ISSN 1070-3284, Russian Journal of Coordination Chemistry, 2018, Vol. 44, No. 9, pp. 553–558. © Pleiades Publishing, Ltd., 2018.

Crystal Structure and Anti-Ovarian Activity of Two Novel Coordination Polymers $[Cu_2(o\text{-Cpia})(OH)(Bitb)_{0.5}]_n$ and $\{[Zn_7(OH)_4(Bta)_4(H_2O)_2](H_2NMe_2)_2(DMF)_3\}_n$[1]

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Received January 15, 2018

Abstract—Two new coordination polymers, namely $[Cu_2(o\text{-Cpia})(OH)(Bitb)_{0.5}]_n$ (**I**) (H_3o-Cpia = 5-(2-carboxy-phenoxy)-isophthalic acid, Bitb = 1,4-bis(1,2,4-triazol-1-yl)-butane) and $\{[Zn_7(OH)_4(Bta)_4(H_2O)_2](H_2NMe_2)_2(DMF)_3\}_n$ (**II**) (H_3Bta = biphenyl-3'-nitro-3,4',5-tricarboxylic acid, DMF = *N*,*N*'-dimethylformamide), have been successfully constructed under solvothermal conditions. The structures of the two complexes have been successfully determined by single crystal X-ray diffraction (CIF files CCDC nos. 1811807 (**I**) and 1811808 (**II**)). In addition, in vitro antitumor activity of compounds **I** and **II** on four human ovarian cancer cells (OV2, 3AO, OVCA420, OVCA429) was further determined and the results show that the two compounds showed promising activity.

Keywords: coordination polymer, X-ray diffraction, cancer cell

DOI: 10.1134/S1070328418090026

INTRODUCTION

Cancer is one of the major causes of mortality worldwide [1]. Despite tremendous efforts to create effective chemotherapy drugs, there is still a huge toxicity and selectivity issue. The toxicity of modern chemotherapy and cancer cell resistance to anticancer agents leads us to seek new treatments and prevention methods of this insidious disease [2–4]. Over the last years, organometallic compounds have been studied with respect to various biological applications. The majority of them are related to anticancer therapy, while less attention has been devoted to organometallics as antibacterial and antiparasite agents [5, 6].

The design and synthesis of Cu(II) and Zn(II) complexes is of significant interest due to the rich structural chemistry and potential applications in molecular light switches, DNA foot-printing agents, nucleic acid probes, chemotherapy, and biological investigation [7, 8]. Geometry is a very important factor in studying the properties of these complexes. Ligands derived from various modifications of aromatic polyacid and triazole have been employed to address different issues [9]. In this work, we prepared two new coordination polymers, namely $[Cu_2(o\text{-Cpia})(OH)(Bitb)_{0.5}]_n$ (**I**) (H_3o-Cpia = 5-(2-carboxy-phenoxy)-isophthalic acid, Bitb = 1,4-bis(1,2,4-triazol-1-yl)-butane) and $\{[Zn_7(OH)_4(Bta)_4(H_2O)_2](H_2NMe_2)_2(DMF)_3\}_n$ (**II**) (H_3Bta = biphenyl-3'-nitro-3,4',5-tricarboxylic acid, DMF = *N*,*N*'-dimethylformamide) under solvothermal conditions and then investigated their in vitro antitumor activity. Schematic representation of the ligands used in this research:

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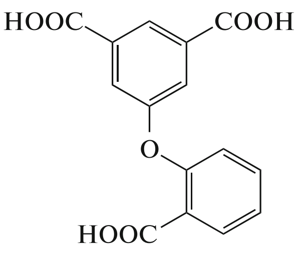
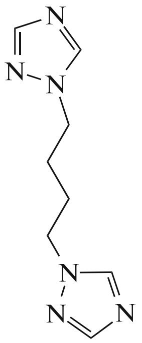
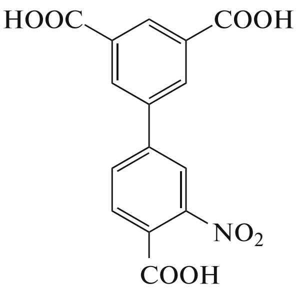


H_3*o*-Cpia



Bitb



H_3Bta

EXPERIMENTAL

Apparatus and materials. All the starting materials and reagents used in this work were obtained commercially and used without further purification. Element analyses (C, H and N) were determined with an elemental Vairo EL III analyzer. Single crystal X-ray diffraction was carried out by an Oxford Xcalibur E diffractometer.

