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Diorganotin(IV) Alkylcyclohexyldithiocarbamate Compounds: Synthesis, Characterization and Biological Activities

(Sebatian Diorganostanum(IV) Alkilsikloheksilditiokarbamat: Sintesis, Pencirian dan Aktiviti Biologi)

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ABSTRACT

Three new compounds of dibutyltin(IV) with N-alkylcyclohexyldithiocarbamate were successfully synthesized using in situ *methods. Elemental analysis data of these complexes were in agreement with the general formula of* $(C_4H_9)_2Sn[S_2CNR(C_6H_{11})]_2$ *(R =* CH_3, C_2H_5, $i\text{-}C_3H_7$*). Infrared spectra showed that the thioureide bands, ν(C=N) appeared in the region of 1475 - 1479* cm^{-1}*, ν(C=S) bands in the region of 978 - 998* cm^{-1} *and ν(Sn-S) bands in the region of 375 – 389* cm^{-1}*. Crystal structure of dibutyltin(IV) ethylcyclohexyldithiocarbamate showed a triclinic system and space group P-1. The crystal structure of the dithiocarbamate ligands were bidentically chelated to the tin atom with Sn-S unsymmetrical: Sn(1)-S(1) = 2.9255(11) and Sn(1)-S(2) = 2.5419(10); Sn(1)-S(3) = 2.8922(9) and Sn(1)-S(4) = 2.5293(10)Å. These compounds were screened for antibacterial activity against four bacteria species using the disc diffusion method. The results showed that* $(C_4H_9)_2Sn[S_2CN(i\text{-}C_3H_7)(C_6H_{11})]_2$ *was mildly active against those three bacteria. Whereas all of these compounds exhibited* in vitro *cytotoxicity activity toward human leukemic promyelocites HL-60 cell line with* CD_{50} *values lower than 1.00 µg/mL.*

Keywords: Biological activities; dibutyltin(IV); dithiocarbamate

ABSTRAK

Tiga sebatian baru dibutilstanum(IV) dengan ligan N-alkilsikloheksilditiokarbamat telah berjaya disintesis menggunakan kaedah in situ. *Data analisis unsur sebatian ini bersetuju dengan formula umum* $(C_4H_9)_2Sn[S_2CNR(C_6H_{11})]_2$ *(R =* CH_3, C_2H_5, $i\text{-}C_3H_7$*). Spektrum inframerah menunjukkan jalur tioureida, ν(C=N) berada pada julat 1475 - 1479* cm^{-1}*, ν(C=S) berada dalam julat 978 - 998* cm^{-1} *dan ν(Sn-S) berada pada julat 375 – 389* cm^{-1}*. Struktur hablur sebatian dibutilstanum(IV) etilsikloheksilditiokarbamat adalah bersistem triklinik dengan kumpulan ruang P-1. Ligan ditiokarbamat mengkelat kepada logam stanum secara bidentat dengan ikatan Sn-S yang tidak simetri: Sn(1)-S(1) = 2.9255(11) dan Sn(1)-S(2) = 2.5419(10); Sn(1)-S(3) = 2.8922(9) dan Sn(1)-S(4) = 2.5293(10) Å. Sebatian ini telah diuji ke atas empat spesies bakteria dan didapati* $(C_4H_9)_2Sn[S_2CN(i\text{-}C_3H_7)(C_6H_{11})]_2$ *mempunyai aktiviti yang sederhana terhadap tiga bakteria. Ketiga-tiga sebatian ini menunjukkan aktiviti sitotoksik secara* in vitro *terhadap titisan sel leukemia promielositi manusia, HL-60 dengan nilai* CD_{50} *kurang daripada 1.0 µg/mL.*

Kata kunci: Aktiviti biologi; dibutilstanum(IV); ditiokarbamat

INTRODUCTION

In recent years much attention have been paid to the synthesis, characterization and biological activities of various organotin(IV) derivatives with sulfur ligands such as thione or dithiocarbamate (Pellerito & Nagy 2002; Saxena 1989; Xanthopoulou et al. 2003). The dithiocarbamates ($R_2NCS_2^-$) are half-amides of dithiocarbonic acid and sulphur analogues of carbamates ($R_2NCO_2^-$). The strong metal binding properties analogues of carbamates were directly related to two donor sulfur atoms.

Organotin dithiocarbamate have a wide range of applications and they were amongst the most widely used organometallic compounds. The biological activity of organotin compounds was well known owing to their practical applications as fungicides, bactericides, biocides and pesticides (Sharma et al. 2002). Moreover, one of the areas that have been intensively studied was the activity against cancer (Crowe 1994; Gielen et al. 2005; Nath et al. 2001). Those with biologically active ligands have attracted more attention towards the design of potential antitumor agents (Barbaric et al. 2005; Raymond 1990).

