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Synthesis, Characterization and Antimicrobial Evaluation of Schiff base Complexes Derived from [2,2´-(ethylenedioxy)bis(ethylamine)] and 5-Chlorosalicylaldehyde

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ABSTRACT

In this abstract a brief account is given of the synthesis, stereochemistry and antibacterial behavior of organotin (IV) complexes of Schiff base derived from 2,2'-(ethylenedioxy)bis(ethylamine) and 5-chlorosalicylaldehyde in 1:2 molar ratio. The compounds have been characterized by spectroscopic techniques (UV-Vis, IR and NMR). The penta coordinated complexes were obtained which coordinate through azomethine nitrogen and hydroxyl oxygen. The synthesized compounds have been investigated for their antimicrobial activity against Gram positive bacteria viz. Staphylococcus epidermidis, Staphylococcus hominis and Gram negative bacteria viz. Pseudomonas aeruginosa and Klebsiella pneumonia and fungus Aspergillus niger. The studies established that phenyl derivatives exhibited better antibacterial activities than standard drug ciprofloxacin. For most of the complexes, higher activity was displayed on coordination with silicon atom than respective ligand due to lipophilic nature of tin atom which favours the permeation of the complexes in the cell to be used as the bactericides.

Keywords: Organotin complexes, 5-chlorosalicylaldehyde, 2,2′-(ethylenedioxy)bis(ethylamine), Antimicrobial, Spectral studies

INTRODUCTION

The chemistry of compounds containing N, O and S donor atoms is of great significance since they exhibit a wide range of physicochemical properties and biological activities [1,2]. The coordination chemistry of Schiff base ligands has also achieved attention due to different coordination mode associated with them. It has been also reported that metal complexes of biologically active compounds have superior activities compared to the non-coordinated ligands [3-6]. Among N and O donor ligands, Schiff base of 5-chlorosalicylaldehyde with 2,2′-(ethylenedioxy)bis(ethylamine) are known to possess a wide variety of biological applications, including antimicrobial, antitubercular, antimalarial and anti-inflammatory activities [7-9]. The salicylaldehyde nucleus has been incorporated into a wide variety of therapeutically interesting molecules to convert them into improved drugs [10-12].

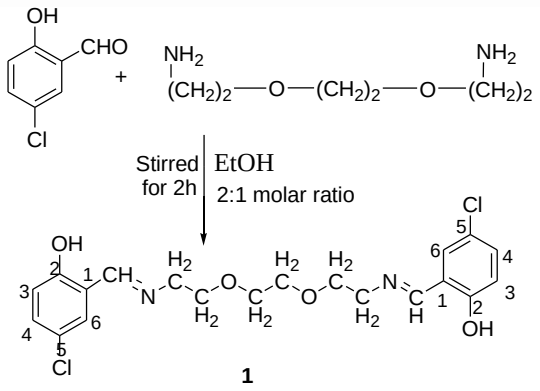
In this study we report synthesis, characterization and antibacterial activity of tin complexes derived from [2,2´-(ethylenedioxy)bis(ethylamine)] and 5-chlorosalicylaldehyde Schiff base. The ligand and their organotin (IV) complexes have been characterized with the help of conductance measurements, elemental analyses, UV-Vis, IR, NMR (^{1}H, ^{13}C and ^{119}Sn) spectroscopy. All the synthesized compounds have been evaluated against bacterial and fungal strains.

MATERIALS AND METHODS

All of the chemicals were of reagent grade (supplied by Sigma-Aldrich and Qualigen) and used as received without further purification. All the reactions were carried out in dry atmosphere and solvents were dried before use [13]. The IR spectra were recorded using a Spectrum BX Series FT-IR spectrophotometer in the range 400-4000 cm^{-1}, using KBr pellets. The NMR (^{1}H, ^{13}C and ^{119}Sn) spectra were recorded on a Bruker Avance II 300 MHz NMR Spectrometer and all chemical shifts (δ) were reported in parts per million (ppm) downfield from the internal standard Tetramethylsilane (TMS) in $CDCl_3$ and DMSO-d_6. The electronic spectra were recorded in methanol and DMF on a UV-Vis-NIR Varian Cary-5000 spectrometer. Elemental analyses were carried out on a Perkin Elmer 2400 analyzer. Molar conductance was measured with conductivity bridge type model-306 Systronics in DMSO solvent. Powder XRD was carried out on Rigaku-miniflex-II with a source of radiation Cu-K_a (1.54 Å).

