Synthesis, Characterization and Biological Activities of Organotin (IV) Methylcyclohexyldithiocarbamate Compounds

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Abstract: Problem statement: The growing interest in the chemistry of sulphur donor ligands are due to their encouraging anticancer, antibacterial and antifungal activities as well as their widespread industrial application. Dithiocarbamates belong to this class and much attention has been paid to them.

Approach: Novel organotin compounds with the molecular formula $R_mSn[S_2CN(CH_3)(C_6H_11)]_{4-m}$ (where $m = 2$, $R = CH_3$, $C_2H_5$; $m = 3$, $R = C_6H_5$) have been synthesized using in situ method. These compounds were characterized by elemental analysis, IR, $^1H$ and $^{13}C$ NMR spectroscopy.

Results: Elemental analysis revealed that all compounds were of good purity. Infrared spectra of the compounds showed that the thioureide $\nu(C-N)$ band was in the region 1450-1500 cm$^{-1}$. The unsplitting band of $\nu(C-S)$ in the region 974-979 cm$^{-1}$ indicated the bidentate nature of the chelated dithiocarbamate legends. The $^{13}C$ NMR chemical shift of the carbon atom in the N-CS$_2$ group appeared in the range of 196.29-199.82 ppm. Single crystal analysis from one of these compounds showed that the chelating mode of the dithiocarbamate groups was isobidentate. These compounds have been screened for antibacterial activity against four bacteria; *Staphylococcus aureus*, *Salmonella typhimurium*, *Pseudomonas aeruginosa* and *Bacillus subtilis*. Only one of these compounds shows promising results against *S. aureus* and *S. typhi*. Cytotoxicity screening on human leukemic promyelocyte HL-60 cells found that two of these compounds were very active with CD$_{50}$ values of 0.87 and 0.18 µg mL$^{-1}$.

Conclusion: The studied compounds were found to have the potential in biological activity especially in cytotoxicity where this possibly can be used for clinical trials after further research.

Key words: *Salmonella typhimurium*, infrared spectra, biological activities, *staphylococcus aureus*, antibacterial activity, synthesized compounds, disc diffusion, elemental analysis

INTRODUCTION

Organotin compounds have a wide range of applications and they are amongst the most widely used organometallic chemicals. The organotin (IV) compounds possess significant biological activities (Kang *et al*. 2009; Wu *et al*. 2009; Alama *et al*. 2009; Affan *et al*. 2009). These compounds have been found as antitumor (Mohan *et al*., 1988; Ruan *et al*., 2011), antibacterial (Maiti *et al*., 1988; Gleeson *et al*. 2008), antifungal (Manav *et al*., 2000; Singh and Kaushik, 2008) and antiviral (Singh *et al*., 2000). These compounds have been widely used as agrochemicals and antifouling paints due to their low phototoxicity and favourable environmental degradation to non-toxic inorganic residues. Organotin(IV) compounds are extensively studied due to its coordination geometries as well as structural diversity (Amini *et al*. (2009).

The dithiocarbamates ($R_2NCS_2^-$) are the half-amides of dithiocarbonic acid. These are the sulphur analogs of carbamates ($R_2NCO_2^-$). The strong metal binding properties of dithiocarbamates are directly related to their possession of two donor sulphur atoms. Dithiocarbamates are the main group of fungicides used to control approximately 400 pathogens of more than crops and registered in all the EU member states and many other countries.
In this study, we report on the synthesis, characterization, antibacterial and cytotoxicity activities of some new organotin (IV) compounds using N-methylcyclohexylamine, which consist of dimethyltin (IV) dichloride, dibutyltin (IV) dichloride and triphenyltin (IV) chloride. The structure of dimethyltin (IV) methylcyclohexylidithiocarbamate (compound 1) also has been reported in this study.

**MATERIALS AND METHODS**

**Reagents:** Dimethyltin(IV) dichloride, dibutyltin(IV) dichloride, N-methylcyclohexylamine and ethanol (95%) were obtained from Fluka Chemical. Carbon disulphide and methanol (99.5%) from Ajax Chemical Ltd. Chloroform was purchased from Merck. All the chemicals were used as supplied without purification.

