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Synthesis, Structural Investigation and Biological Studies of New Macrocyclic Complexes of Tin(II)

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Macrocyclic complexes of bivalent tin were synthesized by the template condensation method using benzildihydrazone with malonic, succinic, glutaric, adipic and phthalic acids. The reaction proceeded smoothly to completion. These macrocyclic complexes were characterized by elemental analyses, molecular weight determinations, infrared and ^{1}H-NMR spectral analyses. The elemental analyses are consistent with the formation of complexes $[Sn(Mac_n)Cl_2]$ where $n = 1-5$ and Mac represents a macrocyclic ligand moiety. All the complexes are stable in open atmosphere. The spectral studies confirmed the proposed framework of new macrocyclic complexes and indicated an octahedral geometry around the central metal atom. The complexes were screened *in vitro* against a number of pathogenic fungi and bacteria to assess their growth inhibiting potential. The antifertility activity is also discussed with positive findings.

Keywords: tin(II) macrocyclic complexes; antifungal activity; antibacterial activity; antifertility activity

1 Introduction

The importance of macrocyclic complexes is now well recognized (1, 2). In the past, attention has been paid to the design and synthesis of small molecular complexes that mimic aspects of spectral and chemical properties of metal site proteins, catalysis, extraction of metal ions from solution and the activation of small molecules. 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 stabilize 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), e.g. in the food industry, dyes industry, analytical chemistry, catalysis, fungicides and agrochemical fields, and importance in the development of industrial areas (6). Among the various synthetic strategies proposed, template condensation is one of the most highlighted methods. Metal template condensation often provides selective routes towards products that are not obtainable in the absence of the metal ion (7). The number and relative position of the donor atoms and the cavity size in the macrocyclic ligands present these molecules with special reactivity (8). Organotin compounds have good biological activity which includes bactericidal, fungicidal, antitumor and acaricidal activity (9). Our ongoing work on tin derivatives and biochemistry of synthetic organometallics has generated active research relating to their biochemical significance. In this paper, we report the synthesis and characterization of tin complexes derived from the template condensation of benzildihydrazone and dicarboxylic acids.

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2 Experimental

2.1 Methods and Materials

2.1.1 Preparations of Benzildihydrazone

Benzildihydrazone (m.pt 172°C) was prepared by the literature method (10) by mixing benzil and hydrazine hydrate.

2.1.2 Preparation of the Complexes

The reaction was carried out in a 1:2:2 molar ratio. A weighed amount of benzildihydrazone (0.3345 g, 5.5 mmol) was dissolved in methanol (25 ml) in a 100 ml round bottom flask. This was followed by the addition of a methanolic solution of malonic (0.5793 g, 5.5 mmol), succinic (0.5513 g, 4.6 mmol), glutaric (0.5239 g, 3.9 mmol), adipic (0.5123 g, 3.5 mmol) or phthalic acid (0.5435 g, 3.2 mmol). The reaction mixture was stirred continuously for 5 h, after which a methanolic solution of $SnCl_2$ (0.4935 g, 2.78 mmol) was added. The reaction was

Table 1. Physical properties and analytical data of the macrocyclic complexes of tin(II) along with different diacids used

Compounds	Color	MP (°C)	Yield %	Analysis (%) found (calcd.) C	H	N	Cl	Sn	Mol wt. found (calcd.)
$[Sn(Mac_1)Cl_2]$ (malonic) ($C_{34}H_{28}N_8O_4Cl_2Sn$)	Orange	148	43	50.45 (50.90)	3.38 (3.51)	13.50 (13.96)	8.50 (8.83)	14.53 (14.79)	799 (802)
$[Sn(Mac_2)Cl_2]$ (succinic)($C_{36}H_{32}N_8O_4Cl_2Sn$)	Orange	155	48	52.00 (52.07)	3.50 (3.88)	13.01 (13.49)	8.23 (8.53)	14.01 (14.29)	809 (830)
$[Sn(Mac_3)Cl_2]$ (glutaric) ($C_{38}H_{36}N_8O_4Cl_2Sn$)	Orange	180	51	53.01 (53.17)	4.01 (4.22)	13.98 (13.05)	8.01 (8.26)	13.50 (13.82)	828 (858)
$[Sn(Mac_4)Cl_2]$ (adipic) ($C_{40}H_{40}N_8O_4Cl_2Sn$)	Orange	200	56	54.01 (54.19)	4.28 (4.54)	12.45 (12.64)	7.68 (7.99)	13.01 (13.39)	845 (886)
$[Sn(Mac_5)Cl_2]$ (phthalic) ($C_{44}H_{32}N_8O_4Cl_2Sn$)	Orange	240	60	57.02 (56.98)	3.01 (3.51)	11.99 (12.09)	7.50 (7.65)	12.65 (12.81)	903 (926)

