

Biologically Active Organotin (IV) Complexes of Schiff Bases Derived from Indoline-2,3-dione and 2-aminobenzoic Acid

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Abstract: Organotin (IV) complexes with the general formulae R_3SnL (R: alkyl and L: Schiff base) were prepared using a novel ligand (1) and their antibacterial activity was investigated by using the agar well diffusion methods. The synthesized compounds were capable of showing biocidal activity against *Staphylococcus aureus*. The order of increasing activities was ligand < Me_3SnL < Bz_3SnL < Ph_3SnL . The results provided evidence that the studied complexes might indeed be potential sources of antimicrobial agents and these would further enable us to evaluate their utility in biomedical field. On the basis of (¹H, ¹³C) NMR, IR and Elemental analysis the trigonal bipyramidal geometry is proposed for the synthesized compounds.

Key words: Organotin • Schiff base • Complexes • Spectral studies • Antibacterial activity

INTRODUCTION

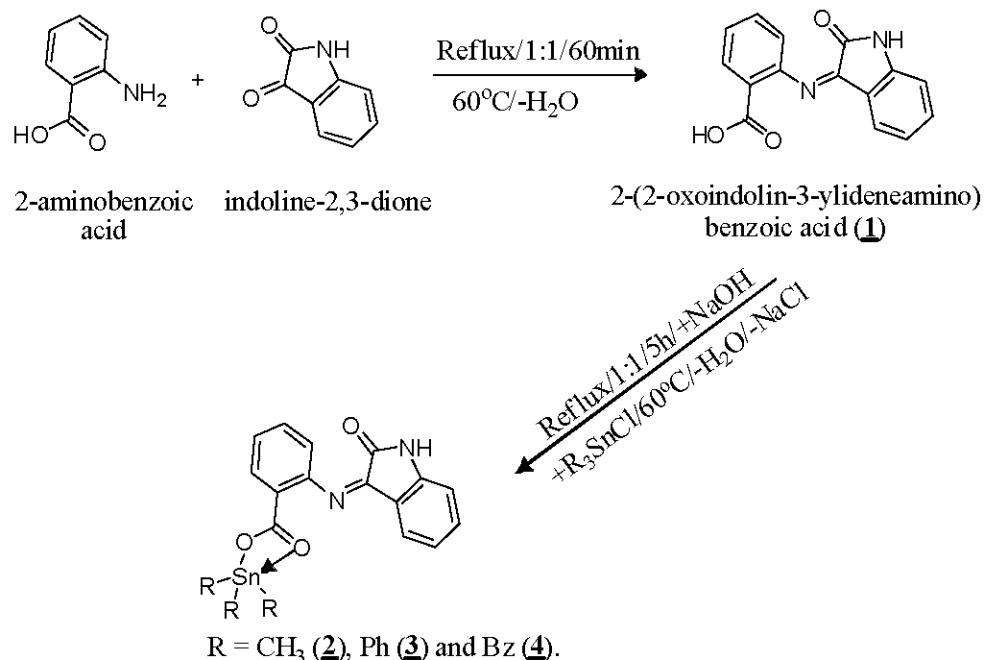
Organometallic compounds containing lead, tin and mercury are all commercially significant [1]. Organotins with three organic groups can be powerful fungicides and bactericides, depending on the organic group (R) and their demand increased the worldwide production of organotin compounds during the last 50 years [2]. In recent years, the most active bioinorganic chemistry research area as concerns organotin(IV) compounds is the investigation of their antimicrobial activity [3]. Organotin compounds have also been found to be biologically active as they show antitumour, antifouling and antimicrobial activities [4]. *Staphylococcus aureus* is a spherical gram-positive bacterium, can cause a wide variety of infections in humans and other animals through either toxin production or invasion [5]. Food poisoning and Staphylococcal scalded skin syndrome are a common cause of *Staphylococcus aureus* [6]. The treatment of choice for *Staphylococcus aureus* infection is Penicillin, but in most countries, penicillin-resistance is extremely common [7,8]. Several authors have been studied the organotin complexes [9,10] while some have also studied the extracts of plant for antibacterial activities against

Staphylococcus aureus [11,12]. Bacterial diseases pose a greater threat; hence the need to find cheap and effective antibacterial agents is necessary [13]. The uses of natural and synthetic compounds are important in the control of bacteria diseases [14].