**Synthesis of dithiocarbamate complexes:** Dimethyltin(IV), dibutyltin(IV) and triphenyltin(IV) methylcyclohexylidithiocarbamate compounds (compound 1-3) were synthesized by the method given by Thirumaran et al. (1998) with some modifications. To a stirred solution of N-methylcyclohexylamine (30 mmol) in 30 mL of ethanol was added carbon disulphide and methanol (99.5%) from Ajax Chemical Ltd. Chloroform was purchased from Merck. All the chemicals were used as supplied without purification.

**Physical measurements:** Melting points were determined in a capillary tube using electrothermal melting point apparatus model MP-D Mitamura Riken Kogyo (Japan). Elemental analysis was carried out on Fison EA 1108 CHN analyzer. IR and far IR spectra were recorded on a Perkin Elmer FTIR Model GX spectrometer in the frequency range 4000-500 cm\(^{-1}\), free and labeled C-H and C-C NMR spectra were recorded using Joel JNM-LA 400 spectrometer.

**X-ray crystallography:** Room-temperature diffraction data were collected on a Bruker SMART APEX area-detector diffractometer (Mo K\(\alpha\) radiation, \(\lambda = 0.71073\) Å) on a crystal with size of 0.27×0.22×0.16 mm over the range 1.76< \(\theta\) <27.0. The structure was solved and refined by using the SHELXS-97. The final R (I>2s(I)) and Rw values were 0.07 and 0.1820 respectively. All non-hydrogen atoms were refined anisotropically. The perspective view of the molecule was obtained using SHELXTL. Selected bond distances and angles are listed in Table 6.

**Cytoxicity screening:** The synthesized compounds (1-3) were screened for the preliminary in vitro anticancer activity against human leukemic promyelocyte HL-60 cell line by MTT (3-(4,5-dimethylthiazole-2-y1)-2,5-diphenyl-tetrazolium bromide) assay reported by Mosmann (1983). The human leukemic promyelocyte 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 cm\(^{-3}\)) by serial dilution in RPMI-1640 to give a volume of 100 \(\mu\)L in each well of a microtiter plate as described by Ali et al. (1999). Each well was filled with 100 \(\mu\)L of cell suspension in a complete growth medium (CGM) at 1-2×10\(^5\) cells cm\(^{-3}\). The CD\(_50\) value represents the concentration, which results in a 50% decrease in cell growth after 24 hrs of incubation. Etoposide was used as control.

**Disc diffusion antimicrobial assay:** The bacterial species used in this study were Staphylococcus aureus, Salmonella typhimurium, Pseudomonas aeruginosa and Bacillus subtilis. In the screening of antibacterial activity, the disc diffusion method (Andrews, 2001) was employed. Sterile study discs (Whatman No. 1, 6 mm diameter) were loaded with 100 ml of each of the stock solution (10 mg mL\(^{-1}\)) 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. Streptomycin (10 mg/disc) was used as standard antibiotic agent, whereas PBS was used as a negative control. The plates of all bacteria strains were then incubated at 37°C for 24 h. On the other hand, the plates of dermatophytes were incubated at 27°C for duration between 48-72 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.

**RESULTS**

The direct reaction of N-methylcyclohexylamine with organotin (IV) chloride yields the organotin (IV) methylcyclohexylidithiocarbamate compounds in a good percentage. Elemental analysis and physical properties data for compound 1-3 are given in Table 1. The reaction schemes for the above preparation are given in Fig. 1.
Fig. 1: The Reactions between N-methyl-N-cyclohexylamine, Carbon Disulfide and Organotin(IV) Chloride

Fig. 2: ORTEP plot of compound 1 at the 50% probability level

Table 1: Physical and Elemental analysis data of organotin(IV) N-methyl-N-cyclohexylthiocarbamate compounds

| Molecular formula | Color       | Yield (%) | Melting point (°C) | Found (Calculated) (%) |
|-------------------|-------------|-----------|--------------------|------------------------|
|                   |             |           | C     | H     | N     | S     | Sn    |
| (CH₃)₂Sn[S₂CN(CH₃)] | Colorless   | 89        | 147.7- | 40.66 | 6.46  | 5.30  | 26.43 | 23.12 |
| (C₆H₁₁)₂Sn[S₂CN(CH₃)] | Colorless  | 83        | 122.6- | 47.15 | 8.08  | 4.62  | 22.72 | 17.92 |
| (C₄H₉)₂Sn[S₂CN(CH₃)] | Colorless  | 76        | 136.8- | 57.71 | 4.98  | 2.57  | 11.26 | 23.05 |

