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Synthesis, Crystal Structures, and Antimicrobial Activity of Copper(II) and Zinc(II) Complexes Derived from 2-Bromo-4-Chloro-6-[(2-Morpholin-4-Ylethylimino)methyl]phenol[1]

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Abstract—An end-to-end azido-bridged dinuclear copper(II) complex $[Cu_2L_2(\mu_{1,3}\text{-}N_3)](NO_3)$ (**I**) and a mononuclear zinc(II) complex $[ZnCl_2(HL)] \cdot CH_3OH$ (**II**), where L is 2-bromo-4-chloro-6-[(2-morpholin-4-ylethylimino)methyl]phenolate, have been prepared and characterized by elemental analyses, IR, and single crystal X-ray crystallographic determination (CIF files CCDC nos. 1415217 (**I**), 1415218 for (**II**)). The crystal of **I** is monoclinic: space group $C2/c$, $a = 28.684(2)$, $b = 7.1787(5)$, $c = 18.292(1)$ Å, $\beta = 117.887(3)°$, $V = 3329.1(4)$ Å^3, $Z = 4$. The crystal of **II** is monoclinic: space group $P2_1/c$, $a = 10.8207(9)$, $b = 12.3398(7)$, $c = 14.9477(7)$ Å, $\beta = 93.473(3)°$, $V = 1992.2(2)$ Å^3, $Z = 4$. The Schiff base ligand in **I** coordinates to the Cu atom through the phenolate O, imine N, and morpholine N atoms, while the Schiff base ligand in **II** coordinates to the Zn atom through the phenolate O and imine N atoms, with the morpholine N atom protonated. The effect of these complexes on the antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* was studied.

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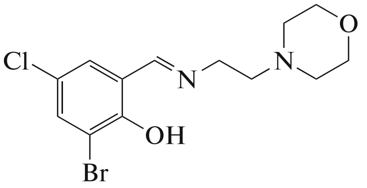
INTRODUCTION

Schiff bases bearing characteristic C=N bonds are a kind of versatile ligands in coordination chemistry [1–3]. In recent years, metal complexes of Schiff bases have attracted considerable attention due to their interesting biological activity, such as antifungal, antibacterial and antitumor [4–6]. Schiff base complexes derived from salicylaldehyde and its derivatives with primary amines, bearing the N_2O, N_2S, NO_2 or NSO donor sets, have particular biological activities [6–10]. Halide substitute groups are reported to improve the antibacterial activities [11]. In the present work, an end-to-end azido-bridged dinuclear copper(II) complex, $[Cu_2L_2(\mu_{1,3}\text{-}N_3)](NO_3)$ (**I**), and a mononuclear zinc(II) complex, $[ZnCl_2(HL)] \cdot CH_3OH$ (**II**), where L is 2-bromo-4-chloro-6-[(2-morpholin-4-ylethylimino)methyl]phenolate, are reported.



(HL)

EXPERIMENTAL

Material and methods. 3-Bromo-5-chlorosalicylaldehyde and 2-morpholin-4-ylethylamine were purchased from Fluka. Other reagents and solvents were analytical grade and used without further purification. Elemental (C, H, and N) analyses were made on a Perkin-Elmer Model 240B automatic analyser. Copper and zinc analyses were carried out by EDTA titration. Infrared (IR) spectra were recorded on an IR-408 Shimadzu 568 spectrophotometer. X-ray diffraction was carried out on a Bruker SMART 1000 CCD area diffractometer.

Synthesis of HL. The Schiff base was prepared by the condensation of equimolar quantities of 3-bromo-5-chlorosalicylaldehyde (0.235 g, 1.0 mmol) with 2-morpholin-4-ylethylamine (0.130 g, 1.0 mmol) in methanol (30 mL) at ambient temperature for 1 h. Then the methanol was evaporated by distillation, yielding yellow solid of the Schiff base.

For $C_{13}H_{16}N_2O_2ClBr$

anal. calcd, %:	C, 44.92;	H, 4.64;	N, 8.06.
Found, %:	C, 44.77;	H, 4.72;	N, 8.13.

Synthesis of complex I. The Schiff base (0.35 g, 1.0 mmol) was dissolved by methanol (20 mL), to which was added with stirring a methanol solution

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[1] The article is published in the original.

