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Melting temperature and heat of fusion of cytosine revealed from fast scanning calorimetry

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ABSTRACT

Thermophysical properties in the melting range of cytosine, one of the five nucleobases of DNA and RNA, are hard to determine because of the low thermal stability of the compound and the high vapor pressure. As for other biomolecules fast heating rates allow melting of cytosine without detectable decomposition. By applying fast scanning calorimetry with the heating rate at 6000 K s^{-1} we succeeded to avoid decomposition and determine the melting temperature of cytosine (extrapolated to zero heating rate), as T_{fus} = (606 ± 4) K, the glass transition temperature of the supercooled liquid state as T_g = (388 ± 3) K, cold-crystallization temperature as T_{cryst} = (448 ± 8) K, and the liquid state molar heat capacity $C^{\circ}_{p,m}(l)$ = (272 ± 2) J mol^{-1} K^{-1} at 423 K. Taking into account the temperature dependent mass loss of the nanogram sized sample (up to 25% during the melting scan) we obtained the molar enthalpy of fusion of cytosine as $\Delta^{l}_{cr}H(T_{fus})$ = (35 ± 4) kJ mol^{-1} in good agreement with the adjusted molar enthalpy of crystallization $\Delta^{cr}_{l}H(T_{fus})$ = (34 ± 2) kJ mol^{-1}.

1. Introduction

Cytosine is a derivative of pyrimidine and one of the four nucleobases which form the main core of Deoxyribonucleic acid (DNA). The four nitro-containing nucleobases cytosine (C), adenine (A), thymine (T) and guanine (G) hold the whole genetic instruction used in growth, development, reproduction and functioning of the organism and even viruses. The particular chemical nature of nucleobases allows for the precise replication of DNA molecules during the cell division process [1–3]. Cytosine, for example, is a relatively small molecule (MW 111.1 g mol^{-1}) however it contains several functional groups (a carbonyl oxygen, primary amine nitrogen, secondary amine ring nitrogen, and a double bonded ring nitrogen), which determine the hydrogen-bonding within its crystal structure [4]. Compounds based on cytosine, such as citicoline [5,6], cytarabine [7,8], and 5-azacytidine [9] have found pharmacological applications. The chemical industry produces a diverse range of pyrimidine derivatives which find application in the pharmaceutical, agrochemical and dye industries [10,11].

Nowadays, computational approaches are widely used for simulation and prediction of the behavior of biological systems starting from small biomolecules [12–15] up to living cell [16,17]. Those thermodynamic data allow for further development and improvement of processes in biopharmaceutical engineering [18–20]. Nevertheless, computational approaches require critical assessments regarding their validity by experimental thermophysical data.

Thermodynamic data on the melting behavior are of high practical importance for the development of pharmaceuticals [18–20]. Modeling approaches were developed for the estimation of melting and solubility properties of organic compounds [21–23]. Such models, however, are only accurate within the range of experimentally studied compounds used for training [24]. Cytosine as a molecule containing several functional groups and as a parent compound for a number of pharmaceutical products therefore represents an important compound indispensable for the model-training datasets.

Cytosine, as other nucleobases, commonly decomposes during melting [25–27]. The thermal properties of cytosine in the liquid state are therefore not available. In fact, thermal studies of cytosine or other biomolecules using slow heating rates are often accompanied by thermal decomposition during melting and possible sublimation/evaporation at high temperatures. These processes are making the

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