Synthesis of a New Heteroleptic Copper(II) Complex: Structural Elucidation, DNA Binding and *In-vitro* Alpha Glucosidase Inhibition Studies

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Summary: A new dimeric heteroleptic Cu(II) complex with formula $[Cu_2(2\text{-}CH_3\text{-}3\text{-}NO_2C_6H_3CH_2COO)_4(2\text{-}Cl\text{-}py)_2]$, where Cl-py = 2-chloropyridine, has been synthesized and characterized by FT-IR, UV-Visible spectroscopy and single crystal XRD. The single crystal XRD revealed that the complex crystallized in monoclinic space group P2/n with square pyramidal geometry around each copper atom and adopted paddlewheel conformation with Cu….Cu intra-dimer distance of 2.66 Å. The DNA binding studies of the complex were carried out through UV-Visible spectroscopy where a high value of the binding constant ($K_b = 1.51 \times 10^4\ M^{-1}$) suggested its strong affinity towards DNA molecule. Moreover, *in-vitro* α-glucosidase inhibition assay of the complex with acarbose as control revealed its anti-diabetic potential with IC_{50} value of 13.1 μM.

Keywords: Heteroleptic Copper(II) complex; Single Crystal XRD; DNA Binding.

Introduction

Copper complexes have been known since decades because of their vast industrial as well as biological applications. They are known to act accelerators for number of chemical reactions such as oxidation, reduction, coupling and C-H insertion [1-3]. With N- and/or O-donor ligands, copper forms variety of mononuclear to polynuclear complexes adopting different geometries like square planar, distorted square planar, trigonal pyramidal, square pyramidal and distorted octahedral [4]. Copper is an essential trace element found in all living organisms with multifaceted roles. Within human body it binds with different proteins *i.e.*, ceruloplasmin, albumin and actively participates in various biochemical processes mainly electron transfer reactions [5]. Cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, angiogenin, S-adenosylhomocysteine, blood clotting factors V and VIII and dopamine β-monoxygenase are copper dependent enzymes within the human body [6, 7]. During last two decades, greater interest in Cu(II) complexes has emerged because of their potential use as antimicrobial, antiviral, anti-inflammatory, antiulcer, antidiabetic, anticonvulsant and antitumor agents [8]. They are found to interact strongly with DNA with reduced side effects attributed to their superoxide dismutase (SOD) mimetic activity [9]. Some of copper complexes reported so far exhibited comparable anti-cancer activity as cis-platin with reduced side effects [10].

In our work, rationale behind the selection of phenylacetic acid and pyridine, is composition of $[Cu(tmphen)_2]Cl_2$, where tmphen stands for 3,4,7,8-tetramethyl-1,10-phenanthroline, the first reported copper complex with remarkable *in-vivo* anti-cancer activity and the *Casiopeınas,* a famous class of Cu(II) mixed-ligand complexes containing both N- and O-donor ligands [11, 12]. Furthermore, the carboxylate ligands can adopt multi-binding modes that provide required flexibility to develop different geometries which dictate reactivity and redox properties of central metal atom [13, 14]. It also increases the solubility of resultant metal complex in aqueous medium which enhances the biological importance of a complex. This arrangement when coupled with ligands of hard base character such as substituted pyridine will further furnish a complex with required planarity for a biological system and also increase its stability [15, 16].

Keeping in view all these facts the present study has been designed with an aim to synthesize biologically active copper(II) complex. The DNA binding and enzyme inhibition capacity of herein reported complex confirmed its biological importance. This data reflects that such complexes can provide a foundation in future to design metal based drugs to cure diseases like cancer and diabetes.

Experimental

Materials and Chemicals

Analytical grade $CuSO_4.5H_2O$, 2-Chloro-pyridine and 2-methyl-3-nitrophenylacetic acid were purchased from Fluka, Switzerland. Methanol was

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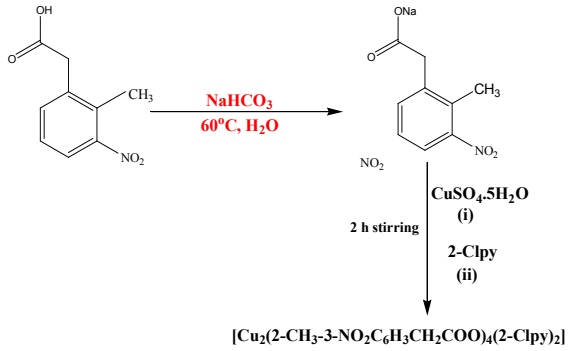
purchased from Merck, Germany and used as received without further purification. Distilled water was used for synthesis of complex. Melting point of the complex was recorded by capillary tube method on a Gallenkamp, serial number C040281, U.K. electrothermal melting point apparatus. FT-IR spectrum of the complex was recorded on a Nicolet-6700 FT-IR spectrophotometer, Thermoscientific, USA, in the range of 4000 to 400 cm^{-1}.

