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Synthesis, Crystal Structures, and Antibacterial Activity of Two Isostructural Trinuclear Zinc(II) Complexes with 2-[(3-Dimethylaminopropylimino)methyl]-6-ethoxyphenol

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Two isostructural azido-bridged trinuclear zinc(II) complexes with the Schiff base 2-[(3-dimethylaminopropylimino)methyl]-6-ethoxyphenol were synthesized and structurally characterized by elemental analysis (C, H, N), FT-IR spectra, and single crystal X-ray diffraction. Both complexes possess crystallographic two-fold rotation axis symmetry. The central Zn atom in each complex is six-coordinated in an octahedral geometry, while the terminal Zn atoms in each complex are five-coordinated in distorted square pyramidal geometries. The antibacterial activity of the complexes and the Schiff base against the bacteria *Staphylococcus aureus*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, and *Streptococcus agalactiae* was investigated.

Keywords antibacterial, crystal structure, Schiff base, synthesis, zinc

INTRODUCTION

Schiff base compounds are readily synthesized from the condensation reaction between aldehydes with primary amines, which have been widely investigated for their biological activities, such as antibacterial, antifungal, and antitumor.[1–5] The imine N atom and some other donor atoms of the Schiff base compounds easily coordinate to metal atoms, forming versatile complexes.[6–8] A number of studies show that the antibacterial activities of the metal complexes were increased when compared with the corresponding Schiff bases.[9,10] It was also reported that salicylaldehyde derivatives with halide atoms in the aromatic rings showed good antibacterial activities.[11] In the present work, two isostructural halide-coordinated zinc complexes, $[Zn\{ZnClL(\mu_{1,1}\text{-}N_3)\}]_2$ (**1**) and $[Zn\{ZnBrL(\mu_{1,1}\text{-}N_3)\}]_2$ (**2**), where L is the deprotonated form of 2-[(3-dimethylaminopropylimino)methyl]-6-ethoxyphenol (HL), were synthesized and structurally characterized. The antibacterial activity of the complexes and the Schiff base against the bacteria *Staphylococcus aureus*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, and *Streptococcus agalactiae* was investigated.

EXPERIMENTAL

Materials and Measurements

3-Ethoxysalicylaldehyde and *N*, *N*-dimethylpropane-1,3-diamine were purchased from Aldrich. Other chemicals were commercially available and were used without further purification. Elemental analyses (C, H, N) were carried out using Elemental CHN Analyzer Vario El III. FT-IR spectra were recorded using KBr discs on a Nicolet AVATAR 360 spectrophotometer. The ^{1}H NMR spectrum was recorded on a Varian INOVA300 (300 MHz) pulse Fourier-transform NMR spectrometer in $CDCl_3$.

Synthesis of the Schiff Base HL

A methanol solution (20 mL) of 3-ethoxysalicylaldehyde (1 mmol, 166 mg) was added to a methanol solution (20 mL) of *N*, *N*-dimethylpropane-1,3-diamine (1 mmol, 102 mg) to give yellow solution. The solution was evaporated to give yellow micro-crystals which were washed with methanol and dried in air. Yield: 87%. Anal. calcd. for $C_{14}H_{22}N_2O_2$: C, 67.2; H, 8.9; N, 11.2%. Found: C, 66.8; H, 8.9; N, 11.0%. IR data (cm^{-1}): 3423 w, 2931 m, 2851 w, 1645 s, 1520 m, 1483 m, 1459 m, 1398 w, 1339 w, 1290 m, 1218 s, 1165 m, 1116 m, 1030 w, 965 w, 835 m, 692 w, 650 w, 616 w, 466 w. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.31 (t, 3H), 1.73 (m, 2H), 2.29 (s, 6H), 2.37 (t, 2H), 3.54 (t, 2H), 3.95 (q, 2H), 6.62–7.03 (m, 3H), 8.12 (s, 1H).

Synthesis of the Complex (1)

To the methanol solution (10 mL) of HL (0.1 mmol, 25.0 mg) and NaN_3 (0.1 mmol, 6.5 mg) was added a methanol solution (10 mL) of $ZnCl_2$ (0.1 mmol, 13.7 mg) with stirring and the mixture was stirred under refluxed for 30 min. The clear colorless solution was left at room temperature to give colorless block-shaped single crystals. Yield: 37 % with respect to $ZnCl_2$. Analysis calcd. for $C_{28}H_{42}Cl_2N_{10}O_4Zn_3$: C, 39.6; H, 5.0; N,

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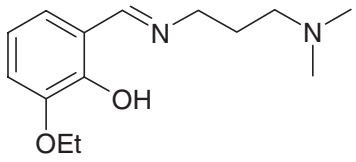


SCH. 1. The Schiff base HL.

