxide (0.422 g, 1.15 mmol) in benzene (45 ml) was added a solution of mefenamic acid (0.241 g, 1 mmol). The reaction mixture was refluxed for 24 h with azeotropic removal of water via a Dean–Stark trap. The resulting yellow clear solution was rotary evaporated under vacuum to a small volume, chilled and triturated with *n*-pentane to give a yellow solid. The yellow powder was filtered, washed with diethyl ether and was dried *in vacuo* over silica gel; m.p. 160–162 °C. Yield 80%. Anal. Found: C, 66.51; H, 4.96; N, 2.15. Calc.: C, 66.28; H, 4.85; N, 2.34%.

*[SnPhOL]$_n$ (**2**)*

Diphenyltin(IV) oxide (0.332 g, 1.15 mmol), mefenamic acid (0.241 g, 1.00 mmol) and 40 ml of benzene were refluxed for 24 h with azeotropic removal of water *via* a Dean–Stark trap. The resulting clear solution was rotary evaporated under vacuum to a small volume. Drops of *n*-pentane were added and, after slow evaporation, a yellow powder was isolated; m.p. >300 °C. Yield 37%. Anal. Found: C, 55.43; H, 4.49; N, 3.59. Calc.: C, 55.80; H, 4.23; N, 3.10%.

*[Bu$_2$SnL$_2$] (**3**)*

Di-*n*-butyltin(IV) oxide (0.249 g, 1.0 mmol), mefenamic acid (0.519 g, 2.15 mmol) and 40 ml of benzene were refluxed for 24 h with azeotropic removal of water via a Dean–Stark trap. The resulting clear solution was rotary evaporated under vacuum to a small volume, chilled and triturated with *n*-pentane. Slow evaporation of the solution gives a white–yellow powder; m.p.: 78–79 °C. Yield 69%. Anal. Found: C, 63.76; H, 6.69; N, 3.92. Calc.: C, 64.00; H, 6.45; N, 3.93%.

X-ray crystallography

Crystal data for **1** are given in Table 1, together with refinement details. All measurements of crystal were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. The crystal was positioned at 65 mm from the KM4CCD camera. 612 frames were measured at 0.75° intervals with a counting time of 30 s. The data were corrected for Lorentz and polarization

Table 1. Crystal data and structure refinement for **1**

Empirical formula	$C_{33}H_{29}NO_2Sn$
Formula weight	590.26
Temperature/K	100(2)
Wavelength/Å	0.71073
Crystal system	Triclinic
Space group	P_1
a/Å	8.840(1)
b/Å	9.624(1)
c/Å	17.281(1)
α/°	104.81(1)
β/°	92.43(1)
γ/°	107.09(1)
Volume/Å^3	1347.6(2)
Z	2
D_c/Mg m^{-3}	1.455
Absorption coefficient μ/mm^{-1}	0.978
$F(000)$	600
Crystal size/mm^3	$0.15 \times 0.12 \times 0.12$
Diffractometer	Kuma KM4CCD
θ range for data collection/°	3.69–28.59
Ranges of h,k,l	$-11 \rightarrow 11$, $-12 \rightarrow 8$, $-23 \rightarrow 23$
Reflections collected	9600
Independent reflections (R_{int})	6045 (0.0310)
Data/parameters	6045/450
Goodness-of-fit (F^2)	1.076
Final R_1/wR_2 indices ($I > 2\sigma_I$)	0.0328/0.0636
Largest diff. peak/hole/e$^-$ Å^{-3}	1.193/−0.581

effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs. The structure was solved by direct methods (program SHELXS97[30–33]) and refined by the full-matrix least-squares method on all F^2 data using the SHELXL97[30–33] programs. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were included from the geometry of the molecules and $\Delta\rho$ maps and were refined with isotropic thermal parameters.

Crytallographic data for the structural analysis of compound **1** have been deposited with the Cambridge Crystallographic Data Centre, CCDC 175682. Copies of this information may be obtained from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033, e-mail: deposit@ccdc.cam.ac.uk; www: http://www.ccdc.cam.ac.uk.

Biological activity—*in vitro* evaluation of anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv

Anti-tubercular activity was determined using the modified BACTEC 460 system. A screen was conducted at 6.25 μg ml^{-1} against *M. tuberculosis* H37Rv in BACTEC 12B medium using the BACTEC 460 radiometric system. Compounds effecting <90% inhibition in the primary screen (minimum inhibitory concentration (MIC) >6.25 μg ml^{-1}) were not evaluated further. Compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentration (MIC) in a broth microdilution assay with alamar blue (MABA). The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls. Rifampicin was included as a positive drug control; the MIC value for Rifampicin is 0.25 μg ml^{-1} with 95% inhibition of H37Rv strain.

