第 36 卷第 3 期
2020 年 3 月

无 机 化 学 学 报
CHINESE JOURNAL OF INORGANIC CHEMISTRY

Vol.36 No.3
515-520

由氟哌酸构筑的铜(Ⅱ)配合物的合成、结构和抑菌性能

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摘要:通过水热法合成了 2 种铜配合物$[Cu_2(HNOR)_2Cl]_n$ (**1**)和$[Cu_2Cl_3]\cdot H_3NOR\cdot H_2O$ (**2**)(H_2NOR=氟哌酸),并对其结构进行了 X 射线单晶衍射测定。结果表明,虽然反应物相同,但在酸度和碱度条件下分别生成具有不同结构的配合物。通过氢键和 π-π 相互作用,2 种配合物形成了稳定的二维结构。同时,选择大肠杆菌和金黄色葡萄球菌作为革兰氏阳性和革兰氏阴性进行了抑菌活性实验。抑菌活性表明,2 种配合物对大肠杆菌和金黄色葡萄球菌都有很好的抑制作用。

关键词:氟哌酸;铜配合物;抑菌活性;二维结构

中图分类号:O614.121 **文献标识码**:A **文章编号**:1001-4861(2020)03-0515-06

DOI:10.11862/CJIC.2020.054

Synthesis, Crystal Structure, and Antibacterial Activity of Copper(Ⅱ) Complexes Based on Norfloxacin

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Abstract: Two copper complexes $[Cu_2(HNOR)_2Cl]_n$ (**1**) and $[Cu_2Cl_3]\cdot H_3NOR\cdot H_2O$ (**2**) (H_2NOR=norfloxacin) were prepared by hydrothermal process and their structures were determined by single-crystal X-ray diffraction. The results showed that although the reactants are the same, the complexes with different structures are formed under acidic and basic conditions. Through the hydrogen bonding interactions and π-π interactions, two complexes form stable two-dimensional structure. At the same time, *Escherichia coli* and *Staphylococcus aureus* were selected as Gram positive and Gram negative for antibacterial activity experiments. Bacteriostatic activity showed that both complexes had a good inhibitory effect on *Escherichia coli* and *Staphylococcus aureus*. CCDC: 1863124, **1**; 1911638, **2**.

Keywords: norfloxacin; copper complexes; antibacterial activity; two-dimensional structure

0 Introduction

Norfloxacin has the chemical name 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid[1]. Norfloxacin of possessing numerous coordination sites in the structure of quinolone, with a carboxyl and a piperazynyl, oxygen and nitrogen containing lone pair electrons can coordinate with metals with empty orbits to form complexes. Furthermore, oxygen and nitrogen have large electronegativity and small radius, and can form hydrogen bonds, increasing the stability of complexes. So norfloxacin

收稿日期:2019-07-22。收修改稿日期:2019-11-10。

通化师范学院学生创新与技能训练项目(No.cs2019036)资助。

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can assemble into a series of metal complexes[2-5].

Norfloxacin is broad spectrum antibiotics widely used for the treatment of numerous diseases. The recent research results indicate the inhibitory activity of the metal complex will increase because of the cooperation between the metals and ligands. Therefore, much attention has been paid to the metal complexes with norfloxacin in recent years[6-7]. Important bio-metal interaction of copper[8] is mainly due to its biological role in its potential synergetic activity with drugs[9]. Numerous copper (Ⅱ) complexes with diverse drugs with potential antibacterial[10] and antifungal[11] activity have been reported[12-13]. The synthesis and characterization of new metal complexes with norfloxacin are of great importance for understanding the drugmetal ion interaction and for their potential pharmacological use. And herein, we selected it as ligand to synthesize two metal complexes, namely $[Cu_2(HNOR)_2Cl]_n$ (**1**) and $[Cu_2Cl_3]\cdot H_3NOR\cdot H_2O$ (**2**), characterized their crystal structures and determined their antibacterial activity. The distinct advantage of the complexes is that their single crystals are relatively stable and pure.

