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Synthesis, Crystal Structures, and Urease Inhibitory Activity of Cooper(II) Complexes with Schiff Bases[1]

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Abstract—A new end-to-end thiocyanato-bridged polynuclear copper(II) complex, $[Cu(CP)(\mu_{1,3}\text{-}NCS)]_n \cdot n$MeOH (I), and a new mononuclear copper(II) complex, $[Cu(MP)(ONO_2)(OH_2)]$ (**II**) (CP = 4-chloro-2-[(pyridin-2-ylmethylimino)methyl]phenolate, MP = 5-methoxy-2-[(pyridin-2-ylmethylimino)methyl]phenolate), were prepared and structurally characterized by elemental analyses, infrared spectroscopy, and single-crystal X-ray diffraction. The crystal of **I** is orthorhombic: space group *Pbca*, a = 10.6161(16) Å, b = 16.340(3) Å, c = 18.840(3) Å, V = 3268.0(9) Å^3, Z = 8. The crystal of II is triclinic: space group $P\bar{1}$, a = 7.5645(2), b = 8.9811(2), c = 11.9412(3) Å, α = 74.4610(10)°, β = 80.5040(10)°, γ = 71.0940(10)°, V = 736.71(3) Å^3, Z = 2. The Cu atoms in the complexes are in square-pyramidal coordination. The biological test shows that both complexes have strong urease inhibitory activity.

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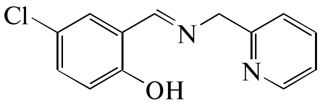
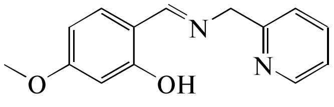
INTRODUCTION

During the last few years, there has been a great effort to identify the biological role of copper, primarily through techniques associated with the interface of biology, biochemistry, and coordination chemistry [1–3]. It appears that the biological role of copper is primarily in redox reactions and as a biological catalyst, although much remains to be understood [4, 5]. An extensive effort has been made to prepare and characterize a variety of copper(II) complexes in an attempt to model the physical and chemical behavior of copper-containing enzymes [6]. The peculiarity of copper lies in its ability to form complexes with coordination numbers four, five, and six [7–9]. Urease is an important class of enzyme involved in the degradative processing of urea [10–12]. They are ubiquitous in nature and directly associated with the formation of infection stones and contribute to 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 [13, 14]. Therefore, urease inhibitors have recently attracted much attention as potential new anti-ulcer drugs. A recent research indicated that the Schiff base complexes, especially for the copper(II) complexes, had potent urease inhibitory activity [15, 16]. As a further study of the urease inhibitors, in this paper, two new copper(II) complexes, $[Cu(CP)([Cu(CP)(\mu_{1,3}\text{-}NCS)]_n \cdot n$MeOH (**I**) and $[Cu(MP)(ONO_2)(OH_2)]$ (**II**), where CP and MP are the new Schiff bases 4-chloro-2-[(pyridin-2-ylmethylimino)methyl]phenolate and 5-methoxy-2-[(pyridin-2-ylmethylimino)methyl]phenolate, respectively, were prepared and structurally characterized. The urease inhibitory activities of the complexes were determined.



(CP)



(MP)

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 FT-IR spectrophotometer in the

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

Parameter	Value	
	I	**II**
M	399.3	384.8
Crystal shape/color	Block/blue	Block/blue
Crystal size, mm	0.32 × 0.32 × 0.30	0.23 × 0.20 × 0.20
Crystal system	Orthorhombic	Triclinic
Space group	*Pbca*	$P\bar{1}$
a, Å	10.6161(16)	7.5645(2)
b, Å	16.340(3)	8.9811(2)
c, Å	18.840(3)	11.9412(3)
α, deg	90	74.4610(10)
β, deg	90	80.5040(10)
γ, deg	90	71.0940(10)
V, Å^3	3268.0(9)	736.71(3)
Z	8	2
μ_{Mo}, mm^{-1}	1.639	1.521
T_{min}	0.622	0.721
T_{max}	0.639	0.756
Reflections/parameters	19044/210	4448/224
Independent reflections	3560	3104
Observed reflections	2614	2556
Restraints	0	3
F(000)	1624	394
Goodness-of-fit on F^2	1.009	1.022
R_1, wR_2 ($I \geq 2\sigma(I)$)*	0.0369, 0.0890	0.0348, 0.0766
R_1, wR_2 (all data)*	0.0585, 0.1021	0.0471, 0.0830

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

range 4000–400 cm^{-1}. Conductance measurements were performed using a DDS-307 conductivity meter.

