European Journal of Medicinal Chemistry 45 (2010) 3196–3199

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis, structures, and urease inhibitory activities of three copper(II) and zinc(II) complexes with 2-{[2-(2-hydroxyethylamino)ethylimino]methyl}-4-nitrophenol

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ARTICLE INFO

Article history:
Received 8 May 2009
Received in revised form
4 March 2010
Accepted 10 March 2010
Available online 16 March 2010

Keywords:
Schiff base
Complex
Crystal structure
Urease inhibition

ABSTRACT

In order to explore novel urease inhibitors, three new mononuclear complexes of Cu(II) and Zn(II) with Schiff base 2-{[2-(2-hydroxyethylamino)ethylimino]methyl}-4-nitrophenol have been prepared and structurally characterized by X-ray crystallography. Among the three complexes, two Cu(II) complexes show strong urease inhibitory activities with the IC_{50} values being much lower than that of the acetohydroxamic acid, while the Zn(II) complex shows no activity at the concentration of 100 μM.

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1. Introduction

Urease (urea amidohydrolase; E.C.3.5.1.5) is a nickel-containing metalloenzyme that catalyzes the hydrolysis of urea to form ammonia and carbamate [1,2]. The resulting carbamate spontaneously decomposes to yield a second molecule of ammonia and carbon dioxide. High concentrations of ammonia arising from these reactions, as well as the accompanying pH elevation, have important negative implications in medicine and agriculture [3–6]. Control of the activity of urease through the use of inhibitors could counteract these negative effects. In recent years, urease inhibitors play an important role in the treatment of the infections caused by urease producing bacteria [7]. Inhibitors of urease can be broadly classified into two fields: (1) organic compounds, such as acetohydroxamic acid, humic acid, and 1,4-benzoquinone [8–10]; (2) heavy metal ions, such as Cu^{2+}, Zn^{2+}, Pd^{2+}, and Cd^{2+} [11,12]. The metal complexes as urease inhibitors have seldom been reported, which indicates that the metal complexes of organotin(IV), vanadium(IV), bismuth(III), copper(II), and cadmium(II) bearing interesting urease inhibitory activities [13–17]. In this paper, three copper(II) and zinc(II) complexes, [$CuLNO_3$] (**1**), [CuClL] (**2**), and [Zn(CH_3COO)L] (**3**) (HL = 2-{[2-(2-hydroxyethylamino)ethylimino]methyl}-4-nitrophenol) were synthesized and structurally characterized. The urease inhibitory activities of the complexes were investigated.

2. Results and discussion

2.1. Chemistry

HL was synthesized by the reaction of equimolar quantities of 5-nitrosalicylaldehyde with N-(2-hydroxyethyl)ethylenediamine in a methanol solution (Scheme 1). All the complexes were synthesized by the reaction of the methanol solutions of HL with the corresponding metal salts (copper nitrate for **1**, copper chloride for **2**, and zinc acetate for **3**; Scheme 2). The compounds have been characterized by elemental analysis and IR spectra. Structures of the complexes were further confirmed by X-ray crystallography (CCDC − 730 768 for **1**, 730 769 for **2**, and 730 770 for **3**).

2.2. Structure description of the complexes

X-ray crystallography reveals that the structures of the three complexes are similar mononuclear compounds. In each complex, the metal atom is in a square-pyramidal geometry, coordinated by the four donor atoms of L at the basal plane, and with the apical position occupied by the anion comes from the corresponding

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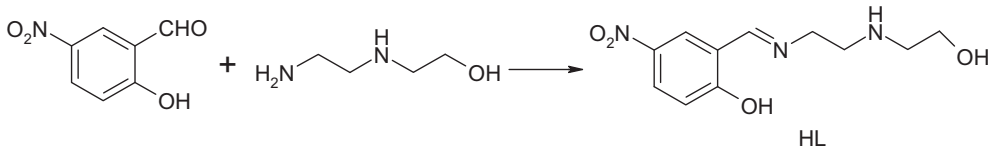
doi:10.1016/j.ejmech.2010.03.012



Scheme 1. Synthesis of HL.

