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1,3,4-Thiadiazole-based diamides: synthesis and complexation properties

Natalia Łukasik[a*], **Elżbieta Luboch**[a], **Jarosław Chojnacki**[b], **Ewa Wagner-Wysiecka**[a*]
[a]Department of Chemistry and Technology of Functional Materials, [b]Department of Inorganic Chemistry; Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland
**Corresponding authors: E-mail: ewa.wagner-wysiecka@pg.gda.pl; natalia.lukasik@pg.gda.pl*

Abstract

Aromatic diamides, derivative of 2,6-pyridinedicarboxylic acid and isophthalic acid, bearing 1,3,4-thiadiazole residue were prepared with satisfactory yields in conventional procedures and microwave stimulated reactions. X-ray structure of *N*,*N′*-bis (1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide (**2**) DMSO solvate (**2**·DMSO) was described. Selective zinc(II), lanthanum(III), terbium(III) and L-tyrosine recognition was found for *N*,*N′*-bis(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide in DMSO and its mixture with water. The IDA (Indicator Displacement Assay) system for metal cations sensing was proposed. The binding properties of **2** were compared with newly synthesized *N*,*N′*-bis(1,3,4-thiadiazol-2-yl)-1,3-benzenedicarboxamide **1.**

Keywords: 1,3,4-thiadiazole-based amide, microwave assisted synthesis, X-ray structure, metal cation complexation, tyrosine recognition, spectroscopic methods

1. Introduction

Modern supramolecular chemistry is nowadays a multidisciplinary field of science taking its early inspiration from nature [1]. One of its current aspects concerns the synthesis of receptors for selective recognition of biologically and environmentally important species. The information about the intermolecular interactions makes possible to predict how some natural systems work. It is also important for development of new selective ligands for analytical purposes or to study of the properties of pharmaceuticals in which ion biding site can be crucial. One of the essential trace element in living organisms is zinc. It plays a role in many life processes e.g. RNA and DNA metabolism, signal transduction, gene expression, apoptosis regulation, brain and nervous system functions regulation [2]. Therefore, the search and study of the properties of zinc ion affinity to artificial, especially biomimetic systems is of great importance.

On the other hand, a significant part of interdisciplinary supramolecular research focuses on the studies of lanthanide complexes (lanthanum(III), terbium(III)) because of their unique optical properties such as large Stokes shifts, long luminescence lifetimes, as well as narrow emission bands [3]. For instance, a terbium(III) – single stranded DNA complex was proposed for luminescent detection of MSC-7 breast cancer cells [4].

Other important group of guests are amino acids, among others tyrosine. L-Tyrosine is a precursor in the synthesis of neurotransmitters - dopamine, noradrenaline, and thyroxin thyroid hormones [5]. Its presence in toxin-sensitive brain channels and absence in toxin-insensitive cardiac channels indicates its crucial role in toxin binding. Tyrosine is also involved in selective transport of K^+ through ion channels [6]. Disorders in tyrosine transport mechanism through blood-brain barrier may be involved in the physiopathology of manic-depressive illness and schizophrenia [7]. Therefore, receptors capable of tyrosine binding have a significant importance in amino acids sensing and analysis [8]. However, under physiological conditions the effective amino acids recognition is a challenging task because of zwitterionic character of guest and competing action of water [9].

Among potential molecular receptors interesting group seems to be heterocyclic compounds, namely thiadiazoles, five membered ring systems with one sulfur and two nitrogen atoms. They occur in four isomeric forms differing in possible arrangements of heteroatoms: 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-thiadiazoles. Derivatives of 1,3,4-thiadiazole being hydrogen binding site and two electron donor system exhibit a wide variety of bioactivities [10]. For example, cefazolin, cephalosporin antibiotic, contains 2-methyl-1,3,4-thiadiazole-5-thiol residue [11]. Biologically active 1,3,4-thiadiazole residue is also a component of acetazolamide – a drug used in the treatment of glaucoma and epilepsy [12]. Derivatives of 1,3,4-thiadiazole show also antibacterial [13], antimicrobial [14], antifugal [15], and insecticidal [16] properties. Anticancer activity of 1,3,4-thiadiazole containing compounds was also documented [17]. This class of compounds has found application also in other field of life and science, for example as corrosion inhibitors [18] or in dye preparation [19]. 1,3,4-Thiadiazole residue can be also used as a part of supramolecular sensing systems. Thiadiazole-based receptors for both metal cations e.g. gold(III) [20], copper (II) [21], zinc(II) [22], as well as anions [23] were reported.

Another example of molecular receptors are pyridine-2,6-dicarboxamides [24]. *N*,*N*'-bis(4-nitrophenyl)pyridine-2,6-dicarboxamide, studied as chromogenic anion receptor, was found to transport chloride ions through phospholipid bilayers and exhibit evidence of channel activity

[25]. Moreover, pyridine-2,6-dicarboxamides show antifungal, antibacterial, and antitubercular properties [26].

Considering the above aspects we have decided to prepare diamide bearing two mentioned in introduction building blocks: 2,6-substituted pyridine ring and 1,3,4-thiazole moiety and compare its binding properties with analogous compound derived from isophthalic acid. The object of studies were metal cations, anions, and amino acids. Complexation studies were carried out in DMSO.

2. Experimental

2.1. Materials

All chemicals of highest available purity were purchased from commercial sources and used without further purification. For reaction progress monitoring aluminum sheets covered with silica gel 60F$_{254}$ purchased from Merck were used. Spectroscopic measurements were carried out in DMSO (dimethylsulfoxide, Sigma-Aldrich) of gradient grade. Substrates for syntheses (2-amino-1,3,4-thiadiazole, pyridine-2,6-dicaboxylic acid dichloride, isophthalic acid dichloride, triethylamine) and all salts used in spectroscopic studies (tetra-*n*-butylammonium (TBA) salts, perchlorates, chlorides) were purchased from Sigma-Aldrich. DMF (*N*,*N*-dimethylformamide) was purchased from POCH S.A.

2.2. Apparatus

Microwave-assisted syntheses were carried out in microwave reactor Plazmatronika RW800. ^{1}H NMR and ^{13}C NMR spectra were recorded at a Varian instrument at 500 and 125 MHz respectively. Chemical shifts are reported as δ [ppm] values in relation to TMS (tetramethylsilane). FTIR (Fourier Transform Infrared) spectra were recorded on a Mattson Genesis II and IS10 Nicolet instruments. Mass spectra were recorded on an AMD-604 (EI method, 70 eV) and a GCT Premier (TOF MSFD^{+}) instruments. For UV-vis measurements an UNICAM UV 300 apparatus was used. In UV-vis spectrophotometry deionized water (conductivity $< 1\ \mu S \cdot cm^{-1}$, Hydrolab, Poland) was applied. All measurements were carried out at room temperature.