Synthesis of complex I. A mixture containing H_3*o*-Cpia (0.04 g, 0.13 mmol), $CuCl_2 \cdot 6H_2O$ (0.15 g, 0.63 mmol), and Bitb (0.020 g, 0.11 mmol) in 3 mL of water and 0.1 mL of 1 M NaOH solution were sealed in a Teflon-lined autoclave and heated under autogenous pressure to 180°C for 3 days and then allowed to cool to room temperature at the rate of 1°C/min. Block-shaped green crystals of **I** were collected in 48% yield. The crystals were washed with water followed by acetone and air-dried.

For $C_{19}H_{14}N_3O_8Cu_2$

Anal. calcd., %	C, 42.31	H, 2.62	N, 7.79
Found, %	C, 42.66	H, 2.32	N, 7.62

Synthesis of complex II. A mixture of $Zn(OAc)_2 \cdot 2H_2O$ (82 mg), H_3Bta (43 mg), DMF (4 mL) and H_2O (1 mL) was sealed in a 25 mL, Teflon-lined, stainless-steel autoclave and heated at 150°C for 4 days. The autoclave was subsequently cooled to room temperature. Light yellow crystals were recovered by filtration, which were washed with DMF and ethanol and finally dried at ambient temperature (42% yield based on H_3L).

For $C_{60}H_{30}N_4O_{38}Zn_7$

Anal. calcd., %	C, 38.49	H, 1.61	N, 2.99
Found, %	C, 38.12	H, 1.92	N, 3.04

X-ray structure determination. Suitable single crystal of compounds **I** and **II** was carefully selected under optical microscope and glued on thin glass fibers. The intensity data of **I** and **II** was collected on Oxford Xcalibur E diffractometer. The empirical absorption corrections were applied to the data using the SADABS system. This structure was solved by direct method and refined by full-matrix least-squares method on F^2 using the SHELXS-97 program [10]. All non-hydrogen atoms of **I** and **II** were refined anisotropically, and all the hydrogen atoms attached to carbon atoms were fixed at their ideal positions. Pertinent crystal data and structural refinement results for compounds **I** and **II** were summarized in Table 1.

Supplementary material for structures has been deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 1811807 (**I**) and 1811808 (**II**); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Antitumor activity. Four human ovarian cancer cells (OV2, 3AO, OVCA420, OVCA429) were grown in a RPMI 1460 medium supplemented with 10% fetal calf serum, 100 μg/mL penicillin and 100 μg/mL streptomycin. They were incubated at the temperature of 37°C in a moist incubator and 95% air and 5% CO_2. Cells at the exponential growth were diluted to 5 × 10^4 cells/mL with RPMI 1640, and then seeded in 96-well cell culture at a volume of 100 μL per cell, respectively, and incubated for 24 h at 37°C in 5% CO_2. After incubation of cells for up to 96 h, medium was removed from each cell and 150 μL of MTT (0.5 mg/mL) solution, diluted 10-fold by RPMI 1460 was subsequently added. The IC_{50} values were measured by depicting the ratio viability versus concentration on a logarithmic chart and reading off the concentration where 50% of cells viable involved in the control. In order to get the mean values, it is requested that each experiment was conducted at least three times in the same way.

