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Synthesis, characterization and antibacterial activity of 3-(2-methoxyphenyl)-2-sulfanylpropenoic acid and di-isopropylammonium [3-(2-methoxyphenyl)-2-sulfanylpropenoato] triphenylstannate(IV). The crystal structure of [HQ][$SnPh_3$(*o*-mpspa)]

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Reaction of 3-(2-methoxyphenyl)-2-sulfanylpropenoic acid [H_2(*o*-mpspa)] with $SnPh_3OH$ in the presence of di-isopropylamine resulted in the formation of the complex [HQ][$SnPh_3$(*o*-mpspa)] (where HQ = di-isopropylammonium cation and *o*-mpspa = 3-(2-methoxyphenyl)-2-sulfanylpropenoato), which was characterized by mass spectrometry and vibrational spectroscopy, as well as by ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy. The single-crystal X-ray structural analysis of the new complex shows a trigonal-bipyramidal coordination geometry around the Sn atom where *o*-mpspa behaves as a bidentate chelating ligand. Dimeric units arise from the existence of N–H...O hydrogen bonds between the NH_2 group of the di-isopropylammonium cation and the oxygen atoms of the two neighbouring carboxylato groups. The bacteriostatic activity of the complex is also reported.

KEYWORDS: tin; triphenyltin complexes; 3-(2-aryl)-2-sulfanylpropenoic acids; X-ray; antibacterial activity

INTRODUCTION

Besides the important uses of organotin(IV) compounds for industrial and agricultural purposes,[1,2] they have a range of pharmacological applications.[3–6] In this respect, the most active bioinorganic chemistry research area in recent years, as concerns this kind of compounds, is perhaps their antitumour activity, well established for adducts of the type $R_2SnX_2L_2$ (X = halogen or pseudohalogen, L = O- or N-donor ligand), even though not subjected until now to clinical trials in humans. Nevertheless, the antibacterial activity of organotin(IV) derivatives is also a research field of increasing interest, since they have been shown to be especially active against unicellular organisms such as *Entamoeba histolytica* and *tropozoites*.[7] The mode of biological action of the organotin(IV) compounds and their derivatives may vary from one compound to another, depending (according to Nath *et al.*[8]) on the number of leaving groups available around the tin atom and the consequent geometry and strength of the Sn–ligand bonds.

On the basis of our previous experience in this area,[9,10] we describe in this paper the synthesis and characterization

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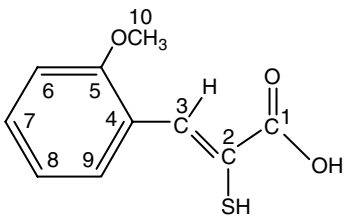
of the 3-(2-methoxyphenyl)-2-sulfanylpropenoic acid [H_2(*o*-mpspa)] (depicted in Scheme 1) and the complex isolated from its reaction with triphenyltin(IV) hydroxide in the presence of di-isopropylamine, as well as their bacteriostatic activities against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.

EXPERIMENTAL

Methods and materials

Triphenyltin(IV) hydroxide, rhodanine and di-isopropylamine (Aldrich-Chemie) were used as supplied. Elemental analyses were performed with a Carlo Erba 1108 apparatus. The IR spectra were recorded on a Bruker IFS 66v FT-IR spectrometer, and the Raman spectra were recorded on the same spectrometer using an FRA-106 accessory. ^{1}H and ^{13}C NMR spectra were obtained in deuterated dimethyl sulfoxide (DMSO-d_6) with a Bruker AMX300 spectrometer operating at 300.14 and 75.48 MHz, respectively (referenced to $SiMe_4$). The ^{119}Sn NMR spectrum of the complex in the same solvent was recorded on a Bruker AMX500 apparatus operating at 186.50 MHz (referenced to $SnMe_4$), all at room temperature. Mass spectra were recorded on a Kratos MS50TC spectrometer connected to a DS90 data system and operating under EI (70 eV, 250 °C) and FAB conditions (Xe, 8 eV) using as liquid matrix 3-nitrobenzyl alcohol. Crystallographic data were collected at 296(2) K on an Enraf-Nonius CAD-4 apparatus using Cu–K_α radiation (λ = 1.54178 Å). $C_{34}H_{39}NO_3SSn$, M = 660.41, monoclinic, *Cc*, a = 25.333(4), b = 13.5870(10), c = 20.768(3) Å, β = 111.738(10)°, V = 6639.8(15) Å^3, Z = 8, R [4774 data with $I \geq 2\sigma(I)$; θ_{max} 67.0] = 0.040, wR (all 6076 data) = 0.119. The structure resolution was carried out using the SHELXS-97 program.[11] Molecular graphics were obtained with ORTEP.[12] CCDC reference number 616291 contains the supplementary crystallographic data for this paper.

