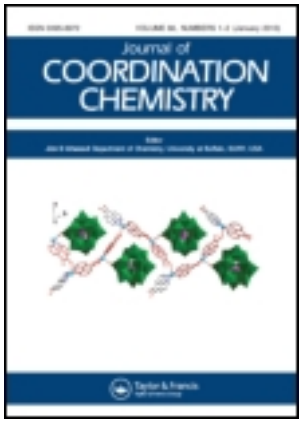

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

Synthesis, structure, and biological evaluation of three Cu(II) and Ni(II) (E)-3-(3,4-dimethoxyphenyl)acrylate complexes with organic diamines as potential urease inhibitors

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Accepted author version posted online: 01 Jul 2013.Published online: 30 Jul 2013.

To cite this article: Hui Zhu, Zi-Zhen Wang, Bing Qi, Tao Huang & Hai-Liang Zhu (2013) Synthesis, structure, and biological evaluation of three Cu(II) and Ni(II) (E)-3-(3,4-dimethoxyphenyl)acrylate complexes with organic diamines as potential urease inhibitors, Journal of Coordination Chemistry, 66:17, 2980-2991, DOI: 10.1080/00958972.2013.821198

To link to this article: http://dx.doi.org/10.1080/00958972.2013.821198

Journal of Coordination Chemistry, 2013
Vol. 66, No. 17, 2980–2991, http://dx.doi.org/10.1080/00958972.2013.821198

Synthesis, structure, and biological evaluation of three Cu(II) and Ni(II) (*E*)-3-(3,4-dimethoxyphenyl)acrylate complexes with organic diamines as potential urease inhibitors

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(*Received 27 September 2012; in final form 29 May 2013*)

Three new complexes (**1**–**3**) have been synthesized and characterized by X-ray single crystal determination and evaluated for inhibitory activity on *jack bean* urease. All the complexes contained a new cinnamic acid derivative as the ligand ($C_{11}H_{12}O_4$), (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid, and crystallized in monoclinic *C2*/*c* space group. Complex **1** $(C_{11}H_{11}O_4)_4(C_3N_2H_8)_2Cu_2$ ($C_3N_2H_8$ = 1,2-diaminopropane) was obtained with $a = 20.488(2)$, $b = 19.596(2)$, $c = 15.2500(13)$, $\beta = 93.502(2)°$, $V = 6111.2(10)$ Å^3, $Z = 4$, $R_1 = 0.0616$, and $wR_2 = 0.2059$. Complex **2** $(C_{11}H_{11}O_4)_4(C_3N_2H_8)_2Cu_2$ ($C_3N_2H_8$=1,3-diaminopropane) was obtained with $a = 20.2494(12)$, $b = 19.5732(12)$, $c = 14.8940(8)$, $\beta = 96.884(2)°$, $V = 5860.6(6)$ Å^3, $Z = 4$, $R_1 = 0.0409$, and $wR_2 = 0.1107$. Complex **3** $(C_{11}H_{11}O_4)_2(C_2N_2H_6)_2Ni_2{\cdot}H_2O$ ($C_2N_2H_6$ = ethylenediamine) was obtained with $a = 28.359(2)$, $b = 6.5422(5)$, $c = 16.8587(14)$, $\beta = 101.359(2)°$, $V = 3066.5(4)$ Å^3, $Z = 4$, $R_1 = 0.0422$, and $wR_2 = 0.1190$. It was found that copper(II) complexes **1** [$IC_{50} = 4.71$ μM] and **2** [$IC_{50} = 3.15$ μM] showed strong inhibitory activity against *jack bean* urease compared with acetohydroxamic acid [$IC_{50} = 10.01$ μM] as a positive reference. Unfortunately, **3** exhibited no inhibitory activity.

Keywords: Cinnamic acid ligand; Transition metal complexes; Crystal structures; Urease inhibitors

1. Introduction

Transition metals have biological activity for many biochemical processes [1]. Commonly used transition metals include nickel, copper, cobalt, zinc, etc. Copper and nickel act as cofactors in some important enzymatic and organ functions, resulting in increased activities of these enzymes. Cinnamic acid is a derivative of phenylalanine. In nature, cinnamic acid derivatives are important metabolic building blocks in the production of lignins for higher plants [2]. A derivative of cinnamic acid is an important pharmaceutical for high blood pressure and stroke prevention and possesses antitumour activity [3], even showing antibacterial, antitubercular, antifungal [4–7], and antiglycation activities [8]. Functional activity may be optimized by combining transition metals with organic acids. Biological activity of metal complexes is a focus and been reported many times [9–11]. Urease is an important enzyme, causing many human diseases [12] and affecting soil nitrogen

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fertilization and ammonia volatilization and root damage [13]. It is important to find an excellent inhibitor.

In view of the biological importance of transition metal complexes, we designed a new cinnamic acid derivative, the (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid, and synthesized new complexes with the cinnamic acid derivative as ligand. In this paper, we synthesized and evaluated the structure and biological activities.