Table 2: The important infrared absorption bands (cm⁻¹)

| Compounds | v(C-H) | v(C-S) | v(N-C) | v(C-S-S) | v(Sn-C) | v(Sn-S) |
|-----------|--------|--------|--------|----------|---------|---------|
| 1         | 2927   | 1475   | 1147   | 974      | 554     | 357     |
| 2         | 2925   | 1459   | 1147   | 975      | 532     | 359     |
| 3         | 2938   | 1478   | 1148   | 979      | 261     | 349     |
The results for IR, $^1$H and $^{13}$C NMR spectroscopy of each compound were presented in Table 2-4, whereas the data for single crystal analysis obtained from compound 1 was shown in Table 5-6. The ORTEP plot of compound 1 is also given in Fig. 2.

Out of three compounds tested for antibacterial activity, only compound 3 showed inhibitory zones against two bacterial strains (Table 7) while in vitro cytotoxicity test indicated that compound 2-3 gave cytotoxic effect when tested on human leukemic cells, HL-60 (Table 8).

### Table 3: $^1$H NMR spectra data of compound 1-3 (δ, ppm)

| Compound | Sn-R (R = CH$_3$; C$_4$H$_9$; C$_6$H$_5$) | H$_a$, H$_b$, H$_c$, H$_d$ | N-C$_6$H$_{11}$ | N-CH$_3$
|-----------|-----------------------------|-----------------------|-----------------|------------------|
| 1 | CH$_3$: 1.56 | 4.87 | 3.24 |
| 2 | α-CH$_2$: 1.40 | 4.91 | 3.27 |
| 3 | C$_6$H$_5$: 7.38-7.82 | 4.76 | 3.28 |

### Table 4: $^{13}$C NMR spectra data of compound 1-3 (δ, ppm)

| Compound | NCSS | Sn-R (R = CH$_3$; C$_4$H$_9$; C$_6$H$_5$) | N-C$_6$H$_{11}$, Ca, Cb, Cd, Cc | N-CH$_3$ |
|-----------|-------|-----------------------------|---------------------|----------------|
| 1 | 198.73 | 15.35 | 63.39; 29.91; 25.44; 25.31 | 32.03 |
| 2 | 199.82 | 34.57; 28.78; 26.69; 14.06 | 63.50; 30.14; 25.69; 25.57 | 36.72 |
| 3 | 196.29 | 142.81; 136.71; 128.99; 128.44 | 65.32; 30.03; 25.36; 25.27 | 36.72 |

### Table 5: Crystallographic data and refinement parameters for compound 1

| Compound 1 | Empirical Formula | C$_{18}$H$_{34}$N$_2$S$_4$Sn |
|------------|------------------|-------------------------|
| Formula weight | 525.40 |
| Crystal system | Orthorhombic |
| Space group | Pnma |
| Crystal size (mm) | 0.27×0.22×0.16 |
| a (Å) | 13.200(9) |
| b (Å) | 19.965(14) |
| c (Å) | 8.950(6) |
| α (%) | 90 |
| β (%) | 90 |
| γ (%) | 90 |
| V (Å$^3$) | 2358.7(3) |
| Z | 4 |
| D/Mgm$^{-3}$ | 1.480 |
| μ (mm$^{-1}$) | 1.442 |
| F (000) | 1080 |
| Color | Colorless |
| Temperature (K) | 293(2) |
| θ range (°) | 2.04-27.56 |
| Index ranges (h, k, l) | -17/16, -25/25, -11/11 |
| Reflection collected/unique | 15359/2795 |
| Completeness to theta = 27.53 | 99.7% |
| Max. and min. transmission | 0.8020 and 0.6968 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data/restraints/parameters | 2795/0/118 |
| Goodness-of-fit on F$^2$ | 0.900 |
| Final R indices [I > 2σ(I)] | R$_1$ = 0.0338, wR$_2$ = 0.1087 |
| R indices (all data) | R$_1$ = 0.0400, wR$_2$ = 0.1165 |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.867 and -0.321 |
Table 6: Selected bond lengths (Å) and angles (°) for compound 1

