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两个 3-甲基-2-乙酰吡嗪缩 4-苯基氨基脲双核铜(Ⅱ)配合物的晶体结构及与 DNA 的相互作用

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摘要:合成并通过单晶 X 射线衍射、元素分析及红外光谱表征了配合物[$Cu_2(L)_2Cl_2$](**1**)和[$Cu_2(L)_2(OAc)_2$](**2**)的结构(HL 为 3-甲基 2-乙酰吡嗪缩 4-苯基氨基脲)。单晶衍射结果表明,2 个配合物中,每个拥有四方锥配位构型的 Cu(Ⅱ)离子与来自 1 个阴离子配体 L^-的 N_2O 电子供体和 2 个阴离子配位(**1** 中为氯离子,**2** 中为醋酸根离子),其中 1 个阴离子为 μ^2 桥联配位模式。荧光光谱结果表明,配合物与 DNA 的相互作用强于配体。

关键词:缩氨基脲;铜配合物;吡嗪;晶体结构;DNA 相互作用

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Two Binuclear Cu(Ⅱ) Complexes with 1-(3-Methylpyrazin-2-yl)ethylidene-4-phenylsemicarbazide: Crystal Structures and DNA Interaction

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Abstract: Two binuclear complexes, namely [$Cu_2(L)_2Cl_2$] (**1**) and [$Cu_2(L)_2(OAc)_2$] (**2**) (where HL is 1-(3-methylpyrazin-2-yl)ethylidene-4-phenylsemicarbazide), have been synthesized and characterized by single crystal X-ray diffraction, elemental analysis and IR spectroscopy. X-ray diffraction analysis results show that in both binuclear complexes, each central Cu(Ⅱ) ion with a distorted square pyramid coordination geometry is surrounded by one independent anionic ligand with N_2O donor set and two coordinated anions (chloride for **1**, whilst acetate for **2**), one of which acts as a μ^2-bridge. In addition, the fluorescence spectra indicate that the interactions of the complexes with DNA are stronger than that of the ligand HL. CCDC: 1455421, **1**; 1455422, **2**.

Keywords: semicarbazone; Cu(Ⅱ) complex; pyrazine; crystal structure; DNA interaction

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[1-8]. It has been demonstrated that the presence of heterocyclic ring in the synthesized Schiff bases plays a major role in extending their pharmacological properties [8]. As a result, a sizable number of transition metal complexes with acylhydrazones and thiosemicarbazones derived from

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actyl-pyridine/pyrazine have been extensively investigated as potential anticancer agents [3,8-10]. However, as their structurally analogous, semicarbazones have been paid much less attention[6].

On the other hand, the previous studies revealed 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[1,5]. Therefore, in this paper, two Cu(Ⅱ) complexes with a semicarbazone ligand derived from 2-acetyl-3-methylpyrazine and 4-phenylsemicarbazide have been synthesized and structural determined by single-crystal X-ray diffraction. In addition, the interactions between three compounds and ct-DNA have been studied by ethidium bromide(EB) fluorescence probe.

1 Experimental

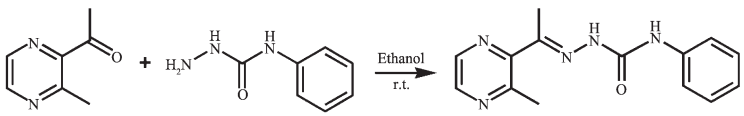
1.1 Materials and measurements

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 FTIR spectrophotometer. ^1H NMR spectra of L was acquired with Bruker AV400 NMR instrument in DMSO-d_6 solution with TMS as internal standard. The interactions between three compounds and ct-DNA are measured using literature method [11] via emission spectra on a Varian CARY Eclipse spectrophotometer.

1.2 Preparations of the ligand HL, complexes 1 and 2

As shown in Scheme 1, the ligand HL was produced by condension of 2-acetyl-3-methylpyrazine (1.36 g, 0.01 mol) and 4-phenylsemicarbazide (1.51 g, 0.01 mol) in ethanol solution (30 mL) with continuous stirring at room temperature for 5 h. The white solid was filtered and washed three times by cold ethanol. Yield: 2.21g (85%). m.p. 178~180 ℃. Elemental analysis Calcd. for $C_{14}H_{15}N_5O$ (%): C 62.44, H 5.61, N 26.01. Found (%): C 62.56, H 5.39, N 25.89. FTIR (cm^{-1}): $\nu(C=O)_{semicarbazone}$ 1 702, ν(C=N) 1 604, $\nu(C=N)_{pyrazine}$ 1 593. ^1H NMR (400 MHz, DMSO-d_6): δ 10.03 (1H, s, NH), 8.77 (1H, s, NH), 8.45~8.48 (2H, m, pyrazine-H), 7.54~7.56 (2H, m, phenyl-H), 7.23~7.27 (2H, m, phenyl-H), 6.95~6.99 (1H, m, phenyl-H), 2.75 (3H, s, CH_3), 2.28 (3H, s, CH_3).

