Journal of Molecular Structure 1128 (2017) 44–50

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Isolation and spectroscopic characterization of Zn(II), Cu(II), and Pd(II) complexes of 1,3,4-thiadiazole-derived ligand

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ARTICLE INFO

Article history:
Received 23 April 2016
Received in revised form
6 July 2016
Accepted 15 August 2016
Available online 17 August 2016

Keywords:
Thiadiazole ligand
Complexation
Spectroscopy
Zinc
Copper
Neurodegeneration

ABSTRACT

A series of complexes incorporating Zn(II), Cu(II), and Pd(II) ions, and 4-(5-heptyl-1,3,4-thiadiazol-2-yl) benzene-1,3-diol (L1) as model ligand, was synthesized in order to examine the nature of potential interactions between biologically active ligands, 1,3,4-thiadiazoles and metal ions with proven biological relevance. The structures of the compounds isolated were characterized using a number of spectroscopic methods including IR, Uv–vis, AAS, steady state and time-resolved fluorescence (TRF). The results obtained suggest that the L1-Zn(II) and L1-Pd(II) complexes consist of one molecule of L1 and one acetate ion acting as ligands, while the L1-Cu(II) complex adapts a 2:1 (L1: metal) stoichiometry. The coordination of L1 to metal ions occurs most likely *via* one of the deprotonated hydroxyl groups of the resorcinyl moiety and one of the N atoms of the thiadiazole heterocycle.

1. Introduction

Derivatives of 1,3,4-thiadiazole are a relatively new class of compounds which demonstrate a broad array of biological activity, which makes these compounds of interest to a number of fields in medicinal chemistry and pharmacology worldwide [1–5]. Due to their high fungicidal potency against phytopathogenic fungi the 1,3,4-thiadiazole derivatives are considered as potential pesticides [6]. Also, their significant antiproliferative activity against a number of cancer cell lines has been reported in parallel with the analgesic and antinociceptive properties [7]. Several other properties of thiadiazole derivatives such as their solvatomorphism, crystal structures, dual fluorescence emission, molecular organization in lipid membranes and various other solvent-dependent interactions were extensively studied by our group [5,8–11].

A relatively small number of reports refer to the use of various thiadiazoles as ligands in the synthesis of biologically active metal complexes [12–15], which prompted us to carry out a more in depth study on coordination chemistry of thiadiazole derivatives. In particular, a recent report has identified 1,3,4-thiadiazoles as inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [16], enzymes which are responsible for cholinergic deficiency and resulting progress of neurodegenerative diseases such as Alzheimer's [17,18].

The progress of neurodegenerative disorders such as Alzheimer's or Parkinson's disease has been shown to be accompanied by an altered metal ion homeostasis [19–23]. For instance, the accumulation of redox-active metal ions, such as Cu(I) and Cu(II), is responsible for an increased concentration of toxic reactive oxygen

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http://dx.doi.org/10.1016/j.molstruc.2016.08.042
0022-2860/

species (ROS), while the generally redox-inactive Zn(II) ions interact with amyloid-β proteins (Aβ) and induce their aggregation, leading to the formation Aβ plaques. Both ROS and Aβ aggregates are thought to contribute to the progress of neurodegeneration processes within the brain [24]. Therefore, the design of therapeutic agents with the ability to bind and expel the accumulated excess metal ions is considered as a promising strategy in the therapy of neurodegenerative disorders. This in turn requires the detailed knowledge about the structures of metal complexes, which may form *in vivo* as result of the therapeutic action.

The main aim of this work is the structural elucidation of complexes which may form upon the interaction of thiadiazole derivatives with metal ions, and especially those involved in neurodegenerative disorders. In order to examine these structures 4-(5-heptyl-1,3,4-thiadiazol-2-yl)benzene-1,3-diol (L1) was employed as ligand for the synthesis of Zn(II), Cu(II) and Pd(II) complexes. The selection of Zn(II) and Cu(II) ions was dictated by their well-known role of essential trace elements in human physiology as well as their relevance to the progress of neurodegenerative disorders. As the formation of Aβ plaques is often accompanied with coordination of Zn(II) and Cu(II) ions *via* carboxylic groups [24], simple acetate salts were considered as convenient source of these ions. The well-known and good catalytic properties of numerous Pd(II)-based compounds together with the high potency of some Pd(II) complexes as photosensitizers in photodynamic therapy [25] were main choice-determining factors for the selection of Pd(II) ion for this study.

2. Materials and methods

All solvents were of 99% purity or higher (HPLC grade). Methanol (MeOH), acetonitrile (ACN) were purchased from Rathburn Chemicals (UK). DMSO-d_6 and $Zn(CH_3COOH)_2$ were purchased from Sigma (Germany), $Cu(CH_3COOH)_2$ was purchased from Avantor (Poland), and $Pd(CH_3COOH)_2$ was purchased from ABCR (Germany).

