Proceedings of the Pakistan Academy of Sciences: B. Life and Environmental Sciences 58(2): 91-98 (2021)

ISSN (Print): 2518-4261; ISSN (Online): 2518-427X
http://doi.org/10.53560/PPASB(58-2)633

Pakistan Academy of Sciences

Research Article

Thermogravimetric and Biological Studies of Organotin(IV) Complexes with 4-(Hydroxymethyl)piperidine-1-Carbodithioic Acid

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Abstract: Present studies were conducted to perform thermogravimetric characterization and biological activity investigations of organotin dithiocarbamates of general formulae R_3SnL (R = *n*-Bu, 1; Ph, 2; Cy, 3), $R_2Sn(Cl)L$ (R = Me, 4; Ph, 5) and R_2SnL_2 (R = Me, 6) where L = 4-(hydroxymethyl)piperidine-1-carbodithioate. A novel procedure was also developed for the synthesis of product 2 by direct reflux of 4-(hydroxymethyl)piperidine-1-carbodithioic acid (HL) with triphenyltin(IV) hydroxide. HL was decomposed at low temperatures as compared to the metal complexes. The coordinated products were degraded leaving behind the tin or SnOCl inorganic residues. The products1-6 have shown excellent antimicrobial activities against the tested bacterial (*Escherichia coli, Salmonella typhi, Staphylococcus aureus*, and *Bacillus subtilis*) and fungal (*Fusarium solani, Aspergillus niger, Alternaria solani,* and *Fusarium verticillioides*) strains. The biological activities were found to depend upon the substitution pattern at the central tin atom.

Keywords: Organotin Dithiocarbamates; 4-(Hydroxymethyl) Piperidine-1-Carbodithioic Acid; Thermogravimetry; Antibacterial; Antifungal.

1. INTRODUCTION

Metal complexes have been found to possess biological and medicinal properties especially anti-cancer, anti-inflammatory, anti-proliferative, anti-malarial, anti-fungal, and antibacterial activities [1, 2]. Organotin(IV) products [3] with different ligands find numerous applications as antimicrobial and anticancer agents [4, 5]. They display fantastic biological potential against several microorganisms [6]. They have been applied in various biocidal formulations as wood preservatives, surface disinfectants, marine antifouling paints, molluscicides, miticides, and fungicides [7]. The biological activities of such complexes are chiefly affected by the nature of the organic substituents. The compounds shaving the general formula $R_nSn^{+(4-n)}$ (where n = 3 or 2) can easily be bound to cellular proteins, glycoproteins, or membrane proteins [8] and also affect the DNA directly [9]. The structure of an organotin molecule and the coordination number of a central metal atom affect its biochemical activity. Their synthesis finds an interest in medicinal, pharmaceutical, and inorganic fields to develop the new drugs [10].

In continuation to our previous investigations on tin products [5, 11], the present studies are focused on thermal and antimicrobial investigations of organotin(IV) p of 4-(hydroxymethyl)piperidine-1-carbodithioate. A novel procedure for the synthesis of triphenyltin(IV) 4-(hydroxymethyl)piperidine-1-carbodithioate (2) has also been discussed.

2. MATERIALS AND METHODS

The precursor materials namely 4-piperidine methanol, carbon disulfide, diphenyltin(IV) dichloride (Ph_2SnCl_2), dimethyltin(IV) dichloride (Me_2SnCl_2), triphenyltin(IV) chloride (Ph_3SnCl), tricyclohexyltin(IV) chloride (Cy_3SnCl), tri-n-butyltin(IV) chloride (n-Bu_3SnCl) and

Received: December 2020; Accepted: June 2021
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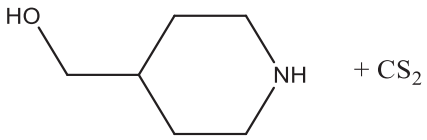
triphenyltin(IV) hydroxide (Ph_3SnOH) were procured from Sigma Aldrich. The solvents (ethanol and toluene) of Merck origin were employed.

