Synthesis, Spectroscopic Studies and Antifungal Activity of 2-[(4(3-Chlorophenyl) piperazine-1-yl)methyl]-3-[8-hydroxy quinolin-5-yl]- 3(*H*)-quinazolin-4-one Ligand and its Chelates

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Abstract: The novel ligand HL₆ was synthesized using anthranilic acid and it was undergo the chelating reaction with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) to prepare transition metal chelates. These chelates were characterized by physicochemical methods such as elemental analysis, conductometric studies, magnetic susceptibility, FT-IR, NMR and electronic spectra. The stoichiometry of the complexes has been found to be 1: 2 (Metal: ligand). An octahedral geometry around Co(II), Ni(II) and Mn(II), distorted octahedral geometry around Cu(II) and tetrahedral geometry around Zn(II) have been proposed. The antifungal activity of ligand and its metal chelates were conducted against various fungi.

Keywords: 8-Hydroxy quinoline ligand, Complexes, NMR spectral studies, Antifungal activity

Introduction

8-Hydroxyquinoline or 8-quinolinol is well known as an analytical reagent¹. The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs². Quinazolin-4-one derivative possesses biological activities such as antifungal^{3,4}. The 8-hydroxyquinoline and quinazolin-4-one molecules into one molecule have not received any attention in spite of well-defined applications of both the molecules. Hence it was thought to explore the study of quinazolin-4-one 8-hydroxyquinoline merged molecules as ligand HL₆ with their complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) metal ion. Antimicrobial activities of the ligand and chelates have also been studied.

General structure of formation of chelates is shown in Scheme1:

Scheme 1

Experimental

All the chemicals used were of pure grade (Merck and B.D.H). Double distilled water was used throughout the experiment. The melting points of all complexes were determined by open capillary method and were uncorrected.

Synthesis of ligand HL₆

The anthranilic acid was converted into *N*-chloroacetyl anthranilic acid by means of chloroacetyl chloride then it refluxed with 5-amino-8-hydroxy quinolin and phosphorous trichloride in dry 1, 4-dioxane under anhydrous condition for 4 h. The reaction mixture was allowed to cool and phosphorous trichloride was decomposed by titrating with cold water. Then, 1, 4-dioxane was distilled off to get the product, 2-Chloromethyl -3-(8-hydroxy quinolin-5-yl)-3(*H*)-quinazolin-4-one. It was filtered and washed with small portion of sodium bicarbonate solution (10%) after then extensively with cold water. The mixture of 2-chloromethyl -3-(8-hydroxy quinolin-5-yl)-3(*H*)-quinazolin-4-one and 1-(3-chlorophenyl)-piperazine in dry pyridine was refluxed for 12 h. Pyridine was distilled off as much as possible and the residue was poured into little crushed ice with stirring. The product, HL₆ was separated out, filtered and washed with water and finally with ethanol. The air dried product was quantitative. Melting point for HL₆ was > 230 °C.

Synthesis of chelates

A dried ligand sample HL₆ (0.01 M) was stirred in 85 % (v/v) formic acid and then it was diluted by water until complete dissolution. The resultant solution was designated as reagent solution. This solution was used for preparation of chelates with particular ligand with transition metal ions. The formic acid solution of ligand was added drop wise to a solution of Cu(NO₃)₂.6H₂O, Ni(NO₃)₂.6H₂O, Co(NO₃)₂.6H₂O, MnCl₂.6H₂O, Zn(NO₃)₂.6H₂O (0.005 mole) in 100 mL of water with rapid stirring. The resultant pH 4.5 [for Cu(II),] pH 6.0 [for Ni(II) and Co(II)] and pH 5.6 [for Mn(II) and Zn(II)] were maintained by addition of sodium acetate. A dark colored solid precipitated out. It was allowed to settle and digested on water bath at 70 °C for about 2 h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone then dried. The percentage yield of chelates was in the range of 65-80%. All the chelates were powdered well and dried at 70 °C over a period of 24 h.

