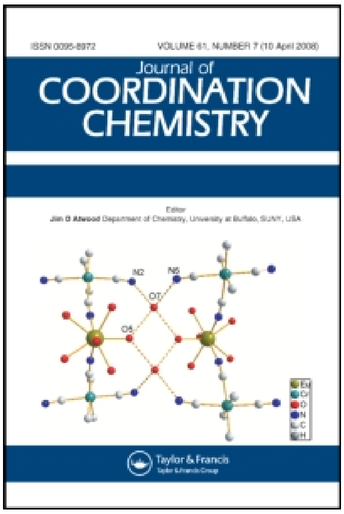

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Syntheses, crystal structures, and urease inhibitory properties of copper(II) and zinc(II) complexes with 2-bromo-4-chloro-6-[(2-dimethylaminoethylimino)methyl]phenol

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Syntheses, crystal structures, and urease inhibitory properties of copper(II) and zinc(II) complexes with 2-bromo-4-chloro-6-[(2-dimethylaminoethylimino)methyl]phenol

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A new copper(II) complex, $[\mathrm{CuL}(\mu_{1,1}\text{-}\mathrm{N}_3)]_n$ (**1**), and a new zinc(II) complex, $[\mathrm{ZnL}(\mu_2\text{-acetato-}O,O')_2]_n$ (**2**) (HL = 2-bromo-4-chloro-6-[(2-dimethylaminoethylimino)methyl]phenol), were prepared and characterized by elemental analyses, infrared spectroscopy, and single-crystal X-ray diffraction. Complex **1** is an end-on azide-bridged polynuclear copper(II) complex and **2** is a *syn–anti* bidentate acetate-bridged polynuclear zinc(II) complex. Each metal in the complex is five-coordinate with square-pyramidal geometry. Complex **1** shows good urease inhibitory properties, while **2** does not.

Keywords: Schiff base; Copper; Zinc; Crystal structure; Urease inhibitory property

1. Introduction

Much effort has been made to prepare and characterize a variety of copper(II) and zinc(II) complexes to model the physical and chemical behavior of some metalloenzymes, such as Cu–Zn superoxide dismutase, phosphatase, and aminopeptidase [1–5]. The peculiarity of copper and zinc lies in their ability to form complexes with coordination numbers 4, 5, and 6 [6–9]. Urease (urea amidohydrolase, E.C. 3.5.1.5) is a nickel-containing metalloenzyme that catalyzes the hydrolysis of urea to form ammonia and carbamic acid. The resulting carbamic acid spontaneously decomposes, yielding 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 implications in medicine and agriculture [10, 11] and inhibition of urease is a challenging topic. Metal complexes have been widely used as enzyme inhibitors [12] and copper(II) complexes with Schiff bases have excellent urease inhibitory activity [13]. In this article, a new copper(II) complex, $[\mathrm{CuL}(\mu_{1,1}\text{-}\mathrm{N}_3)]_n$ (**1**), and a new zinc(II) complex, $[\mathrm{ZnL}(\mu_2\text{-acetato-}O,O')_2]_n$ (**2**) (HL = 2-bromo-4-chloro-6-[(2-dimethylaminoethylimino)methyl]phenol), were prepared and structurally characterized. The urease inhibitory properties of the complexes were investigated.

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2. Experimental

2.1. *Materials and methods*

3-Bromo-5-chlorosalicylaldehyde and *N*,*N*-dimethylethane-1,2-diamine were purchased from Lancaster. *Jack bean* urease was supplied by Sigma. Other reagents and solvents (AR grade) were purchased from Beijing Chemical Co. Ltd. (China). Elemental analyses for C, H, and N were performed on a Perkin–Elmer 240C elemental analyzer. Infrared spectra were recorded on a Nicolet AVATAR 360 spectrophotometer as KBr pellets from 4000–400 cm^{-1}. Melting points were determined on a Beijing X4 microscopic apparatus.

