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吡嗪双腙配体铜配合物的合成、结构和 DNA 结合性质

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摘要: 合成并通过单晶衍射、元素分析及红外光谱表征了配合物$[Cu_4(L)_2(CH_3O)_2(CH_3OH)_4(SO_4)_2]SO_4\cdot 6CH_3OH$ (**1**)的结构(L 为 3-乙基-2-乙酰吡嗪双缩水合肼)。单晶衍射结果表明,在配合物 **1** 中,每个 Cu(Ⅱ)离子与来自半个腙配体的 2 个 N 原子和分别来自配位甲醇、桥联甲氧基及 2 个不同硫酸根的单齿配位和桥联氧原子配位,形成扭曲的八面体配位构型。4 个 Cu(Ⅱ)离子通过对称操作形成理想的平面四核铜簇。此外,荧光光谱表明配合物 **1** 与 DNA 的相互作用强于配体 L。

关键词: 双腙; 晶体结构; Cu(Ⅱ)离子配合物; DNA 相互作用; 吡嗪
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Synthesis, Crystal Structure and DNA Interaction of a Cu(Ⅱ) Complex with Bis-hydrazone Ligand Bearing Pyrazine Unit

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Abstract: A complex, namely $[Cu_4(L)_2(CH_3O)_2(CH_3OH)_4(SO_4)_2]SO_4\cdot 6CH_3OH$ (**1**) (L=*N*,*N*′-bis-(1-(3-ethyl-pyrazin-2-yl)-ethylidene)-hydrazine) has been synthesized and characterized by single-crystal X-ray diffraction, elemental analysis and IR spectroscopy. X-ray diffraction analysis results show that in complex **1**, each Cu(Ⅱ) center with a distorted octahedron geometry is coordinated by two N atoms from one pyrazin-2-yl-ethylideneamine subunit, and four O atoms involving one O atom from one neutral methanol, one μ_2-bridged O atom from one methoxy anion, one μ_2-bridged O and one monodentate O atoms from two independent sulfate anions, thus forming an ideal planar four-membered Cu_4 core. In addition, the fluorescence spectra indicate that the interaction of complex **1** with DNA is stronger than that of the ligand L. CCDC: 1844807, L; 1844806, **1**.

Keywords: bis-hydrazone; crystal structure; Cu(Ⅱ) complex; DNA interaction; pyrazine

In the past few decades, Schiff bases and their metal complexes have been a focus of chemists and biologists because of their noteworthy antibacterial, antifungal, anticancer, urease inhibition, antioxidant and antiglycation activities[1-5]. It has been demonstrated that the presence of heterocyclic ring in the synthesized Schiff bases plays a major role in extending their pharmacological properties[2,6-7]. Since pyrazines are an important class of nitrogen heterocyclic compounds with a variety of biological activities, metal complexes of Schiff bases bering pyrazine unit, including semicarbazones[8-9], thiosemicarbazones[10-11] and acylhydrazone[12-13], have attracted more and more attention. However, to the best of our knowledge, the

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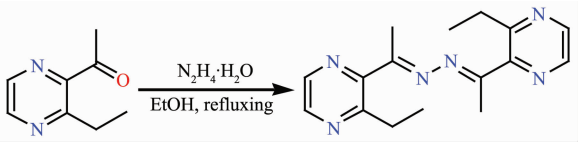
studies on the coordination behavior of bis-hydrazones containing pyrazine ring are relatively scarce[14].

On the other hand, it is noted that Cu(Ⅱ)containing anticancer agents are promising leads for next generation metal-based anticancer agents because Cu(Ⅱ) plays a significant role in biological systems[15-16]. Herein, we present here the crystal structures of a bis-hydrazone (L, Scheme 1) derived from 3-ethyl-2-acetylpyrazine and its Cu(Ⅱ) complex. In addition, the interactions between both compounds and ct-DNA have been studied by ethidium bromide (EB) fluorescence probe.



