

Synthesis, Physico-chemical Characterization And Antimicrobial Studies On 7-Diethylaminosalicyl-8-hydroxyquinoline And Its Metal Complexes

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Abstract: A novel Mannich base of 8-hydroxyquinoline viz. 7-diethylaminosalicyl-8-hydroxyquinoline and its coordination complexes with bivalent Mn, Co, Ni, Cu, Zn, Cd and Hg ions have been synthesized and characterized. The structure of the ligand (L) was established on the basis of micro-elemental analysis, UV, IR, ¹H and ¹³C NMR and mass spectral data. The synthesized coordination complexes were characterized by elemental analysis (C,H,N), wet chemical analysis of metal and chloride, IR, UV-visible, conductivity and magnetic susceptibility measurements. The ligand is found to act as a neutral bidentate chelating one binding through one phenolic O and tertiary amino N atoms. All the complexes studied are assigned a tetrahedral stereochemistry. Both the ligand and its bivalent Mn, Co, Ni, Cu and Zn chloro complexes were tested for antimicrobial properties. They all possess moderate to excellent antimicrobial activity.

Keywords: 8-hydroxyquinoline, Mannich base complexes, tetrahedral stereochemistry, antimicrobial activity.

INTRODUCTION

Compounds containing quinoline moiety are of great interest to synthetic and medicinal chemists due to their unique chemical and biological properties¹. 8-Hydroxyquinoline (oxine) is a bicyclic aromatic and is toxic if injected. However its derivatives have long been used for their antibacterial, antiamoebic and antifungal activity^{2,3}. It is also an important analytical reagent due to its chelating ability. When 8-hydroxyquinoline is subjected to Mannich condensation it yields Mannich bases which could display more potent pharmacological properties like antipsychotic, anticonvulsant, anthelmintic, cytotoxic, antibacterial, antiprotozoal and antimalarial activities^{3,4}. The rise in antibiotic-resistant micro-organisms in recent years has led to an increasing search for new antimicrobial agents. Further the complexation of Mannich bases with metal ions may enhance their antimicrobial properties and the metal complexes may also be used as potent drugs in the treatment of infectious diseases⁵⁻⁷. Keeping this in mind, an attempt has been made to synthesize a novel Mannich base of 8-hydroxyquinoline and its metal complexes with bivalent Mn, Co, Ni, Cu, Zn, Cd and Hg chlorides, to characterize them and to screen their antimicrobial activities.

EXPERIMENTAL

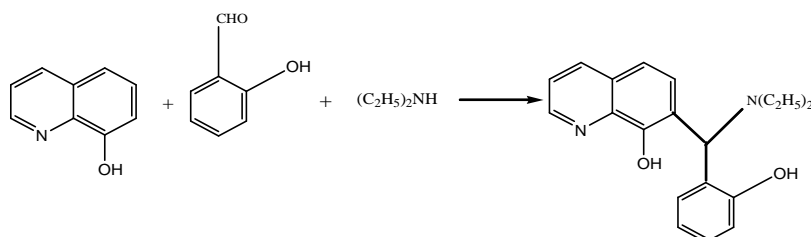
Materials and methods

All the reagents and solvents used were of AnalaR grade (Merck) and were used as such without further purification. Elemental analyses were carried out using Carlo Erba 1108 CH analyzer and Coleman N analyzer. Metal and chloride and sulphate contents of the complexes were determined by standard volumetric and gravimetric procedures⁸. Conductivities of the metal complexes were measured in $\sim 10^{-3}$ M DMF solutions at room temperature using Systronics direct reading conductivity meter 304. Nicolat Avator FT IR 360 spectrophotometer

was used for recording the infrared spectra of the compounds taken as KBr pellets. Bruker AMX 400 MHz instrument was used for recording ¹H and ¹³C NMR spectra of the compounds in DMSO-d₆ and TMS was used as the internal standard. Mass spectrum of the ligand was recorded by using JEOL GC Mate II mass spectrometer. The UV-visible spectra of the compounds were measured on a Perkin Elmer EZ 301 spectrophotometer. Magnetic susceptibility measurements were made at room temperature using a Gouy magnetic balance. Mercury(II) tetrathiocyanatocobaltate(II) was used as a standard and diamagnetic corrections were made with Pascal's constants. Antimicrobial screening of the test compounds was carried out employing disc diffusion method.

