

*Dedicated to the memory of
Professor Maria Brezeanu (1924–2005)*

MIXED-LIGAND COMPLEXES. TERNARY COPPER(II) COMPLEXES WITH AMINOACIDS

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This paper describes the synthesis and characterization of five Cu(II) complexes $[\text{CuL}_1\text{L}_2(\text{NO}_3)] \cdot n\text{H}_2\text{O}$, where $n = 1, 2, 3$, L_1 is 2,2'-bipyridine or albandazole (abd = methyl [5-propyl-thio-1-H-benzimidazole-2-yl] carbamate), and L_2 is L-tyrosine, or L-tryptophan or L-histidine. Characterization of the newly prepared complexes was made by EPR, IR and UV-VIS spectroscopy, thermal analysis and molar electrical conductivity.

INTRODUCTION

Protein phosphorylation is recognized as an important step in information transfer and control of various biological processes such as enzyme activity.^{1,2} X-ray structural studies have revealed that serine phosphorylation of the active and less active forms of an allosteric enzyme muscle phosphorylase induces a conformational transition due to electrostatic or hydrogen bonds involving the phosphate moiety and histidine and arginine residues.^{3,4} A classical example of electrostatic interactions that play a vital role in enzyme activity is that revealed for a zinc enzyme carboxypeptidase A. In its complex with a substrate, glycyl-L-tyrosine, it fixes the substrate by electrostatic interactions between the carboxylate group of the substrate and the arginine guanidinium group of the enzyme.⁵ Ternary Cu(II) complexes containing aromatic heterocycles such as phen and aromatic amino acids like phenylalanine (Phe) and L-tyrosine (Tyr) have been shown to be stabilized by stacking interactions.⁶ Many works describe the presence of π - π intermolecular interactions stacking in mixed ligand complexes.⁷⁻¹³

X-ray crystal structure analysis of ternary Cu(II) complexes containing a coordinated aromatic heterocycle and an aromatic amino acid has revealed that the intramolecular stacking exists in the complex in the solid state.¹⁴⁻¹⁷

This paper describes the synthesis and characterization of five Cu(II) complexes $[\text{CuL}_1\text{L}_2(\text{NO}_3)] \cdot \text{H}_2\text{O}$, where L_1 is 2,2'-bipyridine or albandazole (abd = methyl [5-propyl-thio-1-H-benzimidazole-2-yl] carbamate), and L_2 is L-tyrosine, or L-tryptophan or L-histidine.

RESULTS AND DISCUSSION

The molar conductivity in nitrobenzene was determined for the $[\text{Cu}(\text{bpy})(\text{L-Tyr})\text{NO}_3] \cdot 3\text{H}_2\text{O}$, $[\text{Cu}(\text{bpy})(\text{L-Trp})\text{NO}_3] \cdot \text{H}_2\text{O}$, $[\text{Cu}(\text{bpy})(\text{L-histidine})\text{NO}_3] \cdot 2\text{H}_2\text{O}$ and $[\text{Cu}(\text{abd})(\text{L-histidine})\text{NO}_3] \cdot 2\text{H}_2\text{O}$ complexes. The molar conductivity values ($\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$) indicate that these complexes are non-electrolytes in nitrobenzene. These complexes have a low solubility in chloroform, acetone, ethanol and water but they are insoluble in dimethylformamide (DMF), except $[\text{Cu}(\text{abd})(\text{L-histidine})\text{NO}_3] \cdot 2\text{H}_2\text{O}$ complex which decomposes in DMF.

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IR Spectra. In IR spectra of newly prepared complexes there are 3 bands assigned to the NO_3^- ion bound to the Cu(II) center in the 1451–1456 cm^{-1} (ν_1), 1378–1393 cm^{-1} (ν_2), 1016–1040 cm^{-1} (ν_3) ranges. The splitting of the bands situated at higher wave numbers (ν_1 – ν_2) is about 60–70 cm^{-1} indicating the coordination of the nitrate ion in a monodentate fashion.¹⁸ Also, the ν_{COO^-} bands shifts towards lower wave numbers while the $\nu_{\text{COO}^-}(\text{as})$ frequencies shift towards higher wave numbers compared to the positions of these bands in the IR spectrum of the free aminoacid. The Δ values [$\nu_{\text{as}}(\text{COO}^-) - \nu_{\text{s}}(\text{COO}^-)$] are about 213–316 cm^{-1} .

