Journal of Molecular Structure xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Study of the thermal behavior of choline ibuprofenate using differential scanning calorimetry and hot-stage microscopy

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HIGHLIGHTS

- Two polymorphs with very different thermal behaviors are reported.
- The most stable crystal displays a sharp crystallization and a broad melting.
- A crystal-to-crystal transition was detected on cooling by both DSC and POM.
- Dry [chol][ibu] is thermally stable up to 130 °C without mass loss evidence.

ARTICLE INFO

Article history:
Received 21 October 2013
Received in revised form 22 January 2014
Accepted 11 February 2014
Available online xxxx

Keywords:
Ionic liquids
Phase transformations
DSC
Differential scanning calorimetry
Hot-stage microscopy

ABSTRACT

The phase transformations in choline ibuprofenate, [chol][ibu], have been studied by differential scanning calorimetry (DSC) and hot-stage microscopy (HSM). Two crystalline forms, α and β, were identified that are very different in their thermal behavior, and thus probably very different in their crystal structures. The melting temperatures of the two crystal polymorphs differ as much as 50°. The higher temperature polymorph, α, presents a sharp and fast crystallization process, while the melting transformation displays a very slow dynamics. The β polymorph forms on cooling through a broad crystal-to-crystal transformation, and displays a melting process that is sharp compared with that of α polymorph.

1. Introduction

The behavior of the chemical substances upon crystallization and melting, as observed by differential scanning temperature (DSC), is very diversified [1]. In general, four types of behavior are observed:

1. The substance crystallizes on cooling from the melt (exothermic peak), melts when the crystal is heated up (endothermic peak), the onset temperatures of the two process are very similar, and they are not very dependent on the heating or cooling rate; the enthalpy changes for crystallization and melting are equal in magnitude but opposite in sign, and this corresponds to so-called normal behavior. Examples of this behavior are indium, benzoic acid and caffeine [1].
2. The substance also crystallizes on cooling from the melt and melts when the crystal is heated up, but now the onset temperatures of the two process are different; the onset temperature of the crystallization peak is lower than that of the melting peak, and these temperatures can be markedly different (tens of degrees); the onset of crystallization is variable (even for the same cooling rate) and the shapes of the peaks can also vary; this shows super-cooling, where the melt enters a metastable state at temperatures lower than the melting temperature. Examples of such a behavior are *p*-cresol (or *p*-methylphenol) [1], 1-butyl-2,3-dimethylimidazolium bromide and iodide [2], and 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl) imide [3].
3. In the third type of behavior the substance shows a weak tendency to crystallize on cooling, it is easily supercooled and it is relatively easy to vitrify. After melting, the melt is cooled to a glassy state; on the subsequent heating three features are observed as temperature increases: (a) a glass transition signal, (b) a generally broad exothermic signal that is the result of

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http://dx.doi.org/10.1016/j.molstruc.2014.02.031
0022-2860/

crystallization occurring during the heating cycle, and called "cold crystallization", and (c) the endothermic (melting) signal; the temperature location of this endothermic melting peak can vary as a result of crystal polymorphism. Phenyl salicylate [1] and 1-butyl-3-methylimidazolium bromide [2] display this type of behavior.

4. Finally, some substances show, once melted, a very strong resistance to crystallization. The melt cools without crystallization to form a supercooled liquid that can be molded and stress fractured. No normal means of inducing crystallization, including crystal seeding, are effective in these materials. Only dissolution and re-crystallization yields the crystalline solid. A glass transition signal is observed, but no cold crystallization occurs. This is the behavior found for salicyl salicylate [1], 1-butyl-3-methylimidazolium iodide [2] and 1-propyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [3].

Polymorphism is often observed, and polymorphs convert each other as temperature increases, so that the most stable polymorph is the one that displays an higher melting temperature. Ionic liquids (ILs) also display this wide variety of crystallization and melting behaviors, but no one is known to belong to the type 1 previously described. The observed phase behaviors are often rather complex, and a slow dynamics at the phase changes of several ionic liquids have been frequently observed and reported [4]. As a result, they show characteristic features such as a wide pre-melting range and an excessive supercooling. In the present work we analyze the phase behavior of choline ibuprofenate, [chol][ibu], an ionic liquid (IL) that is also potentially an active pharmaceutical ingredient (API) [5–7]. An interesting feature of this IL is that its phase behavior does not exactly fit to any of the four types previously described. We will use DSC and hot-stage optical spectroscopy in order to try to understand this complex behavior.

2. Experimental

2.1. Materials

The ionic liquid choline ibuprofenate [chol][ibu], molecular weight 307.43 g mol^{-1}, was purchased to Solchemar and has a purity >98%. The molecular structure is shown in Fig. 1.