Melting points of the products were found by an electrochemical melting point apparatus (Stuart SMP3). A Bruker ARC 300 MHz-FT-NMR spectrometer was used to record ^1H and ^{13}C NMR spectra at 300 and 75 MHz, respectively. Thermogravimetric analyses were performed by TGA-7 Perkin-Elmer USA under nitrogen. Agar well diffusion method was employed to evaluate the antimicrobial potential of compounds against bacteria (*Echerichia coli, Salmonella typhi, Staphylococcus aureus,* and *Bacillus subtilis*) and fungal (*Fusarium solani, Aspergillus niger, Alternaria solani,* and *Fusarium verticillioides*)

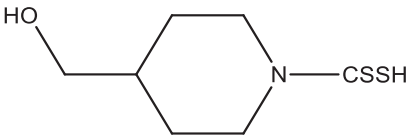
2.1 Syntheses

A solution of 4-piperidine methanol (1 mmol) in ethanol was stirred in a round bottom one-necked flask fitted in an ice bath with the dropwise addition of CS_2 (1 mmol). The precipitated product namely 4-(hydroxymethyl)piperidine-1-carbodithioic acid (Scheme 1) was filtered after 2 hours and recrystallized from ethanol: petroleum ether.



4-piperidine methanol

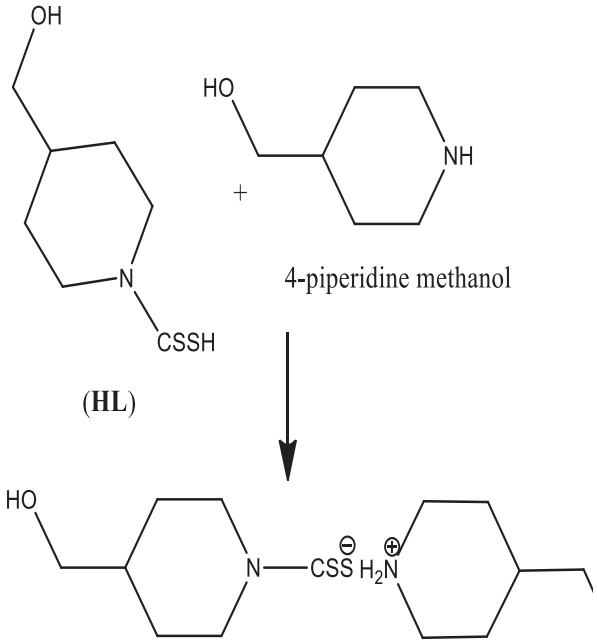
Ethanol



4-(hydroxymethyl)piperidine-1-carbodithioic acid

(**HL**)

Scheme 1: Synthesis of 4-(hydroxymethyl) piperidine-1-carbodithioic acid During the reaction, the intermediate 4-(hydroxymethyl)piperidine-1-carbodithioic acid (HL) was further reacted with the un-reacted form of 4-piperidine methanol to produce a salt (Scheme 2).



