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DNA BINDING AND ANTIBACTERIAL ACTIVITY OF TRANSITION METAL COMPLEXES WITH PREORGANIZED HEXADENTATE LIGAND

K. Anuja, K. Hussain Reddy *, D. Dhanalakshmi, K. Srinivasulu and Y. B. Nagamani

Department of Chemistry, Sri Krishnadevaraya University, Ananthapuramu - 515003, Andhra Pradesh, India.

Keywords:

Transition metal complexes, Hexadentate ligand, Spectral studies. DNA binding, Antibacterial activity

Correspondence to Author:
K. Hussain Reddy

Professor,
Department of Chemistry,
Sri Krishnadevaraya University,
Ananthapuramu - 515 003, Andhra Pradesh, India.

E-mail: khussainreddy@yahoo.co.in

ABSTRACT: A new preorganized ligand, benzil bis [2-(2-amino-ethylamino) ethanol)] (H_2BAE) has been synthesized and characterized for the first time. Copper (II) and cobalt (II) complexes of H_2BAE have been synthesized and characterized based on molar conductivity data IR, UV-Vis spectroscopy. The complexes are found to have general formula $M(BAE)_2$ (where, M = Cu (II) and Co (II). IR spectral data indicate that H_2BAE acts as hexadentate ligand. The complexes are 6-coordinate and found to have octahedral structure. The copper complex is investigated using ESR spectroscopy at room temperature (RT) and liquid nitrogen temperature (LNT). The spin Hamiltonian, orbital reduction, and bonding parameters are calculated for the complex. The interactions of these complexes with calf thymus DNA have been investigated using absorption spectrophotometry. Groove binding of complexes to DNA is suggested on the basis of deoxyribonucleic acid (DNA) binding constants and the variations in the absorption spectra of metal complexes in the presence of DNA. The copper complex binds DNA more strongly than cobalt complexes. Metal complexes are screened for their antibacterial activity by using the agar well diffusion method. The complexes inhibit bacteria more strongly than H_2BAE ligand.

INTRODUCTION: There has been significant progress in the coordination chemistry of preorganized ligands due to their selectivity to form complexes [1, 2]. Transition metal complexes of preorganized ligands play pivot role in bioinorganic chemistry. Applications of azomethines and metal complexes reviewed [3, 4] recently. The metal complexes exhibit interesting properties and hence have versatile applications. These complexes show anti microbial [5, 6], antifungal [7], antiviral, anti tumor [8, 9] and anti-fertility [10, 11] activities. The complexes are also used as insecticides [12], plant growth regulators [13] and dyes [14]. The complexes of preorganized ligands have been regarded as 'models' for respiratory proteins and vitamin B_{12} [15]. Benzil is an interesting precursor for the preparation of bi-, tri and tetradentate ligands. Benzil –α-monoxime [16], benzil –α- monoxime- 2-aminoethanethiol [17], benzil dithiosemi- carabzone [18], benzil –α- monoxime thiosemicarbazone [19] and bis (benzil) ethlenediimine [20] and their transition metal complexes have been investigated using spectral methods.

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Benzil -α-monoxime iso-nicotinoyl hydrazone has been used [21, 22] for the derivative spectro-photometric determination of heavy metal (Cd^{2+} and Pb^{2+}) ions in environmental samples. Metal complexes have been used as tools for understanding DNA structure, as agents for mediation of DNA or as chemotherapeutic agents. Metal complexes provide an opportunity to explore the effects of a central metal atom, ligands and the coordination geometries on the binding event. Moreover, the activity of complex depends on its binding ability to DNA strands [23-25]. Platinum-based complexes had been primary focus of research on chemotherapy agents [26-28]. Since, platinum complexes are expensive and show side effects, the interests in this field have been shifted to non-platinum-based agents. Essential transition metal complexes appear to be upcoming agents for anticancer therapy, having effective cytotoxic activities [29-32]. The literature survey revealed that metal complexes' DNA binding and antibacterial activities with preorganized hexadentate ligands are not investigated so far.

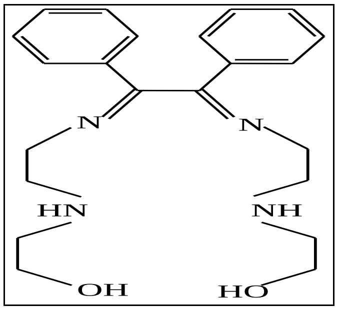


FIG. 1: STRUCTURE OF BENZIL BIS 2-(2 AMINOETHYLAMINO) ETHANOL)

