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Synthesis, Crystal Structure, and Antitumour Activities of Cobalt(II) Complex Based on 2,6-*bis*(1-Phenylbenzimidazol-2-yl)pyridine[1]

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Abstract—A new cationic complex, $[Co(Bpbp)_2](ClO_4)_2 \cdot DMF \cdot H_2O$, was synthesized by treatment $Co(ClO_4)_2 \cdot 6H_2O$ with 2,6-*bis*(1-phenylbenzimidazol-2-yl)pyridine (Bpbp) in DMF solvent at room temperature. Its structure was characterized by element analysis, IR, and X-ray single crystal structure analyses (CIF file CCDC no. 970498). For complex, crystal system, triclinic, space group, $P\bar{1}$, $a = 11.585(13)$, $b = 13.939(16)$, $c = 19.236(2)$ Å, $\alpha = 97.938(2)°$, $\beta = 102.814(2)°$, $\gamma = 90.556(2)°$, $V = 2861.1(6)$ Å^3, $Z = 2$. The Co^{2+} ion octahedral geometry is coordinated by six nitrogen atoms from two ligand (Bpbp). The antiproliferative activities of the complex were screened by MTT assay against HepG2, Huh7, Eca109 and Eca9706 cancer cell. The complex exhibits inhibition on Eca9706 and Eca109 cancer cell but no HepG2 and Huh7 cancer cell.

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INTRODUCTION

The widespread success of cisplatin in the clinical treatment of various types of neoplasias has placed metal-based drugs in the frontline against cancer [1, 2]. The cure with cisplatin is still limited by dose-limiting side effects and inherited or acquired resistance phenomena, only partially amended by employment of new platinum drugs [3–5]. Intensive efforts have been made to develop new metal complexes that are effective against cancer cells either by changing the metal or the ligand type. Various transition metals combined with a variety of ligand classes, such as schiff bases, amino acids, and extended polypyridine have been proposed to improve the efficacy of cancer treatment [6–10].

Benzimidazole derivatives are important pharmacophores in drugs that display a diversity of pharmacological activities, such as anti-inflammatory, antioxidant, gastroprotective and antiparasitic activities [11–15]. In our recent study, some zinc complexes based on benzimidazole derivatives have been evaluated for in vitro anticancer activities [16, 17]. Cobalt is an essential element present in biological systems either as metal center in vitamin B_{12} and other cobalamines or as an ion involved in cellular oxidative stress through mitochondrial mediated apoptosis [18]. Herein we synthesized a new cobalt(II) complex based on 2,6-*bis*(1-phenylbenzimidazol-2-yl)pyridine (**Bpbp**) and investigated its antitumor activities. The result demonstrates that perchlorate *bis*[2,6-*bis*(1-phenylbenzimidazol-2-yl)pyridine] cobalt(II) complex $[Co(Bpbp)_2](ClO_4)_2 \cdot DMF \cdot H_2O$ (**I**) has high proliferation inhibition toward Eca9706 and Eca109 cancer cells *in vitro*.

EXPERIMENTAL

Materials and instrument. *o*-Phenylenediamine, pyridine-2,6-dicaboxyl acid and bromobenzene were purchased from Shanghai Aladdin Reagent Company. All the chemicals and solvents used were analytically pure and without further purification. The analyses (C, H, and N) were made on a Perkin-Elmer 240C elemental analyzer. The solid infared spectra (IR) were obtained from a Bruker IFS66V vacuum-type FT–IR spectrophotometer by using KBr pellets. The synthesis of 2,6-*bis*(-phenylbenzimidazol-2-yl)pyridine (Bpbp) was accorded to the literature method [16].

Synthesis of I. $Co(ClO_4)_2 \cdot 6H_2O$ (730 mg, 2.0 mmol) and Bpbp (926 mg, 2.0 mmol) were mixed in N,N-dimethylformamide (DMF) (35 mL) and stirred for 20 min at room temperature. After the resulting solution was standing in air for two weeks, brown crystals were obtained. The yield was 1393 mg (54.6%).

For $C_{65}H_{51}N_{11}O_{10}Cl_2Co$			
anal. calcd., %:	C, 61.18;	H, 4.03;	N, 12.07.
Found, %:	C, 60.99;	H, 4.01;	N, 12.11.

[1] The article is published in the original.