2. Results and discussion

2.1. *Synthesis*

Cinnamic acid (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid ($C_{11}H_{12}O_4$) was prepared by reaction of malonic acid and veratraldehyde in a solution of absolute ethanol in 70–80% yield. Each new complex was synthesized by (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid and copper sulfate pentahydrate and nickel sulfate heptahydrate in 50–60% yield. We obtained three complexes in different solvents by the cinnamic acid metal salts and different

Table 1. Crystal data and refinement parameters for **1–3**.

Complex	**1**	**2**	**3**
CCDC deposit no.	876276	899450	899449
Molecular formula	$C_{50}H_{60}N_4O_{16}Cu2$	$C_{50}H_{64}N_4O_{16}Cu2$	$C_{26}H_{34}N_4O_8Ni$
Molecular weight	1154.17	1228.25	643.31
Temperature (K)	296	293	296
Radiation λ	Mo Kα (0.71073 Å)	Mo Kα (0.71073 Å)	Mo Kα (0.71073 Å)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*C2/c*	*C2/c*	*C2/c*
a/Å	20.488(2)	20.2494(12)	28.359(2)
b/Å	19.596(2)	19.5732(12)	6.5422(5)
c/Å	15.2500(13)	14.8940(8)	16.8587(14)
β/°	93.502(2)	96.884(2)	101.359(2)
V/Å^3	6111.2(10)	5860.6(6)	3066.5(4)
Z	4	4	4
D_{calc} (g cm^{-3})	1.255	1.392	1.393
Crystal size (mm)	0.21 × 0.23 × 0.27	0.22 × 0.23 × 0.28	0.20 × 0.23 × 0.25
Crystal color	Blue	Blue	Blue
Abs. coefficient (mm^{-1})	0.779	0.771	5.743
Abs. correction T_{min} and T_{max}	0.8172 and 0.8534	0.8130 and 0.8486	0.3278 and 0.3930
F (0 0 0)	2416	2584	1360
Reflections collected/unique	5985/22,482 [R_{int} = 0.037]	6070/29,729 [R_{int} = 0.024]	2852/15,414 [R_{int} = 0.020]
Range/indices (*h*, *k*, *l*)	−24, 25; −24, 24; −18, 18	−25, 23; −24, 24; −18, 18	−34, 34; −7, 7; −20, 20
θ limit (°)	2.1–26.0	2.5–26.5	2.46–25.50
No. of observed data, $I > 2\sigma(I)$	4148	5136	2695
No. of restraints	5985	6070	2852
Goodness of fit on F^2	1.056	1.096	1.051
Largest diff. peak/hole (e Å^{-3})	0.99/−0.42	0.66/−0.34	0.54/−0.52
R_1, wR_2 [$I \geqslant 2\sigma(I)$][a]	0.0616, 0.2059	0.0409, 0.1107	0.0422, 0.1190
R_1, wR_2 (all data)[a]	0.0960, 0.2257	0.0506, 0.1172	0.0441, 0.1216

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

Table 2. Selected bond distances (Å) and angles (°) for **1–3**.

1			
Cu1–N1	1.991(5)	Cu1–O2	1.950(3)
Cu1–N2	1.989(4)	Cu1–O6	1.976(3)
Cu1–O6a	2.372(3)	N2–Cu1–O6	90.21(16)
O2–Cu1–O6	89.96(13)	O2–Cu1–N2	179.13(15)
O6–Cu1–N1	173.15(15)	N1–Cu1–N2	84.62(18)
O6–Cu1–O6a	82.56(11)	N2–Cu1–O6a	88.01(14)
2			
Cu1–N1	1.985(2)	Cu1–O4	1.9568(17)
Cu1–N2	2.0148(19)	Cu1–O5	2.3568(16)
Cu1–O5a	1.9934(16)	N2–Cu1–O5	90.28(7)
N2–Cu1–O5a	85.11(8)	N1–Cu1–N2	95.95(8)
O4–Cu1–N1	90.69(8)	O4–Cu1–N2	173.25(8)
O4–Cu1–O5	90.45(7)	O4–Cu1–O5a	88.40(7)
3			
Ni1–O1	2.1267(18)	Ni1–N1	2.106(2)
Ni1–N2	2.094(2)	O1–Ni1–N1	89.91(7)
O1–Ni1–N2	88.28(8)	N1–Ni1–N2	82.38(9)

diamines in different conditions. The details of the crystallographic data are summarized in table 1. Selected distances and angles are listed in table 2.

2.2. *Discussion*

We designed and synthesized a new cinnamic acid, (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid. With a series of diamines, new coordination compounds could be synthesized. We used many combination experiments, but only three crystalline complexes were obtained. The ligand had two electron-donating groups and the methoxy.

Molecular structure and atomic numbering scheme of **1**, **2**, and **3** are shown in figures 1–3, respectively. Complexes **1** and **2** contain one molecule in the asymmetric unit, while the crystal of **3** is composed of one mononuclear unit and two lattice waters. As shown in table 3, the cinnamic acid ligand has no influence on the activity of *jack bean* urease. Under the same conditions, **1** and **2** showed better inhibitory activity with IC_{50} values of 4.71 and 3.15 μM, respectively. In contrast, **3** showed no urease inhibitory activity. This indicates that urease inhibitory activities of cinnamic acid metal complexes depend on more than the organic ligand, including the central ions.