Table 1. Crystallographic data and structure refinements for compounds **I** and **II**

Parameter	Value	
	I	**II**
Formula	$C_{19}H_{14}N_3O_8Cu_2$	$C_{60}H_{30}N_4O_{38}Zn_7$
Mr	539.41	1872.47
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a, Å	9.5272(4)	11.7413(6)
b, Å	10.6671(5)	13.5961(7)
c, Å	11.6450(5)	17.7373(10)
α, deg	100.807(1)	69.843(2)
β, deg	98.542(1)	89.463(2)
γ, deg	115.054(1)	68.464(2)
V, Å^3	1017.95(8)	2450.2(2)
Z	2	1
ρ_{calcd}, g cm^{-3}	1.760	1.269
$\mu(MoK_{\alpha})$, mm^{-1}	2.143	1.757
θ Range deg	3.03–25.01	3.01–25.01
Reflections collected	18268	43146
Reflections unique (R_{int})	3582 (0.0741)	8596 (0.1380)
Reflections with $I \geq 2\sigma(I)$	2949	5392
R indices ($I > 2\sigma(I)$)	$R_1 = 0.0355$, $wR_2 = 0.0901$	$R_1 = 0.0800$, $wR_2 = 0.2166$
R indices (all data), R_1, wR_2	$R_1 = 0.0473$, $wR_2 = 0.0966$	$R_1 = 0.1395$, $wR_2 = 0.2508$
Largest diff. peak/hole, e Å^{-3}	1.19/–0.53	2.48/–0.78

RESULTS AND DISCUSSION

Compound **I** could be hydrothermally synthesized by reaction of H_3o-Cpia, $CuCl_2 \cdot 6H_2O$ and Bitb in water at 180°C for three days. The X-ray study shows that complex **I** has a 3D mixed-ligand framework structure. The asymmetric unit of **I** contains two independent Cu^{2+} ions, one o-Cpia^{3-} ligand, one hydroxyl group, and a half of Bitb molecule. As shown in Fig. 1a, the Cu(1) atom adopts a [$CuNO_4$] pentacoordination provided by three O atoms from three bridging carboxylates (Cu–O 1.949(2)–2.128(3) Å), one N atom from Bitb ligand (Cu–N 2.001(3) Å) and one μ_3-OH group (Cu–O 1.959(3) Å). The Cu(2) center, on the other hand, shows a distorted [CuO_5] coordination from three bridging carboxylates of o-Cpia^{3-} ligands (Cu–O 1.943(3)–2.135(2) Å) besides two μ_3-OH groups (Cu–O 1.984(2)–2.014(2) Å). Both the metal ions (Cu(1) and Cu(2)) show distorted square pyramidal geometry ($\tau = 0.46$–0.48) as calculated by the SHARP software. Two symmetry-related Cu(1) and Cu(2) atoms are held together by two symmetry-related OH groups to afford a butterfly-like tetranuclear [$Cu_4(\mu_3\text{-}OH)_2$]$^{6+}$ cluster (Fig. 1b). The tetranuclear core propagates in all directions via bridging carboxylates of o-Cpia^{3-} and N atoms of the Bitb ligands into a 3D network (Fig. 1c). From the topological point of view, each [$Cu_4(\mu_3\text{-}OH)_2$]$^{6+}$ cluster could be viewed as an eight-connected node, each o-Cpia^{3-} ligand could be judged as a three connected node and the Bitb ligand could be considered as a two-connected node, so the whole network of **I** can be simplified into a 3D (3,8)-connected tfz-d net with a point symbol of $(4^3)_2(4^6{\cdot}6^{18}{\cdot}8^4)$ (Fig. 1d).

Reaction of $Zn(OAc)_2 \cdot 2H_2O$ with and H_3Bta ligand in a mixed solvent of DMF–H_2O system afforded light yellow crystals of **II** in a moderate yield, which was structurally characterized by single-crystal X-ray diffraction. The asymmetrical unit of **II** consists of three and a half crystallographic independent Zn(II) atoms, two Bta^{3-} ligands, two μ_3-OH atoms, one coordinated water and one disordered H_2NMe_2 cation. As shown in Fig. 2a, the Zn(1) atom is coordinated by three carboxylate oxygen atoms from three different Bta^{3-} ligands and one μ_3-OH atom, forming a distorted tetrahedral geometry; the Zn(2) atom locating in the two-fold axis is bonded with four μ_3-OH atoms and two carboxylate oxygen atoms from two