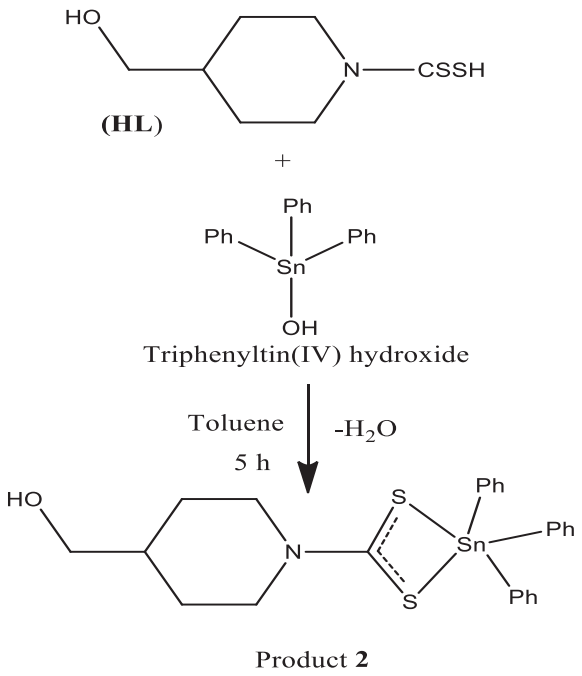
Salt form

Scheme 2: Synthesis of a salt form of **HL**

The salt form (in ethanol) was further treated at room temperature in 1:1 molar ratio with tricyclohexyltin(IV) chloride, triphenyltin(IV) chloride, tri-n-butyltin(IV) chloride, dimethyltin(IV) dichloride and diphenyltin(IV) dichlorideto produce the complexes n-Bu_3SnL (1), Ph_3SnL (2), Cy_3SnL (3), $Me_2Sn(Cl)L$ (4), $Ph_2Sn(Cl)L$ (5), respectively or it was reacted with Me_2SnCl_2in 2:1 molar ratio to produce the coordinated product Me_2SnL_2 (6) by a reported procedure [11].

However, we have also developed an alternate novel procedure for the synthesis of complex 2 by an acid-base reaction. In this procedure 4-(hydroxymethyl)piperidine-1-carbodithioic acid acts as an acid while triphenyltin(IV) hydroxide acts as a base when both are refluxed in Dean and Stark apparatus using dry toluene solvent for the removal of side product which is water. After 5 h, the reaction mixture was rotary evaporated leaving behind the solid product 5 which was recrystallized from ethanol:petroleum ether in 5:1 ratio.

Product 2 was analyzed by NMR (^1H and ^{13}C) spectroscopy. The spectroscopic results of complex 2 were found identical to those already reported [11]. The ^1H and ^{13}C NMR spectra have been displayed in Figures 1 and 2, respectively.



Product **2**

2.2 Antibacterial Activities

The investigated complexes1-6 were evaluated for antibacterial potential by the agar well diffusion method [12] against 4 strains of bacteria, two gram-negative (*S. typhi* and *E. coli*) and two gram-positive (*B. subtilis* and *S. aureus*). The imipenem was used as a standard antibacterial drug. To the 75 mL of nutrient agar medium at 37 °C, there was an addition of 0.75 mL of the broth culture containing~10^5 colony forming units per mL of the test strain; then the mixture was added into a 14 cm sterile petri plate. After solidifying the media, a sterile metallic borer having 8mm diameter was used to dig the wells. Then the solution of each test sample in dimethyl sulphoxide having 1mg/mL concentration was poured into the wells. The plates were allowed to incubate for 24h at 37 °C. The zones of inhibitions were measured by a vernier caliper (precision ± 0.1 mm).

2.3 Antifungal Activities

The investigated compounds 1-6were tested for their antifungal activities against various fungi i.e., *F. solani, A. niger, A. species,* and *F. moniliformis* by agar tube dilution method [12]. The standard drug clotrimazole (200 μgmL–[1]) and DMSO were used as positive and negative controls, respectively. The tubes were allowed to incubate for 7days at 28 °C and growth was found by measuring linear growth (mm). Vincent equation was used to measure the growth inhibition with reference to growth in vehicle control:

$$\text{Inhibition \%} = 100(C\text{-}T)/C$$

where C and T are the diameters of fungal growth for control and the sample, respectively.

3. RESULTS AND DISCUSSION

Organotin dithiocarbamates of general formulae R_3SnL (R = *n*-Bu, 1; Ph, 2; Cy, 3), $R_2Sn(Cl)L$ (R = Me, 4;Ph, 5) and R_2SnL_2 (R = Me, 6) where L = 4-(hydroxymethyl) piperidine-1-carbodithioate were prepared by a reported method [11]. However, a novel procedure was also developed for the synthesis of product 2. The synthesized products showed sharp melting points and excellent solubility in some organic solvents.

3.1 Thermal Analysis

Thermal analysis of the synthesized compounds HL (salt form), 2, 5, and 6 was made to study their thermal stability, degradation pattern, and percentage purity. Some kinetic parameters such as activation energy (Ea), order of reaction (n), enthalpy and entropy were also calculated by the use of data of thermally decomposed products. The results are given in Tables 1 and 2.