Synthesis and characterization of 7-diethylaminosalicyl-8-hydroxyquinoline

8-Hydroxyquinoline (oxine) which is an active hydrogen compound was condensed with salicylaldehyde and diethylamine in 1:1:1 mole ratio at room temperature in ethanol medium⁹. Thus an amount of 14.5 g of oxine in 20 mL of ethanol was mixed with 12.2 g of salicylaldehyde and 7.3 g of diethylamine and the mixture was continuously stirred with a magnetic stirrer for getting a clear solution. The clear solution became a semi solid after a few hours and then a hard cake after two days. The crude product was crushed into a powder and washed repeatedly with cold water and then ethanol. The purity of the product was tested by TLC using methanol as eluent. The single spot in TLC indicated the purity of the product. It was recrystallized from hot ethanol (yield 86%, m.p. 60°C). The formation of the new Mannich base is shown in Scheme 1. The aminobenzyl substitution is found to exhibit regioselectivity at the ortho position of the hydroxyl group in the quinoline moiety.



Scheme 1 Synthesis of the Mannich base

The analytical and spectral data obtained for the ligand (L) are furnished below:

Analysis: Calculated for $C_{20}H_{22}N_2O_2$: C 74.53, H 6.83, N 8.69 % Found: C 74.70, H 6.79, N 8.72 %; UV (MeOH nm): 259, 220; IR (KBr cm^{-1}): 3389 (OH), 3025, 2908 (CH), 1590, 1454, 1369 (C=C Aromatic), 1590 (C=N), 1221 ($H_5C_2-N-C_2H_5$), 1084 (C-O); 1H NMR ($CDCl_3$, ppm): 0.39 (t, CH_3), 1.46 (m, CH_2), 1.98 (s, CH), 6.19-6.94 (m, br, phenyl H), 7.22-7.63 (m, quinoline H), 3.30 and 8.23 (s, OH); ^{13}C NMR ($CDCl_3$, ppm): 13.84, 39.0, 110.8, 117.2, 121.3, 127.0, 135.6, 147.7, 152.8; Mass (m/z): 322.0 (M^+ peak)

Synthesis of metal complexes

The hot ethanolic solution (20mL) of the Mannich base ligand L (0.01 mole) was added to the hot ethanolic solution (20 mL) of the metal chloride (0.01 mole) taken in a 100 mL beaker with vigorous stirring. The content of the beaker

was digested on a water bath for an hour. The solid complex formed in each case was filtered, washed with ethanol and dried at $60^\circ C$ under vacuum in a desiccator and preserved in the desiccator itself. The metal chloro complexes thus obtained were subjected to physical, chemical and biological studies.

RESULTS AND DISCUSSION

Based on the analytical and spectral data the structure of the new Mannich base ligand (L) is confirmed as provided in Scheme 1. The analytical, magnetic, molar conductance and electronic spectral data of the metal complexes of L are provided in **Table 1**. These data indicate that the isolated metal complexes show 1:1 stoichiometry and non-ionic behaviour¹⁰. The non-electrolytic behaviour of the metal complexes suggests that the anions of the salts have coordinated to the metal ions.

Table 1 Analytical, conductance, electronic spectral and magnetic data of the metal complexes of the Mannich base (L)

Compound	Colour & μ_{eff} (B.M)	Analytical (%) found (calculated)					$]_M$ ($l^{-1} cm^2 mol^{-1}$)	Electronic Absorptions (cm^{-1})
		C	H	N	M	Cl		
MnCl ₂ .L	Yellow green 4.37	53.02 (53.58)	5.04 (4.91)	6.21 (6.25)	12.58 (12.26)	15.94 (15.85)	11.50	21850 (ν_1) 27480 (ν_2) 28520 (ν_3)
CoCl ₂ .L	Green 3.89	53.00 (53.11)	5.10 (4.87)	6.29 (6.19)	13.56 (13.04)	16.08 (15.71)	10.84	6750 (ν_2) 15170 (ν_3) 27475 (CT)
NiCl ₂ .L	Green 3.16	53.32 (53.13)	4.92 (4.87)	6.38 (6.20)	13.42 (12.99)	15.99 (15.92)	20.40	9345 (ν_2) 15340 (ν_3)
CuCl ₂ .L	Dark green 2.31	52.86 (52.57)	4.97 (4.82)	6.00 (6.13)	14.08 (13.92)	15.95 (15.55)	15.04	12230
ZnCl ₂ .L	Yellow	52.62 (52.36)	4.90 (4.80)	6.05 (6.11)	14.66 (14.26)	15.84 (15.49)	15.82	-
CdCl ₂ .L	Yellow	47.74 (47.49)	4.86 (4.35)	5.64 (5.54)	22.70 (22.24)	14.60 (14.05)	16.54	-
HgCl ₂ .L	Yellow	40.82 (40.43)	3.68 (3.71)	4.96 (4.72)	34.00 (33.79)	12.08 (11.96)	16.80	-

Infrared spectra

The characteristic IR absorption bands of the free ligand L have been compared with those of the metal complexes in order to get information regarding the actual donor atoms/ bonding sites of the coordinated ligand molecules¹¹. The significant IR absorption frequencies measured for the metal complexes are provided in Table 2. A broad absorption band observed at 3329 cm⁻¹ in the spectrum of the free ligand is ascribed to the presence of the phenolic OH groups in the phenyl ring as well as the quinoline moiety. In the spectra of the metal complexes the band at 3329 cm⁻¹ has split and shifted to 3432- 3205 cm⁻¹ region indicating the coordination of one of the two phenolic oxygens to the metal ion. However it is not clear which of the two oxygens is bound to the metal ion. Normally in aqueous medium the quinoline N and O chelate to a metal ion to precipitate the complex. But in ethanolic medium this behaviour of ionization of OH into O may not be possible. Hence we predict the

coordination of the phenyl OH and tertiary amino N to the metal centre.