Synthesis

The complex was prepared by adding 5 mmol (0.974 g) of 2-methyl-3-nitrophenylacetic acid to 5 mmol of $NaHCO_3$ (0.42 g) in 25 ml of distilled water at 60° C with stirring till complete neutralization of acid. Then 2.5 mmol of $CuSO_4.5H_2O$ (0.72 g) dissolved in 5 ml of distilled water was added dropwise to the above reaction mixture and stirring was continued for next 2 h. Finally, 2.5 mmol (0.23 ml) of 2-Cl-py was added to the mixture. The stirring was continued until the complex was completely precipitated. The complex was collected by filtration and then air dried. It was recrystallized in methanol. Melting point: 208-210℃.



Scheme-1: Reaction scheme of the Cu(II)-complex synthesis.

UV-Visible Spectroscopy

UV-Visible spectrum of the complex was recorded on UV-1800 Shimadzu spectrometer within wavelength range of 190-800 nm with lower cut off at 220 nm. 0.2 M solution of the complex was prepared in methanol at room temperature. Bands in the region of 400 nm to 800 nm were assigned to *d-d* transitions and in the region of 220 nm to 400 nm assigned to π→π*, n→π* and ligand to metal charge transfer transitions. Value of ε for complex is 146 L $mol^{-1}cm^{-1}$ [17].

X-ray Diffraction (XRD)

Crystallographic data of the complex was collected at 296 K using an Oxford Gemini Ultra S CCD diffractometer using graphite monochromatic Mo-Kα radiations (λ=0.71073 Å). Data reduction and empirical absorption corrections were accomplished using CrysAlisPro (Oxford diffraction version 171.33.66). Crystal structure of complex was solved using SHELXS-86 and refined by full matrix least squares analysis against F^2 with SHELXL-2014/7 within the WinGX package. The drawing of the complex was created using ORTEP3 [18, 19].

DNA Binding Studies by Absorption Spectroscopy

Protein free salmon sperm DNA (SSDNA) solution was prepared by using overnight stirred solution of DNA and recording its absorbance at 260 nm and 280 nm. The ratio of (A_{260}/A_{280}) was 1.7 confirming protein free nature of prepared SSDNA solution [20]. The concentration of SSDNA was calculated using molar absorption co-efficient of 6600 $M^{-1}cm^{-1}$ at 260 nm for SSDNA. 0.1 mM solution of the complex was prepared in methanol. The absorption titrations were performed by successive addition of 0.172 mM aqueous SSDNA solution at the rate of 150µl for each measurement in both complex and reference solutions to eliminate the absorbance of SSDNA itself. Both solutions were incubated for 30 mins at room temperature before each measurement. Absorption spectra were recorded using cuvettes of 1cm path length at room temperature.

α-Gucosidase Inhibition Study

α-Glucosidase enzyme inhibition assay was performed by employing previously reported procedure with modifications [21]. Solution of commercial α-glucosidase enzyme (1unit/ml) and the substrate (20 mM) *p*-nitrophenyl-α-D-glucopyranoside (PNG) was prepared in 50 mM phosphate buffer (pH 6.8). 96-Well plates were used to perform the assay in triplicates with Acarbose as control. The assay was performed by mixing 25 µl of PNG, 65 µl of buffer and 5 µl of enzyme along with 5 µl of complex solution in DMSO with final concentrations of 200, 100 and 50 ppm, respectively. These mixtures were incubated at 35 °C for 30 min. After incubation, 0.5 mM sodium bicarbonate (100 µl) was added as stopping reagent. Percentage inhibition was calculated by the given formula and taking absorbance (Abs.) at 405 nm with microplate reader (BioTek Elx-800). IC_{50} value was calculated by using GraphPad Prism 5 [22].

