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Synthesis and structural studies on penta and hexa coordinated organotin (IV) complexes of alkyl pyruvate aroyl hydrazones

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ABSTRACT

A series of five and six coordinated diorganotin(IV) complexes of the type $R_2Sn(L)_n\ Cl_{2-n}$ [R = butyl and phenyl, n = 1 or 2, HL = Schiff base derived from the condensation of methyl/ethyl pyruvate with substituted acid hydrazides [salicylhydrazide, p-toluic acid hydrazide and napthoic acid hydrazide] have been synthesized. The mode of bonding in the complexes has been suggested on the basis of analytical and spectroscopic techniques (IR, ^{1}H, ^{13}C and ^{119}Sn NMR) spectra, where the ligands are coordinating to metal through oxygen and nitrogen of carbonyl and azomethine group respectively. The ligands and their organotin complexes have been tested for antimicrobial activity against phytopathogenic fungi Candida albicans, Aspergillus niger at 25±1°C and bacteria Bacillus subtilis, Escherichia coli and Staphylococcus aureus at 37±1°C compared with Tetracycline, Chloramphenicol, Kanamycin, Cefazolin Sodium, Cefotaxime as reference drugs. The activity of the ligands is enhanced on complexation.

Keywords: Organotin(IV); Schiff base; Antimicrobial activity; Hydrazone.

INTRODUCTION

A large chemistry of organotin(IV) complexes of Schiff bases have been synthesized and extensively studied because they have some characteristics properties like manifestations of novel structures, thermal stability, relevant biological properties, high synthesis flexibility and medicinal utility [1]. Schiff bases have been used in the preparation of many potential drugs and possess a broad spectrum of biological activities such as antiviral [2] antifungal [3] antibacterial [4] antiparasitic [5] anti-inflammatory [6] antitumor [7] antiHIV [8] and anticancer [9] activities. Moreover, some research groups also have been reported that the schiff base metal complexes derived from the salicylaldehyde can specially cleave the DNA [10]. In addition to their special antitumor activities, organotin(IV) compound with Schiff bases present an interesting variety of

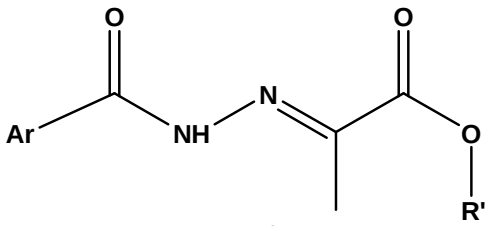
structural possibilities, so that a remarkable diversity in structure may be observed even when only a small change in the chemistry occurs. Hydrazones possessing an azomethine –NHN=CH- proton constitute an important class of compounds for new drug development. Metal complexes of Schiff base derived from aromatic carbonyl compounds have been widely studied in connection with metalloprotein models and asymmetric catalysis, due to versatility of their steric and electronic properties[11]. Keeping these developments in mind, we report here the synthesized a series of 1-24 new organotin(IV) complexes of methyl/ethyl pyruvate salicylhydrazone, p-tolyl hydrazone and napthoyl hydrazone. The detail of structural and spectroscopic characterization of complexes reported here in.

MATERIALS AND METHODS

All the syntheses were carried out in dry nitrogen atmosphere on vacuum lines using Schlenk tubes technique. Dialkyltindichloride and diphenyltindichloride (Aldrich) were used as received. Various hydrazides were prepared according to method reported in literature. Tin and chloride were estimated gravimetrically. All solvents were dried prior to their use. IR spectra were expressed in the range 4000-400 cm^{-1} was recorded on Perkin-Elmer spectrum RX-1 instrument. ^{1}H NMR, ^{13}C and ^{119}Sn NMR were obtained on Bruker Avance II 400 MHz spectrometer in DMSO-d_6 as solvent, using TMS as internal reference and chemical shift (δ) are expressed in ppm. Elements C, H and N analysis of samples were performed on a Perkin-Elmer 2400 CHN analyzer. Synthetic pathway is presented in scheme 1. Analytical and spectral data for synthesized compound are given in tables I, II and III. The antimicrobial activity of the tested compounds is given in the table IV. Molar conductance measurements were carried out using a Model-306 Systronics conductivity bridge in DMSO solvent.

