Synthesis, Spectral Characterization, and Antibacterial Activity of Some New Azomethine-Metal Complexes Derived from Vanillin

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Abstract: Synthesis and characterization of Schiff base with solid metal complexes derived from Vanillin and 2-amino-2-ethyl-1, 3-propanediol (VAEPD) has been carried out. Structural elucidation of the Schiff base and its metal complexes [Cu(II) and Co(II)] were analyzed on the basis of various spectra like IR, electronic absorption spectra, NMR, ESR, TG-DTA and magnetic moments. From the spectral study, monomeric structures of the complexes showed a six-cordinated metal center moiety with an octahedral geometry. In addition the metal complexes were screened for antibacterial activities and the metal complexes showed moderate activity against the organisms *Escherichia coli* (E.C), *Bacillus subtilis* (B.S) and Enterobacter aerogenes.

Keywords: Schiff bases, metal complexes, characterization, antibacterial activity, spectral studies.

1. INTRODUCTION

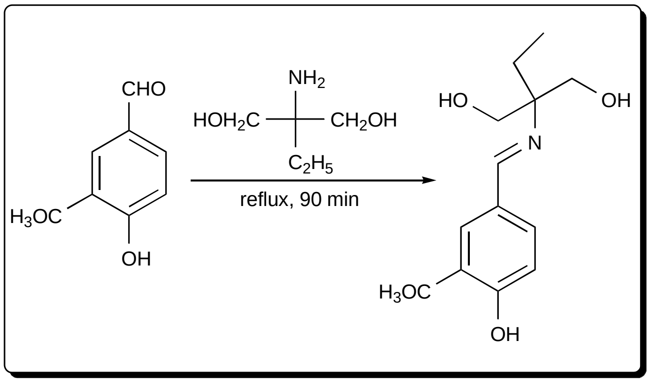
Schiff bases come under the important class of organic compounds containing characteristic group like >C=N. As they contain basic site namely >C=N, they can exhibit spectacular application in many important fields of interest. Schiff bases or azomethines and their metal complexes are known to be biologically important [1, 2] and of interest in the catalysis [3] of various chemical and photochemical reactions. Schiff bases containing polyfunctional groups have produced stable metal complexes of transition metal ions [4, 5]. The azomethine metal complexes were used as anticancer [6], as proteasome inhibitors in human prostate cancer cells [7], antifungal [8], tuberculostically [9], antiinflammatory [10], antiviral, fungicidal, insecticidal [11] and also found a place in the technological fields like electroplating, photography [12], hair spray, cosmetic and perfumes [13], printing technology and environmental science. In this paper, we made Copper and Cobalt Schiff base metal complexes and study the biological activity. Vanillin methoxy group can enhance the biological activity of the metal complexes.

2. EXPERIMENTAL

All reagents and solvents were purchased from commercial sources and used without further purification. Solvents were of analytical or anhydrous grade (Sigma-Aldrich). ^{1}H NMR spectra were recorded on a Varian Unity 400 instrument. Chemical shifts (δ) are reported in *ppm* downfield from solvent references.

Preparation of Azomethine

A mixture of 4-hydroxy-3-methoxybenzaldehyde (1.0 g, 6.57 mmol) and 2-amino-2-ethylpropane-1,3-diol (0.783 g, 6.57 mmol) in methanol (30 mL) was refluxed at 70 °C on water bath with constant stirring for about 90 min. Reaction was monitored by TLC, after completion of the reaction, on cooling, yellow crystalline solid was separated out. The filtered solid was washed with ether and dried. Recrystallization was performed in methanol. To obtained the product (E)-2-ethyl-2-((4-hydroxy-3-methoxybenzylidene)amino) propane-1,3-diol (1.223 g, 4.73 mmol, 72 % yield) as a yellow solid. The yield, color, melting point and molecular formula of the compound were presented in the Table **1**.



