

Scientific paper

Syntheses, Characterization and Crystal Structures of Dicyanamide Bridged Polynuclear Copper(II) and Zinc(II) Complexes with Urease Inhibitory Activity

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Abstract

A pair of structurally similar dicyanamide bridged copper(II) and zinc(II) complexes $[\text{CuL}(\text{dca})]_n$ (**1**) and $[\text{ZnL}(\text{dca})]_n$ (**2**), were prepared from the fluorine containing Schiff base 5-fluoro-2-(((2-hydroxyethyl)imino)methyl)phenol (HL). The compounds were characterized by physico-chemical methods. Structures of the complexes were confirmed by single crystal X-ray diffraction. The Cu atom in complex **1** is in square pyramidal coordination, whereas the Zn atom in complex **2** is in trigonal bipyramidal coordination. The copper complex has effective *Jack bean* urease inhibitory activity, with IC_{50} value of $0.14 \pm 0.12 \mu\text{mol L}^{-1}$.

Keywords: Schiff base; copper and zinc complexes; crystal structure; urease inhibition

1. Introduction

Schiff bases derived from salicylaldehyde and its analogues with various primary amines represent indispensable ligands in coordination chemistry because of their diversified coordination modes with a large number of inorganic salts.¹ Schiff bases as interesting chemotherapeutic agents have received considerable attention in recent years. Schiff base complexes have interesting pharmaceutical applications such as antifungal, antitumor, antibacterial and bio-modeling techniques.²

Urease (amidohydrolase; EC 3.5.1.5) is a nickel-containing enzyme that catalyzes the hydrolysis of urea to NH_3 and CO_2 . The catalyzed reaction rate is about 10^{14} times faster than the uncatalyzed. Urease enzyme is widely found in fungi, bacteria and plants.³ The high efficiency of urease increased the hydrolysis of urea into NH_3 , which leads to severe toxicity in air and disgusting economic damages.⁴ In human, urease may produce several health concerns including hepatic coma, pyelonephritis, gastric and peptic ulcer.⁵ In recent years, various kinds of

urease inhibitors such as dithiobisacetamides, thioureas, thiosemicarbazides, hydroxamic acids are reported in the fields of medicine.⁶ However, most of them are not applicable due to the low efficiency and side effects. Therefore, it is of great interest to explore new urease inhibitors. Some Schiff bases have been reported to have urease inhibitory activities.⁷ Our research group has pioneered the work on urease inhibitors with complexes derived from Schiff bases, and found that some copper, nickel, and zinc complexes have effective activities.⁸ Schiff bases with halide groups are reported to have enhanced urease inhibitory activity.⁹ Xiao and coworkers reported that the introduction of fluorine atom in the hydroxamic acid compounds can increase their urease inhibitory activities.¹⁰ In addition, dicyanamide anion is an interesting ligand in coordination chemistry, which can lead to the formation of metal complexes with versatile structures.¹¹ In order to construct new structures of dicyanamide bridged complexes, and explore new urease inhibitors, two copper(II) and zinc(II) complexes, $[\text{CuL}(\text{dca})]_n$ (**1**) and $[\text{ZnL}(\text{dca})]_n$ (**2**), were prepared from

the fluorine containing Schiff base 5-fluoro-2-(((2-hydroxyethyl)imino)methyl)phenol (HL).

2. Experimental

2.1. Materials and Measurements

4-Fluorosalicylaldehyde and 2-aminoethanol were purchased from TCI Inc. (Japan). Other reagents and solvents were obtained from Xiya Reagent Company of China. *Jack bean* urease was purchased from Sigma-Aldrich. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. IR spectra were recorded on a Jasco FT/IR-4000 spectrometer as KBr pellets in the 4000–400 cm^{-1} region. UV-Vis spectra were recorded on a Perkin-Elmer Lambda 900 spectrometer. Conductivity measurements were performed using a Metrohm 712 conductometer at 25 °C. The urease inhibitory activity was measured on a Bio-Tek Synergy HT microplate reader. Single crystal structures were determined by Bruker D8 Venture single crystal diffraction.

