J. Iran. Chem. Soc., Vol. 7, No. 2, June 2010, pp. 495-499.

JOURNAL OF THE
Iranian
Chemical Society

Biologically Active Organotin(IV) Schiff Base Complexes

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(Received 14 February 2009, Accepted 13 August 2009)

Organotin(IV) complexes with the general formulae R_3ML [R: alkyl (Et, Ph and Bz), M: Sn and L: 1,3-bis(2-hydroxybenzylidene)thiourea were synthesized. The newly synthesized schiff base and its complexes were characterized by elemental analysis, melting point, molecular weight determination, IR and NMR [^1H, ^{13}C and ^{119}Sn] spectral methods. In the light of these techniques, a tetrahedral geometry around the tin atom is proposed for the synthesized complexes. The experimental data have been compared with those in the literature which were found to coincide very well with the assigned structures. The ligands and their tin(IV) complexes were screened *in vitro* for their antibacterial activities. It was found that they possessed significant antibacterial activity and the effect of Ph_3SnL was possibly superior to those of Et_3SnL, Bz_3SnL and ligand. These findings add new insights onto the synthesis of antibacterial drugs as the synthesized compounds showed promising antimicrobial activity.

Keywords: Organotin(IV) complexes, Schiff base, Spectroscopic studies, Antibacterial activities

INTRODUCTION

The first organotin compound was diethyltindiiodide-discovered by Edward Frankland in 1849 [1]. Recently, a great deal of public attention has been focused on the toxicological and ecotoxicological aspects of organotins. Organometallic compounds containing lead, tin, and mercury are all commercially significant [2]. A large number of organotin compounds, for example, are used as pharmaceuticals, pesticides, stabilizers, fire retardants, miticides, molluscicides, marine antifouling paints, surface disinfectants and wood preservatives [3]. Organotins with three organic groups can be powerful fungicides and bactericides, depending on the organic group [4]. Tin has a large number of organometallic derivatives that are used commercially [5]. The demand for them increased the worldwide production of organotin compounds during the last 50 years [6]. Unlike their carbon analogues, tin compounds can also be coordinated to five and even six atoms instead of the regular four [7]. These may accumulate in the food chain and induce imposex in several marine species as well as neurotoxic and immunotoxic effects in higher animals [8]. The discovery of several new organotin species and new applications has led to a renewed interest in organotin complexes.

Shahzadi *et al*., (2005) [9], Echevarria, *et al*., (1999) [10] and Zahid *et al*., (2006) [11] have studied Schiff base ligands and their complexes of Sn(IV), Cu(II), Ni(II), Mn(II), Zn(II) and VO(II) and their effect as antibacterial and antifungal activities. Some of these researchers [12-15] studied the same types of complexes; however, they did not investigate their biological activities. Very little work has however been carried out on the formation of triorganotin(IV) complexes. It is our

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intention to screen these complexes for wide spectrum antimicrobial activities against *Staphylococcus aureus, Escherichia coli and Mycobacterium leprae*.

EEPERIMENTAL

Material and Methods

Analytical grade solvents (methanol, chloroform, petroleum ether, acetone and benzene) supplied by Merck, Germany, were used. Organotin chlorides and NaOH were obtained from Aldrich Chemicals and dimethyl sulphoxide (DMSO) from Fluka Chemicals. The melting points were measured on a Reichert thermometer of F. G. Bode Co. Austria. IR spectra were obtained using an FTIR-165 Bio-Rad Marlin FTIR spectrophotometer in the range 4000-400 cm^{-1}. Elemental analysis was carried out on a Yanaco MT-3 high-speed CHN analyzer with antipyrene as a reference compound. ^{1}H, ^{13}C NMR and ^{119}Sn NMR spectra were recorded on a Brucker AM 270 instrument at 50 MHz using TMS as an internal standard. The conductance of the complexes was measured on a Conductometer HANNA equipped with microprocessor HI 9835 at 17.4 °C. Antibacterial activities were measured by Agar well diffusion method [16]. All reactions were carried out under oxygen-free nitrogen atmosphere. All the glassware were thoroughly washed and dried at 105 °C.

