

STUDIES OF SOME MORPHOLINO- AND METHYLPIPERAZIN-1-YL MANNICH LIGANDS AND THEIR Cu(II) AND Ni(II) COMPLEXES.

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ABSTRACT

The Mannich bases 5-methyl[2-morpholinomethyl]phenol (PA1), 4-methyl[2-morpholinomethyl]phenol (PA2), 5-methyl-2-[[4-methylpiperazin-1-yl]methyl]phenol (PA3) and 4-methyl-2-[[4-methylpiperazin-1-yl]methyl]phenol (PA4) were synthesized by the condensation of m-,p-methylphenols, morpholine and N-methylpiperazine and complexed with metals. The ligands and metal complexes were characterized by IR, ¹H NMR, ¹³C NMR and UV spectroscopy. Complexes of these ligands of general formulae M(PAx)_nX₂ (M = Cu(II), Ni(II); n=2) were reported. Modes of bonding and overall geometry of the complexes were determined through physico-chemical and spectroscopic methods. These studies revealed both octahedral and four-coordinate geometries for the metal complexes.

Keywords: Mannich reaction, Morpholine, N-methylpiperazine

INTRODUCTION

Studies of Mannich base complexes have grown over the years due to the selectivity and sensitivity of the ligands to various metal ions. Several media have been reported to operate for the reaction including acidic, basic and neutral media (Syamala, 2009). In practice, phenols can serve as substrate for Mannich reaction to obtain aminomethylate by treatment with formaldehyde and amines or nitrogen heterocyclic compounds (Peng-Gao *et al.*, 2005)

Ketonic Mannich bases (e.g. from acetophenone) for example are of considerable importance as intermediates in the synthesis of condensed heterocyclic systems (Roman *et al.*, 2002). Mannich bases have demonstrated great antimicrobial, antitumor, cytotoxic and anti-corrosion properties according to several studies (Muthumani *et al.*, 2010).

This research was carried out to examine the influence of meta- and para-substitution on properties like stretching frequency of some characteristic bands and yield. The synthesis using one-pot process involving condensation of meta- and para-methylphenols, morpholine/N-methylpiperazine and formaldehyde and spectroscopic properties of the ligand and its metal complexes are reported.

MATERIALS AND METHODS

All reagents were obtained commercially (Aldrich) and used without further purification. IR spectra were recorded as KBr disc using Shimadzu FTIR spectrophotometer in the range (4000 – 250) cm⁻¹. NMR spectra (¹H, ¹³C NMR) were acquired in DMSO using Bruker AMX400 MHz spectrometer with tetramethylsilane (TMS) as an internal standard for ¹H. Percentage metal composition of the complexes was determined through complexometric titration using EDTA and murexide indicator. Electronic spectra were recorded for the solutions of the synthesized compounds in DMSO on a Perkin Elmer UV-Vis spectrophotometer model Lambda 25.

Preparation of 5-methyl-2-(morpholinomethyl)phenol (PA1)

The mixture of 3-methylphenol (10 ml, 0.096 mol), morpholine (8.3 ml, 0.096 mol) and formaldehyde (8 ml, 0.192 mol) in 50 ml of methanol was stirred and refluxed for 12 hours. A further 4 ml of formaldehyde was added after 6 hours to ensure that the reaction is taken to completion. A viscous liquid separated from the reaction mixture on standing for about 48 hours. This was extracted with chloroform. The crude compound was purified by column chromatography using chloroform: methanol (9:1) and a red viscous liquid was collected and the yield was 14.86 g (75 %). The ¹H NMR (δ ppm in

CDCl₃) showed the following: (**CH₃-Ar**, 2.26; s), (**CH₂** morpholine 3.71, 2.52; t), (**CH₂-N**, 3.63; s) and (aromatic protons, 6.83 – 6.60; m) while the ¹³C (δ ppm in CDCl₃) were assigned as follows: 20.93 (**CH₃-Ar**), 52.65, 66.53 (**CH₂**, morpholine) 61.31(**CH₂-N**) and 116.50 – 157.08 (aromatic carbons). λ_{max}(nm) in DMSO: 278nm. All other ligands were similarly prepared as above.

4-methyl-2-(morpholinomethyl)phenol (PA2)

The yield was 1.36 g (57 %). The ¹H NMR (δ ppm in CDCl₃) were assigned as follows: (**CH₃-Ar**, 2.26; s), (**CH₂** morpholine, 3.56, 2.54; t), (**CH₂-N**, 3.62; s) and (aromatic protons, 6.93 – 6.67; m) while the ¹³C (δ ppm in CDCl₃) were assigned as follows: 20.20 (**CH₃-Ar**), 52.18, 61.10 (**CH₂**, morpholine), 58.57(**CH₂-N**) 115.57 – 155.06 (aromatic carbons). λ_{max}(nm) in DMSO: 276nm.

