J. Chem. Thermodynamics 108 (2017) 18–25

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Physico-chemical characterization antituberculosis thioacetazone: Vapor pressure, solubility and lipophilicity

Angelica Sharapova *, Marina Ol'khovich, Svetlana Blokhina, German Perlovich

Institute of Solution Chemistry of Russian Academy of Sciences, 1 Akademicheskaya Street, 153045 Ivanovo, Russia

ARTICLE INFO

Article history:
Received 25 July 2016
Received in revised form 26 December 2016
Accepted 31 December 2016
Available online 3 January 2017

Keywords:
Thioacetazone
Solubility
Partition coefficient
Vapor pressure
Thermodynamics

ABSTRACT

Vapor pressure of thioacetazone (TAZ) has been determined in the temperature range of 404.15–429.15 K by the transpiration method. The obtained data were used to calculate the standard molar enthalpy of sublimation that was found to be 164.1 kJ/mol at T = 298.15 K. The drug solubility was measured at seven temperatures from 288.15 to 318.15 K in modeling solvents: octanol, hexane and aqueous buffers pH 2.0 and 7.4 by the saturation shake-flask method by using spectrophotometric analysis. It has been found that TAZ has poor solubility in hexane and buffer solutions and limited solubility in octanol. The experimental data were well correlated by van't Hoff and modified Apelblat equations. A temperature dependence of TAZ partition coefficient in the octanol/buffer pH 7.4 system has been derived. The partition coefficient value in this system (logP = 1.82) refers to the optimal interval for oral absorption drugs. The thermodynamic parameters of sublimation, solubility, solvation and transfer have been determined based on experimental data. The dominant effect of enthalpy and entropy contributions to the Gibbs energy of the investigated processes has been revealed.

1. Introduction

Thioacetazone (TAZ, 4-acetylaminobenzaldehyde thiosemicarbazone) (Fig. 1) one of the oldest known antibacterial agents with a pronounced activity against *Mycobacterium tuberculosis* and leprosy pathogen [1]. This drug is effective if the pathogenic bacteria are resistant to the main antituberculosis agents and is widely used in developing countries because of its low cost and accessibility, especially in combination with other drugs [2,3]. Despite the fact that the TAZ has been used in medicine since the middle of the previous century, there is practically no data about its physicochemical properties in the literature and in databases [4–6].

The first basic step in physicochemical studies of a compound is solubility determination. This is a very important property for pharmaceutical product design because it affects drug efficacy, its future development and formulation efforts, and also influences the pharmacokinetics, such as the release, transport and degree of absorption in the body. Solubility of compounds depends on two factors: thermodynamic aspects of molecular interaction both in the crystal lattice (sublimation) and in the solvent (solvation). The values of thermodynamic functions of sublimation, dissolution and solvation are not only of theoretical interest to those studying different types of intermolecular interactions, but may also serve as the basis for development of predictive models and for calculating physico-chemical properties, or designing separation and synthetic processes.

It is possible to estimate bioavailability of drug compounds and their formulations along with their characteristics such as solubility and crystal lattice energy by determining the capability of a substance to pass through the cell membrane. This ability can be assessed by using lipophilicity, the numerical characteristic of which is the partition coefficient in the system octanol/water. This parameter is considered to be a property of utmost importance because of its high physiological relevance and its resemblance to real biological partitions. Partition coefficient is accepted by most scientists as one of the most relevant lipophilicity descriptors to be applied in absorption, distribution, metabolism, excretion and toxicity (ADMET) studies [7]. It is therefore not surprising to find that log*P* is a key parameter in quantitative structure–activity relationship studies (QSAR).

The goal of our research is to present more complete and systematic information about the physico-chemical properties of TAZ: sublimation and dissolution, solvation, and partition in pharmaceutically relevant media. We report here temperature dependence of saturated vapor pressure, solubility in aqueous and organic solvents, partition coefficients in the system octanol/buffer

* Corresponding author.
E-mail address: avs@isc-ras.ru (A. Sharapova).

http://dx.doi.org/10.1016/j.jct.2016.12.034
0021-9614/

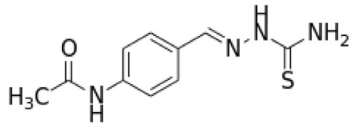

Fig. 1. Molecular structure of thioacetazone.

pH 7.4 and estimated thermodynamics function of the above mentioned processes.

