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Synthesis, Structure and Antimicrobial Studies of the Mannich Base N-(Dicyclohexylamino) (Phenyl) Methyl benzamide and its Metal Complexes

A.BALAKRISHNAN[1], **A.SANKAR**[2]*, **V.NANDINI**[3]
[1]Assistant Professor, PG & Research Department of Chemistry, Govt Arts College, Dharmapuri, Tamilnadu, India
[2]Assistant Professor, PG & Research Department of Chemistry, Kandaswami Kandars College, P.Velur, Tamilnadu, India
[3]PG & Research Department of Chemistry, Govt Arts College, Dharmapuri, Tamilnadu, India.
***Corresponding Author E-Mail:** sankbala16@gmail.com
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Abstract

Mannich bases derived from Amides and aldehydes possess structural features, which confer on them potential biological activities and pharmaceutical applications. A novel Mannich base has been synthesized from benzamide and its transition metal complexes also were prepared. The Mannich base ligand was synthesized by using benzamide, benzaldehyde and dicyclohexylamine. The ligand as well as the metal complexes were characterized by various physical methods. The structure of the synthesized compounds are confirmed by UV, IR, and ^{1}H NMR spectroscopic techniques. The antibacterial activity of the ligand and the complexes were examined using different gram positive and gram negative bacterias by disc diffusion technique.

Key words: Mannich base, Benzamide, transition metal complex, and antibacterial study

Introduction

The field of coordination chemistry has grown from a readily defined and limited area into the most active research arena particularly in drug designing due to their applications in pharmaceutical chemistry. Mannich bases have been studied extensively in recent years , due to the selectivity of ligands towards various metal ions [1-3]. Mannich base complexes with transition metals can exhibit enhanced biological activities due to the presence of metal atoms or other variations of structural factors. Introduction of the metal ions play important role in metabolic activities of living organisms[4]. Brass chelates of Mannich bases having both oxygen and nitrogen as potential donors have been increased much interest in biochemistry because of their multipurpose use as antibacterial[5], anticancer[6], analgesic, anti-inflammatory[7], anticonvulsant[8], antimalarial[9], antiviral[10], antioxidant[11] and CNS depressant activities[12]. The widespread use of Mannich base metal complexes in biological field lies in the fact that the synthesis of Mannich base ligand introduces the basic future which can provide a molecule soluble in aqueous solvents and they can easily be transformed into a number of compounds. Many research articles are available in the literature for the synthesis of Mannich bases using indole[13,14], benzaldehyde and substituted benzaldehydes[15]. In view of all these, it has been decided to synthesize a new Mannich base by the condensation of benzaldehyde, benzamide and dicyclohexylamine.The so synthesized base is made to undergo complexation with first row transition metals.The characterization of the ligand as well as the metal complexes were done by various physico-chemical and spectral methods.They are all tested for their antimicrobial activity against certain selected bacterial species and the results are discussed in this article

Materials and Methods

General

All the reagents used for synthesizing the ligand and its complexes were of A.R. grade. The solvents used were commercial products of the highest available purity and were further purified by distillation. IR spectra were recorded using Perkin Elmer FT-IR spectrometer by using KBr pellets. Absorbance in UV-Visible region was recorded in DMF solution using UV-Visible spectrometer. The ^{1}H NMR of the ligand were recorded on a Bruker instrument employing TMS as internal reference and DMSO-d6 as solvent.

Synthesis of the ligand N-Dicyclohexylamino Phenyl Methyl Benzamide (DCAPMB)

0.05 mol of Benzamide , and 0.05 mol of Benzaldehyde are dissolved in 100 mL of ethanol and taken in a 250mL RB flask. Then 0.05 mol of the Dicyclohexylamine dissolved in 50 mL ethanol added in small aliquots to the reaction mixture kept in icebath and the stirring was continued for about 3hrs. Then it is cooled in refrigerator for overnight. After cooling it for a night, the contents are refluxed for about 4 hrs, again kept in refrigerator. Next day, a turbidity was formed and the solvent was recovered from the mixture by distillation. Mannich base separates out as colourless precipitate. It is filtered and washed with hot water, recrystallised in alcohol and dried in air-oven at 60°C.The yield is found out to be about 72%.

