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Synthesis, Spectroscopy, and Biological Activity of Heterobimetallic Complexes Containing Sn(IV) and Pd(II) with 4-(Hydroxymethyl)piperidine-1-carbodithioic Acid[1]

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Abstract—4-(Hydroxymethyl)piperidine-1-carbodithioic acid has been synthesized by reacting 4-piperidinemethanol with carbon disulfide at room temperature. The synthesized ligand was treated with organotin(IV) chlorides to yield organotin complexes. These complexes by further treatment with palladium chloride afford heterobimetallic complexes containing Sn(IV) and Pd(II). The synthesized complexes along with ligand has been characterized by elemental analysis, FTIR, NMR (^{1}H, ^{13}C) spectroscopy. The IR data confirmed the complexation through the sulfur and oxygen donor sites of the ligand. NMR data revealed the tetrahedral geometry in the solution. Biological activity was checked against selected bacterial and fungal strains. All complexes along with the ligand were found to be biologically active with few exceptions.

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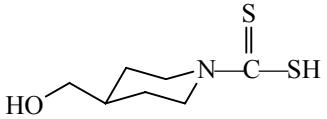
INTRODUCTION

Tin possesses a large number of organometallic derivatives that are commercially [1] used. Organotin(IV) derivatives form an important series of compounds and have been receiving increasing attention in recent year not only because of their intrinsic properties but also owing to their importance as tin-based antitumour drugs [2]. Organotin(IV) complexes are extensively studied due to their structural diversity as well as coordination geometry which are well documented from the single crystal X-ray structural studies [3]. Organotin compounds are toxic against a variety of microorganisms and find widespread application in biocidal compositions [4]. Organotin(IV) complexes are used in different fields [5] and show potential biological application [6] such as insecticidal and antitumor activities. Organotin compounds are now the active components in a number of biocidal formulations, finding application in such diverse areas as fungicides, miticides, molluscides, marine antifouling paints, surface disinfectants, and wood preservatives [7, 8]. Organopalladium chemistry has become one of the most active areas of organometallic chemistry directed towards organic synthesis [9]. Organopalladium is widely used as catalyst in industry in the synthesis of different types of the compound. Complexes of palladium have proved to be the most useful among other transition metals in promoting specific carbon-carbon, carbon-oxygen, and carbon-nitrogen bond formation under mild conditions [10]. Owing to the wide range of applications of heterobimetallic complexes [11–12], we are reporting here the synthesis, characterization, and antimicrobial activity of heterobimetallic complexes containing Sn(IV) and Pd(II) with 4-(hydroxymethyl)piperidine-1-carbodithioic acid HL.



EXPERIMENTAL

Chemicals and instrumentation. 4-Piperidinemethanol, carbon disulfide (CS_2), organotin(IV) chlorides, and palladium chloride were purchased from Sigma-Aldrich (UK). Methanol, ethanol, chloroform, acetone, and dimethyl sulfoxide (DMSO) were of Merck (USA) origin. Nutrient agar, nutrient broth, potato dextrose agar were purchased from Oxoid (UK).

[1] The text was submitted by the authors in English.

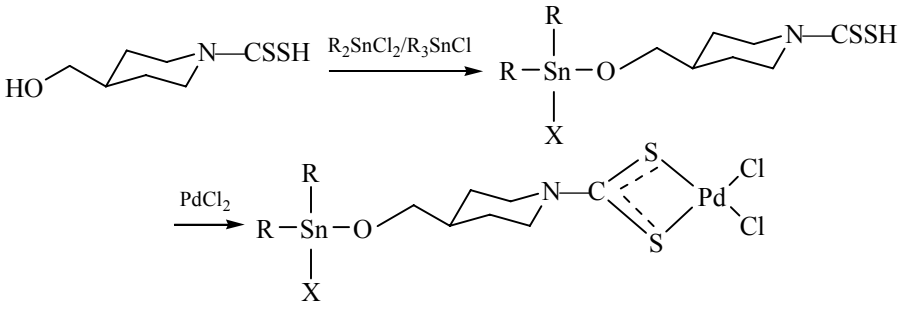
The melting point of samples were determined with electrothermal melting point apparatus, model stuart (SMP3) (USA). Elemental analysis was done on a CHNS elemental analyzer Leco (USA). IR spectra were recorded by using Elmer-1000 spectrophotometer as KBr pellets in the range 4000–250 cm^{-1}.

Bruker 300 MHz-FT-NMR spectrometer was used to record the ^{1}H and ^{13}C NMR spectra using the $CDCl_3$ as internal reference.

