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Biologically important 26-32-membered macrocyclic complexes of manganese (II): *In situ* one pot template synthesis (IOPTS), characterization and bio-efficacy

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Abstract
Twenty six to thirty two membered tetraazamacrocyclic complexes of manganese (II) have been synthesized by template condensation of $MnCl_2.4H_2O$ with dicarboxylic acid (malonic, succinic, glutaric or adipic acid) and 1,8-diaminooctane in 1:2:2 molar ratios. The new products with octahedral geometry have been characterized by elemental analyses, molecular weight determinations, molar conductance, magnetic moment and spectral studies *viz.*, infrared and electronic. On the basis of the spectral studies the binding sites are proposed as the nitrogen atom of the macrocycles. The formulation of the complexes as $[Mn(Mac^n)Cl_2]$ (where n = 1 - 4) has been established on the basis of chemical composition. To assess the growth inhibiting potential of the manganese (II) complexes biological screening has been undertaken.

Keywords: Manganese (II) complexes, macrocyclic, spectral studies and bioactivity

Introduction
In the present scenario chemistry of the macrocyclic complexes is becoming a field of larger significance and interest all around the world due to their importance in the field of inorganic chemistry and biology. Macrocyclic ligands and their metal complexes are of much significance being their existence in many important biotic systems [1–4]. The multifarious role of transition metals in biochemistry suggested that consideration potential exists for the development of new chemistries with these metals in ligand systems specifically designed to serve these roles [5-9]. The enormous interest in the synthesis of the transition metal complexes of the nitrogen donor ligands arises due to the wide range of pharmacological activities of these compounds, which in several cases are known to have been enhanced by the presence of transition metals [10-11]. The synthesis of a series of tetraamide macrocycles which have been designed to afford strongly donating tetraamido-N ligands upon tetradeprotonation and to be resistant to oxidative degradation has been described. It is demonstrated by the preparation and characterization of an unprecedented class of square-planar cobalt compounds with high positive formal reduction potentials that the macrocycles possess the rare property of being compatible with strongly oxidizing coordination environment [12]. The complexes of the metal ions are significant because of their resemblance with many natural systems, such as porphyrins and cobalamines. The biological activity of this class of compounds is associated with the chelation [11]. They are known to function as antimicrobial [13], antifertility, antimalaria and antileukemic agents [14]. Many of these transition metal ions in living systems work as enzymes carriers in a macrocyclic ligand field environment.
Macrocyclic ligands display a number of features of chemical interest. Research into the synthesis, structure and properties of transition metal macrocyclic complexes to model a wide variety of metalloprotein active sites or to mimic their chemistry is well established [15-16]. Macrocycles have wide applications in medicine, cancer diagnosis and in the treatment of tumors Macrocyclic complexes of Mn (II) exhibit a broad spectrum of biological activity [17-18]. No work has been reported on the manganese (II) complexes with such type of tetraazamacrocyclic ligands. Therefore, the importance of the metal-nitrogen bonding and

their prominence in agriculture, medicinal and industrial activity led us to synthesize and screen these compounds for their antifungal and antibacterial activities.

2. Experimental

The chemicals include, malonic acid, succinic acid, glutaric acid and adipic acid (Fluka), 1,8-Diaminooctane (E. Merck), $MnCl_2.4H_2O$ (BDH).

2.1 Analytical Methods and Physical Measurements

Conductivity measurements of 10^{-3} M solutions were made with a Systronic Model 305 conductivity bridge in dry dimethylformamide at room temperature (28 °C). Molecular weights were determined by the Rast Camphor Method. IR spectra were obtained as KBr pellets on a Perkin-Elmer 577 grating spectrophotometer in the range 4000-200 cm^{-1} and far IR spectra were also recorded on the same spectrophotometer in Nujol Mulls using CsI cell. Electronic spectra in dimethylsulphoxide were recorded on a Hitachi W-2000 spectrophotometer. Magnetic moment of the complexes were determined by the Gouy's method at the room temperature. Carbon and hydrogen analyses were performed at the Central Drug Research Institute, Lucknow.

