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The impact of structural modification of 1,2,4-thiadiazole derivatives on thermodynamics of solubility and hydration processes†

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The influence of a structural modification on thermodynamic aspects of solubility and hydration processes of 1,2,4-thiadiazole drug-like compounds was investigated. A substitution in the phenyl ring of the 1,2,4-thiadiazole molecule leads to a significant decrease of the solubility of these compounds. In order to rationalize the relationship between the structures of 1,2,4-thiadiazoles and their solubility, the latter was considered in terms of two fundamental processes: sublimation and hydration. It was found that for most of the compounds solubility decline is a result of a differently directed action of the sublimation and hydration contributions, *i.e.*, the introduction of substituents leads to the simultaneous growth of the sublimation Gibbs energy and decrease in the hydration Gibbs energy.

Introduction

Alzheimer's disease is the most common form of dementia in the elderly and is, along with cardiovascular diseases and cancer, one of the most serious health problems in the developed countries. A large amount of information about the possible mechanisms of pathologies such as Alzheimer's creates a wide range of approaches to its pharmacological correction, which is explained by the complex nature of the disease. Indeed, these diseases are developed with the participation of a wide range of different intra- and extra-cellular biological systems that can be the subject to the pharmacological effects of potential drugs. In addition to this "direct" intervention in the pathogenesis of neurodegenerative diseases, there is a possibility of correcting the developed pathology due to the activation of compensatory mechanisms of the central nervous system, which significantly increases the total set of potential ways in their therapy. Heterocyclic compounds having a 1,2,4-thiadiazole moiety in the structure are of great interest to the pharmaceutical and medicinal chemistry because of their high specific activity within a wide concentration range. Synthesis of new heterocyclic derivatives of 1,2,4-thiadiazole continues to be the most important area in the field of highly effective neuroprotective drugs for medicine. The high therapeutic potential of the 1,2,4-thiadiazole system has been reported since the end of the last century for the receptors of cardiovascular[1] and central nervous systems,[2] as well as G-protein coupled receptors.[3] And the effect of drugs on the basis of 1,2,4-thiadiazole on the cardiovascular system has been revealed at the structural, metabolic and functional levels and consists in affecting both the blood vessels and the heart itself. It is interesting to note that the application of a series of thiadiazole compounds as antiinflammatory agents helps to avoid gastrointestinal side effects, typical of many antiinflammatory drugs.[4] Besides, the authors who created more effective antibiotics[5,6] noted the advantages of incorporating a 5-amino-1,2,4-thiadiazol-3-yl moiety as a substituent to improve the antipseudomonal and methicillin-resistant Staphylococcus aureus activities. Thiadiazole fragments are the basis of a whole series of synthetic agents having biological activity towards receptors determining neurodegenerative diseases and disorders of the central nervous system, which allows their use in developing new drug compounds for treatment and prevention of Alzheimer's disease.[7–9]

One of the key problems of creating effective drugs is poor solubility, so the physicochemical study of newly synthesized drug-like compound includes, first and foremost, the elucidation of solubility behavior. Poor solubility of a potential drug compound significantly reduces the bioavailability, leads to the growth of therapeutic doses and, as a consequence, to the appearance of side effects.

From a thermodynamic point of view, solubility of the compounds is determined by the difference between the energy

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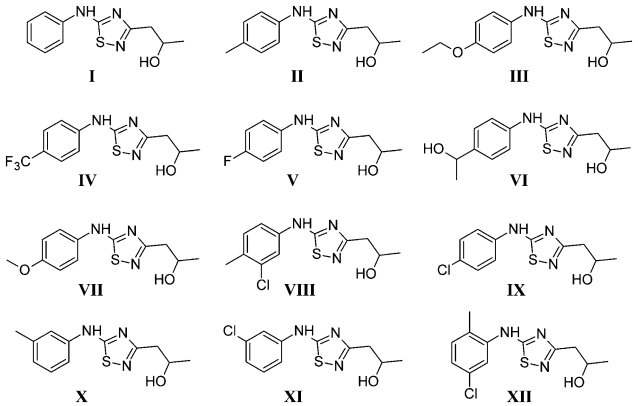

Fig. 1 Molecular structure of the studied compounds.

necessary to disrupt the crystal lattice to bring it into solution (sublimation process) and that of solvation/hydration. Small changes to the substituents on the drug molecule can yield significant changes in its crystal structure and lattice energy. Therefore, it is important to consider the sublimation part of the thermodynamic cycle in order to identify compounds with the desired physicochemical properties, as well as biological activity. Unfortunately, the latter issue is routinely ignored by *in silico* studies, guided only by structure–activity relationships to find the best compound for a particular target, *e.g.* see ref. 10 There are computational approaches for the solubility prediction, however, that consider both sublimation and solvation aspects of the process.[11]

The present study is a continuation of our investigations into the solubility,[12,13] crystal structures[14] and biological activity[15] of 1,2,4-thiadiazole derivatives (Fig. 1). The aim of the present investigation is to measure the solubility of novel 1,2,4-thiadiazole drug-like compounds (**VII–XII**) and elucidate the influence of the molecular structure features on the solubility behavior in the phosphate buffer solution pH 7.4 modeling the blood plasma medium.

Experimental

Compounds and solvents

The buffer solutions pH 7.4 were prepared by mixing solutions of appropriate sodium and potassium salts of phosphoric acid, manufactured in Kchimmed (Moscow, Russia), as described elsewhere.[13] Ionic strength was adjusted by adding potassium chloride. All the chemicals were of AR grade. The pH values were measured by using an Electroanalytical Analyser, Type OP-300, Radelkis, Budapest, standardized with pH 1.68, 6.86 and 9.22 solutions.

