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

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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.

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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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species (ROS), while the generally redox-inactive Zn(II) ions interact with amyloid- β proteins (A β) and induce their aggregation, leading to the formation A β plaques. Both ROS and A β 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 A β 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(CH₃COOH)₂ were purchased from Sigma (Germany), Cu(CH₃COOH)₂ was purchased from Avantor (Poland), and Pd(CH₃COOH)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 fluorescence lifetimes τ_f 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

Fig. 1. Structure of 4-(5-Heptyl-1,3,4-thiadiazol-2-yl)benzene-1,3-diol (L1) free ligand and proposed structures of its corresponding L1-Zn(II), L1-Pd(II), and L1-Cu(II) complexes (M=Zn(II), or Pd(II)). The structure of L1 shows the numbering system of carbons used for the spectroscopic characterization.

Fig. 2. FT-IR (ATR) spectra of free ligand L1 (top) and its corresponding L1-Zn(II) complex (bottom).

the maxima at 3107, 3117, 3158 cm^{-1} in L1-Zn(II), L1-Cu(II), and L1-Pd(II), respectively. This, together with the practically unchanged aliphatic C–H stretching vibrations, suggests that the complexation takes place near the resorcinyl ring. This assignment is supported by the shifts of the bands arising from aromatic C–C stretching, which in the free L1 have maxima at 1475 and 1434 cm^{-1} . In the L1-Zn(II) complex these bands are shifted to 1465 and 1412 cm^{-1} , while in the L1-Cu(II) and L1-Pd(II) complexes these changes are even more significant. Both L1-Cu(II) and L1-Pd(II) complexes show in this region a strong and sharp band at $\sim 1460 \text{ cm}^{-1}$, and a pair of sharp signals within the range of 1550–1500 cm^{-1} . Also the thiadiazole ring is strongly affected by the complexation, which manifests in broadening of –C=N– stretching signal. Additionally, the maximum of this band is shifted from 1601 to 1620, 1606, and 1604 cm^{-1} , in of L1-Cu(II) and L1-Pd(II), and L1-Zn(II) complexes, respectively.

Based on guidelines established by Deacon et al. [27,28], it was expected for the L1-Zn(II) and L1-Pd(II) complexes that the presence of an acetate ion would give rise to a symmetrical and asymmetrical stretching vibrations, which are usually seen between 1600 and 1400 cm^{-1} . Due to a significant broadening of the –C=N– stretching vibration and high intensity of the aromatic C–C stretching bands the assignment and examination of acetate-related signals remained unsuccessful. Nevertheless, an

incorporation of the acetate ligand is confirmed by NMR spectroscopy and supported by results of CHN and AAS analyses.

4.3. NMR spectroscopy

The ^1H NMR spectrum of the free ligand in $\text{DMSO}-d_6$ (Fig. 3) consists of five signals in the downfield region, assigned to the resorcinyl moiety. The two most downfield-positioned peaks are singlets assigned to the phenolic –OH groups present at C11 and C13 carbons. The origin of both –OH signals is additionally confirmed by D_2O exchange experiment (not shown) [26]. The remaining signals present in the aromatic region are assigned to the phenolic ring protons at the positions 12, 14, and 15. The doublet at 9.99 ppm with the coupling constant $J = 8.62 \text{ Hz}$ represents the C15 atom, while the one at 6.47 ppm with $J = 2.23$ originates from the C12 proton. The coupling of both C15 and C12 to C14 results in its signal present as double doublet at 6.41 ppm with J_1 and J_2 values correlated with the respective protons coupled. The upfield region of the spectrum is occupied by a series of signals arising from the aliphatic chain of the heptyl residue. The triplet at 3.05 ppm is the most “deshielded” aliphatic signal and is assigned to the C7 methylene group. It couples to neighboring C6 methylene with $J = 7.55 \text{ Hz}$, which is additionally split as result of coupling to another methylene group C5, giving rise to a quintet at 1.73 ppm.

Fig. 3. ^1H NMR ($\text{DMSO}-d_6$) spectra of free 4-(5-Heptyl-1,3,4-thiadiazol-2-yl)benzene-1,3-diol ligand L1 (bottom) and its corresponding L1-Zn(II) complex (top).

The chemical shift of the C5 methylene group is similar to those of C2–C4, and effects in a multiplet of overlapped signals in the range of 1.4–1.2 ppm. Hence their assignment is based mainly on COSY and HSQC correlation experiments (see [Supplementary Material](#)) and additionally supported by integration of the ^1H NMR peaks. The triplet at 0.86 ppm arises from a terminal $-\text{CH}_3$ group of the heptyl chain.

