第 31 卷第 5 期
2015 年 5 月

无 机 化 学 学 报
CHINESE JOURNAL OF INORGANIC CHEMISTRY

Vol.31 No.5
1019-1026

N′-(2-羟基-5-甲氧基苯甲基)-4-二甲氨基苯甲酰肼及其氧钒(Ⅴ)配合物:合成、晶体结构和脲酶抑制活性

叶玉婷[1] 牛 芳[1] 孙 迎[1] 曲 丹[1] 赵新璐[1]
王 佳[1] 献冬梅[1] Hauser Jürg[3] 由忠录*,[1,2]
([1]辽宁师范大学化学化工学院,大连 116029)
([2]南京大学配位化学国家重点实验室,南京 210093)
([3]伯尔尼大学化学和生物化学系,伯尔尼 3012)

摘要:制备了一个苯甲酰腙化合物 *N*′-(2-羟基-5-甲氧基苯甲基)-4-二甲氨基苯甲酰肼(H_2L)。利用 H_2L、乙酰氧肟酸(HAHA)和 $VO(acac)_2$ 在甲醇中反应得到了配合物[VOL(AHA)]。通过元素分析、红外和紫外光谱,以及单晶 X-射线衍射对 H_2L 和其配合物进行了表征。苯甲酰腙配体作为二价阴离子,利用其酚羟基氧原子、亚胺基氮原子、以及烯醇氧原子与 V 原子进行配位。乙酰氧肟酸配体利用其羰基氧原子和去质子化的羟基氧原子进行配位。配合物中的 V 原子为八面体配位构型。测试了 H_2L、HAHA 和钒配合物的脲酶抑制活性。在浓度为 100 μmol·L^{-1} 时,钒配合物对幽门螺旋杆菌脲酶的抑制率为 63%,其 IC_{50} 值为 45μmol·L^{-1}。还利用分子对接技术研究了配合物分子与脲酶的作用方式。

关键词:苯甲酰腙;乙酰氧肟酸;氧钒配合物;晶体结构;脲酶抑制剂
中图分类号:O614.51+1 **文献标识码**:A **文章编号**:1001-4861(2015)05-1019-08
DOI:10.11862/CJIC.2015.135

N′-(2-Hydroxy-5-methoxybenzylidene)-4-dimethylaminobenzohydrazide and Its Oxovanadium(Ⅴ) Complex: Syntheses, Crystal Structures, and Urease Inhibitory Activity

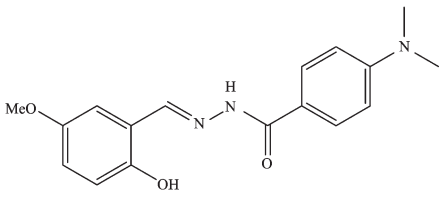
YE Yu-Ting[1] NIU Fang[1] SUN Ying[1] QU Dan[1] ZHAO Xin-Lu[1] WANG Jia[1]
XIAN Dong-Mei[1] Hauser Jürg[3] YOU Zhong-Lu*,[1,2]
([1]*Department of Chemistry and Chemical Engineering, Liaoning Normal University, Dalian, Liaoning* 116029, *China*)
([2]*State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing* 210093, *China*)
([3]*Departement of Chemistry and Biochemistry, University of Bern, Bern* 3012, *Switzerland*)

Abstract: A benzohydrazone compound *N*′-(2-hydroxy-5-methoxybenzylidene)-4-dimethylaminobenzohydrazide (H_2L) was prepared. Reaction of H_2L and acetylhydroxamic acid (HAHA) with $VO(acac)_2$ in methanol gave complex [VOL(AHA)]. Both H_2L and the oxovanadium complex were characterized by elemental analysis, IR and UV-Vis spectra, and single crystal X-ray diffraction. The benzohydrazone ligand, in its dianionic form, coordinates to V atom through the phenolate oxygen, imino nitrogen and enolate oxygen. The acetohydroxamic acid coordintes to V atom through the carbonyl oxygen and deprotonated hydroxyl oxygen. The V atom is in octahedral coordination. H_2L, HAHA and the oxovanadium(Ⅴ) complex were tested for their urease inhibitory activities. The inhibition rate at concentration of 100 μmol·L^{-1} on *Helicobacter pylori* urease is 63% for the oxovanadium complex. The IC_{50} value for the complex is 45 μmol·L^{-1}. Molecular docking study was performed to study the inhibition. CCDC: 1042493, H_2L; 905427, the complex.