Solubility determination

All the experiments were carried out by the isothermal saturation method at several temperature points: 293.2, 298.2, 303.2, 310.2, 315.2 ± 0.1 K. The solid phase was removed by isothermal filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size, Carrigiwohill Co., Cork, Ireland) or centrifugation (Biofuge pico, Thermo Electron LED GmbH, Germany) at 2000 rpm for 5 min. The experimental results are reported as an average value of at least three replicated experiments. The solubility of drugs were measured spectrophotometrically with an accuracy of 2–2.5% and expressed as mole fractions using a protocol described previously.[16]

The standard Gibbs energies of dissolution processes $\Delta_{sln}G^{\circ}$ (in kJ mol^{-1}) were calculated using the following equation:

$$\Delta_{sln}G^{\circ} = -RT\ln a_2 \quad (1)$$

where $a_2 = \gamma_2 \cdot x_2$ is the activity of the solute molecule; x_2 is the drug mole fraction in the saturated solution; and γ_2 is the activity coefficient of the solute molecule. The standard solution enthalpies $\Delta_{sln}H^{\circ}$ (in kJ mol^{-1}) and solution entropies $\Delta_{sln}S^{\circ}$ (in J mol^{-1} K^{-1}) were calculated from the temperature dependencies of drug solubility within the chosen temperature interval, which can be described by the linear function:

$$\ln x_2 = -\Delta_{sln}S^{\circ}/R + (\Delta_{sln}H^{\circ}/RT_{ref})\cdot(T_{ref}/T) \quad (2)$$

where T_{ref} is the reference temperature equal to 298.2 K. Due to the poor solubility of the studied drugs, the activities of the compounds were approximated by mole fractions. It was assumed that the solution enthalpies were independent of the concentration.

Synthesis of compounds

The synthesis of 1-[5-phenylamino-1,2,4-thiadiazol-3-yl]propan-2-ols was based on the method of Vivona *et al.*[17] and described by us earlier.[15]

1-[5-(4-Methoxy-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol (VII). 1-[(5-Methoxy-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-one (10 mmol) was dissolved in 20 mL of methanol. $NaBH_4$ (15 mmol) was added portion wise to the mixture that was stirred for 30 min at the same time the hydrogen gassing was stopped. The solvent was removed until the resulted residue was dry and then taken up in dichloromethane/water. The organic layer was separated, dried (over Na_2SO_4) and filtered. The solvent was evaporated resulting in the product (2.1 g, 79.2%) with Mp 363 K.[14] Anal.: found, %: C 54.32; H 5.70; N 15.84. $C_{12}H_{15}N_3O_2S$ (C, H, N); calcd, %: C 54.15; H 5.67; N 15.86.

^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.27 (d, J = 6.51 Hz, 3H, CH_3), 2.65–3.04 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 4.26 (t, J = 5.58 Hz, 1H, CH), 4.62 (br. s, 1H, OH), 6.96 (d, J = 8.38 Hz, 2, HCH_2, HAr), 7.24 (d, J = 8.38 Hz, 2H, HAr), 8.62 (br. s, 1H, NH).

1-[5-(3-Chloro-4-methyl-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol (**VIII**) was obtained from 1-[5-(3-chloro-4-methyl-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-one (2.3 g, 81.0%). Mp 402 K.[14] Anal.: found, %: C 50.79; H 4.97; N 14.81. $C_{12}H_{14}ClN_3OS$ (C, H, N); calcd, %: C 50.88; H 5.08; N 14.96.

^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.29 (d, J = 6.17 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.69–3.09 (m, 2H, CH_2), 4.36 (br. s, 1H, OH), 6.98–7.14 (m, 1H, HAr), 7.18–7.34 (m, 3H, HAr), 8.82 (br. s, 1 NH).

1-[5-(4-Chloro-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol (**IX**) was obtained from 1-[5-(4-chloro-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-one (2.1 g, 77.8%). Mp 408 K.[14]

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Anal.: found, %: C 48.98; H 4.48; N 15.58. $C_{11}H_{12}ClN_3OS$ (C, H, N); calcd, %: C 49.15; H 4.60; N 15.66.

^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.33 (d, J = 6.51 Hz, 3H, CH_3), 2.76–3.12 (m, 2H, CH_2), 4.17–4.44 (m, 1H, CH), 4.62 (br. s, 1H, OH), 7.24 (m, J = 8.38 Hz, 2H, CH_2, HAr), 7.42 (m, J = 8.38 Hz, 2H, CH_2, HAr), 8.62 (br. s, 1H, NH).

1-[5-(3-Methyl-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol (**X**) was obtained from 1-[5-(3-methyl-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-one (1.9 g, 74.1%). Mp 361 K.[14] Anal.: found, %: C 57.81; H 6.06; N 16.85. $C_{12}H_{15}N_3OS$ (C, H, N); calcd, %: C 57.49; H 6.16; N 16.88.

^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: (d, J = 6.17 Hz, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.70–3.07 (m, 2H, CH_2), 4.27 (br. s, 1H, OH), 4.42 (br. s, 1H, CH), 6.92–7.15 (m, 3H, HAr), 7.27–7.41 (m, 1H, HAr), 8.98 (br. s, 1 NH).

1-[5-(3-Chloro-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol (**XI**) was obtained from 1-[5-(3-chloro-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-one (2.0 g, 74.1%). Mp 390 K.[14] Anal.: found, %: C 48.98; H 4.48; N 15.58. $C_{11}H_{12}ClN_3OS$ (C, H, N); calcd, %: C 48.88; H 4.62; N 15.46.