Synthesis of CP

A methanolic solution (10 ml) of 2-aminomethylpyridine (1.0 mmol, 108.2 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 was washed with methanol and dried in air. The yield was 96%.

For $C_{13}H_{11}N_2OCl$

anal. calcd., %:	C, 63.3;	H, 4.5;	N, 11.4.
Found, %:	C, 63.0;	H, 4.6;	N, 11.3.

Synthesis of MP

A methanolic solution (10 ml) of 2-aminomethylpyridine (1.0 mmol, 108.2 mg) was added with stir-

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

Bond	d, Å	Bond	d, Å
		I	
Cu(1)–O(1)	1.919(2)	Cu(1)–N(1)	1.947(2)
Cu(1)–N(2)	2.015(3)	Cu(1)–N(3)	1.962(3)
Cu(1)–S(1)^i	2.7944(11)		
		II	
Cu(1)–O(1)	1.8917(17)	Cu(1)–N(1)	1.926(2)
Cu(1)–N(2)	1.982(2)	Cu(1)–O(3)	1.9851(18)
Cu(1)–O(4)	2.601(2)		
Angle	**ω, deg**	**Angle**	**ω, deg**
		I	
O(1)Cu(1)N(1)	92.85(10)	O(1)Cu(1)N(3)	90.41(10)
N(1)Cu(1)N(3)	161.96(11)	O(1)Cu(1)N(2)	173.24(10)
N(1)Cu(1)N(2)	82.36(10)	N(3)Cu(1)N(2)	92.71(11)
O(1)Cu(1)S(1)^i	91.51(7)	N(1)Cu(1)S(1)^i	100.24(7)
N(3)Cu(1)S(1)^i	97.40(9)	N(2)Cu(1)S(1)^i	94.04(8)
		II	
O(1)Cu(1)N(1)	93.73(8)	O(1)Cu(1)N(2)	176.14(8)
N(1)Cu(1)N(2)	83.17(9)	O(1)Cu(1)O(3)	88.38(7)
N(1)Cu(1)O(3)	172.67(8)	N(2)Cu(1)O(3)	94.41(8)
O(1)Cu(1)O(4)	102.48(8)	N(1)Cu(1)O(4)	104.68(8)
N(2)Cu(1)O(4)	80.59(8)	O(3)Cu(1)O(4)	81.67(8)

* Symmetry code: ^{i} $-1/2 + x$, $3/2 - y$, $1 - z$.

Table 3. Geometric parameters of hydrogen bond for complexes **I** and **II***

Contact D–H···A	Distance, Å			Angle D–H···A, deg
	D–H	H···A	D···A	
		I		
O(2)–H(2)···O(1)	0.82	2.00	2.806(4)	168
		II		
O(3)–(3*B*)···N(3)^{ii}	0.84(3)	2.67(2)	3.431(3)	150(3)
O(3)–(3*B*)···O(5)^{ii}	0.84(3)	1.873(11)	2.714(3)	174(4)
O(3)–(3*A*)···O(1)^{ii}	0.84(4)	1.86(4)	2.692(3)	168(4)

* Symmetry code: ^{ii} $1 - x$, $1 - y$, $1 - z$.

ring to a methanolic solution (20 ml) of 4-methoxysalicylaldehyde (1.0 mmol, 152.2 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 was washed with methanol and dried in air. The yield was 92%.