Scheme 1 Synthesis route of L

1 Experimental

1.1 Materials and measurements

Solvents and starting materials for synthesis were purchased commercially and used as received. Elemental analysis was carried out on an Elemental Vario EL analyzer. The IR spectra (ν=4 000~400 cm^{-1}) were determined by the KBr pressed disc method on a Bruker V70 FT-IR spectrophotometer. ^1H NMR spectra of L was acquired with Bruker AV400 NMR instrument in DMSO-d_6 solution with TMS as internal standard. The UV spectra were recorded on a Purkinje General TU-1800 spectrophotometer. The interactions between three compounds and ct-DNA are measured using literature method [17] via emission spectra on a Varian CARY Eclipse spectrophotometer.

1.2 Preparations of the ligand L and complex 1

As shown in Scheme 1, the ligand L was produced by condensation of 3-ethyl-2-acetylpyrazine (3.02 g, 0.02 mol) and 85% hydrazine hydrate (0.59 g, 0.01 mol) in anhydrous ethanol solution (30 mL) with continuous stirring under refluxing for 3 h. After cooled to room temperature, colorless rod crystals were filtered and washed three times by cold ethanol. Yield: 2.13 g (72%). m.p. 119.0~120.2 ℃. Elemental analysis Calcd. for $C_{16}H_{20}N_6$(%): C: 64.84; H: 6.80; N: 28.36. Found(%): C: 64.92; H: 6.76; N: 28.15. FT-IR (cm^{-1}): ν(C=C) 1 653, ν(C=N-N) 1 620, $\nu(C=N)_{pyrazine}$ 1 650, $\nu(C=N)_{pyrazine}$ 1 560. ^1H NMR (400 MHz, DMSO-d_6): δ 8.59~8.65 (2H, d, pyrazine-H), 3.14~3.19 (2H, q, CH_2, J=8.0 Hz), 2.27 (3H, s, CH_3), 1.28~1.32 (3H, t, CH_3, J=8.0 Hz).

The crystals of complex **1** suitable for X-ray diffraction analysis were obtained by slow evaporating the methanol solution (5 mL) of the ligand L (5 mmol) with equimolar of $CuSO_4$ at room temperature.

1: green plates. Anal. Calcd. for $C_{44}H_{86}N_{12}O_{24}S_3Cu_4$ (%): C: 34.82; H: 5.71; N: 11.08. Found(%): C: 34.62; H: 5.85; N: 10.94. FT-IR (cm^{-1}): ν(C=C) 1 654, ν(C=N-N) 1 600, $\nu(C=N)_{pyrazine}$ 1 647, $\nu(C=N)_{pyrazine}$ 1 510.

1.3 X-ray crystallography

The X-ray diffraction measurements for L and complex **1** were performed on a Bruker SMART APEX Ⅱ CCD diffractometer equipped with a graphite monochromatized Mo $K\alpha$ radiation (λ=0.071 073 nm) by using φ-ω scan mode. Semi-empirical absorption correction was applied to the intensity data using the SADABS program[18]. The structures were solved by direct methods and refined by full matrix least-square on F^2 using the SHELXTL-97 program[19]. All non-hydrogen atoms were refined anisotropically. The C6 atom of **1** occupied two positions, with the occupancy value of C6/C6A being 0.718/0.282. The H atoms of disordered methanol molecule (C12-O8, occupancy value being 0.5) in **1** were not added. All the other H atoms were positioned geometrically and refined using a riding model. Details of the crystal parameters, data collection and refinements for L and complex **1** are summarized in Table 1.

CCDC: 1844807, L; 1844806, **1**.

2 Result and discussion

2.1 Crystal structures description

Selected bond distances and angles for L and complex **1** are listed in Table 2. The asymmetric unit of L contains half of the molecule (Fig.1a). According to C4-C7 bond, the imine C7-N3 and pyrazine C4-N1 bonds exist in *trans*-manner. As shown in Fig.1b, complex **1** includes one discrete tetrameric Cu(Ⅱ) cations, one free sulfate anion for charge balance, and