Key words: benzohydrazone; oxovanadium complex; crystal structure; urease inhibition

收稿日期:2014-12-03。收修改稿日期:2015-03-19。
辽宁省高校优秀青年人才支持计划(No.LR2014032)资助项目。
*通讯联系人。E-mail:youzhonglu@126.com

Urease has negative effects on human, stockbreeding, and agriculture[1-4]. Control of the activity of urease through use of inhibitors could counteract these negative effects. Metal complexes have been proved to be a kind of versatile enzyme inhibitors[5]. In recent years, metal complexes with hydrazone ligands have received particular attention in biological and medicinal chemistry, as well as catalysis[6-9]. Vanadium complexes have also been reported to normalize the high blood glucose levels and act as models of halo-peroxidases[10-13]. It is notable that Ara and co-workers reported that some binuclear vanadium(Ⅳ) complexes possess effective urease inhibitory activities[14]. Aslam and co-workers reported that the Schiff bases of hydrazone type also possess urease inhibitory activities[15]. Recently, our research group has reported a few vanadium complexes with urease inhibitory activities [16-17]. As an extension on this work, in the present paper, a benzohydrazone ligand *N′*-(2-hydroxy-5-methoxybenzylidene)-4-dimethylaminobenzohydrazide (H_2L, Scheme 1) and its oxovanadium(Ⅴ) complex with acetylhydroxamate (AHA) as co-ligand were prepared and investigated from their coordination and biolgoical aspects.



Scheme 1 Hydrazone ligand H_2L

1 Experimental

1.1 General methods and materials

Starting materials, reagents and solvents were purchased from commercial suppliers with AR grade, and used without purification. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. IR spectra were recorded on a Jasco FT/IR-4000 spectrometer as KBr pellets in the 4 000~200 cm^{-1} region. UV-Vis spectra were recorded on a Perkin-Elmer Lambda 900 spectrometer. ^1H NMR spectra for H_2L and the complex were recorded on a Bruker spectrometer at 300 and 400 MHz, respectively. X-ray diffraction was carried out on a Bruker SMART 1000 CCD diffractometer.

1.2 Synthesis of H_2L

2-Hydroxy-5-methoxybenzaldehyde (1.52 g, 0.01 mol) and 4-dimethylaminobenzohydrazide (1.79 g, 0.01 mol) were reacted in 30 mL of methanol. The mixture was stirred at room temperature for 1 h to give a clear colorless solution. The solution was allowed to stand in air for a few days until three quarter of the solvent was evaporated. Colorless block-shaped crystals of H_2L, suitable for X-ray single crystal diffraction, were formed at the bottom of the vessel. The crystals were isolated by filtration, washed three times with cold methanol and dried in air. Yield: 67%. Anal. Calcd. for $C_{17}H_{19}N_3O_3$ (%): C, 65.2; H, 6.1; N, 13.4. Found (%): C, 65.4; H, 6.0; N, 13.4. IR data (cm^{-1}): 3 434 (br, w), 3 207 (sh, w), 3 033 (w), 2 905 (w), 2 828 (w), 1 614 (s), 1 525 (s), 1 492 (s), 1 363 (m), 1 280 (s), 1 201 (m), 1 150 (m), 1 040 (m), 950 (m), 886 (w), 821 (m), 763 (m), 679 (w), 593 (w), 473 (w). UV (λ / nm, ε / ($L\cdot mol^{-1}\cdot cm^{-1}$)): 250, 1.83×10^4; 282, 1.68×10^4; 327, 1.78×10^4; 376, 2.18×10^4; 456, 1.07×10^4. ^1H NMR (300 MHz, DMSO-d_6): δ 11.81 (s, 1H, O*H*), 10.91 (s, 1H, N*H*), 8.56 (s, 1H, C*H*=N), 7.82 (d, 2H, Ar*H*), 7.07 (s, 1H, Ar*H*), 6.90~6.75 (m, 4H, ArH), 3.73 (s, 3H, OCH_3), 3.00 (s, 6H, N(CH_3)$_2$).

