A Brief Insight into Versatility of Macrocyclic Complexes of tin(II) in Biomedical Domain

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Abstract: Macrocyclic chemistry is a scientific field with increasing significance in both therapeutic and diagnostic directions of medicine. This field in its broadest sense encompasses the chemistry of biomolecules and biologically active compounds. A wide array of macrocyclic compounds has applications in various areas, including catalysis, medicinal chemistry, bioanalysis and material science. These facts have led us to design a new series of tin(II) macrocyclic complexes of type $[Sn(L^n)Cl_2]$ derived from dicarboxylic acids with diamines. These complexes have also been synthesized under microwave irradiation. The mode of bonding and overall geometry of the compounds was determined through physiochemical and spectroscopic methods. On the basis of IR, multinuclear NMR and X-Ray spectral studies, an octahedral geometry around tin has been proposed. The synthesized complexes have been tested for their antifertility activity in male albino rats. The marked reduction in sperm motility and density resulted in infertility. Significant alterations were found in biochemical parameters of reproductive organs in treated animals as compared to control group. It is concluded that all these effects may finally impair the fertility of male rats. With a look to the future regarding how this technology might be improved with respect to biomedical applications of macrocycles containing modified backbones will also be carried out further.

Keywords: Macrocyclic, Spectral, Antifertility, Dicarboxylic acids, Diamines

1. INTRODUCTION

The development of the field of bioinorganic chemistry has also been the other important factor in spurring the growth interest in complexes of macrocyclic compounds. Macrocyclic ligand systems often exhibit unusual properties and sometimes mimic related natural macrocyclic compounds. There is considerable current interest[1] in complexes of polydentate macrocyclic ligands because of the variety of geometrical forms available and the possible encapsulation of the metal ion.[2]

Rapidly expanding population and limited sources are thought to be the most pressing global problems today. This rapid increase in the world population has multiplied the benefits of economic and technological advancement. Fertility control is very essential for maintaining

satisfactory standards in the developing countries. There is an increasing international recognition for the need to control human fecundity. Needless to say there is an immediate need for an inexpensive, safe and effective as well as universally acceptable contraceptive. For the evolution of such an ideal method for control of human fertility it is necessary that the reproductive process of both i.e., male and female should be more intensively investigated.

The male, an integral part of the family unit, has largely been sidelined by family planners. Currently, efforts are being made to develop a male contraceptive agent, which would inhibit fertility without affecting sex accessory function and libido. In this endeavor, a variety of synthetic compounds have been evaluated in males of laboratory species of mammals[3,4]. The results obtained are also encouraging. Therefore, this approach may form the basis for clinical regulation of male fertility in future. Inorganic compounds have also been investigated and applied for antifertility activity only and have not been screened for toxicological effect[5-8]. In this context, to create a new class of biologically active polyazamacrocyclic complexes, we initiated the molecular modelling and antifertility activity of some bivalent tin macrocycles, resulting from the condensation reaction of dicarboxylic acids and diamines. The present communication deals with the synthesis, spectroscopic characterization and contraceptive efficacy of macrocyclic complexes of tin.

2. EXPERIMENTAL

2.1. Synthesis

An ice cold solution of $SnCl_2$ in dry methanol was added to the solution of 1,4-diaminobutane and various dicarboxylic acids (malonic, succinic, glutaric and adipic acid) in 1:2:2 molar ratios in dry methanol. The reaction mixture was stirred continuously for 10-12 hours so as to complete the reaction. The precipitate so formed was filtered off, washed with dry and cold methanol and dried *in vacuo*.

2.2. Antifertility activity

Thirty male albino rats of wister strain, weighing 170 to 190g (90 – 100 days old) were used for the experiments. They were housed in an air conditioned animal room at 24 + 2^{o}C with 14 hours light and water and food was given *ad libitum*. These were divided into five groups containing six animals each. The group A served as vehicle (olive oil) treated control. In the group B, C, D and E, 50 mg/kg suspended in olive oil was given orally for a period of 60 days. The animals of groups B, C, D and E received same doses of macrocyclic complexes of tin(II) for the same period.

Figure1. Test animal male albino rat

Fertility Test and Autopsy Schedule

The fertility test of individual rat was done before the experiment and after 55 days of the experiment. Each rat was cohabited with progesterone female in 1:2 ratios. Vaginal smear was examined every morning for positive mating and number of litters delivered was recorded. The rats were sacrificed within 24 hours after the last administration of the compounds, i.e. on 61st day of experiment. The testes, epididymis, seminal vesicle and ventral prostate were removed, cleared off fat, blood vessels and connective tissue before weighing.

Sperm motility and sperm density were assayed in cauda epididymis and testes. The parts of testes, epididymis, seminal vesicles and ventral prostate from each rat were kept at 20^{o}C until assayed for protein, sialic acid, cholesterol and fructose. Student 't' test was used for the assessment of the significance of variation and the data are presented as Mean + 5 EM.