In the spectrum of the L1-Zn(II) complex all peaks are significantly broaden, most likely as a result of coordination to the Zn(II) ion. However, all signal-to-noise ratios remain high and the correct assignment is possible with support from additional experiments such as COSY, HSQC and HMBC correlations ([Figs. 3 and 4](#), and [Supplementary Material](#)). The broadening of aromatic peaks is particularly strong, indicating coordination of the zinc ion is likely *via* the resorcinyl residue. In addition, compared to the spectrum of free ligand, all signals are shifted to lower frequencies and only one $-\text{OH}$ signal is observed. The most significant shielding effect is observed for the aromatic protons, signals, which together with the disappearance of one of the $-\text{OH}$ peaks suggests that the complexation with L1 occurs most likely *via* one of the hydroxyl groups and one of the thiadiazole N atoms ([Fig. 1](#)). A new signal present in the aliphatic region of the spectrum, namely the sharp singlet at 1.83 ppm is characteristic of the $-\text{CH}_3$ group of the acetate [29] and shows a long range correlation (HMBC) with characteristic highly de-shielded carboxylic carbon ([Fig. 4 D](#)). This suggests an involvement of the acetate in the complexation and is consistent with the AAS and IR spectroscopic data as well as with the elemental analysis results.

The ^{13}C NMR signals of the ligand are even more strongly affected by the presence of central metal ion compared to the corresponding protons in the ^1H NMR spectrum. The ^{13}C NMR spectrum of L1-Zn(II) complex ([Fig. 4 A](#) and [Supplementary Material](#)) does not give a full set of expected signals as only the aliphatic C1–C7 and the acetate carbons are clearly visible. The assignment of C1–C7 carbons is additionally supported by the DEPT (D135), HSQC and HMBC experiments ([Fig. 4 B, C, and D](#), and [Supplementary Material](#)). The carbons that constitute the aromatic and heterocyclic ring give extremely weak signals and their assignment is made based mainly on the 2D correlation spectroscopy. The aromatic C12, C14, and C15 carbons are assigned based on HSQC spectrum ([Fig. 4C](#)). Neither does the HMBC correlation give a spectrum of satisfactory quality and only aliphatic signals gave rise

to strong cross-signals ([Fig. 4 D](#)). Nevertheless, the HMBC spectrum allows for the assignment of the C8 carbon of the thiadiazole and gives evidence for the acetate ion present in the L1-Zn(II) complex, by showing the long distance interaction between singlet at 1.83 ppm and highly de-shielded carboxylic carbon at 176.74 ppm ([Fig. 4D](#)). Chemical shifts of the remaining four quaternary carbons, namely the C9–11 and C13, were calculated using the available tabular data [26].

Low solubility of the L1-Pd(II) is a major obstacle in the acquisition of satisfactory quality ^1H NMR spectrum of this complex (not shown). In spite of the significant broadening of all signals, a pattern of chemical shifts similar to that of the Zn(II) complex is observed. The structural similarity to L1-Zn(II), including the presence of the acetate ion is in agreement with the results obtained from the IR and CHN analyses. Due to the solubility problems, the acquisition of ^{13}C NMR spectrum of L1-Pd(II) was not feasible.

4.4. UV–vis absorption spectroscopy

The electronic absorption spectra of free ligand and its metallo-complexes are shown in [Fig. 5](#). The spectrum of free ligand consists of two intense $\pi \rightarrow \pi^*$ transition bands with their maxima at $\lambda_1 = 286$ and $\lambda_2 = 318$ nm. Coordination to L1-Zn(II) and L1-Cu(II) ions results in only a slight bathochromic shift of the λ_1 (287 and 288 nm, respectively), while in L1-Pd(II) complex this band is significantly shifted towards higher energy (265 nm). In all complexes, λ_2 shifts hipsochromically from 318 nm (free ligand) to 316, 303, and 305 nm, in L1-Zn(II), L1-Cu(II), and L1-Pd(II) complex, respectively. The formation of complexes manifests most notably by new absorption bands λ_3 appearing at the lower energy side of the spectra, with the absorption maxima at 363, 365, and 378 nm, respectively. Additionally, the $d \rightarrow d^*$ transitions λ_4 are visible in the spectra of L1-Cu(II) and L1-Pd(II) complexes as low intensity broad bands centered at approximately 660 and 580 nm, respectively.

