



Studying the sublimation thermodynamics of ethionamide and pyridinecarbothioamide isomers by transpiration method



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ABSTRACT

Temperature dependences of saturated vapor pressure for crystalline phases of 2-ethyl-4-pyridinecarbothioamide (ethionamide) and two parent compounds 2- and 4-pyridinecarbothioamide isomers were measured by the transpiration method. The results were used to determine the standard molar enthalpies, entropies and Gibbs energies of sublimation at $T = 298.15$ K. HYBOT descriptors application has shown an increase in the donor–acceptor ability of the molecules of the studied compounds to form hydrogen bonds to result in their crystal lattice energy growth. The obtained standard molar sublimation enthalpies have been compared with the literature results for 2- and 4-substituted pyridine isomers.

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1. Introduction

Thermodynamic parameters of sublimation—the process of compound transition from the solid state to the gas phase are of particular importance in the study of compounds crystal structure. The sublimation enthalpy values characterize the crystal lattice energy and usually help to study polymorphism and analyze molecular packing and intermolecular interactions [1]. These data serve as reference values for normalizing the functions of the pair potentials used for theoretical calculations of the crystal lattice energies [2]. Measuring the sublimation enthalpy is closely linked to the determination of the saturated vapor pressure as the effusion and other dynamic methods remain the main sources of the experimental data [3]. Being an important molecular property of the substances vapor pressure arouses interest in diverse areas of material, physical, pharmaceutical and environmental research [4]. Furthermore, the solubility of the compounds is known to depend on the ratio between the energy of the crystal lattice and the solvation energy [5].

This work continues our study of the crystal structure and pharmaceutically relevant physicochemical properties of drugs and drug-like compounds [6,7]. The objects of the investigation are the heterocyclic primary carbothioamides:

2-ethyl-4-pyridinecarbothioamide or ethionamide ($2\text{-C}_2\text{H}_5\text{-4-CSNH}_2\text{Py}$) and two parent compounds: 4-pyridinecarbothioamide ($4\text{-CSNH}_2\text{Py}$) and 2-pyridinecarbothioamide ($2\text{-CSNH}_2\text{Py}$). Ethionamide is an important and effective drug in the treatment of multidrug-resistant tuberculosis [8]. The compounds of this series are widely known as drugs of different pharmacological effects: antibacterial, antifungal, antisecretorial and others. [9]. The thioamide group included in the heterocycle structure is considered to be a pharmacophore responsible for biological activity. The physicochemical properties of thioamides depend on many factors, including the molecular structure of the substances and thermodynamic stability of the crystalline state. Despite constant attention of researchers to the compounds containing a thioamide group [10–12], there are little experimental data on sublimation of these substances [13]. The aim of the present investigation is to study the relationship of the molecular structure of ethionamide and 2- and 4-pyridinecarbothioamide isomers with sublimation parameters and to optimizing the search of compounds with desired properties.

2. Experimental

2.1. Materials

2-Ethyl-4-pyridinecarbothioamide (Ethionamide), 4-pyridinecarbothioamide and 2-pyridinecarbothioamide were obtained from commercial sources. The origin, CAS numbers and purity of all the samples are presented in Table 1.

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Table 1
Source, CAS numbers and purity of the compounds studied.

Chemical name	CAS register no.	Source	Purity (%)
2-Ethyl-4-pyridinecarbothioamide (Ethionamide)	536-33-4	BOC sciences	≥99
4-Pyridinecarbothioamide	2196-13-6	BOC sciences	≥99
2-Pyridinecarbothioamide	5346-38-3	Alfa chemistry	≥99

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 cm³ min⁻¹ dry helium gas of high purity 0.99996 (mass fraction) using standard aluminum sample pans and a heating rate of 2 K min⁻¹. The accuracy of weight measurements was 0.005 mg. The DSC was calibrated with an indium sample from Perkin-Elmer (P/N 0319-0033). The value determined for the enthalpy of fusion corresponded to 28.48 J g⁻¹ (reference value 28.45 J g⁻¹). The fusion temperature was 429.5 ± 0.1 K (determined by at least ten 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 the sublimated material and the volume of the inert gas used.

