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Full Length Research Paper

Synthesis and characterization of organotin(IV) complexes derived of 4-(diethylamino) benzoic acid: *In vitro* antibacterial screening activity

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Four organotin(IV) carboxylate complexes derivative of 4-(diethylamino)benzoic acid have been successfully synthesized and characterized quantitatively and qualitatively. The complexes obtained are screened for their *in vitro* antibacterial screening activity. Monomeric $\{4\text{-}[N(C_2H_5)_2]C_6H_4COO\}_2(R)_2Sn$ (R = methyl 1, butyl 2), $[\{4\text{-}[N(C_2H_5)_2]C_6H_4COO(C_4H_9)_2Sn\}_2O]_2$ dimer 3 and $4\text{-}[N(C_2H_5)_2]C_6H_4COO(C_6H_5)_3Sn$ 4 are obtained in solid state. The tin atom of complex 2 is six-coordinated, complex 4 is four-coordinated and the tin atoms of complex 3 are five and six-coordinated. With the exceptional case of tin atom of complex 1 exhibited five and six coordination in solution state which may be attributed from the dynamic stage or partial disassociation bonding of carboxylate anion. From the *in vitro* antibacterial screening activities, complex 1 is active against all the five tested bacterial strains compared to complexes 2 - 4.

Key words: Organotin(IV) complexes, synthesis, characterization, antibacterial activity.

INTRODUCTION

Although the first organotin(IV) compound was successfully isolated in 1850s, it did not gain any commercial significance in industrial application until almost a hundred years later (Blunden et al., 1985). From 1950s onwards, organotin(IV) carboxylate complexes became commercially relevant when the polyvinyl chloride (PVC) industry began to expand tremendously (Blunden et al., 1985; Evans and Karpel, 1985). Since then, the study of organotin(IV) complexes received considerable attention due to the vast applications in industrial as well as its biological properties against bacterial, fungal and cancer cells line (Molloy et al., 1984; Willem et al., 1997; Teoh et al., 1997; Novelli et al., 1999; Gielen et al., 2000; Crouse et al., 2004).

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Up to date, organotin(IV) complexes are still extensively studied due to its structural diversity as well as coordination geometries which are well documented from the single crystal X-ray structural study (monomer, dimeric, hexameric and oligomeric) (Zhang et al., 2005; Win et al., 2007, 2010; Amini et al., 2009). In this paper, we report on the synthesis and structural characterization of new organotin(IV) carboxylate complexes derived from 4-(diethylamino)benzoic acid. Moreover, the *in vitro* antibacterial screening activities of the complexes obtained are carried out and the results are reported.

MATERIALS AND METHODS

General and instrumental

All the reagents, starting materials as well as the solvents were purchased commercially and used without any further purification. The melting points were determined in an open capillary and were

uncorrected. Elemental C, H and N analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyzer. Tin was determined gravimetrically by igniting a known quantity of each complex to SnO_2. Infrared spectra were recorded using a Perkin-Elmer System 2000 FTIR Spectrophotometer as a KBr disc in the frequency range of 4000 - 400 cm^{-1}. The spectra for ^{1}H, ^{1}H-^{13}C HMQC and ^{119}Sn NMR were recorded on a Bruker AC-P 400 MHz FTNMR Spectrometer and ^{13}C NMR was recorded on a Bruker AC-P 300 MHz FTNMR Spectrometer using deuterated $CDCl_3$ as the solvent and tetramethylsilane, TMS as the internal standard.

In vitro antibacterial screening activity

The synthesized complexes and parent acid were screened for their *in vitro* antibacterial activity against three gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*] and two gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) bacterial strains, by Inhibition Zone Method using agar well diffusion method. The seeded agar (nutrient agar medium) was prepared by cooling the molten agar to 40°C and then adding bacterial inoculums containing approximately 10^4 - 10^6 colony forming units (CFU)/mL. The bacterial inoculums were spread on the plate containing agar medium and even coverage was ensured before the agar solidified. The complexes were dissolved in DMSO to prepare 1.0 mg/mL concentration. By using a sterile metallic borer, the wells (6 mm in diameter) were dug and the standard drugs and complexes were introduced into the respective wells. The plates were incubated immediately at 37°C for 20 - 24 h. The activity was determined by measuring the diameter of the inhibition zone (in mm).