Antibacterial activity was initially assayed for the acid and the complex by Müller–Hinton agar diffusion methods. Discs of paper 5 mm in diameter were loaded with 20 µl of a 2 mg ml^{-1} solution of the substance to be tested in 9 : 1 ethanol–water; control discs were loaded with solvent alone. The discs were placed on dishes of Müller–Hinton agar inoculated with *Escherichia coli* (CECT 101), *Pseudomonas aeruginosa* (CECT 110) or *Staphylococcus aureus* (CECT 240) and incubated for 24 h at 37 °C. The bacterial growth inhibition zones were recovered. All the assays were carried out in duplicate. For those products which showed activity, minimum inhibitory concentration (MIC), defined as the lowest concentration of active compound which inhibits the growth of the tested organism under optimal concentration, was determined using serial dilutions in Müller–Hinton broth as described in the literature.[13] A portion of 0.1 ml of nutrient broth containing 10^8 cells ml^{-1} of the sensitive bacterial culture was added to solutions of the compounds at concentrations from 80 to 0 µg ml^{-1}. Results were observed after 18 h of incubation at 35 °C. Serial dilutions of 90% ethanol were assayed as experimental control. Minimal bactericidal concentration (MBC), defined as the lowest concentration of compound that totally kills the tested bacterium, was also assayed by spreading with a swab on Müller–Hinton agar plates with subcultures of tubes incubated for 24 h at 35 °C.



Scheme 1.

Synthesis of the compounds

H_2(o-mpspa)

The acid (Scheme 1) was prepared[14] by condensation of 2-methoxybenzaldehyde with rhodanine, subsequent hydrolysis in NaOH 1 M and ulterior acidification with aqueous HCl (1 M). Colour: yellow. Yield: 49%. Melting point 130 °C. Anal. found: C, 56.5; H, 4.6; S, 15.2; calcd for $C_{10}H_{10}O_3S$: C, 57.1; H, 4.8; S, 15.2%. IR and Raman (in parentheses) (cm^{-1}): 1663 vs, ν(C=O); 1418s, δ(OH); 1282vs, ν(C–O); 2560m (2561w), ν(S–H); 2835m, ν(O–CH_3). The main signals in the EI spectrum are at m/z (ion, intensity): 210 $[M]^+$ (26.87); 192 $[M-H_2O]^+$ (4.15); 228 $[M-H_2O-CO]^+$ (5.23); 230 $[M-COOH]^+$ (5.23); 168 $[M-H_2O-2CO-SH]^+$ (2.65); 164 $[M-H_2O-CO]^+$ (100) and the FAB spectrum shows the same signals. ^{1}H NMR (see atom numbering in Sheme 1): δ(ppm) = 13.00 [sbr, 1H, C(1)OH]; 7.92 [s, 1H, C(3)H]; 7.70 [d, 1H, C(6)H]; 7.02 [t, 1H, C(7)H]; 7.40 [t, 1H, C(8)H]; 7.08 [d, 1H, C(9)H]; 3.82 [s, 3H, C(10)OCH_3]. ^{13}C NMR: δ(ppm) = 166.2 C(1)OH, 128.9 C(2)SH, 139.5 C(3), 119.9 C(4), 157.6 C(5), 111.1 C(6), 131.6 C(7), 122.4 C(8), 130.4 C(9), 55.6 C(10)OCH_3.