The precipitation of each type of coordination compound was subject to different environments; solvents used in the synthesis were important. The most suitable solvents were methanol, ethanol, acetonitrile, and a mixed solution; temperature, pH, and volatibility also influenced crystal growth [14].

2.3. *Crystal structure description*

Figures 1–3 give perspective views of the crystal structures of the complexes with the atomic labels. Single crystal X-ray diffraction reveals that **1** and **2** are binuclear structures. Each contained a centrosymmetric dinuclear unit with an inversion center at the center of planar arrangement of Cu and O. On the contrary, **3** was a mononuclear nickel(II)

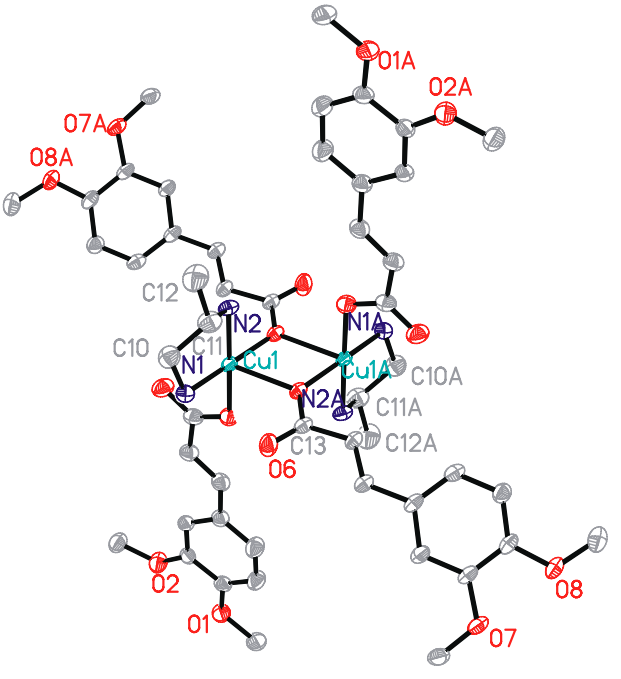

Figure 1. An ORTEP diagram showing the structure of **1** with atom labeling. The thermal ellipsoids are plotted at 30% probability and hydrogens are omitted for plot clarity.

compound. The structures of two copper crystals were similar, as shown in figures 1 and 2. For **1**, the asymmetric unit consists of one copper cation, two (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid molecules and one 1,2-diaminopropane. Two copper(II) were in the middle of an eight-coordinate distorted monocapped structure. Cu(II) was five-coordinate with two carboxyl O from two (*E*)-3-(3,4-dimethoxyphenyl)acrylic acids and two diamine N from 1,2-diaminopropane. For **2**, similar to **1**, except using 1,3-diaminopropane instead of 1,2-diaminopropane. In the crystal structure, for **1**, methoxy O8 is a hydrogen-bond acceptor to N1 of diamine in another molecule at $(1-x, -y, -z)$. Diamine N1 also is a donor to methoxy O8 in another molecule at $(-x, -y, -z)$, respectively, forming intermolecular hydrogen bonds. The molecules are further linked through intermolecular and intramolecular N–H···O and O–H···O hydrogen bonds, forming chains along the *a*-axis. For **2**, two diamine nitrogens also are hydrogen bond donors to methoxy O1, O7, and O8 at $(-x, -y, 1-z)$ and $(1/2+x, -1/2+y, z)$. Diamine nitrogen N2 is a hydrogen bond donor to methoxy O4 at $(1/2-x, ½-y, 1-z)$, forming intramolecular hydrogen bonds. The dihedral angle between the two aromatic rings plane in **2** is 46.75(11)°. Single crystal X-ray diffraction analysis showed that **3** consists of a mononuclear unit and two lattice H_2O as shown in figure 3. Ni is six-coordinate by two carboxyl oxygens of (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid and four diamine nitrogens. The H from H_2O participated in the formation of intermolecular hydrogen bond (table 4). The bond angles subtended at Ni are 82.38(9)–89.91(7)°, indicating a distorted octahedral geometry. C10–C11 in the complex is slightly twisted. In **1**, molecules were mainly connected by intermolecular hydrogen bond between N from 1,2-diaminopropane and methoxy O from another molecule (figure 4). Similarly in **2**, the primary intermolecular hydrogen bond was

