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Syntheses, Crystal Structures, and Urease Inhibitory Activity of Two Zinc Complexes with 2-[(3-Cyclohexylaminopropylimino)methyl]-6-alkoxyphenol

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Two new Schiff base zinc(II) complexes, $[ZnL1IN_3]$ (1) and $[ZnL2(N_3)_2]$ (2) (L1 = 2-[(3-cyclohexylaminopropylimino)methyl]-6-ethoxyphenol, L2 = 2-[(3-cyclohexylaminopropylimino)methyl]-6-methoxyphenol), were prepared and structural characterized by elemental analyses, infrared spectroscopy, and single-crystal X-ray diffraction. Both complexes are mononuclear zinc(II) compounds. The Zn atom in each complex is four-coordinated in a tetrahedral geometry. Both complexes show urease inhibitory activities.

Keywords crystal structure, urease inhibition, Schiff base, synthesis, zinc

INTRODUCTION

Ureases are an important class of enzymes involved in the degradative processing of urea.[1–3] They are ubiquitous in nature and are directly associated with the formation of infection stones and contribute to the pathogenesis of pyelonephritis, urolithiasis, ammonia encephalopathy, hepatic coma and urinary catheter encrustation. High concentration of ammonia arising from these reactions, as well as the accompanying pH elevation, have important implications in medicine and agriculture.[4,5] Therefore, urease inhibitors have recently attracted much attention as potential new anti-ulcer drugs. A recent research indicated that the Schiff base complexes had potent urease inhibitory activity.[6] Zinc complexes with Schiff bases have attracted much attention in coordination chemistry and bioinorganic chemistry due to their versatile structures and interesting biological properties.[7–12] In this paper, two new zinc(II) complexes, $[ZnL1IN_3]$ (**1**) and $[ZnL2(N_3)_2]$ (**2**), where L1 and L2 are 2-[(3-cyclohexylaminopropylimino)methyl]-6-ethoxyphenol and 2-[(3-cyclohexylaminopropylimino)methyl]-6-methoxyphenol, respectively, were prepared and structural characterized. The urease inhibitory activities of the complexes were determined.

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EXPERIMENTAL

Materials and Methods

All chemicals and reagents used for the preparation of the ligands and the complexes were commercial products (Lancaster) and were used without further purification. *Jack bean* urease was obtained from Sigma-Aldrich Co. (St. Louis, MO, USA). C, H and N analyses were performed with a Perkin-Elmer 2400 series II analyzer. The infrared spectra (KBr pellet) were recorded using a FTS165 Bio-Rad FTIR spectrophotometer in the range 4000–400 cm^{-1}.

Synthesis of L1 and L2

The Schiff bases L1 and L2 were prepared according to the literature method.[13] Anal. calcd for $C_{18}H_{28}N_2O_2$ (L1, %): C, 71.0; H, 9.3; N, 9.2. Found: C, 70.7; H, 9.3; N, 9.3. Anal. Calcd for $C_{17}H_{26}N_2O_2$ (L2, %): C, 70.3; H, 9.0; N, 9.6. Found: C, 70.5; H, 9.2; N, 9.5.

Synthesis of (1)

To a methanol solution (10 ml) of L1 (0.1 mmol, 30.4 mg) and sodium azide (0.1 mmol, 6.5 mg) was added with stirring a methanol solution (5 ml) of ZnI_2 (0.1 mmol, 31.9 mg). The mixture was stirred for 30 min at room temperature and filtered. Upon keeping the filtrate in air for a few days, colorless block-shaped crystals of (**1**), suitable for X-ray single-crystal diffraction, were formed at the bottom of the vessel. The crystals were collected by filtration, washed three times with cold methanol and dried in air. Yield: 45%. Anal. calcd for $C_{17}H_{26}N_8O_2Zn$ (%): C, 46.4; H, 6.0; N, 25.5. Found: C, 46.0; H, 6.2; N, 25.2.

Synthesis of (2)

To a methanol solution (10 ml) of L2 (0.1 mmol, 29.0 mg) and sodium azide (0.1 mmol, 6.5 mg) was added with stirring

TABLE 1
Crystal data for (**1**) and (**2**)

