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A Water Soluble Zinc(II) Coordination Polymer Containing Pyridazine-4,5-Dicarboxylic Acid: The Crystal Structure and Binding Properties with DNA[1]

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Abstract—New water soluble complex $[Zn(HPDDA)_2(H_2O)_2(4,4'\text{-Bipy})_2]_n$ (**I**), where H_2PDDA is pyridazine-4,5-dicarboxylic acid, 4,4'-Bipy = 4,4'-bipyridine), has been prepared by hydrothermal reaction and structurally characterized by X-ray single-crystal diffraction analysis (CIF file CCDC no. 835525) and elemental analysis. In **I**, each Zn^{2+} ion is six-coordinated by two oxygen atoms from the two HPDDA ligands, two nitrogen atoms from two 4,4'-Bipy and two oxygen atoms from two water molecules. The interactions of **I** with calf thymus DNA were studied by circular dichroism spectroscopy. The results indicated that this water soluble zinc complex show moderate binding with DNA and could be used for candidate for therapy of cancer.

Keywords: pyridazine-4,5-dicarboxylic acid, zinc complex, DNA

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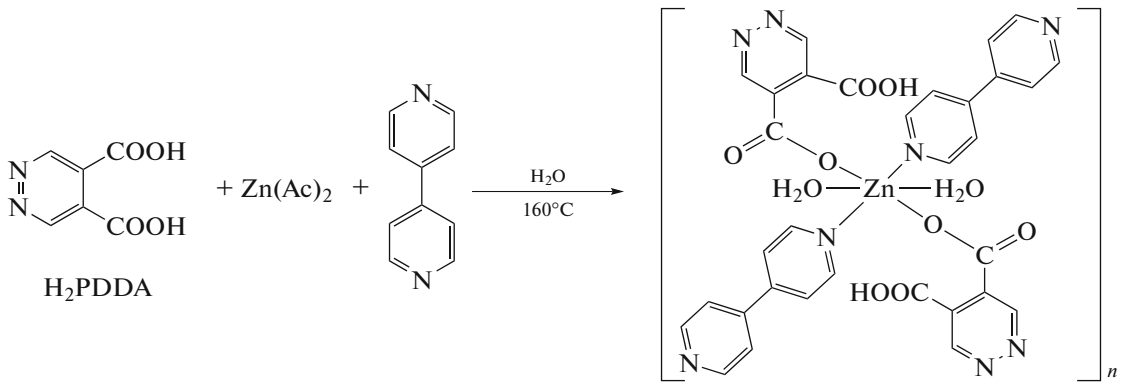
INTRODUCTION

A lot of people are suffering from cancers each year and cancers continue to be the second killer of people globally now. Actually cancers account for one in every seven deaths worldwide. Conventional treatment for cancers includes the use of chemotherapeutic drugs, radiation therapy and surgical treatment [1]. As the most widely used anticancer chemotherapeutics, platinum agents, however, are hindered by systemic toxicities such as nephrotoxicity, neurotoxicity and ototoxicity as well as serious drug resistance either natural or gradually acquired to several cancers [2].

Metal anticancer complexes are being developed to overcome drawbacks of platinum anticancer chemotherapeutics. They block DNA replication in tumor cells by interacting with DNA. In particular, complexes of zinc(II) are of increasing interest, since zinc is the second most abundant trace element in the biological intracellular environment of living organisms [3] which plays critical roles in important physiological process. In addition, Zn complexes can adopt diverse geometries with different coordination numbers. Moreover, they have good pharmacological profiles [4]. To date, Zn complexes have been reported to work as radio-protective agents and tumor photosensitizers [5]. Simultaneously, the use of coordination polymer has led to some remarkable results including $[Zn(4\text{-Me-5-CHOIm})_2(HCOO)(ClO_4)]$, which has been reported to bind with DNA and can be used as potential metal-based drugs [6]. However, there is a lack between DNA-binding nature and its possible relation to the observed cytotoxic activity [7]. Therefore, research interest is ongoing in this field.

