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Synthesis and Crystal Structures of Cobalt(III) and Zinc(II) Complexes Derived from 4-Chloro-2-[(2-Morpholin-4-ylethylimino)methyl]phenol with Urease Inhibitory Activity[1]

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Abstract—A new mononuclear cobalt(III) complex, $[CoL_2(N_3)]_2 \cdot CH_3OH$ (**I**), and a new mononuclear zinc(II) complex, $[ZnLCl(CH_3OH)]$ (**II**) (HL = 4-chloro-2-[(2-morpholin-4-ylethylimino)methyl]phenol), were prepared and structurally characterized by elemental analyses, infrared spectroscopy, and single-crystal X-ray diffraction. The crystal of **I** is monoclinic: space group $P2_1/c$, $a = 18.742(2)$ Å, $b = 15.197(2)$ Å, $c = 25.646(2)$ Å, $\beta = 125.996(3)°$, $V = 5909.8(11)$ Å^3, $Z = 4$. The crystal of II is monoclinic: space group $P2_1/c$, $a = 7.257(1)$ Å, $b = 24.707(2)$ Å, $c = 9.637(1)$ Å, $\beta = 101.557(2)°$, $V = 1692.9(3)$ Å^3, $Z = 4$. The Co atom in **I** is in an octahedral coordination, and the Zn atom in **II** is in a trigonal-bipyramidal coordination. The urease inhibitory test shows that complex **I** has strong urease inhibitory activity, while complex **II** has no activity.

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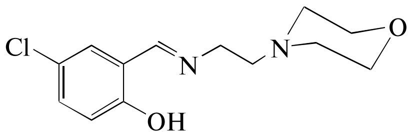
INTRODUCTION

Cobalt and zinc complexes with Schiff bases have been attracted much attention in coordination chemistry and bioinorganic chemistry due to their versatile structures and biological properties [1–6]. Ureases are an important class of enzymes involved in the degradative processing of urea [7–9]. They are ubiquitous in nature and 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 accompanying pH elevation, has important implications in medicine and agriculture [10, 11]. Therefore, urease inhibitors have recently been attracted much attention as potential new anti-ulcer drugs. A recent research indicated that the Schiff base complexes had potent urease inhibitory activity [12]. Schiff bases derived from the condensation of salicylaldehyde and its derivatives with primary amines represent an important class of chelating ligands, the metal complexes of which have been widely studied. However, no complexes with the Schiff base 4-chloro-2-[(2-morpholin-4-ylethylimino)methyl]phenol (**HL**) have been reported. In this paper, a new mononuclear cobalt(III) complex, $[CoL_2(N_3)]_2 \cdot CH_3OH$ (**I**), and a new mononuclear zinc(II) complex, $[ZnLCl(CH_3OH)]$ (**II**), were prepared and structurally characterized. The urease inhibitory activities of the complexes were determined.



(HL)

EXPERIMENTAL

Materials and measurements. All chemicals and reagents used for the preparation of the ligands and complexes were commercial products (Lancaster) and 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 PerkinElmer 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 HL. A methanolic solution (10 ml) of 2-morpholin-4-ylethylamine (130.2 mg) was added with stirring to a methanolic solution (20 ml) of 5-chlorosalicylaldehyde (1.0 mmol, 156.6 mg). The mixture was stirred at reflux for 30 min to give a yellow solution. The solution was evaporated to give a yellow powder, which

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[1] The article is published in the original.

