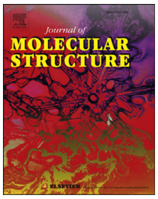
Journal of Molecular Structure 1145 (2017) 329–338

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc



# Binary and ternary copper(II) complexes of a new Schiff base ligand derived from 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone: Synthesis, spectral, thermal, antimicrobial and antitumor studies

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A R T I C L E I N F O

*Article history:*
Received 22 December 2016
Received in revised form
12 May 2017
Accepted 14 May 2017
Available online 18 May 2017

*Keywords:*
Pyridazinone
Binary and ternary complexes
Schiff base
Thermodynamic parameters
Antimicrobial activity
Antitumor activity

A B S T R A C T

A new Schiff base ligand was synthesized by the reaction of 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone with ethylenediamine. A series of binary copper(II) Schiff base complexes have been synthesized by using various copper(II) salts; $AcO^-$, $NO_3^-$, $ClO_4^-$, $Cl^-$ and $Br^-$. Ternary complexes were synthesized by using auxiliary ligands (L′) [N,O-donor; 8-hydroxyquinoline and glycine or *N,N*-donor; 1,10-phenanthroline, bipyridyl and 2-aminopyridine]. The structures of the Schiff base and its complexes were characterized by elemental and thermal analyses, IR, electronic, mass, $^1$H NMR and ESR spectra in addition to conductivity and magnetic susceptibility measurements. The obtained complexes include neutral binuclear complexes as well as neutral and cationic mononuclear complexes according to the anion used and the experimental conditions. The ESR spin Hamiltonian parameters of some complexes were calculated and discussed. The metal complexes exhibited octahedral and square planar geometrical arrangements depending on the nature of the anion. Kinetic parameters (Ea, A, ΔH, ΔS and ΔG) of the thermal decomposition stages were evaluated using Coats–Redfern equations. The antimicrobial activity of the Schiff base and its complexes was screened against Gram–positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram–negative bacteria (*Salmonella typhimurium* and *Escherichia coli*), yeast (*Candida albicans*) and fungus (*Aspergillus fumigatus*). The antitumor activity of the Schiff base and some of its Cu(II) complexes was investigated against HepG-2 cell line.

## 1. Introduction

Schiff bases are considered to be the most important chelating agents in coordination chemistry. Schiff bases and their metal complexes have attracted an enormous consideration because of their various applications including antimicrobial [1], antioxidant [2], anti-inflammatory [3], anticancer [4], antiviral [5] and anti-HIV [6] activities.

There is a considerable interest in heterocyclic diazines including pyrazine, pyrimidine and pyridazine as excellent bidentate chelating agents [7]. Pyridazines, and particularly 3-pyridazinone derivatives possess antibacterial [8], antifungal [9], anticancer [10], antitubercular [9], anti-inflammatory and analgesic [11], antihypertensive [12] as well as various pharmacological activities [13].

Copper(II) ion plays very important roles in several biological processes. It has a significant role in the action of different enzymes that catalyze a great variety of reactions [14]. Copper(II) complexes have been extensively studied because of their biological and pharmaceutical properties [15]. It has also been reported that the biological activity of copper(II) complexes is enhanced in the presence of a nitrogen donor heterocyclic ligand, such as 1,10-phenanthroline, 2,2′-bipyridine or 2,2′-dipyridylamine [16].

The present study aims to study the chelating behavior of the new Schiff base, *N,N*′-bis[5,6-diphenyl-3-oxo-2H-pyridazin-3-yl-ethylidene]ethane-1,2-diamine (Scheme 1) towards copper(II) ion. A series of binary and ternary complexes have been synthesized and characterized by elemental and thermal analyses, IR, electronic, ESR and mass spectra as well as conductivity and magnetic susceptibility measurements. The antimicrobial activity of the ligand and its complexes was screened against selected kinds of bacteria and fungi. The antitumor activity of the ligand and some of its Cu(II) complexes was investigated against HepG2 cell line.

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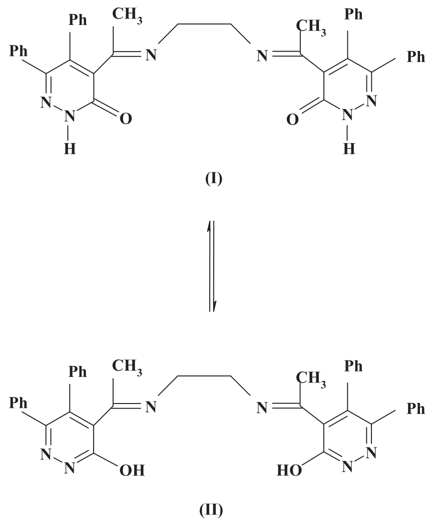
http://dx.doi.org/10.1016/j.molstruc.2017.05.064