2.2. Synthesis of HL and the Complexes

2.2.1. 5-Fluoro-2-(((2-hydroxyethyl)imino)methyl)phenol (HL)

4-Fluorosalicylaldehyde (0.010 mol, 1.4 g) and 2-aminoethanol (0.010 mol, 0.61 g) were mixed in methanol (30 mL). The mixture was stirred for 30 min at reflux. The solvent was evaporated by distillation to give yellow solid, which was recrystallized from ethanol to give yellow crystalline product. The product was washed three times with cold ethanol and dried in air. Yield: 1.5 g (82%). Characteristic IR data (KBr, cm^{-1}): 3372 (OH), 1635 (C=N). UV-Vis data (methanol, λ/nm): 230, 335. Anal. Calcd for $\text{C}_9\text{H}_{10}\text{FNO}_2$: C, 59.01; H, 5.50; N, 7.65. Found: C, 58.87; H, 5.58; N, 7.73%.

2.2.2. *catena*-(μ_2 -Dicyanamide)(5-fluoro-2-(((2-hydroxyethyl)imino)methyl)phenolate)copper(II) (1)

The Schiff base HL (1.0 mmol, 0.18 g) was dissolved in methanol (20 mL), to which was added dropwise $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (1.0 mmol, 0.24 g) and $\text{NaN}(\text{CN})_2$ (1.0 mmol, 0.089 g) dissolved in methanol (20 mL). The mixture was stirred for 20 min at room temperature. The filtrate was kept in air for a few days, to form deep blue crystals suitable for single crystal X-ray diffraction. The isolated crystals were washed three times with cold methanol and dried in air. Yield: 0.17 g (55%). Characteristic IR data (KBr, cm^{-1}): 3438 (OH), 2304, 2243, 2175 ($\text{N}(\text{CN})_2$), 1648 (C=N). UV-Vis data (methanol, λ/nm): 270, 352. Anal. Calcd for $\text{C}_{11}\text{H}_9\text{CuFN}_4\text{O}_2$: C, 42.38; H, 2.91; N, 17.97. Found: C, 42.51; H, 3.02; N, 17.83%. Λ_M (10^{-3} mol L^{-1} in methanol): 35 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$.

2.2.3. *catena*-(μ_2 -Dicyanamide)(5-fluoro-2-(((2-hydroxyethyl)imino)methyl)phenolate)zinc(II) (2)

The zinc complex was prepared with the same method as described for the copper complex, but with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ replaced with $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (1.0 mmol, 0.30 g). Colorless block shaped crystals suitable for single crystal X-ray diffraction were obtained after 5 days. Yield: 0.20 g (64%). Characteristic IR data (KBr, cm^{-1}): 3420 (OH), 2341, 2273, 2199 ($\text{N}(\text{CN})_2$), 1643 (C=N). UV-Vis data (methanol, λ/nm): 272, 345. Anal. Calcd for $\text{C}_{11}\text{H}_9\text{FN}_4\text{O}_2\text{Zn}$: C, 42.13; H, 2.89; N, 17.87. Found: C, 42.02; H, 2.97; N, 17.75%. Λ_M (10^{-3} mol L^{-1} in methanol): 28 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$.

2.3. X-ray Crystallography

Diffraction intensities for the complexes were collected at 298(2) K using a Bruker D8 Venture diffractometer with MoK α radiation ($\lambda = 0.71073$ Å). The collected data were reduced with SAINT,¹² and multi-scan absorption correction was performed using SADABS.¹³ Structures of the complexes were solved by direct methods and refined against F^2 by full-matrix least-squares method using SHELXTL.¹⁴ All of the non-hydrogen atoms were refined anisotropically. The hydroxyl H atoms of the Schiff base ligands in the complexes were located from difference Fourier maps and refined isotropically, with O–H distances restrained to 0.85(1) Å. The remaining hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. Crystallographic data for the complexes are summarized in Table 1.