Table 1. Crystallographic parameters and summary of data collection and refinement for the complexes **I** and **II**

Parameter	Value	
	I	**II**
M	1304.9	400.6
Crystal shape/color	Block/red	Block/colorless
Crystal size, mm	0.18 × 0.17 × 0.15	0.23 × 0.20 × 0.20
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a, Å	18.742(2)	7.257(1)
b, Å	15.197(2)	24.707(2)
c, Å	25.646(2)	9.637(1)
β, deg	125.996(3)	101.557(2)
V, Å^3	5909.8(11)	1692.9(3)
Z	4	4
μ_{Mo}, mm^{-1}	0.809	1.778
T_{min}	0.868	0.685
T_{max}	0.888	0.717
Reflections/parameters	12699/741	3666/203
Independent reflections	6278	3151
F(000)	2712	824
Goodness-of-fit on F^2	1.019	1.044
R_1, wR_2 ($I \geq 2\sigma(I)$)*	0.0551, 0.1295	0.0298, 0.0749
R_1, wR_2 (all data)*	0.1347, 0.1849	0.0366, 0.0780

* $R_1 = S||F_o| - |F_c||/S|F_o|$, $wR_2 = [Sw(F_o^2 - F_c^2)^2/Sw(F_o^2)^2]^{1/2}$.

was washed with methanol and dried in air. The yield was 93%.

For $C_{13}H_{17}ClN_2O_2$
anal. calcd., %: C, 58.1; H, 6.4; N, 10.4.
Found, %: C, 58.5; H, 6.3; N, 10.6.

Synthesis of [CoL$_2$(N$_3$)] · CH$_3$OH (I). A methanolic solution (5 ml) of $Co(ClO_4)_2 \cdot 6H_2O$ (0.1 mmol, 36.6 mg) was added with stirring to a methanolic solution (10 ml) of HL (0.1 mmol, 26.8 mg) and sodium azide (0.1 mmol, 6.5 mg). The mixture was stirred for 30 min at room temperature and filtered. Upon keeping the filtrate in air for a few days, red block-shaped crystals of I, suitable for X-ray single-crystal diffraction, were formed on the bottom of the vessel. The crystals were collected by filtration, washed three times with cold methanol, and dried in air. The yield was 37% based on HL.

For $C_{53}H_{68}Cl_4Co_2N_{14}O_9$
anal. calcd., %: C, 48.8; H, 5.3; N, 15.0.
Found, %: C, 48.3; H, 5.5; N, 15.3.

Synthesis of [ZnLCl(CH$_3$OH)] (II). A methanolic solution (10 ml) of HL (0.1 mmol, 26.8 mg) was added with stirring to a methanolic solution (5 ml) of $ZnCl_2$ (0.1 mmol, 13.6 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 **II**, suitable for X-ray single-crystal diffraction, were formed on the bottom of the vessel. The crystals were collected by filtration, washed three times with cold methanol, and dried in air. The yield was 62% based on HL.

For $C_{14}H_{20}Cl_2N_2O_3Zn$
anal. calcd., %: C, 42.0; H, 5.0; N, 7.0.
Found, %: C, 41.5; H, 5.1; N, 6.7.

Crystal structure determination. A suitable single crystal of each complex was mounted on a glass fiber. The diffraction experiments were carried out on a Bruker AXS SMART CCD diffractometer. The program SMART was used for collecting frames of data, indexing reflections, and determination of lattice parameters [13]. SAINT was used for integration of the intensity of reflections and scaling [13], SADABS was used for absorption correction [14], and SHELXTL was applied for space group and structure determination and least-squares refinements on F^2 [15]. All non-hydrogen atoms were refined anisotropically. The H(3*A*) atom attached to O(3) in **II** was located from a difference Fourier map and refined isotropically with O–H distance restrained to 0.85(1) Å. Other hydrogen atoms were placed in 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.

Atomic coordinates and other structural parameters of the complexes have been deposited with the Cambridge Crystallographic Data Center (nos. 740909 (**I**) and 740910 (**II**); deposit@ccdc.cam.ac.uk).

Measurement of urease. The assay mixture containing 25 μl 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 a microplate 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 [16].

