American Journal of Applied Sciences 7 (3): 301-308, 2010
ISSN 1546-9239

Synthesis and Characterization of Organotin(IV) Complexes Derived of 3-(Dimethylamino)benzoic Acid: Cytotoxic Assay on Human Liver Carcinoma Cells (HepG2)

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Abstract: Problem statement: Many studies have been carried out on organotin(IV) complexes derivative of carboxylate anions. However, the synthesis and characterization as well as the cytotoxic assay of organotin(IV) carboxylate derived of 3-(dimethylamino)benzoic acid have not been studied. **Approach:** Organotin(IV) carboxylate complexes derivative of 3-(dimethylamino)benzoic acid, 3-$[N(CH_3)_2]C_6H_4COOH$ have been successfully synthesized. Two types of diorganotin(IV) complexes, $[\{3\text{-}[N(CH_3)_2]C_6H_4COO(R)_2Sn\}_2O]_2$ dimer (R = methyl **1**, butyl **3**) and $\{3\text{-}[N(CH_3)_2]C_6H_4COO\}_2(C_4H_9)_2Sn$, **2** (monomer) as well as $3\text{-}[N(CH_3)_2]C_6H_4COO(C_6H_5)_3Sn$, **4** were successfully synthesized and obtained in solid state. The acid and complexes **1-4** obtained were characterized quantitatively using C, H, N and Sn elemental analysis as well as spectroscopic methods such as infrared (FTIR) and nuclear magnetic resonance (^1H, ^{13}C, ^1H-^{13}C HMQC and ^{119}Sn NMR). In addition, complexes **1-4** obtained were screened for their cytotoxicity activity against HepG2 cells line. **Results:** Infrared spectroscopy showed that the coordination took place via oxygen atoms from the carboxylate anions. This indicated that the carboxylate anion acts as monodentate ligand in complexes **2** and **4**. However, for distannoxane dimer (complexes **1** and **3**), the carboxylate anions are found to exhibit monodentate and bidentate manner. In ^{119}Sn NMR solution study, the tin atoms of complexes **1-3** were five-coordinated and four-coordinated in complex **4**. From the ^{119}Sn NMR, the tin atom of complex **2** was five-coordinated, this might be upon dilution, the crystal lattice were broken up resulting the carboxylate anions assembly self-arrangement. Hence, one of the carboxylate anions was located close to the tin atoms and exhibited bidentate chelation while the other carboxylate anion exhibited monodentate chelation in complex **2**. **Conclusion:** Pure complexes **1-4** have been successfully obtained and complex **4** possessed promising biological screening activity compared to the parent acid and complexes **1-3**.

Key words: Organotin(IV) carboxylate, preparation, biological activity

INTRODUCTION

Organotin(IV) complexes are extensively studied due to the applications in industrial as well as biocidal properties (Molloy *et al*., 1984; Willem *et al*., 1997; Gielen *et al*., 2000). Numerous studies on organotin(IV) complexes have been carried out in order to study its biological properties against bacterial, fungus and cancer cells line (Teoh *et al*., 1997; Novelli *et al*., 1999; Gielen *et al*., 2000; Crouse *et al*., 2004). Moreover, the biological activity of organotin(IV) carboxylate complexes are greatly influenced by the structure of the molecule as well as the coordination number of the tin moiety (Parulekar *et al*., 1990). The search for

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organometallic compounds as a new alternative drug in combating human cancers has been initiated due to certain side-effects of *cis*-platin and carboplatin as antitumour drugs (Khan *et al*., 2000). Hence, organotin(IV) compounds with general formula $R_2SnX_2.L_n$ or R_2SnL_2 (R = alkyl, aryl or phenyl, X = halogen, L = coordinated ligands and n = 1 or 2) belong to the largest group including organotin(IV) carboxylate complexes selected for the anti cancer screening (Gielen *et al*., 2000; Ronconi *et al*., 2002; Pruchnik *et al*., 2003). In fact, organotin(IV) complexes are extensively studied due to its coordination geometries as well as structural diversity (monomer, dimeric, hexameric and oligomeric) (Zhang *et al*., 2005; Win *et al*., 2007a; 2008a; Amini *et al*., 2009).