16.5 %. Found: C, 39.1; H, 5.3; N, 16.8 %. IR data (cm^{-1}): 2930 w, 2853 w, 2038 vs, 1628 s, 1532 m, 1445 w, 1286 m, 1223 m, 1181 m, 1169 w, 1123 m, 1027 w, 977 w, 823 w, 745 m, 640 w, 577 w.

Synthesis of the Complex (2)

The preparation of complex (**2**) was similar to that described for complex (**1**), which was obtained from HL, NaN_3 and $ZnBr_2$. Yield: 43 % with respect to $ZnBr_2$. Analysis calcd. for $C_{28}H_{42}Br_2N_{10}O_4Zn_3$: C, 35.8; H, 4.5; N, 14.9 %. Found: C, 35.5; H, 4.9; N, 14.4 %. IR data (cm^{-1}): 2930 w, 2853 w, 2039 vs, 1628 s, 1532 m, 1445 w, 1285 m, 1222 m, 1181 m, 1168 w, 1123 m, 1026 w, 973 w, 825 w, 741 m, 640 w, 573 w.

TABLE 1
Crystal data and structural refinement details for complexes (**1**) and (**2**)

Complex	(**1**)	(**2**)
Chemical formula	$C_{28}H_{42}Cl_2N_{10}O_4Zn_3$	$C_{28}H_{42}Br_2N_{10}O_4Zn_3$
Formula weight	849.73	938.65
Color and habit	colorless, block	colorless, block
T(K)	298(2)	298(2)
Radiation (λ, Å)	Mo Kα (0.71073)	Mo Kα (0.71073)
Crystal system	Monoclinic	Monoclinic
Space group	$C2/c$	$C2/c$
a(Å)	23.061(4)	23.117(4)
b(Å)	10.568(2)	10.5868(16)
c(Å)	17.306(3)	17.271(3)
β (^{o})	120.967(2)	121.111(2)
V (Å^3)	3616.3(12)	3618.9(9)
Z	4	4
d_{calcd} (g cm^{-3})	1.561	1.723
μ (mm^{-1})	2.169	4.228
F(000)	1744	1888
No. of unique data	3742	3906
No. of restraints	0	0
No. of parameters	216	216
GOF on F^2	1.030	1.034
R_1^a [$I \geq 2\sigma(I)$]	0.0377	0.0331
R_1^a (all data)	0.0858	0.0766
wR_2^b [$I \geq 2\sigma(I)$]	0.0535	0.0463
wR_2^b (all data)	0.0931	0.0816

$^a R_1 = \sum ||Fo| - |Fc|| / \sum |Fo|$, $^b wR_2 = [\sum w(Fo^2 - Fc^2)^2 / \sum w(Fo^2)^2]^{1/2}$.

TABLE 2
Selected bond lengths (Å) and angles (°) for complexes (**1**) and (**2**)