2.2. *Synthesis of HL*

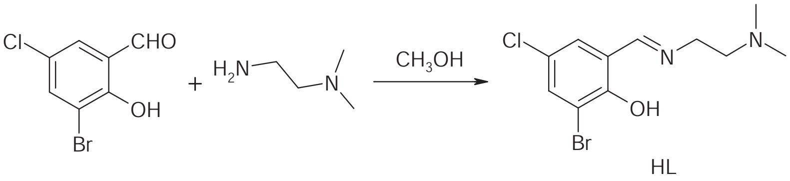
The Schiff base HL was prepared by condensation of 3-bromo-5-chlorosalicylaldehyde (1.0 mmol, 235.5 mg) with *N*,*N*-dimethylethane-1,2-diamine (1.0 mmol, 88.1 mg) in methanol (30 mL) at room temperature (scheme 1). Yield: 97%; m.p. 53.0–54.5°C. Anal. Calcd for $C_{11}H_{14}BrClN_2O$ (%): C, 43.2; H, 4.6; N, 9.2. Found(%): C, 43.5; H, 4.5; N, 9.3.

2.3. *Synthesis of 1*

To a methanol solution (10 mL) of HL (0.1 mmol, 30.5 mg), a methanol solution (5 mL) of $Cu(CH_3COO)_2 \cdot H_2O$ (0.1 mmol, 20.0 mg) and an aqueous solution (2 mL) of sodium azide (0.1 mmol, 6.5 mg) ware added with continuous stirring. The mixture was stirred for 30 min at room temperature and filtered. Upon keeping the filtrate in air for a week, blue block-shaped crystals of **1**, suitable for single-crystal X-ray diffraction, were formed. The crystals were collected by filtration, washed three times with cold methanol and dried in a vacuum desiccator containing anhydrous $CaCl_2$. Yield: 78%; m.p. >250°C. Anal. Calcd for $C_{11}H_{13}BrClCuN_5O$ (%): C, 32.2; H, 3.2; N, 17.1. Found(%): C, 31.8; H, 3.4; N, 17.3.

2.4. *Synthesis of 2*

To a methanol solution (10 mL) of HL (0.1 mmol, 30.5 mg), a methanol solution (5 mL) of $Zn(CH_3COO)_2 \cdot 2H_2O$ (0.1 mmol, 22.0 mg) was added with stirring. The mixture was stirred for 30 min at room temperature and filtered. Upon keeping the filtrate in air for 12 days, colorless block-shaped crystals of **2**, suitable for single-crystal X-ray diffraction, were formed. The crystals were collected by filtration, washed three times



Scheme 1. Synthetic route of the ligand HL.

with cold methanol and dried in a vacuum desiccator containing anhydrous $CaCl_2$. Yield: 83%; m.p. >250°C. Anal. Calcd for $C_{13}H_{16}BrClN_2O_3Zn$ (%): C, 36.4; H, 3.8; N, 6.5. Found(%): C, 36.0; H, 3.8; N, 6.7.

Caution! Although the samples we prepared never exploded during handling, azide metal complexes are potentially explosive: only a small amount of material should be prepared, and it should be handled with care.

2.5. *X-ray crystallography*

Diffraction data for **1** and **2** were determined at 293(2) K on a Bruker SMART 1000 CCD area-detector diffractometer with Mo-Kα radiation ($\lambda = 0.71073$ Å). The collected data were reduced using SAINT [14] and empirical absorption corrections were performed using SADABS [15]. Both structures were solved by direct methods and refined against F^2 by full-matrix least-squares using the SHELXTL package [16]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms in the two complexes were generated geometrically. The crystallographic data for the complexes are summarized in table 1. Selected bond lengths and angles are listed in table 2.

2.6. *Urease inhibitory tests*

The measurement of urease inhibitory properties was carried out according to the method provided in [17]. The assay mixture, containing 25 µL of *jack bean* urease (10 kU L^{-1}) and 25 µL of the test materials of various concentrations (dissolved in

Table 1. Crystal data for **1** and **2**.