As part of our interest and research on organotin(IV) work, we have synthesized and characterized organotin(IV) complexes derived of 3-(dimethylamino)benzoic acid. In addition, the cytotoxic assay of the complexes obtained was screened against human liver carcinoma cells, HepG2 and the results are reported herein.

MATERIALS AND METHODS

General and instrumental: Triphenyltin(IV) hydroxide, Ph_3SnOH was purchased from Aldrich Chemical. Dibutyltin(IV) oxide, Bu_2SnO, dimethyltin(IV) dichloride, Me_2SnCl_2 and 3-(dimethylamino)benzoic acid, 3-$[N(CH_3)_2]C_6H_4COOH$ were obtained from Fluka Chemika. All reagents and solvents were purchased commercially and used without any further purification. 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 ^1H 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 300MHz FTNMR Spectrometer using deuterated $CDCl_3$ as the solvent and tetramethylsilane, TMS as the internal standard. 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. The melting points were determined in an open capillary and were uncorrected.

***In vitro* cytotoxic assay:** The *in vitro* cytotoxic assay was carried out on human liver carcinoma cells line, HepG2. The cells were maintained in Eagle's Minimum Essential Medium (MEM) supplemented with 2 mM of L-glutamine, 1 mM of sodium pyruvate, 0.1 mM of non-essential amino acid, 1.5 μg mL^{-1} sodium bicarbonate, 100 IU mL^{-1} penicillin and 100 μg mL^{-1} streptomycin. The cytotoxicity assay was determined using the microtitration 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay (Mosmann, 1983). The assay of each concentration for each compound was performed in triplicate. The fraction of surviving cells was measured relative to the untreated cell population by measuring the absorbance values at 570 nm with reference at 630 nm using an ELISA microplate reader (Bio Tek EL 340, USA). Cytotoxicity was expressed as fifty percent cytotoxic dose (IC_{50}), i.e., the concentration causing 50% inhibition of cell growth with reference to the control (untreated cells). The IC_{50} and the S.E.M. (standard error of the mean) were determined using Probit Analysis (SPSS, version 12.0.1).

Preparation of sodium salt and dimethyltin(IV) oxide, Me_2SnO: 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 mmole) and 3-(dimethylamino)benzoic acid, 3-$[N(CH_3)_2]C_6H_4COOH$ (0.50 g, 3 mmole) in ethanol (50 mL) for two hours. After a few days, white precipitates were obtained. Dimethyltin(IV) dichloride, Me_2SnCl_2 was dissolve in distilled water and stirred overnight which later gave colorless solution. Ammonia solution (60%) was added into the colorless solution and finally fine white precipitates were obtained, filtered and dried in oven (60°C) for a day.

Preparation of complexes:

Bis[3-(dimethylamino)benzoato]tetramethyldistannoxane(IV) dimer, $[\{3\text{-}[N(CH_3)_2]C_6H_4COO(CH_3)_2Sn\}_2O]_2$ (**1**)

Complex **1** was obtained by heating under reflux a 1:2 molar mixture of dimethyltin(IV) oxide (0.49 g, 3 mmole) and 3-(dimethylamino)benzoic acid (0.99 g, 6 mmole) in methanol (50 mL) for two hours. A clear brown transparent solution was isolated by filtration and kept in a bottle. After few days, brown solids (0.59 g, 61.3% yield) were collected.

Bis{3-(dimethylamino)benzoato}dibutyltin(IV), $\{3\text{-}[N(CH_3)_2]C_6H_4COO\}_2(C_4H_9)_2Sn$ (**2**)

This complex was obtained by heating under reflux a 1:2 molar mixture of dibutyltin(IV)oxide, (0.75 g, 3 mmole) and 3-(dimethylamino)benzoic acid, (0.99 g, 6 mmole) in acetonitrile (60 mL) for four hours. A clear brown solution was separated by filtration and kept in a

bottle. After two weeks, some brown crystals (1.31 g, 74.0% yield) were collected.

