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Vapor pressures and sublimation enthalpies of novel bicyclic heterocycle derivatives

Svetlana V. Blokhina [a,*], Marina V. Ol'khovich [a], Angelica V. Sharapova [a], German L. Perlovich [a], Alexey N. Proshin [b]

[a] Institute of Solution Chemistry, Russian Academy of Sciences, 1 Akademicheskaya Street, 153045 Ivanovo, Russia
[b] Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Russia

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ABSTRACT

The vapor pressures of five novel bicyclic heterocycle derivatives were measured over the temperature 341.15 to 396.15 K using the transpiration method by means of an inert gas carrier. From these results the standard enthalpies and Gibbs free energies of sublimation at the temperature 298.15 K were calculated. The effects of alkyl- and chloro-substitutions on changes in the thermodynamic functions have been investigated. Quantitative structure–property relationship on the basis HYBOT physico-chemical descriptors for biologically active compounds have been developed to predict the sublimation enthalpies and Gibbs free energies of the compounds studied.

1. Introduction

Saturated vapor pressure and sublimation thermodynamic parameters are among the most important characteristics of the solid state of organic compounds. Sublimation enthalpy values reflect the degree of molecular interactions in the crystalline state and largely determine the solubility of a substance [1].

The objects of this research are new bicyclic heterocycle derivatives which can be viewed as agents to exhibit antitumoral, neurodegenerative and antioxidant properties [2–4]. The great interest of science to the substances of this class can be explained by their high physiological activity similar to that of natural molecules, for example alkaloids quinine and cytisine [5]. The main goal of this work is to study the influence of the substituents on the sublimation and fusion properties of the alkyl- and chlorine-derivatives [3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine synthesized by us. This work continues our studies of crystal structure, sublimation, solubility and distribution of pharmaceutically relevant drug and drug-like substances [6,7].

2. Experimental

2.1. Materials

We use five novel bicyclic heterocycle derivatives: (3-Methyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**1**); (4-Ethyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**2**); (4-Chloro-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**3**); (3,4-Dihloro-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**4**); (3-Chloro-4-methyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine (**5**). The alkyl- and chloro-derivatives [3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine were synthesized as indicated in scheme 1.

To a stirred solution of 3,4-dichlorophenylisothiocyanate (2.04 g, 10 mmol) and (3-bromomethyl)piperidine hydrobromide (2.56 g, 10 mmol) in 30 ml of methanol a solution of sodium bicarbonate (1.85 g, 22 mmol) in a minimal amount of water was added dropwise. When formation of the precipitate was over, it was filtered and recrystallized from dioxane to yield 2.1 g (70 percent) of the obtained compound as a white solid [8]. The purity of the bicyclic heterocycle derivatives are presented in table 1. The X-ray molecular structure of the compound **4** were determined and their molecular packing in the crystals was revealed [9].

* Corresponding author. Tel.: +7 (4932)351545; fax: +7 (4932)336246.
E-mail address: svb@isc-ras.ru (S.V. Blokhina).

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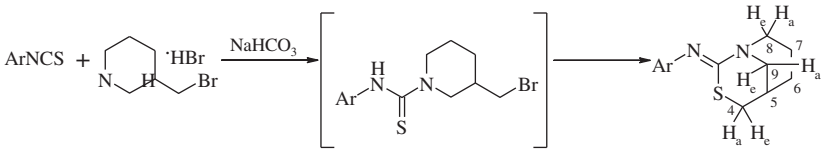

SCHEME 1. Scheme of synthesis of the bicyclic heterocycle derivatives studied.

TABLE 1
Purity of the bicyclic heterocycle derivatives studied.

