Structural, computational and cytotoxic studies of square planar copper(II) complexes derived from dicyandiamide

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ABSTRACT

In this study, two new copper(II) complexes, $[Cu(L^1)_2](ClO_4)_2$ and $[Cu(L^2)_2](ClO_4)_2$ derived from dicyandiamide were synthesized and characterized by the analytical and spectroscopic methods such as elemental analyses, infrared and mass, spectra. The ligands L^1 and L^2 formed within the course of the complex formation by nucleophilic attach of alcohols to the nitrile group of the ligand in the presence of Cu(II) ion. In the spectra of the complexes, the absence of the $v(C\equiv N)$ band at ca. 2157 cm^{-1} and appearance of new bands characteristic of $v_a(C–O–C)$ at ca. 1265 cm^{-1} suggested that the alcohols have added across the nitrile group of the ligand. This was further confirmed by single crystal X-ray analysis of the complexes. In the structure of the complexes, copper(II) ion has square planar geometry, coordinated to the imine nitrogen atom with no significant interactions above or below the plane. The coordinated nitrogen donors show convincing imine (C=N) bond character. Computational studies are performed on $[Cu(L^1)_2](ClO_4)_2$ and $[Cu(L^2)_2](ClO_4)_2$ complexes. Optimized geometries, frontier molecular orbitals (FMO) and non-linear optical (NLO) properties of the complexes were studied. Cytotoxic effects of the synthesized copper(II) complexes at various concentrations were also studied against 3 different cell lines, mouse connective tissue fibroblast (L929), breast cancer (MCF-7) and bone cancer (MG63).

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1. Introduction

Metal complexes have been widely applied in clinics for centuries, although their molecular mechanism has not yet been entirely understood [1–3]. Nitrogen-donor based copper complexes are of great interests since they may mimic active sites of many copper-containing enzymes and also for their potential usage as metallo-drugs [1–4]. Copper as an essential element for human with its bioessential activity and oxidative nature has attracted numerous inorganic chemists to address Cu(II) complexes with the aim of medical applications [4–8]. There are several papers in literature regarding the biological activities of synthetic these complexes. The copper(II) complexes can interact with nucleic acids by intercalation, however, their interactions depends on their molecular structure. In this respect the design of functional bio-materials has taken great attention due to their potential applications as pharmaceutical materials [9–12].

Dicyandiamide is a compound having an active nitrile group and has taken attention in research in the view of both fundamental and application. The nitrile group in this compound is susceptible to nucleophilic attach by water, alcohols and amines in the presence of transition metals [13–20]. In particular, no reaction occurs between alcohols and dicyandiamide in the absence of Cu(II) or Ni(II), even at drastic experimental conditions. In a typical reaction, alcohol addition to the nitrile group of the dicyandiamide in the presence of Cu(II) with reflux results in high yields and pure square planar mononuclear complexes [21]. However, in the presence of Ni(II) the same reaction requires a base and longer reaction times [22].

In recent years, experimental studies are supported by quantum chemical computational studies. Hartree–Fock (HF) and Density Functional Theory (DFT) methods are widely used in calculations of molecular geometry, vibrational frequencies and chemical shifts [23]. In this study molecular geometries, frontier molecular orbitals (FMO) and non-linear optical (NLO) properties of mentioned complexes are predicted by using HF method.

Recently, we have reported the synthesis and characterization of azo-chromophore group containing ligands and their copper

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(II) complexes and evaluated their photophysical and biological activities [24–28]. Because of the importance of metal complexes and in continuance of our interest in synthesis of new ligands and their transition metal complexes, two Cu(II) complexes derived from dicyandiamide were prepared and characterized by spectroscopic and analytic methods. Molecular structures of the copper(II) complexes were also determined by single crystal X-ray diffraction studies. Cytotoxic properties of the structurally characterized complexes were carried out on mouse connective tissue fibroblast (L929), breast cancer (MCF-7), bone cancer (MG63) cell lines.

2. Experimental

2.1. Chemicals

Dicyandiamide and $Cu(ClO_4)_2 \cdot 6H_2O$ were purchased from Aldrich and Merck, respectively. All reagents and solvents for synthesis and analysis were purchased from commercial sources and used as received unless otherwise noted.

2.2. Physical measurements

The IR spectra were obtained ($4000–450\ cm^{-1}$) using a Perkin Elmer spectrum 100 FT-IR spectrophotometer. ESI mass spectra were recorded on a Thermo Fisher Exactive+Triversa Nanomate mass spectrometer. Carbon, hydrogen and nitrogen elemental analyses were performed with a model CE-440 elemental analyzer. Data for X-ray crystallography for the copper(II) complexes were collected at 150(2) K on a Bruker ApexII CCD diffractometer using Mo Kα radiation ($\lambda = 0.71073\ Å$). Data reduction was performed using Bruker SAINT [29]. SHELXS97 was used to solve and SHELXL2014/6 to refine the structure [30].