The $\delta_{\text{NH}(1)}$ and $\delta_{\text{NH}(2)}$ frequencies shift towards higher wave numbers in the IR spectra of the complexes together with the vanishing of the ν_{NH} frequencies. This behavior suggests the coordination of the aminoacid through the $-\text{NH}_2$ and $-\text{COO}^-$ groups in a bidentate fashion.

Table 1

IR spectral data for the ligands and their complexes (cm^{-1})

Compound	$\nu_{\text{COO}^-}(\text{s})$	$\nu_{\text{COO}^-}(\text{as})$	ν_{NH}	$\delta_{\text{NH}(1)}$	$\delta_{\text{NH}(2)}$	$\nu_{\text{C-O-C}}$	$\nu_{\text{C-N-C}}$	$\nu_{\text{C-S}}$	$\nu_{\text{C=N}}$	ν_{NO_3}
L- Tyrosine	1415(vs)	1583(m)	3121(vs)	1662(m)	1535(m)	-	-	-	-	-
2,2'- bipyridine	-	-	-	-	-	-	-	-	1572(vs)	-
[Cu(bpy)(L-Tyr)NO ₃] \cdot 3H ₂ O	1380(m)	1621(m)	-	1705(w)	1578(m)	-	-	-	1528(w)	1456(m) 1393(m) 1040(m)
L-Tryptophan	1393(m)	1608(m)	3103(vs)	1645(vs)	152(vs)	-	1108(m)	-	-	-
[Cu(bpy)(L-Trp)NO ₃] \cdot H ₂ O	1344(m)	1630(m)	-	1683(m)	1568(m)	-	1104(m)	-	1530(m)	1451(m) 1382(m) 1020(m)
L-histidine	1387(m)	1610(m)	3112(vs)	1638(vs)	1517(m)	-	1115(w)	-	1580(vs)	-
[Cu(bpy)(histidine)NO ₃] \cdot 2H ₂ O	1339(m)	1652(m)	-	1672(m)	1560(m)	-	1110(w)	-	1580(w)	1453(m) 1541(m) 1378(m) 1534(m) 1024(m)
albendazole	1408(vs)	1632(m)	-	-	-	1092w	1130(w)	712w)	1568(vs)	-
[Cu(abd)(histidine)NO ₃] \cdot 2H ₂ O	1342(m)	1658(m)	-	1704(w)	1593(m)	1095w	1126(m)	710w)	1580(w)	1454(m) 1542(m) 1386(m) 1535(w) 1016(m)
(dark-brown)										
[Cu(abd)(histidine)NO ₃] \cdot 2H ₂ O	1344(m)	1655(m)	-	1708(w)	1597(m)	1096w	1123(m)	674w)	1580(w)	1453(m) 1540(m) 1381(m) 1531(w) 1021(m)
(red-brown)	1407(m)	1620(m)								

The $\nu_{\text{C=N}}$ frequency of 2,2'-bipyridine ligand shifts by 30–40 cm^{-1} towards lower wave numbers in the IR spectra of complexes compared to the IR spectrum of the free ligand, thus indicating the coordination to Cu(II) through the two sp^2 hybridized nitrogen atoms. The same feature was observed in the case of Cu(II) complexes with methyl [5-propyl-thio-1-H-benzimidazol-2-yl] carbamate. In the IR spectra of Cu(II) complexes with L-histidine, there is an additional $\nu_{\text{C=N}}$ frequency in the 1531–1535 cm^{-1} range.

This behavior indicates the coordination of L-histidine ligand through the sp^2 hybridized nitrogen atom. In the IR spectrum of the red-brown [Cu(abd)(histidine)NO₃] \cdot 2H₂O complex the $\nu_{\text{C-S}}$ frequency shift towards lower wave numbers suggesting the coordination of the methyl [5-propyl-thio-1-H-benzimidazol-2-yl] carbamate ligand through the sulfur atom.