1 Experimental

1.1 Materials, instruments and measurements

All reagents (such as norfloxacin, $CuCl_2\cdot 2H_2O$, NaOH) were analytical grade and used as received without further purification. *Escherichia coli* and *Staphylococcus aureus* are stored on the agar slope and preserved at 4 ℃. The species are activated in the nutrient broth under 37 ℃ culture 24 h.

Elemental analysis was carried out with a Perkin-Elmer 240C analyzer; The infrared (IR) spectrum was recorded from KBr pellets in a range of 4 000~400 cm^{-1} on a Nicolet FT-IR 170SX spectrometer.

1.2 Syntheses

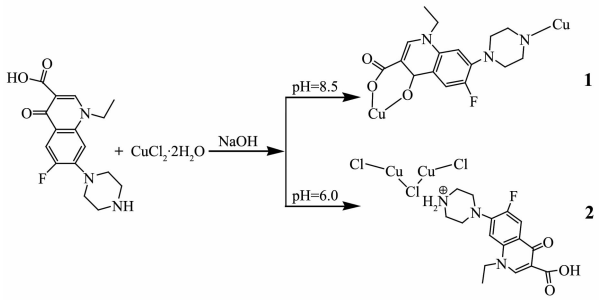
1.2.1 Synthesis of $[Cu_2(HNOR)_2Cl]_n$ (**1**)

The complex **1** was prepared from a mixture of $CuCl_2\cdot 2H_2O$ (0.170 5 g, 1.0 mmol), norfloxacin (0.958 0 g, 0.3 mmol) and H_2O (15.0 mL) stirred at room temperature. When the pH value of the mixture was adjusted to about 8.5 with NaOH, the cloudy solution was put into a 30 mL Teflon-lined autoclave under autogenous pressure at 160 ℃ for five days. After cooling to room temperature, light green block crystals of **1** were collected by filtration and washed with distilled water in 71% yield based on Cu (0.283 0 g, 0.355 mmol). Anal. Calcd. for $C_{32}H_{34}ClCu_2F_2N_6O_6$(%): C, 48.09; H, 4.29; N, 10.52. Found(%): C, 48.12.70; H, 4.24; N, 10.54. IR (KBr, cm^{-1}): 3 117m, 3 043w, 1 609s, 1 556m, 1 481s, 1 023m, 936m, 833w, 745m.

1.2.2 Synthesis of $[Cu_2Cl_3]\cdot H_3NOR\cdot H_2O$ (**2**)

Complex **2** was synthesized by a method similar to that of **1**, except that the pH value of the reaction was adjusted to 6.0 with NaOH, green block crystals of **2** were collected by filtration and washed with distilled water in 75% yield based on Cu (0.214 1 g, 0.375 mmol). Anal. Calcd. for $C_{16}H_{21}Cl_3Cu_2FN_3O_4$(%): C, 33.61; H, 3.70; N, 7.35. Found (%): C, 33.66; H, 3.74; N,7.35. IR (KBr, cm^{-1}): 3 063w, 1 681s, 1 573m, 1 509w, 1 423m, 1 284s, 933m, 903w, 780m, 733m.

The same reactants, only with different pH values, produce complexes **1** and **2** with different structure (Scheme 1). That may be related to the different states of H_2NOR at different pH values, because H_2NOR has two pK_a values (pK_1=6.22, pK_2=8.51)[14]. High pH value is good for piperazynyl reaction.



Scheme 1 Syntheses of the complexes

1.3 Crystal structure determination and physical measurements

Crystallographic data of the complexes were collected at about 293 K on a Bruker SMART 1K CCD X-ray diffractometer with a graphite-monochromatic Mo $K\alpha$ radiation (λ=0.071 073 nm) by using φ-ω scan mode in a 2θ range of 6.36°~56.74° (**1**) and 6.62°~56.64° (**2**). The structures of the complexes **1** and **2** were solved by direct methods and subsequent Fourier and difference Fourier syntheses, followed by

full-matrix least-squares techniques on F^2 using the program SHELXTL[15]. Crystallographic data of the two complexes are summarized in Table 1.

