

Synthesis, Characterization and Biological Activity of Metal Complexes of 2-Picolinic Acid

S. Prema¹ and A. Pasupathy²

¹Asst. Prof., Department of Chemistry, Urumu Dhanalakshmi College, Trichy

²Head, Asso. Prof., Department of Chemistry, Urumu Dhanalakshmi College, Trichy

1. Introduction

Picolinic acid is a derivative of pyridine with a carboxylic acid substituent at the 2-position. It acts as a bidentate chelating agent with elements such as Chromium, Zinc, Manganese, Copper, Iron and Molybdenum in the human body. Many of the complexes are neutral and, thus lipophilic. The Zinc dipicolinate dietary supplements became popular as they were shown to be an effective means of introducing Zinc into the body. It is a catabolite of the amino acid tryptophan through the Kynurenine pathway. It is a precursor to the enzyme NAD⁺ in addition; it is suggested to assist in the absorption of Zinc (II) ions and other divalent or trivalent ions through the small intestine.

Picolinic acid acts as a bidentate ligand in which the metal complex is formed by coordination between the pyridine nitrogen and the carbonyl oxygen on the adjacent carboxylic acid group. Thus, at physiological pH, picolinic acid is fully dissociated and forms very stable complexes with biologically essential metals such as Copper, Iron and Zinc^[1]. Van Campen, D and House, W.A first demonstrated and revealed that Zinc absorption is influenced by endogenous picolinic acid^[2]. It is identified in a pancreatic extract and in human milk^[3]. It should be a useful agent in understanding cell growth control and possible different mechanism of transformation^[4]. Picolinic acid and its metal complexes have been subjected to intense research activity recently due to their broad spectrum of physiological activity as well as for the design of new metallopharmaceuticals. A literature survey of the reported crystal structures of picolinic acid with diverse metal ions indicates picolinic acid exhibits bidentate through nitrogen and oxygen atom of carboxylate anion. N, O- chelating bonding mode and H-bonding between the carboxylate moiety and water molecules are predominant. The crystal structure, chemical properties and biological activities of picolinic acid and some of its metal complexes have been reported^[5-8]. Metal complexes of biologically active ligands are a target for the development of new drugs. An antimicrobial activity of some metal complexes of the mixed ligands 1,10- phenanthroline and 2,2'-bipyridine, hexamethylene tetramine and 4,4'- bipyridine was reported^[9]. Spectral and Thermal analysis of copper (II) complex of 6-hydroxypicolinic acid and 3-picoline, metal chelates of 1-nitroso-2-naphthol and 8-hydroxyquinoline with picolinic acid were reported^[10,11] and electro-chemical behaviour of bispicolinate copper(II)

complex also reported^[12]. In this paper, we reported the synthesis, characterization and its anti-microbial activity against some resistant fungal and bacterial strain.

2. Experimental Techniques

The FTIR spectra were recorded as KBr pellets using Fourier transform infrared spectrometer Shimadzu 24 FTIR 8400S. Electronic spectra of the prepared complexes were taken in the region (300-1100) nm for 10^{-3} M solution in ethanol and methanol at 25°C using Shimadzu UV-160.A-Ultraviolet-visible spectrometer with 1.000 ± 0.001 cm matched quartz cell. The electrical conductivity of the complexes were recorded at the room temperature for 10^{-3} M solution of the samples in acetonitrile using deep vision digital conductivity meter. The melting points are recorded by using Stuart melting point apparatus. The magnetic susceptibility measurements were measured by Gouy's method. ESR spectra were recorded on a JOEL ESR spectrometer at liquid nitrogen temperature operating at X-band frequency (9.1GHz). Electrochemical behavior of the metal complex was investigated with CV instrument Device VSP(SN 0147) electrochemical analyzing. $[\text{Bu}_4\text{N}]\text{ClO}_4$ as the supporting electrolyte. The three electrode system consists of glassy carbon electrode, $\text{Ag}/\text{AgCl}/\text{KCl}$ (Sat'd) (0.197V) as the reference electrode and a Platinum wire as the auxiliary electrode was used. All the Voltammetric experiments were made at room temperature.

Anti-Microbial Test

Anti-microbial activities of the ligand and its complexes have been carried out against three types of pathogenic fungal and four types of pathogenic bacteria, two types of bacteria was gram positive which is *Staphylococcus aureus* and *Bacillus anthrax* and another two types of bacteria was gram negative which is *Klebsiella pneumoniae* and *E. coli* using nutrient agar medium by disc diffusion method. The test solutions were prepared in DMSO and soaked in filter paper having 5 mm diameter and 1mm thickness. These discs were placed on the already seeded plates and incubated at 37°C for 24 hours. The diameter (mm) of the inhibition zone around each disc was measured after 24 hours.