again stirred continuously for 10 h. The colored solids were separated and dried in vacuum. Their physical properties and analytical data are recorded in Table 1.

3 Results and Discussion

All the complexes are colored solids. They are slightly soluble in cold methanol and benzene, but fully soluble in DMF, DMSO and THF. The metal derivatives are stable at room temperature and are non-hygroscopic.

3.1 Infrared Spectra

The IR spectra of the complexes do not show any band corresponding to the amino group in benzildihydrazone and hydroxide protons in dicarboxylic acid (11, 12). This clearly indicates that cyclization has taken place. The presence of a strong absorption band in the region 1555–1590 cm^{-1} corresponds to the ν(C═N) group (13, 14) (Table 2). In addition, four amide bands were also observed, in the regions 1669–1701, 1543–1586, 1254–1274 and 627–684 cm^{-1}, assigned to amide I, amide II, amide III and amide IV vibrations, respectively, similar to those reported for other tetraazamacrocyclic complexes. The νNH group appears in the region 3216–3218 cm^{-1} and it remains unchanged which clearly showed that it is not participating in the coordination (15). The band present in the region 1685–1699 cm^{-1} may be assigned to the C═O group of the CONH moiety (16). This indicates that the oxygen of the carbonyl group is not coordinated to the metal atom. The band present in the range 1000–1350 cm^{-1} is assigned due to the C-N vibration. The band in the region 435–479 cm^{-1} in the spectra of the complexes may be assigned to the Sn-N stretching vibration (17) (Table 2).

3.2 ^{1}H-NMR Spectra

^{1}H-NMR spectra of the complexes showed that the proton resonance signals due to -NH_2 and -OH groups were absent in the respective metal complexes suggesting that the proposed macrocyclic skeleton was formed through a condensation reaction (Table 3). In the spectra of all the complexes, a broad signal, observed in the region δ 7.01–8.13 ppm, is due to the amide (CO-NH) protons (18). On the other hand, singlets appeared at δ 2.90 ppm, δ 3.15 ppm, δ 3.21 ppm and δ 3.30 ppm, from the malonic, succinic, glutaric and adipic acids, respectively are due to the -CH_2- protons. The aromatic protons of phenyl group appear in the region δ 7.52–8.18 ppm.

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

Compound	ν(C═N)	ν(NH)	Amide I	Amide II	Amide III	Amide IV	ν Sn-N
$[Sn(Mac_1)Cl_2]$	1555	3218	1669	1543	1264	664	435
$[Sn(Mac_2)Cl_2]$	1584	3216	1684	1566	1270	627	449
$[Sn(Mac_3)Cl_2]$	1569	3216	1674	1572	1265	660	461
$[Sn(Mac_4)Cl_2]$	1585	3217	1701	1581	1274	676	470
$[Sn(Mac_5)Cl_2]$	1590	3216	1693	1586	1254	684	479

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

Compound	(CO-NH)	CH_2	-$(CH_2)_2$-	-$(CH_2)_3$	-$(CH_2)_4$	-Ph
$[Sn(Mac_1)Cl_2]$	7.01	2.9	—	—	—	7.52
$[Sn(Mac_2)Cl_2]$	7.96	—	3.15	—	—	7.69
$[Sn(Mac_3)Cl_2]$	8.01	—	—	3.21	—	7.78
$[Sn(Mac_4)Cl_2]$	8.03	—	—	—	3.3	7.90
$[Sn(Mac_5)Cl_2]$	8.13	—	—	—	—	8.18