In the free ligand spectrum the absorption band measured at 1221 cm⁻¹ is attributed to the C-N-C stretching vibration of the N(C₂H₅)₂ moiety. But in the spectra of the metal complexes, this vibration has shifted to the lower region of 1200 – 1150 cm⁻¹ indicating the binding of the aliphatic tertiary amino nitrogen to the metal ion. Further the appearance of new non-ligand bands in the regions of 546 – 510 and 462- 440 cm⁻¹ are due to ν_{M-O} and ν_{M-N} vibrations respectively. The ν_{M-Cl} vibrations are noticed in the range of 365 – 358 cm⁻¹ in the case of Mn, Co, Ni, Cu and Zn chloro complexes while ν_{Cd-Cl} and ν_{Hg-Cl} are observed around 310 and 285 cm⁻¹ respectively. Thus on the basis of IR spectral studies it is established that the Mannich base ligand acts as a neutral bidentate chelating type binding through the aliphatic tertiary amino nitrogen and the phenolic oxygen atoms.

Table 2 Important IR spectral bands (cm⁻¹) of L and its metal complexes

Compound	ϵ_{OH} (Phenolic)	ϵ_{CNC} (aliphatic)	$\epsilon_{C=C}$ & $\epsilon_{C=N}$ (aromatic)	ϵ_{M-O}	ϵ_{M-N}	ϵ_{M-X}
L	3329	1221	1590, 1454	-	-	-
MnCl ₂ .L	3345, 3295	1190	1592, 1452	541	462	365
CoCl ₂ .L	3390	1200	1597, 1448	538	461	360
NiCl ₂ .L	3294	1182	1594, 1446	535	458	355
CuCl ₂ .L	3420, 3205	1150	1592, 1450	540	460	365
ZnCl ₂ .L	3432, 3300	1195	1593, 1440	546	462	358
CdCl ₂ .L	3425, 3305	1187	1592, 1450	520	451	310
HgCl ₂ .L	3380, 3296	1160	1590, 1450	510	440	285

Electronic spectra and magnetic moments

This organic ligands containing hetero atoms such as N and O have non-bonding electrons in addition to σ and π electrons. Hence the electronic spectrum of the free ligand shows absorptions at 220 and 259 nm. The band at 220 nm is attributed to $n \rightarrow \pi^*$ transition and that at 259 nm is attributed to $\pi \rightarrow \pi^*$ transition¹².

The colours, magnetic moments and electronic spectral data of the bivalent Mn, Co, Ni and Cu complexes are summarized in Table 1. The freshly formed $MnCl_2 \cdot L$ was yellow coloured and it changed into yellowgreen slowly on standing. For Mn(II) in the tetrahedral environment the electronic transitions are still spin forbidden but no longer parity forbidden¹³. Therefore the electronic transitions for the tetrahedral Mn(II) are ~100 times stronger than that of octahedral Mn(II) and the compounds have yellow-green colour. The high spin d^5 configuration of Mn(II) gives spin only magnetic moment of 5.8 BM. The absorptions observed at 21850 (ν_1), 27480 (ν_2) and 28520 cm^{-1} (ν_3). Indicate tetrahedral environment of Mn(II) in the complex.

Tetrahedral cobalt(II) complexes are high spin and three spin allowed quartet- quartet transitions are expected. They are $^4A_2(F) \rightarrow ^4T_1(P)$ (ν_3), $^4A_2(F) \rightarrow ^4T_1(F)$ (ν_2) and $^4A_2(F) \rightarrow ^4T_2(F)$ (ν_1). The absorptions observed at 6750 (ν_2) and 15170 cm^{-1} (ν_3) and the charge transfer transition found at 27475 cm^{-1} point to the tetrahedral environment of Co(II) in its chloro complex¹⁴. The green colour as well as the determined magnetic moment at 3.92 BM also confirm the tetrahedral geometry of Co(II) chloro complex.

