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Synsthesis, Crystal Structure, Photoluminescence, DNA Cleavage, and Cytotoxicity in Vitro of the Binuclear Ce(III) Complex with Quinaldic Acid[1]

E. J. Gao*, M. C. Zhu, W. Z. Zhang, and Y. G. Sun

Coordination Chemistry Laboratory, Shenyang Institute of Chemical Technology, Shenyang, Liaoning 110142, P.R. China

**E-mail: ejgao@yahoo.com.cn*

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Abstract—A novel binuclear complex $[Ce_2(Qina)_6(H_2O)_3] \cdot 3H_2O$ has been synthesized by the reaction of $Ce(NO_3)_3$ and quinaldine acid (Qina) under hydrothermal conditions. The central ion shows 9-coordination with four Qina and three H_2O molecules, in which Qina adopts three coordination modes. The 2D and 3D framework is constructed via intermolecular hydrogen bonds and π–π stacking interactions. The complex displays an obvious photoluminescent emission upon excitation at 300 nm in solid. Gel electrophoresis assay demonstrates the ability of the complexes to cleave the pBR322 plasmid DNA. The cytotoxic activity of the complex was tested against two different cancer cell lines. The result exhibited cytotoxic specificity and significant cancer cell inhibitory rate.

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Novel coordination polymer and metal-organic materials are of great current interest, because of their perfect framework and the excellent properties such as magnetic, luminescent, catalysis, anticancer activity, etc. [1–5]. The structure of the complexes depends on the coordination number of the metal ion and the structure of ligands. The coordination modes of ligands and the structure of noncoordination groups are the key factor to form the intramolecularly or intermolecularly weak interaction. These weak interactions include metal–metal [6–11], π–π stacking [12, 13], hydrogen bonds [14–17], unconventional hydrogen bonds [18–20], CH···π [21] and multiweak interactions [22–29]. Quinaldine acid (**Qina**) is structurally similar to picolinic acid and pipecolinic acid, which has potentially three coordination sites, two oxygens of carboxylate groups and pyridinic nitrogen, displaying many different coordinate modes with central metal ions. We and other teams synthesized and structurally characterized a series of transition metal complexes with these ligands and found that the ligands have single coordination mode, chelating to central ions by carboxylate and pyridinic nitrogen [30–34]. Lanthanide ions generally adopt higher than six coordination sites and are important building blocks in designing novel organic–inorganic hybrid materials, also its complexes can be potentially usefull as luminescent materials [35, 36]. So we selected Qina and rare-earth metals Ce(III) to synthesize the complexes $[Ce_2(Qina)_6(H_2O)_6] \cdot 3H_2O$ (**I**), in which three coordination modes of the ligand Qina and intramolecularly or intermolecularly weak interaction are observed. The title complex exhibits obvious fluorescence at room temperature in the solid state. Gel electrophoresis assay demonstrates the ability of the complexes to cleave the pBR322 plasmid DNA. The cytotoxic activity of the complexes was tested against two different cancer cell lines.

[1] The article is published in the original.

EXPERIMENTAL

Materials and measurements. All reagents were obtained from commercial sources and used without further purification. The Hep-G2 (human hepatocellular carcinoma) cells and the AGZY–83a (human lung carcinoma) cells were obtained from American Type Culture Collection. Elemental analyses (C, H, and N) were performed on a model Finnigan EA 1112 instrument. IR spectra were run as KBr pellets on a Nicolet IR–470. Emission spectrum was recorded on a Perkin-Elmer LS55 spectrofluorometer.

DNA cleavage. For gel electrophoresis experiments, pBR322 plasmid DNA (0.33 μg/μl) was treated with the complexes in Tris buffer (50 mM Tris–acetate, 18 mM NaCl buffer, pH 7.2), and the contents were incubated for 1 h at room temperature. The samples were electrophoresed for 3 h at 90 V on 0.8% agarose gel in Tris-acetate buffer. After eletrophoresis, the gel was stained with 1 μg/ml ethidium bromide and photographed under the UV-light.