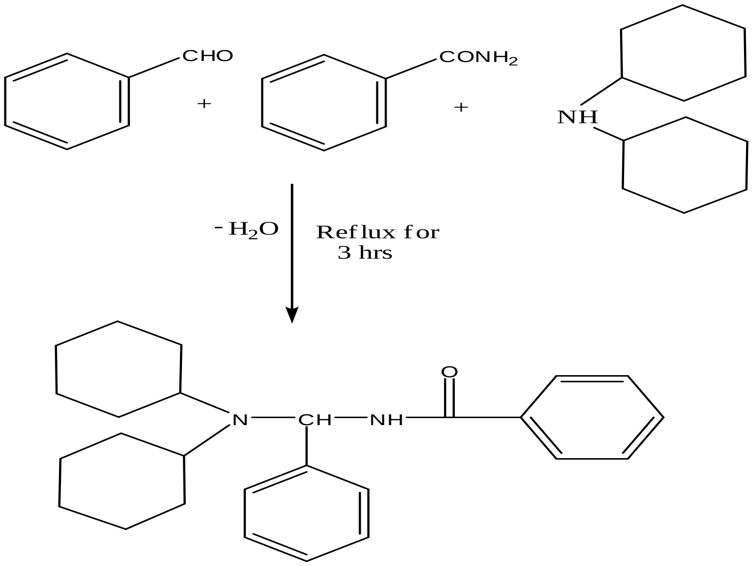


Fig.1: Reaction Scheme for the synthesis of the ligand

Synthesis of Metal complexes

0.01 mol of the ligand is dissolved in 10mL of ethanol taken in a 50mL RB flask and with this 0.01 mol of the metal chloride dissolved in 10mL of distilled water was added. Then the contents of the flask were refluxed for about 3 hrs. A characteristic coloured precipitate settles at the bottom. It was filtered, dried in air oven at 60˚C and recrystallised from alcohol.

Table 1: Physical data of the ligand and the complexes

Compund	Yield (%)	Colour	Mp (°C)
DCAPMB -Ligand	72	Colorless	247
DCAPMB -Co	71	Pale pink	210
DCAPMB -Ni	67	Pale green	214
DCAPMB -Cu	78	Pale blue	236

Antibacterial activity

For the antibacterial study, nutrient agar was used as the medium. The ligand as well as the complexes were screened for antibacterial activity against certain pathogenic bacteria by disc diffusion method at concentration of 10µg / ml in DMSO using *Bascillus subtilis, Staphaylococcus aureus, Escherichia coli and Pseudomonas aeruginosaa.*The paper disc containing the compound (10, 20 and 30 µg/disc) was placed on the surface of the nutrient agar plate previously spread with 0.1 mL of sterilized culture of microorganism. After incubating this at 37^{o}C for 24 hrs, the diameter of inhibition zone around the paper disc was measured.

The zone of inhibition was measured in mm and the activity was compared with Gentamycin in 1 µg / disc A comparison of the diameters of inhibition zones of the compounds investigated shows that Cu(II) complex exhibit highest antibacterial activity against all the bacterial species studied .The results are tabulated in Table.2.

Table 2: Antibacterial activity

Samples	*Escherichia coli* (mm)	*Staphylococcus aureus* (mm)	*Bacillus subtilis* (mm)	*Pseudomonas aeruginosaa* (mm)
Ligand (50µl)	1.90±0.13	1.50±0.10	1.20±0.08	1.00±0.07
Co Complex(50µl)	0.70±0.04	0.60±0.04	0.20±0.01	0.40±0.02
Ni Complex (50µl)	1.00±0.07	0.80±0.05	0.30±0.02	0.50±0.03
Cu Complex (50µl)	4.10±0.28	2.30±0.16	2.10±0.14	3.10±0.21
Standard (30µl)	9.20±0.64	9.00±0.63	8.10±0.56	8.90±0.62
Control (Solvent) (30µl)	0	0	0	0

Result and Discussion

^{1}H NMR spectra

The signals observed in the ^{1}H NMR spectra of the Mannich base under study are shown in Fig.2. The signals between 1.0-1..2 ppm corresponds to the hydrogens of the cyclohexyl ring. The appearance of peak at 4.3 ppm indicates the methylene hydrogens attached to the nitrogen. Further, the formation of the ligand is ascertained by the disappearance of a signal corresponding to the –NH proton of secondary amine as it was eliminated in the Mannich reaction.

