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Copper Complexes with 4(3*H*)-Quinazolinone: Thermal Gravimetric Analysis and Anticancer Activity of $[Cu(L)_2(H_2O)_2(NO_3)_2]$, $[Cu(L^-)(NO_3)]_n$, and $[Cu(L)_2(H_2O)_2(Cl)_2]$[1]

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Abstract—The title complexes $[Cu(L)_2(H_2O)_2(NO_3)_2]$ (**I**), $[Cu(L^-)(NO_3)]_n$ (**II**), and $[Cu(L)_2(H_2O)_2(Cl)_2]$ (**III**), where L = 4(3*H*)-quinazolinone, had been synthesized and characterized by elemental analysis, and single crystal X-ray diffraction analysis (CIF files CCDC nos. 1409899 (**I**), 1409901 (**II**), 1409900 (**III**)). The results show that complex **I** belongs to the triclinic system, space group $P\bar{1}$; complex **II** belongs to the orthorhombic system, space group *Pbca*; complex **III** belongs to the monoclinic system, space group $P2_1/c$. TG curves show that complex **II** is more stable than complex **I** and complex **III**. Anticancer activity of the complex **I** was 25.92, 9.70, 13.58 and 18.56 μg mL^{-1} against the human cancer cells 7404, A549, HepG2 and NCI-H1650, respectively.

Keywords: 4(3*H*)-quinazolinone, complex, anticancer activity, synthesis

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INTRODUCTION

With the development of bio-inorganic chemistry and analytical tools to continuously improve, more and more studies show that coordination compounds play an important role in our life [1–5]. Heme in mammals, such as chlorophyll in plants, animals and plants are complex organic molecules and metal magnesium, iron formation, natural organic molecules of protein complexes containing copper execution of invertebrates in the blood oxygen function. Pharmacological tests proved that 4(3*H*)-quinazolinone has antibacterial [6, 7], anti-virus [7], cancer [8, 9], antihypertensives [10], anti-high blood cholesterol [11], as well as resistance to high cholesterol [12]. Copper complexes anticancer activity also attracted people's attention. For example, Yin [13] synthesized two copper complexes based on 2,2'-bipyridine and demethylcantharate, and the compounds were tested in vitro against human tulnor cells, HL-60, BGC-823, Bel-7402 and HeLa, and displayed high activity. Easmon [14] and Palanimuthu [15] both also synthesized copper complexes, and tested their anticancer activity. Meanwhile, 4(3*H*)-quinazolinone (L) has a planar structure, it is very easy to form the flat-type complex. Such complex has easy way to insert a DNA tumor or viral action, so as to achieve anti-tumor, anti-viral purpose. Therefore, study the pharmacological active of 4(3*H*)-quinazolinone complexes have important significance. In this paper, ligand L and $Cu(NO_3)_2 \cdot 3H_2O$ as a raw material, in the same ratio material, solvent and under different reaction temperatures, we synthesized three new complexes: $[Cu(L)_2(H_2O)_2(NO_3)_2]$ (**I**), $Cu(L^-)(NO_3)]_n$ (**II**), and $[Cu(L)_2(H_2O)_2(Cl)_2]$ (**III**).

EXPERIMENTAL

Physical measurements. All solvents, chemicals and ligand L were commercial reagents and used without further purification. Elemental analyses (C, H, and N) were performed with a Perkin-Elmer 240 elemental analyzer. The crystal structure was determined by Agilent supernova diffractometer. The thermal stability of complexes was studied in the range of 45–1000°C under a nitrogen atmosphere with 5°C min^{-1} heating rate on Pyris Daimond TG-DTG Analyzer.

Synthesis of I. The 0.2 mmol (0.0292 g) L and 0.1 mmol (0.0241 g) $Cu(NO_3)_2 \cdot 6H_2O$ were dissolved in 10 mL of acetonitrile, stirred for 2 min at room temperature, filtered, the filtrate was collected in 50 mL of beaker, partial evaporated at room temperature for 2 h,

[1] The article is published in the original.

blue bulk crystal were obtained. The yield was for 78.1% (based on copper).

