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SYNTHESIS AND X-RAY CRYSTAL STRUCTURE OF A COPPER(II) COMPLEX WITH PYRIDOXAL-AMINOGUANIDINE (PLAG) LIGAND

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Abstract: With the reaction of warm water mixture of pyridoxal hydrochloride (PL·HCl), and Aminoguanidine-hydrogencarbonate (AG·H_2CO_3) in presence of $Na_2CO_3 \cdot 10H_2O$, pyridoxal-aminoguanidine (PLAG; H_2L) was obtained. Ligand and appropriate salt $CuCl_2$ are coordinate, and form the following complex: green-brown, hexa-coordinated, octahedral structure, dimmer-complex Cu(II) formula $[Cu(PLAG)(NCS)_2]_2$. This paper presents a synthesis and crystal structure of complex with Schiff-based ligand.

Keywords: pyridoxal-aminoguanidine Cu(II) complex, synthesis, crystal structure.

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 it not only prevents vitamin B6 deficiency, but also is better 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 we attempted to evaluate the chelating ability of PL-AG inhibitor in order to cast more light on the role of copper chelation in the mechanism of action of AGEs inhibitors.

2. EXPERIMENTAL MATERIALS AND METHODS

2.1. Reactants

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

2.2. Measurements

Elemental (C, H, N) analysis of air-dried samples was carried out by standard micromethods in

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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 fibber in random orientation. Data collection was performed at temperature 150 K on a computing data collection Nonius Kappa CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å). Data collection and cell refinement were carried 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 the CCDC, 12 Union Road, Cambridge CB2 IEZ, 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 complex.

Identification code	0018vjdv010
Empirical formula	$C_{10}H_{16}CuN_6O_{10}$
Formula weight	443.814
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a=8.5771(2) Å α=90° b=10.1164(3) Å β=101.1742(11)° c=19.0567(5) Å γ=90°
Volume	1622.19(7) $Å^3$
Z	4
Density (calculated)	1.817 Mg/m^3
Absorption coefficient	1.417 mm^{-1}
Crystal size	0.060 x 0.120 x 0.190 mm^3
Theta range for data collection	5.166 to 27.464°.
Index ranges	-11<=h<=11, -13<=k<=13, -24<=l<=24
Reflections collected	0
Independent 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^2
Data / restraints / parameters	3477 / 0 / 244
Goodness-of-fit on F^2	1.0110
Final R indices [I>2sigma(I)]	R1=0.0509, wR2=0.1186
R indices (all data)	R1=0.0805, wR2=0.1277
Largest diff. peak and hole	0.84 nd -1.09 e.$Å^{-3}$

2.4. Preparation of the ligand and complex $[Cu(PLAG)(NCS)_2]$

2.4.1. $PLAG{\cdot}HCl{\cdot}H_2O$

The ligand ($PL\text{-}AG{\cdot}HCl{\cdot}H_2O$), 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. $[Cu(PLAG)(NCS)_2]$

Warm 0.28g (1 mmol) PLAG in 20cm^3 MeOH and add mixture 0.26g (1.2 mmol) $CuCl_2$ in 10cm^3 MeOH, was added followed by 0.12 g (1.6 mmol) NH_4NCS. Green mixture is formed which is left behind on room temperature for about 50 hours, followed by separation of green monocrystals. Green crystals started to form after a couple of hours, which were then washed with methanol. Yield: 0.18 g.

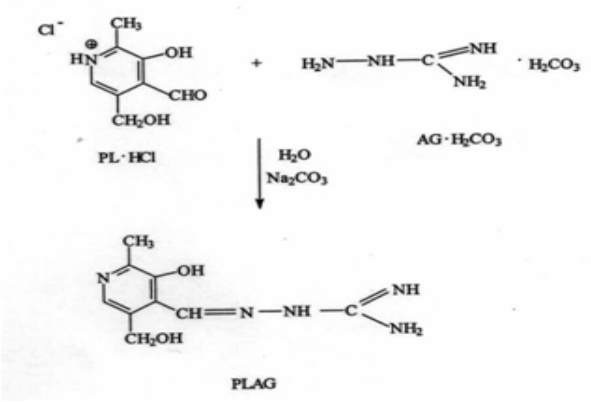
3. RESULTS AND DISCUSSION

3.1. Synthesis and characterization of ligand and complex

Neutral form of the ligand pyridoxal-aminoguanidine (PLAG), is synthesized according to formely described action [10], reaction with water mixture $PL{\cdot}HCl$ and $AG{\cdot}H_2CO_3$ [1:1] in presence $Na_2CO_3{\cdot}10\ H_2O$ (Scheme 1.).