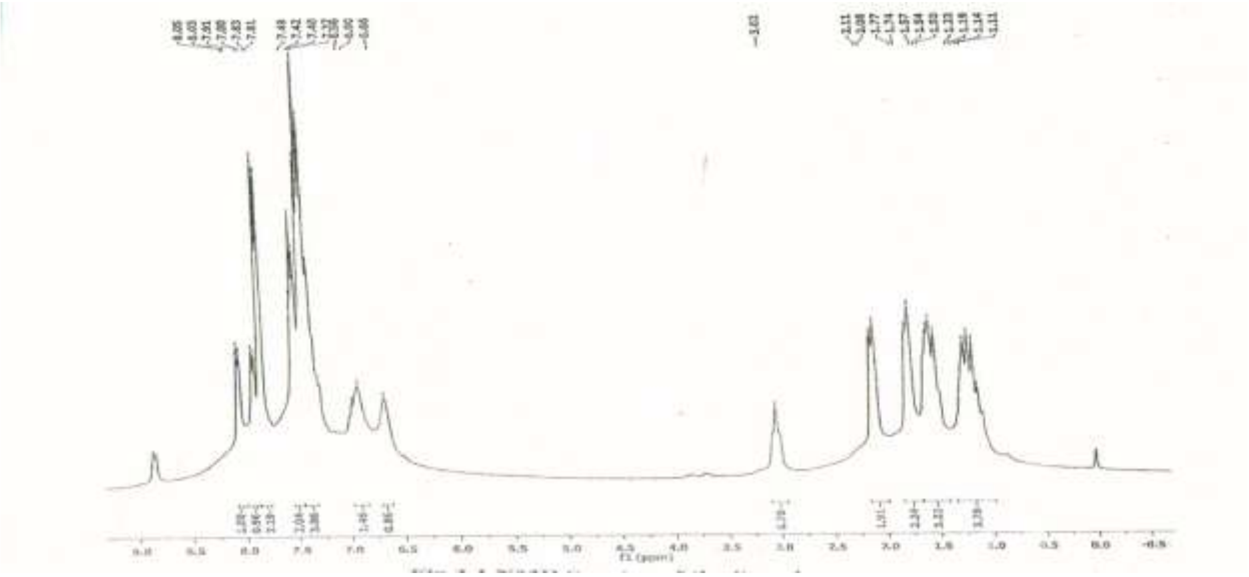


Fig. 2: 1H NMR spectra of the ligand

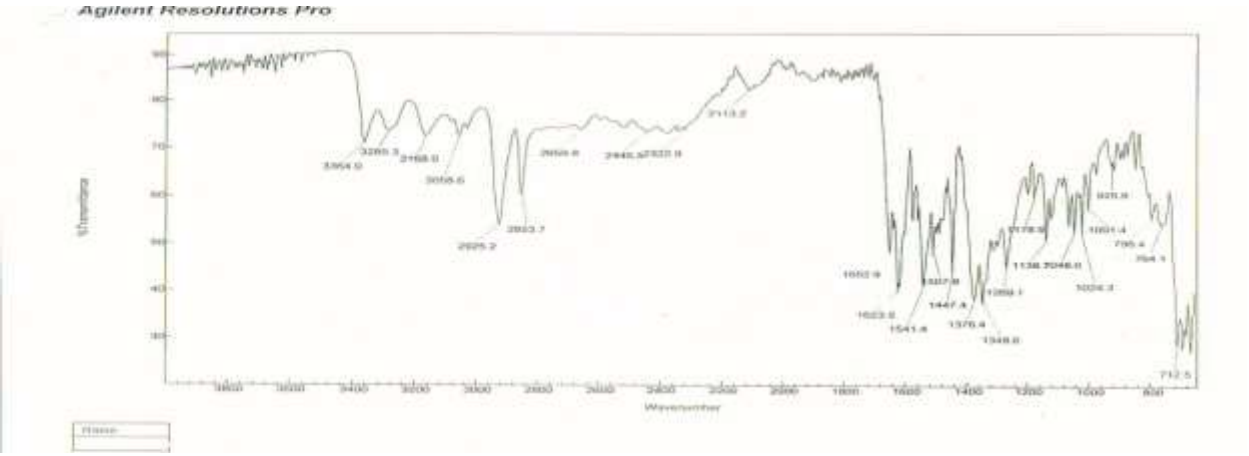


Fig 3: IR Spectra of the ligand

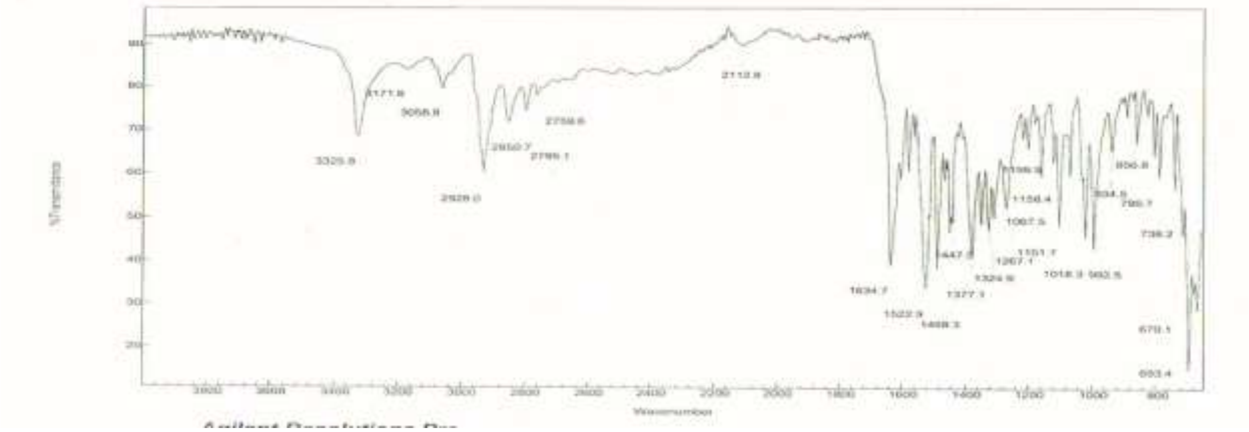


Fig 4: IR Spectra of the metal complex

Table 3: IR Spectral data of the ligand and the complexes

IR SIGNALS	INTERPRETATION
1652 cm^{-1}	>C=O bond
1178 cm^{-1}	–C–N-C stretching
1447 cm^{-1}	Angular deformation of C-H
2925 cm^{-1}	Ring –C-H stretching

The important observation is the presence of an intense band at ~ 1652 cm^{-1} which is due to νC=O carbonyl group. The most notable change in the IR spectra is the disappearance of the – NH stretching vibration and appearance of an intense band at 1178 cm^{-1} due to νC-N-C stretching which is formed due to the aminomethylation. The absence of band at 3300 cm^{-1} due to amino -NH disappears implying its condensation after deprotonation. These results confirms the formation of the Mannich base.
. In all the complexes, band due to νC=O and νC-N shifted towards lower frequency clearly indicating the nitrogen and carbonyl oxygen are involved in coordination with metal ions. Further, the appearance of new bands around 760cm^{-1} corresponding to M-O bond and a signal around 660 cm^{-1} corresponding to M-Nbond confirms the formation of the metal complex.