2.3. Synthesis

General procedure of **c**onventional **s**ynthesis (**cs**):

To a magnetically stirred solution of 2-amino-1,3,4-thiadiazole (0.40 g, 4 mmol) and triethylamine (0.56 mL, 4 mmol) in dry DMF (20 mL) the respective acid dichloride (dipicolinic or isophthalic acid chloride) (2 mmol) was added in portions. The reaction mixture was stirred at 60 °C for twelve hours. Addition of distilled water to a cooled (room temperature) reaction mixture resulted in white precipitate formation which was filtered off under reduced pressure and washed with distilled water. The pure product was obtained by crystallization of the white solid from propan-2-ol.

General procedure of **m**icrowave-**a**ssisted **s**ynthesis (**m-as**):

A mixture of respective acid chloride (dipicolinic or isophthalic acid chloride) (2 mmol), 2-amino-1,3,4-thiadiazole (4 mmol) and imidazole (4 mmol was exposed to microwave irradiation for 15 minutes at 60ºC (power 400 W). Reactions were carried out under solvent-free conditions. After that time, reaction mixture was dissolved in DMF (20 mL) and further purification procedure was similar to the one described above.

***N*,*N′*-bis(1,3,4-thiadiazol-2-yl)-1,3-benzenedicarboxamide (1)** Yield: 0.207 g, 31% (**cs**); 0.467 g, 70% (**m-as**); white solid; mp> 300 °C; TLC: R_f = 0.73 (dichloromethane:methanol, 15:2, v/v); ^{1}H NMR (500 MHz, *d*-DMSO, δ [ppm]): 7.76 (1H, t, *J* = 7.7 Hz); 8.34 (2H, d, *J* = 7.7 Hz); 8.86 (1H, s); 9.26 (2H, s); 13.22 (2H, s). ^{13}C NMR (125 MHz, *d*-DMSO, δ [ppm]): 165.2 (C=O); 160.0, 149.6 (C-thiadiazole); 133.0, 132.6, 129.7, 129.1 (C-aromatics). FT-IR (KBr pellet) cm^{-1}: 3160, 3030, 2934, 1673, 1541, 1304, 1249, 878, 712. HRMS (ESI) $[M-H]^-$: found 331.0073 calculated for $C_{12}H_7N_6O_2S_2$ 331.0072.

***N*,*N′*-bis(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide (2)** Yield: 0.445 g, 70% (**cs**); 0.490 g, 77% (**m-as**); white solid; mp> 300 °C; R_f = 0.69 (dichloromethane:methanol, 15:2, v/v); ^{1}H NMR (500 MHz, *d*-DMSO, δ [ppm]): 8.41 (1H, t, *J* = 7.8 Hz); 8.51 (2H, d, *J* = 7.3 Hz); 9.36 (2H, s); 13.72 (2H, s). ^{13}C NMR (125 MHz, *d*-DMSO, δ [ppm]): 162.7 (C=O); 159.5, 150.0 (C-thiadiazole); 147.4, 140.9, 127.7 (C-aromatics). FT-IR (KBr pellet) cm^{-1}: 3276, 3061, 1693, 1680, 1526, 1291, 1030, 882, 654. HRMS (EI): found 333.00883, calculated for $C_{11}H_7N_7O_2S_2$: 333.01027.

2.4. Complexation studies

Complexation studies were performed by UV-vis titration of the ligand solution in DMSO and its mixture with water with the respective metal perchlorates (for metal cations) or chlorides (for lanthanides) or tetra-*n*-butylammonium (TBA) salts (for anions). *Caution! Perchlorate salts should be regarded as potentially explosive and handled with care.* The stock solutions of ligands (~10^{-4} M) and metal perchlorates/chlorides or TBA salts (~10^{-2} M) were prepared by weighing the respective quantities of them and dissolving in pure DMSO or its mixture with water (DMSO : H_2O= 9:1 v/v) in volumetric flasks. In order to prepare tyrosine solution the weighted quantities of amino acid were dissolved in deionized water. Titrations were carried out in a quartz cuvette with path length of 1 cm using starting volume of the ligand solution (2.3 mL). The stability constant values were calculated with the use of OPIUM software on the basis of titration experiment data [27]. The symbol R in caption of UV-Vis titration spectra is defined as molar ratio of salt (or the amino acid) and respective ligand. The limit of detection (LOD) were calculated from plots A=f (concentration of metal perchlorate) using equation:

$$\mathrm{LD} = \frac{3\sigma}{\mathrm{K}}$$

Where σ is the standard deviation of the blank and K is the slope of the linear calibration range.

2.5. Complexes preparation

Complexes for spectroscopic studies were prepared by dissolving equimolar amounts of reagents: amide **1** or **2** and metal salts (molar ratio 1:1) as well as amide **2** and tyrosine (molar ratio **2**:Tyr is 1:2) in methanol. All components were refluxed until complete dissolution. For spectral analysis samples were used after solvent evaporation (reduced pressure).

2.6. X-ray single crystal structural analysis

Single crystals of **2**·DMSO suitable for X-ray analysis were obtained by very slow dimethylsulfoxide evaporation at room temperature.

X-ray diffraction measurements were carried out with a Diffraction intensity. Data were collected on an IPDS 2T dual-beam diffractometer (STOE&Cie GmbH, Darmstadt, Germany) at 120.0(2) K with Mo-Kα radiation of a microfocus X-ray source (GeniX 3D Mo High Flux, Xenocs, Sassenage, France, 50 kV,1.0 mA, λ = 0.71069 Å). The crystal was thermostated in nitrogen stream at 120K using CryoStream-800 device (Oxford CryoSystem, UK) during the entire experiment. Data collection and data reduction were controlled by X-Area 1.75 program [28]. The structure was solved by direct methods and refined anisotropically using the program packages WinGX 2013.3 [29] and SHELX-2014 [30]. Hydrogen atoms were placed in idealized positions and refined within the riding model, except the N-H type, which were found in the Fourier difference map and refined with N-H bond length restrained to 0.88(2) Å.

3. Results and discussions

3.1. Synthesis

Diamides **1** and **2** were prepared according to the simple synthetic method using the respective acid dichlorides and 2-amino-1,3,4-thiadiazole as substrates in reaction carried out in DMF in the presence of triethylamine as a base (Fig. 1) [24b, 31]. Amide **2,** being derivative of pyridine-2,6-dicarboxylic acid, was obtained with satisfactory yield (70%), however isophthalic acid-derived compound **1** was gained with only 31% of yield. *N*,*N′*-di(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide **2** has been previously synthesized by Hou *et al.* (70% yield, solvent: pyridine) [32]. Amide **1** has not been described so far (according to Chemical Abstracts, Web of Science and Scopus data bases).