		(**1**)	
		Bond lengths	
Zn1-O1	2.350 (2)	Zn1-O2	2.013 (2)
Zn1-N3	2.066 (3)	Zn2-O2	2.080 (2)
Zn2-N1	2.096 (3)	Zn2-N2	2.114 (3)
Zn2-N3	2.180 (3)	Zn2-Cl1	2.2708 (11)
		Bond angles	
O2A-Zn1-O2	175.3 (1)	O2A-Zn1-N3	99.1 (1)
O2-Zn1-N3	78.2 (1)	N3-Zn1-N3A	111.3 (2)
O2A-Zn1-O1	110.7 (1)	O2-Zn1-O1	73.1 (1)
N3-Zn1-O1	145.4 (1)	N3A-Zn1-O1	92.1 (1)
O1-Zn1-O1A	80.6 (1)	O2-Zn2-N1	84.6 (1)
O2-Zn2-N2	118.6 (1)	N1-Zn2-N2	91.8 (1)
O2-Zn2-N3	74.2 (1)	N1-Zn2-N3	158.1 (1)
N2-Zn2-N3	93.4 (1)	O2-Zn2-Cl1	133.0 (1)
N1-Zn2-Cl1	99.6 (1)	N2-Zn2-Cl1	108.1 (1)
N3-Zn2-Cl1	99.0 (1)		
		(**2**)	
		Bond lengths	
Zn1-O1	2.0159 (18)	Zn1-O2	2.347 (2)
Zn1-N3	2.059 (2)	Zn2-O1	2.0752 (19)
Zn2-N1	2.096 (2)	Zn2-N2	2.111 (3)
Zn2-N3A	2.174 (2)	Zn2-Br1	2.4053 (6)
		Bond angles	
O1A-Zn1-O1	175.6 (1)	O1A-Zn1-N3	78.2 (1)
O1-Zn1-N3	99.3 (1)	N3-Zn1-N3A	111.3 (2)
O1A-Zn1-O2	110.5 (1)	N3-Zn1-O2A	145.3 (1)
N3-Zn1-O2	92.5 (1)	O1-Zn1-O2	73.1 (1)
O2-Zn1-O2A	79.9 (1)	O1-Zn2-N1	84.5 (1)
O1-Zn2-N2	117.0 (1)	N1-Zn2-N2	91.4 (1)
O1-Zn2-N3A	74.4 (1)	N1-Zn2-N3A	158.4 (1)
N2-Zn2-N3A	94.3 (1)	O1-Zn2-Br1	133.7 (1)
N1-Zn2-Br1	99.1 (1)	N2-Zn2-Br1	109.1 (1)
N3A-Zn2-Br1	98.6 (1)		

Crystal Structure Determination

Crystals with dimensions 0.27 × 0.25 × 0.25 mm^3 for (**1**) and 0.18 × 0.17 × 0.17 mm^3 for (**2**) were mounted and data were collected at 298(2) K on a Bruker SMART 1000 CCD area-detector with Mo Kα radiation (λ = 0.71073 Å). A total of 14159 reflections were collected in the range $2.06^\circ < \theta < 26.50^o$ ($-28 \leq h \leq 28$, $-13 \leq k \leq 13$, $-21 \leq l \leq 21$). A total of 14632 reflections were collected in the range $2.06^\circ < \theta < 27.00^\circ$ ($-29 \leq h \leq 29$, $-13 \leq k \leq 13$, $-21 \leq l \leq 22$). Empirical absorption corrections were applied using the SADABS program.[12] Both structures were solved by direct methods and refined by a full matrix least-squares technique based on F^2 using the SHELXL 97 program.[13] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were

refined as riding atoms. Selected crystallographic data and structure determination parameters for complexes (**1**) and (**2**) are given in Table 1. Selected bond lengths and angles for (**1**) and (**2**) are listed in Table 2. X-ray crystallographic data for the complexes have been deposited with the Cambridge Crystallographic Data Centre (The Director, CCDC, 12 Union Road, Cambridge, CB2 1 EZ, UK; e-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk; fax: +44-(0)1223-336033) and are available free of charge on request, quoting the deposition number CCDC 752998 for (**1**) and 752999 for (**2**)).

Antibacterial Test

The two complexes and the Schiff base were determined against the bacteria *Staphylococcus aureus*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, and *Streptococcus agalactiae*. Microorganisms were cultured on Müller–Hinton agar medium. The gentamicin was used as a reference. After drilling wells on medium using a 6 mm cork borer, 100 μL of solution from different compound were poured into each well. The plates were incubated at 37°C overnight. The diameter of the inhibition zone was measured to the nearest. Each test was carried out in triplicate, and the average was calculated for inhibition zone diameters. A blank containing only methanol showed no inhibition in a preliminary test. The macro-dilution broth susceptibility assay was used for the evaluation of minimal inhibitory concentration (MIC). By including 1 mL Müller-Hinton broth in each test, and then adding 1 mL extract with concentration 100 mg mL^{-1} in the first tube, we made a serial dilution of this extract from first tube to last tube. Bacterial suspension prepared to match the turbidity of 0.5 Mcfarland turbidity standards. Matching this turbidity provides a bacterial inoculum concentration of 1.5×10^8 cfu mL^{-1}. Then 1 mL of bacterial suspension was added to each test tube. After incubation at 37°C for 24 h, the last tube was determined as the MIC without turbidity.