2.2. Synthesis of ligands

The Schiff bases were prepared by the condensation of metyl/ethyl substituted pyruvate (0.40 g, 3.50 mmol) and salicylhydrazide (0.53 g, 3.50 mmol) in minimum amount of ethanol (30mL). The solution was refluxed for 2-3 h. A yellow solid product so obtained was purified by repeated washing with petroleum ether (bp 40-60 ˚C) to ensure the purity of the product and finally dried under vacuum. The analytical data of all ligands were listed in Table I.

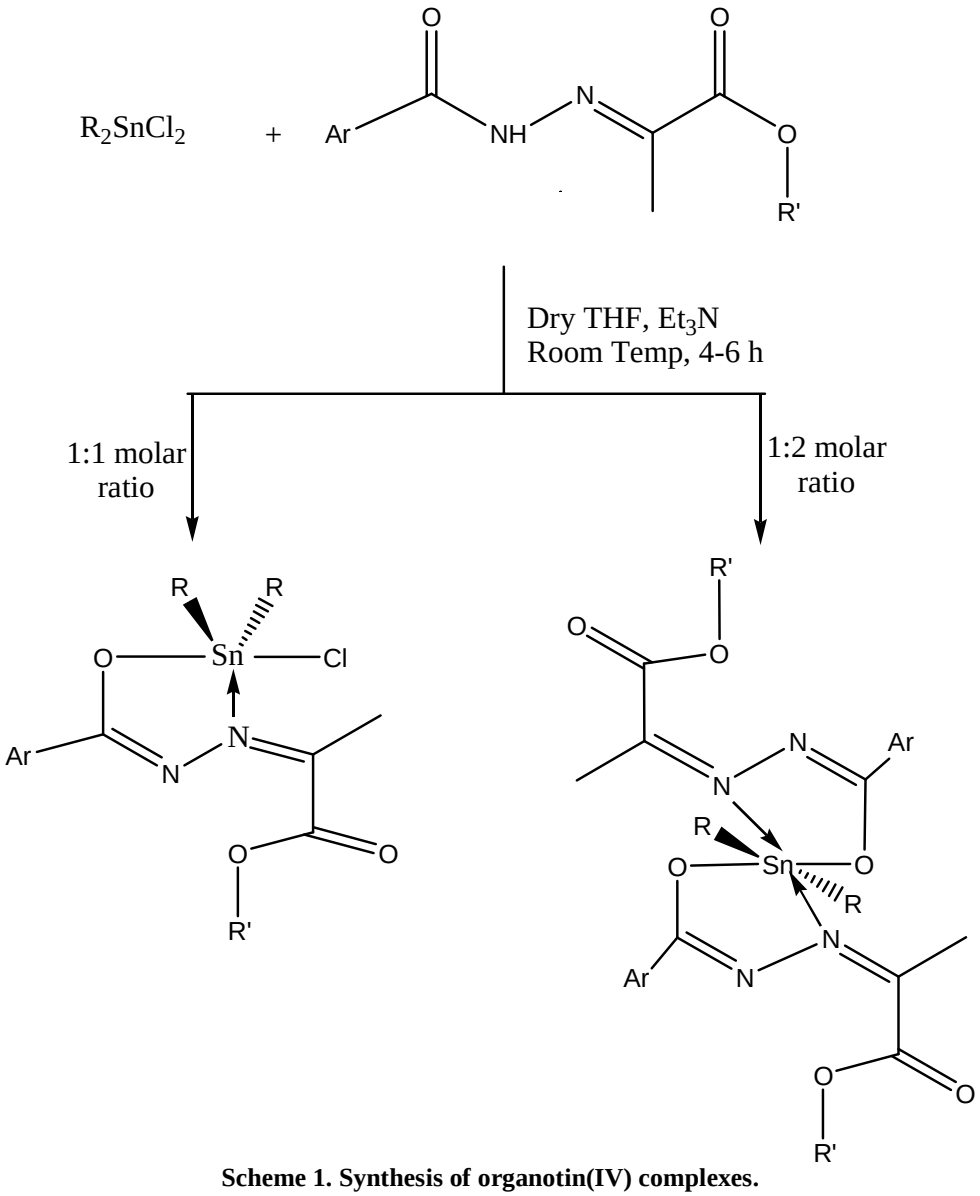


Structure of ligand

Ligands	Ar	R′	Yield
1	2-OHC_6H_4	CH_3	77
2	2-OHC_6H_4	C_2H_5	79
3	4-$CH_3C_6H_4$	CH_3	75
4	4-$CH_3C_6H_4$	C_2H_5	90
5	$C_{10}H_7$	CH_3	81
6	$C_{10}H_7$	C_2H_5	84

2.3. Synthesis of complexes

The schiff base ((2.52 g, 10.7mmol) and dibutyltindichloride (1.62 g, 5.355 mmol) was added in the solvent of tetrahydrofuran with triethylamine at room temperature. The mixture was stirred for 4-6 hours and the precipitate of Et_3N-HCl so formed was filtered off. The solvent was removed under vacuum and the solid product was washed with THF/Hexane mixture subsequently to remove any excess of reactants and dried over phosphorous(V) oxide under vacuum.



