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Copper(II) Complexes of Mono-Condensed N,O-Donor Schiff Base Ligands: Synthesis, Crystal Structures, and Antibacterial Activity[1]

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Abstract—Two new copper(II) complexes, $[Cu(L^1)_2]$ (**I**) and $[Cu(L^2)_2]$ (**II**), where L^1 = 2-bromo-4-chloro-6-(isopropyliminomethyl)phenolate and L^2 = 2-bromo-4-chloro-6-[(2-hydroxyethylimino)methyl]phenolate, have been prepared and structurally characterized by X-ray crystallography (CIF files CCDC nos. 1445936 (**I**) and 1445935 (**II**)). In both complexes, the Cu atoms are coordinated by two phenolate oxygen and two imino nitrogen, giving square planar geometry. The complexes have been tested on various strains of bacteria to study their antibacterial effects.

Keywords: Cu(II) complexes, N,O-donor bidentate Schiff base, X-ray structure, antibacterial activity

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INTRODUCTION

Schiff bases are a kind of biological active compounds, which are reported to show a variety of interesting biological actions, including antibacterial [1–3], antifungal [4, 5], anticancer [6–8], etc. Schiff bases derived from salicylaldehyde and its derivatives usually possess two or more donor atoms, which can chelate to transition metal atoms, to form a variety of complexes [9–12]. Metal complexes with Schiff base ligands have attracted much attention in the fields of magnetic, catalytic, as well as biological materials [13–19]. Thus, in this paper, we report the synthesis, characterization, and antibacterial activities of two new copper(II) complexes derived from Schiff bases 2-bromo-4-chloro-6-(isopropyliminomethyl)phenol (HL^1) and 2-bromo-4-chloro-6-[(2-hydroxyethylimino)methyl]phenol (HL^2).

EXPERIMENTAL

Materials and physical measurements. All chemicals were of reagent grade, purchased from commercial sources, and used without further purification. Elemental analysis (carbon, hydrogen, and nitrogen) was performed using a Perkin-Elmer 240C elemental analyzer. IR spectra in KBr (4000–400 cm^{-1}) were recorded using a Perkin-Elmer RXI FT-IR spectrophotometer. Electronic spectra in acetonitrile were recorded in a Lambda 35 spectrophotometer.

[1] The article is published in the original.

Syntheses of the Schiff bases HL^1 and HL^2 were carried out in a similar way by refluxing 3-bromo-5-chlorosalicylaldehyde (1.0 mmol, 235.5 mg) with isopropylamine (1.0 mmol, 59.1 mg) and 2-aminoethanol (1.0 mmol, 61.1 mg), respectively, in methanol (20 mL) for 1 h. The Schiff bases were not isolated. The methanolic solutions were used for the syntheses of the complexes.

Synthesis of complexes I and II. A methanol solution (10 mL) of copper(II) chloride dihydrate (1.0 mmol, 17.0 mg) was added to the methanol solution (10 mL) of HL^1 (1.0 mmol, 27.6 mg) and HL^2 (1.0 mmol, 27.8 mg), respectively, and refluxed for 1 h. Single crystals suitable for X-ray diffraction were obtained from the filtrate by slow evaporation in a refrigerator.

Complex **I**: yield, 175 mg (57%). λ_{max}, nm (ε_{max}, L mol^{-1} cm^{-1})) (acetonitrile) 272 (17210), 295 (10365), 375 (10230), 763 (210). IR data (KBr; ν, cm^{-1}): 1624 m (CH=N), 1450 s, 1353 m, 1162 s, 1072 s, 949 s, 860 s, 743 w, 545 m, 521 m, 465 w.

For $C_{20}H_{20}N_2O_2Cl_2Br_2Cu$			
anal. calcd., %:	C, 39.08;	H, 3.28;	N, 4.56.
Found, %:	C, 39.21;	H, 3.37;	N, 4.45.

Complex **II**: yield, 132 mg, 43%. λ_{max}, nm (ε_{max}, L mol^{-1} cm^{-1})) (acetonitrile) 275 (16380), 292 (9878), 367 (8560), 750 (273). IR data (KBr; ν, cm^{-1}): 3325 w,

1623 m (CH=N), 1452 s, 1357 m, 1161 s, 1087 w, 1066 s, 953 s, 860 s, 745 w, 532 m, 505 m, 440 w, 421 w.

