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Synthesis, microbiological study and X-ray structural characterisation of a tri-*n*-butylstannyl-2[4(diethylamino)arylazo]benzenecarboxylate

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Abstract

Organostannyl carboxylates adopt an interesting range of structural variations leading to different structure–activity relationship. Organostannyl-2(arylazo)benzenecarboxylates, reported here, inhibit Gram-positive bacterial growth with an average MIC 10–20 μg ml^{-1}, which is below the lethal dose. The discrete molecular units of this series of compounds function as an anisobidentate chelating ligand, thus rendering the Sn atom five coordinated and adopt a polymeric form. The present work reports the X-ray crystallographic structure of tri-*n*-butylstannyl-2[4(diethylamino)arylazo]benzenecarboxylate and microbial studies in order to get insight into the mode of action of such compounds in biology.

Keywords: Crystal structures; Tributyltin analogs; Triorgano stannyl; Structure–activity

1. Introduction

Organostannyl carboxylates are one of the most extensively investigated class of organometallics known since early 1950s obviously for their biocidal properties and unique structural features [1–4]. Organotin carboxylates are known to adopt an interesting range of structural variations leading to different structure–activity relationships (SAR), sometimes for compounds with very similar chemical formulae [5]. When the carboxylate residue contains additional potential donor atoms, such as oxygen and nitrogen, other structural possibilities arise. Several substituted organotin carboxylates are known to exhibit significant biological activities [6,7]. Organotin compounds, diimine ligands of diphenyltin dichloride [8] and diorganotin compounds are known to possess significant antitumor activity [9–12]. With this in view, we focussed attention on molecules of the general formula (Fig. 1) containing elements of structural rigidity, because rigidity restricts conformational options and reduces the ambiguity in stereochemical assignments for functional groups. Organostannyl-2[4(diethylamino)arylazo]benzenecarboxylates have shown great promise in inhibiting the growth of Gram-positive bacteria with an average MIC 10–20 μg ml^{-1} which is below the lethal dose.

Compounds of this series comprise discrete molecular units, in which the carboxylato-group functions as an anisobidentatate chelating ligand, thus rendering the tin atom five coordinated and adopt a polymeric form [13].

In continuation of our earlier work [14] on the structure–activity relationship (SAR) of a series of organostannyl-2[4(diethylamino)arylazo]benzenecarboxylates, we extended our study with synthesis, microbiological activity, spectroscopic analysis, X-ray crystallographic studies and computer modelling to correlate their unique structural properties with their activities. The present paper reports the full details of the X-ray crystallographic structure of a tri-*n*-butylstannyl-2[4(diethylamino)arylazo]benzenecarboxylate and microbiological studies in order to get an insight into the mode of action of such compounds in respect to biological activity.

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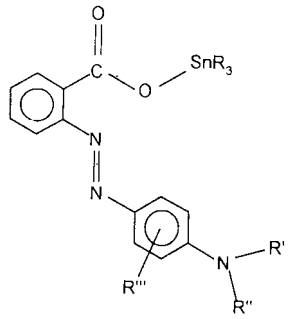

Fig. 1. General schematic diagram of organostannylarylazobenzenecarboxylates.

2. Experimental

2.1. Microbial studies

The microbiological activity of these compounds was tested following the Agar-Cup bioassay method. Bacterial suspension (1 ml) was mixed with sterilised NA (nutrient agar) at 45 °C and plated. The plates were chilled for 30 min and then with the aid of a sterile cork borer, an 8 mm diameter cup was made. The same volume of solution of the compound was added to each cup and incubated at 37 °C for 24 h. The diameters of the inhibition zones were recorded. All apparatus and materials were sterilised where necessary using standard procedures.

2.2. Synthesis and spectroscopic studies

The title compound was prepared by stannylation of 2[4-(diethylamino)arylazo]benzenecarboxylic acid with hexa-*n*-butyl-distannoxane in dry benzene at the reflux temperature of the solvent (at 80 °C) for a period of 34 h, using 2:1 mole ratio of the substrate to reagent. Removal of solvent followed by crystallisation from light petroleum afforded the desired product as beautiful orange red needles, m.p. 102 °C. It was characterised by IR, UV–vis spectral data and elemental analysis. The stannyl carboxylate asymmetric stretching frequency which occurred at 1610 cm^{-1} in the solid phase did not show a great change in solution phase indicating thereby the existence of a typical five coordinate stannyl carboxylate bridged structure (Fig. 2) in the solid state.

