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Synthesis, Characterisation and Antibacterial Activity of New Diorganotin(IV) Bis(2-Methoxyethyl)dithiocarbamate Complexes.

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ABSTRACT

The strong and selective biological activities induced by the organotin(IV) and dithiocarbamate derivatives in pathogenic microorganisms could probably lead to the new formulation of antimicrobial drugs for therapeutic application. In this study, two new diorganotin(IV) dithiocarbamate complexes of the type R_2SnL_2 (R = CH_3 or C_6H_5; L = bis(2-methoxyethyl)dithiocarbamate) were synthesised with good yields. Both complexes were prepared using an *in situ* method and suitably characterised by elemental analysis, FT-IR, ^{1}H, ^{13}C, and ^{119}Sn NMR spectroscopes. Elemental analysis data (carbon, hydrogen, nitrogen, and sulphur) showed an agreement with the suggested formula structures. The infrared spectra of these complexes showed three important peaks for ν(C=N), ν(C=S) and ν(Sn-S) in the region of 1482–1489, 985–987 and 386–425 cm^{-1}, respectively. Data for ^{13}C NMR spectroscopy showed an important peak in the region of 200 ppm that corresponded to the NCS_2 group. The ^{119}Sn NMR expected the six coordinated tin atom in both complexes. These complexes were evaluated for their antibacterial activities and showed good activities towards *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Keywords: organotin(IV), dithiocarbamate, antibacterial, *Staphylococcus aureus, Pseudomonas aeruginosa*

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INTRODUCTION

Organotin(IV) compounds have attracted much attention owing to their potential biocidal activities besides their potential industrial and agricultural applications. In general, the biochemical activity of organotin(IV) compounds is influenced greatly by the structure of the molecule and the coordination number of the tin atoms [1]. The toxicity towards microorganisms depends on the number and nature of the organic groups bonded to the metal centre, which, in general, decreases in the order $R_3SnX > R_2SnX_2 > RSnX_3$. However, the order of toxicity depends on the microorganism and varies from strain to strain [2].

Well-documented in the field of coordination chemistry, dithiocarbamates are a class of metal-chelating, antioxidant compounds with various applications in medicine for the treatment of bacterial and fungal infections and possible treatments of AIDS [3]. Apart from the ability to stabilise metal cations in a variety of oxidation states, the dithiocarbamate ligand is also known for its applications in pharmaceuticals. This ligand is used to remove excess of copper due to Wilson's disease and is also able to reduce the nephrotoxicity of platinum-based drug used in chemotherapy [2].

Metal dithiocarbamates have encouraged a lot of interests due to their structural chemistry and biocidal applications [4]. Dithiocarbamates with organotin(IV) are among the metal dithiocarbamates that have been studied extensively for their wide applications in biology and agriculture as well as in catalysis and for organic syntheses [5]. Organotin complexes have received much attention because of their extensive and potential therapeutic use as antifungal, antibacterial, and antitumoural, antimalarial, and schizonticidal agents [4]. In view of the wide-range applications of organotin(IV) dithiocarbamate complexes, we report in this article the synthesis, characterisation, and antibacterial activity of two new complexes namely dimethyltin(IV) and diphenyltin(IV) with bis(2-methoxyethyl)dithiocarbamate ligand.

MATERIALS AND METHODS

Materials

The secondary amine, bis(2-methoxyethyl) amine and diorganotin(IV) chloride were purchased from Sigma Aldrich; carbon disulphide and chloroform were purchased from Merck; and ethanol was purchased from Marcon. All the chemicals were used without purification.

Instrumentations

The melting points were determined in open capillary tubes using an electrothermal 9300 digital melting point apparatus. The percentage compositions of the elements carbon, hydrogen, nitrogen, and sulphur were determined using an elemental analyser CHNS-O Model LECO 932. Solid state infrared spectra of the compounds were recorded in the range of 4000–370 cm^{-1} and 350–200 cm^{-1}. The infrared spectra were recorded as potassium bromide discs using a Perkin-Elmer Spectrum GX and Perkin-Elmer Spectrum BX. The ^{1}H, ^{13}C, and ^{119}Sn nuclear magnetic resonance spectra were recorded in DMSO and $CDCl_3$ using BRUKER Avance lll 400. Tetramethylsilane was used as an internal standard.

