

Spectroscopic Studies, Crystal Structure and Biological Activity of {ethyl 4-(2-hydroxy-benzylideneamino) benzoate} Schiff Base and its Copper Complex

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Abstract: Ethyl4-(2-hydroxy-benzylideneamino) benzoate Schiff base ($C_{16}H_{15}NO_3$), was synthesized and the structure was elucidated on the bases of elemental analysis, 1H NMR, X-ray, UV-VIS, IR, and Mass spectroscopy. The X-ray establish the conformation of the molecule, which indicate the compound is crystalline in the monoclinic $C2/c$ with $a = 16.0916(5)\text{\AA}$, $b = 6.0315(2)\text{\AA}$, $c = 29.0072(10)\text{\AA}$, $\alpha = 90.00^\circ$, $\beta = 101.856(2)^\circ$, $\gamma = 90.00^\circ$, $V = 2755.3(2)\text{\AA}^3$, $Z = 8$ and $R_{int} = 0.032$. Also, the Cu complex was prepared and its structure was elucidated on the bases of elemental analysis, electronic, IR spectra, and conductance measurements. Also, the biological activity of the Schiff base and its Cu complex were studied.

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1. Introduction

Schiff base compounds containing the azomethine (imine) group ($-RC=N-$) are usually prepared by the condensation of a primary amine with an active carbonyl compound ⁽¹⁾.

It has been often used as chelating agents (ligands) in the field of coordination chemistry and their metal complexes are of great interest for many years. It is well known that O, N and S atoms play a key role at the active sites of numerous metallobiomolecules in the coordination with metals ⁽²⁾.

Schiff bases are well known for their biological applications as antibacterial, antifungal, anticancer and antiviral agents ^(3,4). Also, Schiff base metal complexes have been widely studied because they have industrial, antifungal, antibacterial, anticancer herbicidal applications ⁽⁵⁾, antitubercular activities ⁽⁶⁾ and chelating abilities which give it attracted remarkable attention ⁽⁷⁾. Benzocaine was prepared by direct esterification of p-aminobenzoic acid with absolute ethanol, in the presence of sulfuric acid as dehydrating agent ⁽⁸⁾.

In the present work, the Schiff base (ethyl 4-(2-hydroxybenzylidene-amino) benzoate) and its Cu complex were prepared and X-ray crystal structure of the Schiff base was studied. The nature of bonding in the isolated Schiff base and its Cu complex were elucidated by examining the elemental analysis, UV-VIS, IR and molar ratio methods.

2. Experimental

2.1. Materials

Benzocaine (BZC) was obtained from pharco Co for pharm, Egypt. Salicylaldehyde (SA) was

obtained from Morgan chemical IND Co, Egypt. Triethylamine was obtained from Scharlau chemical, European Union. Glacial acetic acid was obtained from El-Nasr pharmaceutical chemicals Co, Egypt. Ethanol 99% was obtained from Technolgene Corp, Dokki, Egypt. Diethyl ether and N,N-dimethyl formamide (DMF) were obtained from Sd finne-Chem limited India.

2.2. Instruments

IR spectrum for Schiff base (I) and its Cu complex (I_a) were recorded on a Perkin Elmer spectrophotometer 57928 RXIFT-IR system. The electronic spectra for Schiff base (I) and its Cu complex (I_a) were recorded by Perkin Elmer Lambda 35 Spectrophotometer using DMF as solvent.

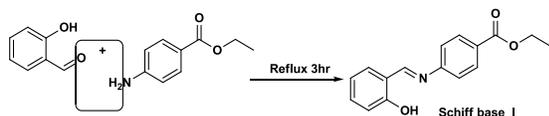
Conductance TDS Engineered system, U.S.A, was employed for the conductometric titration in Al-Azhar university, Cairo, Egypt. 1H NMR spectra of Schiff base were recorded by a Varian, USA, Gemini 200 MHz instrument using TMS as an internal standard and DMSO-d₆ as solvent, and microanalysis for Schiff base and its Cu-complex were carried out in the Micro-analytical Center, Cairo University, Cairo, Egypt.

Metal analyses were determined by atomic absorption (AAS Vario6 in spectroscopy analytical lab. Faculty of Science, Al-Azhar University, Cairo, Egypt.