Preparation of Complexes

Metal complexes were prepared by adding requisite (2.0 mmol) amount of Schiff base in 50ml of 50% methanol to the copper and cobalt metal ions respectively (1.0 mmol) in 1:2 (metal:ligand) molar ratio. Then, the reaction mixture was refluxed for four hours on a water bath and then, the reaction mixture

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Table 1: Analytical Data of the Ligand and its Solid Metal Complexes

Molecular Formula $X=H_2O$	Molecular weight	Colour	Yield (%)	Melting Point (M.P) in °C
$L=C_{13}H_{19}NO_4$	253.29	Yellow	72	171-74
$[Cu.L_2.X_2]$	387.85	Light green	70	311-14
$[Co.L_2.X_2]$	383.24	Dark brown	65	343-46

was poured in excess of cold water. Colored precipitates of metal complexes were obtained with good yield. These products were washed several times with hot water and cold methanol to free them from unreacted metal and ligand respectively and finally washed with ether and dried in a vacuum dessicator.

3. RESULTS AND DISCUSTION

Conductivity Measurements

The molar conductance of complexes in DMF (~10^{-3} M) were determined at 27 ± 2^0C using Systonic 303 direct reading conductivity bridge. These complexes are easily soluble in dimethylformamide (DMF). Therefore, these metal chelates are dissolved in DMF to perform conductivity measurements. Known amount of solid matter is transferred into 25 mL standard flask and dissolved in dimethylformamide (DMF). The molar conductance values of these metal complexes are given in Table **2**. These values suggest non-electrolytic nature [14] of the present complexes, i.e., the overall charge on the complex is zero. Hence the ligand besides being coordinated to the metal (II) ion also neutralizing. It is possible only when the ligand looses one proton from alcoholic –OH of $(-CH_2OH)_2$. The participation of one of the alcoholic OH's in chelation has been reported [15]. The conductivity measurements thus help in confirming 1:2 complex formation and behavior of the ligand as bidentate.

Electronic (UV-Visible) Absorption Spectra

In UV-Visible electromagnetic radiation, the transitions are associated with the electronic energy levels of the compound under investigation. The electronic spectra were recorded on a Thermo Spectronic Heylos α-Spectrophotometer. The transition metal ions occur in a variety of structural environments. Because of this, the electronic structures are extremely varied. The electronic structures have been identified with UV-Visible spectroscopy.

Table 2: Molar Conductivity of Copper and Cobalt Complexes

Metal Complexes	Molar conductance ($ohm^{-1}\ cm^2\ mol^{-1}$)
$Cu(VAEPD)_2$	14
$Co(VAEPD)_2$	8

Interpretation of Electronic Spectra to VAEPD and its Metal Complexes

The electronic spectra of the aqueous solutions of Cu^{2+} and Co^{2+} individual ions are compared with the corresponding complexion nature. The data is summarized in Table **3**. The data indicates that the energy of the d-d transitions in the complexes is slightly less when compared to the corresponding aqua ions, either because of slight covalent interaction of the 3d vacant orbital with ligands, leading to some delocalization with consequent reduction in interelectronic repulsion [16], or by increased nuclear shielding of the orbital due to slight covalent ligand-metal electron drift. The $\Pi\rightarrow\Pi^*$ transitions occur at 290 nm for the ligand, but on complexation with the different metal ions like copper and cobalt, new bands appeared at 328nm, 336nm respectively corresponding to the intra ligand transition and a charge transfer from the ligand to the different metal ions are observed[17]. Bands occurring in the region of 26882 cm^{-1} to 30585 cm^{-1} for all complexes are assigned to charge transfer transition (L→M). Based on the above results octahedral structures were proposed for Cu^{2+} and Co^{2+} complexes [18].

Infrared Spectra

Infrared spectra were recorded with a Perkin-Elmer IR 598 Spectrometer (4000-400 cm^{-1}) using KBr pellet (done at IICT Hyderabad). Infrared spectroscopy is one of the many valuable analytical techniques currently available to the chemist which is based on the interaction of electromagnetic radiation with the matter. By utilizing this spectroscopy, the presence of

Table 3: Electronic (UV-Visible) Spectral Data of Copper and Cobalt Metal Complexes

Metal Complexes	λ max of metal ions in cm^{-1} and nm	λ max of the complex in cm^{-1} and nm	λ max of the ligand in cm^{-1} and nm
$Cu(VAEPD)_2$	30581.04, 327	30487.80, 328	34482.75, 290
$Co(VAEPD)_2$	29940.12, 334	29761.90, 336	34482.75, 290

important functional groups in the compound, can be identified.