In the light of lacuna identified in the literature and in continuation of our ongoing research work [16-22] on ligands derived from benzil and metal-DNA interactions [33, 34], herein we report the synthesis, spectral characterization, and DNA binding studies of Cu(II) and Ni(II) complexes with new preorganized ligand, *viz.* benzil bis [2-(2-aminoethyl-amino) ethanol)] (H_2BAE). The structure of H_2BAE is shown in **Fig. 1.**

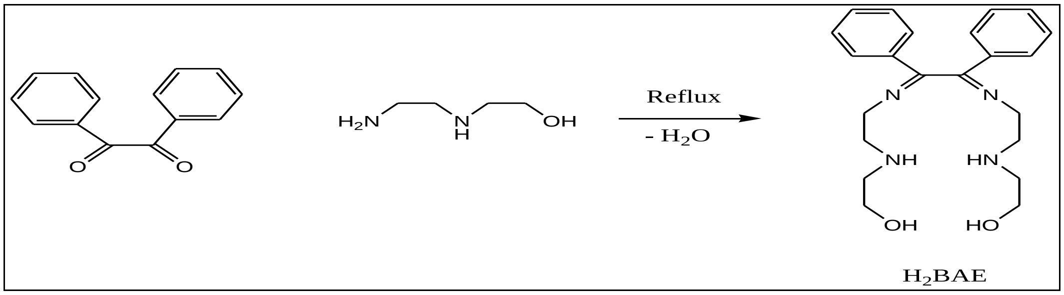
EXPERIMENTAL: Materials and Methods: The chemicals used in the preparation of ligand, benzil and 2-(2-aminoethylamino) ethanol were of reagent grads (Aldrich) and were used without further purification. Metal salts used in the synthesis of complexes were of reagent grade (Merck). Solvents used in the present study were distilled before use. Calf thymus DNA was purchased from Genie Bio labs, Bangalore, India. All other chemicals were of AR grade and used without purification.

Synthesis of ligand:

Synthesis of benzil bis[2-(2-aminoethylamino) ethanol] (H_2BAEA): Synthesis of the ligand is shown in **Scheme 1.** The preparation of BAEA ligand is shown in **Fig. 2.**

A 2.1 g benzyl (0,01 mol) was dissolved in 20 ml of ethanol 0.01 mol in 20 ml of ethanol) was mixed with 2-(2-aminoethylamino) ethanol (0.02 mol in 20 ml of ethanol) in a round bottom flask.

The contents were heated under reflux over a water bath for 1h and cooled. On slow evaporation of the solvent. A white crystalline product was formed. It was collected by filtration, washed with methanol and dried in vacuum. **Yield, 50%, m.p 116-120 °C.**



SCHEME 1: SYNTHESIS OF H_2BAE LIGAND

Synthesis of Complexes: The complex was prepared by mixing hot methanolic solution (20 ml) of (H_2BAE). (1.0g, 0.026 mol) and Metal salt ($CuCl_2.2H_2O$/ $CoCl_2.6H_2O$; 0.026 mmol) dissolved in methanol (20ml) in 1:1 ratio in a clean 100 ml round bottom flask and the contents were refluxed on water bath for 3 h. The resulting solution was allowed to stand at room temperature and after slow evaporation, coloured complex which separated out was collected by filtration, washed with methanol followed by hexane, and dried in vacuum. Yield and melting point data of complexes are given in **Table 1**.

Physical Measurements: The conductivity measurements at 298±2 in dry and purified DMF were carried out on CM model 162 conductivity cell (ELICO). ESI-Mass spectral data were obtained from Karunya Institute of Technology and Sciences, Coimbatore, India. The electronic spectra of metal complexes were recorded in DMF with an ELICO spectrophotometer. The infrared spectra were recorded in the range 4000-400 cm^{-1} with Perkin Elmer spectrum 100 spectrometer in KBr discs. ESR spectra were recorded in solid state and in DMF at 298 K and at liquid nitrogen temperature (L.N.T) on a Varian E-112 spectrometer with 100 KHz field modulation. The $g_{\|}$ and $g_{\perp}$ values are computed from the spectrum using tetracyano-ethylene (TCNE) free radical as 'g' marker.

DNA Binding Experiments: DNA binding experiments [35, 36] were done in tris-buffer (0.5mM NaCl/5mM Tris-HCl; pH = 7.0). A solution of CT-DNA in the buffer medium gave a ratio of UV absorbance at 260 and 280 nm (A_{260}/A_{280}) of 1.8-1.9, indicating that the CT-DNA was apparently free of proteins. Concentration of CT-DNA was estimated by using the ε value of 6600 M^{-1} cm^{-1} at 260 nm and stock solution of DNA was always stored at 4 ºC. The electronic spectra of metal complexes in aqueous solutions were monitored in the absence and presence of CT-DNA. Absorption titrations were performed by maintaining the metal complex concentration 10 $x10^{-6}$ M and varying the nucleic acid concentration (0 to7.36 $\times 10^{-6}$ M). Absorption titration experiments were performed by varying the concentration of CT-DNA with each addition of 10 µL DNA while the fixed metal complex concentration.