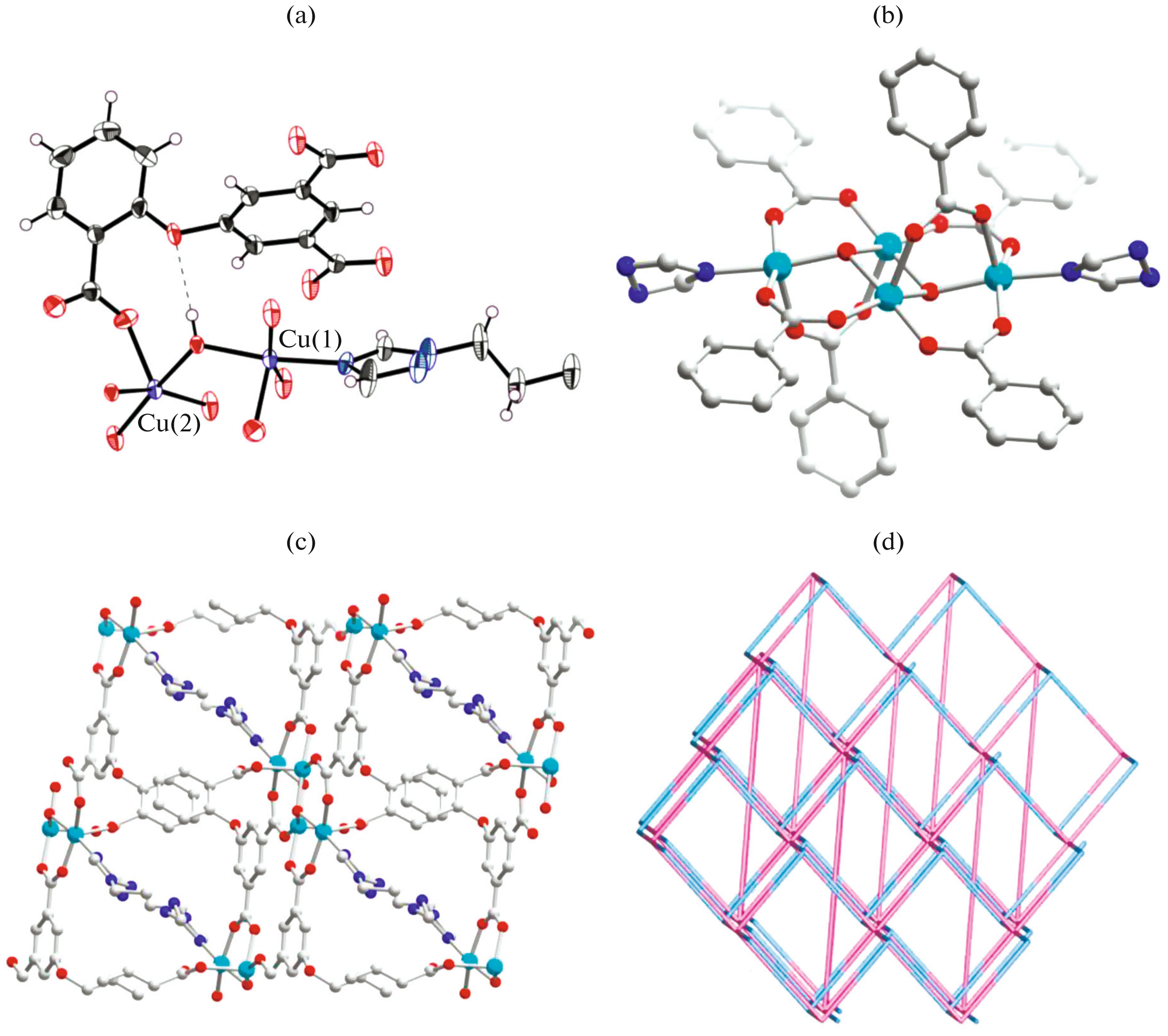


Fig. 1. View of the asymmetric unit of **I** (a); view of the tetranuclear $[Cu_4(\mu_3\text{-}OH)_2]^{6+}$ cluster of **I** (b); view of the 3D framework of **I** (c); view of the (3,8)-connected tfz-d net of **I** (d).