3. RESULT AND DISCUSSION

3.1 Physical properties, analytical data and spectral studies

The resulting complexes are solids and soluble in methanol, benzene, tetrahydrofuran and carbontetrachloride. The molar conductance values 14-22 ohm^{-1} cm^{2} mol^{-1} in dimethylformaamide solution of these complexes are indicative of their non-electrolytic nature. The monomeric nature of these complexes has been deduced on the basis of molecular weight determinations. The physical properties and analytical data of the resulting compounds are recorded in Table 1.

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

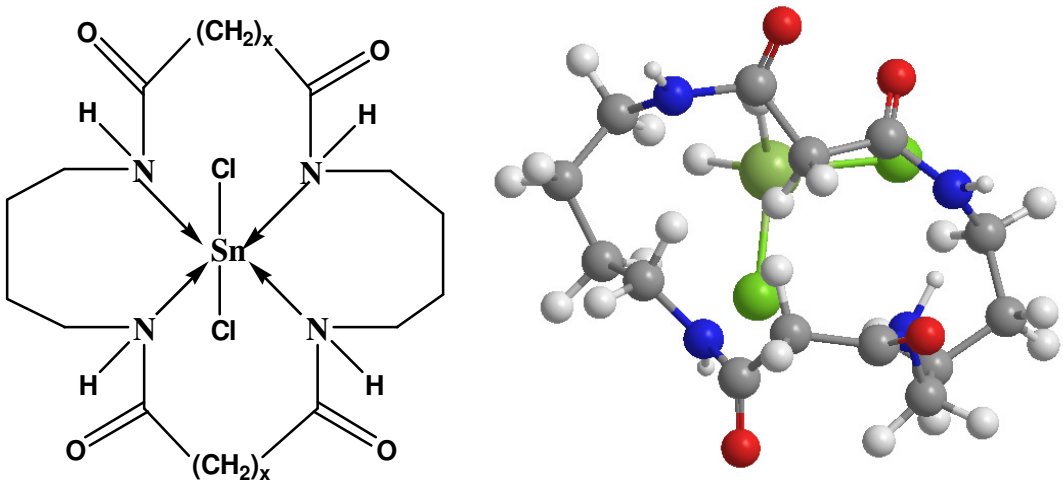
S. No.	Compound	M.P. (°C)	Colour	Analyses Found (Calcd.) %					Mol. Wt. Found (Calcd.)
				C	H	N	Cl	Sn	
1.	$[Sn(L^1)Cl_2]$	225	White	33.12 (33.50)	4.46 (4.82)	10.94 (11.16)	14.02 (14.13)	23.49 (23.61)	504 (510.96)
2.	$[Sn(L^2)Cl_2]$	201	White	36.10 (36.26)	5.16 (5.32)	10.24 (10.57)	13.16 (13.38)	22.14 (22.39)	521 (530.02)
3.	$[Sn(L^3)Cl_2]$	219	White	38.42 (38.74)	5.36 (5.78)	9.83 (10.04)	12.54 (12.71)	21.06 (21.27)	549 (558.07)
4.	$[Sn(L^4)Cl_2]$	198	Cream	40.68 (40.98)	5.82 (6.09)	9.21 (9.56)	11.78 (12.01)	20.08 (20.25)	579 (586.12)

The geometry and the mode of bonding of the resulting coloured complexes have been inferred from the IR, ^{1}H NMR and ^{119}Sn NMR spectral studies.

The IR spectra of all complexes exhibit a single sharp absorption band in the 3265-3240 cm^{-1} region, attributed to the coordinated -NH. The bands characteristics of amino -NH_2 and -OH of dicarboxylic acids were not observed. The bands appearing in the regions 2930-2890 and 1450-1410 cm^{-1} in all the complexes may be due to the C-H stretching and C-H bending vibrations respectively[9]. The spectra of the complexes exhibited additional bands around 440 and 390 cm^{-1} due to the Sn-N and Sn-Cl bonds. In addition to it, four amide bands have also been observed which appeared in the regions 1700-1670, 1540-1460, 1270-1240 and 680-660 cm^{-1}.

The bonding pattern discussed above gets further support by the ^{1}H NMR spectral studies of the starting materials and their complexes in DMSO-d_6. The ^{1}H NMR spectra of the complexes exhibited the broad signal in the region δ7.95-8.60 ppm which may be assigned to an amide proton (-CONH). In the complexes a multiplet observed at δ1.98-2.15 ppm is due to the middle methylene protons [C-(CH_2)-C] of 1,4-diaminobutane. Singlet appeared in the regions δ2.80-2.91 ppm and δ3.09-3.11 ppm attributed to the methylene protons of the malonic and succinic acids. Multiplet at δ3.12-3.20 and δ3.21-3.25 ppm are assigned to the methylene protons of glutaric and adipic acids, respectively.[10,11] The absence of carboxylic protons (-COOH) of the carboxylic acid and NH_2 protons of the diamine moiety supports the proposed macrocyclic framework.