For $C_{18}H_{16}N_2O_4Cl_2Br_2Cu$			
anal. calcd., %:	C, 34.95;	H, 2.61;	N, 4.53.
Found, %:	C, 34.82;	H, 2.73;	N, 4.60.

X-ray crystallography. Unit cell parameters and the intensity data for the crystals of both complexes were measured with MoK_α radiation using the Bruker Apex II diffractometer. Data were collected at 298(2) K with a scan width of 0.3° in ω and an exposure time of 10 s/frame. The SMART software was used for data acquisition, and the SAINT software was used for data extraction [20]. In each case, an absorption correction was performed with the help of the SADABS program [21]. The structures were solved by direct methods and refined on F^2 by full-matrix least-squares procedures. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms in the structures were included at idealized positions by using a riding model. The SHELX-97 [22] program was used for structure solution and refinement. A summary of the crystallographic data is given in Table 1.

Supplementary material for structures has been deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 1445936 (**I**) and 1445935 (**II**); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Antibacterial activity. The antibacterial activities were tested against *B. subtilis* ATCC 6633, *E. coli* ATCC 35218, *P. putida* TS 1138 and *S. aureus* ATCC 25923 using MH medium (Mueller–Hinton medium: casein hydrolysate 17.5 g, soluble starch 1.5 g, beef extract 1000 mL). The MICs (minimum inhibitory concentrations) of the test compounds were determined by a colorimetric method using the dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide]. A stock solution of the synthesized compound (50 μg mL^{-1}) in DMSO was prepared and quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. A specified quantity of the medium containing the compound was poured into microtitration plates. A suspension of the microorganism was prepared to contain approximately 10^5 cfu mL^{-1} and applied to microtitration plates with serially diluted compounds in DMSO to be tested and incubated at 37°C for 24 h. After the MICs were visually determined on each of the micro-titration plates, 50 μL of PBS (phosphate buffered saline 0.01 mol L^{-1}, pH 7.4: Na_2HPO_4 2.9 g, KH_2PO_4 0.2 g, NaCl 8.0 g, KCl 0.2 g, distilled water 1000 mL) containing 2 mg of MTT per mL^{-1} was added to each well. Incubation was continued at room temperature for 4–5 h. The content of each well was removed and 100 μL of isopropanol containing 5% 1 mol L^{-1} HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density (OD) was measured with a microplate reader at 550 nm.

RESULTS AND DISCUSSION

Both Schiff bases and their copper complexes were synthesized in a very facile and essentially identical way. 3-Bromo-5-chlorosalicylaldehyde and the respective primary amines were mixed in a 1 : 1 stoichiometric ratio in methanol and refluxed. The methanolic solution of the Schiff bases thus prepared was added to a methanolic solution of copper chloride, and refluxed for 1 h. The two Schiff bases are very similar; both complexes have the same general formula $[CuL_2]$. The two complexes were air stable and soluble in ethanol, methanol, DMF and DMSO. None of the complexes are electrically conducting in acetonitrile solutions.

The structure determination reveals that both complexes are similar mononuclear copper compounds (Fig. 1). The complex molecule in each of the complexes is perfectly planar as it possesses crystallographic inversion center symmetry. The bidentate Schiff base ligands coordinate to the copper ion via the phenolate oxygen and imino nitrogen, forming two six-membered chelate rings. The chelate bite angles for the six-membered rings formed by the Schiff base ligands are in the range 88.94(8)°–91.06(8)°. The Cu–O(phenolate) and the Cu–N(imino) bond lengths in the complexes are very similar, and comparable to those reported for Schiff base copper(II) complexes [23–25]. For example, Cu(1)–O(1) 1.907(3), Cu(1)–N(1) 2.031(4) Å; angle O(1)Cu(1)N(1) 90.84(15)° (for **I**) and Cu(1)–O(1*A*) (symmetry code for *A*: 2 − *x*, −*y*, −*z*) 1.8896(17), Cu(1)–N(1) 2.020(2) Å; angle O(1)Cu(1)N(1) 91.06(8)° (for **II**).

The crystal packing structures of complexes **I** and **II** are shown as Fig. 2. In the packing structure of **I**, molecules are stack along the *z* axis, with weak π···π interactions. While for the packing structure of **II**, the presence of hydroxyl groups leads to interesting architectural packing mode. Molecules are linked through intermolecular C–H···Br and O–H···O hydrogen bonds, to form 2D sheets.