Table 1. Crystallographic data and refinement parameters for structures **I** and **II**

Parameter	Value	
	I	**II**
Habit, color	Block, blue	Block, colorless
Formula weight	924.4	511.9
Temperature, K	298(2)	298(2)
Crystal size, mm	0.20 × 0.20 × 0.15	0.27 × 0.27 × 0.26
Radiation (λ, Å)	MoK_α (0.71073)	MoK_α (0.71073)
Crystal system	Monoclinic	Monoclinic
Space group	$C2/c$	$P2_1/c$
Unit cell dimensions:		
a, Å	28.684(2)	10.8207(9)
b, Å	7.1787(5)	12.3398(7)
c, Å	18.292(1)	14.9477(7)
β, deg	117.887(3)	93.473(3)
V, Å^3	3329.1(4)	1992.2(2)
Z	4	4
ρ_{calcd}, g cm^{-3}	1.844	1.707
F(000)	1840	1016
Absorption coefficient, mm^{-1}	3.895	3.655
θ Range for data collection, deg	2.95–25.50	2.91–25.50
Index ranges, h, k, l	$-34 \leqslant h \leqslant 34$; $-8 \leqslant k \leqslant 8$; $-22 \leqslant l \leqslant 22$	$-13 \leqslant h \leqslant 9$; $-14 \leqslant k \leqslant 14$; $-18 \leqslant l \leqslant 17$
Reflections collected	14654	9757
Independent reflections	3100	3677
Data/parameters	2297/219	2423/238
Restraints	0	27
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0728$, $wR_2 = 0.1767$	$R_1 = 0.0609$, $wR_2 = 0.1336$
R indices (all data)	$R_1 = 0.0954$, $wR_2 = 0.1949$	$R_1 = 0.1070$, $wR_2 = 0.1570$
Goodness-of-fit on F^2	1.047	1.075

(10 mL) of $Cu(NO_3) \cdot 3H_2O$ (0.24 g, 1.0 mmol) and an aqueous solution (3 mL) of NaN_3 (0.065 g, 1.0 mmol). The mixture was stirred for 1 h at ambient temperature to give a blue solution. Blue block-shaped single crystals suitable for X-ray diffraction were formed by slow evaporation of the solution in air for several days. The yield is 53% (based on the Schiff base).

For $C_{26}H_{30}N_8O_7Cl_2Br_2Cu_2$

anal. calcd, %:	C, 33.78;	H, 3.27;	N, 12.12;	Cu, 13.75.
Found, %:	C, 33.62;	H, 3.41;	N, 12.03;	Cu, 13.96.

Synthesis of complex II. The Schiff base (0.35 g, 1.0 mmol) was dissolved by methanol (20 mL), to which was added with stirring a methanol solution (10 mL) of $ZnCl_2$ (0.14 g, 1.0 mmol). The mixture was stirred for 1 h at ambient temperature to give a colorless solution. Colorless block-shaped single crystals suitable for X-ray diffraction were formed by slow evaporation of the solution in air for several days. The yield was 72% (based on the Schiff base).

For $C_{14}H_{16}N_2O_3Cl_3BrZn$

anal. calcd, %:	C, 32.85;	H, 3.15;	N, 5.47;	Zn, 12.77.
Found, %:	C, 32.67;	H, 3.41;	N, 5.36;	Zn, 12.95.

X-ray structure determination. Data were collected from selected crystals mounted on glass fibres. The data for the two complexes were processed with SAINT [12] and corrected for absorption using SADABS [13]. Multi-scan absorption corrections were applied with ψ-scans [14]. The structures were solved by direct methods using the program SHELXS-97 and were refined by full-matrix least-squares techniques on F^2 using anisotropic displacement parameters [15]. The amino hydrogen atom in **II**

Table 2. Selected bond lengths (Å) and bond angles (deg) for compounds for **I** and **II**

Bond	*d*, Å	Bond	*d*, Å
		I	
Cu(1)–O(1)	1.907(4)	Cu(1)–N(1)	1.923(5)
Cu(1)–N(2)	2.069(5)	Cu(1)–N(3)	1.975(5)
		II	
Zn(1)–O(1)	1.931(4)	Zn(1)–N(1)	2.018(5)
Zn(1)–Cl(2)	2.242(2)	Zn(1)–Cl(3)	2.234(2)
Angle	**ω, deg**	**Angle**	**ω, deg**
		I	
O(1)Cu(1)N(1)	92.2(2)	O(1)Cu(1)N(3)	90.7(2)
N(1)Cu(1)N(3)	159.2(3)	O(1)Cu(1)N(2)	178.0(2)
N(1)Cu(1)N(2)	85.8(2)	N(3)Cu(1)N(2)	91.3(2)
		II	
O(1)Zn(1)N(1)	95.9(2)	O(1)Zn(1)Cl(3)	114.3(2)
N(1)Zn(1)Cl(3)	106.0(2)	O(1)Zn(1)Cl(2)	113.6(2)
N(1)Zn(1)Cl(2)	114.2(2)	Cl(2)Zn(1)Cl(3)	111.7(1)