Preparation of sodium salt and dimethyltin(IV) oxide, Me_2SnO

Dimethyltin(IV) dichloride (Me_2SnCl_2) was dissolve in distilled water and stirred overnight. Colourless solution was obtained. Ammonia solution (60%) was added into the colourless solution and finally fine white precipitate was obtained and filtered. The precipitate was dried in oven (60°C) for a day until dry white precipitate was obtained. The sodium salt of the acid was obtained by heating under reflux a 1:1 molar mixture of sodium hydroxide, NaOH (0.12 g, 3 mmoles) and 4-(diethylamino)benzoic acid, 4-$[N(C_2H_5)_2]C_6H_4COOH$ (0.58 g, 3 mmoles) in ethanol (50 mL) for two hours. After a few days, white precipitates were obtained. FTIR as KBr disc (cm^{-1}): selected data: $\nu(COO)_{as}$ 1604, $\nu(COO)_s$ 1356.

Synthesis of complexes

Bis{4-(diethylamino)benzoato}dimethyltin(IV), {4-$[N(C_2H_5)_2]C_6H_4COO\}_2(CH_3)_2Sn$ (1) Bis{4-(diethylamino)benzoato}dimethyltin(IV), 1 was obtained by heating under reflux a 1:2 molar mixture of dimethyltin(IV) oxide (0.49 g, 3 mmoles) and 4-(diethylamino)benzoic acid (1.16 g, 6 mmoles) in ethanol (50 mL) for two hours. A clear colourless transparent solution was isolated by filtration and kept in a bottle. After four days, fine colourless crystals (1.07 g, 67.0% yield) were collected. Melting point: 185.3 - 186.1°C. Analysis $C_{24}H_{34}N_2O_4Sn$: C, 54.05; H, 6.38; N, 5.15; Sn, 22.06%. Calculated $C_{24}H_{34}N_2O_4Sn$: C, 54.05; H, 6.43; N, 5.25; Sn, 22.26%. FTIR as KBr disc (cm^{-1}): ν(C-H) aromatic 3079, ν(C-H) saturated 2970, 2925, 2910, 2871; $\nu(COO)_{as}$ 1605, $\nu(COO)_s$ 1353, ν(C-N) 1272, ν(O-Sn-O) 612, ν(Sn-C) 553, ν(Sn-O) 428. ^{1}H-NMR (ppm) ($CDCl_3$): δ: benzene protons 6.66 (d, 9.0 Hz, 4H); 7.99 (d, 6.6 Hz, 4H); N-$(CH_2CH_3)_2$ 1.22 (t, 7.0 Hz, 12H); 3.45 (q, 7.1 Hz, 8H); methyl, CH_3 1.11 (s, 6H). ^{13}C-NMR (ppm) ($CDCl_3$): δ: benzene carbons 110.54, 115.90, 132.92, 151.62; methyl 5.16, $^{1}J(^{119}Sn - ^{13}C)$ = 670.3 Hz; N-$(CH_2CH_3)_2$ 12.90, 44.90; COO 176.76. ^{119}Sn-NMR (ppm) ($CDCl_3$): δ: -137.25. Bis{4-(diethylamino)benzoato}dibutyltin(IV), {4-$[N(C_2H_5)_2]C_6H_4COO\}_2(C_4H_9)_2Sn$ (2). Complex 2 was prepared by a similar method to those described for complex 1, except substituting dimethyltin(IV) oxide with dibutyltin(IV) oxide. Acetonitrile (50 mL) was used as solvent and the mixture was heated under reflux for three hours. A clear transparent solution was isolated by filtration and kept in a bottle. After twelve days, colourless crystals (1.52 g, 82.0% yield) were collected. Melting point: 136.9-137.7 °C. Analysis $C_{30}H_{46}N_2O_4Sn$: C, 58.37; H, 7.28; N, 4.61; Sn, 19.05 %. Calculated $C_{30}H_{46}N_2O_4Sn$: C, 58.36; H, 7.51; N, 4.54; Sn, 19.22 %. FTIR as KBr disc (cm^{-1}): ν(C-H) aromatic 3080, ν(C-H) saturated 2969, 2929, 2871, 2856; $\nu(COO)_{as}$ 1603, $\nu(COO)_s$ 1352, ν(C-N) 1273, ν(O-Sn-O) 610, ν(Sn-C) 559, ν(Sn-O) 442. ^{1}H-NMR (ppm) ($CDCl_3$): δ: benzene protons 6.66 (d, 9.1 Hz, 4H); 8.02 (d, 9.0 Hz, 4H); N-$(CH_2CH_3)_2$ 1.22 (t, 7.0 Hz, 12H); 3.44 (q, 7.0 Hz, 8H); butyl, CH_3 0.91 (t, 7.4 Hz, 6H); CH_2 1.36-1.46 (m, 4H); CH_2 1.68-1.87 (m, 8H). ^{13}C-NMR (ppm) ($CDCl_3$): δ: benzene carbons 110.43, 119.98, 132.37, 150.74; butyl 14.12, 27.29, 27.92, 28.46; N-$(CH_2CH_3)_2$ 12.95, 44.89; COO 173.44. ^{119}Sn-NMR (ppm) ($CDCl_3$): δ: -214.50.