In the present study, we report the hydrothermal synthesis and structural studies of a new zinc(II) polymer of pyridazine-4,5-dicarboxylic acid (H_2PDDA), namely, $[Zn(HPDDA)_2(H_2O)_2(4,4'\text{-Bipy})_2]_n$ (**I**) (Scheme 1) which has a 4,4'-bipyridine (4,4'-Bipy) as the auxiliary ligand. In addition, the interactions of **I** with calf thymus DNA were investigated by circular dichroism (CD) spectroscopy.

[1] The article is published in the original.



Scheme 1.

EXPERIMENTAL

Materials and measurements. All starting materials were of AR grade and were used aspurchased without further purification. Calf-thymus DNA (CT-DNA) and Tris were from Sigma. Elemental analyses of C, H, N were carried out on a Pekin-Elmer model 240C Elemental Analyzer.

Synthesis of complex I. $Zn(Ac)_2 \cdot 2H_2O$ (110 mg, 0.5 mmol), H_2PDDA (84 mg, 0.5 mmol) and water (9 mL) were stirred at room temperature until all the starting materials dissolved. The pH value of the resulting mixture was adjusted to 8.0 with 4,4'-Bipy and then sealed in a 25 mL Teflon lined autoclave. The autoclave was kept at 433 K for 96 h. The bomb was cooled naturally to room temperature. After filtration, colorless block microcrystals of **I** were obtained from the solution at room temperature in a few days (the yield was 42%).

For $C_{16}H_{18}N_4O_8Zn$			
Anal. calcd., %	C, 41.80	H, 3.95	N, 12.19
Found, %	C, 41.72	H, 3.78	N, 12.30

X-ray diffraction analysis. Data collections were performed on a Rigaku Mercury CCD diffractometer with graphite-monochromated MoK_α radiation (λ = 0.071073 nm) at 296(2) K with a maximum 2θ value of 51.1°. The intensities were corrected for Lorentz and polarization effects. The structures were solved with direct methods using the SHELXS-97 program and the refinement was performed against F^2 using SHELXL-97 [8]. All the nonhydrogen atoms were refined anisotropically. The H atoms on C and N atoms were positioned with idealized geometry and refined with fixed isotropic displacement parameters, while H atoms of water molecules were located in a difference map. The final cycle of refinement gave $R_1 = 0.039$ and $wR_2 = 0.099$ with $w = 1/[\sigma^2(F_o^2) + (0.0454P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. The details of the crystal parameters, data collection and refinement for the title compound are summarized in Table 1. Selected bond lengths and angles relevant to the zinc center are listed in Table 2.

Supplementary material for structure **I** has been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 835525; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Interaction with DNA. The CT-DNA stock solution was prepared as reported [9]. CD spectra were recorded at room temperature in the wavelength range of 220–320 nm after CT-DNA (1.0×10^{-4} M) was incubated with **I** in different molar ratios in the buffer (5 mM Tris-HCl/50 mM NaCl, pH 7.4) at 310 K for 24 h in the dark. Three scans were performed for each spectrum and the buffer background was subtracted.

RESULTS AND DISCUSSION

As the crystal structure shows (Fig. 1), complex **I** is aneutral polymer. The coordination of the Zn(II) center is a centro symmetric octahedron and Zn(II) is six-coordinated. Each Zn^{2+} ion is coordinated by two O atoms from the two HPDDA ligands, two N atoms from two 4,4'-Bipy and two O atoms from two water molecules. This coordinated unit is extended by 4,4'-Bipy and HPDDA to form a coordinated polymer. Figure 2 is the packing diagram of **I** and there are four molecular structure of **I** in one cell. Perhaps owing to the two coordinated H_2O molecules, the solubility of **I** in water is good and this prompts us to develop biological properties of **I**.

DNA replication is the crucial event for cell division and its accumulation in cells plays an important role in the demise of cell apoptosis [10, 11]. The structure of the molecules plays important roles in interaction mode with DNA. To infer the effects of **I** binding on DNA conformation, we studied the binding affinity and the mode of binding by CD spectroscopy, which is a powerful method for investigation of the interaction between small molecules and DNA [12]. It

