Synthesis and characterization of 2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-methoxyphenyl)-3(H)-quinazolin-4-one and its metal complexes with Cu(II), Ni(II), Mn(II), Co(II) and Zn(II) ions

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Abstract

Synthesis and characterization of 2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-methoxyphenyl)-3(H)-quinazolin-4-one ligand called HAMQ (HL₃) was studied. To prepare this ligand, anthranilic acid was converted into 2-chloromethyl-3(4-methoxyphenyl)-3(H)-quinazoline-4-one. This compound was finally condensed with 5-amin-8-hydroxyquinoline. The transition metal complexes of Cu²⁺, Ni²⁺, Zn²⁺, Mn²⁺ and Co²⁺ of this ligand HAMQ were prepared and characterized by reflectance, NMR as well as IR spectroscopy, elemental analysis and magnetic measurements. The stoichiometry of the complexes has been found to be 1:2 (Metal : ligand). The data suggested an octahedral geometry around Co²⁺, Ni²⁺ and Mn²⁺ complexes, a distorted octahedral geometry around Cu²⁺ and a tetrahedral geometry around Zn²⁺ have been proposed. These complexes have been tested for their antifungal activities.

Keywords: Ligand, 8-hydroxyquinoline, IR and NMR spectral studies, magnetic moment, antifungal study.

Introduction

The chemistry of heterocyclic compounds continuously to be an explore field in the organic chemistry. Infectious diseases caused by micro and micro organisms; viz. bacteria, fungi, viruses and parasites are still a major threat to human health, despite tremendous inventions in drug chemistry. The emergence of wide spread drug resistance, particularly multi-drug resistance [1] against gram-positive bacteria is a major concern.

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs [2]. A Quinazolin-4-one derivative possesses biological activities such as antifungal [3-4]. The formation of 8-hydroxyquinoline and
Quinazolin-4-one molecules into one molecule has not received any attention in spite of well-defined applications of both the molecules. Hence the initial work in this direction has been carried out [5]. Thus in the extension of this work [5] present communication comprises the synthesis, characterization and chelating properties of novel quinazolin-4-one-8-hydroxyquinoline derivatives. The whole work is summarized in scheme-1.

Results and Discussion

The synthesis of Ligand HL₃ was performed by method reported for 2-chloromethyl–3-phenyl-3(H)-quinazoline-4-one. The C, H and N of ligand are consistent with predicted structure.

NMR spectra: The ¹H NMR spectra of ligand HL₃ (Fig.1) gave the multiplate between 6.88-7.8 \( \delta \) ppm for aromatic protons, signal at 5.74-5.98 \( \delta \) ppm for phenolic –OH group, 3.35-3.77 \( \delta \) ppm
due to CH$_2$ bridge and 11.1-11.35 δ ppm due to –NH group. The non-aqueous conductometric titration of ligand gave the proton of –CH$_2$ and –OH group in ligand.

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. Very low molar conductance ($\Lambda$$_M$) values in the range of 8.15 to 22.52 ohm$^{-1}$cm$^2$ mol$^{-1}$ in Mn$^{2+}$, Ni$^{2+}$, Cu$^{2+}$ and Zn$^{2+}$ complexes indicates that they are non-electrolytic and monomeric in nature (ML$_2$ type complexes). The low $\Lambda$$_M$ values may be attributed to the large cations [6]. The electrical conductivity of these complexes found in the order: Co > Ni > Cu > Mn > Zn.

Table – 1 Analytical and physical data of metal chelates of HL$_3$ [HAMQ]

