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Synthesis, Characterization and Biological Evaluation of Cobalt(II), Nickel(II) and Copper(II) Complexes of Schiff Base

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A new Schiff base ligand, 4-[{[4-(benzyloxy)phenyl]-imino} methyl]benzene-1,3-diol (bmbH), has been synthesized by the condensation reaction of *p*-benzyloxyaniline with 2,4-dihydroxybenzaldehyde in EtOH solution at boiling point. A mononuclear complexes of bmbH bidentate schiff base ligand with Co(II) acetate, Ni(II) acetate and Cu(II) acetate salts have been synthesized. All the complexes have been characterized by several techniques using elementel analyses conductivity measurements, IR and electronic spectral. ^{1}H NMR specrum of the bmbH ligand was also recorded. The mononuclear Co(II), Ni(II) and Cu(II) complexes of the Schiff base ligand, bmbH have a metal/ligand ratio of 1:2 and the ligand coordinates through the N and O atoms. The molar conductivities in DMF solution indicate non-electrolytic nature for the metal complexes. In addition, the ligand and its metal complexes were screened for antibacterial and antifungal activities by agar well diffusion techniques using DMF as solvent.

Key Words: Synthesis, Biological activiites, Spectroscopic techniques, Schiff base, Transition metal complexes.

INTRODUCTION

Schiff Bases derived from an amine and aldehyde are an important class of ligands that coordinate to metal ions *via* azomethine nitrogen and have been studied extensively[1-3]. Coordination compounds of Schiff bases with various transition metals have been investigated for their coordinating capability, pharmaceutical and biological activities[4-9]. These complexes are used as catalysts for water photolysis or for oxygen reduction at a modified carbon cathode[10,11]. Some compounds have been used for catalytic hydrogenation of unsaturated hydrocarbons[12]. Schiff bases have also been used for analytical purposes in the determination of metal ions, and some Schiff base derivatives have been used in the solvent extraction of metals[13,14]. Schiff bases offer versatile and flexible ligands capable of binding with metal cations to yield complexes, some of them have suitable properties for practical applications[15-17]. Previously, the synthesis and characterization of various transition metal complexes of novel bidentate compounds have been reported[18-26]. In this article, we reported the syntheses, complex formation, characterization using different techniques of 4-[{[4(benzyloxy)-phenyl]imino}methyl]benzene-1,3-diol, (bmbH) which was synthesized by the reaction of *p*-benzyloxyaniline with 2,4-dihydroxybenzaldehyde in EtOH solution at boiling point. The ligand may be represented as shown in Fig. 1. Its complexing ability with Co(II), Ni(II) and Cu(II) salts is also examined.

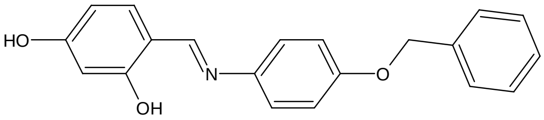


Fig. 1. Structure of 4-[{[4-(benzyloxy)phenyl]imino}methyl]benzene-1,3-diol

EXPERIMENTAL

$Co(OAc)_2.4H_2O$, $Cu(OAc)_2.H_2O$ (Merck) and $Ni(OAc)_2.4H_2O$ (Fluka) were used as purchased. 2,4-Dihydroxybenzaldehyde and *p*-benzyloxy-aniline were purchased from Merck. All solvents were reagent grade and used without further purification.

Infrared spectra were recorded on a Shimadzu FT-IR 8300 Spectrometer. The electronic absorbtion spectra of DMF solutions of the ligand and its complexes in the range 200-800 nm were measured on a Shimadzu UV-160A spectrometer. Elemental analyses for carbon, hydrogen and nitrogen and ^{1}H NMR spectrum of the ligand were determined at the Tubitak (Center of Science and Technology Research of Turkey). The melting points of the ligand and complexes were recorded in open capillaries in a capillary melting point appratus. In the study, *Klebsiella pneumoniae* 13883, *Micrococcus luteus* LA 2971, *Streptococcus faecalis, Enterobacter cloaca* ATCC 13047 and *Bacillus megaterium* DSM 32 bacteria and antifungal activity against *Candida albicans* CCM 314, *Kluyveromyces fragilis* DC 98 and *Rhodotorula rubra* fungi were used.