One-step decomposition in the compound HL (salt form) was observed; it was stable up to 147.1 ^{0}C and showed the 90.59 % weight loss due to the evolution of H_2S, N_2, CO_2, $2C_6H_{12}$, and 1/8 S at 147.71-226.75 ^{0}C leaving 7/8 S (9.41% of the compound HL) as residue. Three-step decomposition in compound 2 was observed. This compound was stable up to 164.47 ^{0}C. It showed a loss of $C_6H_{12}O$ (18.955 % weight loss) in the first step (164.47-286.14 0C) and a loss of $3C_6H_5$, CS_2 (56.95 % weight loss) in the second step (288.05-372.32 ^{0}C). The third step (411.61-528.81 ^{0}C) showed the loss of ½ N_2 (2.55 % weight loss) leaving Sn (21.54 % of the compound 1) as residue.

Two-step decomposition in compound 5 was observed. This compound was stable up to 191.74 ^{0}C. It showed a loss of C_6H_{12}, 1/2 N_2,

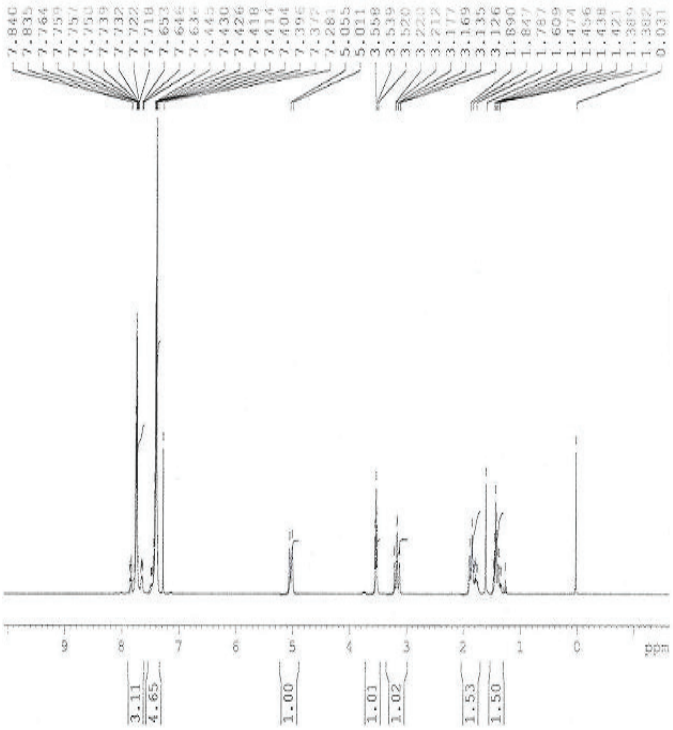


Fig. 1. [1]H NMR spectrum of Compound **2**

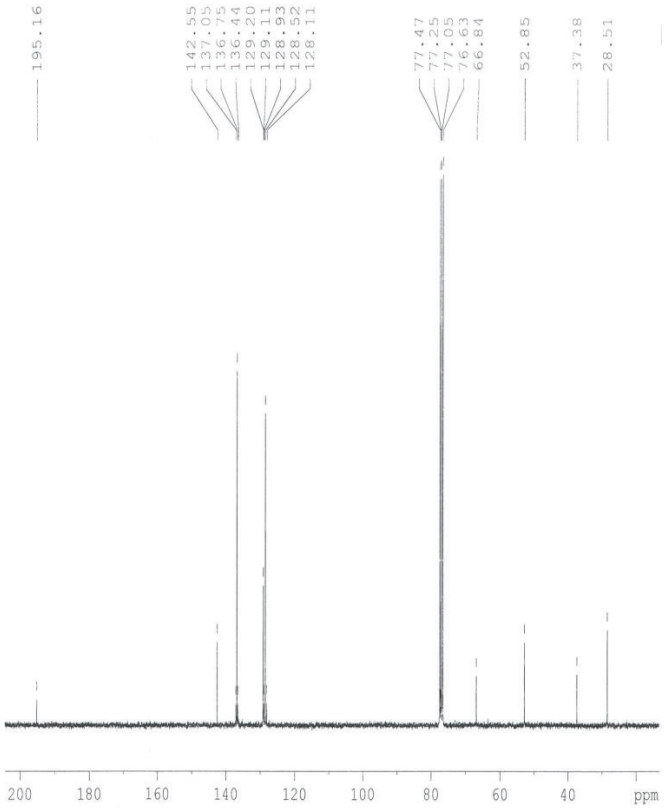


Fig. 2. [13]C NMR spectrum of Compound 2

7/8CS_2, C_6H_5 (48.63 % weight loss) in the first step (191.74-332.91 ^{0}C) and a loss of 1/8 CS_2, C_6H_5 (17.67% weight loss) in the second step (288.05 - 372.32 ^{0}C) leaving SnOCl (33.7 % of the compound 2) as residue.

Compound 6 was decomposed into four steps. It lost 1/2CH_3 (1.43% weight loss) in the first step (104.90-149.0 ^{o}C) and 1/2CH_3, CH_3 (42.96 % weight loss) in the second step (195.35-256.91 ^{o}C). CS_2 and ½ N_2 (30.43 % weight) were lost in the third step (257.70-371.64 ^{o}C). The final step was the loss of ½ N_2, 1/5Sn (7.24 % weight) at 440.94-570.83 ^{o}C leaving behind 4/5 Sn as the residue (17.94 % weight).

HL is decomposed at low temperature leaving the sulphur. The reason is that it is a pure organic compound. However, when it becomes attached with organotin moiety, the decomposition becomes difficult leaving behind Sn or SnOCl which are inorganic species.

3.2 Antibacterial Activities