Synthesis of Schiff Base

1,3-Bis(2-hydroxy-benzylidene)thiourea (1). The Schiff base was prepared according to the literature method from thiourea (760 mg, l0 mmol) and salicyaldehyde (2.44 g, 20 mmol) in 50 ml methanol in a 1:2 ratio [17]. This mixture was refluxed for 60 min. The water formed during the reaction was removed by a Dean/Stark trap. Then the mixture was cooled to room temperature and the solvent was removed under reduced pressure. The extract was thoroughly washed with chloroform. The solid complexes were recrystallized from a 1:2 (v/v) mixture of methanol and petroleum ether/chloroform and the residue was eluted from a column of silica gel to give 70% yield as a white solid. m.p.: 140 °C. Molecular mass: 284.33 g mol^{-1}. Molar conductance: 10.04 µs cm^{-1} at 17.4 °C. Anal. for $C_{15}H_{12}N_2O_2S$; Calcd. (%): [C] 63.36. [H] 4.25. [N] 9.85. Found (%): [C] 63.60. [H] 4.68. [N] 9.44. ^{1}H NMR (ppm): δ; 5 (s, 2H, OH). δ; 6.8-7.3 (m, 8H, Ar). δ; 8.1 (s, 2H, CH). ^{13}C NMR (ppm); δ 118-129, 161, 163, 210. IR (cm^{-1}): υ(OH); 3310. υ(CH); 2964. υ(CS); 1600. υ(CN); 1650.

Synthesis of Complexes

1,3-Bis(2-(triethylstannyloxy)benzylidene)thiourea (1a). 1,3-Bis(2-hydroxy-benzylidene)thiourea (**1**) (2.94 g, l0 mmol) was dissolved in 50 ml methanol in a three-necked round bottom flask equipped with a reflux condenser, a thermometer and a drying tube. NaOH (800 mg, 20 mmol) and triethyltin(IV)chloride (4.82 g, 20 mmol) in anhydrous methanol/chloroform (100 ml) were added drop-wise with constant stirring for 30 min. The reaction mixture was then refluxed for 5 h under nitrogen. The reaction was centrifuged and filtered to remove the NaCl. The filtrate was concentrated under vacuum. The combined extracts were washed with brine (50 ml) and the residual was eluted from a column of silica gel with (8:2) Cloroform: acetone solution. All the complexes were recrystallized from a 1:2 (v/v) mixture of methanol and chloroform at low temperature [18]. Yield: 75% as a white solid. m.p.: 178 °C. Molecular mass: 706 g mol^{-1}. Molar conductance: 1228 µs cm^{-1} at 17.4 °C. Anal. for $C_{27}H_{40}N_2O_2SSn_2$; Calcd. (%): [C] 46.72. [H] 5.81. [N] 4.04. Found (%): [C] 46.40. [H] 5.44. [N] 4.34. ^{1}H NMR (ppm): δ 0.5 (q, 18H, CH_3). δ 1.9 (t, 12H, CH_2). δ 6.2-7.0 (m, 8H, Ar). δ 8.6 (s, 2H, CH). ^{13}C NMR (ppm): δ 1.9, 8.7, 118-135, 165, 169, 215. IR (cm^{-1}): *v*(CH): 2990. *v*(CS): 1620. *v*(CN): 1638. *v*(SnC): 525. *v*(SnO): 435. ^{119}Sn-NMR (ppm): δ -47.5.

1,3-Bis(2-(triphenylstannyloxy)benzylidene)thiourea (1b). The procedure for the synthesis of 1,3-bis(2-(triphenylstannyloxy)benzylidene)thiourea (**1b**) was the same as the one described above. The reactants used were 1,3-bis(2-hydroxy-benzylidene)thiourea (**1**) (2.94 g, l0 mmol), NaOH (800 mg, 20 mmol) and (7.60 g, 20 mmol) triphenyltin chloride. Yield: 70% as a white solid. m.p.: 139 °C. Molecular mass: 982 g mol^{-1}. Molar conductance: 1300 µS cm^{-1} at 17.4 °C. Analysis for $C_{51}H_{40}N_20_20SSn_2$; Calculated (%): [C] 62.35. [H] 4.10. [N] 2.85. Found (%): [C] 62.70. [H] 4.37. [N] 2.53. ^{1}H NMR (ppm): δ 6.0-7.7 (m, 38H, Ar). δ 8.5 (s, 2H, CH). ^{13}C NMR (ppm): δ 118-140, 167, 169, 220. IR (cm^{-1}): *v*(CH): 2900. *v*(CS): 1625. *v*(CN): 1635. *v* (SnC): 550. *v*(SnO): 460. ^{119}Sn-NMR (ppm): δ -46.5.

