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Impact of structural modification of 1,2,4-thiadiazole derivatives on thermodynamics of solubility and solvation processes in 1-octanol and *n*-hexane

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ABSTRACT

Influence of a structural modification on thermodynamic aspects of solubility and solvation processes of the 1,2,4-thiadiazole drug-like compounds in pharmaceutically relevant solvents *n*-hexane and 1-octanol was investigated. The solubility of the compounds in 1-octanol does not substantially depend on the nature and position of the substituent in the phenyl moiety. In *n*-hexane, however, the introduction of any substituent in the phenyl ring of the 1,2,4-thiadiazole molecule reduces the solubility in the solvent. 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 solvation. It was found that for the most of the compounds the solubility change in both solvents is a consequence of competition between the sublimation and solvation contributions, i.e. the introduction of substituents leads to growth of the sublimation Gibbs energy and increase in the solvation Gibbs energy. Thermodynamic parameters of the transfer process of the compounds from *n*-hexane to 1-octanol, which is a model of the blood–brain barrier (BBB), were also analyzed.

1. Introduction

Heterocyclic compounds containing structural fragments specific for natural biologically active substances can be considered as a database for creating new drugs [1]. The synthetic derivatives of 1,2,4-thiadiazole are widely used in the therapy of different pathologies [2–6], among which an important place is taken by the neurodegenerative ones including the Alzheimer's disease [7,8].

The interaction of a drug substance molecule with the receptors on a target organ is the key issue in the design of new pharmaceutical formulations. However, other factors such as solubility in biological fluids are also significant for successful delivery of the drug to the target organ. Model solvents – 1-octanol and *n*-hexane – are often used along with aqueous buffer solutions to predict drug compounds solubility, their distribution in internal environments and membrane permeability. 1-Octanol is an appropriate solvent for simulating the lipid layer of the cell membrane. Moreover, the water–octanol distribution coefficient is widely applied to forecasting the pharmacokinetic properties of drugs [9].

The system of the immiscible solvents – *n*-hexane-buffer pH 7.4 – which can model the blood–brain barrier properties is successfully used for the drug substances that are biological active to the receptors in the brain cortex including compounds based on 1,2,4-thiadiazole structural fragment. As *n*-hexane can interact only non-specifically, it imitates the non-polar regions of the brain, whereas the buffer solution pH 7.4 can model the blood plasma. According to its ability to interact specifically with the dissolved substance, *n*-hexane (along with cyclohexane, carbon tetrachloride, benzene etc.) belongs to the non-polar aprotic solvents group and is usually used as an inert solvent due to its inability to create hydrogen bonds either as a proton donor or as a proton acceptor [10]. The interaction of the *n*-hexane molecule with the molecules of the dissolved substances occurs due to the van-der-Waals forces alone. Thus, the investigation of the dissolution and solvation processes of the compounds in *n*-hexane and the quantitative analysis of the thermodynamic functions of the transfer from *n*-hexane to other solvents allows dividing the contributions of the specific/non-specific interactions to the total Gibbs energy of the solvation processes.

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As the solvation process cannot be evaluated directly from the experimental data, its investigation requires information on the numerical values of the thermodynamic parameters of the dissolution process and crystal lattice energies. These parameters enable determination of the quantitative characteristics of the solvation process and their analysis on an absolute energy scale. Thus, it becomes possible to study the correlations between the thermodynamic values which characterize the solubility process and the structure and physicochemical properties including lipophilicity and hydrophobicity parameters.

The present study is a continuation of our investigations into the solubility [11,12], crystal structures [13] and biological activity [14] of newly synthesized drug-like compounds based on 1,2,4-thiadiazole fragment (figure 1). The aim of the present study is to measure the solubility of a series of 1,2,4-thiadiazole derivatives in 1-octanol and *n*-hexane in order to analyze the influence of structural modifications on thermodynamic aspects of solubility, solvation and distribution processes.