[HQ][SnPh$_3$(o-mpspa)]

The complex was synthesized by treating H_2(*o*-mpspa) (0.10 g, 0.5 mmol) in ethanol (10 ml) with triphenyltin hydroxide (0.17 g, 0.5 mmol) in 10 ml of the same solvent, and in the presence of di-isopropylamine (0.15 g, 0.5 mmol). After refluxing for 5 h, yellow crystals suitable for X-ray crystallographic study were isolated and dried *in vacuo*. Yield: 50%. Melting point 167 °C. Anal. found: C, 61.6; H, 6.0; N, 5.0; S, 2.2; calcd for $C_{34}H_{39}NO_3SSn$: C, 61.8; H, 5.9; N, 4.8; S, 2.1%. The main signals in the EI spectrum are at m/z (ion, intensity): 351 $[SnPh_3]^+$ (11); 197 $[SnPh]^+$ (74); 121 $[SnH]^+$ (17); 120 $[Sn]^+$ (100%). Besides these signals the EI spectrum shows signals for H_2(*o*-mpspa) and its fragments and the FAB spectrum shows the same metallated signals and another one at 560 $[M]^+$ (0.3%). IR (Raman) (cm^{-1}): 1525s, $\nu_{asym}(CO_2)$; 1349s (1347w), $\nu_{sym}(CO_2)$; 270s, ν_{asym}(Sn–C); 233sh (235w), ν_{sym}(Sn–C); 346m, ν(Sn–S);

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2836w, ν(O–CH$_3$). [ν_{asym}(CO$_2$)–ν_{sym}(CO$_2$)] = 176. ^{1}H NMR: δ(ppm) = 7.94 [s, 1H, C(3)H]; 6.93 [m, 1H, C(7)H]; 7.35 [m, 1H, C(8)H]; 7.56 [d, 1H, C(9)H]; 3.78 [s, 3H, C(10)H]; 7.52 (m, 6H, Ph$_o$, ^2J = 53.9 Hz); 6.90–7.40 (m, 9H, Ph$_{m,p}$); 8.02 (s,br, 2H, NH$_2$[HQ]); 3.30 (sp, 1H, CH[HQ]); 1.16 (d, 12H, CH$_3$[HQ]). ^{13}C NMR: δ(ppm) = 168.6 C(1), 128.5 C(2), 137.0 C(3), 136.7 C(4), 157.2 C(5), 110.8 C(6), 127.7 C(7), 127.2 C(8), 119.6 C(9), 55.2 C(10), 148.1 C$_i$ (^1J = 584.5 Hz), 136.3 C$_o$ (^2J = 43.9 Hz), 127.8 C$_m$ (^3J = 54.2 Hz), 127.6 C$_p$, 46.2 CH[HQ], 18.8 CH$_3$[HQ]. ^{119}Sn NMR: δ(ppm) = −218 (s).

RESULTS AND DISCUSSION

The crystal structure of [HQ][SnPh$_3$(*o*-mpspa)]

Figure 1 shows an ORTEP representation of the structure for the complex with the numbering scheme, and Table 1 lists some selected bond lengths and angles.

The structure crystallizes in the non-centrosymmetric space group Cc (no. 9) with two independent complexes per asymmetric unit, forming a nearly centrosymmetric dimer stabilized by hydrogen bonds (Table 2). A vector overlap of the two independent complexes performed by the method of W. Kabsch[15] gives an improper rotation matrix relating the complexes and an overall rms deviation between homologous atoms of 0.21 Å. The inversion centre is a local (approximate) symmetry element, the position of which ($x = 0.1129, y = -0.2012$ and $z = 0.5765$) is not consistent with that of the glide plane so as to give rise to the centrosymmetric supergroup C2/c (no. 15).