The ratio of r = Complex / DNA values vary from 23.41 to 2.60.

Evaluation of Antibacterial Activity: The pathogenic bacterial strains were purchased from National Chemical Laboratory (NCL), Pune, India. Antibacterial activity of compounds were screened against bacterial strains such as Gram–ve bacteria such as *Escherichia coli, Klebsiella pneumoniae and* Gram +ve bacteria such as *Bacillus cereus* and *Staphylococcus aureus* by using agar well diffusion method. Nutrient agar (NA) plates were prepared using sterile nutrient agar medium was poured into sterile Petri-dishes and allowed to solidify. About 6mm wells are made in each nutrient agar plate using a sterile cork borer. Different concentrations of compounds (100, 200 and 300 µg /well) were used to assess the dose-dependent activity of the product. The metal complexes were dissolved in 10% dimethyl sulfoxide (DMSO) and micropipettes were used for the addition of compounds into the wells. Simultaneously the standard antibiotics (Ciprofloxacin used as a positive control) are tested against the pathogenic bacterial strains. Then the plates were incubated at 37 °C for 36 h. After incubation, the zone of inhibition of each well was measured and the values were noted. The experiments were carried out in triplicates with each compound and the average values were calculated for determining the antibacterial activity.

RESULTS AND DISCUSSION:

Characterization of Ligand: The ligand (H_2BAEA) is characterized based on FT-IR, ^{1}H-NMR Mass spectral data.

IR spectra (cm^{-1}): 3285, 3056, 2931, 2887, 1634, 1156 are assigned to ν (O-H), ν (N-H), ν (C-H, aromatic), ν (C-H, methylene) ν (C=N) and ν (C-O) stretching vibrations respectively.

NMR spectra (δ, ppm): 7.72 (m, 2H, OH), 7.29 (m, 10H, Phenyl H); 3.67 (m. 4H, O-CH_2); 3.65 (m. 4H, >N-CH_2), 2.91 (m. 4H, N-CH_2); 2.74(m, 4H, >C=N-CH_2) and 2.0 (m, 2H, >NH). Mass spectrum of the ligand is shown in **Fig. 2.** Fragmentation pattern **Fig. 3** confirms the synthesis of H_2BAE ligand.

