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Kinetics of the (solid + solid) transformations for the piracetam trimorphic system: Incidence on the construction of the *p*–*T* equilibrium phase diagram

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ABSTRACT

The three common polymorphs of piracetam have been characterized by associating thermal analysis, X-ray diffraction and densimetry. DSC experiments showed that the (solid + solid) transition temperature between Forms II and I and between Forms III and I is scan-rate dependent. The transition temperatures decrease when the DSC scan rate decreases and the thermodynamic temperatures were confirmed by isothermal X-ray diffraction.

These new results in terms of temperature and enthalpy of transition allow us to propose a new equilibrium phase diagram establishing the relative thermodynamic stability of the three common polymorphs of piracetam as a function of the temperature and the pressure.

The diagram suggests that Form II presents a small stability domain located just above the stability domain of Form I. As a consequence, Form I should transform into Form II, which itself can turn into Form III when placed under pressure.

1. Introduction

Piracetam, $C_6H_{10}N_2O_2$, is a nootropic drug whose chemical name is 2-oxo-1-pyrrolidine acetamide (Scheme 1). It is used as adjunctive therapy against chronic pathological cognitive and neurosensory deficits. This drug is usually administered in solid form.

No less than five polymorphs of this substance have been characterized and subsequently reported in the literature [1–8]. The most commonly studied polymorphic forms are referenced as I, II and III. The first solid form crystallizes in a monoclinic lattice and is the stable form at high temperature [3–7,9–11]. Its melting point is $T = \sim 435$ K. The second and the third polymorphs are reported to crystallize in triclinic and monoclinic systems, respectively [2]. Throughout the literature, there is some conflicting evidence about the stability hierarchy of Forms II and III. However, Form III is the usual commercial sample and this could suggest that this form is the thermodynamically most stable phase under normal conditions of temperature and pressure, as attested by former studies [3,5–11]. However, a previously reported state diagram of piracetam revealed that, due to a measured III–I transition temperature lower than that of the II–I, Form II was the most stable form at ordinary pressures [4]. Moreover, the authors claimed that Form III was a high-pressure phase and that form II could transform into Form III under increased pressure. This statement is thus in contradiction with the fact that Form III was proven to be the most stable form under normal conditions. On this basis, one may wonder what the exact stability hierarchy between Forms II and III is, taking into account the temperature and the pressure effect.

Forms IV and V have been described as high-pressure polymorphs [3,6]. Form IV was obtained by crystallization under high pressure and structurally characterized by *in situ* high-pressure X-ray diffraction [5]. According to these authors, when decreasing the pressure, Form IV undergoes a polymorphic transformation into Form II. As far as Form V was concerned, it was obtained by direct compression of Form II and structurally characterized by *in situ* high-pressure X-ray diffraction [6]. On decreasing the

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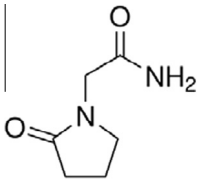

SCHEME 1. chemical structure of piracetam.

pressure, Form V reversibly transforms into Form II. As for Form IV, no data, such as temperature and enthalpy of transition and/or melting, are available.

In the present paper, thermal analyses are coupled with isothermal X-ray diffraction to provide new thermodynamic data regarding the piracetam (solid + solid) transitions, which are proven to be kinetically-dependent. From these new results, new thermodynamic relative stabilities between the three polymorphs I, II and III of piracetam are established as a function of temperature and pressure. This thermodynamic approach describes the equilibrium states between these three polymorphs in a two-dimensional space where pressure and temperature are used as variables. The knowledge of the p–T phase diagram of a substance is particularly important for drugs since external pressure exerted on a drug during tableting may result in polymorphic transformations as well as in changes of physico-chemical properties [12].

2. Experimental

2.1. Chemicals

Piracetam was obtained from Sigma (purity higher than 99.5%) and was used without further purification. N-octadecane with a purity higher than 99% was purchased from Alfa-Aesar. Table 1 reports the purities stated by the supplier for all the materials used in this work.