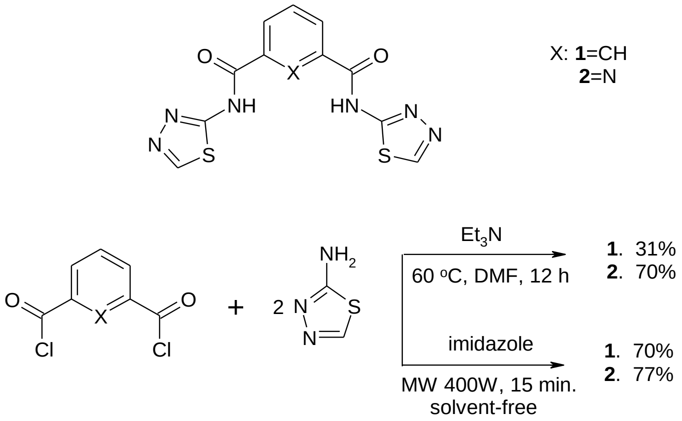


Fig. 1. Classic and microwave assisted (MW) synthesis of 2-amino-1,3,4-thiadiazole diamides from acid dichlorides.

Although the yield of the above reactions can be considered as satisfactory we carried out tests for preparation of the diamides **1** and **2** in well proved in amide synthesis [33] microwave stimulated reactions using both dicarboxylic acids and their chlorides as substrates. It was found that the use of the exactly the same substrates as for classic heated procedure, microwave stimulated process (400 W) gave amides with significantly lower yields. The yield varied from 30-57% depending on reaction time and the applied microwave power. The change of reaction conditions to solvent free and the use of imidazole as a base allowed synthesis of diamides from acid dichlorides with more than 70% within 15 minutes.

Amides **1** and **2** were also synthesized from respective inactivated carboxylic acids. In-reactions carried out with the use of imidazole under solvent-free conditions (90 °C, 600 W) the desired compounds **1** and **2** were gained with low yield 7.3% and 5.5% respectively.

The positive microwave effect in reactions, where acid dichlorides were used as substrates, is particularly evident in the case of compound **1** – the derivative of isophthalic acid. Solvent-free conditions and the use of imidazole allowed for more than 2-fold increase of reaction yield and shortening the reaction time from 12 hours to 15 minutes. The impact of microwaves on the formation of amide **2** is a bit less significant. The microwave-assisted procedure gave the product with comparable yield to the classic synthesis. However, the reaction time was significant shorter what is an advantage of this procedure.

The positive effect of microwave irradiation for reaction involving isophthalic acid chloride may result from a change in polarity of the reactants under synthesis conditions. It can be assumed that the first step of the reaction is protonation of oxygen carbonyl atom, what causes that resulting acyl derivative of imidazole is more active for nucleophilic attack. The created carbocation increases the polarity of the system and thus the absorption of microwave irradiation is more effective. In a consequence, generated heat accelerates the reaction. The presence of a lone electron pair on the nitrogen atom in the pyridine-2,6-dicarboxylic acid dichloride structure, makes the compound more polar than the isophthalic acid chloride. Therefore, the change in polarity due to the formation of carbocation is less significant, and the observed microwave effect is smaller. This hypothesis is supported by the experiment in which under MW conditions amides **1** and **2** were prepared directly from the corresponding carboxylic acids. Despite the very low yields of the products obtained by this method, it can be seen that isophthalic acid more effectively interacts with microwave radiation than pyridine-2,6-dicarboxylic acid.

3.2. X-ray structure of 2·DMSO

Crystal data, data collection and structure refinement details are summarized in Table 1. Compound **2** *N*,*N*'-bis(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide crystallizes from DMSO as dimethylsulfoxide monosolvate, $C_{11}H_7N_7O_2S_2 \cdot C_2H_6SO$ = **2**·DMSO, in the monoclinic system in the space group $P2_1/c$ with four independent complexes **2**·DMSO in the asymmetric unit, so the unit cell contains 16 such residues. Each symmetry independent complex is chemically identical and comprises of the flat diamide **2** molecule with both NH groups directed towards each other and to the oxygen atom, belonging to a solvent dimethylsulfoxide molecule, forming two rather strong intermolecular N-H...O hydrogen bonds. Molecular structure of the solvate is shown in Fig. 2.

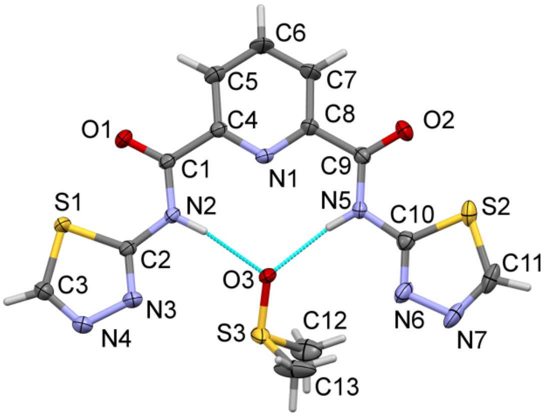


Fig. 2. Molecular structure and hydrogen bonding in complex of *N,N*'-bis(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide and dimethylsulfoxide.

Table 1

Crystal data, data collection and structure refinement details for **2**·DMSO

Chemical formula	$C_{11}H_7N_7O_2S_2{\cdot}C_2H_6OS$
M_r	411.48
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	120
a, b, c (Å)	16.418 (2), 23.413 (4), 18.0874 (19)
β (°)	93.605 (9)
V (Å^3)	6938.9 (17)
Z	16
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.46
Crystal size (mm)	0.21 × 0.09 × 0.03
Data collection	
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	33733, 12599, 8025
R_{int}	0.034
$(\sin \theta/\lambda)_{\text{max}}$ (Å^{-1})	0.606
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.046, 0.134, 1.01
No. of reflections	12599
No. of parameters	984
No. of restraints	8
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e Å^{-3})	1.50, -1.34

X-ray structure of several related coordination compounds, containing the ligand **2** in N-H deprotonated form, have been determined for Zn, Co, Fe and Ni [34], and for Cu [35] and Pb [36]. Metal-free structure has not been reported yet. The most natural difference in the protonated form is increased separation of amide nitrogen atoms (N2...N5 in Fig. 2). Current value is *ca* 4.6 Å (Table SM1, Supplementary Material), and was usually found in the range of 4.4 – 4.1 Å for metal complexes, but also as short as 4.04 Å in the case of Cu complex [35]. Naturally it depends on radius and coordination mode of the metal ion. If we regard C-H donors' participation in hydrogen bonding, we see a large number of such intermolecular interactions. Full list of hydrogen bonds is given in Supplementary Material (Table SM1).