2.3. Synthesis of Schiff base (I)

The Schiff-bases was prepared as in (scheme 1) by the usual condensation reaction ⁽⁹⁾, in which salicylaldehyde (SA) (0.1 mol) was drop wisely added to the amine (benzocaine) (0.1 mol) with

continuous stirring, (drops of glacial acetic acid⁽¹⁰⁾ was added). After complete addition the reaction mixture was heated under reflux for about three hours. The products (imines) were separated after cooling at room temperature by filtration. The isolated compound was purified by recrystallization from ethanol. orange prisms of compound (I) were obtained (scheme 1). The melting point was found to be 88°C.



Scheme 1. Synthesis of Schiff base (I).

2.4. Synthesis of complex

2.4.1. Studying the Molar ratio

2.4.1.1. Conductometric Titration

The conductometric titration Figure (1), is performed by titrating 10 ml of 1×10^{-3} M copper ion solution with increasing volume of 1×10^{-3} M complexing agent solution of Schiff-base, using DMF as solvent, and the conductance was then recorded after stirring the solution for about 2 minutes. By plotting the conductance value Vs. milliliter of the reagent added, and applying the least square equation the ratio was 1:1 as shown in figure 1⁽¹¹⁾.

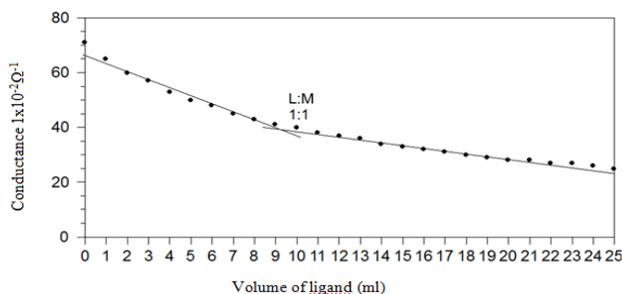


Figure 1. Conductometric titration of Schiff base (I) (1×10^{-3} M) with $(\text{CH}_3\text{COO})_2 \cdot \text{Cu} \cdot \text{H}_2\text{O}$ (1×10^{-3} M) system.

2.4.1.2. Spectroscopic Molar ratio testing

In the present investigation, 2 ml solution Cu^{+2} ion concentration were kept constant at 1×10^{-3} M, while that the ligands were regularly varied from 0.2×10^{-3} to 2×10^{-3} M using DMF as solvent. The absorbance of the mixed solutions was measured and plotted Vs the molar ratio [ligand] / [metal ion]. The results obtained are represented graphically in Figs. (2)⁽¹²⁾. Which indicate the formation of the complex by 1:1 metal to ligand.

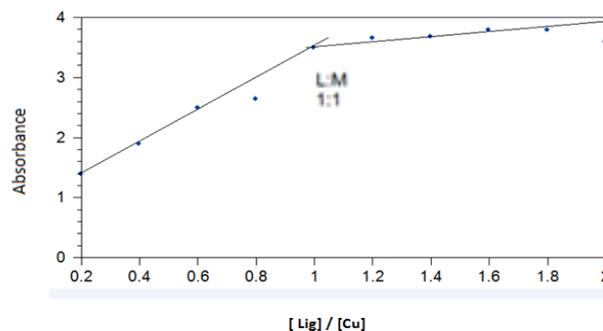
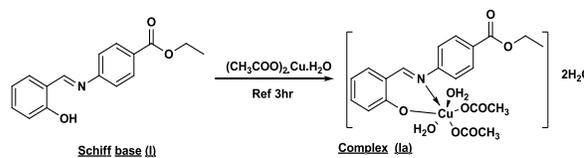


Figure 2. Absorption spectra of Cu (II) complex molar ratio method.

2.4.2. Preparation of Schiff-base metal complexes

Molar ratio and conductance data indicate the formed complex are 1:1, the prepared complex was carried out according to these data, a solution of the copper acetate monohydrate $(\text{CH}_3\text{COO})_2 \cdot \text{Cu} \cdot \text{H}_2\text{O}$ (0.001 mol) in absolute ethyl alcohol was added drop wise to a well stirred equimolar amount of Schiff-base (I). After complete addition of the metal salt the reaction mixture was heated under reflux for about three hours. Then, the product separated immediately, and recrystallized from DMF to give solid products (I_a) (scheme 2).



Scheme 2. Synthesis of Cu-complex (I_a).

3. Results and Discussion

3.1. The structure of Schiff base (I) was elucidated on the bases of:

3.1.1. Elemental analysis.

The percent of C, H and N of Schiff base (ethyl 4-(2-hydroxy-benzylideneamino) benzoate) were found (70.30, 6.87 and 5.12, respectively) which compatible with that required (71.36, 5.61 and 5.20, respectively).

3.1.2. ¹H-NMR spectrum.

