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A Novel Coordinated Polymer $[Cu(En)_2][(PzTp)Fe(CN)_3]_2$: Synthesis, Crystal Structure, and Inhibiting Left Atrial Myxoma Cell Activity in vitro[1]

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Abstract—A new cyanide-bridged neutral centrosymmetric cluster $[Cu(En)_2][(PzTp)Fe(CN)_3]_2$ (**I**), where En = ethylenediamine, PzTp = tetra(pyrazol-1-yl)borate) was synthesized by a programmed self-assembly of preformed building blocks. Characterization with single crystal X-ray diffraction (CIF file CCDC no. 1555334) showed that the Cu^{2+} center was located in a large distorted octahedral environment due to the obvious Jahn–Teller effect, which was demonstrated by continuous shape measures with the SHAPE program. Furthermore, no coordinated or free solvent molecules existed in the clusters, showing good room-temperature stability. In addition, in vitro anticancer activity of compound **I** on three human cancer cells (SKOV3, A2780, and OVCAR) was further determined.

Keywords: cyanide-bridged, X-ray, anticancer activity

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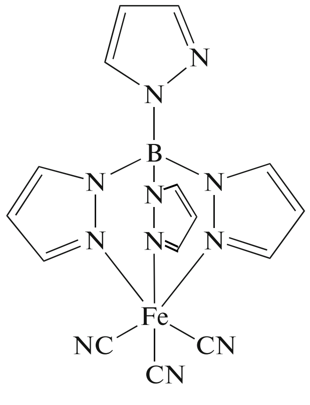
INTRODUCTION

Globally cancer is the second largest cause of death after cardiovascular disease [1]. More seriously, epidemiological evidence indicates that cancer incidence rates are still increasing in many parts of the world [2]. Drug therapy has an important position in the treatment of malignant tumors, and it is worth noting that discoveries of tumor-resistant pharmacological drugs have mainly resulted from screening of artificial drugs [3]. Artificial antitumor drugs have also proven effective and less toxic for cancer therapy [4].

The design and synthesis of the coordination polymers and supramolecular with transition metal have caused much attention in the past few years [5]. The aims of the research of this field are the discovery and synthesis of new complexes and materials with practical function and application value, for example, transition metal coordination complexes have applied in the field of light, electricity, magnetism, new materials, catalyst, bionics, and biology [6–8]. Recently, this kind of compounds have been studied and recognized for their ability with anti-tumor property. In this study, a new cyanide-bridged trinuclear cluster $[Cu(En)_2][(PzTp)Fe(CN)_3]_2$ (**I**) was synthesized through a bottom-up strategy with a tetra(pyrazol-1-yl)borate (PzTp) building block, ethylenediamine (En) and copper ions. The anticancer activity of the title compound **I** was then evaluated on three human cancer cells in vitro.



PzTp building block

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 ele-

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[1] The article is published in the original.

Table 1. Crystallographic data and structure refinements for compound **I**

Parameter	Value
Mr	1009.78
Crystal system	Monoclinic
Space group	$P2_1/c$
a, Å	20.9015(9)
b, Å	7.8798(4)
c, Å	13.6017(6)
β, deg	100.736(3)
V, Å^3	22010(2)
Z	2
ρ_{calcd}, g cm^{-3}	1.524
$\mu(\text{Mo}K_\alpha)$, mm^{-1}	1.190
θ Range, deg	2.77–25.00
Reflections collected/unique	12160/3879
R_{int}	0.0240
Reflections with $I \geq 2\sigma(I)$	3517
R_1, wR_2 (all data)	0.0380, 0.1110
Goodness-of-fit on F^2	0.987
$\Delta\rho_{\max}/\Delta\rho_{\min}$, *e* Å^{-3}	1.01/–0.72

mental Vairo EL III analyzer. Powder X-ray diffraction (PXRD) data were collected using PANalytical X'Pert Pro powder diffractometer with CuK_α radiation and $5° \leq 2\theta \leq 50°$. Single crystal X-ray diffraction was carried out by an Oxford Xcalibur E diffractometer.

