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Physico-chemical study of bioactive N-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide: Sublimation, solubility and distribution

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ABSTRACT

Novel experimental data for physicochemical properties of the bioactive compound N-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide have been obtained. The saturated vapor pressure of the studied compound has been measured within the temperature range of 431.15–457.15 K by the inert gas transpiration method. The shake flask method has been used to determine the solubility in buffer pH 7.4, n-hexane, ethanol, 1-octanol and distribution coefficients in the 1-octanol/buffer system at different temperatures. The van't Hoff and modified Apelblat models have been used to correlate the experimental solubility. The thermodynamic functions of sublimation and transfer have been investigated and discussed.

1. Introduction

Despite a big variety of available medicinal drugs, the problem of developing new highly efficient and low-toxicity compounds remains quite urgent. This is due to worse drug efficiency caused by the appearance of drug-resistant microorganism forms, possible side effects and limited shelf life of the drugs. Heterocyclic compounds based on 1,3,4-thiadiazole are of great interest to scientists as they have a broad potential for practical applications. For example, some representatives of this class have a high anti-microbial [1], anti-inflammatory [2], analgetic [3], anti-cancer [4], anti-tubercular [5] effects, anticonvulsant action [6] and many other valuable properties [7,8]. The authors of [9] have found out that adding a phenyl ring to a 1,3,4-thiadiazole molecule improves the molecule biological activity, and compounds that have a phenyl ring with electron-acceptor groups have the highest antimicrobial action. The results of a pharmacological study have shown that compound N-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide (Fig. 1) has anti-inflammatory, broncholytic, anti-tubercular activities as good as the reference drugs such as budesonide and isoniazid [10].

Physicochemical properties largely determine drug compound applications and peculiarities of their action inside the body. Learning of solubility has an important meaning at all stages of drug research. At the discovery stage, solubility plays the role of a screening parameter together with the other physicochemical properties (ionization, lipophilicity and permeability). At the development stage, knowledge of solubility is essential for placing the compound in the biopharmaceutical classification, as well as for composition optimization and salt selection. Compound solubility depends on two factors: thermodynamic aspects of molecular interaction in the crystal lattice (sublimation) and in the solvent (solvation) [11].

A very important feature of organic compound solid state is sublimation enthalpy that reflects both the degree of intermolecular interactions in the crystalline form and to a large extent the character of molecule interaction while solving [12]. Studies of solubility and sublimation properties of compounds allow us to calculate solvation characteristics which provide valuable information about the nature of drug compound interaction with solvents modeling different biological environments.

A large influence on the pharmacokinetics of drug compounds is exerted by lipophilicity and hydrophilicity of substances. Hydrophilic substances have worse pharmacokinetic properties than lipophilic ones. They are characterized by low bioavailability usually not exceeding 10% of the dose taken, high metabolism degree and quick excretion. Because of these drawbacks, therapeutic concentrations are only achieved by introduction of big drug doses. The quantitative characteristic of drug lipophilicity is the distribution coefficient of the dissolved compound between water and model organic solvent. As the model, *1*-octanol (that is practically insoluble in water and a neutral compound) is the closest to the phospholipid membrane in its polarity and structure [13,14].

The objective of this study was to determine some physicochemical properties of biologically active N-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-nitrobenzamide:

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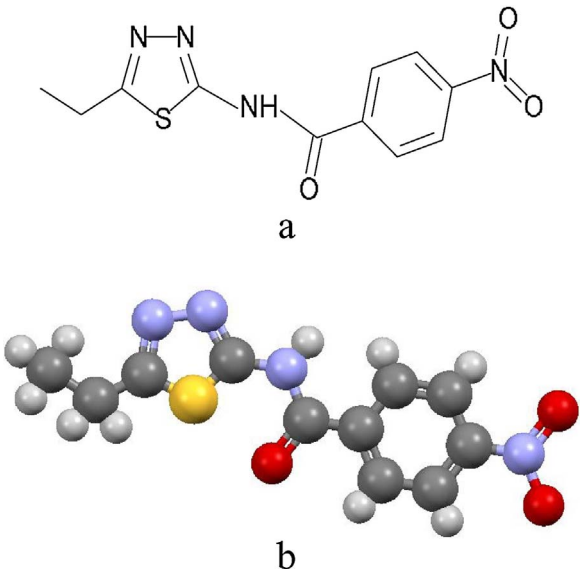

Fig. 1. Chemical structure (a) and three-dimensional structure (b) of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-nitrobenzamide.

- saturated vapor pressure at 431.15–457.15 K using the transpiration method;
- solubility in four pharmaceutically relevant solvents at 288.15–318.15 K using the shake-flask method;
- distribution coefficient in the *1*-octanol/water system at 293.15–313.15 K using the shake-flask method,
- thermodynamic function of sublimation, solubility, solvation and transfer.