CCDC: 1863124, **1**; 1911638, **2**.

Table 1　Crystallographic data for complexes 1 and 2

Complex	1	2
Empirical formula	$C_{32}H_{34}ClCu_2F_2N_6O_6$	$C_{16}H_{21}Cl_3Cu_2FN_3O_4$
Formula weight	799.20	571.81
Crystal system	Monoclinic	Triclinic
Space group	*C*2/*c*	$P\bar{1}$
Crystal size / mm	0.18×0.20×0.26	0.18×0.20×0.26
a / nm	3.844 2(2)	0.679 08(5)
b / nm	1.022 49(5)	0.916 70(7)
c / nm	0.835 84(4)	1.776 63(14)
α / (°)		80.301(2)
β / (°)	92.692(2)	86.390(2)
γ / (°)		71.645(1)
D_c / (g·cm^{-3})	1.617	1.835
μ(Mo *K*α) / mm^{-1}	1.443	2.480
θ range for data collection / (°)	3.18~28.37	3.3~28.3
Limiting indices	$-40 \leqslant h \leqslant 51, -13 \leqslant k \leqslant 13, -11 \leqslant l \leqslant 10$	$-9 \leqslant h \leqslant 9, -12 \leqslant k \leqslant 11, -21 \leqslant l \leqslant 23$
V / nm^3	3.281 8(3)	1.034 64(14)
Z	4	2
R_1, wR_2 [$I>2\sigma(I)$]	0.036 4, 0.104 4	0.047 9, 0.122 5
F(000)	1 636.1	576
Reflection collected, unique	13 371, 4 112	8 224, 5 144
Goodness-of-fit (GOF) on F^2	1.076	1.040

1.4　Antimicrobial experiments

The antibacterial activity of two complexes against *Escherichia coli* and *Staphylococcus aureus* was determined based on the diameter of inhibition zone that was measured by the disc diffusion method.

Sterilized nutrient broth medium (20 mL) was poured into the Petri dish. After solidification, 100 μL bacteria solution was added, evenly coated and held for 5 min. The filter paper was made into a round piece with a diameter of 6 mm and was sterilized. The filter sheets containing 5 μL solution of complexes **1** and **2** were placed on the surface of Petri dish for 5 min. After incubating in the petri dish at 37 ℃ for 24 h, the size of inhibition zone diameter was measured with a cursor caliper.

2　Results and discussion

2.1　Description of crystal structures

2.1.1　Structure of $[Cu_2(HNOR)_2Cl]_n$ (**1**)

Single-crystal X-ray diffraction analysis reveals that complex **1** crystallizes in *C*2/*c* space group and consists of a one-dimensional chain structure. There are two copper ions, two $HNOR^-$ ligands and one coordination chloride ion in the asymmetric unit (Fig.1). The Cu1 ion coordinates with four oxygen atoms (O1, O3, O1a, O3a) from $HNOR^-$ ligands and its symmetric ligands. The John-Teller effect is most often encountered in octahedral structure complexes of Cu(Ⅱ) ions. The Cu1-O1 bond length is 0.195 04(15) and Cu1-O3 bond lengths is 0.192 33(15) nm. The distance between Cu1 and O2 is 0.267 70(17) nm, slightly longer than Cu-O bond lengths, and the O-Cu1-O angles range from 88.33(7)° to 180.0°, forming a plane quadrangle structure (Fig.2a). The Cu2 is monovalent copper ion and coordinated with three atoms (N1, N1b and Cl1). The Cu-N bond lengths is 0.195 28(18) nm, and the Cu2-Cl1 bond length is 0.239 45(12) nm. The N-Cu2-