^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.30 (d, J = 6.17 Hz, 3H, CH_3), 2.68–3.11 (m, 2H, CH_2), 4.30 (m, 1H, CH), 4.37 (br. s, 1H, OH), 7.14 (d, J = 7.50 Hz, 2H, CH_2, HAr), 7.27 (s, 1H, CH, HAr), 7.30–7.46 (m, 1H, CH, HAr), 9.02 (br. s, 1 NH).

1-[5-(5-Chloro-2-methyl-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol (**XII**) was obtained from 1-[5-(5-chloro-2-methyl-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-one (2.1 g, 73.9%). Mp 374 K.[14] Anal.: found, %: C 50.79; H 4.97; N 14.81. $C_{12}H_{14}ClN_3OS$ (C, H, N); calcd, %: C 50.78; H 5.02; N 14.76.

^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.24 (d, J = 6.17 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.63–3.07 (m, 2H, CH_2), 4.17 (d, J = 13.67 Hz, 1H, CH), 4.25 (d, J = 5.73 Hz, 1H, CH), 7.04–7.16 (m, 1H, CH, HAr), 7.16–7.24 (m, 1H, CH, HAr), 7.42 (d, J = 1.76 Hz, 1H, CH, HAr), 8.26 (br. s, 1 NH).

Calculation procedure

All physicochemical descriptors for the compounds studied were calculated by the program package HYBOT-PLUS (version of year 2003) in Windows.[18]

Results and discussion

The thermodynamic parameters of the solubility and hydration processes of compounds **I–VI** are described in our previous papers[12,13] (Tables S1 and S2 of the ESI†). The temperature dependences of the solubility of thiadiazoles **VII–XII** in a buffer solution pH 7.4 are presented in Table 1. The dissolution and hydration thermodynamic functions at 298 K are shown in Table 2.

Dissolution and hydration processes in buffer solution

In order to reveal the effect of the substituents inserted in the phenyl fragment of the tested compounds on the Gibbs free energy of hydration and dissolution, we analyzed the difference between the mentioned thermodynamic functions of the substituted and unsubstituted 1,2,4-thiadiazole. For this purpose, we used the diagram approach which allows revealing the change in the thermodynamic functions upon molecule structure modification.

The differences between the thermodynamic functions of the substituted and unsubstituted compounds were utilized as the characteristics to be analyzed. Fig. 2a shows a diagram of the dissolution process, while Fig. 2b presents a diagram of the hydration process in a buffer solution pH 7.4.

The diagram is divided into eight sectors, each corresponding to a different ratio of the enthalpy and entropy contributions to the Gibbs energy. The sector is formed by two lines: on the one side – the line corresponding to the zero ΔH° or $T\Delta S^\circ$-value; on the other side – the bisector of the angles formed at the intersection of the coordinates (ΔH°; $T\Delta S^\circ$). Isoenergetic curves of Gibbs energy are marked by the dotted lines.

Thus, the diagram can be divided into the following areas: ($T\Delta S^\circ > \Delta H^\circ > 0$) ≡ sector **A**, ($\Delta H^\circ < 0$; $T\Delta S^\circ > 0$; $|T\Delta S^\circ| > |\Delta H^\circ|$) ≡ sector **B**, ($T\Delta S^\circ < \Delta H^\circ < 0$) ≡ sector **E**, and ($\Delta H^\circ > 0$; $T\Delta S^\circ < 0$; $|T\Delta S^\circ| > |\Delta H^\circ|$) ≡ sector **F** belonging to the entropy determined processes. The segments of the diagram where ($\Delta H^\circ < 0$; $T\Delta S^\circ > 0$; $|\Delta H^\circ| > |T\Delta S^\circ|$) ≡ sector **C**, ($\Delta H^\circ < 0$; $T\Delta S^\circ < 0$; $|\Delta H^\circ| > |T\Delta S^\circ|$) ≡ sector **D**, ($\Delta H^\circ > T\Delta S^\circ > 0$) ≡ sector **H** и ($\Delta H^\circ > 0$; $T\Delta S^\circ < 0$; $|\Delta H^\circ| > |T\Delta S^\circ|$) ≡ sector **G** correspond to the enthalpy determined processes.

Table 1 Temperature dependencies of solubility, x_2 (mol. fraction), of the compounds **VII–XII** in buffer pH 7.4

	VII	**VIII**	**IX**	**X**	**XI**	**XII**
T, K	$x_2 \times 10^5$	$x_2 \times 10^6$	$x_2 \times 10^5$	$x_2 \times 10^5$	$x_2 \times 10^5$	$x_2 \times 10^5$
293.2	4.11	0.74	0.77	1.75	0.97	0.70
298.2	5.48	0.87	0.83	2.04	1.02	0.80
303.2	6.73	1.08	0.93	2.35	1.08	0.88
310.2	9.02	1.39	1.07	2.93	1.22	1.07
315.2	10.95	1.57	1.16	3.33	1.29	1.19
A^a	3.7 ± 0.4	3.0 ± 0.4	−5.6 ± 0.2	−1.7 ± 0.2	−7.2 ± 0.3	−4.2 ± 0.2
B^a	4049 ± 130	3260 ± 119	1806 ± 63	2721 ± 44	1272 ± 81	2239 ± 61
R^b	0.999	0.998	0.998	0.999	0.994	0.999
$\sigma \times 10^{2\,c}$	2.49	2.27	1.20	0.84	1.56	1.18

[a] Parameters of the correlation equation: $\ln x_2 = A - B/T$. [b] R: pair correlation coefficient. [c] σ: standard deviation.