Synthesis of Organotin(IV) Dithiocarbamate Complexes

Organotin(IV) dithiocarbamate complexes were prepared by adding the diorganotin(IV) dichloride (0.01 mol) in ethanol into ligand-containing solution of bis(2-methoxyethyl)amine (0.01 mol). The reaction mixture was then stirred. The white powder products were filtered and washed with cold ethanol and then dried in a desiccator. The general reaction scheme for the synthesis of dimethyltin(IV) and diphenyltin(IV) with bis(2-methoxyethyl)dithiocarbamate is shown in Figure 1.

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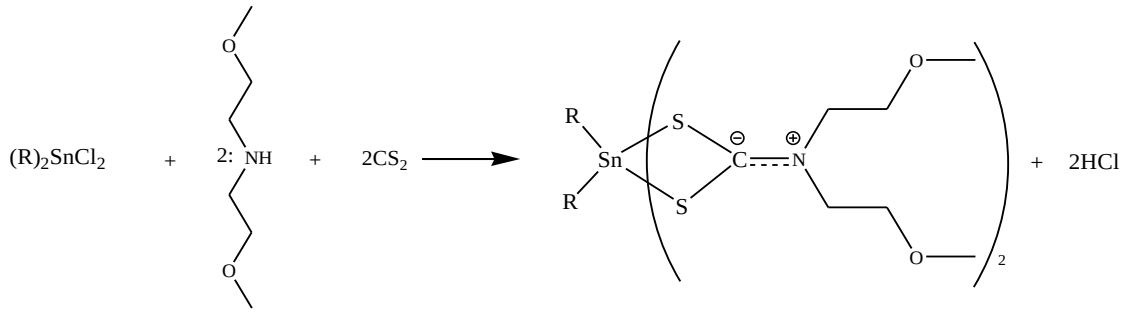

R= CH_3 and C_6H_5

Figure 1 Reaction scheme of complex 1 (R=methyl) and complex 2 (R=phenyl)

Antibacterial Activity

Microorganism: The microorganisms were obtained from the culture collection of the Department of Biomedical Science, Faculty of Health Sciences, Universiti Kebangsaan Malaysia. The stock cultures were grown on Mueller-Hinton agar for bacteria. The microbial strains were *Staphylococcus aureus* (ATCC 25923), *Klebsiella pneumoniae*, *Enterobacter aerogenes* (ATC 51697), *Enterobacter raffinosus* (ATCC 49464), and *Pseudomonas aeruginosa* (ATCC 27853).

Assay for Antibacterial Activity

Disc Diffusion Method: Antibacterial activity of the complexes 1 and 2 was tested using disc diffusion (Kirby-Bauer) method according to Bou (2007), which is a recommended standard of Clinical Laboratory Standard Institute. The discs (6 mm in diameter) were prepared by impregnating them with 10 µL of each compound solution (10 mg/mL), and the solvent was allowed to dry off in an aseptic hood until the discs contained 100 µg of compound. The discs were then evenly spaced on the agar surface previously inoculated with the suspension of each microbe (10^6–10^8 CFU/mL) to be tested. Standard disc of ampicillin (10 µg/mL per disc) was used as a positive control, while 5% DMSO disc was used as a negative control. The plates were incubated at 37 °C for 24 h. The antimicrobial activity was recorded by measuring the diameter of the clear inhibition zones around each disc. Each assay in this experiment was repeated in triplicate.

RESULTS AND DISCUSSION

Synthesis

Organotin(IV) dithiocarbamate complexes were prepared by using direct reaction between 0.01 mol carbon disulphide and an ethanolic solution of bis(2-methoxyethyl)amine (0.01 mol). The reaction mixture was then stirred for 1 h at 277 K temperature and organotin(IV) (0.005 mol) in ethanol added dropwise to the solution. The precipitates formed were filtered and washed with cold ethanol and then dried in desiccator. Both complexes formed as white powders, were stable in air and highly soluble in dimethylsulfoxide and chloroform. The elemental analysis (C, H, N, and S) showed that the experimental values were in agreement with the theoretical values based on their chemical formula (see Table 1).