The ¹H-NMR spectrum of the ligand in DMSO exhibits signals at δ 11.00 (s), 8.647 (s), 4.40 (q), and 1.40 (t) ppm, attributed to $-\text{OH}$, $-\text{CH}=\text{N}-$, $-\text{CH}_2$ and $-\text{CH}_3$ protons, respectively. The multi-signals within the range at $\delta = 6.95-7.79$ (m) ppm are assigned to the aromatic protons of the two benzene rings.

3.1.3. Electronic spectrum.

Electronic spectrum - in (DMF) as a solvent - exhibits the absorption band structure at $\lambda_{\max} = 267$ nm corresponds to $\pi-\pi^*$ transitions of the C=N group. The broad band at $\lambda_{\max} = 332$ nm corresponds to $n-\pi^*$ transitions of the azomethine and carbonyl groups.

3.1.4. IR spectrum.

The IR spectrum of Schiff-base (I) exhibits a broad band at 3254 cm^{-1} characteristic to the stretching vibrations of phenolic O-H group. The breadth of this band indicates the presence intra hydrogen bonds involving the hydroxyl O atom and azomethine N atom. The band at 1608 cm^{-1} may be assigned as ν -CH=N stretching mode of vibration of the azomethine group^(13, 14). A sharp peak at 1704 cm^{-1} is due to C = O stretching mode of vibrations. And stretching vibration of aromatic C = C at 1455 and 1568 cm^{-1} . Finally the bands at 2973 , 2750 and 1361 cm^{-1} may be assigned as ν C-H aromatic, C-H aliphatic and C-N respectively⁽¹⁵⁾.

3.1.5. X-ray crystal structure.

X-ray crystal structure view of the asymmetric unit is shown in Fig. (3) and table (1). The asymmetric unit contains one crystallographically independent Schiff bases.

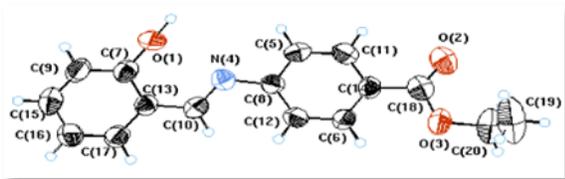


Figure 3. ORTEP view of the title compound (I) showing 30% Probability displacement ellipsoids. CCDC 816670

3.2. The structure of Schiff base Copper complex (Ia) was elucidated on the bases of:

3.2.1. Elemental analysis

The elemental analysis show that the percent of N = 2.54% and Cu = 12.05% which are compatible with required (N= 2.68 % and Cu = 12.17%). It founds that; yield = 51.73% (0.27g), and m.p = 189°C .

3.2.2. Electronic spectra and magnetic moment measurements.

The electronic spectra (UV- VIS) of the Schiff-base complexes (Figure 4) were carried out in DMF solutions at a concentration of 10^{-3} M. The spectrum of the complex exhibits the absorption bands at $\lambda_{\max} = 267$ nm corresponds to $\pi-\pi^*$ transitions of the C=N group. The sharp band at $\lambda_{\max} = 317$ nm corresponds

to $n-\pi^*$ transitions of the acetate group. The sharp band at $\lambda_{\max} = 357$ nm corresponds to $n-\pi^*$ transitions of the azomethine group. Where the band at $\lambda_{\max} = 366-450$ corresponds to d-d transition ion. The measured value of the magnetic moment for Cu(II) complex was 1.80 BM which confirms the octahedral structure of Cu (II) complex(Ia)⁽¹⁶⁾.

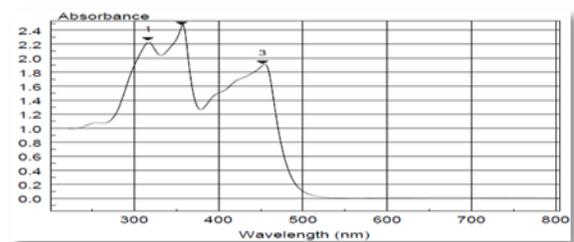


Figure 4. UV-Visible spectrum of complex I_a.

3.2.3. IR spectrum.

The spectra of Schiff base (I) show a broad band at 3254 cm^{-1} in the ligand (I) which assigned the intra-molecular hydrogen bonded OH group⁽¹⁵⁾, was disappeared indicating OH group act as covalent site. The complex (I_a) exhibit a broad band at 3540 cm^{-1} simultaneously appeared with a bands at 888 cm^{-1} attributed to coordinated water molecules^(17, 18).