3. Results and Discussion

3.1 Synthesis

Metal complexes of picolinic acid were prepared by the refluxion of metal salts and picolinic acid in ethanol taking 1:3 molar ratio for 6 hours. The solutions were concentrated and cooled, to crystallize out the complexes. The complexes were washed with ether to remove the excess ligand. The prepared complexes were characterized by conductance, magnetic behaviour, IR, EPR, Electronic spectral studies and antimicrobial activity.

3.2 Conductance Studies

Molar conductance studies helped in assigning the composition of the prepared complexes.

Table 1. Physical properties, conductance and magnetic studies of metal complexes

Complex	Conductance values $\text{Ohm}^{-1}\text{cm}^2\text{mol}^{-1}$	Type of Electrolyte	μ_{eff}	Melting Point $^{\circ}\text{C}$	Colour of the Complex
$[\text{MnL}_2\text{Cl}_2]$	40.091	1:0	6.05	180	White
$[\text{CoL}_3]^{2+}[\text{CoCl}_4]^{2-}$	104.92	1:1	4.5	280	Green
$[\text{NiL}_2\text{Cl}_2]$	33.26	1:0	2.85	285	Pale Blue
$[\text{CuL}_2\text{Cl}_2]$	40.091	1:0	1.85	230	Dark Blue
$[\text{ZnL}_2\text{Cl}_2]$	19.62	1:0	-	197	White

L=Picolinic acid

By the conductance studies, we found out the complexes belong to 1:0 electrolyte in which anions are inside the coordination. The cobalt complex exhibit 1:1 electrolyte. The magnetic moments, μ_{eff} of the complexes are given in the table 1. The magnetic moment of the metal ion is within the expected value.

3.3 IR Spectroscopy

By the conductance studies, we found out the complexes belong to 1:0 electrolyte in which anions are inside the coordination. The cobalt complex exhibit 1:1 electrolyte. The magnetic moments, μ_{eff} of the complexes are given in the Table 1. The magnetic moment of the metal ion is within the expected value.

The comparison of IR spectra of the ligand and its complexes confirmed the coordination of the ligand atoms with the metal ion. The presence of chloride ion, OH stretch of the spectra of the complex, absence of symmetric and asymmetric stretch of the carboxylate ion confirmed that the carboxylic acid group of the picolinic acid is not ionized and the shift of the C=O group stretch to lower frequency in the spectra of complexes suggests that the acid group is not ionized and the carbonyl oxygen of the acid group is coordinated to the metal ion. Moreover the C=N stretch of the pyridine ring is also shifted to lower frequency suggests that the picolinic acid acts as a bidentate ligand from which carbonyl oxygen of the acid group and nitrogen of the pyridine ring are coordinated to the metal ion. The FTIR spectra of the metal complexes are summarized in the Table 2.

Table 2. FTIR spectra of metal complexes

Compound	ν_{O-H} stretching cm^{-1}	$\nu_{C=O}$ acid cm^{-1}	$\nu_{C=N}$ cm^{-1}	$\nu_{C=C}$ cm^{-1}	ν_{C-H} stretching cm^{-1}	ν_{O-H} deformation cm^{-1}	ν_{M-O} cm^{-1}	ν_{M-N} cm^{-1}
Ligand	3396	1742	1675	1599	3099	941	-	-
[Mn(PA) ₂ Cl ₂]	3447	1702	1658	1601	3081	953	550	458
[Co(PA) ₃] ²⁺ [CoCl ₄] ²⁻	3442	1713	1658	1604	3113	965	515	451
[Ni(PA) ₂ Cl ₂]	3487	1721	1641	1599	3115	990	516	461
[Cu(PA) ₂ Cl ₂]	3426	1710	1643	1603	3072	982	527	458
[Zn(PA) ₂ Cl ₂]	3454	1715	1644	1592	3091	950	565	468