2.2. Thermal analysis

The differential scanning calorimetry experiments were performed using an 822e thermal analyzer from Mettler-Toledo (Switzerland). Indium and zinc (purity higher than 99.9%, table 1), from Mettler-Toledo, were used for temperature and enthalpy calibration of the DSC device. For all the experiments, an empty aluminum pan was used as a reference. The DSC experiments were carried out at different scan rates from (0.1 to 10) °C·min^{-1} in the T = (300 to 450) K temperature range. Each transition temperature was determined at the onset of the corresponding thermogram signal. Sample masses around 10 mg were used for each experiment and measured with an analytical balance (Mettler Toledo, Switzerland) with an accuracy of ±0.01 mg.

2.3. X-ray powder diffraction

X-ray data collection was performed on a home-made diffractometer with a Rigaku RA-HF18 rotating anode generator (50 kV, 300 mA). The home-made goniometer was set as previously described [13]. Monochromatic Cu Kα1 (λ = 1.54056 Å) radiation was selected by means of a nickel filter. The sample was placed on a cryofurnace (TBT – Air Liquide) with a temperature range between −190 and 210 °C, using liquid nitrogen. Each data scan was recorded between 5° and 60° in 2θ, with a step of 0.02° and a counting time of 1 s per step.

The cryofurnace was calibrated in temperature using a powder sample of Y_2O_3 for which the lattice parameters are known as a function of the temperature [14]. Then, for a given set temperature, the lattice parameters were refined and compared to the lattice parameters obtained at the true temperature. The standard uncertainty on the temperature is estimated to be 0.1 °C.

Cell parameters were obtained by pattern matching using JANA2006 software [15].

2.4. Liquid molar volumes

The molar volume of liquid piracetam was determined as a function of the temperature with a DMA-4500 densimeter coupled with a DMA HP density-measuring cell from Anton-Paar (Austria). Data were collected from T = (420 to 473) K. The standard uncertainty on the temperature is estimated at 0.01 °C. The period oscillation of the measurement cell of the densimeter was calibrated using two reference samples, namely dry air and N-octadecane, as a function of temperature.

3. Results and discussion

3.1. Transition points determination

The commercial sample was first characterized by X-ray powder diffraction (XRPD) performed at T = 300 K. The experimental XRPD pattern was found to fit with that of Form III [2], calculated from single crystal data at T = 300 K (table 2).

The estimated uncertainties on the lattice parameters are standard uncertainties. The standard uncertainty on the temperature is estimated at u(T) = ±0.1 K.

Form III was then heated by DSC at different scan rates from (0.1 to 10) °C·min^{-1}. It was observed that Form III transformed into Form I (figure 1, curve a) at a temperature decreasing from 123.7 °C at 10 °C·min^{-1} to 100.9 °C at 0.1 °C·min^{-1} (table 3). XRPD experiments were performed as a function of the temperature from 27 °C (300 K) to 147 °C (420 K) with a 24-h acquisition time for a given temperature. We observed that Form I began to appear at 97 °C. This value has to be considered as the thermodynamic transition temperature corresponding to the DSC value when scan rate tends to zero.

Randomly, for some experiments carried out by DSC on Form III at 10 °C·min^{-1}, we get a transformation of Form III at a higher temperature, *i.e.* 127.5 °C (figure 1, curve b). This could not be ascribed to a transformation into Form I, the latter occurring at a lower temperature. We therefore hypothesized that this transformation could be the Form III toward Form II transformation, followed by the melting of Form II and recrystallization into Form I.

Interestingly, a direct melting of Form III has been randomly observed by DSC (figure 1 curve c), as previously reported [4],

TABLE 1
Sample purity description.

Component	Source	Mass fraction Purity from supplier	Purification method
Piracetam	Sigma	>0.995	None
N-octadecane	Alfa-Aesar	>0.99	None
Indium	Mettler-Toledo	>0.99999	None
Zinc	Mettler-Toledo	>0.99998	None