Free ligand and its stannic complexes1-6 were tested against 4 bacterial strains by the agar well diffusion method. The observed data are displayed in Table 3. The samples were tested at a recommended concentration of 1mg/ml in DMSO [13]. The salt of free ligand has shown no activity against any bacterium. The organotin(IV) products exhibited significant antibacterial activities against all the tested strains of bacteria. The coordination of the ligand with the metal has resulted in the biological activities of the tested products [13]. This antimicrobial potential of the complexes can be interpreted based on chelation theory which clarifies that the coordination results in a reduction of the polarity of central tin after coordination with the ligand and thus lipophilic character of the resultant product is also increased so the lipid bilayer of bacterial strains is dissolved and ultimately destroyed. This reduction in polarity is thought to be achieved due to partial sharing of metal positive

Table 1. Thermal decomposition pattern of synthesized dithiocarbamates

Compound No.	Molecular formula	Temperature Range (^{0}C)	Evolved Components	% Loss Calculation	% Loss Observation
Salt form of HL	$C_{13}H_{26}S_2N_2O_2$	147.71-226.75	H_2S, N_2, CO_2, $2C_6H_{12}$, 1/8 S	90.85	90.59
			Residue left behind = 7/8 S		
2	$C_7H_{12}S_2NOSn(C_6H_5)_3$	164.47-286.14	$C_6H_{12}O$	18.52	18.955
		288.05-372.32	$3C_6H_5$, CS_2	56.85	56.95
		411.61-528.81	½ N_2	2.59	2.55
			Residue left behind = Sn		
5	$C_7H_{12}S_2NOSn(C_6H_5)_2Cl$	191.74-332.91	C_6H_{12}, 1/2N_2, 7/8CS_2, C_6H_5	48.49	48.63
		541.45-681.34	1/8CS_2, C_6H_5	17.37	17.67
			Residue left behind = SnOCl		
6	$(C_7H_{12}S_2NO)_2Sn(CH_3)_2$	104.90-149.0	1/2CH_3	1.42	1.43
		195.35-256.91	1/2CH_3,CH_3	42.53	42.96
		257.70-371.64	CS_2, ½ N_2	31.38	30.43
		440.94-570.83	½ N_2, 1/5Sn	7.13	7.24
			Residue left behind = 4/5Sn		

Table 2. Kinetic parameters calculated from TG curves of complexes

Compound No.	Energy of activation ($KJmol^{-1}$)	Enthalopyof reaction ($KJmol^{-1}$)	Entropy of reaction ($KJmol^{-1}$)	Order of reaction	Temperature (^0C)
HL	35.75	34.09	+0.141	0.89	198.3
2	31.66	29.16	-0.042	3.31	301
5	3.08	0.78	-0.301	1.03	275.7
6	28.96	26.94	-0.008	3.43	243.3