5-methyl-2-((piperazin-1-yl)methyl)phenol (PA3)

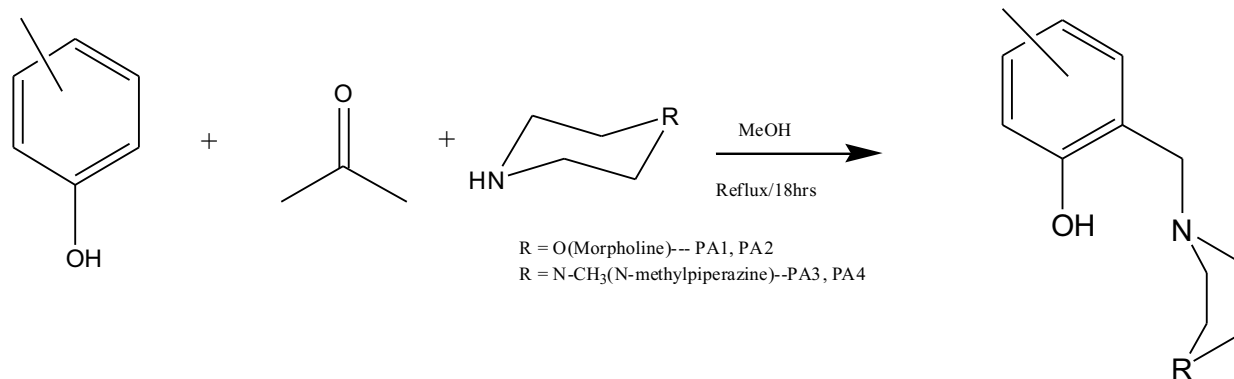
The yield was 15.13 g (72 %). The ¹H NMR (δ

ppm in CDCl₃) were assigned as (**CH₃-N**, 2.22; s), (**CH₃-Ar**, 2.52; s), (**CH₂N**-methylpiperazine 3.50, 2.52; t), (**CH₂-N**, 3.71; s) and (aromatic protons, 6.99 – 6.57; m), while the ¹³C (δ ppm in CDCl₃) are 20.17 (**CH₃-Ar**), 52.69, 66.52 (**CH₂N**-methylpiperazine), 59.11(**CH₂-N**), 61.59 (**CH₃-N**) 114.99 – 154.86 (aromatic carbons). λ_{max}(nm) in DMSO: 278nm.

4-methyl-2-((piperazin-1-yl)methyl)phenol (PA4)

The yield was 11.15 g (53 %) and the ¹H NMR (δ ppm in CDCl₃) were assigned as: (**CH₃-N**, 2.23; s), (**CH₃-Ar**, 2.53; s), (**CH₂N**-methylpiperazine 3.63, 2.52; t), (**CH₂-N**, 3.73; s) and (aromatic protons, 6.96 – 6.70; m) and the ¹³C (δ ppm in CDCl₃) are 20.20 (**CH₃-Ar**), 52.72, 66.56 (**CH₂** N-methylpiperazine), 59.11(**CH₂-N**), 61.59 (**CH₃-N**), 115.01 – 154.87 (aromatic carbons). λ_{max}(nm) in DMSO: 278nm.

The synthesis of the ligands is summarized in scheme 1 below:



Scheme 1. Synthesis of Ligands

Synthesis of the Metal Complexes

A solution of the appropriate Mannich base (10 mmol) in methanol was stirred for 10 minutes and methanolic solution of the appropriate metal acetate (5 mmol) was then added. The resulting mixture was refluxed for 4 hours, resulting in the formation of a solid mass which was recrystallized from acetonitrile. The % metal composition, colours and yield of the complexes are given in Table 1. The proposed structures of the complexes are given in Scheme 2. The IR spectroscopic data of the ligands and metal complexes are summarized in Table 2. Table 3

contains the UV-Vis spectrum data of the metal complexes recorded in DMSO.

RESULTS AND DISCUSSION

Physical Properties

All the complexes were stable at room temperature and were non-hygroscopic. On heating, they decompose at moderately high temperatures (> 150°C). The complexes were insoluble in diethyl ether, but soluble in DMF and DMSO while demonstrating varying degree of solubility in water, ethanol and chloroform.

The Mannich bases PA1, PA2, PA3 and PA4 were obtained in good yields (53 – 75 %). The Mannich bases were characterized by IR and ^1H , ^{13}C spectroscopy. The IR spectra of the free Mannich bases showed characteristic bands due to $\nu(\text{C}=\text{C})$, $\nu(\text{C}=\text{O})$ and $\nu(\text{N}-\text{H})$ functional groups. The ^1H and ^{13}C NMR spectra of the Mannich bases showed the expected signals.

