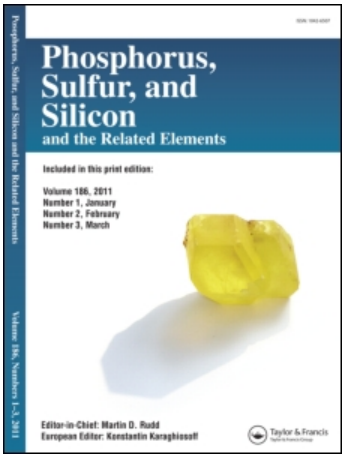

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SYNTHETIC, STEREOCHEMICAL, AND BIOLOGICAL ASPECTS OF MANGANESE (II) COMPLEXES WITH UNSYMMETRICAL SULFUR CONTAINING BIDENTATE SCHIFF BASES

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SYNTHETIC, STEREOCHEMICAL, AND BIOLOGICAL ASPECTS OF MANGANESE (II) COMPLEXES WITH UNSYMMETRICAL SULFUR CONTAINING BIDENTATE SCHIFF BASES

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The synthesis and characterization of tetracoordinated manganese (II) complexes of unsymmetrical sulpha drug azomethines having general formula (MnL^1L^2) are reported. The 1:1:1 reactions of hydrated manganese chloride with unsymmetrical monobasic bidentate azomethines resulted in the formation of coloured solids. The complexes have been characterized by elemental analysis, molecular weight determinations, magnetic measurements, IR, ESR, and UV spectral studies. The magnetic and spectral studies indicate tetrahedral geometry for the resulting complexes. The ligands along with their complexes have been screened in vitro against a number of pathogenic fungal and bacterial strains. The antifertility activity of some representative ligands and their manganese complexes have been studied and important parameters like testicular biochemistry, sperm dynamics, and reproductive organ weights have been discussed. The studies indicate that the metal chelates are more potent than the parent ligands.

Keywords: Antifertility activity; biological aspects; manganese (II) complexes; Schiff bases; unsymmetrical ligands

There is currently a resurgence of interest in the coordination chemistry of manganese mainly due to the involvement of the element in a number of biological systems.[1,2] Of these systems there is little doubt that the most important is the water oxidation centre (WOC) within the photosystem II (PS II) of green plants and cyanobacteria. It is a system that has created and necessarily maintains our environment. An understanding of it represents one of the greatest challenges to bio-inorganic chemists.

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Several Schiff base complexes of manganese have been synthesized as models for some of these metalloproteins.[3] Manganese dust was shown to exhibit anticarcinogenic effect upon the tumerigenic action by α-Ni_3S_2.[4] Imines are an important class of ligands in coordination chemistry and there complexing ability containing different donor atoms is widely reported.[5,6] The mechanism of sulfur toxicity has intrigued the scientific curiosity ever since sulfur was found to have "pest averting" qualities. An elaborate study of the metal complexes with nitrogen and sulfur donor ligands is because of their widespread applications in industry, agriculture, and pharmacology.[7,8] Sulphonamides long have been used as drugs for disorders like cancer, tuberculosis, malaria, diabetes, leprosy, and convulsions. They also have been found to be active against different types of bacteria and viruses. It now has been observed that some of these drugs show increased activity when administered in the form of metal complexes. Our effort in this area have focused on the preparation and characterization of new manganese (II) complexes with sulfur containing unsymmetrical bidentate ligands derived from sulphadrugs with various aldehydes and ketones.

RESULTS AND DISCUSSION

The reactions of hydrated manganese (II) chloride with monobasic bidentate, unsymmetrical sulpha drug Schiff bases (N$\cap$NH) have been carried out in 1:1:1 molar ratio in dry methanol and resulted in the successive replacement of chlorine and a water molecule. The reactions may be represented by Eq. 1.

$$MnCl_2{\cdot}4H_2O + L^1H + L^2H \xrightarrow[1:1:1]{MeOH} [Mn(L^1)(L^2)] + 2HCl + 4H_2O \quad (1)$$

The resulting complexes (Table I) are coloured solids and are nonelectrolytes as evidenced by their molar conductance values of 10–15 ohm^{-1} cm^2 mol^{-1} of their 10^{-3} M solutions in dry DMF. The complexes are soluble in MeOH, DMSO, and DMF. The reactions are quite facile and can be completed within 8–10 h of refluxing. The yields of these reactions are almost quantitative. The methods used for the preparation and isolation of the resulting complexes give products of good purity as supported by their analyses.