Procedure for the synthesis of 4-(hydroxymethyl)piperidine-1-carbodithioic acid (HL). The ligand was synthesized by the reported method [13]. 4-Piperidinemethanol (1 mmol) and carbon disulfide (1 mmol) were stirred in ethanol in a round-bottom flask at 0°C for 3 h. Yellow precipitate formed was filtered off and dried in air.

General procedure for the synthesis of heterobimetallic complexes. *a.* The synthesized ligand HL (1 mmol) was dissolved in ethanol (15 mL) in a round-bottom two neck flask at stirring. To the above solution, a solution of R_2SnCl_2/R_3SnCl (R= methyl, butyl, phenyl) in acetone (30 mL) was added in 1 : 1 molar ratio, and the resulting reaction mixture was refluxed for 4 h with continuous stirring. The solvent was slowly evaporated at room temperature and the product obtained was dried in air.

b. The product obtained in *a* (1 mmol) was dissolved in acetone (20 mL) with continuous stirring. Then solution of $PdCl_2$ in distilled water (50 mL) was added dropwise in 1 : 1 molar ratio and the reaction mixture was stirred for 6 h. The solvent was slowly evaporated at room temperature and the product obtained was dried in air.



X = Cl for chlorodiorganotn; X = R for triorganotin
I: R = Mep; **II**: *n*-Bu; **III**: Me; **IV**: *n*-Bu; **V**: Ph.

Antibacterial activity. Disc diffusion method was used to determine the antibacterial activity [14]. The active complexes inhibit the growth of bacteria and a clear zone is formed. Zone reader was used to measure the zone of inhibition [15]. Nutrient agar medium was prepared by suspending 28 g nutrient agar in one liter of distilled water. The medium was autoclaved for 15 min at 121°C. Nutrient agar medium (100 mL) was placed in a beaker. To the medium, 100 μL of inocula was added and mixed well. Transfer The mixture (medium and inocula) was transferred to the Petri dish. Flat paper discs were laid on the growth medium having fungal strains and 100 μL of complexes and standard solution was applied on each disc and incubated at 37°C for 24 h for the growth of bacteria.

Antifungal activity. Disc diffusion method was used to determine the antifungal activity of complexes [16]. Zone reader was used to measure the inhibition zone [17]. The sterilized medium was transferred to the Petri dish, 100 μL of fungal inocula was added to each Petri dish and was homogenized with medium. Flat paper disc was laid on the growth medium having fungal strain and 100 μL of complexes and standard solution was applied on each disc. Petri dishes were incubated at 28°C for 48 h.

RESULTS AND DISCUSSION

The synthesized complexes have sharp melting points and are soluble in organic solvents. The observed values of elemental analysis are in good agreement with the calculated values. Physical data are given in Table 1.

Infrared spectroscopy. The IR spectra of 4-(hydroxymethyl)piperidine-1-carbodithioic acid and complexes were recorded in the range of 4000–250 cm^{-1}. The characteristic vibration frequencies have been

Table 1. Physical data for the heterobimetallic complexes

Comp. no.	Formula	Molecular weight	mp, °C	Yield, %		Elemental analysis , %	
				C calculated (found)	H calculated (found)	N calculated (found)	S calculated (found)
HL	$C_7H_{13}NOS_2$	191.0	80	43.97 (43.93)	7.32 (7.36)	7.32 (7.36)	33.50 (33.54)
I	$C_9H_{18}NOS_2SnPdCl_3$	551.6	56	19.57 (19.61)	2.53 (2.46)	2.53 (2.46)	11.60 (11.64)
II	$C_{15}H_{30}NOS_2SnPdCl_3$	635.6	58	28.31 (28.39)	2.20 (2.24)	2.20 (2.24)	10.07 (10.12)
III	$C_{10}H_{21}NOS_2SnPdCl_2$	531.1	55	22.59 (22.63)	2.63 (2.64)	2.63 (2.64)	12.05 (12.01)
IV	$C_{19}H_{39}NOS_2SnPdCl_2$	657.1	61	34.70 (34.70)	2.13 (2.09)	2.13 (2.09)	9.74 (9.79)
V	$C_{25}H_{27}OS_2SnPdCl_2$	717.0	64	41.84 (41.86)	1.95 (1.99)	1.95 (1.99)	8.92 (8.97)

Table 2. IR data (cm^{-1}) for heterobimetallic complexes

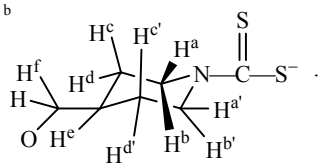
Comp. no.	ν(SH)	ν(C–N)	ν(C=S)	ν(C–S)	ν(OH)	ν(M–C)	ν(M–O)	ν(M–Cl)
HL	2550	1020	1050	940	3600	–	–	–
I	–	1021	1040	943	–	545	443	312
II	–	1020	1055	943	–	542	435	323
III	–	1020	1060	945	–	542	430	328
IV	–	1021	1045	943	–	543	448	320
V	–	1020	1050	945	–	540	440	331