Table 1. Crystallographic data and details of the experiment and refinement of structure **I**

Parameter	Value
Empirical formula	$C_{60}H_{54}Ce_2N_6O_{21}$
Formula weight	1475.33
T, K	293(2)
Wavelength, Å	0.71073
Crystal system	Triclinic
Space group:	$P\bar{1}$
a, Å	8.1966(4)
b, Å	15.1496(7)
c, Å	24.1618(11)
α, deg	78.6420(10)
β, deg	87.4960(10)
γ, deg	79.0220(10)
V, Å^3	2887.7(2)
Z	2
ρ_{calcd}, mg/m^3	1.697
Absorption coefficient, mm^{-1}	1.643
F(000)	1480
Crystal size, mm	$0.37 \times 0.23 \times 0.12$
θ Range for data collection, deg	1.49–26.03
Index ranges	$-10 \le h \le 9$, $-18 \le k \le 18$, $-29 \le l \le 25$
Reflections collected	16250
Independent reflections	11071
Data/restraints/parameters	11071/0/802
Goodness-of-fit on F^2	1.046
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0307$, $wR_2 = 0.0772$
R indices (all data)	$R_1 = 0.0349$, $wR_2 = 0.0798$
Largest diff. peak and hole, e Å^{-3}	0.813 and –0.771

Cell line and culture. The cell lines used in this experiment were routinely maintained in a RPMI–1640 medium supplemented with 10% (v/v) heat-inactivated fetal bovine serum, 2 mmol/l of glutamine, 100 U/ml of penicillin, and 100 μg/ml of streptomycin in a highly humidified atmosphere of 95% air with 5% CO_2 at 37°C.

Cytotoxicity assay. The growth inhibitory effect of the metal complexes on the HeLa, Hep-G2, KB, and AGZY–83a cells was measured by the microculture tetrazolium [3-(4,5-dimethyl-thiazol–2-yl)–2,5-diphenyltetrazolium bromide, **MTT**] assay [37]. In brief, the cells were seeded into a 96-well culture plate at 2×10^5 cells/well in a 100 μl culture medium. After incubation for 24 h, the cells were exposed to the tested complexes of serial concentrations. The complexes were dissolved in DMSO and diluted with RPMI 1640 or DMEM to the required concentrations prior to use (0.1% DMF final concentration). The cells were incubated for 24 and 72 h, followed by the addition of 20 μl of a MTT solution (5 mg/ml) to each well and further cultivation for 4 h. The media with MTT were removed, and 100 μl of DMSO was added to dissolve formazan crystals at room temperature for 30 min. The absorbance of each cell at 450 nm was determined by the analysis with a microplate spectrophotometer. The IC_{50} values were obtained from the results of quadruplicate determinations of at least three independent experiments.

Synthesis of $[Ce_2(Qina)_6(H_2O)_6] \cdot 3H_2O$. A mixture of $Ce(NO_3)_3$ (1.0 mmol), Qina (1.8 mmol) and 10 ml of H_2O were sealed in a 25-ml stainless steel reactor with teflon liner, heated at 180°C for 5 days, and then cooled to room temperature. Accordingly, white crystals were recovered by filtration and washed with distilled water three times.

For $C_{60}H_{54}C_6O_{21}$			
anal. calcd, %:	C, 48.84;	H, 3.69;	N, 5.70.
Found: %:	C, 48.89;	H, 3.61;	N, 5.74.

IR spectrum (ν, cm^{-1}): 3362 m, 3080 m, 2424 w, 2358 w, 1658 s, 1613 s, 1561 s, 1505 w, 1465 s, 1384 s, 1218 m, 1174 m, 1151 m, 1116 w, 1037 w, 958 w, 898 m, 855 m, 806 s, 780 s, 742 m, 633 m, 596 m, 551 m, 523 w, 479 w.