The conclusions drawn from the IR and ^{1}H NMR spectra are parallel with the carbon-13 spectral data regarding the authenticity of the proposed structures. The considerable shifts in the positions of the carbon atoms adjacent to the diamino nitrogen further supported the proposed coordination in the complexes. The ^{119}Sn NMR spectrum of $[Sn(L^{1})Cl_2]$ gives signal at δ623 ppm indicating coordination number six in this complex around the tin atom.[12] The structures shown below may be suggested for these complexes (Fig.2).



(a) Where, x=1,2,3 or 4 (b)

Figure2. (a) Proposed structure of the complexes and (b) Energy minimized MM2 structure of $[Sn(L^{1})Cl_2]$

3.2 Antifertility activity

3.2.1 Body and Organ Weights

Administration of all four macrocyclic complexes did not cause any significant change in the body weights of treated rats. The weights of testes, epididymis, seminal vesicle and ventral prostate were reduced significantly when compared with the vehicle treated control (Figure 3).

3.2.2 Sperm Motility and Sperm Density

A sharp decline ($P < 0.001$) in the sperm motility was noticed in rats treated with all four macrocyclic complexes. Sperm density in cauda epididymis was also reduced significantly ($P < 0.0010$ in all treated groups (Figure 4).

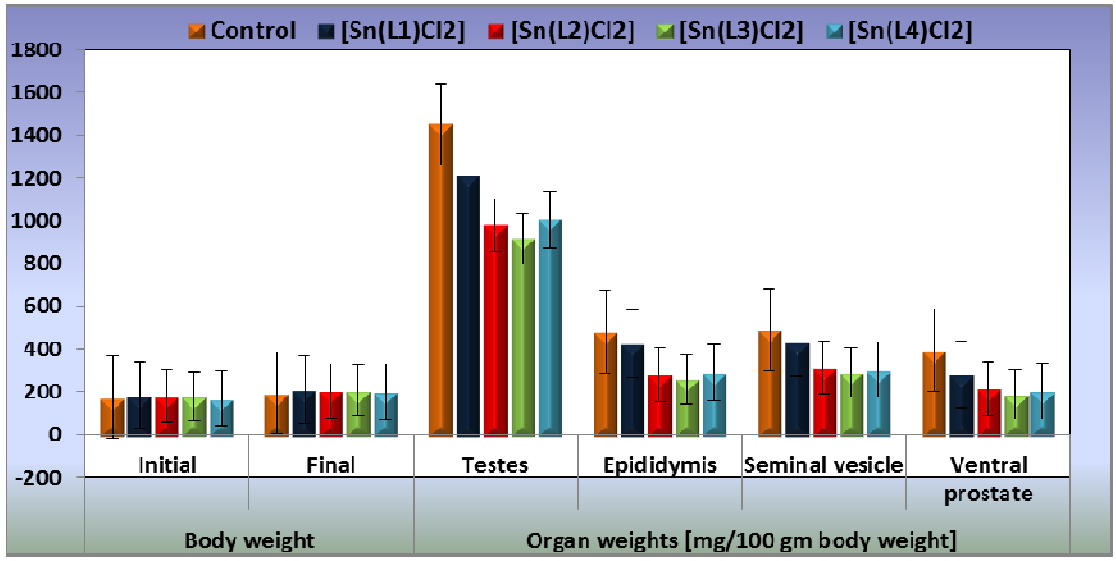


Figure 3. Changes in the body weight and weights of the reproductive organs after the treatment with macrocyclic tin(II).