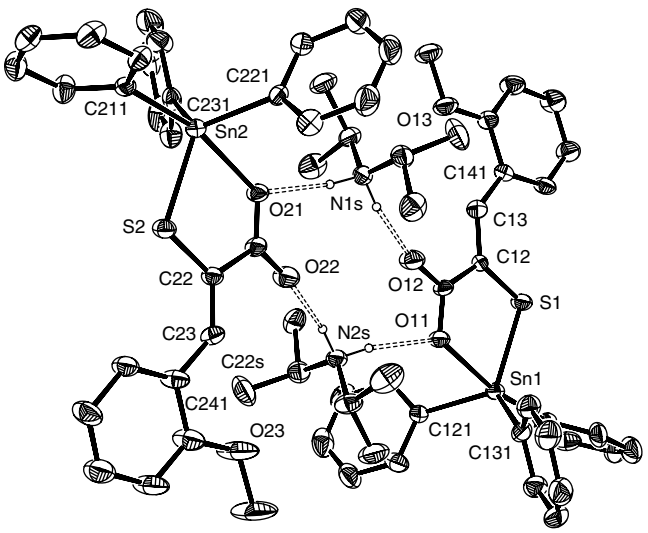

Figure 1. Displacement ellipsoid plot for [SnPh$_3$(*o*-mpspa)] showing the hydrogen-bonding interactions (dashed bonds) between the two independent molecules comprising the asymmetric unit and showing the atom numbering scheme (hydrogen atoms not involved in hydrogen-bonding are omitted for clarity). Ellipsoids are shown at the 30% probability level.

Table 1. Selected bond lengths (Å) and angles (deg)

Sn1–C111	2.174(11)	Sn2–C211	2.192(10)
Sn1–C121	2.159(10)	Sn2–C221	2.111(10)
Sn1–C131	2.124(11)	Sn2–C231	2.149(10)
Sn1–S1	2.419(3)	Sn2–S2	2.439(3)
Sn1–O11	2.435(7)	Sn2–O21	2.379(7)
S1–C12	1.745(10)	S2–C22	1.753(10)
O11–C11	1.277(11)	O21–C21	1.249(11)
O12–C11	1.279(12)	O22–C21	1.238(11)
C111–Sn1–C121	105.2(4)	C211–Sn2–S2	90.4(3)
C111–Sn1–C131	102.4(4)	C211–Sn2–C221	105.0(4)
C121–Sn1–C131	113.9(4)	C211–Sn2–C231	102.4(4)
C111–Sn1–S1	93.1(3)	C221–Sn2–C231	115.7(4)
C121–Sn1–S1	118.1(3)	C221–Sn2–S2	118.0(3)
C131–Sn1–S1	118.9(3)	C231–Sn2–S2	118.7(3)
C111–Sn1–O11	168.8(3)	C211–Sn2–O21	165.7(3)
C121–Sn1–O11	79.5(3)	C221–Sn2–O21	82.9(3)
C131–Sn1–O11	84.4(3)	C231–Sn2–O21	84.2(3)
S1–Sn1–O11	75.83(17)	O21–Sn2–S2	75.34(17)
O11–C11–O12	118.1(10)	O22–C21–O21	122.1(9)

The asymmetric unit contains two diisopropylammonium cations and two [SnPh$_3$(*o*-mpspa)]$^-$ anions, in which (*o*-mpspa) behaves as a bidentate chelating ligand via one O atom of the carboxylato group and the S atom of the deprotonated thiol group, resulting in a distorted trigonal-bipyramidal environment for both Sn atoms. In these two trigonal bipyramids the oxygen atom and one C phenyl atom are apical, whereas the S atom and the other two C phenyl atoms lie in the equatorial plane. The Sn1–O11 and Sn2–O21 bond lengths [2.435(7) and 2.379(7) Å, respectively] are quite longer than the sum of their covalent radii (2.13 Å).[16] Moreover, the expected difference between the equatorial and the apical positions in their distances to the central atom is in this case especially pronounced, since whereas for the apical phenyl groups the Sn–C bond lengths are 2.174(11) and 2.192(10) Å (i.e. in the upper limit of the range 2.12–2.18 Å reported for other triphenyltin compounds[17]), for the equatorial sites these bond lengths are 2.111(10) and 2.149(10) Å (in one bipyramid), 2.124(11) and 2.159(10) Å (in the other). On the other hand, the Sn–S bond lengths [2.419(3) and 2.439(3) Å] are in keeping with the sum of the covalent radii (2.42 Å),[16] and they are in the range found in other triphenyltin thiolates (2.40–2.48 Å).[17–20] Regarding the bond angles, it is noteworthy that the distortion of the polyhedron in respect of the regular geometry is made evident in both cases by the values of the angles in the equatorial plane, which sum is around 352°, and by the C–Sn–O angle, that is quite smaller than 180° [168.8(3)° in one case and 165.7(3)° in the other]. Finally, the S–Sn–O angle is much narrower [75.83(17), 75.34(17)°] than the others around the metal atom, because of the *bite* of the bidentate ligand.

