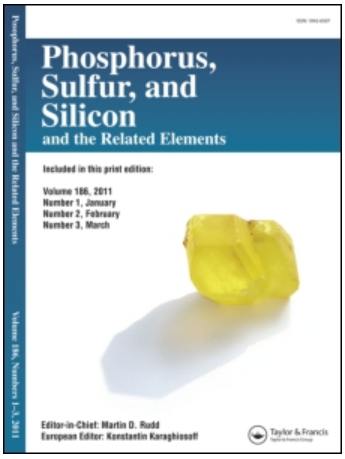

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Synthesis, Structure, Antimicrobial, and Hepatotoxic Behavior of 28-and 32-Membered Bearing Tetra Amide Functions and Their Tin(II) Complexes

Shikha Chauhan[a]; Ashu Chaudhary[b]; R. V. Singh[a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, India [b] Department of Chemistry, Indian Institute of Technology-Delhi, New Delhi, India

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Shikha Chauhan
Department of Chemistry, University of Rajasthan, Jaipur, India

Ashu Chaudhary
Department of Chemistry, Indian Institute of Technology–Delhi, New Delhi, India

R. V. Singh
Department of Chemistry, University of Rajasthan, Jaipur, India

Tin(II) complexes of 1,8-diaminooctane and dicarboxylic acids (succinic acid and adipic acid) have been synthesized and studied. These complexes have been characterized by chemical analysis and IR, ^{1}H NMR, ^{13}C NMR, and ^{119}Sn NMR spectral studies, as well as X-ray powder diffraction, molecular weight determinations, and conductivity measurements. An octahedral geometry around the tin atom is suggested for $[Sn(MacL^{n})Cl_{2}]$ complexes. The pathogenicity of certain microbial infections associated with the complexes made it obligatory to distinguish between a parent counter part and their tin(II) complexes. To make the subject interesting, biomedical applications of the complexes have been discussed.

Keywords Biomedical applications; biologically potent ligands; bivalent tin(II) complexes; hepatotoxic behavior

INTRODUCTION

Interest in exploring metal ion complexes with macrocyclic ligands has been continuously increasing owing to the recoginition of the role

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Address correspondence to R. V. Singh, University of Rajasthan, Department of Chemistry, Jaipur, 302004 India. E-mail: singh-rv@uniraj.ernet.in

played by these structures in metalloprotiens. Schiff-base macrocycles have been of great importance in macrocyclic chemistry. They were the first artificial metal macrocyclic complexes to be synthesized. Metal complexes containing synthetic macrocyclic ligands have attracted a great deal of attention because they can be used as models for more intricate biological macrocyclic systems as metalloporphyrins (haemoglobin, myoglobin, cytochromes chlorophyll), corrins (vitamin B_{12}), and antibiotics (valinomycin, nonaction). These discoveries have created supramolecular chemistry and its enormous diversity.[1–5] Recognition of the importance of the complexes containing macrocyclic ligands for supramolecular science, bioinorganic and encapsulation processes, as well as the formation of compounds with unusual properties and structure has led to considerable effort to develop methods for the synthesis of these complexes.

Ideally, macrocyclic complexes are formed by adding the required metal to a performed macrocycle, which often results in a very low yield of the desired products with the domination of competing linear polymerization or other side reactions. Therefore, we have designed and developed tin complexes with macrocyclic ligands ($MacL^n$) consisting of 1,8-diaminooctane with dicarboxylic acids (succinic acid and adipic acid).

EXPERIMENTAL

All solvents used were of high purity and distilled before use. $SnCl_2$ (BDH), succinic acid, adipic acid, and 1,8-diaminooctance (E. Merck, Darmstadt, Germany) were used as obtained.

Synthesis of the Ligand ($MacL^1$)

In a 100-mL short-necked round-bottom flask, a weighed amount of 1,8-diaminooctane (1.30 g, 10 mmol) in methanol (40 mL) was taken, and to this a corresponding amount of succinic acid (0.60 g, 10 mmol) in methanol (40 mL) was added. The reaction was carried out in 2:2 molar ratios and heated under reflux for 12 h. The reaction mixture was cooled off, and the white compound obtained was recrystallized from methanol.

The same procedure has been used for the synthesis of $MacL^2$. The reagents used were adipic acid in place of succinic acid. The physical properties and analytical data of the ligands are given in Table I.

