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Synthesis, Crystal Structure and Antibacterial Activity of *N'*-(2,4-Dichlorobenzylidene)-4-methylbenzohydrazide

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A Schiff base compound, *N'*-(2,4-dichlorobenzylidene)-4-methylbenzohydrazide ($C_{15}H_{12}N_2OCl_2$) has been synthesized by the condensation of 4-methylbenzohydrazide and 2,4-dichloro benzaldehyde in an ethanol solution. The Schiff base was characterized by ^{1}H NMR, MS and single crystal X-ray diffraction. The crystal structure and antibacterial activity of the compound are reported herein. The crystal belongs to the triclinic system, space group $P\bar{1}$ with a = 6.9796 (4), b = 11.5134 (6), c = 12.5679 (7) Å, α = 115.274(1)°, β = 97.009 (1)°, γ = 94.578 (1)°, Z = 2, V = 896.60 (9) Å, D_c = 1.375 g/cm^3, Mr = 371.25, λ(Mok$_\alpha$) = 0.71073 Å, μ = 0.379 mm^{-1}, F (000) = 388. The final R = 0.0344, wR = 0.0984 for 2955 observed reflections with I >2σ (I). The two benzene rings are nearly coplanar with the dihedral angle 1.56°. Three classical intermolecular hydrogen bonds exist in the crystal. The compound molecules are connected through hydrogen bonds to generate a two-dimensional network. The results of preliminary biological activity assay showed that the title compound exhibited good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

Keywords: Schiff base, Crystal structure, Antibacterial activity.

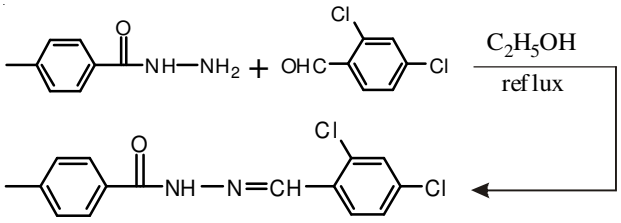
INTRODUCTION

Over the past decades, Schiff base and their metal complexes have been extensively investigated because of their wide range of applications including catalysts[1,2], medicine[3,4] and anti-corrosion agents[5]. Schiff bases are also important intermediates in synthesis of some bioactive compounds[6,9] and are potent antibacterial, antifungal, antiviral, antiinflammatory and anti-tumor agents[10-15]. Besides, Schiff base ligands play an important role in the development of coordination chemistry, which could be attributed to their strong coordination ability and versatile coordination modes[16,17]. They can easily form stable complexes with most transition metal ions[18,19]. Induced by a wide variety of biological activities[20,21] exhibited by Schiff bases and in continuation of our efforts in search of potent molecules exhibiting antibacterial activity, we have synthesized *N'*-(2,4-dichlorobenzylidene)-4-methylbenzohydrazide by the condensation of 4-methylbenzohydrazide and 2,4-dichlorobenzylidene in an ethanol solution and its crystal structure was determined by X-ray crystallography. Furthermore, preliminary antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* was tested.

EXPERIMENTAL

Reagents and measurements: All chemicals and reagents were of analytical grade and used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE-400 MHz NMR spectrometer using TMS as internal standard. Mass spectrum was obtained with a Thremo LCQ DECA XP spectrometer (APCI).

Synthesis of *N'*-(2,4-dichlorobenzylidene)-4-methylbenzohydrazide: The synthesis procedure is shown in **Scheme-I**. 4-Methylbenzohydrazide (0.30 g, 2 mmol) and 2,4-dichlorobenzaldehyde (0.35 g, 2 mmol) were dissolved in ethanol (10 mL). The mixture was refluxed for 2 h until the disappearance of the starting materials (monitored by TLC) to give a clear white solution. The excess ethanol was evaporated under reduced pressure, the mixture was filtered. Then, the crude product was recrystallized from methanol to give 0.38 g colorless crystals with a yield of 61.93 %. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.44 (s, 3H, CH_3), 7.22-7.33 (m, 3H, ArH), 7.39 (d, *J* = 1.9 Hz, 1H, ArH), 7.84 (d, *J* = 7.8 Hz, 2H, ArH), 8.09 (s, 1H, ArH), 8.65 (s, 1H, NH-N), 9.79 (s, 1H, CH=N); APCI MS: (*m/z*) 372.4 (M + 1, 100). Single crystals suitable for X-ray



Scheme-I: Synthesis route of the title compound

structural determination were obtained by slowly evaporating the methanol solution of the product under room temperature.