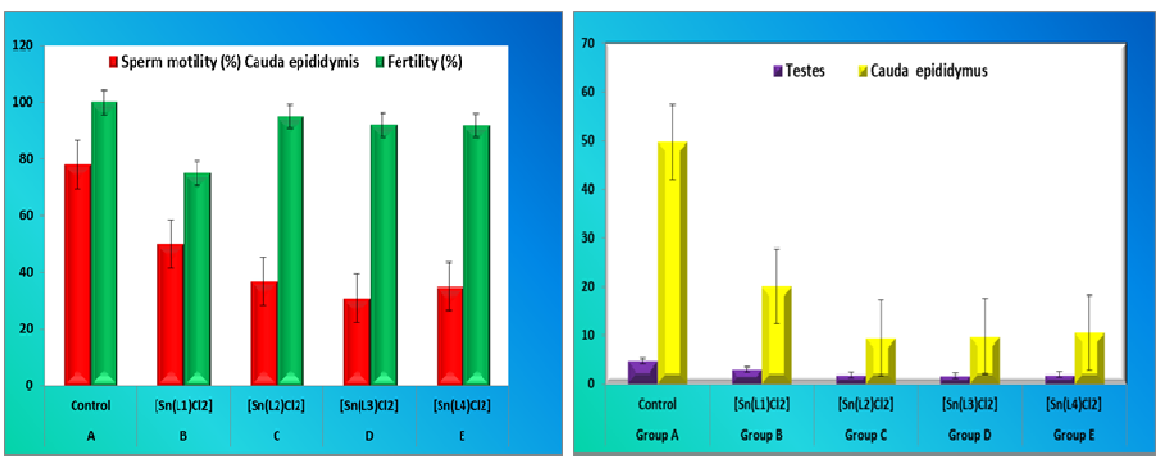


Figure 4. Effects of macrocyclic tin(II) complexes on sperm motility and fertility in rats.

3.3 Tissue Biochemistry

3.3.1. Protein and Sialic Acid

Protein and sialic acid contents in testes, epididymis, seminal vesicle and ventral prostate were significantly decreased after the treatment with macrocyclic tin(II) complexes (Figure 5).

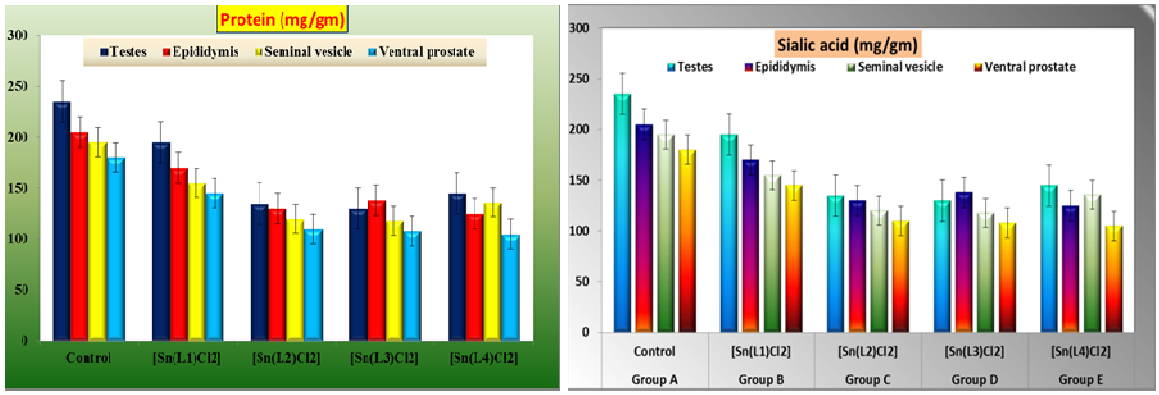


Figure 5. Testicular biochemistry of macrocyclic tin(II) complexes.

3.3.2. Testicular Cholesterol

Testicular cholesterol was increased significantly ($P < 0.001$) after the treatment with the ligands and its tin(II) complexes.

3.3.3. Fructose

Fructose contents of seminal vesicle was decreased ($P < 0.001$) in rats treated with the ligand and its tin(II) complexes. In the present study a significant decrease was observed in the weight of testes, epididymis, seminal vesicle and ventral prostate after the treatment with macrocyclic tin(II) complexes. Significant decrease in testes weight may be due to the decrease in the number of spermatogenic elements and spermatogenia[13] that is cell death which leads to regression of these organs.[14] Reduction in the weight of the accessory reproductive organs directly support the reduced availability of androgens.[15] Treatment with the ligand and its tin(II) complexes resulted in the sharp decline in sperm motility of cauda epididymis. On the other hand the low caudal epididymal sperm density may be due to the alteration in the androgen metabolism.[16]

The low motility and negative fertility test may be attributed to the lack of the forward progression and reduction in density of spermatozoa and altered biochemical millieu of cauda epididymis. Treatment with the various complexes also alters the biochemical parameters of the reproductive tract. Reduction in sialic acid contents in testes, epididymis, ventral prostate and seminal vesicle in treated rats may be correlated with the loss of the androgen.[17] Reduced contents of the proteins in testes and sex accessory organ, probably due to the absence of spermatogenic stages in the testes[18]. A significant increase of testicular cholesterol indicates that pituitary gonadotropins may not be available for steroidogenesis.[19] Our study suggest that addition of macrocyclic tin(II) complex $[Sn(L^4)Cl_2]$ is more effective in regulating the fertility in male rats.

4. CONCLUSION

Here, we propose a new approach for design of multitalented series of macrocyclic complexes of tin(II). The results suggested that all the complexes are effective in reducing fertility and addition of addition of macrocyclic tin(II) complex $[Sn(L^4)Cl_2]$ is more effective in regulating the fertility in male rats.

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