PLAG is yellow microcrystalline compound very soluble in MeOH and DMF, but slightly less in H_2O and EtOH. The resulting compound is stable in air and at high temperature. The elemetal analysis data and some physical-chemical characteristics are given in Table 2.

By using reaction of warm MeOH mixture of $CuCl_2$ and PLAG, the mole ratio of 1:1, with the addition of NH_4NCS, we obtained a dark-green monocrystal dimeric complex $[Cu(PLAG)(NCS)_2]_2$ (Scheme 2).



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

$$PLAG+CuCl_2+NH_4NCS\rightarrow[Cu(PLAG)(NCS)_2]_2$$

Scheme 2. Syntheses of the complex$[Cu\ (PLAG)(NCS)_2]_2$.

The resultant 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_2O, MeOH and EtOH. The elemental analysis data and some physical-chemical characteristics are given in Table 2.

IR spectra of ligand and complex indicate that the coordination of oxygen atom of deprotonated phenolic hydroxyl points ν(C-O) peak at ~1330 cm^{-1} in the spectrum of the complex (Figure 1.), which is in the spectrum of ligand in lower energy (~1290 cm^{-1}) (Figure 1.). Intense peak in the spectrum of the complex in 1650 cm^{-1} originate from ν(C=N) azomethine group vibrations, which are due to the effect of coordination moved to lower energy relative to their position in the spectrum of ligand (Figure 2.).

Bands that can be attributed to the spectra of guanido group in the complex are located at ~1552 cm^{-1} in the spectrum of the complex, and ~1631 cm^{-1} in the spectrum of ligand.

Table 2. The elemental analysis data and physical-chemical characteristics for the ligand and complex.

Ligand/Complex	Mr	Gross formula	Found/calculated (%)		
			C	H	N
$PLAG{\cdot}HCl{\cdot}H_2O$	223,23	$C_9H_{13}N_5O_2$	47,91	5,11	31,18
			(48,29)	(5,87)	(31,37)
$[Cu(PLAG)(NCS)_2]$	401,94	$C_{11}H_{12}CuN_7O_2S_2$	32,61	2,06	24,23
			(32,87)	(2,99)	(24,38)

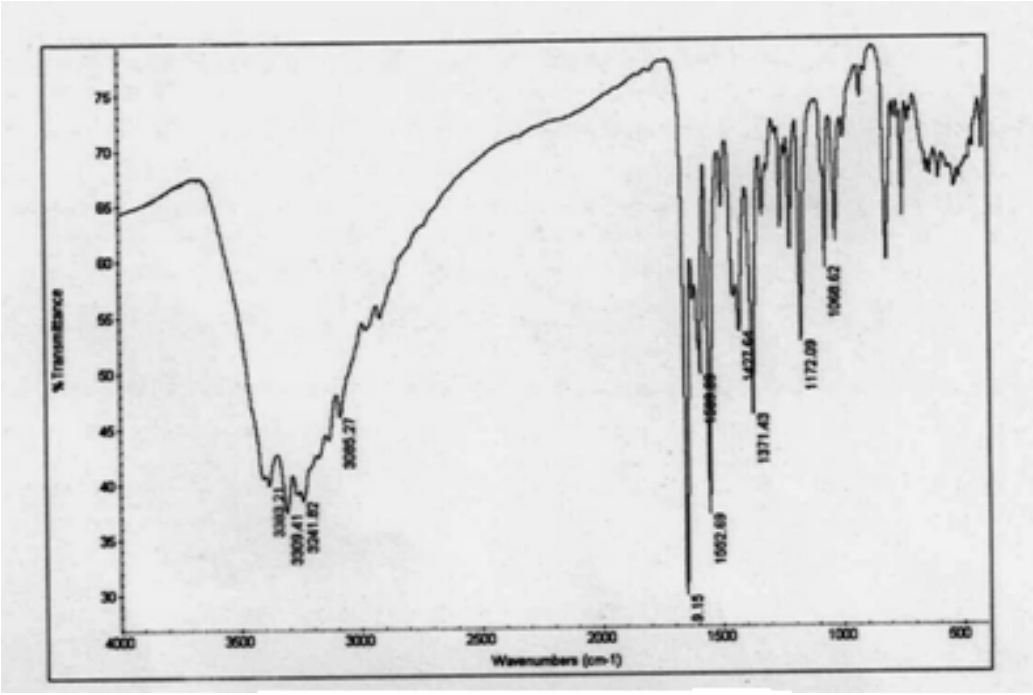


Figure 1. IR spectra of complex.

