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Synthesis, spectral, antimicrobial, and antifertility studies of tetraaza macrocyclic complexes of tin(II)

Abstract: A novel family of tetraazamacrocyclic complexes of Sn(II) has been synthesized by template condensation using 1,9-diaminononane with different dicarboxylic acids (malonic, succinic, glutaric, and adipic). The complexes were characterized by elemental analysis, conductivity measurements, molecular weight determinations, infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and tin nuclear magnetic resonance (^{119}Sn NMR) spectral studies. The compounds were found to be monomeric in nature, having an octahedral geometry. The *in vitro* antibacterial activity of macrocyclic complexes against *Escherichia coli* and *Staphylococcus aureus* were tested to assess their inhibiting activities. The antifungal activity of starting materials and their metal complexes were studied by screening the compounds against *Fusarium oxysporum* and *Aspergillus niger*. The testicular sperm density, sperm morphology, sperm motility, density of cauda epididymis, spermatozoa, and fertility in mating trials and the biochemical parameters of the reproductive organs of the rats were examined and are discussed.

Keywords: antibacterial activity; macrocyclic complexes; monomeric; octahedral geometry.

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Introduction

Macrocyclic complexes have attracted increasing interest owing to their role in the understanding of molecular processes occurring in biochemistry, material science, and catalysis (Kumar et al., 2012). Studies on macrocyclic complexes have shown that some of them are involved in important biological processes, such as photosynthesis and dioxygen transport, in addition to their catalytical properties, which may lead to important industrial applications (Pawar et al., 2011). A number of nitrogen donor macrocyclic derivatives have long been used in analytical, industrial, and medical applications (Singh and Kumar, 2010). Macrocyclic complexes are considered to mimic the synthetic models of metalloporphyrins and metallocorrins due to their intrinsic structural properties (Sharma et al., 2010). Macrocyclic metal complexes are of great importance due to their resemblance with many natural system antibacterial activity, such as porphyrins and cobalamines, and their use in DNA recognition oxidation and cleavage (Arockiadoss and Amaladason, 2012). The synthesis and characterization of coordination compounds with macrocyclic ligand have evolved during the last years as one of the main research areas in coordination chemistry (Al Obaidi and Al Hiti, 2012). There has been a spectacular growth in interest in metal complexes with the tetraazamacrocyclic ligands, followed by an extensive work on the metal-controlled template synthesis of the macrocyclic species (Herlinger et al., 1994). The development in the field of bioinorganic chemistry has also been the other important factor in spurring the growing interest in the complexes of the macrocyclic ligands (Melson, 1979). Macrocyclic ligand systems often exhibit unusual properties, and sometimes, mimic-related natural macrocyclic ligands are at the forefront of bioinorganic chemistry due to their variety of geometrical forms available and the possible encapsulation of the metal ion (Melson, 1979). It has been reported that macrocyclic complexes with tetraazamacrocyclic ligands such as cyclan, cyclam, or bycyclam exhibit antitumor or anti-HIV activity, which stimulates researchers to do more exploitation on their derivatives (Chaudhary and Singh, 2008). Organotin complexes have a range of pharmacological applications. The use of organotin halides as antiinflammatory agents against different types of edema in mice has been reported (Sembdner and Parthier, 1993). Organotin complexes are also used in agriculture. They are efficient fungicides and bactericides (Ranjan and Lewak, 1995; Tsai and Rao, 1996). Macrocylicpolyamines have attracted increasing attention because of their unique property, namely, to form very

stable chelates with various heavy metal ions. The potential of macrocyclic ligand systems with their central cavity for use as metal ion selective reagent has been widely recognized (Sharma et al., 2013).

Results and discussion

The elemental analyses and analytical data of the prepared complexes are given in Table 1. All the complexes are stable at room temperature and are nonhygroscopic. They are soluble in most organic solvents such as methanol, benzene, dichloromethane, tetrahydrofuran, and carbon tetrachloride. The low values of their molar conductivities (14–22 Ω^{-1} cm^2 mol^{-1}) in anhydrous dimethylformamide show them to be nonelectrolyte. The molecular weights of the complexes indicated the monomeric nature of the complexes.