Two DMSO solvent molecules (S3, S9) are fully ordered, but the other two with S6 and S12 atoms have proximate locations in crystal and were found disordered synchronically over two positions with occupation factors of methyl groups C25 and C52 of 0.530 (6)/0.470(6).

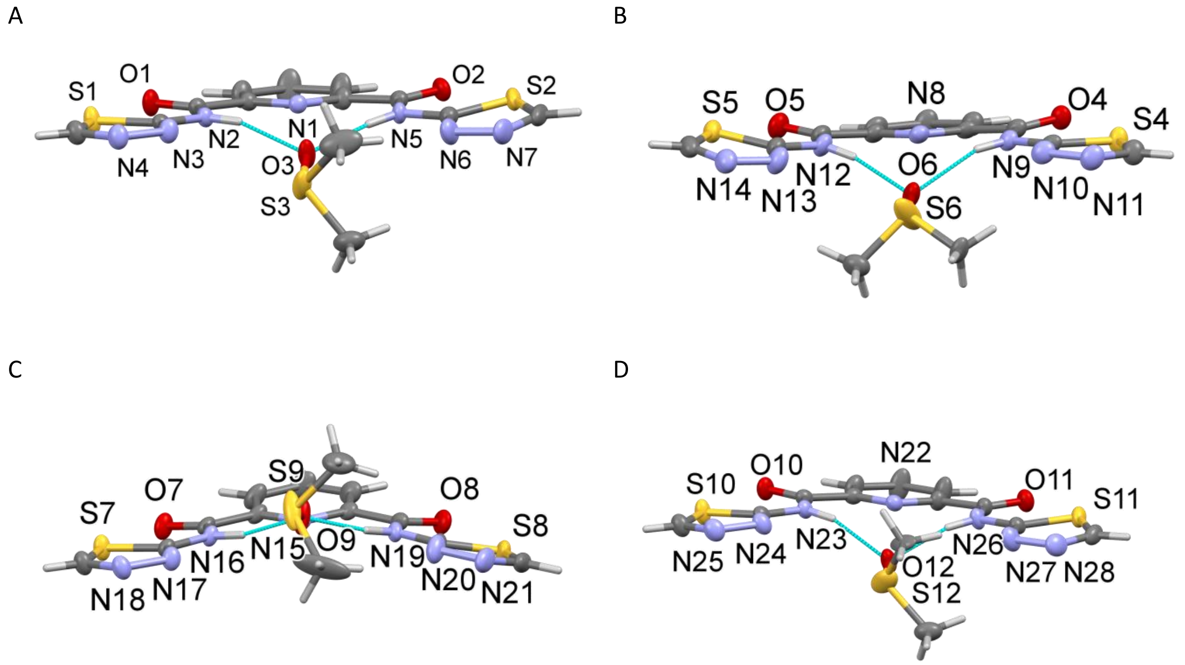


Fig. 3. The four symmetry independent **2**·DMSO complexes (called A, B, C, D respectively) with heteroatom numbering schema. Only the more populated parts of solvent are shown for molecules with S6 and S12 atoms.

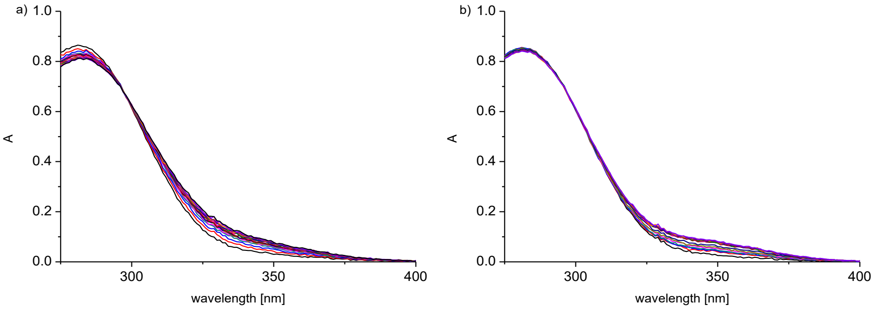
In fact, mutual orientation of a flat diamide molecule **2** and the bound DMSO molecule is the most prominent difference between the four complexes (Fig. 3). In the case of S6-O6 molecule both methyl groups are placed on one side of the flat diamide (notably one of the CH_3 groups belongs to the more populated part), in the case of S12-O12 the less populated methyl group is placed on the same side of L as the second Me group. Two remaining DMSO are in positions with one CH_3 group above and one below the mean plane of the flat part of the complex. Rotational freedom of Me_2SO (about the S–O axis) is probably limited (constrained) giving rise to the increased number of symmetry independent molecules and the disorder observed in the solid state. The molecules of *N*,*N*'-bis(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide differ also in deviations from planarity. As a measure of those deformations we selected improper torsion angles of the O-C...C-S type (like O1-C1...C2-S1 in Figure 3) which should be close to zero in true flat conformation. The angles are gathered in Supplementary Material (Table SM2).

3.3. Complexation studies

Amide **1** derived from isophthalic acid is a new compound and its binding abilities have not been explored yet. The affinity of ligand **2** - the derivative of pyridine-2,6-dicarboxylic acid to transition metal cations is known and its multinuclear complexes with metal cations have been characterized by X-ray crystallography and magnetic measurements [34]. However, interactions of **2** with ions in solution have not been studied so far. Both ligands are very hardly soluble, thus all measurements were carried out in DMSO.

Metal cation complexation

Complexing properties of described here amides **1** and **2** were tested towards metal cations (as alkali, alkaline earth and heavy metal perchlorates) in dipolar, aprotic DMSO. The binding affinity towards lanthanides taking as their representatives lanthanum(III) and terbium(III) chlorides was also studied. For ligand **1** – the derivative of isophthalic acid –changes in absorption spectra were observed only in the presence of a large excess of zinc(II), nickel(II), lanthanum(III), terbium(III) (addition of solid salts) (Fig. SM1, Supplementary Material). Due to insignificant changes upon spectrophotometric titration with metal salts determination of a reliable binding constant values for amide **1** was not possible. In the case of pyridine-2,6-carboxamide (**2**) changes in UV-vis spectra were observed only in the presence of zinc(II) perchlorate, lanthanum(III) and terbium(III) chlorides among all investigated salts, what is shown in Fig. 4a-c. The largest spectral changes can be seen in the presence of terbium salt, what is also accompanied with the largest value of stability constant (logK, Fig. 4d) of the formed 1:1 complex.