IR spectra of the free ligands show a broad and strong band in the region of 3392–3150 cm^{-1}. This band is attributed to ν(NH), which does not appear in the complexes, showing the deprotonation of this group. A sharp and strong band at 1600–1620 cm^{-1} assignable to ν(C=N) is shifted to a higher wave number in the spectra of the complexes indicating the coordination of the ligand through a nitrogen atom of the

TABLE I Physical and Analytical Data of Manganese (II) Complexes

Complex	Color	m.p. (°C)	mol. wt. found (calcd)	Elemental analysis (%) found (calcd)				
				C	H	Mn	N	S
$Mn(L^1)(L^2)$	Brown	90	712.21 (739.17)	53.58 (53.62)	3.96 (3.95)	7.10 (7.43)	15.02 (15.16)	8.24 (8.67)
$Mn(L^4)(L^6)$	Brown	98	743.26 (765.58)	54.89 (54.91)	3.70 (3.68)	7.12 (7.17)	12.62 (12.80)	8.28 (8.37)
$Mn(L^1)(L^6)$	Brown	103	712.23 (729.66)	51.00 (51.02)	3.78 (3.73)	7.42 (7.50)	15.28 (15.36)	8.54 (8.78)
$Mn(L^3)(L^4)$	Brown	101	701.12 (716.66)	50.12 (50.28)	3.78 (3.38)	7.45 (7.66)	13.55 (13.68)	13.26 (13.42)
$Mn(L^3)(L^5)$	Brown	110	779.14 (801.66)	47.91 (47.94)	3.81 (3.77)	6.54 (6.85)	13.61 (13.97)	7.54 (7.99)

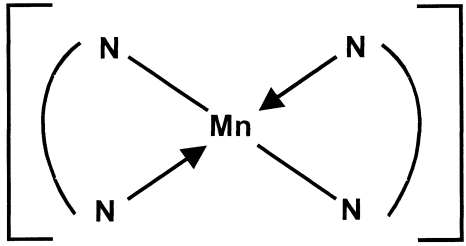
azomethine group. Two medium bands of sharp intensity observed in the spectra of the complexes in the region around 400 and 310 cm^{-1} have been assigned to ν(Mn—N) and ν(Mn $\leftarrow$ N), respectively, which are not observed in the spectra of the Schiff bases (Table II).

The UV spectra of the ligands and their complexes show bands at ca 270 and 300 nm, assignable to π-π^* electronic transitions within the benzene ring. Another band observed at ca 370 nm in the spectra of the said ligands is due to n-π^* transitions of the azomethine (>C=N) group. However, in the spectra of the complexes, this band shifts to lower wavelength due to coordination of the azomethine nitrogen to the metal atom, indicating a delocalisation of the electronic charge within the chelate ring and thereby stabilising the resulting complex (Table II).

TABLE II IR (cm^{-1}) and UV (nm) Data of the Ligands and Their Manganese Complexes

Compound	ν(NH)	ν(C=N)	ν(Mn—N)	ν(Mn $\leftarrow$ N)	$\pi - \pi^*$		n-π^*
L^1H	3150	1620	—	—	270	300	370
L^2H	3158	1615	—	—	266	288	369
L^3H	3296	1605	—	—	271	304	320
L^4H	3258	1608	—	—	267	292	370
L^5H	3392	1600	—	—	265	294	370
L^6H	3320	1604	—	—	266	299	366
$Mn(L^1)(L^2)$	—	1625	390	310	269	294	364
$Mn(L^4)(L^6)$	—	1615	398	310	266	294	356
$Mn(L^1)(L^6)$	—	1622	396	312	268	300	360
$Mn(L^3)(L^4)$	—	1620	398	315	270	296	358
$Mn(L^3)(L^5)$	—	1620	400	315	270	300	350

The ESR spectra of manganese complexes at room temperature showed only one isotropic signal centered at g = 2.0, suggesting a four-coordinated geometry for these complexes.



