



COORDINATION BEHAVIOUR AND BIOLOGICAL ACTIVITY OF UNSYMMETRICAL BIS-HYDRAZONE TOWARDS MANGANESE (II) ION

PRATIBHA MITTAL and V. UMA*

P. G. Department of Chemistry, Faculty of Science, Govt. College, AJMER (Raj.) INDIA

ABSTRACT

Bis-hydrazones were prepared by condensation of cinnamaldehyde monohydrazone with p-anisaldehyde, p-chlorobenzaldehyde and m-nitrobenzaldehyde. Manganese (II) complexes of these (Schiff base) bis hydrazones were prepared in 1 : 2 ratio. Elemental analysis, IR, ¹H NMR, UV spectral studies and conductance measurement reveals that bis-hydrazones are bidentate ligands with N, N-donor atoms. A tetrahedral geometry was suggested for all the complexes. The Schiff base ligands, and their complexes were tested against different bacteria as well as fungi. The metal complexes exhibited higher antibacterial activities, than the parent ligand and their biopotency is discussed.

Key words: Schiff base, Bis-hydrazones, Antimicrobial activity, IR, Conductance.

INTRODUCTION

During recent years, the transition elements have attracted increasing attention on account of their complex forming ability and due to biocidal activity of the resulting complexes. Manganese Schiff base complexes have subsequently been found to play an important role in many biological processes such as transamination, decarboxylation, condensation and -elimination and racemization Angadi et al.¹ gave complexes of various metals with Schiff bases derived from thiazoles and their carbohydrazones having antimicrobial activity. Seleem² reported stability constants and thermodynamic parameters of some complexes with Schiff base hydrozones containing pyrimidine moiety.

Tofazzal et al.³, have reported the biological activity of Schiff base complexes derived from the condensation of s-bezylidithiocarbamate with salicylaldehyde.³ while Shi et. al. have reported the urease inhibitory activity of manganese⁴, while Hotchandani et al.⁵ have studied the redox characteristic of Schiff base manganese and cobalt complexes⁵.

* Author for correspondence; E-mail: drvuma@gmail.com, Phone No. 91-0145-2460946

Structural studies have shown that bis-hydrazone exhibits different types of bonding depending on the reaction conditions⁶⁻⁹. The interest in such complexes continues due to the possibility of their use as models to explain some intricate reactions in biological systems¹⁰⁻¹⁷. In view of this and our continuous interest in synthesizing biologically active complexes, we are reporting in this paper the synthesis, characterization and biological activity of manganese (II) complexes of bis-hydrazones derived from cinnamaldehyde and p-anisaldehyde, p-chlorobenzaldehyde or m-nitrobenzaldehyde.

EXPERIMENTAL

Synthesis of the ligands

Cinnamaldehyde (1m mol; 1.32 mL) dissolved in absolute ethanol (10 mL) was added to the hydrazine hydrochloride (1m mol; 1.04 g.) dissolved in absolute ethanol (10 mL). The mixture was refluxed for 4 hrs. The golden yellow precipitate (**I**) was filtered and washed with absolute ethanol (5 mL) and recrystallised from ether to give the compound. (80% yield, mp 120°C).

The resultant product (**I**) was again condensed with p-anisaldehyde, p-chlorobenzaldehyde and m-nitrobenzaldehyde, respectively. The reaction mixture was refluxed for 4 hrs. After cooling, the yellow precipitate was collected, filtered and finally washed with absolute ethanol (10 mL) and purified by recrystallization from ether (Fig. 1) (77% yield mp130°C). The physical properties and analytical data are given in Table 1.

Synthesis of metal complexes

The requisite amount of bis-hydrazone (3.0 gm) to methanolic solution of 40 mL of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (1.97 g; 0.1 mmol) was added. The reaction mixture was shaken thoroughly, refluxed for 2-4 hrs and then cooled at the room temperature. The precipitated complexes (Fig. 2) were washed with diethyl ether and dried in vacuum over anhydrous CaCl_2 . The purity of the compounds was checked by TLC using benzene-water mixture (3 : 1). Micro-analytical and physical data of the complexes are reported in Table 1.

Biological activity

The bacterial strains studied were obtained from J. L. N. Medical College, Ajmer.

