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The solubility of ethionamide and structural analogues in buffer solutions, octanol and hexane at several temperatures

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ABSTRACT

The solubility of antituberculosis drug ethionamide and structural analogues in buffer solutions, octanol and hexane within the temperature range from (293.15–313.15) K was measured using the shake-flack method. All the compounds studied appeared to have the solubility neither more than 10^{-3} mol fraction in aqueous solutions. At that the solubility in buffer pH 7.4 is lower than that in pH 2.0 which is determined by the ionization state. The solubility in octanol was estimated to be essentially higher than in hexane that is explained by the specific interactions of the compounds with the solvent. Thermodynamic solubility and solvation functions for the substances in the solvents studied were calculated. The partition coefficients of the compounds were measured in the octanol – buffer pH 7.4 system. The solubility values of the unionized molecular species of the investigated compounds using the partition coefficients and HYBOT descriptors for the biologically active substances were calculated. Comparison of the experimental and calculated solubility values showed the acceptability of the proposed approach for predicting the solubility of the compounds of aromatic thioamide series.

1. Introduction

Pulmonary tuberculosis is currently one of the major health problems worldwide. A variety of drugs with good efficiency have applied against tuberculosis, including ethionamide, which is an important second-line antituberculosis drug used for the treatment of patients infected with multidrug-resistant Mycobacterium. Although ethionamide is a structural analogue of isoniazid, both are pro-drugs that need to be activated by mycobacterial enzymes to exert their antimicrobial activity [1]. It is used in combination with other agents in cases where the first-line drugs are ineffective or are contraindicated. Its effective bacteriostatic action against organisms having resistance to isoniazid has been demonstrated by animal experiment and clinical trials by many authors [2–4]. Despite the fact that ethionamide and its structural analogues are commonly used in therapeutics and the literature contains information about their crystal structure [5,6], to date, the information on their important physicochemical parameters such as solubility, partitioning in pharmaceutically important solvents, and membrane permeability is rather limited [7,8].

It is well known that the solubility of organic compound in aqueous solutions is determined both by the solid state structure and the interactions of the solute with the solvent. In its turn, the solubility dramatically depends on the molecules being either in the ionized or unionized state due to the presence of donor and acceptor fragments. The ionization degree of the substance is determined by the solution pH and the ionization constants (pK_a), which influence the passive transport of the drug compound through the membranes: at that, a single form of the compound – either neutral or ionized reveals an affinity to the biological receptor.

The objects of the present investigation were the compounds of aromatic thioamide series: 2-ethyl-4-pyridinecarbothioamide (ethionamide), 2-pyridinecarbothioamide, and 4- pyridinecarbothioamide. The last two are the parent compounds of ethionamide. Thioamide group in the structures of the studied compounds determines the biological activity of a broad spectrum of drugs. So, the investigation of physicochemical properties of the compounds studied in the present work is important for the design of effective antituberculosis drug substances.

This study is a continuation of our investigations on the relationship of the structure of drug and drug-like substances with solubility, lipophilic-hydrophilic properties and biological activity [9,10]. The aim of the present work: studying the solubility of the compounds of aromatic thioamide series in pharmaceutically rele-

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vant solvents: phosphate buffer pH 7.4 and muriatic buffer pH 2.0 solutions, octanol and hexane; as well as measuring the partitioning coefficients of the investigated substances in octanol/buffer pH 7.4 system.

2. Apparatus and procedure

2.1. Materials

All the compounds studied in this work were obtained from commercial sources. The origin, CAS numbers, and purity of all samples are presented in Table 1. All chemicals were used without additional purification.

Bidistilled water (with electrical conductivity 2.1 $\mu S\,cm^{-1}$) was used for preparation of buffer solutions. Phosphate buffer pH 7.4 (I = 0.15 mol/l) was prepared by combining the KH_2PO_4 (9.1 g in 1 L) and $Na_2HPO_4{\cdot}12H_2O$ (23.6 g in 1 L) salts. For the preparation of the buffer solution pH 2.0 (I = 0.10 mol/l) 6.57 g of KCl was dissolved in water, 119.0 mL of 0.1 M hydrochloric acid was added and the volume of the solution was adjusted to 1 L with water [11]. The pH values were measured by using pH meter FG2-Kit (Mettler Toledo, Switzerland) standardized with pH 1.68, 6.86 and 9.22 solutions.