(Where, N⌒N is the donor set of the ligand)
Proposed structure of the complexes

Antimicrobial Studies

All the complexes and free ligands studied were tested on various fungi and bacteria. The results show that the activity is enhanced on complexation. The greater toxicities of the metal complexes compared to the free ligands can be explained on the basis of chelation theory. Chelation reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with the donor groups and possible π-electron delocalisation over the whole chelate ring. The manganese complexes with sulphadiazene and sulphaguanidine were found to be most toxic against bacterial and fungal species (Table III).

Antifertility Screening

No significant change in the body weights of rats treated with various ligands and Mn complexes was observed. Ligands and their Mn complexes decreased the weights of testes, epidymis, seminal vesicle, and ventral prostate significantly ($P \leq 0.01$ to $P \leq 0.001$) (Table IV).

The sperm motility in cauda epidymis declined significantly ($P \leq 0.01$ to $P \leq 0.001$) in animals treated with various ligands and their Mn complexes. A severe impairment of sperm density in testes and cauda epidymis was observed after treatment with ligands and their Mn complexes (Table V).

A marked reduction ($P \leq 0.01$ to $P \leq 0.001$) in protein and sialic acid contents of testes were observed after administration of ligands and their Mn complexes. However, testicular glycogen, cholesterol, acid, and alkaline phosphatase contents were decreased significantly

TABLE III Microbocidal Screening Data of Manganese Complexes

	Antibacterial: zone of inhibition (mm)				Antifungal: inhibition (%) after 96 h			
	Staphylococcus aureus		*Escherichia coli*		*Alternaria alternata*		*Fusarium oxysporum*	
Compound	500	1000	500	1000	100	200	100	200
L^1H	4	6	5	7	46	57	46	55
L^2H	4	7	5	7	49	56	48	57
L^3H	7	8	7	9	61	66	62	69
L^4H	5	6	4	7	51	54	49	53
L^5H	6	7	6	9	58	63	59	66
L^6H	4	6	4	7	49	52	47	54
$Mn(L^1)(L^2)$	6	7	6	8	59	66	57	60
$Mn(L^4)(L^6)$	7	9	6	9	60	72	53	62
$Mn(L^1)(L^6)$	8	10	7	9	77	83	60	74
$Mn(L^3)(L^4)$	9	11	8	11	80	83	79	83
$Mn(L^3)(L^5)$	11	13	10	11	83	89	85	91
Standard[a]	16	17	13	14	100	100	100	100

[a]Standard for antibacterial activity is *Streptomycin*. Standard for antifungal activity is *Bavistin*.

($P \leq 0.01$ to $P \leq 0.001$) in animals treated with ligands and their Mn complexes (Table VI).

Administration of ligands and their Mn complexes (20 mg/kg b·wt) orally to rats for 60 days caused a significant reduction in the weights of testes, epidymis, seminal vesicles, and ventral prostates. This indicates a suppression in the endocrine activity of testes.[9,10] Sperm count has been considered to be an important parameter for assessment of male fertility.[11] The reduction of sperm count in epidymis indicates inhibition of spermatogenesis and fertility. Furthermore, the loss of motility of spermatozoa also might be associated with impairment of energy metabolism.[12] Increased levels of testicular cholesterol suggest suppression of androgenesis and impairment of spermatogenesis.[13] An increase in testicular alkaline phosphatase[14] and acid phosphatase activity[15] of rats treated with ligands and their Mn complexes suggest an impairment of the functional integrity of the testes. Furthermore, an accumulation of glycogen in the testes of treated rats might be associated with poor utilization of glycogen due to decrease phosphorylase activity.[16] The results of the present study clearly demonstrated that the (ligand L^5H) is the most potent among the ligands, and the addition of a Mn moiety to the ligand enhanced its effects on fertility reduction in male rats.

