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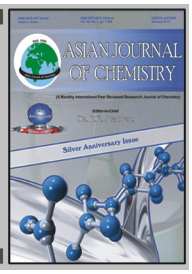

Synthesis, Spectroscopic and Antimicrobial Studies on Copper(II), Cobalt(II), Nickel(II) and Manganese(II) Complexes of *N*-(2-Ethylphenyl) *N*'-Picolinoyl Hydrazine

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Novel ligand *N*-(2-ethylphenyl)*N*'-picolinoyl hydrazine (L) has been synthesized from pyridine-2-acetyl chloride and *N*-(2-ethylphenyl) hydrazine by condensation in ethanol. The ligand and its Cu(II), Co(II), Ni(II) and Mn(II) complexes have been characterized by microanalysis, magnetic susceptibility, FT-IR, ^{1}H and ^{13}C NMR, mass spectrum and UV-visible spectroscopy techniques. It is suggested that two ligands coordinate to the metal ion by hydrazine nitrogen atoms and pyridine nitrogen atoms to form square-planar geometry of $[Cu(L)_2]Cl_2$ but the complexes of cobalt(II), nickel(II) and manganese(II) have octahedral geometry. Newly synthesized ligand and its metal complexes have been screened against *S. aureus* (ATCC 25923), *S. aureus* (ATCC 3160) bacterial species and *C. albicans* (227) and *S. cereviscae* (361) fungal species.

Key Words: Hydrazine ligand, Metal(II) complexes, Spectral and biological studies.

INTRODUCTION

Coordination chemistry is the most active research area in inorganic chemistry. Several thousands of coordination complexes[1-3] have been synthesized and investigated during the past few decades. Ever since the importance of coordination phenomenon in biological processes[4-7] was realized, a number of metal containing macromolecules have been synthesized and studied to understand the mechanism of complex in biological reactions. This has resulted in the emergence of an important branch of inorganic chemistry *viz*. bioinorganic chemistry. Similarly the importance of coordination of substrate molecules on metal ions in catalysis was understood and a lot of research work[8-10] is being carried out on this aspect.

Keeping in view the medicinal and biological importance of hydrazones and of pyridine and its derivatives, they thought it is worthwhile to synthesize and characterize pyridine hydrazides[11] and their transition metal complexes. Preparation and characterization of some 3*d* metal complexes with pyridine-3-benzhydrazide and pyridine-3-(2-hydroxybenz hydrazide) were reported[12].

In this article, we synthesized hydrazine derivative ligand and their metal complexes and were characterized by IR, NMR, molar conductance and magnetic moments, elemental analysis, mass spectrum and UV-visible spectroscopy.

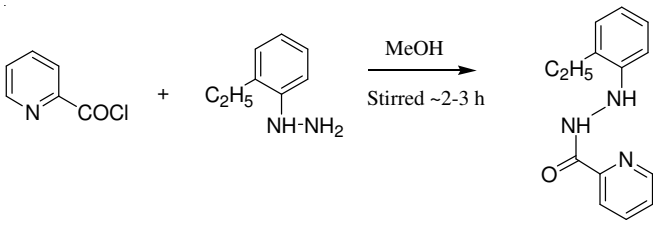
EXPERIMENTAL

All the chemicals used in the present investigation were of the analytical reagent grade (AR). Pyridine-2-acetyl chloride (Fisher Scientific), *N*-(2-ethylphenyl) hydrazine (Sigma, Germany), all metal salts and solvents (Qualigens Fine Chemicals, India) were purchased and used as received. The elemental analysis (C, H, N) done at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow. ^{1}H NMR and ^{13}C NMR spectra of the samples were measured in DMSO-d_6 at IIT Delhi, India. The IR spectra were recorded as KBr pellets using a Perkin-Elmer 783 spectrophotometer in the range 4000-400 cm^{-1}. UV-visible spectra of the complexes were recorded on a Shimadzu UV-1601 spectrophotometer.

Synthesis of ligand *N*-(2-ethylphenyl) *N*'-Picolinoyl hydrazine: This ligand was prepared by the coupling of pyridine-2-acetyl chloride with the *N*-(2-ethylphenyl)hydrazine. In a round bottom flask (100 mL), *N*-(2-ethylphenyl)hydrazine (0.01 mol, 1.15 g) in distilled hot water (10.0 mL) and pyridine-2-acetyl chloride (0.01 mol, 1.38 mL) in ethanol (95 %, 10 mL) were taken and this solution was brought to 5 ºC by cooling in an ice bath, stirred for 2-3 h. Temperature should be maintained at 5 ºC by keeping in ice bath. The product obtained was filtered, washed with water, the organic layers were

collected and then evaporate the solvent under reduced pressure to afford the product; a yellow crystalline solid was obtained (**Scheme-I**). The product was well characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry and physico-chemical techniques.