Complex	(1)	(2)
Formula	$C_{17}H_{26}N_8O_2Zn$	$C_{18}H_{28}IN_5O_2Zn$
Fw	439.8	538.7
Crystal shape/colour	block/colorless	block/colorless
Crystal size (mm^3)	0.28 × 0.27 × 0.27	0.32 × 0.30 × 0.27
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
a (Å)	11.045(2)	12.434(3)
b (Å)	13.129(2)	12.755(3)
c (Å)	16.644(2)	14.464(3)
β (°)	120.94(1)	103.49(3)
V ($Å^3$)	2070.2(5)	2230.6(8)
Z	4	4
λ (Mo-Kα) (Å)	0.71073	0.71073
T (K)	298(2)	298(2)
μ (Mo-Kα) (mm^{-1})	1.216	2.506
T_{min}	0.727	0.501
T_{max}	0.735	0.551
Reflections collected	12302	13402
Data/restraint /parameters	4489/0/254	5004/0/245
R_{int}	0.0425	0.0488
Goodness of fit on F^2	1.058	1.028
R_1, wR_2 $[I \geq 2\sigma(I)]^a$	0.0554, 0.1503	0.0563, 0.1351
R_1, wR_2 (all data)^a	0.0930, 0.1716	0.0992, 0.1549

$^a R_1 = \sum ||Fo| - |Fc|| / \sum |Fo|$, $wR_2 = [\sum w(Fo^2 - Fc^2)^2 / \sum w(Fo^2)^2]^{1/2}$

a methanol solution (5 ml) of $Zn(CH_3OO)_2 \cdot 2H_2O$ (0.1 mmol, 22.0 mg). The mixture was stirred for 30 min at room temperature and filtered. Upon keeping the filtrate in air for a few days, colorless block-shaped crystals of (**2**), suitable for X-ray single-crystal diffraction, were formed at the bottom of the vessel. The crystals were collected by filtration, washed three times with cold methanol and dried in air. Yield: 37%. Anal. calcd for $C_{18}H_{28}IN_5O_2Zn$ (%): C, 40.1; H, 5.2; N, 13.0. Found: C, 40.5; H, 5.3; N, 12.8.

X-ray Crystallography

Suitable single crystals were mounted on glass-fibers. The diffraction experiments were carried out on a Bruker AXS SMART CCD diffractometer. The program SMART[14] was used for collecting frames of data, indexing reflections and determination of lattice parameters, SAINT[14] for integration of the intensity of reflections and scaling, SADABS[15] for absorption correction, and SHELXTL[16] for space group and structure determination and least-squares refinements on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at idealized positions and allowed to ride on the connecting atoms. The crystallographic data for the complexes are summarized in Table 1. Selected bond lengths and angles are listed in Table 2. Hydrogen bonds are listed in Table 3.

TABLE 2
Selected bond lengths (Å) and bond angles (°) for (**1**) and (**2**)

(1)			
Bond lengths			
Zn1–O1	1.927(3)	Zn1–N1	1.982(4)
Zn1–N3	1.983(5)	Zn1–N6	1.967(4)
Bond angles			
O1–Zn1–N6	110.0(2)	O1–Zn1–N1	97.1(2)
N6–Zn1–N1	119.3(2)	O1–Zn1–N3	114.7(2)
N6–Zn1–N3	107.3(2)	N1–Zn1–N3	108.5(2)
(2)			
Bond lengths			
Zn1–O1	1.948(4)	Zn1–N1	1.998(4)
Zn1–N3	1.975(5)	Zn1–I1	2.5734(9)
Bond angles			
O1–Zn1–N3	111.3(2)	O1–Zn1–N1	96.3(2)
N3–Zn1–N1	112.5(2)	O1–Zn1–I1	116.5(2)
N3–Zn1–I1	108.3(2)	N1–Zn1–I1	111.6(2)

Measurement of Urease

The assay mixture, containing 25 μL (4U) of *jack bean* urease and 25 μL (100 μg) of the test compound, was preincubated for 0.5 or 3 h at room temperature in a 96-well assay plate. After preincubation, 0.2 mL of 100 mM phosphate buffer pH 6.8 containing 500 mM urea and 0.002% phenol red were added and incubated at room temperature. The reaction time was measured by micro plate reader (570 nm), which was required for enough ammonium carbonate to form to raise the pH of a phosphate buffer from 6.8 to 7.7.[17] The results are listed in Table 4.

TABLE 3
Distances (Å) and angles (°) involving hydrogen bonding of the complexes

D–H···A	d(D–H)	d(H···A)	d(D···A)	Angle(D–H···A)
(**1**)				
N2–H2A···O1	0.90	1.91	2.762(4)	157(5)
N2–H2A···O2	0.90	2.34	2.978(4)	128(5)
N2–H2B···N8	0.90	2.04	2.921(6)	167(5)
(**2**)				
N2–H2A···N5	0.90	2.18	2.990(7)	149(5)
N2–H2B···O1	0.90	2.02	2.801(6)	145(5)
N2–H2B···O2	0.90	2.25	3.003(6)	140(5)

TABLE 4
Inhibitory activities against urease

Tested materials	IC_{50} (μM)
(**1**)	72.31 ± 0.31
(**2**)	56.05 ± 0.82
L1	>100
L2	>100
ZnI_2	>100
Acetohydroxamic acid	45.37 ± 0.31