2.3. Synthesis of $[Cu(L^1)_2](ClO_4)_2$

The complex was prepared according to the reported method [31]. A solution of copper(II) perchlorate hexahydrate (75 mg, 0.30 mmol) in 5 mL of ethanol was added dropwise to a solution of dicyandiamide (137 mg, 0.60 mmol) in 25 mL of ethanol. The reaction mixture was refluxed for 4 h at room temperature. Then, the solution was allowed to evaporate at room temperature until pink-violette crystals appear. The solid was filtered and washed with cold methanol (5 mL) and diethyl ether (5 mL).

Single crystals were grown by slow vapor phase diffusion of diethylether into the methanolic solution of the complex. Elemental analyses for $C_8H_{20}Cl_2CuN_8O_{10}$: Calc. C, 18.38; H, 3.86; N, 21.44. Found: C, 18.63; H, 3.893; N, 21.49%. ESI Mass Spect. (m/z): 322.09 (100%) $[Cu(L^1)_2]^+$, 252.03 (90%) $[Cu(C_4H_{12}N_8O)]^+$. IR (cm^{-1}): 3428, 3233 (N–Hs), 3347 (NH_2), 2986 (aliphatic C–H), 1656 (C≡N), 1266 (C–O–C), 1060 (ClO_4), 621 (ClO_4).

2.4. Synthesis of $[Cu(L^2)_2](ClO_4)_2$ complex

Copper(II) perchlorate hexahydrate (2.18 g, 5.95 mmol) dissolved in 20 mL of CH_3CN was added to dicyandiamide (1 g, 12 mmol) in CH_3CN (15 mL). To this solution, $PhCH_2OH$ (5 mL) dissolved in 10 mL of CH_3CN was added dropwise. The reaction mixture was refluxed for 4–6 h and then left to cool. Pink-violette crystals were separated and washed with methanol and diethyl ether. Elemental analyses for $C_{18}H_{28}Cl_2CuN_8O_{12} \cdot 2H_2O$: Calc. C, 31.66; H, 4.13; N, 16.41. Found: C, 31.82; H, 4.150; N, 17.15%. ESI Mass Spect. (m/z): 446.12 (100%) $[Cu(L^2)_2]^+$, 356.08 (50%) $[Cu(C_{11}H_{17}N_8O)]^+$, 313.07 (10%) $[Cu(C_{11}H_{17}N_6O)]^+$. IR (cm^{-1}): 3463, 3353, 3226 (N–H), 1665 (C = N), 1268 (C-O-C), 1058 (ClO_4), 621 (ClO_4).

*Caution: Perchlorate salts of metal complexes are potentially explosive and must be handled with care.

2.5. X-ray crystallography

The structures were solved by direct methods and refined on F^2 using all the reflections [30]. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon atoms were inserted at calculated positions using a riding model. Hydrogen atoms bonded to the nitrogen and oxygen atoms were located from difference maps and refined with temperature factors riding on the carrier atom. The N–H and O–H bond distances were fixed to 0.88 and 0.85 Å, respectively. In complex $[Cu(L^1)_2](ClO_4)_2$, perchlorate ion is disordered which was modeled over two positions with the site occupancy of 0.7:0.3. Details of the crystal data and refinement are given Table 1.

2.6. Computational method

Input file of the synthesized Cu(II) complexes were prepared with Gauss View 5.0.8 program [32]. All calculations were made

Table 1
Crystallographic data for the complexes.

Identification code	$[Cu(L^1)_2](ClO_4)_2$	$[Cu(L^2)_2](ClO_4)_2 \cdot 2MeOH$
Empirical formula	$C_8H_{20}Cl_2CuN_8O_{10}$	$C_{20}H_{32}Cl_2CuN_8O_{12}$
Formula weight	522.76	790.18
Crystal size (mm^3)	$0.43 \times 0.14 \times 0.36$	$0.166 \times 0.07 \times 0.063$
Crystal color	pink	pink
Crystal system	monoclinic	triclinic
Space group	$P2(1)/n$	$P\bar{1}$
Unit cell a (Å)	5.3408(4)	5.0390(16)
b (Å)	13.7926(10)	8.822(3)
c (Å)	13.4695(10)	17.476(5)
α (°)	90	82.898(5)°
β (°)	100.1520(10)	89.924(5)°
γ (°)	90	74.453(5)°
V ($Å^3$)	976.68(12)	742.3(4)
Z	2	1
Absorption coefficient (mm^{-1})	1.458	0.988
Reflections collected	10460	7233
Independent reflections [R_{int}]	2677 [0.0273]	3417 [0.0524]
R_1, wR_2 [I > 2σ (I)]	0.0284, 0.0720	0.0494, 0.1016
R_1, wR_2 (all data)	0.0347, 0.0753	0.0902, 0.1158
CCDC number	1482953	1482954