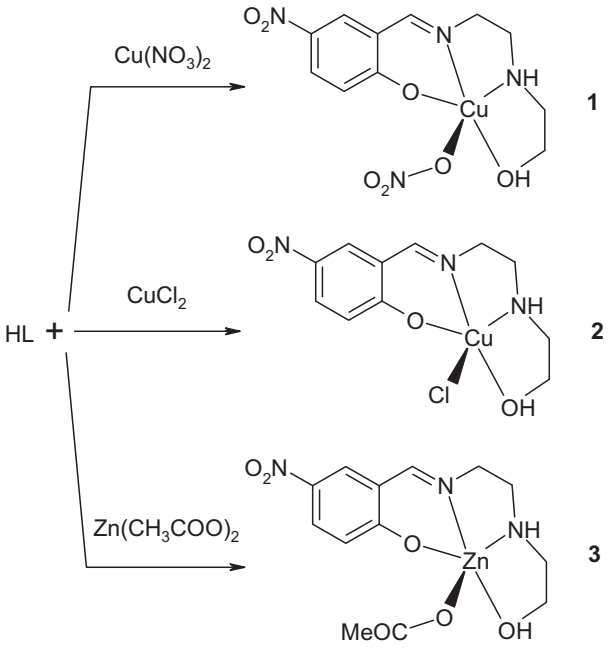
metal salts, viz. nitrate for **1** (Fig. 1), chloride for **2** (Fig. 2), and acetate for **3** (Fig. 3). The metal atoms deviate by 0.160(2) Å in **1**, 0.296(2) Å in **2**, and 0.642(2) Å in **3**, respectively, from the least-squares plane defined by the four basal donor atoms. Close examination of the structures reveal that the Cu–O and Cu–N bond lengths in **1** and **2** are comparable to each other, while the Zn–O and Zn–N bond lengths in **3** are a little longer than the corresponding values in **1** and **2**. All the coordinate bond lengths can be considered as normal by comparison with those reported in the literatures. The crystals of the complexes are stabilized by hydrogen bonds (Table 1).

2.3. Pharmacology

The measurement of jack bean urease inhibitory activity was carried out for three parallel times according to the literature phenol-red method [18]. The results are summarized in Table 2. Complexes **1** and **2** show strong urease inhibitory activity with the IC_{50} values being much lower than that of the acetohydroxamic acid coassayed as a standard urease inhibitor [7], while complex **3** shows no activity. The results in this paper are accordance with those reported previously, that the zinc(II) complexes have much weak urease inhibitory activities [19].

3. Conclusion

The present study reports the synthesis, structures and urease inhibitory activities of three mononuclear copper(II) and zinc(II) complexes with Schiff base HL. The urease inhibitory activities of the copper(II) complexes are superior than that of the acetohydroxamic acid. Considering the copper(II) complexes have interesting biological activities and have been widely used in medicine [20–22], the two copper(II) complexes in this paper may be used in the treatment of infections caused by urease producing bacteria.



Scheme 2. Synthesis of the complexes.

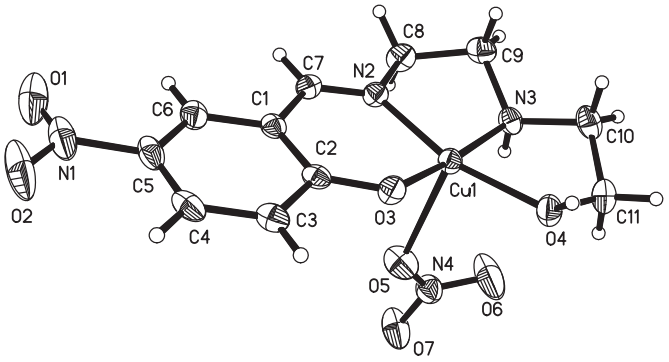


Fig. 1. A perspective view of the molecular structure of **1** with the atom labeling scheme. The thermal ellipsoids are drawn at the 30% probability level.