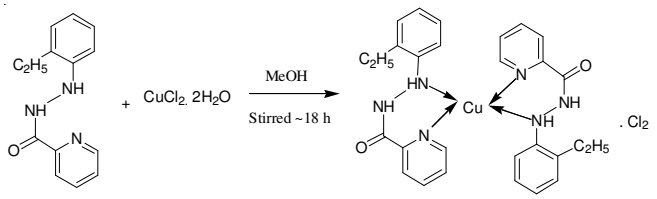
Analytical data of ligand (L): Yield: 60 %; m.p. 240 ºC, m.w. 241, colour: yellow; analytical data for $C_{14}H_{15}N_3O$ found (calc.): C, 69.70 (68.99); H, 6.22 (5.91); N, 17.42 (16.97). IR (KBr, ν_{max}, cm^{-1}): 1637 ν(C-NH), 1690 ν(C=O), 1298 ν(NH-NH). ESI-MS, m/z data found (calcd.): 241 (240), ^{1}H NMR (DMSO-d_6) δ ppm: 7.1 (m, 8H, HC-Ar), 3.8 (s, 2H, NH-NH). ^{13}C NMR (DMSO-d_6) δ ppm: 117.53-121.07 (10C, CH-Ar.), 143.23 (1C, C-N), 153.88 (2C, C=O).



Scheme-I: Synthesis of the N-(2-ethylphenyl)-N'-picolinoyl hydrazine

Synthesis of copper(II) complex [Cu(L)$_2$]Cl$_2$: *N*-(2-ethylphenyl)-*N*'-picolinoyl hydrazine (0.002 mmol, 0.482 g) was dissolved in absolute ethanol and treated with an ethanolic solution of potassium hydroxide till pH about 8 added drop wise to a 0.001 mmol solution of copper chloride (0.170 g)] in methanol solution with continuous stirring and refluxed at 75 ºC for 18 h (**Scheme-II**). After the completion of this reaction; the reaction mixture was monitored by thin layer chromatography. The organic layers were collected, then crude products was taken in chloroform and washed with water and then with brine solution (3 × 20 mL) (thrice) and then evaporate the solvent under reduced pressure to afford the product; a dark bluish crystalline solid was obtained.

Yield: 38 %; m.p.: 260 ºC; m.w. 720; colour: dark bluish; analytical data for [Cu($C_{28}H_{30}N_6O_2$)]Cl$_2$ found (calcd.): C, 46.66 (46.15), H, 4.16 (4.11), N, 11.66 (11.47). IR (KBr, ν_{max}, cm^{-1}) 3402 ν(NH), 1690 ν(C=O), 3015 ν(C-H), 2210 ν(C-N), 411 ν(M-N), ^{1}H NMR (DMSO-d_6) δ ppm: 7.1 (m, 16H, HC-Ar), 3.8 (s, 4H, NH-NH). ^{13}C NMR (DMSO-d_6) δ ppm: 117.53-121.07 (16C, CH-Ar.), 143.23 (4C, C-N), 153.88 (4C, C=O).



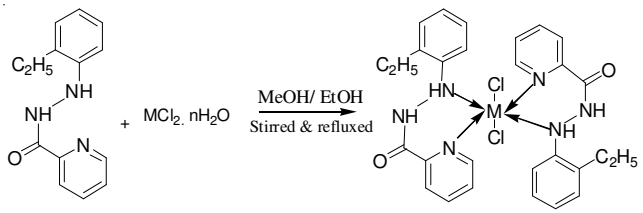
Scheme-II: Synthesis of Copper Complex

Synthesis of cobalt complex [Co(L)$_2$Cl$_2$]: An ethanolic solution of *N*-(2-ethylphenyl)-*N*'-picolinoyl hydrazine (0.002 mmol, 0.482 g) was added dropwise to a solution of cobalt chloride (0.001 mmol, 0.237 g)] in methanol solution with continuous stirring and refluxed at 70 ºC for 12 h. After the completion of this reaction, the reaction mixture was monitored by thin layer chromatography. The organic layers were collected, then crude products was taken in chloroform and washed with water and then with brine solution (3 × 20 mL) (thrice) and then evaporate the solvent under reduced pressure to afford the product; a dirty brownish crystalline solid was obtained (**Scheme-III**).

