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PHARMACEUTICALLY IMPORTANT ORGANOTIN(II) MACROCYCLIC COMPLEXES : SYNTHETIC, SPECTRAL AND ANTIMICROBIAL APPROACH

Ashu Chaudhary[a*] and R. V. Singh[b]
[a]Department of chemistry, Banasthali University, Rajasthan-304022,India.
[b]Department of chemistry, University of Rajasthan, Jaipur-304022, India.
[*]Email : ashuchaudhary21@gmail.com

ABSTRACT

Macrocyclic complex [Sn(MacL)Cl_2] has been prepared by the template synthesis using bis(3-oxo-2-butylidene) propane-1,3-diamine(L) and 1,3-phenylenediamine. The complex has been alkylated using CH_3I / C_2H_5Br in the presence of pyridine to obtain corresponding macrocyclic organotin complexes. The macrocyclic complex [Sn(MacL)Cl_2] and alkylated derivatives have been characterized by elemental analysis, molar conductance, molecular weight determinations, IR, ^{1}H NMR, ^{13}C NMR, ^{119}Sn NMR spectra and X-ray spectral analysis. An octahedral geometry around the tin ion is suggested for these complexes. An octahedral geometry around the tin ion is suggested for these complexes. The pathogenicity and virulence of certain microbial infections associated with the ions of these complexes have been found to be potent and like broad spectrum antibiotics.

Key Words : Macrocyclic complexes, NMR spectra, antimicrobial activity

INTRODUCTION

The coordination chemistry of macrocyclic precursors is a fascinating area which has attracted the attention of inorganic chemists. Macrocyclic polyamines complexes of bivalent transition metals have been of great interest due to their importance as an essentialmetalloenzyme active site[1] and this will help in furthering our understanding of biological systems[2]. These precursors are also of theoretical interest as they are capable of furnishing an environment of controlled geometry and precursor filed strength[3]. The successful application of several 1, 4, 7, 10-tetraazacyclododecane (cyclen) precursors to the synthesis of macrocyclic complexes stems mainly from their use as models for protein- metal binding sites in biological systems[4] and as selective complexing agents for metal ion[5], such as therapeutic reagents for the treatment of metal toxicity[6]. Organotin compounds exhibits a broad spectrum of biological activity which includes bactericidal, fungicida7 antitumor and caricidal derivatives[7]. Our ongoing work of tin (II) derivatives involving such systems led us to describe the synthetic and stereochemical features of some diorganotin complexes. The biochemistry of synthetic organometallic has generated active research relating to their biochemical significance[6]. The importance of metal-nitrogen bonding and their prominence in agricultural, medicinal and industrial chemistry led us to synthesize and screen the precursors and their macrocyclic compounds for their antifungal and antibacterial activities.

EXPERIMENTAL

All reagents were obtained commercially and by standard procedures. All solvents were of reagent grade. $SnCl_2$ was from Sarabhai and Glaxo make. The reactions were carried out under strictly anhydrous conditions.

Preparation of bis(3-oxo-2-butylidene)propane-1,3-diamine

In a 100 ml short necked round bottomed flask, diacetyl was taken in ethanol and to this was added 1,3-diaminopropane in ethanol. The reaction was carried out in 2:1 molar ratio heated under reflux for 12 hours. The reaction mixture was cooled and the reddish brown compound obtained was recrystallised from ethanol (Yield 75%).

Preparation of complexes

The reaction mixture containing bis(3-oxo-2-butylidene)propane-1,3-diamine, diamine and tin chloride in 1:1:1 ratio in methanol was heated under reflux for 36 hours. The reaction mixture was cooled, transferred to an evaporating dish and set aside for a few hours, whereupon a dark coloured compound separated out. The product formed was washed and dried under reduced pressure, which was recrystallised from a 1:1 mixture of toluene and n-hexane in 78% yield. The physical properties and analytical data are summarized in Table I.