The crystal structures of the diorganotin(IV) dithiocarbamate showed that the coordination environments around the central atom ranging from tetrahedral to distorted octahedral with the dithiocarbamate groups can act as either unidentate or bidentate (Sharma et al. 2000). We have reported for $Me_2Sn[S_2CN(CH_3)(C_6H_{11})]_2$, that both of the dithiocarbamate groups act as isobidentate ligand (Awang et al. 2003) and similar properties observed for $Me_2Sn[S_2CNCH_2CH_2CH_2CH_2CH_2]_2$ (Sharma et al. 1996).

In this paper, we report on the synthesis, characterization and biological activities of three new dibutyltin(IV) ethylcyclohexyldithiocarbamates. The crystal structure of

dibutyltin(IV) ethylcyclohexyldithiocarbamate compound was also discussed.

Materials and Methods

All chemicals and solvents were purchased from suppliers as follows: *N*-methylcyclohexylamine, *N*-ethylcyclohexylamine, *N*-isopropylcyclohexylamine and dibutyltin(IV) chloride (Fluka); chloroform and ethanol (Merck). All the chemicals were used as supplied without purification.

The melting points were determined using Electrothermal IA 9100. Elemental analysis was recorded on Fison EA 1108, infrared spectra were recorded using a Perkin Elmer GX spectrophotometer; KBr disc for the range 400-4000 cm^{-1} and nujol in polyethylene tablets for the range 400 - 200 cm^{-1}. The ^{13}C NMR spectra were recorded on Joel JNM-LA 400 in $CDCl_3$ using TMS as internal standard.

Three dibutyltin(IV) alkylcyclohexyldithiocarbamate compounds, $(C_4H_9)_2Sn[S_2CN(CH_3)(C_6H_{11})]_2$ **(1)**, $(C_4H_9)_2Sn[S_2CN(C_2H_5)(C_6H_{11})]_2$ (**2**) and $(C_4H_9)_2Sn[S_2CN(iC_3H_7)(C_6H_{11})]_2$ **(3)** were prepared using direct reaction by addition of carbon disulphide, CS_2 (30 mmol) to an ethanolic solution of corresponding amine (30 mmol). The mixture was stirred for one hour at 0–4°C. After one hour of stirring, the dibutyltin(IV) chloride solution was added and stirred for another one hour. The white precipitate was filtered and washed with cold ethanol and dried in vacuo over silica gel. The yield and melting point were recorded for each compound.

Room-temperature diffraction data for X-ray crystallography studies were collected using a Bruker SMART APEX area–detector diffractometer (Mo Kα radiation). Suitable crystals for X-Ray analysis of $(C_4H_9)_2Sn[S_2CN(C_2H_5)(C_6H_{11})]_2$ was separated after the mixture of chloroform and ethanol solutions were allowed to slowly evaporate for a few days. Data collection: SMART (Bruker 2008). Cell refinement: SAINT (Bruker 2008). Data reduction: SAINT. Programs were used to solve the structure: *SHELXTL* (Sheldrick 2008). Molecular graphics: *SHELXTL* (Sheldrick 2008). The structure was solved and refined by using the SHELXS-97 (Sheldrick 2008). The final R ($I>2/\sigma(I)$) was 0.0470. All non-hydrogen atoms were refined anisotropically.

The synthesized compounds (**1**-**3**) were screened for the preliminary *in vitro* anticancer activity against human leukemic promyelocites HL-60 cell line by MTT (3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide) assay reported by Mosmann (1983). The human leukemic promyelocites HL-60 cell line was obtained from the National Cancer Institute, Frederick, Maryland, USA. The cell was cultured in RPMI-1640 (Sigma) medium supplemented with 10% fetal calf serum (Flow Lab). Solutions of different concentrations were prepared from stock solutions (10 mg/L) by serial dilution in RPMI-1640 to give a volume of 100 μL in each well of a microtiter plate as described by Ali et al. (1998). Each well was filled with 100 μL of cell suspension in a complete growth medium (CGM) at 1-2 × 10^5 cells/L. The CD_{50} value represents the concentration, which results in a 50% decrease in cell growth after 24 hours incubation. Etoposide was used as control.