<table>
<thead>
<tr>
<th>Ligand / Complexes</th>
<th>Molecular Formula</th>
<th>M.W. (g/mol)</th>
<th>Yield (%)</th>
<th>C (%)</th>
<th>H (%)</th>
<th>N (%)</th>
<th>M (%)</th>
<th>$\mu$$_{eff}$ (B.M.)</th>
<th>$\Lambda$$_M$ (ohm$^{-1}$cm$^2$mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL$_3$</td>
<td>C$<em>{25}$H$</em>{20}$N$_4$O$_3$</td>
<td>424.00</td>
<td>87</td>
<td>70.70 (70.75)</td>
<td>4.70 (4.71)</td>
<td>13.10 (13.20)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(HL$_3$)$_2$ Cu$^{2+}$</td>
<td>C$<em>{50}$H$</em>{40}$N$_8$O$<em>6$ Cu$</em>{12}$</td>
<td>945.54</td>
<td>72</td>
<td>63.2 (63.46)</td>
<td>4.20 (4.44)</td>
<td>11.70 (11.85)</td>
<td>6.60 (6.72)</td>
<td>1.87</td>
<td>9.11</td>
</tr>
<tr>
<td>(HL$_3$)$_2$ Ni$^{2+}$</td>
<td>C$<em>{50}$H$</em>{38}$N$_8$O$<em>6$ Ni$</em>{12}$</td>
<td>940.69</td>
<td>76</td>
<td>63.5 (63.78)</td>
<td>4.30 (4.46)</td>
<td>11.80 (11.91)</td>
<td>6.00 (6.24)</td>
<td>2.99</td>
<td>10.20</td>
</tr>
<tr>
<td>(HL$_3$)$_2$ Mn$^{2+}$</td>
<td>C$<em>{50}$H$</em>{38}$N$_8$O$<em>6$ Mn$</em>{12}$</td>
<td>936.93</td>
<td>75</td>
<td>64.0 (64.04)</td>
<td>4.10 (4.48)</td>
<td>11.70 (11.95)</td>
<td>5.70 (5.86)</td>
<td>5.20</td>
<td>8.98</td>
</tr>
<tr>
<td>(HL$_3$)$_2$ Co$^{2+}$</td>
<td>C$<em>{50}$H$</em>{38}$N$_8$O$<em>6$ Co$</em>{12}$</td>
<td>940.93</td>
<td>77</td>
<td>63.5 (63.77)</td>
<td>4.3 (4.46)</td>
<td>11.80 (11.90)</td>
<td>6.1 (6.26)</td>
<td>4.01</td>
<td>22.52</td>
</tr>
<tr>
<td>(HL$_3$)$_2$ Zn$^{2+}$</td>
<td>C$<em>{50}$H$</em>{38}$N$_8$O$<em>6$ Zn$</em>{12}$</td>
<td>947.39</td>
<td>67</td>
<td>63.1 (63.33)</td>
<td>4.20 (4.43)</td>
<td>11.70 (11.82)</td>
<td>6.7 (6.90)</td>
<td>-</td>
<td>8.15</td>
</tr>
</tbody>
</table>
Infrared spectra: IR spectrum of ligand HL₃ (Fig. 2) show a broad band extended from 3700 to 2600 cm⁻¹ which might be responsible to phenolic -OH group bonded to N atom of 8-hydroxyquinoline moieties [7]. The inflextious at 2923, 2856 and 1470 cm⁻¹ are due to aromatic -CH₂- and methylene group of bridge [8-11]. The strong band at 1710 cm⁻¹ is attributed to -C=O of quinazoline 4-one moiety. Several bands appeared between 1500 and 1600 cm⁻¹ region may arised from aromatic breathing. Band at 3400 cm⁻¹ for –NH group. The IR band at 1580 cm⁻¹ (C=N of 8-quinolinol system) of HL₃ ligand shifted to higher frequency side ~1595 cm⁻¹ in the spectra of the metal complexes indicating involvement of nitrogen in the complexes formation [7,12]. Most of bands appeared in the spectra of corresponding ligand are observed at their metal complexes. Only a new band at 1095 cm⁻¹ had appeared in the spectra of metal complexes. This may be assigned to νC-O of C-O-M bond formation. All the complexes show additional bands at 840-830 cm⁻¹ indicating the presence of coordinated water [13].

Fig. 2 IR Spectrum of Ligand HL₃
Magnetic moment and electronic spectra: The room temperature $\mu_{\text{eff}}$ value for the Co$^{2+}$ complexes 4.01 B.M. suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The electronic spectrum of the Co$^{2+}$ complex shows three bands at 8540, 18700 and 24855 cm$^{-1}$, assignable to $^4T_{1g}$ (F) $\rightarrow$ $^4T_{1g}$ (F) ($\nu_1$), $^4T_{1g}$ (F) $\rightarrow$ $^4A_{2g}$ (F) ($\nu_2$) and $^4T_{1g}$ (F) $\rightarrow$ $^4T_{1g}$ (P) ($\nu_3$) transitions, respectively for an octahedral geometry [14]. The value of transition ratio $\nu_2 / \nu_1$ is 2.19 providing further evidences for octahedral geometry for the Co$^{2+}$ complex.

In the Ni$^{2+}$ complexes, $\mu_{\text{eff}}$ values at room temperature are in the range 2.99 B.M. as expected for six coordinated spin free Ni$^{2+}$ species [15]. The reflectance spectra of the Ni$^{2+}$ complex, exhibit two strong bands at 15620 cm$^{-1}$ and 22475 cm$^{-1}$, assignable to $^3A_{2g}$ (F) $\rightarrow$ $^3T_{1g}$ (F) ($\nu_1$) and $^3A_{2g}$ (F) $\rightarrow$ $^3T_{1g}$ (P) ($\nu_2$) respectively. The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier [16-17]. The Cu$^{2+}$ complexes exhibit normal magnetic moments 1.87 B.M. corresponding to one unpaired electron indicating the distorted octahedral geometry, which is in agreement with data reported by other research worker [18]. Electronic spectra of these complex show broad asymmetric bands in the region 14896 cm$^{-1}$ and at 23878 cm$^{-1}$ assignable $^2B_{1g} \rightarrow$ $^2A_{1g}$ and charge transfer transition respectively [19]. These results reveal the distorted octahedral geometry for this complex. The former band may be due to $^2E_g \rightarrow$ $^2T_{2g}$ accounted due to John Teller effect suggesting thereby a distorted octahedral geometry for these complexes. Zn$^{2+}$ complex is diamagnetic in nature and its electronic spectra do not furnish any characteristic d-d transitions except charge transfer (C.T.) bands as expected for d$^{10}$ systems and may have tetrahedral geometry [20]. There is no evidence for the characteristic bands of coordinated water in IR spectra.