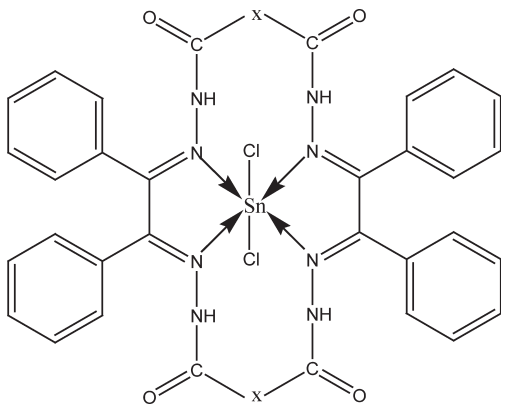

Fig. 1. Structure of the complexes.

3.3 ^{119}Sn NMR Spectra

The ^{119}Sn NMR spectra of the tin complexes give signals at $-\delta$ 586–595 ppm indicating a coordination number of six for the tin atom in the complexes (19).

Thus, on the basis of the above discussions, Figure 1 is proposed (15) for the complexes.

Where, Complex x; $[Sn(Mac_1)Cl_2]$ (CH_2); $[Sn(Mac_2)Cl_2]$ $(CH_2)_2$; $[Sn(Mac_3)Cl_2]$ $(CH_2)_3$; $[Sn(Mac_4)Cl_2]$ $(CH_2)_4$; $[Sn(Mac_5)Cl_2]$ (C_6H_4).

3.4 Microbial Assay

3.4.1 Antifungal Activity

The antifungal activity of the metal complexes was evaluated against *Fusarium oxysporum* and *Aspergillus niger*. Fungicidal activity was measured by the radial growth method (20), using Czapek's agar medium with the composition glucose 20 g, starch 20 g, agar-agar 20 g and distilled water 1000 ml. The complexes were mixed directly with the medium in different concentrations. The spores of fungi were placed on the medium with the help of an inoculums needle. The Petri dishes were wrapped in polythene bags containing a few drops of alcohol and placed in an incubator at $25 \pm 2^{\circ}$C. Controls were also run and three replicates were used in each case. The radial growth of the fungus was obtained by measuring the fungus colony diameter after 4 days. The amount of growth inhibition was calculated by the equation, Percent inhibition $= (C - T) \times 100/C$ where C is the diameter of the fungal colony in the control plate and T is the diameter of the fungal colony in the test plate.

3.4.2 Antibacterial Activity

The activity against bacteria was evaluated by the paper disc plate method (21). For this purpose, pure cultures of the organism were dissolved in peptone:water (1:1) and then uniformly seeded on the nutrient agar plates having the composition peptone 5 g, beef extract 5 g, NaCl 5 g, agar-agar 20 g and distilled water 1000 ml. The compounds were dissolved in 500 and 1000 ppm concentrations. Paper discs of Whatman No. 1 with a diameter of 5 mm were soaked in these solutions. These discs were placed on the medium previously seeded with the organisms in Petri dishes at suitable distances. The Petri dishes were stored in an incubator at $30 \pm 2^{\circ}$C for 24 h. The zone of inhibition that formed around each disc containing the test compound was measured accurately in mm. The organisms used in the

Table 4. Antifungal activity of the macrocyclic complexes of tin(II)

	Fusarium oxysporum (concentration in ppm)			*Aspergillus niger* (concentration in ppm)		
Compound	50	100	200	50	100	200
$[Sn(Mac_1)Cl_2]$	53	65	74	53	76	80
$[Sn(Mac_2)Cl_2]$	61	65	78	66	79	89
$[Sn(Mac_3)Cl_2]$	68	70	79	70	79	91
$[Sn(Mac_4)Cl_2]$	73	80	84	80	90	96
$[Sn(Mac_5)Cl_2]$	78	84	88	83	91	97
Bavistin	85	100	100	86	100	100

Table 5. Antibacterial activity of the macrocyclic complexes of tin(II)