different Bta^{3-} ligands, resulting in an octahedral geometry; the Zn(3) atom is six-connected with three carboxylate oxygen atoms, two μ_3-OH atoms and one water molecule to give rise to the an octahedral geometry; the four-coordinated Zn(4) atom is joined with three carboxylate oxygen atoms and one μ_3-OH atom to furnish a tetrahedral coordination geometry. The Zn–O bond lengths for Zn(1), Zn(2), Zn(3), and Zn(4) ions are varying from 1.894(5) to 2.138(4) Å, which are comparable to those documented values in the previous heptanuclear $\{Zn_7\}$ clusters. More interestingly, two pairs of Zn(1), Zn(2), Zn(3), Zn(4) and their symmetry-related ones are held together by four μ_3-OH atoms to give an uncommon heptanuclear $[Zn_7(HO)_4]^{10+}$ cluster. The Bta^{3-} ligands in **II** exhibits two similar coordination modes and bond with five Zn ions using its five carboxylic O atoms (Fig. 2b). Each heptanuclear zinc cluster in **II** is 12-coordinated to twelve neighboring clusters by twelve Bta^{3-} ligands to extend into an infinite 3D MOF. There exists 1D rhombus channels (edge length of ~7.6 Å, atom to atom distance) running along the *b* axis (Fig. 2c). Complex **II** is porous and possesses a solvent-accessible volume of 36.2% as calculated using PLATON without considering the lattice charge-balance ions. To understand the net of **II** more clearly, we use the TOPOS software to simplify the framework connection, each $\{Zn_7\}$ cluster could be viewed as a 12-connected node and each Bta^{3-} ligand could be judged as a 3-connected node, so the whole network of **II** could be viewed as a (3,12)-connected net with the point symbol of $(4^{20}.6^{28}.8^{18})(4^3)_4$ (Fig. 2d).