Synthesis complex I. A 10.0 mL methanol solution containing 0.10 mmol (65.5 mg) of $Bu_4N[PzTpFe(CN)_3]$ [9] and 0.20 mmol (12.0 mg) of En was added dropwise to a 10.0 mL aqueous solution containing 0.10 mmol (25.0 mg) of $CuSO_4 \cdot 5H_2O$. The resulting suspension was stirred for 3 h and then filtrated to remove the precipitate. After filtration, slow evaporation of the filtrate in air gave black crystals after several days.

For $C_{34}H_{40}B_2N_{26}Fe_2Cu$

anal. calcd., %	C, 40.44	H, 3.99	N, 36.07
found, %	C, 40.32	H, 4.14	N, 36.22

X-ray structure determination. According to the evaporation of chloroform solution, suitable single crystals of compound **I** come to hand. The diffraction data were acquired on a Bruker Smart Apex CCD area detector using a graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 293(2) K. The structure was solved by using the program SHELXL-97 [10] and Fourier difference techniques, and refined by full-matrix least-squares method on F^2. All hydrogen atoms were added academically. Crystallographic data for compound **I** have been showed in Table 1.

Supplementary material for structure **I** has been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 1555334; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Antitumor activity. Three human tumor cells (SKOV3, A2780, and OVCAR) and one normal cell line (MDCK) were determined by using the MTT assay as described previously [11, 12]. In this study, the cells were plated on 96-wells at 5 × 10^3. After attachment (24 h), the cells reaching 70–80% confluency were treated for 48 h with each compound at different concentrations or 1% DMSO as a negative control. After 48 h incubation, 20 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (5 mg/mL in phosphate buffered saline (PBS)) was added and incubated for an additional 4 h. Subsequently, the medium was aspirated carefully, and 150 μL of DMSO was added. After incubation for 15 min, the optical density was measured at 490 nm using FlexStation 3 benchtop multi-mode microplate reader (Molecular Devices, USA). This assay measures the amount of formazan produced from MTT by the dehydrogenase enzymes of metabolically active cells. Thus, the quantity of formazan produced is directly proportional to the number of living cells. Absorbance values of the treated cells were compared with the absorbance values of untreated cells. The half-maximal inhibitory concentration (IC_{50}) value was determined from non-linear regression equation. The results are presented as the average percentage viability to the negative control (1% DMSO).

RESULTS AND DISCUSSION

Structure **I** consists of neutral trinuclear entities of $[Cu(En)_2][(PzTp)Fe(CN)_3]_2$ (Fig. 1a). In this trinuclear cluster, the $[(PzTp)Fe(CN)_3]^-$ unit acts as a monodentate ligand through one of its three cyano groups toward a central $[Cu(En)_2]^{2+}$ motif in *trans* position, while each $[Cu(En)_2]^{2+}$ unit is linked to two $[(PzTp)Fe(CN)_3]^-$ units, forming a neutral centrosymmetric linear cluster. Each Fe^{3+} atom is coordinated in N_3C_3 octahedral environment with three PzTp nitrogen atoms and three cyano carbon atoms, taking a C_{3v} symmetry. The Fe–C bond lengths are 1.915(4)–1.925(3) Å, and the Fe–N distances are 1.965(3)–1.987(3) Å, respectively. The Fe–C≡N linkages are closer to linearity with bond angles of 174.4(4)°–177.1(3)°. Such structure characteristics indicated that the iron center is low-spin Fe^{3+} ion [13]. The Cu^{2+} ion is located in a distorted N_6 octahedral coordination, occupied by two cyanide N atoms and four N atoms from two En ligands. The bond lengths are 2.511(6) Å for Cu–N(11), 1.990(3) and 2.035(3) Å for Cu–N(12) and Cu–N(13), respectively, which is