TABLE IV Effects of Various Ligands and Their Manganese Complexes on Body and Reproductive Organ Weights of Male Rats

		Body weight (g)		Organ weight (mg)			
Group	Treatment	Initial	Final	Testis	Epidymis	Seminal vesicle	Ventral prostate
A	Control (olive oil)	225.0 ± 15.8	236.0 ± 18.3	132.5 ± 30.7	480.0 ± 12.8	520 ± 18.5	480.5 ± 21.8
B	L^3H	220.5 ± 10.8	228.7 ± 8.8	108.0 ± 38.5[b]	390.8 ± 27.5[b]	410 ± 10.8[b]	405.3 ± 10.3[b]
C	L^4H	238.5 ± 13.3	245.5 ± 15.0	121.0 ± 10.7[a]	410.0 ± 15.8[a]	470 ± 20.0[a]	422.5 ± 10.8[a]
D	L^5H	227.8 ± 10.8	240.0 ± 9.0	970.0 ± 30.5[b]	300.0 ± 25.8[b]	390 ± 10.5[b]	390.0 ± 15.5[b]
E	$Mn(L^3)(L^4)$	200.8 ± 10.5	210.9 ± 10.8	905.0 ± 19.5[b]	298.0 ± 17.6[b]	370 ± 10.7[b]	310.0 ± 115.8[b]
F	$Mn(L^3)(L^5)$	210.8 ± 10.5	225.0 ± 10.6	890.0 ± 20.5[b]	270.0 ± 18.9[b]	305 ± 20.8[b]	300.0 ± 15.6[b]

[a] $P \leq 0.01$
[b] $P \leq 0.001$
Groups B, C, and D, compared with group A.
Group E compared with groups B and C.
Group F compared with groups B and D. (Mean ± SEM of 5 animals).

TABLE V Altered Sperm Dynamics and Fertility of Ligands of Male Rats Treated with Manganese Complexes

Group	Treatment	Sperm motility (Cauda epidymis) (%)	Sperm density (million/ml)		Fertility tests (%)
			Testes	Cauda epidymis	
A	Control (olive oil)	80.0 ± 4.5	4.95 ± 0.50	56.5 ± 3.9	100 positive
B	L^3H	38.0 ± 7.8^b	2.90 ± 0.10^b	35.5 ± 6.5^b	80 negative
C	L^4H	49.0 ± 7.5^b	3.15 ± 0.20^a	40.5 ± 6.7^a	75 negative
D	L^5H	36.7 ± 6.5^b	2.10 ± 0.10^b	30.0 ± 3.5^b	88 negative
E	$Mn(L^3)(L^4)$	30.0 ± 6.8^b	1.50 ± 0.15^b	28.1 ± 3.8^b	95 negative
F	$Mn(L^3)(L^5)$	28.5 ± 4.8^b	1.20 ± 0.10^b	20.1 ± 3.9^b	98 negative

$^a P \leq 0.01$.
$^b P \leq 0.001$.
Groups B, C, and D, compared with group A.
Group E compared with groups B and C.
Group F compared with groups B and D. (Mean ± SEM of 5 animals).

EXPERIMENTAL

All the chemicals used were dried and purified before use. The chemicals used were of analytical reagent or equivalent grade. Glass apparatus with standard quick fit joints and adequate precautions were taken to exclude moisture from the system.

Preparation of Ligands

Sulpha drug Schiff bases were prepared by the condensation of different sulpha drugs with various aldehydes or ketones in 1:1 molar ratio in refluxing ethanol. On cooling, the crystals formed were filtered, recrystallized in the same solvent, and finally dried in vacuo. The ligands used are

L^1H: 2-Fluorobenzaldehyde sulphaguanidine
L^2H: 2-Acetylnaphthalene sulphaguanidine
L^3H: Thiophene-2-carbaldehyde sulphaguanidine
L^4H: 2-Fluorobenzaldehyde sulphapyridine
L^5H: 3,4,5-Trimethoxybenzaldehyde sulphadiazine
L^6H: Furfuraldehyde sulphamethazine

Preparation of the Complexes

The unsymmetrical imine complexes of hydrated manganese dichloride were prepared by the reaction of $MnCl_2 \cdot 4H_2O$ with sulphadrug

TABLE VI Testicular Biochemistry of Ligands of Male Rats Treated with Manganese Complexes