Analytical Methods and Physical Measurements

Conductivity measurements in dry DMF were performed with a Systronics conductivity bridge type 305 and molecular weights were determined by the Rast Camphor method. IR spectra were recorded on Perkin - Elmer 577 Grating Spectrophotometer. ^{1}HNMR spectra were recorded on a Jeol FX-90Q Spectrometer in methanol and DMSO-d_6 using TMS as internal standard. ^{119}Sn NMR spectra were recorded on a Jeol FX-90Q Spectrometer at 33.35 MHz. The chemical shifts were determined relative to the external reference tetramethytin. Nitrogen and chlorine were estimated by Kjeldahl's and Volhard's method, respectively. Tin was estimated gravimetrically as SnO_2. Carbon and hydrogen analyses were performed at CDRI, Lucknow.

RESULTS AND DISCUSSION

The elemental analyses and analytical data of the prepared complexes are given in Table I. All the complexes are stable at room temperature and non-hygroscopic. The products so obtained are soluble in common organic solvents, DMF and DMSO. Complexes have been found to be monomeric as evidenced by their molecular weight determinations. The low values of their molar conductivities (14-26 Ω^{-1} cm^2 mol^{-1}) in anhydrous dimethylformamide show them to be non-electrolytes.

Spectral Studies:

IR Spectra

The infrared spectra of the precursor and its tin complexes were recorded and important features may be summarized as follows. In the IR spectra of the complexes, the stretching and deformation vibrations of any NH_2 signal are absent, indicating the formation of complexes[8]. Strong bands appearing in the range 1615-1600 cm^{-1} are assigned[17] to the coordinated υC=N stretching vibrations in all the complexes. Two distinct bands of the methyl moiety occurring at 2962 cm^{-1} (υ_{as} CH_3) and 2865 cm^{-1} (υ_s CH_3) are present in all the complexes. Strong and sharp bands in the spectra of the metal complexes for C-H stretching and bending vibrations appear at *ca* 2820 and 1430 cm^{-1}, respectively[8].

^{1}HNMR Spectra

The ^{1}HNMR spectrum of the precursor does not show any NH_2 signal any more indicating that the proposed macrocyclic skeleton has been formed. A singlet observed at δ 3.14 - 3.56 ppm in the complexes may be assigned to methylene protons adjacent to nitrogen. A multiplet in the region 2.15 – 2.25 ppm was assigned as middle methylene protons of 1,3-diaminopropane moiety. The shift of the signals towards lower field is an identification of the coordination of the precursor. A singlet observed at δ1.23-1.68 ppm in complexes and precursor is attributable to methyl protons. The multiplets of aromatic protons were observed at δ7.30-8.30 ppm in the spectra of the precursor as well as complexes.

^{119}Sn NMR Spectra

The ^{119}Sn NMR spectrum of the complex [Sn($C_{15}H_{27}N_5$)Cl_2] shows the signal at δ-568.96 ppm which gives good agreement with a hexacoordinated tin[9]. On the basis of above evidences, structure (*1*) may be proposed.

Antimicrobial Approach

The ligand and its complexes were screened for their antifungal activity against *Fusarium oxysporum* and *Macrophomina phaseolina*. Their antibacterial properties were also evaluated by testing them against *Escherichia coli* and *Staphylococcus aureus*. The experimental results show that there is an increase in the toxicity of the complexes as compared to the ligand.. The bactericidal activity of complexes was greater towards gram positive strain as compared to gram negative strain.

Table-1: Physical Properties and Analytical Data of Precursor and its Compounds

			Analysis(%) Found (Cacd.)					
Compound	**Colour**	**M.P. (°C)**	**Sn**	**N**	**Cl**	**C**	**H**	**Mol.Wt. Found (Calcd)**
$C_{11}H_{18}N_2O_2$	Reddish Brown	167-169	-	13.11 (13.32)	-	62.88 (62.83)	8.61 (8.63)	186.23 (210.28)
$[Sn(C_{17}H_{22}N_4)Cl_2]$	Brown	210-213	25.33 (25.15)	11.95 (11.87)	14.99 (15.02)	43.35 (43.26)	4.67 (4.70)	459.05 (471.98)
$[Sn(C_{16}H_{23}N_5)Cl_2]$	Orange	198-200	25.12 (24.99)	14.63 (14.74)	14.79 (14.93)	40.83 (40.45)	4.84 (4.88)	443.92 (474.98)
$[Sn(C_{15}H_{27}N_5)Cl_2]$	Red	260-262	25.60 (25.42)	14.88 (15.00)	15.05 (15.18)	38.56 (38.58)	5.80 (5.83)	438.98 (466.99)
$[Sn(C_{21}H_{24}N_4)Cl_2]$	Dark Brown	Above 300	22.80 (22.73)	10.82 (10.73)	13.43 (13.57)	48.29 (48.30)	4.60 (4.63)	494.59 (522.13)

