

# Synthesis, Characterization and X-ray Analysis of a Copper(II) Complex with Pyridoxal-aminoguanidine Ligand

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**Abstract** The reaction between pyridoxal hydrochloride (PL-HCl) and aminoguanidine-hydrogencarbonate (AG·H<sub>2</sub>CO<sub>3</sub>) in the presence of Na<sub>2</sub>CO<sub>3</sub>·10H<sub>2</sub>O resulted in the formation of pyridoxal-aminoguanidine (PLAG; H<sub>2</sub>L) ligand. The ligand's coordination chemistry with CuCl<sub>2</sub> yielded a green-brown, octahedral dimer of Cu (II) with the general formula of [Cu(PLAG)(NCS)<sub>2</sub>]<sub>2</sub>. This paper presents the synthesis and the structural analysis of this complex with the Schiff-based ligand.

**Keywords** Pyridoxal-aminoguanidine Cu(II) complex, Synthesis, Crystal structure, Characterization

## 1. Introduction

Hyperglycemia has been identified as a major risk factor for the development of diabetic complications[1]. Aminoguanidine (AG) has been extensively studied as one of the most promising compounds for the treatment of diabetic complications, because the compound has both advanced glycation inhibitory activity[2] and antioxidant activity[3,4]. It has been reported that a pyridoxal-aminoguanidine (PL-AG) Schiff base adduct exhibits advanced glycation inhibitory activity comparable to that of AG, while causing no decrease in the liver pyridoxal phosphate content of normal mice[5,6]. Also, PL-AG is more potent than AG in preventing nephropathy in streptozotocin-induced diabetic mice[7]. These findings suggest that PL-AG is superior to AG for the treatment of diabetic complications because not only it prevents vitamin B6 deficiency, but it is also superior at controlling diabetic nephropathy. The preventive effect of this adduct against diabetic nephropathy is mediated via inhibition of both oxidation and glycation[8]. The inhibition of advanced glycation end products (AGEs) at millimolar concentrations of AGEs inhibitors, used in many in vitro studies, results primarily from the copper chelating or antioxidant activity of the AGEs inhibitors, rather than their carbonyl trapping activity[9]. Defining the chelating activity of AGEs inhibitors is essential for understanding the mechanism of action of drugs and possible benefits of chelation therapy in

diabetes, as well as for developing more effective clinically useful inhibitors of diabetic complications. Bearing in mind the biological and medicinal importance of AG and PL-AG adduct and the influence of copper (II) ions on their inhibitory activity, in the present study evaluation of the chelating ability of PL-AG inhibitor was attempted in order to cast more light on the role of copper chelation in the mechanism of action of AGEs inhibitors.

## 2. Experimental Section

### 2.1. Reactants

All commercially obtained reagent-grade chemicals were used without further purification, except for the ligand, which was prepared according to the previously described procedure[10<sup>a,b</sup>].

### 2.2. Physical Measurements

Elemental (C, H, N) analysis of air-dried samples was carried out by standard micromethods in the Center for Instrumental Analysis, Faculty of Chemistry, Belgrade. The X-ray analysis was performed in the Oxford Chemical Crystallography Service.

### 2.3. Crystal Data Collection and Processing

A single crystal was mounted on a glass fiber in random orientation. Data collection was performed at temperature 150 K on a computing data collection Nonius Kappa CCD diffractometer using graphite mono-chromated MoK $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Data collection and cell refinement we details concerning data collection and structure re carried

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out using DENZO and COLLECT[11,12]. The structures were solved with SIR-92 and refined using CRYSTALS [13,14]. In general, the hydrogen atoms were visible in the difference map. Therefore, they were positioned geometrically and refined in a separate hydrogen cycle (with soft restraints) before inclusion in the refinement using a riding model. For more information see the Supplementary information. Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge by writing to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk. The CCDC deposition numbers are 828036. Crystal data and details concerning data collection and structure refinement are given in Table 1.

**Table 1.** Crystal data and structure refinement details of the complex

Empirical formula	C <sub>10</sub> H <sub>16</sub> CuN <sub>6</sub> O <sub>10</sub>
Formula weight	443.814
Temperature	150K
Wavelength	0.71073Å
Crystalsystem	Monoclinic
Spacegroup	P121/c1
Unitcell dimensions	a=8.5771(2)Å α=90° b=10.1164(3)Å β=101.1164(3)° c=19.0567(5)Å γ=90°
Volume	1622.19(7)Å <sup>3</sup>
Z	4
Density (calculated)	1.817Mg/m <sup>3</sup>
A Absorption coefficient	1.417mm <sup>-1</sup>
Crystalsize	0.060x0.120x0.190mm <sup>3</sup>
Theta range for data collection	5.166to27.464°
Indexranges	-11<=h<=11,-13<=k<=13, -24<=l<=24
Reflections collected	1018
Independent reflection reflections	3669[R(int)=0.046]
Completeness to theta=26.915°	99.2%
Absorption correction	Semi-empirical from equivalents
Max. and min. Transmission	0.76 and 0.00
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data/restraints/parameters	3477/0/244
Goodness-of-fit on F <sup>2</sup>	1.0110
Final R indices [I>2σ(I)]	R1=0.0509, wR2=0.1186
R indices (all data)	R1=0.0805, wR2=0.1277
Largest diff. peak and hole	0.84 and -1.09 e.Å <sup>-3</sup>