Preparation of Schiff base ligand

The Schiff base ligand were prepared by reacting *p*-benzyloxyaniline (1.393 g, 7 mmol) with 2,4-dihyrdroxybenzaldehyde (0.966 g, 7 mmol) in EtOH (100 mL) under reflux (4 h). The yellow solid compound was recovered by filtration, washed with EtOH and dried over anhydrous $CaCl_2$ under vacuum with 75% yield. The ligand is soluble in MeOH, EtOH and highly soluble in DMF. ^{1}H NMR (DMSO-d_6 δppm): 10.35 (s, 1 H, 2-O-H), 9.50 (s, 1 H, 4-OH), 8.65 (s, 1 H, CH=N), 7.75 (d, 2 H, Ar-H), 7.70 (d, 2 H, Ar-H), 7.60 (d, 2 H, Ar-H), 7.60 (d, 2 H, Ar-H) 7.45 (d, 2 H, Ar-H), 3.80 (s, 2 H, OCH_2-).

Preparation of metal complexes

The following general procedure was used. Ethanolic solution of acetates of Co(II), Ni(II) and Cu(II) were added to the hot ethanolic solution of the ligand in (1:2) molar ratio, which resulted in the precipitation of metal derivatives in all the cases. The product formed were filtered, washed with warm water, cold ethanol and finally with acetone and dried on water bath, then *in vaccuo*. The yield ranged from 65 and 80 %.

Biological studies

New Schiff base and its complexes (i) bmbH, (ii) $[Co(bmb)_2]$, (iii) $[Ni(bmb)_2]$ and (iv) $[Cu(bmb)_2]$ were evaluated for their *in vitro* antibacterial activity against *Klebsiella pneumoniae*, *Micrococcus luteus*, *Streptococcus faecalis*, *Enterobacter cloaca*, *Bacillus megaterium* and antifungal activity against *Candida albicans*, *Kluyveromyces marxianus* and *Rhodotorula rubra* by agar-well diffusion method. All the bacteria mentioned above were incubated at 30 ± 0.1ºC for 24 h by inoculation into Nutrient Broth (Difco), and the fungi studied were incubated in malt extract broth (Difco) for 48 h. Mueller Hinton agar (Oxoid), sterilized in a flask and cooled to 45-50ºC, was distributed in to sterilized Petri dishes having a diameter of 9 cm, by using pipettes in the amount of 15 cm^3 after injecting cultures of bacteria prepared as mentioned above and mold for 24 h in the amount of (10^5 bacteria per cm^3 and 10^3 fungi spores per cm^3) and providing the distribution of food medium in Petri dishes homogenously. By using a sterilised cork borer (11 mm diameter), wells were dug in the culture plates. Compounds dissolved in DMF were added (50 µL) to these wells. The compounds to be tested were dissolved in DMF to a final concentration of 1000 ppm. Petri dishes so obtained were placed at 4ºC for 2 h, plates inoculated with fungi were incubated at 25 ± 0.1ºC for 24 h. At the end of the period, values for the diameter of the inhibition zones for the growth of various microorganisms, created in response to treatment with the compounds. These studies works were performed in triplicate. Gentamicin (Bioanalyse) and nystatin (Oxoid) were used as a standards.

RESULTS AND DISCUSSION

The condensation of 2,4-dihydroxybenzaldehyde with *p*-benzyloxyaniline in boiling ethanol yields one Schiff base compound. The purity of the Schiff base and its complexes were assured by TLC techniques. The chemical equation concerning the formation of the metal complexes represented as follows:

$$M(OAc)_2 \cdot xH_2O \ + \ 2\ bmbH \longrightarrow [M(bmb)_2] \ + \ 2AcOH \ + \ xH_2O$$

[M = Co^{2+}, Ni^{2+} and Cu^{2}]

bmbH = 4-[{[4-(Benzyloxy)phenyl]imino}methyl]benzene-1,3-diol.

The elementel analyses data of the Schiff base compounds are given in Table-1. The molar conductance values of complexes measured in DMF at the concentration 10^{-3} M are in the range 6.15-11.5 $\Omega^{-1}cm^{2}\ mol^{-1}$, for all the Schiff base coordination compounds (Table-1). The low values of the molar conductance measured in DMF solution of the complexes indicate the non-electrolytic nature of the complexes.