Scheme 1. Synthesis of organotin(IV) complexes.

Similar procedure was employed for the reaction of dibutyl and diphenyltindichloride with other hydrazones in 1:1 and 1:2 molar ratios. The physical and analytical data of complexes are given in Table-1

Complexes	Molar ratio	Ar	R′	R	Yield
7	1:1	2-OHC_6H_4	CH_3	C_4H_9	72
8	1:2	2-OHC_6H_4	CH_3	C_4H_9	78
9	1:1	2-OHC_6H_4	C_2H_5	C_4H_9	84
10	1:2	2-OHC_6H_4	C_2H_5	C_4H_9	88
11	1:1	4-$CH_3C_6H_4$	CH_3	C_4H_9	87
12	1:2	4-$CH_3C_6H_4$	CH_3	C_4H_9	76
13	1:1	4-$CH_3C_6H_4$	C_2H_5	C_4H_9	72
14	1:2	4-$CH_3C_6H_4$	C_2H_5	C_4H_9	69
15	1:1	$C_{10}H_7$	CH_3	C_4H_9	79
16	1:2	$C_{10}H_7$	CH_3	C_4H_9	86
17	1:1	$C_{10}H_7$	C_2H_5	C_4H_9	78
18	1:2	$C_{10}H_7$	C_2H_5	C_4H_9	83
19	1:1	2-OHC_6H_4	CH_3	C_6H_5	71
20	1:2	2-OHC_6H_4	CH_3	C_6H_5	88
21	1:1	2-OHC_6H_4	C_2H_5	C_6H_5	84
22	1:2	2-OHC_6H_4	C_2H_5	C_6H_5	67
23	1:1	4-$CH_3C_6H_4$	CH_3	C_6H_5	77
24	1:2	4-$CH_3C_6H_4$	CH_3	C_6H_5	81
25	1:1	4-$CH_3C_6H_4$	C_2H_5	C_6H_5	91
26	1:2	4-$CH_3C_6H_4$	C_2H_5	C_6H_5	79
27	1:1	$C_{10}H_7$	CH_3	C_6H_5	89
28	1:2	$C_{10}H_7$	CH_3	C_6H_5	87
29	1:1	$C_{10}H_7$	C_2H_5	C_6H_5	77
30	1:2	$C_{10}H_7$	C_2H_5	C_6H_5	70