Infrared spectra

The IR spectra of the starting materials and their metal complexes were recorded, and their comparative studies confirmed the formation of macrocyclic complexes with the proposed coordination pattern. The bands observed in the regions 3500–3410 and 3000–2500 cm^{-1} were attributed to the -NH_2 of amino acid and -OH of dicarboxylic acid, respectively. Both of these bands (-NH_2 and -OH) disappeared in case of all the complexes, confirming the cyclization (Colthup et al., 1964). The appearance of four amide bands in the regions 1690–1650, 1560–1465, 1259–1230, and 680–630 cm^{-1} in the plane deformation vibrations also suggests the proposed cyclization (Anastasi et al., 1998; Choi et al., 1998; Hay and Fraser, 1998). A single sharp absorption band in the region 3220–3180 cm^{-1} is attributed to ν(N-H) of the amide group. The absorption bands appearing in the regions 2930–2880 and 1460–1410 cm^{-1} in all the complexes may reasonably be assigned to the C-H stretching and C-H bending vibrational modes, respectively. The bands in the region 470–450 cm^{-1} in the spectra of the complexes may be attributed to ν(Sn-N) vibration. The (Sn-Cl) stretching vibrations of the complexes have been assigned at 420–350 cm^{-1} (Shakir and Varshney, 1995; see Table 2).

NMR spectral studies

The ^{1}H NMR spectra of the tin(II) complexes were recorded in DMSO-d_6, and the chemical shift values δ for the different protons are given in Table 3. The following points, which confirm the suggested structures for the tin(II) complexes, are worth mentioning. The ^{1}H NMR spectra of the complexes do not show any signal corresponding to the amino and hydroxyl groups. The broad signal

Table 1 Physical properties and analytical data of tin(II) macrocyclic complexes.

S. No.	Reactants (g)			Complex empirical formula	M.P. (°C)	Color	Analyses found (calcd.) %					Mol. wt. found (calcd.)
	$SnCl_2$	1,9-Diaminononane	Acid				C	H	N	Cl	Sn	
1	1.06	1.77	Malonic 1.16	$C_{24}H_{44}N_4O_4Cl_2Sn$	230	White	44.63 (44.88)	6.78 (6.90)	8.58 (8.72)	10.88 (11.04)	18.2 (18.48)	638 (642.33)
2	1.02	1.70	Succinic 1.27	$C_{26}H_{48}N_4O_4Cl_2Sn$	225	White	46.46 (46.59)	7.15 (7.22)	8.22 (8.36)	10.42 (10.69)	17.63 (17.71)	668 (670.28)
3	0.96	1.60	Glutaric 1.34	$C_{28}H_{52}N_4O_4Cl_2Sn$	210	White	48.32 (48.16)	7.64 (7.50)	7.96 (8.02)	10.02 (10.15)	16.08 (16.99)	702 (698.34)
4	0.94	1.57	Adipic 1.45	$C_{30}H_{56}N_4O_4Cl_2Sn$	215	White	49.54 (49.60)	7.68 (7.77)	7.64 (7.71)	9.66 (9.76)	16.21 (16.34)	720 (726.39)

Table 2 IR spectral data (cm^{-1}) of tin(II) macrocyclic complexes.

Compound	ν(N-H)	Amide bands				C-H		ν(Sn-N)	ν(Sn-Cl)
		I	II	III	IV	Stretching	Bending		
$[Sn(Mac_1)Cl_2]$	3180	1662	1465	1252	630	2925	1450	465	410
$[Sn(Mac_2)Cl_2]$	3200	1669	1560	1240	656	2920	1440	456	380
$[Sn(Mac_3)Cl_2]$	3220	1690	1495	1230	680	2880	1410	450	350
$[Sn(Mac_4)Cl_2]$	3210	1650	1532	1259	642	2930	1460	470	420

Table 3 ^{1}H NMR spectral data (ppm) of tin(II) macrocyclic complexes.

Compound	(CO-NH)	(CO-N-CH_2)	C-CH_2-C	CO-(CH_2)x-CO
[Sn(Mac_1)Cl_2]	7.90	3.36	2.03	2.90
[Sn(Mac_2)Cl_2]	7.96	3.32	2.05	3.05
[Sn(Mac_3)Cl_2]	8.04	3.41	2.09	3.23
[Sn(Mac_4)Cl_2]	8.17	3.44	1.97	3.28

observed in all the complexes at δ=7.90–8.17 ppm is due to the amide (CO-NH) protons (Shakir and Varshney, 1995). In the spectra of the complexes, a multiplet observed in the region δ=1.97–2.09 ppm may be ascribed to the middle methylene protons of the 1,9-diaminononane moiety. In the spectra of the complexes, a multiplet arising due to the methylene protons (CO-N-CH_2) appeared in the region δ=3.32–3.44 ppm. Similar data have been reported by several authors (Woon and Fairlie, 1992) showing the presence of the NH group in the macrocyclic ring system. Singlets appearing in the regions δ=2.90–3.05 ppm were assigned to methylene protons of malonic and succinic acid moiety, respectively, while multiplets observed in the regions δ=3.23–3.28 ppm were ascribed to the methylene proton of glutaric acid and adipic acid, respectively. The conclusions drawn from the IR and ^{1}H NMR spectra are in agreement with the ^{13}C NMR spectral data regarding the authenticity of the proposed structure. The shift observed in the carbons attached with nitrogen atoms is indicative of their coordination with the central tin atom.