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Table 2 Thermodynamic solubility and hydration functions of compounds **VII–XII** in buffer 7.4 at 298 K

	x_2^{298}	$\Delta_{sln}G^\circ$ [kJ mol^{-1}]	$\Delta_{sln}H^\circ$ [kJ mol^{-1}]	$T_{ref}\Delta_{sln}S^\circ$ [kJ mol^{-1}]	$\Delta_{sln}S^\circ$ [J mol^{-1} K^{-1}]	ΔH_{sln}[a] [%]	ΔTS_{sln}[b] [%]	$\Delta_{hyd}G^\circ$ [kJ mol^{-1}]	$\Delta_{hyd}H^\circ$ [kJ mol^{-1}]	$T_{ref}\Delta_{hyd}S^\circ$ [kJ mol^{-1}]	$\Delta_{hyd}S^\circ$ [J mol^{-1} K^{-1}]	ΔH_{hyd}[c] [%]	ΔTS_{hyd}[d] [%]
VII	5.48×10^{-5}	24.3	33.7 ± 1.1	9.3	31 ± 4	78.2	21.8	−36.5	−95.3	−59.0	−198	61.8	38.2
VIII	0.87×10^{-6}	34.6	27.1 ± 1.0	−7.4	−25 ± 3	78.3	21.7	−28.0	−93.6	−65.6	−220	58.8	41.2
IX	0.83×10^{-5}	29.0	14.8 ± 0.5	−14.2	−48 ± 2	51.7	48.3	−35.5	−117.6	−82.2	−276	59.2	40.8
X	2.04×10^{-5}	26.8	22.7 ± 0.4	−4.1	−14 ± 1	84.3	15.7	−33.4	−114.7	−81.3	−273	58.5	41.5
XI	1.02×10^{-5}	28.5	10.3 ± 0.7	−18.1	−61 ± 2	37.2	62.8	−31.9	−105.0	−73.3	−246	59.0	41.0
XII	0.80×10^{-5}	29.1	18.6 ± 0.5	−10.5	−35 ± 2	63.9	36.1	−28.5	−83.3	−54.9	−184	60.3	39.7

[a] $\Delta H_{sln} = (|\Delta_{sln}H^\circ|/(|\Delta_{sln}H^\circ| + |T_{ref}\Delta_{sln}S^\circ|)) \times 100\%$. [b] $\Delta TS_{sln} = (|T_{ref}\Delta_{sln}S^\circ|/(|\Delta_{sln}H^\circ| + |T_{ref}\Delta_{sln}S^\circ|)) \times 100\%$. [c] $\Delta H_{hyd} = (|\Delta_{hyd}H^\circ|/(|\Delta_{hyd}H^\circ| + |T_{ref}\Delta_{hyd}S^\circ|)) \times 100\%$. [d] $\Delta TS_{hyd} = (|T_{ref}\Delta_{hyd}S^\circ|/(|\Delta_{hyd}H^\circ| + |T_{ref}\Delta_{hyd}S^\circ|)) \times 100\%$.

Dissolution processes

Fig. 3 contains a diagram in which the solubility values in a buffer pH 7.4 at 298.2 K are illustrated in decreasing order.

It is clear that the introduction of any substituent in the phenyl ring of the 1,2,4-thiadiazole molecule reduces the solubility of the substance. It should be noted that even within a small sampling of structurally similar compounds, the solubility depends considerably on the nature and position of the substituent in the phenyl fragment. The maximum solubility decrease in the series of the investigated compounds is $x_{2,max}$(**I**)/$x_{2,min}$(**VIII**) = 104 times. At the same time, the most significant solubility reduction is observed in the group of halogen-substituted 1,2,4-thiadiazoles (**XI**, **XII**, **IX**, **IV**, and **VIII**).

As shown in Table 2, the process of dissolving the compounds in a buffer solution is endothermic. This suggests that the hydration enthalpy does not compensate for the crystal lattice energy. The dissolution enthalpies of 1,2,4-thiadiazoles vary over a wide range. The solubility of compound **V** is essentially independent of the temperature, whereas the presence of a complex hydroxyl group in the phenyl ring of molecule **VI** increases $\Delta_{sln}H^\circ$ up to 50 kJ mol^{-1}. Obviously, this could be due to the presence of an additional hydrogen bonding center in molecule **VI** involved in the intermolecular interactions both in the crystal and in the solution. The entropic characteristics of the dissolution of the investigated compounds should be given particular attention. Negative entropy values of the majority of compounds indicate a manifestation of the so-called ''hydrophobic effects'', *i.e.* increasing the ordering of hydration shells and neighboring water molecules.

Analysis of the thermodynamic characteristics of dissolution by the diagram approach (Fig. 2a) shows that all the compounds are unevenly distributed over the three diagram sectors with different ratios of Gibbs energy enthalpy and entropy terms: there are two compounds in sector **H** (representing 18.2% of the studied compounds), three compounds in sector **F** (27.3%) and, finally, six substances in sector **E** (54.6%). The dissolution processes are mainly determined by the entropy (9 compounds), but the enthalpy terms of the compounds lying in sectors **E** and **F** have different signs. Thus, the introduction of peripheral substituents in the phenyl ring of the molecule more significantly affects the entropic factor of the dissolution process. It is evident that for compounds in sectors **F** and **E** a dramatic solubility decrease (growth of $\Delta_{sln}G^\circ$) is determined by the significant decrease in the $\Delta_{sln}S^\circ$ value, whereas the change in $\Delta_{sln}H^\circ$ is not considerable or not enough to balance the entropy contribution. And the maximal solubility decline was observed for compounds **VIII** and **IV** due to a ''differently directed'' action of the enthalpy and entropy terms: the introduction of these substituents leads to the simultaneous growth of $\Delta_{sln}H^\circ$ and decrease in $\Delta_{sln}S^\circ$.