In the present contribution a complexation of Sn(IV) with a novel Schiff base ligand is reported. Furthermore, it was also intended to screen these complexes for antibactericidal activities against *Staphylococcus aureus*. Thus the present results will add new information in pharmaceutical industry to synthesize antibacterial and antifungal drugs as the synthesized compounds showed promising antimicrobial activity.

RESULTS AND DISCUSSION

The schiff base, [2-(2-oxoindolin-3-ylideneamino) benzoic acid] derived from indoline-2,3-dione and 2-aminobenzoic acid has been prepared. This novel ligand was then used to form complexes with different tin(IV) compounds. These complexes were synthesized by the reaction of organotin(IV) halide with ligand in the presence of a base. The reaction was carried out at a reflux temperature 60°C using benzene/methanol in 30:70 ratios.



Scheme 1: Structure of schiff base (1) and complexes (2, 3, 4)

The complexes were in a good yield of 75-80% yield. On the basis of IR, NMR [¹H, ¹³C and ¹¹⁹Sn] spectral studies, trigonal bipyramidal geometry around the tin atom has been proposed through oxygen atom of the ligand moiety (Scheme 1). The analytical data of the newly formed complexes agrees very well with the proposed molecular structure [15]. These results encourage us to report these compounds.

The biological activities of the complexes were also tested against staphylococcus which was close to the standard drug. Molar conductance values of the complexes and schiff bases show very low values of molar conductance indicating their non-electrolytic nature [16].

Spectroscopy: The IR spectra of the free ligand was 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. Shahzadi *et al.*, have successfully employed infrared spectroscopy for identification of organotin [17]. The IR spectra in schiff base shows deprotonation. When spectra of schiff base and complex were compared, more bands were observed in the complexes. The peaks lie in the range 1700-1750 cm⁻¹ and 2964 cm⁻¹ in the ligand (1) and complexes (2)(3)(4) confirm the presence of ν(C=O) and ν(C-H) group respectively. The explicit feature in the spectra of complexes was the presence of bands at 400-600 cm⁻¹ for

ν(Sn-O) and ν(Sn-C) indicating the complex formation. The ν(Sn-C) and ν(Sn-O) vibrations were observed in the range of 500-560 cm⁻¹ and 450-480 cm⁻¹ respectively. The IR spectra of schiff base (1) and complexes (2)(3)(4) showed strong absorption bands at 1600-1700 cm⁻¹, which can be attributed to ν(C=O) and ν(C=N) stretching frequency respectively, these two peaks lie in the same region, so it is difficult to distinguish between them which are the characteristics of Schiff base [18]. On the basis of the IR results discussed, we can propose the trigonal bipyramidal geometry to the synthesized compounds as reported in the literature [19].

Tin-alkyl protons due to the ¹H-NMR are observed in the regions 0.31-8.5 (ppm) while ¹³C-NMR are observed in the regions 10.0-200 (ppm). In ¹H-NMR spectra -OH signal observed at 5 ppm which were absent in the complexes (2)(3)(4) indicated the deprotonation of alcoholic proton and the complexation of the schiff base. In ¹H-NMR the chemical shift at 6.5-7.5 (ppm) is due to aromatic ring in the ligand, which shifts to 6.3-7.9 (ppm) on complexation and some additional peaks have been observed due to benzyl group at 7.5-8.0 (ppm). The C=N and C=O peaks were observed at 163 ppm and 191-193 (ppm) in ligand and complexes which indicated that these bonds were not involved in the bonding. The NMR data are listed in experimental section and the results conclude that deshielding of protons is observed in all the complexes,

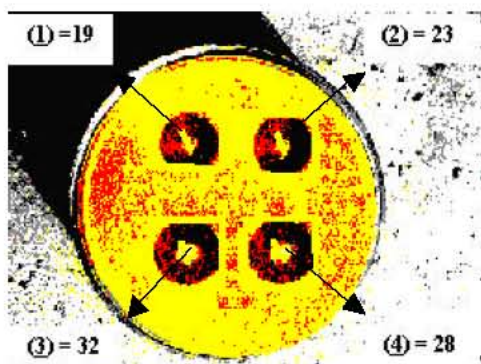


Fig. 1: Antistaphylococcus activities (millimeter inhibition zone)