2.3. Crystallography

Suitable orange–red good needle shaped crystals of tri-*n*-butyl-2[4(diethylamino)arylazo]benzenecarboxylate for X-ray study were obtained by slow evaporation from petroleum ether (boiling range 333–353 K); dimensions $0.34 \times 0.25 \times 0.15$ mm. Cell parameters were obtained from least-squares refinement of setting angles of 25 reflections.

A total of 1851 [1756 with $I > 2\sigma(F)$] unique reflections were collected in an Enraf–Nonius CAD4 diffractometer with Ni-filtered Cu–K_α radiation and $\omega - 2\theta$ step scan mode. Ranges of h, k and l are -17 to 17, 0 to 12, and 0 to 13, respectively, and maximum 2θ was

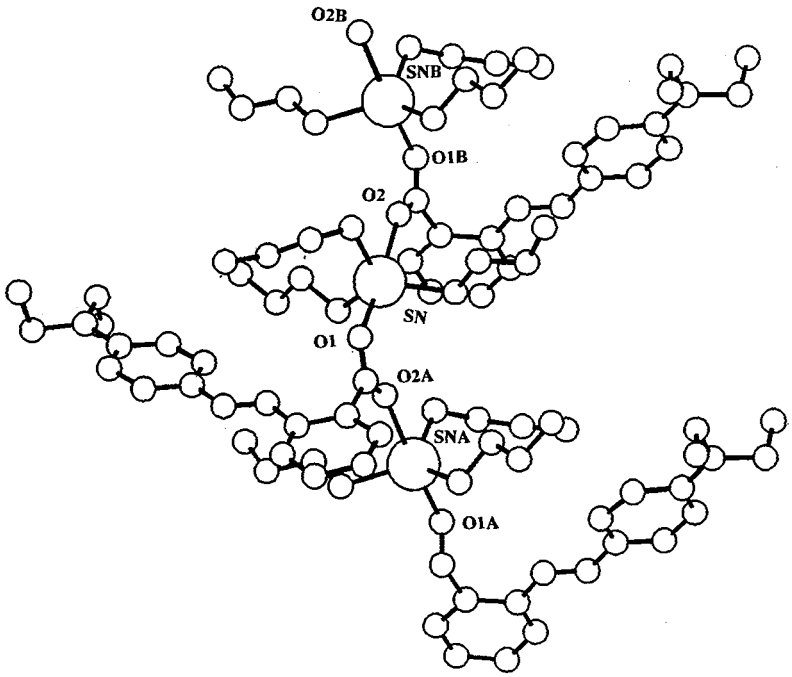

Fig. 2. The polymeric structure of tri-*n*-butyl 2[4(diethylamino)arylazo]benzenecarboxylate.

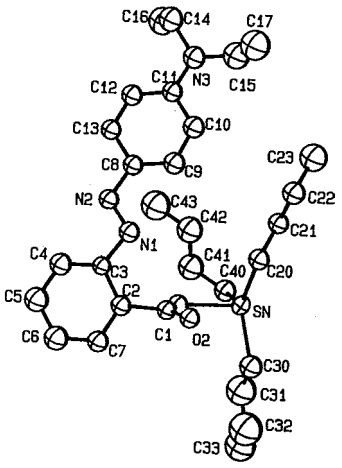

Fig. 3. ORTEP plot of the molecule with displacement ellipsoids at the 30% probability level.

156°. Three standard reflections measured for every 100 reflections showed 0.5% variation of intensity. The data sets were corrected for Lorentz & Polarisation effects, and for absorption. The crystal data are given in Table 3. The structure was solved by direct methods, SHELXS-86 [15] in the space group $P2_1/m$ and refined by full-matrix least-squares on F_o^2 using SHELXL-93 [16]. The refinement converged to $R = 0.0499$ ($wR = 0.11237$). The ORTEP diagram is shown in Fig. 3.

3. Results and discussion

The organotin carboxylates were obtained in good yield via the stannylation of 2-[4(diethylamino)-arylazo]benzenecarboxylic acid with hexa-*n*-butyl-distannoxane in dry benzene.