Electronic spectra. The electronic spectroscopy data for the complexes in the solid state are presented in Table 2. The UV-VIS spectra of the [Cu(bpy)(L-Tyr)NO₃] \cdot 3H₂O and [Cu(bpy)(L-Trp)NO₃] \cdot H₂O complexes show two distinct bands at 11435 cm^{-1} and 14980 cm^{-1} for the former and at 11790 cm^{-1} and 15120 cm^{-1} for the latter complex. The position of these two bands is a strong indication of a square-pyramidal geometry.¹⁹

The UV-VIS spectrum of the [Cu(bpy)(L-histidine)NO₃] \cdot 2H₂O complex shows two absorption bands at 16300 cm^{-1} and 17230 cm^{-1} and a third weak absorption band at 13215 cm^{-1} , suggesting a distorted octahedral geometry. The UV-VIS spectra of the other complexes containing histidine as a secondary ligand show medium absorption bands, for which the position indicates an octahedral geometry.¹⁹ The coordination of the sp^2 hybridized heterocyclic nitrogen atom of histidine in the axial position (for Cu(II) complexes with histidine) increases the splitting between the d_z^2 and $d_{x^2-y^2}$ orbitals as well as between the d_{xz}, d_{yz} and $d_{x^2-y^2}$ orbitals.²⁰

Table 2

Electronic spectral data for complexes in solid state (cm⁻¹)

Compounds	Assignments	d-d (cm ⁻¹)		Geometry
		$xy \rightarrow x^2 - y^2$	$xz, yz \rightarrow x^2 - y^2$	
[Cu(bpy)(L-Tyr)NO ₃] \cdot 3H ₂ O	11435	-	14980	Square-pyramidal
[Cu(bpy)(L-Trp)NO ₃] \cdot H ₂ O	11790	-	15120	Square-pyramidal
[Cu(bpy)(histidine)NO ₃] \cdot 2H ₂ O	13125	16300	17230	Octahedral
[Cu(abd)(histidine)NO ₃] \cdot 2H ₂ O (dark-brown)	-	16820	17934	Octahedral
[Cu(abd)(histidine)NO ₃] \cdot 2H ₂ O (red-brown)	-	16170	18140	Octahedral

EPR spectra. EPR spectra in the X-band for the Cu(II) complexes **(1),(2),(3)** were recorded using ethanolic solutions at 77K. The frozen ethanolic solution spectra of [Cu(bpy)(L-Tyr)NO₃] \cdot 3H₂O and [Cu(bpy)(L-Trp)NO₃] \cdot H₂O are identical, Fig. 1(A), with g_{\perp} = 2.03, g_{\parallel} = 2.18 and A_{\parallel} = 152 Gauss, respectively g_{\perp} = 2.02, g_{\parallel} = 2.20 and A_{\parallel} = 150 Gauss. The seven lines of the hypersuperfine structure of the EPR spectra indicate the presence of 3 nitrogen atoms around the Cu(II) ion.²¹ The frozen ethanolic solution spectra of [Cu(bpy)(L-histidine)NO₃] \cdot 2H₂O, Fig 1(B), indicate that there are 4 nitrogen atoms around the Cu(II) ion.²¹

Table 3

EPR parameters of the complexes

Compounds	g_{\perp}	g_{\parallel}	A_{\parallel}	A_{\perp}
[Cu(bpy)(L-Tyr)NO ₃] \cdot 3H ₂ O	2.03	2.18	152	13.8
[Cu(bpy)(L-Trp)NO ₃] \cdot H ₂ O	2.02	2.20	150	14.5
[Cu(bpy)(histidin)NO ₃] \cdot 2H ₂ O	2.09	2.29	185	17
[Cu(abd)(histidin)NO ₃] \cdot 2H ₂ O (dark-brown)	2.07	2.27	-	-
[Cu(abd)(histidin)NO ₃] \cdot 2H ₂ O (red-brown)	2.08	2.25	-	-

The splitting parameters, g_{\perp} and g_{\parallel} values depend on the ground level occupied by the paramagnetic electron of Cu(II). Thus, if the ground state of Cu(II) is $B_{1g}(d_{x^2-y^2})$, then the two parameters are related by the following relationship: $g_{\parallel} > g_{\perp} > 2.002$ and the complex shows an axial distortion.²² The EPR spectra recorded at room temperature of the polycrystalline powder of the [Cu(abd)(L-histidine)NO₃] \cdot 2H₂O complex both dark-brown and red-brown forms with g_{\perp} = 2.07, g_{\parallel} = 2.29 for the former and g_{\perp} = 2.08, g_{\parallel} = 2.25 for the latter, show typical axial absorption.