Complex	**1**	**2**
Formula	$C_{11}H_{13}BrClCuN_5O$	$C_{13}H_{16}BrClN_2O_3Zn$
Molecular weight	410.2	429.0
Crystal shape/color	Block/Blue	Block/Colorless
Crystal size (mm^3)	0.32 × 0.30 × 0.30	0.35 × 0.33 × 0.32
Crystal system	Monoclinic	Monoclinic
Space group	P_21/c	Cc
Unit cell dimensions (Å, °)		
a	11.267(2)	13.162(3)
b	6.963(3)	36.981(2)
c	19.312(2)	9.245(3)
β	102.121(2)	133.941(3)
V (Å^3)	1481.3(7)	3240.2(13)
Z	4	8
λ (Mo-Kα) (Å)	0.71073	0.71073
T (K)	293(2)	293(2)
μ (Mo-Kα) (cm^{-1})	4.354	4.156
$T_{\min}$	0.336	0.324
$T_{\max}$	0.355	0.350
Reflections/parameters	3218/184	6763/385
Goodness-of-fit on F^2	1.044	1.024
R_{int}	0.0368	0.0374
R_1, wR_2 [$I 2\sigma(I)$][a]	0.0287, 0.0692	0.0426, 0.0954
R_1, wR_2 (all data)[a]	0.0423, 0.0744	0.0576, 0.1032

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

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

1			
Cu1–O1	1.925(2)	Cu1–N1	1.948(2)
Cu1–N2	2.066(2)	Cu1–N3	1.979(2)
Cu1···N3^{i}	2.729(2)		
O1–Cu1–N1	92.4(1)	O1–Cu1–N3	90.0(1)
N1–Cu1–N3	174.1(1)	O1–Cu1–N2	176.9(1)
N1–Cu1–N2	84.5(1)	N3–Cu1–N2	93.1(1)
O1–Cu1···N3^{i}	90.1(1)	N1–Cu1···N3^{i}	85.2(1)
N3–Cu1···N3^{i}	100.1(1)	N2–Cu1···N3^{i}	89.9(1)
2			
Zn1–O1	2.005(4)	Zn1–O3	1.993(4)
Zn1–O4^{ii}	2.024(4)	Zn1–N1	2.084(5)
Zn1–N2	2.256(5)	Zn2–O2	2.002(4)
Zn2–O5	2.015(4)	Zn2–O6^{ii}	2.022(4)
Zn2–N3	2.092(5)	Zn2–N4	2.238(5)
O3–Zn1–O1	100.23(2)	O3–Zn1–O4^{ii}	102.60(2)
O1–Zn1–O4^{ii}	91.25(2)	O3–Zn1–N1	140.35(2)
O1–Zn1–N1	86.75(2)	O4^{ii}–Zn1–N1	116.32(2)
O3–Zn1–N2	93.20(2)	O1–Zn1–N2	165.56(2)
O4^{ii}–Zn1–N2	90.97(2)	N1–Zn1–N2	79.5(2)
O2–Zn2–O5	98.62(2)	O2–Zn2–O6^{ii}	96.94(2)
O5–Zn2–O6^{ii}	102.79(2)	O2–Zn2–N3	86.92(2)
O5–Zn2–N3	154.44(2)	O6^{ii}–Zn2–N3	101.26(2)
O2–Zn2–N4	164.63(2)	O5–Zn2–N4	91.25(2)
O6^{ii}–Zn2–N4	92.29(2)	N3–Zn2–N4	79.22(2)

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

Table 3. Inhibitory properties against urease.

Tested materials	IC_{50} (μM)
1	13.0 ± 0.4
2	>100
HL1	>100
HL2	>100
Copper acetate	18.7 ± 0.2
Zinc acetate	>100
Sodium azide	>100
Acetohydroxamic acid	46.5 ± 0.3

DMSO : H_2O solution 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*′-[2-ethanesulfonic acid]) buffer at pH 6.8 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 micro-plate reader (570 nm) with the end-point determined by the color of the phenol red indicator. The results are listed in table 3.