X-ray crystallographic determination. The crystal structure of **I** was determined by singe-crystal X-ray diffraction. A suitable single crystal was mounted in a glass fibrse capillary. Data were collected on a Brucker Smart 1000 CCD X-ray single-crystal diffractometer with MoK_α radiation (λ = 0.71073 Å) at 293(2) K in a range of $1.49° < \theta < 26.03°$ in the ω-scan mode. The structure was solved by direct methods using SHELXL–97 [38, 39] and refined by full-matrix least-squares methods on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from different Fourier maps. Structure solution and refinement based on 11071 independent reflections with $I > 2\theta$ (I) gave $R_1 = 0.0349$, $wR_2 = 0.0798$. Crystal data and structure refinement details are listed in Table 1.

Supplementary material has been deposited with the Cambridge Crystallographic Data Centre (no. 634406; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam. ac.uk).

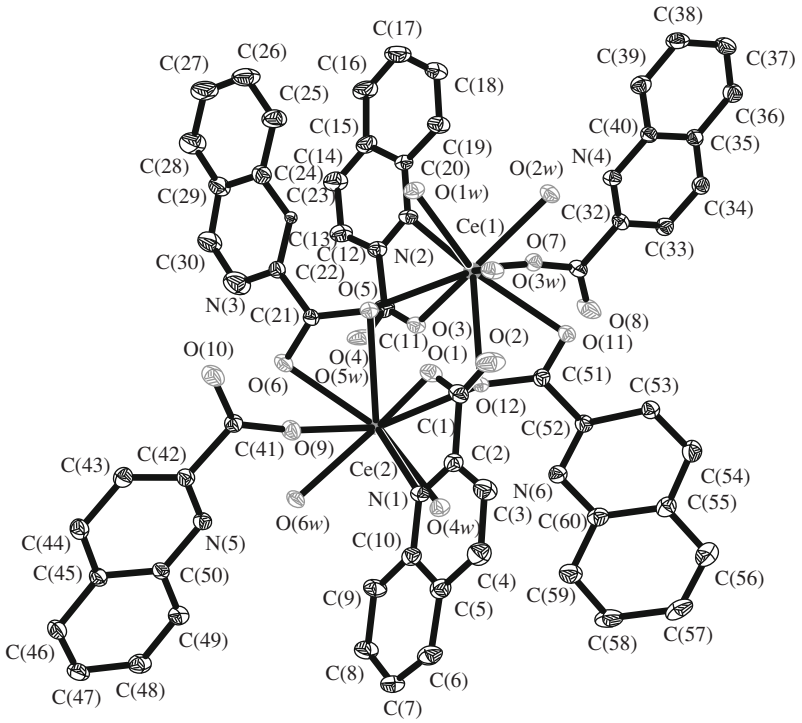
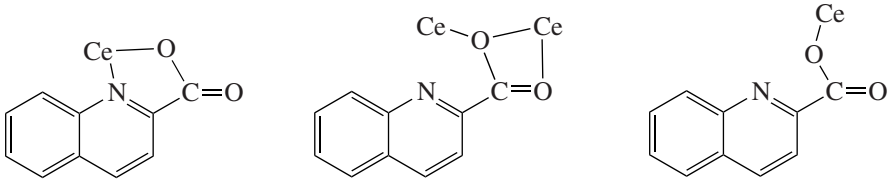


Fig. 1. Coordination environments of Ce(III) in the complex **I** (thermal ellipsoids are at 50% probability, Hydrogen atoms are omitted for clarity)

RESULTS AND DISCUSSION

The single crystal X-ray diffraction revealed that each central Ce^{3+} ion of the complex is coordinated by five oxygen atoms, one nitrogen atom from four Qina, and three water molecules (Fig. 1), which are similar with the Nd-Qina complex [40]. Selected bond distances and angles for complex **I** are collected in Table 2. The Qina ligand adopts three coordination modes **a–c**:



(a) nitrogen atom and carboxylic oxygen atoms (C–O) from Qina chelate with Ce(III), forming a five-membered ring (Ce(2)–O(1) 2.475 Å, Ce(2)–N(1) 2.814 Å); (b) the Qina adopts tridentate bridging mode to link two Ce(III), while two carboxylic oxygen atoms of Qina chelate with one Ce(III), forming a four-membered ring, one of them also bonds to the other Ce(III) (Ce(2)–O(5) 2.789 Å, Ce(2)–O(6) 2.582 Å, Ce(1)–O(5) 2.588 Å); (c) Qina offers only one carboxylic oxygen atom coordinating with Ce(III) (Ce(2)–O(5) 2.372 Å). The distance between Ce(1) and Ce(2) is 4.482 Å. The Ce(III)–O and Ce(III)–N distances are similar to those found in other Ce(III) complexes [41]. Comparing with Co(II), Pb(II), Ga(III) complexes containing a single coordination mode of ligand Qina [32, 34], the structure of the title complex is distinct and infrequent formed by the single ligand because of the coordination environments of Ce(III) and the different synthesis methods.

The intramolecular hydrogen bonds (O(2*w*)···N(4) 2.829, O(4*w*)···N(6) 2.777, O(6*w*)···N(5) 2.747, O(3*w*)···O(1) 2.758, O(5*w*)···O(3) 2.752 Å) between coordinated water with coordinated nitrogen or coordinated carboxylate oxygen are observed in the complex, and intramolecular π–π stacking in the face-to-face model (C(12)···C(22) 3.597, C(12)···N(3) 3.674, C(13)···C(30) 3.641, C(14)···C(29) 3.767, C(20)···C(24) 3.708, N(2)···C(23) 3.468 Å), and strong C–H···π (the distance between C(59) with C(5), C(9), C(10) is 3.600, 3.939, 3.468 Å, respectively) also exist in the complex.

Table 2. Selected bond lengths and angles for **I**

Bond	*d*, Å	Bond	*d*, Å
Ce(1)–O(7)	2.356(2)	Ce(1)–O(2*w*)	2.457(2)
Ce(1)–O(3)	2.472(2)	Ce(1)–O(1*w*)	2.477(2)
Ce(1)–O(11)	2.531(2)	Ce(1)–O(3*w*)	2.580(2)
Ce(1)–O(5)	2.588(2)	Ce(1)–O(12)	2.818(2)
Ce(1)–N(2)	2.847(3)	Ce(1)–C(51)	3.034(3)
Ce(2)–O(9)	2.372(2)	Ce(2)–O(6*w*)	2.460(2)
Ce(2)–O(4*w*)	2.469(2)	Ce(2)–O(1)	2.475(2)
Ce(2)–O(12)	2.523(2)	Ce(2)–O(6)	2.582(2)
Ce(2)–O(5*w*)	2.596(2)	Ce(2)–O(5)	2.789(2)
Ce(2)–N(1)	2.814(3)	Ce(2)–C(21)	3.044(3)
Angle	ω, deg	Angle	ω, deg
O(7)Ce(1)O(3)	77.82(8)	O(7)Ce(1)O(11)	75.18(8)
O(3)Ce(1)O(11)	101.16(8)	O(7)Ce(1)O(5)	147.98(7)
O(3)Ce(1)O(5)	70.17(7)	O(11)Ce(1)O(5)	111.49(7)
O(7)Ce(1)O(12)	105.62(7)	O(3)Ce(1)O(12)	72.33(7)
O(11)Ce(1)O(12)	48.09(7)	O(5)Ce(1)O(12)	65.85(6)
O(7)Ce(1)N(2)	70.16(8)	O(3)Ce(1)N(2)	60.83(7)
O(11)Ce(1)N(2)	143.48(8)	O(5)Ce(1)N(2)	92.78(7)
O(12)Ce(1)N(2)	132.92(7)	O(9)Ce(2)O(1)	78.01(8)
O(9)Ce(2)O(12)	148.03(7)	O(1)Ce(2)O(12)	70.92(7)
O(9)Ce(2)O(6)	72.20(9)	O(1)Ce(2)O(6)	106.06(8)
O(12)Ce(2)O(6)	109.05(7)	O(9)Ce(2)O(5)	96.02(7)
O(1)Ce(2)O(5)	70.98(7)	O(12)Ce(2)O(5)	67.11(6)
O(6)Ce(2)O(5)	48.12(7)	O(9)Ce(2)N(1)	69.00(8)
O(1)Ce(2)N(1)	61.29(7)	O(12)Ce(2)N(1)	101.31(7)
O(6)Ce(2)N(1)	140.90(8)	O(5)Ce(2)N(1)	131.83(7)

Table 3. Cytotoxicity of the complexes and cisplatin against selected human tumor cells after 72 h of incubation*

Tumor cells	In vitro activity (IC_{50} ±SD, μM)	
	complex **I**	cisplatin
Hep-G2	6.87 ± 1.24	1.89 ± 0.27
AGZY-83a	1.32 ± 0.23	2.35 ± 0.43

* Data are expressed as mean ±SD ($n = 4$).