2. Experimental

2.1. Materials

Detailed information about all chemicals used in this work is listed in Table 1. Bidistilled water (with electrical conductivity 2.1 μS cm^{-1}) was used to prepare 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. In order to prepare 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 mol/dm^3 hydrochloric acid was added and the volume of the solution was adjusted to 1 l with water. 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

Fusion temperatures and enthalpies of the compounds under investigation have been determined using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin-Elmer Analytical Instruments, Norwalk, Connecticut, USA) with Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing 20 $cm^3{\cdot}min^{-1}$ dry helium gas of high purity 0.99996 (mass fraction) using standard aluminum sample pans and a heating rate of 2 $K{\cdot}min^{-1}$. The accuracy of weight measurements was 0.005 mg. The DSC was calibrated using a two-point calibration, measuring the onset temperatures of indium and zinc standards. Onset of melting was used for calibration because it is almost independent on scan rate. Temperatures of melting for indium and zinc were 429.7 K and 419.5 °C, respectively (determined by at least ten measurements). The enthalpy scale was calibrated using the heat of fusion of indium. The value measured for the enthalpy of fusion corresponded to 28.69 $J{\cdot}g^{-1}$ (reference value 28.66 $J{\cdot}g^{-1}$ [8]). The standard uncertainty on the melting temperature was determined as twice standard deviation of five independent measurements.

2.3. Vapor pressure determination

The temperature dependence of TAZ vapor pressure was measured by the gas saturation method, also known as the transpiration method. The detailed description of the apparatus had been presented previously [9]. In brief: approximately 0.5 g of the investigated compound was blended with Pyrex balls and placed into a thermostated tube. At a constant temperature, the flow of inert gas (N_2) transported the saturated vapor of the sample under investigation through the tube until it was completely condensed at some point downstream. The vapor pressure of the sample at this temperature was calculated from the amount of sublimated sample and the volume of the inert gas used. The stability of the gas flow was supported by a mass flow controller MKS type 2179A. It is a prerequisite of the method that within the temperature interval used and during the whole experiment the compound does not get chemically decomposed in the measuring cell and in the sublimated products, and the stripping gas vapor pressure does not depend on the temperature.

The equipment was tested using benzoic acid. The details of verification experiment and the comparison the obtained results with literature data were described previously [10]. The standard value of the sublimation enthalpy at T = 298.15 K obtained in our experiments was $\Delta^g_{cr}H^O_m = 90.5 \pm 0.3$ kJ·mol^{-1}. This was in good agreement with the value recommended by IUPAC ($\Delta^g_{cr}H^O_m = 89.7 \pm 0.5$ kJ·mol^{-1}) [11].

From the experimentally determined pressure – flow rate relationship, the optimal flow rate of 1.2–1.8 $dm^3{\cdot}h^{-1}$ was revealed. At this flow rate, the saturated vapor pressure was independent of the flow rate and, thus, the thermodynamic equilibrium was reached.

The saturated vapor pressures values were measured five times at each temperature with the standard deviation of no more than 5%. Because the saturated vapor pressure of the investigated compounds was low, it may be assumed that the heat capacity change of the vapor with temperature was so small that it could be neglected. Thus, the experimentally determined vapor pressure data may be described in the following way:

$$\ln(p/\mathrm{Pa}) = \mathrm{A} + \mathrm{B}/T \tag{1}$$

The value of the sublimation enthalpy at the mean temperature T was calculated by the Clausius–Clapeyron equation:

$$\Delta^g_{cr}H^o_m(T) = -R\left(\frac{\partial(\ln p)}{\partial(1/T)}\right) \tag{2}$$

where as the sublimation entropy at the given temperature T was calculated from the following relation:

$$\Delta^g_{cr}S^o_m(T) = \frac{\left(\Delta^g_{cr}H^o_m(T) - \Delta^g_{cr}G^o_m(T)\right)}{T} \tag{3}$$

with $\Delta^g_{cr}G^o_m(T) = -RT\ln(p/p_0)$, where $p_0 = 1{\cdot}10^5$ Pa.

2.4. Solubility

The saturated equilibrium solubility of TAZ was determined by the shake flask method at atmospheric pressure and in the temperature range from 288.15 K to 318.15 K. The essence of the above mentioned method consists in determination of the compound concentration in the saturated solution. An excess amount of

Table 1
Sample table.

Chemical name	CAS register No.	Source	Mass fraction purity*	Method of purification
Thioacetazone	104-06-3	Acros Organics	⩾0.98	None
1-Octanol	111-87-5	Sigma-Aldrich	⩾0.99	None
n-Hexane	110-54-3	Sigma-Aldrich	⩾0.97	None
Potassium dihydrogen phosphate	7778-77-0	Merck	⩾0.99	None
Disodium hydrogen phosphate dodecahydrate	10039-32-4	Merck	⩾0.99	None
Potassium chloride	7447-40-7	Aldrich	⩾0.99	None
Hydrochloric acid 0.1 mol/dm^3 fixanal	7647-01-0	Aldrich	–	None

*As stated by the supplier