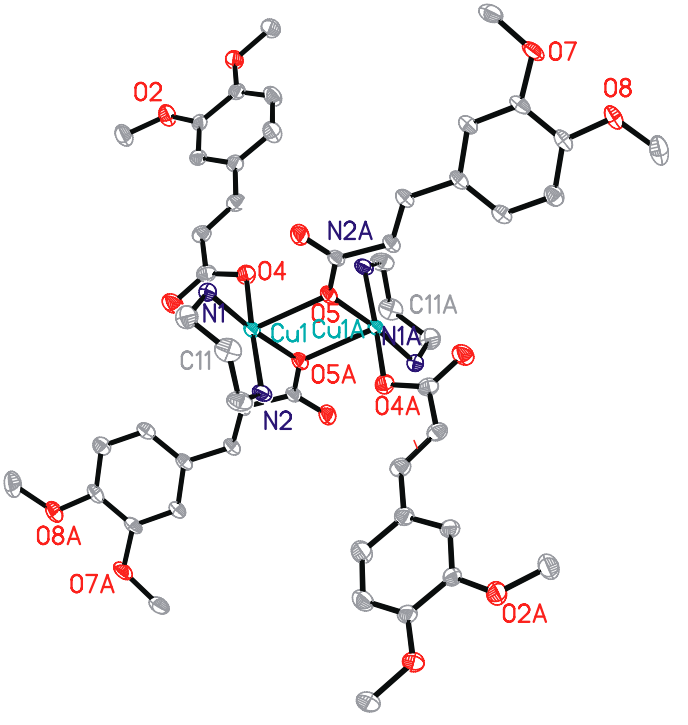

Figure 2. An ORTEP diagram showing the structure of **2** with atom labeling. The thermal ellipsoids are plotted at 30% probability and hydrogens are omitted for clarity.

between N from 1,3-diaminopropane and methoxy O from another molecule (figure 5). Figure 6 showed that in **3**, the connection between each molecule was by water.

There were π–π interactions in **1** and **2**. These π–π interactions and hydrogen bonds played roles in the formation, stability, and crystallization of these complexes. The π–π interactions in **3** were weaker than in the other two complexes.

2.4. *IR spectra*

The separation between the asymmetric and symmetric carboxylate stretches have been compared to determine carboxylate binding with metal. In **1**–**3**, the $\nu_{as}(COO^-)$ of asymmetric carboxylates are 1551.7, 1586.0, and 1585.5 cm^{-1}. The $\nu_s(COO^-)$ of symmetric carboxylates are 1385.9, 1368.0, and 1376.8 cm^{-1}. The Δ values are 165.8, 218.0, and 208.7 cm^{-1}, respectively. All Δ values are higher than the value for sodium cinnamate (143 cm^{-1}) [15]. This suggests monodentate coordination of (*E*)-3-(3,4-dimethoxyphenyl) acrylic acid in **1**–**3**.

2.5. *Inhibitory activity against* jack bean *urease*

As shown in table 3, transition metal ions as enzyme inhibitors exhibit different abilities to inhibit urease, $Cu^{2+} > Ni^{2+}$. This is in accord with inhibitory efficiency of metal ions toward urease, $Cu^{2+} > Ni^{2+} > Co^{2+} > Zn^{2+}$, reported in the literature [16, 17]. Compared

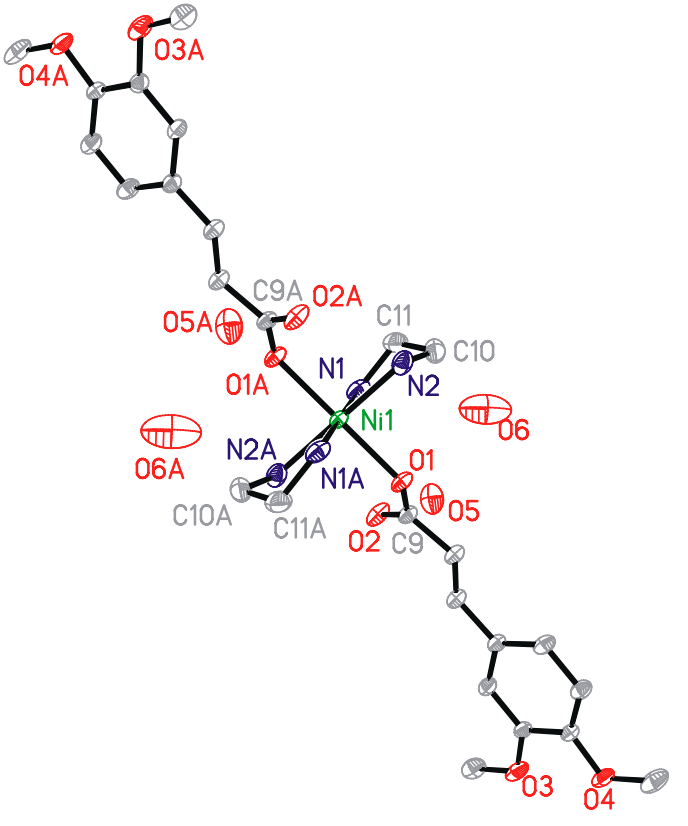

Figure 3. An ORTEP diagram showing the structure of **3** with atom labeling. Thermal ellipsoids are plotted at 30% probability and hydrogens are omitted for clarity.

Table 3. Inhibition of *jack bean* urease by **1–3**, cinnamic acid ligand and metal ions.

Tested materials	IC_{50} (μM)
Cinnamic acid ligand	>100
Complex **1**	4.71
Complex **2**	3.15
Complex **3**	>100
Acetohydroxamic acid	10.01

with the standard inhibitor acetohydroxamic acid, (*E*)-3-(3,4-dimethoxyphenyl) acrylate has no influence on the activity of *jack bean* urease. Under the same condition, Cu(II) complexes **1** and **2** showed better inhibitory activity with IC_{50} of 4.71 and 3.15, respectively. In contrast, Ni(II) and its (*E*)-3-(3,4-dimethoxyphenyl) acrylate complex **3** showed no urease inhibitory activities ($IC_{50} > 100\,\mu M$).

