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RESEARCH ARTICLE

One-Pot Synthesis of copper (II) complex of Curcumin di Ketimines as models for blue copper Protein

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ABSTRACT:
One pot synthesis of curcumin Schiff's metal complex is successfully achieved. The synthesized complex is compared with blue copper protein by electron paramagnetic studies. The formed complex is characterized using absorption studies, IR and EPR studies. The distorted structure of the molecule make the complexes suitable for biological system.

KEYWORDS: Curcumin, Schiff's, EPR, One pot.

INTRODUCTION:

The design and synthesis of small molecules that bind to and cleavenucleic acids are still a major challenge for researchers. These artificial nucleases have important applications as tools in molecular biology and as potential therapeutic agents for the treatment of cancer and viral diseases. There has been substantial interest in the rational design of novel transition metal complexes which bind and cleave duplex DNA with high sequence or structure selectivity [1–3]. The characterization of DNA recognition by small transition metal complexes has been substantially aided by the DNA cleavage chemistry that is associated with redox active or photo activated metal complexes. Indeed, there is already a considerable literature involving the practical use of transition metal complexes as chemical nucleases [4–6].

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Curcumin (1,7-bi(4-hydroxy-3-methoxyphenyl)-1,5-heptadiene-3,5-dione), is a natural orange dye extracted from the *Rhizome* of the plant *Curcuma Longa*. Curcumin has an interesting structure with two phenolic groups and one active methylene function. The double bonds are essential for proper conformational flexibility of the molecule. The remarkable antioxidant properties of curcumin [7] are thought to arise from the hydroxyl groups in the aromatic side chains or from the CH2 group of the β-diketone moiety [8]. Jovanoic *et al.* have indicated that hydrogen abstraction from the methylene -CH2 group is responsible for the remarkable antioxidant activity of curcumin [9]. Recently, Priyadarsini *et al.* have reported that phenolic OH is mainly responsible for the activity of curcumin [10,11]. However, modifications in the β-diketone are less explored except where this moiety is modified with hydrazide [12] and cyclohexanone groups [13]. Preliminary studies in appending the β-carbonyl functionality in curcumin with known pharmacophore amine have shown to enhance its antioxidant potential [14].

Schiff bases derived from an amine and any aldehyde or ketone are a class of compounds which coordinate to metal ions *via* the azomethine nitrogen. Schiff base chelating ligands containing O and N donor atoms show broad biological activity and are of special interest because of the variety of ways in which they are bonded to metal ions [15]. Transition metal complexes derived from Schiff base ligands have been among the most widely studied coordination compounds, since they are becoming increasingly important as biochemical,

analytical and antimicrobial reagents. These complexes containing certain metal ions are active in many biological processes. Synthesis and characterization of new copper (II) complexes are important to develop models for copper proteins and to understand the factors affecting the distortions from regular coordination geometry observed in various copper (II) complexes [16, 17]

In the present study we discuss about the successful synthesize of new copper schiffs complex of curcumin derived from curcumin and ethanolamine. The complex is characterized using UV-visible, IR and electron paramagnetic resonance studies (EPR).

Experimental:

Electronic absorption spectra were obtained with Ocean optics optical fiber (400 μm) spectrophotometer SD1000 using 10 mm quartz cell. X-band EPR spectra were recorded with JEOL JES-TES 100 ESR spectrometer having 100 kHz field modulation. Spectra at liquid nitrogen temperature were performed in a cold finger Dewar. IR spectra were recorded on ABB Bomem MB 104 spectrometer using KBr disks. Elemental (C, H and N) analysis was performed with Heraus Rapid analyzer.

Curcuma longa (turmeric) fresh root and organic turmeric powder were obtained from organic shop. Analar grade ethanolamine, ethanol, methanol, chloroform, silica gel (Column and TLC) and Cu $(SO_4).5H_2O$ are obtained from SD fine India and used directly for the reaction.

Extraction of Curcumin from Curcuma longa:

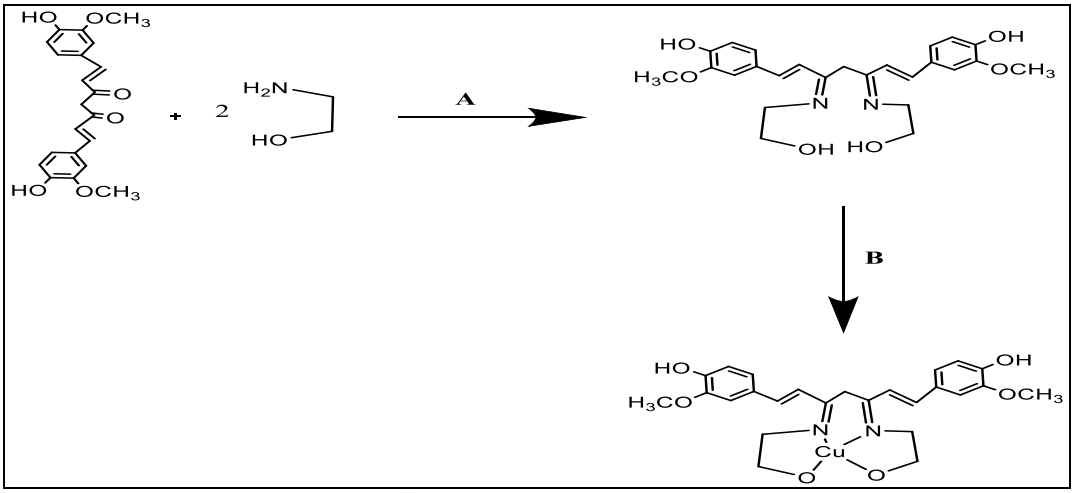
10 g of small slices of fresh rhizomes in 50 mL of ethanol was magnetically stirred and heated under reflux for 1 h. The mixture was suction-filtered and the filtrate was concentrated in hot-water bath maintained at 50°C.The reddish yellow oily residue was triturated with hexane. TLC analysis (3% methanol-97% chloroform) showed the presence of three components. The crude material obtained after trituration with methanol was dissolved in a minimum amount of chloroform and loaded into a column packed with 30 g of silica gel. The column was eluted with the same solvent. TLC analyses of the various fractions showed the presence of three components. The fractions containing the least polar color component were combined and the solvent was removed on water bath to give a yellow solid. Yield 76%, melting point 184-187 °C.

Isolation of Curcumin from Turmeric Powder:

About 20g of organic turmeric powder was soaked in 50mL of ethanol for 48hrs. The solution was then filtered and distilled to get reddish yellow oily residue. Purification or isolation of curcumin was done as before and the yield is found to be 60%.

Synthesis of Schiff's base ligand and its copper complex:

A methanolic solution of curcumin(0.5 g, 1.4mmol, 25 mL) was slowly added to a methanolic solution of ethanolamine (0.18g, 3mmol, 25 mL) with constant stirring as shown in Scheme I. This reaction mixture was stirred for 6 h. This reaction mixture is then transferred into a refluxing unit which contained a solution of copper sulphate (1.1mmol) in 25 mL of methanol and then refluxed for 2 h on water bath. Removal of solvent at reduced pressure gave the crude product. The product was washed twice with diethyl ether and recrystallized from chloroform. The yield was found to be 17% [M-H=514] (Scheme-1).



Scheme I: A) Methanol, stirred, 6hr; B) CuSO4, Methanol, reflux, 2hr

RESULT AND DISCUSSION:

Electronic Spectral studies:

The electronic spectra of ligand and its copper complex were recorded in methanol. Curcumin in methanolic solution showed a broad characteristic UV-visible absorption at around 300-500 nm with maximum absorption band at wavelength 424 nm and shoulder near 360 and 460 nm, and a weak absorption band at 262 nm. The maximum absorption is due to the electronic dipole allowed π-π* type excitation of its extended conjugation system. Since there is electrostatic interaction between polar solvent (methanol) and polar chromophores in curcumin molecule, this solvent tends to stabilize both the bonding electronic ground states and the π* excited states. This interaction causes the n-π* transition which occurs at lower energy than the π-π* transitions to move to higher energy and π-π* transition to move to lower energy. Thus, the π-π* and n-π* absorptions of curcumin move close to each other [18].

The copper complex shows a broad d–d band with unusually high intensity at 520–550 nm (Fig 1), assigned to the combination of d-d transitions in a distorted planar geometry. The spectral feature of these complexes is comparable [18] to the natural blue copper proteins. In the absence of a sulphur donor the unusual increase in intensity in the d-d transition may be due to its possible overlap with the conjugated (Cu) LMCT transition. The ligand π* -orbitals may function as the empty dπ orbitals of the sulphur in blue copper and, hence, an increase in intensity is observed. The intralig and π–π* entities in the complexes are observed in the 400 nm range with higher intensities comparable to their free ligands, which may be due to the presence of imine functions [18].

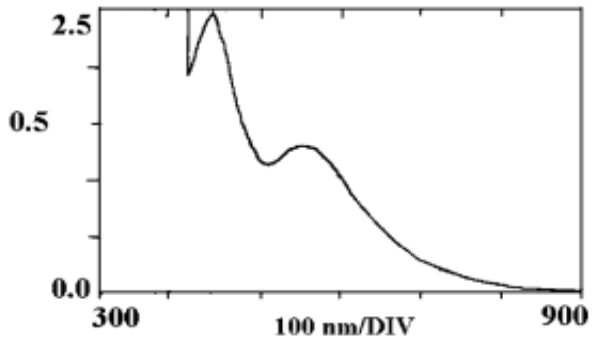


Fig 1.Electronic absorption spectrum of Copper schiffs ligand in methanol.