Table 1: Physical and elemental analysis data of complexes 1 and 2

Complex	Yield (%)	Melting point (°C)	Elemental analysis % Found (% Calculated)			
			Carbon	Hydrogen	Nitrogen	Sulphur
1	54	**62.1-63.8°C**	34.06 (33.99)	7.00 (6.06)	5.23 (4.95)	22.78 (22.68)
2	76	**59.6-62°C**	47.17 (45.29)	6.62 (5.55)	4.20 (4.06)	18.84 (18.60)

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Infrared Spectroscopy

The important infrared absorption bands of complexes **1** and **2** are presented in Table 2. The presence of thioureide band of the chelated dithiocarbamates can be found in the region 1,470–1,500 cm^{-1} [6]. The infrared spectra of both diorganotin(IV) bis(2-methoxyethyl)dithiocarbamate showed an intense peak in the region 1,482–1,489 cm^{-1}, thus confirming the presence of chelated dithiocarbamates.

The band at around 985 cm^{-1} can be assigned to the C=S stretching frequency. The monodentate or bidentate nature of the dithiocarbamate ligand can be determined by the presence of a single or double ν(C=S) peak. A bidentate chelate shows only one intense band as both sulphur atoms are bonded to the metal centre rendering both the C-S bonds almost equivalent [7]. The infrared spectra of both complexes showed a single peak at 985–987 cm^{-1}, indicating that the bis(2-methoxyethyl)dithiocarbamate ligands bond as bidentate chelate [7]. Other than the stretching bands C- N and C-S, the Sn-sulphur coordination is supported by the presence of a new medium to weak absorptions in the region 386–425 cm^{-1} [4]. In the spectra, this peak was observed at 381–407 cm^{-1}. The vibration band due to Sn-C stretching usually appeared in the region 475–625 cm^{-1}, indicating that that the tin metal is still in contact with the organic groups [8]. This peak was observed at 513–571 cm^{-1}.

Table 2: IR spectra data of complexes 1 and 2

Complex	IR spectra (cm^{-1})				
	ν(C-N)	ν(C=S)	ν(C-H)	ν(Sn-C)	ν(Sn-S)
1	1,489	987	2,885	513	407
2	1,482	985	2,988	571	381

NMR Spectroscopy

^1H NMR spectra for both complexes were recorded in DMSO and $CDCl_3$ solution, respectively, and tetramethylsilane was used as an internal standard at room temperature. The proton of methoxy group for both complexes exhibited sharp singlet signals at 3.252 and 3.352 ppm (see Table 3). The protons of ethylene group, N-CH_2 and –CH_2 attached to nitrogen atom exhibited singlet signals at 3.568 and 3.987 for dimethyltin(IV) complex and triplet signals at 3.770 and 4.065 for diphenyltin(IV) complex. The methyl protons attached to tin atom in dimethyltin(IV) complex exhibited a sharp singlet signal at 1.407 ppm. A multiplet was observed at 7.38–7.89 ppm corresponding to the presence of aromatic protons in diphenyltin(IV) complex. The position of methyl and aromatic protons was in agreement with reported data [9].

Table3: ^1H NMR data of complexes 1 and 2

Complex	^1H NMR (ppm)			
	Sn-R (R= C_4H_9, C_6H_5)	N-CH_2	O-CH_2	O-CH_3
1	CH_3: 1.407 (3H)	3.568 (2H)	3.987 (2H)	3.252(3H)
2	$CH_{aromatic}$: 7.38–7.892 (5H)	3.770 (2H)	4.065 (2H)	3.352 (3H)

The important data of ^{13}C NMR of these complexes are depicted in Table 4. The ^{13}C NMR spectra exhibited signals for the carbon of N(CH_2) at 55.01 (complex 1) and 56.72 (complex 2) ppm, while the methylene carbon bound to the oxygen atom was found to resonate at 58.74 and 59.02 ppm in complex 1 and 2, respectively. The CS_2 resonances were observed at 200.8 and 200.16 ppm, clearly indicating the chelation of tin [9]. The signals for the O-CH_3 carbon resonated accordingly at 58.74 and 59.02 ppm in both complexes. Methyl carbon attached to the tin atom appeared at 18.38 ppm. The signal appearing at the region 128.26–150.89 ppm was assigned to the aromatic carbons attached to the tin atom of complex 2 [9].