X-ray crystal structure determination: A yellow single crystal of the title compound (0.48 × 0.41 × 0.36 nm) was selected and mounted on the top of a glass fiber. X-ray single-crystal diffraction measurement was carried out at 273 (2) K on a Bruker Smart APEX 1000 CCD area diffractometer equipped with a graphite-monochromatic MoK_α radiation (λ = 0.71073 Å) for data collection. The structure was solved by direct methods with SHELXS-97 program and refined by full-matrix least-squares techniques on F^2 with SHELXL-97 program[22,23]. All non-H atoms were refined anisotropically and allowed to ride on their parent carbon atoms. A full-matrix least-squares refinement gave the final R = 0.0344 and wR = 0.0984 ($w = 1/[\sigma^2(F_o^2) + (0.0564P)^2 + 0.2789P]$, where $P = (F_o^2 + 2F_c^2)/3$). S = 1.077, $(\Delta/\sigma)_{max}$ = 0.005, $(\Delta\rho)_{max}$ = 0.313 e Å^{-3}, $(\Delta\rho)_{min}$ = -0.213 e Å^{-3}. All calculations were performed using the crystal structure crystallographic software package except for the refinement. All H atoms were placed in the geometrically idealized positions and allowed to ride on their respective parent atoms, with the C-H distance of 0.9500-0.9800 Å and U_{iso} (H) = 1.2 or 1.5 U_{eq} (C/O). The crystallographic data and experimental details for structural analysis are summarized in Table-1.

Antibacterial activity measurement: The antibacterial activity of the present compound was tested against *S. aureus* and *E. coli* by the agar diffusion method[24]. The compound was dissolved in DMF. After encapsulation, autoclave sterilization at 121 °C for 20 min, nutrient agar was transferred to Petri dish and frozen after cooling. The test strains were spread on the solid nutrient agar surface and then three stainless steel tubes (7.8 × 6 × 10 mm) were placed on the surface vertically. 100 µL compound with certain concentration was injected into each steel tube. The inhibition was labeled as the diameter of transparent bacteriostatic circle after an incubation period of 24 h at 37 °C. All the samples were tested for three times with the average value as the final result.

RESULTS AND DISCUSSION

The selected bond lengths and bond angles are summarized in Table-1. The hydrogen bond lengths and bond angles are presented in Table-2. The molecular structure and packing diagram of title compound are shown in Figs. 1 and 2, respectively. The two benzene rings are nearly coplanar with the dihedral angle 1.56°. The N-N bond length of 1.373 (2) Å is somewhat shorter than that observed in related literature[25]. The N(1)-C(7) bond length is 1.362 (2) Å which is shorter than the isolated N-C single bond (1.471 Å) and longer than the N=C double bond (1.273 Å) because of the conjugation effects in the molecule, indicating that a partially conjugated system operates in this Schiff base. While the N(2)-C(8) bond length is 1.279(2) Å agree with the N=C double bond (1.273 Å). The torsion angle C(7)-C(1)-C(2)-C(3), C(1)-C(7)-N(1)-N(2) and C(9)-C(8)-N(2)-N(1) are 178.83 (12)°, -179.32 (11)°and -179.85 (13)°, respectively. From these results, it is known that all the bond lengths and bond angles are in normal ranges as compared to those observed in a similar Schiff base.

In the structure, the three classical intermolecular hydrogen bonds link the molecule into a two-dimensional network which further stabilizes the crystal structure. The distances between the donor and acceptor are 2.9309(18) Å (N(1)-H(1A)···O(3), symmetry code: -x + 2, -y + 2, -z), 2.7858(17) Å (O(2)-H(2A)···O(1), symmetry code: -x + 2, -y + 2, -z) and 2.7387(18) Å (O(3)-H(3A)···O(2), symmetry code: -x + 2, -y + 2, -z), respectively.

The antibacterial activity of the present Schiff base was evaluated against *S. aureus* and *E. coli*. The test results are

TABLE-1
SELECTED BOND LENGTHS (Å) AND BOND ANGLES (°)