2.2 Synthesis of the complexes [Mn (Mac^n)Cl_2]

The reaction is carried out in 1:2:2 molar ratios. For the preparation of metal complexes, an ice cold solution of $MnCl_2.4H_2O$ in methanol (50 ml) was reacted with 1,8-diaminooctane at 0 °C and put in magnetically stirred 100ml round-bottom flask. This is followed by the addition of methanolic solution of malonic, succinic, glutaric or adipic acid). The reaction mixture was stirred continuously at room temperature for 10 h. The resulting solid product was recovered by filtration, washed with methanol and dried in vacuo. These were recrystallized from a 1:1 solution of methanol and chloroform.

The purity of the compounds was checked by TLC on Silica Gel-G using anhydrous tetrahedrofuran as a solvent. Each of the compound moves as a single spot indicating the presence of only one component and hence their purity.

3. Results and Discussion

The resulting new macrocyclic complexes are brown solids having sharp melting points. These are soluble in most of the organic solvents. The conductivity measured for 10^{-3} M solution in anhydrous DMF are in the range 9-29 ohm^{-1} cm^2 mol^{-1} showing them to be non-electrolytes. Elemental analyses agree well with the stoichiometry and chemical formulae of the compounds [Mn(Mac^n)Cl_2]. The molecular weight determinations indicated that all the complexes are monomers. The physical properties and analytical data of the complexes are given in Table 1.

Table 1: Physical Properties And Analytical Data of the Manganese(II) Complexes

Compound	M.P. (°C) and Colour	Analysis, Found (Calcd.) %					Mol. Wt. Found (Calcd.)
		C	H	N	Cl	Mn	
[Mn(Mac^1)Cl_2]	168 Brown	52.16 (52.36)	7.21 (7.32)	9.25 (10.18)	12.27 (12.88)	9.95 (9.97)	527 (550.49)
[Mn(Mac^2)Cl_2]	144 Brown	53.47 (53.98)	7.60 (7.61)	8.75 (9.61)	11.55 (12.16)	9.01 (9.42)	554 (582.88)
[Mn(Mac^3)Cl_2]	159 Brown	54.48 (54.69)	7.76 (7.87)	8.22 (9.11)	10.85 (11.53)	8.44 (8.93)	589 (614.96)
[Mn(Mac^4)Cl_2]	162 Brown	55.58 (55.69)	8.09 (8.09)	7.75 (8.66)	10.29 (10.96)	8.03 (8.48)	619 (647.05)

3.1 IR Spectra

The formation of the complexes has been revealed by the absence of $–NH_2$ stretching vibrations of 1,8-diaminooctane and OH groups of the dicarboxylic acids. The amide groups are present at 1665 – 1680, 1435 – 1475, 1245 – 1275 and 590 – 640 cm^{-1} in the complexes [19]. It provides a strong evidence for the presence of a closed cyclic product. Strong and sharp absorption bands appearing in the regions 2840 – 2878 and 1410 – 1449 cm^{-1} in the complexes were assigned to the C-H stretching and bending vibrational modes, respectively [20]. A single sharp band observed for the complexes in the region 3280-3292 cm^{-1} may be assigned to n(N-H) of amide group. This is further substantiated by the fact that all the complexes show a medium intensity band in the region 425-432 cm^{-1} which is attributed to the Mn-N stretching vibrations [21]. The characteristic IR frequencies of the synthesized macrocyclic complexes reported in Table 2.

Table 2. IR Spectral Data (Cm^{-1}) of the Manganese (II) Complexes

Compound	Amide bands				ν(NH)	ν(Mn-Cl)	ν(Mn-N)
	I	II	III	IV			
[Mn(Mac^1)Cl_2]	1665	1475	1275	590	3280	315	425
[Mn(Mac^2)Cl_2]	1675	1446	1252	655	3288	321	430
[Mn(Mac^3)Cl_2]	1669	1457	1245	640	3292	325	432
[Mn(Mac^4)Cl_2]	1680	1435	1267	669	3283	312	428

3.2 Electronic Spectra

The electronic spectra of all the complexes display weak absorption bands in the regions 580-595, 420-435 and 380-386 nm for $^6A_{1g}$ ® $^4T_{1g}$, $^6A_{1g}$ ® $^4T_{2g}$ and $^6A_{1g}$ ® $^4A_{1g}$, respectively. The values obtained correspond to these compounds reported earlier for the octahedral complexes [22]. The electronic spectral data of manganese (II) complexes are given in Table 3. The μ_B values for all the complexes are in the range 5.73-5.90 B.M. and suggest the high spin d^5 configuration for the complexes [23].