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Table 4: ^{13}C NMR data of complexes 1 and 2

Complex	Chemical shift, δ (ppm)				
	$N^{13}CS_2$	O-CH_3	Sn-R (R=C_4H_9 or C_6H_5)	-O-CH_2-	-N-CH_2-
1	200.8	58.74	18.38	69.18	55.01
2	200.16	59.02	128.26, 134.28, 135.77, 150.89	69.90	56.72

The ^{119}Sn NMR spectra of the compounds at room temperature showed a sharp signal in the case of dimethyltin complex, while diphenyltin complex showed more than one sharp signal. In the later, an associated structure namely stereoisomer species was present in solution similar to the spectra reported by [10]. The single signal appeared at −380.96 ppm in complex 1, while in complex 2, the signal appeared at −321.54 and −491.69 ppm. Both spectra showed that the tin atom is six coordinated at room temperature in both complexes [1]. Table 5 shows the chemical shift for ^{119}Sn NMR.

Table 5: ^{119}Sn NMR data for complexes 1 and 2

Complex	Chemical shift, δ (^{119}Sn)
1	−380.96
2	−321.54, −491.69

Antibacterial Activity

Antibacterial activity of the complexes was screened using disc diffusion method. The formation of inhibition zone was observed and measured from the filter paper as a result of the antibacterial activity by the compounds. Based on the size of inhibition zone, the complexes were categorised into weak inhibition (1–9 mm), medium inhibition (10–14 mm), or strong inhibition (15–19 mm) [11]. The complexes that inhibited the tested microbe with the size of zone of inhibition of more than 15 mm were considered to have an active antimicrobial activity [12, 13].

Table 5 shows the diameter of zone of inhibition for complex 1 and 2 against the bacteria tested. Based on the inhibition zones, complex 2 showed a promising antibacterial activity against the tested isolates. Complex 2 had a strong inhibition activity towards *S. aureus* with the diameter of zone inhibition of more than 15 mm and had a bigger zone than the commercial antibiotic ampicillin against *P aeruginosa*. The inhibition activity of complex 1 was also in good agreement with the previous study, but with better antibacterial activity compared to some complexes reported in the study on the same type of *S. aureus* [8,14] and *P. aeruginosa* [15]. Meanwhile, complex 2 exhibited a weak inhibition against *S. aureus* and *P. aeruginosa* with an inhibition zone of less than 10 mm. However, these two complexes were not active against three types of bacteria (*K. pneumoniae*, *E. aerogenes*, and *E. raffinosus).* Dissimilarities of bioactivity formed by the complexes indicated that some of them were specific to certain groups of bacteria [14].

Table 6: Inhibition zone of complexes 1 and 2 against tested bacteria

Strain	Inhibition Zone (mm)		
	Positive control (ampicillin 10 mg/mL)	Complex 1	Complex 2
S. aureus (ATCC 25923)	36.7 ± 0.115	9.0 ± 0.173	16.3 ± 0.709
K. pneumoniae	9.7 ± 0.058	NA	NA
E. aerogenes (ATCC 51697)	14.0 ± 0.1	NA	NA
E. raffinosus (ATCC 49464)	19.7 ± 0.058	NA	NA
P. aeruginosa (ATCC 27853)	8.7 ± 0.84	9.7 ± 0.07	7.0 ± 0.0

NA= No inhibition zone detected

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CONCLUSION

Two new organotin(IV) complexes with ligand bis(2-methoxyethyl)dithiocarbamate were successfully synthesised and characterised. Spectroscopic analyses suggested that both complexes were chelated via bidentate coordination mode with a tin atom possessing six coordination number. Antibacterial activity of the synthesised complexes showed that both complexes demonstrated an inhibition towards *S. aureus* and *P aeruginosa*. Complex **2** namely diphenyltin(IV) bis(2-methoxyethyl)dithiocarbamate was more active and more promising to be developed as an antibacterial agent.

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