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Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsrt20</u>

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To cite this article: Da-Hua Shi, Lin Zhang, Li-Li Ni, Shun Bai & Zhong-Lu You (2010) Synthesis, Crystal Structures, and Urease Inhibitory Activities of Two Isostructural Schiff Base Cadmium(II) Complexes, Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry, 40:5, 359-363

To link to this article: <u>http://dx.doi.org/10.1080/15533174.2010.487057</u>

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Synthesis, Crystal Structures, and Urease Inhibitory Activities of Two Isostructural Schiff Base Cadmium(II) Complexes

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Two isostructural cadmium(II) complexes, $[Cd(L1)(NO_3)_2(H_2O)] \cdot CH_3OH$ (1) and $[Cd(L2)(NO_3)_2(H_2O)] \cdot CH_3OH$ (2), derived from the Schiff bases 4-bromo-2-[(2-piperazinylethylimino)methyl]phenol (L1) and 4-chloro-2-[(2-piperazinylethylimino)methyl]phenol (L2), respectively, were prepared and structurally characterized by X-ray diffraction. Each complex consists of a mononuclear cadmium(II) complex molecule and a methanol molecule of crystallization. The Cd atom in each complex is six-coordinated by one phenolate O, one imine N and one amine N atoms of the Schiff base ligand, two O atoms from two nitrate anions, and one water O atom, forming distorted octahedral coordination. The urease inhibitory activities of the complexes were evaluated.

Keywords cadmium, crystal structure, schiff base, synthesis, urease inhibitory activity

INTRODUCTION

Urease (urea amidohydrolase; E.C.3.5.1.5) is a nickelcontaining metalloenzyme that catalyzes the hydrolysis of urea to form ammonia and carbon dioxide.^[1,2] The enzyme is found in many plants, selected fungi, and a wide variety of prokaryotes.^[3] High concentrations of ammonia arising from these reactions, as well as the accompanying pH elevation, have important negative implications in medicine and agriculture.^[4–6] Control of the activity of urease through the use of inhibitors could counteract these negative effects. Recently, we have reported the urease inhibitory activities of some Schiff base complexes.^[7,8] Among which, the cadmium complexes show strong urease inhibitory activities. In order to further investigate the urease inhibitory activities of Schiff base complexes, we report herein the synthesis, crystal structures, and urease inhibitory activities of two isostructural cadmium(II) complexes. It is notable that only one nickel(II) complex derived from L1 has been reported,^[9] and no complexes derived from L2 have been reported so far.

EXPERIMENTAL

Materials and Methods

5-Bromosalicylaldehyde, 5-chlorosalicylaldehyde, and 2piperazinylethylamine with AR grade were purchased from Lancaster. Cadmium nitrate and solvents were purchased from Beijing Chemical Reagent Company and were used as received. Elemental analyses for C, H and N were performed on a Perkin-Elmer 240C elemental analyzer.

Synthesis of L1

To a methanol solution (20 mL) of 5-bromosalicylaldehyde (1.0 mmol, 201.0 mg) was added a methanol solution (20 mL) of 2-piperazinylethylamine (1.0 mmol, 129.2 mg), with stirring. The mixture was stirred for 30 min at room temperature to give a yellow solution. Then the methanol was evaporated to give yellow precipitation of L1. Yield: 97%. Anal. calcd. $C_{13}H_{18}BrN_3O$: C, 50.0; H, 5.8; N, 13.5%. Found: C, 50.4; H, 6.0; N, 13.8%.

Synthesis of L2

L2 was prepared according to the procedure as described for L1, with 5-bromosalicylaldehyde replaced by 5-chlorosalicylaldehyde (1.0 mmol, 156.6 mg). Yield: 95%. Anal. calcd. $C_{13}H_{18}ClN_3O$: C, 58.3; H, 6.8; N, 15.7%. Found: C, 57.8; H, 6.7; N, 15.4%.

Synthesis of $[Cd(L1)(NO_3)_2(H_2O)] \cdot CH_3OH (1)$

L1 (0.1 mmol, 31.2 mg) and Cd(NO₃)₂·4H₂O (0.1 mmol, 30.8 mg) were mixed and stirred in a methanol solution (15 mL) for 30 min at room temperature. The mixture was filtered and the colorless block-shaped crystals of **1**, suitable for X-ray

Received 15 August 2009; accepted 16 April 2010.

This work was financially supported by the Natural Science Foundation of Huaihai Institute of Technology (Z2008022), and by the Education Office of Liaoning Province (Project No. 2007T092).