Table 2. Selected bond lengths and bond angles for the complexes

Bond	d, Å	Bond	d, Å
		I	
Co(1)–O(1)	1.894(3)	Co(1)–O(3)	1.880(3)
Co(1)–N(1)	1.958(4)	Co(1)–N(3)	1.901(4)
Co(1)–N(4)	2.074(4)	Co(1)–N(5)	1.927(4)
Co(2)–O(5)	1.910(3)	Co(2)–O(7)	1.888(3)
Co(2)–N(8)	1.953(4)	Co(2)–N(10)	1.895(4)
Co(2)–N(11)	2.067(4)	Co(2)–N(12)	1.927(4)
		II	
Zn(1)–O(1)	2.070(2)	Zn(1)–O(3)	2.026(2)
Zn(1)–N(1)	2.017(2)	Zn(1)–N(2)	2.515(2)
Zn(1)–Cl(2)	2.219(1)		
Angle	**ω, deg**	**Angle**	**ω, deg**
		I	
N(1)Zn(1)O(3)	114.3(1)	N(1)Zn(1)O(1)	89.4(1)
O(3)Zn(1)O(1)	89.7(1)	N(1)Zn(1)Cl(2)	130.3(1)
O(3)Zn(1)Cl(2)	114.6(1)	O(1)Zn(1)Cl(2)	98.5(1)
N(1)Zn(1)N(2)	76.9(1)	O(3)Zn(1)N(2)	92.1(1)
O(1)Zn(1)N(2)	165.7(1)	Cl(2)Zn(1)N(2)	93.6(1)
		II	
O(3)Co(1)O(1)	90.0(2)	O(3)Co(1)N(3)	94.4(2)
O(1)Co(1)N(3)	85.7(2)	O(3)Co(1)N(5)	91.0(2)
O(1)Co(1)N(5)	172.4(2)	N(3)Co(1)N(5)	86.7(2)
O(3)Co(1)N(1)	86.2(2)	O(1)Co(1)N(1)	94.7(2)
N(3)Co(1)N(1)	179.3(2)	N(5)Co(1)N(1)	92.9(2)
O(3)Co(1)N(4)	178.6(2)	O(1)Co(1)N(4)	88.6(2)
N(3)Co(1)N(4)	85.4(2)	N(5)Co(1)N(4)	90.4(2)
N(1)Co(1)N(4)	94.0(2)	O(7)Co(2)N(10)	93.2(2)
O(7)Co(2)O(5)	89.8(2)	N(10)Co(2)O(5)	84.7(2)
O(7)Co(2)N(12)	92.8(2)	N(10)Co(2)N(12)	88.5(2)
O(5)Co(2)N(12)	172.8(2)	O(7)Co(2)N(8)	85.6(2)
N(10)Co(2)N(8)	178.6(2)	O(5)Co(2)N(8)	94.4(2)
N(12)Co(2)N(8)	92.4(2)	O(7)Co(2)N(11)	179.0(2)
N(10)Co(2)N(11)	86.3(2)	O(5)Co(2)N(11)	90.9(2)
N(12)Co(2)N(11)	86.3(2)	N(8)Co(2)N(11)	94.9(2)

RESULTS AND DISCUSSION

The Schiff base HL was readily synthesized via Schiff base condensation using equimolar quantities of 5-chlorosalicylaldehyde with 2-morpholin-4-ylethylamine. Complex **I** was synthesized by mixing equimolar quantities of HL, NaN_3, and $Co(ClO_4)_2 \cdot 6H_2O$ in a methanolic solution, yielding an azide-coordinated octahedral cobalt(III) complex. It is notable that the Co atom was oxidized during the process. Complex **II** was synthesized by a similar procedure as that described for **I**, but with $Co(ClO_4)_2 \cdot 6H_2O$ replaced by $ZnCl_2$, yielding a chloride-coordinated trigonal bipyramidal zinc(II) complex.

The Schiff base HL is soluble in DMF, DMSO, methanol, ethanol, chloroform, and acetonitrile. The elemental analyses are in good agreement with the chemical formula proposed for the compound. Both complexes are stable in air at room temperature. They are soluble in DMF, DMSO, methanol, ethanol, and acetonitrile, and insoluble in water.