Bis[3-(dimethylamino)benzoato]tetrabutyldistannoxane (IV) dimer, $[\{3\text{-}[N(CH_3)_2]C_6H_4COO(C_4H_9)_2Sn\}_2O]_2$ (**3**)

This title complex was prepared by similar method to those described for complex **1**, except substituting with Bu_2SnO and the reaction was heating under reflux for three hours. After five days, brown crystals (2.14 g, 66.1% yield) were collected.

3-(dimethylamino)benzoatotriphenyltin(IV), $3\text{-}[N(CH_3)_2]C_6H_4COO(C_6H_5)_3Sn$ (**4**)

Complex **4** was prepared by heating under reflux a 1:1 molar mixture of triphenyltin(IV) hydroxide (1.10 g, 3 mmole) and 3-(dimethylamino)benzoic acid (0.50 g, 3 mmole) in acetonitrile (50 mL) for two hours. Clear brown solution was isolated by filtration and kept in a bottle. After eight days, brown crystals (1.01 g, 65.7% yield) were collected.

RESULTS

Physical and elemental analysis: An outline of the proposed structure for complexes **1-4** are depicted in Fig. 1. The melting points and elemental analytical data of complexes **1-4** are given in Table 1.

Structural and cytotoxic assay: The characteristic infrared absorption frequencies (cm^{-1}) and assignments of important absorption bands of the acid, sodium salt and complexes **1-4** are listed in Table 2. The ^1H NMR spectral data of complexes **1-4** are summarized in Table 3, ^{13}C and ^{119}Sn NMR data are listed in Table 4. From the spectroscopy methods, the structure of complexes **1-4** are characterized and the cytotoxic activity of complexes **1-4** are given in Table 5.

Table 1: Melting points and elemental analytical data (%) of complexes **1-4**

		Elemental (%)			
Complexes	Melting points	C	H	N	Sn
1	246.3-247.8	41.11 (41.17)	5.02 (5.03)	4.23 (4.36)	36.50 (36.98)
2	113.3-114.1	55.63 (55.64)	6.77 (6.82)	4.90 (4.99)	20.75 (21.15)
3	137.3-138.2	50.62 (50.40)	6.52 (6.97)	3.44 (3.46)	29.53 (29.30)
4	140.2-141.5	63.05 (63.07)	4.91 (4.90)	2.67 (2.72)	23.00 (23.08)

Calculated value are given in parentheses

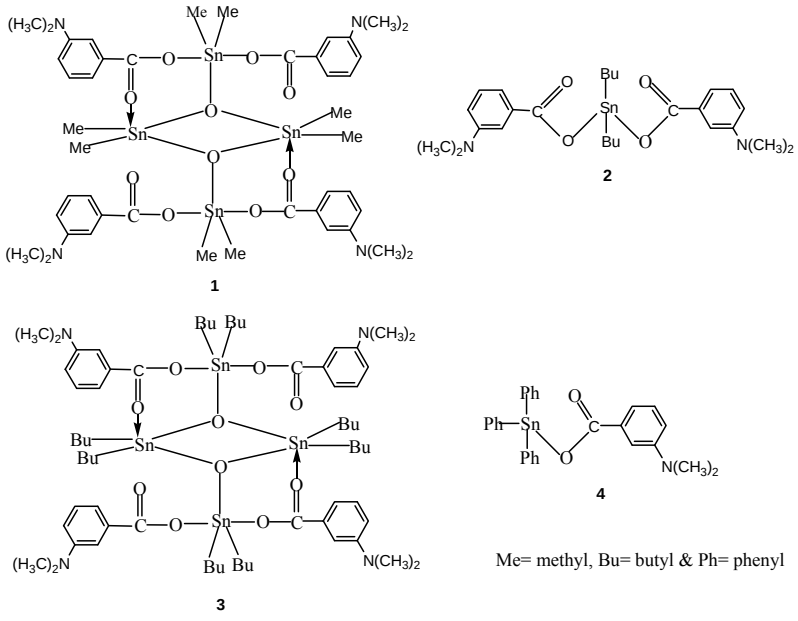

Fig. 1: The proposed structure for complexes **1-4**

Table 2: Important infrared data of acid, salt and complexes **1-4**

	Wavelength (cm^1)						
Complexes	ν(OH)	ν(COO)as	ν(COO)s	Δν	ν(Sn-O)	ν(O-Sn-O)/ν(Sn-O-Sn)	ν(Sn-C)
Acid	2885-2544	1677	1360	317	-	-	-
Salt	-	1569	1387	2182	-	-	-
1	-	1597	1333	264	426	658	575
		1541	1365	176			
2	-	1608	1360	248	459	679	551
3	-	1595	1330	265	420	635	572
		1573	1368	205			
4	-	1625	1322	303	445	-	-