RESULTS AND DISCUSSION

Compounds **1–3** were obtained by azeotropic removal of water from the reaction between the triorganotin hydroxide (for **1**) or diorganotin oxide (for **2** and **3**) and mefenamic acid (1:1 Molar ratios for **1** and **2**; 1:2 Molar ratio for **3**) conducted in benzene according to Eqns (1–3).

$$SnPh_3OH + HL \xrightarrow{C_6H_6} SnPh_3L + H_2O \quad (1)$$

$$n SnPh_2O + n HL \xrightarrow{C_6H_6} [SnPh(O)L]_n + n C_6H_6 \quad (2)$$

$$SnBu_2O + 2HL \xrightarrow{C_6H_6} [SnBu_2L_2] + H_2O \quad (3)$$

A facile dearylation of diphenyltin(IV) oxide takes place in the presence of mefenamic acid, Eqn. (2). This may be presumably mediated by traces of water in the (nominally dry) solvents. In an attempt to prepare the diphenyl derivative of mefenamic acid, a relatively insoluble white solid resulted that had a high melting point, >300 °C, compared with **1**, and an elemental analysis indicated the loss of a benzene molecule. Such dearylations have previously been reported and found to have a role in the interconversion of phenyltin trichloroacetate complexes.[29] Monoorganotin derivatives are the least studied. There are two basic structural types adopted by these compounds, and their chemistry has been documented in the literature.[34] The 'drum' hexameric structure having six chemically equivalent tin atoms was found for the monophenyl derivatives, $[PhSn(O)(O_2C\text{-}c\text{-}C_6H_{11})]_6$,[35] and $[PhSn(O)(O_2CCl_3)]_6$,[29] and the 'open drum' or 'ladder' structure for $Sn_6Ph_6(O_2CCCl_3)_{10}O_4{\cdot}2C_6H_6$.[29] In the drum structure, the sides are composed of Sn_2O_2 stannoxane rings and the faces of Sn_3O_3 planes, whereas the 'open drum' or 'ladder' structure is constructed about a central Sn_4O_4 core.

The crystal structures of a number of triorganotin carboxylates have been determined by X-ray diffraction.[34–40] In the crystalline state, these compounds generally adopt either a polymeric structure with a five-coordinated tin atom, e.g. trimethyltin benzoates mainly assume one-dimensional associated arrangements, whereas triphenyltin benzoates generally exist in a discrete five-coordinated form.

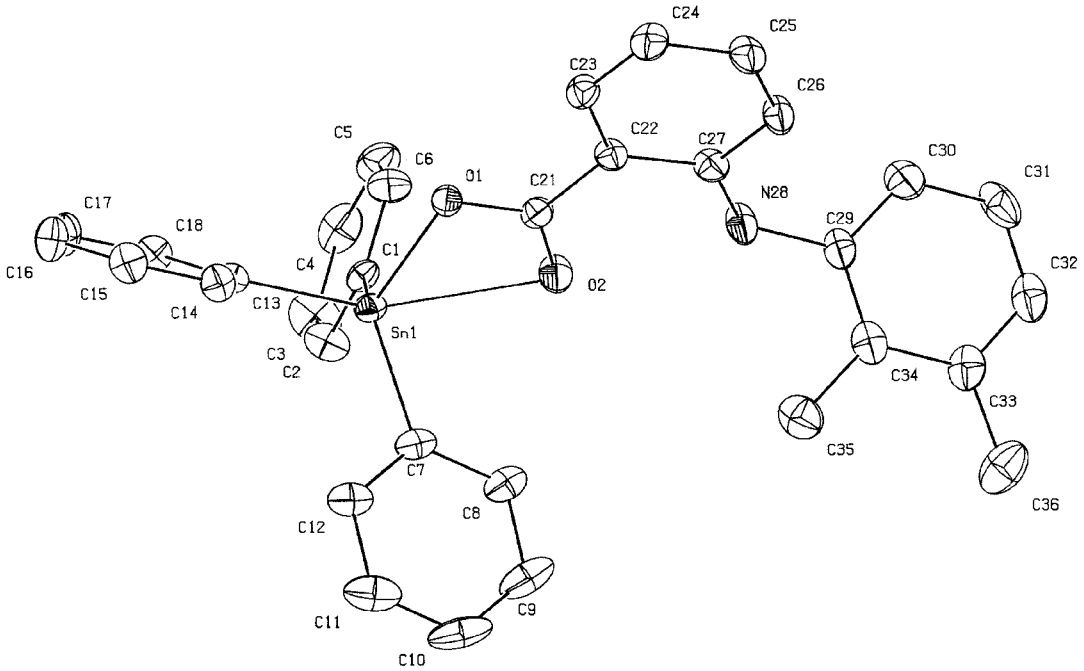

Figure 1. An ORTEP representation of **1** with the atom numbering scheme.

