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2-氨基-5-巯基-1,3,4-噻二唑乙酸及其锌(Ⅱ)配位聚合物的合成、晶体结构及性质研究

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摘要:用 2-氨基-5-巯基-1,3,4-噻二唑乙酸(Hatma)为配体合成出一种金属锌配合物$[Zn(atma)_2]_n$,其结构通过 IR、TGA、元素分析和 X-射线单晶衍射法确定。从结构中看出,配合物通过 π-π 作用、分子间氢键作用和基团间的嵌合作用,由二维层状结构自组装形成一个三维的超分子骨架。电化学研究表明配合物中的 Zn^{2+}/Zn^{+}对的氧化还原是一个不可逆过程。抗菌试验表明,该配合物比配体表现出更好的生物活性。

关键词:配位聚合物;晶体结构;循环伏安法;抗菌
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Synthesis of Zinc(Ⅱ) Complex of [5-Amino-1,3,4-thiadiazol-2-yl]thioglycolic and the Study of Its Crystal Structure and Properties

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Abstract: A complex of Zinc(Ⅱ), $[Zn(atma)_2]_n$ in which the Hatma=[5-amino-1,3,4-thiadiazol-2-yl]thioglycolic acid has been synthesized and structurally characterized. The structure of the complex was determined by IR, TGA, elemental analysis and single crystal X-ray diffraction. In crystal, the title compound self-assembled from 2D layers to 3D surpramolecular framework by π-π interaction, hydrogen bonding and intercalation of groups. The cyclic voltammetry behaviors of the complex on glass carbon electrode showed a typical irreversible process. The antibacterial assays indicate that the complex shows better activities than ligand. CCDC: 805509.

Key words: coordination polymer; crystal structure; cyclic voltammetry; antibacterial

0 Introduction

Zinc, a transition metal with antioxidant properties, is the second most prominent trace metal in the human body after iron which is an important essential cofactor in transcription factors and enzymes, fulfilling cell replication, protein synthesis and extracellular remodeling[1]. Zinc plays an important role in various

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biological systems, since it is critical for numerous cell processes and is a major regulatory ion in the metabolism of cells[2]. In the literature, diverse zinc complexes with biological activity have been reported, but only zinc complexes with drugs are used for the treatment of Alzheimers disease[3], while others show antibacterial[4], anticonvulsant[5], antidiabetic[6], anti-inammatory[7], antimicrobial[8] and antiproliferative-antitumor[9] activity.

A wide variety of heterocyclic systems have been explored for developing pharmaceutically important molecules. Among them the derivatives of thiadiazoles have played an important role in the medicinal chemistry. These heterocycles have been found to have good effects on inflammation[10], analgesic[11], hypertension[12]. They also possess broad-spectrum antimicrobial activity[13] and have been used as antidepressant agents[14].

As most drugs contain either acidic functions or nitrogen heterocycles they are all potential ligands for the metals in the human body. In order to make research on the interaction between transition metals and heterocyclic amino acid and to continue the research in thiadiazoles of biological and coordination polymer interests[15-17], we have synthesized a novel MOFs, $[Zn(atma)_2]_n$ by using versatile ligand-[5-amino-1,3,4-thiadiazol-2-yl] thioglycolic acid (Hatma) incorporating both nitrogen-containing heterocyclic thiadiazole core and carboxylic acids groups and using $Zn(NO_3)_2\cdot 4H_2O$ as zinc nitrate ion donor. The complex self-assembled to three-dimensional porous structure by π-π interaction, hydrogen bonding and intercalation of groups. The resulting complex was characterized by IR, elemental analysis, single crystal X-ray diffraction measurements and thermo-gravimetric analyses (TGA). Moreover, the antibacterial activities of the both free ligand and its metal complex have also been studied. The metal complex was found to possess broad-spectrum antibacterial activity.