The technique details are given in the literature [14]. The inert gas (nitrogen) from the tank flows through a column packed with silica to adsorb the gas humidity. The gas temperature is stabilized in a water thermostat. The stability of the gas flow with the precision over 0.01% is maintained by using a mass flow controller MKS type 1259CC-00050SU. The inert gas of constant temperature and velocity passes then to the glass tube, which is placed in an air thermostat. Three zones of the glass tube can be distinguished: a starting zone for inert gas stabilization; a transitional zone in which the sublimation process takes place ensuring slow sublimation of the investigated substance, and the finishing zone in which the inert gas together with the sublimated substance is overheated by 4 to 5 K, controlled by a platinum resistance thermometer. The determined temperature of the air thermostat is kept constant with a precision of 0.01 K by the temperature controller PID type 650 H UNIPAN equipped with a resistance thermometer. The finishing zone is coupled with a condenser built from glass helix, placed outside the thermostat located in a Dewar vessel filled with liquid nitrogen. To avoid humidity adsorption from the air, the condenser is connected to a vessel filled with CaCl₂.

The equipment was tested with benzoic acid. The vapor pressure values were measured in the temperature range of 307–355 K and were consistent with the results of works [15–17] within the limits of experimental error. The standard value of the sublimation enthalpy obtained in our experiments was $\Delta_{\text{cr}}^{\text{g}}H_m^{\text{o}} = 90.5 \pm 0.3 \text{ kJ mol}^{-1}$. This is in good agreement with the value recommended by IUPAC ($\Delta_{\text{cr}}^{\text{g}}H_m^{\text{o}} = 89.7 \pm 0.5 \text{ kJ mol}^{-1}$) [18].

From the experimentally determined pressure–flow rate relationship, the optimal flow rate of 1.2 to 1.8 dm³ h⁻¹ has been revealed. At this flow rate, the saturated vapor pressure is independent of the flow rate and, thus, the thermodynamic equilibrium is realized.

Each experiment was repeated five times at fixed temperature with the standard deviation of up to 5%. At the assumption of independence of the sublimation enthalpy on the temperature the experimentally determined vapor pressure data may be described in the following way:

$$\ln\left(\frac{p}{\text{Pa}}\right) = A + \left(\frac{B}{T}\right) \quad (1)$$

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

$$\Delta_{\text{cr}}^{\text{g}}H_m^{\text{o}}(T) = -R \left(\frac{\partial(\ln p)}{\partial(1/T)} \right) \quad (2)$$

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

$$\Delta_{\text{cr}}^{\text{g}}S_m^{\text{o}}(T) = \frac{(\Delta_{\text{cr}}^{\text{g}}H_m^{\text{o}}(T) - \Delta_{\text{cr}}^{\text{g}}G_m^{\text{o}}(T))}{T} \quad (3)$$

with

$$\Delta_{\text{cr}}^{\text{g}}G_m^{\text{o}}(T) = -RT \ln\left(\frac{p}{p_0}\right), \text{ where } p_0 = 10^5 \text{ Pa.}$$

For the calculation of the standard Gibbs energy of the experimental values of the vapor pressure were extrapolated at 298.15 K. In order to determine the standard enthalpy of sublimation, we estimated the heat capacities ($C_{p,m}^{\text{o}}(\text{cr})$ value) of the crystals using the additive scheme proposed by Chickos et al. [19]. Heat capacity was introduced to adjust the enthalpy of sublimation to the temperature 298.15 K according to the following equation [20]:

$$\begin{aligned} \Delta_{\text{cr}}^{\text{g}}H_m^{\text{o}}(298.15) \\ = \Delta_{\text{cr}}^{\text{g}}H_m^{\text{o}}(T) + (0.75 + 0.15 \cdot C_{p,m}^{\text{o}}(\text{cr})) \cdot (T - 298.15) \end{aligned} \quad (4)$$

2.4. Computational details

The existence of an intramolecular hydrogen bond in 2-pyridinethioamide molecules in gas phase was established by topological analysis of electron density (Bader analysis) [21] using AIM2000 software [22]. The geometry was optimized in MP2/6-311+G** approximation in Gaussian09 package [23]. The starting geometry was taken from crystal structure. Normal mode analysis was performed to confirm that the conformation corresponds to local minimum. In order to quantitatively estimate the strength of hydrogen bond, the correlation the energy of particular non-covalent interaction (E_{int}) with local kinetic energy density in bond critical point (G_b) was used [24]:

$$E_{\text{int}} = 0.429 * G_b \quad (5)$$

3. Results and discussion

Three pyridinecarbothioamides were used as the objects of the research; their molecular structures and thermophysical parameters are shown in Table 2. The melting points of the substances obtained by DSC are in good agreement with the literature data [10,25]. The common elements of these compounds' structure are: a pyridine ring and a thioamide group. Ethionamide is different from 2- and 4-pyridinecarbothioamides as it contains an ethyl-group in

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