Table 1　Crystal data and structure refinement for L and complex 1

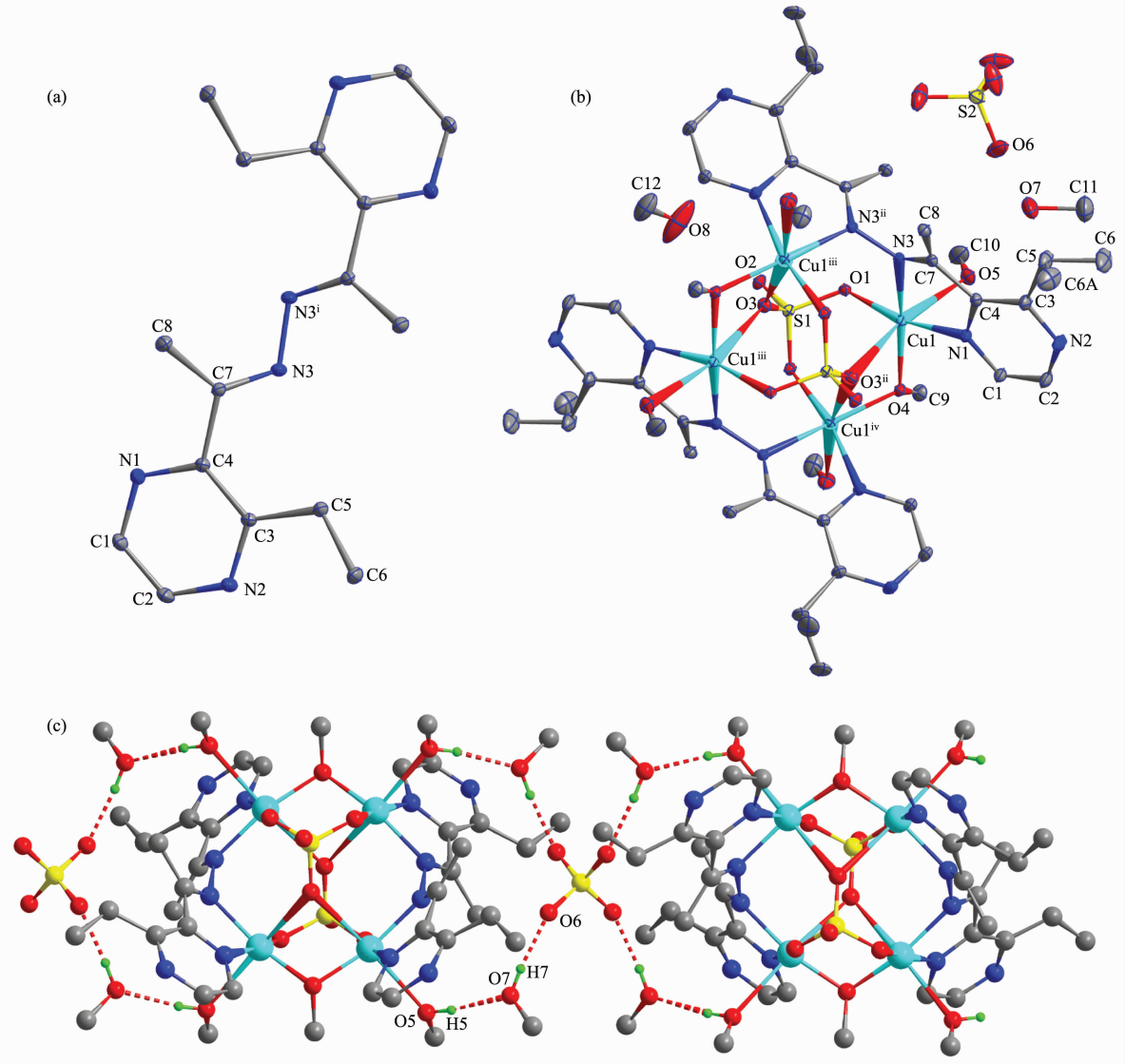
	L	**1**
Empirical formula	$C_{16}H_{20}N_6$	$C_{44}H_{86}N_{12}O_{24}S_3Cu_4$
Formula weight	296.38	1 517.58
T / K	296(2)	296(2)
Crystal system	Monoclinic	Orthorhombic
Space group	*I*2/*a*	*Ibam*
a / nm	1.830 1(2)	1.170 59(6)
b / nm	0.392 13(5)	1.891 69(11)
c / nm	2.189 5(4)	3.000 61(17)
β / (°)	96.673(2)	
V / nm^3	1.560 7(4)	6.644 5(6)
Z	4	4
F(000)	632	3 160
D_c / (g·cm^{-3})	1.261	1.517
Unique reflection	1 374	2 998
R_{int}	0.022 2	0.028 7
Goodness-of-fit (GOF) on F^2	1.054	1.038
R indices [$I>2\sigma(I)$]	R_1=0.044 6, wR_2=0.119 2	R_1=0.040 9, wR_2=0.116 4
R indices (all data)	R_1=0.061 0, wR_2=0.130 3	R_1=0.050 5, wR_2=0.123 9