TABLE-1
ANALYTICAL DATA AND PHYSICAL PROPERTIES OF THE SCHIFF BASE LIGAND AND ITS METAL COMPLEXES

Compound	m.f.	m.w.	Colour	m.p. (°C)	MC	Calcd (Found) %			λ_{max} (nm, in DMF)
						C	H	N	
bmbH	$C_{20}H_{17}NO_3$	319	Bright Yellow		–	75.24 (75.44)	5.33 (5.13)	4.39 (4.51)	391, 284
$[Co(bmb)_2]$	$C_{40}H_{32}N_2O_6Co$	699.5	Dark Brown	251	8.95	68.62 (68.47)	4.57 (4.74)	4.00 (4.17)	360, 346, 246
$[Ni(bmb)_2]$	$C_{40}H_{32}N_2O_6Ni$	694.7	Green-Yellow	225	6.15	69.09 (69.35)	4.61 (4.43)	4.03 (4.22)	364, 362, 248
$[Cu(bmb)_2]$	$C_{40}H_{32}N_2O_6Cu$	694.9	Black	279	11.5	69.07 (68.87)	4.60 (4.46)	4.03 (4.18)	601, 368, 347, 248, 228

MC = Molar conductivity ($\Omega^{-1}\ cm^{2}\ mol^{-1}$)

^{1}H NMR spectrum of the Schiff base ligand bmbH in DMSO-d_6 exhibits its singlet signals in the 10.35, 9.50 and 8.65 ppm which are attributed to the 2-OH, 4-OH and azomethine group (CH=N) protons, respectively[3,28]. The 2-OH and 4-OH signals disapeared upon addition of D_2O to the solution indicating that is an acidic proton. ^{1}H NMR spectrum of (1) bmbH resulted in peaks corresponding to the aromatic protons at 7.75, 7.70, 7.60, 7.45, 6.95, 6.80, 6.70 ppm as singlet or doublets[28]. The spectrum of the bmbH showed singlet signals at 3.80 ppm due to hydrogens of the methylene group of the Schiff base.

Infrared spectral data of the ligand bmbH and its metal complexes are listed in Table-2. Since there are no (C=O) and $-NH_2$ absorptions in the IR spectra of bmbH ligand, this peak indicates the formation of the expected compound. The strong band observed at 3382 cm^{-1} for the ligand can be attributed to the -OH group vibration[28]. Aromatic C-H and aliphatic C-H bands occured at 3059 and 2934 cm^{-1}, respectively. The ligand exhibits broad medium intensity bands in the 2700-2550 cm^{-1} range, which are assigned to the intramolecular hydrogen-bonding O-H···N vibration. This situation is common for aromatic azomethine compounds containing *o*-OH groups and in the complexes this bands disappear completely[29]. The azomethine group (CH=N) vibration of the free ligand occurs at 1626 cm^{-1} as a strong band. This band was not observed at the same frequency in the spectra of all the compexes. It shifted to lower frequency region indicating coordination of Schiff base through azomethine nitrogen[24]. The bands at 1242 and 1168 cm^{-1} in spectrum of the bmbH correspond to the asymetric and symetric stretching of the ether group, respectively. Conclusive evidence of the banding is also shown by the observation that new bands in the spectra of the coordination compounds appear at 570-534 and 484-424 cm^{-1} range assigned to ν(M-O) and ν(M-N) bands stretching vibrations which are not observed in the spectra of the Schiff base ligand[30].

TABLE-2
CHARACTERISTIC IR BANDS (cm^{-1}) OF THE SCHIFF BASE LIGAND AND ITS METAL COMPLEXES

Compound	ν(OH)	ν(ArC-H)	ν(R-C-H)	ν(CH=N)	ν(R-O-C)	ν(R-O-C)	ν(M-O)	ν(M-N)
bmbH	3382 vs	3059 m	2934-2877 m	1626 s	1242 m	1168 w	-	-
$[Ni(bmb)_2]$	3377 s	3034 m	2930-2876 m	1611 s	1240 m	1180 w	570 w	424 w
$[Co(bmb)_2]$	3421 s	3034 m	2928-2877 m	1607 s	1236 m	1172 w	619 w	453 w
$[Cu(bmb)_2]$	3363 s	3036 m	2930-2878 m	1614 s	1202 m	1186 m	534 w	484 m