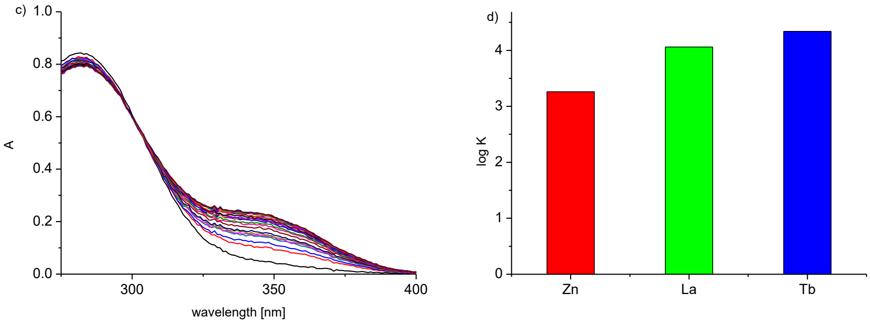


Fig. 4. Changes in UV-vis spectra of ligand **2** solution ($c_L = 5.68\times10^{-5}$ M) upon titration with a) zinc(II) perchlorate ($0\leq R\leq4.38$), b) lanthanum(III) chloride ($0\leq R\leq3.39$), c) terbium(III) chloride ($0\leq R\leq6.63$) in DMSO. d) The comparison of the stability constant values for 1:1 complexes of **2** with zinc(II), lanthanum(III) and terbium(III) salts in DMSO.

Interactions of pyridine-2,6-dicarboxamides with metal cations were studied by us before [24b, 31b]. Investigated previously naphthyl- and anthryl- analogs of studied here *N*,*N′*-bis(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide, showed affinity towards lead(II) and copper(II) in acetonitrile. No spectral response (UV-vis, ^{1}H NMR) towards these metal cations in DMSO was found. The presence of 1,3,4-thiadiazole residue in described here compounds **1** and **2** probably increases ligands affinity to metal cations in competitive solvent – DMSO. To find information about nature of interactions between tested ligands and cations ^{1}H NMR experiments were performed. In Fig. 5 spectra of ligand **1** and **2** solutions in the presence of the strongest bounded terbium(III) cation (according to UV-vis measurements) are shown. In the case of both ligands the presence of terbium(III) cation causes signals extending, as terbium has paramagnetic properties. Even so, shifts of proton signals can be noticed. In the spectrum of ligand **1** solution NH signal is shifted from 13.22 (free ligand) to 13.46 ppm in the presence of terbium(III) cations, what may suggest the creation of stronger hydrogen bonds in the complex. Differences are also observed in the range of aromatic proton signals. In spectrum of ligand **2** registered in the presence of terbium salt, signal of NH proton remains almost unchanged after addition of metal salt. More significant changes are observed for aromatic protons signals, which are shifted to lower value of ppm in the presence of terbium(III).

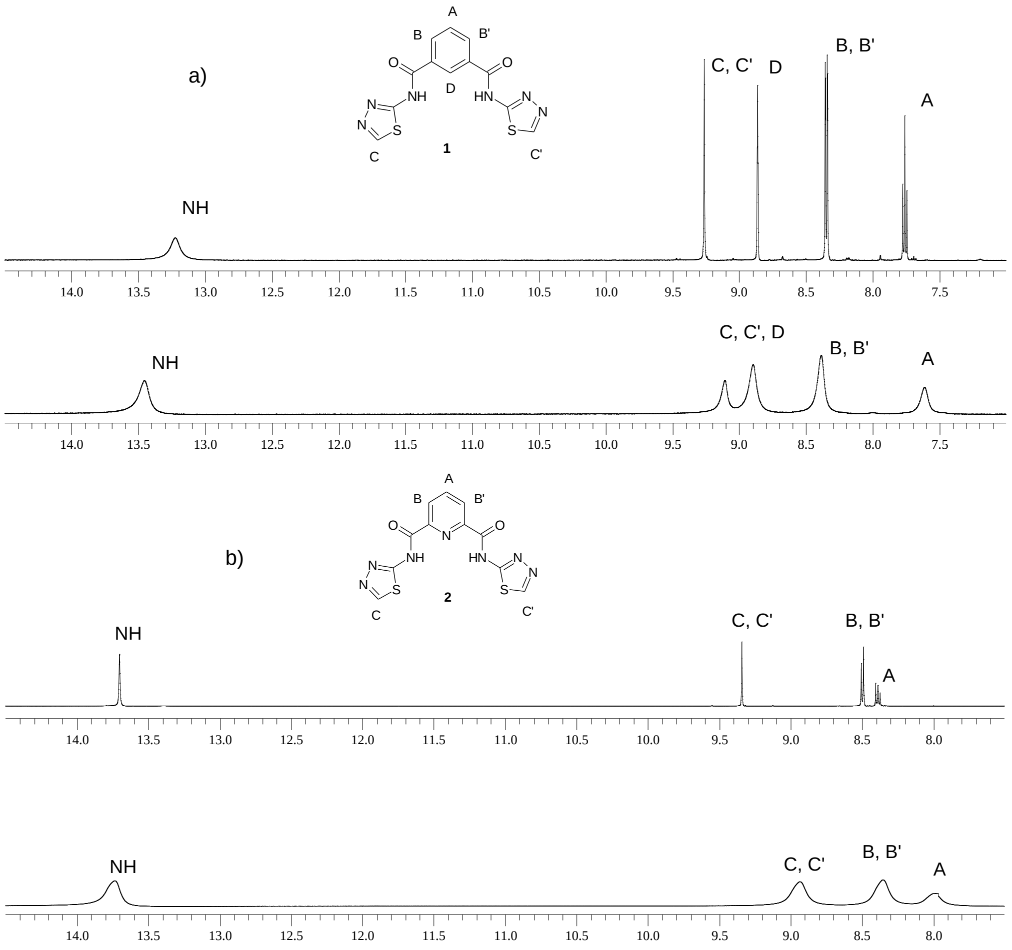


Fig. 5. Comparison of ^{1}H NMR spectra of solution of ligand a) **1** ("free" ligand, $c_1 = 3.98 \times 10^{-2}$ M, upper spectrum) and in the presence of terbium(III) chloride ($c = 7.98 \times 10^{-2}$ M, bottom spectrum), b) **2** ("free" ligand, $c_2 = 3.97 \times 10^{-2}$ M, upper spectrum) and in the presence of terbium(III) chloride ($c = 7.96 \times 10^{-2}$ M, bottom spectrum) registered in DMSO-*d*$_6$.