Organostannyl-2(arylazo)benzenecarboxylates under investigation were screened in vivo for their biological activity against several microorganisms using Agar-Cup method. These compounds were found to exhibit considerable activity against several Gram-positive bacteria (Table 1). From the results, it was found that the nature of the substituents (R′, R″ and R‴) at various positions (Fig. 1) in the phenyl ring was found either to increase or to decrease the biological activity of the organostannyl-2-(arylazo)benzenecarboxylates. The results may be explained as being due to the variation of electron density environment on the β-azoic nitrogen brought about by the substituents. These observations led us to consider that the β-azoic nitrogen to be the active site in organostannyl carboxylates under investigation. This is not surprising, because the azoic nitrogen is capable of forming a hydrogen bond which is established for this series by IR, UV–vis and ^{1}H-NMR spectral studies.

The significant inhibition of bacterial growth by organostannyl-2(arylazo)benzenecarboxylates in the present study also proved the presence of the metal in the reactive site of the substrate. The observed enhanced biological activity of the organostannyl carboxylates as compared to that of their corresponding 2(arylazo)benzenecarboxylic acids and the complete loss of biological potency of the corresponding ethyl/methylcarboxylates provide further support to this view.

The unique structural feature of the organostannyl-2(arylazo)benzenecarboxylates [1], which is involved in complexation with solvents of variable nucleophilicity as evident from UV–vis spectra (Table 2) and others [10], can perhaps be successfully exploited in explaining similar coordination with enzymatic protein molecules also. The enzymatic proteins in their relatively rigid planar peptide structures possess carbonyl group capable of forming metal–oxygen bond with the stannyl groups of organostannyl carboxylate and the bond formation is further augmented by the nearby β-azoic nitrogen and stannyl carboxylate carbonyl oxygens

Table 1
Antimicrobial activities of organostannyl-2(arylazo)benzenecarboxylates

Compound	R	R′	R″	R‴	S. a	B. m	S. l	B. p	M. f	B. s
1	Ph	H	Me	3-Cl	15.0	15.0	13.0	15.0	15.0	14.0
2	n-Bu	H	Me	3-Cl	15.0	15.0	15.0	15.0	15.0	15.0
3	Ph	H	Me	3-Me	15.0	15.0	15.0	15.0	15.0	15.0
4	n-Bu	H	Me	3-Me	15.0	16.0	15.0	16.0	15.0	15.0
5	Ph	Me	Me	2-Cl	15.0	15.0	16.0	16.0	16.0	15.0
6	n-Bu	Me	Me	2-Cl	16.0	16.0	16.0	17.0	17.0	16.0
7	Ph	Me	Me	2-Br	16.0	17.0	18.0	17.0	17.0	18.0
8	n-Bu	Me	Me	2-Br	19.0	19.0	19.0	19.0	19.0	18.0
9	Ph	Et	Et	H	19.0	18.0	18.0	19.0	19.0	19.0
10	n-Bu	Et	Et	H	19.0	19.0	20.0	19.0	19.0	19.0
11	Ph	Et	Et	2-Me	20.0	19.0	20.0	19.0	19.0	20.0
12	n-Bu	Et	Et	2-Me	20.0	20.0	21.0	19.0	20.0	21.0

S. a: *Staphylococcus aureus*; B. m: *Bacillus cereus* var. *mycoides*; S. l: *Sarcina lutea*; B. p: *Bacillus pumilus*; M. f: *Micrococcus flavus*; B. s: *Basillus subtilis*.

Table 2
UV–vis spectra of organostannyl-2(arylazo)benzenecarboxylates in different nucleophilic solvents [λ (nm)]

Compound	R	R′	R″	R‴	MeOH	Pyridine	DMSO
1	Ph	H	Me	3-Cl	391	397	398
2	n-Bu	H	Me	3-Cl	395	395	401
3	Ph	H	Me	3-Me	400	405	410
4	n-Bu	H	Me	3-Me	402	400	407
5	Ph	Me	Me	2-Cl	407 498	415	421
6	n-Bu	Me	Me	2-Cl	412 500	412	416
7	Ph	Me	Me	2-Br	410 510	417	418
8	n-Bu	Me	Me	2-Br	410 512	420	421
9	Ph	Et	Et	H	412 510	432 518	422
10	*n*-Bu	Et	Et	H	415 512	432 510	420

which form bifurcated hydrogen bonds with the peptide NH groups [14] thus enhancing the electron density of the peptide oxygen. This binding through peptide bonds is not unusual since the affinity of the stannyl group for oxygen coordination [17] is believed to be greater than that of the peptide nitrogen. This complexation results in ceasing the bacterial growth. Spectral evidence also supports the fact by a rapid change in λ_{max} and ε-values in the UV–vis spectroscopy in different solvent [14].