For $C_{16}H_{16}N_6O_{10}Cu$

anal. calcd., %:	C, 37.21;	H, 3.12;	N, 16.28
Found, %:	C, 37.33;	H, 3.21;	N, 16.21.

Synthesis of II. The 0.2 mmol (0.0292 g) L and 0.1 mmol (0.0241 g) $Cu(NO_3)_2 \cdot 6H_2O$ were added to 8 mL of acetonitrile and 2 mL of water, stirred for 20 min, sealed with a stainless steel jacket placed in drying oven after reaction at 150°C for 24 h and then cooled to 130°C, the reaction was continued for 24 h, turn off the oven was slowly cooled to room temperature, open the Teflon liner, yellow and green flake crystal obtained. The yield was for 10.1% (based on copper).

For $C_8H_5N_3O_4Cu$

anal. calcd., %:	C, 35.49;	H, 1.85;	N, 15.53
Found, %:	C, 35.52;	H, 1.83;	N, 15.49.

Synthesis of III. The 0.2 mmol (0.0292 g) L and 0.1 mmol (0.0170 g) $CuCl_2 \cdot 2H_2O$ were dissolved in 10 mL of acetonitrile, stirred at room temperature for 20 min, filtered, the filtrate was collected in 50 mL beaker, natural volatile at room temperature for 48 h, green bulk crystal obtained. The yield was for 68.1% (based on copper).

For $C_{16}H_{16}CuN_4O_4Cl_2$

anal. calcd., %:	C, 41.51;	H, 3.46;	N, 18.16
Found, %:	C, 41.56;	H, 3.44;	N, 18.21.

Anticancer activity assay. The in vitro cytotoxicities of the ligands L, complexes **I** and **II** were evaluated by MTT [16] assay on 7404 (human hepatoma cells), A549 (human non-small cell lung cancer), HepG2 (human hepatoma cells), NCI-H1650 (human non-small cell lung cancer cells) cell line. All of complexes dissolved in DMSO were tested. Under the same experimental conditions, 5-fluorouracil (5-FU) was used as a positive control drug.

X-ray crystallography. Diffraction intensities were collected on a Bruker Apex CCD area-detector diffractometer (MoK_α, $\lambda = 0.71073$ Å). The structure was solved with direct methods and refined with a full-matrix least-squares technique with the SHELXTL program package [17]. The hydrogen atoms were placed at calculated positions and refined as riding atoms with isotropic displacement parameters. Crystallographic crystal data and structure processing parameters for **I**–**III** are summarized in Table 1. Selected bond lengths and bond angles for complexe **I**–**III** are listed in Table 2. Hydrogen bonds for complexes **I**–**III** are listed in Table 3.

Supplementary material for **I**–**III** has been deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 1409899 (**I**), 1409901 (**II**), 409900 (**III**); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

In this paper, we used 4(3*H*)-quinazolinone (L) and Cu(II) salts as raw material, the same molar ratio material and solvent and different reaction temperatures. Complex **I** was obtained at room temperature. 3D coordination polymer **II** was obtained by hydrothermal synthesis, at that we used different synthesis temperature to achieve a zero-dimensional complex transition to a three-dimensional complex.

The molecular structure of complex **I** was shown in Fig. 1a. The Cu^{2+} ion in **I** is coordinated by two nitrogen atoms from different ligands L, two oxygen atoms from two nitrates, and two oxygen atoms from two aqua ligands. The center Cu^{2+} ion is six-coordinated. Because of Jahn–Teller effect, the exceptional longer distances are Cu–O(2), which defines *z* axis of the coordination. The Cu–N bond length is 2.064 (3) Å, Cu–O bond length range from 1.957(3) (Cu(1)–O(2)) to 2.447(3) Å (Cu(1)–O(1)), which is in the normal range [18]. Since the introduction of the water molecules takes place, there are not only the intramolecular hydrogen bond in **I** but also intermolecular hydrogen bonds—the O atom in carbonyl group on the ligand formed O–H···O intramolecular hydrogen bonds with water molecule; O atoms on the other nitrate ions of 1 formed O–H···O intermolecular hydrogen bonds with water molecules (Fig. 1b).