1,3-Bis(2-(tribenzylstannyloxy)benzylidene)thiourea (1c). The procedure for the synthesis of 1,3-bis(2-(tribenzylstannyloxy)benzylidene)thiourea (**1b**) was the same as the one described above. The reactants used were 1,3-bis(2-hydroxy-benzylidene)thiourea (**1**) (l0 mmol, 2.94 g), NaOH (800 mg, 20 mmol) and (8.55 g, 20 mmol) tribenzyltin chloride. Yield: 70% as a white solid. m.p.: 120 °C. Molecular mass: 1068 g mol^{-1}. Molar conductance: 982 µs cm^{-1} at 17.4 °C. Anal. for $C_{57}H_{52}N_20_2SSn_2$; Calcd. (%): [C] 64.19. [H] 4.91. [N] 2.63. Found (%): [C] 64.49. [H] 4.57. [N] 2.28. ^{1}H NMR (ppm): δ 1.4 (t, 12H, CH_2). δ 6.3-8.0 (m, 38H, Ar). δ 8.1 (s, 2H, CH). ^{13}C NMR (ppm): δ 12.5, 108-137, 161, 166, 218. IR (cm^{-1}): *ν*(CH): 2066. *ν*(CS): 1610. *ν*(CN): 1649. *ν*(SnC): 535. *ν*(SnO): 480. ^{119}Sn-NMR (ppm): δ -40.5.

Agar Well Diffusion Method

The antibacterial activity was determined using the agar well diffusion method [19]. Imipinem was used as the standard drug. The well was dug in the media with a sterile metallic borer with the centers at least 24 mm apart and eight-hour bacterial inoculum containing *ca.* 10^4-10^6 colony-forming units (CFU)/ml was spread on the surface of the nutrient agar using a sterile cotton swab. The recommended concentration of the best sample (2 mg ml^{-1} in DMSO) was introduced into the respective wells. Other wells containing DMSO and the reference antibacterial drug served as negative and positive controls, respectively. The plates were incubated immediately at 37 °C for 20 h. The activity was determined by measuring the diameter of the inhibition zones (in mm) showing complete inhibition. Growth inhibition was calculated with reference to the positive control.

RESULTS AND DISCUSSION

Molar Conductance

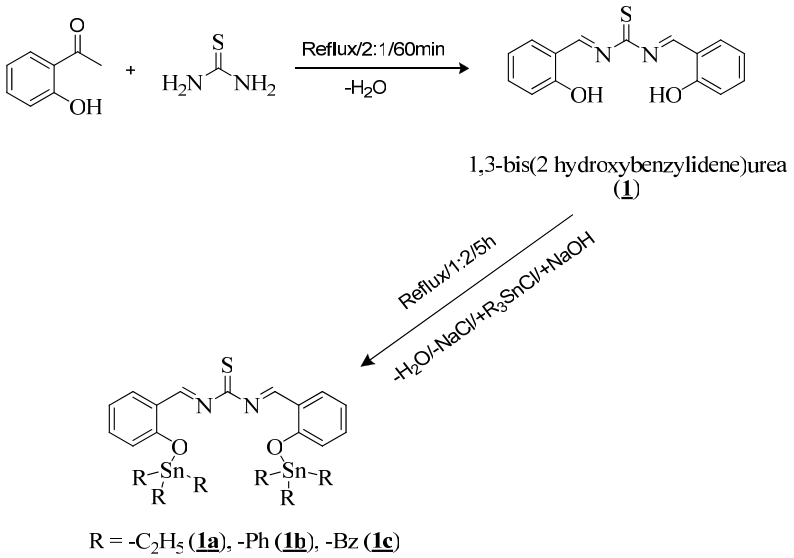
Molar conductances were measured in methanol/DMSO depending upon the solubility. Molar conductances of the synthesized compounds (**1**) (**1a**) (**1b**) (**1c**) showed very low values indicating their non-electrolytic nature. [20].