Table 1: Colour, (%) Yield, Melting Points, °C and % Metal Composition

Compounds	Colour	Yield (%)	Melting point (°C)	Found (Calcd) (%)
$\text{Cu}(\text{PA1})_2\text{X}_2$	Green	60	196	10.49 (10.66)
$\text{Cu}(\text{PA2})_2\text{X}_2$	Light green	63	152	10.57 (10.66)
$\text{Cu}(\text{PA3})_2\text{X}_2$	Dark green	56	201	10.18 (10.22)
$\text{Cu}(\text{PA4})_2\text{X}_2$	Brown	54	220	10.16 (10.22)
$\text{Ni}(\text{PA1})_2\text{X}_2$	Green	42	>300	10.00 (9.94)
$\text{Ni}(\text{PA3})_2\text{X}_2$	Light brown	48	>300	9.60 (9.52)
$\text{Ni}(\text{PA4})_2\text{X}_2$	Green	47	292	9.75 (9.52)

Table 2: IR Wavenumbers (cm^{-1}) of the Compounds

Compound	$\nu_{\text{O-H}}$	$\nu_{\text{C=C}}$	$\nu_{\text{C-N-C}}$	$\nu_{\text{C-O-C}}$	$\nu_{\text{M-O}}$	$\nu_{\text{M-N}}$
PA1	3567	1584, 1456	1275	1119		
$\text{Cu}(\text{PA1})_2\text{X}_2$	3457(b)	1570, 1456 (s)	1161 (w)	1115 (s)	617 (w)	473 (w)
$\text{Ni}(\text{PA1})_2\text{X}_2$	3476 (b)	1541, 1420 (s)	1057 (w)	1119 (s)	625 (w)	473 (w)
PA2	3392	1600, 1456	1258	1119		
$\text{Cu}(\text{PA2})_2\text{X}_2$	3210 (b)	1568, 1427 (s)	1227 (w)	1119 (s)	610 (w)	517 (w)
PA3	3443	1587, 1458	1248, 1285	-----		
$\text{Cu}(\text{PA3})_2\text{X}_2$	3422 (b)	1576, 1458 (s)	1182, 1223 (w)	-----	517 (w)	457 (w)
$\text{Ni}(\text{PA3})_2\text{X}_2$	3385 (b)	1559, 1458 (s)	1150, 1246 (w)	-----	517 (w)	461 (w)
PA4	3567	1590, 1458	1258, 1285			
$\text{Cu}(\text{PA4})_2\text{X}_2$	3364 (b)	1559, 1466(s)	1146, 1182 (w)	-----	577 (w)	457 (w)
$\text{Ni}(\text{PA4})_2\text{X}_2$	3385 (b)	1559, 1456 (s)	1140, 1161 (w)	-----	571 (w)	451 (w)

s: strong, w: weak, and b: broad

Table 3: Electronic Spectral Data (cm^{-1}) of Metal Complexes

Compound	Intraligand / Charge transfer transitions (cm^{-1})	d-d transitions (cm^{-1})
$\text{Cu}(\text{PA1})_2\text{X}_2$	33557, 20000 (sh)	13774
$\text{Cu}(\text{PA2})_2\text{X}_2$	32468, 20408	13908
$\text{Cu}(\text{PA3})_2\text{X}_2$	34483, 21459 (sh)	10341
$\text{Cu}(\text{PA4})_2\text{X}_2$	34483, 26316	10132
$\text{Ni}(\text{PA1})_2\text{X}_2$	34843, 29240, 24631	14556, 11223
$\text{Ni}(\text{PA3})_2\text{X}_2$	32895, 24631	10060, 11274
$\text{Ni}(\text{PA4})_2\text{X}_2$	34247, 24570	14388, 13228

sh: shoulder

The IR Spectra of the Metal Complexes

The IR spectra provided valuable information regarding the nature of functional groups attached to the metal atom. In order to study the bonding mode of Mannich bases to the metal complexes, the IR spectra of the free ligands were compared with the spectra of the complexes. The main IR bands and their assignments are listed in Table 2 (Mounika *et al.*, 2010).

In PA1 and PA2 complexes, coordination via the phenolic OH and the N-atom of the morpholine moiety was indicated by the decrease in the frequencies assigned to these bands compared to those of the free ligands. The bands assigned to $\nu(\text{C-O-C})$ in the ligands remained unchanged in the metal complexes and this showed that morpholine acted as a monodentate ligand coordinating only through the N-atom while the N-methylpiperazine acted as a bidentate ligand as evident by the decrease in the $\nu(\text{C-N-C})$ of the ligands containing the moiety upon coordination (Bharathi *et al.*, 2009).