$\Delta\nu = \nu(COO)_{as}-\nu(COO)_{s}$

Table 3: ^{1}H NMR data of acid and complexes **1-4**

	Chemical shift, δ(ppm)		
Compounds	Benzene	Amino-$N(CH_3)_2$	Sn-R (R = Me, Bu and Ph)
Acid	7.00 (d, 9.3 Hz, 1H) H4	3.03 (s, 6H) Hy	-
	7.35 (t, 8.1 Hz, 1H) H5		
	7.54 (d, 7.8 Hz, 2H) H2 & H6		
1	6.93 (d, 8.0 Hz, 4H) H4	3.04 (s, 24H) Hy	0.97 (s, 12H) Ha
	7.33 (t, 7.6 Hz, 4H) H5		1.06 (s, 12H) Ha
	7.40 (d, 7.7 Hz, 8H) H2 & H6		
2	6.94 (dd, 2.4 Hz, 7.9 Hz, 2H) H4	3.01 (s, 12H) Hy	0.88 (t, 7.3 Hz, 6H) Hd
	7.33 (t, 8.0 Hz, 2H) H5		1.34-1.44 *(m, 4H) Hc
	7.50 (d, 8.5 Hz, 4H) H2 & H6		1.69-1.84 *(m, 8H) Ha & Hb
3	6.94 (d, 6.8 Hz, 4H) H4	3.04 (s, 24H) Hy	0.81-0.93 *(m, 24H) Hd
	7.34 (t, 7.3 Hz, 4H) H5		1.32-1.45 *(m, 16H) Hc
	7.43 (d, 7.5 Hz, 8H) H2 & H6		1.71-1.78 *(m, 32H) Ha & Hb
4	6.87 (dd, 2.7 Hz, 8.3 Hz, 1H) H4	2.95 (s, 6H) Hy	7.42-7.49 *(m, 9H) H*m* & H*p*
	7.26 (t, 7.8 Hz, 1H) H5		7.79-7.81 *(m, 6H) H*o*
	7.52 (d, 7.6 Hz, 2H) H2 & H6		

s: Singlet; d: Doublet; t: Triplet; dd: Doublet of doublet; m: Multiplet; o: Ortho; m: Meta; p: Para; Coupling constant: Hz, *: overlap

Table 4: ^{119}Sn and ^{13}C NMR data of complexes **1-4**

	Chemical Shift (ppm)				
Compounds	^{119}Sn	Benzene	Amino $N(CH_3)_2$	Sn-R (R = Me, Bu and Ph) $^nJ(^{119}Sn-^{13}C)$ (n = 1, 2, 3 and 4)	COO
Acid	-	114.11 (C2), 118.06 (C4),	40.97 (Cy)	-	
	173.29				
		118.69 (C6), 129.53 (C5),			
		130.37 (C1), 150.87 (C3)			
1	-178.82	113.70 (C2), 116.30 (C4),	40.89 (Cy)	7.40 (^{1}J = 779.3 Hz) (Ca)	173.8
	-183.19	118.05 (C6), 128.83 (C5),		9.40 (^{1}J = 795.3 Hz) (Ca)	
		133.66 (C1), 150.90 (C3)			
2	-156.4	114.42 (C2), 117.40 (C4),	41.02 (Cy)	13.98 (Cd), 25.85 (Cb)	
	177.25				
		119.02 (C6), 129.36 (C5),		26.82 (Cc), 27.11 (Ca)	
		131.09 (C1), 150.86 (C3)			
3	-195.35	114.29 (C2), 116.42 (C4),	41.09 (Cy)	14.04 (Cd),	
	173.79				
	-207.95	118.58 (C6), 129.11 (C5),		26.84 (Cc), 27.26 (Cc), 27.96 (Cb),	
		131.52 (C1), 150.90 (C3)		28.24 (Cb), 29.06 (Ca), 30.99 (Ca)	
4	-114.19	114.84 (C2), 117.18 (C4),	41.04 (Cy)	139.01 (^{1}J = 648.9 Hz) (Ci),	
	174.05				
		119.31 (C6), 129.57 (C5),		137.36 (^{2}J = 47.9 Hz) (Co),	
		134.59 (C1), 150.85 (C3)		129.31 (^{3}J = 63.2 Hz) (Cm),	
				130.51 (Cp)	