Table 3. ^{1}H NMR chemical shifts[a,b] for the heterobimetallic complexes

Proton no.	Chemical shift, δ, ppm					
	HL	**I**	**II**	**III**	**IV**	**V**
SH	5.64 s	–	–	–	–	–
a, a'	2.82–2.86m	2.82–2.87m	2.81–2.85m	2.80–288m	2.82–2.87m	2.83–.86m
b, b'	3.22–3.31m	3.21–3.32m	3.22–3.38m	3.21–3.31m	3.20–3.35m	3.22–3.33m
c, c'	1.32–1.36m	1.31–1.35m	1.31–1.34m	1.31–1.36m	1.31–1.36m	1.31–1.37m
d, d'	1.74–1.78m	1.72–1.79m	1.72–1.78m	1.74–1.77m	1.74–1.78m	1.73–1.77m
e	1.58–1.61m	1.58–1.62m	1.57–1.61m	1.58–1.62m	1.54–1.62m	1.55–1.61m
f	5.64–5.68m	5.66–5.70m	5.62–5.69m	5.64–5.69m	5.62–5.68m	5.62–5.69m

[a] **I**: Sn–CH_3, 0.38 s [77]; **II**: Sn–CH_2–CH_2–CH_2–CH_3, 0.87 t (7.2), 1.26–1.34 m, 1.61–1.87 m; **III**: Sn–CH_3 1.10 s [96]; **IV**: Sn–CH_2–CH_2–CH_2–CH_3, 0.92 t (7.7), 1.63–1.68 m, 1.72–1.77 m; **V**: Sn–C_6H_5, 7.69–7.87 m, 7.39–7.41 m.

[b]



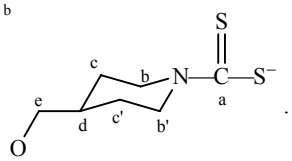
identified by comparing the spectra of the complexes with the ligand. The disappearance of OH band at 3600 cm^{-1} in the complexes confirms complexation through the oxygen atom. Similarly the disappearance of S–H band at 2550 cm^{-1} in the complexes confirms the complexation through sulfur. A band due to ν(C–S) stretching vibrations is also important and is used to differentiate between mono and bidentate mode of

Table 4. ^{13}C NMR data[a] for heterobimetallic complexes

Carbon no.	Chemical shift, δ, ppm					
	HL	**I**	**II**	**III**	**IV**	**V**
a	211.3	204.2	200.5	205.6	205.6	205.6
b, b'	65.5	65.1	65.3	65.2	65.2	65.3
c, c'	29.2	28.6	28.6	28.6	28.6	28.9
d	38.9	38.5	38.5	38.5	38.5	37.3
e	49.8	48.1	48.4	47.2	47.2	44.8

[a] **I**: Sn–CH_3, (C^{α}) 2.2; **II:** Sn–$CH_2CH_2CH_2CH_3$, (C^{α}) 26.0, (C^{β}) 28.1, (C^{γ}) 27.6, (C^{δ}) 14.1; **III**: Sn–CH_3, 14.2; **IV**: Sn–$CH_2CH_2CH_2CH_3$ (C^{α}) 21.5, (C^{β}) 28.2, (C^{γ}) 27.2, (C^{δ}) 14.1; **V**: Sn–C_6H_5 (C^{α}) 136.6, (C^{β}) 129.2, (C^{γ}) 128.7, (C^{δ}) 137.0.

[b]



ligand. The presence of a single band due to ν(C–S) stretching vibrations lying in the range 940–943 cm^{-1} confirms that the ligand acts as a bidentate one [18]. The explicit feature in the spectra of complexes was the presence of bands in the range of 430–448 and 540–545 cm^{-1} due to Sn–O and Sn–C, respectively [19]. The new band due to ν(M–Cl) that appears in the range of 312–331 cm^{-1} also confirms the complexation. These results are compiled in Table 2.