On thorough examination it was observed that while these organostannyl carboxylates are active against Gram-positive bacteria, none possess any activity against Gram-negative bacteria and pathogenic fungi. Gram-negative bacteria are resistant to this group of organostannyl carboxylates possibly due to the inability of these larger polar molecules to cross the outer membrane and reach the target site.

3.1. Crystal structure

The structure of tri-*n*-butylstannyl-2[4(diethylamino)-arylazo]benzenecarboxylate is shown in Fig. 2 (see Table 3 for crystal data), and selected interatomic parameters are listed in Table 4. The structure reported here for tri-*n*-butylstannyl-2[4(diethylamino)arylazo]-benzenecarboxylate is in agreement with that reported earlier by us [1] and others [18]. The crystallographic asymmetric unit comprises one centrosymmetric molecule about a symmetric plane, which associate as a result of mutual intermolecular Sn→O contacts, afforded by bidentate bridging carboxylate groups as shown in Fig. 2. The resultant structure is therefore polymeric, that is the crystals of the compound com-

Table 3
Crystal data and structure refinement parameters for tri-*n*-butylstannyl[2(4diethylaminoarylazo)]benzenecarboxylate

Colour/shape	Orange–red/needle shaped
Empirical formula	C29H43N3O2Sn
Formula weight	586.068
Temperature (K)	293(2)
Radiation	Cu–K_α
Wavelength (Å)	1.54182
Crystal system	Monoclinic
Space group	$P2_1/m$
Unit cell dimensions	
a (Å)	14.135(2)
b (Å)	10.252(3)
c (Å)	10.802(2)
α (°)	90
β (°)	99.93(2)
γ (°)	90
V (Å^3)	1541.9(6)
Z	4
D_{calc} (g cm^{-3})	2.526
Absorption coefficient (mm^{-1})	13.584
$F(000)$	1224
Crystal size (mm)	$0.34 \times 0.25 \times 0.15$
Theta range for data collection (°)	3.17–78.01
Index ranges	$-17 \le h \le 17$, $0 \le k \le 12$, $0 \le l \le 13$
Reflections collected	1851
Independent reflections	1756 [$R_{int} = 0.0288$]
Refinement method	Full-matrix least-squares on F_o^2
Data/restraints/parameters	1756/0/316
Goodness-of-fit on F_o^2	1.088
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0494$, $wR_2 = 0.1232$
R indices (all data)	$R_1 = 0.0499$, $wR_2 = 0.1237$
Extinction coefficient	0.00037(6)
Largest differential peak and hole (e Å^{-3})	0.954 and −0.632

Table 4
Selected bond lengths (Å) and bond angles (°) for tri-*n*-butylstannyl[2(4diethylaminoarylazo)]benzenecarboxylate