The complexes **1** and **2** were generated by reaction of the ligand HL (5 mmol) with equimolar of $CuCl_2\cdot 2H_2O$ and Cu $(OAc)_2\cdot H_2O$ in methanol solution (10 mL), respectively. Crystals suitable for X-ray diffraction analysis were obtained by evaporating the corresponding reaction solutions at room temperature.



Scheme 1 Synthesis route of HL

1: Green blocks. Anal. Calcd. for $C_{28}H_{28}N_{10}O_2Cl_2Cu_2$ (%): C 45.78, H 3.84, N 19.07. Found(%): C 45.65, H 4.00, N 18.94. FTIR (cm^{-1}): ν(N=C-O) 1 619, ν(C=N) 1 594, $\nu(C=N)_{pyrazine}$ 1 548.

2: Black blocks. Anal. Calcd. for $C_{32}H_{34}N_{10}O_6Cu_2$ (%): C 49.16, H 4.38, N 17.92. Found (%): C 49.36, H 4.52, N 17.74. FTIR (cm^{-1}): ν(N=C-O) 1 595, ν(C=N) 1 579, ν $(C=N)_{pyrazine}$ 1 544, ν_{as1} (COO^-) 1 509, $\nu_{as4}(COO^-)$ 1 435 and 1 352.

1.3.1 X-ray crystallography

The X-ray diffraction measurement for complexes **1** and **2** 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[12].

The structures were solved by direct methods and refined by full matrix least-square on F^2 using the SHELXTL-97 program [13]. All non-hydrogen atoms were refined anisotropically. All the H atoms were positioned geometrically and refined using a riding

model. Details of the crystal parameters, data collection and refinements for complexes **1** and **2** are summarized in Table 1.

CCDC: 1455421, **1**; 1455422, **2**.

Table 1　Crystal data and structure refinement for complexes 1 and 2

	1	**2**
Empirical formula	$C_{28}H_{28}Cl_2N_{10}O_2Cu_2$	$C_{32}H_{34}N_{10}O_6Cu_2$
Formula weight	734.58	781.77
T / K	296(2)	296(2)
Size / mm	0.15×0.10×0.08	0.20×0.16×0.12
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
a / nm	0.863 6(4)	0.803 2(14)
b / nm	1.303 5(6)	0.857 78(16)
c / nm	1.521 6(5)	2.328 4(4)
β / (°)	118.14(2)	98.320(3)
V / nm^3	1.510 4(11)	1.587 3(5)
Z	2	2
D_c / (g·cm^{-3})	1.615	1.636
Unique	2 661	2 795
R_{int}	0.067 1	0.022 6
GOF	1.047	1.081
R indices [$I>2\sigma(I)$]	R_1 = 0.045 6	R_1 = 0.030 7
	wR_2 = 0.081 2	wR_2 = 0.082 4
R indices (all data)	R_1 = 0.086 4	R_1 = 0.036 3
	wR_2 = 0.093 8	wR_2 = 0.085 5
Largest peak and hole / (e·nm^{-3})	384 and −359	336 and −362