Table 1. Micro-analytical data of the LH1, LH2, and LH3 and their manganese (II) complexes

Compounds	LH ₁	LH ₁ -Mn ²⁺	LH ₂	LH ₂ -Mn ²⁺	LH ₃	LH ₃ -Mn ²⁺
C% Found	(77.27)	(71.32)	(68.81)	(61.32)	(79.49)	(78.32)
(calculated)	77.21	70.63	62.60	62.63	71.64	78.63
H% Found	(6.06)	(5.59)	(4.65)	(3.59)	(5.83)	(4.59)
(Calculated)	5.98	5.25	4.07	3.25	4.85	4.25
N% Found	(10.60)	(9.79)	(15.05)	(14.79)	(10.51)	(9.79)
(Calculated)	10.22	9.32	16.26	14.32	10.44	9.32
Mn% Found	-	(8.74)	-	(8.65)	-	(8.53)
(Calculated)	-	8.34	-	8.34	-	8.34
Magnetic moment	-	4.38	-	4.85	-	4.83
Conductivity mol ⁻¹ cm ⁻¹	-	3.48	-	4.48	-	4.38
Melting point	130°C	200°C	180°C	190°C	210°C	230°C
Molecular weight	(264)	(572)	(279)	(578)	(268)	(586)
Found (Calculated)	261	569	271	570	261	579
Yield (%)	77	69	75	69	78	68
Colour	Yellow	Black	Yellow	Black	Yellow	Black

Antibacterial studies (*in vitro*)

Antibacterial activity of the complexes/ligands was investigated by a previously reported method against different bacterial strains such as *E. Coli*, *Klebsiella*, *S. Aureus*, *Enterococci* and fungi species like *Candida Albicans* and *Candida Krusei*.

The nutrient agar medium (Peptone, Beef extract, NaCl and Agar-Agar) and 5 mm diameter paper discs (Whatman No. 1) were used. The investigated compounds, i.e. ligands and their complexes, were dissolved (30 μg) in DMF (0.01 mL). The filter paper discs were soaked in solutions of ligands as well as complexes, dried, and then placed in petri plates previously seeded with the test organisms. The plates were incubated for 24 h at 37°C and the inhibition zone around each disc was measured. The results obtained are tabulated in Table 3.

Antifungal activity (*in vitro*)

Antifungal activities of all compounds were studied against fungal cultures like - *Candida Albicans*, and *Candida Krusei*. Sabouraud dextrose agar was seeded with 10⁵ (cfu) mL⁻¹ fungal spore suspensions and was transferred to petri plates. Discs soaked in 20 mL (10 $\mu\text{g}/\text{mL}$ in DMSO) of all compounds were placed at different positions on the agar surface. The plates were incubated at 32°C for seven days. The results were recorded as zones of inhibition in % and were compared with standard drugs. The data are presented in Table 4.

Manganese (II) chloride hexahydrate were obtained from BDH. Organic solvents used were purified from computational methods.^{18, 19} Manganese (II) was estimated complexometrically using Erichrome black-T as indicator²⁰. Chlorine was estimated argentometrically by the Volhard's method. The solution spectra of the ligand and its metal complexes were recorded on a Perkin-Elmer -15 UV/VIS spectrophotometer in the 200-900 nm range in methanol. IR spectra were recorded using KBr discs on a FT-IR spectrophotometer, Shimadzu 8201 PC in the range of 4000-400 cm^{-1} . ¹H NMR spectra were recorded in CDCl_3 at room temperature using TMS as internal standard on a Bruker Advance 400 MHz FT N.M.R. Elemental analysis were carried out on a Vario EL III Elementar Carlo- Erba 1108. Conductance measurements of 10⁻³ M solutions of the complexes in DMF were carried out on an Equiptronics model No Eq-660A. Melting points of the ligand and its metal complexes were determined by open capillary method using Sunsim electric melting point apparatus. Molecular weight was determined by Rast camphor method. The data show that they are monomeric in nature. The conductivity

measurements of the complexes in anhydrous DMF at (295 K) show that these are non-electrolytic in nature.