For $C_{14}H_{14}N_2O_2$

anal. calcd., %:	C, 69.4;	H, 5.8;	N, 11.6.
Found, %:	C, 69.6;	H, 5.8;	N, 11.5.

*Synthesis of **I***

A methanolic solution (5 ml) of $Cu(NO_3)_2 \cdot 3H_2O$ (0.1 mmol, 24.2 mg) was added with stirring to a methanolic solution (10 ml) of CP (0.1 mmol, 24.7 mg) and ammonium thiocyanate (0.1 mmol, 7.6 mg). The mixture was stirred for 30 min at room temperature and filtered. Upon keeping the filtrate in air for few days, blue block-shaped crystals of **I**, suitable for X-ray single-crystal diffraction, were formed on the bottom of the vessel. The crystals were collected

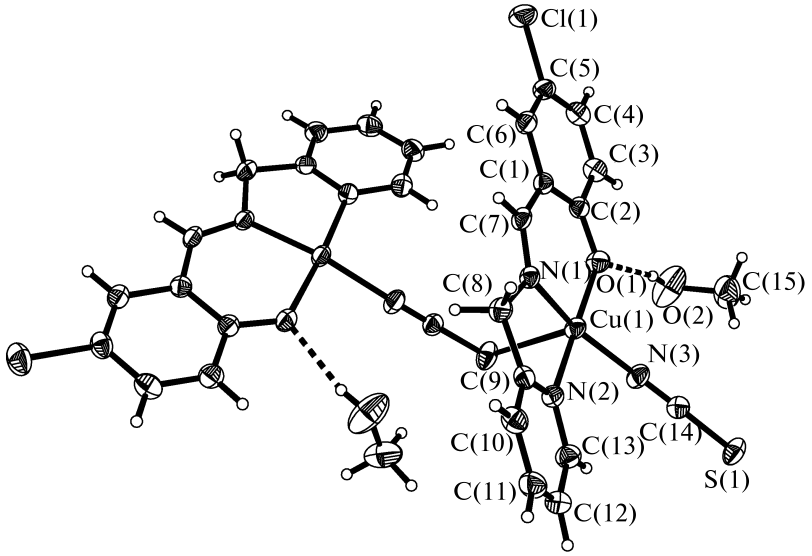

Fig. 1. Molecular structure of **I** at 30% ellipsoid. Hydrogen bonds are shown as dashed lines.