was located from a difference Fourier map and refined isotropically with N–H distance restrained to 0.90(1) Å. The remaining hydrogen atoms were placed at the calculated positions. Idealized H atoms were refined with isotropic displacement parameters set to 1.2 (1.5 for methyl groups) times the equivalent isotropic *U* values of the parent atoms. The crystallographic data for the complexes are listed in Table 1, selected bond lengths and bond angles for **I** and **II** are given in Table 2.

A full detail of data collections and structure determinations has been deposited with the Cambridge Crystallographic Data Centre (nos. 1415217 (**I**), 1415218 for (**II**); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

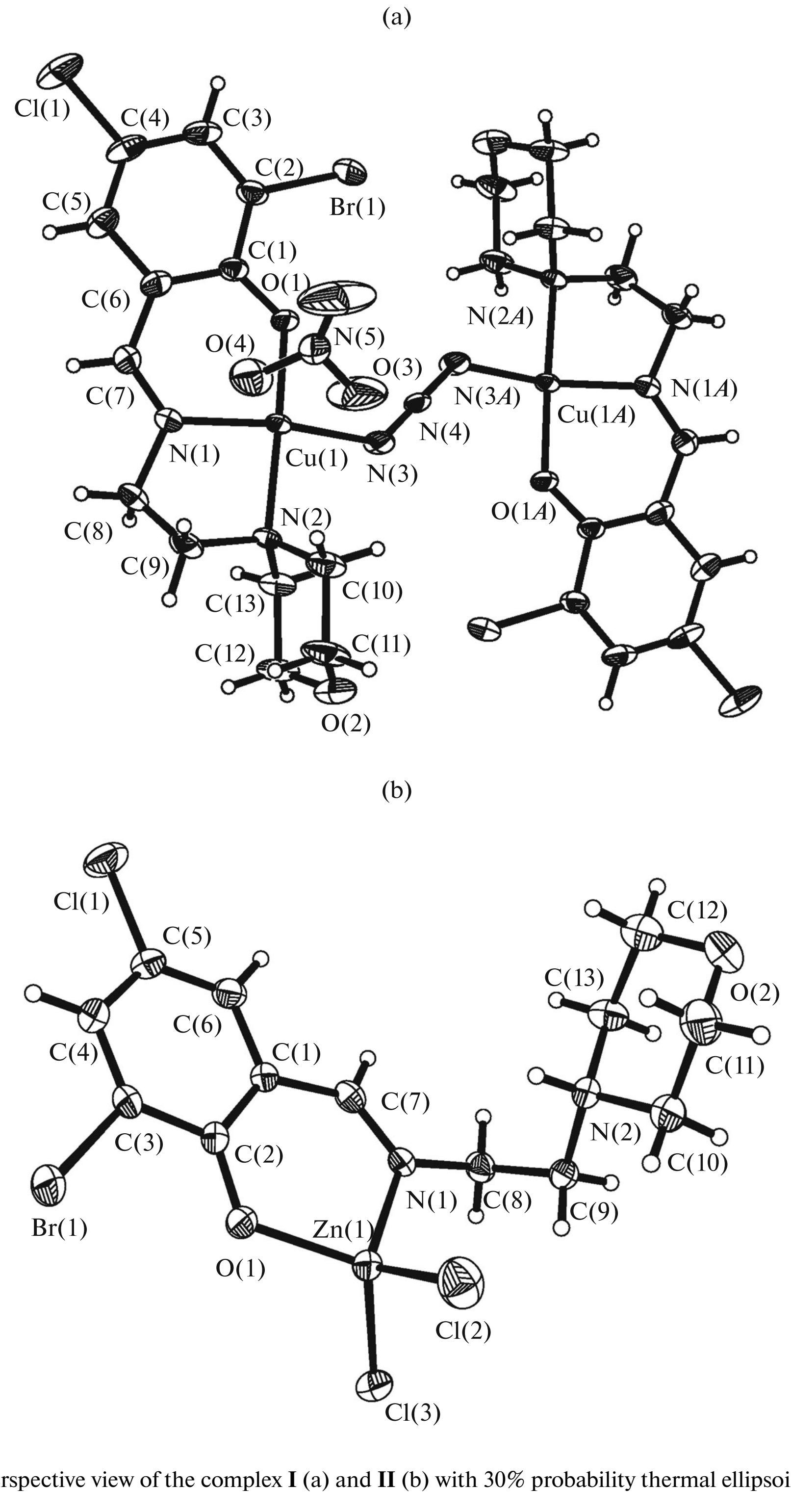
The Schiff base was prepared by the condensation of equimolar quantities of 3-bromo-5-chlorosalicylaldehyde with 2-morpholin-4-ylethylamine in methanol at ambient temperature [10]. The Schiff base prepared in this way was formed in nearly quantitative yield and is of high purity. The complexes were readily synthesized by reaction of the Schiff base and metal salt in methanol at ambient temperature. All the compounds are very stable at room temperature in the solid state, and soluble in common organic solvents, such as methanol, ethanol, and acetonitrile. The results of the elemental analyses are in accord with the composition suggested for the Schiff base and the complexes.