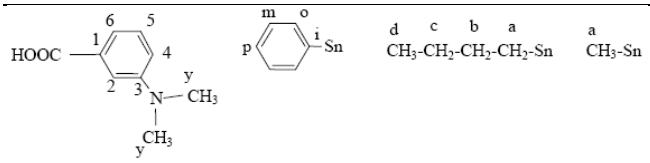

Table 5: Cytotoxicity assays, IC_{50} of acid and complexes **1-4**

Complexes	IC_{50} (μg mL^{-1}) Human liver hepatocellular carcinoma cells, HepG2
Acid	Inactive (start at 1.0)
1	Inactive (start at 1.0)
2	0.602±0.033
3	0.541±0.027
4	0.153±0.010
Vincristine sulphate	0.042±0.013

IC_{50} (μg mL^{-1}): The concentration that yields 50% inhibition of the cell compared with untreated control. The cytotoxicity values are expressed as mean ± S.E.M. from the triplicate. Reference drug = Vincristine sulphate

DISCUSSION

In this study, complexes **1-4** derived of 3-$[N(CH_3)_2]C_6H_4COOH$ have been obtained in solid state. Complexes **2** and **4** were obtained as single brown crystals and the X-ray crystal structure of both complexes have been reported (Win *et al*., 2007b; 2008b). Elemental analysis C, H, N and Sn data obtained were in agreement with the predicted formula and complexes **1-4** gave a sharp melting points which indicate the isolation of fairly pure complexes.

The ν(O-H) bands which appeared in the range 2885-2544 cm^{-1} for the acid, were absent in the infrared spectra of salt and complexes **1-4** also showed the deprotonation and coordination of the carboxylate anion. The infrared spectra of 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.

The magnitude of $\Delta\nu = [\nu(COO)_{as}-\nu(COO)_s]$ is a useful indicator in the correlation of the coordination modes of the carboxylate anion to the tin atoms. Sandhu and Verma (1987) have shown that the Δν value of complexes greater by 65-90 cm^{-1} than in their sodium salts indicates either asymmetric or monodentate bonding of the carboxylate group to tin(IV) atom. Complex **2** was isolated as a monomer type and its Δν value indicated that the carboxylate anions were bonded to tin atom moiety in a monodentate mode. Two Δν values for the organodistannoxane dimer type complexes indicate that the carboxylate anions were coordinated to the tin atom moiety in either a monodentate or bidentate manner (Win *et al*., 2008a). For complex **1**, the first Δν value (264 cm^{-1}) was larger than the Δν value of the sodium salt while the second Δν value (176 cm^{-1}) was comparable to the sodium salt (182 cm^{-1}). Hence a pair of carboxylate anions bonded to tin atom in monodentate manner and another pair of carboxylate anions bonded to tin atom in bidentate manner respectively resulting the tin atoms in complex **1** exhibited distorted trigonal bipyramid geometry. Complex **3** was also isolated as bulky organodistannoxane dimer types and were found to be similar to complex **1**. Moreover, 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, carboxylate anion in complex **4** would be expected to bond to the tin atom in monodentate manner since the Δν above 200 cm^{-1}.

Further evidence for the coordination to Sn via O atoms was revealed by the presence of the Sn-O stretching bands in the spectra of complexes **1-4** in the region of 459-420 cm^{-1}. The presence of a medium absorption band at 679-635 cm^{-1} in the infrared spectra of complex **1-3** was ascribed to ν(Sn-O-Sn)/ν(O-Sn-O) which further supported the coordination of the oxygen atoms to the tin atom moiety (Gielen *et al*., 1989; Win *et al*., 2008a). Generally, ν(Sn-O-Sn) band was fit in the assignment of additional Sn-O bonding in organodistannoxane dimer type since the centrosymmetry of the complexs were occupied by Sn_2O_2 (complexes **1** and **3**).