3. Results and discussion

The air-stable Schiff base is an orange oil, soluble in common polar organic solvents, such as DMF, DMSO, methanol, ethanol, and acetonitrile. The elemental analyses are

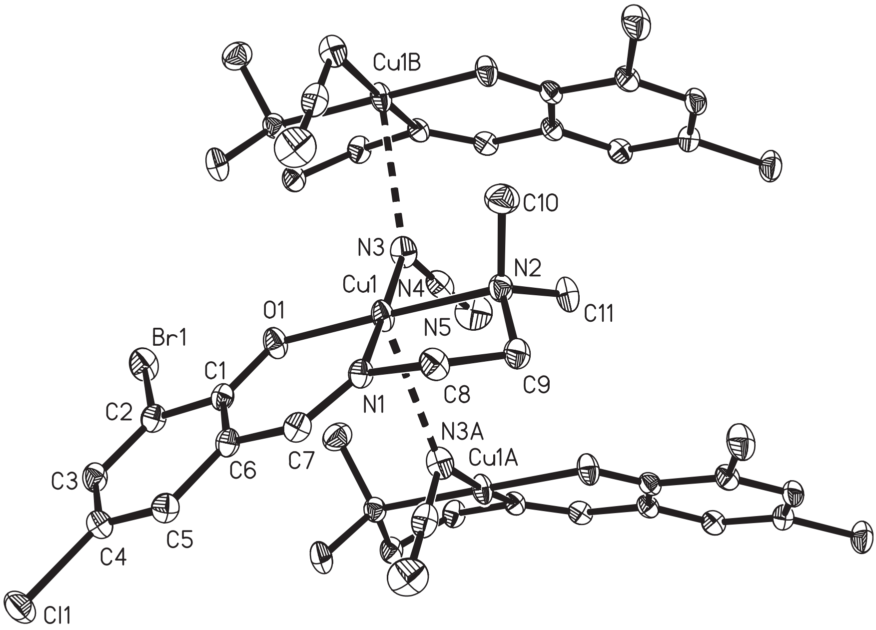


Figure 1. The structure of **1**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity. Weak apical coordinate bonds are shown as dashed lines.

in good agreement with the chemical formula proposed for the compounds. Both complexes are stable in air at room temperature and soluble in DMF, DMSO, methanol, ethanol, and acetonitrile.

The Schiff base ligand readily coordinates to the copper or zinc through the phenolate O, imine N, and amine N; azide or acetate coordinate to the remaining sites of the metals.

3.1. *Structure description of 1*

Complex **1** is an end-on azide-bridged polynuclear copper(II) complex (figure 1), which is structurally similar to the azide-bridged copper(II) complex with 4-bromo-2-[2-(dimethylamino)ethyliminomethyl]phenol [18]. The smallest repeat unit contains one CuL and one end-on bridging azide. The Cu is five-coordinate in a square-pyramidal geometry with the three donor atoms of the Schiff base ligand, a terminal N of a bridging azide defining the basal plane, and a different terminal N of another bridging azide occupying the apical position. The apical coordination is very weak, with bond length of 2.729(2) Å. The deviation of Cu1 from the best-fit square plane towards the apical position is 0.050(2) Å. The coordinate bond lengths are comparable with those previously reported in [18]. The Cu $\cdots$ Cu separation is 4.292(2) Å.

In the crystal structure, the CuL moieties are linked by the bridging azide groups, forming polymeric chains running along the *b*-axis. Adjacent chains are further linked by weak C5–H5 $\cdots$ N5^a [d(C5–H5) = 0.93 Å, d(H5 $\cdots$ N5) = 2.51(3) Å, d(C5 $\cdots$ N5) = 3.367(5) Å; symmetry code for a: $x, 3/2 - y, 1/2 + z$] interactions in the *c* direction into a sheet (figure 2).