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The geometry of the ligand, on the other hand, remains practically unchanged upon coordination to the metal, even around the donor atoms. For instance, the O–C–O angle in both carboxylate anions [118.1(10), 122.1(9)°] hardly differs from 120°, and both C–O bond lengths are almost identical to each other [1.277(11), 1.279(12) Å], despite the presence of the metal.

Finally, the existence of N–H. . .O hydrogen bonds between the NH_2 group of the di-isopropylammonium cation and the oxygen atoms of the two neighbouring carboxylato groups (Table 2) leads to dimeric units [N–O distances: 2.918(13), 2.758(13) Å]. This hydrogen bond weakens the oxygen–carbon bond and makes the C–O distance similar to the bond length between C and the donor O atom, as stated above.

Vibrational spectra

Vibrational spectra of the ligand show the characteristic band of the SH group at 2560 and 2561 cm^{-1} in the IR and Raman spectra, respectively, together with the (C=O) and (C–O) very strong stretching bands in the IR spectrum at 1663 and 1282 cm^{-1}, respectively. In the case of the IR spectrum of the complex, the lack of the SH and OH ligand bands is concordant with its coordination to the metal via both S and O atoms, while the carboxylato bands lie in the wavenumber range found in other similar compounds[9,10] with a $\Delta\nu[= \nu_{as}\ (CO_2) - \nu_{sym}(CO_2)]$ value of 176 cm^{-1}. This value is small compared with those found in other complexes in which the carboxylato group coordinates via just one of the oxygen atoms.[21,22] This fact may be attributed to the N–H. . .O hydrogen bond, which leads to a significant weakening of the bond between the non-coordinating oxygen and the carbon atom. Finally, the presence of the di-isopropylammonium cation is made evident by a strong band at 1616 cm^{-1} in the IR spectrum, attributed to $\delta(NH_2^+)$.

NMR spectroscopy

The NMR studies were carried out in DMSO-d_6, due to the low solubility of both compounds in $CDCl_3$. In the ^1H NMR spectrum of the complex, the absence of signals for C(1)OH and SH is indicative of di-deprotonation of the ligand. Moreover, the presence of the di-isopropylammonium cation is revealed by signals at 1.16 (d, 12H, CH_3), 3.30 (m, 4H, CH) and 8.02 ppm (s, 2H, NH_2^+), while the multiplets in the range 6.90–7.40 ppm may be attributed to the $SnPh_3$ moiety. In the spectrum of the free ligand, no signal attributable to C(2)SH was found, probably due to the existence of a proton–deuterium exchange process with the solvent. Regarding the ^{13}C NMR spectrum of the complex, the signals attributable to C(1) and C(2) are slightly shifted downfield, whilst the C(3) signal is shielded, compared with that found in the spectrum of the free ligand. These facts confirm the subsistence in dissolution of the coordination via S and O atoms. The chemical shift value in the ^{119}Sn NMR spectrum lies close to the upper limit of the range accepted for five-coordinated tin compounds (−180 to −260 ppm),[23] and is very similar to those reported previously for other $SnPh_3$ compounds.[9,10,24]

Table 2. Hydrogen bonds (Å)

	D–H	H. . .A	D. . .A
N1S–H111. . .O21	0.90	2.03	2.918(13)
N1S–H111. . .O22	0.90	2.46	3.125(13)
N1S–H117. . .O12	0.90	1.87	2.758(13)
N2S–H221. . .O22	0.90	1.90	2.786(13)
N2S–H227. . .O11	0.90	2.02	2.907(13)
N2S–H227. . .O12	0.90	2.44	3.105(14)

Antibacterial activity

No antibacterial activity was exhibited either by di-isopropylammonium hydrochloride, the ligand or solvent. The complex showed to be active against the Gram-positive bacterium *Staphylococcus aureus* (diameter of growth inhibition zone 1.8 mm), but not against standard strains of the Gram-negative bacteria *E. coli* and *P. aeruginosa*. In the case of the only sensitive strain (*S. aureus*), the minimal inhibitory and bactericide concentrations were also determined. The MIC and MBC results, 10 and 40 μg ml^{-1}, respectively, are in accordance with those found for other similar triphenyltin(IV) complexes.[9,10,25]

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