Table 1 Crystal data for the complexes

	1	2
Formula	$\text{C}_{11}\text{H}_9\text{CuFN}_4\text{O}_2$	$\text{C}_{11}\text{H}_9\text{FN}_4\text{O}_2\text{Zn}$
FW	311.76	313.59
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
<i>a</i> (Å)	7.6028(11)	7.5125(9)
<i>b</i> (Å)	15.340(2)	10.8296(12)
<i>c</i> (Å)	10.6785(15)	16.1164(19)
α (°)	90	90
β (°)	91.869(2)	94.623(2)
γ (°)	90	90
<i>V</i> (Å ³)	1244.7(3)	1306.9(3)
<i>Z</i>	4	4
<i>T</i> (K)	298(2)	298(2)
μ (MoK α) (cm^{-1})	1.770	1.894
Reflections/parameters	7343/175	6740/175
Unique reflections	2321	2425
Observed reflections	2055	2016
[$I > 2\sigma(I)$]		
Restraints	1	1
Goodness of fit on F^2	1.059	1.051
R_1, wR_2 [$I > 2\sigma(I)$]	0.0356, 0.0952	0.0309, 0.0826
R_1, wR_2 (all data)	0.0405, 0.0985	0.0393, 0.0870

2. 4. Urease Inhibitory Activity Assay

The measurement of urease inhibitory activity was carried out according to the literature method.¹⁵ The compounds (0.100 mmol) and the reference drug acetohydroxamic acid, as well as copper and zinc perchlorate were first dissolved by 5.0 mL DMSO, then diluted to 1.0 L by distilled water. The assay mixture containing 75 μL of *Jack bean* urease and 75 μL of tested compounds with various concentrations (100 $\mu\text{mol L}^{-1}$, 50 $\mu\text{mol L}^{-1}$, 25 $\mu\text{mol L}^{-1}$, 12.5 $\mu\text{mol L}^{-1}$, 6.25 $\mu\text{mol L}^{-1}$, 3.12 $\mu\text{mol L}^{-1}$, 1.56 $\mu\text{mol L}^{-1}$, 0.78 $\mu\text{mol L}^{-1}$) pre-incubated for 15 min on a 96-well assay plate. Then 75 μL of phosphate buffer at pH 6.8 containing phenol red (0.18 mmol L^{-1}) and urea (400 mmol L^{-1}) were added and incubated at room temperature. The reaction time required for enough ammonium carbonate to form to raise the pH phosphate buffer from 6.8 to 7.7 was measured by micro-plate reader (560 nm) with end-point being determined by the color change of phenol-red indicator.

3. Results and Discussion

3. 1. Chemistry

The Schiff base HL was facile synthesized from 4-fluorosalicylaldehyde with 2-aminoethanol in methanol. The complexes **1** and **2** (Scheme 1) were synthesized according to the similar method from the Schiff base, sodium dicyanamide with copper nitrate and zinc nitrate, respectively, in methanol. If copper or zinc nitrate was replaced with chloride or bromide salt, the same structures for the complexes can be obtained. Molar conductivities of the complexes in methanol are within the normal values 20–40 $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$, indicate their non-electrolytic nature.¹⁶

3. 2. Structure Description of the Complexes

Complex 1

Molecular structure of the polymeric copper complex **1** is shown in Figure 1. Selected bond lengths and

angles are given in Table 2. The smallest repeat unit of the complex contains $[\text{CuL}(\text{N}(\text{CN})_2)]$, which is bridged by dicyanamide ligands to form one dimensional chain structure. The Cu atom is in square pyramidal geometry, with the phenolate oxygen (O1), imino nitrogen (N1) and hydroxyl oxygen (O2) atoms of the Schiff base ligand, and the N2 atom of the dicyanamide ligand located at the basal plane, and with the N4A (symmetry code for A: $-1 + x, y, z$) atom of the symmetry related dicyanamide ligand located at the apical position. The Cu atom deviates from the least-squares plane defined by the four basal donor atoms by 0.250(1) Å. The coordination geometry can be defined as distorted square pyramid because the structural index τ value is 0.30.¹⁷ The bond lengths of the Cu–O (1.9271(19)–2.035(2) Å) and Cu–N (1.937(2)–1.977(2) Å) in the basal plane of the complex are comparable to those observed in the copper(II) complexes with Schiff base ligands.¹⁸