The ^{119}Sn NMR spectrum of the complex [Sn(Mac_3)Cl_2] shows the signal at δ=-568.96 ppm, indicating coordination number 6 in the complexes around tin (Winter et al., 1963).

Biochemical studies

Antifungal activity

The starting materials and their metal complexes have been screened for their antifungal activities by the radial growth method (Bansal et al., 2004) using potato dextrose agar medium. The pathogenic fungi used during the investigations were *Fusarium oxysporum* and *Aspergillus niger*. The compounds were directly mixed with the medium in concentrations of 50, 100, and 200 ppm. Controls were also run, and three replicates were used in each case. The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after 4 days (Table 4). The percentage growth inhibition was calculated by using the following formula:

Table 4 Antifungal screening data of tin(II) macrocyclic complexes.

Compound	Average % inhibition after 96 h (conc. in ppm)					
	Fusarium oxysporum			*Aspergillus niger*		
	50	100	200	50	100	200
$SnCl_2$	53	57	61	44	46	49
Malonic acid	30	33	36	29	30	30
Succinic acid	32	35	38	30	32	33
Glutaric acid	33	35	39	31	32	34
Malonic acid	33	36	39	33	34	36
1,9-diaminononane	34	36	40	33	34	35
[Sn(Mac_1)Cl_2]	77	83	95	59	63	74
[Sn(Mac_2)Cl_2]	86	92	97	66	73	82
[Sn(Mac_3)Cl_2]	89	96	98	69	76	87
[Sn(Mac_4)Cl_2]	91	99	100	72	79	89
Standard (Bavistin)	86	100	100	82	100	100

$$\% \text{ Growth inhibition} = \frac{dc\text{-}dt}{dc} \times 100$$

where *dc* is the diameter of the fungal colony in the control plate and *dt* is the diameter of the fungal colony in the test plate.

The experimental results show that there is an increase in the toxicity of the complexes as compared with the starting materials. The evaluation of antifungal studies further revealed that the fungi toxicity of the complexes also depends on the nature of the metal ion (Bansal et al., 2004). In general, the activity of these metal complexes increases as their concentration is increased in the test solution.

Antibacterial activity

The starting materials and their complexes were screened for their antimicrobial activity against gram-negative as well as gram-positive microorganisms such as *Escherichia coli* and *Staphylococcus aureus*. For antibacterial activity, inhibition zone technique (Chaudhary et al., 2002) was used. Solutions of the test compounds in methanol in concentrations of 500 and 1000 ppm were prepared in which discs were dipped in solution of the test sample and then placed on seeded plates. The Petri plates having these discs on the seeded agar is placed at low temperature for 2–4 h to allow for the diffusion of chemicals before being incubated at a suitable optimum temperature of 28±2°C for 24–30 h. After the expiry of their incubation period, the zone of inhibition associated with the treated disc was measured in mm (Table 5).

The data revealed that the antibacterial activity of the complexes was superior to that of the starting material. Further, on the basis of chelation theory (Sharma et al., 2010), the antibacterial activity of the metal chelates can be explained. Chelation may enhance the biochemical potential of bioactive species. Because of chelation, the polarity of the metal ion will be reduced due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Hence, macrocyclic complexes become very stable due to delocalization of π-electrons. It enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell, thus blocking the synthesis of the proteins, which restricts further growth of organisms (Raman et al., 2009).

Antifertility activity

The antifertility activity of the starting materials and their complexes was studied on the adult male albino rats of Sprague Dawley strain. The rats were divided into four groups of five animals each.

Group A received the vehicle (olive oil) only. Animals of groups B and C received succinic acid and 1,9-diaminononane, respectively (20 mg/kg b.wt.), orally for 60 days, whereas the animals of groups D received their complexes, i.e., $C_{26}H_{48}N_4O_4Cl_2Sn$ (20 mg/kg b.wt.), orally for a period of 60 days. The animals were screened for fertility test and were autopsied for detailed pathological and biochemical studies.

Table 5 Antibacterial screening data of tin(II) macrocyclic complexes.