NMR spectroscopy. The ^1H NMR spectra were recorded in DMSO and the data are given in Table 3. The presence of SH proton at 5.64 ppm in HL and its disappearance in the complexes indicate the coordination of sulfur with Sn moiety. In complex **V** the phenyl protons exhibit two multiplets in the range of 7.39–7.87 ppm, while methyl protons in complexes **I** and **III** give sharp singlets at 0.38 and 1.10 ppm with $^nJ(^{119}Sn–^1H)$ value of 77 and 96 Hz, respectively. All protons have been identified in position and number using calculations by the incremental method [20]. The ^{13}C NMR data are presented in Table 4. The –CSS group gives a signal at 211.3 ppm in the free ligand, while it shows an upfield shift in the complexes **I**–**V** to the range of 200.5–205.6 ppm indicating the coordination of sulfur to the metal. The upfield shift is due to lowering of C=S bond order upon coordination with the metal atom and a shift N→C of electron density

Table 5. Antibacterial activity[a–d] data for heterobimetallic complexes

Comp. no.	Bacteria zone size, mm			
	B. subtilus	*P. multocida*	*S. aureus*	*E. coli*
HL	14±1.2	16±1.2	14±1.2	16±1.4
I	20±1.3	21±1.0	19±1.1	22±1.3
II	18±1.3	19±1.0	17±1.2	18±1.3
III	14±1.3	14±1.3	17±1.2	20±1.4
IV	22±1.6	21±1.4	21±1.4	22±1.3
V	17±1.2	19±1.3	18±1.4	19±1.3
Rifampicin	24±1.4	25±1.3	22±1.3	23±1.2

[a] Concentration. [b] Standard drug (Rifampicin). [c] Values are mean ±SD of three samples analyzed individually in triplicate at $p < 0.05$. [d] Different letters in superscript indicate significant and insignificant differences with sample.

Table 6. Antifungal activity[a–d] data for heterobimetallic complexes

Comp. no.	Fungal zone size, mm			
	A. niger	*A. flavus*	*A. alternata*	*G. lucidum*
HL	12.25	12.25	12.25	12.25
I	13.5±1.5	13.5±1.5	13.5±1.5	13.25±1.0
II	–	–	–	–
III	–	–	–	–
IV	16±1.5	16±1.5	16±1.5	14.5±1.0
V	–	–	–	–
Fluconazol	18. 5±1.0	18. 5±1.0	18. 5±1.0	18.5±1.0

[a] Concentration. [b] Standard drug (Fluconazol). [c] Values are mean ±SD of three samples analyzed individually in triplicate at $p < 0.05$. [d] Different letters in superscript indicate significant and insignificant differences with sample.

producing a partial double bond character in the C–N bond as reported earlier [21, 22]. The R group attached to tin(IV) give the signals in the expected range.

Antibacterial activity. The synthesized complexes along with ligand were screened for antibacterial activity against *Bacillus subtilis, Escherichia coli, Pseudomonas multocida* and *Staphylococcus aureus*. Disc diffusion method was used [14]. The antibacterial activity of the standard drug Rifampicin (positive control) was used for comparison. The results are given in Table 5.

It is clear from the tabulated values that the antibacterial activity of the ligand is markedly low as compared to the standard drug (Rifampicin) and the complexes. The antibacterial activity of the synthesized complexes is higher as compared to the ligand with few exceptions and lower than that of the standard drug. The results show that activity increases on chelation of ligand with metal. There is a direct relation between the activity and the coordination environment of the metal. All complexes show tetrahedral geometry in solution, which is consistent with the known data that species generating tetrahedral geometry in solution are more active [23, 24]. The activity of the ligand is affected by the nature of substituent and this is in relation to the lipophilicity of the ligand. This can be attributed to the difference in the structure of the cell walls. The walls of Gram (–) cells are more complex than those of Gram (+) cells. The lipopolysaccharide forms an outer-lipid membrane and contributes to the complex antigenic specificity for the Gram (–) cells.

Antifungal activity. The antifungal activity of synthesized complexes along with the ligand were checked against selected fungal strains *Aspergillus niger, Aspergillus flavus, Ganoderma lucidum* and *Alternaria alternaria*. Complexes **II**, **III,** and **V** were found to be inactive against all four fungi [14]. The results are given in Table 6. The synthesized complexes were found to be active and showed more significant activity as compared to the ligand. It can be noted that ligand and complex **I** exhibit moderate activity, while complex **IV** shows a significant activity. However, the complexes are more toxic than ligand, which may be due to the chelation and the presence of sulfur atoms [25].

Mechanism of action. The mechanism of action is not yet fully understood. But it is assumed that organic ligand supports the transport of active organotin moiety to the site of action where it is released by hydrolysis. The anionic ligand also plays an important role in determining the degree of activity of organotin compounds [25, 26].

CONCLUSIONS

The disappearance of OH band in the IR spectra of the complexes confirms the complexation through oxygen atom with tin(IV). The absence of SH band in the complexes also confirms the coordination of sulfur with the palladium atom. The NMR data confirmed the tetrahedral geometry in solution. The results of biological activity showed that complexes are biologically active against different bacterial and fungal strains with few exceptions.

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