Bond	Dist.	Bond	Dist.	Bond	Dist.
C(1)-C(6)	1.394(2)	C(8)-N(2)	1.279(2)	C(16)-O(2)	1.413(2)
C(1)-C(2)	1.392(2)	C(8)-C(9)	1.463(2)	C(17)-O(3)	1.418(2)
C(1)-C(7)	1.492(2)	C(9)-C(10)	1.398(2)	N(1)-N(2)	1.373(2)
C(2)-C(3)	1.387(2)	C(9)-C(14)	1.396(2)	N(1)-H(1A)	0.8800
C(3)-C(4)	1.393(2)	C(10)-C(11)	1.385(2)	O(2)-H(2A)	0.8400
C(4)-C(15)	1.507(2)	C(11)-C(12)	1.378(2)	O(3)-H(3A)	0.8400
C(7)-O(1)	1.230(2)	C(12)-C(13)	1.386(2)	Cl(1)-C(10)	1.739(2)
C(7)-N(1)	1.362(2)	C(13)-C(14)	1.382(2)	Cl(2)-C(12)	1.741(2)
Angle	(°)	Angle	(°)	Angle	(°)
C(2)-C(1)-C(6)	118.46(14)	O(1)-C(7)-N(1)	121.31(14)	C(12)-C(11)-C(10)	118.07(15)
C(2)-C(1)-C(7)	124.58(14)	O(1)-C(7)-C(1)	121.73(14)	C(11)-C(12)-C(13)	121.87(15)
C(6)-C(1)-C(7)	116.95(14)	N(1)-C(7)-C(1)	116.96(13)	C(11)-C(12)-Cl(2)	118.99(13)
C(3)-C(2)-C(1)	120.15(14)	N(2)-C(8)-C(9)	120.00(14)	C(13)-C(12)-Cl(2)	119.13(13)
C(2)-C(3)-C(4)	121.69(15)	C(14)-C(9)-C(10)	117.24(14)	C(14)-C(13)-C(12)	118.79(15)
C(5)-C(4)-C(3)	117.68(15)	C(14)-C(9)-C(8)	121.23(14)	C(13)-C(14)-C(9)	121.68(15)
C(5)-C(4)-C(15)	121.38(15)	C(10)-C(9)-C(8)	121.53(14)	C(7)-N(1)-N(2)	118.16(13)
C(3)-C(4)-C(15)	120.93(16)	C(11)-C(10)-C(9)	122.35(15)	C(8)-N(2)-N(1)	116.00(13)
C(6)-C(5)-C(4)	121.15(15)	C(11)-C(10)-Cl(1)	117.13(12)	—	—
C(5)-C(6)-C(1)	120.86(15)	C(9)-C(10)-Cl(1)	120.52(12)	—	—

TABLE-2
HYDROGEN BOND LENGTHS (Å) AND BOND ANGLES (°)

D-H···A	D(D-H)	D(H···A)	D(D···A)	∠DHA/(°)
N(1)-H(1A)···O(3)	0.88	2.08	2.9309(18)	162.9
O(2)-H(2A)···O(1)	0.84	1.99	2.7858(17)	157.0
O(3)-H(3A)···O(2)#1	0.84	1.90	2.7387(18)	175.5

Symmetry transformation used to generate the equivalent atoms: (#1) – x + 2, -y + 2, -z

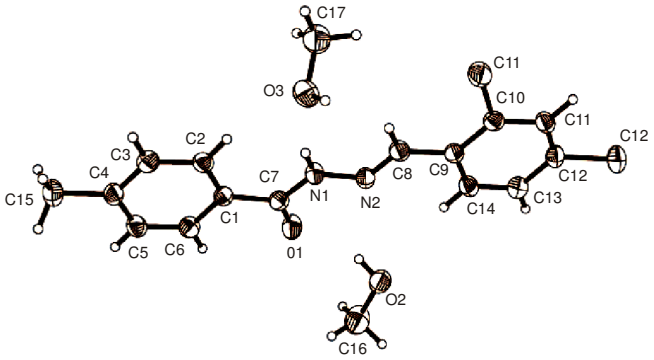


Fig. 1. Molecular Structure of the title compound

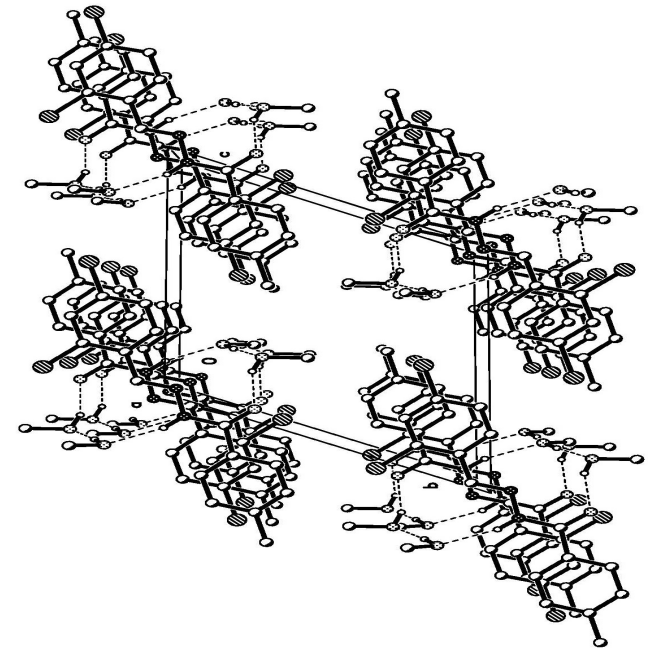


Fig. 2. Packing diagram of the title compound

reported in Table-3. It can be observed that the title compound exhibits antibacterial activity against both test bacterial organisms. The inhibition effect is strengthened with the increase of the concentration in the test range. Besides, the title compound shows nearly the same antibacterial activity against *E. coli* and *S. aureus*.

TABLE-3
ANTIBACTERIAL ACTIVITY OF THE TITLE COMPOUND

Compound	Concentration (mg/mL)	Diameter of inhibition zone (mm)	
		S. aureus	*E. coli*
Title compound	5.0	13.0	13.0
	2.5	12.8	12.7
	1.25	12.3	12.3
	0.625	11.7	11.8
DMF (control)		11.5	11.7

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