IR Spectroscopy

The IR spectra of free Schiff base were compared with the spectra of the tin(IV) complexes in order to study the binding mode of the Schiff base to tin(IV) in the new complexes. The lR spectra of Schiff base (**1**) and complexes (**1a**) (**1b**) (**1c**) showed strong absorption bands at 1635-1650 cm^{-1}, which can be attributed to *ν*(C=N) stretching frequency. The IR spectral vibrations in the range of 1700-1600 cm^{-1} is assigned to *ν*(C=N) and *ν*(C=S). These two peaks lie in the same region, so it is difficult to distinguish between them which is a characteristics of schiff base [21]. The IR spectra in schiff base (**1**) of *ν*(OH) shows strong band in the 3310 cm^{-1}, which was found to be absent in the complexes (**1a**) (**1b**) (**1c**). The presence of new bands at 400-600 cm^{-1} for *ν*(Sn-O) and *ν*(Sn-C) in the complexes (**1a**) (**1b**) (**1c**) confirm the complex formations respectively [22]. On the basis of these IR results, we can propose a tetrahedral geometry for the synthesized compounds congruent with those reported in the literature [23].

NMR Spectroscopy

The NMR data are listed in the experimental section, The results indicate that deshielding of protons is observed in all the complexes, which is probably due to electrophilic character of Sn atom [24,25]. The ^{1}H NMR spectra signal at 5 ppm observed in the schiff base (**1**) is assigned to alcoholic protons which is absent in the spectra of complexes (**1a**) (**1b**) (**1c**) indicating the complexation of the ligand moiety to tin [26]. The ^{13}C NMR signals due to the carbon atoms attached to the thionic and the azomethine groups in ligands appear at 163 ppm and 210 ppm which remain at the same position in the spectra of the complexes (**1a**) (**1b**) (**1c**) indicating that these bonds were not involved in the bonding respectively [27]. Protons of the phenyl group were absorbed in the usual region and some additional signals were observed in benzyl derivative (**1c**) [28]. The ^{119}Sn data were compared with those in the literature which were found to be coinciding [29]. The prediction of the geometry can be made by coupling. Such couplings are not observed in the complexes due to overlapping of the signals [30]. According to Rehman *et al*., (2004) triorganotin complexes adopt a tetrahedral geometry in both solution and solid states [18]. The main NMR spectral data of the compounds are in good agreement with the expected structure. On the basis of NMR [^{1}H, ^{13}C and ^{119}Sn] spectral studies, a tetrahedral geometry around the tin atom is proposed through oxygen atom of the ligand moiety [31]. On



Scheme 1. Procedure for the synthesis of schiff base (**1**) and complexes (**1a**) (**1b**) (**1c**)

Table 1. Growth Inhibition Zone (Diameter in Millimeter)

Species	**(1)**	**(2)**	**(3)**	**(4)**	**Imipinem**
M. leprae	+	7	23	7	30
S. aureus	22	29	28	25	31
E. coli	20	30	31	27	35

the basis of the observed spectral evidence, the tentative structures are shown in Scheme 1.

Antibacterial Activities

The antibacterial activity of the synthesized compounds was tested against three different pathogenic bacteria [32]. Growth inhibition studies of the standard drug ((Imipinem) and the synthesized compounds (**1a**) (**1a**) (**1b**) (**1c**) against the different species are as follows.

The data in Table 1 indicate that the schiff base (**1**) and their complexes (**1a**) (**1b**) (**1c**) have a profound antibacterial activity against the two species; namely *E. coli* and *S. aureus*. Among the complexes, the activity of the complex (**1a**) remained lower than those of the complexes (**1b**) and (**1c**). It can be noted that compounds with phenyl groups showed the greatest inhibitory effect on one or more types of bacteria as compared to alkyl groups in the same position. The results compared with the standard drug (Imipinem) indicate that the compounds are active, however, their activity is less than that of the standard drug [33]. Trialkyltin complexes have previously been reported to have an effective control against *E. coli* and *S. aureus*, which is similar to the activity of the compounds synthesized in this study [34]. The order of increasing antibacterial activities was schiff base < Me_3SnL < Bz_3SnL < Ph_3SnL, which matches with the previously reported data for the biological activity of organotin complexes [35]. Bacteria are very resilient and have already developed resistance to many commonly used antibiotics [36]. This may open up new avenues for exploiting new drugs [37,38]. The goal of this paper was to focus specifically on the scientific challenges of antibacterial research; hence, it could be used as a model for specialists around the world [39,40].

AKNOWLEDGEMENTS

We thank Hazara University, Mansehra, Pakistan, Quaid-i-

Azam University, Islamabad, Pakistan, COMSATS Institute of Information Technology, Abbottabad, Pakistan and Sarghoda University, Sarghoda, Pakistan for the provision of laboratory facilities and financial assistance.

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