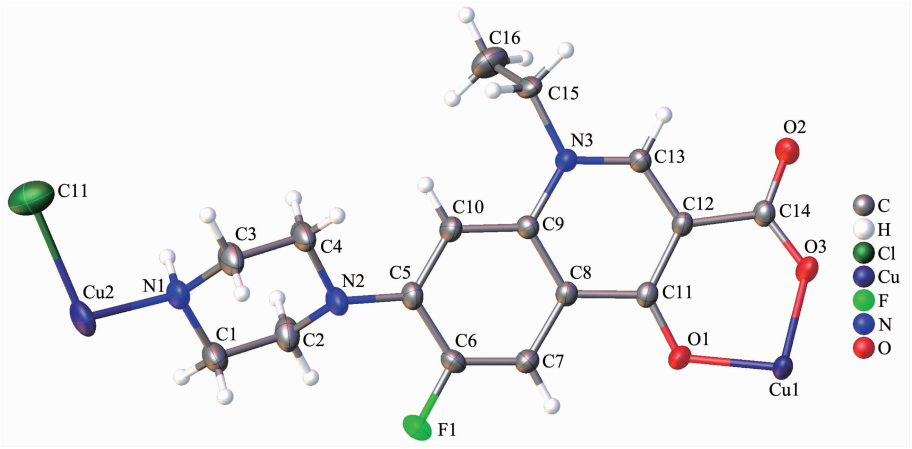
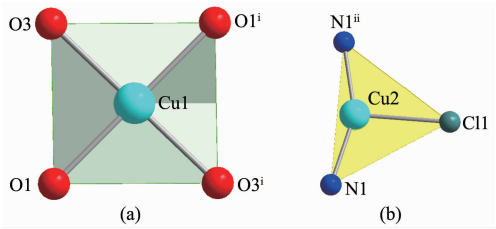


Fig.1 Asymmetric unit of complex **1** with ellipsoids at 50% probability

N(Cl) angles range from 102.85(7)° to 154.31(14)° and the coordination environment can be described as a slightly distorted flat triangle (Fig.2b).



Symmetry codes: ⁱ 3/2−*x*, 5/2−*y*, 1−*z*; ⁱⁱ 1−*x*, *y*, −1/2−*z*

Fig.2 Local coordination environment of Cu1 (a) and Cu2 (b) of complex **1**

Atoms with large electronegativity and small radius are prone to form hydrogen bonds, and hydrogen bonding interactions are usually important in stabilizing the chain structure and controlling the orientation of ligands. There are persistent weak C−H⋯O hydrogen bonding interactions between $HNOR^-$ ligands with the hydrogen-bonding geometry of C13⋯O13 being 0.315 5(2) nm, ∠C13−H13⋯O13 being 152°. At the same time, the aromatic ring of ligands and symmetry of two adjacent equivalents of aromatic rings have *π*-*π* interactions with Cg(4)→Cg(5) centroid distance being 0.370 30(12) nm, dihedral angle being 8.31(10)° and Cg(5)→Cg(4) centroid distance being 0.370 30(12) nm, dihedral angle being 8.31(10)° (Cg(4): N3→C9→C8→C11→C12→C13, Cg(5): C5→C6→C7→C8→C9→C10). Through the hydrogen bonding interactions and *π*-*π* interactions, complex **1** forms stable two-dimensional layer structure (Fig.3).

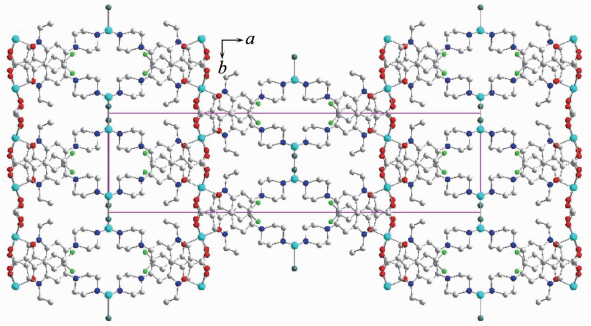


Fig.3 Two-dimensional layer structure of complex **1**

2.1.2 Structure of $[Cu_2Cl_3]\cdot H_3NOR\cdot H_2O$ (**2**)

Single-crystal X-ray diffraction analysis reveals that complex **2** crystallizes in $P\bar{1}$ space group and consists of copper cluster structure. There are two copper ions, three chlorine atoms, one free H_3NOR^+ ligand and one free water molecule in the asymmetric unit (Fig.4a).