Selected bond length (Å) and bond angles (deg) for complex **I**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
Co(l)–N(2)	2.138(3)	Co(l)–N(3)	2.080(3)	Co(l)–N(4)	2.124(3)
Co(l)–N(7)	2.138(3)	Co(l)–N(8)	2.072(3)	Co(l)–N(9)	2.120(3)
Angle	ω, deg	Angle	ω, deg	Angle	ω, deg
N(3)Co(l)N(7)	97.34(10)	N(3)Co(l)N(2)	76.29(11)	N(7)Co(l)N(2)	89.53(10)
N(3)Co(l)N(4)	76.15(11)	N(9)Co(l)N(4)	87.89(10)	N(8) Co(l)N(7)	76.83(10)

IR data (KBr; ν, cm^{-1}): 3432, 3070, 2765, 1667, 1592, 1506, 1449, 1389, 1338, 1297, 1092, 873, 816, 753, 695, 620, 500, 425.

X-ray structure determination. A brown single crystal of the title compound with dimensions of 0.12 mm × 0.24 mm × 0.45 mm was selected for X-ray diffraction analysis. Data collection was performed on a Bruker P4CCD diffractometer equipped with a graphite-monochromatic MoK_α radiation (λ = 0.71073 Å) by using φ-ω scan mode at 173.15 K. The empirical