| Bond length (Å) | Compound 1         | Compound 2         | Compound 3         | Sn(1)-C(10) | 2.099(5) | S(1)-C(8) | 1.749(3) |
|-----------------|--------------------|--------------------|--------------------|--------------|----------|----------|----------|
| Sn(1)-C(9)      | 2.116(5)           |                    |                    | 2.099(5)     | 2.116(5) | S(2)-C(8) | 1.695(3) |
| Sn(1)-S(1)      | 2.5173(7)          |                    |                    | 2.5173(7)    | 2.5173(7) | N(1)-C(7) | 1.456(3) |
| Sn(1)-S(2)      | 2.9785(6)          |                    |                    | 2.9785(6)    | 2.9785(6) | N(1)-C(6) | 1.485(3) |
| Sn(1)-C(10)     |                    |                    |                    |              |          |          |          |

Table 7: The diameter of inhibitory zone (mm) of compound 1-3 at 10 mg mL⁻1 against selected bacterial strains

| Microorganisms          | Compound 1 | Compound 2 | Compound 3 | Standard (Streptomycin) |
|-------------------------|------------|------------|------------|-------------------------|
| Staphylococcus aureus   | -          | -          | 8          | 19.0                    |
| Salmonella typhimurium  | -          | -          | 10         | 15.0                    |
| Pseudomonas aeruginosa  | -          | -          | -          | 20.0                    |
| Bacillus subtilis       | -          | -          | -          | 20.0                    |

Table 8: CD₅₀ values of the compounds 1-3

| Compound | CD₅₀ (μg mL⁻¹) |
|----------|---------------|
| 1        | Inactive      |
| 2        | 0.87          |
| 3        | 0.18          |
| Etoposide| 0.60          |

DISCUSSION

The elemental analysis as shown in Table 1 revealed that compounds were in good purity and in agreement with the general formula RₘSn[S₂CN(CH₃)(C₆H₁₁)]₄₋ₘ (where m = 2, R = CH₃, C₂H₅, m = 3, R = C₆H₅). All the synthesized compounds were soluble in chloroform solvent and stable in air.

The important IR peaks of the compounds determined by the infrared spectra test were shown in Table 2. The ν(C–N) modes appeared in the region of thioureide band (1450-1550 cm⁻¹), while ν(C=S) modes appeared in the region 950-1002 cm⁻¹ (Ajibade et al. 2011). These indicated that dithiocarbamate legends were coordinated to the tin atom through thiol sulphur. The absence of any splitting to the ν(C-S) bands that appeared in the range 974-979 cm⁻¹ indicated a bidentate nature of the chelation of the dithiocarbamate ligands (Brown et al., 1976; Nomura et al., 1987; Mamba et al. 2010). The highest ν(C-N) and ν(C = S) observed for compound 3 may be due to the electron donating effect of the phenyl group compared to the other groups.

The proton magnetic resonance spectra (¹H NMR spectra) of the organotin(IV) methylcyclohexyldithiocarbamate compounds were recorded in CDCl₃ as shown in Table 3. The results showed that signals for methylene proton bound to nitrogen atom in the compounds in the range 3.24-3.29 ppm. The aromatic protons of the phenyl group directly attached to the Sn atom in compound 3 were observed in the range 7.38-7.82 ppm. The ¹H NMR spectra of compound 1 exhibited a sharp singlet at 1.52 ppm corresponding to the protons of methyl groups attached to the Sn atom (Yin et al. 2008). However, in the case of compound 2, four sets of signals were observed. As the butyl group is attached to electropositive Sn atom via carbon nuclei, a shielding effect was experienced through the carbon chain (Gomez-Ortiz et al., 2002). The methyl protons of the butyl group were observed as a triplet at 0.93 ppm while broad signals were observed at 2.09, 1.89 and 1.40 ppm for the methylene protons.

The ¹³C NMR spectrum of the organotin(IV) methylcyclohexyldithiocarbamate compounds exhibited a signal for N-CH₃ carbon in the range 35.81-36.72 ppm while the methyl carbon which directly attached to the Sn atom in compound 1 was found at 15.35 ppm (Table 4). The CS₂ resonances for compound 1 and 2 were observed at 198.73 and 199.82 ppm respectively while in the compound 3 it was shifted to up field to about 3 ppm.