Interpretation of Infrared Spectra to VAEPD and its Metal Complexes

The infrared spectrum of the ligand is compared with the spectra of copper and cobalt complexes. The data is summarized in Table **4**. Along with their assignments the typical I.R. spectra are presented in Supplementary. The infrared spectra of the ligand has shown a strong band at 1640 cm^{-1} due to the (C=N) stretching vibration of the azomethine group. On complexation this band is shifted to 1599 cm^{-1} and 1576 cm^{-1} for copper(II) and cobalt(II) complexes respectively, suggesting the involvement of azomethine group (>C=N-) in complexation. Conjugation of this group with the metal ion on complexation shifts this band to lower wave numbers due to the reduction in electron density thereby indicating the coordination of the metal ion through the nitrogen atoms [19]. The shift in the broad band observed at 2560-3000 cm^{-1} due to the hydroxyl group indicates the participation of this group also in complexation. The strong bands present at 1350 cm $^{-1}$ in the ligand due to hydroxyl in plane bending vibrations are absent in the IR spectra of complexes, also further confirms the participation of this group in complexation. The bonds appearing in the regions 415-425 cm^{-1} and 490-510 cm^{-1} are assigned to the stretching frequencies of M-N and M-O [20] of the metal-ligand bonds respectively. The aromatic ether had showed the absorption peaks at 1240 cm^{-1}, 1226 cm^{-1} corresponding to the ligand and metal complexes respectively. The IR spectra of Cu(II) and Co(II) complexes exhibited a broad band around 3400 cm^{-1} which can be assigned to (OH) of water molecules associated in the complex formation. The two weaker bands at 800-750 cm^{-1} and 720-700 cm^{-1} are assigned to OH rocking and wagging vibrations respectively. These results indicate that the ligand nitrogen coordinated with metal ion and the deprotonated oxygen of the hydroxyl group suggested that structures of the ligand and complexes are likely to be that given in Figure **1**. And other peaks are also shown in Table **4**.

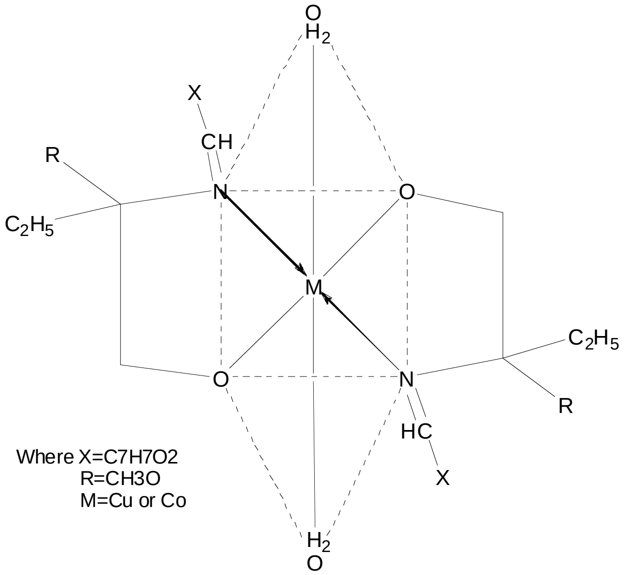

Figure 1: Proposed Octahedral Structure of the VAEPD Schiff base metal complexes.