Chemical name	Mass fraction
(3-Methyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine	>0.98
(4-Ethyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine	>0.98
(4-Chloro-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine	>0.98
(3,4-Dihloro-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine	>0.98
(3-Chloro-4-methyl-phenyl)-[3-thia-1-aza-bicyclo[3.3.1]non-2-ylidene]-amine	>0.98

2.2. Apparatus and procedure

Temperatures and enthalpies of fusion 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 with an indium sample from Perkin–Elmer (P/N 0319–0033). The value determined for the enthalpy of fusion corresponded to 28.48 $J \cdot g^{-1}$ (reference value 28.45 $J \cdot g^{-1}$). The fusion temperature was 429.5 ± 0.1 K (determined from ten 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 the saturation state of the gas with the substance's vapor. Then the vapor was condensed and the sublimed quantity determined. The vapor pressure over the sample at this temperature can be calculated from the amount of sublimed material and the volume of the inert gas used.

Details of the technique are given in the literature [10]. The inert gas (nitrogen) from a tank flows through a column packed with silica to adsorb any humidity from the gas. The stabilization of the gas temperature occurs in a thermostated water bath. The stability of the gas flow with precision better than 0.01 percent is realized by use of a mass flow controller, MKS type 1259CC-00050SU. The inert gas of constant temperature and velocity passes then to a glass tube, which is placed in a temperature controlled air bath. Three zones of the glass tube can be distinguished the starting zone for stabilizing of the inert gas; the transitional zone in which the sublimation process occurs; ensuring slow sublimation of the substance investigated; the finishing zone in which the inert gas together with the sublimed substance is overheated by 4 to 5 K, controlled by a platinum resistance thermometer. The temperature of the air thermostat is kept constant with a precision of 0.01 K by means of the temperature controller, PID type 650 H UNIPAN equipped with a resistance thermometer. The finishing zone is coupled to a condenser built from glass helices, placed (outside the thermostat) located in a Dewar vessel filled with a liquid nitrogen. To avoid adsorption of water from the air, the condenser is connected to a vessel filled with $CaCl_2$.

The equipment was calibrated using benzoic acid. The measured value of the vapor pressure at this apparatus is 0.962 Pa at T = 317.15 K. This value is in good agreement with the literature data: p = 0.99 Pa [11]. The standard value of the sublimation enthalpy obtained was $\Delta^g_{cr}H^o_m$ = 90.5 ± 0.3 $kJ \cdot mol^{-1}$.This is in good agreement with the value recommended by IUPAC ($\Delta^g_{cr}H^o_m$ = 89.7 ± 0.5 $kJ \cdot mol^{-1}$) [12].

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

The saturated vapor pressures were measured five times at each temperature with the standard deviation of no more than 5 percent. Because the saturated vapor pressure of the investigated compounds is low, it may be assumed that the heat capacity change of the vapor with temperature is so small that it can be neglected.

The amount of sublimed substance is determined by following procedure. The condensed substance is dissolved in a defined volume of solvent V_{sol}. The determination of the mass of the substance is based on the measuring of absorbance A of its solution by means of CARY 1E UV–Visible Spectrophotometer, Varian. Knowing a value of the extinction coefficient ε ($dm^3 \cdot mol^{-1} \cdot cm^{-1}$) of the studied compound dissolved in the solvent one can express the concentration of the solution c ($mol \cdot dm^{-3}$) according to the Lambert–Beer law, by the following relation:

$$A = ecl, \tag{1}$$

whereas the mass of sublimed substance is calculated from:

$$m = cV_{sol}M, \tag{2}$$

where l is an absorbing path length; M is a molar mass of studied substance. Considering that the vapor pressure of the substance is very low, the ideal gas rule can be applied:

$$pV_x = nRT, \tag{3}$$

where V_x is a total inert gas volume at temperature T, of the measurement corrected with the thermal expansivity coefficient; R is the gas constant; $n = m/M$ is the number of moles of sublimed substance. The V_x value is calculated from equation (4):

$$V_x/V_{gas} = T/T_r, \tag{4}$$

where T_r is a temperature of the water thermostat, V_{gas} (dm^3) is the gas volume at temperature T_r, calculated by equation (5):

$$V_{gas} = vt, \tag{5}$$

where v (dm^3/h) is a gas flow velocity; t (h) is the sublimation period. Taking into account (2)–(5) we then obtain:

$$P = cV_{sol}V_{gas}RT_r. \tag{6}$$