The independent dimers units are linked to each other via kinds of hydrogen bonds, resulting in a perfect 1D chain. The lattice water molecule O(7w) forms three hydrogen bonds with coordinated carboxylate oxygen O(3), uncoordinated carboxylate oxygenO(8) and coordinated water O(2*w*) with O···O distances of 3.010 (O(7*w*)···O(3)), 2.685 (O(7*w*)···O(8)), 2.646 Å (O(7*w*)···O(2*w*)). The other lattice water molecule O(8*w*) forms two hydrogen bonds with coordinated carboxylate oxygen O(1), and coordinated water O(6*w*) with O···O distances of 2.954 (O(8*w*)···O(1)), 2.704 Å (O(8*w*)···O(6*w*)). In addition, strong hydrogen bonds formed by coordinated water with uncoordinated carboxylate oxygen (O(4*w*)···O(2) 2.746, O(1*w*)···O(4) 2.708 Å) also play an important role in the formation of the 1-D chains. The 1D chains stacked to the 2D framework via aromatic π–π interactions (the average distance of carbons of the adjacent aromatic ring is 3.571 Å). The 2D and 3D frameworks constructed by hydrogen bonds and π–π stacking interactions are shown in Figs. 2 and 3.

The Photoluminescent property of **I** is shown in Fig. 4. In the solid state, intense photoluminescent emission bands at 422 and 484 nm (λ_{exac} = 300 nm) are observed, while there is no obvious emission observed for free Qina under the same experimental conditions. The fluorescent emissions of **I** may be attributed to cerium transition $5d \longrightarrow {}^2F_{5/2}$ and $5d \longrightarrow {}^2F_{7/2}$ according to literature reported before [42].

The degree to which the complex can function as DNA cleavage agents was examined using supercoiled pBR 322 plasmid DNA as the target. The efficiency of cleavage of the molecule was probed using agarose gel electrophoresis [43, 44]. The complex was found to promote the cleavage of pBR322 plasmid DNA from supercoiled Form I to the nicked Form II (Fig. 5). A little DNA cleavage was observed for the control in which the metal complex was absent (Fig. 5, lane 0); with increasing concentration of the four complexes, the amount of Form I of pBR322 DNA diminished gradually, whereas Form II increased.

We have performed in vitro cytotoxicity tests of the complex using selected human tumor cell lines. The IC_{50} values are listed in Table 3. The complex exhibited a high level of resistance against conventional chemotherapeutic agents, especially against the AGZY–83a cells. The viability rate by day 3 to less than 50% of the