1 Experimental

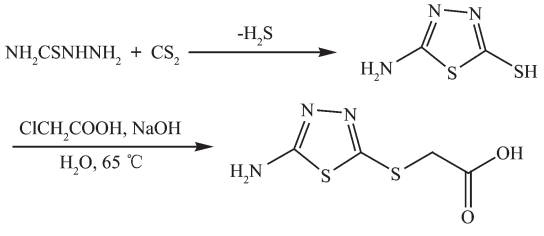
1.1 Materials and general procedures

All of the chemicals are commercially available and used without further purification. Elemental analyses were performed with a Perkin-Elmer 240 elemental analyzer. The IR (KBr pellet) spectra were recorded on a Perkin-Elmer FT-IR spectrometer in the 4 000~400 cm^{-1} range. Thermogravimetric analyses (TGA) were carried out in an N_2 atmosphere with a heating rate of 10 ℃·min^{-1} on a CA Instruments DTA-TGA 2960 type simultaneous analyzer. Voltammetry was performed by using a CHI 650D electrochemical analysis system with a three-electrode system consisting of a glass carbon (GC) electrode (U=5 mm) as the working electrode, a saturated calomel electrode (SCE) as the reference electrode, and a platinum wire as the auxiliary electrode. All the electrochemical measurements were carried out in a 10 mL electrolyte cell with 0.04 mol·L^{-1} pH 4.74 NaAc-HAc buffer solution as electrolyte.

1.2 Synthesis of Hatma (Scheme 1)

1.2.1 Synthesis of 2-amino-5-mercapto-1,3,4-thiadiazole

The 2-amino-5-mercapto-1,3,4-thiadiazole was synthesized by literature method[18]. The reactant mixture of 0.08 mol aminothiourea, 30 mL DMF (Dimethyl Formamide) and 0.10 mol carbon sulfide was heated at 45 ℃ for 40 min, then gradually to 80 ℃ and kept for 6 h until there was no hydrogen sulfide. The solvent was removed by rotary evaporation and the residue was dissolved in 45 mL sodium hydroxide solution with a concentration of 2 mol·L^{-1}, then decolorized by active carbon and filtered. The filtrate was acidified by hydrochloric acid to obtain the crude product, which was purified by recrystallization in ethanol to get yellow needle crystals, with a yield of 80%. The melting point of the product crystal is within 231 to 232 ℃ (230 to 232 ℃ in Ref.[19]).



1.2.2 Synthesis of [5-amino-1,3,4-thiadiazol-2-yl] thioglycolic acid (Hatma)

To the stirred mixture of 1.0 g 2-amino-5-mercapto-1,3,4-thiadiazole and the solution of 0.4 g NaOH in 10 mL distilled water in a reaction flask at room temperature, the solution of 0.9 g choroacetic acid and 0.4 g NaOH in 10 mL distilled water was added dropwise, then the mixture was stirred at 50 ℃ for 5 h. After cooled, the reacting mixture was acidified by 2 mol·L^{-1} hydrochloric acid to form a precipitation. The precipitation was filtered, rinsed, dried and finally became faint yellow powder[20], with a yield of 78%, which was purified by recrystallization in ethanol-water to get yellow crystals, melting point within 237 to 238 ℃.

1.3 Synthesis of 1

A mixture of $Zn(NO_3)_2·4H_2O$ (0.100 g, 0.5 mmol), Hatma (0.096 g, 0.5 mmol), C_2H_5OH (10 mL) and H_2O (5 mL) was sealed in a 23 mL Teflon-lined stainless steel vessel and heated to 180 ℃ for 3 days and then cooled to room temperature at a rate of 5 ℃·h^{-1}. Yellow rectangular block crystals suitable for single-crystal X-ray diffraction were obtained. The products were washed with H_2O and dried in air (54% yield based on Zn(Ⅱ)). Elem anal. Calcd. for $C_8H_{10}N_6O_5S_4Zn$ (%): C, 20.71; H, 2.17; N, 18.12; S, 27.62. Found(%): C,20.72; H, 2.18; N, 18.08; S, 27.63.

1.4 Crystal structure determination

Crystal data for complex were collected on a Bruker SMART Apex Ⅱ CCD diffractometer using graphite-monochromated Mo $K\alpha$ radiation (λ=0.071 073 nm) at 296 K. The structures were solved using a direct method and refined by full-matrix leastsquares on F^2 using the SHELXTL crystallographic software package. The crystal data collection and refinement processes are summarized in Table 1. Selected bond lengths and angles are listed in Table 2. Hydrogen bonding parameters are given in Table 3.

CCDC: 805509.

