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Synthesis, Crystal Structure, and Urease Inhibition of [N'-(3,5-Dibromo-2-Hydroxybenzylidene)isonicotinohydrazido]-(Benzohydroxamato)oxovanadium(V)[1]

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Abstract—A new oxovanadium(V) complex [VOL(BZH)] was prepared by the reaction of $[VO(Acac)_2]$ (Acac = acetylacetonate) with N'-(3,5-dibromo-2-hydroxybenzylidene)isonicotinohydrazide (H_2L) and benzohydroxamic acid (HBZH) in methanol. Crystal and molecular structure of the complex was determined by elemental analysis, infrared spectra and single crystal X-ray diffraction. The complex crystallizes in the monoclinic space group $P2_1/c$, with unit cell dimensions $a = 11.424(1)$, $b = 12.012(1)$, $c = 19.565(2)$ Å, $\beta = 93.487(3)°$, $V = 2679.8(4)$ Å^3, $Z = 4$, GOOF = 1.152, $R_1 = 0.0593$, and $wR_2 = 0.1942$. The V atom is in octahedral coordination. Thermal stability and the inhibition of urease of the complex were studied.

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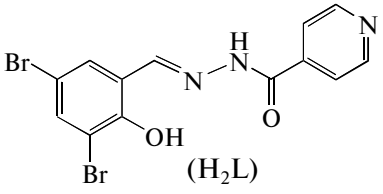
INTRODUCTION

Urease has important negative effects on human, stockbreeding, and agriculture [1–4]. Control of the activity of urease through the use of inhibitors could counteract these negative effects. Metal complexes have been proved to be a kind of versatile enzyme inhibitors [5]. Among versatile metal complexes, those derived from hydrazones have been received particular attention in biological and medicinal chemistry [6–9]. In recent years, vanadium complexes have been reported to have interesting biological activities such as normalizing the high blood glucose levels and acting as models of haloperoxidases [10–12]. It is notable that Ara and co-workers reported that some binuclear vanadium(IV) complexes possess interesting urease inhibitory activities [13]. Aslam and co-workers reported that the Schiff bases of hydrazone type also possess urease inhibitory activities [14]. Recently, our research group has reported a few vanadium complexes with urease inhibitory activities [15, 16]. In order to explore more potent urease inhibitors, in the present paper, a new oxovanadium(V) complex [VOL(BZH)] (H_2L = N'-(3,5-dibromo-2-hydroxybenzylidene)isonicotinohydrazide, HBZH = benzohydroxamic acid, has been presented.



(H_2L)

[1] The article is published in the original.

EXPERIMENTAL

Materials and measurements. Commercially available 3,5-dibromosalicylaldehyde, isonicotinohydrazide and benzohydroxamic acid were purchased from Aldrich and used without further purification. Other solvents and reagents were made in China and used as received. C, H, and N elemental analyses were performed with a PerkinElmer elemental analyser. Infrared spectra were recorded on a Nicolet AVATAR 360 spectrometer as KBr pellets in the 4000–400 cm^{-1} region. Thermal stability analysis was performed on a PerkinElmer Pyris Diamond TG-DTA thermal analyses system.

Synthesis of H_2L. 3,5-Dibromosalicylaldehyde (1.0 mmol, 0.28 g) and isonicotinohydrazide (1.0 mmol, 0.14 g) were dissolved in methanol (30 mL) with stirring. The mixture was stirred for about 30 min at room temperature to give a clear solution. The solvent was evaporated to give colorless crystalline products. The yield was 87%.

For $C_{13}H_9N_3O_2Br_2$			
anal. calcd., %:	C, 39.1;	H, 2.3;	N, 10.5.
Found, %:	C, 39.3;	H, 2.2;	N, 10.4.

Synthesis of [VOL(BZH)]. A methanolic solution (10 mL) of $[VO(Acac)_2]$ (0.1 mmol, 26.5 mg) was added to a methanolic solution (10 mL) of H_2L (0.1 mmol, 39.9 mg) and benzohydroxamic acid (0.1 mmol, 13.7 mg) with stirring. The mixture was stirred for 30 min at room temperature to give a deep brown solution. The resulting solution was allowed to