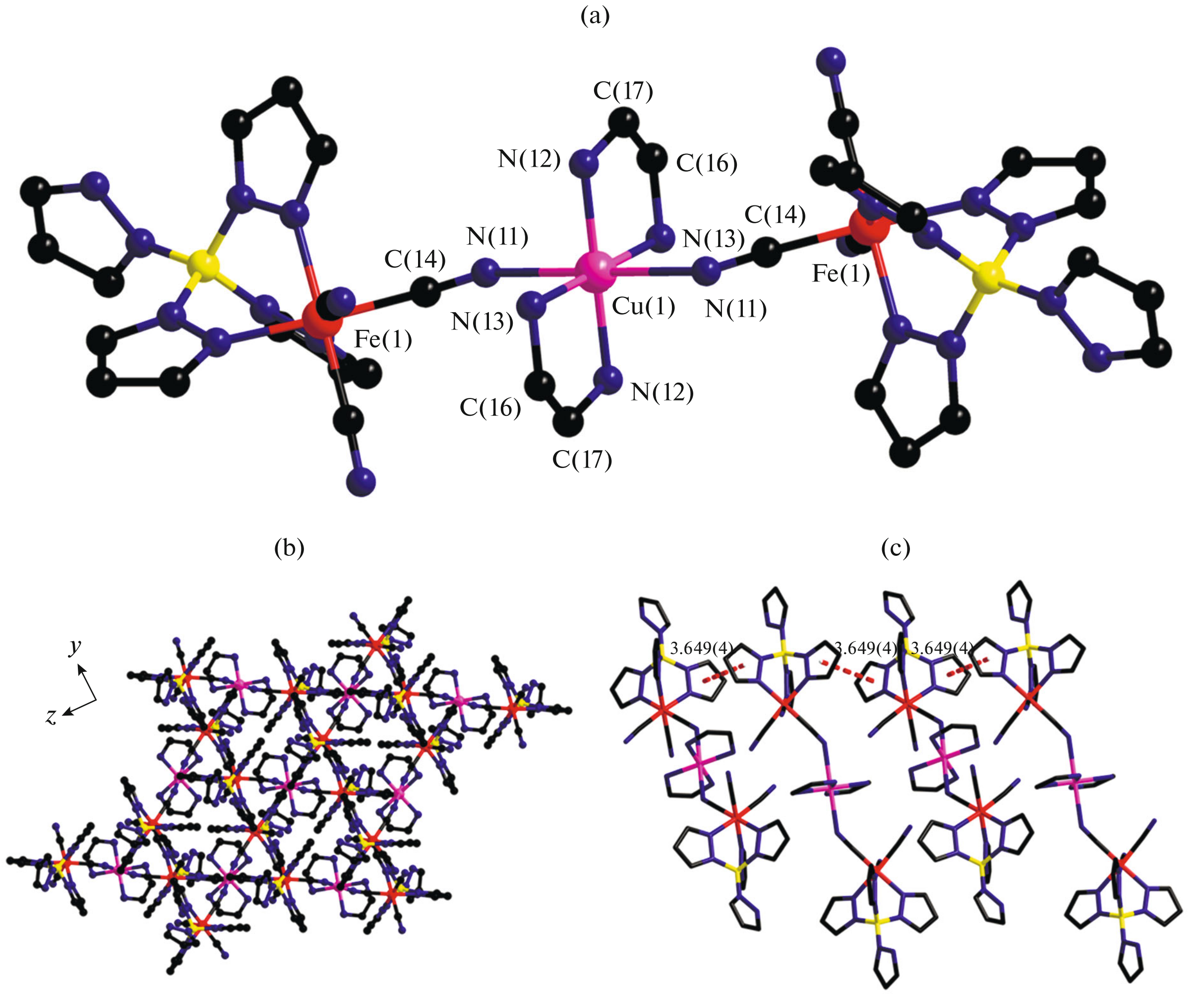

Fig. 1. Crystal structure of **I**: view of the trinuclear cluster (a); packing diagram along the *x* axis (b); intercomplex π···π interactions between two PzTp ligands (c).