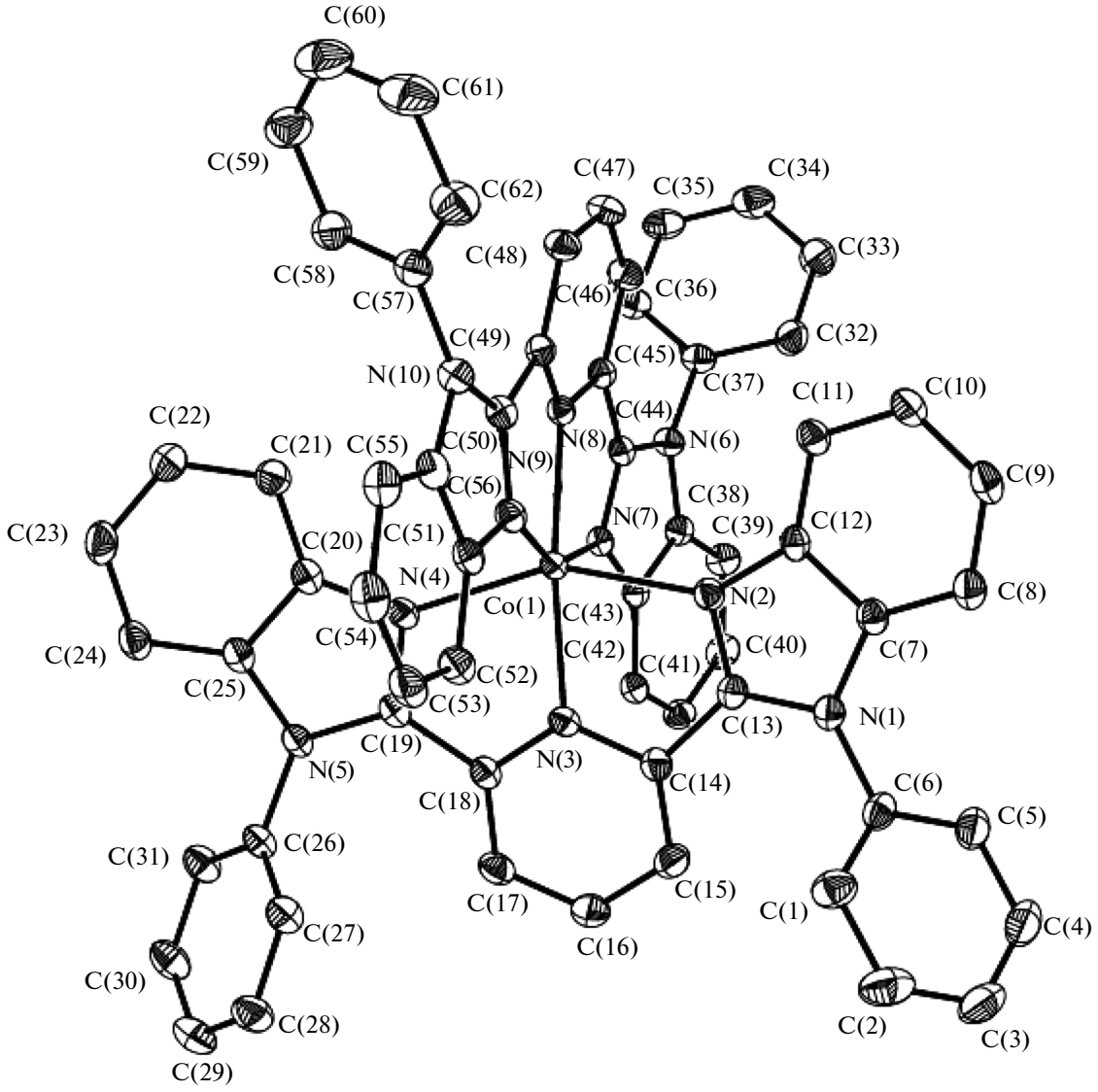

Fig. 1. Molecular structure of $[Co(Bpbp)_2]^{2+}$.

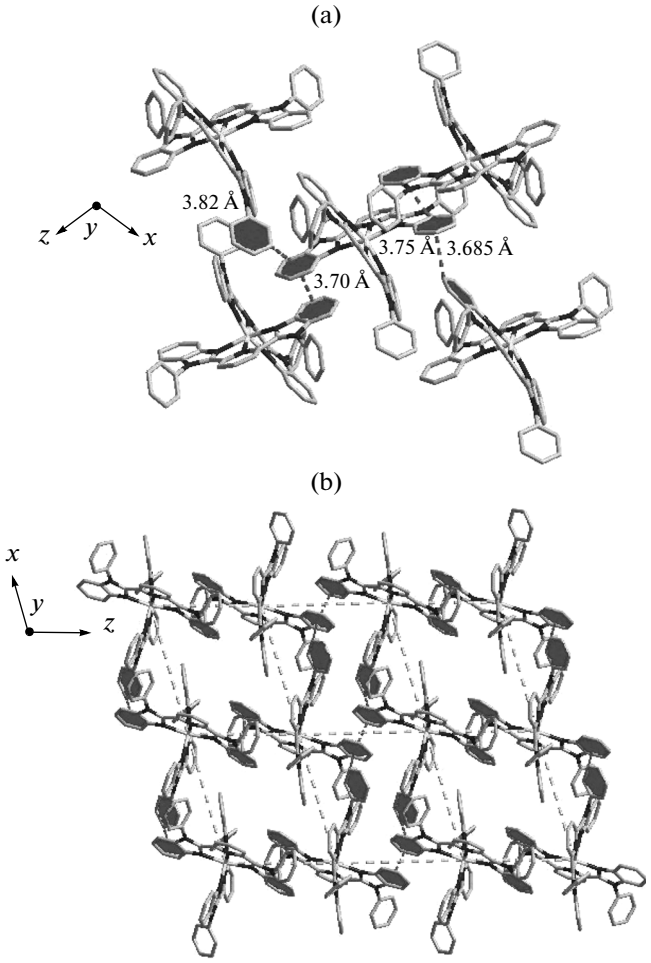

Fig. 2. π···π Stacking interactions of the adjacent mononuclear complexes (a); 2D (4,4) network formed through π···π stacking interactions (b).

absorption was applied to the intensity data. A total of 24118 reflections were collected in the range of $1.58° < \theta < 26.0°$, of which 12311 were independent with $R_{int} = 0.030$ and 9414 were observed with $I > 2\sigma(I)$. The structure was solved by direct methods with SHELXS–97 and refined by full-matrix least squares techniques on F^2 with SHELXL–97 [19, 20]. H atoms were positioned geometrically and constrained with riding model position parameters and fixed isotropic thermal parameters. The final $R = 0.0661$, $wR = 0.2058$ ($w = 1/[\sigma^2(F_o^2) + (0.1110P)^2 + 3.7024P]$, where $P = (F_o^2 + 2F_c^2)/3$, $(\Delta/\sigma)_{max} = 0.025$, $S = 1.097$, $(\Delta\rho)_{max} = 1.994$ and $(\Delta\rho)_{min} = -0.766$ $e/Å^3$. All calculations were performed on a computer with SHELXTL–97 program package.