In conclusion, the urease inhibitory activities revealed that **1** and **2** have significantly enhanced inhibitory activities compared to parent ligand. Coordination, locking the polar electronegative atoms in the inner core around the metal and confining the apolar residues in an external lipophilic envelope, favors diffusion through biomembranes [18]. Factors such as solubility, conductivity, and dipole moment (influenced by the presence of metal ions) may

Table 4. Geometrical parameters for hydrogen bonds.

Hydrogen bonds	*D*–H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*–H···*A* (°)
Complex **1**				
N1–H1···O1$^{\#1}$	0.86	2.41	3.236(6)	162
N1–H1B···O8$^{\#2}$	0.86	2.34	3.052(6)	140
Complex **2**				
N1–H1B···O1$^{\#3}$	0.90	2.37	3.206(3)	155
N2–H2A···O7$^{\#4}$	0.90	2.50	3.122(3)	127
N2–H2A···O8$^{\#4}$	0.90	2.26	3.089(3)	154
N2–H2B···O4$^{\#5}$ (Intra)	0.90	2.36	3.218(3)	159
Complex **3**				
O6–H6B···O5$^{\#6}$	0.85	2.20	2.778(3)	125
O6–H6A···O5	0.85	2.19	2.778(3)	126
O5–H5B···O1$^{\#7}$	0.85	2.27	2.724(3)	114

Symmetry codes: $^{\#1}1-x, -y, -z$; $^{\#2}-x, -y, -z$; $^{\#3}-x, -y, 1-z$; $^{\#4}1/2+x, -1/2+y, z$; $^{\#5}1/2-x, 1/2-y, 1-z$; $^{\#6}-x, y, 1/2-z$; $^{\#7}x, -1+y, z$.

contribute to the increase in activity [19]. However, **3** showed no urease inhibitory activities; maybe the performance of the metal, steric, and pharmacokinetic factors may also play roles in potency of an antiturease agent.

3. Experimental

3.1. *Materials and measurements*

Unless otherwise stated, all solvents were of reagent grade and purchased commercially. All chemicals were also commercially available and used without purification. (*E*)-3-(3,4-Dimethoxyphenyl)acrylic acid was obtained according to literature method [20]. C, H, O, and N elemental analyses were performed on a Perkin-Elmer 240 C elemental analyzer. IR spectra were recorded (400–4000 cm^{-1}) on a FT-IR Nicolet 5700 spectrometer.

3.2. *Synthesis of* (E)-*3-(3,4-dimethoxyphenyl)acrylic acid*

Malonic acid (0.05 M, 5.30 g) and veratraldehyde (0.05 M, 8.30 g) were added to a solution of absolute ethyl alcohol with stirring, then piperidine (0.2 mL) was added. The mixture was stirred and heated under reflux for 8 h. The solution was added in ice-water, precipitate was obtained and then dissolved in lye. The supernatant was obtained and then acidification. The white precipitate was separated by filtration, washed three times with water and dried at 50 °C. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; N, 30.74%. Found: C, 63.23; H, 6.02; N, 30.95%.

3.3. *Synthesis of* $Cu[C_{11}H_{11}O_4]_2$ *and* $Ni[C_{11}H_{11}O_4]_2$

(*E*)-3-(3,4-Dimethoxyphenyl)acrylic acid (10 mM, 2.08 g) dissolved in a solution of sodium hydroxide (pH was controlled at 7) was added to solution of $CuSO_4 \cdot 5H_2O$ (5 mM, 0.81 g) or $NiSO_4 \cdot 7H_2O$ (5 mM, 1.315 g). The precipitates were filtered and dried at 40 °C. Anal. Calcd for $C_{22}H_{22}CuO_8$: C, 55.29; H, 4.64%. Found: C, 55.45; H, 5.01%. Anal. Calcd for $C_{22}H_{22}NiO_8$: C, 55.85; H, 4.69%. Found: C, 55.61; H, 4.93%.