Table 3. Antibacterial activity data[a] of the ligand **LH** and complexes **1-6**

Compound No.	Bacterial inhibition zone (mm)			
	E. coli	***S. typhi***	***S. aureus***	***B. subtilis***
LH	0	0	0	0
1	27	26	29	33
2	28	28	31	29
3	24	23	27	24
4	22	21	28	24
5	24	21	26	26
6	21	19	24	21
Imipenem	30	32	36	30

[a]Concentration = 1mg/ml in DMSO; 26-40 = Strong activity, 11-25 = Moderate activity, 5-10 = Activity present, 0 = No activity

charge with donor groups and secondly due to pi electrons delocalization within the whole chelating ring [14].

The triorganotin(IV) complexes 1-3, in general, were found more active as compared to the diorganotin(IV) derivatives 4-6. The results can be justified due to an increase in the number of alkyl groups attached to the tin atom which causes a rise in lipophilicity of the triorganotin(IV) compounds. The effect of various compounds varies depending upon the nature of microorganisms. Due to variations in the structures of target microbial cells, the tested compounds have shown different effects on different microorganisms [15]. The investigated complexes exhibited low-sized zones against gram-negative bacteria as compared to gram-positive bacteria. This is because the outer wall of gram-negative bacteria is thicker as compared to the gram-positive bacteria. The activities also differ depending upon the substitution pattern at tin because the number and nature of the alkyl group attached to tin play an important role in this regard [16]. The high activity of chloromethyldiorganotin(IV) derivatives 4 and 5 than the corresponding diorganotin(IV) compound6 may be described based on the labile nature of the chlorogroup and also due be the Efflux effect.

3.3 Antifungal Activities

The antifungal activities of the free ligand and the coordinated products were tested by the agar tube dilution protocol method; the results have been summarized in Table 4. All the chlorodimethyltin(IV), triorganotin(IV), and diorganotin(IV) derivatives were found active against the tested microbes. The biological activities of a few compounds were found even higher than that of the standard drug (Clotrimazole). Generally, thetriorganotin(IV) complexes were found comparatively more active

Table 4. Antifungal activity data[a] of the ligand **LH** and complexes **1-6**

Compound **No.**	**Fungal inhibition zone (mm)**			
	F. solani	***A. niger***	***A. species***	***F. moniliformis***
LH	0	0	0	0
1	23	29	31	27
2	36	21	33	23
3	19	20	22	21
4	24	26	18	26
5	19	20	25	29
6	22	18	25	19
Clotrimazole	35	37	30	28

[a]Concentration = 1mg/ml in DMSO; 26-40 = Strong activity, 11-25 = Moderate activity,5-10 = Activity present, 0 = No activity

than chlorodiorganotin(IV) complexes against all the tested four fungal strains. The high activity of triorganotin(IV) and chlorodimethylorganotin(IV) is probably due to high lipophilicity and feasible permeability to the cytoplasm where compounds interact to cause extensive K^+ discharge and the organism dies. Since few of our synthesized compounds are more active as compared to the standard drug (Clotrimazole) against fungi these compounds have the potential to be used as antifungal drugs in the future. Further investigations are required in this regard.

4. CONCLUSION

Organotin derivatives of 4-(hydroxymethyl) piperidine-1-carbodithioic acid (LH) can be successfully characterized by thermogravimetric analysis (TGA). The thermal decomposition pattern agrees well with the chemical composition of the coordinated products. The triphenyltin(IV) derivative of HL can be synthesized by direct reflux of 4-(hydroxymethyl)piperidine-1-carbodithioic acid (LH) with triphenyltin(IV) hydroxide in Dean and Starck apparatus. All the synthesized complexes were tested against different fungal and bacterial and fungal strains and were found to be biologically active. The biological activities greatly differ depending upon the substitution pattern at tin. The nature of alkyl/aryl groups and the coordinated metal play the main role in the biological activities of the coordinated products. as compared to the free ligand.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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