## 2.4. Preparation of the Ligand and Complex [Cu(PLAG)(NCS)<sub>2</sub>]<sub>2</sub>

### 2.4.1. PLAG•HCl•H<sub>2</sub>O

The ligand (PL-AG•HCl•H<sub>2</sub>O), synthesized in a similar manner as described for PL-AG[6], is a yellow microcrystalline compound which is moderately soluble in

water and sparingly soluble in MeOH, EtOH and DMF[10].

### 2.4.2. [Cu(PLAG)(NCS)<sub>2</sub>]<sub>2</sub>

To a warm methanol (20cm<sup>3</sup>) solution containing 0.28g (1 mmol) of PLAG 0.26g (1.2 mmol) of CuCl<sub>2</sub> in 10cm<sup>3</sup> MeOH was added followed by 0.12 g (1.6 mmol) of NH<sub>4</sub>NCS. Green mixture was formed which was left behind at room temperature for about 50 hours. Green crystals started to form after a couple of hours. After the sedimentation has completed the product was isolated by vacuum filtration and was then washed with methanol. Yield: 0.18 g.

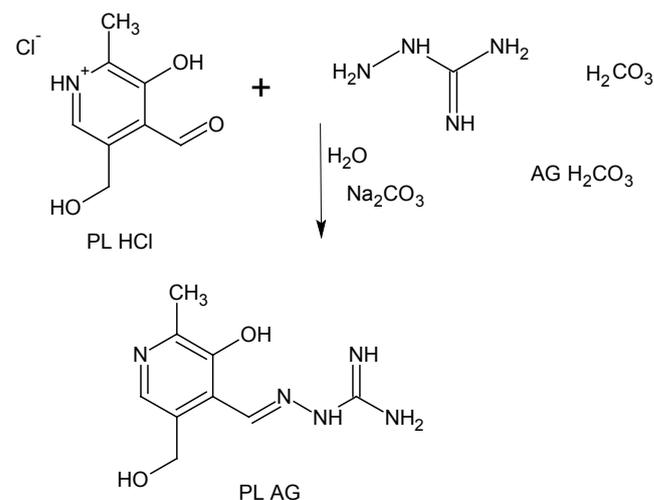
## 3. Results and Discussion

### 3.1. Synthesis and Characterization of the Ligand and the Complex

Neutral form of the ligand pyridoxal-aminoguanidine (PLAG), is synthesized according to a previously described procedure[10], involving a reaction of water mixture between PL-HCl and AG-H<sub>2</sub>CO<sub>3</sub>[1:1] in the presence of Na<sub>2</sub>CO<sub>3</sub>•10H<sub>2</sub>O (Scheme 1).

PLAG is a yellow microcrystalline compound very soluble in MeOH and DMF, but slightly less in H<sub>2</sub>O and EtOH. The resulting compound is stable in air and at high temperatures. The elemental analysis data are given in Table 2.

By using reaction of a warm MeOH mixture of CuCl<sub>2</sub> and PLAG, the mole ratio of 1:1, with the addition of NH<sub>4</sub>NCS a dark-green monocrystalline dimeric complex [Cu(PLAG)(NCS)<sub>2</sub>]<sub>2</sub> (Scheme 2) was obtained.