1.3 Synthesis of the complex

A methanolic solution (30 mL) of $VO(acac)_2$ (0.27 g, 1.0 mmol) was added to a methanolic solution (20 mL) of H_2L (0.31 g, 1.0 mmol) and HAHA (0.075 g, 1.0 mmol) with stirring. The mixture was stirred at room temperature for 30 min to give a brown solution. The resulting solution was allowed to stand in air for a few days until three quarter of the solvent was evaporated. Brown block-shaped crystals of the complex, suitable for X-ray single crystal diffraction were formed at the bottom of the vessel. The crystals were isolated by filtration, washed three times with cold methanol and dried in air. Yield: 55%. Anal. Calcd. for $C_{19}H_{21}N_4O_6V$ (%): C, 50.5; H, 4.7; N, 12.4. Found (%): C, 50.3; H, 4.8; N, 12.3. IR data (cm^{-1}): 3 213 (sh, w), 1 602 (s), 1 550 (m), 1 473 (s), 1 427 (w), 1 376 (s), 1 266 (m), 1 189 (s), 1 034 (w), 963 (m),

821 (m), 750 (w), 679 (w), 595 (m), 569 (m), 473 (w). UV(λ / nm, ε / (L·mol^{-1}·cm^{-1})): 227, 3.15×10^4; 250, 2.65×10^4; 280, 2.44×10^4; 327, 2.56×10^4; 377, 3.16×10^4; 455, 1.55×10^4. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 13.80 (s, 1H, N*H*), 8.94 (s, 1H, C*H*=N), 7.72 (d, 2H, Ar*H*), 7.32 (d, 1H, Ar*H*), 7.14 (t, 1H, Ar*H*), 6.77 (m 3H, Ar*H*), 3.75 (s, 3H, OCH$_3$), 3.00 (s, 6H, N(C*H*$_3$)$_2$), 2.07 (s, 3H, C*H*$_3$CONHO).

1.4 X-ray crystallography

Diffraction intensities for H_2L and the complex were collected at 298(2) K using a Bruker SMART 1000 CCD area-detector diffractometer with Mo $K\alpha$ radiation (λ=0.071 073 nm). The collected data were reduced with SAINT [18], and multi-scan absorption correction was performed using SADABS[19]. Structures of the compounds were solved by direct methods and refined against F^2 by full-matrix least-squares method using SHELXTL[20]. All of the non-hydrogen atoms were refined anisotropically. The hydrogen atom attached to N atom of the complex was located from a difference Fourier map and refined isotropically, with N-H distance restrained to 0.090(1) nm. The remaining hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. The C18 ~C24-O4-O6-C34 moiety of H_2L is disordered over two sites, with occupancies of 0.53 and 0.47, respectively. Crystallographic data for H_2L and the complex are summarized in Table 1. Selected bond lengths and angles are given in Table 2.

CCDC: 1042493, H_2L; 905427, the complex.