Synthesis of Schiff base ligand

Schiff base ligand H_2L was prepared by reaction of 1.46 ml (10 mmol) 2,2′-(ethylenedioxy)bis(ethylamine) and 1.56 g (20 mmol) 5-chlorosalicylaldehyde [1:2 molar ratio] in dry ethanol and stirred for 2 h (Scheme 1). Light yellow colored crystalline product obtained was recrystallized from ethanol and dried under vacuum. Progress of reaction was monitored by Thin Layer Chromatography (TLC).

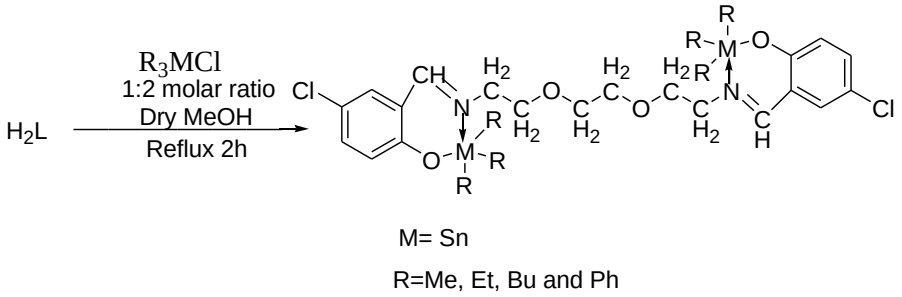


Scheme 1: Synthesis of ligand

H_2L [1] Yield: (88%). Anal. Calcd. for $C_{20}H_{22}Cl_2N_2O_4$: C (56.48); H (5.21); N (6.59). Found: C, 56.50; H, 5.20; N, 6.58%. ^{1}H-NMR [400 MHz, DMSO, δ(ppm)]: 11.22 (s,1H, OH), 10.80 (s,1H,-N=C-H), 8.57-8.59 (d, H-3), 7.81-7.83 (d, H-4), 7.39 (s, H-6), 4.21-4.29 (t, 2H, Hb), 2.49-2.52 (t, 2H, Ha), 2.32 (s, 2H, Hc). ^{13}C-NMR [400 MHz, DMSO δ (ppm)]: δ=166.40 (HC=N), 161.20 (C-OH), 138.03 (C-4), 134.93 (C-6), 129.66 (C-1), 127.54 (C-5), 119.27 (C-3), 70.57 (C-b), 66.84 (C-c), 59.07 (C-a). FT-IR (*v*, cm^{-1}): 3041 (br), 1618 (m).

Synthesis of complexes

R_3SnCl was added slowly to the weighed amount of Schiff base ligand H_2L in 2:1 molar ratio and reaction mixture was refluxed for 2 h (Scheme 2). After completion of reaction the final product obtained was recrystallized from dry hexane and finally dried under reduced pressure.



Scheme 2: Synthesis of complexes

$Me_3Sn(L)$ [2] Yield: (84%). Anal. Calcd. for $C_{26}H_{38}Cl_2N_2O_4Sn_2$: C, 41.49; H, 5.10; N, 3.73; Sn, 31.62. Found: C, 41.51; H, 5.12; N, 3.70; Sn, 31.61%. ^{1}H NMR [400 MHz, $CDCl_3$, δ(ppm)]: 8.65 (s,1H,-N=C-H), 7.83 (s, H-6), 7.64-7.66 (d, H-4), 6.87-6.90 (d, H-3), 3.67-3.69 (t, 2H, Hb), 3.59-3.61 (t, 2H, Ha), 1.61 (s, 2H, Hc), 0.07 (s, 6H, Me), ^{13}C-NMR [400 MHz, $CDCl_3$, δ (ppm)]: 188.21 (C=N), 168.55 (C-OH), 132.93 (C-4), 131.67 (s, C-6), 118.99 (C-1), 118.72 (C-5), 117.09 (C-3), 70.00 (C-b), 60.22 (C-c), 45.88 (C-a), 8.05 (Me), ^{119}Sn NMR [300 MHz, $CDCl_3$, δ (ppm)]: −309. FT-IR (*v*, cm^{-1}): 1600 (m), 440 (Sn-N), 621 (Sn-O).