Bis[4-(diethyl amino)benzoato]tetrabutyldistannoxane(IV) dimer, $[\{4\text{-}[N(C_2H_5)_2]C_6H_4COO(C_4H_9)_2Sn\}_2O]_2$ **(3).** Complex **3** was obtained by heating under reflux a 1:1 molar mixture of dibutyltin(IV) oxide (0.49 g, 2 mmoles) and 4-(diethylamino)benzoic acid (0.39 g, 2 mmoles) in ethanol (50 mL) for two hours. A clear transparent solution was isolated by filtration and kept in a bottle. After five days, colourless crystals (2.96 g, 85.3% yield) were collected. Melting point: 208.3 - 209.9°C. Analysis $C_{76}H_{128}N_4O_{10}Sn_4$: C, 52.78; H, 7.07; N, 3.19; Sn, 27.37%. Calculated $C_{76}H_{128}N_4O_{10}Sn_4$: C, 52.68; H, 7.45; N, 3.23; Sn, 27.41 %. FTIR as KBr disc (cm^{-1}): ν(C-H) aromatic 3082, 3052; ν(C-H) saturated 2957, 2925, 2869; $\nu(COO)_{as}$ 1604, 1576; $\nu(COO)_s$ 1350, 1394; ν(C-N) 1269, ν(Sn-O-Sn) 634, ν(Sn-C) 548, ν(Sn-O) 468. ^{1}H-NMR (ppm) ($CDCl_3$): δ: benzene protons 6.66 (d, 6.9 Hz, 8H); 7.91 (d, 7.3 Hz, 8H); butyl, CH_3 0.88 (t, 7.3 Hz, 24H); CH_2 1.37-1.41 (m, 16H); CH_2 1.57-1.74 (m, 32H); N-$(CH_2CH_3)_2$ 1.23 (t, 6.5 Hz, 24H); 3.44 (q, 6.8 Hz, 16H). ^{13}C-NMR (ppm) ($CDCl_3$): δ: benzene carbons 110.43, 120.03, 132.36, 150.78; butyl 14.09, 26.83, 27.13, 27.27, 27.42, 27.90, 28.45; N-$(CH_2CH_3)_2$ 12.95, 44.87; COO 173.44. ^{119}Sn-NMR (ppm) ($CDCl_3$): δ: -171.65, -221.43. 4-(Diethylamino)benzoatotriphenyltin(IV), 4-$[N(C_2H_5)_2]C_6H_4COO(C_6H_5)_3Sn$ (4). Complex 4 was prepared by heating under reflux a 1:1 molar mixture of triphenyltin(IV) hydroxide (0.73 g, 2 mmoles) and 4-(diethylamino)benzoic acid (0.39 g, 2 mmole) in acetonitrile (50 mL) for two hours. A clear transparent solution was isolated by filtration and kept in a bottle. After four days, colourless crystals (1.30 g, 79.9% yield) were obtained. Melting point: 113.5 - 113.8°C. Analysis $C_{29}H_{29}N_1O_2Sn$: C, 64.28; H, 5.00; N, 2.63; Sn, 21.31%. Calculated $C_{29}H_{29}N_1O_2Sn$: C, 64.24; H, 5.39; N, 2.58; Sn, 21.89%. FTIR as KBr disc (cm^{-1}): ν(C-H) aromatic 3067, 3053; ν(C-H) saturated 2967, 2927, 2903, 2869; $\nu(COO)_{as}$ 1603, $\nu(COO)_s$ 1347, ν(C-N) 1270, ν(Sn-O) 448. ^{1}H-NMR (ppm) ($CDCl_3$): δ: phenyl protons 7.48 - 7.53 (m, 9H); 7.86 - 7.88 (m, 6H); benzene 6.66 (d, 8.9 Hz, 2H); 8.06 (d, 9.1 Hz, 2H); N-$(CH_2CH_3)_2$ 1.22 (t, 7.2 Hz, 6H); 3.43 (q, 7.1 Hz, 4H). ^{13}C-NMR (ppm) ($CDCl_3$): δ: phenyl carbons C_{ipso} 139.75, C_{ortho} 137.39 (48.1 Hz), C_{meta} 129.20 (63.2 Hz), C_{para} 130.28; benzene 110.53, 116.29, 133.25, 151.41; N-$(CH_2CH_3)_2$ 12.92, 44.92; COO 173.95. ^{119}Sn-NMR (ppm) ($CDCl_3$): δ: -127.33. 4-(diethylamino)benzoic acid, 4-$[N(C_2H_5)_2]C_6H_4COOH$.