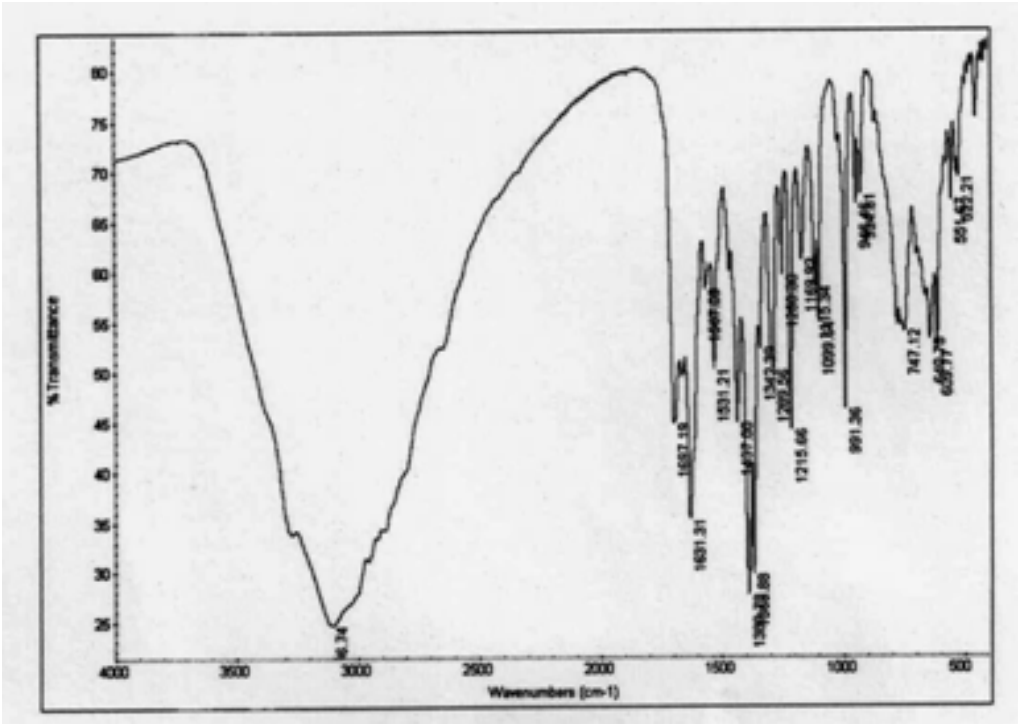


Figure 2. IR spectra of PLAG.

3.2. X-ray crystallography

As shown in the formula of the complex, the complex contains a neutral ligand form PLAG. Neutral form of the ligand represent transfer of protons from the phenolic hydroxyl on the pyridine nitrogen atom. Doubly deprotonated form occurs from deprotonation, except phenolic hydroxyl and deprotonation of hydrazine nitrogen atoms, similar to a series of ligands with pyridoxal carbazones [15].

In the study complex $[Cu(PLAG)(NCS)_2]_2$ the hexa-coordination of the central copper ion was completed with the usual tridentate ONN coordination of ligand PLAG, coordination of two NCS^- groups and band with nearby central Cu atom (Figure 3.). Chelating ligand coordination is achieved through the oxygen atom of deprotonated phenolic hydroxyl, azomethine group nitrogen atom and guanido group nitrogen atom.