Two adjacent copper atoms are connected by Cl2 to form a cluster structure (Fig.4b). It is similar with $(C_{17}H_{22}FN_3O_3)[CuCl_4]$, but $CuCl_4^{2-}$ is not copper cluster structure[16]. The bond lengths of complex **2** are 0.217 95(10)~0.238 96(10) nm for Cu-Cl. The angles range from 49.64(3)° to 137.17(5)°. There are persistent classic intramolecular hydrogen bonds N(O)−H⋯O (O1⋯O3 0.255 1(4) nm, ∠O1−H1⋯O3=153° and N2⋯O4 0.282 7(4) nm, ∠N2−H2b⋯O4=167°). Through the hydrogen bonding interactions, the complex forms two-dimensional structure. At the same time, aromatic ring ligands and symmetry of the adjacent equivalent of aromatic ring ligands (Symmetry code: ⁱ 1−*x*, −*y*, 1−*z*) have *π*-*π* interactions (Cg(2)→Cg(2)ⁱ 0.353 27(17)

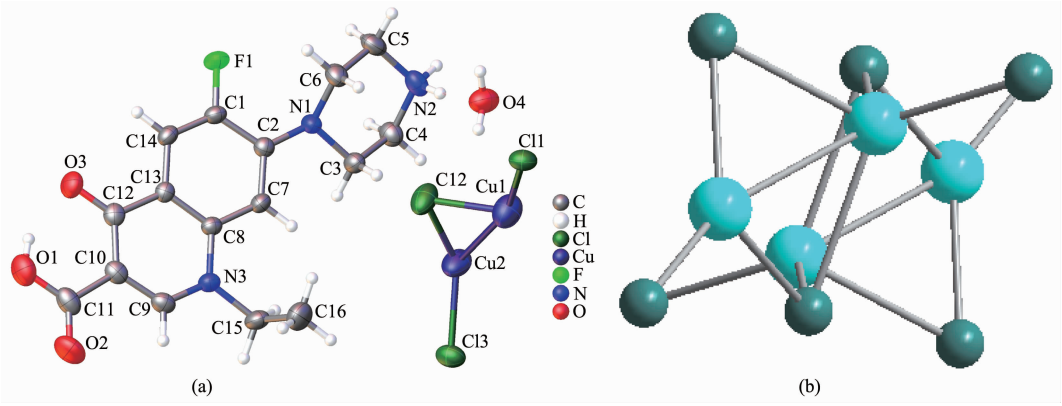


Fig.4　Asymmetric unit with ellipsoids at 50% probability (a) and cluster structure (b) of complex **2**

nm, dihedral angle=0°; Cg(2)→Cg(3) 0.356 86(17) nm, dihedral angle=1.83(14)°; Cg(3)→Cg(2) 0.356 86(17) nm, dihedral angle=1.83 (14)°. defined rings Cg(2): N3→C8→C13→C12→C10→C9 and Cg (3): C1→C2→C7→C8→C13→C14). π-π interactions played an important role in stabilizing the structure and controlling the orientation of ligands (Fig.5).