2 Results and discussion

2.1 Description of crystal structures

A single-crystal X-ray diffraction study reveals that the crystal belongs to the monoclinic space group $P\bar{1}$, with one Zn^{2+} ion and four Hatma ligand in the asymmetric unit (Fig.1). Every Zn^{2+} ion is four-

Table 1　Crystallographic data, data collection and refinement for 1

Empirical formula	$C_8H_{10}N_6O_5S_4Zn$	D_c / (g·cm^{-3})	1.916
Formula weigh	463.83	Z	2
Temperature / K	296(2)	μ / mm^{-3}	2.081
Crystal system	Triclinic	F(000)	468
Crystal colour	Yellow	Crystal size / mm	0.35×0.33×0.25
Space group	$P\bar{1}$	θ range / (°)	2.53~25.50
a / nm	8.456(6)	Reflections collected / unique (R_{int})	5 877 / 2 958 (0.034 8)
b / nm	8.859(6)	Data / restraints / parameters	2 958 / 3 / 225
c / nm	12.439(9)	Goodness-of-fit on F^2	0.999
α / (°)	86.456(7)	R/wR (I>2σ(I))	0.042 8 / 0.084 6
β / (°)	71.444(6)	R/wR (all data)	0.063 2 / 0.091 1
γ / (°)	65.929(6)	Largest diff. peak and hole / (e·nm^{-3})	450 and −349
V / nm^3	804.0(9)		

Table 2　Selected bond distances (nm) and angles (°) for 1

Zn(1)-O(1)^{i}	0.197 3(3)	Zn(1)-N(4)	0.202 4(3)	O(1)-Zn(1)^{iii}	0.197 3(3)
Zn(1)-O(3)^{ii}	0.200 2(3)	Zn(1)-N(1)	0.203 2(4)	O(3)-Zn(1)^{iv}	0.200 2(3)
O(1)^{i}-Zn(1)-O(3)^{ii}	107.79(14)	O(1)^{i}-Zn(1)-N(1)	98.71(13)	C(4)-O(1)-Zn(1)^{iii}	117.6(3)
O(1)^{i}-Zn(1)-N(4)	115.43(14)	O(3)^{ii}-Zn(1)-N(1)	131.05(15)	C(8)-O(3)-Zn(1)^{iv}	106.2(3)
O(3)^{ii}-Zn(1)-N(4)	99.02(13)	N(4)-Zn(1)-N(1)	105.73(13)		

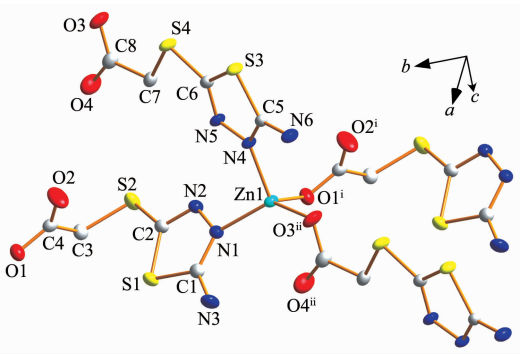
Symmetry transformations used to generate equivalent atoms: ^{i} x, y−1, z; ^{ii} x+1, y−1, z; ^{iii} x, y+1, z; ^{iv} x−1, y+1, z.

Table 3 Hydrogen bonding distances and angles

D–H···A	*d*(D–H) / nm	*d*(H···A) / nm	*d*(D···A) / nm	∠DHA / (°)
O(5)–H(1W) ···O(5)^{v}	0.083(3)	0.217(3)	0.286 0(5)	141(6)
N(3)–H(3C) ···O(4)^{ii}	0.086	0.222	0.287 5(6)	133
N(3)–H(3D) ···O(5)^{vi}	0.086	0.208	0.288 7(7)	156
N(6)–H(6A)···O(3)^{ii}	0.086	0.21	0.287 6(6)	150
N(6)–H(6B)···O(2)^{vii}	0.086	0.199	0.278 9(6)	154
C(3)–H(3B)···O(1)^{viii}	0.097	0.249	0.343 0(6)	162

Symmetry codes: ^{v} 1–*x*, 1–*y*, 1–*z*; ^{ii} 1+*x*, –1+*y*, *z*; ^{vi} 1+*x*, *y*, *z*; ^{vii} 2–*x*, 1–*y*, –*z*; ^{viii} 2–*x*, 2–*y*, 1–*z*.