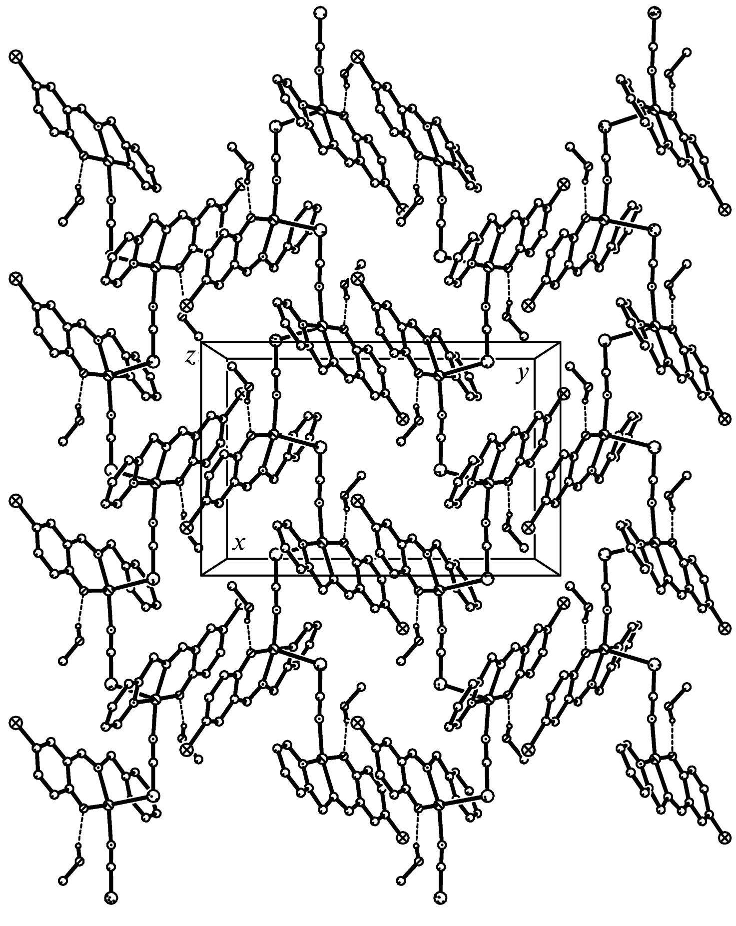

Fig. 2. Molecular packing diagram of **I**. Hydrogen bonds are shown as dashed lines.

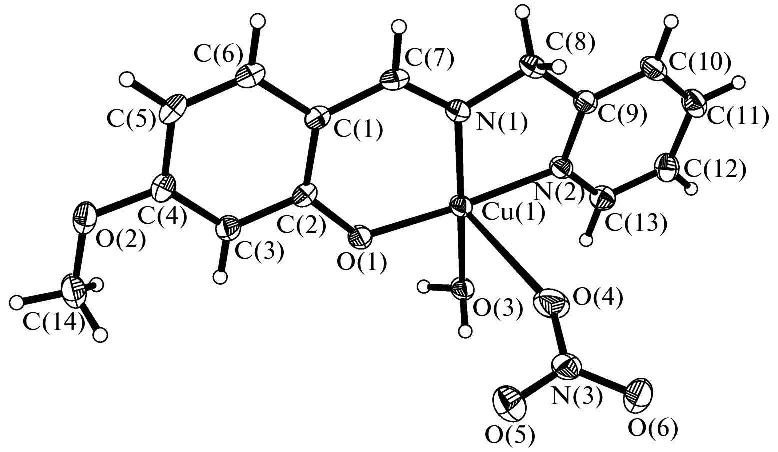

Fig. 3. Molecular structure of **II** at 30% ellipsoid. Hydrogen bonds are shown as dashed lines.

by filtration, washed three times with cold methanol, and dried in air. The yield was 53% based on CP.

For $C_{15}H_{14}N_3O_2SClCu$

anal. calcd., %:	C, 45.1;	H, 3.5;	N, 10.5.
Found, %:	C, 45.4;	H, 3.7;	N, 10.3.

Synthesis of II

A methanolic solution (5 ml) of $Cu(NO_3)_2 \cdot 3H_2O$ (0.1 mmol, 24.2 mg) was added with stirring to a methanolic solution (10 ml) of MP (0.1 mmol, 24.2 mg). The mixture was stirred for 30 min at room temperature and filtered. Upon keeping the filtrate in air for few days, blue 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 72% based on MP.

For $C_{14}H_{15}N_3O_6Cu$

anal. calcd., %:	C, 43.7;	H, 3.9;	N, 10.9.
Found, %:	C, 43.4;	H, 4.1;	N, 11.0.

X-ray 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 [17]. SAINT was used for integration of the intensity of reflections and scaling [17], SADABS was used for absorption correction [18], and SHELXTL was applied for space group and structure determination and least-squares refinements on F^2 [19]. All non-hydrogen atoms were refined anisotropically. The water H atoms in **I** were located from a difference Fourier map and refined isotropically with O–H and H···H distances restrained to 0.85 and 1.37 Å, respectively. Other hydrogen atoms were placed in idealized positions and allowed to ride on the connecting atoms. The