In the crystal structure of complex **1**, the $[\text{CuL}]$ units are linked by dicyanamide ligands, to form one dimensional chain structure along the a axis. The chains are

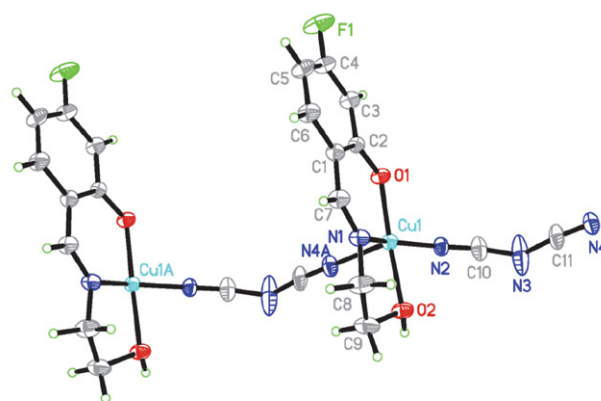
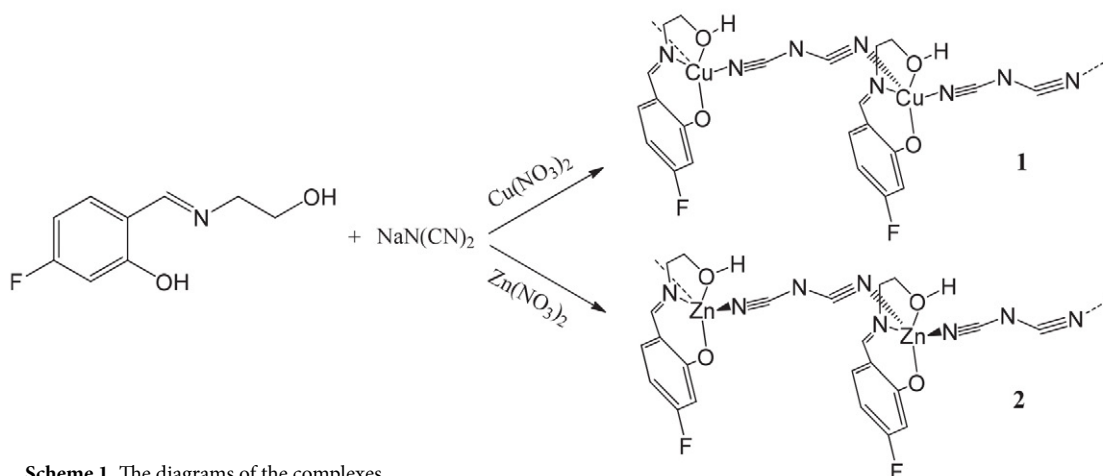


Figure 1. Molecular structure of **1**, showing the atom-numbering scheme. Displacement ellipsoids for non-hydrogen atoms are drawn at 30% probability level. Atoms labeled with the suffix A are related to the symmetry operation $-1 + x, y, z$.



Scheme 1. The diagrams of the complexes.

further linked through intermolecular hydrogen bonds of O–H...O hydrogen bonds ($O2-H2 = 0.85(1) \text{ \AA}$, $H2...O1^i = 1.90(1) \text{ \AA}$, $O2...O1^i = 2.734(3) \text{ \AA}$, $O2-H2...O1^i = 170(4)^\circ$, symmetry code for $i: \frac{1}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z$), to form two-dimensional network along the ac plane (Figures 2 and 3).