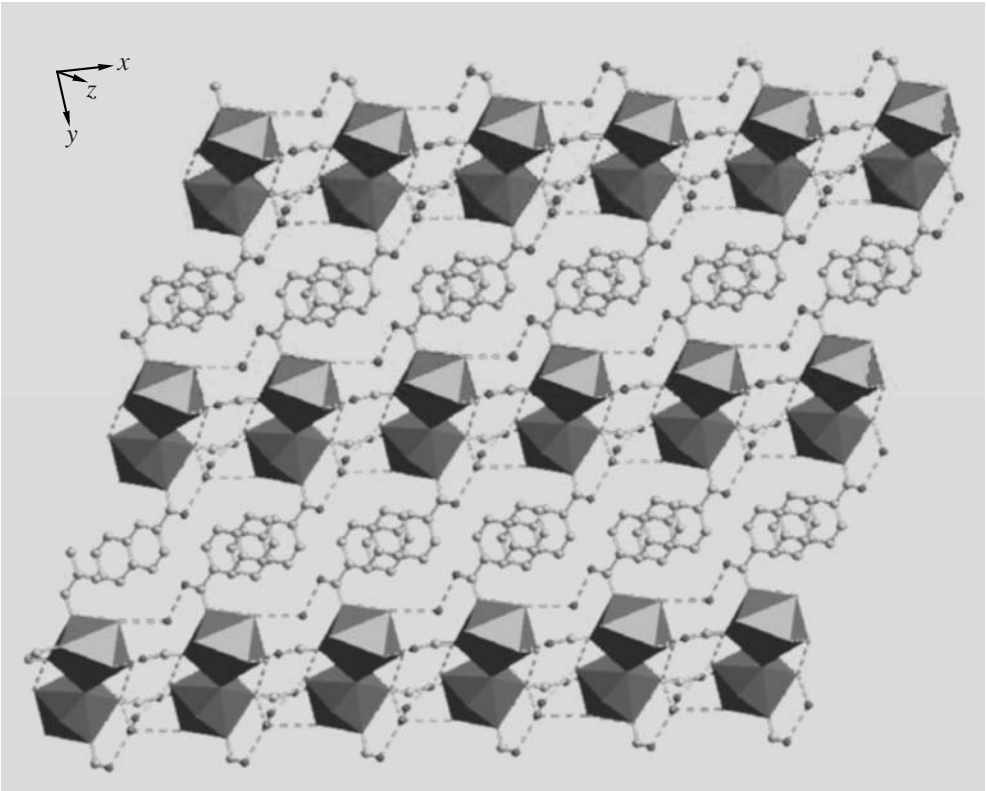


Fig. 2. Two-dimensional framework diagram of the title complex **I**.

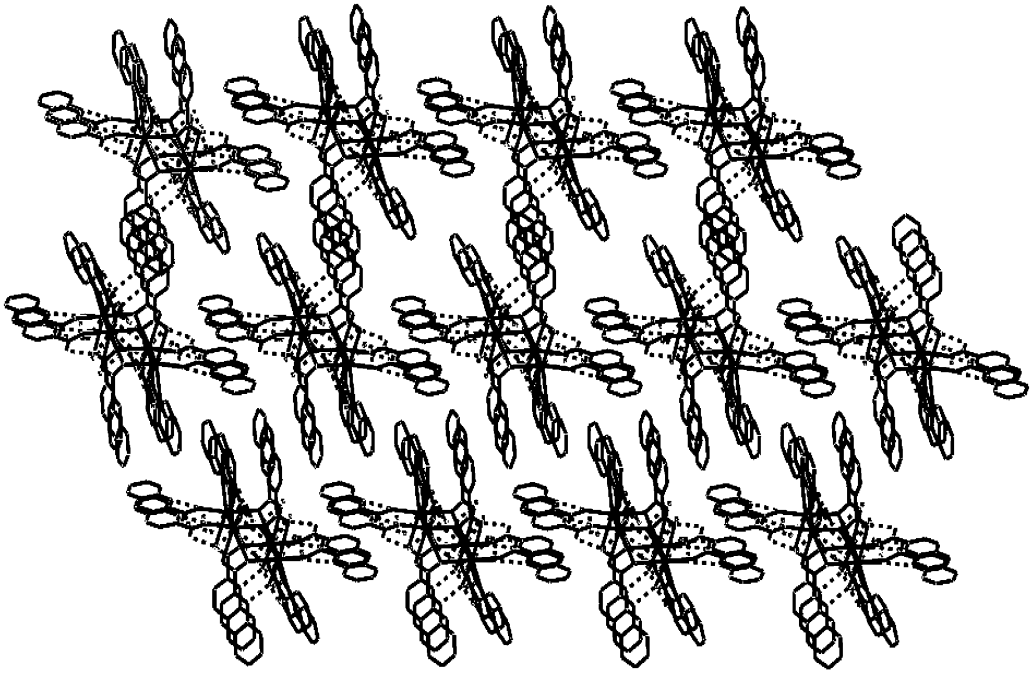


Fig. 3. Three-dimensional framework diagram of the title complex **I**.