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diffraction, were formed on slow evaporation of the filtrate in air. Yield: 45%. Anal. calcd. $C_{14}H_{24}BrCdN_5O_9$: C, 28.1; H, 4.0; N, 11.7%. Found: C, 27.5; H, 4.3; N, 12.1%.

Synthesis of [Cd(L2)(NO₃)₂(H₂O)]·CH₃OH (2)

Complex **2** was synthesized in methanol solution by a similar procedure as that described for **1**, with L1 replaced by L2 (0.1 mmol, 26.7 mg). Yield: 63%. Anal. calcd. $C_{14}H_{24}CdClN_5O_9$: C, 30.3; H, 4.4; N, 12.6%. Found: C, 30.8; H, 4.5; N, 12.2%.

X-ray Crystallography

Diffraction intensities for the two complexes were collected at 298(2) K using a Bruker SMART 1000 CCD area-detector with MoK α radiation ($\lambda = 0.71073$ Å). The collected data were reduced with the SAINT program,^[10] and multi-scan absorption corrections were performed using the SADABS program.^[11] Both structures were solved by direct methods. The complexes were refined against F^2 by full-matrix least-squares methods using the SHELXTL package.^[12] All of the non-hydrogen atoms were refined anisotropically. The water H atoms were located from a different Fourier map and refined isotropically, with O-H and H···H distances restrained to 0.85(1) and 1.37(2) Å, respectively. Other hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. The crystallographic data for both complexes are summarized in Table 1. Selected bond lengths and angles are given in Table 2. Hydrogen bonds are listed in Table 3. Crystallographic data for the complexes have been deposited with the Cambridge Crystallographic Data Center (CCDC 744025 for 1 and 744026 for 2).

Urease Inhibition Assay

The measurement of urease inhibitory activities was carried out according to the method reported by Tanaka.^[13] Generally, the assay mixture, containing 25 μ L of jack bean urease (10 kU/L) and 25 μ L of the tested complexes of various concentrations (dissolved in the solution of DMSO:H₂O = 1:1 (v/v)), was preincubated for 1 h at 37°C in a 96-well assay plate. Then 0.2 mL of 100 mM Hepes [N-(2-hydroxyethyl)piperazine-N'-