In the infrared spectra of the Schiff base HL, the weak and broad absorption band centered at 3350 cm^{-1} is assigned to the stretching vibration of the O–H bond, which absent in the complexes. The strong absorption band at 1645 cm^{-1} for HL is assigned to the azomethine group, ν(C=N) [17], which is shifted to lower frequencies in the complexes (1627 cm^{-1} for **I** and 1623 cm^{-1} for **II**). The strong absorption of the azide group in **I** is at 2043 cm^{-1}.

Figure 1 gives a perspective view of complex **I**. The asymmetric unit of **I** consists of two $CoL_2(N_3)$ complex molecules and one methanol molecule of crystallization. The methanol molecule is linked to the complex molecules through the O(9)–H(9)···O(5) hydrogen bond.

In each complex molecule, the Co atom is six-coordinated and is best described as having an octahedral coordination. One Schiff base coordinates to the Co atom through the phenolate O, imine N, and amine N atoms, and another base coordinates to the Co atom through the phenolate O and imine N atoms. The remaining position of the octahedral geometry is occupied by the N atom of the terminal coordinated azide group. The three *trans* angles are ranged from 172.4(2)° to 179.3(2)° for Co(1) and 172.8(2)° to

Table 3. The geometric parameters of hydrogen bonds and bond angles for complexes **I** and **II***

Contact D–H···A	Distance, A			Angle D–H···A, deg
	D–H	H···A	D···A	
		I		
O(9)–H(9)···O(5)	0.82	2.08	2.889(6)	172
		II		
O(3)–H(3*A*)···O(1)^i	0.845(10)	1.782(11)	2.623(2)	173(4)

* Symmetry code: $^i 2 - x, 1 - y, 1 - z$.

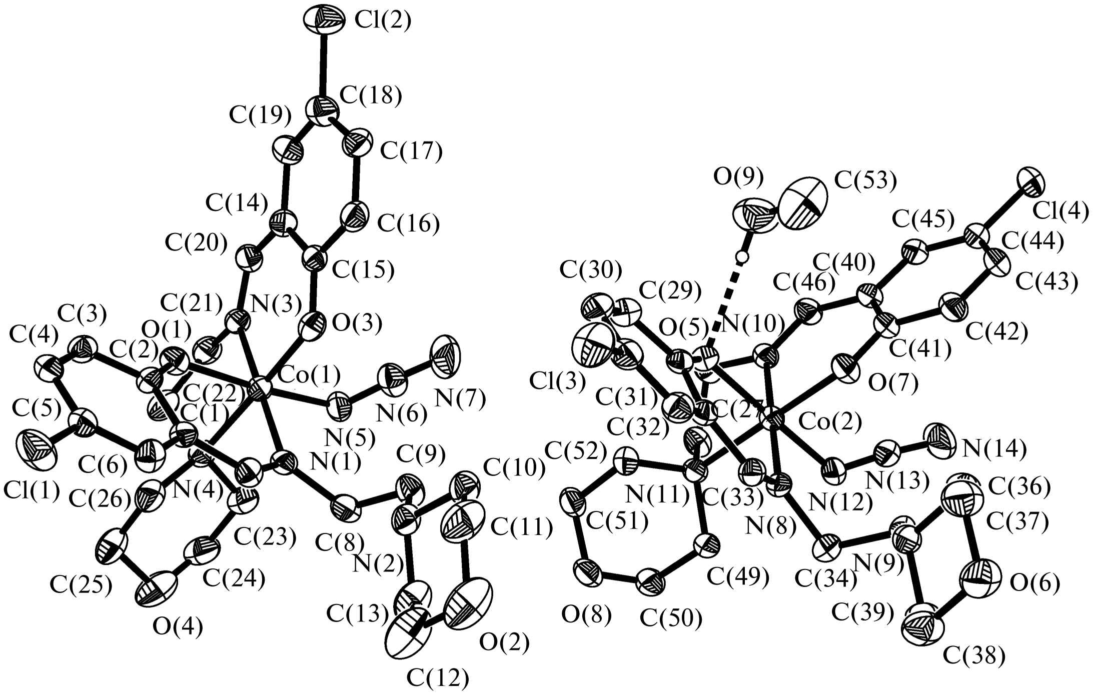

Fig. 1. Molecular structure of **I** at 30% ellipsoid. H atoms unrelated to hydrogen bond are omitted.