A delicate energy balance is present between these two forms, although the greater electronegativity of the phenyl group over the methyl group has been cited as a factor influencing the formation of the discrete form, as it gives more access to an axial position of a trigonal bipyramid.[34,35,38–40] A polymeric structure for tributyl or triphenyl carboxylates is associated with the R′ group, R′COO− being electron withdrawing. The contribution of either steric or electronic factors has been discussed by Molloy *et al.*[41] From structural data accumulated so far, the relative ligand electronegativity appears to be an important factor in determining whether the discrete structural form or the chain form is observed. The axial tin–ligand bond lengths in both forms are subject to variations depending on the substituent electronegativity, ring strain, hydrogen bond, and steric interactions.

Crystal structures of 1

The molecular structure of **1** is shown in Fig. 1, and selected interatomic parameters are collected in Table 2. The triphenyltin ester of mefenamic acid **1** comprises discrete molecular units, in which the carboxylato group functions as an anisobidentate chelating ligand [Sn—O(1), 2.079(2) Å, Sn—O(2), 2.615(2) Å], thus rendering the tin atom five-coordinated (Fig. 1). The intramolecular coordinate Sn···O(2) distance, 2.615(2) Å, is considered too long to indicate significant bonding interactions; however, the range of Sn···O distances of 2.61–3.02 Å has been confidently reported for intramolecular bonds.[42,43] The intramolecular hydrogen

Table 2. Selected bond lengths (Å) and angles (°) for **1**

Sn(1)—O(1)	2.079(2)
Sn(1)—O(2)	2.615(2)
Sn(1)—C(7)	2.118(3)
Sn(1)—C(1)	2.120(2)
Sn(1)—C(13)	2.132(3)
O(1)—C(21)	1.309(3)
O(2)—C(21)	1.243(3)
C(27)—N(28)	1.376(3)
N(28)—C(29)	1.420(4)
O(1)—Sn(1)—C(7)	110.78(8)
O(1)—Sn(1)—C(1)	109.25(9)
C(7)—Sn(1)—C(1)	120.8(1)
O(1)—Sn(1)—C(13)	96.71(8)
C(7)—Sn(1)—C(13)	107.8(1)
C(1)—Sn(1)—C(13)	108.71(9)
O(1)—Sn(1)—O(2)	54.41(2)
O(2)—Sn(1)—C(13)	151.10(2)
C(21)—O(1)—Sn(1)	104.8(1)
C(2)—C(1)—C(6)	118.6(3)
C(2)—C(1)—Sn(1)	120.7(2)
C(6)—C(1)—Sn(1)	120.6(2)
C(12)—C(7)—Sn(1)	118.3(2)
C(8)—C(7)—Sn(1)	122.9(2)
C(18)—C(13)—Sn(1)	120.1(2)
C(14)—C(13)—Sn(1)	122.0(2)
O(2)—C(21)—O(1)	118.9(2)
O(2)—C(21)—C(22)	123.5(2)

Table 3. The donor bond parameters for pentacoordinated derivatives (discrete forms) containing the Ph_3Sn group

Compound	Sn—O1	Sn—O2	Sn—(O1) − Sn—(O2)	∠O2—Sn—C_{axial}	Ref.
$Ph_3Sn[(o-OH)C_6H_4CO_2]$	2.083(2)	3.071(2)	0.988	138.1(1)	38
$Ph_3Sn[(p-Cl)C_6H_4CO_2]$	2.048(4)	2.861(4)	0.713	145.6(2)	34
$Ph_3Sn[(o-NH_2)C_6H_4CO_2]$	2.043(3)	2.823(3)	0.780	146.6(1)	40
$Ph_3Sn[(p-SMe)C_6H_4CO_2]$	2.060(2)	2.783(3)	0.723	149.2(1)	38
$Ph_3Sn[(o-OMe)C_6H_4CO_2]$	2.054(3)	2.781(3)	0.727	145.9(1)	38
$Ph_3Sn[(p-NH_2)C_6H_4CO_2]$	2.072(2)	2.629(2)	0.557	151.3(1)	38
$Ph_3Sn[(o-NMe_2)C_6H_4CO_2]$	2.115(6)	2.564(7)	0.449	143.7(3)	40
$Ph_3Sn[(o-NH_2)C_6H_4CO_2]$	2.070(5)	2.463(7)	0.293		45
1	2.079(2)	2.615(2)	0.536	151.1(1)	This work