TABLE 1						
Crystallographic data for the complexes						

TABLE 2Selected bond lengths (Å) and angles (°) for the complexes

omplex	1	2		1	1	1
Formula	C ₁₄ H ₂₄ BrCdN ₅ O ₉	C ₁₄ H ₂₄ CdClN ₅ O ₉	-	Bond lengths	Bond lengths	Bond lengths
W	598.7	554.2		CdI-OI	Cd1-O1 2.205 (3)	Cd1-O1 2.205 (3) Cd1-O2
Crystal shape/color	Block/colorless	Block/colorless		Cd1-O5	Cd1-O5 2.202 (3)	Cd1-O5 2.202 (3) Cd1-N1
Crystal size (mm)	$0.20\times0.18\times0.18$	$0.20\times0.18\times0.18$		Cd1-N2	Cd1-N2 $2.557(4)$	Cd1-N2 2.557 (4) Cd1-O6
T (K)	298(2)	298(2)		Bond angles	Bond angles	Bond angles
$\lambda (MoK\alpha) (Å)$	0.71073	0.71073		O5-Cd1-O1	O5-Cd1-O1 108.92 (13)	O5-Cd1-O1 108.92 (13) O5-Cd1-N1
Crystal system	Monoclinic	Monoclinic		O1-Cd1-N1	O1-Cd1-N1 85.41 (14)	O1-Cd1-N1 85.41 (14) O5-Cd1-O2
space group	$P2_{1}/c$	$P2_{1}/c$	0	1-Cd1-O2	1-Cd1-O2 89.98 (13)	1-Cd1-O2 89.98 (13) N1-Cd1-O2
ı (Å)	9.043(2)	8.964(2)	O5-Cd1	-N2	-N2 95.56 (14)	-N2 95.56 (14) 01-Cd1-N2
v (Å)	11.116(2)	11.168(3)	N1-Cd1-N2	2	2 74.87 (15)	2 74.87 (15) O2-Cd1-N2
c (A)	21.343(4)	21.280(5)	01-Cd1-O6		74.4 (2)	74.4 (2) O2-Cd1-O6
β (°)	98.227(2)	99.194(4)	O5-Cd1-O6		76.0 (2)	76.0 (2) N1-Cd1-O6
V (A ³)	2123.5(7)	2102.9(9)	N2-Cd1-O6		116.4 (2)	116.4 (2)
$(\mathbf{M}_{0}\mathbf{K}_{0})$ (cm ⁻¹)	4	4	2			
$L(MOK\alpha)(CIII)$	2.900	0.792	Bond lengths			
r _{min} T	0.588	0.810	Cd1-O1		2.205 (3)	2.205 (3) Cd1-O2
$D_c (g \text{ cm}^{-3})$	1.873	1.751	Cd1-O5		2.357 (4)	2.357 (4) Cd1-O8
Measured reflections	16789	12730	Cd1-N1		2.194 (4)	2.194(4) Cd1-N2
Unique reflections and R _{int}	4397 and 0.0584	4769 and 0.0538	Bond angles		,	
Observed reflections	3207	3288	N1-Cd1-O8		149.90 (15)	149.90 (15) N1-Cd1-O1
Data/restraints/parameters	4397/3/279	4769/4/281	08-Cd1-O1		108.75 (12)	108.75 (12) N1-Cd1-O5
Goodness of fit on F^2	1.033	1.008	O8-Cd1-O5		81.83 (12)	81.83 (12) 01-Cd1-O5
$R_1 \left[I \ge 2\sigma(I) \right]$	0.0459	0.0505	N1-Cd1-N2		74.96 (14)	74.96 (14) 08-Cd1-N2
$WK_2 \left[I \ge 2\sigma(I) \right]$	0.0932	0.10/4	O1-Cd1-N2		155.09 (12)	155.09 (12) O5-Cd1-N2
$\pi_1(an a a a)$ w $R_2(a a b a)$	0.0710	0.0608	N1-Cd1-O2		81.79 (15)	81.79 (15) 08-Cd1-O2
I arge diff neak and hole	0.745 -0.806	0.879 -0.665	O1-Cd1-O2		75.13 (12)	75.13 (12) O5-Cd1-O2
$(e Å^{-3})$	0.713, -0.000	0.077, -0.005	N2-Cd1-O2		116.03 (13)	116.03 (13)

D–H···A	<i>d</i> (<i>D</i> –H)	$d(\mathrm{H}\cdots A)$	$d(D\cdots A)$	Angle $(D-H\cdots A)$
1				
O5−H5A· · · O9 ^{#1}	0.850 (10)	1.829 (16)	2.670 (5)	170 (6)
$O5-H5B\cdots O1^{#2}$	0.852 (10)	1.784 (14)	2.628(4)	171 (5)
$N3-H3B\cdot\cdot\cdot N5^{\#3}$	0.90	2.63	3.486 (7)	160
$N3-H3B\cdots O2^{\#3}$	0.90	2.55	3.225 (6)	132
$N3-H3B\cdots O4^{\#3}$	0.90	1.95	2.849 (6)	172
$N3-H3A\cdots N4^{#4}$	0.90	2.49	3.348 (6)	160
N3–H3A· · · O6 ^{#4}	0.90	2.34	3.010 (6)	132
N3–H3A· · · O7 ^{#4}	0.90	1.96	2.845 (6)	168
O9−H9· · · N4 ^{#5}	0.82	2.68	3.439 (6)	154
O9−H9· · · O7 ^{#5}	0.82	2.55	3.184 (6)	135
O9−H9· · · O8 ^{#5}	0.82	2.12	2.891 (6)	157
2				
$O8-H8D \cdot \cdot \cdot O2$	0.845 (10)	2.37 (4)	3.029 (5)	135 (5)
$O8-H8D\cdot\cdot\cdot O9^{\#1}$	0.845 (10)	2.12 (5)	2.690 (5)	125 (5)
O8–H8C· · · O1 ^{#6}	0.851 (10)	1.782 (15)	2.625 (4)	170 (5)
O9–H9· · · O8 ^{#7}	0.844 (10)	1.89 (3)	2.690 (5)	157 (6)
N3−H3B· · · N5 ^{#8}	0.90	2.64	3.493 (7)	159
N3−H3B· · · O5 ^{#8}	0.90	2.57	3.233 (6)	131
N3−H3B· · · O7 ^{#8}	0.90	1.95	2.847 (6)	173
$N3-H3A\cdots N4^{#4}$	0.90	2.47	3.339 (6)	163
N3−H3A· · · O2 ^{#4}	0.90	2.31	2.998 (6)	134
N3−H3A· · · O4 ^{#4}	0.90	1.98	2.857 (5)	166