The sharp band found at 1742 cm^{-1} is assigned to C=O stretch of carboxylic acid in the spectra of ligand^[13], which is shifted to lower frequency 1718 cm^{-1} suggesting that the carbonyl oxygen of the carboxylic acid group is coordinated to the metal ion^[14]. In the spectrum of ligand, the stretch found out as 1675 cm^{-1} is assigned to C=N stretch of pyridine ring which is shifted to 1640 cm^{-1} in the spectra of complexes, suggesting that the nitrogen of the pyridine ring also coordinated to the metal ion. The OH stretch of the acid group is found at 3396 cm^{-1} is shifted to higher frequency in the spectra of complexes which indicates that the acid group is not ionized. The stretches of the ligand especially the C=C stretch at 1600 cm^{-1} , 1520 cm^{-1} are not much affected in the spectra of the complexes. The new band in the spectra of complexes found at the range of 550-511 cm^{-1} are assigned to the metal-oxygen bonding and bands at the range of 468-451 cm^{-1} due to metal-nitrogen bonding in the corresponding complexes which are absent in the spectra of the ligand. Thus the comparison of IR spectra of the ligand and complexes confirmed the mode of coordination and the ligand is a bidentate ligand.

3.4 Electronic Spectra of Metal Complexes

Here the nickel complex exhibit a band at 23,365 cm^{-1} (428 nm) assigned to $^3A_2g \rightarrow ^3T_1g(P)$ transition of octahedral geometry of the complexes.

The electronic spectra of Co(II) chloride complex displays bands at 19,581 cm^{-1} (510 nm) and 14,806 cm^{-1} (675 nm). The first band is assigned to $^4T_1g(F) \rightarrow ^4T_1g(P)$ transition of octahedral geometry and the other band is assigned to $^4A_2(F) \rightarrow ^4T_1(F)$ transition of tetrahedral geometry. This suggests that this complex is a mixture of octahedral and tetrahedral geometries with the

composition of the type $[\text{Co}(\text{BBA})_3]^{2+}[\text{CoCl}_4]^{2-}$ which is supported by the conductance data.

The complex shows an absorption band in 600-900 nm regions (They are blue or green in colour). The octahedral complex shows a unique band due to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ transition. The copper complex showed a broad band at $15,479 \text{ cm}^{-1}$ (646 nm) due to Jahn-Teller distortion and has a distorted octahedral geometry.

3.5 EPR spectral studies

The X- band EPR spectrum of the Cu(II) complex was recorded in DMSO at liquid nitrogen temperature shows five peaks on the parallel component due to the interaction of unpaired electron of Cu(II) ion with Cu having nuclear spin $I = 3/2$ for the complex ($g_{\parallel} > g_{\perp}$) suggesting that the system is axial. The trend in the g value ($g_{\parallel} > g_{\perp} > 2.0023$) and the value of exchange interaction term ($G > 4$) suggested that the unpaired electron of Cu(II) ion is present in $d_{x^2-y^2}$ orbital.

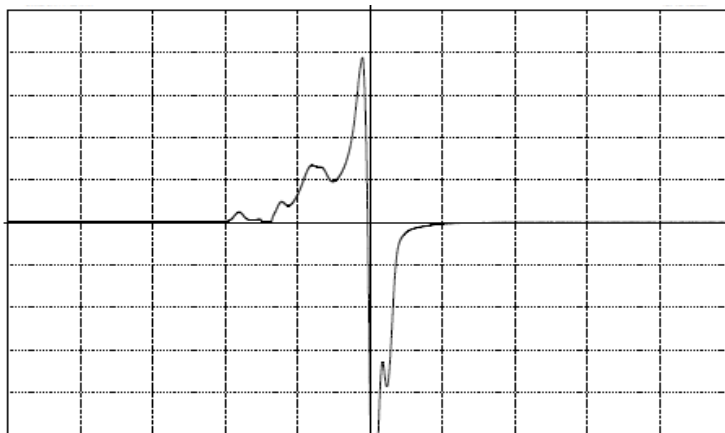


Fig 1. EPR spectrum of $[\text{Cu}(\text{PA})_2\text{Cl}_2]$ complex in DMSO solution

Table 3. EPR parameter of Cu(II) complex

Complex	Medium and Temperature	g_{\parallel}	g_{\perp}	G
$[\text{Cu}(\text{PA})_2\text{Cl}_2]$	Solution state LNT	2.32	2.05	6.4

However, chloride molecule is present in the coordination sphere suggested that Cu(II) complex posses distorted octahedral geometry.

3.6 Thermal Analysis

TGA and DTA curves of Mn(II) complex showed that it is stable upto 180°C. The first stage of degradation occurs at 237.9 °C with the removal of chloride ligand at about 14.1% (calc 14.3%). The second stage is from 237.9- 313.8°C with the mass loss of about 39% (calc 37.6) corresponds to the gradual decrease in the mass of the ligand accompanied by an endothermic peak at 305.4°C on DTA shows that the complex melts. From 493.1°C of TGA curve represents the decomposition of another ligand and an exothermic peak with 521.9°C on DTA which corresponds to the decomposition of the ligand. The mass of the final residue corresponding to stable MnO is 18% (calc 19%).