The coordination environment of Cu^{2+} ions in **II** are given in Fig. 2a. The Cu^{2+} ion in **II** is five-coordinated by two nitrogen atoms from two ligands L, one oxygen atom from ligand L, and two oxygen atoms from two nitrates. The Cu–N bond length are in the range from 2.221(9) to 2.270(10) Å, Cu–O bond length are in the range from 2.279(10) to 2.467(11) Å, which is in the normal range [19].

The smallest structural unit of polymer **II** has three ligands coordinated by one of the ligand to provide O atom (from carbonyl group); another offer N anion (H atom has lost) on the carbonyl group of the *ortho*, the last offer N atom on the carbonyl group of the contraposition. Thus, in **II**, the three coordination sites on the ligand are involved in the coordination, so ligand taken μ_3-η1:η1:η1 bridging. Notably, there are π···π stacking interactions in coordination polymer **II** (Fig. 2b). These intramolecular π···π effect on the stability of the molecular structure plays an important role. As the ligand adopts a μ_3-η1:η1:η1 bridging style and nitrate takes a μ_2-η1:η1 bridging style, the polymer **II** exhibits a very special 3D structure (Fig. 2c). The polyhedron of Cu^{2+} ions in **II** can more clearly saw from Fig. 2d.

Table 1. Crystallographic data and refinements of complexes **I**–**III**

Parameter	Value		
	I	**II**	**III**
Temperature, K	293(2)	293(2)	293(2)
Crystal system	Triclinic	Orthorhombic	Monoclinic
Space group	$P\bar{1}$	*Pbca*	$P2_1/c$
a, Å	6.5381(6)	10.1242 (5)	6.7441(3)
b, Å	7.3762(6)	7.6747 (5)	18.5130(4)
c, Å	10.1314(11)	23.8171 (15)	6.78147(15)
α, deg	83.532(8)	90	90
β, deg	74.312(9)	90	90.707(3)
γ, deg	88.204(7)	90	90
Volume, Å ^{3}; *Z*	467.40(8); 1	1850.59(19); 4	846.62(5); 2
ρ_{calc}, g/cm^3	1.833	1.929	1.815
Crystal size, mm	0.40 × 0.20 × 0.12	0.44 × 0.18 × 0.11	0.41 × 0.21 × 0.12
Limiting indices	$-8 \le h \le 8$, $-9 \le k \le 9$, $-12 \le l \le 13$	$-12 \le h \le 11$, $-10 \le k \le 8$, $-29 \le l \le 31$	$-8 \le h \le 8$, $-23 \le k \le 23$, $-8 \le l \le 9$
F(000)	263.4894	1075.2259	471.44384
μ, mm^{-1}	1.24	2.36	1.64
θ Range, deg	3.2–28.3	3.2–28.4	3.2–28.4
Collected reflections	5117	5469	9139
Independent reflections	2138	2134	2005
R_{int}	0.027	0.044	0.028
R ($F^2 > 2\sigma(F^2)$)	0.056	0.082	0.031
wR (F^2)	0.180	0.231	0.080
Reflections/parameters	2138/151	2134/144	2005/126
S	1.33	1.07	1.04
$(\Delta/\sigma)_{max}$	0.536	0.002	0.053
$\Delta\rho_{max}/\Delta\rho_{min}$, *e* Å^{-3}	1.29/–0.75	2.07/–1.55	0.66/–0.55

The structure of the complex **III** (Fig. 3) is similar to that published in [20]. However, the synthesis method is not the same. We use the simple and rapid method for the synthesis of complex **III**. The center Cu^{2+} ion is six-coordinated. The Cu–N bond length is 2.0225(17) Å, Cu–Cl bond length is 2.3468(5) Å. These bond lengthes are in the normal range [20].

We studied the thermal stability of these complexes. TG curves are given in Fig. 4. Thermalgravimetric (TG) curve of complex **I** has an obvious platform between 45 to 164°C (weight loss of two coordinate H_2O: obsed. 6.98%; calcd. 6.982%), indicating that within this temperature range complex **I** loses two coordinated water molecules. Weight loss 32.27% at 164 to 256°C may be complex ligand starts portion to split and finally 30% CuO remains.