The C, H and N contents of metal chelates were determined on elemental analyzer Thermo Finigan 1101 Flash EA. The metal contents were estimated using standard methods⁵. The molar conductance of the complexes in DMF (10⁻³ M) solutions were measured at room temperature using Systronics model 305 direct reading conductivity bridge. ¹H NMR spectra of ligand was recorded on Bruker NMR spectrophotometer. PMR chemical shifts are recorded in δ-value using TMS as an internal standard in CDCl₃/D₆-DMSO. The IR spectra (KBr) were recorded in the range 4000-600 cm⁻¹ on a Nicolet -760 spectrophotometer. Electronic spectra of the metal chelates were recorded on a Beckman-DK-2A spectrophotometer using MgO as reference. Magnetic susceptibility 'χ_m' was measured by Gouy's method⁶ at room temperature (300 K) using Hg [Co(CNS)₄] as calibrant⁷ and the effective magnetic moment from relation⁸, μ_{eff} = 2.84 √χ_m × T, where T is the absolute temperature. Diamagnetic corrections were made by using Pascal's constants.

The ligand and its metal chelates were screen at 1000 ppm concentration *in vitro* for their antifungal activity against five fungi viz. *Botrydepladia thiobromine*, *Nigrospora sp.*, *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. The antifungal activity of the compounds was measured by plate method⁹. Five days old cultures were suspended in potato dextrose agar (PDA) medium and autoclaved at 1200 °C for 15 minutes and 15 atmospheric pressure. The percentage inhibition of fungi was calculated after 5 days using the formula given below:

$$\text{Percentage of inhibition} = 100 (X-Y) / X$$

Where X= area of colony in control plate (without sample) and Y = area of colony in test plate.

Results and Discussion

The complexes are microcrystalline colored powders having melting points higher than the ligand. They are stable in air at room temperature. All compounds gave satisfactory elemental analysis, suggesting 1:2 (metal: ligand) stoichiometry. Elemental and molar conductance data are shown in Table 1. The result indicates that they are less polar in DMF.

The molar conductance values found to be 25.69, 9.79, 8.28, 8.22 and 7.68 ohm⁻¹ cm² mol⁻¹ for Co(II), Ni(II), Mn (II), Zn(II) and Cu(II) respectively. So, the electrical conductivity of these chelates was found in the decreasing order: Co > Ni > Mn > Zn > Cu. The very low values of chelates indicates that they are non-electrolytic¹⁰ and monomeric in nature. The low conductance values may be attributed to the large cations¹¹.

Table 1. Analytical and physical data of metal chelates of ligand HL₆

Ligand / Mol. Formula	M. W. g/mole	Yield %	Elemental Analysis, %				Observed μ_{eff} , B.M (Expected)	Λ_{M} , $\text{Ohm}^{-1} \text{cm}^2$ mol^{-1}
			Found, Calc.					
			C	H	N	M		
HL ₆	497.50	79	67.40 (67.53)	4.70 (4.82)	14.00 (14.07)	-	-	-
C ₂₈ H ₂₄ N ₅ O ₂ Cl (HL ₆) ₂ Cu ²⁺	1092.54	69	65.70 (65.78)	4.60 (4.69)	13.60 (13.70)	6.20 (6.22)	2.09 (1.7-2.2)	7.68
(HL ₆) ₂ Ni ²⁺	1087.69	76	65.00 (66.09)	4.60 (4.70)	13.60 (13.77)	5.60 (5.77)	3.12 (2.9-3.4)	9.79
C ₅₆ H ₅₀ N ₁₀ O ₆ Ni ²⁺ Cl ₂ (HL ₆) ₂ Co ²⁺	1087.90	59	66.00 (66.08)	4.70 (4.72)	13.70 (13.76)	5.70 (5.79)	5.10 (4.4-5.2)	25.69
C ₅₆ H ₅₀ N ₁₀ O ₆ Co ²⁺ Cl ₂ (HL ₆) ₂ Mn ²⁺	1083.93	65	66.30 (66.34)	4.70 (4.73)	13.00 (13.82)	5.30 (5.36)	5.32 (5.2-6.0)	8.28
C ₅₆ H ₅₀ N ₁₀ O ₆ Mn ²⁺ Cl ₂ (HL ₆) ₂ Zn ²⁺	1094.39	72	65.60 (65.66)	4.60 (4.70)	13.60 (13.77)	6.10 (6.20)	-	8.22