4.5. Steady state and time-resolved fluorescence spectroscopy

The fluorescence spectrum of each compound consists of only one emission band, with the maximum at approximately 440 nm ([Fig. 6](#)). Although there are no significant differences between the

Fig. 4. Assignment of ^{13}C NMR signals in the L1-Zn(II) complex: A) ^{13}C NMR spectrum of free ligand L1 (bottom) v.s. L1-Zn(II) complex (top); B) Aliphatic region of ^{13}C NMR spectrum of L1-Zn(II) complex (bottom) v.s. DEPT (D135) (top); C) HSQC spectrum of L1-Zn(II) complex; D) HMBC spectrum of L1-Zn(II) complex.

Fig. 5. UV-Vis spectra of free L1 ligand and its corresponding metal complexes in MeOH. All spectra are normalized to the a.u. value of 1 at the λ_2 maxima.

positioning of emission maxima, the intensities vary widely depending on type of the central metal ion. The greatest emission intensity is observed in the L1-Zn(II) complex, while the emission from L1 is less intensive. The lower intensity of fluorescence emission in the free ligand may have several reasons, including the possibility of free rotation (*cis-trans* isomerization), intramolecular rearrangements, or various structural distortions, which may contribute to non-radiative relaxation [30–32]. Moreover, the hydrogen bonding or other interactions with environment (solvent), may additionally favor a non-radiative dissipation of the excitation energy [33]. Coordination with metal ions utilizes a number of substituents able to form hydrogen bonds, thus disfavoring the non-radiative dissipation of the excitation energy. Also, the formation of complex effects in an increased rigidity of the whole molecule which usually results in an increase in the fluorescence intensity. Additionally, the electron-rich metal ions such as Zn(II), with fully occupied *d* valence orbital and relatively low mass prefer most likely the radiative relaxation pathway rather than non-radiative one. The opposite effect is observed in the L1-Cu(II) and L1-Pd(II) complexes, in which emission of fluorescence

Fig. 6. Steady state fluorescence spectra of free L1 and its metal complexes in MeOH.

is strongly quenched. Compared to those of L1-Zn(II), and free L1 ligand, the weak fluorescence of L1-Cu(II) complex may be as result of internal conversion from the excited MLCT state [34], while in L1-Pd(II) results most likely from an increased spin-orbit coupling, which favors the relaxation via intersystem crossing (ISC) [35].

Most compounds show monoexponential fluorescence decays, except the L1-Pd(II) complex (Fig. 7), which shows a multi exponential decay and which may be associated with the sample scattering caused by the poor solubility, which in turn may result in an incorrect identification of its intrinsic decay kinetics [36]. L1 has the longest fluorescence lifetime of 2.95 ns. Among the complexes the L1-Zn(II) has the longest fluorescence lifetime (2.76 ns), which is only slightly shorter than that of the free ligand (Table 1). The fluorescence lifetime of L1-Cu(II) complex is shorter by 1 ns than that of L1, while the results obtained for L1-Pd(II) are unreliable.

5. Conclusions

In conclusion, we have synthesized a series of metal complexes with 4-(5-heptyl-1,3,4-thiadiazol-2-yl)benzene-1,3-diol (L1). Based on the set of spectroscopic experiments we were able to propose the structures of the complexes, which adapt a distorted square planar or tetrahedral coordination geometry. The spectroscopic

Fig. 7. Fluorescence decays of free L1 and its corresponding metal complexes in MeOH.

Table 1

Absorption and emission maxima and fluorescence lifetimes of free L1 and its corresponding metal complexes in MeOH.

Compound	λ_{Abs} [nm]	$\lambda_{\text{Em}} (\lambda_{\text{Ex}})$ [nm]	τ_{fl} [ns]
L1 free ligand	286 318	442 (365)	2.95
L1–Zn (II) complex	287 316 363	440 (365)	2.76
L1–Cu (II) complex	288 303 365 650	430 (365)	1.92
L1–Pd (II) complex	265 305 378 580	430 (365)	3.49 (61%) 0.19 (39%)

data suggest that the L1–Zn(II) and L1–Pd(II) complexes comprise one L1 and one acetate ion as ligands, while the L1–Cu(II) complex shows 2:1 stoichiometry (L1: metal). The coordination of L1 to metal ions occurs most likely *via* one of the hydroxyl groups of the resorcinyl moiety and one of the N atoms of the thiadiazole heterocycle. All compounds were isolated with high yields and satisfactory purities, giving the that the evidence that 1,3,4-thiadiazole derivatives are effective metal chelators. This in turn may suggest that the anti-neurodegenerative properties of these compounds not only are associated with AChE and BuChE inhibition but also may emerge from their metal binding ability, similar to that

observed for a number of other potential AChE inhibitors [37]. The high yields and purities of complexes enable the possibility of further studies aimed at more detailed examination of their biological activity.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.molstruc.2016.08.042>.

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