The electronic spectra of the Mn$^{2+}$ complex exhibited three spin allowed bands in the region 15999 cm$^{-1}$, 18000 cm$^{-1}$ and 24310 cm$^{-1}$ assigned to the transitions $^6A_{1g} \rightarrow$ $^4T_{1g}$ ($^4G$)($\nu_1$), $^6A_{1g} \rightarrow$ $^4T_{2g}$ ($^4G$)($\nu_2$) and $^6A_{1g} \rightarrow$ $^4E_g$, $^4T_{1g}$ ($^4P$) ($\nu_3$) respectively, indicating octahedral geometry [21]. The observed magnetic moment of the Mn$^{2+}$ complexes are 5.20 B.M. corresponding to five unpaired electrons indicates high spin octahedral environment [22].

Antifungal activity: Ligand and its metal complexes were found more or less toxic against fungi. The antifungal activity of the metal complexes was found to be in the order: Cu (II) > Zn (II) > Co (II) > Ni(II) > Mn (II). Copper complex exhibit more toxicity than other metal complexes. Hence such type of complexes may find as agricultural and garden fungicides.

Materials and Methods

All the chemicals used were of pure grade (Merck and B.D.H). The melting points of ligand HL$_3$ was determined by DSC method and was uncorrected.

Synthesis of ligand HL$_3$: A mixture of N-chloroacetyl anthranilic acid (2.13 g, 0.1 M) and P-anisidine (1.20 g, 0.01 M) and PCl$_5$ (1.86 g, 0.01 M) in dry 5-Amino-8-hydroxy quinoline solvent was refluxed under anhydrous condition for 4 hrs. The reaction mixture was allowed to cool and PCl$_5$ was decomposed by titrating with cold water. 5-Amino-8-hydroxy quinoline was distilled off to get the product. It was filtered, washed with saturated sodium bicarbonate solution and then with cold water and air-dried. The product was in form of amorphous dark brown color
powder. The air dried products were quantitative. Melting point of HL₃ was 207.8°C (Uncorrected).

**Synthesis of Complexes:** A dried ligand sample HL₃ 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 complexes with transition metal ions. The formic acid solution of ligand was added drop wise to a solution of cupric nitrate hexahydrate, nickel nitrate hexahydrate, cobalt nitrate hexahydrate, manganese chloride hexahydrate, Zinc nitrate hexahydrate (0.005 moles) in 100 ml of water respectively with rapid stirring. The resultant pH 4.5 (for Cu²⁺), pH 6.0 (for Ni²⁺ and Co²⁺) and pH 5.6 (for Mn²⁺ and Zn²⁺) were maintained by adding 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 hrs. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone, dried. The percentage yield of complexes was in the range of 59-82 %. All the complexes were powdered well and dried at 70°C over a period of 24 hrs.

**Measurements:** The C, H and N contents of metal complexes were determined on elemental analyzer Thermofiniggan 1101 Flash EA (ITALY). The metal contents were estimated using standard methods [23]. ¹H NMR spectra of ligand was recorded on Bruker NMR spectrophotometer using TMS as an internal standard in CDCl₃/DMSO-d₆ [24]. The molar conductance of the complexes in DMF (10⁻³M) solutions were measured at room temperature using Systronics model 305 direct reading conductivity bridge. The infrared spectra (KBr) were recorded in the range 4000-600 cm⁻¹ with a Nicolet-760 spectrophotometer. Reflectance spectra of complexes were recorded on a Beckman–DK-2A spectrophotometer using MgO as reference. Magnetic susceptibility was measured by Gouy’s method [25] at room temperature (300 K) using Hg [Co(CNS)₄] as calibrant [26], and the effective magnetic moment from relation [24], \( \mu_{\text{eff}} = 2.84\sqrt{Xm \times T} \), where T is the absolute temperature. Diamagnetic corrections were made by using Pascal’s constants.

The ligand and its metal complexes were screen at 1000 ppm concentration in vitro for their antifungal activity against five fungi viz. Erysiphe pisi, Nigrospora sp., Trichoderma sp., Aspergillus niger, Cuvularia lunata. The antifungal activity of the compounds was measured by plate method. 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,

\[
\text{Percentage of Inhibition} = 100 \left( \frac{X-Y}{X} \right)
\]

Where, \( X = \) area of colony in control plate (without sample)

\( Y = \) area of colony in test plate.

**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$^{2+}$, Co$^{2+}$ and Mn$^{2+}$ complexes, tetrahedral polymeric structure for Zn$^{2+}$ and distorted octahedral for Cu$^{2+}$ 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