Additional information may bring analysis of FTIR spectra. In the spectrum of **1**-Tb^{3+} the band of C=O vibration is observed as two spllited signals at 1683 and 1670 cm^{-1} whereas in the spectrum of "free" ligand **1** it is seen as one signal at 1674 cm^{-1} (Fig. SM2). It may indicate that the presence of terbium(III) cation has influence on ligand symmetry. More significant changes are seen in spectra registered for the derivative of pyridine-2,6-dicarboxylic acid **2** (Fig. 6). Due to presence of water in used salt only partial FTIR spectra are shown (range 2000 – 600 cm^{-1}). Complex bands are strongly overlapped by water bands in the region above 3000 cm^{-1} what makes this region less useful for interpretation. Amide I ν(C=O) band in "free" ligand is observed as splitted signals at 1694 and 1680 cm^{-1}, what may suggest different involvement of carbonyl groups in hydrogen bond creation. In the **2**-Tb^{3+} spectrum this band appears as a single, sharp signal at 1684 cm^{-1}, what may point out the change of the molecule symmetry upon terbium(III) complexation. A relatively broad band at 1526 cm^{-1} in the spectrum of "free" ligand which can be assigned to overlapping of δ(N-H) band and vibration of aromatic ring band, in complex is shifted to higher frequency, what can be a result of increasing C-N double bond character or of involvement of aromatic ring in metal cation binding. For the second postulate speaks also analysis of other region of the spectra. Characteristic for pyridine ring bands (C-H bending vibration in plane) at around 1030 cm^{-1} in the presence cationic guest are slightly shifted and their relative intensity comparing spectra of **2** and its complex is changed.

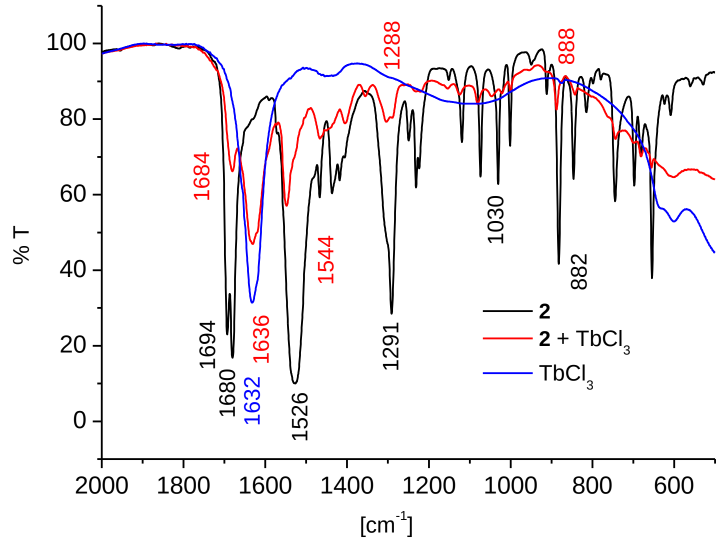


Fig. 6. Comparison of partial (2000-500 cm^{-1}) FTIR spectra (0.5% w/w of substance in KBr pellet) of "free" amide **2**, its complex with terbium(III) chloride (**2**:Tb^{3+} = 1:1), and "free" salt.

However, spectral changes for **2** are well observed upon spectrophotometric titration with some metal salts, this system suffers from the fact, that metal cation complexation is not connected with significant color changes - important from analytical point of view. To overcome this disadvantage the possibilities of formation of Indicator Displacement Assay (IDA) with the involvement of **2** were tested. Alkali Blue 6b (**AB6b**) - commercially available acid base indicator, for this purpose was used. Colourless solution of **2** in DMSO in the presence of equimolar amount of indicator (**AB6b**, purple in pure DMSO) - is observed as grey-bluish. Addition to this solution of zinc(II) perchlorate and lanthanide(III) chlorides results in color change (Fig. 7) to intensively blue, with characteristic cornflower blue for zinc(II) salt.

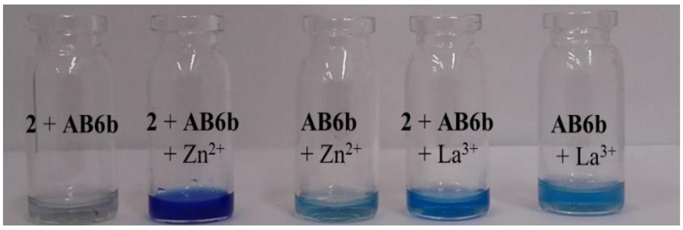


Fig. 7. Color change of the solutions of **2** in the presence of **AB6b** (first from the left) and after addition of metal salts in DMSO.

The color of solutions **2-AB6b**-metal salts is stable for more than 24 hours, whereas solutions where only indicator and metal salts were present (without amide **2**) after that time became colourless. It can point out higher stability of three-component systems. Titration of **2** with solution of **AB6b** shows that system obeys Lambert-Beer's law in a wide range of indicator concentration (Fig. 8a). Upon addition to **2-AB6b** system metal salts new absorption band in visible range of spectrum appears, what is exemplified here with zinc(II) cation (Fig. 8b).