The parent acid, 4-(diethylamino)benzoic acid, 4-$[N(C_2H_5)_2]$

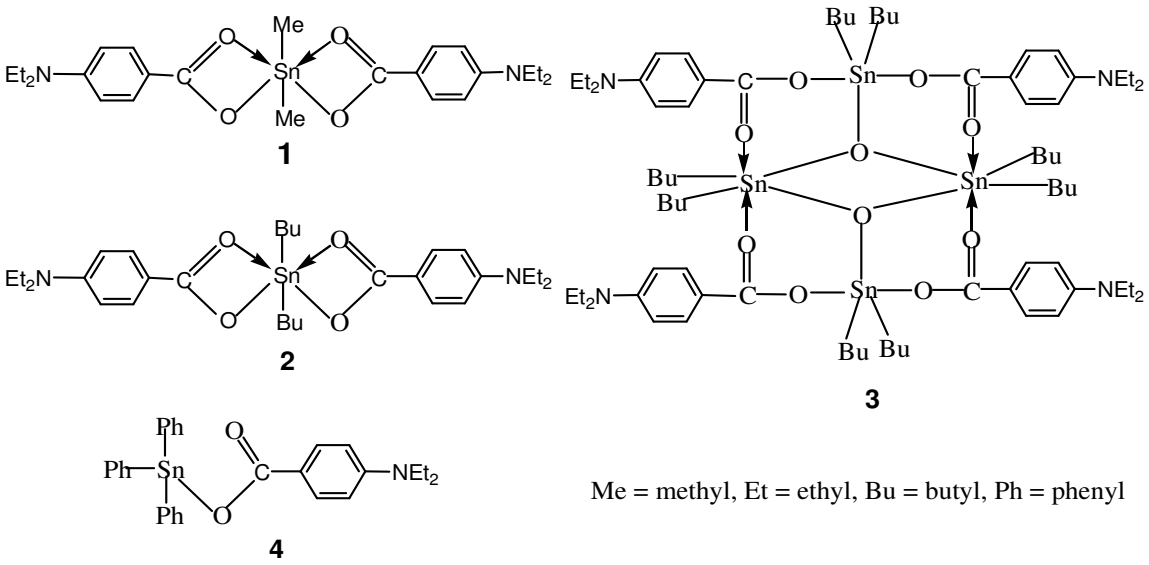

Figure 1. The proposed structure for complexes 1 – 4.

C_6H_4COOH was purchased from Merck Schuchardt and used without any further purification. FTIR as KBr disc (cm^{-1}): selected data: ν(OH) 2899 - 2545, $\nu(COO)_{as}$ 1663, $\nu(COO)_s$ 1357. ^{1}H-NMR (ppm) ($CDCl_3$): δ: benzene protons 6.66 (d, 9.1 Hz, 2H); 7.97 (d, 9.1 Hz, 2H); N-$(CH_2CH_3)_2$ 1.22 (t, 7.1 Hz, 6H); 3.44 (q, 7.1 Hz, 4H). ^{13}C-NMR (ppm) ($CDCl_3$): δ: benzene carbons 110.54, 115.45, 132.73, 151.96; N-$(CH_2CH_3)_2$ 12.88, 44.93; COO 173.02.