bond formed from the imino group [O(2)···H(28) = 2.02(3) Å] contributes in causing the longer Sn—O(2) bond. A similar hydrogen-bonded situation was found in the structure of $Ph_3Sn[(o\text{-}OH)C_6H_4CO_2]$.[34,35,38–40] Analysis of the shape-determining angles for **1**, using the approach of Reedijk and coworkers[44] yields a τ ($(\alpha - \beta)/60$) value of 0.50 for Sn (τ = 0.0 and 1.0 for *sp* and *tbp* geometries respectively). The geometry at the tin atom is intermediate between tetrahedral and *cis*-trigonal bipyramidal, in which the carboxylato ligand spans equatorial and axial sites. Other examples of this stereochemistry are shown in Table 3. The two C—O bond distances of the carbonyl group are unequal [1.309(3) and 1.243(3) Å] with the longer C—O distance being associated with the shorter Sn—O bond and *vice versa*. The phenyl rings are planar. The dihedral angle between the planes of the phenyl rings in **1** is 62.61(14)°.

The crystal structure of **1** shows C—H–π interactions and intramolecular hydrogen bonds. The polar imino hydrogen atoms on N(28) for **1** participate in an intramolecular hydrogen bond; Table 4. Complex **1** is self-assembled *via* C—H–π interactions. Views of the crystal packing along the *a* and *b* axes for **1** are shown in Figs 2 and 3.

Spectroscopy

IR spectroscopy

IR bands corresponding to the bridging carboxylato groups and the Sn—O stretching vibration are very useful in discriminating between the drum and the ladder forms. For drum structures the carboxylato absorption appears as a symmetric doublet centered near 1550 cm^{-1}, whereas the ladders have an unsymmetrical doublet absorption in the same region. A very strong band around 600 cm^{-1} characteristic of the Sn—O—Sn linkage is assigned to ν(Sn—O) for the drum form.[39] The IR data recorded for **2** are consistent with the drum structure. The IR of **1** and **2** gave bands at ~3340 and 3290 cm^{-1} attributable to intramolecular hydrogen bonds NH···O. The ν_{as}(COO) and ν_{sym}(COO) bands appear at 1576 cm^{-1} and 1269 cm^{-1} respectively for **1**. The difference between these two bands for **2** and **3** (307 cm^{-1} and 318 cm^{-1} respectively) is close to that observed for

Table 4. Distances (Å) and angles (°) of C—H–π and intramolecular hydrogen bonds for **1**[a]

X-H(*I*) → Cg(*J*)	H···Cg	C···Cg	∠C—H···Cg		
C(2)—H(2) → Cg(3)^{i}	2.84	3.726	157		
C(5)—H(5) → Cg(4)^{ii}	3.12	3.976	147		
C(10)—H(10) → Cg(3)^{iii}	3.08	3.674	123		
C(17)—H(17) → Cg(2)^{i}	2.95	3.603	126		
C(25)—H(25) → Cg(5)^{iv}	2.78	3.471	131		
C(35)—H(35C) → Cg(5)	2.86	3.618	146		
D[b]	H	A[b]	H···A	D···A	∠D — H···A
N(28)	H(28)	O(2)	2.02(3)	2.666(3)	136(3)
C(8)	H(8)	O(2)	2.44(4)	3.092(4)	127(3)
C(23)	H(23)	O(1)	2.42(3)	2.751(3)	102(2)

[a] Cg(2) and Cg(5) are referred to the centroids C(7)···C(12) and C(29)···C(34) respectively and Cg(3) and Cg(4) are referred to the centroids C(13)···C(18) and C(22)···C(27) respectively; symmetry transformations: (i) $-x, -y, -z$; (ii) $x, -1+y, z$; (iii) $-1+x, y, z$; (iv) $1-x, 2-y, 1-z$; (v) $-x, 1-y, 1-z$.
[b] D is donor and A is acceptor.