3.3 UV-Visible spectra

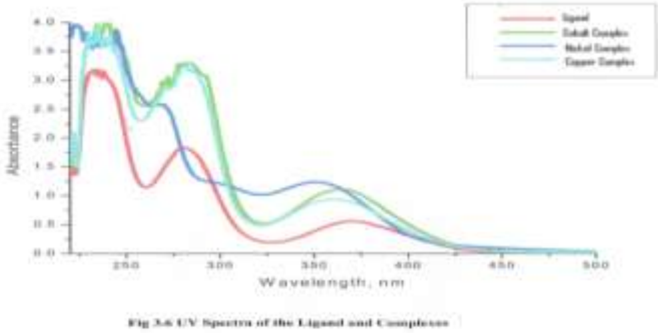
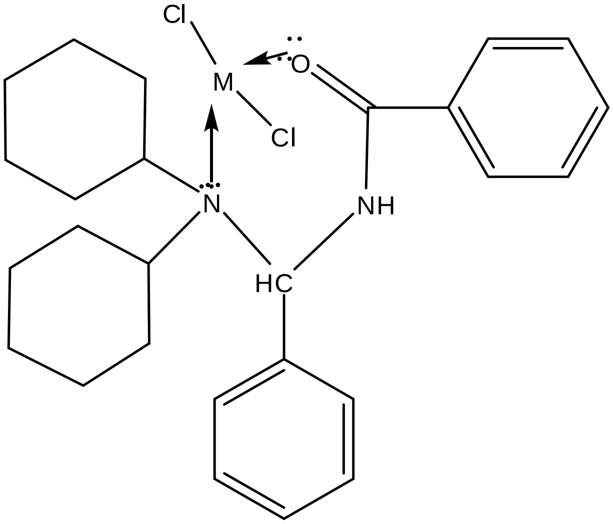


Fig 5: UV Spectra of the ligand and the metal complexes

The UV-Visible spectra of the complexes were recorded in the range of 200-1100 nm. In the case of the Cobalt complex, the signals at 6853 cm^{-1}, 14786 cm^{-1},and 18575 cm^{-1} corresponds to the transitions $^4T_{1g}$ (F) → $^4T_{2g}$(F), $^4T_{1g}$ (F) → $^4A_{2g}$ and $^4T_{1g}$ (F) → $^4T_{1g}$ (P) respectively. Further, the shoulder at 25120 cm-1 is due to charge transfer (Ligand → Metal). These observations confirms that the so formed cobalt complex have octahedral geometry. For Nickel complex, the signals at 7124 cm^{-1}, 15224 cm^{-1},and 18487 cm^{-1} corresponds to the transitions $^3T_{1g}$ (F) → $^3T_{2g}$(F), $^3T_{1g}$ (F) → $^3A_{2g}$, and $^3T_{1g}$ (F) → $^3T_{1g}$ (P) respectively. Further, the shoulder at 24140 cm-1 is due to charge transfer (Ligand → Metal). These observations confirms that the so formed nickel complex have tetrahedral geometry.The UV spectra of Copper complex shows bands at 9230 cm^{-1}, 9578 cm^{-1} due to the transitions $^2B_{1g}$ → $^2A_{1g}$, and $^2B_{1g}$ → $^2A_{2g}$ respectively and at 10430 cm-1 due to $^2B_{1g}$ → $^2B_{2g}$ .the band at 24675 cm-1 is dueto charge transfer (Ligand → Metal). These observations confirms that the so formed copper complex have octahedral geometry. Likewise, in the Cobalt complex too, same observations are made.

Based on the foregoing observations from the NMR spectral data and the IR spectral data of both the ligand and the metal complexes, the structure of the so formed complexes can be concluded as given below.



Where M- Cu, Co or Ni

Antimicrobial activity

The ligand as well as the complexes were screened for antibacterial activity against certain pathogenic bacteria by disc diffusion method at concentration of 10µg / ml in DMSO using *Bascillus subtilis, Staphaylococcus aureus, Escherichia coli and Pseudomonas aeruginosaa.*The zone of inhibition was measured in mm and the activity was compared with Gentamycin in 1 µg / disc.The results showed that the chelating tends to make the ligand act as more potent bactericidal agents,thus destroying more bacteria than the free ligand. Such increased activity of metal chelates can be explained on the basis of overtone concept and chelation theory. According to the overtone concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid-soluble materials in which liposolubility is an important factor that controls the anti microbial activity. On chelation it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of complexes. This lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding sites in enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism.

Conclusion

A new Mannich base ligand has been syntesised using Succinimide and made complexation with three transition metals. All the four compounds were characterized by physicochemical and spectroscopic methods.It has been observed that the ligand behaves as a bidentate chelating agent thro the N and O donor sites and the spectroscopic data is in support of our expected structure. The cobalt and copper complexes were of octahedral geometry whereas the nickel complex exhibits tetrahedral geometry.The antimicrobial property of the the ligand and the complexes were studied and found that complexes possess better antibacterial activity than that of the free ligand .

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