which is probably due to electrophilic character of Sn atom and coordination of the carbonyl oxygen atom in all complexes [20,21-]. The prediction of geometry can be assigned by coupling such coupling are not observed in complexes due to overlapping of signals [22]. According to Rehman *et al.*, triorganotin complexes adopt trigonal bipyramidal geometry in solution and solid states [23]. It is generally accepted that compounds with different geometries about the tin atom produce shifts in moderately well defined charges -90 to -190 (ppm) for trigonal bipyramidal complexes. Sn-NMR chemical shifts of compounds are in the -ive ranges which are in consistent with the literature reported data for trigonal bipyramidal complexes [24]. Hence, on the basis of NMR [^1H , ^{13}C and ^{119}Sn] spectral studies the tin(IV) atoms are five coordinated in case of complexes (2)(3)(4) and therefore the expected geometry arrangement around triorganotin(IV), in solution, is suggested as trigonal bipyramidal which is in accordance with earlier reports [25].

Antibacterial Activities: Agar well diffusion method has been used for the activity of Schiff base ligand and complexes against *Staphylococcus aureus*. Data revealed that the ligand and complexes had significant antimicrobial activities against the pathogenic bacteria. The results compared with standard drug (Imipinim) have indicated that compounds were active but activity was lesser than the standard drug. Figure 1 shows the antistaphylococcus activities and the assessment is based on % inhibition.

This activity might be due to the presence of a hydroxyl and phenyl groups [26]. The increased activity in the organotin complexes may be due to the coordination and polarity of a tin (IV) atom with oxygen of the ligand [27]. The order of increasing activities is;

ligand < Me_3SnL < Ph_3SnL < Bz_3SnL , the results matched with the previously reported data for the biological activity of organotin complexes [28]. Further, it has been concluded that the organotin compounds are more active than the free ligands, which indicate that metallation increases antibacterial activity which is in accordance with earlier reports [29]. The novel synthesized compounds are cost effective and are easy to synthesize. It is likely that the new complexes might be more environments friendly. There have been several reports dealing with the impact of organotin chemistry in the biosphere. Controlling resistant bacteria is an increasingly challenging endeavor and is a major concern for specialists around the world [30]. Likewise, the results provided evidence that the studied complexes might indeed be potential sources of antimicrobial agents [31].

Experimental: The melting points were measured on a Reichert thermometer of F. G. Bode Co. Austria. Molar conductance of the organotin (IV) complexes has been measured in methanol on a Conductometer HANNA equipped with microprocessor HI 9835 at 17.4°C. IR spectra were obtained while using a FTIR-1605 Bio-Rad Marlin FTIR spectrophotometer in the range 4000-400 cm^{-1} . ^1H , ^{13}C NMR and ^{119}Sn NMR spectra were recorded on a Bruker AM 270 instruments at 50 MHz using TMS as an internal standard. Analytical grade solvents (Methanol, chloroform, petroleum ether, acetone and benzene) supplies by Merck, Germany were used. Organotin chlorides and NaOH were obtained from Aldrich Chemicals. Organotin chlorides and NaOH by Aldrich chemicals and dimethyl sulphoxide DMSO by Fluka chemicals were used and antimicrobial activities of the organotin (IV) complexes have been measured in DMSO or methanol of Fluka Chemicals.

Synthesis of Schiff Base:

2-(2-oxoindolin-3-ylideneamino) Benzoic Acid (1): The [2-(2-oxoindolin-3-ylideneamino) benzoic acid (1) was prepared from indoline-2,3-dione (2.94g, 20mmol) and 2-aminobenzoic acid (2.74g, 20mmol) according to method of Kadir [32]. This mixture was refluxed in anhydrous methanol for 1h. The water formed during the reaction was removed by a Dean/Stark trap. Then the mixture was cooled to room temperature and the mixture was extracted with acetone (3x30mL) and the solvent was removed under reduced pressure. The combined extracts were washed with brine (50mL) and the residual was eluted from a column of silica gel with chloroform: acetone solution (8:2). The residue was eluted from a column of

silica gel to give 70% yield as a white solid. m.p; 129°C. Mol. wt.: 266.25g/mol. Molar conductance. 10.04 μ S at 17.4°C. Analysis for C₁₅H₁₀N₂O₃. Calculated (%): C, 67.67; H, 3.79; N, 10.52. Found (%): C, 67.60; H, 3.24; N, 10.24. IR (cm⁻¹): ν (OH) = 3313. ν (CH) = 2920. ν (C=O) = 1710. ν (C=N) = 1650. ¹H-NMR (ppm): δ 11 (s, 1H, -OH). δ 7.3-8 (m, 8H, Ar). δ 8.0 (s, 1H, N-H). ¹³C-NMR (ppm): δ 117-154, 163, 167, 169, 193.