^{1}H Nuclear Magnetic Resonance Spectra

^{1}H Nuclear magnetic resonance (^{1}H NMR) spectroscopy is an analytical technique based on the magnetic properties of nuclei. By using this spectroscopy, the nature of protons and the number protons present in a particular environment can be deterermined. In this principle, chemical shifts are measured in parts per million (ppm). For measuring chemical shifts, internal reference standard

Table 4: Important Infrared (IR) Absorption Bands (cm^{-1}) of the Ligand and their Metal Complexes

Ligand and Metal complexes	Free υ(OH)	υ(C=N)	υ(M-O)	υ(M-N)	υ(H_2O)
VAEPD	1350	1640 s	-----	-----	-----
$Cu(VAEPD)_2$	-----	1599 s	490-510 w	415-425 w	3400 b
$Co(VAEPD)_2$	-----	1576 s	480-495 w	420-435 w	3400 b

tetramethylsilane (TMS) is needed. TMS is chosen for several reasons. i.e., it contains 12 equivalent protons and four equivalent carbons and also it is chemically inert, soluble in most organic compounds, and sufficiently volatile to be easily removed from the sample after the spectrum has been recorded.

Interpretation of NMR Spectra to VAEPD and its Metal Complexes

Typical NMR spectra are given Supplementary, and the important chemical shifts values of ligand and metal complexes were summarized in Table **5**. The ^{1}H NMR spectrum of the ligand showed a multiplet between 6.82-7.34 ppm due to the aromatic protons of the Vanillin moiety, a singlet at 9.76 ppm due to resonance peak of the of the azomethine proton and another singlet at 3.7 ppm due to the methoxyl protons present in the aromatic ring system. Two closely peaks are observed at 5.2 ppm due to the two hydroxyl protons of the two hydroxymethyl groups. A group of peaks are observed between 3.37 to 3.63 ppm due to the methyl protons of the two hydroxymethyl groups. In addition to this two multiplets are observed in between 1.48 to 1.60 and 0.76 to 0.90 ppm due to the methylene methyl protons of the ethyl group respectively. In the case of Cu (II) and Co (II) complexes only one peak is observed at 5.2 ppm indicating deprotonation of one hydroxyl proton of one of the hydroxyl methyl group thereby indicating the involvement of that oxygen atom in the coordination. The signal due to the azomethine proton has shifted to 9.2 ppm and 9.25 ppm for copper and cobalt complexes respectively compared to 9.76 ppm in the case of ligand. This up field shift indicates shielding of the azomethine proton on coordination through nitrogen atom of the azomethine group. The singlet at 3.46 ppm in the case of Cu (II) and Co (II) complexes indicates the complexation of water by coordination with metal ions. The NMR data indicates the peaks corresponding to methoxyl and azomethine hydrogens undergo a slight downfield and up field [21] shift respectively, for the Copper and Cobalt complexes. These results indicate that the ligand is behaving in a bidentate manner, bonding to the metals through the alcoholic oxygen and azomethine nitrogen atoms.

Electron Spin Resonance Spectra (ESR)

In the present study the X-band (~9.3 GHz) ESR spectra for all the Cu (II) and Co (II) complexes in DMF were recorded at room temparature and at liquid nitrogen temperature (LNT) on a Bruker ESP 300E spectrometer. The ESR spectrum obtained from the instrument is a plot of the first derivative of the absorption curve as a function of the magnetic field which was calibrated with an NMR gauss meter and the exact frequency was determined using DPPH radical as a field maker.

Interpretation of ESR Spectra to Copper and Cobalt Complexes of VAEPD Azomethine

The ESR spectra of the complex in polycrystalline state exhibit only one broad signal which is attributable to dipolar broadening and enhanced spin – lattice relaxation. Anisotropic spectra are obtained for all complexes in DMF at LNT and representative ESR spectra of Cu (II) and Co (II) ion complexes are presented in Supplementary. In this low temperature spectrum, four peaks of small intensity have been identified which are considered to originate from gII compound. The spin Hamiltonian, orbital reduction and bonding parameters of all the complexes are presented in Table **6**. The $g_{\parallel}$ and $g_{\perp}$ are computed from the spectrum using DPPH free radical as g marker. Kivelson & Neiman [22] have reported that $g_{\parallel}$ value is less than 2.3 for covalent character and is greater than 2.3 for ionic character of the metal- ligand bond in complexes. Applying this criterion, the covalent bond character can be predicted between the metal and ligand for the complexes understudy. The trend $g_{\parallel} > g_{\perp} > g_{ave} > 2.0023$ observed for the complex suggests that the unpaired electron is localized in $d_{x^2-y^2}$ orbital of the copper (II) and cobalt (II) ions for these complexes and, g_{ave} results suggest that, these metal complexes possess octahedral geometry. The G values for all complexes are given in Table **6**. The G values for all these complexes are > 4 suggesting that