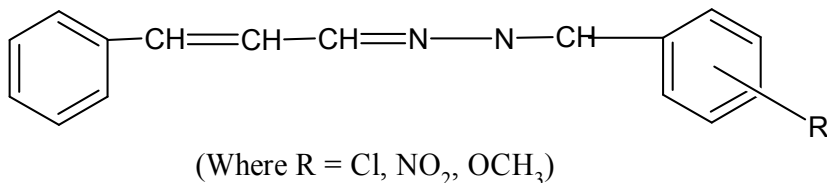


Fig. 1: Structure of ligand

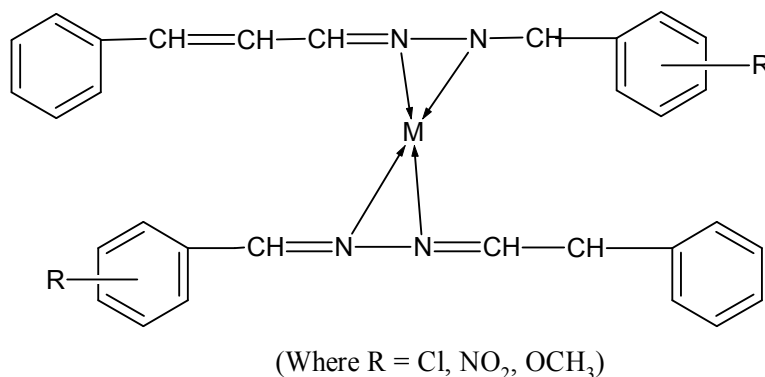


Fig. 2: Structure of Mn-complexes

IR Spectra of ligand and metal complexes

The IR spectra of the ligands HL₁, HL₂ and HL₃ show a peak at 3045, 3018 and 3028 due to (Ar-CH). Peaks at 1629, 1608 and 1615 are due to (C=N-) of HL₁, HL₂ and HL₃, respectively.

In IR spectra of mononuclear complexes (Table 2) the band due to -C=N has shifted to lower wave number due to the Coordination of the azomethine nitrogen atom with metal. Spectra of metal complexes, show new bands at 560-720, 580-750 and 680-850 that due to (M-N) coordination.

Table 2. IR, ¹H NMR and UV spectral data of ligands (LH₁, LH₂ and LH₃) and their manganese (II) complexes

Compound	IR spectra (cm ⁻¹)				¹ H NMR spectra (ppm)		UV spectra (nm)	
	(M-N)	(C=N)	(Ar-CH)	-(OC-)	(Ar-H)	(N=H)	(-C=C-)	(-C=N)
HL ₁	-	1629	3045	1612	7.08-7.1	8.76	260	300
HL ₂	-	1608	3018	1620	6.98-7.1	8.56	280	320
HL ₃	-	1615	3028	1640	6.88-7.0	8.58	270	350
HL ₁ -Mn ²⁺	575	1615	3036	1612	6.20-6.8	8.49	260	210
HL ₂ -Mn ²⁺	625	1595	2996	1620	6.15-6.8	8.19	280	279
HL ₃ -Mn ²⁺	702	1603	3008	1640	6.15-6.5	8.18	270	268

Table 3. Antibacterial activity of bis-hydrazones and their Mn (II) complexes

Compounds	Micro-organisms											
	<i>Staphylococcus aureus</i> (mm)			<i>Klebsiella</i> (mm)			<i>Enterococci</i> (mm)			<i>E. coli</i> (mm)		
	0.01 mg/mL	0.1 mg/mL	1 mg/mL	0.01mg/mL	0.1mg/mL	1mg/mL	0.0 1mg/mL	0.1mg/mL	1mg/mL	0.0 1mg/mL	0.1mg/mL	1mg/mL
LH ₁	14	16	18	13	15	20	14	16	19	15	17	20
LH ₂	22	23	25	19	20	23	18	20	22	16	18	20
LH ₃	16	17	18	19	21	22	21	22	23	15	16	17
LH ₁ -Mn ⁺²	20	21	28	15	17	27	18	20	23	14	16	20
LH ₂ -Mn ⁺²	24	28	33	20	25	29	23	18	36	22	23	28
LH ₃ -Mn ⁺²	24	28	34	21	25	27	24	30	32	20	25	33

Table 4. Antifungal activity of LH₁, LH₂ and LH₃ and their manganese (II) metal complexes

Compounds	Micro-organisms					
	<i>Candida albicans</i> (%)			<i>Candida krusei</i> (%)		
	0.01 mg/mL	0.1 mg/mL	1.0 mg/mL	0.1 mg/mL	0.1 mg/mL	1.0 mg/mL
HL ₁	60	68	76	49	56	63
HL ₂	80	84	88	66.5	70	73.5
HL ₃	76	80	92	59.5	63	70
HL ₁ -Mn ²⁺	72	76	80	73.5	77	80.5
HL ₂ -Mn ²⁺	76	80	88	69	79	76.5
HL ₃ -Mn ²⁺	86	90	98	62.5	69.5	80

NMR spectra of ligands and their metal complexes

The ¹H NMR spectra of the ligands (Table 2) HL₁ HL₂ and HL₃ in CDCl₃ showed signals at 8.76, 8.56 and 8.58 ppm corresponding to the N=CH- group. The signals at 7.08-7.18, 6.98-7.18 and 6.88-7.08 is due to aromatic -CH. The signals due to the aromatic rings appeared at 6.20 -6.80 6.15 -6.82 and 6.15-6.52 ppm in spectra of Mn (II) complexes. The -CH-N signal appeared at 8.49, 8.19 and 8.18 ppm in the spectra of Mn (II) complexes.