The NMR spectra, were acquired on a Bruker Avance III spectrometer (500 MHz), using DMSO-d_6 as solvent. Signal assignments were made using standard techniques including DEPT/COSY/HSQC/HMBC experiments. The infrared spectra were recorded in the region of 4000 cm^{-1} to 600 cm^{-1} on a Nicolet Impact 410 Fourier-Transform Infrared spectrophotometer equipped with the ATR adapter and Omnic software. The electronic absorption spectra were recorded on a Cary 50 Bio (Varian, USA) spectrophotometer. The steady state emission spectra were measured on a Fluorolog Max-P spectrofluorometer (Horiba Jobin Yvon, Japan) in MeOH using the excitation wavelengths equal to the absorption maxima of the compounds tested and concentration of 0.005 g/l. The florescence lifetimes τ_{fl} were measured on a time-domain Chronos BH fluorometer (ISS, USA) using a laser diode (374 nm, pulse duration of 42 ps, output power of 1070 mW, and frequency of 10 MHz) for the excitation, and a H7422P-50 (Hamamatsu, Japan) photomultiplier was applied to detect emission. A diffraction cuvette was applied as the reference scattering sample. Fitting of theoretical curves to the experimental data was performed using the bundled ISS Vinci software.

3. Synthesis

4-(5-Heptyl-1,3,4-thiadiazol-2-yl)benzene-1,3-diol (L1) was synthesized according to the previously described procedure [6].

3.1. Synthesis of L1-Zn(II), L1-Cu(II), and L1-Pd(II) complexes

All complexes were synthesized according to the following general procedure: the free ligand L1 (200 mg, 0.7 mmol) was dissolved in hot MeOH (15 ml) and a solution of Zn(II) acetate (74 mg, 0.35 mmol) in MeOH (10 ml) was added. The mixture was heated under reflux for 3 h. A fine light-yellow solid, which precipitated upon cooling the mixture was then filtered off, rinsed with water and air-dried. The crude product was recrystallized using ACN. The synthesis of L1-Cu(II) complex was carried out in a similar manner, except that Cu(II) acetate was used and the mixture was heated to reflux and stirred for 1.5 h. The L1-Pd(II) complex was synthesized in a similar manner, using Pd(II) acetate as a source of the Pd(II) ions and ACN as solvent in which the reaction mixture was heated to reflux while stirring for 6 h (See Supplementary Material for experimental details).

4. Results and discussion

Although the synthesis and structure of L1 has been reported [6], its extensive spectroscopic characterization is given in this work. The structures of free L1 and its complexes were characterized using a number of spectroscopic methods including IR, Uv–vis, AAS, steady state and time-resolved fluorescence (TRF), and NMR (both 1D and 2D) as well as by elemental analysis (C, H, and N). Regardless of the numerous attempts made, the isolation of single crystals suitable for an X-Ray diffraction remained unsuccessful.

4.1. Elemental analysis (CHN) and atomic absorption (AAS) spectroscopy

The CHN analyses of both L1-Zn(II) and L1-Pd(II) complexes suggest a structure consisting of one L1 ligand molecule and one acetate ion being bound to the central metal and such a structure is supported by NMR spectroscopic data. In the L1-Cu(II) complex, the Cu: L1 ratio of 1:2 suggest the lack of an acetate ion in the complex. The proposed structures are supported by the AAS results with only one L1 molecule in the L1-Zn(II) complex, while there are two L1 ligands in the L1-Cu(II) complex (Fig. 1). All complexes were isolated with high yields. Sharp melting points of the complexes give evidence for their high purities (See Supplementary Material).

4.2. IR spectroscopy

The IR (ATR) spectrum of free L1 (Fig. 2 top), shows a relatively sharp band at 3345 cm^{-1} and a neighboring, less intensive one at 3220 cm^{-1}, assigned to the stretching vibrations of the resorcinyl –OH groups [16,26]. One of those bands is broadened probably due to an intramolecular hydrogen bond with one of the thiadiazole heteroatoms (either S or N). The sharp and moderately intensive band at 3035 cm^{-1} is assigned to aromatic C–H stretching, while the aliphatic C–H stretching vibrations manifest as a series of highly intensive and sharp bands in the region of 2950–2850 cm^{-1}. The most characteristic band, namely the –C=N- stretching vibration of the thiadiazole moiety is present at ~1600 cm^{-1} [6,16] and is neighbored by three sharp bands at 1520, 1475, and 1434 cm^{-1}, assigned to the aromatic C–C stretches of the resorcinyl moiety. Another pair of sharp and moderately intensive bands at 1342, 1317 cm^{-1} corresponds to an in-plane bending vibrations of the O–H bond, while the sharp and intensive band at 1276 cm^{-1} is characteristic of the phenolic C–O stretching vibrations [26]. This signal is slightly broaden, most likely due to an overlap of two resorcinyl –OH signals. The series of signals representing C–S–C stretching of the thiadiazole is present at ~660 cm^{-1} and is accompanied by a number of other weak signals arising from out-of-plane bending vibrations of the hydroxyl O–H bonds [26].

In the spectra of the metallo-complexes (Fig. 2, bottom) the region of 3400–3000 cm^{-1} is dominated by one broad band, with