Infrared spectra

FT-IR spectrum of ligand HL₆ show a broad band extended from 3400 to 2600 cm⁻¹ which might be responsible to phenolic group bonded to N atom of 8-hydroxy quinoline moiety¹². The inflexions at 2923, 2852 and 1470 cm⁻¹ are due to aromatic CH and methylene group of bridge and piperazine ring¹³. The strong band at 1705 cm⁻¹ is attributed to C=O of quinazoline 4-one moiety. Several bands appeared between 1500-1600 cm⁻¹ region may arise from aromatic breathing. The IR band at ~ 1580 cm⁻¹ (C=N of 8-quinolinol system) of HL₆ ligand shifted to higher frequency side ~1600 in the spectra of the metal chelates indicating involvement of nitrogen in the chelate formation^{12,14}. Most of bands appeared in the spectra of corresponding ligand are observed at their metal chelates. Only a new band at 1095 cm⁻¹ had appeared in the spectra of metal chelates. This may be assigned to ν c-o of C-O-M bond formation. All the complexes show additional bands at 840-830 cm⁻¹ indicating the presence of coordinated water¹⁵.

NMR spectra

¹H NMR spectra of ligand was depicted in Figure 1, which shows results in δ ppm as follows: 1.0 (-CH₃), 2.4 (-CH₂), 3.47 (CH₂ bridge) 3.44 to 3.52 (triplet -CH₂ of piperazine), 3.47 (-CH₂ bridge), 4.82 (singlet of phenolic -OH), and 7.1 to 8.84 (multiplet, quinazoline).

Magnetic moment and Electronic spectra

At room temperature the magnetic moment ' μ_{eff} ' values for the Co(II) complex is 5.10 B.M (Table 1) suggest high spin octahedral geometry, which was further supported by the electronic spectral data. The electronic spectra of the Co(II) complex display three absorption bands in the range 8452, 19586 and 23215 cm⁻¹, assigned to the transitions ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{2g}(\text{F})$ (ν_1), ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{2g}(\text{F})$ (ν_2) and ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})$ (ν_3) respectively¹⁶. The values of transition ratio ν_2 / ν_1 is 2.31 providing further evidences for octahedral geometry for the Co(II) complexes.

In the Ni(II) complex, μ_{eff} value at room temperature is observed to be 3.12 B.M. as expected for six coordinated spin free Ni(II) species. The reflectance spectra of the Ni(II) complex, exhibit two strong bands at 15009 cm⁻¹ and 24515 cm⁻¹, assignable to ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$ respectively. The ν_2/ν_1 ratio for the chelate is 1.63 occurs in the usual range (1.60- 1.82) for octahedral Ni(II) chelates¹⁷. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier¹⁸.

The Cu(II) complex exhibit normal magnetic moments (2.09 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers¹⁹⁻²⁰. These complex show broad asymmetric bands in the region 14589 cm⁻¹ and at 24856 cm⁻¹ assignable to $^2B_{1g} \rightarrow ^2A_{1g}$ and charge transfer transition respectively²¹. These results reveal the distorted octahedral geometry for these complexes. The former band may be due to $^2E_g \rightarrow ^2T_{2g}$ accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes²². The values of transition ratio ν_2/ν_1 is 1.70. Zn(II) complexes are diamagnetic as expected for d¹⁰ systems and may have tetrahedral geometry²³.

The electronic spectra of the Mn(II) exhibited three spin allowed bands in the region 15896, 17954 and 24768 cm⁻¹ assigned to the transitions $^6A_{1g} \rightarrow ^4T_{1g} (^4G)$, $^6A_{1g} \rightarrow ^4T_{2g} (^4G)$ and $^6A_{1g} \rightarrow ^4E_g, ^4T_{1g} (^4G)$ respectively, indicating octahedral geometry²⁴. The observed magnetic moment (5.32 B.M.) of the complexes indicates high spin octahedral environment²⁵.