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

Parameter	Value
M	459.73
Crystal system	Triclinic
Space group	$P\bar{1}$
a, Å	7.100(4)
b, Å	9.224(6)
c, Å	15.154(9)
α, deg	88.732(7)
β, deg	84.429(7)
γ, deg	69.959(7)
V, Å^3	927.9(10)
Z	2
ρ_{calcd}, g cm^{-3}	1.645
$\mu(MoK_\alpha)$, mm^{-1}	1.38
F(000)	472
GOOF	1.11
Crystal size, mm	0.20 × 0.18 × 0.17
θ_{max}, deg	25.5
Reflections collected	6818
Unique reflections	3395
Observed reflections ($I > 2\sigma(I)$)	2605
Largest difference peak and hole, e Å^{-3}	0.46 and −0.36

is also used for the determination of the secondary structural changes of DNA after binding with small molecules. As shown in Fig. 3, the CD spectrum of CT-DNA demonstrates a positive band at 277 nm due to base stacking and a negative band at 245 nm due to right-hand helicity. These are characteristics of the B-DNA [13]. On addition of increasing amount of **I** (the ratio of [complex]/[DNA] changed from 0 to 0.8), the intensity of the positive increases whereas that of the negative bands decreases. Additionally, a slight red shift in the maximum wavelength for negative bands was observed which suggests not only the unwinding of the DNA helix by **I** but also a tendency of the conformational deviation from B-DNA to A-DNA. Moderate increase of positive and negative signal were observed by some other Zn(II) complexes

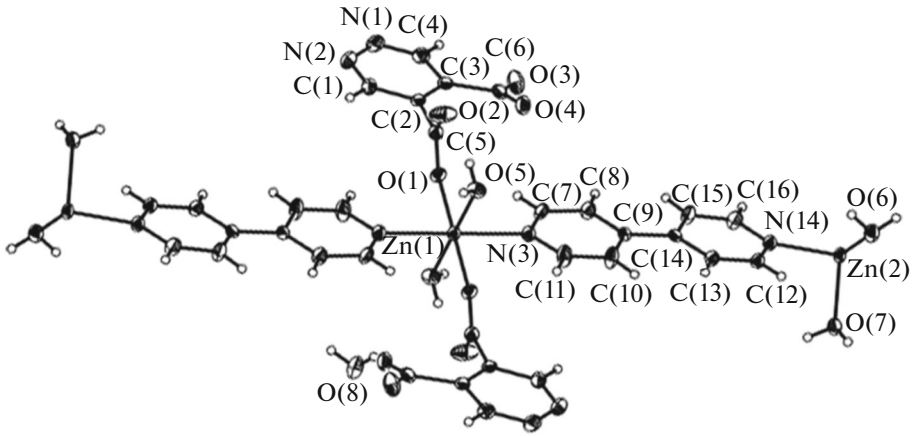


Fig. 1. Molecular structure of **I**.

Table 2. Selected bond lengths (Å) and angles (deg) for **I**

Bond	*d*, Å	Bond	*d*, Å
Zn(1)–O(1)	2.155(2)	Zn(2)–O(6)	2.159(2)
Zn(1)–O(5)	2.052(2)	Zn(2)–O(7)	2.133(2)
Zn(1)–N(3)	2.197(2)	Zn(2)–N(4)	2.123(2)
Angle	ω, deg	Angle	ω, deg
O(1)Zn(1)O(5)	92.29(8)	O(7)Zn(2)O(6)	93.28(10)
O(5)Zn(1)N(3)	87.81(9)	O(7)Zn(2)N(4)	89.51(10)
O(1)Zn(1)N(3)	89.45(10)	O(6)Zn(2)N(4)	90.10(10)
C1(3)C(14)C(9)	121.7(3)	C(8)C(9)C(14)	122.8(3)
C(15)C(14)C(9)	121.9(3)	C(10)C(9)C(14)	121.3(3)
C(11)N(3)Zn(1)	122.6(2)	C(12)N(4)Zn(2)	119.8(2)
C(7)N(3)Zn(1)	121.8(2)	C(16)N(4)Zn(2)	123.9(2)
C(5)O(1)Zn(1)	127.6(2)	N(2)C(1)C(2)	124.7(3)
C(11)N(3)C(7)	115.6(3)	C(1)N(2)N(1)	119.3(3)
C(3)C(2)C(1)	116.0(3)	C(3)C(2)C(1)	116.0(3)
C(3)C(2)C(5)	126.0(3)	C(1)C(2)C(5)	118.0(3)
C(2)C(3)C(4)	116.5(3)	C(2)C(3)C(6)	124.8(3)
C(4)C(3)C(6)	118.7(3)	N(1)C(4)C(3)	125.3(3)
C(12)N(4)C(16)	116.1(3)	O(2)C(5)O(1)	128.1(3)
O(2)C(5)C(2)	116.4(3)	O(1)C(5)C(2)	115.3(3)
O(4)C(6)O(3)	127.0(3)	O(4)C(6)C(3)	117.8(3)
O(3)C(6)C(3)	115.1(3)	N(3)C(7)C(8)	123.2(3)
C(7)C(8)C(9)	121.0(3)	C(8)C(9)C(10)	115.8(3)
C(11)C(10)C(9)	120.0(3)	N(3)C(11)C(10)	124.3(3)
N(4)C(12)C(13)	123.6(3)	C(12)C(13)C(14)	120.3(3)
C(13)C(14)C(15)	116.3(3)	C(16)C(15)C(14)	119.8(3)
N(4)C(16)C(15)	123.7(3)	C(4)N(1)N(2)	118.2(3)