Compound	Diameter of inhibition zone (mm) after 24 h (conc. in ppm)			
	Staphylococcus aureus		*Escherichia coli*	
	500	1000	500	1000
$SnCl_2$	6	7	4	5
Malonic acid	4	7	4	6
Succinic acid	5	6	4	5
Glutaric acid	5	5	3	5
Adipic acid	5	6	4	5
1,9-diaminononane	6	8	5	6
$[Sn(Mac_1)Cl_2]$	10	12	7	7
$[Sn(Mac_2)Cl_2]$	11	13	8	11
$[Sn(Mac_3)Cl_2]$	13	15	10	12
$[Sn(Mac_4)Cl_2]$	14	17	12	14
Standard(Streptomycin)	15	17	17	18

The sperm motility in cauda epididymis and the density of testicular and cauda epididymis in suspended sperm were calculated. Reproductive organs were excised, blotted free of blood, and weighed. The testes were frozen for biochemical estimations. Total protein, glycogen, total cholesterol, sialic acid, acid and alkaline phosphatase activities were estimated by using the standard laboratory techniques. Student's *t* test was applied in comparing the means.

Sperm motility and density

Oral administration of the starting materials and tin complexes resulted in a significant ($p<0.01$ to $p<0.001$) decline in the sperm motility in cauda epididymis and sperm density in the testes and cauda epididymis (Table 6).

Fertility test

While conducting fertiility test, the sluggish motile sperms were unable to fertile normal cyclic females. The test was 70%–98% negative in treated animals (Table 7).

Testicular biochemistry

A significant reduction ($p \leq 0.01$ to $p \leq 0.001$) in the protein and sialic contents of the testes was observed in the rats treated with starting materials and their complexes, whereas the testicular cholesterol, glycogen, acid and alkaline phosphatase contents were increased significantly ($p \leq 0.01$ to $p \leq 0.001$; see Table 8).

The present study showed that the oral administration of the starting materials and their Sn complex for 60 days in male rats resulted in a significant reduction in the weights of the testes and other reproductive organs. The reduction in the weight of the testes reflects regressive changes in the seminiferous tubules, which are associated with azoospermia and germinal aplasia.

A reduction in the number of germinal cells leads to the reduction in the weight of the testes (Naqvi and Vaishnavi, 1993). The reduction in the weight of accessory sex organs may be due to the reduced androgen availability by these compounds. The reduction in the sperm density in the cauda epididymis may be due to the alteration in the androgen metabolism (Chitra et al., 2001). Suppression of gonadotropins might have caused a decrease in the sperm density in the testes. Further, the reduction in fertility by these compounds may be

Table 6 Effect of starting materials and their tin(II) complex on body and reproductive organ weights of male rats.

Groups	Treatment	Body weight (g)			Organ weight (mg)		
		Initial	Final	Testes	Epididymis	Seminal vesicle	Ventral prostate
A	Control	225±22.5	238±21.5	1390±30.0	450.0±18.9	485.0±22.2	478.0±21.8
B	Succinic acid	220±18.5	232±15.7^{ns}	1180±30.5^{a}	390±15.0^{a}	405±18.9^{b}	408±16.5^{a}
C	1,9-Diaminononane	222±14.0	230±18.6^{ns}	1190±28.7^{b}	380±14.5^{b}	410±9.8^{b}	413±18.9^{a}
D	$C_{26}H_{48}N_4O_4Cl_2Sn$	228±13.4	240±12.5^{ns}	740±20.5^{b}	225±15.6^{b}	225±13.5^{b}	232±14.5^{b}

Data are mean±SEM of five animals.
ns=nonsignificant.
$^{a}p \leq 0.01$, group B and C compared with group A.
$^{b}p \leq 0.001$, group B and C compared with group D.

Table 7 Altered sperm dynamics of the starting materials and their tin(II) complex on treated rats.

Groups	Treatment	Sperm motility (cauda epididymis) (%)	Sperm density (million/cm^3)		Fertility tests (%)
			Testes	Epididymis	
A	Control	86.0±4.9	5.10±0.30	97.9±4.5	100 positive
B	Succinic acid	50.0±4.3^{a}	3.9±0.15^{a}	45.5±3.9^{a}	70 negative
C	1,9-Diaminononane	52.0 ± 5.4^{a}	3.75±0.17^{a}	43.5±3.1^{a}	75 negative
D	$C_{26}H_{48}N_4O_4Cl_2Sn$	28.5±6.5^{a}	2.1±0.11^{a}	20.5±2.8^{a}	98 negative

Data are mean±SEM of five animals.
$^{a}p \leq 0.001$, group B compared with group A, group C compared with group B, group D compared with group C.

due to a lack of forward progression and reduction in the density of the spermatozoa and altered biochemical million of cauda epididymis. These complexes also induce biochemical changes in the reproductive tract. A significant reduction in the total protein and sialic acid contents of the testes after treatment indicated reduced androgen supply to those organs and a decrease in the number of spermatozoa in lumen (Bedwal et al., 1994). The increase in the cholesterol contents of the testes may be due to nonutilization of substances for androgen biosynthesis by fewer Leyding cells present or due to damage.

