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UNSYMMETRICAL MACROCYCLIC ORGANOTIN COMPLEXES AS ANTIINFLAMMATORY AGENTS : SYNTHETIC, SPECTROSCOPIC AND MEDICINAL ASPECTS

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ABSTRACT

Unsymmetrical macrocyclic complex [Sn(MacL)Cl_2] has been prepared by template synthesis using bis(benzyl)propylenediamine(L) and 1,8–diaminonaphthalene. The complex has been alkylated using CH_3I/C_2H_5Br in the presence of pyridine to obtain corresponding macrocyclic organotin complexes. The marcocyclic complex [Sn(MacL)Cl_2] and the alkylated derivatives have been characterized by elemental analyses, molar conductance, molecular weight determinations, IR, ^1H NMR and ^{119}Sn NMR studies. An octahedral geometry around the tin atom is suggested for these complexes. The ligand and their complexes have been screened for their antiinflammatory activity and their positive findings have been discussed.

Key words : Unsymmetrical macrocycles, Organotin complexes, Spectral studies, Antiinflammatory activity.

INTRODUCTION

The importance of macrocyclic complexes is now well recognised.[1,2] In the past, attention has been paid on the design and synthesis of small molecular complexes that mimic aspects of the spectral and chemical properties of metal sites proteins. Catalysis, extraction of metal ions from solution and the activation of small molecules gave impetus to this endeavor. In view of the presence of two possible potential donor atoms, viz. nitrogen and oxygen, the coordination chemistry of amide macrocyclic deserves special attention. It has been shown that amide macrocyclic compounds bear the dual structural features of macrocyclic tetraamines and oligopeptides and can stablize higher oxidation states in some of the metal ions.[3] There are many examples of macrocyclic synthesis, mixtures of two or more donor sites have also been employed to tune of the selectivity and stability.[4] The current interest is inspired by some other applications[5] and importance in the development of industrial area.[6]

Organotin compounds have good biological activity which includes bactericidal, fungicidal, antitumor and caricidal activity.[7] Our ongoing work on tin derivatives on biochemistry of synthetic organometallics has generated active research relating to their biochemical significance. This communication deals with the synthesis, spectroscopic characterization and

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some new biodimensions in the structural and bioactivity patterns with the applied potential of some macrocyclic organotin complexes.

EXPERIMENTAL

Materials and Methods

All reagents were obtained commercially and purified by standard procedures. All solvents were of reagent grade. The reactions were carried out under strictly anhydrous conditions.

Synthesis of bis(benzil) propylenediamine (L)

The reaction was carried out in 2 : 1 molar ratios. Bis(benzil)propylenediamine was prepared from ethanolic solutions (35 mL) of benzil and 25 mL solution of propylenediamine in ethanol. The reaction mixture was refluxed for 4 h. After reducing the solvent, the solution was cooled and the reddish yellow crystalline compound was obtained.

Synthesis of the macrocyclic tin complex [Sn(MacL)Cl_2]

The reaction mixture containing L, 1,8–diaminonaphthalene and tin chloride in 1 : 1 : 1 ratio in methanol was heated under reflux for 42 hours. The reaction mixture was cooled, transferred to an evaporating dish and set aside for a few hours where upon a off white compound separated out. The product formed was washed and dried under reduced pressure, which was recrystallized from a 1 : 1 mixture of toluene and n–hexane.

Synthesis of macrocyclic organotin complexes

The reaction was carried out in 1 : 1 molar ratio. In a Schlenk tube, a saturated methanolic solution of [Sn(MacL)Cl_2] was taken and stirred and pyridine was then added. The stirred suspension was then cooled to –5°C and stirred for 30 minutes. The sodium hydroxide (0.006 mol) followed by CH_3I/C_2H_5Br (0.003 mol) was added. The solution was gradually warmed to 20 °C and stirred further for 45 minutes. The solution was refluxed to half the volume, stirred, filtered and dried *in vacuo*. The physical properties of the ligand and their complexes are given in Table 1.