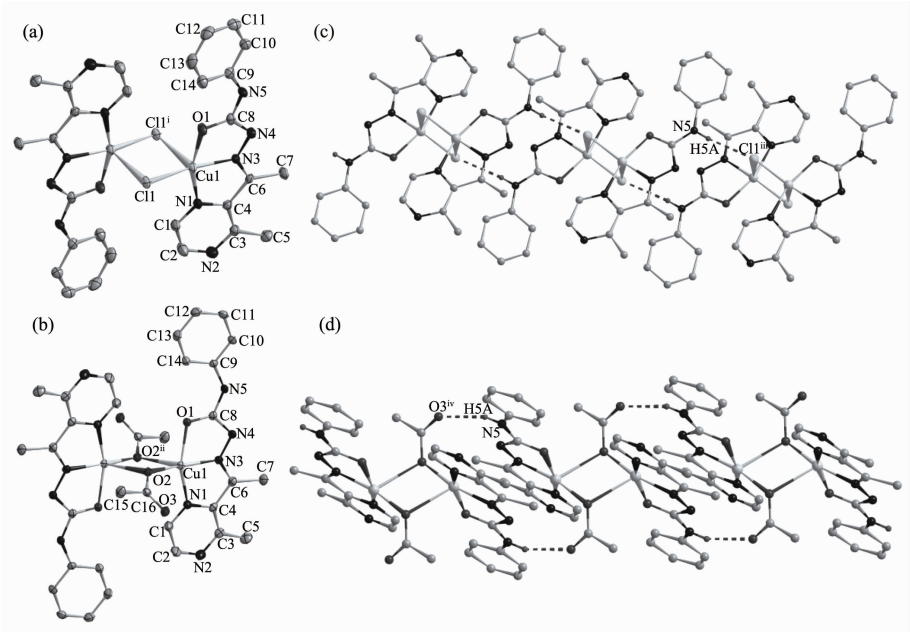
2　Results and discussion

2.1　Crystal structure description

A diamond drawing for complexes **1** and **2** is shown in Fig.1. Selected bond distances and angles are listed in Table 2. The lengths of C-O bond of the semicarbazone moiety are 0.127 9(5) and 0.126 9(3) nm in complexes **1** and **2**, respectively, clearly showing that the ligand HL has enolizated and deprotonated in both complexes[8].

As shown in Fig.1a, complex **1** contains one discrete dimeric Cu (Ⅱ) molecule in the unit cell. Two Cu atoms of the dimer were separated by 0.352 4 nm and doubly bridged by two chloride anions to form an ideal planar four-membered Cu_2Cl_2 core. Each of the Cu(Ⅱ) ions is penta-coordinated by one independent anionic ligand with N_2O donor set and two chloride anions, one of which acts as a μ^2-bridge, thus giving a distorted square pyramid coordination geometry (τ = 0.122)[14]. In the solid state, the discrete Cu (Ⅱ) dimers of **1** were further linked into a one-dimensional chain along a axis (Fig.1c) by intermolecular N-H⋯Cl (N5-H5A⋯Cl1^{iii}, with D⋯A distance being 0.343 1(4) nm, D-H⋯A angle being 170.1°, Symmetry codes: ^{iii} x+1, y, z) hydrogen bonds between the amine nitrogen atoms from one dimer and chloride anions from the adjacent one.

The structure of **2** is similar as that of **1**, while the chloride anion is replaced by monodentate acetate, in which one oxygen atom of the carboxyl group bridges two Cu(Ⅱ) ions to form μ-O. One-dimensional chain (Fig.1d) along a axis formed by intermolecular N-H⋯O (N5-H5A⋯O3^{iv}, with D⋯A distance being 0.288 6 (3) nm, D-H⋯A angle being 157.8°, Symmetry codes: ^{iv} 2 −x, 2 −y, 2 −z) hydrogen bonds are also present in the crystal of **2**.



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

Fig.1 Diamond drawing of **1** (a) and **2** (b) with 30% thermal ellipsoids and extend 2D supramolecular structure along *a* axis in complexes **1** (c) and **2** (d)

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

			1		
Cu1-N1	0.199 6(3)	Cu1-N3	0.192 9(3)	Cu1-O1	0.195 6(3)
Cu1-Cl1	0.225 76(16)	Cu1-Cl1^{i}	0.274 18(18)	Cl1-Cu1-Cl1^{i}	90.90(4)
N3-Cu1-O1	80.40(13)	N3-Cu1-Cl1	167.33(11)	N3-Cu1-Cl1^{i}	101.75(10)
N3-Cu1-N1	79.71(14)	O1-Cu1-Cl1	97.68(9)	O1-Cu1-Cl1^{i}	96.35(10)
O1-Cu1-N1	160.00(12)	N1-Cu1-Cl1	101.26(10)	N1-Cu1-Cl1^{i}	89.77(11)
			2		
Cu1-N1	0.201 5(2)	Cu1-N3	0.193 7(2)	Cu1-O1	0.203 32(17)
Cu1-O2	0.194 09(17)	Cu1-O2^{ii}	0.245 84(18)	O1-Cu1-O2^{ii}	92.15(6)
N3-Cu1-O2	167.46(8)	N3-Cu1-O1	78.44(7)	N3-Cu1-O2^{ii}	118.45(7)
N3-Cu1-N1	78.76(8)	O2-Cu1-O1	100.27(7)	O2-Cu1-O2^{ii}	73.96(7)
O2-Cu1-N1	103.82(8)	N1-Cu1-O1	155.68(8)	N1-Cu1-O2^{ii}	91.30(7)