TABLE I Physical Properties and Analytical Data of Macrocyclic Ligands and Their Tin(II) Complexes

Compounds	M.P. °C Color	Analysis, Found (Calcd.) % C	H	N	Cl	Sn	Mol. Wt. Found (Calcd.)
$MacL^1$	156°C (Cream)	63.00 (63.36)	9.63 (9.84)	11.58 (12.43)	15.15 (15.73)	25.81 (26.33)	419.05 (450.64)
$MacL^2$	163°C (Cream)	66.00 (66.10)	10.1 (10.30)	10.12 (11.01)	13.39 (13.93)	22.88 (23.33)	483.04 (508.784)
$[Sn(MacL^1)Cl_2]$	182°C (White)	44.50 (44.71)	6.82 (6.92)	7.86 (8.75)	10.38 (11.01)	19.13 (18.53)	607.546 (640.236)
$[Sn(MacL^2)Cl_2]$	194°C (White)	47.90 (48.15)	7.30 (7.50)	7.21 (8.02)	9.51 (10.15)	16.48 (16.99)	669.04 (698.38)

Synthesis of the Complex $[Sn(MacL^1)Cl_2]$

The reaction mixture containing $MacL^1$ (1.26 g, 5 mmol) and $SnCl_2$ (0.88 g, 5 mmol) in a 1:1 molar ratio in methanol (40 mL) was heated under reflux for 42 h. The reaction mixture was cooled, transferred to an evaporating dish, and set aside for a few hours, whereupon a white compound separated out. The product formed was washed and dried under reduced pressure and recrystallized from a 1:1 mixture of toulene and n-hexane. The same procedure has been used for the synthesis of $[Sn(MacL^2)Cl_2]$ using $MacL^2$ as ligand.

Physical Measurements

Molecular weights were determined by the Rast Camphor method. Conductivity measurements in dry dimethylformamide were performed with a conductivity bridge type 305 Systronics. Infrared spectra were recorded on a Nicolet Magna FTIR 550 spectrophotometer in KBr pellets. ^1H NMR spectra were recorded on a JEOL FX-90 Q spectrometer in $CDCl_3$ using TMS as the internal standard. ^{13}C and ^{119}Sn NMR spectra were also recorded on the same spectrometer using MeOH as the solvent at 22.49 MHz and 33.35 MHz, respectively. Nitrogen and chlorine were estimated by Kjeldahl's and Volhard's method, respectively. Tin was estimated as tin oxide gravimetrically. Carbon and hydrogen analyses were performed at Central Drugs Research Institute, Lucknow, India. The physical properties and analytical data of the metal complexes are listed in Table I.

RESULTS AND DISCUSSION

The resulting macrocyclic complexes are solids and are soluble in teterahydrofuran and dimethylformamide. The conductivity values measured for 10^{-3}M solution in anhydrous DMF are in the range 13–22 ohm^{-1} cm^2 mol^{-1}, showing them to be nonelectrolytes.

Infrared Spectra

The preliminary identification of macrocyclic ligands and their complexes have been obtained from their infrared spectra. The first feature of all the complexes that attracted attention was the absence of -NH_2 stretching vibrations of the amine and -OH groups of dicarboxylic acids. A single sharp band observed for amide ligands $MacL^1$ and $MacL^2$ in the region 3125–3295 cm^{-1} may be assigned to ν(N-H) of the amide group. The amide I, amide II, amide III, and amide IV groups of ligands were present at 1655–1685, 1444–1481, 1245–1265, and 630–650 cm^{-1}, respectively.[6–7] They provide strong evidence for the presence of a closed cyclic product. Strong and sharp absorption bands appeared in regions 2890–2935 and 1450–1482 cm^{-1} in both the ligands, and their complexes were assigned to a C-H stretching and C-H bending vibrational mode respectively.[8] However, a slight negative shift in the N-H stretching vibration was observed. All other bands did not show appreciable change.

In the spectra of macrocyclic complexes $[Sn(MacL^1)Cl_2]$ and $[Sn(MacL^2)Cl_2]$ as compared to their tetraazamacrocycles, the slight negative shift in the ν(N-H) band that appeared in the region 3236–3240 cm^{-1} was noticed. It is ascribed to the coordinated N-H stretching vibration. This is further sustained by the fact that both complexes showed a medium intensity band in the region 415–424 cm^{-1}, which is attributed to the Sn-N stretching vibrations. The Sn-Cl stretching vibrations of the compounds have been assigned at 313–325 cm^{-1} as reported earlier also.[9] The infrared spectral data of the ligands and their complexes are listed in Table II.