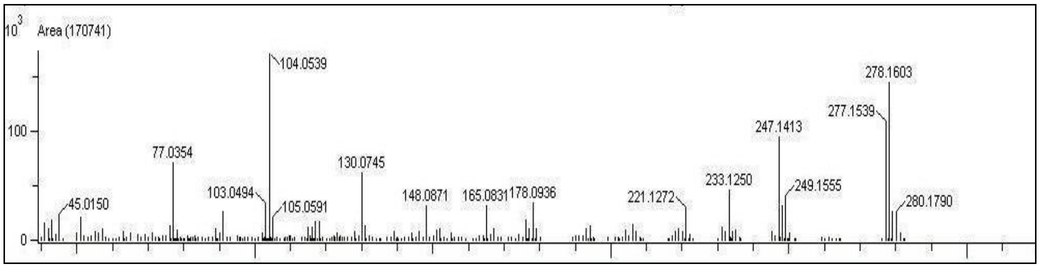


FIG. 2: MASS SPECTRUM OF H_2BAE LIGAND

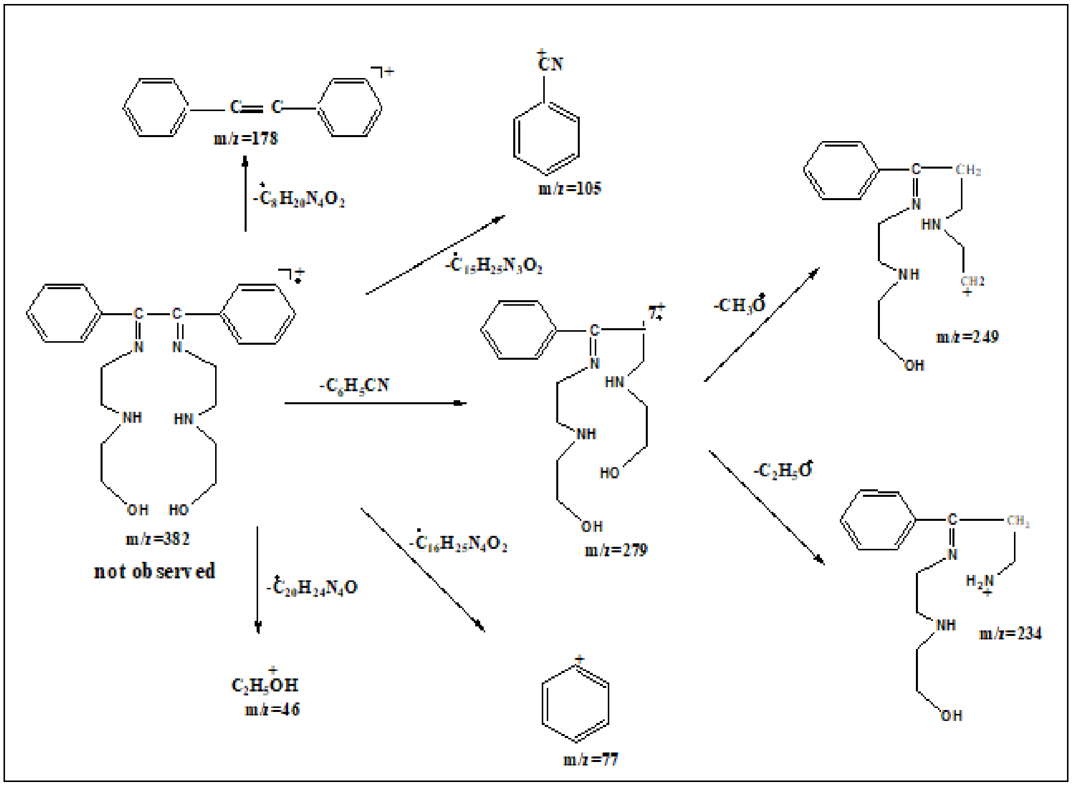


FIG. 3: FRAGMENTATION PATTERN OF H_2BAE LIGAND

Characterization of Complexes: The reaction of (H_2BAEA) with metal chlorides yielded in the formation of mononuclear complexes. All the complexes are non-hygroscopic, coloured, and freely soluble in ethanol, and soluble in many organic solvents. Physicochemical data of complexes are given in **Table 1**. Molar conductivity data of the complexes suggest the non-electrolytic [37] nature of complexes.

TABLE 1: PHYSICOCHEMICAL AND ANALYTICAL DATA OF CU (II) AND CO (II) COMPLEXES

S. no.	Complex	Colour (Yield %)	ESI-MS (F.W)	Molar Conductivity ($\Omega^{-1}cm^2mol^{-1}$)
1	Cu(BAE)	Purple colour (71)	431	32.24
2	Co(BAE)	Light Green (89)	426	39.24

Electronic Spectra: The electronic spectra of copper and cobalt complexes are shown in **Figs. 4** and **5,** respectively. Spectral data and assignment of peaks are given in **Table 2.** The presence of a single d-d band at 11560 cm-1 in the spectrum of copper complex **Fig. 5** may be assigned to $^2Eg \rightarrow {}^2T_2g$ electronic transition in favour of octahedral structure.

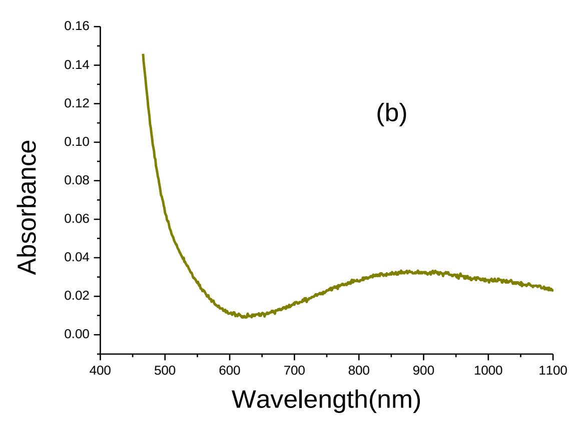


FIG. 4: SPECTRUM OF Cu COMPLEX

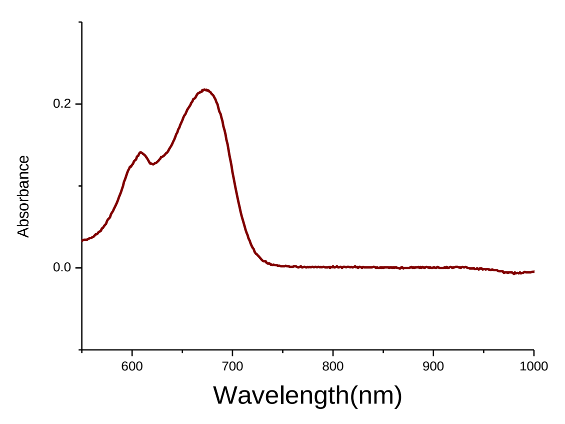


FIG. 5: SPECTRUM OF Co COMPLEX

TABLE 2: ELECTRONIC SPECTRAL DATA FOR CU (II) AND CO (II) COMPLEXES

S. no.	Complex	λ max (nm)	Frequency (*cm*$^{-1}$)	Assignment
1	[Cu(BAEA)]	865	11560	d-d Transition
		385	25773	CT Transition
		268	37174	$\pi \rightarrow \pi^*$Transition
2	[Co(BAEA)]	672	14880	d-d Transition
		608	16450	d-d Transition
		316	25773	$\pi \rightarrow \pi^*$Transition