The TGA and DTA of Co(II) complex at 153.5°C on TGA curve indicates the release of one chlorine atom with 7.09% (cal 5.6%). The second stage of degradation from 153.5°C – 303.8°C indicates the decomposition of trichloro cobalt anion with 26.33% (cal 26.27%) ,accompanied by an endothermic peak with 296°C on DTA curve where the the complex melts before decomposition. The third stage of decomposition on TGA, gradually decreases from 303.8 - 621°C with 48.25% (calc 51%) mass loss of the ligand and an exothermic peak with 477.9°C on the DTA which may be attributed to the decomposition of the ligand. The mass of the final residue corresponds to stable cobalt trioxide with 15.92% (calc 17%).

The TGA and DTA of Ni(II) complex is stable upto 263.8°C. The first stage of degradation was observed at 263.8°C with loss of one chlorine at 8.75% (cal 9.4%). The second and third stage of degradation at 264-466.6°C with 64.85% (cal 65.5%) shows the gradual decomposition of two picolinic acid ligand. The mass of the final residue to 10% (cal 19.8%) does not corresponds to any stiochiometry of the end product, as the residue obtained is not close to that expected for metal oxide. The residue CO₂ with 11.85% (cal 11.7%) is expected.

3.7 Cyclic Voltammetry studies

The redox property of the Mn(II) complex was studied in the potential range of -2V to +2V. The Mn(II) complex is electroactive with respect to the metal center and exhibited two redox process, where each reduction is associated with a single electron transfer at the room temperature. The two well defined quasi-reversible one electron cyclic process were observed at $E_{pc} = -0.7878V$ with the corresponding oxidation peak at $E_{pa} = -0.5833V$ at a scan rate of about 50mV/sec and at $E_{pc} = 0.875V$ with the corresponding oxidation peak at $E_{pa} = 1.213V$. The ΔE_p value for the first redox couple is 0.2045V, which is less than the second redox couple of about 0.335V.

The Cyclic voltammogram of cobalt complex which has been studied in the methanol solution under nitrogen atmosphere is also electroactive with respect to the metal center with the scan rate of about 50mv/s. The Co(II) complex

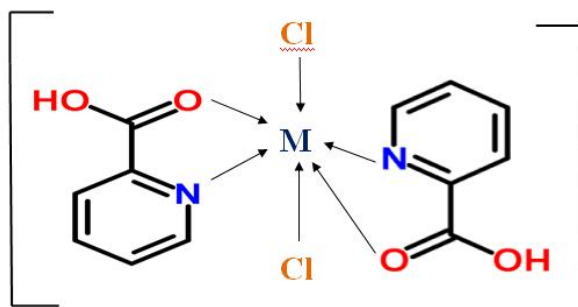
exhibits one electron quasi-reversible transfer process with an oxidation peaks at -0.9114V and -0.5059V, also having a corresponding reduction peak at -1.051V. The peak separation ΔE_p is 0.139V. The voltammogram of copper complex displays an oxidation peak at $E_{pa} = -0.618V$ with an associated reduction peak at $E_{pc} = -0.9117V$ and at $E_{pa} = 1.214V$ with the corresponding reduction peak at $E_{pc} = -0.492V$, at a scan rate of about 50mV/sec. The ΔE_p value for the first redox couple is 0.293V, which is less than the second redox couple of about 1.706V. The E_p value is higher for the complex due to the difference between the original complex and the reduced complex.

The cyclic voltammogram of Zinc complex displays an oxidation peaks at $E_{pa} = -0.5303V$ and 1.389V with an associated reduction peak at $E_{pc} = -0.83055V$ at a scan rate of about 50mV/sec. The peak separation is at 0.3002V.