	Escherichia coli (−) (concentration in ppm)		*Staphylococcus aureus* (+) (concentration in ppm)	
Compound	500	1000	500	1000
$[Sn(Mac_1)Cl_2]$	8	10	9	13
$[Sn(Mac_2)Cl_2]$	6	9	10	12
$[Sn(Mac_3)Cl_2]$	5	8	7	11
$[Sn(Mac_4)Cl_2]$	9	12	6	9
$[Sn(Mac_5)Cl_2]$	10	12	10	13
Streptomycin	17	18	15	17

present investigations included *Escherichia coli* and *Staphylococcus aureus.*

3.5 Mode of Action

Chelation theory (22) accounts for the increased activity of the metal complexes. Chelation reduces the polarity of the metal atom, because of partial sharing of its positive charge with the donor groups and possible π electron delocalization within the whole chelate ring. The chelation increases the lipophilic nature of the central atom, which subsequently favors its permeation through the lipid layer of cell membranes. The results of fungicidal and bactericidal screening of the metal complexes against some pathogenic fungi and bacteria are recorded in Tables 4 and 5. The results show that the activity was enhanced on undergoing chelation. It is a well known fact that the concentration plays a vital role in increasing the degree of inhibition. As the concentration increased, the activity increased. The fungicidal activity was better as compared to the bactericidal activity.

3.6 Antifertility Activity

The antifertility activity in male rats was carried out using 60 adult male Swiss albino rats (*Rattus norvegicus*) weighing 180–200 g. The animals were randomly divided into six groups of 10 animals each. Throughout the experiment they were kept in standard conditions (12 h light/12 h night, 26 ± 2°C), fed a standard diet and provided water *ad libitum.* After completion of the respective treatment, each male was cohabited with two pro-estrous females for fertility test and the number of litters was recorded (22). These females were used only for mating with those treated male rats and were other than 60 male rats taken for the experiment. These females were also kept in standard conditions. Group A was used as a control and each animal of this group received 0.5 ml olive oil per day orally. The complexes were suspended in olive oil separately and were given at a dose level of 2 mg/kg body weight per day for 60 days. 24 h after the last dosing the animals were sacrificed, autopsied and the reproductive tract was dissected out (23). The sperm motility and density (24) in cauda epididymis and testes were measured within a few seconds after sacrificing the animals.

4 Conclusions

The results reported in Table 6 reveal that there is a significant decrease in the motility from 82.54 ± 4.6 to 32.23 ± 3.8 in

Table 6. Effects of tin(II) complexes on sperm dynamics and fertility of male rats (values are expressed as mean plus/minus SEM)

			Sperm density (million/ml)		
Group	Compound	Sperm motility (%) (Cauda epididymis)	Testes	Cauda epididymis	Fertility
A	Control (vehicle treated) 0.5 ml olive oil/day	82.54 ± 4.6	4.2 ± 0.36	59.08 ± 4.9	100% (positive)
B	$[Sn(Mac_1)Cl_2]$	48.96^a ± 3.7	2.4^a ± 0.31	41.35^a ± 1.3	80% (negative)
C	$[Sn(Mac_2)Cl_2]$	46.63^a ± 2.9	2.2^a ± 0.48	40.69^a ± 2.6	83% (negative)
D	$[Sn(Mac_3)Cl_2]$	40.28^a ± 4.1	1.9^a ± 0.29	38.22^a ± 3.3	86% (negative)
E	$[Sn(Mac_4)Cl_2]$	36.19^a ± 2.7	1.5^a ± 0.25	36.68^a ± 4.5	90% (negative)
F	$[Sn(Mac_5)Cl_2]$	32.23^a ± 3.8	0.9^a ± 0.16	30.22^a ± 3.0	95% (negative)

(Mean ± SEM of 10 Animals), $^a p < 0.001$–Highly significant, $^b p < 0.01$–Significant, $^c p < 0.01$–Non-significant.

animals treated with the complexes. The sperm density also decreased significantly ($P < 0.001$) from 4.2 ± 0.36 to 0.9 ± 0.16 in testes and from 59.08 ± 4.9 to 30.22 ± 3 in cauda epididymis. The fertility test fluctuates between 80% negative to 95% negative. Thus it can be postulated that the chelation through complexes induces antispermetogenic activity. The present study suggests that the complex $[Sn(Mac_5)Cl_2]$ is the most effective fertility inhibitor in male rats.

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