Table 1. Physical properties and analytical data of the compounds

Compound	Colour and M.P. (°C)	Analysis (%) Found (Calcd.)					Mol. Wt. Found (Calcd.)
		C	H	N	Cl	Sn	
L	Brownish yellow	80.72 (81.12)	5.56 (5.71)	5.69 (6.10)	–	–	431 (459.0)
[Sn(MacL)Cl_2]	White	63.60 (63.74)	4.24 (4.44)	6.88 (7.77)	8.70 (9.18)	14.96 (15.36)	741 (772.6)
[CH_3Sn(MacL)C_5H_5N]	Off white	70.54 (70.94)	5.20 (5.33)	8.57 (9.42)	–	14.44 (14.92)	763 (795.8)
[C_2H_5Sn(MacL)C_5H_5N]	Off white	71.00 (71.20)	5.28 (5.48)	8.31 (9.26)	–	14.25 (14.66)	781 (809.8)

Physical measurements and analytical methods

The molecular weights were determined by the Rast Camphor Method. Conductivity measurements in dry DMF were performed with a conductivity Bridge type 305. Nitrogen and chlorine were estimated by the Kjeldahl's and Volhard's method, respectively. Tin was estimated as tin oxide gravimetrically. Infrared spectra of the precursors, ligand and the complexes were recorded in the range 4000–200 cm^{-1} with the help of a Nicolet–Magna FTIR–550 spectrophotometer as KBr pellets. ^{1}H NMR spectra were recorded in methanol, using TMS as the standard and ^{119}Sn NMR spectra were recorded on a JEOL FX – 90Q spectrometer at 33.35 MHz. Carbon and hydrogen analyses were performed at Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow.

Antiinflammatory activity

Antiinflammatory activity of the compounds were performed using a plethysmometer to measure carrageenan induced rat paw volume.[8] Adult male wister albino rats (100 – 150 g) were fasted for 18 h but with free access to water. Each treatment i.e. standard drug and compounds were administered at a dose of 100 mg/kg body weight orally in 0.5% CMC suspension. Half an hour following the treatment 0.1 mL of 1% solution of a carrageenan was injected in the right hand paw planter aponeurosis. The paw volume was measured immediately before giving carrageenan and again 3 hour later by means of plethysmometer. Edema was measured in a precalibrated plethysmometer as the difference between the volume of the paw measured before and 3 hour after giving carrageenan. The present inhibition of inflammation after 3 hours was calculated by the method of Newbould.[9]

RESULTS AND DISCUSSION

The elemental analysis and spectral data suggested the formation of the Ligand L alongwith the macrocyclic complex. $[Sn(MacL)Cl_2]$ and organotin complexes $[CH_3Sn(MacL)C_5H_5N]$ and $[C_2H_5Sn(MacL)\ C_5H_5N]$. A proposed scheme of synthetic route is given in Fig. 1.

The resulting complexes are stable at room temperature. These complexes are soluble in common organic solvents, dimethylformamide and dimethylsulphoxide without change in colour. The molar conductance of the compounds in distilled dimethylformamide ($10^{-3}M$), are in 14–19 $cm^2\ ohm^{-1}\ mol^{-1}$ range, which corresponds to non–electrolytes.

SPECTRAL STUDIES

IR Spectra

The infrared spectra of the precursors and their tin complexes were recorded and important features have been summarized. The IR spectrum of the ligand L has a band due to ν(C=O) at 1675 cm^{-1}. In the IR spectra of all the complexes, lack of any ν (NH_2) and ν (C=O) vibrations confirms that cyclization[10] has occurred and characteristic bands of imine groups ν(C=N)[11]