4. Experimental protocols

Starting materials, reagents and solvents were purchased from commercial suppliers and purified before use. Elemental analyses were performed on a Perkin–Elmer 240C elemental analyzer. The IR spectra were recorded on a Jasco FT/IR-4000 spectrometer as KBr pellets in the 4000–200 cm^{-1} region. X-ray diffraction was carried out at a Bruker SMART 1000 CCD area diffractometer equipped with MoKα radiation, and the structures were solved by direct methods using SHELXTL 97 software [23]. The crystallographic data for the complexes are summarized in Table 3. Selected bond lengths and angles are given in Table 4.

4.1. Synthesis of HL

To the methanol solution (50 mL) of 5-nitrosalicylaldehyde (1.0 mmol, 0.167 g) was added a methanol solution (30 mL) of

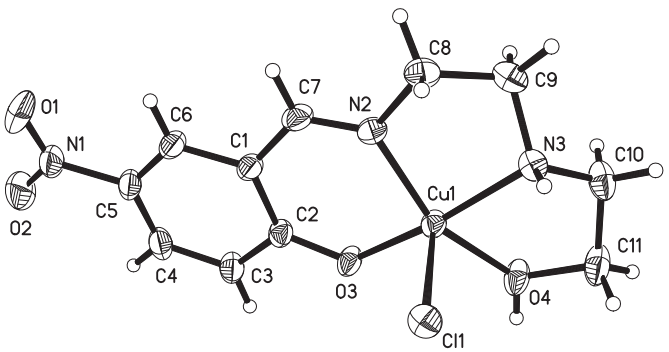


Fig. 2. A perspective view of the molecular structure of **2** with the atom labeling scheme. The thermal ellipsoids are drawn at the 30% probability level.

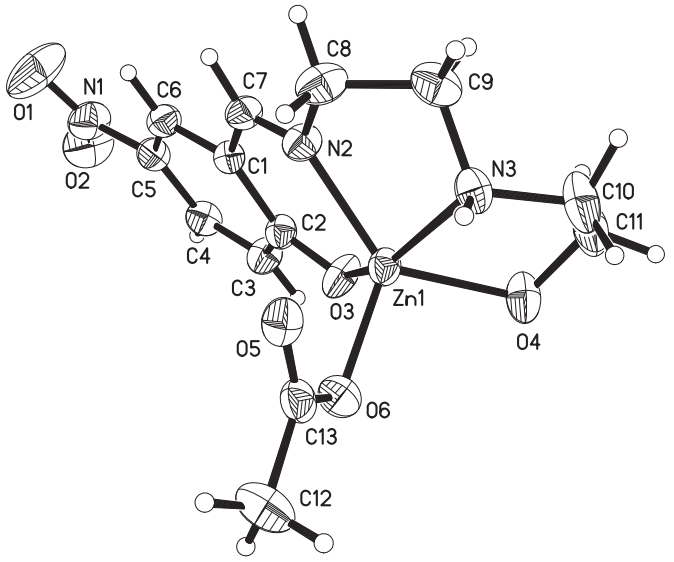


Fig. 3. A perspective view of the molecular structure of **3** with the atom labeling scheme. The thermal ellipsoids are drawn at the 30% probability level.

Table 1
Hydrogen bond distances (Å) and bond angles (°) for the complexes.

D–H···A	d(D–H)	d(H···A)	d(D···A)	Angle (D–H···A)
1				
N_3–H_3A···O_7^i	0.90(2)	2.64(4)	3.118(4)	114(3)
N_3–H_3A···O_6^i	0.90(2)	2.61(2)	3.393(4)	146(3)
O_4–H_4A···N_4^{ii}	0.85(2)	2.65(2)	3.442(4)	156(4)
O_4–H_4A···O_7^{ii}	0.85(2)	1.82(2)	2.632(3)	158(4)
2				
N3–H3A···Cl1^{iii}	0.90(2)	2.68(2)	3.365(2)	134(2)
O4–H4A···Cl1^{iv}	0.85(2)	2.22(2)	3.061(2)	173(3)
3				
N3–H3A···O6^{v}	0.90(2)	2.54(3)	3.237(3)	136(3)
O4–H4A···O5^{vi}	0.85(2)	1.783(5)	2.595(3)	159(4)

Symmetry codes: (i) $1-x, 2-y, -z$; (ii) $x, 3/2-y, 1/2+z$; (iii) $1-x, -y, 1-z$; (iv) $1\,x, 1/2-y, -1/2+z$; (v) $2-x, -1/2+y, 1/2-z$; (vi) $2-x, 1/2+y, 1/2-z$.