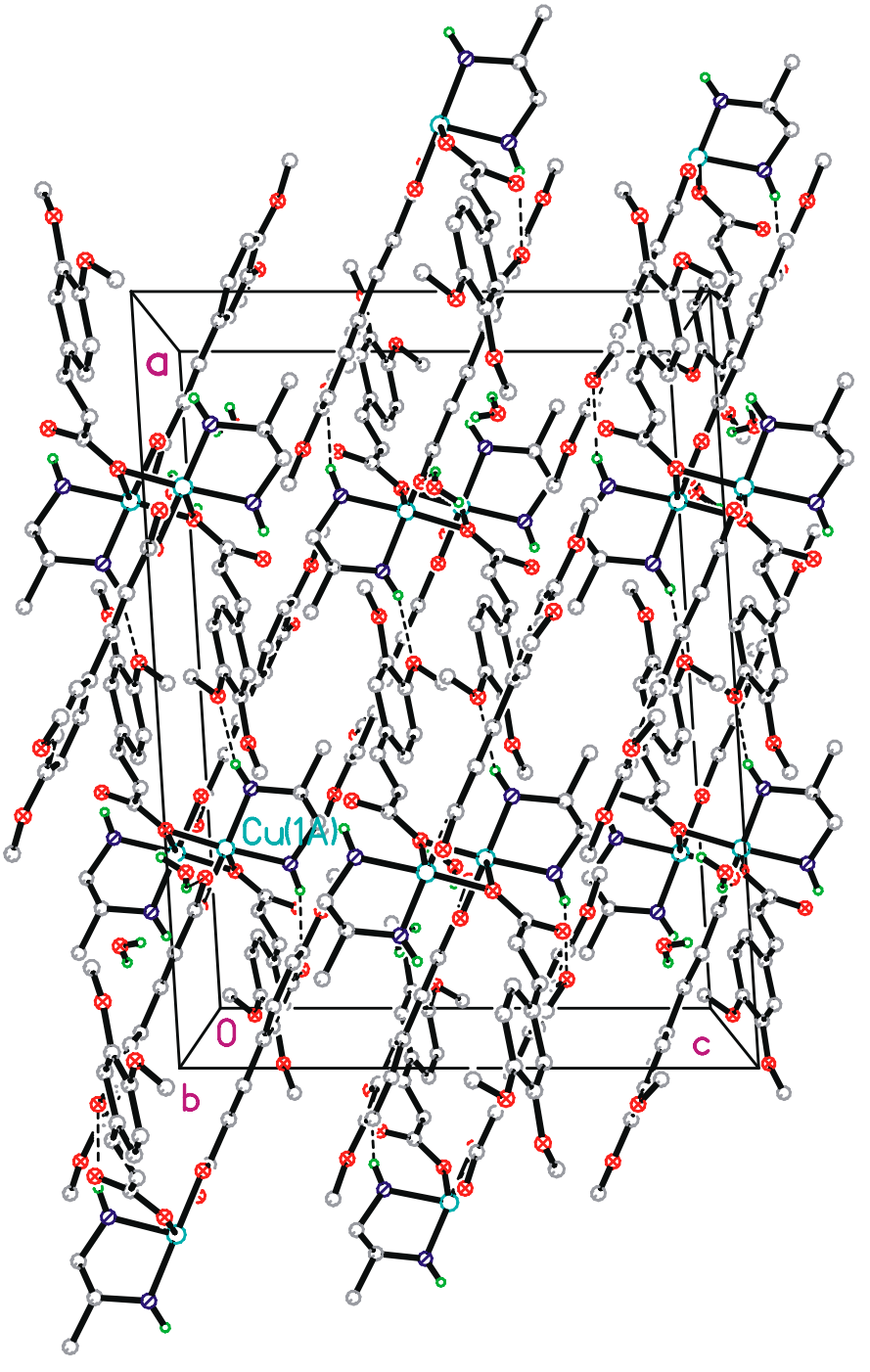

Figure 4. Molecular packing of **1**, viewed along the *c* axis. Intermolecular hydrogen bonds are shown as dashed lines.