$Et_3Sn(L)$ [3] Yield: (75%). Anal. Calcd. for $C_{32}H_{50}Cl_2N_2O_4Sn_2$: C, 46.02; H, 6.04; N, 3.35; Sn, 28.43. Found: C, 46.00; H, 6.06; N, 3.36; Sn, 28.46%. ^{1}H-NMR [400 MHz, $CDCl_3$, δ (ppm)]: 8.80 (s, 1H, -N=C-H), 7.92 (s, H-6), 7.79-7.84 (d, H-4), 7.01-7.05 (d, H-3), 3.70-3.75 (t, 2H, Hb), 3.61-3.62 (t, 2H, Ha), 2.00 (s, 2H, Hc), 1.20-1.30 (t, 6H, Et), 0.21-0.31 (m, 4H, Et). ^{13}C-NMR [400 MHz, $CDCl_3$, δ(ppm)]: 188.65 (C=N), 168.43 (C-OH), 132.76 (C-4), 131.55 (C-6), 118.92 (C-1), 118.47 (C-5), 117.67 (C-3), 70.87 (C-b), 61.81 (C-c), 49.88 (C-a), 45.58 (Et), 10.71 (Et), ^{119}Sn NMR [300 MHz, $CDCl_3$, δ (ppm)]: −311. FT-IR (*v*, cm^{-1}): 1599 (m), 439 (Sn-N), 620 (Sn-O).

$Bu_3Sn(L)$ [4] Yield: (79%). Anal. Calcd. for $C_{44}H_{74}Cl_2N_2O_4Sn_2$: C, 52.67; H, 7.43; N, 2.79; Sn, 23.66. Found: C, 52.65; H, 7.45; N, 2.80; Sn, 23.69%. ^{1}H-NMR [400 MHz, $CDCl_3$, δ (ppm)]: 8.83 (s, 1H, -N=C-H), 8.00 (s, H-6), 7.81 (d, H-4), 7.09-7.12 (d, H-3), 3.70-3.74 (t, 2H, Hb), 3.63-3.65 (t, 2H, Ha), 2.05 (s, 2H, Hc), 0.62-0.66 (t, 6H, Bu), 0.92-0.96 (m, 8H, Bu), 1.47-1.51 (t, 4H, Bu). ^{13}C-NMR [300 MHz, $CDCl_3$, δ (ppm)]: 186.20 (C=N), 169.88 (C-OH), 132.49 (C-4), 131.51 (C-6), 119.06 (C-1), 118.89 (C-5), 117.82 (C-3), 67.22 (C-b), 59.01 (C-c), 45.08 (C-a), 45.89 (Bu), 26.81 (Bu), 19.49 (Bu), 9.89 (Bu). ^{119}Sn NMR [300 MHz, $CDCl_3$, δ (ppm)]: −312. FT-IR (*v*, cm^{-1}): 1598 (m), 442 (Sn-N), 621 (Sn-O).

$Ph_3Sn(L)$ [5] Yield: (80%). Anal. Calcd. for $C_{56}H_{50}Cl_2N_2O_4Sn_2$: C, 59.88; H, 4.49; N, 2.49; Sn, 21.14. Found: C, 59.86; H, 4.51; N, 2.53; Sn, 21.10%. ^{1}H-NMR [400 MHz, $CDCl_3$, δ (ppm)]: 8.91 (s, 1H, -N=C-H), 8.11 (s, H-6), 7.91-7.99 (m, 10H, Ph), 7.83-7.86 (d, H-4), 7.16-7.18 (d, H-3), 3.74-3.77 (t, 2H, Hb), 3.67-3.70 (t, 2H, Ha), 2.11 (s, 2H, Hc). ^{13}C-NMR [300 MHz, $CDCl_3$, δ (ppm)]: 187.22 (C=N), 169.73 (C-OH), 137.87 (Ph), 135.95 (Ph), 130.35 (Ph), 128.97 (Ph), 132.65 (C-4), 131.26 (C-6), 119.20 (C-1), 118.68 (C-5), 117.55 (C-3), 67.38 (C-b), 59.38 (C-c), 46.08 (C-a). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: -307. FT-IR (*v*, cm^{-1}): 1600 (m), 440 (Sn-N), 621(Sn-O).

Biology

Test microorganisms

Two Gram-positive bacteria *viz. Staphylococcus epidermidis* (MTCC 3086), *Staphylococcus hominis* (MTCC 4435) and two Gram-negative bacteria *viz. Pseudomonas aeruginosa* (MTCC 7453) and *Klebsiella pneumonia* (MTCC 4030) and fungus *Aspergillus niger* (MTCC 1344) were used for antibacterial assay. All the bacterial strains were procured from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), and Chandigarh. The strains were cultured at 37°C on nutrient agar medium in aerobic conditions for 24 h.