RESULTS AND DISCUSSION

Physical and elemental analysis

In this study, complexes 1 - 4 derived from 4-(diethylamino)benzoic acid have been obtained in solid state. Complex 4 is obtained as colourless crystals and the X-ray crystal structure of complex 4 has been reported (Win et al., 2007). The micro-elemental analysis for C, H, N and Sn data obtained were in agreement with the predicted formula for complexes 1 - 4. Complexes 1 - 4 gave a sharp melting point which indicated the isolation of fairly pure complexes. An outline of the proposed structure for complexes 1 - 4 are depicted in Figure 1.

Infrared and NMR spectral studies

The ν(O-H) bands for the acid were absent in the infrared spectra of salt and complexes 1 - 4 showed the deprotonation and coordination of the carboxylate anion. Complexes 1 - 4 revealed that the $\nu(COO)_{as}$ was shifted to a lower wave length number compared to the parent acid which signify that the coordination took place via the oxygen atoms of the carboxylate anion. Complexes 1 - 4 showed the $\nu(COO)_{as}$ and $\nu(COO)_s$ are in the range of 1605 - 1579 and 1394 - 1347 cm^{-1} respectively. Generally, the $\Delta\nu = [\nu(COO)_{as} - \nu(COO)_s]$ value is used to determine the bonding properties of carboxylate anion to tin atom in organotin(IV) carboxylate complexes (Sandhu and Verma, 1987).

Complexes 1 - 3 showed that the Δν is comparable to the sodium salt of the acid indicating bidentate bonding of the carboxylate group to tin(IV) atom. For complexes derived from triphenyltin(IV) carboxylate, Δν below 200 cm^{-1} would be expected for bridging or chelating carboxylates, but greater than 200 cm^{-1} for the monodentate bonding carboxylate anions (Yeap and Teoh, 2003). Hence, the carboxylate anion in complex 4 would be expected to bond to the tin atom in monodentate manner since the Δν above 200 cm^{-1}. As a result, the tin atom moiety in complexes 1 and 2 exhibited six-coordinated; complex 3 (organodistannoxane dimer) exhibited five- and six-coordinated and complex 4 exhibited four-coordinated.

The ^{1}H NMR spectrum of 4-(diethylamino)benzoic acid exhibited two sets of signals [6.66 and 7.97 ppm] with the integration values of 2:2 and another two set of signals [1.22 and 3.44 ppm] with integration values of 6:4. Both signals are also observed in the ^{1}H NMR spectra of complexes 1 - 4 arising from the aromatic protons of the benzene ring and the -ethylamino protons attached at the *para* position at the benzene ring. Moreover, these signals did not show any significant shifting indicating that the benzene and -ethylamino did not involve in the coordination to tin atom moiety in the complexes. In the upfield regions of the ^{1}H NMR spectra of the complexes 1 - 3 showed the signal of the methyl and butyl protons in the range of 1.11 and 0.88 - 1.87 ppm respectively. For complex 4, the resonances appeared as two well separated sets of multiplets in the regions centering around δ≈ 7.50 and 7.87 ppm (downfield) ascribed to