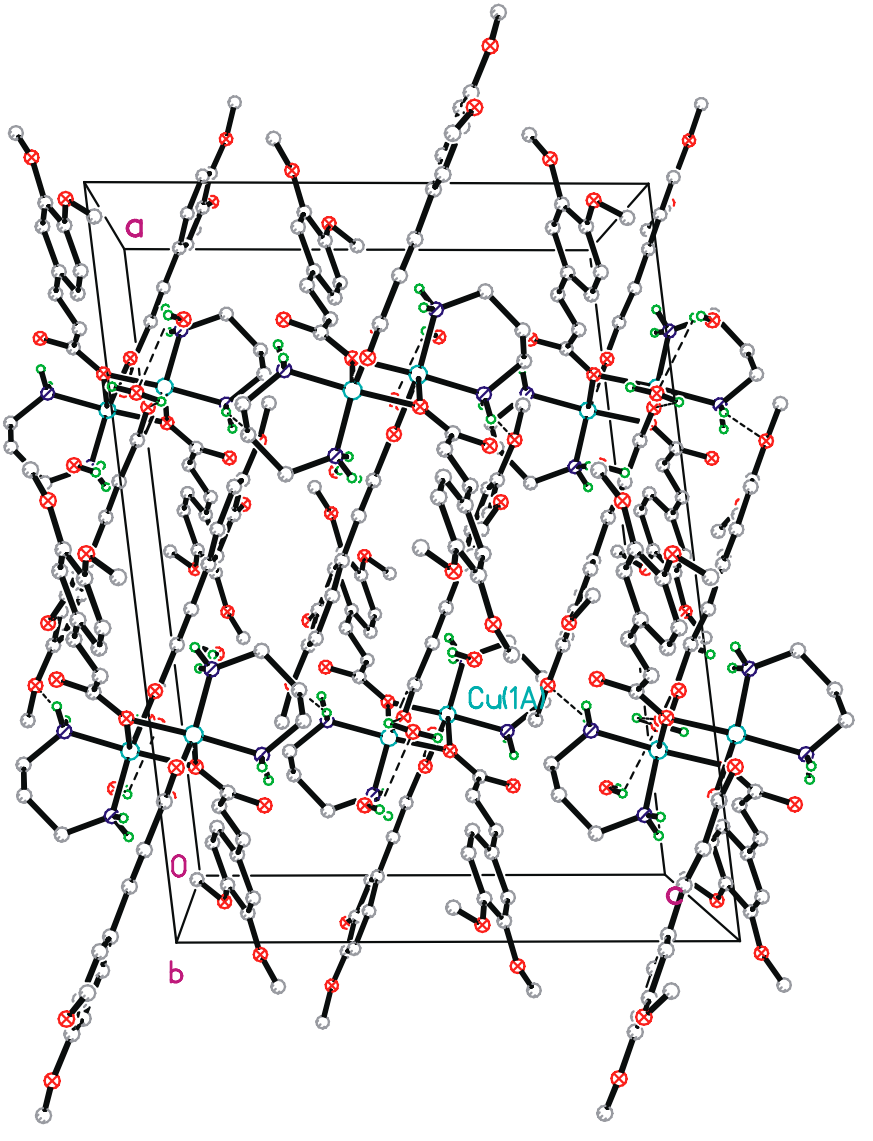

Figure 5. Molecular packing of **2**, viewed along the *c* axis. Intermolecular hydrogen bonds are shown as dashed lines.

3.4. *Synthesis of 1*

To a MeOH solution of 1,2-diaminopropane (0.5 mM, 0.04 g) was added a MeOH solution of (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid copper salt (0.5 mM, 0.24 g). The mixture was stirred for 10 min at room temperature and filtered. Upon keeping the filtrate in air for five days, suitable blue, block-shaped single crystals of **1** for structure determination were obtained by slow evaporation of the solution in air. Anal. Calcd for $C_{25}H_{30}CuN_2O_8$: C, 54.59; H, 5.50; N, 5.09%. Found: C, 54.25; H, 6.01; N, 5.39%. IR (KBr, ν/cm^{-1}): 3302.2 ν(NH, stretching), 1466.0 ν(O–CH_3), 1640.5 ν(NH, deformation), 1551.7 ν_{as}(COO^-), 1424.0 ν(Ar–C=C), 1385.9 ν_s(COO^-), 1139.7 ν(C–N).

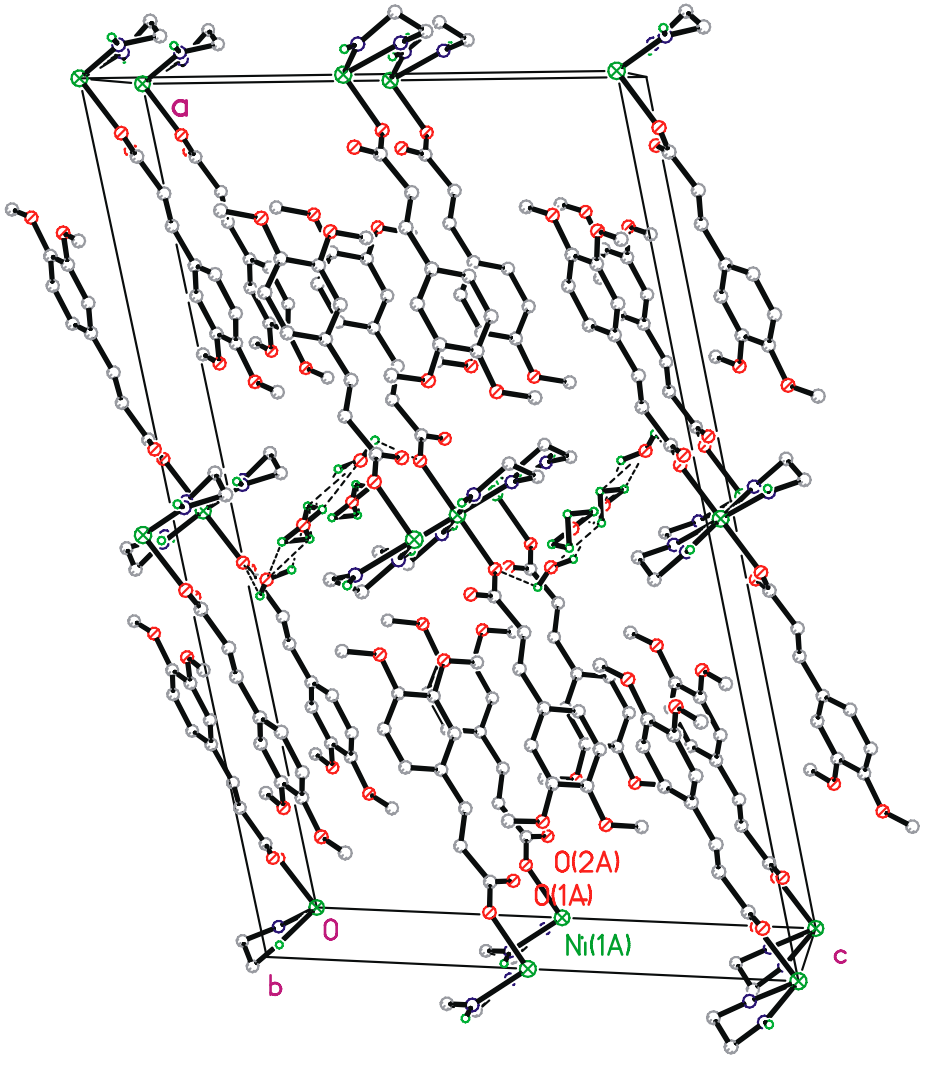

Figure 6. Molecular packing of **3**, viewed along the *c* axis. Intermolecular hydrogen bonds are shown as dashed lines.