RESULTS AND DISCUSSION

The alkyl pyruvate substituted aroyl hydrazone (L-1 to L-6) have been prepared by the condensation of alkyl pyruvate with substituted acid hydrazides. The progress of the reaction was constantly monitored by using conventional method TLC. The reactions of R_2SnCl_2 (R= Bu, Ph) with alkyl pyruvate aroylhydrazones in 1:1 and 1:2 molar ratios in dry THF in the presence of triethylamine at room temperature afforded the complexes which were characterized by elemental analysis, IR, ^1H, ^{13}C, and ^{119}Sn NMR. All the complexes have been obtained as solids, soluble in common polar organic solvents, such as ethanol, chloroform, dimethylformamide and dimethyl sulphoxide but insoluble in saturated hydrocarbons, such as hexane and petroleum ether. The low values of molar conductivity (7.0-15.0 ohm^{-1} cm^2 mol^{-1}) of the complexes in dry DMF indicate their non-electrolytic nature.

IR Spectra

The infrared spectra of the ligand consistent with N-H stretching vibration was appeared as a strong sharp band at 3219-3232 cm^{-1}, a medium intensity band at 1620-1623cm^{-1} for azomethine ν(C=N) group. A strong band in the ligands at 1655-1670 cm^{-1} assigned to carbonyl ν(C=O) is indicative of their ketonic nature in the solid state. The band at 992 cm^{-1} was due to ν(N-N) group which seems to have origin in the conjugate system >C=N-N=C< [12]. In the ligand medium intensity broad band was due to ν(OH) in the region 2300-2700 cm^{-1} is due to intramolecular hydrogen bonds. On comparison of the vibrational spectra of the ligand and its diorganotin(IV) complexes was the disappearance of the ν(N-H) carbonyl ν(C=O) band along with the appearance of four new bands at about 1600, 1586 1353 and 1238 cm^{-1} arising from ν(C=N-N=C), ν(NCO), and ν(C-O) was consistent with enolization and coordination of the

ligand to tin after deprotonation [13]. Of the two nitrogens of the azomethine group, coordination through N(2) nitrogen of terminal substituted acid hydrazide was suggested as it gives rise to stable five membered ring which would be formed on coordination through other nitrogen. The band appeared at 1715 cm^{-1} due to ν(C=O) of ester group remain unaltered suggested non participation of this group in coordination (Table-II). The band between 540-584 cm^{-1} was due to ν (Sn-C) and the weak or medium intensity band in the region 452-478 cm^{-1} can be assigned to the ν $(Sn\leftarrow N)$ stretching vibration [14]. The explicit feature in the infrared spectra of all complexes, a strong absorption at 652-671 cm^{-1} which was absent in the free ligands, is assigned to the Sn–O stretching mode of vibration. The infra red spectra of compounds show strong broad band at 3414-3486cm^{-1} related to phenolic hydrogen indicated that the phenolic oxygen atoms does not participate in coordination to the atoms.

NMR Spectra

The coordinating modes of the ligands was confirmed by comparing ^{1}H, ^{13}C and ^{119}Sn NMR spectra of the ligands and the complexes which were recorded in $CDCl_3$ containing small amount of DMSO(d_6) using TMS as an internal standard and tetramethyltin as external standard. The relevant spectroscopic data were collected in (Table III). A strong single resonance was appeared in the region 11.24-11.43 ppm suggested that due to salicylic hydroxyl group remain unaltered indicating non participation of the hydroxyl group in coordination [15]. A broad singlet was appeared at 11.28-13.45 ppm of –NH proton in the ligand which disappeared in the spectra of complexes containing that the ligand was coordinated to tin in enolic form after deprotonation. The phenyl group protons were appeared in complex pattern in the range of 6.80-7.95 ppm. The singlet of methyl proton attachment to azomethine group was observed at 2.21-2.39 ppm. The methyl protons of methoxy group of methyl pyruvate aroyl hydrazones was appeared at 3.82-3.91 ppm while ethyl protons of the ethoxy group of the ethyl pyruvate aroyl hydrazone show a quartet at 4.28-4.39 ppm and a triplet at 1.34-1.49 ppm respectively.