**Scheme 1.** Tautomeric forms of the Schiff base ligand.

## 2. Experimental

### 2.1. Measurements

Elemental analyses (C, H and N) were carried out using Vario El-Elementar at the Ministry of Defense, Chemical War Department. Analysis of the metal content followed the decomposition of the complexes with conc. nitric acid then copper(II) ion was estimated by EDTA. Melting points of the complexes were determined using a Stuart SMP3 melting point apparatus. IR spectra were recorded using KBr discs on FT IR Nicolet IS10 spectrometer. Electronic spectra were recorded at room temperature on a Jasco model V-550 UV/Vis spectrophotometer as Nujol mulls and/or solutions in DMF. $^1$H NMR spectra were recorded at room temperature on a Bruker WP 200 SY spectrometer. Dimethylsulfoxide, DMSO-$d_6$, was used as a solvent and tetramethylsilane as an internal reference. ESR spectra of the complexes were recorded at Elexsys, E500, Bruker company. The magnetic field was calibrated with 2,2′-diphenyl-1-picrylhydrazyl (DPPH) sample purchased from Aldrich. Mass spectra were recorded at 70 eV on a Gas chromatographic GCMSqp 1000 ex Shimadzu instrument. The magnetic susceptibility measurements were carried out at room temperature using a magnetic susceptibility balance of the type Johnson Matthey, Alfa product, Model No. (MKI). Effective magnetic moments were calculated and corrected using Pascal's constants for the diamagnetism of all atoms in the compounds [17]. Molar conductivities were measured for $10^{-3}$ M solution of the solid complexes on the Corning conductivity meter NY 14831 model 441. TGA-measurements were carried out from room temperature up to 800 °C at a heating rate of 10 °C/min on a Shimadzu-50 thermal analyzer.

### 2.2. Materials

4-Acetyl-5,6-diphenyl-3(2H)-pyridazinone was prepared according to literature [18]. Metal salts, 8-hydroxyquinoline, glycine, 1,10-phenanthroline, bipyridyl, 2-aminopyridine and EDTA disodium salt, ammonium hydroxide, mureoxide and nitric acid were either Aldrich, BDH or Merck products. Organic solvents were reagent grade chemicals and were used without further purification. Crystal violet and trypan blue dye were purchased from Sigma (St. Louis, Mo., USA). Fetal Bovine serum, DMEM, RPMI-1640, HEPES buffer solution, L-glutamine, gentamycin and 0.25% Trypsin-EDTA were obtained from Lonza. HepG-2 cells (human Hepatocellular carcinoma) were obtained from VACSERA Tissue Culture Unit.

*Caution*! Perchlorate salts are potentially explosive especially in the presence of organic ligands. Only a small amount should be prepared and handled with care.

### 2.3. Synthesis of the Schiff base ligand

The Schiff base ligand was synthesized by adding ethylenediamine (0.1 g, 1.66 mmol) dissolved in absolute ethanol (10 mL) to 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone (1 g, 3.44 mmol) in absolute ethanol (20 mL). The reaction mixture was heated under reflux for 2 h. The obtained yellow product was filtered off and washed with few amounts of ethanol then diethylether, air-dried and recrystallized from methanol-DMF. The crystalline ligand was kept in a desiccator until used. The yield was 0.8 g (38%).

### 2.4. Synthesis of the metal complexes

The metal salt and the ligand, both in ethanol, were mixed in the molar ratio 1:2 (L:M) and heated under reflux for 4 h. In order to investigate the experimental conditions, reactions of the ligand with copper(II) chloride or bromide were carried out using stirring conditions in addition to the regular reflux method. The resulting precipitates were filtered, washed with ethanol then ether and finally air-dried. The complexes were kept in a desiccator over anhydrous calcium chloride. As representative examples, the following synthetic methods are provided in details.

#### 2.4.1. Synthesis of $[(L)Cu_2(OAc)_4(H_2O)_4]\cdot EtOH$ (**1**)

0.264 g (1.32 mmol) of $Cu(OAc)_2\cdot H_2O$ dissolved in 30 mL ethanol was added gradually to 0.4 g (0.66 mmol) of the ligand, suspended in 30 mL ethanol. The reaction mixture was heated under reflux for 4 h which resulted a dark brown precipitate and was filtered off, washed several times with ethanol, diethylether and finally air-dried. The yield was 32%.

#### 2.4.2. Synthesis of $[(L)Cu_2(OAc)_2(8\text{-}HQ)_2(H_2O)_2]$ (**8**)

0.66 g (3.3 mmol) of $Cu(OAc)_2\cdot H_2O$ dissolved in 40 mL ethanol was added gradually to 1 g (1.65 mmol) of the ligand, suspended in 40 mL ethanol. The reaction mixture was heated under reflux for 30 min and then 0.48 g (3.3 mmol) of 8-hydroxyquinoline (8-HQ) dissolved in ethanol was added to the above mixture. The resulting mixture was heated under reflux 7 h which resulted a dark green precipitate and was filtered off, washed several times with ethanol, diethylether and finally air-dried. The yield was 29%.

#### 2.4.3. Unsuccessful trials

Trials to prepare the binary Cu(II) complex of the Schiff base ligand by using Cu(II) sulphate were unsuccessful.

### 2.5. Biological activity

#### 2.5.1. Antimicrobial activity

The standardized disc-agar diffusion method [19] was followed to determine the activity of the Schiff base and its metal complexes against the sensitive organisms *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6635) as Gram positive bacteria, *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922) as Gram negative bacteria and *Candida albicans* (ATCC 10231) and *Aspergillus fumigatus* as fungus strain. The antibiotic chloramphenicol was employed as reference in the case of Gram-positive bacteria, cephalothin in the case of Gram-negative bacteria and cycloheximide in the case of fungi.