Antifungal activity

The ligand and chelates were used for their antimicrobial studies by means of fungi, such as *Candida albicans*, *Botrydepladia thibromine*, *Nigrospora sp*, *Aspergillus fumigatus* and *Rhizopur nigricums*. Antifungal activity of ligand and complexes shown in Table 2 was in following decreasing order:

Table 2. Antifungal activity of ligand HL₆ and its metal chelates

Sample	Zone of inhibition at 1000 pm, %				
	<i>Candida albicans</i>	<i>Botrydepladia thibromine</i>	<i>Nigrospora sp.</i>	<i>Aspergillus fumigatus</i>	<i>Rhizopur nigricums</i>
HL ₆	73	56	65	74	72
(HL ₆) ₂ Cu ²⁺	88	79	75	89	87
(HL ₆) ₂ Ni ²⁺	78	75	79	82	80
(HL ₆) ₂ Co ²⁺	69	68	59	58	77
(HL ₆) ₂ Mn ²⁺	56	56	69	68	67
(HL ₆) ₂ Zn ²⁺	77	75	72	72	73

The substitutions of phenyl rings by chlorine have much more effect on the fungicidal activity. The results suggest that variation in structure on coordination affects the growth of micro organisms and may result in to inhibitory or reduction in toxicology of metal ions towards some organisms²⁶.

Conclusion

The ligand molecule acts as a hexadentate ligand in all the studied cases of complex. Bonding either among N (4) depending upon the nature of the metal ions. Octahedral structures for Ni(II), Co(II) and Mn(II) complexes, tetrahedral polymeric structure for Zn(II), and distorted octahedral for Cu(II) complex have been tentatively proposed. Present work will contribute in the field of new antifungal for some plant pathogenic organisms.

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References

1. Gribov L A, Sawin S B and Raikhstat M M, *Zh Anal Khim.*, 1980, **35**, 1469.
2. Patel N B and Chaudhari R C, *J Indian Chem Soc.*, 2006, **83**, 838-841.
3. Robert J A and Russel H E, *J Med Chem.*, 1972, **15**, 335.
4. Vashi R T and Patel S B, *E-J Chem.*, 2009, **6 (S1)**, S445-S451.
5. Vogel A I, Text book of Quantitative Inorganic Analysis. 3rd Ed., ELBS, London, 1978.
6. Lewis J and Wilkins R G, Modern Coordination Chemistry, *New Science*, New York, 1964.
7. Figgis B N and Lewis J, The Magneto Chemistry of Chelates in Modern Coordination Chemistry, InterScience, New York, 1960.
8. Williams J O, *Adv Phys Org Chem.*, 1979, **16**, 159.
9. Barry A L, Antibiotics in Laboratory Medicine, Williams and Wilkins, Baltimore, 3rd Ed., 1996.
10. Geary W J, *Coord Chem Rev.*, 1971, **81**.
11. Upadhyay R K, *J Indian Chem Soc.*, 1977, **74**, 535-537.
12. Bellamy L J, Infrared spectra of complexes molecules, Chapman and Hall, London, 1957.
13. Silvestein R M, Spectrometric identification of organic compounds, 5th Ed., John Wiley, 1991, 123.
14. Nakamoto K, Infrared and Raman Spectra of Inorganic and Coordination Compounds, 3rd Ed., Wiley- InterScience, New York, 1975.
15. Nakamoto K, Infrared and Raman Spectroscopy of Inorganic and Coordination Compounds, 3rd Ed., Wiley, Inter Science, New York, 1978.
16. Lever A B P, Inorganic Electronic Spectroscopy, Elsevier, New York, 1968.
17. Syamal A and Maurya M R, *Synth React Inorg Metal Org Chem.*, 1986, **16**, 39.
18. Singh D P, Shishodia N, Yadav B P and Rana V B, *Polyhedron*, 1997, **16(13)**, 2229-2232.
19. Vashi R T, Patel S B and Kadiya H K, *Der Pharma Chemca.*, 2010, **2(1)**, 109-116.
20. Reddy S N and Agarwal B V, *Syn React Inorg Chem.*, 1987, **17**, 10.
21. Chaudhary G L, Prasad S R and Rahman A, *J Indian Chem Soc.*, 1997, **74**, 683-685.
22. Satapathy K C, Dash D C, Pradhan G C and Naik A, *J Indian Chem Soc.*, 1989, **66**, 292.
23. Yidiz M, Dulger B, Koyuncu S Y K and Yanpici M B, *J Indian Chem Soc.*, 2004, **81**, 7.
24. Aswar A S and Bhava N S, *J. Indian Chem Soc.*, 1997, **4**, 75.
25. Sahu B K and Mahapatra B K, *J Indian Chem Soc.*, 1979, **56**, 825.
26. Patel M M and Patel H R, *J Indian Chem Soc.*, 1996, **73**, 313- 317.