The coupling constant (J) for the ligand HL_1 and HL_2 for C_3-H was 8.16 Hz while for C_6-H it was 7.28 Hz for HL_3 and HL_4 (J) value appeared for C_5-H and C_6-H at 8.20 Hz. In case of HL_5 and HL_6 coupling constant (J) for C_4-H at 8.16 Hz, C_5-H at 11.2 Hz and C_8-H at 8.20 Hz [16]. The ^{13}C NMR spectra show a significant downfield shift of all carbon resonances. The shift is a consequence of an electron density transfer from the ligand to the acceptor. In the free ligand methyl pyruvate aroyl hydrazone the vinyl methyl carbon was appeared at 12.5 ppm and methoxy carbon resonates at 46.6 ppm, while in the complexes it was appeared at 13.4 ppm and at 52.4 ppm. The carbonyl carbon was appeared at 170.2 ppm in the ligand it was appeared at 174.1 ppm suggested that ligand was coordinated to tin atom. Not much variation was observed in complexation in the vinyl methyl carbon of ethyl pyruvate aroyl hydrazone which was at 8.24 ppm while ethoxy carbon appeared at (-CH_3 13.0), (-CH_2 41.6) in the ligand and slightly downfield shift was appeared at (-CH_3 13.5), (-CH_2 46.0). The signal due to butyl groups (≡Sn-$^{1}CH_2$-$^{2}CH_2$-$^{3}CH_2$-$^{4}CH_3$) attached to tin atom appeared at 28.4 (C_1), 26.9 (C_2), 26.0 (C_3), and 13.7 (C_4) ppm respectively while the carbon of phenyl group attached to tin atom appeared at 152.0, 133.7, 129.8, and 130.4 ppm.

In ^{119}Sn NMR spectra single resonance was observed in the range of -151 to -159 ppm and -331 to -359 ppm for 1:1 and 1:2 tin complexes of formula $R_2Sn(L)_nCl_{2-n}$ where R= butyl and phenyl. The appearance of chemical shift values in this region indicated pentacoordinated for 1:1

and hexacoordinated for 1:2 environment [17]. Since the chemical shift of ^{119}Sn was affected by the nature of R group directly attached to the tin atom when R = phenyl, the localized system of this group allows for pπ-dπ interaction to dominate shielding of the ^{119}Sn values. The high field chemical shifts for the phenyltin derivatives being a concequence of anisotropic shielding effects in addition with pi interactions.

4. Antimicrobial Activity

In vitro evaluation of antimicrobial activity of the ligands and their corresponding dichlorodiorganotin (IV) complexes were subjected to *in vitro* antimicrobial studies. Antibacterial activity was done by the serial dilution method [18] on the following strains i.e. *Bacillus subtilis* (MTCC no. 2063) *Staphylococcus aureus* (MTCC no. 2901) & *Escherichia coli* (MTCC no. 1652), under the standard conditions of Temperature 37˚C±1˚C and Relative Humidity 40%±5% for 24 hours. The standards used for comparative study for antibacterial studies are Tetracycline, Chloramphenicol, Kanamycin, Cefazolin Sodium, Cefotaxime, which all are pharmacologically very much potent, broad spectrum antibiotic agents *in vitro* as well as *in vivo*. Media used to determine antibacterial activity is sterile double strength nutrient broth I.P. Antifungal activity was also done by the serial dilution method; on Aspergillus niger (MTCC no1344) under the temperature 25˚C±1˚C, Relative Humidity 40%±5% for 7 days & on *Candida albicans* (MTCC no.183) under the standard conditions of 37˚C±1˚C, Relative Humidity 55%±5% for 36 hours. The standards used for antifungal activity are Fluconazole (a therapeutic broad spectrum antifungal agent), Cycloheximide (a fungicide antibiotic for *in vitro* use only), and Carbendazim Hydrochloride (a fungicide with antitumor property). Media used to screen antifungal activity is sterile Sabouraud dextrose broth I.P.