RESULTS AND DISCUSSION

The Schiff base HL was synthesized by the condensation of 3-ethoxysalicylaldehyde with *N*, *N*-dimethylpropane-1,3-diamine in a methanol solution with good yield and high purity. The two zinc complexes were synthesized by the reaction of equimolar quantities of the Schiff base, NaN_3 and zinc halide in methanol (Scheme 2). The Schiff base and the two complexes were stable at room temperature in air. The molar conductivities at 10^{-3} mol L^{-1} concentration for the complexes in acetonitrile were in the expecting range for non-electrolytes.[14]

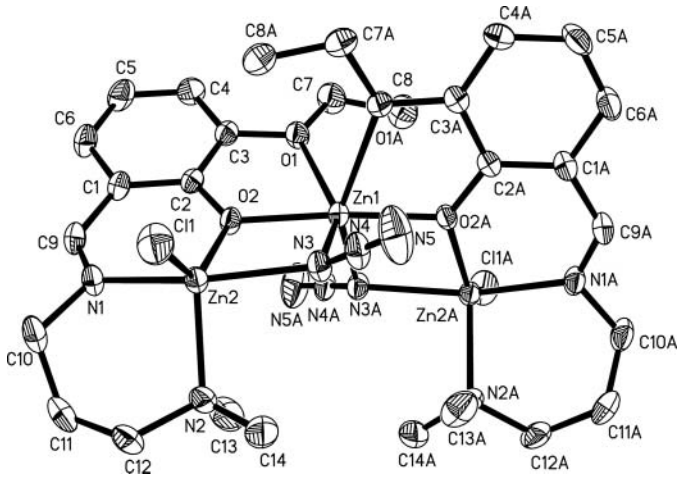
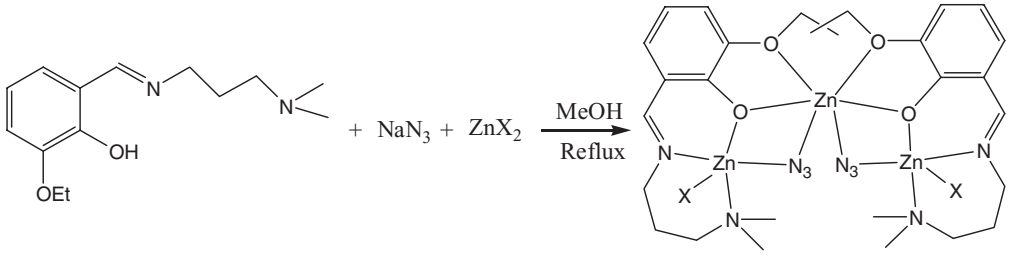


FIG. 1. Molecular structure of (**1**) at 30% probability displacement.

Structure Description of the Complexes

The molecular structures of the isostructural azido-bridged trinuclear zinc(II) complexes (**1**) and (**2**) are shown in Figures 1 and 2, respectively. Both complexes possess crystallographic two-fold rotation axis symmetry. The azide ligands adopt end-on coordination mode. The Zn···Zn distances are 3.276(2) Å in (**1**) and 3.268(2) Å in (**2**).

The central Zn atom in each complex is six-coordinated by two phenolic O and two ether O atoms from two Schiff base ligands, and by two terminal N atoms from two bridging azide groups, forming an octahedral coordination. The coordinate bond lengths and angles about the central Zn atoms in both complexes are comparable to each other. The octahedral coordinations in the complexes are distorted, as evidenced by the bond angles. The three *trans* angles subtended at Zn1 are in the range 145.4(1)–175.3(1)° in (**1**) and 145.2(1)–175.6(1)° in (**2**), and the other angles subtended at Zn1 are in the range 73.1(1)–111.3(2)° in (**1**) and 73.1(1)–111.3(2)° in (**2**), all of which are much deviated from the values for an ideal octahedral geometry.



SCH. 2. The synthesis procedure of the complexes [X = Cl for (**1**) and Br for (**2**)].