UV spectra of bis-hydrazone

The UV-VIS spectra of ligands (HL₁, HL₂ and HL₃) showed two bands between 250-270 nm and 300-360 nm (Table 2). The first band may be due to π-π* transition within the aromatic ring. The second band would be due to n-π* transition within the -C=N group.

Molar conductance of the metal complexes

The conductance measurements, recorded for 10⁻³M solutions of the metal complexes in DMF are listed in Table 1. All complexes are non-electrolyte in nature.

Magnetic moment

The magnetic susceptibilities of manganese (II) complexes have been determined by Guoy method. The magnetic moment value of Mn (II) complexes have been found between 5.87-6.12 BM, which suggest the high spin nature for these complexes with a four coordinate tetrahedral geometry²¹.

ESR spectra

The ESR spectra of 1 : 2 manganese (II) complexes of p-anisaldehyde, p-chloro benzaldehyde and m-nitrobenzaldehyde at the room temperature showed only one isotropic signal centered at $g = 2.022 - 2.012$, which further suggests a four coordinated geometry for these complexes²².

Biological activity

The antifungal and antibacterial activities of ligands and their Mn (II) complexes were evaluated by the agar plate techniques²³ at three different concentrations. The numbers of replications in each case were three and the inhibition zones were measured in mm.

The results of antibacterial and antifungal activity are given in (Tables 3 and 4) show that these compounds exhibit greater antibacterial and antifungal activity against the *E. Coli*, *Klebsiella*, *Enterococci*, *S. Aureus* and *Candida Albicans*, *Candida Krusei* at all the three concentrations. Further the antibacterial and antifungal activity of ligands and their metal complexes decreases on lowering the concentrations. The increased antibacterial and antifungal activity of the complexes as compared to the ligand may be due to the presence of the metal ion²⁴⁻²⁶. In antifungal activity, the number of replications in each case were three and the percentage inhibition (Table 4) was calculated by using the formula:

$$\% \text{ Inhibition} = \frac{C - T \times 100}{C}$$

RESULTS AND DISCUSSION

The reactions between manganese dichloride and bidentate unsymmetrical bis-hydrazone were carried out in bimolar ratio in methanol. The successive replacement of chlorine by the ligands resulted in the formation of the product $[\text{MnL}_2]$ as shown below.

These reactions have been found to be quite facile and could be completed in 2-4 hrs for refluxing. The resulting complexes were obtained in the form of colored solids and soluble in methanol, benzene, DMF and DMSO. The cryoscopic determinations of molecular weights of these complexes S. M. E. Khalil and M. Shebl have reported the potentiometric and spectrophotometric studies of the complexation of Schiff-base hydrazones containing the pyrimidine moiety.²

CONCLUSIONS

The results of this investigation support the suggested structures of all the metal complexes. Tetrahedral geometry has been suggested for all the complexes The Schiff base ligands were found to be biologically active and their metal complexes display enhanced antimicrobial activity against one or more strains. Chelation tends to make the ligands act as more powerful and potent bactericidal agents.

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REFERENCES

1. S. D. Angadi, R. K. Shikkargoi, N. N. Millikarjuna, K. Siddapa and V. H. Kulkarni, *E. Journal Chem.*, **5**, 566 (2003).
2. H. S. Seleem, Stability Constants and Thermodynamic Parameters of Mn^{2+} , Co^{2+} , Ni^{2+} Complexes with Some Schiff Base Hydrazones Containing the Pyrimidine Moiety, *Ann. Chem.*, (2003) pp. 305-314.
3. M. Tofazzal, H. Tarafdar, A. Manaf, D. Ali, Juan Wee and Kasbollah Azahri Complexes of a Tridentate ONS Schiff Base, *Synthesis and Biological Properties, Transition Met. Chem.*, **10**, 456 (2004),
4. Da-Hua Shi, Zhong-Lu You, Chen Xu Quing Zhang and Hai- Liang Zhu Synthesis, Crystal Structure and Urease Inhibitory Activities of Schiff Base Metal Complexes, *Inorg. Chem.*, **10**, 404 (2007).