The ^1H NMR spectra of complexes **1-4** revealed similarities to their parent acid, 3-(dimethylamino)benzoic acid. The ^1H NMR spectrum of 3-(dimethylamino)benzoic acid exhibited three sets of signals at downfield region [7.00 ppm, 7.35 ppm and 7.54 ppm] with integration values of 1:1:2 which was also observed in the ^1H NMR spectra of complexes **1-4** arising from the aromatic protons of the benzene ring. The upfield regions of the ^1H NMR spectra of the complexes **1-3** showed the signal of the methyl and butyl protons in the range of 0.97-1.11 and 0.88-1.78 ppm respectively. Complexes **2** and **3** consisted of dibutyl groups (monomer and distannoxane dimer types) and found in the upfield region in the NMR spectra. Theoretically, the butyl groups should exhibit four signals corresponding to the protons of butyl groups, with multiplicities of triplet, sextet, quintet and triplet with integration values of 3:2:2:2, respectively. However, these complexes only exhibited three sets of signals in the range of 0.81-0.93 ppm (CH_3, triplet or multiplet), 1.32-1.45 ppm (CH_2, multiplet) and 1.69-1.84 ppm (CH_2, multiplet) respectively, due to the methylene protons having very similar environment causing their signals to overlap with each other in the ^1H NMR spectra (Danish *et al*.,

1995; Teoh *et al*., 1996a; 1996b). Complex **1** was derived from dimethyltin(IV) complexes and isolated as an organodistannoxane dimer type and exhibited two sharp singlets at 0.97 and 1.06 ppm which corresponded to the methyl groups attached to the tin atom moiety. For complex **4**, the occurrence of multiplets in the regions centering around δ≈7.45 and 7.80 ppm with integration values of 9:6 respectively were ascribed to the aromatic protons of the phenyl group (Sau and Holmes, 1981; Willem *et al*., 1997; Nath *et al*., 2006).

The formation of the complexes were evident from the δ(COO) value in the ^{13}C NMR spectra. All the complexes exhibited a δ(COO) signal in the range of 173.80-177.25 ppm. The ^{13}C NMR spectra of complexes **1-4** showed that the chemical shift of the δ(COO) signal in each complex was shifted downfield compared to that of their parent acids (173.29 ppm), indicating the participation of the carboxylate anions in the coordination to the tin(IV) atom (Win *et al*., 2007b; 2008a). The occurrence of six resonances in the range of 114.11-150.90 ppm and a single resonance in the range of 40.89-41.09 ppm in the ^{13}C NMR spectra of the complexes and acid defined as benzene and -methylamino carbons signals respectively. Complex **1** (organodistannoxane dimer type) exhibited two sharp signals at 7.40 and 9.40 ppm indicating the presence of the methyl groups in the $SnMe_2$ moiety with $^1J(^{119}Sn-^{13}C)$ satellites values at 779.3 and 795.3 Hz (Careri *et al*., 1989; Gomez *et al*., 2003). Together with the application of the Lockhart-Manders equation, [$|^1J| = 11.4\theta-875$]; the C-Sn-C angles were 145.1 and 146.5° (Lockhart and Manders, 1986). With the help of the ^{119}Sn solution studies, the tin atoms in complex **1** were confirmed to be five-coordinated and each exhibited a distorted trigonal bipyramid geometry. Complexes **2** and **3** were derivative of dibutyltin(IV) showed the occurrence of CH_3 and CH_2 in the range of 13.98-14.04 and 25.85-30.99 ppm respectively (Danish *et al*., 1995; Win *et al*., 2008a). In addition, complex **3** exhibited two sets of butyl signals in ^{13}C NMR spectra which attributed to the butyl groups linked to the exo- and endo-cyclic tin atom respectively. Complex **4** revealed the chemical shifts of the $\delta(^{13}C)_{ipso}$ at 139.01 ppm indicative of a four-coordinated Sn atom (Holecek *et al*., 1983a; 1983b; Baul *et al*., 2001).