Table 1. Crystallographic data and refinement parameters for the complex

Parameter	Value
M	600.1
Crystal color, habit	Brown, block
Crystal size, mm	0.20 × 0.20 × 0.17
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell parameters:	
a, Å	11.424(1)
b, Å	12.012(1)
c, Å	19.565(2)
β, deg	93.487(3)
V, Å^3	2679.8(4)
Z	4
ρ_{calcd}, g cm^{-3}	1.487
Temperature, K	298(2)
μ, mm^{-1}	3.385
F(000)	1176
Number of unique data	4981
Number of observed data ($I > 2\sigma(I)$)	3428
Number of parameters	292
Number of restraints	1
R_1, wR_2 ($I > 2\sigma(I)$)	0.0593, 0.1942
R_1, wR_2 (all data)	0.0922, 0.2171
Goodness of fit on F^2	1.152
Largest difference peak/hole, e Å^{-3}	1.187/−0.529

stand in air for a few days. Brown block-shaped crystals suitable for X-ray single crystal diffraction were formed at the bottom of the vessel. The isolated products were washed three times with cold methanol and dried in air. The yield was 37%.

For $C_{20}H_{13}N_4O_5Br_2V$			
anal. calcd., %:	C, 40.0;	H, 2.2;	N, 9.3
Found, %:	C, 39.8;	H, 2.3;	N, 9.5.

X-ray crystallography. Diffraction intensities for the complex were collected at 298(2) K using a Bruker D8 VENTURE PHOTON diffractometer with MoK_α radiation (λ = 0.71073 Å). The collected data were reduced using the SAINT program [17], and multi-scan absorption corrections were performed using the SADABS program [18]. The structure was solved by direct method and refined against F^2 by full-matrix least-squares method using the SHELXTL [19]. All of the non-hydrogen atoms were refined anisotropically. The amino H atom was located from a difference Fourier map and refined isotropically, with N–H distance restrained to 0.90(1) Å. The remaining H atoms were placed in idealized positions and constrained to ride on their parent atoms. The crystallographic data for the complexes are summarized in Table 1. Selected bond lengths and angles are given in Table 2.

Supplementary material for structure of complex [VOL(BZH)] has been deposited with the Cambridge Crystallographic Data Centre (no. 978239; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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°C 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 [20]. Briefly, broth cultures (50 mL, 2.0×10^8 CFU mL^{-1}) were centrifuged (5000 *g*, 4°C) to collect the bacteria, and after washing twice with phosphate-buffered saline (pH 7.4), the *Helicobacter pylori* precipitation was stored at −80°C. While the *Helicobacter pylori* was returned to room temperature and mixed with 3 mL of distilled water and protease inhibitors, sonication was performed for 60 s. Following centrifugation (15000 *g*, 4°C), the supernatant was desalted through SephadexG-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°C until used in the experiment. The mixture, containing 25 μL (4 U) 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 by measuring ammonia production by the indophenol method.

RESULTS AND DISCUSSION

Replacement of two acetylacetonate ligands in [VO(Acac)$_2$] by hydrazone and benzohydroxamate ligands in methanol resulted in the formation of the complex. The complex is soluble in DMF, DMSO, methanol, ethanol, and acetonitrile. Molar conductance of the complex at a concentration of 10^{-4} mol/L is 30 Ω^{-1} cm^2 mol^{-1}, indicating it is a non-electrolyte [21].

The molecular structure and atom numbering scheme of the complex is shown in Fig. 1. The V atom in the complex is in octahedral coordination with the three donor atoms of the hydrazone ligand and the hydroxyl O atom of the benzohydroxamate ligand defining the equatorial plane, and with one oxo O atom and the carbonyl O atom of the benzohydroxamate ligand occupying the axial positions. The distance between atoms V(1) and O(5) is 1.59 Å, indicating it is a typical V=O double bond. The V(1)–O(3) bond in the complex is significantly longer than the remaining coordinate bonds, yet, it is not uncommon for such complexes [22, 23]. The coordinate bond

lengths in the complex are comparable to those observed in the mononuclear oxovanadium(V) complexes with octahedral coordination [22–26]. The angular distortion in the octahedral environment around V comes from the five- and six-membered chelate rings taken by the hydrazone ligand. For the same reason, the *trans* angles significantly deviate from the ideal values of 180°. Distortion of the octahedral coordination can be observed from the coordinate bond angles, ranging from 75.2(2)° to 102.8(2)° for the perpendicular angles and from 156.4(2)° to 172.2(2)° for the diagonal angles. The displacement of the Vatom from the equatorial plane is 0.280(1) Å. The formation of the coordinate bonds with the V atom, together with the delocalization of the ligand, leads to the planarity of the hydrazone moiety. The dihedral angle between the C(1)–C(6) benzene ring and the V(1)–N(1)–N(2)–C(8)–O(2) chelate ring is 5.3(2)°. The dihedral angle between the benzene ring and the pyridine ring of the hydrazone ligand is 19.0(3)°. The hydrazone ligand and the benzohydroxamate ligand are almost perpendicular to each other with a dihedral angle of 87.7(5)°.