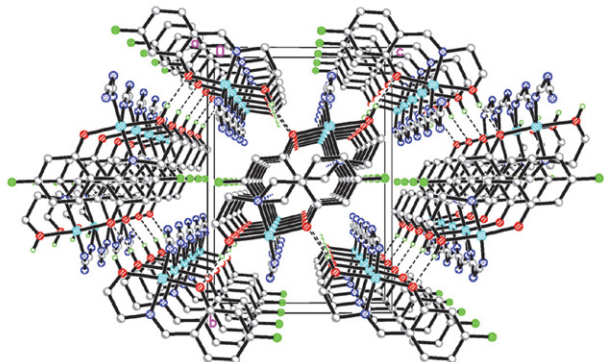


Figure 2. Molecular packing diagram of **1**, viewed along the a axis. Hydrogen bonds are shown as dashed lines.

Table 2 Selected bond lengths (\AA) and angles ($^\circ$) for the complexes

	1	2
M1–N1	1.937(2)	2.002(2)
M1–N2	1.977(2)	2.016(2)
M1–O1	1.927(2)	1.988(2)
M1–O2	2.035(2)	2.246(2)
M1–N4A	2.249(3)	1.993(2)
O1–M1–N1	93.95(9)	92.26(8)
O1–M1–N2	92.28(9)	96.06(10)
N1–M1–N2	155.31(11)	120.66(10)
O1–M1–O2	173.23(8)	169.53(8)
N1–M1–O2	81.51(9)	77.28(9)
N2–M1–O2	89.87(10)	89.21(10)
O1–M1–N4A	95.48(10)	98.15(10)
N1–M1–N4A	101.08(11)	128.85(9)
N2–M1–N4A	102.06(10)	107.86(10)
O2–M1–N4A	90.34(10)	88.78(10)

M = Cu for **1**, Zn for **2**.

Complex 2

Molecular structure of the polymeric zinc complex **2** is shown in Figure 4. The smallest repeat unit of the complex contains $[\text{ZnL}(\text{N}(\text{CN})_2)]$, which is bridged by dicyanamide ligands to form one dimensional chain structure. The Zn atom is in trigonal bipyramidal geometry, with the imino nitrogen (N1) atom of the Schiff base ligand, and two nitrogen (N2 and N4A, symmetry code for A: $-1 + x, y, z$) atoms from two dicyanamide ligands located at the equatorial plane, and with the phenolate oxygen (O1) and hydroxyl oxygen (O2) atoms of the Schiff base ligand located at the axial positions. The Zn atom deviates from the

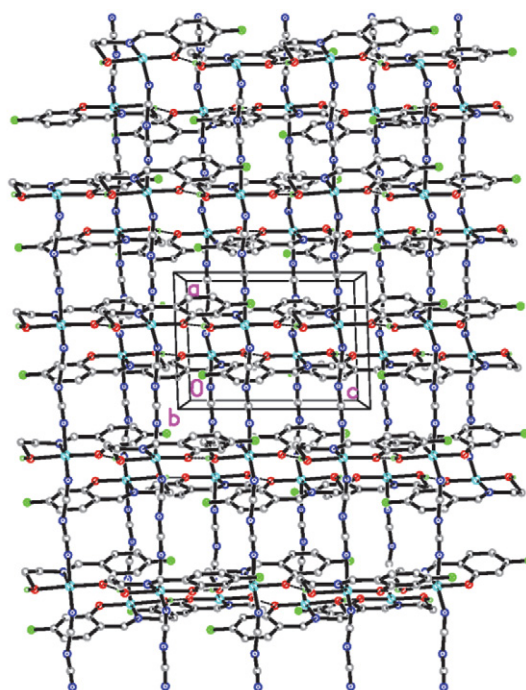


Figure 3. Molecular packing diagram of **1**, viewed along the b axis. Hydrogen bonds are shown as dashed lines.

least-squares plane defined by the three equatorial donor atoms by $0.187(1) \text{ \AA}$. The coordination geometry can be defined as distorted trigonal bipyramid because the structural index τ value is 0.68.¹⁷ The bond lengths of the Zn–O ($1.988(2)$ – $2.247(2) \text{ \AA}$) and Zn–N ($1.993(2)$ – $2.016(2) \text{ \AA}$) of the complex are comparable to those observed in the zinc(II) complexes with Schiff base ligands.¹⁹