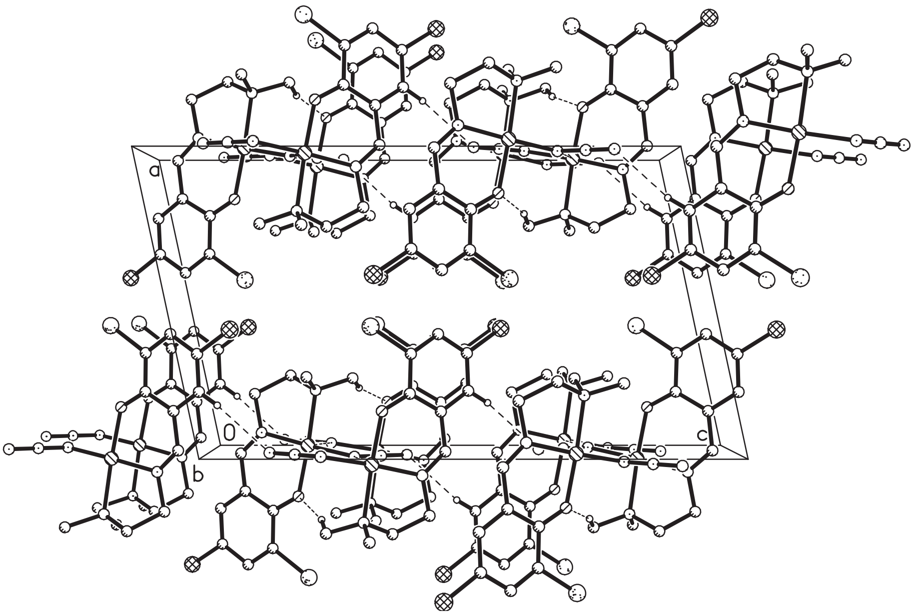


Figure 2. Molecular packing of **1**, viewed along the *b*-axis. Intermolecular C–H···N hydrogen bonds are shown as dashed lines.

3.2. *Structure description of 2*

Zinc is generally four or six coordinate, tetrahedral or octahedral. However, there are few reports of five-coordinate zinc complexes [19, 20] with distorted square-pyramidal or trigonal-bipyramidal geometries.

Complex **2** is a *syn–anti* μ_2-acetate-bridged polynuclear zinc(II) complex (figure 3). The smallest repeat unit contains one ZnL and a bidentate bridging acetate. Each Zn is five-coordinate in a square-pyramid with the three donor atoms of the Schiff-base ligand and one O of a bridging acetate defining the basal plane, and a different O of another bridging acetate occupying the apical position. The deviations of Zn1 and Zn2 from the best-fit square planes towards the apical positions are 0.346(2) and 0.303(2) Å, respectively. The coordinate bond lengths are comparable with those observed in similar Schiff-base zinc(II) complexes [19, 20]. The Zn···Zn separations are 4.760(2) and 4.627(2) Å, respectively.

Zn1 moieties are bridged by acetate groups, forming chains running along the *a*-axis, and the Zn2 moieties are bridged by acetate groups, forming chains running along the *c*-axis. The perpendicular chains are further linked by weak Br···Cl [$d(\mathrm{Br1}\cdots\mathrm{Cl2^b}) =$ 3.928(3) Å, $d(\mathrm{Br2}\cdots\mathrm{Cl1}) = 3.723(3)$ Å; symmetry code for b: $-1 + x, y, z$] interactions, forming a 3-D network (figure 4).

3.3. *IR spectra of 1 and 2*

The infrared spectra of the Schiff base and the two complexes provide information about the metal-ligand bonding. The weak and broad absorption band, observed for the Schiff base at 3323 cm^{-1}, is assigned to the stretching of the O–H bond, absent in the complexes. The strong absorption band at 1645 cm^{-1} for HL is assigned to the

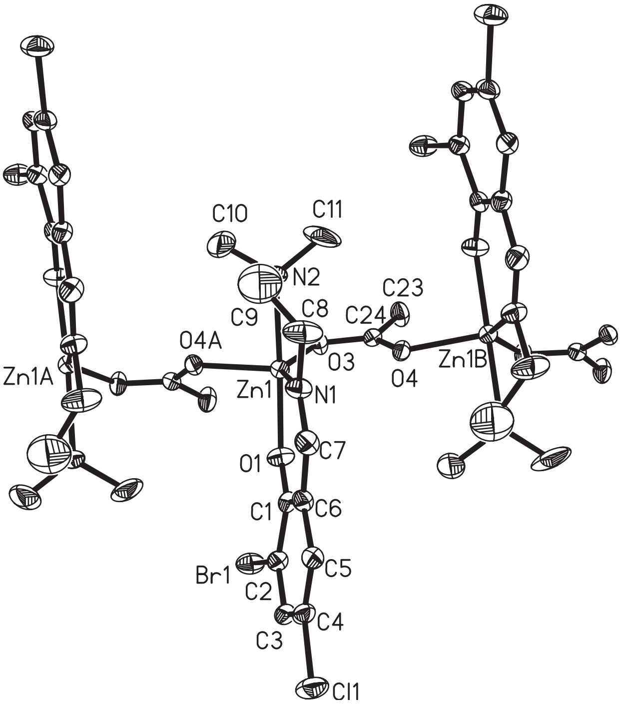


Figure 3. The structure of **2**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity.