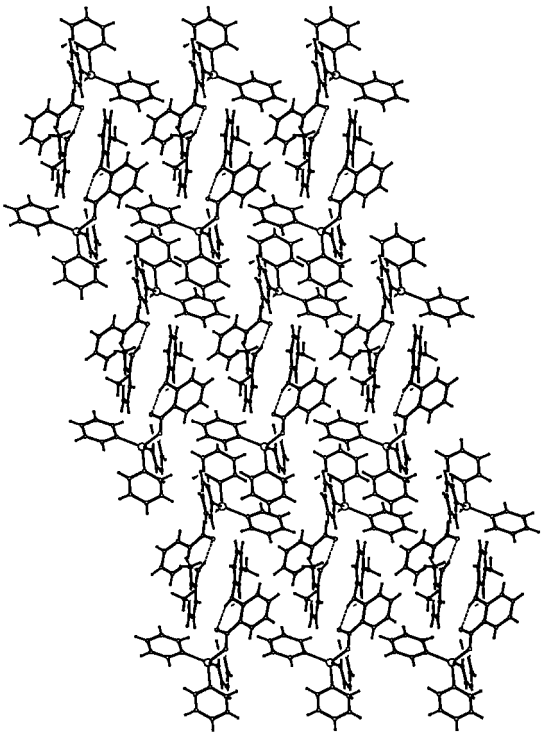

Figure 2. Packing diagram of complex **1** viewed along the *a* axis of the unit cell.

asymmetric bidentate chelate mode.[39] The bands at 260–190 cm^{-1} are assigned to the tin–oxygen (COO) stretching modes.[3,46]

^1H and ^{13}C NMR spectra

The ^1H and ^{13}C NMR data for mefenamic acid, Scheme 1, and the complexes are summarized in Table 5. These results, together with the published data on mefenamic acid[5–7,47] allowed complete assignment of all signals in the spectra of the mefenamic acid and complexes **1** and **3**. The downfield chemical shift for HN in mefenamic acid indicates that this proton is involved in hydrogen bonding. The crystal structure of mefenamic acid suggests the presence of hydrogen-bonded dimers linked by two intermolecular O···H—O hydrogen bonds.[10] The downfield chemical shift for HN in **1** and **3** indicates that this proton is involved in an intramolecular hydrogen bond between the HN group and the carbonyl oxygen of the carboxylato group. Deshielding of protons H(3), H(4) and H(6) is observed, which should be related to the electrophilicity of the tin. A σ-charge donation from the COO— donor to the tin center removes electron density from the ligand and produces this deshielding, which will attenuate at positions remote from the metal. All shifts are downfield except for that due to H(5), which is shifted upfield. The upfield shift observed for H(5) and its corresponding carbon atom C(5), para to the tin center, could be due to the flow of charge from the tin into the aromatic ring.[45] Involvement of the carboxyl group in bonding to tin is confirmed by the resonances ascribed to C(2), which exhibits the greatest shift upon coordination. The remaining resonances due to the aromatic carbon atoms do not shift significantly on binding to tin. In the ^{13}C NMR spectra of **1**, the greatest downfield shift is exhibited by the carbonyl C (4.0 ppm), whereas the C(3), C(4) and C(6) atoms shift slightly downfield. The C(5) resonance shifts upfield.