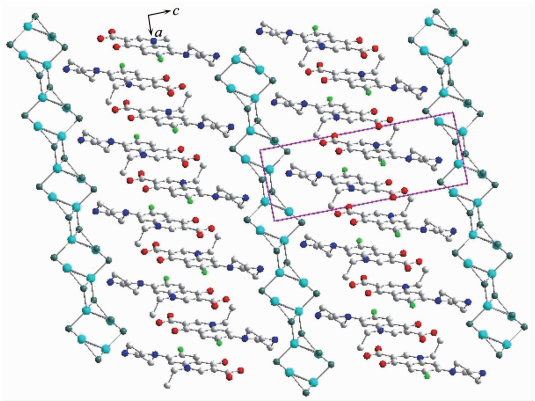


Fig.5　Two-dimensional structure of complex **2**

2.2　Antibacterial activity

Complexes **1** and **2** have a good antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. The inhibition zone diameter of the complexes, norfloxacin, central ion and solvent water are summarized in Table 2. As shown in Table 2, complex **1** with a one-dimensional chain structure has stronger antibacterial activity than **2**.

Table 2　Diameter of the inhibition zone for complexes 1 and 2

mm

Compound	**1**	**2**	Norfloxacin	$CuCl_2·2H_2O$	H_2O
Escherichia coli	16±1	15±1	11±1	8±1	4±1
Staphylococcus aureus	14±1	13±1	12±1	0	4±1

2.3　Thermal analyses

The curves of simultaneous TG-DTA of complexes **1** and **2** in nitrogen atmospheres were presented in Fig.6. in the TG curves of complex **1** (Fig.6a), we did not find clearly weight loss for the crystallization water under low temperature conditions, indicating no water on the surface of the complex. Under high temperature conditions, the complex began to lose weight due to that the ligand was decomposed to form gaseous products. The residue was metal oxide after thermal decomposition. However, the TG curves of complex **2** (Fig.6b) exhibited that the loss befell in successive and overlapping steps. The first decomposition step of weight loss mainly correspond to the loss of water molecules, whereas weight loss during the second step corresponds to the decomposition of the H_2NOR, leaving behind metal oxide as residue at the last and slow step. Meanwhile, the corresponding to endothermic events in the DTA curve was also presented. The events are mainly attributed to dehydration, thermal decomposition and reduction reactions, and exothermic events are ascribed to oxidation of the organic matter and/or of the gaseous products related during the thermal decompositions.

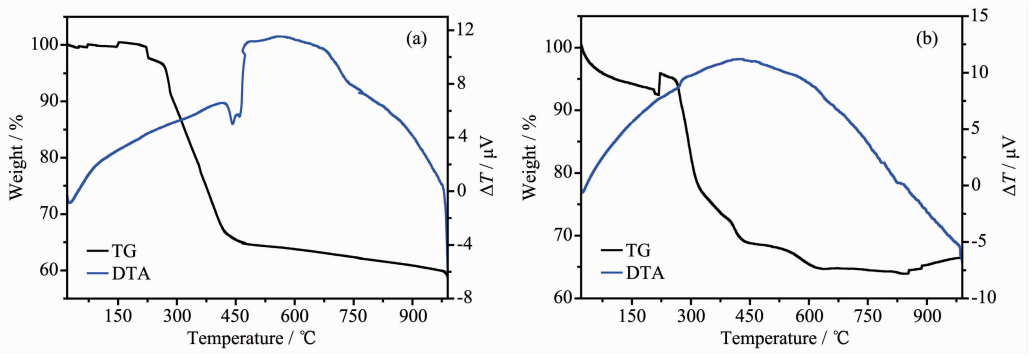


Fig.6 TG-DTA curves of complexes **1** (a) and **2** (b)

These analysis and results are consistent with the previous reports[17-18].

3 Conclusions

In summary, we have prepared two complexes by the combination of $CuCl_2 \cdot 2H_2O$, and norfloxacin. Different pH values in preparation lead to two complexes with different structures. The complexes form three-dimensional supramolecular structures through hydrogen bonding interaction and π-π stacking interactions. Complexes **1** and **2** can inhibit well the *Escherichia coli* and *Staphylococcus aureus*.

Supporting information is available at http://www.wjhxxb.cn

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