In the infrared spectrum of **II**, there displays a weak band centered at 3325 cm^{-1}, which is due to the O–H vibration. The band corresponding to the azomethine (CH=N) group is distinct in both complexes; it occurs at 1624 cm^{-1} for **I** and 1623 cm^{-1} for **II** [26].

The electronic spectra of the complexes were recorded using the acetonitrile as solvent. The spectral profiles are very similar. There display a single absorption band at 763 nm for **I** and 750 nm for **II**. The positions of these bands are consistent with the observed square planar geometry around the copper center. Several intense absorptions appear in the range 370–

Table 1. Crystallographic data and refinement details for complexes **I** and **II**

Parameter	Value	
	I	**II**
Formula weight	614.64	618.59
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
a, Å	8.2572(13)	13.1337(9)
b, Å	17.101(3)	4.6586(3)
c, Å	8.3151(14)	16.9665(12)
β, deg	102.983(2)	90.9650(10)
V, Å^3	1144.1(3)	1037.94(12)
Z	2	2
ρ_{calcd}, g cm^{-3}	1.784	1.979
Crystal size, mm	0.17 × 0.12 × 0.10	0.18 × 0.18 × 0.17
$\mu(MoK_\alpha)$, mm^{-1}	4.699	5.188
Minimum and maximum transmission	0.5022 and 0.6508	0.4553 and 0.4725
$F(000)$	606	606
$\lambda(MoK_\alpha)$	0.71073	0.71073
Scan mode	ω	ω
Reflections collected	5777	5219
Unique reflections	2105	1936
Observed reflections ($I > 2\sigma(I)$)	1763	1610
Refinement parameters	135	134
R_{int}	0.0259	0.0234
Goodness of fit on F^2	1.075	1.040
R_1, wR_2 ($I > 2\sigma(I)$)	0.0508, 0.1130	0.0254, 0.0551
R_1, wR_2 (all data)	0.0631, 0.1191	0.0363, 0.0590