Such behavior of the thiadiazole derivatives is probably caused by the following factors: (a) there are no structural changes (the introduction of substituents) in the thiadiazole fragment, where the centers of hydrogen bonding, *i.e.* the potential sources of enthalpy change are situated, but such changes are observed at the periphery of the molecule (the phenyl moiety) which is hydrophobic and does not have such centers; (b) the substituents used do not contain hydrogen bonding centers either, which ''enhances'' the hydrophobicity of the molecules and affects the value of the entropy contribution. The exceptions are compounds in sector **H** containing the substituents (4-iso-EtOH and 4-OMe) capable of participating in the intermolecular interactions with water molecules. The diagram (Fig. 2a) shows that the insertion of these groups has a positive effect on the change in the entropy term, however, it is accompanied by a substantial increase in the dissolution enthalpy. Di-substituted isomers according to their solubility are ranged in the following order: 2-Me-5-Cl-(**XII**) ($x_2 = 0.8 \times 10^{-5}$) > 3-Cl-4-Me-(**VIII**) ($x_2 = 0.87 \times 10^{-6}$). In 2-Me-5-Cl-(**XII**) both the entropy and the enthalpy of dissolution decrease as compared to the unsubstituted compound (**I**). In turn, the enthalpy of 3-Cl-4-Me-(**VIII**) increases but its entropy diminishes, just as those of 2-Me-5-Cl-(**XII**).

For methyl-phenyl-isomers of compounds (4-Me (**II**) and 3-Me (**X**)), the solubility of the *para*-isomer is 2-fold greater than the solubility of the *meta* isomer. For the pair of Cl-isomers (4-Cl (**IX**) and 3-Cl-(**XI**)), the opposite pattern is observed: the solubility of the *meta*-isomer is approximately 1.3 times higher than the same value of the *para*-isomer. It should be noted that a common regularity is observed in the considered methyl- and Cl-isomers: the entropy and enthalpy of dissolution decrease compared to those of the unsubstituted compound. An exception is the 3-Me-derivative whose dissolution enthalpy practically coincides with the corresponding value of compound **I**.

The substitution of the Cl-atom by a methyl-group in the *meta*-position of the phenyl ring increases the solubility by two times, whereas a similar replacement in the *para*-position leads to a 5-fold solubility enhancement. Introducing a methyl-fragment in

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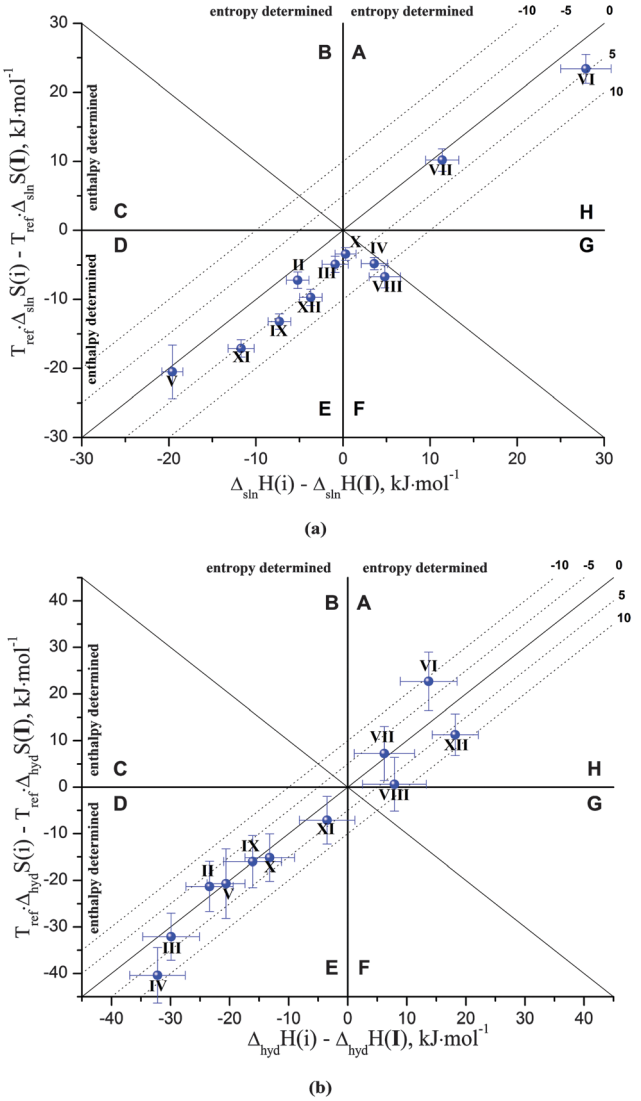

Fig. 2 Relationship between the thermodynamic functions of (a) the dissolution and (b) hydration processes for the substituted 1,2,4-thiadiazole (i) relative to the unsubstituted compound **I**. The isoenergetic curves of the Gibbs energy are marked by dotted lines. See Fig. 1 for numbering of the compounds.

the *para*-position of compound (**II**) instead of the CF_3-group (compound **IV**) decreases the solubility by 13 times, with the substances located in different sectors of the diagram (**II** – in **E**, and **IV** – in **F**). In sector **E** the dissolution enthalpy declines in comparison with that of the unsubstituted compound and in sector **F**, the enthalpy grows.