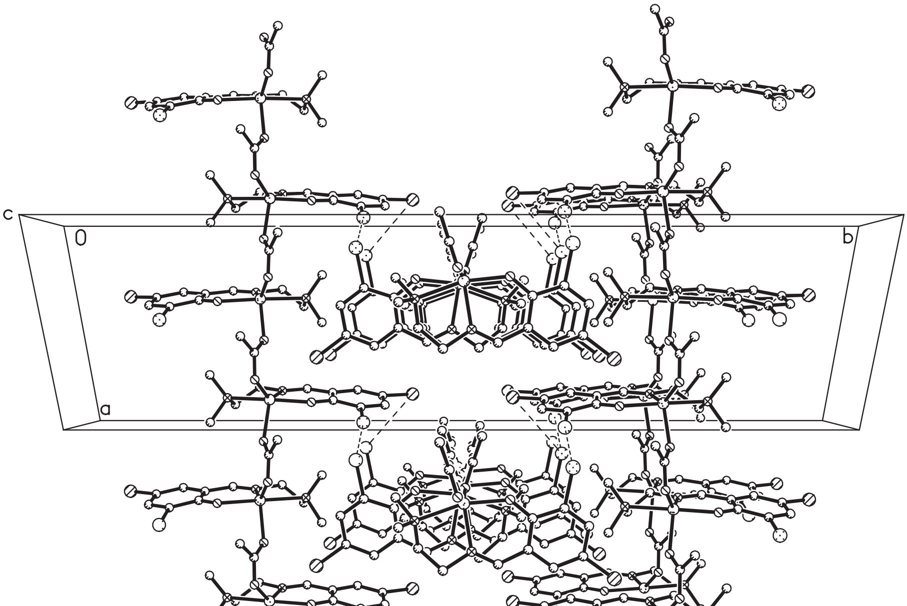


Figure 4. Molecular packing of **2**, viewed along the *c*-axis. Weak Br···Cl interactions are shown as dashed lines.

azomethine group, ν(C=N) [21]. This band shifts in the complexes to 1637 cm^{-1} for **1** and 1630 cm^{-1} for **2**, attributed to coordination of the imine N to the metal [22]. This conclusion is further supported by the presence of weak ν(M–N) at low wavenumbers, 578 cm^{-1} for **1** and 556 cm^{-1} for **2**. Weak bands indicative of formation of M–O are observed at 472 cm^{-1} for **1** and 443 cm^{-1} for **2** [23]. The strong absorption band at 2046 cm^{-1} for **1** is assigned to azide. Complex **2** exhibits the following important acetate infrared strong absorption bands: $\nu_{as}(CO_2)$ at 1553 and $\nu_{sym}(CO_2)$ at 1451 cm^{-1}. The separation between $\nu_{as}(CO_2)$ and $\nu_{sym}(CO_2)$ is 102 cm^{-1}, indicating bidentate acetate [24, 25]. The results of the infrared spectra agree with the single-crystal X-ray analysis.

3.4. *Urease inhibitory properties*

From table 3, we find that complex **1** exhibits strong urease inhibitory property, with the median inhibition concentration (IC_{50}) value being much lower than that of acetohydroxamic acid coassayed as a standard reference against urease. The zinc(II) complex, **2**, shows no urease inhibitory property. The urease inhibitory property of **1** is much stronger than those of the Schiff base and copper acetate. Since **1** contains azide, the urease inhibitory property of sodium azide was also tested, indicating no urease inhibitory property.

4. Conclusions

Schiff base copper(II) and zinc(II) complexes with azide or acetate co-ligands have been synthesized and their structures were characterized by single-crystal X-ray crystallography. The copper(II) complex shows strong urease inhibitory property, while there is none for the zinc(II) complex.

Supplementary material

Crystallographic data for both complexes have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos 713677 and 713678).

Acknowledgements

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