Table 1　Crystallographic and experimental data for H_2L and the complex

	H_2L	Complex
Formula	$C_{17}H_{19}N_3O_3$	$C_{19}H_{21}N_4O_6V$
Formula weight	313.3	452.3
Crystal system	Monoclinic	Orthorhombic
Space group	*C*2/*c*	*Pbca*
a / nm	3.548 8(2)	1.505 05(5)
b / nm	1.043 8(1)	1.406 98(5)
c / nm	1.852 0(2)	1.981 75(7)
β / (°)	109.470(2)	
V / nm^3	6.467 9(12)	4.196 5(3)
Z	16	8
D_c / (g·cm^{-3})	1.287	1.432
μ / mm^{-1} (Mo $K\alpha$)	0.090	0.516
F(000)	2 656	1 872
Independent reflections	8 024	4 349
Observed reflections ($I\geqslant 2\sigma(I)$)	3 705	3 519
Parameters	522	278
Restraints	191	1
Final *R* indices ($I\geqslant 2\sigma(I)$)	R_1=0.060 1, wR_2=0.143 0	R_1=0.036 9, wR_2=0.110 2
R indices (all data)	R_1=0.148 4, wR_2=0.187 1	R_1=0.048 5, wR_2=0.121 1
GOF on F^2	0.977	1.091

Table 2　Selected bond lengths (nm) and angles (°) for H_2L and the complex

H_2L					
C7-N1	0.128 2(3)	N1-N2	0.136 0(2)	N2-C8	0.136 2(3)
C8-O2	0.123 4(2)	C24-N4	0.127 4(8)	N4-N5	0.137 3(2)
N5-C25	0.136 1(2)	C25-O5	0.122 9(2)		

Continued Table 2

Complex					
V1-N1	0.208 71(17)	V1-O2	0.184 35(15)	V1-O3	0.194 77(15)
V1-O4	0.220 53(15)	V1-O5	0.185 32(14)	V1-O6	0.158 78(16)
C8-N1	0.128 8(3)	N1-N2	0.138 6(2)	N2-C9	0.131 5(2)
C9-O3	0.129 9(2)	O6-V1-O2	100.49(9)	O6-V1-O5	96.86(8)
O2-V1-O5	100.87(7)	O6-V1-O3	98.94(8)	O2-V1-O3	152.77(7)
O5-V1-O3	95.53(6)	O6-V1-N1	97.77(8)	O2-V1-N1	83.81(7)
O5-V1-N1	163.55(7)	O3-V1-N1	74.79(6)	O6-V1-O4	173.24(7)
O2-V1-O4	81.90(7)	O5-V1-O4	76.44(6)	O3-V1-O4	81.01(6)
N1-V1-O4	88.75(6)				

1.5 Urease inhibitory activity assay

Helicobacter pylori (ATCC 43504; American Type Culture Collection, Manassas, VA) was grown in brucella broth supplemented with 10% heat-inactivated horse serum for 24 h at 37 ℃ under microaerobic condition (5% O_2, 10% CO_2, and 85% N_2). The method of preparation of *Helicobacter pylori* urease by Mao was followed[21]. Briefly, broth cultures (50 mL, 2.0×10^8 CFU·mL^{-1}) were centrifuged (5000 g, 4 ℃) to collect the bacteria, and after washing twice with phosphate-buffered saline (pH 7.4), the *Helicobacter pylori* precipitation was stored at −80 ℃. After the *Helicobacter pylori* was cooled to room temperature, and mixed with 3 mL of distilled water and protease inhibitors, sonication was performed for 60 s. Following centrifugation (15 000 g, 4 ℃), the supernatant was desalted through Sephadex G-25 column (PD-10 columns, Amersham-Pharmacia Biotech, Uppsala, Sweden). The resultant crude urease solution was added to an equal volume of glycerol and stored at 4 ℃ until use in the experiment. The mixture, containing 25 μL (4U) of *Helicobacter pylori* urease and 25 μL of the test compound, was pre-incubated for 3 h at room temperature in a 96-well assay plate. Urease activity was determined for three parallel times by measuring ammonia production using the indophenol method as described by Weatherburn[22].