For the IR spectra of both complexes, the strong bands observed at 1617 cm^{-1} for **I** and 1615 cm^{-1} for **II** are assigned to the azomethine group vibration. The strong absorption at 2072 cm^{-1} in the spectrum of **I** is assigned to the stretching vibration of the azide group. The weak and sharp absorption at 3213 cm^{-1} in the spectrum of **II** can be attributed to the vibration of N–H group of the Schiff base ligand.

The molecular structure of complex **I** is shown in figure a. The complex is an end-to-end azido-bridged centrosymmetric dinuclear copper(II) compound. The Cu atom is coordinated by one phenolate O, one imine N, and one morpholine N atoms from a Schiff base ligand, and an azide N atom, forming a square planar geometry. The Schiff base ligand acts as a tridentate ligand, forming a five- and a six-membered chelate rings. The azide anion acts as an end-to-end bidentate ligand, which coordinates to two Cu atoms through two terminal N atoms. The bond distances subtended at the Cu atoms are comparable to those observed in the similar copper(II) complexes with Schiff bases [16–18].

The molecular structure of complex **II** is shown in figure b. The Zn atom in the mononuclear complex is coordinated by one phenolate O and one imine N atoms of the Schiff base ligand and by two chloride atoms, forming a tetrahedral geometry. The Schiff base ligand acts as a bidentate ligand, forming a six-membered chelate ring. The coordinate bond angles are in the range 95.9(2)°–114.3(2)°, as well as the coordinate bond distances are typical and comparable with those observed in the similar zinc(II) complexes with Schiff bases [19, 20], suggesting a slightly distorted tetrahedral coordination of the Zn atom.

Qualitative determination of antimicrobial activity was done using the disk diffusion method [21, 22]. The results are summarized in Table 3. A comparative



Perspective view of the complex **I** (a) and **II** (b) with 30% probability thermal ellipsoids.

study of minimum inhibitory concentration (MIC) values of the Schiff base and the two complexes indicate that the complexes have better activity than the free Schiff base. Generally, this is caused by the greater lipophilic nature of the complexes than the ligand. Such increased activity of the metal chelates can be explained on the basis of chelating theory [23]. On chelating, the polarity of the metal atoms will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of positive charge of the metal atoms with donor atoms. Further, it increases the delocalization of *p*-electrons over the

Table 3. MIC values (μg/mL) for the antimicrobial activities of the tested compounds

Compounds	*Staphylococcus aureus*	*Escherichia coli*	*Candida albicans*
The Schiff base	128	64	>512
I	0.5	4.0	64
II	2.0	8.0	256
Tetracycline	0.32	2.12	>1024

whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membrane and blocks the metal binding sites on enzymes of microorganisms.

From Table 3, it is obvious that the copper complex shows greater antibacterial and antifungi activities against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* when compared to the Schiff base and the zinc complex. Complex **I** has effective activity against *Staphylococcus aureus* and *Escherichia coli*, which is comparable to Tetracycline. Complex **II** also has effective activity against *Staphylococcus aureus* and *Escherichia coli*, but it is much more weak when compared to Tetracycline. It is interesting that the free Schiff base and Tetracycline have no activity against *Candida albicans*, yet the complexes showed weak activity.

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