The comparison of 4-Cl-(**IX**) and 4-F-(**V**) phenyl-derivatives has shown that compound **V** is 7-time more soluble ($x_2 = 6.13 \times 10^{-5}$) than **IX**. Fig. 2a demonstrates a decrease in both the dissolution entropy and enthalpy in comparison with the unsubstituted compound when Cl- or F-atoms are introduced in the *para*-position of the phenyl ring.

Inserting a methoxy-fragment in the *para*-position (compound **VII**) instead of the methyl-group (compound **II**) (*i.e.* an additional oxygen atom) leads to 1.4 time solubility growth.

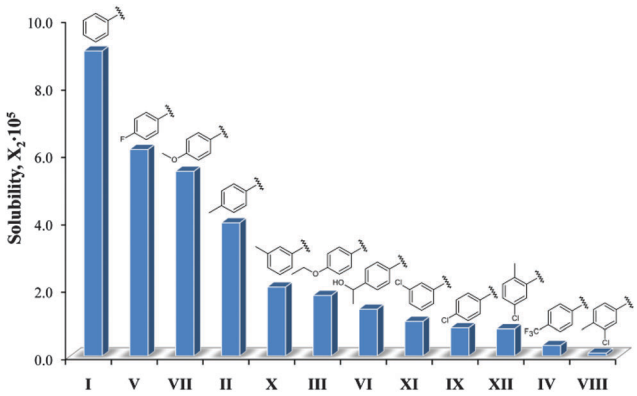

Fig. 3 Solubility of 1,2,4-thiadiazoles at 298.2 K in decreasing order.

As it follows from Fig. 2a, the dissolution entropy and enthalpy of 4-Me-(**II**) decrease, whereas those of 4-OMe-(**VII**) increase as compared to the unsubstituted compound.

For the substances with *para*-substituents tending to form hydrogen bonds, the solubility values can be ranged in the following order: x_2(4-OMe-(**VII**)) = 5.48×10^{-5} > x_2(4-OEt-(**III**)) = 1.79×10^{-5} > x_2(4-iso-EtOH-(**VI**)) = 1.45×10^{-5}. It should be noted that the chain length of the substituent in the phenyl ring was found to essentially affect the dissolution thermodynamic functions. The addition of the methyl-fragment $-CH_2-CH_2$ to the substituent 4-OMe-(**VII**) (the result is 4-OEt-(**III**)) does not only lead to increasing the dissolution Gibbs energy, but also results in a considerable change in the ratio of the entropy and enthalpy terms of the process. As a result, for 4-Me-(**VII**) the entropic and enthalpic terms increase in comparison with those of compound (**I**), whereas for 4-OEt-(**III**), they decrease.

Hydration processes

In order to estimate the interaction of compounds with solvents/water on an absolute energy scale, the solvation thermodynamic functions were calculated for the compounds on the basis of the sublimation and solubility experiments results:

$$\Delta_{hyd}Y^\circ = \Delta_{sln}Y^\circ - \Delta_{sub}Y^\circ \quad (3)$$

where Y is one of the thermodynamic functions G, H or S. The sublimation thermodynamics of compounds **I–XII** were studied in our previous studies,[12–14] and experimental data are collected in Table S3 of the ESI.† The thermodynamics of hydration of **I–VI** in buffer 7.4 at 298 K is shown in Table S2 (ESI†).

Thermodynamic functions of the hydration process for compounds **VI–XII** are presented in Table 2. As in the dissolution process, the insertion of terminal substituents in the phenyl ring of the molecule affects the entropic term of the hydration process to a larger extent (Fig. 2b). As all the hydration parameters are negative, the diagram sectors where the negative signs are observed correspond to the increase in the absolute values of the considered values in comparison with those belonging to the unsubstituted compound. In turn, the regions with the positive sign show an enhancement of the absolute values of the thermodynamic functions. Further, only

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the absolute values are considered when the changes in the hydration processes are discussed.

The diminution of the hydration enthalpy is observed in di-substituted isomers (2-Me-5-Cl-(**XII**) and 3-Cl-4-Me-(**VIII**)) in comparison with the unsubstituted compound. Thus, the molecules of these compounds have weaker interactions with the water molecules in the hydrate shell than the molecules of the unsubstituted compound. The possible explanation of this phenomenon can be the steric hindrances and respective decrease in the molecule surface available for the interactions with water (in comparison with **I**) due to the presence of bulky hydrophobic substituents. The entropy of the process for 2-Me-5-Cl-(**XII**) decreases by about 38 J mol^{-1} K^{-1}, and for 3-Cl-4-Me-(**VIII**) the difference is close to zero. This testifies to a different extent of water molecules ordering in the hydrate shell of these isomers.

The introduction of the methyl-group in the *meta*- or *para*-position of the phenyl ring (resulting in the formation of compounds 3-Me-(**X**) and 4-Me-(**II**), respectively) increases both the entropy and enthalpy of hydration compared to the unsubstituted compound. And the growth in these values is bigger in the *para*-substituted compound (**II**) than in the *meta*-substituted one (**X**). This phenomenon is fully repeated when a Cl-atom is inserted in the *meta*- or *para*-position (resulting in the formation of compounds 3-Cl-(**XI**) and 4-Cl-(**IX**), respectively). Thus, the introduction of the substituents (methyl-group, Cl-atom) enhances the interaction of the substance molecule with water and, consequently, the degree of water molecules ordering in the hydrate shells of the molecules. It can be assumed that in the hydrate shells the forces of the hydrogen bonds between the molecules of these isomers and water molecules are stronger than those in compound (**I**).