TABLE 3
Zone of growth inhibition of the test compounds against the bacteria

	Zone of growth inhibition (mm)			
Compound	*Staphylococcus aureus*	*Bacillus anthracis*	*Pseudomonas aeruginosa*	*Streptococcus agalactiae*
HL	9	13	19	11
(**1**)	20	27	32	17
(**2**)	17	22	25	15
gentamicin	30	35	17	15

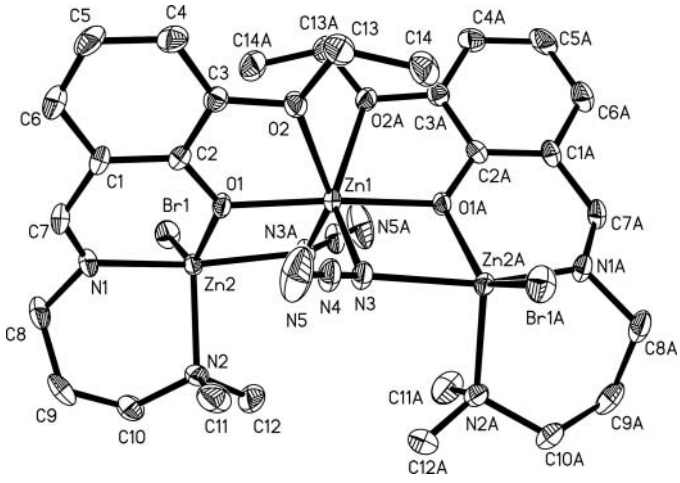


FIG. 2. Molecular structure of (**2**) at 30% probability displacement.

The terminal Zn atom in each complex is five-coordinate in a square pyramidal geometry, with the basal plane defined by one phenolic O and one imine N atoms of a Schiff base ligand, one terminal N atom of an azide group, and a halide atom (Cl for (**1**) and Br for (**2**)), and with the apical position occupied by one amine N atom of a Schiff base ligand. The square-pyramidal geometry is distorted, with the τ value of 0.418 for (**1**) and 0.412 for (**2**).[15] The Zn-O and Zn-N bonds in the square pyramidal coordinations in both complexes are comparable to each other. The Zn-Cl bonds in (**1**) are much shorter than the Zn-Br bonds in (**2**). The bond angles among the apical and the basal donor atoms are in the range 91.8(1)–118.6(1)° for (**1**) and 91.4(1)–117.0(1)° for (**2**), which are deviate from the values for an ideal square pyramidal geometry.

In both complexes, the coordinate bond lengths are comparable to the corresponding values observed in other Schiff base zinc complexes.[16–18]

IR Spectra

Compared with the IR spectrum of the Schiff base ligand, it was shown that the ν(C=N) absorption band at 1645 cm^{-1} are shifted to lower frequencies by 17 cm^{-1} in the complexes, indicating that the Schiff base ligand is coordinated to the Zn atoms through the imine N atom. The absence of the OH bands of the free Schiff base ligands in the complexes indicates that the phenol groups have been deprotonated and coordinated to the Zn atoms. The strong absorption bands at 1218 cm^{-1} in the Schiff base ligand assigned to the phenolic C–O linkage, which is shifted towards lower wave numbers of 1181 cm^{-1} for the complexes, confirming the involvement of OH groups in coordination. The strong absorption bands indicative of the azide groups are at 2038 cm^{-1} for (**1**) and 2039 cm^{-1} for (**2**).

Antibacterial Activity

The antibacterial activity of the Schiff base, the two complexes, and the reference gentamicin against the bacteria *Staphylococcus aureus*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, and *Streptococcus agalactiae* as zone of growth inhibition is summarized in Table 3. The MIC values are listed in Table 4.

The antibacterial activities of the two complexes are stronger than those of the Schiff base HL. It is notable that the antibacte-

TABLE 4
MIC values of the test compounds against the bacteria

	MIC (mg mL^{-1})			
Compound	*Staphylococcus aureus*	*Bacillus anthracis*	*Pseudomonas aeruginosa*	*Streptococcus agalactiae*
HL	13.0	11.5	9.0	12.0
(**1**)	5.5	3.5	5.5	7.5
(**2**)	7.0	5.0	4.0	11.0
gentamicin	3.5	3.0	7.0	20.0

rial activity of the chloride-coordinated complex (**1**) is stronger than that of the bromide-coordinated complex (**2**), and even comparable with the gentamicin.

CONCLUSION

Two isostructural azido-bridged trinuclear zinc(II) complexes with the Schiff base 2-[(3-dimethylaminopropylimino)-methyl]-6-ethoxyphenol has been synthesized and structurally characterized. The Schiff base coordinates to the Zn atoms through the phenolic O, imine N and amine N atoms. Both complexes show stronger antibacterial activity than that of the free Schiff base, and the antibacterial activity of the chloride-coordinated zinc complex is stronger than that of the bromide-coordinated zinc complex.

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