Yield: 28 %; m.p.: 285 ºC; m.w. 789; colour: dirty brownish; analytical data for [Co($C_{28}H_{30}N_6O_2$)Cl$_2$] found (calcd.): C, 42.58 (42.15); H, 3. 80 (3.55); N, 10.64 (10.47); IR (KBr, ν_{max}, cm^{-1}) 3412 ν(NH), 1690 ν(C=O), 3015 ν(C-H), 2220 ν(C-N), 419 ν(M-N), 380 ν(M-Cl); ^{1}H NMR (DMSO-d_6) δ ppm: 7.3 (m, 16H, HC-Ar), 3.2 (s, 4H, NH-NH). ^{13}C NMR (DMSO-d_6) δ ppm: 117.53-121.07 (16C, CH-Ar.), 140.20 (4C, C-N), 153.21 (4C, C=O).

Synthesis of nickel complex [Ni(L)$_2$Cl$_2$]: In the round bottom flask (100 mL), *N*-(2-ethylphenyl)-*N*'-picolinoyl hydrazine (0.01 mmol, 3.21 g) in an aqueous ethanolic solution (15 mL) and a solution of nickel chloride (0.001 mmol, 0.238 g) in the methanolic solution (10 mL) were mixed dropwise with constant stirring and the reaction mixture was refluxed on heating mental at 60 ºC for 14 h. The resulting solution was cooled at 4 ºC, after the completion of this reaction; the reaction mixture was monitored by thin layer chromatography (**Scheme-III**). After this, the reaction mixture was taken in methanol and washed with water and then with brine solution (3 × 20 mL) (thrice). The organic layers were collected and then evaporate the solvent under reduced pressure to afford the product; a dark greenish crystalline solid was obtained.

Yield: 32 %; m.p.: 290 ºC, m.w. 790; colour: dark greenish; analytical data for [Ni($C_{28}H_{30}N_6O_2$)Cl$_2$] found (calcd.): C, 42.53 (41.27); H, 3.79 (3.61); N, 10.63 (10.35). IR (KBr, ν_{max}, cm^{-1}) 3411 ν(NH), 1690 ν(C=O), 3015 ν(C-H), 2223 ν(C-N), 415 ν(M-N), 391 ν(M-Cl). ^{1}H NMR (DMSO-d_6) δ ppm: 7.4 (m, 16H, HC-Ar), 3.2 (s, 4H, NH-NH). ^{13}C NMR (DMSO-d_6) δ ppm: 117.53-121.07 (16C, CH-Ar.), 140.20 (4C, C-N), 150.08 (4C, C=O).



where M = Ni(II), Co(II) and Mn(II), n = 2-6

Scheme-III: Synthesis of the metal complexes

Synthesis of manganese complex [Mn(L)$_2$Cl$_2$]: An ethanolic solution of *N*-(2-ethylphenyl)-*N*'-picolinoyl hydrazine (0.002 mmol, 0.482 g) was added drop wise to a solution of manganese chloride (0.001 mmol, 0.197 g) in methanol and refluxed at 70 ºC for 10 h. After the completion of this reaction the reaction mixture was monitored by thin layer chromatography. The organic layers were collected, then crude products was taken in chloroform and washed with water and then with brine solution (3 × 20 mL) (thrice) and then evaporate the solvent under reduced pressure to afford the product; a brownish crystalline solid was obtained (**Scheme-III**).

Yield: 63 %; m.p.: 265 ºC, m. w. 749; colour: dirty brownish; analytical data for [Mn($C_{28}H_{30}N_6O_2$)Cl$_2$] found (calcd.): C,

44.85 (44.21); H, 4.11 (4.01); N, 11.21 (11.07). IR (KBr, ν_{max}, cm^{-1}) 3411 ν(NH), 1690 ν(C=O), 3015 ν(C-H), 2222 ν(C-N), 415 ν(M-N), 351 ν(M-Cl). ^{1}H NMR (DMSO-d_6) δ ppm: 7.4 (m, 16H, HC-Ar), 3.2 (s, 4H, NH-NH). ^{13}C NMR (DMSO-d_6) δ ppm: 117.53-121.07 (16C, CH-Ar.), 140.20 (4C, C-N), 150.08 (4C, C=O).