The replacement of the methyl-group (4-Me) in the *para*-position of compound **II** with a CF_3-group (compound **IV**) increases the hydration entropy and enthalpy of compound **II** itself. In both compounds (**II** and **IV**), the discussed values grow compared to **I**. Therefore, the molecules of these compounds interact with water molecules in the hydrate shells better than the molecule of compound (**I**) and the degree of ordering the system increases. Apparently, the following regularity is observed: the stronger the interaction between the solvent molecules, on the one part, and the molecules of the drug compounds – on the other, the more ordered their hydration shell is. It should be noted that the alterations of the entropy and enthalpy terms differ from each other. As a result, the hydration Gibbs energy of compound 4-Me-(**II**) increases by 2.2 kJ mol^{-1} in comparison with the unsubstituted compound. In turn, in compound 4-CF_3-(**IV**), the driving force of the process falls by 8.1 kJ mol^{-1}.

By the driving force of the process, the halogen-mono-substituted compounds (4-Cl-(**IX**)/4-F-(**V**)) are similar to compound **I**. The difference in the Gibbs energies between the substituted compounds and the unsubstituted one is equal to zero. This fact indicates an equal ability of the considered compounds to be hydrated by the water molecules. In turn, the entropy and enthalpy terms of these contributions grow as compared to compound **I**.

For compounds with an additional presence of hydrogen bonding centers, the alteration tendencies of the entropy and enthalpy terms are different in comparison with the unsubstituted thiadiasole. Fig. 2b clearly demonstrates that compound 4-OEt-(**III**) contrasts with 4-iso-EtOH-(**VI**) and 4-OMe-(**VII**). The introduction of an ethoxy-group (**III**) leads to the hydration enthalpy and entropy increase and the driving force of the process decrease, which is analogous to the behavior of the molecules with no potential centers of hydrogen bonding. For compounds 4-iso-EtOH-(**VI**) and 4-OMe-(**VII**), the situation is opposite: the diminution of the Gibbs energy of the process in comparison with **I** (growth of the driving force) is accompanied by a decrease in the enthalpy and entropy terms. It can be proposed that the oxygen-atom in the 4-OEt-(**III**) molecule is ''shielded'' to a great extent by the ethyl-fragment and does not participate in the interactions with the water molecules. On the other hand, the increment in the hydration driving force for 4-iso-EtOH-(**VI**) and 4-OMe-(**VII**) in comparison with the unsubstituted compound results from the considerable decrease in the entropy impact. Table 2 indicates that the relative contribution of the enthalpy term (ΔH_{hyd}) in the hydration Gibbs energy is maximal for compounds under consideration (66.9 and 61.8%, respectively), in spite of small $\Delta_{hyd}H^{\circ}$ absolute values. All the above mentioned information indicates the specific features of the hydration process in 4-iso-EtOH-(**VI**) and 4-OMe-(**VII**), probably accompanied by solute–solvent interactions different from those in the other compounds.

We tried to construct a correlation model with the help of HYBOT physicochemical descriptors in order to predict the hydration Gibbs energy for the thiadiazole class compounds.[18] The analysis of various descriptors showed that the most appropriate descriptor is the sum of donor and acceptor ability of the atoms in the molecule to form hydrogen bonds normalized by the polarizability of the molecule. Fig. 4 presents the respective dependence of the Gibbs energy on the $\sum(C_{ad})/\alpha$-parameter. The values of $\sum(C_{ad})$ and α for all the 1,2,4-thiadiazoles are tabulated in Table S4 of the ESI.†

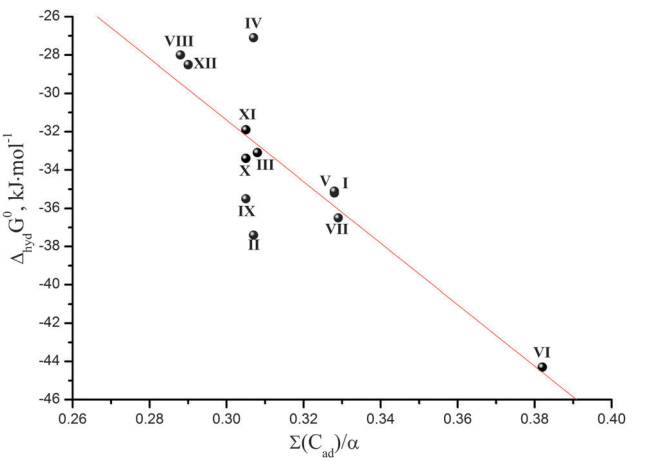

Fig. 4 Relationship between the hydration Gibbs free energy ($\Delta_{hyd}G^{\circ}$) and the $\sum(C_{ad})/\alpha$ descriptor of the compounds studied.