The electronic spectrum of cobalt complex **Fig. 6** shows bands at 16450 and 14880 cm^{-1}. These peaks are respectively assigned to $^4T_{1g} \rightarrow {}^4T_{2g}$ and $^4T1g \rightarrow {}^4A_{2g}$ transitions respectively in favour of octahedral structure. IR spectrum of H_2BAE ligand is compared with those of metal complexes to determine donor atoms of ligand. The IR spectrum of the ligand shows several prominent bands due to $\nu_{O\text{-}H}$, $\nu_{N\text{-}H,}$ and $\nu_{C=N}$ stretching modes. The first band disappeared in spectra of complexes due to deprotonation followed by bonding with metal covalently. The $\nu_{C=N}$ is shifted to a lower frequency in the spectra of all complexes suggesting the involvement of azomethine nitrogen in chelation. The band due to N-H vibration is shifted to lower frequency. In summary, IR data suggest that H_2BAE acts as dianionic hexadentate ligand in metal complexes. The non- ligand bands around 540 and 495 cm^{-1} are tentatively assigned to $\nu_{(M\text{-}O)}$, and $\nu_{(M\text{-}N)}$ vibrations, respectively. Based on physicochemical and spectral data, a general structure **Fig. 6** is proposed.

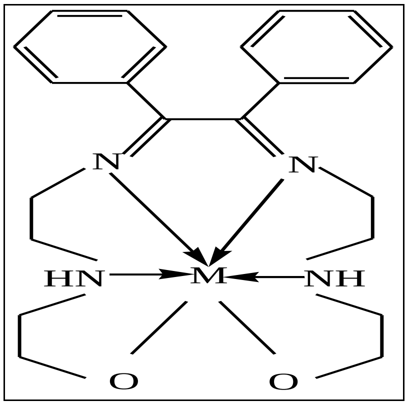


FIG. 6: PROPOSED GENERAL STRUCTURE FOR COMPLEXES [Where M = Cu (II), Co (II)].

ESR Spectra of Copper Complex: ESR spectrum of copper complex in DMF solvent recorded at room liquid nitrogen temperature (LNT) is shown in **Fig. 7.** ESR spectral data are given in **Table 3.**

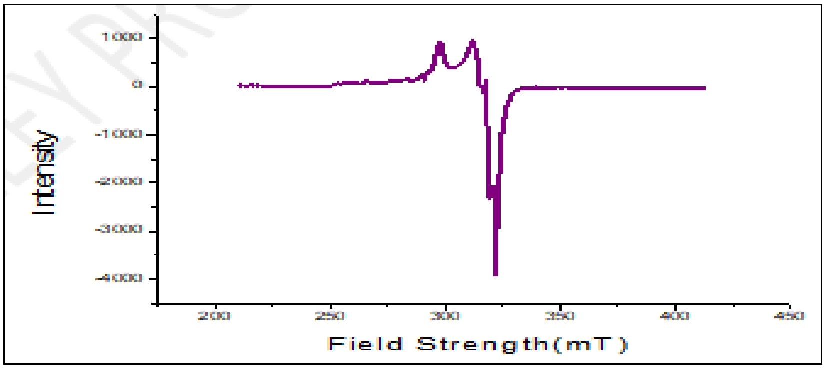


FIG. 7: ESR SPECTRUM OF Cu COMPLEX AT LNT

TABLE 3: ESR SPECTRAL PARAMETERS OF Cu-BAE COMPLEX

In DMF at RT				In DMF at LNT									
$g_\parallel$	$g_\perp$	$g_\parallel$	$g_\perp$	$g_\parallel$	$g_\perp$	$g_\parallel$	$g_\perp$	$g_\parallel$	$g_\perp$	$g_\parallel$	$g_\perp$	$g_\parallel$	$g_\perp$
2.20	2.08	2.20	2.08	2.20	2.08	2.20	2.08	2.20	2.08	2.20	2.08	2.20	2.08

The g values were computed from the spectrum using tetracyanoethylene (TCNE) free radical as the g marker.