Nickel(II) complexes which are blue in colour have tetrahedral geometry. Occasionally they are green or red in colour due to charge transfer absorption tailing into visible region from UV region¹⁴. The present Ni(II) chloro complex is green in colour and exhibits electronic absorptions at 15340 cm^{-1} due to $^3T_1(F) \rightarrow ^3T_1(P)$ (ν_3) and at 9345 cm^{-1} due to

$^3T_1(F) \rightarrow ^3A_2(F)$ (ν_2). The transition $^3T_1(F) \rightarrow ^3T_2(F)$ (ν_1) is not observed in the visible region and is masked by the absorptions of the organic ligand in the IR region. The magnetic moment of Ni(II) in the chloro complex is measured at 3.76 BM which is much higher than the spin only value due to orbital contribution. Thus on the basis of spectral and magnetic data the Ni(II) chloro complex is assigned a tetrahedral geometry.

The present Cu(II) chloro complex shows an absorption at 12230 cm^{-1} . The absorption band is attributed to $^2E \rightarrow ^2T_2$ transition of Cu(II) in a pseudo tetrahedral environment. The magnetic moment for Cu(II) ion in this complex is measured at 2.31 BM. This high value of magnetic moment is also supportive of the pseudo tetrahedral stereochemistry of Cu(II).

Stereochemistry of Zn(II), Cd(II) and Hg(II) complexes

The d^{10} metal ion complexes do not display electronic transitions and they are diamagnetic in nature. However on the basis of 1:1 stoichiometry, molar conductance and IR spectral data all the complexes of Zn(II), Cd(II) and Hg(II) are tentatively assigned the usual 4-coordinated tetrahedral geometry.

Antimicrobial activity

The Mannich base ligand and its Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) chloro complexes have been screened for their *in vitro* antibacterial activity¹⁵ against *E.coli* and *S. aureus* and for antifungal activity against *C.albicans* and *A. niger* by using disc diffusion method¹⁶. Ciprofloxacin and nystatin were used as standard antibiotics. The Muller Hindun agar was used as basal medium and DMSO was used as the solvent. The inhibitory activity was measured as the diameter of zone of inhibition and the results are shown in Tables 3 and 4.

Table 3 Antibacterial activity of L and its metal complexes

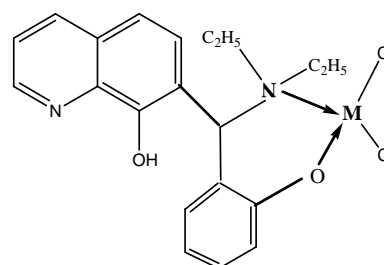
Compound	Zone of Inhibition (mm)			
	E.coli		S.aureus	
	50 (µg/mL)	100 (µg/mL)	50 (µg/mL)	100 (µg/mL)
L (C ₂₀ H ₂₂ N ₂ O ₂)	3.5	3.8	3.2	3.6
MnCl ₂ .L	1.5	1.8	1.3	1.6
CoCl ₂ .L	-	1.2	-	1.1
NiCl ₂ .L	1.0	1.2	1.3	1.6
CuCl ₂ .L	2.1	2.5	2.2	2.7
ZnCl ₂ .L	1.8	2.1	1.8	2.0
Ciproflaxacin (std)	1.8	-	2.0	-

Table 4 Antifungal activity of L and its metal complexes

Compound	Zone of Inhibition (mm)			
	C. albicans		A. niger	
	50 (µg/mL)	100 (µg/mL)	50 (µg/mL)	100 (µg/mL)
L (C ₂₀ H ₂₂ N ₂ O ₂)	1.5	1.9	2.5	3.4
MnCl ₂ .L	-	1.8	-	1.4
CoCl ₂ .L	-	1.2	1.0	1.6
NiCl ₂ .L	-	-	1.2	1.5
CuCl ₂ .L	1.1	1.3	1.1	1.4
ZnCl ₂ .L	1.0	1.2	1.2	1.7
Ciproflaxacin (std)	1.0	--	1.0	-

CONCLUSION

The new Mannich base (L) of 8-hydroxyquinoline and its metal complexes were synthesized and characterized by elemental analysis, IR, UV-visible, NMR, mass, conductivity and magnetic susceptibility measurements. The IR studies indicate that the ligand involves in bidentate coordination through the tertiary amino nitrogen and the phenolic OH group. On the basis of stoichiometry, electronic and magnetic data tetrahedral stereochemistry is tentatively assigned to all the metal complexes studied (Fig 1). All the compounds tested show excellent to moderate antibacterial and antifungal activities against the pathogenic strains *E.coli*, *S. Aureus*, *C.albicans* and *A. niger*. The pronounced antimicrobial activity of the compounds be due to the presence of the heterocyclic system as well as the metal chelation¹⁷. The inhibitory potency of Zn(II), Cu(II) and Co(II) complexes is higher than that of Mn(II) and Ni(II) complexes.



(M = Bivalent Mn, Co, Ni, Cu, Zn, Cd and Hg)

Fig 1 Tetrahedral structure of the metal complex

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