Also, the complexes of ligands PA3 and PA4 showed reduced frequencies for $\nu(\text{C-N})$ and $\nu(\text{O-H})$ bands compared to those of the free ligands. This was also an evidence of the coordination of these groups.

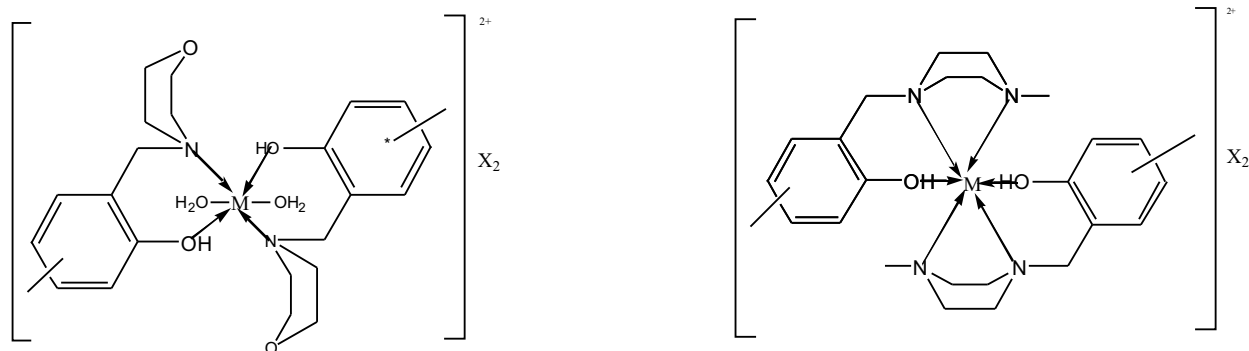
The spectra of the complexes also exhibited bands around 625–517 and 517–451 cm^{-1} which could be assigned to the $\nu(\text{M-O})$ and $\nu(\text{M-N})$ vibration modes, respectively (Raman *et al.*, 2004). Due to the larger dipole moment change for the M–O

bond compared to the M–N bond, the $\nu(\text{M-O})$ band usually appeared a higher wavenumbers than the $\nu(\text{M-N})$ band (Chkaku and Nakamoto, 1971; Nakamoto, 1996).

The Electronic Spectra of the Metal Complexes

The electronic spectra of the ligands and metal complexes were recorded in DMSO. There was a shift in the absorption bands (35971 – 36232 cm^{-1}) observed in spectrum of the free ligand to lower frequencies due to the coordination of the ligand with metal ions (El-Behery and El-Twigry, 2007). Copper complexes containing morpholine moiety had observed transitions at higher wavenumbers than those containing N-methylpiperazine which could be attributed to the more electronegative nature of oxygen than nitrogen. The metal based d-d transitions for the copper conjugates were observed in the region (10132 – 13908 cm^{-1}) characteristics of square-planar / octahedral geometry with dx^2-y^2 ground state.

The electronic spectrum of Nickel complex of PA1 showed absorption bands at 11223 and 14556 cm^{-1} which were characteristic of Ni^{2+} assigned to $\rightarrow^3A_{2g} \rightarrow ^3T_{1g}$, $^3A_{2g} \rightarrow ^3T_{1g}(\text{P})$ in an octahedral environment. While the electronic spectrum of the Nickel complexes of PA3 and PA4 showed two absorption bands at 10060 – 14556 cm^{-1} assigned to $\rightarrow^3A_{2g} \rightarrow ^3T_{2g}$, $^3A_{2g} \rightarrow ^3T_{1g}$ which are characteristic of octahedral Ni^{2+} (Higgs and Carrano, 1997).



Scheme 2: Proposed octahedral structure of metal complexes, where M = Cu and Ni

CONCLUSION

All the Cu(II) and Ni(II) complexes were synthesized except the Ni(II) complex of 4-methyl[-2-morpholinomethyl]phenol which tended to dissociate into the starting materials during isolation. This observation could mean that the complex was thermodynamically unstable or that other pathways should be utilized to bring about the formation of the complex. Results from IR studies, % metal determination and UV spectroscopy suggested a metal: ligand ratio of 1:2 and octahedral structures for all the metal complexes.

In this study, it was discovered that the metal ions of interest were capable of forming stable and high-melting point complexes with the Mannich ligands. From the results obtained for coordination abilities of the Mannich ligands, the conclusion that the position of substitution (meta- or para-) of the methyl group on the aromatic ring of the Mannich ligands/bases had no orderly effect on properties like UV-Vis absorption, position of prominent IR bands (particularly O-H) and other physical properties of the Mannich bases and their metal complexes obtained could be drawn. The differences observed in the metal complexes have been shown to be due to the nature of the heteroatom of the Mannich bases.

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