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Synthesis, characterization and biological studies of diorganotin(IV) complexes with *tris*[(hydroxymethyl)aminomethane] Schiff bases

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ABSTRACT

Several Schiff base ligands derived from *tris*(hydroxymethyl)aminomethane were synthesized and a series of diorganotin(IV) complexes were obtained from the reaction of diorganotin dichlorides or oxides with Schiff base ligands. The ligands and complexes have been characterized by elemental analysis, IR, ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopies. Single-crystal X-ray diffraction analysis reveals that *bis*[(2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenolato)]dimethyltin(IV), **1** and *bis*[(2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]iminomethyl}-4-bromophenolato)]dimethyltin(IV), **7** are dimeric structures, in which the central tin atom is rendered six-coordinate while (2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]iminom ethyl}-4-bromophenolato)diphenyltin(IV), **9**, (2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]iminomethyl}-4-chloropenolato)dimethyltin(IV), **13**, (2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]imino methyl}-4-chlorophenolato)diphenyltin(IV), **15** and (2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]iminomethyl}-4-chlorophenolato)dicyclohexyltin(IV), **16** are monomeric structures, whereby the tin atom is in a distorted trigonal–bipyramidal configuration. The Schiff bases and their corresponding diorganotin(IV) complexes have been evaluated against three human carcinoma cell lines, namely HT29 (human colon carcinoma cell line), SKOV-3 (human ovarian cancer cell line) and MCF-7 (hormone-dependent breast carcinoma cell line), for its *in vitro* cytotoxic activities. The dibutyltin and dicyclohexyltin derivatives of the Schiff base ligands display good cytotoxic activities against the tested cell lines.

1. Introduction

Organotin(IV) compounds have been actively studied due to their medical, industrial and agricultural applications [1–5]. Among these compounds, the chemistry and applications of organotin(IV) complexes with monodentate, bidentate, tridentate and multidentate Schiff bases are extensively studied because of their structural diversity, thermal stability and biological properties such as antimicrobial [6], antifungal [7,8], antibacterial [7,8], anti-tumour [7,9–11], antioxidant [11], anti-insecticidal [12] and anti-inflammatory [11,13]. The biological activities of the organotin(IV) complexes are largely influenced by the structure of the complexes, coordination number at the tin atom and by the alkyl/aryl groups in the complexes [14,15].

Schiff bases play an important role as chelating ligands in both main group metal and transition metal coordination chemistry. This is due to their stability in a variety of oxidative-reductive condition and their structural versatilities [16]. *Tris*(hydroxymethyl)aminomethane (TRIS) has been widely used in biochemistry, physiology and medicine as an inexpensive buffer in the physiological pH range. From literature, *tris*(hydroxymethyl)aminomethane (TRIS) and its Schiff base derivatives are known to have a broad spectrum of biological activities including anti-tumour, antibiotic, anticancer, antihistamine, antifungal, anti-inflammatory and many others [16–19]. Some metal complexes with TRIS Schiff base have been reported. For example, TRIS Schiff bases with dioxomolydenum(VI) complexes have been investigated and used as catalysts in epoxidation of alkenes while its dioxovanadium(IV) complexes have been studied as potential biomimetics [20,21].

The coordination chemistry of diorganotin(IV) complexes with *ONO*, *ONS* and *NNO* terdentate ligands is widely discussed for its biological and pharmacological properties. In the current article, we report the synthesis and structural studies of diorganotin complexes with terdentate *ONO* Schiff bases prepared from the condensation reaction of *tris*(hydroxymethyl)aminomethane with substituted salicylaldehydes. The prepared diorganotin complexes could be a monomeric or dimeric structure with coordination geometries which are close to trigonal–bipyramidal, octahedral

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and pentagonal-bipyramidal. The *in vitro* cytotoxicity of the Schiff bases and their diorganotin complexes against three human carcinoma cell lines (HT29, SKOV-3 and MCF7) is evaluated and discussed.

2. Experimental

2.1. Materials and physical measurements

The reagents used were of reagent grade quality and used as supplied. Dibenzyltin dichloride and di(*p*-chlorobenzyl)tin dichloride were prepared according to the literature method [22]. The solvents used in the reaction were of AR grade and were dried using standard literature procedures [23]. The melting points of the ligands and complexes were determined using an Electrothermal digital melting point apparatus and were uncorrected. The IR spectra for the compounds were recorded using KBr pellets on a Perkin-Elmer Spectrum RX1 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM GX-270 FT NMR SYSTEM spectrometer while ^{119}Sn NMR spectra were recorded on a JEOL ECA-400 MHz NMR spectrometer and were referenced against Me_4Sn. The chemical shifts were recorded in ppm with reference to Me_4Si for ^{1}H NMR and ^{13}C NMR. Microanalyses were carried out on an Eager 300 CHNS Elemental Analyzer and a Perkin-Elmer EA2400 CHNS Elemental Analyzer.

2.2. Preparation of the ligands

2.2.1. 2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenol, H_2L1

Tris(hydroxymethyl)aminomethane (1.21 g, 0.01 mol) and salicylaldehyde (1.07 mL, 0.01 mol) were added to 100 mL of ethanol. The solution mixture was refluxed for 2 h. A yellow solid was obtained upon cooling to room temperature, and was used without further purification. Yield: 1.90 g (84.5%); m.p. 139–140 °C. *Anal.* Calc. for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.11; H, 6.33; N, 6.70%. IR (cm^{-1}): 3321 ν(O–H), 1636 ν(C=N), 1189 ν(C–O).

The preparation method used for ligand **H_2L1** was repeated for ligands **H_2L2** and **H_2L3** with the respective substituted salicylaldehydes.