Dry [chol][ibu] is solid at room temperature and does not display any glass transition signal in the DSC thermogram. However, wet [chol][ibu] can form an amorphous solid by temperature quenching from room temperature down to ~ −80 °C. Depending of the amount of absorbed water, the glass transition temperature was found in the range from −45 °C to −65 °C. Heating up to 120 °C is not sufficient to completely dry the [chol][ibu] samples, and vacuum is required. Furthermore, for precaution, we decided to fill the DSC pans with [chol][ibu] inside a glove box with pure nitrogen (Air Liquide N45) for the experiments described below.

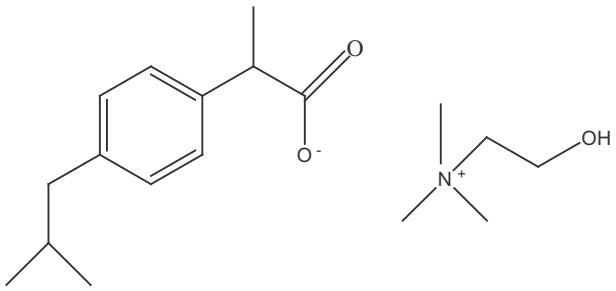

Fig. 1. Chemical structure of the ions in the ionic liquid choline ibuprofenate, [chol][ibu].

2.2. Methods

2.2.1. Conventional differential scanning calorimetry (DSC)

The calorimetric measurements were performed with a 2920 MDSC system from TA Instruments Inc. The samples of ~5–10 mg were introduced in aluminium pans. The measuring cell was continuously purged with dry high purity helium gas at a flow rate of 30 mL min^{-1}. An empty aluminium pan, identical to that used for the sample, was used as the reference. Cooling was achieved with a liquid nitrogen cooling accessory which presents automatic and continuous programmed sample cooling down to −150 °C (123 K). The baseline was calibrated scanning the temperature domain of the experiments with an empty pan. Details of the calibration procedures are given elsewhere [8,9].

2.2.2. Step by step scanning calorimetry

The experimental procedure in the step by step scanning calorimetry is a heating or cooling process composed by successive isothermal steps: the temperature changes, not in a linear ramp, but rather in a stepwise manner, with isothermal stages that alternate with short time heating or cooling stages. The advantage of this experimental procedure is that it allows looking differently to the observed thermal events, and to enhance their details. To facilitate the interpretation of the experimental results we use a sample of benzoic acid as a reference. This substance is often used as a standard in calorimetric investigations because melting behaves as a single step process determined solely by thermodynamic factors. The melting of benzoic acid is a first order thermodynamic transition according to the Ehrenfest classification, it occurs at a definite temperature, and is accompanied by a discontinuous and sharp change in thermodynamic properties such as enthalpy and density. That is why we use it as a reference or standard to discuss the nature of the observed phase transformations. The results of the step by step scanning calorimetry on the melting transformation of benzoic acid have been reported elsewhere [10,11] and are recalled here very briefly.

In the experimental result reported in Fig. 2, one can identify two manifestations of the melting process: (i) isothermal melting, which occurs in each step of the stairs; and (ii) melting on heating, which occurs in the heating process that leads from one step to the next. This melting process that occurs between two successive

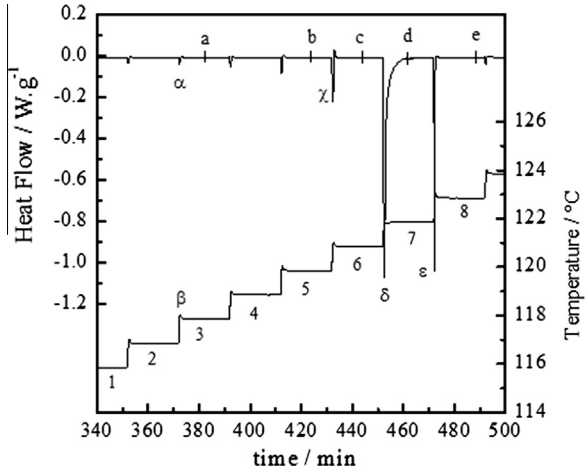

Fig. 2. Melting of benzoic acid obtained in a DSC experiment where the heating process is carried out by successive isothermal steps. The upper line shows the experimental result of the experiment (heat flux as a function of time), while the stair-like line schematically displays the experimental procedure (temperature as a function of time). The temperature at step 1 is 115.9 °C (389.1 K), the temperature jumps are $\Delta T = 1$ K, and the duration of the isothermal steps is $\Delta t = 20$ min. The values of the heat flow in the marked points are as follows: *a* – 0.0077 W g^{-1}; *b* – 0.0078 W g^{-1}; *c* – 0.0087 Wg^{-1}; *d* – 0.0146 W g^{-1} and *e* – 0.0077 W g^{-1}.