Table -2: Fungicidal Screening Data of Precursor and its Compounds (percentage inhibition after 96 h)

Compound	*Fusarium oxysporum*			*Macrophomina phaseolina*		
Conc.	*50*	*100*	*200*	*50*	*100*	*200*
$C_{11}H_{18}N_2O_2$	33	46	56	30	42	47
$[Sn(C_{17}H_{22}N_4)Cl_2]$	47	65	74	42	53	60
$[Sn(C_{16}H_{23}N_5)Cl_2]$	66	70	78	52	66	71
$[Sn(C_{15}H_{27}N_5)Cl_2]$	34	41	69	39	47	58
$[Sn(C_{21}H_{24}N_4)Cl_2]$	71	77	84	59	69	81
Standard (Bavistin)	86	100	100	82	100	100

Table-3: Antibacterial Activity of Precursor and its Compounds [percentage inhibition (mm) after 24 h] (Conc. in ppm)

Compound	***Escherichia coli (-)***		***Staphylococus aureus (+)***	
Conc.	*500*	*1000*	*500*	*1000*
$C_{11}H_{18}N_2O_2$	3	5	4	6
$[Sn(C_{17}H_{22}N_4)Cl_2]$	6	7	8	9
$[Sn(C_{16}H_{23}N_5)Cl_2]$	9	10	11	12
$[Sn(C_{15}H_{27}N_5)Cl_2]$	4	6	5	7
$[Sn(C_{21}H_{24}N_4)Cl_2]$	11	12	13	15
Standard (Streptomycin)	17	18	15	17

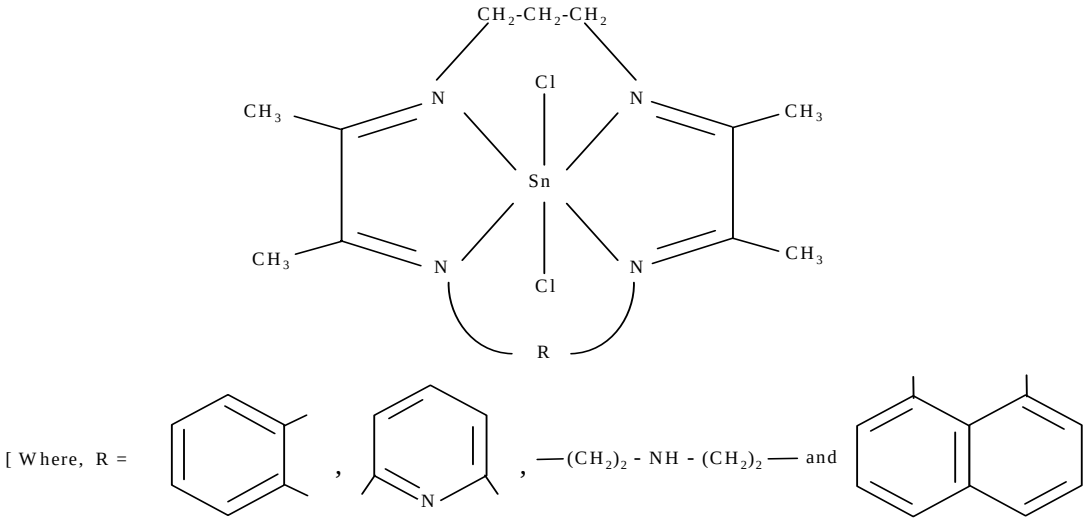

Fig.-1

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