TABLE II IR Spectra of Macrocyclic Ligands and Their Tin(II) Complexes

		Amide bands				C-H			
Compound	ν(N-H)	I	II	III	IV	Stretching	Bending	ν(Sn-Cl)	ν(Sn-N)
$MacL^1$	3195	1655	1444	1265	630	2910	1450	—	—
$MacL^2$	3225	1685	1481	1245	650	2890	1482	—	—
$[Sn(MacL^1)Cl_2]$	3240	1642	1500	1235	637	2915	1464	313	424
$[Sn(MacL^2)Cl_2]$	3236	1750	1499	1261	640	2935	1475	325	415

TABLE III ^{1}H NMR Spectra of Macrocyclic Ligands and Their Tin(II) Complexes

Compound	CO-NH (bs)	CO-N-CH_2 (m)	N-CH_2-CH_2	OC-CH_2-CO	OC-$(CH_2)_4$-CO
$MacL^1$	8.04	3.36	2.08	2.88	—
$MacL^2$	8.12	3.22	1.97	—	3.18
$[Sn(MacL^1)Cl_2]$	8.14	3.30	1.98	2.90	—
$[Sn(MacL^2)Cl_2]$	8.02	3.40	2.06	—	3.27

^{1}H NMR Spectra

^{1}H NMR spectra of the ligands and their macrocyclic complexes (Table III) revealed the signals expected for the given figures. In the spectra of both complexes, no band could be assigned for hydroxyl or amino groups, suggesting that the proposed macrocyclic complexes formed after condensation. Broad signals were observed at δ 8.04 and 8.12 ppm due to amide protons[10,11] in macrocyclic ligands $MacL^1$ and $MacL^2$, respectively. A multiplet appearing in the region δ 3.22–3.36 ppm could be ascribed to methylene protons (CO-N-CH_2) adjacent to the nitrogen atom. A multiplet observed in the region δ 1.97–2.08 ppm is attributed to the methylene protons (N-CH_2-CH_2) of an acid moiety. $MacL^1$ showed a multiplet at δ 2.88 ppm due to central methylene protons [C-(CH_2)-C], and $MacL^2$ showed another multiplet at δ 3.18 ppm ascribed to methylene protons of adipic acid. According to the previously discussed interpretation, we can say that the ligands act as tetradentate chelating agents having four coordination sites. Second, since the anions Cl remained bonded with the tin atom, a hexacoordinated environment around the tin metal atom seems to be reasonable (Figure 1).

^{13}C NMR Spectra

The conclusions drawn from the IR and ^{1}H NMR spectra are in agreement with the ^{13}C NMR spectral data (Table IV) regarding the authenticity of the proposed structure.

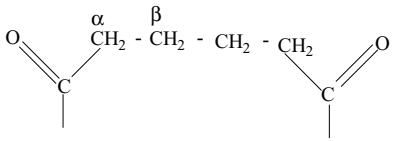
X-Ray Studies

Cell dimensions of the complex $[Sn(MacL^2)Cl_2]$ were successfully calculated, which were found to be a = 20.0649, b = 19.1956, c = 15.1674, and $\alpha = \beta = \gamma \simeq 90^\circ$.

All these data agree with the orthorhombic system of the complex.

TABLE IV ^{13}C NMR Spectra of Macrocyclic Ligands and Their Tin(II) Complexes

Compound	>C=O	C-CH_2-C	>N-CH_2	C_α	C_β
$MacL^1$	170.11	36.45	45.80	32.45	—
$MacL^2$	172.02	36.68	44.70	32.68	26.50
$[Sn(MacL^1)Cl_2]$	171.92	36.70	46.22	32.70	—
$[Sn(MacL^2)Cl_2]$	170.88	36.50	45.10	33.50	28.10



^{119}Sn NMR Spectra

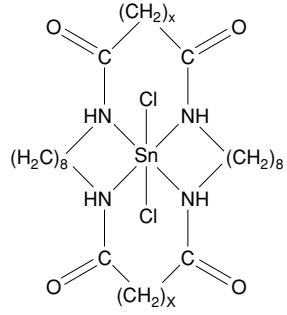
^{119}Sn NMR spectra of the tin (II) complexes gave signals at δ 585–596 ppm, indicating coordination number six around the tin atom in complexes.[12]

On the basis of the previously discussed results, the structure shown in Figure 1 is proposed for the complexes.

MICROBIAL ASSAYS

The dehydrated plate count medium (g/100 mL) distilled water:glucose 0.1, yeast extract 0.25, tryptone 0.5) and sabouraud's dextrose agar (g/100 mL distilled water:glucose, peptone), were used, respectively, for the antibacterial and antifungal activities.