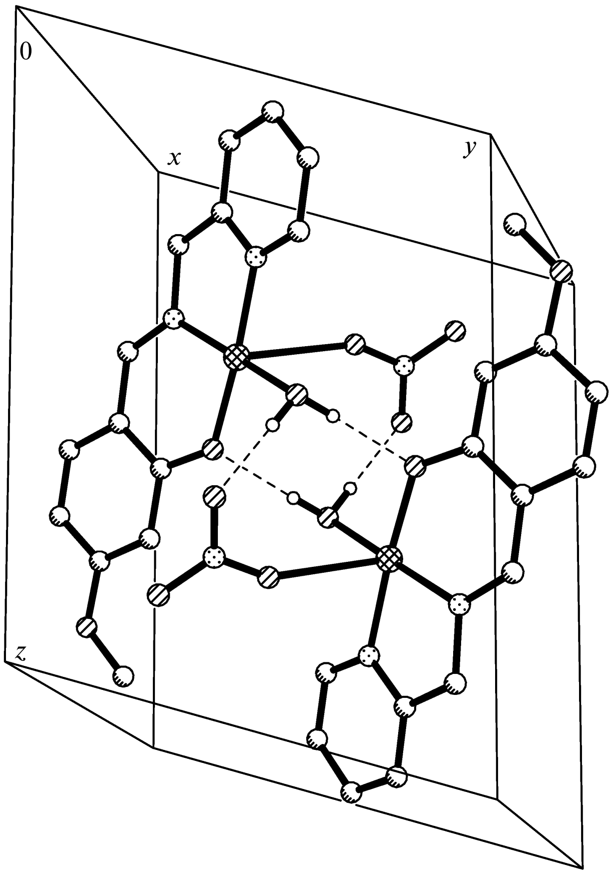

Fig. 4. Molecular packing diagram of **II**. Hydrogen bonds are shown as dashed lines.

crystallographic data for the complexes are summarized in Table 1. Selected bond lengths and angles are listed in Table 2, hydrogen bonds are shown in Table 3.

Atomic coordinates and other structural parameters of the complexes have been deposited with the Cambridge Crystallographic Data Centre (nos. 775269 (**I**) and 775270 (**II**); deposit@ccdc.cam.ac.uk or http://www.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 a 100 mM phosphate buffer (pH 6.8) containing 500 mmol/l 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.

RESULTS AND DISCUSSION

Two new Schiff bases were easily synthesized from the reaction of 2-aminomethylpyridine with 5-chlorosalicylaldehyde and 4-methoxysali-cylaldehyde, respectively, in methanol. The analytical and spectral data are completely consistent with the proposed formulas of the compounds. Complex **I** was synthesized by mixing equimolar quantities of CP, NH_4NCS, and $Cu(NO_3)_2 \cdot 3H_2O$ in methanol, yielding a thiocyanato-bridged polynuclear copper(II) complex. In the preparation of complex **II**, CP and NH_4NCS were replaced by MP, yielding a mononuclear copper(II) complex. Both complexes are stable in air at room temperature. They are soluble in DMF, DMSO, methanol, ethanol, and acetonitrile, and insoluble in water. The molar conductivities of complexes **I** and **II** measured in acetonitrile with concentrations of 10^{-3} mol/l are 17.6 and 117.3 Ω^{-1} cm^2 mol^{-1}, respectively, indicating that complex **I** is a nonelectrolyte, while the nitrate of complex **II** is delocalized in the test solution.

In the infrared spectra of the Schiff bases, the weak and broad absorption bands at 3350–3450 cm^{-1} are assigned to the stretching vibration of the phenolic O–H bonds. The strong absorption bands at 1637 cm^{-1} for CP and .1635 cm^{-1} for MP are assigned to the azomethine groups, ν(C=N) [20], which are shifted to lower frequencies in the complexes (1621 cm^{-1} for **I** and 1618 cm^{-1} for **II**). The weak and broad absorption bands at 3350–3500 cm^{-1} in the complexes are assigned to the stretching vibration of the methanol and water O–H bonds. The strong absorption band of the thiocyanate group in **I** is at 2109 cm^{-1}. The strong absorption band of the nitrate group in **II** is at 1383 cm^{-1}.

Figure 1 gives a perspective view of complex **I**. The compound is an end-to-end thiocyanato-bridged polynuclear copper(II) complex. The asymmetric unit of **I** consists of a Cu(CP)(NCS) moiety and a methanol molecule of crystallization. The methanol molecule is linked to the complex molecules through the O(2)–H(2)···O(1) hydrogen bond.