In the crystal structure of the complex, adjacent two molecules are linked through intermolecular N(4)–H(4)···N(3) hydrogen bonds (N(4)–H(4) 0.90(1), H(4)···N(3)^{i} 1.96(5), N(4)···N(3)^{i} 2.753(7), N(4)–H(4)···N(3)^{i} 147(8)° (symmetry code: $^{i}x, -1/2-y, -1/2+z$), forming dimers (Fig. 2).

Table 2. Selected bond distances (Å) and angles (deg) for the complex

Bond	*d*, Å	Bond	*d*, Å
V(1)–O(1)	1.885(4)	V(1)–O(2)	1.966(4)
V(1)–O(3)	2.184(5)	V(1)–O(4)	1.845(4)
V(1)–O(5)	1.591(5)	V(1)–N(1)	2.091(5)
Angle	ω, deg	Angle	ω, deg
O(5)V(1)O(4)	96.2(2)	O(5)V(1)O(1)	98.9(2)
O(4)V(1)O(1)	100.7(2)	O(5)V(1)O(2)	96.2(2)
O(4)V(1)O(2)	95.6(2)	O(1)V(1)O(2)	156.4(2)
O(5)V(1)N(1)	102.8(2)	O(4)V(1)N(1)	159.5(2)
O(1)V(1)N(1)	83.8(2)	O(2)V(1)N(1)	75.2(2)
O(5)V(1)O(3)	172.2(2)	O(4)V(1)O(3)	76.1(2)
O(1)V(1)O(3)	84.0(2)	O(2)V(1)O(3)	83.4(2)
N(1)V(1)O(3)	84.6(2)		

The hydrazone ligand showed stretching bands attributed to C=O, C=N, C–OH, and NH at about 1653, 1619, 1150 and 1223, and 3211 cm^{-1}, respectively. The complex exhibits typical band at 966 cm^{-1}, assigned to the V=O vibration. The band due to ν(C=O) was absent in the complex, but new C–O stretches appeared at 1288 cm^{-1}. This suggests occurrence of *keto*-imine tautomerization of the ligand dur-

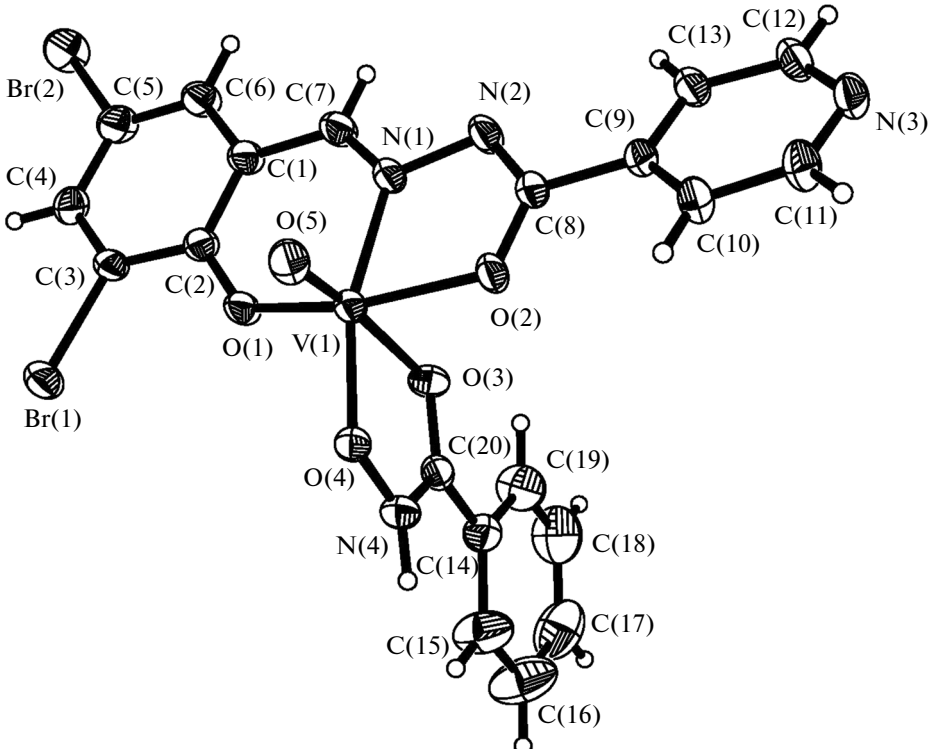


Fig. 1. ORTEP plot of the crystal structure of the complex. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level.