At Room Temperature: The $g_\parallel$ and $g_\perp$ values for Cu complex are respectively found to be 2.20 and 2.08 in DMF at room temperature **Table 3.**

Kivelson and Neiman [38] have reported that the $g_\parallel$ is less than 2.3 for covalent character and greater than 2.3 for the ionic character of the metal-ligand bonding. The $g_\parallel$ value suggests a covalent character for the complex. The trend, $g_\parallel > g_\perp > 2.0023$ suggests that the unpaired electron predominantly in the $d_{x^2-y^2}$ orbital [39] characteristic of octahedral geometry for copper (II) complex. The g_{av} value of the complex suggests the presence of covalent character [40] in M-L bond. The axial symmetry parameter *G* is defined as,

$$G = g - 2.0023 / g - 2.0023$$

The calculated *G* value for the Cu complex is found to be 2.44. The G value is less than 4 for the Cu-BAEA complex which indicates the absence of exchange coupling and misalignment of molecular axes.

At Liquid Nitrogen Temperature: The typical ESR spectrum of Cu-BAE complex in DMF at Liquid nitrogen temperature (LNT) is shown in **Fig. 6.** ESR spectra of complexes in DMF at liquid nitrogen temperature (LNT) exhibit well resolved peaks at low field and at high field corresponding to $g_\parallel$ and $g_\perp$ respectively. The spin Hamiltonian, orbital reduction and bonding parameters of complexes are incorporated in **Table 3**. The $A_\parallel$ and $A_\perp$ are the separation between two adjacent $g_\parallel$ and two adjacent $g_\perp$ peaks, respectively (in cm^{-1}).

The orbital reduction parameters ($K_\parallel$, $K_\perp$) are calculated. Hathaway pointed that that for pure sigma bonding $K_\parallel = K_\perp = 0.77$ and for in-plane pi bonding $K_\parallel < K_\perp$, while for out-plane π- bonding $K_\parallel > K_\perp$. For the present complex under investigation, $K_\parallel$ and $K_\perp$ are 0.983 and 1.00, respectively. These values suggest the presence of in-plane π- bonding in the complex.

Cyclic Voltammetry: Electrochemical Properties of complexes are investigated by cyclic voltammetry in DMF using 0.1 M tetra-butylammonium hexafluorophosphate as supporting electrolyte. The cyclic voltammogram of the complex is shown in **Fig. 8** and the electrochemical data of complexes are summarized in **Table 4.**

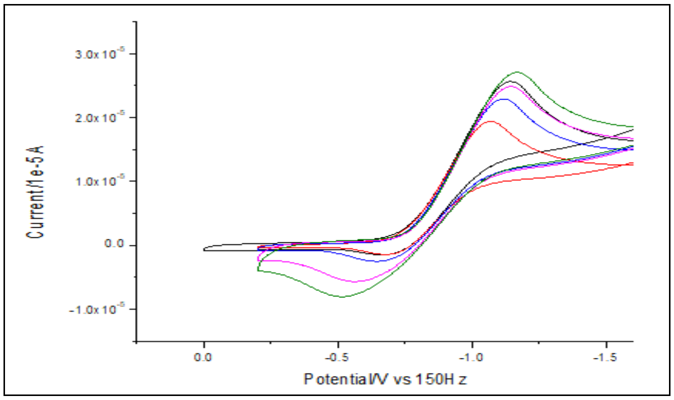


FIG. 8: CYCLIC VOLTAMMOGRAMS OF COBALT COMPLEX AT DIFFERENT SCAN RATES

TABLE 4: CV DATA OF Cu(II) AND Co(II) COMPLEXES

Complex	Redox couple	E_{pc}	E_{pa}	ΔEp(mV)	$E_{1/2}$	$-i_c/i_a$	LogKc[a]	-ΔG°[b]
Cu-BAE	II/I	-0.045	0.452	0.497	0.248	1.509	0.6757	387
Co-BAE	II/I	-1.143	-0.679	0.464	0.911	1.893	0.072	415

[a] $\log K_c = 0.434ZF / RT\Delta E_p$, [b] $\Delta G^o = -2.303RT\log K_c$

The cathodic peak current function values were found to be independent of the scan rate. Repeated scans at various scan rates suggest that the presence of stable redox species in the solution. It has been observed that cathodic (Ipc) and anodic (Ipa) peak currents were not equal. The E½ values of copper (II) and cobalt (II) complexes are +0.248 and -0.911, respectively.

It may be concluded that the bivalent metal complexes undergo one-electron reduction to their respective M (I) complexes. The non-equivalent currents in cathodic and anodic peaks indicate quasi-reversible behavior. The difference, ΔEp in all the complexes, is better than the Nerstian requirement 59/n mV (n = number of electrons involved in oxidation reduction), demonstrating the quasi-reversible character of electron transfer. The complexes show large separation between anodic and cathodic peaks indicating quasi-reversible character.