Antibacterial assays

The synthesized ligand and organotin complexes were screened for antimicrobial activity using microdilution technique [14] and their Minimum Inhibitory Concentration *(*MIC) was determined. The microbial inoculums were prepared in 5 mL nutrient broth and incubated at 37°C for 48 h. The final inoculums were of approximately 1.5×10^6 CFU/ml (Mcfarland standard). Controls with 0.5 ml of culture medium without the test samples compounds and other without microorganisms were used in the tests. Tubes were incubated at 37°C for 24 h. The activity was measured as a function of turbidity. Lack of turbidity was further confirmed by pouring suspension aliquot of 0.1 ml into pre-sterilized petri dishes with nutrient agar medium.

RESULTS AND DISCUSSION

Chemistry

The Schiff base ligand H_2L was prepared by reaction of 2,2′-(ethylenedioxy)bis(ethylamine) and 2-hydroxy benzaldehyde in 1:2 molar ratio in ethanol (Scheme 1). The spectral data and elemental analysis of the synthesized ligand and their complexes were according to their structure. Molar conductance values of 10^{-3} M solution of these compounds fall in the range of 08-17 $ohm^{-1}.cm^2.mol^{-1}$ indicated non-electrolytic nature.

Electronic spectra

The nature of the ligand field around the central atom was assumed from the electronic spectra. The spectra of ligands H_2L exhibited a maxima at 396 nm, which may be due to the n-π* transition of the azomethine group [15]. Blue shift in the complexes was due to metal-ligand interaction caused by polarization within the >C=N─ chromophore group, showing the participation of azomethine nitrogen in coordination with silicon and tin atom. Occurrence of some medium intensity bands at 210-229 nm in Schiff base ligands indicated π-π* transition of benzene ring. These bands remain almost unchanged in the electronic spectra of complexes, indicating non-involvement of benzene ring in bond formation.

IR spectra

IR spectrum of free ligand was compared with complexes and the formation of ligand [H_2L] was confirmed by the absence of important stretching vibrations due to aldehyde *ν*(CHO) and amino *ν*(NH_2) moieties and a strong new band appeared at 1618 cm^{-1} which corresponds to the azomethine *ν* (H-C=N-) group. In the spectra of complexes, *ν*(O-H) stretching modes at 3041 cm^{-1} of ligand, were disappeared in the complexes revealed the deprotonation of the hydroxyl OH group of H_2L [16]. Similarly, band due to the *ν*(C=N) in the ligand, was shifted to lower frequencies on coordination, suggesting the involvement of azomethine group to form five membered chelate rings at Sn centers. The formation of the complexes was also supported by appearance of new bands at 419-450 cm^{-1} and 614-646 cm^{-1} due to *ν*(Sn-N) and *ν*(Sn-O) modes respectively. The spectral region for all the complexes is more or less similar due to the similarity in coordination modes of the ligands with metal centres.

NMR spectra

The signals at *δ* 11.22 due to OH proton of 1 disappeared in the complexes indicating the deprotonation of hydroxyl group on complexation with central metal atom [17]. The azomethine protons of ligands appeared at δ=10.80 and shifted in the complexes suggested the participation of azomethine group in bond formation. Aliphatic protons (Ha, Hb and Hc) of ligand appeared at δ=2.32-4.21 and aromatic protons appeared in the region δ=7.39-8.57 and these remains almost at the same position in the spectra of the complexes, showing non-participation of these protons. However, tin complexes shows additional signals at δ=0.07, 0.21-0.31, 0.62-1.51 and 7.91-7.99 due to the protons of the methyl, ethyl, butyl and phenyl group.

^{13}C-NMR spectra

^{13}C-NMR chemical shifts in all the complexes were in the expected resonance. The appearance of singlet at δ=166.40 in the spectrum confirms the presence of azomethine (–CH=N–) carbon in the ligand and shifted towards higher value in the complexes suggesting again the participation of azomethine carbon in bond formation with central atom. The carbon attached to the hydroxyl group appeared at δ-161.20 and shifted in the complexes suggesting its coordination. Aliphatic carbon atoms of ligand appeared in the range of δ=59.07-57.70 and carbons of aromatic ring appeared at δ=119.27-138.03 which remains unchanged in the complexes, indicating their non-participation in bond formation with central atom. A considerable shift in the position of carbons attached to the different participating groups clearly indicates the bonding of the azomethine nitrogen and hydroxyl oxygen to the tin atom. The signals due to carbon of methyl, ethyl, butyl and phenyl group appeared in the range of δ=8.05, 10.71-45.58, 9.89-45.89 and 128.97-137.87 respectively.