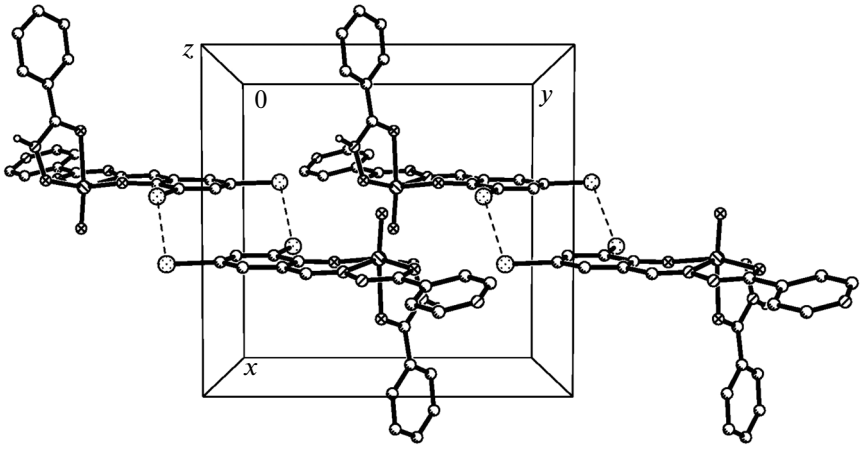


Fig. 2. Packing diagram of the complex. Hydrogen bonds are shown as dashed lines.

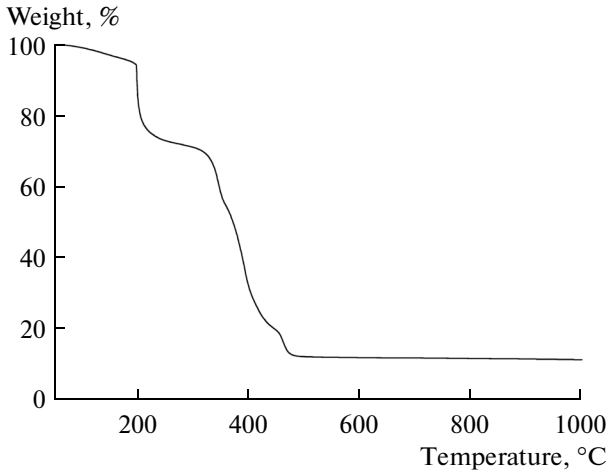


Fig. 3. DT curve of the complex.

ing complexation. The ν(C=N) absorption observed at 1619 cm^{-1} in the free hydrazone ligand shifted to 1601 cm^{-1} for the complex upon coordination to V atom. The weak peaks in the low wave numbers at 495 and 590 cm^{-1} may be attributed to V–O and V–N bonds in the complex.

Differential thermal (DT) analysis was conducted to examine the stability of the complex (Fig. 3). The complex started to decompose at about 70°C and completed at 480°C. The total observed weight loss of 86.1% is close to the calculated value of 84.8% for the formation of V_2O_5 as the final product.

Table 3. Inhibition of urease by the tested materials*

Tested materials	Percent inhibition	IC_{50}, μmol L^{-1}
Complex	73.6 ± 3.5	10.5
H_2L	10.2 ± 2.1	
Vanadyl sulfate	26.5 ± 1.9	220
AHA	88.2 ± 4.0	37.5

* Concentration of the tested material is 100 μmol L^{-1}.

The results of the urease inhibition are summarized in Table 3. Compared with the reference inhibitor acetohydroxamic acid (AHA), the free hydrazone compound and the vanadyl sulfate have very weak interactions against the urease. The complex at concentration of 100 μmol L^{-1} has urease inhibitory activity with percent inhibition of 73.6 ± 3.5 and with IC_{50} value of 10.5 μmol L^{-1}. It is clear that the activity of the complex is stronger than that of vanadyl sulfate and H_2L, and even near to that of AHA.

In summary, a new oxovanadium(V) complex with the tridentate hydrazone ligand N'-(3,5-dibromo-2-hydroxybenzylidene)isonicotinohydrazide and the bidentate ligand benzohydroxamate has been prepared and structurally characterized. The complex may be used as a potential urease inhibitor with the IC_{50} value of 10.5 μmol L^{-1}.

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