1.6 Molecular docking study

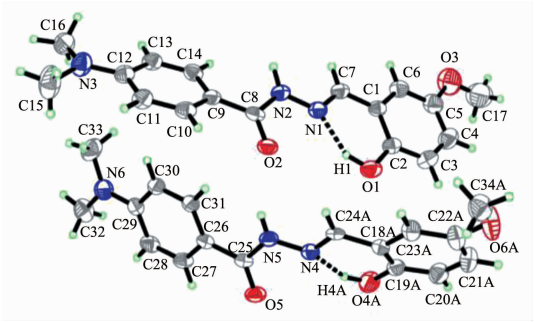
Molecular docking of the complex into 3D X-ray structure of *Helicobacter pylori* urease (entry 1E9Y in the Protein Data Bank) was carried out by using AutoDock 4.2 software as implemented through the graphical user interface AutoDockTools (ADT 1.5.4). The graphical user interface AutoDockTools was employed to setup the enzymes: all hydrogens were added, Gasteiger charges were calculated and non-polar hydrogens were merged to carbon atoms. The Ni initial parameters are set as r=0.117 0 nm, q=+2.0, and van der Waals well depth of 0.420 kJ·mol^{-1} [23]. The molecule of the complex was transferred to a pdb file with the program ChemBio3D. The pdb file was further transferred to a pdbqt file with the AutoDockTools.

The AutoDockTools was used to generate the docking input files. In the docking a grid box size of 7.0 nm×7.0 nm×9.0 nm points in x, y, and z directions was built. The maps were centered on the original ligand molecule in the catalytic site of the protein. A grid spacing of 0.037 5 nm and a distances-dependent function of the dielectric constant were used for the calculation of the energetic map. 100 runs were generated by using Lamarckian genetic algorithm searches. Default settings were used with an initial population of 50 randomly placed individuals, a maximum number of 2.5×10^6 energy evaluations, and a maximum number of 2.7×10^4 generations. A mutation rate of 0.02 and a crossover rate of 0.8 were chosen. The results of the most favorable free energy of binding were selected as the resultant complex structure.

2 Results and discussion

2.1 Structure description of H_2L and the complex

Molecular structure of H_2L is shown in Fig.1. X-ray crystallography reveals that the asymmetric unit of



Thermal ellipsoids are drawn at 30% probability level; Hydrogen bonds are shown as dashed lines

Fig.1 A perspective view of the molecular structure of H_2L with the atom labeling scheme

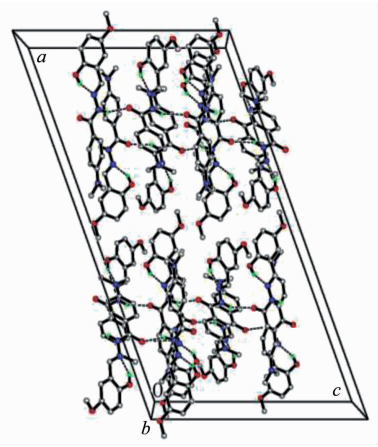
the compound contains two independent molecules. There are intramolecular O-H···N hydrogen bonds (Table 3) in the molecules. The dihedral angle between benzene rings C1~C6 and C9~C14 is 25.4(3)°, and that between benzene rings C18A ~C23A and C26~C31 is 36.7(3)°. All the bond values agree well with those observed in similar structures [24-26]. In the crystal structure of H_2L, molecules are linked through intermolecular N-H···O hydrogen bonds (Table 3), to form chains along *c*-axis direction (Fig.2).

Molecular structure of the oxovanadium complex is shown in Fig.3. The benzohydrazone ligand coordinates to the V atom through the phenolate O, imino N, and enolate O atoms. The V atom in the complex is in an octahedral coordination, with three donor atoms of the benzohydrazone ligand and the

Table 3 Hydrogen bond distances (nm) and bond angles (°) for H_2L and the complex