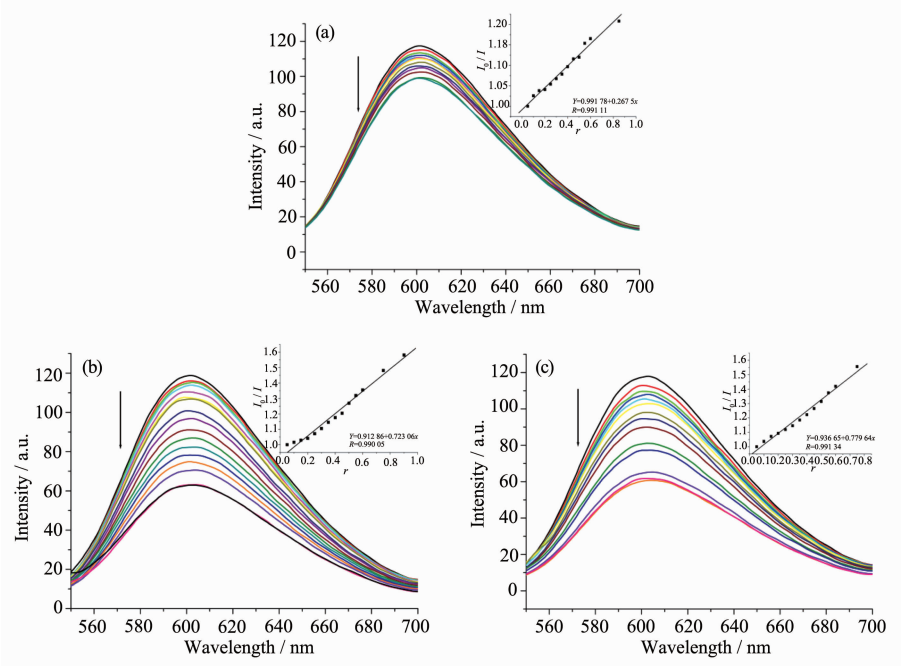
Symmetry codes: [i] $-x, -y, -z$; [ii] $1-x, 2-y, 2-z$

2.2 IR spectra

The $\nu_{\text{semicarbazone}}$ (C=O) of the free ligand is 1 748 cm^{-1}, while it is disappeared in both complexes, meanwhile, new N=C-O stretching vibration absorption is observed at 1 619 and 1 595 cm^{-1} in complexes **1** and **2**, respectively, revealing that the C=O in O=C-N moiety has enolized and the oxygen atom coordinates to the metal ions in both complexes[6-7]. The ν(C=N) bands of the imine group and pyrazine ring in the ligand HL shift to lower frequency values in the complexes, indicating that the N atoms of both units take part in the coordination[8]. Furthermore, the bands at 1 509, 1 435 and 1 352 cm^{-1} in complex **2** could be assigned to the split bands $\nu_{as1}(COO^{-})$ and $\nu_{as4}(COO^{-})$ of the acetate group, respectively, showing that there are bridged and monodentate carboxyl groups in the complex **2** [15]. It is in accordance with the crystal structure study.

2.3 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[16]. The effects of the ligand and complexes on the fluorescence spectra of EB-DNA system are presented in Fig.2, the fluorescence intensities of EB bound to ct-DNA at about 600 nm show remarkable decreasing trends with the increasing concentration of the tested compounds, indicating that some EB molecules are released into solution after the exchange with the compounds. The quenching of EB bound to DNA by the compounds is in agreement with the linear Stern-Volmer equation: $I_0/I = 1 + K_{sq}r$ [11], 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 are 0.268, 0.723 and 0.780 for the ligand HL, complexes **1** and **2**, respectively. The results indicate that interactions of the complexes with DNA are stronger than that of the ligand HL, because the complexes have higher rigidity to bind the base pairs along DNA, which increases their binding abilities. In addition, the complexes **1** and **2** have similar K_{sq} values, showing that the coordination anions are almost irresponsible for the DNA interaction.



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

Fig.2　Emission spectra of EB-DNA system in the absence and presence of ligand HL (a), complexes **1**(b) and **2** (c)

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