2. Experimental

2.1. Materials

Specification of the chemicals used in this study is listed in Table 1. N-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-nitrobenzamide was synthesized by the method described in [10]. The structure of the obtained compound was confirmed by Fourier-transform infrared spectroscopy and element analysis: Anal. Calc. for $C_{11}H_{10}N_4O_3S$: C 47.43%, H 3.59%, N 20.22%, S 11.51%. Found: C 47.48%, H 3.57%, N 20.31%, S 11.49%. FT-IR (KBr, cm^{-1}): ν = 3400 (NH), 1790 (−N═C), 1680 (−C═C arom.), 1520 (CO−NH amide). Graphical ^{1}H NMR spectra of N-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide presented in Fig. S1 (Supporting Information). The purity of the synthesized compound after recrystallisation was determined by HPLC an Agilent 1100 series apparatus with a Kinetex C18, 2.6 μm, 3 × 100 mm (Phenomenex, USA). The mobile phase consisted of a mixture of water-methanol (42/58, v/v). The flow-rate was 0.4 ml/min. The detector was operated at 262 nm. The injection volume was 10 μl. Bidistilled water (with electrical conductivity 2.1 l μ S cm^{-1}) was used for preparation of buffer solution. The phosphate buffer pH 7.4 (I = 0.15 mol l^{-1}) was prepared by combining the KH_2PO4 (9.1 g in 1 l) and $Na_2HPO_4{\cdot}12H_2O$ (23.6 g in 1 l) salts. The pH values were measured by using a pH meter FG2-Kit (Mettler Toledo, Switzerland) standardized with pH 1.68, 6.86 and 9.22 solutions.

2.2. Differential scanning calorimetry

Temperature of melting of compound has been determined using the differential scanning calorimeter of Perkin Elmer Pyris 1 DSC (Perkin Elmer Analytical Instruments, Norwalk, Connecticut, USA). Work of DSC took place in the atmosphere of the drained argon of high cleaning of 99.990% proceeding with a speed of 20 ml/min. DSC was calibrated using a two-point calibration, measuring the onset melting temperatures of indium and bismuth standards from Perkin Elmer. Onset of melting was used for calibration because it is almost independent on scan rate. Temperatures of melting for indium and bismuth were 156.7 °C and 271.4 °C, respectively (determined by at least ten measurements). The enthalpy scale was calibrated using the heat of fusion of indium. Value of an enthalpy of melting was corresponded 28.48 J g^{-1} (the recommended value of 28.45 J g^{-1}). In total DSC-experiments were made at a speed of heating of 10 °C min^{-1} between 25 and 300 °C. Previously dried samples (3–5 mg) were placed into aluminum pan. Accuracy of weighing made ± 0.0005 mg. An empty pan sealed in the same way was used as reference. The standard uncertainty on the melting temperature was determined as standard deviation of five independent measurements.

2.3. Vapor pressures measurements

Sublimation experiments were carried out by the transpiration method. This method consists in passing a stream of an inert gas over a sample at the constant flow rate and temperature, the rate being low enough to achieve practically the saturation state of the gas with the substance vapor. Then the vapor is condensed and the sublimated quantity is determined. The vapor pressure over the sample at this temperature can be calculated from the amount of sublimated material and the volume of the inert gas used.

Details of the technique are given in the literature [15]. The inert gas (nitrogen) from tank flows through a column packed with silica to adsorb a humidity from the gas. The stabilization of the gas

Table 1
Specification of the chemicals used in this study.

Chemical name	CAS register No.	Formula	M/g mol^{-1}	Source	Initial mass fraction purity	Method of purification	Final mass fraction purity	Analysis method
N-(5-ethyl-1,3,4-thiadiazol-2-yl) −4-nitrobenzamide	313662−95-2	$C_{11}H_{10}N_4O_3S$	278.29	synthesis	0.975	recrystallization	≥0.993 ≥0.98	HPLC[a] 1H NMR[c]
Ethanol	64−17-5	C_2H_6O	46.07	Sigma-Aldrich	≥0.99[b]	–	–	–
1-Octanol	111−87-5	$C_8H_{18}O$	130.2	Sigma-Aldrich	≥0.99[b]	–	–	–
n-Hexane	110−54-3	C_6H_{14}	86.18	Sigma-Aldrich	≥0.97[b]	–	–	–
Potassium dihydrogen phosphate	7778−77-0	KH_2PO_4	136.08	Merck	≥0.99[b]	–	–	–
Disodium hydrogen phosphate dodecahydrate	10039−32-4	$Na_2HPO_4{\cdot}12H_2O$	358.14	Merck	≥0.99[b]	–	–	–

[a] High performance liquid chromatography.
[b] As stated by the supplier.
[c] Hydrogen nuclear magnetic resonance.