The bacterial species used in this study were *Stapyhlococcus aureus, Salmonella typhimurium, Bacillus subtilis* and *Pseudomonas aeruginosa*. In the screening for antibacterial activity, the disc diffusion method (Andrews 2001) was employed. Sterile paper discs (Whatman No. 1, 6 mm diameter) were loaded with 100 mL of each of the stock solution (10 mg/mL) to give a final concentration of 1 mg/disc. An even spread of microorganism was prepared by transferring 50 mL of microbial suspension to Mueller-Hinton agar plates for bacteria and SDA plates for yeast using sterile cotton buds. As for the dermatophytes, 100 mL of the spore suspension was added to 20 mL of molten PDA before they were poured out into the sterile plates. The discs were then positioned on the inoculated agar surface. Each compound solution was assayed in triplicate. Streptomycine (10 mg/disc) was used as standard antibiotic agent, whereas PBS was used as a negative control. The plates were then incubated at 37°C for 24 h for all the bacteria strains. On the other hand, the plates for the dermatophytes were incubated at 27°C for duration between 48 h to 72 h. The screening for antibacterial activity was done by measuring the diameter of a clear inhibition zone around the disc. The mean diameter of inhibition zone was measured to the nearest millimeter (mm) based on three readings of the diameter zones of each target microorganism using the vernier caliper. The results were expressed as mean ± S. D.

Results and Discussion

The reaction between $(C_4H_9)_2SnCl_2$ with related amines (methyl-, ethyl- and isopropyl-cyclohexylamine) and carbon disulphide in 1:2:2 molar ratio produced dibutyltin(IV) dithiocarbamates, $(C_4H_9)_2Sn[S_2CNR(C_6H_{11})]_2$ (R = CH_3, C_2H_5, i-C_3H_7) in high yield. The physical and analytical data for the three compounds are given in Table 1. The elemental analysis was in agreement with the proposed molecular formulae. All the three compounds were soluble in chloroform, $CHCl_3$ and stable in air. A general reaction scheme for the synthesis is given in Figure 1.

The infrared (IR) data of the compounds are tabulated in Table 2. The strong bands in the region of 1475-1479 cm^{-1} were attributed to a S_2 ⁻⁻⁻⁻ CN stretching mode of thioureida band (Honda et al. 1968). This band was very sensitive to the substituents on the tin atom, moving to a higher frequency by the introduction of more electronegative substituents. The peak in the region 978-998 cm^{-1} were attributed to ν(C ⁻⁻⁻⁻ S) vibration indicated a bidentate nature of the dithiocarbamate ligand in the compounds (Bonati & Ugo 1967). The presence of a band in the region 375-389 cm^{-1} was attributed to ν(Sn-S), confirming the bonding of the tin with sulfur atom of the dithiocarbamate ligand.

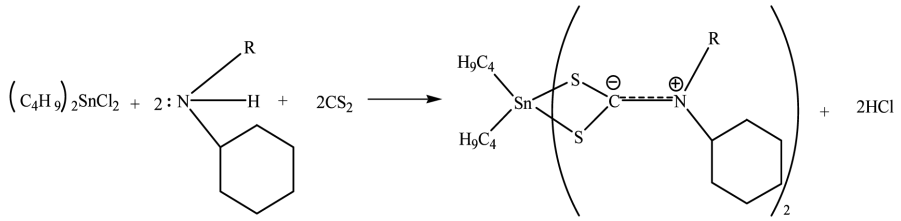

FIGURE 1. The proposed mechanism for reactions between N-alkyl-N-cyclohexylamine, carbon disulfide and dibutyltin(IV) chloride

TABLE 1. Physical and elemental analysis data of (N-alkyl-N-cyclohexyldithiocarbamato) dibutyltin(IV) compounds

Formula	Yield (%)	Melting point (°C)	Found (*Calculated*) (%)				
			C	H	N	S	Sn
$(C_4H_9)_2Sn[S_2CN(CH_3)(C_6H_{11})]_2$ **(1)**	83	122.6-124.0	47.15 *47.29*	8.08 *7.55*	4.62 *4.60*	22.72 *21.02*	17.92 *18.54*
$(C_4H_9)_2Sn[S_2CN(C_2H_5)(C_6H_{11})]_2$ **(2)**	79	110.6-112.0	49.00 *48.98*	8.38 *7.85*	4.11 *4.40*	20.23 *20.09*	20.21 *19.65*
$(C_4H_9)_2Sn[S_2CN(iC_3H_7)(C_6H_{11})]_2$ **(3)**	76	137.7-148.8	49.92 *50.53*	9.19 *8.12*	4.16 *4.21*	18.08 *19.25*	19.48 *18.89*

TABLE 2. The important infrared absorption bands (cm^{-1})

Compound	ν(C⋯N)	ν(C⋯S)	ν(Sn-S)
1	1478s	979m	375m
2	1475s	998m	385s
3	1479s	978w	389s

s = strong, m = medium, w = weak

The most important signal in the ^{13}C NMR spectrum was the chemical shift for $N^{13}CS_2$. The ^{13}C NMR spectra of these compounds was carried out in $CDCl_3$ and showed that the peak for $N^{13}CS_2$ chemical shifts appeared in the region 199.34-199.82 ppm (Table 3). The signals for ^{13}C for dibutyl group have been observed in the same area reported by Farina et al. (2002).