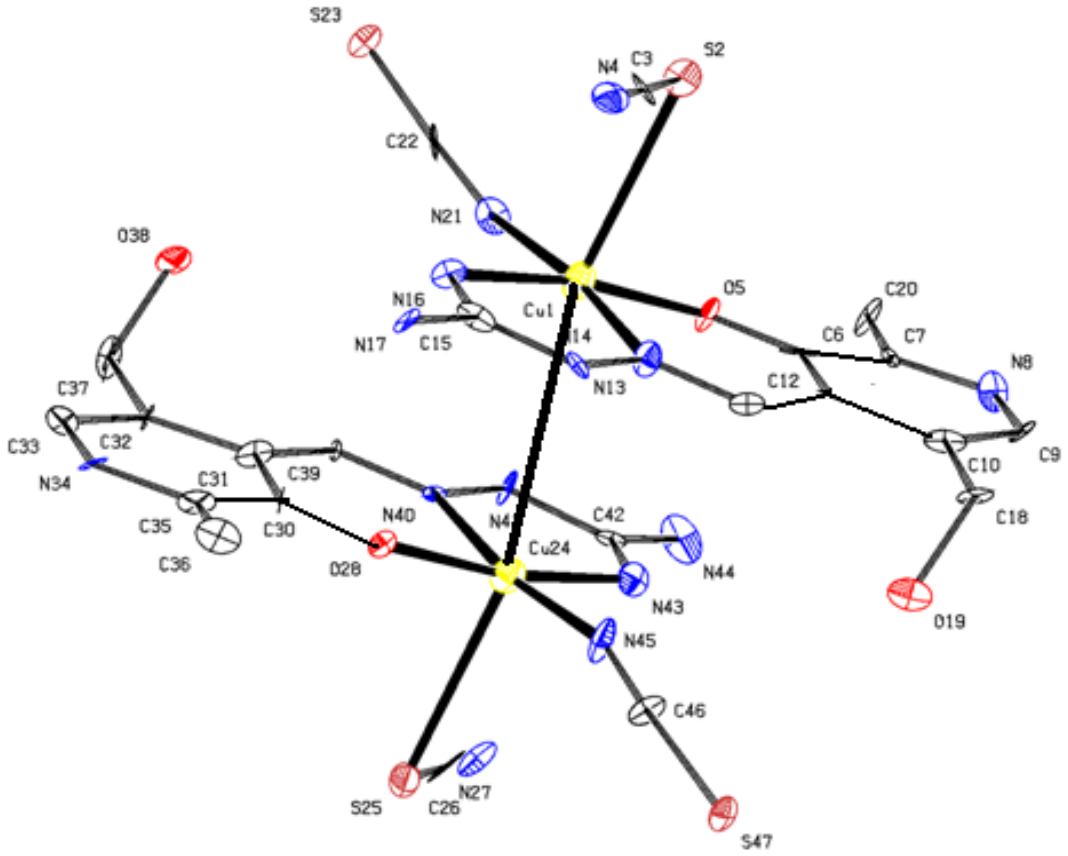


Figure 3. Crystal structure of [Cu(PLAG)(NCS)$_2$]$_2$.

As it can be seen from Table 1., the complex crystallizes in the monoclinic system, with two molecules in the unit cell (Figure 4.). Crystal lattice 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 located in the neutral form is coordinated by building two metallocycles: one six-membered (pyridoksilydene) and one five-membered (aminoguanidine).

The lengths of connections metal-ligand and angles among connections in coordinate sphere of metal are given in Table 3. The lengths of Cu-ligand in 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, witch was expected, because of the negative charge present on the oxygen atom of deprotonated phenolic hydroxyl, while copper has 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)° is close to the theoretical 180°, but the O(5)-Cu(1)-N(16) bond angle is 169.59(15)º due to the chelation rings strain.

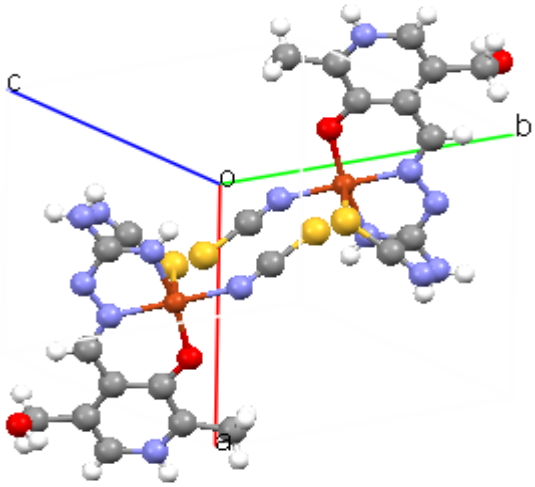


Figure 4. Packing arrangement in the unit cell.

Table 3. Bond lengths [Å] and angles [°] for 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)

4. REFERENCES

[1] D. Giugliano, A. Ceriello, G. Paolisso, *Oxidative stress and diabetic vascular complications*, Diabetes Care 19 (1996) 257−267.