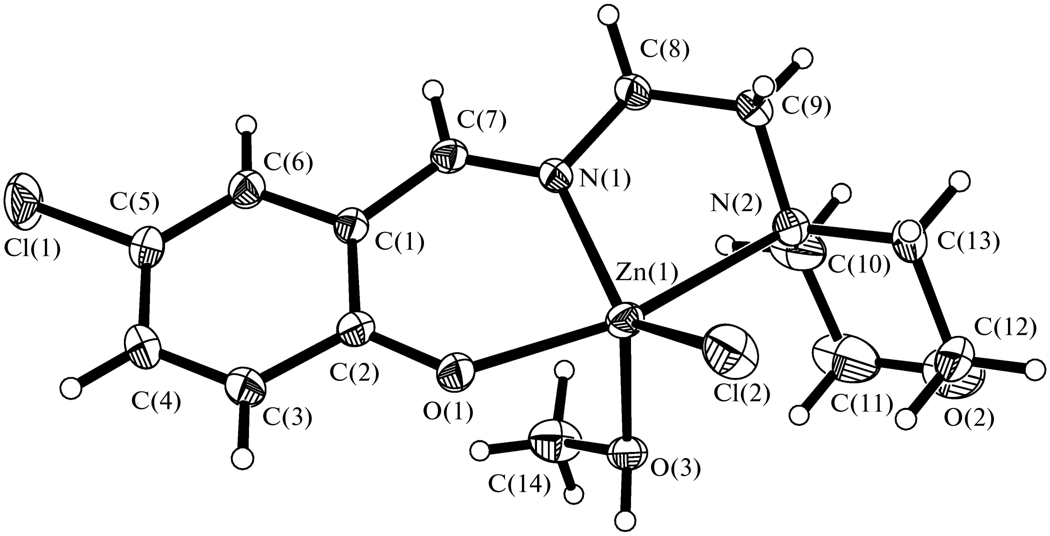

Fig. 2. Molecular structure of **II** at 30% ellipsoid.

179.0(2)° for Co(2), and the remaining coordinate bond angles are close to 90°, indicating that the octahedral coordination is slightly distorted. The coordinate bond lengths for Co(1) and Co(2) are similar to each other and comparable with the values observed in other cobalt(III) complexes with Schiff bases [18–20]. As expected, the morpholine rings in the complex adopt chair conformations.

Figure 2 gives a perspective view of complex **II**. The Zn atom is five-coordinated and is best described as having a trigonal bipyramidal coordination. The equatorial plane of the coordination is defined by one imine N atom of L, one O atom of the methanol molecule, and one CI atom. The two axial positions are occupied by one phenolate O atom and one amine N atom, respectively. The coordinate bond angles in the