In the crystal structure of complex **1**, the $[\text{ZnL}]$ units are linked by dicyanamide ligands, to form one dimensional chain structure along the a axis. The chains are

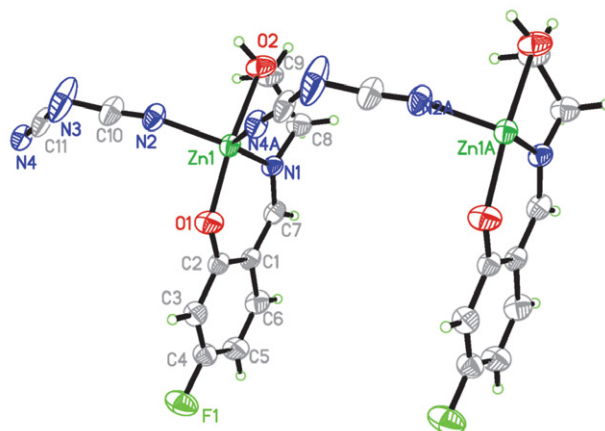


Figure 4. Molecular structure of **2**, showing the atom-numbering scheme. Displacement ellipsoids for non-hydrogen atoms are drawn at 30% probability level. Atoms labeled with the suffix A are related to the symmetry operation $-1 + x, y, z$.

further linked through intermolecular hydrogen bonds of O–H...O hydrogen bonds (O2–H2 = 0.85(1) Å, H2...O1ⁱ = 1.91(1) Å, O2...O1ⁱ = 2.714(3) Å, O2–H2...O1ⁱ = 161(4)°, symmetry code for i: $-x, -1 - y, -z$) along the *b* axis, to form two-dimensional network along the *ab* plane (Figures 5 and 6).

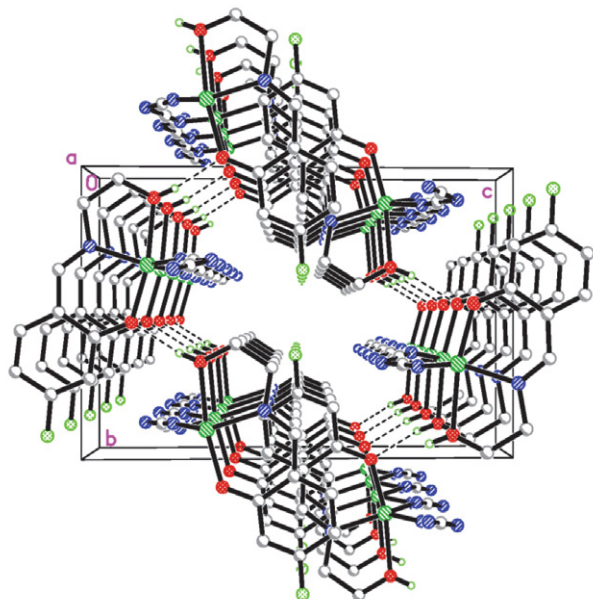


Figure 5. Molecular packing diagram of **2**, viewed along the *a* axis. Hydrogen bonds are shown as dashed lines.

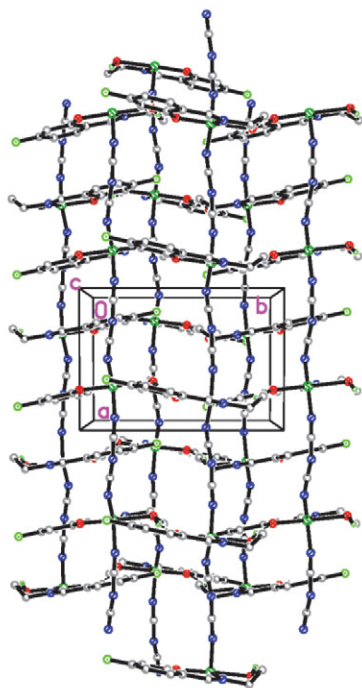


Figure 6. Molecular packing diagram of **2**, viewed along the *c* axis. Hydrogen bonds are shown as dashed lines.