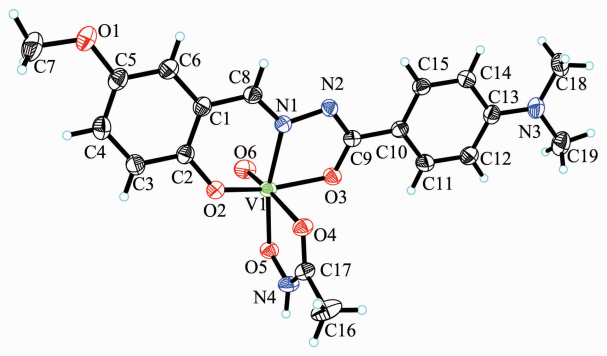
D-H···A	*d*(D-H)	*d*(H···A)	*d*(D···A)	∠D-H···A
		H_2L		
O1-H1···N1	0.095(3)	0.174(3)	0.258 9(2)	147(2)
O4A-H4A···N4	0.095(1)	0.161(4)	0.252 4(7)	159(10)
N2-H2···O5^{i}	0.092(2)	0.197(2)	0.280 9(2)	152(2)
N5-H5···O2	0.082(2)	0.218(2)	0.294 2(2)	155(2)
O4B-H4B···N4	0.095(1)	0.181(7)	0.263 8(8)	144(10)
		Complex		
N4-H4···N2^{iii}	0.090(1)	0.193(1)	0.280 8(2)	166(3)

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



Hydrogen bonds are shown as dashed lines

Fig.2 Molecular packing diagram of H_2L

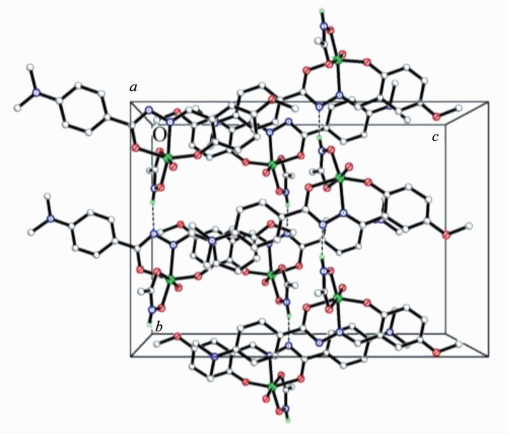


Thermal ellipsoids are drawn at 30% probability level

Fig.3 A perspective view of the molecular structure of the complex with the atom labeling scheme

deprotonated hydroxyl O atom of the acetohydroxamate ligand defining the equatorial plane, and with oxo O atom and carbonyl O atom of the acetohydroxamate ligand occupying the axial positions. The distance between atoms V1 and O6 is 0.158 8(2) nm, indicating it a typical V=O bond. The coordinate bond lengths in the complex are comparable to those observed in mononuclear oxovanadium complexes with octahedral coordination[24-26]. Distortion of the octahedral coordination can be observed from the coordinate bond angles, ranging from 74.79(6)° to 100.87(7) ° for the perpendicular angles, and from 152.77(7)° to 173.24 (7)° for the diagonal angles. The displacement of the V atom from the equatorial plane to the axial oxo O atom is 0.028 3(2) nm. The formation of the coordinate bonds with the V atom, together with the delocalization of the ligand, leads to the planarity of the benzohydrazone molecule. The dihedral angle between the two benzene rings is 7.7 (3)°. In the crystal structure of the complex, molecules are linked through intermolecular N-H⋯N hydrogen bonds, to form 1D chains along *b*-axis direction (Fig.4).

Coordination of H_2L to the V atom results in the change of related bonds. The bond lengths of C7-N1 and C24-N4 in H_2L are 0.128 2(3) and 0.127 4(8) nm, respectively, which are shorter than C8-N1 bond (0.128 8(3) nm) in the oxovanadium complex. The same phenomenon has been observed for N1-N2 and N4-N5 bonds in H_2L and the oxovanadium complex. The N2-C8 and N5-C25 bonds in H_2L are much longer than N2-C9 bond in the oxovanadium complex, and the C8-O2 and C25-O5 bonds in H_2L are much shorter than C9-O3 bond in the complex, indicating the change for the N-C-O groups from carbonyl in H_2L to enolate during coordination.