The target microorganisms included *Aspergillus niger* NCIM 545, *Candida albicans* NCIM 3471, *X. compestris, Pseudomonas aeruginosa*



Where x = 2 and 4

FIGURE 1

TABLE V Antimicrobial Activity* of the Ligands and Their Tin(II) Complexes

Compound	*A. niger*	*C. albicans*	*X. compestris*	*P. aeruginosa*	*S. aureus*
Diclone (standard)	8	16	8	9	15
$MacL^1$	6.9	7.8	9.1	11.3	9
$MacL^2$	8.2	8.8	9.7	—	12.3
$[Sn(MacL^1)Cl_2]$	9.5	10.5	12.4	13.2	15.8
$[Sn(MacL^2)Cl_2]$	13.7	21.2	16.3	18.2	19.7

*Zone of inhibition in mm.

NCIM 2036, and *Staphylococcus aureus* NCIM 2054. These strains were selected because they are routinely used in testing of disinfectants.[13] The stock cultures of these microorganisms were maintained at 20°C in 15% glycerol.[14] The inoculum was prepared from stock cultures by a streaking onto the plate-count agar for bacteria and on Sabouraud's dextrose agar for fungi. After an overnight incubation, a single colony was used to inoculate sterile liquid media. The 5-mL broth was dispensed in the test tube and sterilized in the autoclave. The broths were then inoculated with respective cultures and incubated on an orbital shaker (150 ppm) overnight at 30°C. A_{540} of bacterial cultures and *C. albicans* were adjusted to 0.12 and 0.20, respectively. This corresponds to the 10^6–10^7 colony forming unit (Cfu/mL). The spore inoculum of *A. niger* containing 10^6 spores per mL was used. The solutions of the ligands and complexes were prepared in DMSO,[15] added to the tube containing a 3-mL liquid medium, and inoculated with 30 μL of the cultures.

Incubation was done for 18 h at 37°C. The extent of inhibition of *S. aureus* by the ligand was found to be more pronounced than by their respective complexes, but the reverse was found for the other microorganisms. The experimental data of these complexes are listed in Table V.

Antihepatotoxic Activity

Treatment Schedule

Male albino rats of the Sprague-Dawley strain were used in the present investigation. The rats were fed with a balanced pellet diet, and water was provided *ad libitum*. The rats were divided into six groups containing six animals each, out of which animal of group A served as the control and received only gum asacia (1%) in distilled water. Group B received (CCl_4 [1.5 mL/kg b.w]) and gum asacia to produce hepatotoxicity, whereas as groups C and D received $MacL^2$ and $[Sn(MacL^2)Cl_2]$.

TABLE VI Effect of the Ligand and Its Tin(II) Complexes on Various Liver Enzymes of Albino Rats

		Mean ± SEM (Unit/mL)			Mean ± SEM	
Group	Treatment	Serum Glutamic Oxaloacetic Transaminase (SGOT)	Serum Glutamic Pyruvate Transaminase (SGPT)	Alkaline phosphate (ALKP)	Total protein	Total Albunin
A	Normal control	45.12 ± 1.42	32.80 ± 0.51	25.42 ± 0.96	5.79 ± 0.311	3.55 ± 0.199
B	Toxic control	77.10 ± 2.04	65.54 ± 2.54***	50.14 ± 3.149	4.30 ± 0.167	4.55 ± 0.667
C	$MacL^2$	55.05 ± 1.25***	44.23 ± 3.25***	21.28 ± 1.25***	6.27 ± 0.261***	4.29 ± 0.11*
D	$[Sn(MacL^2)Cl_2]$	36.80 ± 1.98***	39.44 ± 1.25	22.05 ± 2.97***	6.15 ± 2.67***	3.44 ± 0.052
E	Silybon-50 standard	56.76 ± 1.56***	49.66 ± 2.64[x]	26.19 ± 1.417***	6.96 ± 0.371***	3.66 ± 0.59

*$P < 0.05$.

***$P < 0.001$.

The values of biochemical parameters are in mean ± SEM.

Figures in the table that indicate the percent protection in individual biochemical parameter from their elevated values caused by the hepatotoxin.

Assessment of Liver Function

The biochemical parameters such as serum glutamic oxaloacetic transaminase (SGOT),[16] serum glutamic pyruvate transaminase (SGPT), alkaline phosphates (ALKP),[17] and total protein and total albumin[18,19] were estimated by the reported methods (Table VI).

Histopathological Studies of Rat's Liver

The histopathological studies were also carried out by the reported method.[20] The rats were sacrificed under light ether anesthesia after 24 h of the last dosage, and then the liver was removed and washed with normal saline. Small pieces of liver tissue were processed and embedded in paraffin. Sections of 5–6 microns in thickness were cut, stained with haematoxylin eosin, and then studied under an electron microscope. Results of the biochemical estimations are reported as mean ± SE. Total variation presence in a set of data was estimated by one-way analysis of variance (ANOVA). Student t-test and Dennett's test were used for determine the significance.

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