 TABLE 3

 Hydrogen bond distances (Å) and bond angles (°)

Symmetry codes: #1: x, y, -1 + z; #2: 1 - x, 1 - y, -z; #3: -x, 1 - y, -z; #4: -1 + x, y, z; #5: 1 - x, 2 - y, 1 - z; #6: 1 - x, -y, -z; #7: x, y, 1 + z; #8: -x, -y, -z

(2-ethanesulfonic acid)] buffer at pH 6.8.^[14] containing 500 mM urea and 0.002% phenol red were added and incubated at 37°C. The reaction time, which was required to produce enough ammonium carbonate to raise the pH of a Hepes buffer from 6.8

to 7.7, was measured by a micro-plate reader (570 nm) with the end-point being determined by the color of phenol red indicator. The acetohydroxamic acid was used as the standard reference. All the tests were carried out for three times.



FIG. 1. Molecular structure of 1 at 30% probability ellipsoids. The methanol molecule was omitted for clarity.



FIG. 2. Molecular structure of 2 at 30% probability ellipsoids. The methanol molecule was omitted for clarity.



FIG. 3. Molecular packing of 1. Hydrogen bonds are shown as dashed lines.

RESULTS AND DISCUSSION

The Schiff bases L1 and L2 were prepared in excellent yields in methanol solutions. Both compounds are stable in air at room temperature. They are soluble in methanol, ethanol, acetonitrile, but insoluble in water. Both cadmium(II) complexes are colorless crystals; however, they are not very stable in air at room temperature, which might be caused by the lose of the methanol molecules. The complexes are soluble in methanol, ethanol and acetonitrile, insoluble in water.

Structures of the Complexes

Figures 1 and 2 give perspective views of the complexes 1 and 2, respectively. Both complexes are isostructural mononuclear cadmium(II) compounds. Each complex consists of a cadmium(II) complex molecule and a methanol molecule of crystallization. The Cd atom in each complex has an octahedral coordination and is coordinated by one phenolate O, one imine N, and one amine N atoms of the Schiff base ligand, and by one water O atom, defining the basal plane, and by two O atoms from two nitrate anions, occupying the axial positions.

The coordinate bond lengths and angles in both complexes are comparable to each other, and also comparable to those observed in other similar Schiff base cadmium(II) complexes.^[15–17] It is notable that the axial coordinate bond lengths are much longer than those of the basal bonds, indicating that they are weakly coordinate to the metal atoms. As



FIG. 4. Molecular packing of 2. Hydrogen bonds are shown as dashed lines.

TABLE 4 Inhibitory activities of urease

Tested materials	IC ₅₀ (μM)
1	56.51 ± 0.62
2	52.17 ± 0.37
L1	>100
L2	>100
Cadmium nitrate	18.23 ± 0.33
Acetohydroxamic acid	42.12 ± 0.08

expected, the coordinate bonds involving amine N atoms are much longer than those involving imine N atoms.

The molecular packing diagrams for 1 and 2 are shown in Figures 3 and 4, respectively. Both crystals are stabilized by intermolecular $O-H\cdots O$, $O-H\cdots N$, $N-H\cdots O$, and $N-H\cdots N$ hydrogen bonds.

Infrared Spectra

The weak absorptions at about 3371 cm⁻¹ are assigned to the stretching vibration of the phenol groups in the Schiff bases. The strong absorption bands at 1637 cm⁻¹ for L1 and 1638 cm⁻¹ for L2 are assigned to the azomethine groups, ν (C=N), which are shifted to lower wave numbers in both complexes, 1618 cm⁻¹ for **1** and 1620 cm⁻¹ for **2**, respectively. The lower shift of the absorption bands indicating that the coordination of the azomethine N atoms to the Cd atoms. The bands indicative of the nitrate anions in both complexes are at about 1440 and 1315 cm⁻¹.

The close resemblance of the shapes and the positions of the bands suggest similar coordination modes for the complexes.

Urease Inhibitory Activities

The average results concerning the inhibition of the complexes of the Schiff bases, and of cadmium nitrate on jack bean urease, are summarized in Table 4. Both complexes show weak urease inhibitory activities with the IC₅₀ values bigger than that of the standard reference and those reported in the literature.^[7,8] The Schiff bases show no inhibitory activities on jack bean urease (IC₅₀ > 100 μ M), which is in accord with the results we reported recently.^[7]

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