TG curve for complex **II** shows, the complex **II** appears gentle decline between 45 to 404°C (weight loss 12%). There is a very significant decline between 404 to 496°C (weight loss ligands: obsed. 42%; calcd. 45.7%), indicating that at this temperature range ligand most have already started to decompose; there is a relatively flat platform between 496 to 1000°C and finally the remaining 18% CuO.

The complex **III** appears an obvious platform between 45 to 131°C (weight loss of two ligands H_2O: obsed. 7.91%; calcd. 7.78%), indicating that within this temperature range complex **III** loses two coordinated water molecules; weight loss 63.27% at 132 to 657°C may be ligand started a small split, and finally the remaining 30% of CuO.

Complex **I** was evaluated for antitumor activities in vitro against 7404 (human hepatoma cells), A549

Table 2. Selected bond lengths (Å) and bond angles (deg) of complex **I**–**III***

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
		I			
Cu(1)–O(2)	1.957(3)	Cu(1)–N(1)	2.064(3)	Cu(1)–O(1)	2.447(3)
		II			
Cu(1)–O(3*A*)	2.462(10)	Cu(1)–O(2)	2.281(9)	Cu(1)–O(1*C*)	2.287(9)
Cu(1)–N(1)	2.221(9)	Cu(1)–N(2*B*)	2.273(9)		
		III			
Cu(1)–Cl(1)	2.3468(5)	Cu(1)–O(2)	2.4758(18)	Cu(1)–N(1)	2.0225(17)
Angle	ω, deg	Angle	ω, deg	Angle	ω, deg
		I			
N(1)Cu(1)O(2)	88.52(11)	O(1)Cu(1)O(2)	95.34(11)	O(1)Cu(1)N(1)	93.09(11)
		II			
N(1)Cu(1)O(3*A*)	80.5(3)	N(2*B*)Cu(1)N(1)	119.5(3)	O(1*C*)Cu(1)O(2)	89.1(3)
O(2)Cu(1)O(3*A*)	79.8(3)	N(2*B*)Cu(1)O(2)	118.2(3)	O(1*C*)Cu(1)N(2*B*)	87.6(3)
O(2)Cu(1)N(1)	119.6(4)	O(1*C*)Cu(1)O(3*A*)	168.0(3)	N(3)O(3)Cu(1*C*)	113.4(8)
N(2*B*)Cu(1)O(3*A*)	93.6(3)	O(1*C*)Cu(1)N(1)	109.2(3)		
		III			
O(2)Cu(1)Cl(1)	90.72(5)	N(1)Cu(1)O(2)	91.48(6)	N(1)Cu(1)Cl(1)	90.20(5)

* Symmetry codes: (*A*) $-x + 3/2, y + 1/2, z$; (*B*) $x - 1/2, -y + 3/2, -z + 1$; (*C*) $-x + 1, -y + 1, -z + 1$; (*D*) $-x + 3/2, y - 1/2, z$ (see Fig. 2).

Table 3. Geometric parameters of hydrogen bonds of structure **I**, **III***

D–H···A	Distance, Å			Angle D–H···A, deg
	D–H	H···A	D···A	
		I		
O(2)–H(2*A*)···O(5*B*)	0.85(3)	1.95(2)	2.668(5)	141
O(2)–H(2*B*)···O(3*A*)	0.85(3)	1.79(1)	2.569(4)	152
		III		
O(2)–H(2*A*)···O(1)	0.84(3)	1.91(3)	2.723(2)	163

* Symmetry codes: (*A*) $-x + 3/2, y + 1/2, z$; (*B*) $x - 1/2, -y + 3/2, -z + 1$.

(human non-small cell lung cancer), HepG2 (human hepatoma cells), NCI-H1650 (human non-small cell lung cancer cells) by MTT method. The data represent the mean of the three experiments performed in triplicate. The IC_{50} (IC_{50}: 50% inhibitory concentrations) value is the concentration at which 50% survival of the cells is observed. The IC_{50} of title complexes against cancer cell are presented in Table 4.