3. 3. IR and UV-Vis Spectra

The weak bands centered at 3438 and 3420 cm^{-1} in complexes **1** and **2**, respectively, are assigned to $\nu(\text{O-H})$. The intense absorption bands at 2304, 2243 and 2175 cm^{-1} in **1**, and 2341, 2273 and 2199 cm^{-1} in **2**, are assigned to the stretching vibrations of dicyanamide ligands.²⁰ Strong absorptions at 1648 cm^{-1} in **1** and 1643 cm^{-1} in **2** are assigned to azomethine groups, $\nu(\text{C=N})$.^{20b} The phenolic $\nu(\text{Ar-O})$ appear at 1288 cm^{-1} in **1** and 1301 cm^{-1} in **2**. The weak bands in the range of 400–600 cm^{-1} for the complexes can be assigned to $\nu(\text{M-O})$.²¹

The electronic spectra of the complexes were determined with methanol as solvent. The spectra of the complexes reveal intense absorption bands at 270–272 nm are assigned to $n-\pi^*$ transition of the azomethine groups. The bands observed at 340–360 nm in the spectra of the complexes are assigned to ligand to metal charge transfer transitions.²²

3. 4. Urease Inhibitory Activity Assay

The results of the inhibition assays against the urease for the synthetic compounds are listed in Table 3. The copper complex has good inhibitory activity on urease with IC_{50} value of $0.14 \pm 0.12 \mu\text{mol L}^{-1}$, whereas the zinc complex has no activity. The copper complex show better activity than the reference drug acetohydroxamic acid ($\text{IC}_{50} = 37.2 \pm 4.0 \mu\text{mol L}^{-1}$). Both the copper and zinc complexes have better activities than copper and zinc perchlorate. Thus, the copper complex would be a potential urease inhibitor that deserves further study on the treatment of diseases like hepatic coma, pyelonephritis, gastric and peptic ulcer, as well as on the application in the nitrogen containing fertilizer.

Table 3 Inhibition of urease by the tested materials

Tested materials	Percentage Inhibition rate [#]	IC_{50} ($\mu\text{mol L}^{-1}$)
HL	–	> 100
1	99 ± 2.1	0.14 ± 0.12
2	33 ± 1.8	3.4 ± 1.6
Copper perchlorate	87.5 ± 2.6	8.8 ± 1.4
Zinc perchlorate	–	> 100
Acetohydroxamic acid	85.5 ± 3.9	28.1 ± 3.6

[#] The concentration of the tested material is 100 $\mu\text{mol L}^{-1}$.

– indicates no activity.

4. Conclusion

This work reports the syntheses, characterization and crystal structures of two new dicyanamide bridged copper and zinc complexes with fluorine containing Schiff base 5-fluoro-2-(((2-hydroxyethyl)imino)methyl)phenol.

The copper complex has effective urease inhibitory activity. The results indicated that the copper complex can be further optimized and developed as a prospective lead urease inhibitor.

Supplementary data

CCDC 2170031 (1) and 2170032 (2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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Povzetek

Sintetizirali smo dva strukturno sorodna bakrova(II) in cinkova(II) kompleksa z dicianamidnim mostovnim ligandom, [CuL(dca)]_n (**1**) in [ZnL(dca)]_n (**2**), z vezavo fluor vsebujoče Schiffove baze 5-fluoro-2-(((2-hidroksietil)imino)metil) fenol (HL). Spojini smo okarakterizirali s fizikalno-kemijskimi metodami. Strukturi kompleksov smo določili z monokristalno rentgensko difrakcijo. V kompleksu **1** je atom Cu koordiniran kvadratno piramidalno, medtem ko je atom Zn v kompleksu **2** koordiniran trigonalno bipiramidalno. Bakrov kompleks učinkovito zavira ureazo stročnice *Canavalia ensiformis* z vrednostjo IC₅₀ 0,14 ± 0,12 μmol L⁻¹.



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