Hydrogen bonds are shown as dashed lines

Fig.4 Molecular packing diagram of the complex

2.2 IR spectra

The weak and broad absorption centered at 3 434 cm^{-1} in the spectrum of H_2L substantiates the presence of phenol group, which is absent in the complex. The sharp bands indicative of the N-H vibrations are located at 3 207 and 3 213 cm^{-1}, respectively, in the spectra of H_2L and the complex. The typical ν(N-H) absorption band of the free hydrazone ligand is absent in the spectrum of the complex, indicating the enolisation of the amide functionality and subsequent proton replacement by the V atom. The strong absorption bands at 1 614 cm^{-1} for H_2L and 1 602 cm^{-1} for the complex are assigned to the azomethine ν(C=N)[27]. The typical absorption at 963 cm^{-1} can be assigned to the V=O vibration[24].

2.3 Pharmacology

Results of the urease inhibition are summarized in Table 4. Acetohydroxamic acid and vanadyl sulfate were used as references. The free benzohydrazone ligand showed very low inhibition. The oxovanadium complex showed effective inhibition, with IC_{50} value of about 45 $\mu mol \cdot L^{-1}$. The results indicate that the urease inhibition of the complex is much better than vanadyl sulfate (IC_{50}=203 $\mu mol \cdot L^{-1}$), and similar to acetylhydroxamic acid (IC_{50}=39.8 $\mu mol \cdot L^{-1}$).

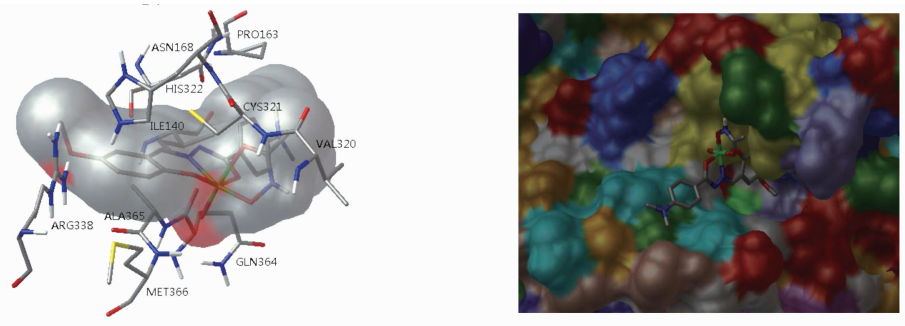
Table 4　Inhibition of urease by the tested materials

Tested materials[a]	Inhibition ratea / %	IC_{50} / ($\mu mol \cdot L^{-1}$)
H_2L	9.1±2.2	–
the complex	63.0±2.5	45.0±3.0
vanadyl sulfate	23.7±2.9	203±6
acetohydroxamic acid	87.5±4.0	39.8±3.4

[a]Concentration of the tested material is 100 $\mu mol \cdot L^{-1}$.

2.4 Molecular docking study

Molecular docking study was performed to investigate the binding effects between the compound and the active sites of *Helicobacter pylori* urease. In the X-ray structure available for the native *Helicobacter pylori* urease, two nickel atoms were coordinated by *HIS*136, *HIS*138, *KCX*219, *HIS*248, *HIS*274, *ASP*362 and water molecules, while in the AHA-inhibited urease, these water molecules are replaced by AHA. In order to give an explanation and understanding of the inhibitory activity of the complex, molecular docking of the complex molecule into the AHA binding site of the urease was performed on the binding model based on *Helicobacter pylori* urease complex structure (1E9Y.pdb). The binding model of the complex and the urease was depicted in Fig.5, which revealed that the complex molecule is well filled in the active pocket of the urease. The binding energy of the complex with urease is –27.55 $kJ \cdot mol^{-1}$, which is lower than that of AHA (–21.04 $kJ \cdot mol^{-1}$). There are interactions among the complex molecule with residues *ASN*168, *HIS*322,



Left: Only the interacting residues are displayed; the interactions are shown as dashed spheres;
Right: The enzyme is shown as surface; the complex is shown as sticks

Fig.5　Binding mode of the complex with the *Helicobacter pylori* urease

*ILE*140, *CYS*321, *VAL*320, *ALA*365, *ARG*338, GLN364, and MET366 of the urease. The results of molecular docking study may explain the activity of the complex against *Helicobacter pylori* urease.