Table 5: **^{1}H NMR Spectral Data of the Ligand and its Metal Complexes in DMSO-d_6 in ppm**

Ligand and Metal complexes	HC=N	OCH_3	H-OR	Vanillin
VAEPD(ligand)	9.76 (1H,s)	3.7 (3H,s)	5.2 (1H,s)	6.8-7.4 (3H,s)
$Cu(VAEPD)_2$	9.20 (1H,s)	4.1 (3H,s)	5.2 (1H,s)	6.6-7.2 (3H,s)
$Co(VAEPD)_2$	9.25 (1H,s)	4.2 (3H,s)	5.2 (1H,s)	6.6-7.2 (3H,s)

Table 6: Spin Hamiltonian and Orbital Reduction Parameters of Copper and Cobalt Complexes in DMF Solution (ESR Values of Metal Complexes)

Metal Complexes	$g_{\parallel}$	$g_{\perp}$	g_{ave}	G	$A_{\parallel}^*$	$A_{\perp}^*$	A_{ave}^*	d –d	$K_{\parallel}$	$K_{\perp}$	P^*	α^2
Cu(VAEPD)$_2$	2.298	2.068	2.145	4.50	.0137	.0015	.0056	16730	.622	.882	.020	.457
Co(VAEPD)$_2$	2.295	2.065	2.141	4.67	.0143	.0017	.0059	15870	.607	.853	.021	.455

there are no interactions between copper - copper and cobalt – cobalt centers in DMF medium. The ESR parameters $g_{\parallel}$, $g_{\perp}$, $A_{\parallel}^*$, and $A_{\perp}^*$ of the complexes and the energies of d-d transitions are used [23,24] to evaluate the orbital reduction parameters ($K_{\parallel}$, $K_{\perp}$), bonding parameters (α^2), dipolar interaction (P). The observed $K\parallel < K_{\perp}$ indicates the presence of out of plane Pi-bonding. The α^2 values for the present chelates lie in the range 0.41 – 0.48 support the covalent nature of these complexes. Giordano and Bereman [25] suggested the identification of bonding groups from the values of dipolar term P. The reduction of P values from the free ion value (0.036cm^{-1}) might be attributable to the strong covalent bonding. The values of P obtained for the present complexes lie in between 0.018 - 0.022 cm^{-1} and are consistent with bonding of copper and cobalt ions to Oxygen and Nitrogen donor atoms. The shape of ESR lines, ESR data together with the electronic spectral data suggest an octahedral geometry for copper and cobalt complexes.

Thermogravimetry (TG and DTA)

The thermal studies of these complexes are done to know the stability of the complexes on thermal decomposition, as well as to know the different final products that are obtained in thermal decomposition having novel catalytic properties. Thermo gravimetric analyses of the metal complexes were carried out by using the METTLER TOLEDO STARe System in thermal analysis center: IICT Hyderabad. All possible precautions were taken to optimize conditions, so as to carry out all the thermo gravimetric analysis experiments under the same conditions. Thermo gravimetric studies of all the complexes were carried out in air at a heating rate of 25^0C per minute. The calibration of the thermo balance and temperature were checked using standard samples supplied by the Mettler Company. It has been observed that all the complexes showed weight loss corresponding to two water molecules in the range 150 to 180^0C [26]. The TGA and DTA curves (supplementary) of $[Cu(VAEPD)_2(H_2O)_2]$ and $[Co(VAEPD)_2(H_2O)_2]$ showed the first weight loss step at 152^0C and 156^0C respectively, which consists of a weight loss of 6.66% and is in good agreement with the theoretical weight loss corresponding to the elimination of two water molecules in Cu(II) and Co(II) complexes. Modes of decomposition of metal chelates were shown in Table **7**. The second (endothermic) weight loss of 84.45% in the temperature range 230- 420^0C was observed due to the loss of ligand molecules. The solid residue at 600 ^{o}C was identified as CuO and CoO. In all the complexes the final products are metal oxides.