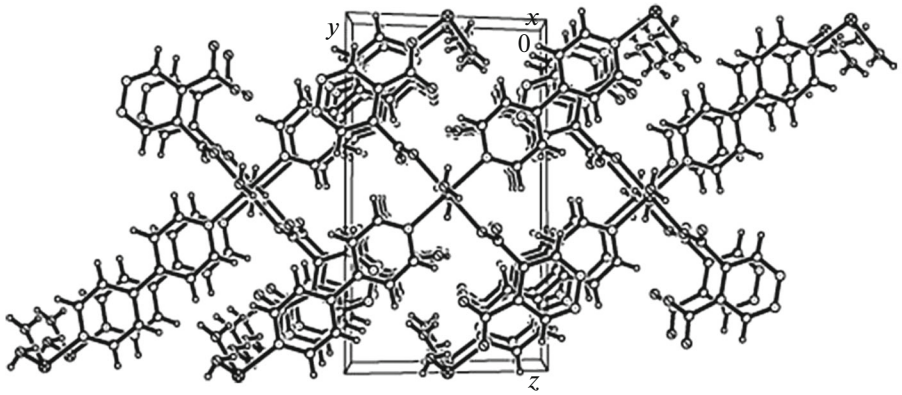


Fig. 2. The packing diagram of **I**.

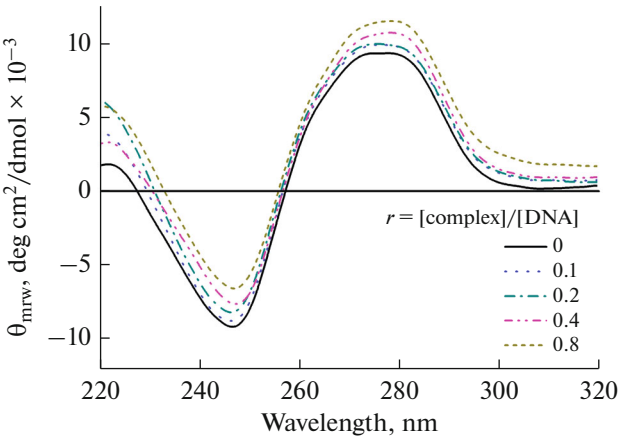


Fig. 3. CD spectra of CT-DNA (0.1 mM) in the presence of **I** at different [complex]/[DNA] molar ratios.

which suggest a weak intercalating mode [14, 15]. In our studies, the planar **I** may also induce a weak intercalation.

Thus, in conclusion, we have synthesized coordination polymer $[Zn(HPDDA)_2(H_2O)_2(4,4'\text{-Bipy})_2]_n$ (**I**) with simple pyridazine-4,5-dicarboxylic acid ligand and 4,4'-Bipy auxiliary ligand hydrothermally. The complex was thoroughly characterized by single crystal XRD techniques. CD spectra studies imply that **I** is involved in groove binding with CT-DNA. Further work is ongoing in the antitumor potential of **I** in cancer cell lines and this will definitely open opportunities to develop more effective zinc anticancer drugs.

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