Percentage inhibition = [(Abs. of control – Abs. of sample)/ Abs. of control] ✕ 100

Results and Discussion

FT-IR Analysis

The FTIR spectrum of the complex was furnished with all the characteristic bands along with number of overtones. Absorption band at 2960 cm^{-1} was assigned to aliphatic C–H while at 1558 cm^{-1} and 1428 cm^{-1} represented asymmetric and symmetric O–C═O stretching modes of fully deprotonated carboxylate group of oxygen donor ligand. Absorption bands at 1588 cm^{-1} and 1427 cm^{-1} reflected C═C stretching [23]. Two absorption bands at 1458, 1349 cm^{-1} were observed due to presence of NO_2 substituent on phenylacetate moiety [24]. Absorption bands at 426 cm^{-1} and 480 cm^{-1} were assigned to (Cu–O) and (Cu–N) bonds, respectively [25, 26].

The difference between asymmetric and symmetric stretching frequencies of carboxylate group, $\Delta\nu\{\nu(OCO)_{asym} - \nu(OCO)_{sym}\}$, calculated for the complex was 130 indicating bidentate binding mode of carboxylate ligand [27]. All these observations were further supported by single crystal XRD analysis of the complex.

XRD Analysis

Crystal's data with structural refinement information are given in Table 1. Selected bond distances and angles for the complex are given in Table 2. ORTEP diagrams of symmetric dimeric unit, asymmetric unit and close packing diagram of the complex are given in Figs. 1a, b and c, respectively. The unit cell of the complex consists of dimeric units with overall paddlewheel conformation. Each metal atom of the dimer is bound to four oxygen atoms from four carboxylate ligands and one nitrogen atom from pyridine moiety thus giving rise to distorted square pyramidal geometry around each metal center of dimer with τ value of 0.19 where (τ = distortion factor = (β˚- α˚/60˚).

Table-1: Crystal's data and structure refinement parameters.

Empirical formula	$C_{46}H_{40}Cl_2Cu_2N_6O_{16}$
Formula weight ($gmol^{-1}$)	1130.82
Temp, K	296(2)
λ (Å)	0.71073
Crystal system	Monoclinic
Space group	P 2/n
a (Å)	10.6865(8)
b (Å)	10.4925(8)
c (Å)	21.2246(17)
α (°)	90
β (°)	101.673(3)
γ (°)	90
Volume ($Å^3$)	2330.7(3)
Z	2
ρ calculated(gcm^{-3})	1.444
μ (mm^{-1})	1.108
F (000)	1156
Crystal size (mm^{-1})	0.40×0.24×0.20
No. of reflections collected	5083
Goodness-of-fit on F^2	1.036
Final R index [I > 2σ(I)]	0.0403
wR_2 (all data)	0.1074

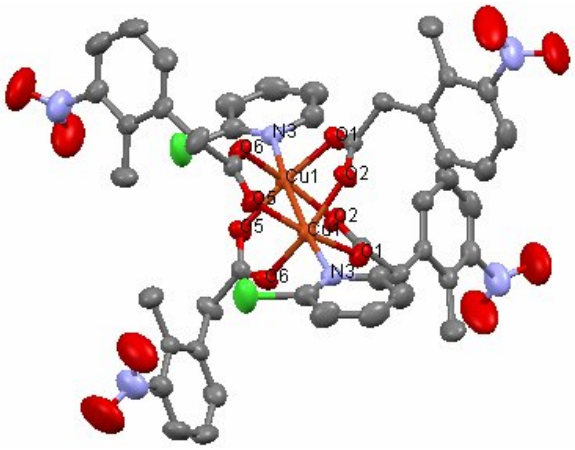


Fig. 1: (a) ORTEP diagram of symmetric dimeric unit of the complex. The H-atoms have been omitted for clarity.