Table 4. CV study of metal complexes

Complex	$E_{pa}(V)$	$E_{pc}(V)$	$E_{1/2}(V)$	$\Delta E_p(V)$	$E_{pa}(V)$	$E_{pc}(V)$	$E_{1/2}(V)$	$\Delta E_p(V)$
Ligand	1.310	-0.690	0.31	2.008	-	-	-	-
[Mn(PA) ₂ Cl ₂]	-0.583	-0.787	-0.685	0.204	1.2133	0.8750	0.425	0.335
[Co(PA) ₃] ²⁺ [CoCl ₄] ²⁻	-0.911	-1.05	-0.983	0.139	-0.505	-	-	-
[Ni(PA) ₂ Cl ₂]	-0.633	-	-	-	1.250	-	-	-
[Cu(PA) ₂ Cl ₂]	-0.618	-0.911	-0.764	0.293	1.214	-0.492	0.361	1.706
[Zn(PA) ₂ Cl ₂]	-0.530	-0.830	-0.680	0.3002	1.389	-	-	-

Structure of the Metal Complex



M = Mn, NiCu, Zn

Fig 2. Structure of [M(PA)₂Cl₂] complexes

The structure of picolinic acid complexes of divalent metals are assigned on the basis of their electronic spectra, their magnetic moment and their analytical data. All the complexes except cobalt(II) complex exhibit octahedral geometry.

The chloride complex of cobalt (II) is a 1:1 electrolytes $[\text{Co}(\text{PA})_3]^{2+}[\text{CoCl}_4]^{2-}$ with octahedral cation and a tetrahedral anion which is well supported by the electronic spectra and conductance data.

Structure of the Cobalt Complex

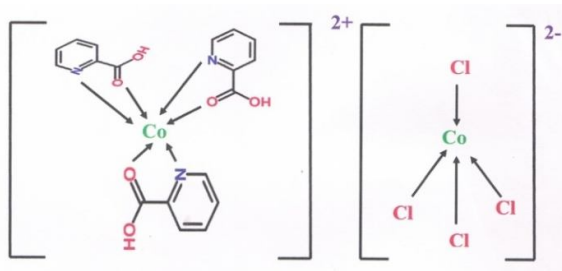


Fig 3. Structure of $[\text{Co}(\text{PA})_3]^{2+}[\text{CoCl}_4]^{2-}$ complex

3.8 Antimicrobial Activity

Table 5. Antifungal activity of metal complexes

Name of Organism	Ligand	$[\text{Co}(\text{PA})_3]^{2+}[\text{CoCl}_4]^{2-}$	$[\text{Ni}(\text{PA})_2 \text{Cl}_2]$	$[\text{Cu}(\text{PA})_2 \text{Cl}_2]$
<i>Aspergillus niger</i>	11	15	15	13
<i>Aspergillus flavus</i>	9	10	15	13
<i>Aspergillus terreus</i>	9	11	19	3

Table 6. Antibacterial activity of metal complexes

Name of Organism	Ligand	$[\text{Co}(\text{PA})_3]^{2+}[\text{CoCl}_4]^{2-}$	$[\text{Ni}(\text{PA})_2 \text{Cl}_2]$	$[\text{Cu}(\text{PA})_2 \text{Cl}_2]$
<i>Klebsiella pneumonia</i>	13	-	17	-
<i>Escherichia coli</i>	14	-	32	-
<i>Bacillus anthrax</i>	-	-	20	-
<i>Staphylococcus aureus</i>	-	-	12	-

In the present study, the antifungal activity of the synthesized metal complexes have been investigated against the three fungal pathogens by disc-diffusion method and the results are summarized in the above Table 5. It is clear that, the inhibition by the comparative study of free ligand and its complexes, the inhibition of growth of fungi due to the metal complex increases. The increase in activity with the concentration is due to the effect of metal ions on the metabolic function of the cell. The action of compounds may involve the formation of hydrogen bonds with the active centre of the cell constituents, resulting in the interference with the normal function of the cell. The antibacterial activity of the ligand shows moderate activity. But its Ni(II) chloride complex exhibited higher activity against four bacterial microorganism. The Co(II) and Cu(II) complexes have less activity against all microorganisms.

4. Conclusion

Picolinic Acid acts as a bidentate ligand in which the mode of coordination is confirmed by the negative shift of carbonyl and C=N stretching frequency in the spectra of complexes. The mode of coordination is confirmed by the negative shift in C=O stretching frequency of carboxylic acid group in the spectra of the complexes. The electronic spectra confirmed the geometry of the complexes. The magnetic moment of the metal ion is within the expected value. Conductance studies show that the complexes are in non-electrolyte except cobalt complex. The ESR spectra of Cu(II) complex confirmed the distorted octahedral with two axial bond elongated. The TGA and DTA studies revealed that the complexes are thermally stable. The electrochemical properties of the metal complexes were investigated in DMF solution by CV revealed the quasi reversible one electron/ two electron transfer redox process. The ligand and some of the complexes were found to be active against fungal and bacterial strains.

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