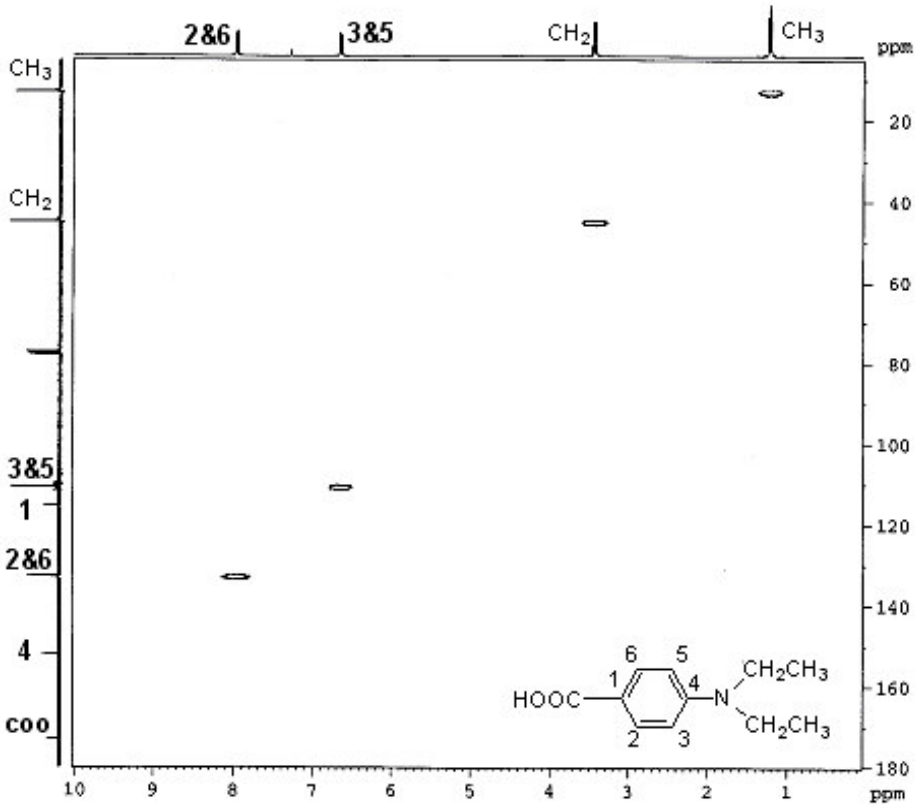

Figure 2. ^{1}H-^{13}C HMQC NMR spectrum of 4-(diethylamino)benzoic acid.

phenyl protons (Sau and Holmes, 1981). Evidence of the formation of the complexes is displayed in the ^{13}C NMR spectra. The ^{13}C NMR spectra of complexes 1 – 4 showed the δ(COO) signal shifted to the downfield region which is lower compared to that of the acid (173.02 ppm) indicating the carboxylate anion is bonded to tin atom. Complex 1 exhibited a sharp signal at 5.16 ppm with the $^{1}J(^{119}Sn\text{-}^{13}C)$ value of 670.3 Hz and the C-Sn-C angle was 135.6°. As a result, the tin atom in complex 1 exhibited a distorted octahedral geometry (Lockhart and Manders, 1986). Complexes 2 and 3 showed the occurrence of terminal CH_3 and CH_2 (methylene) in the range of 14.09 - 14.12 and 26.83 - 28.46 ppm respect-tively (Danish et al., 1995). Complex 4 revealed the chemical shifts of the $\delta(^{13}C)_{ipso}$ at 139.75 ppm indicative of a four-coordinated Sn atom (Holeček et al., 1983a, 1983b; Baul et al., 2001). Generally, the ^{1}H and ^{13}C NMR spectra of the complexes obtain are found to exhibit no additional resonance and thus reflects the purity of the complexes. The ^{1}H-^{13}C HMQC NMR spectra of acid, complexes 2 and 4 are depicted in Figures 2 – 4 as a representative.

For diorganotin (IV) carboxylate complexes, the $\delta(^{119}Sn)$ value for five-coordinated complexes between -90 to -190 ppm and for six-coordinated complexes between -210 to -400 ppm (Holeček et al., 1986). For complex 1, the $\delta(^{119}Sn)$ value was -137.25 ppm, indicating that the tin atom was five-coordinated. This is due to dilution; one of the bonds in complex 1 disassociated resulting to the tin atom exhibiting a five-coordinated geometry.

Complex 2 exhibited a well resolved resonance of $\delta(^{119}Sn)$ at -214.50 ppm respect-tively, indicating that the tin atom was six-coordinated. Complex 3 derivatives of the organodistannoxane dimer type exhibited two well resolved $\delta(^{119}Sn)$ signals attri-buted to the exo and endo-cyclic tin atoms (Danish et al., 1995). Complex 3 exhibited two well resolved signals, one lying in the range of a five-coordinated geometry and the other in the range of a six-coordinated geometry, indicating that the carboxylate anions remained in a bidentate manner in the coordination to the tin atoms in solution state.