On the basis of the said spectral analyses, it is clear that the ligands are acting as tetradentate chelating agents having

four coordination sites. Also since the anions Cl^- remain bonded with tin atom, a hexacoordinated environment for manganes (II) has been proposed.

Table 3: Molar Conductance and Electronic Spectral Data of Manganese (II) Complexes

Compound	Molar conductance (Ohm^{-1} cm^2 mol^{-1})	Electronic spectral bands (nm)			Magnetic moment (B.M.)
		$^6A_{1g}$ ® $^4T_{1g}$	$^6A_{1g}$ ® $^4T_{2g}$	$^6A_{1g}$ ® $^4A_{1g}$	
$[Mn(Mac^1)Cl_2]$	9	592	435	382	5.73
$[Mn(Mac^2)Cl_2]$	17	580	432	386	5.78
$[Mn(Mac^3)Cl_2]$	29	587	420	385	5.90
$[Mn(Mac^4)Cl_2]$	20	595	428	380	5.80

3.3 Bioactivity

The antifungal activities were evaluated against *Collectatrichum capsici*, *Penicillium notatum* and *Sceleratium rolfsii* by the Radial Growth Method [24] using Czapek's agar medium. The compounds were dissolved in 50, 100 and 200 ppm concentrations in methanol and then mixed with the medium. The linear growth of the fungus was determined by measuring the diameter of the colony after 96 hours. The percentage inhibition was calculated as 100 (dc-dt)/dc, where dc and dt are the diameters of the fungus colony in the control and test plates, respectively, shown in Table 4.

Table 4: Fungicidal Screening Data of Manganese Complexes

Compound	% Inhibition after 96 hours (Conc. in ppm)								
	Collectarichium capsici			*Penicillium notatum*			*Sceleratium rolfsii*		
	50	100	200	50	100	200	50	100	200
Bavistin (standard)	90	100	100	88	100	100	87	100	100
$[Mn(Mac^1)Cl_2]$	58	66	82	58	-	-	60	64	-
$[Mn(Mac^2)Cl_2]$	64	76	86	74	81	87	72	79	86
$[Mn(Mac^3)Cl_2]$	80	90	97	82	91	100	81	94	100
$[Mn(Mac^4)Cl_2]$	85	96	100	85	96	100	82	95	100

Bacterial activities were evaluated by the Inhibition Zone Technique [25]. The organism used were *Escherichia coli* (-), *Staphylococcus aureous* (+) and *Klebsiella aerogenous* (-). The nutrient agar medium (Peptone, Beef extract, NaCl and Agar-Agar and 5 mm diameter paper discs, (Whatman No. 1) filter paper were used. The compounds were dissolved in methanol in 500 and 1000 ppm concentrations. The filter paper discs were soaked in these solutions of the compounds, dried and then placed in the petriplates previously seeded with the test organism. The petridishes were stored in an incubator at 30 ± 1 °C for 24 hours. The zone of inhibition thus formed around each disc containing the test compound was measured accurately (Table 5).

Table 5: Bactericidal Screening Data of Manganese Complexes

Compound	Inhibition after 24 hours (Conc. in ppm)					
	Eschrichia coli (-)		*Staphylococcus aureus (+)*		*Klebsiella aerogenous*	
	500	1000	500	1000	500	1000
Standard (Streptomycin)	95	100	88	100	25	42
$[Mn(Mac^1)Cl_2]$	39	56	59	83	84	100
$[Mn(Mac^2)Cl_2]$	47	65	60	69	88	100
$[Mn(Mac^3)Cl_2]$	53	79	55	83	55	88
$[Mn(Mac^4)Cl_2]$	65	76	68	79	65	84

The striking feature seen in the bacterial activity is the remarkable potential of the toxicity, for the gram (+) stain as compared to the gram (-) stain. The reason is the difference in the structure of the cell walls. The walls of the gram (-) cells are more complexes than those of the gram (+) cells. Over all, the result was appreciable when compared with a standard. The bioactivity increased on undergoing complexation but did not reach the efficacy of the standard at lower concentration. However, at higher ppm concentration the results achieved were satisfactory. The aforesaid studies are clearly worthy of further investigation

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5. Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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