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Original article

Syntheses, characterization, interaction with DNA, cytotoxic and apoptosis of two novel complexes of Zn(II) and Mn(II) with 2-methyl-1H-4,5-imidazoledicarboxylic acid

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ABSTRACT

Two new complexes, $Zn(L)_2(H_2O)_2$ (**1**) and $Mn(L)_2(H_2O)_2$ (**2**) [L = 2-Methyl-1H-4,5-imidazoledicarboxylic acid] were synthesized and characterized by elemental analysis, infrared spectroscopy, and single crystal X-ray diffraction. Intramolecular weak interactions, such as hydrogen-bond and intermolecular interactions were presented in the complexes. The activities of the complexes binding with DNA, and cytotoxic activities were studied. The binding of complexes with fish sperm DNA (FS-DNA) was investigated by fluorescence spectra. Gel electrophoresis assay demonstrated the ability of the complexes to cleave the pBR322 plasmid DNA. The cytotoxic activities of the complexes were tested against the KB cell line. Cytotoxic activity studies showed the two complexes exhibited significant cancer cell inhibitory rate. The most active compound was complex 1 with IC_{50} and CC_{50}value of 36.5, 429, with the selectivity index (SI = 11.75) among the tested compounds.

1. Introduction

Inorganic medicinal chemistry was an area of growing significance in both therapeutic and diagnostic medicine [1–5]. Metal based chemotherapy agents were of substantial interest, mainly due to the landmark discovery of the anti-tumor activity of cis-diamminedichloroplatinum(II) (cis-$[PtCl_2(NH_3)_2]$, cisplatin) by Barnett Rosenberg [6,7]. Unfortunately, its severe side effects and intrinsic or acquired resistance in tumor cells limited its application as anti-tumor agents. New areas of researches, which mainly focused on the synthesis of specific, highly functional metal drug complexes with lower toxicity and more improved therapeutic properties, had drawn considerable attentions [8,9]. Thus, many new derivatives had been synthesized and anti-tumor activity against various tumor model systems was determined, in order to discover new drugs [10–16].

2-Methyl-1H-4,5-imidazoledicarboxylic acid with a proton donor was a multifunctional carboxylate ligand, which had various acid-base-type coordination modes, forming specific structures. Herein, we reported the synthesis of the Zn (II) (1) and Mn (II) (2) complexes with it. The two complexes were characterized by elemental analysis, infrared spectrum (IR) as well as the binding behaviors of the complexes with FS-DNA investigated by electronic absorption spectra, fluorescence spectra and gel electrophoresis. The cytotoxic and apoptosis activity of the complexes were also investigated.

2. Experimental

2.1. Materials

2-Methyl-1H-4,5-imidazoledicarboxylic acid ($C_6H_6N_2O_4$), $ZnSO_4 \cdot 7H_2O$, $C_4H_6MnO_4 \cdot 4H_2O$. Fish sperm DNA (FS-DNA) and pBR 322 plasmid DNA were purchased from Sinopharm Chemical Reagent Co., Ltd. The KB cells (human oral epithelial carcinoma cells) was obtained from American Type Culture Collection (ATCC).

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2.2. Preparation of the complexes

2.2.1. Synthesis of complex 1

Complex 1 was synthesized according to the procedure as follows. 3.0 mmol of L was dissolved in ethanol/DMSO (1:1, 2.0 ml) and diluted with water to 10.0 ml. Then, 3.0 mmol of $ZnSO_4 \cdot 7H_2O$ dissolved in 10.0 ml of water was added dropwise. The mixture was stirred for 14 h at room temperature, adjusted pH to 3.9. After five days, colorless transparent crystals were obtained at room temperature by slow evaporation of the mixed solvents. The resulting crystals were filtered, washed with ethanol and dried in vacuo. Anal. Calc. (%): C, 32.93; H, 2.76; N, 12.80. Found (%): C, 32.99; H, 2.83; N, 12.74. IR spectrum (KBr, cm^{-1}): 3232(s), 1545(s), 1426(m), 1265(m), 1120(s), 983(w), 835(w), 784(w),619(m).

2.2.2. Synthesis of complex 2

This complex was synthesized in an identical manner as that described for 1 with $C_4H_6MnO_4 \cdot 4H_2O$ (3.0 mmol, 10.0 ml of water) in place of $ZnSO_4 \cdot 7H_2O$. Anal. Calc. (%): C, 33.74; H, 2.83; N, 13.12. Found (%): C, 33.68; H, 2.75; N, 13.20. IR spectrum (KBr, cm^{-1}): 3246(s), 1725(m), 1539(s), 1421(m), 1270(m), 1053(w), 773(m), 703(w), 677(w), 653(w).