RESULTS AND DISCUSSION

The IR spectrum of the ligand shows a broad band around 3420 cm^{-1} assignable to stretching of -NH groups, which is shifted to the lower frequencies in the spectra of metal complexes. The bands in the region 3100-2900 cm^{-1} can be assigned to -CH stretching vibration of ethyl group. The band at 1690 cm^{-1} is due to free C=O group. The IR spectral bands are in agreement with the proposed structure. The ligand coordination to the metal centre is substantiated by two bands appearing at 425-410 cm^{-1} and 385-350 cm^{-1} for the complexes respectively which are mainly attributed to ν(M-N) and ν(M-Cl) respectively[13]. The low energy pyridine ring in plane and out of plane vibrations observed in the spectrum of the ligand at 625 cm^{-1} whereas the corresponding bands for the complexes are shifted to lower frequencies in region 714-631 cm^{-1} for all complexes, which is a good indication of the coordination of the heterocyclic nitrogen[14].

The ^{1}H NMR and ^{13}C NMR spectra of the title compounds have been recorded in DMSO-d_6 with TMS as internal reference. The present data on comparison support the conclusions derived from the reported similar/substituted pyridine compounds. All these compounds exhibit two peaks in the ^{1}H NMR spectra at δ-3.5 ppm (s) assigned to proton signals of ethylene substituted to benzyl ring system of pyridine moiety. Furthermore, two peaks were found at δ-4.5 ppm (singlet) and δ-4.8 ppm (singlet) assigned to substituted benzyl rings of pyridine. Aromatic proton signals appeared at 7.1-7.8 ppm as multiplet. Similarly, ^{13}C NMR exhibited signals at δ-52.5 due to ethylene carbon and at δ-69.8, 70.4 and 84.3 ppm assigned to benzyl carbons. Aromatic carbon signals were also found to appear at δ-125.7, 130.2, 135.6 and 144.2 ppm values. The electron spray mass spectrum of *N*-substituted pyridine hydrazide ligand was examined to see the fragmentation pattern of the ligand. Mass spectra provide a vital clue for elucidating the structure of compounds. The spectrum shows the molecular ion peak at m/z = 241 ($C_{14}H_{15}N_3O$, calculated atomic mass 240 amu due to ^{13}C and ^{15}N isotopes). The different competitive fragmentation pathways of ligand give the peaks at different mass numbers at 241. The intensity of these peaks reflects the stability and abundance of the ions. The presence of fragments at m/z values 121, 23, 67 and 320 shows that the fragmentation has taken place at NH-NH-. The mass spectrum clearly suggests existence of ligand in the hydrazones form. The electronic spectra of Mn(II) complex show three bands in the regions 485-491, 529-530 and 710-721 nm, which may be assigned to $^6A_{1g} \rightarrow {}^4T_{1g}$, $^6A_{1g} \rightarrow {}^4T_{2g}$(G) and $^6A_{1g} \rightarrow {}^4T_{1g}$ (D) transitions respectively suggesting octahedral environment around the Mn(II) ion[14,15]. The magnetic moment 4.88 is an additional evidence for an octahedral structure. The μ_{eff} value measured for the Co(II) complex is 5.32 B.M, indicating octahedral geometry of the Co(II) ion in the complex. The former band would be due to a $^4T_{1g} \rightarrow {}^4A_{2g}$ electronic transition, indicating an octahedral configuration around Co(II) ions. In all the reflectance spectra of the complexes, four absorption bands appeared at 240, 311, 325 and 348 nm due to the ligand absorptions, which are shifted from those of the parent ligand due to complex formation. The magnetic moment values of Ni(II) complexes are of great help in ascertaining the geometry. The spin only value for octahedral Ni(II) with two unpaired electrons is 2.83 BM. However, octahedral Ni(II) complexes, the magnetic moment value observed is between 2.8-3.3 BM due to spin orbit coupling and higher state mixing with the ground state $^3A_{2g}$. The spectrum of the present Ni(II) complex also shows the ligands band at 350 nm and a charge transfer band at 460 nm. In addition to these bands a d-d band was observed at 550 nm. The electronic transitions expected for octahedral Ni(II) are $^3A_{2g} \rightarrow {}^3T_{2g}$(F); $^3A_{2g} \rightarrow {}^3T_{1g}$(F) and $^3A_{2g} \rightarrow {}^3T_{1g}$(P). These transitions occur at approximately 1000, 600 and 400 nm respectively. The transition $^3A_{2g} \rightarrow {}^3T_{1g}$(P) was probably marked by the charge transfer band. The magnetic data also support such a structure. The spectrum of Cu(II) complex showed absorption band at 665 nm, which could be attributed to the $^2A_{1g}$(F) $\rightarrow {}^2B_{1g}$(P) transitions characterized Cu(II) ion in a square-planar geometry. The square-planar geometry of Cu(II) ion in the complex is confirmed by the measured magnetic moments values, 1.75 B.M. The square-planar geometry is achieved by the coordination of two molecules of ligand, acting as bidentate ligand, to the copper(II) ion.