The electronic spectra (Table-1) of the Schiff base and its metal complexes were measured in DMF at room temperature. The Schiff base ligand is characterized mainly by two absorption bands in the region 275-400 nm. The bands at 391 nm was assigned to the imine $n\rightarrow\pi^*$ transition in the oxybenzyl linked dihydroxy Schiff base ligand, bmbH[24]. The second band located at 284 nm can be assigned to the moderate energy $\pi\rightarrow\pi^*$ transition of the aromatic ring[3]. The peaks belonging to the azomethine in the spectra of the $[Ni(bmb)_2]$, $[Co(bmb)_2]$ and $[Cu(bmb)_2]$ coordination compounds at 362, 346 and 347 nm, respectively.

Biological activity

The antibacterial activity of bmbH and its metal complexes was tested by using agar-well diffusion method[13,32]. The antibacterial and antifungal activities of the compounds against five bacteria namely *Klebsiella pneumoniae*, *Micrococcus luteus*, *Streptococcus faecalis*, *Enterobacter cloaca*, *Bacillus megaterium* and three fungi namely *Candida albicans*, *Kluyveromyces marxianus* and *Rhodotorula rubra* are presented in Table-3.

The results showed that all of the compounds exhibit moderate activity against all species of bacteria. The Schiff base ligand has the highest effect against *Enterobacter cloaca* bacteria in comparison to other five bacteria. The results indicate that the complexes show more activity and the ligand have low activity against same microbes under identical experimental conditions. This would suggest that the chelation could facilitate the ability of a complex to cross a cell membrane and can be explained by Tweedy's chelation theory[31]. Ni(II) complex of the Schiff base ligand showed high effect against fungi especially *Rhodotorula rubra* fungi. The variation in the activity of different complexes against different microorganisms depends either on the impermeability of the cells of the microbes or differences in ribosomes in microbial cells[23,32].

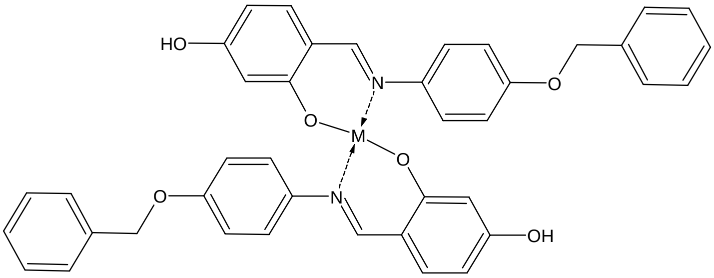
TABLE-3
ANTIMICROBIAL STUDIES OF bmbH AND ITS METAL COMPLEXES
(CONCENTRATION: 1000 ppm; 50 µL/well)

Compound	Diameter of inhibition zone (mm)							
	K. p	*M. l*	*S. f*	*E. c*	*B. m*	*C. a*	*K. m*	*R. r*
bmbH	16	15	17	20	13	14	13	13
$[Ni(bmb)_2]$	16	17	14	16	17	20	18	24
$[Co(bmb)_2]$	12	13	15	15	15	17	17	17
$[Cu(bmb)_2]$	13	13	13	14	14	16	17	16

K. p = Klebsiella pneumoniae, M. l = Micrococcus luteus, S. f = Streptococcus faecalis, E. c = Enterobacter cloaca, B. m = Bacillus megaterium, C. a = Candida albicans, K. m = Kluyveromyces marxianus, R. r = Rhodotorula rubra

Conclusion

In this work, a Schiff base ligand, 4-[{[4-(benzyloxy)phenyl]imino}-methyl]benzene-1,3-diol, derived from *p*-benzyloxyaniline with 2,4-dihydroxybenzaldehyde and its some transition metal complexes is reported. The satisfactory analytical data and the spectroscopic studies presented above suggest that the complexes are of the general formula $[M(bmb)_2]$ (M = Co^{2+}, Ni^{2+} or Cu^{2+}). According to the UV-vis and IR data oxybenzyl linked Schiff base ligand coordinated to the metal ion through the phenolic oxygen and the imino nitrogen. Based on the above results, the structure of the coordination compounds under investigation can be formulated as Fig. 2.



M = Co^{2+}, Ni^{2+} or Cu^{2+}

Fig. 2. Proposed structure of the metal complexes of 4-[{[4-(benzyloxy)phenyl]imino}methyl]benzene-1,3-diol

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