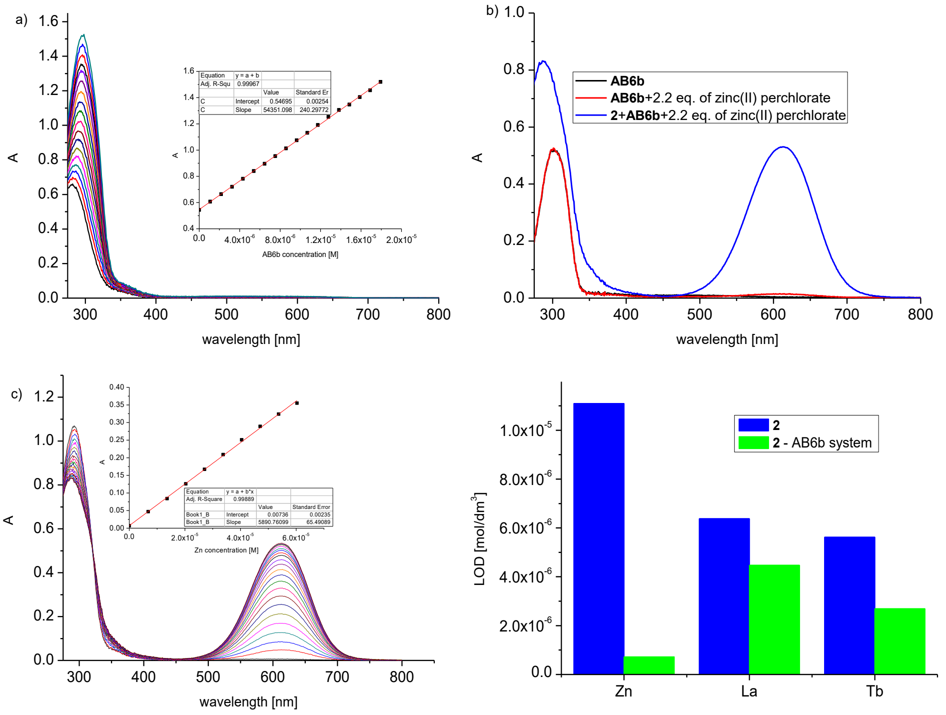


Fig. 8. Changes in UV-vis spectra of: a) **2** (c= 6.24×10^{-5} M) upon titration with **AB6b** solution ($0\leq R\leq 0.30$); (inset A=f(**AB26b**) concentration, at 295 nm), b) comparison of UV-vis spectra registered for: **AB6b** (c=8.58×10^{-6} M) - black line - overlapping with red one; **AB26b** (c=8.58×10^{-6} M) upon addition of 2 eq of zinc(II) perchlorate - red line and **2** (c=6.24×10^{-5} M)-**AB6b** (c=8.58×10^{-6} M) system upon addition of 2.2 eq of zinc(II) salt - blue line in DMSO; c) **2** (c=6.24×10^{-5} M) - **AB6b** (c=8.58×10^{-6} M) upon titration with zinc(II) perchlorate ($0\leq R\leq 2.33$) in DMSO (inset A=f(Zn) concentration, at 603 nm); d) comparison of limits of detection (LOD) for zinc(II), lanthanum(III) and terbium(III) cations.

In Fig. 8c spectrophotometric titration of the system **2-AB6b** with zinc(II) perchlorate is presented with inset showing a linear relationship between absorption and salt concentration. Comparing with spectrophotometric titration of **2** with metal salts a beneficial effect of the use of the additional colored component is shifting of complex absorption band to visible range of spectrum. In Fig. 8d limits of detection (LOD, determined from spectrophotometric measurements) are compared. The most spectacular effect of the presence of **AB6b** is observed for zinc(II) cation with the improvement of LOD from 1.11×10^{-5} to 7.20×10^{-7} mol/dm^3 in the presence of indicator. For lanthanides the LOD values are 6.38 and 5.62×10^{-6} mol/dm^3 for lanthanum and terbium in the absence of indicator and 4.47 and 2.69×10^{-6} mol/dm^3 in a three-component system.

Anion complexation

The presence of NH moieties in ligands' structures makes them potential anion receptors. Among studied anions (as TBA salts) amides **1** and **2** (DMSO) show spectrophotometric response towards fluorides, hydroxides, acetates (AcO^-), benzoates (BzO^-), and dihydrogen phosphates. Taking into account the basic character of anions, especially fluorides in highly dipolar DMSO, observed spectral changes (see Supplementary Material and Fig. SM3) can be considered as a result of ligand deprotonation. Even so, the attempts to evaluate the stability constant values of eventually formed complexes have been taken. Binding constants can be put into order $F^->BzO^->H_2PO_4^->AcO^-$ (Fig. SM3d), which is not in full accordance with basic strength of the anions ($F^->AcO^->H_2PO_4^->BzO^-$). It can suggest that other than just simple deprotonation anion-amide interaction (such as hydrogen bonding) may take place. Although, the anion affinity can be considered, also from observed changes in FTIR spectra (Fig. SM4), for investigated here amides **1** and **2** the nature of spectral changes in DMSO seems not to be clear as it is not strongly supported by ^{1}H NMR spectra where changes suggest rather deprotonation of ligands than hydrogen bond driven interactions.

Amino acids complexation

Due to the fact that 1,3,4-thiadiazole ring as a part of drug acetazolamide is involved in L-tyrosine binding [12] the ability of obtained ligands **1** and **2** to tyrosine and other selected protein amino acids recognition was also tested in DMSO:water solvent system and compared. Among studied L-amino acids (Ala, Phe, Tyr, Lys, Trp, Pro, Cys, Ser) only in the presence of L-tyrosine spectral changes were observed in absorption spectra of **1** and **2** as an appearance of a new band at ~ 350 nm (Fig. 9a,b). In this region both free ligands and L-tyrosine do not absorb what is seen in spectra shown in Fig. 9c, exemplified with amide **2**.

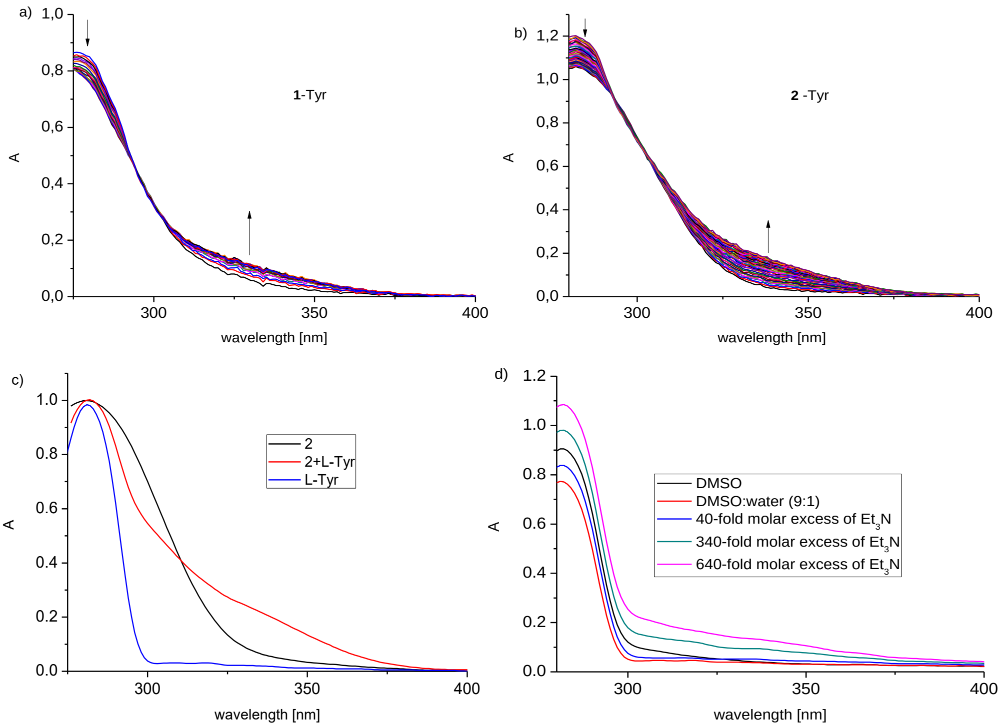


Fig. 9. Changes in the absorption spectra of ligand solution a) **1** (c=5.50×10^{-5} M, 0≤R≤2.23); b) **2** (c=5.68×10^{-5} M, 0≤R≤4.13) in DMSO upon addition aqueous solution of L-tyrosine; c) comparison of normalized spectra of the amide **2**, L-tyrosine and **2** with L-tyrosine in DMSO: H_2O (9:1 v/v); d) absorption spectra of L-tyrosine in pure DMSO, DMSO:H_2O and in the presence of excess of triethylamine.