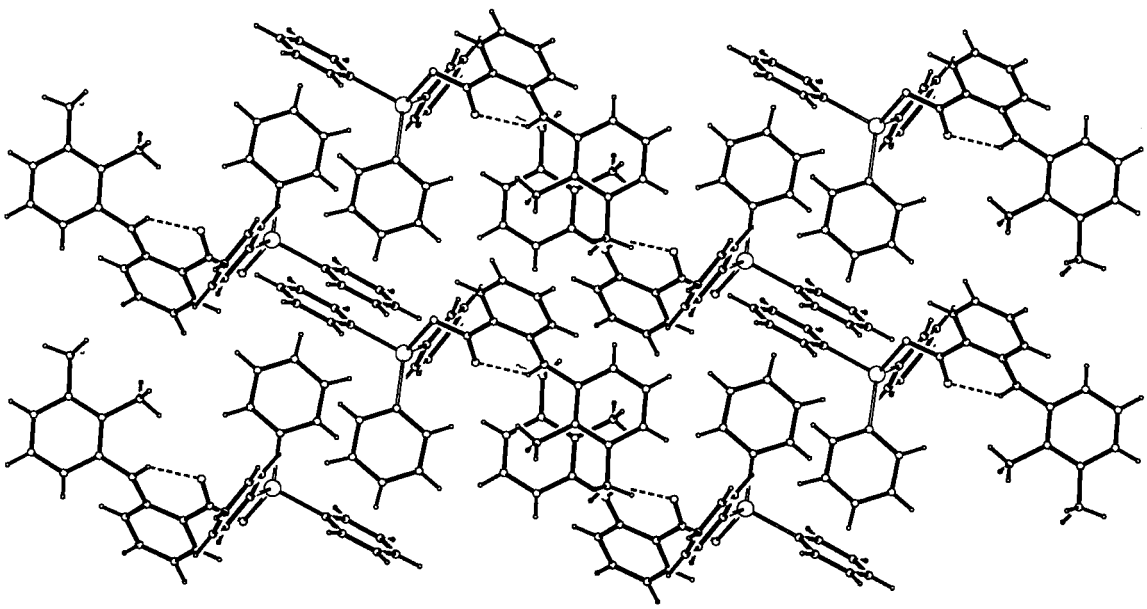

Figure 3. Packing diagram of complex **1** viewed along the *b* axis of the unit cell.

Table 5. ^{1}H and ^{13}C NMR data

	COOH	NH	H3	H4	H5	H6	H4′	H5′	H6′	2′-CH_3 3′-CH_3
Mef[a]	–[c]	9.11s	8.03d	6.69dd	7.28t	6.69dd	7.10m[d]	7.10m	7.10m	2.18s/2.34s
Mef[b]	13.12	9.52s	7.94d	6.71dd	7.32t	6.71dd	7.08m	7.08m	7.08m	2.13s/2.30s
1[a]	Ph_3Sn: H_o 7.72–7.75m; H_m and H_p 7.60–7.64m	9.33s	8.09dd	6.94d	7.04t	6.72d	7.19m	7.19m	7.19m	2.09s/2.29s
3[a]	Bu_2Sn: Hδ 0.88; Hγ 1.24; Hβ 1.77; Hα 1.41	9.17s	8.10dd	6.92d	7.10t	6.82d	7.19m	7.19m	7.19m	2.15s/2.31s

	COOH	C1	C2	C3	C4	C5	C6	C1′	C2′	C3′	C4′	C5′	C6′	2′-CH_3 3′-CH_3
Mef[a,e]	173.05	150.3	109.2	132.4	116.1	135.2	113.7	138.4	132.9	138.8	123.7	126.0	127.2	20.7/14.3
11[a]	175.0 Ph_3Sn: C_o 138.9; C_m 129.8; C_p 128.8	149.9	113.3	132.7	116.5	134.0	113.9	139.6	130.6	137.4	126.9	123.4	126.3	20.6/13.9

[a] Spectrum recorded in $CDCl_3$.
[b] Spectrum recorded in DMSO-d_6.
[c] Carboxyl proton exchanged in $CDCl_3$.
[d] These resonances formed a multiplet.
[e] Refs 5–7 and 47. The ^{1}H and ^{13}C NMR spectra of **2** and the ^{13}C NMR spectrum of **3** could not be recorded because of low solubility in DMSO-d_6, $CDCl_3$ and other common NMR solvents.

Q4 **Table 6.** Anti-tuberculosis activities of compounds **1** and **3**

No.	Compound	Inhibition at 6.25 μg ml^{-1} (%)	Assay	MIC (μg ml^{-1})
1	$SnPh_3L$	98	Alamar	0.39
3	$SnBu_2L_2$	92	Alamar	>6.25

Biological activity

Compounds **1** and **3** were screened against *M. tuberculosis* H37Rv in BACTEK 12B medium using the BACTEC 460 radiometric system at the single concentration of 6.25 μg ml^{-1}. Compound **2** was not screened, since it was not soluble in organic solvents or water. Compounds **1** and **3** exhibited the highest inhibitory activities, 98% and 92% respectively, and are considered as active compounds. The compounds were screened by serial dilution beginning at 6.25 μg ml^{-1}. The final column in Table 6 lists the measured MIC values, viz. 0.39 μg ml^{-1} and >6.25 μg ml^{-1} for compounds **1** and **3** respectively. The significance of these values depends on several factors, such as compound structure, novelty, toxicity, and potential mechanism of action, though generally an MIC ≤1 μg ml^{-1} in a new compound class is considered a good lead. The triphenyltin derivative of mefenamic acid with a value of 0.39 μg ml^{-1} is considered as a very good lead compound and the results of this study represent the discovery of triphenyltin derivatives as a potential new class of anti-tuberculosis agent.

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