Group	Treatment	Glycogen (mg/g)	Total protein (mg/g)	Total cholesterol (mg/g)	Sialic acid (mg/g)	Phosphatase (mg/ip/g/hr)	
						Acid	Alkaline
A	Control (olive oil)	3.27 ± 0.15	210.5 ± 15.8	5.8 ± 0.25	5.3 ± 0.50	3.10 ± 0.18	10.30 ± 0.70
B	L^3H	4.90 ± 0.12^b	150.8 ± 15.3^b	7.3 ± 0.18^b	3.9 ± 0.71^b	4.80 ± 0.19^b	15.00 ± 0.30^b
C	L^4H	4.70 ± 0.10^a	170.0 ± 18.7^a	6.8 ± 0.10^a	4.6 ± 0.60^a	4.20 ± 0.20^a	13.20 ± 0.90^a
D	L^5H	5.10 ± 0.13^b	130.8 ± 15.2^b	7.8 ± 0.19^b	3.5 ± 0.81^b	5.30 ± 0.20^b	15.70 ± 0.30^b
E	$Mn(L^3)(L^4)$	5.20 ± 0.11^b	122.8 ± 17.3^b	8.3 ± 0.19^b	2.8 ± 0.75^b	5.33 ± 0.29^b	16.20 ± 0.31^b
F	$Mn(L^3)(L^5)$	5.17 ± 0.14^b	124.7 ± 18.5^b	8.8 ± 0.16^b	2.2 ± 0.95^b	5.45 ± 0.35^b	16.80 ± 0.35^b

$^a P \leq 0.01$.
$^b P \leq 0.001$.
Groups B, C, and D, compared with group A.
Group E compared with groups B and C.
Group F compared with groups B and D. (Mean $\pm$ SEM of 5 animals).

azomethines in 1:1:1 molar ratio in dry ethanol. The reaction mixture of $MnCl_2 \cdot 4H_2O$ with 2 unsymmetrical ligands was shaken thoroughly and refluxed for 12–14 h on a fractionating column. After the completion of the reaction, excess solvent was distilled off, and the complex was dried in vacuo.

Analytical and Physical Measurements

The conductance was measured with a conductivity bridge type 304 systronics model, and the molecular weights were determined by the Rast camphor method. IR spectra were recorded on a Perkin-Elmer 577 grating spectrophotometer. The electronic spectra were recorded in chloroform on a UV-160A, Schimadzu spectrophotometer in the range of 200–600 nm. The electronic spin resonance spectra were recorded at RSIC, Chennai. Manganese was estimated complexometrically with EDTA using Eriochrome Black T as an indicator. Nitrogen and sulphur were estimated by Kjeldahl's and Messenger's methods respectively (Table I).

Fungicidal and Bactericidal Activity

Bioeffeciency of the parent ligands and their complexes were tested in vitro for the growth inhibiting potential against various fungal and bacterial strains using the agar plate technique and paper disc plate method, respectively. Fungal strains *Alternaria alternata* and *Fusarium oxysporum* and bacterial strains, *Staphylococcus aureus* (+ve) and *Escherichia coli* (−ve) were used. The results of the biocidal activity have been compared with the conventional fungicide, *Bavistin*, and the conventional bactericide, *Streptomycin*, taken as standard in either case (Table III).

Antifertility Activity

Sexually experienced healthy adult crossbred albino rats were used. They were kept in plastic cages under standardized animal house conditions ($24 \pm 2^{\circ}C$ temperature and 12 h light/12 h darkness) with free access of pellated food and tap water. The animals were divided into six groups containing five animals in each group. Group A was administered olive oil to serve as a vehicle-treated control. In the groups B, C, and D, ligands L^3H, L^4H, and L^5H were administered to the animals vehicle to groups E and F complexes $Mn(L^3)(L^4)$ and $Mn(L^3)(L^5)$ (20 mg/kg b.wt/orally) for a period of 60 days. After 55 days of treatment, males were cohabited with proestrous females in the ratio of 1:2 for fer-

tility test. The mated females were separated and implantation sites were recorded. On day 61 of the pregnancy through laprotomy, the animals were sacrificed using light ether anesthesia. Reproductive organs were excised, blotted free of blood, and weighed. The sperm motility and density of cauda epidymis was assessed. The testes were frozen for biochemical estimations. Total protein, cholesterol, glycogen, acid, and alkaline phosphatase were estimated by using standard laboratory techniques.[17] Student's t test was applied in comparing the means.

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