2.3. X-ray structure determination for the complexes

The crystal structures of the two complexes were determined by singe crystal X-ray diffraction. A suitable single crystal of approximate dimension 0.14 * 0.12 * 0.10 mm was mounted in a glass fibre capillary. Data were collected on a Brucker Smart 1000 CCD X-ray single-crystal diffractometer with graphite-monochromated MoKa radiation (k = 0.71073 Å) at 293(2) K in the range of $-17 \le h \le 12$, with the ω-scan technique. The structure was solved by direct methods and refined by means of the full-matrix least squares procedures with SHELXTL 97 systems [17,18]. Structure solution and refinement based on 5024 independent reflections with $I > 2\sigma(I)$ given R1 = 0.0551, wR2 = 0.1507 and R1 = 0.0593, wR2 = 0.1557, respectively. Crystal data and structure refinement details were summarized in Table 1 and selected bond lengths and angles were given in Table 2.

Table 2
Selected bond lengths (A°) and angles (°).

$[Zn(L)_2(H_2O)_2]_n$	D(Å)	$[Mn(L)_2(H_2O)_2]_n$	D(Å)
O(2)···H(3)	1.65	O(3)···H(3)	1.73
O(3)–H(3)···O(2)	170	O(6)···O(4)	3.073(3)
O(6)–H(6A)···O(2)	171	O(1)···H(5A)	176
O(6)–H(6B)···O(1)	173(4)	O(2)–H(3)···O(3)	2.553(2)
O(6)···H(6A)	2.89	O(6)–H(6A)···O(4)	159
O(6)···H(6B)	2.85(3)	O(6)–H(6B)···O(3)	171(4)

2.4. Physical measurements

Fluorescence measurements was performed on a PerkinElmer LS55 fluorescence spectrofluorometer. For all fluorescence measurements, the entrance and exit slits were maintained at 10 nm and 10 nm, respectively. The samples were excited at 526 nm and its emission was observed at 602 nm. The buffer used in the binding studies was 50.0 mM Tris-HCl, pH 6.8–7.3, containing 10.0 mM NaCl. The samples were incubated 4 h at room temperature (20 °C) before spectral measurements. The measurements of EB binding to DNA-Zn(II) and DNA-Mn(II) complexes were studied by increasing the concentrations of the complexes and measuring the change in fluorescence intensity.

For the gel electrophoresis experiments, pBR 322 plasmid DNA

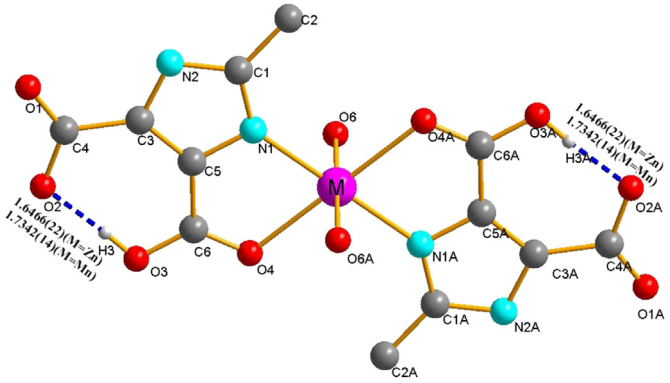

Fig. 1. The molecular structure of the two complexes [M = Zn (II)/Mn (II)].

Table 1
Crystal data and structure refinement for complexes.

Parameter	$[Zn(L)_2(H_2O)_2]$(1)	$[Mn(L)_2(H_2O)_2]$(2)
Formula weight	437.63	427.20
Crystal system, space group	Orthorhombic, Pbca	Monoclinic, P2(1)/c
a, Å	6.848(4)	12.245(7)
b, Å	13.934(8)	9.162(5)
c,Å	8.1006(7)	7.433(4)
β, deg	90	101.662(8)
V, $Å^3$	1596.7(16)	1596.7(16)
Z	4	2
ρ_{calcd}, mg/cm^{-3}	1.737	1.737
Absorption coefficient, mm^{-1}	1.605	0.874
Crystal size, mm	0.12 × 0.10 × 0.08	0.14 × 0.12 × 0.10
θ Range for data collection, deg	3.17 to 27.55	3.40 to 27.53
F(000)	888	434
Limiting indices	$-8 \le h \le 8$, $-18 \le k \le 18$, $-21 \le l \le 21$	$-15 \le h \le 15$, $-11 \le k \le 11$, $-9 \le l \le 9$
Reflections collected/unique	14640/1831 [R(int) = 0.1409]	8098/1878 [R(int) = 0.0512]
Completeness, %	99.6	99.6
Data/restraints/parameters	1831/84/132	1878/0/130
Goodness-of-fit on F^2	1.103	1.058
Final R indices ($I > 2\sigma(I)$)	R1 = 0.0551, wR2 = 0.1507	R1 = 0.0346, wR2 = 0.0951
R indices (all data)	R1 = 0.0593, wR2 = 0.1557	R1 = 0.0374, wR2 = 0.0974
Largest diff. peak and hole, $e.Å^{-3}$	0.878 and −0.929	0.676 and −0.302