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Nicotinamides: Evaluation of thermochemical experimental properties

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ABSTRACT

Vapor pressures of the isomeric 2-, 3-, and 4-pyridinecarboxamides were measured by using the transpiration method. The enthalpies of sublimation/vaporization of these compounds at 298.15 K were derived from vapor pressure temperature dependences. The enthalpies of solution of the isomeric pyridinecarboxamides were measured with the high-precision solution calorimetry. The enthalpies of sublimation of 3- and 4-pyridinecarboxamides were independently derived with help of the solution calorimetry based procedure. The enthalpies of fusion of the pyridinecarboxamides were measured by the DSC. Thermochemical data isomeric pyridinecarboxamides were collected, evaluated, and tested for internal consistency. The high-level G4 quantum-chemical method was used for mutual validation of the experimental and theoretical gas phase enthalpies of formation successfully.

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1. Introduction

Nicotinamide (or 3-pyridinecarboxamide) and its isomers: isonicotinamide (4-pyridinecarboxamide) and picolinamide (2-pyridinecarboxamide) are active pharmaceutical ingredients. Each of these compounds is used in formulation of drugs used against Alzheimer's disease, age-related loss of thinking skills, and depression [1]. Thermodynamics of fusion and sublimation is frequently used for prediction of drug solubility [2–4]. However, the available thermochemical data for nicotinamides are in disarray and spread of the literature values *e.g.* for sublimation enthalpy of 3-pyridinecarboxamide and 4-pyridinecarboxamide of 10–13 kJ mol^{-1} makes any reasonable prediction of solubility impossible.

This paper extends our previous work on thermochemistry of amides and compounds with the related functional groups [5,6]. The experimental and computational study of the pyridinecarboxamides presented in Fig. 1 have been performed, aiming at evaluation of the consistent sets of thermochemical data useful for prediction of drugs solubility, as well as for testing of the high-level quantum-chemical methods.

2. Experimental methods

2.1. Compounds and purity controls

Commercial samples of pyridinecarboxamides (Table 1) with the purity 98–99% were additionally purified with fractional sublimation in vacuum. No impurities (greater than 0.001 mass fractions) were detected in samples used for the thermochemical measurements. The degree of purity was determined using a gas-chromatography (GC) with capillary column HP-5 with a column length of 30 m, an inside diameter of 0.32 mm, and a film thickness of 0.25 μm. The standard temperature program of the GC was T = 333 K for 180 s followed by a heating rate of 0.167 K s^{-1} to T = 523 K.

2.2. Transpiration method. Vapor pressure measurements

Absolute vapor pressures of 2-, 3-, and 4-pyridinecarboxamides were measured by using the transpiration method [7–10]. Small glass beads were covered with the sample under study and placed in a U-shaped saturator. A well-defined nitrogen stream was passed through the saturator at a constant temperature (±0.1 K), and the transported material was collected in a cold trap. The amount of the condensed sample was determined by the GC. The vapor pressure p_i at each temperature T_i was calculated from the amount of the material collected within a definite period. Assuming validity of the Dalton's law applied to the nitrogen stream sat-

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