**Scheme 1.** Synthesis of pyridoxal-aminoguanidine (PLAG)



**Scheme 2.** Syntheses of the complex [Cu(PLAG)(NCS)<sub>2</sub>]<sub>2</sub>

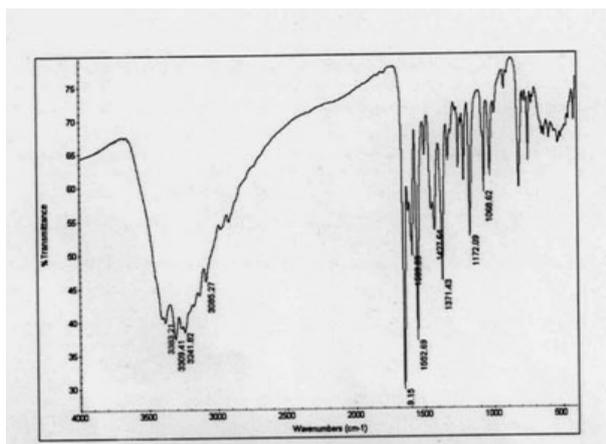
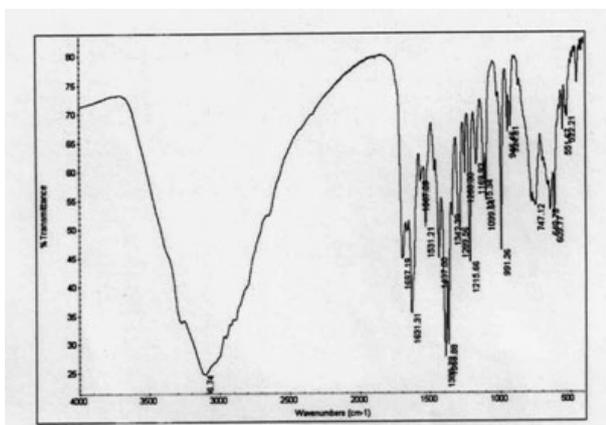
The resulting complex is crystalline solid that is stable in air and at high temperatures (melting point of the complex is 330°C). It is very soluble in DMF, less in H<sub>2</sub>O, MeOH and EtOH. The elemental analysis data are given in Table 2.

**Table 2.** The elemental analysis data for the ligand and complex

Ligand/Complex	Mr	Grossformula	Found/calculated (%)		
			C	H	N
PLAG·HCl·H <sub>2</sub> O	223,23	C <sub>9</sub> H <sub>13</sub> N <sub>5</sub> O <sub>2</sub>	47,91	5,11	31,18
			(48,29)	(5,87)	(31,37)
[Cu(PLAG)(NCS) <sub>2</sub> ]	401,94	C <sub>11</sub> H <sub>12</sub> CuN <sub>7</sub> O <sub>2</sub> S <sub>2</sub>	32,61	2,06	24,23
			(32,87)	(2,99)	(24,38)

Comparison of the  $\nu(\text{C-O})$  signals in the IR spectra of the ligand ( $\nu(\text{C-O}) \sim 1290 \text{ cm}^{-1}$ ) and the complex ( $\nu(\text{C-O}) \sim 1330 \text{ cm}^{-1}$ ) indicated coordination of oxygen and deprotonation of the phenolic hydroxyl moiety (Figures 1 and 2). Intense peak in the IR spectrum of the complex at  $1650 \text{ cm}^{-1}$  originated from  $\nu(\text{C=N})$  or the coordinated azomethine group and the value has been moved to a lower energy with respect to the corresponding value observed for the free ligand.

The bands that could be assigned to the guanido group in the complex are located at  $\sim 1552 \text{ cm}^{-1}$  in the spectrum of the complex, and  $\sim 1631 \text{ cm}^{-1}$  in the spectrum of the ligand.

**Figure 1.** IR spectra of complex**Figure 2.** IR spectra of PLAG

### 3.2. X-ray Crystallography

As shown in the empirical formula, the complex contains a neutral form of PLAG ligand. The neutral form represents a proton transfer from the phenolic hydroxyl to the pyridine nitrogen atom. The doubly deprotonated form occurs from deprotonation of the phenolic oxygen and hydrazine nitrogen atoms, similar to a series of ligands with pyridoxalcarbazon es[15].

The complex  $[\text{Cu}(\text{PLAG})(\text{NCS})_2]_2$  possesses a hexacoordinated copper ion formed with the usual tridentate ONN coordination of ligand PLAG, coordination of two NCS-groups and a bonding interaction with the nearby Cu atom from a different molecule (Figure 3). Chelating ligand coordination is achieved through the oxygen atom of deprotonated phenolic hydroxyl, azomethine group nitrogen atom and guanido group nitrogen atom. As it can be seen from Table 1, the complex crystallizes in the monoclinic system, with four dimer molecules ( $Z=4$ ) in the unit cell. Coordination sphere of the complex was built from the neutral form of the ligand molecule PLAG and two NCS groups. In this complex, as already mentioned, the tridentate ONN ligand in its neutral form is coordinated by building two metalocycles: one six-membered (pyridoxilydene) and one five-membered (aminoguanidine).

The bond lengths of for the metal-ligand distances and the corresponding bond angles are given in Table 3.