The $\delta(^{119}Sn)$ values define the region with different coordination number of the tin atom moiety and the $\delta(^{119}Sn)$ values are summarized in Table 4. For diorganotin(IV) carboxylate complexes, the $\delta(^{119}Sn)$ value for four-coordinated complexes fall in the range between +200 to -60 ppm; for five-coordinated complexes between -90 to -190 ppm and for six-coordinated complexes between -210 to -400 ppm (Holecek *et al*., 1986). Complex derivatives of the organodistannoxane dimer types usually exhibit two well resolved $\delta(^{119}Sn)$ signals. These two low- and high-field resonances were respectively attributed to the exo-and endo-cyclic tin atoms (Danish *et al*., 1995). From Table 4, the exo- and endo-cyclic tin atoms in complexes **1** and **3** were five-coordinated respectively. This indicated that a pair of carboxylate anions was bonded to the tin atom in a monodentate manner while the other two carboxylate anions were bonded to the tin atoms (endo and exo-cyclic tin atom) in a bridging bidentate manner. As a result, all the tin atoms in complexes **1** and **3** were five-coordinated and exhibited a distorted trigonal bipyramid geometry. Complex **4** derivatives of triphenyltin(IV) exhibited $\delta(^{119}Sn)$ values at -114.19 ppm which lie in the range of -40 to -120 ppm, hence, indicating that the tin atom in complexes **4** was four-coordinated and have a distorted tetrahedral geometry (Holecek *et al*., 1983a; 1983b). From the ^{119}Sn NMR solution study, the tin atom of complex **2** was five-coordinated (predominantly). Moreover, based on the infrared spectroscopy and single crystal X-ray structure determination, complex **2** was pure and the tin atom was four-coordinated and existed in a distorted tetrahedral geometry (Win *et al*., 2007b). This might be upon dilution, the crystal lattice were broken up resulting the carboxylate anions assembly self-arrangement (in dynamic state). Hence, one of the carboxylate anions was located close to the tin atoms and exhibited bidentate chelation while the other carboxylate anion exhibited monodentate chelation resulting five-coordinated tin atom in complex **2**.

The IC_{50} values for the acid and complexes **1-4** are given in Table 5. From the data in Table 5, it was found that 3-(dimethylamino)benzoic acid and complex **1** are inactive against HepG2 cells compared to complexes **2-4**. Complex **4** showed a significant cytotoxic activity with a lower IC_{50} value of 0.153 μg mL^{-1} compared to complexes **2** (0.602 μg mL^{-1}) and **3** (0.541 μg mL^{-1}). This was due to complex **4** was derived from triphenyltin(IV) (triorganotin) which is more active compared to the diorganotin(IV) derivatives (complexes **1-3**). In addition, complex **4** existed as monomer and the tin moiety was four-coordinated with distorted tetrahedral geometry consequently enhanced the cytotoxic activity (Ashfaq *et al*., 2004). Hence the biological activities of organotin(IV) obtained in this present study could be arranged as: Triorganotin(IV) > diorganotin(IV).

CONCLUSION

Complexes **1-4** derivative of 3-(dimethylamino)benzoic acid have been successfully synthesized and characterized. Elemental analysis C, H,

N and Sn data obtained were in agreement with the predicted formula. Results of the infrared and NMR spectroscopy on the acid and complexes showed that the coordination took place via oxygen atoms from the carboxylate group. As a result, in solid and liquid state, the tin atoms of complexes **1** and **3** are five-coordinated whereas four-coordinated in complex **4**. With the exceptional case, the tin atom in complex **2** is four-coordinated in solid state and exhibited five-coordinated in solution which may attributed from the dynamic stage and self-rearrangement of one carboxylate anion. Based on the cytotoxic activity, complex **4** showed significant cytotoxic activity compared to complexes **1-3** but lower compared to reference drug and believed to possess a significant role in the medicinal area in the future.

ACKNOWLEDGEMENT

We would like to thank University Tunku Abdul Rahman and University Sains Malaysia and for financial support and technical assistance.

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