^{119}Sn NMR spectra were recorded in DMSO-d_6. The spectra displayed one sharp singlet in each complex indicating the formation of a single species. The chemical shift values of tin complexes were also in the range of penta-coordinated environment, which appears at δ=150.21-156.89. Therefore on the basis of spectroscopic studies, penta coordinated geometries were assumed for all the synthesized complexes (Scheme 2).

Antimicrobial evaluation

The Schiff base ligand and its complexes were evaluated for their inhibitory effects on the growth of Gram-positive bacteria *(S. epidermidis, S. hominis)* and Gram negative bacteria (*P. aeruginosa, K. pneumonia)* and fungus (*A. niger)* using micro dilution technique and their MICs were calculated. The results are summarized in Table 1 and graphical representation for 1-5 compounds is given in Figure 1. Antimicrobial activity was determined by measuring minimum concentration that inhibits the growth of microbes. DMSO was used as negative control which produced no visible inhibitory effect on any of the tested bacteria and ciprofloxacin was used as positive control.

In the whole series MICs of the synthesized compounds were calculated which ranged from 3.75-30 µg/ml. On the basis of results derived, compound 5 was found to be most potent having minimum MIC (3.75 µg/ml) against all the bacterial and fungal strains used. The biological activity of the Schiff base ligand got enhancement on coordination with tin atom against all the strains. This enhancement is explained on the basis of Overtone's concept of cell permeability and Tweedy's chelation theory [18-20]. According to this concept, on coordination the polarity of the metal atom decreases due to partial sharing of its positive charge with the donor groups within the chelate ring system created during coordination and lipophilicity of the complexes is increased. Thus diffusion of the drugs in the lipid layer of the microorganism becomes more efficient and kills them more aggressively by deactivating the respiration process. All the complexes, phenyl derivative was found to be most potent against microbial strains as compared to other derivatives. The order of activity for the compounds were Ph>Bu>Et>Me. Further all compounds were found to be biologically more potent for Gram-positive bacterial strains as compared to Gram negative because outer membrane of Gram-negative bacteria is more complex.

Table 1: Minimum inhibitory concentration of compounds (MIC in µg/ml)

Comp. No.	Compounds	MIC in µg/ml				
		Gram-positive *bacteria*		Gram-negative		Fungus
		Staphylococcus epidermidis	***Staphylococcus hominis***	***Pseudomonas aeruginosa***	***Klebsiella pneumonia***	***Aspergillus niger***
1	H_2L	30	30	30	30	30
2	$Me_2Sn(L)$	15	15	30	30	15
3	$Et_2Sn(L)$	15	15	15	15	7.5
4	$Bu_2Sn(L)$	3.75	7.5	7.5	7.5	7.5
5	$Ph_2Sn(L)$	3.75	3.75	3.75	7.5	3.75

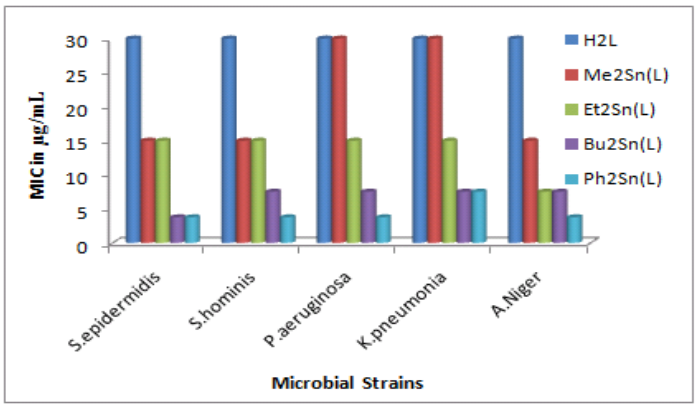


Figure 1: Graphical representation for antimicrobial activities

CONCLUSIONS

In this work we prepared successfully novel Schiff base and their organotin (IV) complexes. The *in vitro* antimicrobial activity of the synthesized compounds was evaluated against Gram-positive and Gram-negative bacterial and fungal strains. Complexes displayed enhanced antimicrobial activity then their respective ligand. Among the synthesized compounds, phenyl derivative possessed the most prominent and consistent activity. Therefore, such compounds would stand for a productive atmosphere for the development of a new class of antibacterial agents.

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Ethical statement

The authors declare that they have no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study

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