Microbial activities: For the antibacterial and antifungal assays, the compounds were dissolved in dimethylformamide. Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities of 500 and 1000 ppm concentrations with dextrose broth. The minimum inhibitory concentrations (MIC) were determined using the two fold serial dilution technique. A control test was also performed containing inoculated broth supplemented at the same dilutions used in our experiments and found inactive in the culture medium. All the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and the fungus. Origins of bacterial strains are *S. aureus* (ATCC 25923), *S. aureus* (ATCC 3160), as Gram-positive. Gentamycin and Amphotericin B were used as control drugs. The data on the antimicrobial activity of the compounds and the control drugs as minimum inhibitory concentrations values are given in Table-1.

The cultures were obtained from SRL broth for all the bacterial strains after 24 h of incubation at 37 ºC. *C. albicans* were maintained in dextrose broth after incubation at 25 ºC for 24 h, testing was carried out in dextrose broth at pH 7.4 and the two fold serial dilution technique was applied. A set of tubes containing only inoculated broth was used as controls. For the antibacterial assay after incubation at 37 ºC for 24 h and after incubation for 48 h at 25 ºC for the antifungal assay, the last tube with no growth of microorganism and/or yeast was recorded to represent the minimum inhibitory concentrations expressed in ppm. Every experiment in the antibacterial and antifungal assays was replicated twice and the data is given in Table-2.

TABLE-1
ANTIBACTERIAL ACTIVITY OF TRANSITION METAL COMPLEXES AGAINST S. *aureus* 25923 AND S. *aureus* 3160

Compounds	Time (h)	*S. aureus* (ATCC 25923)		S. aureus (ATCC 3160)	
		500 ppm Inhibition zone	1000 ppm Inhibition zone	500 ppm Inhibition zone	1000 ppm Inhibition zone
I	24	18.6	20.7	13.8	17.7
	48	18.3	20.3	13.5	17.1
II	24	18.8	20.7	13.9	17.9
	48	18.5	20.1	13.5	17.4
III	24	18.9	20.9	13.5	17.6
	48	18.5	20.4	13.1	17.2
IV	24	18.1	20.3	-	-
	48	18.5	20.4	-	-
DMSO	24	22.4	22.2	21.1	21.2
Gentamycin	48	22.4	22.2	21.1	21.2
(100 ppm)	24	21.1	21.2	22.1	22.2
	48	21.1	21.2	22.1	22.2

TABLE-2
ANTIFUNGAL ACTIVITIES OF NEWLY SYNTHESIZED TRANSITION METAL COMPLEXES AGAINST *S. cereviscae 227* AND *C albicans 361*

Compounds	Time (h)	*C. albicans* (MTT 227)		*S. cereviscae* (MTT 361)	
		500 ppm Inhibition zone	1000 ppm Inhibition zone	500 ppm Inhibition zone	1000 ppm Inhibition zone
I	24	4.7	7.8	6.3	7.4
	48	4.7	7.9	6.5	7.6
II	24	4.2	7.7	6.4	7.6
	48	4.6	7.8	6.6	7.7
III	24	4.3	7.3	6.2	7.4
	48	4.5	7.5	6.5	7.5
IV	24	4.2	7.6	-	-
Amphotericin-B	48	4.5	7.8	-	-
In DMSO	24	15.5	23.4	14.2	22.2
100 ppm	48	15.5	23.4	14.2	22.2

Conclusion

In the present investigations, all the complexes are found to be mononuclear obtained for Cu(II), Mn(II), Co(II) and Ni(II), ions in presence of ligand. An octahedral geometry was suggested for all the complexes, except the Cu(II) ones. All the investigated compounds showed less to good activity against *S. aureus*.

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