DNA Binding Studies: UV- Vis spectroscopy is an important technique to investigate the interaction of DNA with metal complexes. Hence the interaction of metal complexes with calf-thymus DNA was monitored by UV-visible spectroscopy. Absorption spectra were recorded in the range of 200-350 nm. Typical absorption spectra of in presence and in absence of DNA are shown in **Fig. 9.**

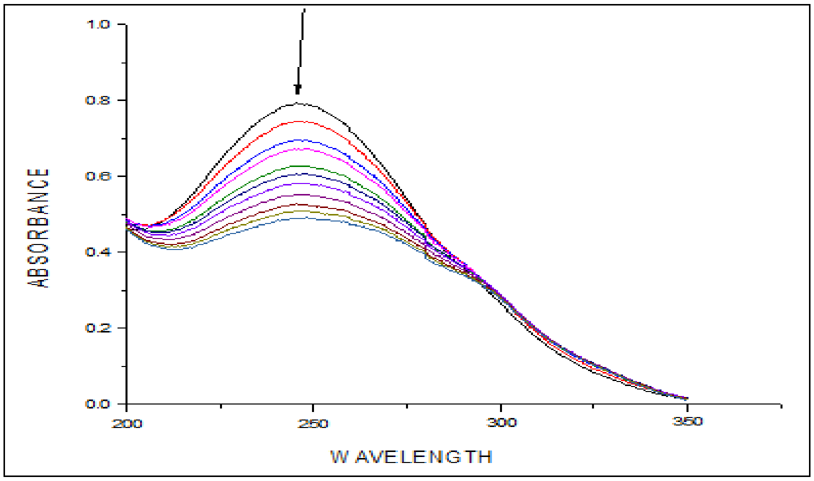


FIG. 9: ABSORPTION SPECTRA OF CO-BAE COMPLEX IN THE PRESENCE AND IN ABSENCE OF DNA

Metal complexes exhibit an intense absorption band in high energy region (345-395 nm) which are attributed to metal-ligand charge transfer (MLCT) transitions The absorption spectra of complexes were compared in the absence and in the presence of CT-DNA.

The change in absorbance values with increasing amounts of CT-DNA was used to evaluate the intrinsic binding constant K_b, for the complexes. Based on the variation in absorption, the intrinsic binding constant or association constant (K_b) of the metal complex can be calculated according to the Benesi-Hildebrand equation, modified by Wolfe *et al* [41].

$$DNA / (\varepsilon_a-\varepsilon_f) = DNA /(\varepsilon_b-\varepsilon_f) + 1/Kb\ (\varepsilon_b-\varepsilon_f)$$

Where, ε_a, $\varepsilon_{f,}$ and ε_b correspond to Aobserved/complex, the extinction coefficient for the free metal complex and the extinction coefficient for the metal complex fully bound to DNA, respectively, Kb represents the binding constant. Electronic absorption spectral data upon the addition of CT-DNA and binding constants of these complexes are given in **Table 5.**

TABLE 5: ELECTRONIC ABSORPTION DATA UPON ADDITION OF C T –DNA TO THE COMPLEXES

S. no.	Complexes	λ max (nm)		Δ λ	H%	K_b [M^{-1}]
		Free	Bound			
1	[Co(BAE]	336	337.5	1.5	-5.9	4.2×10^4
2	[Cu(BAE)]	338	337	1	-9.7	10.4×10^4

In the presence of increasing amounts of CT-DNA, the UV-visible absorption spectra of [Co(BAE] complex shows a small bathochromic shift (Redshift) (Δ λ_{max}: .1.5 nm) with increasing amounts of DNA. The calculated binding constants for Cobalt and Copper complexes are respectively found to be 4.2×10^4 and 10.4×10^4 M^{-1}.

Metal complexes binding to DNA through intercalation usually result in hypochromism and bathochromism or hypsochromism [42-44] while hyperchromism has been attributed to electrostatic attraction, hydrogen bonding and groove (minor or major) binding along the outside of DNA helix [45,46]. The extent of the changes that appear in the metal complex spectrum are usually consistent with the strength of interaction. Such small bathochromic shifts are more in keeping with groove binding, leading to small perturbations. The Kb valuee for present complexes are lower than that reported for classical intercalator for ethidium bromide and $[Ru(Phen)_2\ DPPZ]^{2+}$ complex whose binding constants have been found [47] to be in the order 10^6 - 10^7. The observed binding constants for the present complexes are in accordance with *groove binding* with DNA as reported in the literature [48, 49]. It is pertinent to note that the binding constant for the Cu complex is quite high.