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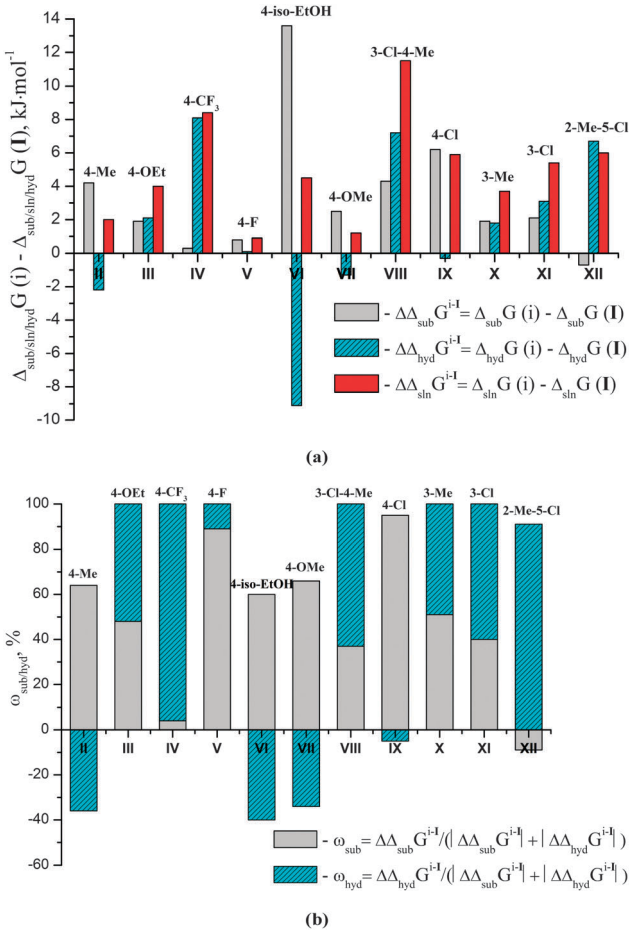

Fig. 5 (a) The Gibbs energy differences between the substituted 1,2,4-thiadiazole and compound **I** for the following processes: sublimation (grey), hydration (cyan), solubility (red); (b) the relative contribution (in percentage) of the sublimation (grey) and hydration (cyan) Gibbs energies to $\Delta\Delta_{sln}G^{i-I}$ of the compounds.

The correlation equation has the following form:

$$\Delta_{hyd}G^{\circ} = (17 \pm 10) - (161 \pm 32)\cdot\sum(C_{ad})/\alpha \; R = 0.846; \quad \sigma = 2.66; \; n = 12 \qquad (4)$$

It should be mentioned that the correlation coefficient of this dependence is not too high; meanwhile, the obtained correlation parameters make it possible to detect the character of the $\Delta_{hyd}G^{\circ}$-value change depending on the chosen descriptor and to predict the Gibbs energy within the network of these correlation characteristics.

As it was mentioned above, the solubility is a result of the imbalance of two fundamental processes: sublimation and hydration. The results of the analysis are presented in Fig. 5a. The introduction of any substituent in the phenyl ring increases the sublimation Gibbs energy (the saturated vapor pressure) in comparison with the unsubstituted compound. An exception is compound **XII** (2-Me-5-Cl-), for which the considered value of Gibbs energy is slightly lower (by 0.7 kJ mol^{-1}). And it is worth mentioning that the dispersion in the sublimation Gibbs energy values as compared to that in the unsubstituted compound is 14.3 kJ mol^{-1}. This value is comparable to the hydrogen bond energy. Thus, we can assume that the design strategy for the compounds belonging to the class of 1,2,4-thiadiazole derivatives should be based on the fact that during the substance dissolution (transition from the crystal to the solution) additional hydrogen bonds were formed. The analysis of the difference in hydration Gibbs energy between the substituted 1,2,4-thiadiazoles and the unsubstituted one showed that the situation is considerably different from the previous case. Four compounds have a negative difference. In other words, the insertion of 4-Me-(**II**), 4-iso-EtOH-(**VI**), 4-OMe-(**VII**) and 4-Cl-(**IX**) substituents enhances the hydration in comparison with the unsubstituted 1,2,4-thiadiazole. The dispersion between the minimal and maximal values among the considered set of the substituents was revealed to be 17.2 kJ mol^{-1}. But, for all the compounds the difference between the dissolution Gibbs energies appeared to be positive. This fact indicates that even the gains of the hydration terms (namely the negative ones) do not exceed the sublimation contributions (interactions of the molecules in the crystal) after the introduction of the substituents in the phenyl fragment of 1,2,4-thiadiazole.

It was also interesting to compare the contributions of the sublimation and hydration Gibbs energy to the dissolution process. The results are presented in Fig. 5b. It is evident from Fig. 5b that the relations of the considered terms vary greatly. In the range of the compounds with the negative values of the hydration contributions, the maximum value of 40% was obtained for 4-iso-EtOH-(**VI**).

Conclusions

The influence of structural modifications on thermodynamic aspects of solubility and hydration processes of a series of 1,2,4-thiadiazole compounds was studied. It was found that the introduction of any substituent in the phenyl ring of the 1,2,4-thiadiazole molecule reduces the solubility of the substance. For most of the compounds this process is accompanied by a significant decrease of the dissolution entropy, whereas the change in $\Delta_{sln}H^{\circ}$ is not considerable or not enough to balance the entropy contribution. In order to rationalize the relationships between the structure of 1,2,4-thiadiazoles and their solubility, the latter was considered in terms of two fundamental processes: sublimation and hydration. As in the dissolution process, the insertion of terminal substituents in the phenyl ring of the molecule affects the entropic term of the hydration process to a larger extent. Analysis of the hydration Gibbs energy revealed that only four substituents (4-Me-(**II**), 4-iso-EtOH-(**VI**), 4-OMe-(**VII**) and 4-Cl-(**IX**)) enhance the hydration of the corresponding compounds in comparison with the unsubstituted 1,2,4-thiadiazole. However, this gain of the hydration term does not compensate the increase of the sublimation contribution (interactions of the molecules in the crystal) induced by the introduction of the substituents in the phenyl fragment, which leads to consequent solubility decrease.

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The correlation analysis of the thermodynamic functions of hydration with HYBOT physicochemical descriptors demonstrated that the Gibbs energy of the process can be estimated using the sum of donor and acceptor ability of the atoms in the molecule to form hydrogen bonds normalized by the polarizability ($\sum(C_{ad})/\alpha$).

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