It may be concluded from the data (Table IV) on the antimicrobial activity that:

i) toxophorically important –CON= group is responsible for the antifungal activity of the ligands [19].

ii) 1:1 complexes $R_2Sn(L)Cl$ are more potent than 1:2 $R_2Sn(L)_2$ complexes against the tested microorganism under identical experimental conditions indicate that active 'Cl' moiety attached to tin is responsible for the higher toxicity.

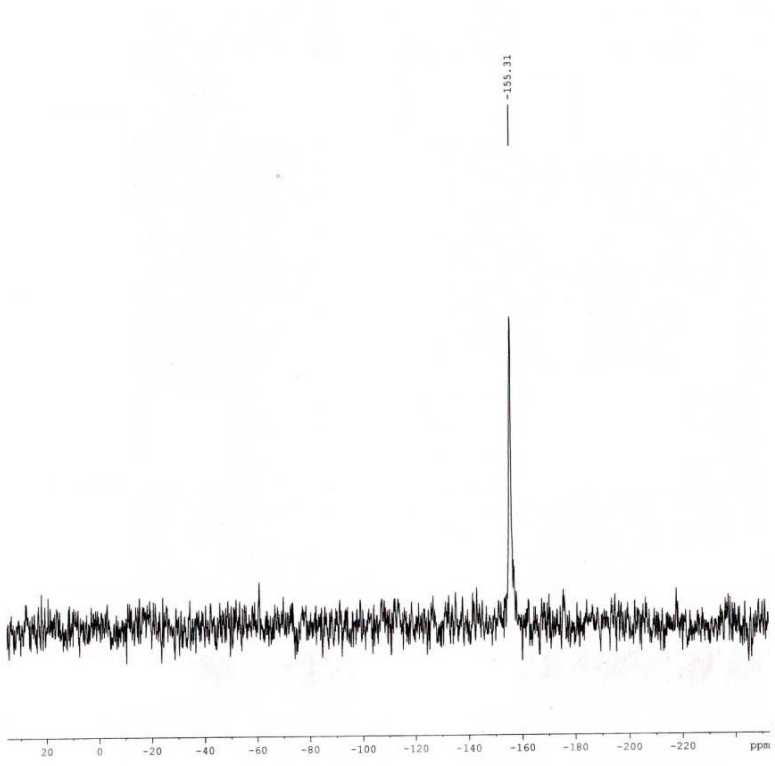
iii) *In vitro* biocidal studies indicate that the organotin(IV) complexes of alkyl pyruvate aroyl hydrazone of type $R_2SnCl_nL_{2-n}$ where[L= 1-napthyl and n= 0,1] are more toxic against the tested bacteria and fungi as compared to their ligands. Some of these compounds have toxicity close to the conventional fungicides and bactericides are more potent than their parent ligands against the same microorganisms under identical experimental conditions. The lipophilic characteristic is essential for deciding the activity of the compound. The increased activity of the complexes may be due to the effect of central ion on the normal cell process, which on chelation increases lipophilic character of the central atom. This favours its permeation through the lipid layer of the membrane, there by resulting in interference with normal cell process [20]. Due to their poor water solubility, *in vivo* studies remain untouched.

iv) Among the complexes $Ph_2SnCl_nL_{2-n}$ are found to be most active, compared to $Bu_2SnCl_nL_{2-n}$ which may be due to the fact that the bulkiness of R group increases the lipophilicity, coupled with the polarity of Sn-C bond which boost to the bioactivity of these complexes.

v) It is evident from the data that the complexes are more toxic towards Gram (+) strains as compared to Gram (-) strains which may be attributed to the fact that the cell wall of Gram (-)

strains have more antigenic properties due to the presence of an outer lipid membrane of lipopolysaccharides.

vi) Conventional fungicide and bactericide showed inhibition at concentration less than 3.12 ppm. No compounds show better inhibitory action than the conventional fungicide and bactericide used. Some of the compounds have toxicity near to the conventional fungicide against bacteria *Bacillus subtilis* and fungi *Aspergillus niger* and *Candida albicans*.