Further, an increase in the acid and alkaline phosphatase activity in the testes of the rats treated with starting materials and their Sn complex suggested an impairment of functional integrity of the testes (Akbarsha et al., 1990).

Conclusion

Macrocyclic complexes of Sn(II) with different dicarboxylic acids and 1,9 diaminononane were synthesized and

Table 8 Testicular biochemistry of the starting materials and their tin(II) complex.

Group	Treatment	Glycogen (mg/g)	Total protein (mg/g)	Total cholesterol (mg/g)	Sialic acid (mg/g)	Phosphatase (mg/ip/g/h)	
						Acid	Alkaline
A	Control	3.95±0.19	228.8±20.3	5.8±0.35	5.7±0.34	3.21±.15	11.39±0.65
B	Succinic acid	4.40±0.20^{a}	182.5±11.0^{a}	6.2±0.11^{a}	4.9±0.45^{b}	4.2±0.16^{a}	13.90±0.65^{a}
C	1,9-Diaminononane	4.45±0.30^{a}	188.5±12.5^{a}	6.4±1.5^{a}	4.7±0.38^{b}	4.1±0.14^{a}	14.2±0.75^{b}
D	$C_{26}H_{48}N_4O_4Cl_2Sn$	6.14±0.14^{b}	130.5±17.5^{b}	8.1±.25^{a}	2.5±0.15^{b}	6.2±0.15^{b}	15.0±0.56^{b}

Data are mean±SEM of five animals.
$^{a}p \leq 0.01$, group B and C compared with group A.
$^{b}p \leq 0.001$, group B and C compared with group D.

characterized by analytical and spectral techniques. Spectroscopic investigations revealed the formation and purity of compounds. These compounds were tested against different bacterial and fungal strains and exhibited promising activity against all the tested microorganisms. The present study also evaluated the effect of succinic acid and 1,9 diaminononane and their Sn(II) complexes on the reproductive functions of the rats and suggests that the macrocyclic complexes are an effective fertility inhibitor in male rats.

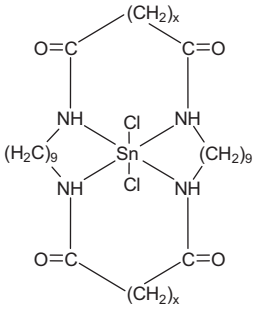

Figure 1 Structures of the tin(II) complexes according to the results of the spectral studies.
x=1, 2, 3, 4.

Materials and methods

The chemicals used include malonic acid, succinic acid, glutaric acid, adipic acid (Fluka, Messerschmittstr, Neu-Ulm, Switzerland), 1,9-diaminononane (E. Merck, Worli, Mumbai), and $SnCl_2$ (BDH, Worli, Mumbai). All solvents used were of high purity and were distilled in laboratory before use. Moisture was excluded from the glass apparatus using $CaCl_2$ guard tubes.

Preparation of the complexes

A weighed amount of $SnCl_2$ was added to the calculated amounts of dicarboxylic acid and 1,9-diaminononane in a 1:2:2 molar ratio using dry MeOH as the reaction medium. The resulting mixture was stirred for 10–12 h. The contents were kept at room temperature for 12 h, resulting in the formation of crystalline compounds (Figure 1). The products were repeatedly washed with methanol to ensure their purity and were dried. These compounds were recrystallized from benzene and dried again *in vacuo*. Yields of the resulting complexes were 65–70%.

Molecular weights were determined by the Rast camphor method (Vogel, 1978). Conductivity measurements were carried out in 10^{-3} M dimethylformamide solutions at 20°C using a Systronic Type-305 conductivity bridge. IR spectra were recorded as KBr discs, using a Nicolet-Magna FTIR-550 spectrophotometer. ^{1}H NMR spectra were recorded in deuterated DMSO-d_6 at 89.55 MHz using TMS as an internal standard. ^{13}C NMR spectra were recorded in dry DMSO using TMS as the internal standard at 22.49 MHz. ^{119}Sn NMR spectra were recorded at 33.35 MHz using DMSO-d_6 as the solvent. The chemical shifts were determined relatively to the external reference tetramethyltin. Nitrogen and chlorine were determined by Kjeldahl's and Volhard's methods, respectively (Vogel, 1991). Tin was estimated gravimetrically as tin oxide. Carbon and hydrogen analyses were performed at CDRI Lucknow .

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