Tyrosine, one of the most hardly soluble in water amino acid, in most proteins occurs in neutral, phenol form under physiological conditions [37]. Thus spectrophotometric response of amide **1** and **2** towards L-tyrosine was investigated just in solvent mixture (DMSO-water) without any buffers. For pyridine-2,6-carboxamide **2** stability constant for **2**-tyrosine was calculated from titration experiments. For system 2:1 (L-tyrosine:**2**) stability constant value logK was found as 7.08±0.04. Due to relatively small spectral changes observed for amide **1** upon titration with tyrosine solution the determination of reliable value of binding constant was not possible under titration measurements.

Tyrosine is known to interact with different ligands *via* side amino acid residue, namely OH phenolic group acting as either proton donor or acceptor or both simultaneously [38]. To test the possible binding of tyrosine *via* phenolic group the spectrophotometric response towards some phenols (phenol, 2,4-dinitrophenol, resorcinol and pyrocatechol) was checked. In all cases spectra of **2** were not changed upon addition of phenols. However, this fact does not exclude participation of phenolic OH group of tyrosine in complex formation with **2**. Phenols, opposite to amino acids are uncharged. DMSO is known to affect proteins by preferentially solvatation of positive ions what influences on ionization of tyrosine by formation of hydrogen bond between phenolic residue and the solvent [39]. The effect of highly dipolar DMSO is stronger than water [40] what is well seen in Fig. 9d. In pure DMSO sharp absorption maximum is observed at 280 nm and additionally at region of 300 nm broad band of low intensity is also present. This broad signal disappears upon addition of water (red line) and is observed again upon addition of excess of triethylamine. These changes can be connected with partial ionization of tyrosine or formation of stronger hydrogen bond with organic base.

Infrared spectra of **2**, its complex with L-tyrosine and L-tyrosine (KBr pellet) were registered (Fig. 10) and compared. Selected signals with proposed assignment are collected in Table 2.

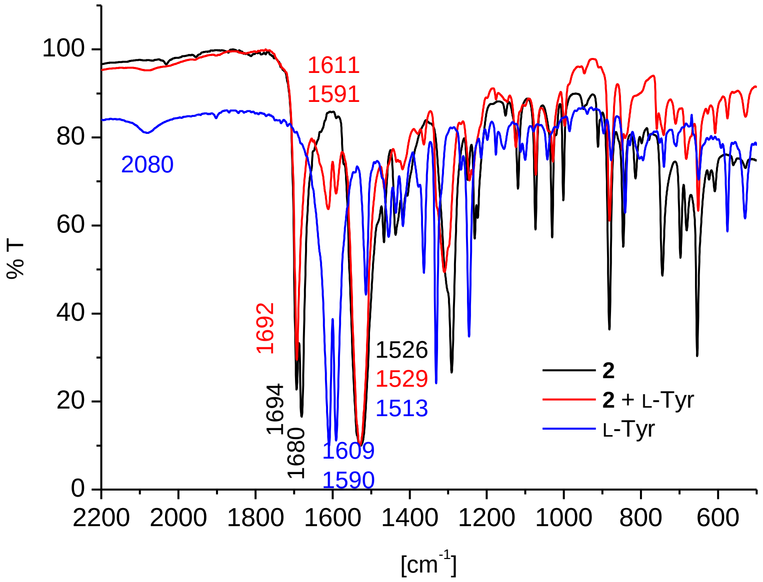


Fig. 10. Comparison of partial FTIR normalized spectra (KBr pellets) of **2** and **2**-L-Tyr complex (molar ratio **2**:L-tyrosine 1:2) and L-Tyr.

Table 2

Selected signals [cm^{-1}] and their proposed assignment for **2**, **2**-L-Tyr and L-Tyr (KBr pellet)

	I amide band (νC=O)	**δNH$_3^+$**	**νCOO$^-$**	**II amide band (δN-H) and νC=C of aromatic rings**	**νC-O**
2	1694 1680	-	-	1526	-
2-L-Tyr	1692	1611	1591;1418	1529	1244;1235 doublet
L-Tyr	-	1609	1590;1416	1513	1246 singlet

In a spectrum of **2** I amide band is observed as two signals at 1694 and 1680 cm^{-1} and II amide band as a broad signal (overlapping of bands) at 1526 cm^{-1}. In a complex of **2** with L-tyrosine C=O band is seen as a sharp signal at 1692 cm^{-1}. δNH$_3^+$ (1611 cm^{-1}) and νCOO$^-$ (1590;1416 cm^{-1}) bands are observed as signals of comparable intensities in L-tyrosine. In complex these bands appear at almost the same wavenumber, but are alerted with a change of relative intensity. Strong signal - singlet - at 1246 cm^{-1} in L-tyrosine spectrum which can be assigned to bending mode of tyrosine hydroxyl group [39] in complex is observed as a doublet (1244, 1235 cm^{-1}) of medium relative intensity.

Taking all together it seems probable that amide **2** interacts with L-tyrosine *via* one of nitrogen atom of thiadiazole moiety by formation of hydrogen bond with OH residue of tyrosine.

4. Conclusions

To sum up, we have shown that the new amide **1** and previously reported in literature amide **2** bearing 1,3,4-thiadiazole residue can be obtained with satisfactory yields. Yield is significantly improved by using more convenient and faster microwave stimulated reactions. In solid state **2** forms four solvates of different geometry with DMSO. Pyridine-2,6-carboxamide **2** seems to be much more effective molecular receptor than isophthalic derived diamide **1** providing the importance of pyridine nitrogen atom in binding processes. A benefit of the introduction of 1,3,4-thiadiazole moiety into the structure of pyridine-2,6-carboxamide **2** comparing its anthracene or naphthalene analogs, is higher affinity towards zinc(II). Moreover, the detection limit for zinc(II) can be improved by formation of IDA system with Alkali Blue 6b. The next interesting advantage is selective, among investigated amino acids, tyrosine binding by *N*,*N'*-bis(1,3,4-thiadiazol-2-yl)-2,6-pyridinedicarboxamide, what has not been described in literature so far.

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Conflict of interest

The authors declare that they have no conflict of interest.

Supplementary Data

CCDC 1531056 contains the supplementary crystallographic data for **2**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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