The IC_{50} values of the complex **I** were 25.92, 9.70, 13.58 and 18.56 μg mL^{-1} against the human cancer

Table 4. Complex **I** anticancer activity (IC_{50})*

Name	IC_{50}, μg mL^{-1}			
Cell (molecular weight)	7404	A549	HepG2	NCI-H1650
5-FU (130)	2.27	2.39	2.64	2.54
Complex **I** (566)	25.92	9.70	13.58	18.56
L (146)	>50	>50	>50	>50

* 5-FU—5-fluorouracil; L—4(3*H*)-quinazolinone.

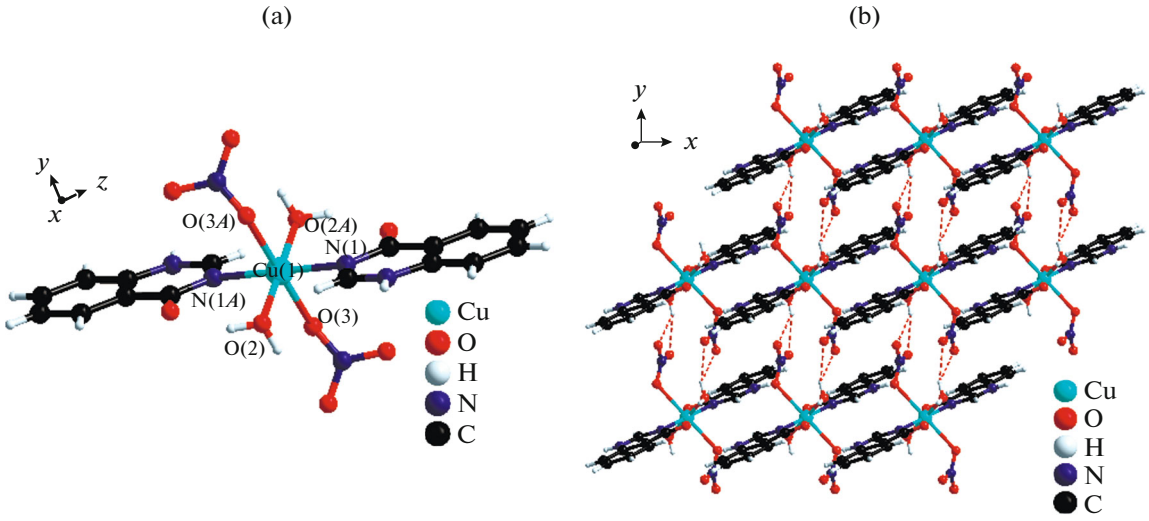

Fig. 1. Coordination environment of Cu^{2+} ions in **I** for clarity with thermal ellipsoids at 50% level (a); by hydrogen bonds formed 2D structure (*z* axis) (b).