Complex 4 showed that the $\delta(^{119}Sn)$ values at -127.33 ppm which lie in the range of -40 to -120 ppm [for triphenyltin(IV) complexes], hence, indicating that the tin atom in complex 4 is four-coordinated with a distorted tetrahedral geometry (Holeček et al., 1983a, 1983b). However, the $\delta(^{119}Sn)$ value of complex 4 obtained is slightly in the upfield region of -40 to -120 ppm and did not lie in the range of five-coordinated tin atom [-180 to -260 ppm for triphenyltin(IV) complexes] indicating the tin atom of complex 4 was still four-coordinated.

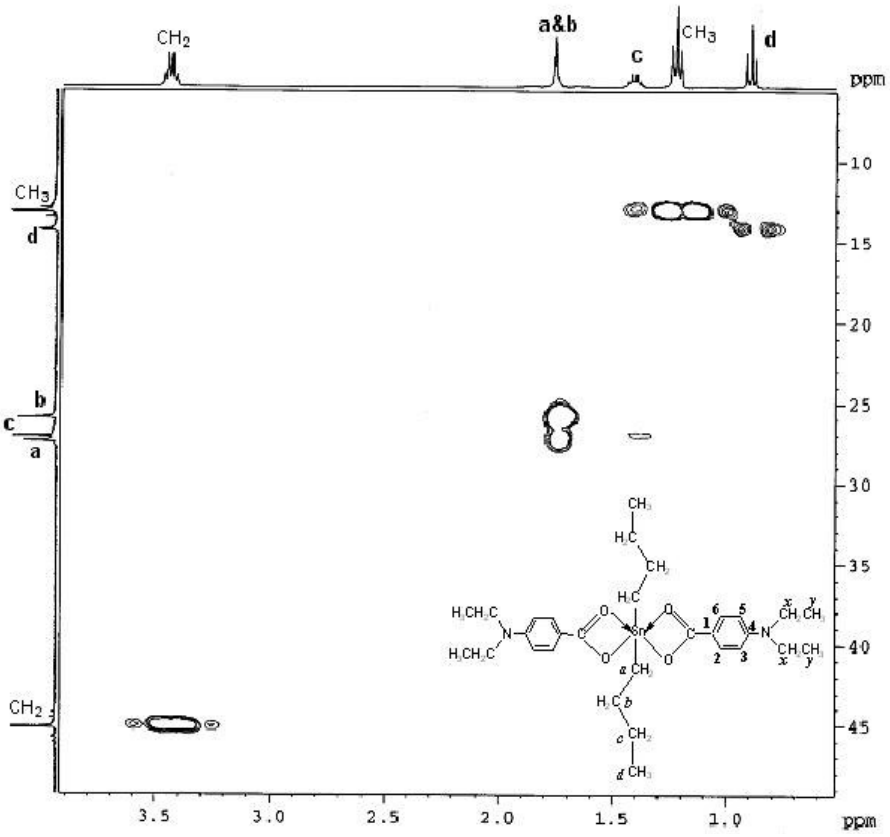

Figure 3. ^{1}H-^{13}C HMQC NMR spectrum of complex 2.