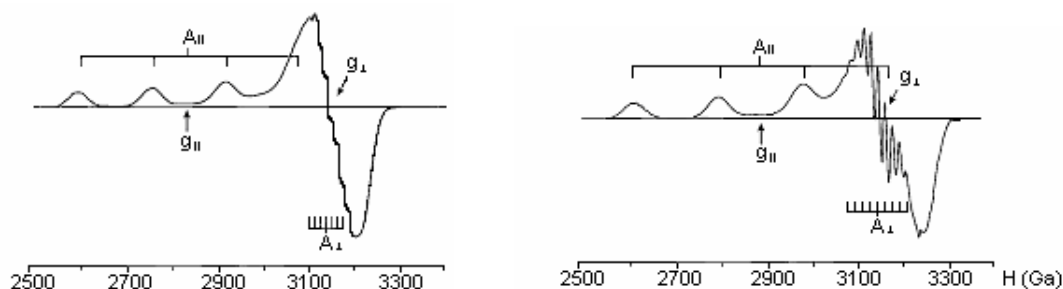


Fig. 1 – Frozen solution EPR-spectra of [Cu(bpy)(L-Tyr)NO₃] \cdot 3H₂O, (A) and [Cu(bpy)(L-histidine)NO₃] \cdot 2H₂O, (B), recorded at 77 K in ethanol.

Thermal decomposition. The reported complexes of this study were investigated by thermogravimetry (TG). Experimental data for thermogravimetric analysis are presented in Table 4. The TG and DTG indicate

a loss of weight from 90–110°C corresponding to 3 molecules of water per mol of complex combination **(1)**, one molecule of water per mol of complex combination **(2)**, and 2 molecules of water per mol of complex combinations **(3),(4),(5)**.

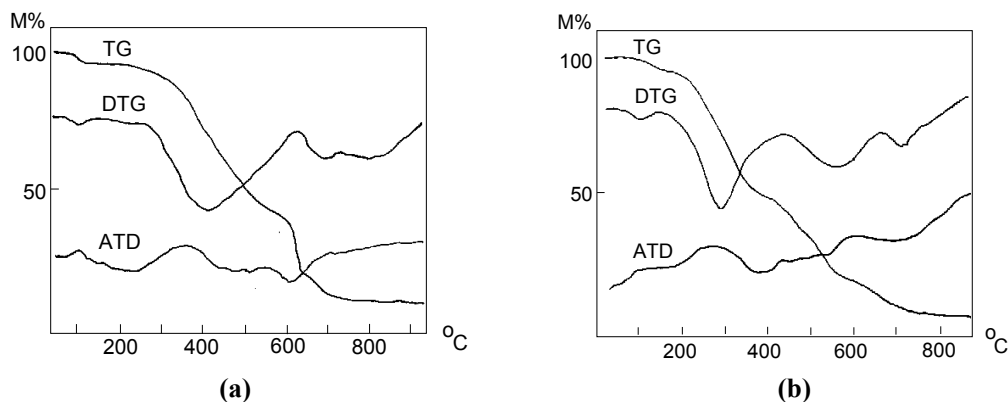
The TG and DTG curves for the **(1)** and **(2)** complex combinations are similar except for the temperature corresponding to the loss of weight, Fig. 2(a). Thus, the second step has two consecutive effects, indicating the loss of one molecule of *bpy* and the heterocyclic fragment of the aminoacid molecule, while the third step corresponds to the loss of the $-C_3NO_2H_5$ fragment of the aminoacid molecule.

