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Synthesis, characterization and biological activity of diorgano and triorganotin (IV) complexes of Chlordiazepoxide, Choline theophyllinate and Phenobarbitone sodium

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ABSTRACT

In an attempt to develop novel metal-based drugs with a different therapeutic profile to cisplatin, a new series of diorganotin (IV) and triorganotin (IV) complexes of R_2SnA_2 (R = Me, *n*-Bu, *n*-Oct and Phenyl) and R_3SnA_2 (R = *n*-Bu) where A is the anion of Chlordiazepoxide (L^1H) {(2*Z*)-7-chloro-2-(methylimino)-5-phenyl-3,4-dihydro-2*H*-1,4-benzodiazepin-4-ol}, Choline theophyllinate (L^2H) {(2-hydroxyethyl)trimethylazanium; 1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-ide} and Phenobarbitone sodium (L^3H) {5-ethyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione} have been synthesized. These resulting complexes were characterized by elemental analysis, UV, IR, NMR (^1H, ^{13}C and ^{119}Sn) studies. On the basis of these spectroscopic studies, it was proposed that diorganotin (IV) complexes of Chlordiazepoxide, Choline theophyllinate and Phenobarbitone sodium having 1:2 stoichiometry show tetrahedral geometry. Triorganotin (IV) complexes of Chlordiazepoxide and Choline theophyllinate having 1:2 stoichiometry show trigonal bipyramidal geometry. The ligand molecules in these complexes appear to be bound to the tin atom through the hydroxyl oxygen in Chlordiazepoxide, Choline theophyllinate and Phenobarbitone sodium. The biological activity of all these complexes was screened against six indicator strains: *Bacteriodes fragilis*, *Salmonella enterica*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Vibrio cholerae*. The antibacterial activity is found maximum for *n*-$Bu_2Sn(L^2)_2$ which is most effective against all indicator strains used. *n*-$Bu_2Sn(L^1)_2$ is effective against *Pseudomonas aeruginosa* and *Vibrio cholerae* while $Me_2Sn(L^3)_2$ and $Ph_2Sn(L^3)_2$ show good inhibitions against *Bacteriodes fragilis* and *Salmonella enterica*.

1. Introduction

Research on medicinal applications of metal complexes is an area of current interest and one of the most studied in biomedical and inorganic chemistry [1,2]. In this context the potent therapeutic properties of tin complexes are well known [3]. Moreover, the organotin (IV) complexes continue to be of interest on account of their interesting structural features [4–6] and also their wide applications as catalysts, anti-fouling agents, agricultural biocides, anti-tumor agents and other biological activities [7–10]. Organometallic complexes of group 14 elements, especially tin (IV) and silicon (IV) derivatives have been the subject of considerable interest [11,12] owing to their unique physical, chemical and structural properties [13] favorable to the environment [14]. We have published a few papers on silicon complexes, silatranes, organolead complexes with amino acids and dipeptides [15–29]. As all the organotin (IV) derivatives degrade by chemical action to produce non-toxic inorganic complexes so we are attempting to explore the chemistry of tin (IV) complexes. For fast and effective relief of pain and inflammation in humans with minimum side effects continue to be a major challenge for medicinal chemistry researchers. Many diorganotin (IV) derivatives have been found to have the potential to be placed in the class of non-steroidal anti-inflammatory drugs [30–34].

Chlordiazepoxide (L^1H) is benzodiazepine derivative with hypnotic action [35] while Choline theophyllinate (L^2H) also known as oxtriphylline, is a cough medicine derived from xanthine which acts as a bronchodilator to open up airways in the lungs [36]. Phenobarbital (L^3H) is a barbiturate and the most widely used anticonvulsant worldwide [37]. In this paper, we are reporting the

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synthesis, spectroscopic characterization and biological activities of series of di- and tri-organotin (IV) complexes of Chlordiazepoxide (Fig. 1), Choline theophyllinate (Fig. 2) and Phenobarbital sodium (Fig. 3).

2. Experimental

2.1. Materials and methods

All the di- and tri-organotin (IV) complexes were purchased from Sigma–Aldrich and were used as such. The reactions were carried out under strict anhydrous conditions and adequate care was taken to keep the organotin (IV) complexes, chemicals and glass apparatus free from moisture. The solvents used were dried before use according to the literature method. Melting points were determined in a capillary tube on an electrothermal melting point apparatus. IR spectra for the complexes **1**–**9** were recorded on a Perkin Elmer FTIR spectrophotometer at 4000–200 cm^{-1}. The ^{1}H, ^{13}C and ^{119}Sn NMR were recorded on a Bruker Avance II 400 NMR Spectrometer. All chemical shift values were reported with respect to tetramethylsilane as internal standard. CHN analysis of the samples was performed on the Perkin Elmer model 2400 C H N analyzer. Cell turbidity for the soluble complexes was measured by taking Optical density on Perkin Elmer UV–Visible spectrophotometer at 600 nm.