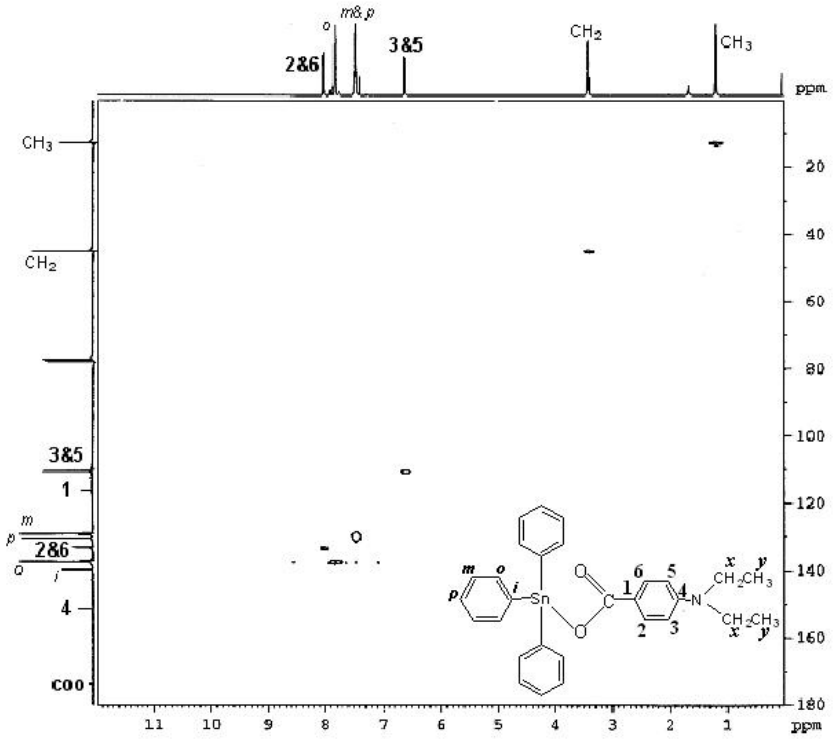

Figure 4. ^{1}H-^{13}C HMQC NMR spectrum of complex 4.

Table 1. *In vitro* antibacterial screening activity of parent acid and complexes 1 – 4.

Complexes	Inhibition Zone (mm)				
	Bacillus subtilis	***Escherichia coli***	***Klebsiella pneumoniae***	***Pseudomonas aeruginosa***	***Staphylococcus aureus***
Acid	-	-	-	-	-
1	16	17	23	18	21
2	15	7	8	-	16
3	14	6	-	-	13
4	19	7	-	-	16
Chloramphenicol	29	-	23	34	30
Doxycycline	34	24	21	40	28
Rifampicin	25	24	23	29	37

Agar well diffusion method (*in vitro*) = 1.0 mg/mL; Reference drug = Chloramphemicol, Doxycycline and Rifampicin.

In vitro antibacterial screening activity

The *in vitro* antibacterial screening activity of parent acid and complexes 1 - 4 are given in Table 1. Inhibition zones with a diameter less than 10 mm are considered as weak; larger than 10 mm but less than 16 mm are considered as moderate and finally larger than 16 mm and above are active (Chohan et al., 2006). Complex 1 is active to all bacterial strains especially against *S. aureus*. Meanwhile, complexes 2 - 4 are found to be significantly active against gram-positive bacterial strains. This contradicts the fact that the increase in the number of organo groups will in turn enhance the biological activity of organotin (IV) complexes. These significant activities of dimethyltin(IV) carboxylate complexes may be due to the ability of the anionic ligands which aid in the transportation of the active organotin(IV) cationic group to the cell or active site (receptor site) (Nath et al., 1999, 2005; Rehman et al., 2005).

The *in vitro* antibacterial activities of complex 2 was slightly higher compared to complex 3. This is because complex 3 is organodistannoxane dimers which is a bulky molecule and in turn restrict their mobility. At 1.0 mg/mL, complex 4 was found to be active against gram-positive bacterial strains such as *S. aureus* (16 mm) and *B. subtilis* (19 mm). However, complex 4 were found to be inactive against *P. aeruginosa* and *K. pneumoniae* bacterial strains. In addition, the adverse result of complexes 1 – 4 was clearly shown in the antibacterial screening against *S. aureus* bacterial strains. Data indicated that the dimethyltin(IV) carboxylate (1 = 21 mm) possessed a higher activity compared to the dibutyltin(IV) (2 = 16 mm and 3 = 13 mm) and triorganotin(IV) (4 = 16 mm) derivatives.

Again, this contradicts the fact that the increase in the number of organo groups enhances the biological activity of the organotin(IV) complexes. This observation may be due to the ability of the anionic ligands which aid the transportation of the active organotin(IV) cationic group to the cell (Nath et al., 1999, 2005; Rehman et al., 2005). Although complexes 1 - 4 showed significant activity on antibacterial screening study but their activities are lower compared to the reference drugs (antibiotic).

Conclusion

Complexes 1 - 4 have been successfully synthesized. The structural as well as the coordination number of tin moieties of complexes 1 - 4 have been successfully characterized quantitatively and qualitatively. Based on the *in vitro* antibacterial screening activity, complex 1 showed significant activity on all five tested bacterial strains compared to complexes 2 - 4 but lower activity compared to the reference drugs.

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