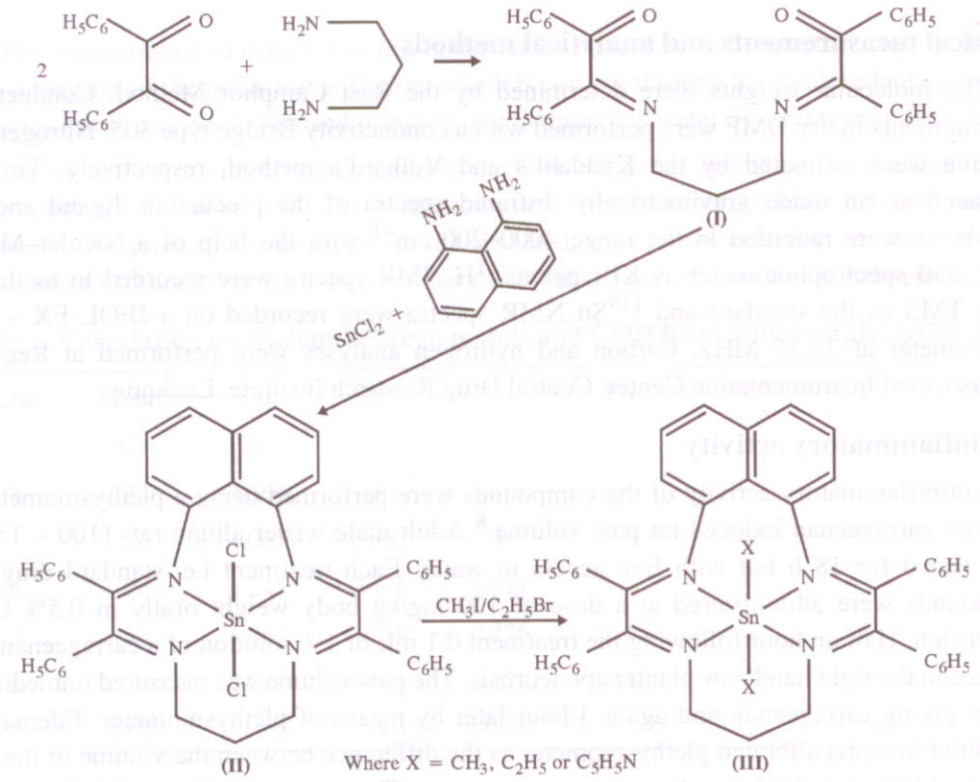

Figure 1. Schematic representation of organotin complexes

appeared. The bands characteristic of the benzil moiety appeared in all the complexes at 1475 – 1490 cm^{-1} (ν_{asy} C_6H_5) and 1375 – 1390 cm^{-1} (ν_{sym} C_6H_5). Strong and sharp bands in the spectra of the metal complexes for C–H stretching and bending vibrations appeared at ca 2820 and 1430 cm^{-1}, respectively.[12] The apperance of new bands in the spectra of tin (II) complexes in the far IR region 429 cm^{-1} due to ν(Sn–N) vibration unequivocally supports the coordination of the imine nitrogens to the tin atom.[13] In the spectra of the complex $[Sn(MacL)Cl_2]$, a band at ca 295 cm^{-1} may be assigned to a ν(Sn–Cl) vibration.[14]

^{1}H NMR

The bonding pattern discussed above gets further support by the proton magnetic resonance spectral studies of the complexes. The ^{1}H NMR spectrum of the ligand L does not show any signal corresponding to primary amino protons indicating that the proposed macrocyclic skeleton has been formed. A singlet observed at 3.36 – 3.40 ppm in the complexes may be assigned to methylene protons adjacent to nitrogen. The shift of the signals towards lower field is an identification of the coordination of the macrocycles. Some other major peaks have been enlisted in Table 2.

Table 2. ^{1}H NMR Spectral data (δ ppm) of the compounds

Compound	>N–CH_2– (t)	–CH_2– (q)	R	Aromatic protons
L	3.14	2.19	–	8.00(d), 7.39 (dd), 7.65(d)
[Sn(MacL)Cl_2]	3.45	2.05	8.03($H_{2,7}$d), 7.30 ($H_{3,6}$d), 7.28 ($H_{4,5}$d)	8.22(d), 7.44(dd), 7.80(d)
[CH_3Sn(MacL)C_5H_5N]	3.36	2.16	8.00($H_{2,7}$d), 7.35 ($H_{3,6}$d), 7.27 ($H_{4,5}$d)	8.34(d), 7.45(dd), 7.86(d)
[C_2H_5Sn(MacL)C_5H_5N]	3.40	2.10	8.02($H_{2,7}$d), 7.33 ($H_{3,6}$d), 7.28 ($H_{4,5}$d)	8.35(d), 7.42(dd), 7.86(d)

^{119}Sn NMR

^{119}Sn NMR spectra of the complexes give signals at 590 – 545 ppm, indicating coordination number six in these complexes around tin atoms.[15]

Thus, on the basis of the above spectral and analytical data, structure (I) for ligand L and (II) and (III) for organotin macrocyclic complexes have been proposed.

Antiinflammatory activity

The values reveal that the ligand and their complexes are more active than the standard dicyclofenac sodium. However, the complex [C_2H_5Sn(MacL)C_5H_5N] show best antiinflammatory activity. The complexes possibly depressed the synthesis of the proinflammatory (vasodilator) prostaglandin, PGE_2 in the carrageenan pouch model of inflammation. This is in consistent with the work of Lee and Lands[16] and recently confirmed by Moddox.[17] The mechanism of action [C_2H_5Sn(MacL)C_5H_5N] of complex may be, at least in part, at the level of the prostaglandin mediation of inflammation. This is to say that all the compounds may play a role in decreasing the synthesis of proinflammatory PGE_2.

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