Magnetic Moment

Copper (II) complex showed magnetic movement of 1.75 BM. It corresponding to the presence of a single unpaired electron with a very slight orbital contribution and it is in octahedral geometry. Its electronic spectrum

Table 7: Mode of Decomposition of Metal Complexes (Thermo Analytical Results of Metal Complexes)

Complexes L=$C_{13}H_{19}NO_4$ X=H_2O	Molecular weight in gms	Weight of the complex taken in mgs	Temperature Range during weight loss ^{0}C	% of weight fraction calc. found	Probable assignment
[Cu.L$_2$]2X	604.16	7.1918	0-152 152-420 420-590	5.95 6.66 83.52 84.45 10.51 10.91	Loss of 2H$_2$O molecule Loss of one L molecule Remaining residue corresponds to CuO
[Co.L$_2$]2X	599.65	6.2221	0-156 156-420 420-600	6.00 6.82 84.15 85.01 9.84 10.63	Loss of 2H$_2$O molecule Loss of one L molecule Remaining residue corresponds to CoO

also proposed for Cu^{2+} is octahedral geometry. $[Co(VAEPD)_2](H_2O)_2$ complex exhibit magnetic movement is 5.11 BM, which fall in the normal range expected for magnetically dilute octahedral complex of the metal ion [27, 28].

Figure 2: Schiff base and its metal complexes Showing zone of inhibition against Escherichia coli, Bacillus Subtilis, and Enterobacter aerogen.

(I). Escherichia coli of a) VAEPD b) $Cu(VAEPD)_2$ and c) $Co(VAEPD)_2$.

(II). Bacillus Subtilis of a) VAEPD b) $Cu(VAEPD)_2$ and c) $Co(VAEPD)_2$.

(III). Enterobacter aerogen of a) VAEPD b) $Cu(VAEPD)_2$ and c) $Co(VAEPD)_2$.

4. BIOLOGICAL ACTIVITY

The antibacterial of the ligand, and the corresponding complexes were assayed against two different bacteria, *Escherichia coli* and *Bacillus Subtilis,* and *Enterobacter aerogen* by the cup-plate method (shown in Figure **2**). The results (Shown in Table **8**) were compared against the standards Norfloxocin and Gressofulvin which were screened simultaneously. Norfloxocin is an antibacterial drug and Gressofulvin drug currently in use. The activity was measured by measuring the diameter of the inhibited zone in millimeters. The data showed that the antifungal activity of the metal complexes as well as that of the ligand is significantly enhanced on complexation. The activity of the newly synthesized metal complexes against *Enterobacter aerogen* is very near to the activity of the standard drug enhanced on complexation. The activity of the newly synthesized metal complexes against *Enterobacter aerogen* is very near to the activity of the standard drug in current use.

Table 8: Antibacterial Activity of Ligand, and its Metal Complexes, and Standard Drugs

S.No	Compound	Diameter of zone of inhibition (mm)		
		E.C	B.S	E.A
(1)	VAEPD	18	15	13
(2)	$[Cu(VAEPD)_2]2X$	22	23	26
(3)	$[Co(VAEPD)_2]2X$	24	21	23
(4)	Norfloxocin	28	25	- -
(5)	Gressofulvin	- -	- -	30

5. CONCLUSIONS

The ligand (E)-2-ethyl-2-((4-hydroxy-3-methoxybenzylidene)amino)propane-1,3-diol was successfully synthesized. The ligand, VAEPD was coordinated to two different metal ions *via* oxygen and nitrogen atoms to afford the corresponding complexes. These complexes were six-coordinated and exhibited octahedral geometry. Antibacterial study indicates that these complexes obtained showed a moderate activity against the known drugs.

SUPPORTING INFORMATION

The supplementary data and analytical spectra can be downloaded from the journal website with the article.

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