N-(2-hydroxyethyl)ethylenediamine (1.0 mmol, 0.104 g) with stirring. The mixture was stirred for 30 min at room temperature to give a yellow solution. The solvent was evaporated to give yellow powder, which was washed with cold methanol and dried in air. Yield: 91%. Characteristic IR data (cm^{-1}): 3351 (m), 3233 (w), 1635 (s), 1356 (s), 1513 (s). Anal. calcd. for $C_{11}H_{15}N_3O_4$: C, 52.2; H, 6.0; N, 16.6; Found C, 51.8; H 6.1; N 16.8%.

4.2. Synthesis of the complexes

A methanol solution (10 mL) of HL (0.1 mmol, 25.3 mg) was added with stirring to a methanol solution (10 mL) of the corresponding metal salt (0.1 mmol), viz. copper nitrate for **1**, copper chloride for **2**, and zinc acetate for **3**. The mixtures were stirred at room temperature for 30 min to give clear solutions. X-ray quality single crystals were formed by slow evaporation of the solutions in air for a few days.

Table 2
Inhibition of urease by the tested materials.

Tested materials	IC_{50}(μM)
1	22.40 ± 0.08
2	24.25 ± 0.05
3	>100
HL	>100
Acetohydroxamic acid	45.32 ± 0.27

Table 3
Crystallographic and experimental data for the complexes.

Complex	**1**	**2**	**3**
Formula	$C_{11}H_{14}CuN_4O_7$	$C_{11}H_{14}ClCuN_3O_4$	$C_{13}H_{17}N_3O_6Zn$
Mr	377.8	351.2	376.7
T (K)	298(2)	298(2)	298(2)
Crystal shape/color	block/blue	block/blue	block/colorless
Crystal size (mm^3)	0.27 × 0.25 × 0.25	0.34 × 0.32 × 0.32	0.32 × 0.32 × 0.27
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	8.256(1)	11.834(2)	11.875(3)
b (Å)	13.040(1)	10.779(2)	9.900(2)
c (Å)	13.409(1)	11.011(2)	14.309(5)
β (°)	99.267(3)	96.75(1)	114.397(12)
V ($Å^3$)	1424.7(2)	1394.7(3)	1532.0(8)
Z	4	4	4
D_c (g cm^{-3})	1.761	1.673	1.633
μ (Mo-Kα) (mm^{-1})	1.578	1.773	1.638
F(000)	772	716	776
Data collected	3073	3017	3441
Unique data ($I \geq 2\sigma(I)$)	2215	2517	2741
Min. and max. transmission	0.675 and 0.694	0.584 and 0.601	0.622 and 0.666
Parameters	214	187	215
Restraints	2	2	2
Goodness-of-fit on F^2	1.030	1.025	1.046
R_1, wR_2 [$I \geq 2\sigma(I)$][a]	0.0368, 0.0941	0.0302, 0.0816	0.0359, 0.0913
R_1, wR_2 (all data)[a]	0.0584, 0.1090	0.0380, 0.0871	0.0478, 0.0977
Large diff. peak and hole (e $Å^{-3}$)	0.603 and −0.304	0.642 and −0.537	0.516 and −0.376

[a] $R_1 = F_o - F_c/F_o$, $wR_2 = \left[\sum w(F_o^2 - Fc^2)/\sum w(F_o^2)^2\right]^{1/2}$

4.2.1. 2-{[2-(2-Hydroxyethylamino)ethylimino]methyl}-4-nitrophenolatonitratocopper(II) (*1*)

Blue single crystals. Yield: 73%. Characteristic IR data (cm^{-1}): 3434 (w), 3231 (w), 1653 (s), 1605 (s), 1550 (s), 1376 (s), 1308 (s),

Table 4
Selected bond lengths (Å) and angles (°) for the complexes.