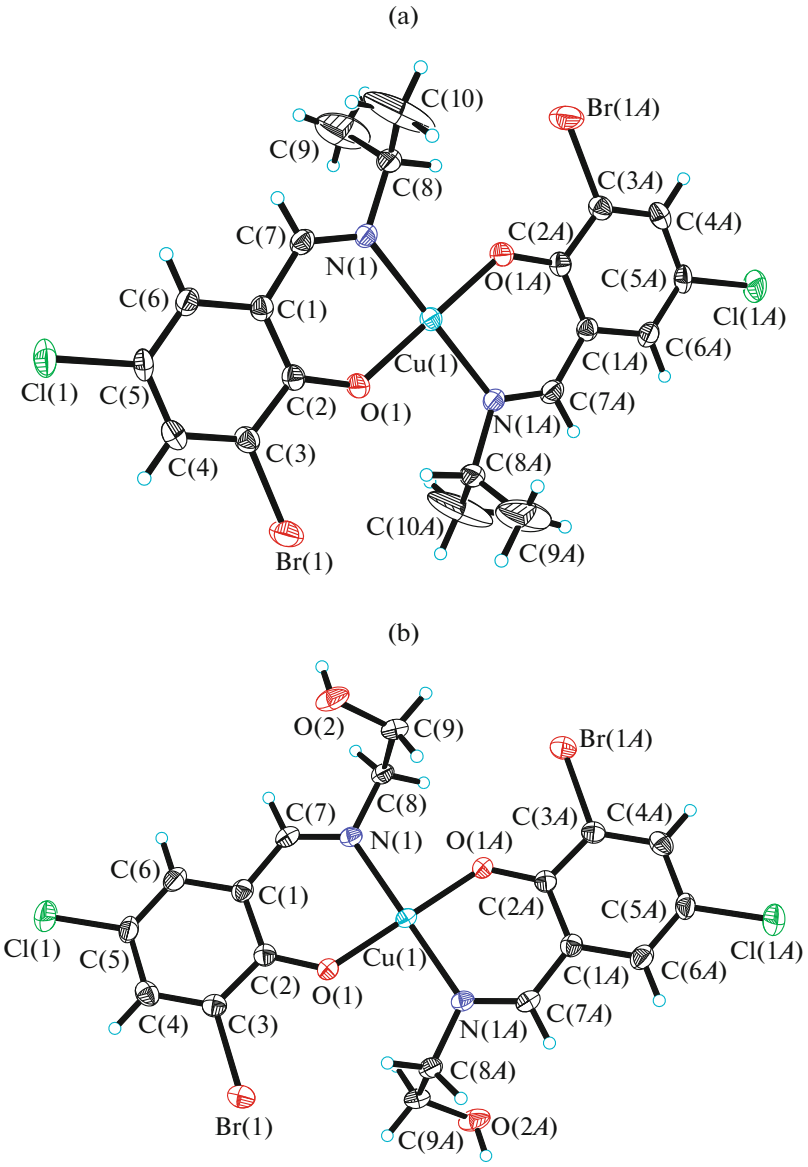

Fig. 1. Molecular structures of complexes **I** (a) and **II** (b). Atoms labeled with the suffix *A* are at the symmetry position $-x$, $1-y$, $1-z$ (for **I**) and $2-x$, $-y$, $-z$ (for **II**).

Table 2. MIC (μg mL^{-1}) values of the antibacterial activity of the complexes

Compound	*B. subtilis*	*E. coli*	*P. putida*	*S. aureus*
I	3.12	1.56	6.25	12.5
II	3.12	1.56	6.25	6.25
Penicillin	0.78	>100	12.5	3.13

270 nm, which is most likely due to the ligand-to-metal charge transfer.

The complexes were screened for antibacterial activity against *B. subtilis* ATCC 6633, *E. coli* ATCC 35218, *P. putida* TS 1138 and *S. aureus* ATCC 25923 by the MTT method. The MIC values of the complexes against these bacteria are presented in Table 2. The antibiotic Penicillin was included as a reference. In general, the two copper complexes have the same activities against the bacteria *B. subtilis*, *E. coli* and *P. putida*. As for *S. aureus*, complex **II** is stronger than complex **I**. The complexes showed a wide range of bactericidal activities against the bacteria, more potent

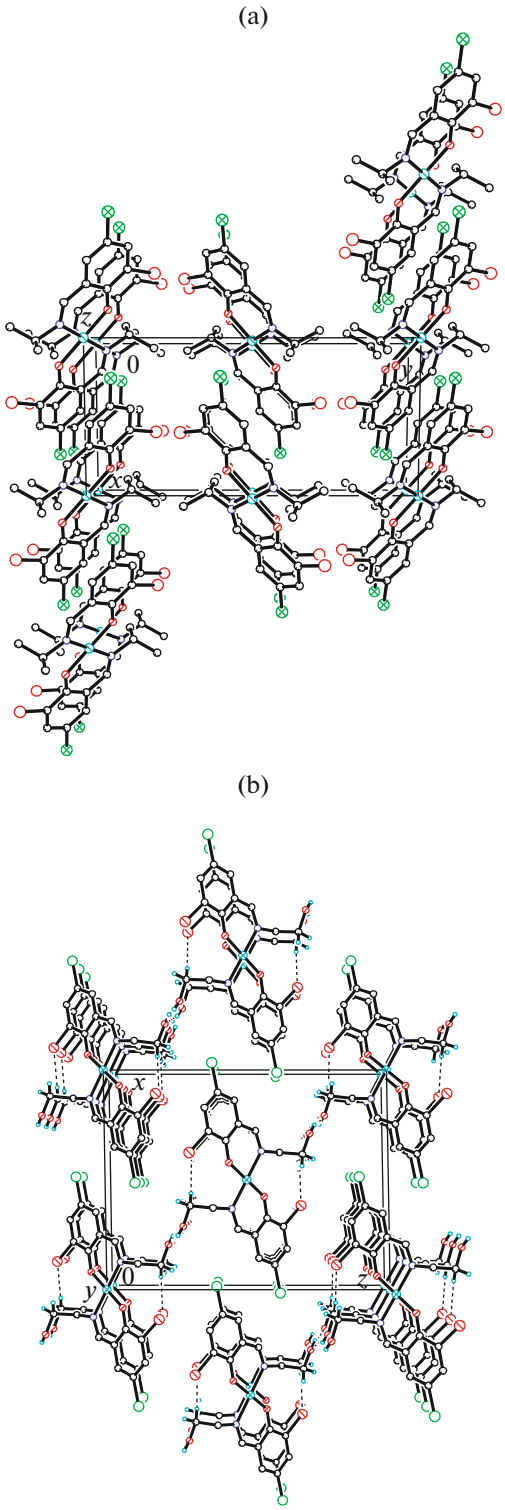

Fig. 2. Molecular packing structure of complexes **I** (a) and **II** (b). Hydrogen bonds are depicted by dashed lines.

than, or similar with, commercial antibiotic Penicillin. So, they are potential antibacterial material.

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