Single crystal of $(C_4H_9)_2Sn[S_2CN(C_2H_5)(C_6H_{11})]_2$ was obtained by slow evaporation of a chloroform:ethanol mixture at room temperature for a few days. The details of the crystal data and refinement parameters are listed in Table 4, while the selected geometric parameters are listed in Table 5. The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-square calculations, using the program system SHELXS-97.

Figure 2 shows the ORTEP plot of molecule in the unit cell which showed that tin was chelated by both of sulphur of the dithiocarbamate group which formed six-coordinated geometry. The coordination geometry of the tin atom can be described as distorted octahedral surrounded by 4 sulphur atoms and 2 butyl groups. The 4 sulphur atoms lie in the equatorial plane and distortion is reflected in S-Sn-S angles. The dithiocarbamate ligand through 4 Sn-S bonds were chelated to tin atom in anisobidentate fashion, with 2 longer and 2 shorter Sn-S bonds (Sn(1)-S(1) = 2.9255(11) Å; Sn(1)-S(3) = 2.8922(9) Å; Sn(1)-S(2) = 2.5419(10) Å; Sn(1)-S(4) = 2.5293(10) Å). The shorter Sn-S bond lengths are very close to the sum of the covalent radii (3.2 Å) of tin and sulfur, the longer Sn-S distances are significantly less than the sum of the van der Waals radii (4.0 Å) (Shahzadi et al. 2008). Furthermore, the longer C-S bonds (S(2)-C(9) = 1.746(3) Å, S(4)-C(18) = 1.743(4)) are associated with the shorter Sn-S bond, and the shorter C-S bonds (C(9)-S(1) = 1.692(4), C(18)-S(3) = 1.692(4)) are associated with the longer Sn-S bond. The C-S bond distances were almost similar to those observed in other dithiocarbamate complexes (Zia-ur-Rehman et al. 2007), which confirms the considerable double bond character associated with the C-S bonds. The short thioureide C-N distance (C(9)–N(1) = 1.328(4) Å and C(18)–N(2) = 1.331(4) Å) indicated that the π-electron density were delocalized over the S_2CN moiety and has a significant double bond character. The Sn-C distances (Sn(1)–C(10) = 2.128(4) and Sn(1)–C(14) = 2.144(5)) were almost similar to those found in $Bu_2Sn[S_2CN(C_7H_7)(i\text{-}C_3H_7)]_2$ (Baba et al. 2009) and $Bu_2Sn[S_2CN(C_6H_{12})]_2$ (Zia-ur-Rehman et al. 2006). The Bu-Sn-Bu angle (C(14)-Sn(1)-C(10) = 144.7(2)°) is intermediate between cis and

TABLE 3. The ^{13}C NMR spectra data of compound 1-3 (δ, ppm)

Compound	$N^{13}CS_2$	$R(C_6H_{11})$	$Sn\text{-}C_4H_9$	N-R' (R' = CH_3, C_2H_5, $i\text{-}C_3H_7$)
1	199.82	63.50	34.57	36.03
		30.14	28.78	
		25.69	26.69	
		25.57	14.06	
2	199.34	63.74	34.37	43.86
		30.69	28.56	14.13
		25.60	26.44	
		25.32	13.87	
3	199.44	66.50	34.56	54.74
		29.59	28.73	19.64
		26.63	28.11	
		26.47	14.15	

TABLE 4. Crystallographic data and refinement parameters

	$(C_4H_9)_2Sn[S_2CN(C_2H_5)(C_6H_{11})]_2$
Empirical formula	$C_{26}H_{50}N_2S_4Sn$
Formula weight	637.71
Crystal system	Trilinic
Space group	P-1
Crystal size(mm^3)	0.35 × 0.25 × 0.25
a (Å)	10.2809(6)
b (Å)	11.435(3)
c (Å)	11.989(3)
α (°)	103.1030(10)
β (°)	108.1250(10)
γ (°)	90.6550(10)
V ($Å^3$)	1591.49(15)
Z	2
D/Mgm^{-3}	1.324
F (000)	662
Temperature (K)	293(2)
θ range (°)	1.65 – 27.53
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.034
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0470$, $wR_2 = 0.1216$

trans, and larger than those observed in $Bu_2Sn[S_2CN(C_7H_7)(i\text{-}C_3H_7)]_2$ (129.0(2) °) (Baba et al. 2009).