Synthesis of Complexes

Trimethylstannyl 2-(2-oxoindolin-3-ylideneamino)

Benzoate (2): The ligand (2.6g, 10mmol) was dissolved in 25mL of methanol in a three-necked round bottom flask equipped with a reflux condenser, thermometer and a drying tube. Stoichiometric amount of NaOH was added, followed by the appropriate amount of trialkyltin chloride in methanol (50mL), drop wise with constant stirring for 10-30 minutes. The reaction mixture was then refluxed for 4-5 hours under nitrogen under TLC control. The reaction was centrifuged and filtered to remove the NaCl. The filtrate was concentrated under vacuum. The solid complexes were recrystallized from a 1:2 (v/v) mixture of methanol and chloroform. Physical state: amorphous solid; m.p = 138°C. Yield: 73%. Mol. wt. 429.06g/mole. Molar conductance: 1132.80 μ S at 17.4°C. Analysis for C₁₈H₁₈N₂O₃Sn. Calculated (%): C, 50.22; H, 4.33; N, 6.89. Found (%): C, 50.40; H, 4.27; N, 6.53. IR (cm⁻¹): ν (CH)=3066. ν (C=O)=1710. ν (C=N)=1660. ν (Sn-C)=521. ν (Sn-O) = 446. ¹H-NMR (ppm): δ 2.34 (q, 9H, CH₃). δ 7-8.1 (m, 8H, Ar). δ 8.2 (s, 1H, N-H). ¹³C-NMR (ppm): δ 28.03, 124-154, 162, 168, 191. ¹¹⁹Sn-NMR (ppm): δ -61.

Triphenylstannyl 2-(2-oxoindolin-3-ylideneamino)

Benzoate (3): The procedure for synthesis of triphenylstannyl 2-(2-oxoindolin-3-ylideneamino) benzoate (2) is the same as described above. Physical state: amorphous solid; m.p = 149°C. Yield: 78%. Mol. wt: 589.27g/mole. Molar conductance: 132.80 μ S at 17.4°C. Analysis for C₃₁H₂₂N₂O₃Sn. Calculated (%): C, 63.22; H, 3.33; N, 4.89. Found (%): C, 63.40; H, 3.27; N, 4.53. IR (cm⁻¹): ν (CH) = 3050. ν (C=O) = 1700. ν (C=N) = 1660. ν (Sn-C) = 555. ν (Sn-O) = 470. ¹H-NMR (ppm): δ 6.7-8.2 (m, 23H, Ar). δ 8.3 (s, 1H, N-H). ¹³C-NMR (ppm): δ 118-160, 163, 168, 190. ¹¹⁹Sn-NMR (ppm): δ -79.

Tribenzylstannyl 2-(2-oxoindolin-3-ylideneamino)

Benzoate (4): The procedure for synthesis of tribenzylstannyl 2-(2-oxoindolin-3-ylideneamino) benzoate (3) is the same as described above. Physical state:

amorphous solid; m.p = 132°C. Yield: 75%. Mol. wt: 656.36g/mol. Molar conductance. 1328 μ S at 17.4°C. Analysis for C₃₆H₃₀N₂O₃Sn. Calculated (%): C, 65.39; H, 4.58; N, 4.58. Found (%): C, 65.19; H, 4.27; N, 4.58. IR (cm⁻¹): ν (CH) = 3092. ν (C=O) = 1719. ν (C=N) = 1630. ν (Sn-C) = 522. ν (Sn-O) = 422. ¹H-NMR (ppm): δ 1.6 (t, 6H, CH₂). δ 6.7-8.2 (m, 23H, Ar). δ 8.3 (s, 1H, N-H). ¹³C-NMR (ppm): δ 13.9. 128-158, 162, 172, 192. ¹¹⁹Sn-NMR (ppm): δ -46.5.

Agar Well Diffusion Method: The antibacterial activity was determined using the agar well diffusion method developed by Rehman [33]. The well was dug in the media with a sterile borer and eight-hour bacterial inoculum containing ca. 104-106 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 (2mg/ml in DMSO) was introduced into 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 20h. The activity was determined by measuring the diameter of the inhibition zone (in mm) showing complete inhibition. Growth inhibition was calculated with reference to the positive control.

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