valentedly coordinated with four atma anionic ligand. Two atma act as O-donor ligand while the other two atma act as N-donor ligand. The complex shows distorted tetrahedron coordination geometry. The Zn-O distances are 0.197 3(3) and 0.200 2(3) nm respectively, while the Zn-N distances are 0.203 2 (4) and 0.202 4(3) nm. As shown in Fig.2, every Zn^{2+} ions is linked by Hatmas ligand, forming an extended 2D layer structure in the ab plane. From the topological view, every Zn^{2+} ion can be considered as a 4-connected node and Hatma ligand as linkers, leading to the (4,4) topology (Fig.3). It is noteworthy to point out that there are various hydrogen bonds between the adjacent chains which make the 2D layer framework more stable. In Fig.4, the 2D layers are further connected by the hydrogen bonds of NH···O with a distance of 0.278 9(6) nm to produce a 3D supramolecular network as depicted. In addition, the thiadiazol rings between the adjacent chains are stacked with each other via intermolecular π-π interactions (the interplanar distance between two neighboring parallel heterocyclic skeletons is 0.358 10 nm and the corresponding centroid-to-centriod distance between two thiadiazol units is 0.376 85(20) nm). Besides, the dihedral angel of thiadiazol-thiadiazol is 0°, showing the completely parallel thiadiazols. Those various intermolecular π-π stacking interactions make the intercalation of groups in 3D surpramolecular



Symmetry codes: ^{i}*x*, *y*–1, *z*; ^{ii}*x*+1, *y*–1, *z*

Fig.1 Coordination environment of Zn in **1** with thermal ellipsoids shown at 30% probability

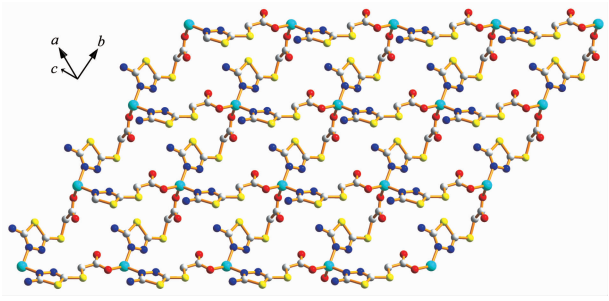


Fig.2 View of the 2D polymer sheet of **1**

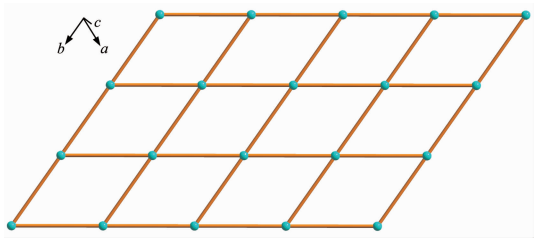
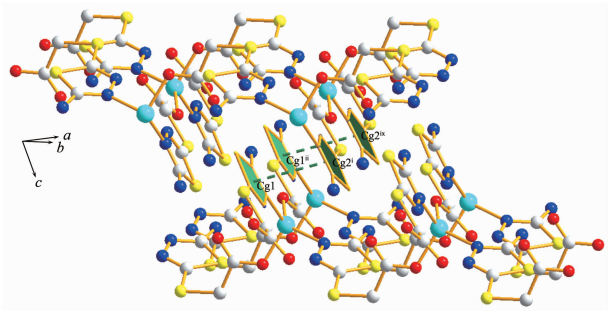


Fig.3 Schematic representation of the 2D distorted sql net of **1**



Symmetry codes: ^{i}2–*x*, 1–*y*, 2–*z*; ^{ii}*x*+1, *y*–1, *z*; ^{ix}3–*x*, –*y*, 2–*z*; Color code: Zn, cyan; O, red; N, blue; S, yellow; C, gray; H atoms are omitted for clarity

Fig.4 View of π-π stacking interaction among 2D layer structure of **1**

framework.

2.2 IR and thermogravimetric analysis

The FTIR spectrum of the compound is consistent with the structural data. The bands of ν(C=O) of complex shift (1 700 cm^{-1}) to a higher wavenumber when compared to the free ligand (at 1 645 cm^{-1}). The band of thiadiazole ring becomes weaker and shifts towards higher wavenumbers (from 1 455 to 1 534 cm^{-1}). Accordingly, it can be concluded that the O-atom of the carboxyl and the N-atom of the thiadiazole in Hatma coordinate with the metal ions, resulting in the novel complex.