Table 2　Selected bond lengths (nm) and angles (°) in L and complex 1

			L		
N1-C4	0.133 2(2)	N3-C7	0.128 1(2)	N3-N3^{i}	0.140 6(2)
			1		
Cu1-O1	0.1945(2)	Cu1-O5	0.224 0(3)	Cu1-N1	0.199 6(3)
Cu1-O4	0.192 79(19)	Cu1-O3^{ii}	0.247 8(3)	Cu1-N3	0.203 3(3)
O4-Cu1-O1	95.02(12)	O4-Cu1-N1	95.42(13)	O1-Cu1-N1	167.48(11)
O4-Cu1-N3	164.98(13)	O1-Cu1-N3	93.14(10)	N1-Cu1-N3	78.92(11)
O4-Cu1-O5	99.15(12)	O1-Cu1-O5	88.92(11)	N1-Cu1-O5	88.260(13)
N3-Cu1-O5	93.59(12)	O4-Cu1-O3^{ii}	76.28(11)	O1-Cu1-O3^{ii}	103.16(11)
O5-Cu1-O3^{ii}	167.34(13)	N1-Cu1-O3^{ii}	86.05(12)	N3-Cu1-O3^{ii}	89.59(10)

Symmetry codes: ^{i} $-x$+0.5, y, $-z$; ^{ii} x+2, y+1, z.

six methanol molecules in the unit cell. The N3-N3^{ii} (Symmetry codes: ^{ii} 2−x, 1−y, z) bridge divides the ligand into two pyrazin-2-yl-methyleneamine subunits, each of which is bound to a different Cu(Ⅱ) ion with N1 and N3 atoms. Compared with free ligand, the configuration of C7-N3 and C4-N1 bonds transfer to *cis*. Each Cu(Ⅱ) center is also coordinated by four O atoms, involving one O atom from one neutral methanol, one μ_2-bridged O atom from one methoxy anion, one μ_2-bridged O and one monodentate O atoms from two independent sulfate anions. In other words, four Cu(Ⅱ) atoms were bridged by two pairs of μ_2-bridged O atoms to form an ideal planar four-membered Cu_4 core with Cu … Cu instance being 0.314 1 and 0.401 2 nm. In the crystal, free sulfate anions and methanol molecules linked the complex cations into one-dimensional chains along c axis (Fig. 1c) via intermolecular O−H…O hydrogen bonds (O5−H5…O7, with D…A distance being 0.267 2(6) nm, D−H…A angle being 169.7°; O7−H7…O6, with D…A distance being 0.259 4(9) nm, D−H…A angle being 171.7°). The intermolecular O−H…O hydrogen bonds



H atoms are omitted for clarity in (a) and (b); H atoms of C-H bonds and disordered methanol molecules are omitted for clarity in (c); Symmetry codes: [i] $-x+0.5, y, -z$; [ii] $x+2, y+1, z$; [iii] $x+2, y+1, z+1$; [iv] $x, y, z+1$

Fig.1 Diamond drawing of L (a) and complex **1** (b) with 10% thermal ellipsoids; (c) Extended chain-like supramolecular structure along *c* axis in complex **1**

between the disordered methanol molecules and the uncoordinated O atom (O2) of the sulfate anion in the complex cations are also present (O8···O2, with D···A distance being 0.256 8 nm).

2.2 IR spectra

The infrared spectral bands most useful for determining the mode of coordination of the ligand are the ν(C=N-N) and $\nu(C=N)_{pyrizine}$ vibrations. As our previous work shows, such two bands of the ligand L are at 1 620 and 1 560 cm^{-1}, while they shift to 1 600 and 1 510 cm^{-1} in the complex **1**, respectively, indicating that imine N and pyrizine N atoms take part in the coordination[14,20]. It is in accordance with the crystal structure study.