The results of the antibacterial activity studies of the three compounds are shown in Table 6. As determined from disc diffusion assays, compound **3** showed antibacterial activity against both of the Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and one of the Gram-negative bacteria (*Salmonella typhimurium*). Based on the inhibition zones, the most susceptible microorganism towards the compound **3** was *Stapyhlococcus aureus* with the inhibition zone of 12.34 ± 0.56 mm.

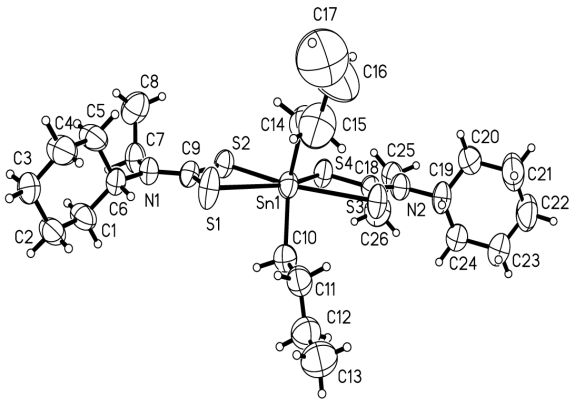

FIGURE 2. The ORTEP plot of (N-alkyl-N-cyclohexyldithiocarbamato)dibutyltin(IV) at the 50% probability level

The results of the *in vitro* cytotoxicity test were given in Table 7. The CD_{50} values of more than 10 μg/mL were considered indicative of weak cytotoxic activities while compounds with CD_{50} values of less than 5.0 μg/mL were considered to be very active (Shier 1991). Those having intermediate values from 5.0 to 10.00 μg/mL were classified as moderately active. Table 7 clearly showed that the three compounds were found to be very active against human leukemic promyelocites HL-60 cells with CD_{50} values of 0.68 – 0.92 μg/mL.

CONCLUSION

The elemental, spectroscopic and supported by crystallographic data approved that dithiocarbamate anions have chelated to the tin atom to form the neutral compounds. The crystallographic information obtained for dibutyltin(IV) ethyldithiocarbamate compound showed that the dithiocarbamate ligand formed bidentate

TABLE 5. Selected bond distances (Å) and angles (°) for $(C_4H_9)_2Sn[S_2CN(C_2H_5)(C_6H_{11})]_2$

Sn(1)–S(1)	2.9255(11)	S(1)–C(9)	1.692(4)
Sn(1)–S(3)	2.8922(9)	S(2)–C(9)	1.746(3)
Sn(1)–S(2)	2.5419(10)	S(3)–C(18)	1.692(4)
Sn(1)–S(4)	2.5293(10)	S(4)–C(18)	1.743(4)
Sn(1)–C(10)	2.128(4)	C(9)–N(1)	1.328(4)
Sn(1)–C(14)	2.144(5)	C(18)–N(2)	1.331(4)
		S(2)–C(9)	1.746(3)
S(4)–Sn(1)–S(2)	85.36(3)	C(14)–Sn(1)–S(4)	103.11(17)
S(3)–Sn(1)–S(1)	144.12(3)	C(18)–S(4)–Sn(1)	93.30(12)
C(10)–Sn(1)–C(14)	144.7(2)	C(18)–S(3)–Sn(1)	82.46(11)
C(10)–Sn(1)–S(4)	102.17(12)	S(3)–C(18)–S(4)	118.60(19)

TABLE 6. The mean diameter of inhibitory zone (mm ± SD) at 10 mg/mL against four bacterial strains

Microorganisms	Mean diameter of inhibiton zone (mm)			
	Compound 1	Compound 2	Compound 3	Standard (Streptomysin)
Stapyhlococcus aureus	-	-	12.27 ± 0.56	19.0
Salmonella typhimurium	-	-	11.16 ± 0.95	15.0
Pseudomonas aeruginosa	-	-	11.62 ± 0.38	20.0
Bacillus Subtilis	-	-	-	20.0

TABLE 7. The CD50 values

Compound	CD_{50} (μg/mL) HL-60
1	0.87
2	0.68
3	0.92
Etoposide	0.60

chelation respectively with non-equivalent Sn-S bond distances. This concluded that the substituent groups of the dithiocarbamate ligands have an influence on the chelation of the dithiocarbamate ligands to the tin atom. The present study also showed that one of these compounds has good potential as antibacterial agent. Cytotoxicity assay of the compounds confirm the potential of these compounds, which can be used for clinical trials after further research.

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