In order to estimate the stability of the frameworks, thermal gravimetric analysis (TGA) of complex was carried out in nitrogen atmosphere from 30 to 800 ℃. For complex, no weight loss is observed until the temperature reaches 253 ℃ and the decomposition of complex occurs. The TGA result suggests that the frameworks of complex are thermally stable under about 250 ℃.

2.3 Electrochemistry

The cyclic voltammogram of the title complex was measured in 0.04 mol·L^{-1} pH 4.74 NaAc-HAc buffer solutions are shown in Fig.5. From the cyclic voltammetry diagram, it was observed that the complex at 0.1 V·s^{-1} has a well-defined reduction peak at −751 mV, ascribing to the reduction of center Zinc(Ⅱ) ion. In addition, there was no corresponding oxidation peak appeared in this experiment, suggesting the electrochemical behaviors of the Zinc(Ⅱ) complex was irreversible.

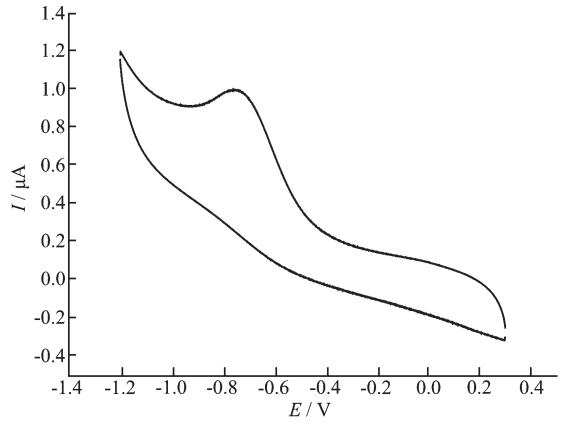


Fig.5　Cyclic voltammetry curve of the title complex

2.4 Antibacterial studies

In order to study the antimicrobial activity of zinc complex, we have tested the antimicrobial ability of the free ligand and its complex against Gram positive bacteria-Staphylococcus aureus and Bacillus subtilis and Gram negative bacteria-Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Shigella dysenteriae and Salmonella choleraesuis.

Minimum inhibitory concentrations (MICs) were determined by broth dilution technique[21]. The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately 5×10^5 c.f.u.·mL^{-1} of actively dividing bacterial cells. The cultures were incubated for 24 h at 37 ℃ and the growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as MIC.

To obtain the minimum bacterial concentration (MBC), 0.1 mL volume was taken from each tube and spread on agar plates. The number of c.f.u. was counted after 18~24 h of incubation at 35 ℃. MBC was defined as the lowest drug concentration at which 99.9% of the inoculums were killed. The minimum inhibitory concentration and minimum bactericidal concentration are given in Table 4.

MIC (μg·mL^{-1})=minimum inhibitory concentration, that is, the lowest concentration of the compound to inhibit the growth of bacteria completely; MBC (μg·mL^{-1})=minimum bacterial concentration, that is, the lowest concentration of the compound for killing the bacteria completely.

The results (Table 4) indicate that the Zinc complex is more active against all Gram-positive and Gram-negative bacterial strains (*S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *S. choleraesuis*, *P. vulgaris*, *S. dysenteriae*) than ligand under identical experimental conditions, although mode of action and mechanism of their antimicrobial activities have not been clarified. The increase in antibacterial activity of the complex may be due to the effect of the metal ion on the normal cell. The MBC in most of the bacterial was two or three folds higher than the corresponding MIC results.

Table 4 MIC and MBC results of Hatma and $[Zn(atma)_2]_n$

Compounds	Gram-positive bacteria								Gram-negative bacteria					
	S. aureus		*B. subtilis*		*E. coli*		*P. aeruginosa*		*S. choleraesuis*		*P. vulgaris*		*S. dysenteriae*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
Hatma	160	640	160	320	80	320	80	160	80	320	80	320	160	640
$[Zn((Hatma))_2]_n$	80	320	80	160	40	160	40	80	40	80	40	160	80	320

3 Conclusions

In conclusion, We have synthesized a novel MOFs, $[Zn(atma)_2]_n$. The 3D supramolecular structure was formed by the self-assembly approach of transition metals with a versatile bridged heterocyclic amino acid ligand-Hatma. The structures have been determined by single crystal X-ray analysis. The antibacterial assays indicate that the complex shows parallel activity against Gram-positive and Gram-negative bacterial with the ligand, and the complex has a better activity than that of the ligand.

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