[2] D. Edelstein, M. Brownlee, *Mechanistic studies of advanced glycosylation end product inhibition by aminoguanidine*, Diabetes 41 (1992) 26−29.

[3] I. Giardino, A.K. Fard, D.L. Hatchell, M. Brownlee, *Aminoguanidine inhibits reactive oxygen species formation, lipid peroxidation and oxidant-induced apoptosis*, Diabetes 47 (1998) 1114−1120.

[4] S.H. Ihm, J.H. Yoo, S.W. Park, J. Ihm, *Effect of aminoguanidine on lipid peroxidation in streptozotocin-induced diabetic rats*, Metabolism 48 (1999) 1141−1145.

[5] T. Taguchi, M. Sugiura, Y. Hamada, I. Miwa, *Inhibition of advanced protein glycation by a Schiff base between aminoguanidine and pyridoxal*, Eur. J. Pharmacol. 378 (1999) 283−289.

[6] T. Taguchi, M. Sugiura, Y. Hamada, I. Miwa, *In Vivo Formation of a Schiff Base of Aminoguanidine with Pyridoxal Phosphate*, Biochem. Pharmacol.55 (1998) 1667−1671.

[7] H. Miyoshi, T. Taguchi, M. Sugiura, M. Takeuchi, K. Yanagisawa, Y. Watanabe, I. Miwa, Z. Makita, T. Koike*, Aminoguanidine Pyridoxal Adduct is Superior to Aminoguanidine for Preventing Diabetic Nephropathy in Mice*, Horm. Metab. Res. 34 (2002) 371−377.

[8] A.S. Chen, T. Taguchi, S. Aoyama, M. Sugiura, M. Haruna, M.W. Wang, I. Miwa, *Antioxidant activity of a Schiff base of pyridoxal and aminoguanidine*, Free Radical. Bio. Med. 35 (2003) 1392−1403.

[9] D.L. Price, P.M. Rhett, S.R. Thorpe, J.W. Baynes, *Chelating Activity of Advanced Glycation End-product Inhibitors*, J. Biol. Chem. 276 (2001) 48967−48972.

[10] V. M. Leovac, M. D. Joksovic, V. Divjakovic, Lj. Jovanovic, Z. Saranovic, A. Pevec, *Synthesis, spectroscopic and X-ray characterization of a copper(II) complex with the Schiff base derived from pyridoxal and aminoguanidine: NMR spectral studies of the ligand*, J. of Inorg. Bioch. 101 (2007) 1094−1097.

[11] Z. Otwinowski, W. Minor, *in Methods Enzymology*, edited by C.W. Carter and M.R. Sweet Academic Press, New York, USA 1996.

[12] Nonius BV, Delft, The Netherlands, 1997.

[13] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M.C.Burla, G. Polidori, M. Camalli, *SIR 92-a program for automatic solution of crystal structures by direct methods*, J Appl Crystallogr. 27 (1994) 435.

[14] P.W. Betteridge, J.R. Carruthers, R.I. Cooper, J. Prout, D.J. Watkin, *CRYSTAL version 12: software for guided crystal structure analysis*, J App Crystallogr 36 (2003) 1487.

[15] V. Jevtovic, *Cu, Fe, Ni and V complexes with pyridoxal semicarbazones. Syntheses, physical and chemical properties, structural analyses and biological activities*, Monograph, Lambert Academic Publishing, Germany (2010).

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СИНТЕЗА И РЕНДГЕНСКА КРИСТАЛНА СТРУКТУРА КОМПЛЕКСА БАКРА (II) СА ПИРИДОКСАЛ-АМИНОГУАНИДИН (PLAG) ЛИГАНДОМ

Сажетак: Реакцијом воденог раствора пиридоксал-хидрохлорида (PL·HCl) и аминогуанидин-хидрогенкарбоната ($AG·H_2CO_3$), у присуству $Na_2CO_3·10H_2O$, добили смо пиридоксал-аминогуанидин (PLAG; H_2L). Лиганд и одговарајућа со бакра $CuCl_2$ се координују и образују комплекс: тамнозелено обојен, хекса-координован, октаедарске структуре, димер-комплекс Cu(II) формуле $[Cu(PLAG)(NCS)_2]_2$. У овом раду дата је синтеза и кристална структура комплекса са лигандом у неутралној, Zwitter јонској форми.

Кључне речи: пиридоксал-аминогуанидин, Cu(II) комплекс, синтеза, кристална структура.

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