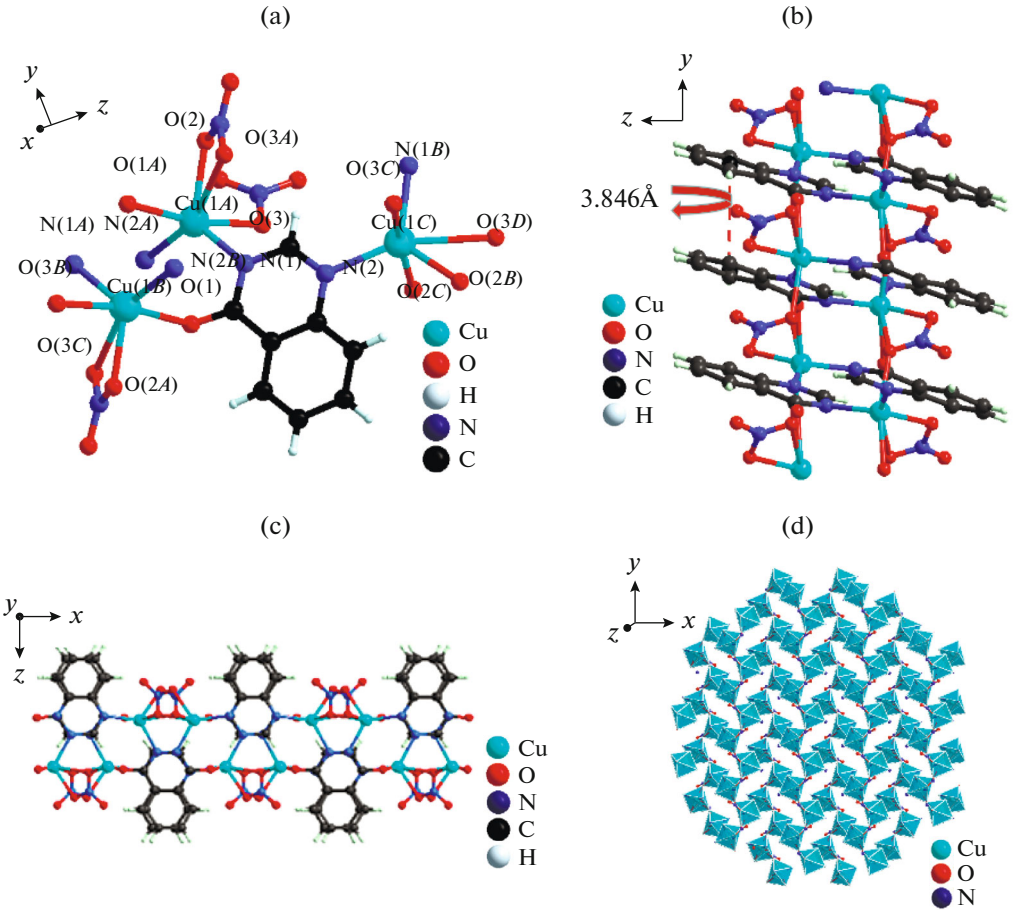

Fig. 2. Coordination environment of Cu^{2+} ions in **II** for clarity with thermal ellipsoids at 60% level (a); π···π stacking interactions in **II** (*x* axis) (b); a very special 3D structure (c); the polyhedra of Cu^{2+} ions in **II** (*z* axis), C and H have been removed (d) (symmetry codes see in Table 2).

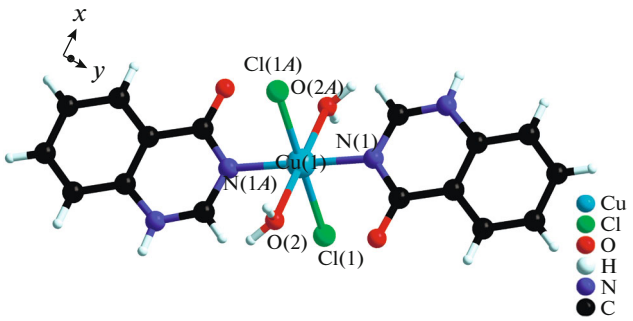

Fig. 3. Coordination environment of Cu^{2+} ions in **III** for clarity with thermal ellipsoids at 50% level (a).

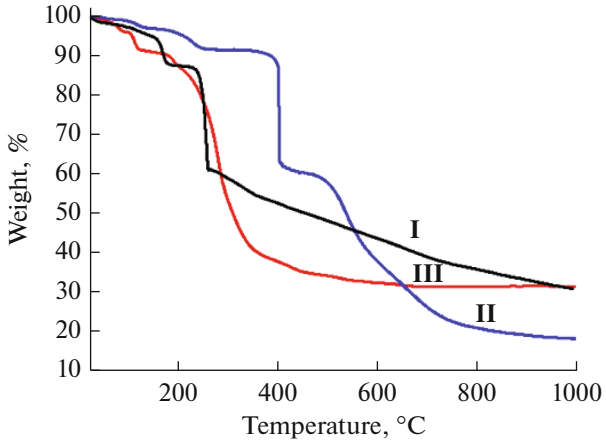

Fig. 4. TGA curves of complexes **I**–**III**.

cells 7404, A549, HepG2 and NCI-H1650, respectively. According [21], the compounds with the IC_{50} values more than 10–25 μg mL^{-1} exhibit weak inhibitory activity while those with values less than 5 μg mL^{-1} are considered to be very active. Those having intermediate values ranging from 5 to 10 μg mL^{-1} are classified as moderately active. The results have been compared with an anticancer drug 5-FU. Among the present complex, ligand L and complex **I** are less effective than 5-FU.

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