Suitable crystal for X-ray analysis of compound 1 was obtained by slow evaporation of a chloroform: Ethanol mixture at room temperature for a few days. The proton magnetic resonance spectra (¹H NMR spectra) of the organotin(IV) methylcyclohexyldithiocarbamate compounds were recorded in CDCl₃ as shown in Table 3. The results showed that signals for methylene proton bound to nitrogen atom in the compounds in the range 3.24-3.29 ppm. The aromatic protons of the phenyl group directly attached to the Sn atom in compound 3 were observed in the range 7.38-7.82 ppm. The ¹H NMR spectra of compound 1 exhibited a sharp singlet at 1.52 ppm corresponding to the protons of methyl groups attached to the Sn atom (Yin et al. 2008). However, in the case of compound 2, four sets of signals were observed. As the butyl group is attached to electropositive Sn atom via carbon nuclei, a shielding effect was experienced through the carbon chain (Gomez-Ortiz et al., 2002). The methyl protons of the butyl group were observed as a triplet at 0.93 ppm while broad signals were observed at 2.09, 1.89 and 1.40 ppm for the methylene protons.

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The compound showed a partial double bond. The IR spectrum of the above compound (N(1)-C(7) = 1.456(3) Å; N(1)-C(6) = 1.485 Å) were manifestation due to the presence of a double bond. The central Sn1 atom is surrounded axially by S1, S2, S1A and S2A. The angle of axial C(9)-Sn(1)-C(10) is 137.00 (2)°, deviating from 180°, which showed that this compound has a distorted octahedron geometry.

The antibacterial activity of the synthesized compounds solution in dimethylsulfoxide (DMSO) was tested against gram positive and gram negative bacteria consisting of Staphylococcus aureus, Salmonella typhimurium, Pseudomonas aeruginosa and Bacillus subtilis. The activity of the compounds was evaluated by measuring the diameter of the inhibition zone around the respective wells. The activity was then compared with the standard drug (Streptomycin). The results as been presented in Table 7 revealed that only compound 3 had antibacterial activity but its activity was lower than the standard drug used. The presence of phenyl groups in compound 3 bonded to tin atom is responsible for the toxicity.

The results for in vitro cytotoxicity test of compounds 1-3 were given in Table 8. Following the suggestion, CD50 values of more than 10 µg mL⁻¹ are considered as indicative of weak cytotoxic activities while compounds with CD50 values of less than 5.0 µg mL⁻¹ are considered to be very active. Those having intermediate values between 5.0-10.00 µg mL⁻¹ are classified as moderately active. Table 8 clearly showed that compounds 2-3 were found to be very active against human leukemic promyelocyte HL-60 cells with CD50 values of 0.87 and 0.18 µg mL⁻¹ respectively. As compared to compound 2, compound 3 was found to be much more active to posses cytotoxicity at lower dose. This was supported by previous study tested on HepG2 cells which showed those complex derived from triphenyltin(IV) is more active than diorganotin(IV) derivatives (Win et al. 2010). Other research tested for in vitro cytotoxicity by using organotin(IV) also share the same results (Xanthopoulou et al., 2008, Hadjikakou and Hadjiliadis 2009). It has been suggested that these behaviors are exhibited due to the interaction of organotin compounds with DNA at the level of phosphate group, which may be followed by the intercalation of the legend into DNA (Casini et al., 2001).

CONCLUSION

On the basis of elemental analysis, spectral (IR, ¹H NMR and ¹³C NMR) data supported by crystallographic data approved that dithiocarbamate anions have chelated to the tin atom to form the neutral compounds. The crystallographic information obtained for dimethyltin (IV) methylcyclohexylidithiocarbamate compound showed that the dithiocarbamate ligand formed bidentate chelation respectively with non-equivalent Sn-S bond distances. The screening results indicate that not all compounds exhibited antibacterial activity. It can be noted that compound with phenyl groups showed inhibitory effect on selected types of bacteria. Cytotoxicity assays of the compounds confirm the potential of these compounds, which can be used for clinical trials after further research.

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