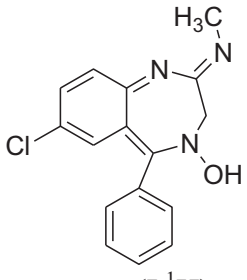
2.2. Synthesis and biological activity

2.2.1. Synthesis of dibutyltin, dioctyltin and bis(tributyltin)oxide complexes of Chlordiazepoxide (L^1H) and Choline theophyllinate (L^2H)

Dialkyl/trialkyltin (IV) oxide [1 mmol] and ligands (L^1H, L^2H) [2 mmol] were dissolved in benzene–methanol (3:1) mixture. The reaction mixture was refluxed for about 4 h until a clear solution was obtained. The contents were then filtered and benzene was added to remove the water produced due to condensation. Excess of solvent was removed by distillation to leave behind a solid complex. All the solid complexes were recrystallized from the mixture of methanol and hexane (5:1) and dried in *vacuo* at 40–50 °C for 2–3 h. The purity of the complexes was checked by TLC using silica gel-G as adsorbent.

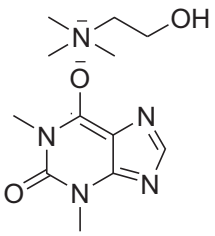
2.2.2. Synthesis of dimethyltin, dibutyltin and diphenyltin dichloride complexes of Phenobarbitone sodium (L^3H)

Dialkyltin (IV) dichloride [1 mmol] and the sodium salt of the ligand (L^3H) [2 mmol] were dissolved in benzene–methanol (3:1) mixture. The reaction mixture was refluxed for about 4 h till the whole of white sodium chloride salt separated out which is removed by filtration and the contents were finally cooled. Excess of solvent was removed by distillation and dried under vacuum to obtain a solid complex. All the solid complexes were recrystallized from the mixture of methanol and hexane (5:1) and dried in *vacuo* at 40–50 °C for 2–3 h. The purity of all the complexes was checked by TLC using silica gel-G as an adsorbent.



(L^1H)
Chlordiazepoxide

Fig. 1. Chlordiazepoxide.



(L^2H)
Choline theophyllinate

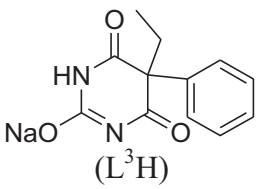
Fig. 2. Choline theophyllinate.

2.2.3. Biological activity

The antimicrobial activity of the soluble organotin (IV) complexes from **1**–**9** have been studied on six indicator strains: *Bacteriodes fragilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Vibrio cholerae* and *Listeria monocytogenes* procured from a Microbial Type Culture Collection, India. The organisms were cultured and incubated at different temperatures as given in Table 1 along with their respective medias. For all the experiments, actively proliferating log phase cells were taken and grown at the final concentration of 100 ppm. 1×10^5 cells of indicator strains as counted by haemocytometer [38] were used per ml of the media as inoculum. Growth of cells was measured by optical density measurements at 600 nm.

The interaction of R_2SnO [R = *n*-Bu, *n*-Oct] and $(R_3Sn)_2O$ [R = *n*-Bu] with Chlordiazepoxide, Choline theophyllinate and R_2SnCl_2 [R = Me, *n*-Bu and Phenyl] with Phenobarbitone sodium respectively in 1:2 metal:ligands (L^1H, L^2H and L^3H) molar ratio lead to the formation of complexes **1**–**9** (Figs. 4–12) with an azeotropic removal of water in complexes **1**–**6** and through the precipitate formation of sodium chloride in complexes **7**–**9** (Scheme 1). All the synthesized organotin (IV) complexes were obtained in a good yield of 67–71% and were found stable towards air and moisture. The physical properties and analytical data of the organotin (IV) complexes were enlisted in Table 2.

The abbreviation L^n refers to the anion of Chlordiazepoxide ($n = 1$), Choline theophyllinate ($n = 2$) and Phenobarbitone sodium ($n = 3$) respectively. All the complexes were obtained as crystalline solids. Complexes **1**–**9** were soluble in chloroform with one drop of dimethyl sulfoxide.



(L^3H)
Phenobarbitone sodium

Fig. 3. Phenobarbitone sodium.