similar to those reported in related complexes [14]. The C≡N–Cu bond angles deviate obviously from linearity with bond angle of 142.52(52)°. The complex is further contacted by π–π stacking of adjacent pyrazolyl rings between the triclusters, forming a pseudochain structure (Fig. 1b). The intermolecular pyrazolyl-pyrazolyl separation is 3.649(4) Å, as shown in Fig. 1c. Continuous shape measures of Cu^{2+} center in the distorted octahedral environment is calculated as 1.245. The calculation result indicates a huge deviation from a regular octahedron, which is attributed to the large Jahn–Teller effect of Cu^{2+} ion.

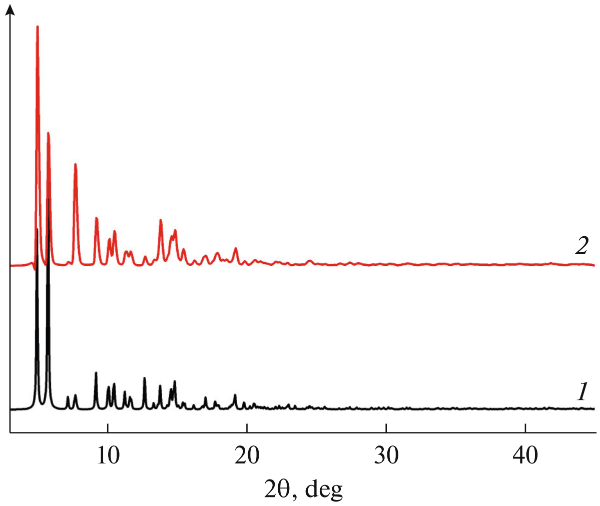

Fig. 2. The PXRD patterns for **I**: simulation (*1*), observed (*2*).

To investigate whether the analyzed crystal structures are truly representative of the bulk materials, PXRD technology has been performed for complex **I** at room temperature (Fig. 2). The main peak positions observed are in good agreement with the simulated ones. Although minor differences can be found in the positions, widths, and intensities of some peaks, it can be still considered that the bulk synthesized materials

Table 2. Growth inhibitory effects of **I** and PzTp on SKOV3, A2780, OVCAR, and MDCK cells

Compound	IC_{50} ± SD, μM[a]			
	SKOV3	A2780	OVCAR	MDCK
PzTp	>100	>100	>100	>100
I	20.2 ± 1.6	25.9 ± 1.9	30.6 ± 2.3	>100
Cisplatin[b]	23.3 ± 2.2	24.1 ± 1.7	29.9 ± 2.1	>100

[a] Data presented is the mean ± SD value of three independent determinations; [b] used as positive control.

and the analyzed crystal are homogeneous. The differences may be due to the preferred orientation of the powder samples.

The cell growth inhibitory activity of the title compound **I** and organic ligand PzTp was evaluated against three human tumor cells (SKOV3, A2780, and OVCAR) using standard MTT assay in vitro with cisplatin as the positive control. Additionally, cytotoxic assays were conducted using normal cell line MDCK. The results of the mean values of experiments from three independent determinations, expressed as IC_{50} values, were summarized in Table 2. Compound **I** showed good antitumor activities ($IC_{50} = 20 \sim 30$ μM), which is similar to that of cisplatin on the three cell lines; while its organic ligand proved to be ineffective against all three cell lines ($IC_{50} > 100$ μM). In addition, it is worth noting that compound **I** indicated no inhibitory activity against MDCK cell lines ($IC_{50} >$ 100 μM), which suggested that the compound exhibit good selectivity towards cancer cells rather normal cells.

According to the above-mentioned data, it shall be concluded that compared with organic ligand PzTp, the anticancer activity of compound **I** has been advanced greatly when its organic ligand PzTp is in coordination with Cu^{2+} ion, respectively. The above data is beneficial to design and synthesize more Cu(II) complexes that show more potent antitumor effects against cancer cells.

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