RESULTS AND DISCUSSION

Synthesis and Characterization

The two Schiff base ligands were readily synthesized *via* Schiff base condensation using equimolar quantities of *N*-cyclohexylpropane-1,3-diamine with 3-ethoxysalicylaldehyde and 3-methoxysalicylaldehyde, respectively. The complex (**1**) was synthesized by mixing equimolar quantities of L1, NaN_3 and ZnI_2 in methanol, yielding an iodide and azide-coordinated tetrahedral zinc(II) complex. The complex (**2**) was synthesized by a similar procedure as that described for (**1**), but with L1 replaced by L2, and with ZnI_2 replaced by $Zn(CH_3COO)_2{\cdot}2H_2O$, yielding an azide-coordinated tetrahedral zinc(II) complex. It can be seen that the coordinate ability of the iodide anion is superior to that of the acetate anion.

In the infrared spectra of the Schiff bases L1 and L2, the weak and broad absorption bands in the region 3280–3400 cm^{-1} are assigned to the stretching vibration of the O–H bonds, which absent in the complexes. The strong absorption bands at 1637 cm^{-1} for L1 and L2 are assigned to the azomethine groups, ν(C=N),[18] which are shifted to lower frequencies in the complexes (1623 cm^{-1} for (**1**) and 1621 cm^{-1} for (**2**)). The strong absorption of the azide groups in both complexes is at about 2035 cm^{-1}.

Structure Description of (1) and (2)

Figures 1 and 2 give perspective views of the complexes (**1**) and (**2**), respectively. In both complexes, the Zn atom is four-coordinated and is best described as having a tetrahedral geometry. Both Schiff bases chelate to the Zn atoms in bidentate fashion employing the phenolate O and imine N atoms. The other two positions are occupied by coordinated I atom and N atoms from the azide groups. The coordinate bond angles, ranging from 97.1(2) to 119.3(2)° for (**1**) and from 96.3(2) to 116.5(2)° for (**2**), support the slightly distorted tetrahedral geometries. The coordinate bond lengths of (**1**) and (**2**) are similar to each other (Table 2), and comparable with the values observed in other similar zinc(II) complexes with Schiff bases.[13,19–21] As expected, the cyclohexyl rings in the complexes adopt chair conformations.

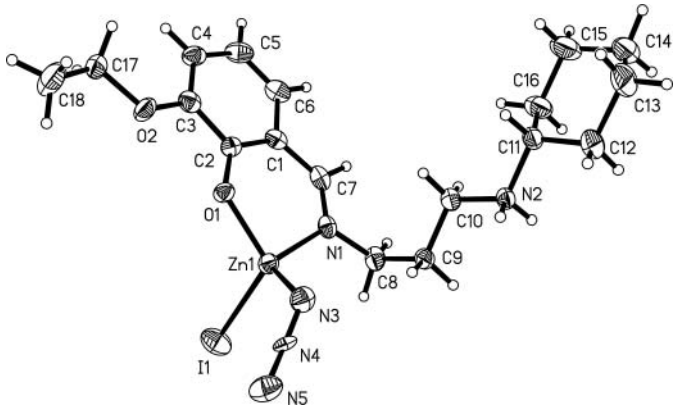

FIG. 1. The structure of (**1**), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

In the crystal structure of (**1**), molecules are linked through intermolecular N–H···N and N–H···O hydrogen bonds, forming a network (Figure 3). In the crystal structure of (**2**), molecules are linked through intermolecular N–H···N and N–H···O hydrogen bonds, forming layers along the *bc* direction (Figure 4).

Urease Inhibitory Activities

From Table 4, it can be seen that both complexes showed weak urease inhibitory activities with the IC_{50} values of 72.31 μM for (**1**) and 56.05 μM for (**2**), respectively, which are larger than that of the acetohydroxamic acid coassayed as a standard reference against the urease. It is notable that both complexes possess stronger urease inhibitory properties than the corresponding Schiff bases and the zinc iodide, but weaker than those of the copper(II) complexes we reported previously.[6,22]