^{119}Sn NMR of pentacoordinated complexesfor 1:1

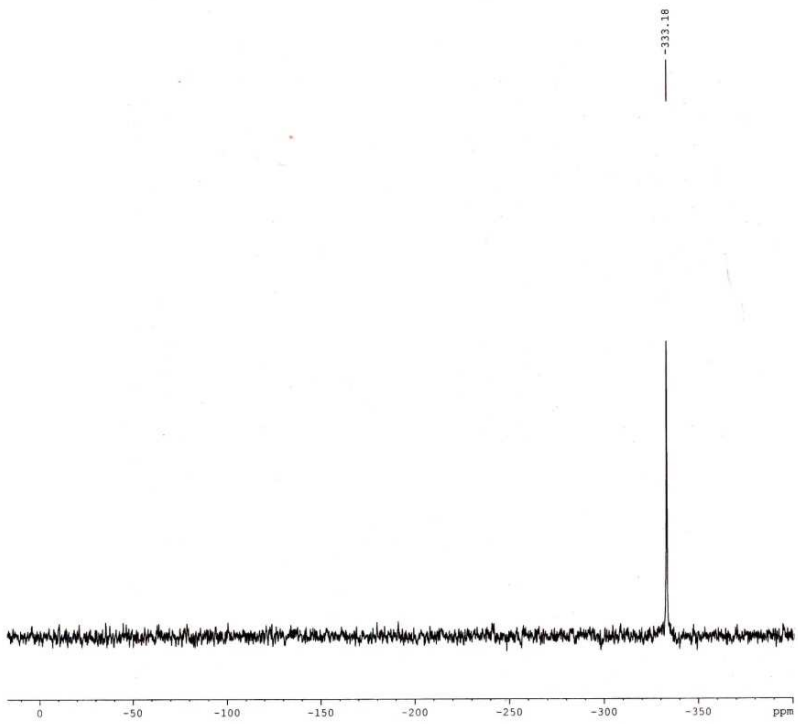
Antibacterial assay

To prepare the stock solution of 100µg/mL for each complex & ligands, the dichlorodiorganotin (IV) complexes & the ligands were dissolved in DMSO separately. This stock solution was serially diluted in tubes containing 1 mL of double strength nutrient broth I.P. to get the required concentrations (i.e. concentration of 50 µg/mL, 25 µg/mL, 12.5 µg/mL, 6.25 µg/mL, 3.12 µg/mL respectively) and then inoculated with 100 µL of suspension of respective organism (*Bacillus subtilis, Staphylococcus aureus & Escherichia coli*) in sterile saline. The inoculated tubes were incubated at 37˚C±1˚C and Relative Humidity 40%±5% for 24 hours and respective minimum inhibitory concentrations (MIC) were determined.

Antifungal Activity

The antifungal activity of the ligands & their dichlorodiorganotin(IV) complexes was determined against the fungal species on Aspergillus niger (MTCC no1344) under the temperature 25˚C±1˚C, Relative Humidity 40%±5% for 7 days & on *Candida albicans* (MTCC no.183) under the standard conditions of 37˚C±1˚C, Relative Humidity 55%±5% for 36 hours. Similar to

antibacterial assay, the serial dilution method was followed, using sterile Sabouraud dextrose broth IP medium for both fungal species.



^{119}Sn NMR of Hexacoordinated complexes for 1:2

CONCLUSION

The complexes of alkyl pyruvate aroyl hydrazone with diorganotin(IV)dichloride of type $R_2SnCl_nL_{2-n}$ were designed, synthesized & characterized. The antimicrobial activity of the ligands & corresponding complexes were evaluated against different phytopathogenic fungi and bacteria and it was found that the complexes exhibit significant antimicrobial activity than the ligands.

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