2.2.2. 2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}-4-bromophenol, H_2L2

Yield: 2.13 g (70.1%); m.p. 141–142 °C. *Anal.* Calc. for $C_{11}H_{14}NO_4Br$: C, 43.44; H, 4.64; N, 4.61. Found: C, 43.01; H, 4.60; N, 4.49%. IR (cm^{-1}): 3357 ν(O–H), 1637 ν(C=N), 1175 ν(C–O).

2.2.3. 2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}-4-chlorophenol, H_2L3

Yield: 1.95 g (75.1%); m.p. 137–138 °C. *Anal.* Calc. for $C_{11}H_{14}NO_4Cl$: C, 50.88; H, 5.43; N, 5.39. Found: C, 51.18; H, 5.42; N, 5.01%. IR (cm^{-1}): 3339 ν(O–H), 1639 ν(C=N), 1175 ν(C–O).

2.3. Preparation of the diorganotin complexes, **1**–**18**

The preparation method used for compound **1** was repeated for compounds **3**, **4**, **7**, **9**, **10**, **13**, **15** and **16** with the appropriate diorganotin oxides and Schiff base ligands. The preparation method used for compound **2** was repeated for compounds **5**, **6**, **8**, **11**, **12**, **14**, **17** and **18** with the appropriate diorganotin chlorides and Schiff base ligands.

2.3.1. Bis[(2-{[1,1-bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenolato)]dimethyltin(IV), **1**

0.23 g (1.0 mmol) of 2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenol, **H_2L1** in 20 mL dry toluene was added to a suspension of 0.17 g (1.0 mmol) of dimethyltin oxide in 50 mL of dry toluene. The mixture was heated under azeotropic removal of water using a Dean–Stark trap. The solvent was gradually removed by evaporation under vacuum to give a yellow precipitate. The precipitate was recrystallized from a 1:1 mixture of ethanol:dichloromethane. Yellow crystals suitable for X-ray crystallographic studies were obtained from the slow evaporation of the filtrate.

Yield: 0.58 g (77.8%); m.p. 196–198 °C *Anal.* Calc. for $C_{26}H_{38}N_2O_8Sn_2$: C, 41.97; H, 5.15; N, 3.77. Found: C, 42.02; H, 5.02; N, 3.98%. IR (cm^{-1}): 3495 ν(O–H), 1614 ν(C=N), 1191 ν(C–O), 669 ν(Sn–O), 419 ν(Sn–N).

2.3.2. (2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenolato)dibutyltin(IV), **2**

0.23 g (1.0 mmol) of 2-{[1,1-*bis*(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenol, **H_2L1**, and 0.14 mL (1.0 mmol) of triethylamine were added to 50 mL of absolute ethanol and the mixture was heated under reflux for 2 h. Dibutyltin dichloride (0.30 g, 1.0 mmol) in 30 mL of absolute ethanol was added and the mixture was further refluxed for 5 h and filtered. The filtrate was evaporated until precipitation was obtained. The precipitation was recrystallized from toluene and the by-products, triethylammonium chloride, was removed through filtration. The yellow precipitate was recrystallized from a 1:1 mixture of ethanol:dichloromethane.

Yield: 0.36 g (79.2%); m.p. 126–127 °C *Anal.* Calc. for $C_{19}H_{31}NO_4Sn$: C, 50.03; H, 6.85; N, 3.07. Found: C, 49.94; H, 7.12; N, 2.79%. IR (cm^{-1}): 3422 ν(O–H), 1611 ν(C=N), 1182 ν(C–O), 678 ν(Sn–O), 422 ν(Sn–N).

2.3.3. (2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenolato)diphenyltin(IV), **3**

Yield: 0.37 g (74.4%); m.p. >350 °C (dec.) *Anal.* Calc. for $C_{23}H_{23}NO_4Sn$: C, 55.68; H, 4.67; N, 2.82. Found: C, 56.00; H, 4.64; N, 2.73%. IR (cm^{-1}): 3281 ν(O–H), 1611 ν(C=N), 1173 ν(C–O), 699 ν(Sn–O), 436 ν(Sn–N).

2.3.4. (2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenolato)dicyclohexyltin(IV), **4**

Yield: 0.38 g (75.5%); m.p. 190–191 °C *Anal.* Calc. for $C_{23}H_{35}NO_4Sn$: C, 54.35; H, 6.94; N, 2.76. Found: C, 53.70; H, 6.87; N, 3.02%. IR (cm^{-1}): 3369 ν(O–H), 1616 ν(C=N), 1149 ν(C–O), 669 ν(Sn–O), 421 ν(Sn–N).

2.3.5. (2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenolato)dibenzyltin(IV), **5**

Yield: 0.34 g (65.2%); m.p. >350 °C (dec.) *Anal.* Calc. for $C_{25}H_{27}NO_4Sn$: C, 57.28; H, 5.19; N, 2.67. Found: C, 56.95; H, 5.57; N, 2.43%. IR (cm^{-1}): 3401 ν(O–H), 1612 ν(C=N), 1174 ν(C–O), 698 ν(Sn–O), 458 ν(Sn–N).

2.3.6. (2-{[1,1-Bis(hydroxymethyl)-2-oxidoethyl]iminomethyl}phenolato)di(p-chlorobenzyltin)(IV), **6**

Yield: 0.39 g (65.0%); m.p. >350 °C (dec.) *Anal.* Calc. for $C_{25}H_{25}Cl_2NO_4Sn$: C, 50.63; H, 4.25; N, 2.36. Found: C, 50.35; H, 3.90; N, 2.20%. IR (cm^{-1}): 3282 ν(O–H), 1610 ν(C=N), 1172 ν(C–O), 688 ν(Sn–O), 420 ν(Sn–N).