2. Experimental section

2.1. Solvents

1-Octanol (CH_3–$(CH_2)_7OH$, MW 130.2, 99%) and *n*-hexane (C_6H_{14}, MW 86.18, HPLC grade) were received from Sigma Chemical and RCI Labscan, respectively, and used without further purification.

2.2. 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. All the experimental data has been presented/recalculated in molar fraction units. 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 molar solubilities of drugs were measured spectrophotometrically with an accuracy of 2% to 2.5% using a protocol described previously [15].

The standard Gibbs energies of dissolution processes ΔG^0_{sol} (in kJ·mol^{-1}) were calculated using the following equation:

$$\Delta G^0_{sol} = -RT \ln a_2, \quad (1)$$

where $a_2 = \gamma_2 x_2$ is the activity of the solute molecule; x_2 is the drug molar fraction in the saturated solution; γ_2 is the activity coefficient of the solute molecule. Considering high solubility of the compounds in 1-octanol, the activity coefficients of the 1,2,4-thiadiazole derivatives in this solvent (γ^o_2) were estimated by concentration dependencies of the distribution coefficients at $T = 298.2$ K using the procedure described elsewhere [11,12]. Details of the experiment are reported in the Supporting Information. Due to the poor solubility of the studied drugs in *n*-hexane, the activities of the compounds were approximated by mole fractions.

The standard solution enthalpies ΔH^0_{sol} (in kJ · mol^{-1}) were calculated using the van't Hoff equation:

$$\partial(\ln a_2)/\partial T = \Delta H^0_{sol}/RT^2. \quad (2)$$

It was assumed that the solution enthalpies were independent of the concentration. The temperature dependencies of drug solubilities within the chosen temperature interval can be described by the linear function:

$$\ln x_2 = A - B/T, \quad (3)$$

where A is the integral coefficient relating to entropy and $B = \Delta H^0_{sol}/R$. This indicates that the change in heat capacity of the solutions with the temperature is negligibly small.

The standard solution entropies ΔS^0_{sol} (in J · mol^{-1} · K^{-1}) were obtained from the well-known equation:

$$\Delta G^0_{sol} = \Delta H^0_{sol} - T\Delta S^0_{sol}. \quad (4)$$

2.3. 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.* [16] and described by us earlier [14]

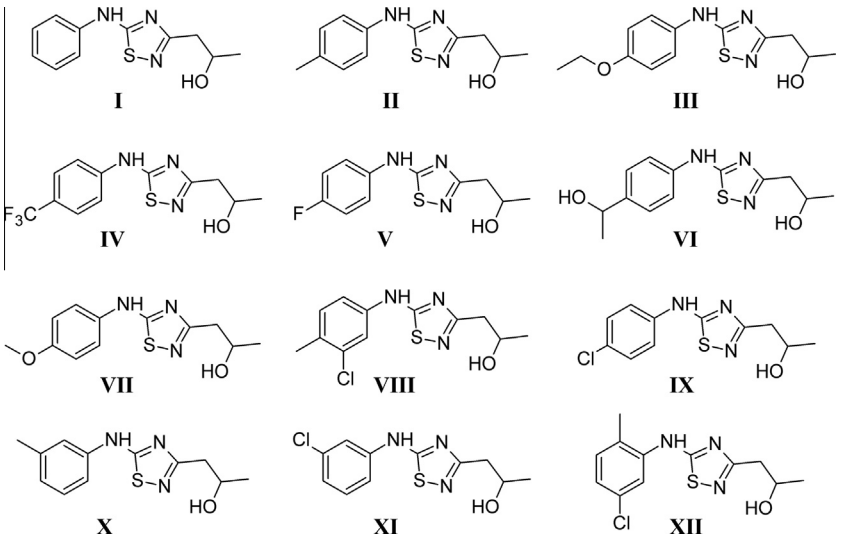

FIGURE 1. Molecular structure of the studied compounds.