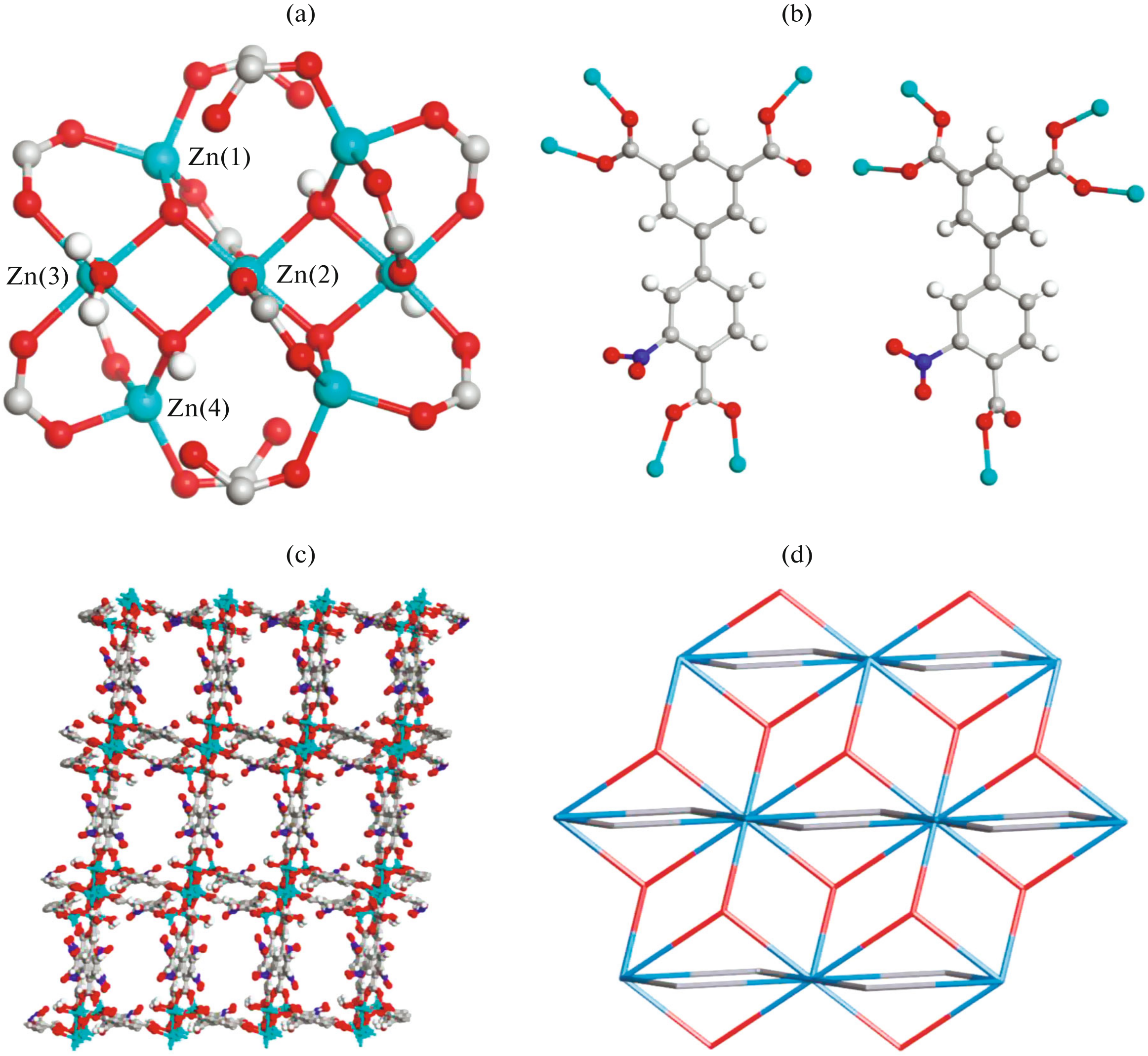


Fig. 2. View of the $\{Zn_7\}$ cluster of **II** (a); view of the coordination mode of the L^{3-} ligand in **II** (b); view of the 1D channel of **II** along the *b* aixs (c); view of the (3,12)-connected net of **II** (d).

The cytotoxicity of the title compounds **I** and **II** and their corresponding organic ligands H_3*o*-Cpia, Bitb and H_3Bta against OV2, 3AO, OVCA420, OVCA429 cell lines were evaluated by MTT assay, and the IC_{50} values derived from the experimental data were concluded in Table 2. It is obvious that the three organic ligands were inactive against all of these cell lines (IC_{50} > 100 μM). At this concentration, they should exert high cytotoxicity against these cells, thus we infered that it did not exert any inhabitation selectivity towards these cell lines. However, after the tumor cells were incubated in the presence of compounds **I** and **II** for 72 h, the IC_{50} values for the compounds ranged from 20 to 35 μM, indicating that the two title compounds **I** and **II** exhibited antitumor activity against all of these cell lines in different degrees.

Table 2. Growth inhibitory effects of **I**, **II**, H_3*o*-Cpia, Bitb and H_3Bta on OV2, 3AO, OVCA420 and OVCA429 cells

Compounds	IC_{50}, μM			
	OV2	3AO	OVCA420	OVCA429
H_3*o*-Cpia	>100	>100	>100	>100
Bitb	>100	>100	>100	>100
H_3Bta	>100	>100	>100	>100
I	28	20	30	32
II	25	23	27	35

Thus, the single-crystal X-ray diffraction study reveals that compound **I** contains a butterfly-like tetranuclear $Cu_4(OH)_2$ cluster that connected by the *o*-$Cpia^{3-}$ and Bitb ligands to afford a (3,8)-connected tfz-d net with a point symbol of $(4^3)_2(4^6{\cdot}6^{18}{\cdot}8^4)$, while compound **II** contains a heptanuclear zinc secondary building unit that is connected by the V-shape aromatic carboxylate ligand gives rise to a three-dimensional porous framework. In addition, antitumor activity of compounds **I** and **II** has been advanced greatly when their related organic ligands are in coordination with Cu or Zn ion respectively.

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