3.5. *Synthesis of 2*

1,3-Diaminopropane (0.5 mM, 0.04 g) was added to a solution of (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid copper salt (0.5 mM, 0.24 g) in a mixed solvent. The mixture was stirred for 10 min at room temperature and filtered. Keeping the filtrate in air for five days, suitable blue, block-shaped single crystals of **2** for structure determination were obtained by slow evaporation of the solution in air. Anal. Calcd for $C_{25}H_{30}CuN_2O_8$: C, 54.59; H, 5.50; N, 5.09%. Found: C, 54.27; H, 6.00; N, 5.37%. IR (KBr, ν/cm^{-1}): 3295.6 ν(NH, stretching), 1464.7 ν(O–CH_3), 1640.3 ν(NH, deformation), 1586.0 ν_{as}(COO^-), 1424.4 ν(Ar–C=C), 1368.0 ν_s(COO^-), 1139.1 ν(C–N).

3.6. *Synthesis of 3*

Complex **3** was obtained from reaction of ethylenediamine (0.5 mM, 0.04 g) dissolved in acetonitrile added to ammonia water solution of (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid nickel salt (0.5 mM, 0.23 g), stirred at room temperature, and then filtered. Keeping the filtrate in air for days, single crystals of **3** for structure determination were obtained by slow evaporation of the solution in air. Anal. Calcd for $C_{13}H_{17}NiN_2O_4$: C, 48.19; H, 5.29; N, 8.65%. Found: C, 47.73; H, 5.36; N, 8.92%. IR (KBr, ν/cm^{-1}): 3351.1 ν(OH, water), 3291.2 ν(NH, stretching), 1462.5 ν(O–CH_3), 1638.2 ν(NH, deformation), 1585.5 ν_{as}(COO^-), 1413.8 ν(Ar–C=C), 1376.8 ν_s(COO^-), 1136.4 ν(C–N).

3.7. *Crystal structure determination*

X-ray diffraction intensities were collected using a Bruker SMART APEX-II CCD area detector equipped with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at 298 (2) K. Absorption correction was applied by *SADABS* [21]. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares using Bruker's *SHELXTL-97* [22]. All nonhydrogen atoms were refined anisotropically. The hydrogens were placed in calculated positions and constrained to ride on their parent. The details of the crystallographic data are summarized in table 1. Selected bond lengths and angles are summarized in table 2. Hydrogen bonds are listed in table 4.

3.8. *Measurement of inhibitory activity against* jack bean *urease*

Jack bean urease was purchased from Sigma Aldrich Co. (St. Louis, MO, USA). The measurement of urease was carried out according to the literature [23, 24]. Generally, the assay mixture, containing 25 mL of *jack bean* urease (10 kU^{-1}L) and 25 mL of the tested complexes of various concentrations [dissolved in the solution of DMSO: H_2O=1 : 1 (v : v)], was preincubated for 1 h at 37 °C in a 96-well assay plate. After preincubation, 0.2 mL of 100 mM HEPES (N-[2-hydroxy-ethyl]piperazine-N'-[2-ethanesulfonic acid]) buffer [25] pH = 6.8 containing 500 mM urea and 0.002% phenol red were added and incubated at 37 °C. The reaction time was measured by microplate reader (570 nm), which was required to produce enough ammonium carbonate to raise the pH of a HEPES buffer from 6.8 to 7.7, the endpoint being determined by the color of phenol red indicator [26]. The abilities of the ligand, (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid, metal ions (M = Cu^{2+}, Ni^{2+}), and complexes **1–3** as inhibitors were studied by the inhibition rate values of the material (25 mL, 100 mg) tested against *jack bean* urease (25 mL, 10 kU^{-1}L) using urea (500 mM) in HEPES buffer (0.2 mL, 100 mM; pH 6.8). The activities are shown in table 3.

4. Conclusions

The present study describes the preparation of (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid and its Ni(II) and Cu(II) complexes. X-ray single crystal determination of the three complexes showed that three mixed-ligand complexes were synthesized and characterized; they crystallize in monoclinic space group *C2*/*c*. The inhibitory activity on *jack bean* urease indicated

that copper(II) complexes (**1** and **2**) exhibit stronger activity to inhibit *jack bean* urease than **3**. The trend in this work is in accord with the studies reported earlier. Detailed investigations are continuing to study the mechanisms of the inhibitory activity reported here.

Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Center (CCDC 876276 for **1**, 899450 for **2** and 899449 for **3**). Copy of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (+44) 1223-336033; E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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