The band of azomethine group (C=N) stretching appear at 1608 cm^{-1} , which is shifted to lower wave length; 1600 cm^{-1} of complexes I_a suggesting that the nitrogen of the azomethine group is coordinated to the metal ion^(13, 14). New bands appear in the region $510-582\text{ cm}^{-1}$ and $450-470\text{ cm}^{-1}$ in the spectra of complexes I_a can be attributed to the vibrations of M← N and M ← O respectively. The band due to C=O at 1704 remind almost on the same place in the complexes and indicate that this group are not taking part in complexation,⁽¹⁵⁾.

3.3. Biological activity

3.3.1. Antifungal activity

Schiff base (I) and its copper complex (I_a) were screened separately *in vitro* for their antifungal activity against various fungi ((*Aspergillus fumigatus* (RCMB 002003), *Geotrichum candidum* (RCMB 052006), *Candida albicans* (RCMB 005002) and *Syncephalastrum racemosum* (RCMB 005003)) on *Sabouraud dextrose agar plates*. The culture of fungi was purified by single spore isolation technique. The antifungal activity was by agar well diffusion method⁽¹⁹⁾ using clotrimazole and itraconazole as antifungal standard drugs.

3.3.2. Antibacterial activity

Antibacterial activity was investigated using agar well diffusion method⁽¹⁹⁾. The activity of Schiff base (I) and its copper complex (I_a) were studied against the *Staphylococcus aureus* (RCMB 000106) and *Bacillus subtilis* (RCMB 000107) (as Gram positive bacteria) while *Pseudomonas aeruginosa*

(RCMB 000102) and *Escherichia coli* (RCMB 000103) (as Gram negative bacteria), using penicillin G and streptomycin for antibacterial as standard. All the selected strains showed sensitivity to compound I and I_a which shown good activity against all the tasted bacterial and fungal except *Syncephalastrum racemosum* (RCMB 005003).

Table 1. Crystallographic details for Schiff base (I).

<p>C₁₆H₁₅NO₃ C₁₆H₁₅NO₃ M_r = 269.300 Monoclinic C2/c a = 16.0916 (5)Å b = 6.0315 (2)Å c = 29.0072 (10)Å α = 90.00° β = 101.856 (2)° γ = 90.00° V = 2755.3 (2)Å³ Z = 8 Data collection Kappa CCD Absorption correction: none 5846 measured reflections 3902 independent reflections 921 observed reflections Criterion: I > 3.00 sigma(I) R_{int} = 0.032</p>	<p>D_x = 1.298 Mg m⁻³ Density measured by: not measured fine-focus sealed tube Mo Kα radiation λ = 0.71073 Cell parameters from 2935 θ = 2.910—27.485 ° μ = 0.09 mm⁻¹ T = 298 K needle pale orange Crystal source: Local laboratory</p> <p>θ_{max} = 27.49 ° h = -20 → 20 k = -7 → 7 l = -37 → 37 h = 0 → 20 k = 0 → 7 l = -37 → 36</p>
<p>Refinement Refinement on F² fullmatrix least squares refinement R(all) = 0.279 R(gt) = 0.062 wR(ref) = 0.111 wR(all) = 0.174</p> <p>Only coordinates of H atoms refined Calculated weights sigma Δ/σ_{max} = 0.00 3 Δρ_{max} = 0.72eÅ³</p>	<p>wR(gt) = 0.112 S(ref) = 2.503 S(all) = 2.128 S(gt) = 2.537 915 reflections 181 parameters 0 restraints</p> <p>Δρ_{min} = -0.77eÅ³ Extinction correction: none Atomic scattering factors from Waasmaier & Kirfel, 1995</p>
<p>Data collection: Kappa CCD Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)⁽²⁰⁾ Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)⁽²¹⁾ Program(s) used to refine structure: maXus (Mackay et al., 1999)⁽²²⁾ Molecular graphics: ORTEP (Johnson, 1976) Software used to prepare material for publication: maXus(Mackay et al., 1999)⁽²⁴⁾</p>	

4. Conclusion

Ethyl4-(2-hydroxy-benzylideneamino) benzoate (Schiff base (I)) was synthesized from condensation of benzocaine and o-hydroxybenzaldehyde, the Schiff base (I) reacted with cupric acetate monohydrate as bidentate ligand one from hydroxyl oxygen and the other from azomethine nitrogen to form octahedral structure.

The result of all previous physiochemical measurements show that the structure of 1:1 complex may be represented as in scheme (2). Finally the two compounds I and I_a show more biological activity on both bacterial and fungal than the basic drug (benzocaine).

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