2.2. Solubility

All the experiments were carried out by the shake flask method [12] at five temperature points: 293.15, 298.15, 303.15, 308.15, 313.15 ± 0.1 K. The essence of the above mentioned method includes determination of the compound concentration in the saturated solution. Glass ampoules containing the tested substance and the solvent were placed into an air thermostat supplied by a stirring device. To ensure the equilibration condition, the dissolution profiles of the compounds were investigated. Thermodynamic equilibrium was determined from the preliminary experiments including measuring the kinetic dependences of the concentration of the saturated solutions for the investigated substances. The time needed for reaching the plateau of drug concentration against time was considered a suitable equilibration time. The incubation time of 24 h was estimated to be high enough for the equilibrium to be reached and all the solubility experiments lasted 24 h before the solubility measurements were performed. The saturated solution was taken and centrifuged (Biofuge stratus, Germany) under the temperature control for 5 min at a fixed temperature. The solid phase was removed through isothermal filtration by the filter MILLEX® HA 0.45 μm (Ireland) at the same temperature. An aliquot of the saturated solution was taken at fixed temperature using the thermostated equipment and then diluted at room temperature by the solvent. The absorbance was measured by means of spectrophotometer Cary-50 (USA) in UV spectral region (λ = 200–400 nm) with an accuracy of 2–4% at room temperature. The experimental results are reported as an average value of at least three replicated experiments. The calibration procedure was made at room temperature using the solutions with known concentrations of each substance in each investigated solvent. The solutions were prepared by adding an appropriate mass of substance and volume of solvent (buffer pH 2.0, buffer pH 7.4, octanol, hexane) to the flask and mixing until the substance was totally dissolved. The absorbance of the solutions was measured and calibration curves were constructed.

In order to converse molarity to mole fraction concentration scale, densities of solutions were measured with a vibrating-tube digital densimeter (model DMA 4500, Anton Paar, Austria). The relative standard uncertainty of the density measurement was 0.004. Experimental densities of the investigated solutions are given in Table S1 (see Supplementary information S1).

2.3. Thermodynamics of dissolution

The standard Gibbs energies of dissolution processes ΔG^0_{sol} were calculated using the following equation:

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

where $a_2 = \gamma_2 \cdot x$ is the activity of the solute molecule; x is the drug molar fraction in the saturated solution; γ_2 is the activity coefficient of the solute molecule. The standard solution enthalpies ΔH^0_{sol} were calculated using the van't Hoff equation:

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

The temperature dependences of drug solubility within the chosen temperature interval can be described by the linear function:

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

This indicates that the change in heat capacity of the solutions with the temperature is negligibly small.

In order to estimate the interactions of the compounds with solvents the solvation thermodynamic functions were calculated on the basis of the sublimation and solubility experimental results:

$$\Delta Y^0_{solv} = \Delta Y^0_{sol} - \Delta Y^{298}_{sub} \quad (4)$$

where Y is one of the thermodynamic functions G or H.

2.4. Partition experiments

The shake flask method was used to determine the partition coefficients (P) in octanol/buffer (pH 7.4) system [13–16]. The procedure was performed as follows. Buffer pH 7.4 and octanol were mixed vigorously for 24 h at 25 °C, to promote solvent saturation in both phases. The solvents were standing long enough to allow the phases to separate, and the compound was dissolved in the octanol phase to obtain stock solution. The buffer saturated octanol phase with the dissolved substance, and octanol saturated buffer phase were placed in a glass vials and mixed during 24 h at 25 °C. Three different volume ratios $V^{O/B}/V^{B/O}$ of the phases were used: 1/6, 1/3, 1/1 for compounds I and II; 2/1, 1/1, 1/2 for compound III. The concentration of the stock solution was approximately 0.01 mol L^{-1}. To obtain the activity coefficients the distribution for at least 5 concentrations of stock solution in the concentration range of 0.005–0.01 mol L^{-1} was studied. The substance concentrations were determined spectrophotometrically using calibration curves. The partition coefficient was calculated using the following equation:

$$P = C^{O/B}/C^{B/O} \quad (5)$$

where $C_{O/B}$ and $C_{B/O}$ are the molar concentrations of solute in the mutually saturated phases of octanol and water. The accuracy of the partition coefficient value was verified by checking the mass balance of the starting amount of compound i compared to the total amount of the compound partitioned between the two phases:

$$m_i = m^{O/B} + m^{B/O} \quad (6)$$

where $m_i = C_i V_i$ is the starting mass (in moles) of the compound, $m^{O/B} = C^{O/B} V^{O/B}$ is the mass of the substance dissolved in the water-saturated octanol phase, and $m^{B/O} = C^{B/O} V^{B/O}$ is the mass of the substance dissolved in the octanol-saturated water phase.

The activity coefficients of the studied compounds were estimated by the concentration dependences of the partitioning coefficients using the following procedure:

$$P^{B/O}_{c(\max)} = \frac{a^{O/B}(C_{\max})}{a^{B/O}(C_{\max})} \quad (7)$$