**Table 3.** Bond lengths[Å] and angles[o] for the complex

Cu(1)-S(2)	2.881(14)	S(2)-Cu(1)-O(5)	90.83(10)
Cu(1)-O(5)	1.915(3)	S(2)-Cu(1)-N(13)	92.27(11)
Cu(1)-N(13)	1.963(4)	O(5)-Cu(1)-N(13)	90.70(15)
Cu(1)-N(16)	1.947(4)	S(2)-Cu(1)-N(16)	96.71(12)
Cu(1)-N(21)	1.973(4)	O(5)-Cu(1)-N(16)	169.59(15)
		N(13)-Cu(1)-N(16)	81.87(16)
		S(2)-Cu(1)-N(21)	95.02(13)
		O(5)-Cu(1)-N(21)	93.42(15)
		N(13)-Cu(1)-N(21)	171.58(17)
		N(16)-Cu(1)-N(21)	93.06(17)

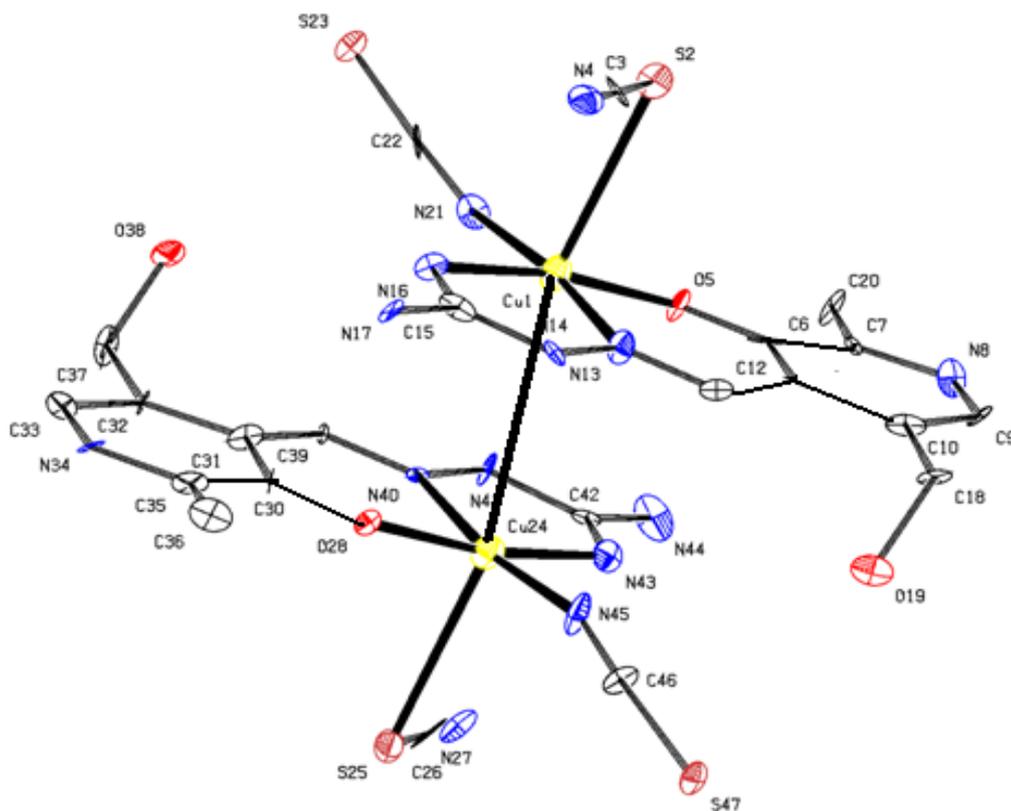


Figure 3. Crystal structure of  $[\text{Cu}(\text{PLAG})(\text{NCS})_2]_2$

The bond lengths of Cu-ligand in the equatorial plane have very similar values: Cu(1)-O(5) 1.915(3) Å, Cu(1)-N(13) 1.963(4) Å and Cu(1)-N(16) 1.947(4) Å. The Cu(1)-O(5) bond distance is the shortest one, which was expected, because of the negative charge present on the oxygen atom of deprotonated phenolic hydroxyl. On the other hand the central copper forms the the longest bond distance with nitrogen atom of azomethine group in equatorial plane (Cu(1)-N(13) 1.963(4) Å). The longest bond distance in the Cu coordination sphere is apical Cu(1)-S(2) bond formed by the central atom with the sulfur atom NCS-group and its value is 2.881(14) Å. The N(13)-Cu(1)-N(21) bond angle of  $171.58(17)^\circ$  is close to the theoretical  $180^\circ$ , but the O(5)-Cu(1)-N(16) bond angle is  $169.59(15)^\circ$  due to the chelation rings strain.

#### 4. Conclusions

The synthesis, characterization and structural analysis of a Cu(II) complex incorporating PLAG ligand is described. The Cu II environment is best described as octahedral. The equatorial plane is formed by the tridentate ONN-coordinated PLAG ligand and one NCS molecule. This compound crystallizes in a monoclinic crystal symmetry with the space group of  $P 1 21/c 1$ .

#### 5. Supplementary Information

Crystallographic data (excluding structure factors) for the structure (1) reported in this paper have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 828036. Copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +441223336033; e-mail: deposit@ccdc.cam.ac.uk <http://www.ccdc.cam.ac.uk>).

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