5. S. Hotchandani, U. Ozdemir, C. Nasr, S. I. Allakherdiev, N. Kaacan, W. Kilmov, P. V. Amot, R. Carentier, Redox Characteristics of Schiff Base Manganese and Cobalt Complexes Related to Water-Oxidizing Complex of Photosynthesis. *Bioelectrochem. Bioenerg.*, **48(1)**, 53 (1998).
6. V. Mirkhani, S. Tangestaninejad, M. Moghadam, M. Moghbel, Rapid and Efficient Oxidative Decarboxylation Ofcarboxylic Acids with Sodium Periodate Catalyzed by Manganese (III) Schiff Base Complexes *Bioorg Med Chem.*, **12(5)**, 903 (2004).
7. S. A. Abdel-Latif, H. B. Hassib, Y. M. Issa, Studies on Some Salicylaldehyde Schiff Base Derivatives and Their Complexes with Cr (III), Mn (II), Fe (III), Ni (II) and Cu (II), *Spectrochim Acta A Mol Biomol Spectrosc.*, **67(3-4)**, 950 (2007).
8. H. L. Singh, A. K. Varshney, Synthesis and Characterization of Coordination Compounds of Organotin (IV) with Nitrogen and Sulphur Donor Ligands., *Applied Organomet. Chem.*, **15(9)**, 762 (2001).
9. V. M. Dembitsky, M. Srebmik, *Tetrahedron*, **59**, 579 (2003).
10. L. Savanmi, L. Chiasserini, A. Gaeta and C. Pellerno Synthesis and Antitubercular Evaluation of 4-Quinolylyhydrazones, *Bioorg. Med. Chem.*, **10**, 2193 (2002).
11. M. B. Ferrari, S. Capacchi, G. Pelosi, G. Reffo, P. Tarasconi, R. Alberlini, S. Pinelli and P. Lunghi, Synthesis, Structural Characterization and Biological Activity of Helicon Thiosemicarbazone Monohydrate and a Copper (II) Complex of Salicaldehyde Thiosemicarbazone, *Inorg. Chem. Acta.*, **286**, 134 (1999).
12. Z. H. Chohan and S. K. A. Sheazi, Synthesis and Characterization of Some Co(II) and Ni(II) Complexes with Nicolinylhydrazine Derivatives and their Biological Role of Metal and Anions (SO_4^{+2} , NO_3^- , C_2O_4 and CH_3CO_2) on the Antibacterial Properties, *Synth. React. Inorg Met-Org Chem.*, **29**, 105 (1999).
13. C. Jayabalakrishnan and K. Natarajan, Synthesis, Characterization and Biological Activities of Ruthenium (II) Carbonyl Complexes Containing Bifunctional Tridentate Schiff Bases. *Synth. React. Inorg. Met. -Org. Chem.*, **30**, 1023 (2001).
14. T. Jeeworth, H. L. K. Wah, M. G. Bhoon, D. Ghoorhoo and K. Babooram, Synthesis and Antibacterial/ Catalytic Properties of Schiff Bases and Schiff Base Metal Complexes Derived from 2, 3-Diaminopyridine, *Synth, React. Inorg. Met. Org. Chem.*, **30**, 1023 (2000).
15. A. I. Vogel, *A Text Book of Quantitative Inorganic Analysis*, Longmans London. (1971)
16. A. I. Vogel, *Practical Organic Chemistry Including Quantitative Organic Analysis*, 3rd Ed., Longmans London. (1956) p. 854.

17. A. I. Vogel, *Quantitative Inorganic Analysis* Third Edition, (1988) p. 434.
18. M. Bandini, P. G. Cozzi and A. Umani-Ronichi, *Chem. Commun.*, (2002) p. 919
19. L. Canali and D. C. Shemngton, *Chem. Soc. Rev.*, **28**, 85 (1999).
20. Antony Harriman, *Coord. Chem. Rev.*, **28-30**, 177 (1979).
21. H. B. Singh, S. Maheshary and W. Nadir, *Synth. React. Inorg. Met-Org. Chem.*, **15 (3)**, 335 (1985).
22. Lallan Mishra, *Synth. React. Inorg. Met. Org. Chem.*, **16 (6)**, 831 (1986).
23. W. H. Leung, E. Y. Y. Chan, E. K. F. Chow, I. D. Williams and S. M. Peng, *J. Chem. Soci. DaltonTrans*, (1996) p. 1229,
24. A. I. Karlov and B. V. Stolyarov *Org. Chem.*, **14**, 2224 (1978).
25. N. Raman, V. Muthuraj, S. Ravichandran and A. Kulandisamy, *Proc. Indian Acad. Society*, **115**, 161 (2003).
26. R. Miao, L. Shuoling, Y. Pudong, Y. Lau and Y. Wenbing. *Indian J. Chem., Sec. A.*, **42**, 318 (2003).

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