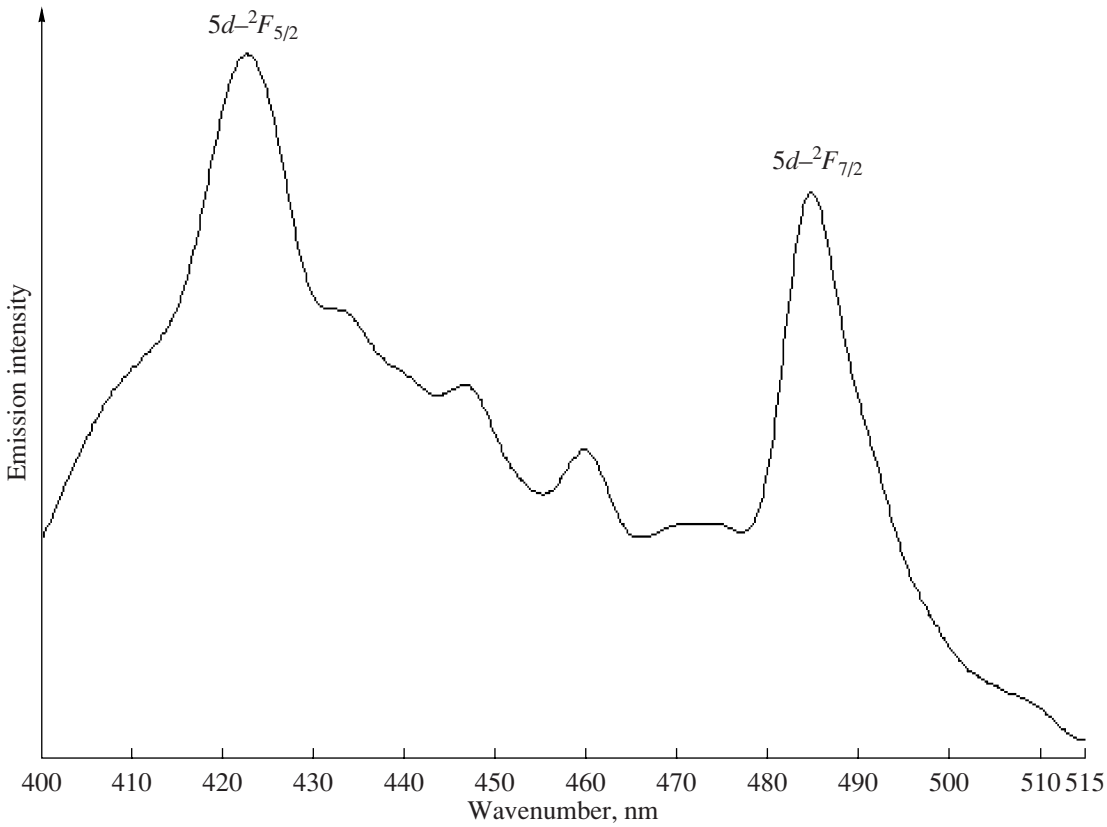


Fig. 4. Solid-state photoluminescence spectrum of the title complex **I**.

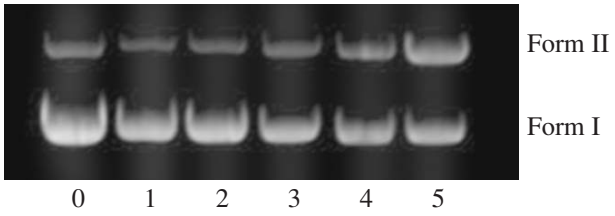


Fig. 5. Cleavage of pBR322 DNA(10 μM) in the presence of the Pd(II) complex in the different concentrations: DNA alone (lane 0) and, of the complex: 20 (*1*), 40 (*2*), 60 (*3*), 80 (*4*), 100 (*5*) μM (lanes *1*–*5*), respectively.

control values was observed for the complex. The complex was more efficient in arresting the growth of AGZY–83a than other lines.

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