IR Studies:

IR spectrum of curcumin (Fig. 2) showed a sharp peak at 3510 cm^{-1} indicating the phenolic O-H stretching with a broad band at a range from 3200-3500 cm^{-1}, which is due to the ν(OH) group (in enol form). The low intensity bands observed in the IR spectrum at 3079–3000 cm^{-1} are assigned to the aromatic ν(C-H), while the lower frequency bands are attributed to the methyl group motions. The important absorption band at 1629 and 1603 cm^{-1} correspond to the mixtures of stretching vibrations of ν (C=C) and ν(C=O) in curcumin. The IR spectrum of copper complex showed peaks characteristic of imine link around 1639 cm^{-1}. IR spectrum of copper complex was not very much clear due to side product formation.

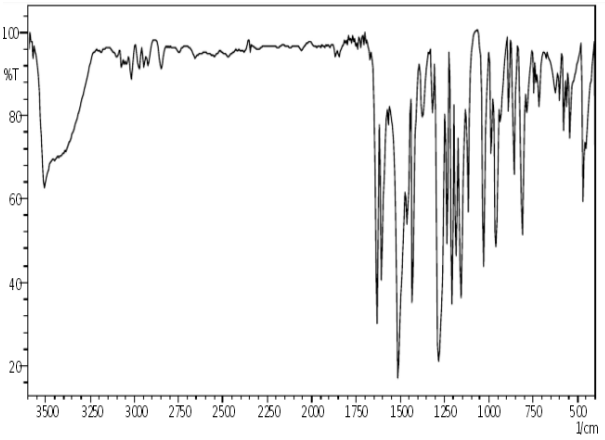
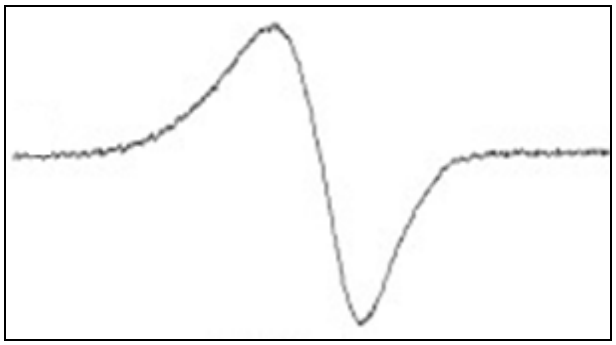


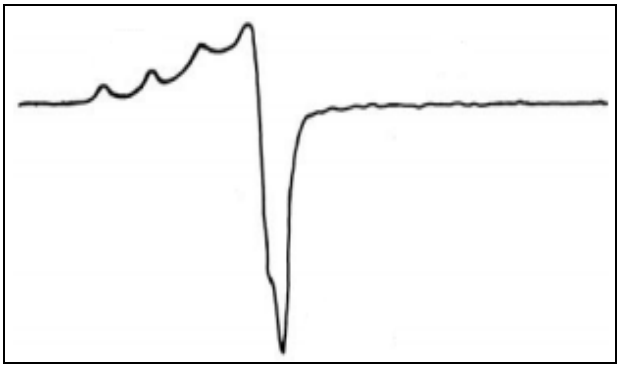
Fig 2. FTIR spectrum of cursumin

EPR Studies

The EPR spectrum of the copper (II) complexes were recorded in DMSO at 300 and 77 K (Fig3). The $g_{\perp}$ values are greater than the corresponding gII values and therefore the unpaired electron occupies the $dx2\text{-}y^2$ molecular orbital [19]. All the spectra exhibit a typical four-line pattern. The spectral data are consistent with typical monomers but with distorted tetrahedral copper (II) geometry [19]. It is known that as the tetrahedral distortion increases, the gπππ will increase with a decrease in Aπππ[19]. For blue copper proteins the Aππ values are in the 15–90 x 10^{-4} cm^{-1} region due to deviation from planarity, towards a suppressed tetrahedron. The observed Aπππvalues (~110 x10^{-4} cm^{-1}) reveal that these complexes largely deviate from the regular square planar geometry. The Aππ values of these complexes are on the borderline between naturally occurring blue copper proteins and typical planar structures. Often the gππ/Aππ quotient is empirically treated as an index of tetrahedral distortion [19]. The gππ / Aππ values are expected to be in the 105–135 and 150–250 range respectively for square planar and tetrahedral distorted copper (II) complexes. In the present case the gππ / Aππ values are between 178 and 209; it is assumed that they have geometry distorted from planarity towards tetrahedral. It is also reflected in the unusual gain in intensity in the visible spectra.



(a)



(b)

Fig 3. EPR spectrum of Copper schiffs ligand a) RT b) LNT in DMSO

CONCLUSION:

A successful extraction of curcumin from natural source has been achieved. Furthermore, the formation of schiffs complex was achieved, though yield was very less. Instrumental studies reveal the formation of complex. The copper complex seems to form more distorted structure from planarity which makes it as applicable to biological systems, yet its application has to be done by us.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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