Complete information on the studied structure **I** has been deposited with the Cambridge Crystallographic Data Centre (no. 970498; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

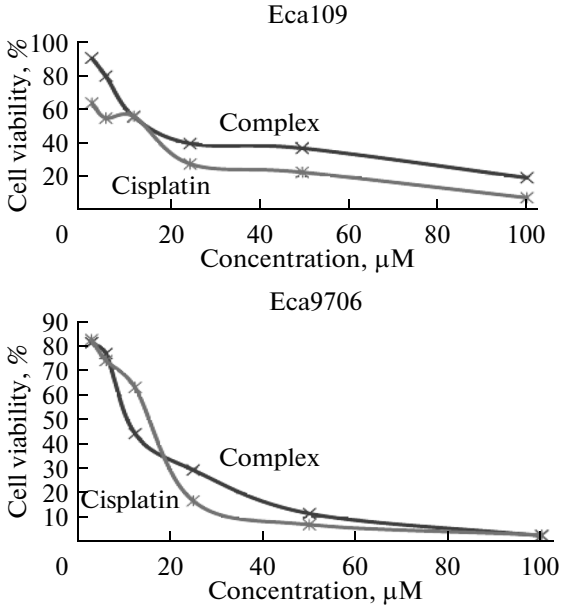

Fig. 3. The complex exhibits inhibition on Eca109 and Eca9706 cancer cell (cisplatin as positive control).

Cell culture. The cell lines were obtained from American Type Culture Collection (ATCC, Manassas, VA) and maintained in DMEM medium supplemented with fetal bovine serum (10%), penicillin (100 units mL^{-1}), and streptomycin (50 units mL^{-1}) at 37°C in a humidified incubator with 5% CO_2 atmosphere.

MTT assay. The effects of the complexe on cell proliferation were determined by MTT assay. Briefly, cells were seeded in 96–well culture plates at different densities. After 24 h, different concentrations of compounds were added and incubated for the indicated time. Then, 20 μL per well of MTT solution (5 mg mL^{-1} phosphate buffered saline) was added and incubated for 5 h. The medium was aspirated and replaced with 200 μL per well of DMSO to dissolve the formazan salt formed. The color intensity of the formazan solution, which reflects the cell growth condition, was measured at 570 nm using a microplate spectrophotometer (VERSA max) . Each IC_{50} value represents the mean ±SD of three independent experiments.

RESULTS AND DISCUSSION

Large negative perchlotate acts as counterion to precipitate coordinated cation $[Co(Bpbp)_2]^{2+}$. The purity of the complex was carefully checked by elemental analysis. Single crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from DMF. The IR spectra of complex **I** show all absorption bands resulting from the skeletal vibration of the Bpbp ligand. In complex, there is a very strong

peak at 1080 cm^{-1}, which shows ClO_4^- in this complex.

The complex includes a coordination cobalt ion, two ClO_4^- ions, a DMF and a water molecule. The ORTEP drawing for the cobalt ion of complex with atom numbering is shown in Fig. 1. The center Co(II) atom has N_6 coordination sphere, being bound by two ligand (Bpbp). In every ligand, the two benzimidazole rings and center pyridine ring and Co(II) atom form a good planar. The dihedron between the planar (N(2), N(3), N(4), Co(1)) and the planar (N(7), N(8), N(9), Co(1)) is 84.7°. Selected bond lengths and angles for complex **I** are listed in table. All the bond length of Co–N is within the range of normal Co–N distance. The average bond length of Co–N is 2.112 Å. The geometry of the CoN_6 coordination is appreciably distorted octahedral. The significant deviation from 90° of the bond angles involving the chelation is observed (table) which is presumably due to formation of five-membered chelate ring.

There are π···π stacking interactions between the discrete mononuclear complexes through benzimidazole ring with the adjacent benzimidazole ring and benzene ring (Fig. 2a). Each mononuclear complex has π···π stacking interactions with four adjacent complexes, serving as 4-connecting nodes, linking up the discrete mononuclear complexes alternately which give rise to a 2D (4,4) topological network (Fig. 2b).

The antiproliferative activities of complex **I** were screened by MTT assay against HepG2, Huh7, Eca109 and Eca9706 cancer cell (cisplatin as positive control). As is shown in Fig. 3, the cobalt complex exhibits inhibition on Eca109 cancer cell (IC_{50} = 16.3 μM) and Eca9706 cancer cell (IC_{50} = 13.3 μM), but no antitumor activities on HepG2 and Huh7 cancer cell. The complex is a promising novel complex with application potential in treatment of Eca9706 and Eca109 cancer.

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