Bond lengths		Bond angles	
Sn–C30	2.14(3)	C30–Sn–C20	121.9(1)
Sn–C20	2.13(4)	C30–Sn–C40	115.0(2)
Sn–C40	2.14(3)	C20–Sn–C40	122.1(1)
Sn–O1	2.20(2)	C30–Sn–O1	96.8(1)
		C20–Sn–O1	94.6(1)
		C40–Sn–O1	88.9(1)
O1–C1	1.27(4)	C1–O1–Sn	120.0(3)
C1–O2	1.17(4)	O2–C1–O1	126.0(4)
C1–C2	1.55(5)	O2–C1–C2	121.0(4)
		O1–C1–C2	113.0(3)
C2–C7	1.33(5)	C7–C2–C3	119.0(4)
		C7–C2–C1	124.0(4)
C2–C3	1.50(6)	C3–C2–C1	117.0(3)
C3–C4	1.35(5)	C4–C3–N1	127.0(4)
		C4–C3–C2	117.0(4)
C3–N1	1.50(5)	N1–C3–C2	116.0(4)
C4–C5	1.35(5)	C3–C4–C5	124.0(4)
C5–C6	1.44(5)	C4–C5–C6	118.0(3)
C6–C7	1.36(5)	C7–C6–C5	121.0(3)
		C6–C7–C2	121.0(4)
N1–N2	1.23(5)	N2–N1–C3	108.0(3)
		N1–N2–C8	112.0(3)
N2–C8	1.39(5)	C9–C8–N2	126.0(3)
C8–C9	1.35(5)	C9–C8–C13	118.0(4)
C8–C13	1.39(5)	N2–C8–C13	116.0(4)
C9–C10	1.37(5)	C8–C9–C10	122.0(3)
C10–C11	1.43(5)	C9–C10–C11	121.0(3)
C11–C12	1.36(5)	C12–C11–N3	126.0(3)
C11–N3	1.40(4)	C12–C11–C10	116.0(3)
		N3–C11–C10	118.0(3)
C12–C13	1.36(5)	C11–C12–C13	122.0(3)
		C12–C13–C8	121.0(4)
N3–C15	1.43(4)	C11–N3–C15	124.0(3)
N3–C14	1.49(4)	C11–N3–C14	118.0(3)
		C15–N3–C14	118.0(2)
C14–C16	1.49(4)	C16–C14–N3	111.0(3)
C15–C17	1.46(4)	N3–C15–C17	113.0(2)
C20–C21	1.49(5)	C21–C20–Sn	116.0(2)
C21–C22	1.57(5)	C20–C21–C22	112.0(3)
C22–C23	1.48(5)	C23–C22–C21	115.0(3)
C30–C31	1.54(4)	C31–C30–Sn	113.0(2)
C31–C32	1.28(3)	C32–C31–C30	127.0(2)
C32–C33	1.41(4)	C31–C32–C33	124.0(2)
C40–C41	1.45(6)	C41–C40–Sn	122.0(3)
C41–C42	1.36(6)	C42–C41–C40	120.0(3)
C42–C43	1.57(5)	C41–C42–C43	118.0(4)

prise discrete molecular units, in which the carboxylato-group functions as an anisobidentate chelating ligands (Sn–O = 2.21 Å and Sn–O = 2.4 Å), thus rendering five coordination to tin atom (Fig. 2). Each of the tin atom exists in a distorted trigonal bipyramidal geometry with the axial positions occupied by the oxygen atoms and the equatorial plane is defined by trigonal plane of three *n*-butyl carbon atoms. The axial carboxylate oxygen atoms are organised in the weakly *syn–anti* bridged fashion. The Sn atom lies 0.147(11) Å out of the trigonal plane of the butyl carbon in the direction of O1 atom. The Sn–C bond in the second axial site trans to the coordinate Sn–O bond is marginally longer (Å), whilst the sum of the equatorial angle at Sn is 345.7°. The C–Sn–C angles are opened up [122(4)°, 115(2)° and 122(4)°] due to the proximity of the carbonyl oxygen atom O2, whereas the O–Sn–C angles are compressed [95(1)°, 89(2)° and 97(2)°], as obtained also in other structures [13]. In this structure the aromatic ring and the carboxylate group are twisted by 79° which is similar to that found in the case of polymeric triphenyltin 2-chlorobenzoate [19]. The two C–O bond distances of the carbonyl group are unequal as expected, with the longer C–O distance being associated with the shorter Sn–O bond, and vice versa. The aryl azobenzenecarboxylate unit exhibits a *trans* geometry at the N=N (C3–N–N2–C8 = 179.4(1)° linkage, with the ligand apparently held in a quite rigid conformation by hydrogen bonds. Atom O1 forms bifurcated hydrogen bond to C41 and C42 by 2.125 and 2.696 Å, respectively, for self-stabilisation while N1 and N3 atoms form intermolecular hydrogen bond with C40 (2.698 Å) and C17 (2.543 Å), respectively.

It is interesting to note that, in spite of the *n*-butyl group attached to Sn and the very large steric demands of the arylazobenzoato group which prevent intermolecular bridging, the carboxyl group prefers to function as a chelating ligand giving the five coordinated structure, rather than as a unidentate ligand.

4. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 163010 for compound tri-*n*-butyl-[2(4diethylamino)arylazo]benzenecarboxylate. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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