The Cu atom is five-coordinated and best described as having a square pyramidal coordination. The basal plane of the square pyramidal coordination is defined by the phenolate O, imine N, and pyridine N atoms of a Schiff base ligand, and one N atom of a thiocyanate bridge. The apical position of the square pyramid is occupied by one S atom of a thiocyanate bridge. The deviation of the atom Cu(1) from the least-squares plane defined by the four basal donor atoms is 0.196(1) Å. The bond lengths subtended at the metal center are comparable to the corresponding values observed in other similar copper(II) complexes [21–23], and, as expected, the bonds involving pyridine N atom is longer than that involving imine N atom. The distortion of the square pyramidal coordination is revealed by the bond angles between the apical and basal donor atoms, which range from 91.5(1)° to 100.2(1)°. The N(1)Cu(1)N(2) bond angle in the complex deviates from 90° by 7.6(1)°, as a result of the strain created by the five-membered chelate ring Cu(1)/N(1)/C(8)/C(9)/N(2). The thiocyanate group is nearly linear and shows bent coordination with the Cu atoms (N(3)–C(14)–S(1)/Cu(1)–N(3)–(C(14)/Cu(1)^i–S(1)–C(14) = 178.8(3)°/161.9(3)°/96.1(1)°, symmetry code for ^{i}: $-1/2 + x$, $3/2 - y$, $1 - z$).

In the crystal structure of **I**, the mononuclear copper(II) complex units are linked by the end-to-end thiocyanate bridges to form polymeric chains running along the x axis, as shown in Fig. 2. The methanol molecules are linked to the chains through O–H···O hydrogen bonds.

Figure 3 gives a perspective view of complex **II**. The Cu atom in the complex is five-coordinated and best described as having a square pyramidal coordination. The basal plane of the square pyramidal coordination is defined by the phenolate O, imine N, and pyridine N atoms of a Schiff base ligand, and one water O atom. The apical position of the square pyramid is occupied by one O atom of a nitrate anion. The deviation of the atom Cu(1) from the least-squares plane defined by the four basal donor atoms is 0.643(1) Å. The basal bond lengths subtended at the metal center are comparable to those in **I**, and the corresponding values observed in other similar copper(II) complexes [21–25]. As expected, the bonds involving pyridine N atom is longer than that involving the imine N atom. It is notable that the apical bond of the square pyramidal coordination is a little longer than usual (Cu(1)–O(4) = 2.601(2) Å), indicating that the O(4) atom is weakly coordinated to the metal atom. The distortion of the square pyramidal coordination is revealed by the bond angles between the apical and basal donor atoms, which range from 81.7(1)° to 104.7(1)°. The N(1)Cu(1)N(2) bond angle in the complex deviates from 90° by 6.8(1)° as a result of the strain created by the five-membered chelate ring Cu(1)N(1)C(8)C(9)N(2).

In the crystal structure of **II**, adjacent two mononuclear copper(II) complex molecules are linked by the coordinate water molecules through four O–H···O hydrogen bonds to form a dimer as shown in Fig. 4.

In both complexes, the square pyramidal coordination can be proved by the structural index τ value [26], which represents the relative amount of trigonality (square pyramid, $\tau = 0$; trigonal bipyramid, $\tau = 1$). The τ values for complexes **I** and **II** are 0.19 and 0.06, indicating that the coordination is best described as trigonal bipyramid.

The biological test indicates that both complexes have satisfactory urease inhibitory activity with the IC_{50} values of 31.3 ± 0.2 μM for **I** and 20.5 ± 0.3 μM for **II**, which are superior to that of the acetohydroxamic acid (37.23 ± 0.27 μM) coassayed as a standard reference against the urease. When compared with those we reported previously, it can be seen that the activity of the two complexes in this paper is comparable to those of the copper(II) complexes [15, 16] and superior to those of the zinc(II) complexes [27]. Further work needs to be done to explore highly efficient urease inhibitors.

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