Table 4

Experimental data for thermo-gravimetric analysis

Compounds	Temperature range (°C)	Eliminated fragment	Weight loss	
			exp.%	calc.%
[Cu(<i>bpy</i>)(L-Tyr)NO ₃] \cdot 3H ₂ O	90-110	3H ₂ O	10.08	10.46
	365-560	<i>bpy</i> ; Ph-OH	47.86	48.25
	650-670	$-C_3NO_2H_5$	16.33	16.86
	785	CuO(residue)	15.89	15.50
[Cu(<i>bpy</i>)(L-Trp)NO ₃] \cdot H ₂ O	93-108	H ₂ O	3.20	3.57
	340-580	<i>bpy</i> ; heterocycle	53.28	54.07
	610-635	$-C_3NO_2H_5$	16.76	17.29
	775	CuO(residue)	16.31	15.90
[Cu(<i>bpy</i>)(histidine)NO ₃] \cdot 2H ₂ O	98-109	2H ₂ O	7.25	7.62
	200-380	<i>bpy</i>	33.69	33.05
	490-680	heterocycle ; $-C_3NO_2H_5$	31.97	32.62
	745	CuO(residue)	16.27	16.94
[Cu(<i>abd</i>)(histidine)NO ₃] \cdot 2H ₂ O (light-brown)	98-105	2H ₂ O	6.76	6.18
	208-360	<i>abd</i>	46.13	45.53
	425-550	heterocycle ; $-C_3NO_2H_5$	25.93	26.46
	735	CuO(residue)	14.36	13.74
[Cu(<i>abd</i>)(histidine)NO ₃] \cdot 2H ₂ O (red-brown)	98-105	2H ₂ O	6.47	6.18
	222-378	<i>abd</i>	46.22	45.53
	427-558	heterocycle ; $-C_3NO_2H_5$	26.82	26.46
	740	CuO(residue)	14.39	13.74

For complexes **(3)**, **(4)** and **(5)** the second step of decomposition corresponds to the loss of L₁, *bpy* or *abd* (depending on the case), in the 200–380°C range which is much smaller than the corresponding temperature range of complexes **(1)** and **(2)**.

Fig. 2 – TG, DTG and ATD curves for (a) [Cu(*bpy*)(L-Trp)NO₃] \cdot H₂O; (b) [Cu(*abd*)(L-histidine)NO₃] \cdot 2H₂O.

The third step of decomposition cumulates two consecutive effects corresponding to the loss of L₂. For all complexes the last decomposition step corresponds to the loss of the NO₃⁻ group in the 675–785°C range. The values of temperature that characterize the weight loss indicate that the stability of complexes decreases

following the sequence: **(1)** \equiv **(2)** > **(4)** = **(5)** > **(3)**. The final residue, for all complexes, was analyzed by IR spectroscopy and was identified as CuO, and the %M corresponds to the calculated one.

EXPERIMENTAL

Materials and methods. The required chemicals were of analytical reagent grade and were purchased from Merck and Chimopar Bucharest and all manipulations were performed using materials as received. The content of the metallic ions was determined by atomic absorption spectroscopy with AAS 1N spectrometer Carl Zeiss Jena; C, H, and N were analyzed with a Carlo Erba elemental analyzer. Elemental analyses were performed after drying the complexes at 60°C. The molar conductivity was determined with CONSORT – C533 conductometer. Electronic spectra were recorded by the diffuse-reflectance technique, using MgO as diluting matrix, on a JASCO V-550 spectrophotometer. IR spectra were recorded with a BioRad FTS 135 spectrophotometer in the 4000-400cm⁻¹ region using KBr pellets. All the complexes were studied by thermogravimetry (TG) in static air atmosphere, with a sample heating rate of 10⁰C/min. using a DuPont 2000 ATG thermo-balance. EPR spectra were obtained with an ART-6, model IFA-Bucharest, X-band spectrometer (9.01 GHz) on line with a PC, equipped with a 100kHz field modulation unit, on polycrystalline powders and solutions at room temperature and 77K.

Synthesis of [Cu(bpy)(L-Tyr)NO₃] \cdot 3H₂O (1). Cu(NO₃)₂ \cdot 3H₂O (1.21g, 5 mmol) and bpy (0.78g, 5mmol) were dissolved in 0.2 M HCl (25mL) by heating, and after cooling a solution of L-Tyr (0.91g, 5mmol) in 1 M NaOH (10 mL) was added. The mixture was concentrated *in vacuo* and kept at room temperature. The separated blue crystals were collected and recrystallized from water. Anal. Calc. for C₁₉H₂₄N₄O₉Cu: C, 44.18; H, 4.65; N, 10.85; Cu, 12.40. Found: C, 44.87; H, 4.08; N, 10.15; Cu, 12.20%.