Antibacterial Activity: Metal complexes are screened for their antibacterial activity by using the agar well diffusion method. The diameters of inhibition of zone were measured with Vernier callipers in mm, and values are depicted in **Table 6.**

TABLE 6: ANTIBACTERIAL ACTIVITY OF DIFFERENT METAL COMPLEXES AGAINST PATHOGENIC BACTERIA

Complex	Treatment	*E. coli*	*K. pneumoniae*	*S. aureus*	*B. cereus*
S-Ciprofloxacin	5µg/µL	10.5±0.3	9.8±0.17	10.03±0.15	12.16±0.16
H_2BAE	100µg/µL	0.8±0.16	0.9±0.34	0.65±0.00	1.2±0.33
	200µg/µL	1.1±0.17	1.0±0.34	0.85±0.32	1.3±0.15
	300µg/µL	1.4±0.50	1.2±0.50	1.2±	1.5±0.25
Cu-BAE	100µg/µL	3.1±0.33	2.9±0.17	3.4±0.33	3.25±0.31
	200µg/µL	3.4±0.32	3.2±0.16	3.5±0.51	3.45±0.50
	300µg/µL	3.6±0.15	3.4±0.31	3.65±0.32	3.6±0.15
Co-BAE	100µg/µL	2.5±0.50	2.2±0.00	1.6±0.31	1.7±0.31
	200µg/µL	2.55±0.17	2.3±0.00	1.8±0.09	1.9±0.31
	300µg/µL	2.7±0.33	2.6±0.17	1.98±0.31	2.21±0.15

Values are the mean ± SE (Standard Error) of inhibition zone in mm.

Antibacterial activity of present complexes is comparable to the standard compound **Fig. 10.** The data indicates that the complexes inhibit bacteria more strongly than the ligand H_2BAE. Among Cu-BAE and Co-BAE complexes the former show higher activity than the latter. The increased activity of metal complexes maybe may be understood on the basis of Overtone's concept [50] and Tweedy's Chelation theory [51]. The cell membrane is a bi-layer. It is composed of both protein and lipid layers. As per the principles of cell permeability, lipid solubility is the prime factor for showing antibacterial activity. In complexes, the polarity of metal greatly decreases due to the delocalization of π-electrons. The low polarity of metal in the complex enhances its penetration ability into the lipid membrane. On entering into the cells, metal derivatives block the microorganisms' enzymes [52, 53], leading to the death of bacteria.

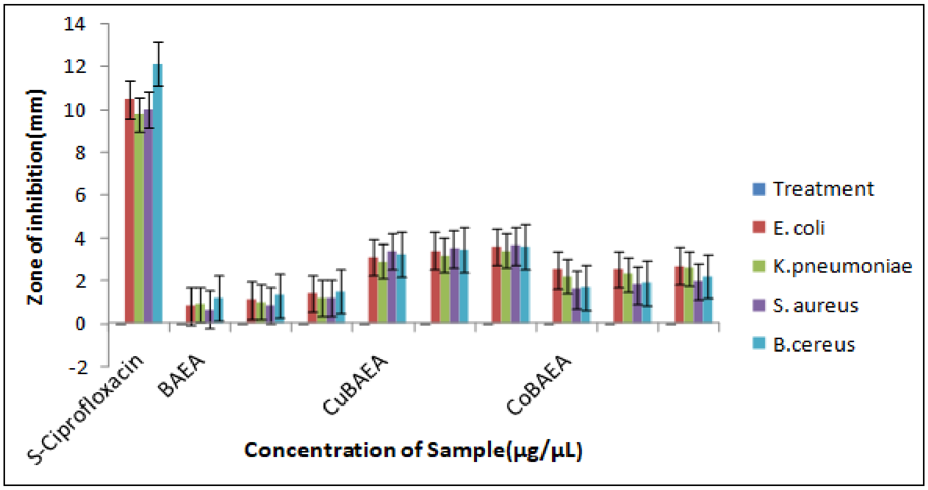


FIG. 10: GRAPHICAL REPRESENTATION OF ANTIBACTERIAL ACTIVITY OF METAL COMPLEXES AGAINST PATHOGENIC BACTERIAL STRAINS

CONCLUSIONS: A new preorganized ligand, benzil bis 2-(2-aminoethylamino) ethanol) (H_2BAE) has been synthesized and characterized for the first time. Preorganized ligands are known to give very stable complexes.

Hence copper (II) and cobalt (II) complexes of H_2BAE have been synthesized and characterized based on physicochemical and spectral data. The complexes are 6-coordinate and have octahedral structures with the central metal ion coordinated by hexadenatate ligand. The copper complex is investigated using ESR spectra. Spectral data suggest the covalent nature of metal-ligand bonding. Groove binding of complexes to DNA is suggested based on binding constants and the variations in the absorption spectra of metal complexes in the presence of DNA. The complexes inhibit bacteria more strongly than the ligand H_2BAEA.

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