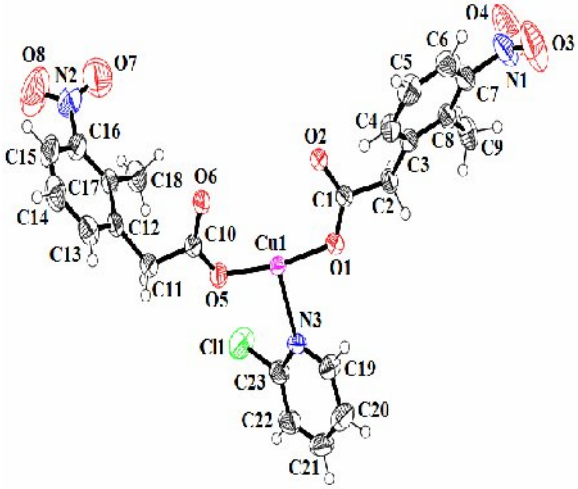


Fig. 1: (b) ORTEP diagram of asymmetric unit of the complex with thermal ellipsoid drawn at 50 % probability level. The H-atoms are shown as small circles of arbitrary size.

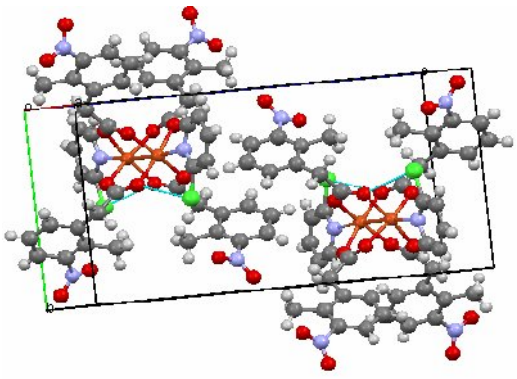


Fig. 1c: 3D close packing diagram of the complex.

Table-2: Selected bond lengths (Å) and angles (˚).

Bonds	Distances (Å)
Cu1 ─ O5	1.948(2)
Cu1 ─ O6	1.9679(19)
Cu1─ O1	1.9749(19)
Cu1 ─ O2	1.9921(19)
Cu1─ N3	2.244(2)
	Angles (˚)
O5─Cu1─ O6	91.80(9)
O5─Cu1─O1	168.04(8)
O6─Cu1─O1	89.10(9)
O5─Cu1─O2	87.56(9)
O6─Cu1─O2	165.56(8)
O1─Cu1─O2	88.61(9)
O5─Cu1─N3	99.27(8)
O6─Cu1─N3	99.93(8)
O1─Cu1─N3	92.31(8)
O2─Cu1─N3	94.40(8)
O5─Cu1─Cu1	83.71(6)
O6─Cu1─Cu1	83.29(6)
O1─Cu1─Cu1	84.55(6)
O2─Cu1─Cu1	82.30(6)
N3─Cu1─Cu1	175.49(6)

Four oxygen atoms occupy equatorial positions and nitrogen atom from substituted pyridine is present at axial position of distorted square pyramid. Cu·····Cu intradimer distance is 2.66 Å which is typical of classical paddlewheel structures [28, 29]. Four carboxylate ligands are attached to metal center in *syn-syn* fashion. Cu─O distances ranges from 1.948(2) to 1.992(3) Å. Cu─N bond distance is 2.244 Å which is relatively longer than usual because of presence of chloro-substituent at *ortho*-position of pyridine. Presence of electron withdrawing group at *ortho*-position lowers the basicity of pyridine which results in elongation of metal─nitrogen bond [30]. The largest bond angle in complex is N3─Cu1─Cu1 with value of 175.49°. O2─Cu1─Cu1 being the smallest one around each metal center with value of 82.30°. This data of bond lengths and angles resembles with the reported structurally similar copper complexes [31-33].

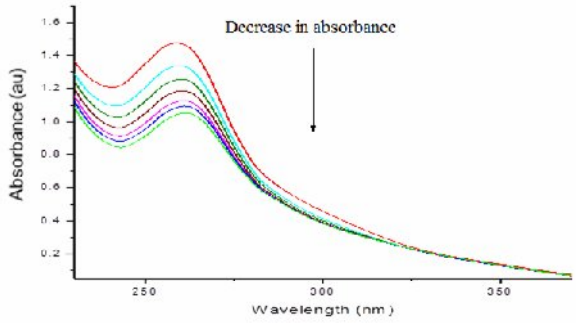
The close packing arrangement of complex is stabilized by two types of intermolecular interactions; one being the hydrogen bond and other one is π─π stacking interaction present between two nearby aromatic rings [34]. The Intramolecular hydrogen bonds are C2─H2A···O4, C6─H6···Cl1 and C19─H19···O1 which are scattered throughout the crystal lattice of the complex. Moreover, π─π stacking interactions between the neighboring aromatic rings is another interesting feature of the synthesized complex. All these interactions provide the backbone to supramolecular structure of the complex [35].