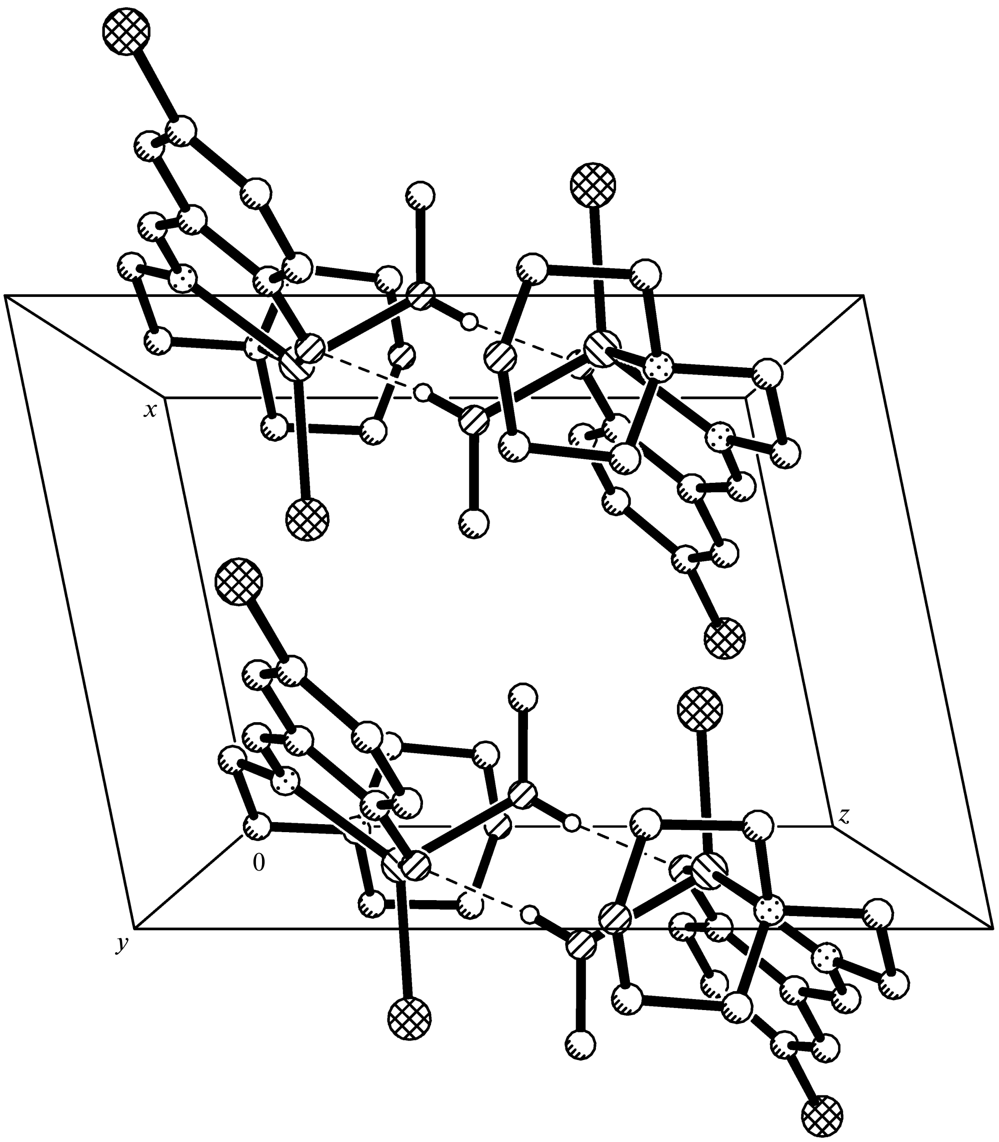

Fig. 3. Molecular packing diagram of **II** viewed along the *y* axis. Hydrogen bonds are shown as dashed lines.

equatorial plane are ranged from 114.3(1)° to 130.3(1)°, and the axial *trans* bond angle is 165.7(1)°, indicating a distorted trigonal bipyramidal coordination. The trigonal bipyramidal coordination can further be proved by the structural index τ value [21], which represents the relative amount of trigonality (square pyramid, $\tau = 0$; trigonal bipyramid, $\tau = 1$). The τ value for this structure is 0.59, indicating that the coordination is severely distorted and best described as a trigonal bipyramid. The coordinate bond lengths are typical of and similar to those observed in other zinc(II) complexes with Schiff bases [22–24]. As expected, the morpholine ring in the complex adopts chair conformation.

In the crystal structure of the complex, adjacent two molecules are linked through intermolecular O–H···O hydrogen bonds, forming a dimer, as shown in Fig. 3.

The cobalt(III) complex **I** shows strong urease inhibitory activity with the IC_{50} value of 27.12 ± 0.73 μM, which is even stronger than that of the acetohydroxamic acid (45.37 ± 0.31) coassayed as a standard reference against the urease. However, zinc(II) complex **II** shows no activity.

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