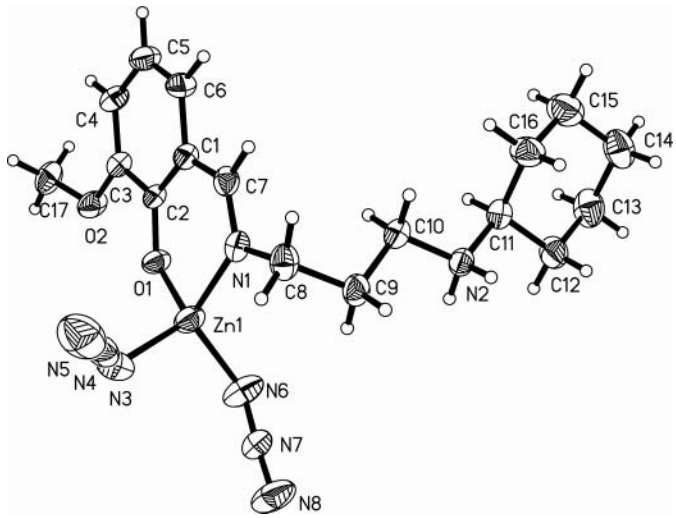

FIG. 2. The structure of (**2**), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

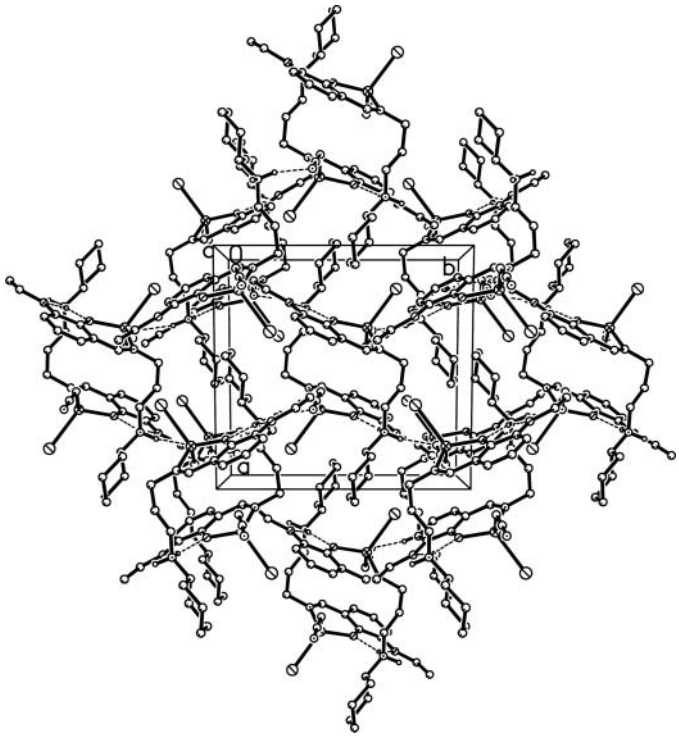

FIG. 3. Molecular packing of (**1**), viewed along the *c* axis. Intermolecular hydrogen bonds are shown as dashed lines.

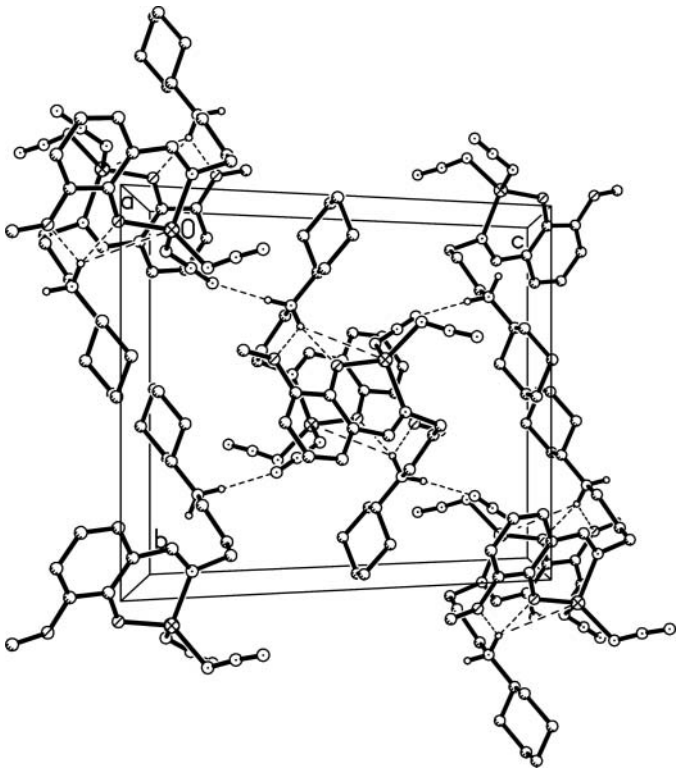

FIG. 4. Molecular packing of complex (**2**), viewed along the *a* axis. Intermolecular hydrogen bonds are shown as dashed lines.

CONCLUSION

Two Schiff base zinc(II) complexes with azide and iodide co-ligands have been synthesized according to the standard procedure, and their structures were characterized by X-ray crystallography. Both complexes showed moderate urease inhibitory activities.

SUPPLEMENTARY MATERIALS

CCDC–739929 and 739930 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk.

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