Synthesis of [Cu(bpy)(L-Trp)NO₃] \cdot H₂O (2) and [Cu(bpy)(L-histidine)NO₃] \cdot 2H₂O (3). These complexes were prepared by the method described above but using 1.02g

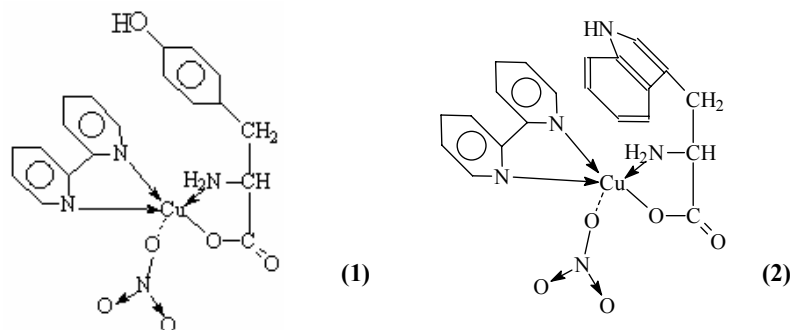
L-Trp (5 mmol) and 0.78g histidine (5mmol). The light-blue crystals which separated were collected and recrystallized from water. Anal. Calc. for [Cu(bpy)(L-Trp)NO₃] \cdot H₂O, C₂₁H₂₁N₅O₆Cu: C, 50.09; H, 4.17; N, 13.91; Cu, 12.72. Found: C, 50.83; H, 3.74; N, 13.78; Cu, 12.47%, and calc. for [Cu(bpy)(histidine)NO₃] \cdot 2H₂O, C₁₅H₁₉N₇O₇Cu: C, 40.67; H, 4.23; N, 17.29; Cu, 13.55. Found: C, 40.89; H, 3.86; N, 16.93; Cu, 13.32%.

Synthesis of [Cu(abd)(L-histidine)NO₃] \cdot 2H₂O. Cu(NO₃)₂ \cdot 3H₂O (1.21g, 5 mmol) and abd (1.32g, 5mmol) were dissolved in 0.2 M HCl (25mL) by heating, and after cooling a solution of histidine (0.78g, 5mmol) in 1 M NaOH (10 mL) was added. The resulting mixture (pH=8.5) was heated under stirring for 2-3 hours and then kept at room temperature for 7 days. The light-brown precipitate **(4)** formed was filtered off and washed with hot water and dried at 60°C. The final product was a microcrystalline powder. A red-brown microcrystalline powder **(5)** was obtained by modifying the pH the resulting mixture to 4.5-5 by adding a 0.2 M HCl solution (30mL). The elemental analysis confirmed the same chemical formulae: [Cu(abd)(L-histidine)NO₃] \cdot 2H₂O, C₁₈H₂₈N₇O₉SCu. Calc.: C, 37.11; H, 4.12; N, 16.83; Cu, 11.00. Found: C, 37.88; H, 3.86; N, 17.12; Cu, 10.83%.

All these final products were obtained as microcrystalline powders.

CONCLUSIONS

EPR spectral, Electronic spectral and IR spectral data led to the conclusion that the [Cu(bpy)(L-Tyr)NO₃] \cdot H₂O **(1)** and [Cu(bpy)(L-Trp)NO₃] \cdot H₂O **(2)** complexes display a square-pyramidal geometry similar to that of [Cu(bpy)(L-Tyr)ClO₄] \cdot H₂O [17], which suggests that the replacement of the ClO₄⁻ ion with the NO₃⁻ ion has no influence on the coordination geometry.



The UV-VIS spectra of the last three complexes containing histidine as a secondary ligand show medium intensity absorption bands specific to an octahedral geometry. The coordination of the sp² hybridized nitrogen atom of the aminoacid heterocycle in the axial position of the Cu(II) complexes with histidine leads to the conclusion that these complexes have an axial distortion [20].