DNA Binding Study

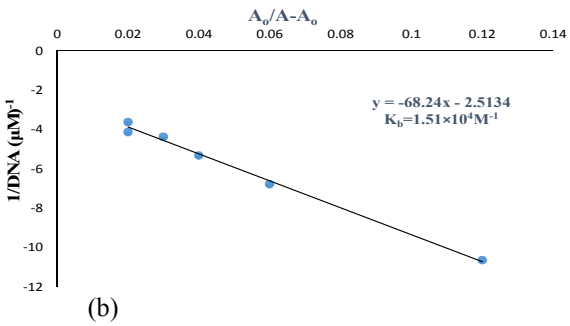
DNA binding ability of the complex was evaluated by using UV-visible spectroscopy. The binding mode of complex with DNA was depicted by peak patterns of recorded spectra while extent of its binding was reflected by calculating its binding constant (K_b) value. Absorption spectra of complex in the presence of SSDNA are shown in Fig.2a. As the concentration of SSDNA was increased, hypochromism (decrease in absorption) and bathochromism (red shift = 3-4 nm) was observed in absorption peak. It suggests that complex binds with DNA molecule through intercalation [36]. On the other hand smaller red shift is also indicative of groove binding mode thus, overall suggesting mixed binding mode of complex with DNA molecule [37]. K_b for the complex was calculated by using famous Benesi-Hildebrand equation which is given as [38]:

$$\mathbf{A_o/A\text{-}A_o = \varepsilon_G/\varepsilon_{H\text{-}G}\text{-}\varepsilon_G + \varepsilon_G/\varepsilon_{H\text{-}G}\text{-}\varepsilon_G.1/K_b[DNA]}$$

where K_b is binding constant, A and A_o are the absorbance of complex-DNA adduct and pure complex solution, respectively. [DNA] is the concentration of SSDNA in mol/l and $\boldsymbol{\varepsilon_{H\text{-}G}}$, $\boldsymbol{\varepsilon_G}$ are molar absorption co-efficients of complex-DNA adduct and pure complex, respectively. The value of K_b was calculated from intercept to slope ratio of the plot of 1/ [DNA] *vs.* $A_o/A\text{-}A_o$ as shown in the Fig. 2b. K_b calculated for the complex was 1.51×10^4 M^{-1} reflecting its DNA binding ability [39, 40].



(a)



(b)

Fig. 2: (a) UV spectrum of the complex showing absorption changes. (b) Linear plot between $A_o/A\text{-}A_o$ along x-axis and 1/[DNA] $(\mu M)^{-1}$ along y-axis for calculating binding constant K_b.

α-Glucosidase Inhibition Study

α-Glucosidase is present in the brush border of small intestine and it catalyzes the last glucose-releasing step in starch digestion. By regulating its action through α-glucosidase inhibitor is an attractive approach for controlling blood glucose levels for the treatment of Type II diabetes in modern era of medicine [41]. In present study, α-glucosidase enzyme inhibition activity of the complex was determined by using PNG as a substrate where acarbose (IC_{50} 20.29 μM) served as positive control. The results showed that the complex exhibited enzyme inhibition activity in dose dependent manner with IC_{50} 13.1 μM. The significant enzyme inhibition activity of the complex represented the positive potential of the complex to be used as anti-diabetic agent [42].

Conclusions

We have successfully synthesized and characterized a heteroleptic Cu(II) complex that has adopted a dimeric paddlewheel structure, where each metal atom is penta-coordinated with distorted square pyramidal geometry. DNA binding ability of the complex has been investigated by absorption spectroscopy. Results showed that the complex binds with DNA *via* intercalative as well as groove binding mode. *In vitro* dose dependent enzyme inhibition activity of the complex revealed its potential as anti-diabetic agents as well.

Acknowledgments

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Supplementry Data

Crystallographic data for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Centre, with CCDC # 1540909. Copies of this information may be obtained free of charge from The Director, CCDC, 12, Union Road Cambridge CB2 1EZ [Fax: +44 (1223)336 033] or e.mail: deposit @ccdc.cam.ac.uk.

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