2.3 UV spectra

The UV spectra of L and complex **1** in CH_3OH solution (concentration: 10 $\mu mol \cdot L^{-1}$) were measured at room temperature (Fig.2). The spectrum of L features only one main band located around 285 nm (ε=15 134 $L \cdot mol^{-1} \cdot cm^{-1}$), which could be contributed to the characteristic π-π^* transition of pyrazine[14]. In complex **1**, the absorbance band has blue-shifted to

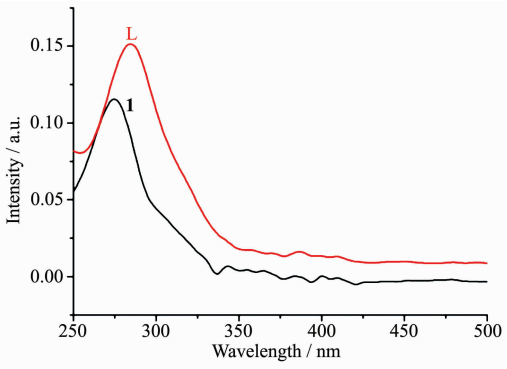
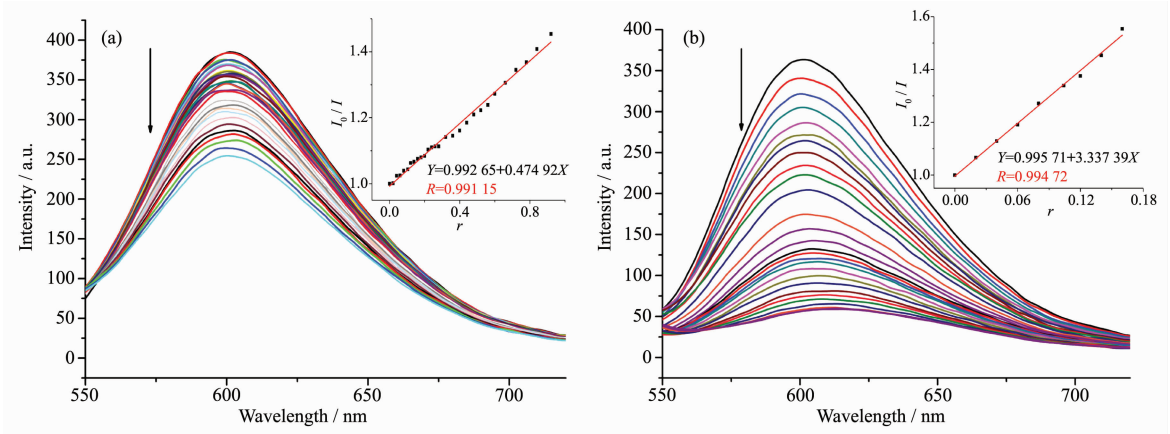


Fig.2　UV spectra of the ligand L and complex **1** in CH_3OH solution at room temperature

275 nm (ε=11 562 L·mol^{-1}·cm^{-1}), confirming the coordination of ligand L in complex **1**.

2.4　EB-DNA binding study by fluorescence spectrum

It is well known that EB can intercalate nonspecifically into DNA, which causes it to fluoresce strongly. Competitive binding of other drugs to DNA and EB will result in displacement of bound EB and a decrease in the fluorescence intensity[9]. As shown in Fig.3, the fluorescence intensities of EB bound to ct-DNA at about 600 nm show remarkable decreasing trends with the increasing concentration of the tested samples, indicating that some EB molecules are exchanged by the tested compounds. The quenching of EB bound to DNA by the compounds is in agreement with the linear Stern-Volmer equation: I_0/I= 1+$K_{sq}r$[9], where I_0 and I represent the fluorescence intensities in the absence and presence of quencher, respectively; K_{sq} is the linear Stern-Volmer quenching constant; r is the ratio of the concentration of quencher and DNA. In the quenching plots of I_0/I versus r, K_{sq} values are given by the slopes. The K_{sq} values of complex **1** is tested to be 3.337, which is much higher than that of the ligand L (0.475). The results indicate that the interaction of the complex with DNA are stronger than that of the ligand L, because complex **1** have higher rigidity to bind the base pairs along DNA.



Arrow shows the fluorescence intensities change of EB-DNA system upon increasing tested complex concentration; Inset: plot of I_0/I versus r

Fig.3　Emission spectra of EB-DNA system in the presence of L (a) and complex **1** (b), respectively

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