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SYNTHESIS AND CHARACTERIZATION OF A NEW DIIMINEDIOXIME LIGAND AND ITS COPPER (II) COMPLEX AS POTENTIAL ⁶⁴Cu(II)-RADIOPHARMACEUTICALS

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Abstract

As a part of effort to an develop ⁶⁴Cu-based radiopharmaceuticals for PET (positron emission tomography) imaging of multidrug resistance in cancer, a new diiminedioxime ligand was prepared. Its Cu(II) complex was synthesized from Cu(OAc)₂ by heating in methanol. The structure of the ligand was established using elemental analysis, UV-Vis, IR, ¹H and ¹³C NMR technique. The isolated complex was characterized by means of elemental analysis, IR and UV-Vis, and its structure was proposed.

Introduction

Positron emission tomography (PET) is a valuable diagnostic tool, but its availability is limited because the half-lives of many PET radionuclides are too short to allow their delivery beyond the site where they are produced. There is, therefore, considerable interest in the development of PET radiopharmaceuticals based on positron-emitting radionuclides with longer half-lives (e.g., ¹²⁴I, t_{1/2} = 4.2 d; ^{94m}Tc, t_{1/2} = 52 min; ⁶⁴Cu, t_{1/2} = 12.7 h). Because of its convenient half-life and ease of production, ⁶⁴Cu is a strong candidate on which to build a family of PET radiopharmaceuticals for a variety of applications to complement ¹⁸F[FDG][1]. On another front, organic scaffolds capable of accommodating PET radionuclides that generate novel metallopharmaceuticals through short synthetic routes have been reported. Based upon rigorous prior contributions [2,3], a stable, monocationic radiolabeled complex of copper(II) was obtained as a potential ⁶⁴Cu PET radiopharmaceutical [4]. The desired diiminedioxime ligand was synthesized from 2,3-dimethyl-propane-1,2-diamine and heptane-2,3-dione-3-oxime. Diiminedioxime as tetradentate ligands can form complexes with transition metal ions, forming a hydrogen bond between the two oxime groups by removing one hydrogen ion [5].

Results and Discussion

Materials and methods: All reagents and solvents used in these studies were obtained from commercial sources without further purification. The ¹³C and ¹H NMR spectral measurements were performed on a Varian Gemini 2000

(200 MHz). The spectra were recorded at room temperature in deuterated dimethyl sulfoxide (DMSO- d_6). IR Spectra were recorded on a Bomem MB 100 FTIR spectrophotometer in the form of KBr pellets. Elemental (C, H, N) analysis of the samples was carried out by standard micromethods in the Center for Instrumental Analysis, Faculty of Chemistry, Belgrade. Spectrophotometric measurements were performed by using a Uvicon 810/820 spectrophotometer.

Preparation of the ligand: 4,9-Diaza-3,10-diethyl-3,9-undecadiene-2,11-dione bis-oxime (LH₂) was prepared using the method described in the literature [6], with a slight modification, which included heating of reaction mixture and crystallization of the product in petroleum-ether.

Preparation of the complex: Cu(II) acetate monohydrate in 10 ml of methanol was added to a hot methanol solution of ligand (1:1 molar ratio). The mixture was then refluxed for 3 h. An aqueous solution of sodium perchlorate was added to the reaction mixture and stirred well. The reaction mixture was allowed to stand at room temperature for 3 days, and brown crystals were formed. The crystals were collected and dried in a desiccator. Spectrophotometric investigation indicated complex formation in methanol (for UV-spectroscopy, min. 99.8 %) with absorption maximum at 240 nm and ratio M:L=1:1, depicted in Fig. 1.

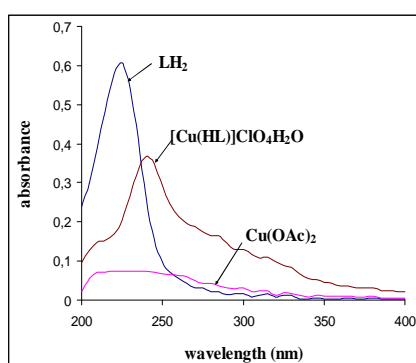


Fig. 1. UV absorption spectrum in methanol: LH₂, [Cu(LH)]ClO₄H₂O, Cu(OAc)₂, each 2×10^{-5} M.

Table 1. ¹H NMR and ¹³C NMR spectral data (δ ppm) for the ligand LH₂.

LH ₂ *	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
¹ H NMR	1.79(s)	3.48(s)	-	2.57(q)	0.96(t)	-	1.91(s)	11.41(s)
¹³ C NMR	28.99	50.29	155.52	19.67	11.69	167.9	9.27	-

s, singlet; t, triplet; q, quartet

* structure of LH₂ with all the protons and carbon atoms is presented in the Fig. 2.

All the protons and carbon atoms were found to be in their expected regions (Table 1). When the complex is formed from ligand, two C-N bonds are distinguishable. Two ν (C-N) are observed at lower frequencies than that in the free ligand, supporting the coordination at oxime and imine nitrogens (Table 2). According to presenting data proposed structures are shown in Fig. 2.

Table 2. Physical properties, elemental analysis and vibrational frequencies for the C-N bond of the ligand and complex.

Compound	m.p. (C°)	Yield (%)	Color	Calcd. (found)%			v (C-N)
				C	H	N	
LH ₂	143	65	white	59.55	9.28	19.84	1622 (s)
				(59.25)	(9.32)	(19.74)	
[Cu(HL)]ClO ₄ H ₂ O	>200	45	brown	36.37	5.89	12.12	1625 (w)
				(36.67)	(5.99)	(12.38)	1524 (m)

s, strong; m, medium; w, weak;

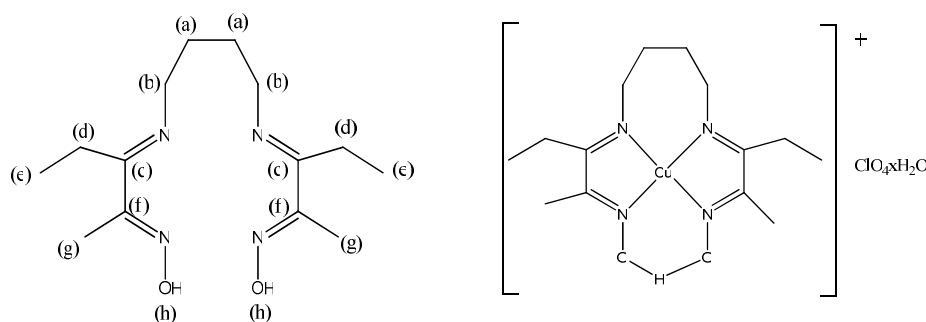


Fig. 2. Structures of LH₂ and Cu(LH)]ClO₄H₂O.

Conclusion

A new tetradentate diiminedioxime (LH₂) was successfully synthesized and characterized as well as its Cu(II) complex. On the basis of the obtained results and the literature data on similar compounds [1,5,7] we proposed structure of complex. Efforts are currently underway to prepare the corresponding ⁶⁴Cu complex.

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