1			
Cu_1–O_3	1.888(2)	Cu_1–O_4	2.005(2)
Cu_1–O_5	2.424(2)	Cu_1–N_2	1.929(2)
Cu_1–N_3	1.986(2)		
O_3–Cu_1–N_2	94.09(9)	O_3–Cu_1–N_3	171.5(1)
N_2–Cu_1–N_3	85.1(1)	O_3–Cu_1–O_4	95.7(1)
N_2–Cu_1–O_4	165.2(1)	N_3–Cu_1–O_4	83.6(1)
O_3–Cu_1–O_5	90.9(1)	N_2–Cu_1–O_5	93.3(1)
N_3–Cu_1–O_5	97.6(1)	O_4–Cu_1–O_5	97.6(1)
2			
Cu_1–O_3	1.913(2)	Cu1–O_4	2.014(2)
Cu_1–N_2	1.935(2)	Cu1–N_3	2.013(2)
Cu_1–Cl_1	2.574(1)		
O_3–Cu_1–N_2	93.8(1)	O_3–Cu_1–N_3	167.3(1)
N_2–Cu_1–N_3	84.8(1)	O_3–Cu_1–O_4	94.7(1)
N_2–Cu_1–O_4	155.4(1)	N_3–Cu_1–O_4	82.0(1)
O_3–Cu_1–Cl_1	102.6(1)	N_2–Cu_1–Cl_1	98.4(1)
N_3–Cu_1–Cl_1	90.1(1)	O_4–Cu_1–Cl_1	102.2(1)
3			
Zn_1–O_3	2.003(2)	Zn_1–O_4	2.082(2)
Zn_1–O_6	1.950(2)	Zn_1–N_2	2.051(2)
Zn_1–N_3	2.161(2)		
O_6–Zn_1–O_3	98.0(1)	O_6–Zn_1–N_2	122.8(1)
O_3–Zn_1–N_2	88.3(1)	O_6–Zn_1–O_4	101.3(1)
O_3–Zn_1–O_4	90.6(1)	N_2–Zn_1–O_4	135.6(1)
O_6–Zn_1–N_3	110.7(1)	O_3–Zn_1–N_3	150.7(1)
N_2–Zn_1–N_3	81.4(1)	O_4–Zn_1–N_3	78.4(1)

1098 (m). Anal. calcd. for $C_{11}H_{14}CuN_4O_7$: C, 35.0; H, 3.7; N, 14.8; Found C, 35.6; H 3.9; N 14.5%.

*4.2.2. Chlorido-2-{[2-(2-hydroxyethylamino)ethylimino]methyl}-4-nitrophenolatocopper(II) (**2**)*

Blue single crystals. Yield: 71%. Characteristic IR data (cm^{-1}): 3446 (w), 3220 (w), 1660 (s), 1601 (s), 1551 (m), 1397 (m), 1312 (vs), 1102 (m). Anal. calcd. for $C_{11}H_{14}ClCuN_3O_4$: C, 37.6; H, 4.0; N, 12.0; Found C, 37.1; H 4.3; N 11.7%.

*4.2.3. Acetato-2-{[2-(2-hydroxyethylamino)ethylimino]methyl}-4-nitrophenolatozinc(II) (**3**)*

Colorless single crystals. Yield: 90%. Characteristic IR data (cm^{-1}): 3436 (w), 3316 (w), 1653 (s), 1604 (s), 1550 (m), 1492 (m), 1390 (m), 1313 (vs), 1103 (m). Anal. calcd. for $C_{13}H_{17}N_3O_6Zn$: C, 41.5; H, 4.5; N, 11.2; Found C, 42.1; H 4.8; N 10.9%.

Acknowledgements

This work was financially supported by the National Science Foundation of China (Project No. 20901036).

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