3 Conclusions

The present study reports synthesis, characterization and crystal structures of a benzohydrazone ligand and its acetohydroxamate coordinated oxovanadium (Ⅴ) complex. The benzohydrazone ligand coordinates to V atom through the phenolate oxygen, imino nitrogen and enolate oxygen. The complex has effective inhibitory activity against *Helicobacter pylori* urease. Considering that oxovanadium(Ⅴ) complexes have interesting biological activities and have been widely used in medicine, the complex described here may be used in treatment of infections caused by urease producing bacteria.

References:

[1] Francisco S S, Urrutia O, Martin V, et al. *J. Sci. Food Agric*., **2011**,**91**:1569-1575

[2] Xiao Z P, Ma T W, Fu W C, et al. *Eur. J. Med. Chem.*, **2010**,**45**:5064-5070

[3] Barros T G, Williamson J S, Antunes O A C, et al. *Lett. Drug Des. Discovery*, **2009**,**6**:186-192

[4] Murtaza G, Badshah A, Said M, et al. *Dalton Trans*., **2011**,**40**:9202-9211

[5] Louie A Y, Meade T J. *Chem. Rev.*, **1999**,**99**:2711-2734

[6] Chew S T, Lo K M, Lee S K, et al. *Eur. J. Med. Chem.*, **2014**, **76**:397-407

[7] Pal R, Kumar V, Gupta A K, et al. *Med. Chem. Res*., **2014**,**23**:3327-3335

[8] Shaabani B, Khandar A A, Mobaiyen H, et al. *Polyhedron*, **2014**,**80**:166-172

[9] Li A M. *J. Coord. Chem.*, **2014**,**67**:2076-2085

[10]Smith T S, Pecoraro V L. *Inorg. Chem*., **2002**,**41**:6754-6760

[11]Zhang X A, Woggon W D. *J. Am. Chem. Soc*., **2005**,**127**: 14138-14139

[12]Pereira M J, Carvalho E, Eriksson J W, et al. *J. Inorg. Biochem.*, **2009**,**103**:1687-1692

[13]Nomiya K, Torii H, Hasegawa T, et al. *J. Inorg. Biochem*., **2001**,**86**:657-667

[14]Ara R, Ashiq U, Mahroof-Tahir M, et al. *Chem. Biodivers*., **2007**,4:58-71

[15]Aslam M A S, Mahmood S, Shahid M, et al. *Eur. J. Med. Chem.*, **2011**,**46**:5473-5479

[16]Huo Y, Ye Y T, Cheng X S, et al. *Inorg. Chem. Commun*., **2014**,**45**:131-134

[17]Cheng X S, Zhang J C, You Z L, et al. *Transition Met. Chem*., **2014**,**39**:291-297

[18]*SMART* and *SAINT*. Bruker AXS Inc., Madison, **2002**.

[19]Sheldrick G M. *SADABS*. University of Göttingen, Germany, **1996**.

[20] Sheldrick G M. *Acta Crystallogr.*, **2008**,A64:112-122

[21]Mao M J, Lü P C, Shi L, et al. *Bioorg. Med. Chem.*, **2009**,**17**:7531-7536

[22]Weatherburn M W. *Anal. Chem*., **1967**,**39**:971-974

[23]Krajewska B, Zaborska W. *Bioorg. Chem.*, **2007**,**35**:355-365

[24]Sangeetha N R, Kavita V, Wocadlo S. *J. Coord. Chem.*, **2000**,**51**:55-66

[25]REN Jin-Qi(任晋琦), JIAO Qing-Zhu(焦庆祝), WANG Yi-Nuo(王艺诺), et al. *Chinese J. Inorg. Chem.*(无机化学学报), **2014**,**30**(3):640-648

[26]ZHAO Yue(赵月), HAN Xiao(韩笑), ZHOU Xiao-Xia(周晓霞), et al. *Chinese J. Inorg. Chem.*(无机化学学报), **2013**,**29**(4):867-874

[27]You Z L, Xian D M, Zhang M. *CrystEngComm*, **2012**,**14**: 7133-7136