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THERMODYNAMIC ANALYSIS OF DSC DATA FOR ACETAMINOPHEN POLYMORPHS

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Abstract

This article provides a thermodynamic analysis of DSC data for acetaminophen polymorphic forms I and II by measurement of heat capacity. Form I is found to have lower heat capacity and free energy and hence better stability than Form II down to at least –30°C. The transition temperature below which Form II becomes more stable was determined to be less than –120°C. Form I is more stable than Form II as a consequence of its higher entropy, since its crystallographic packing arrangement is of larger energy.

Keywords: acetaminophen, heat capacity, physical stability, polymorphism, solid state

Introduction

Acetaminophen exists in three polymorphic forms, but only two of which can be readily isolated. Form I (monoclinic) is the commercially marketed version. Form II (orthorhombic), however, has distinct advantages in its tableting properties due to its plasticity, which enables direct compression without binders [1]. The crystal structures of both forms are known, and Form I [2] does not contain the slip planes present in Form II [3]. Unfortunately, Form II has proven difficult to make on a large scale, although this endeavor is still under investigation and recent advances have transpired [4].

Form II can be easily made on a small scale, either by slow cooling of the Form I melt [5] or by recrystallization [4]. Characterization of the two forms has revealed that Form I is more stable than Form II under ambient temperature conditions. Indeed, the energy-temperature diagram for acetaminophen, which was constructed with minimal data and approximations, suggests that the forms are enantiotropically related and that the transition temperature is near –30°C [6]. In contrast, experiments have determined that Form II crystals stored at –70°C spontaneously converted to Form I [4]. Thus, at this time, the transition temperature for the two forms has proven elusive.

In this article, a thermodynamic analysis of DSC data for both forms is provided to better understand the relative stability of the polymorphic forms. The method in-

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volves measurement of heat capacity from which enthalpy, entropy and free energy are calculated. The point at which the free energy difference between the two forms vanishes provides the transition temperature.

Theory

The molar free energy (G_m) difference between two polymorphic forms at any temperature can be calculated from the equation

$$G_{m,II}-G_{m,I}=H_{m,II}-H_{m,I}-T(S_{m,II}-S_{m,I}) \tag{1}$$

in which H_m, S_m and T are molar enthalpy, molar entropy and temperature, respectively. In turn, the enthalpy and entropy can be calculated from molar heat capacity at constant pressure (c_p) according to

$$\frac{\partial H_m}{\partial T}=c_p \tag{2}$$

$$\frac{\partial S_m}{\partial T}=\frac{c_p}{T} \tag{3}$$

The reference state is selected as the liquid at the melting point of the highest melting form, which in the case of acetaminophen is Form I; the reference temperature is denoted by T_{mI}.

These definitions enable one to derive

$$H_{m,II}(T)-H_{m,I}(T)= \int_{T_{mI}}^{T_{mII}} c_{p,L}\mathrm{d}T+\Delta H_{f,I}-\Delta H_{f,II}-\int_{T_{mI}}^{T} c_{p,I}\mathrm{d}T+\int_{T_{mII}}^{T} c_{p,II}\mathrm{d}T \tag{4}$$

and

$$S_{m,II}(T)-S_{m,I}(T)= \int_{T_{mI}}^{T_{mII}} \frac{c_{p,L}}{T}\mathrm{d}T+\frac{\Delta H_{f,I}}{T_{mI}}-\frac{\Delta H_{f,II}}{T_{mII}}-\int_{T_{mI}}^{T} \frac{c_{p,I}}{T}\mathrm{d}T+\int_{T_{mII}}^{T} \frac{c_{p,II}}{T}\mathrm{d}T \tag{5}$$

in which L is for liquid and ΔH_f is the enthalpy of fusion.

Experimental

Materials

Acetaminophen USP was obtained from Mallinckrodt (Paris, Kentucky) (lot 5543KJKG) at a stated purity of 99.7%. No attempt was made at further purification.

Methods

Heat capacity measurements were made on a DSC (model 2920, TA Instruments, New Castle, DE) with low temperature attachment (Refrigerated Cooling System, TA Instruments) for subambient operation. Three runs were made for each heat capacity experiment: empty pan for baseline determination, sapphire for calibration and sample scans. The general methodology has been previously described [7]. The specific software used for heat capacity calculations in this article was DSC Heat Capacity Program Version 1.2 (TA Instruments). Al hermetic pans and lids were weighed and only those having mass differences within 0.1% tolerance were used in the experiments. All scans were conducted at 10°C min^{-1} with nitrogen purge to minimize oxidative decomposition.

The procedure was as follows. First, the baseline was scanned followed by the sapphire standard (26.265 mg) from –60°C to 200°C. Then Form I (8–10 mg) was heated with the lid off from ambient to 120°C for 5 min to remove residual water. Complete drying of the samples was readily verified by the absence of the water crystallization exotherm upon cooling below 0°C. The lid was hermetically crimped, the sample reweighed and scanned from –60°C to 200°C. After the sample cooled to ambient temperature, which required approximately 30 min, it was scanned to 140°C with an isothermal hold for 5 min to produce pure Form II. The sample was reweighed to ensure no loss of material. Finally, Form II was then scanned from –60°C to 200°C. The entire procedure was repeated 4 times. One sample was assayed by HPLC (UV detection at 244 nm) and no decomposition was observed.

Results

The raw DSC data (heat flow) for Form I, recrystallization and Form II are shown in Fig. 1. The average heat of fusion and melting point for both forms are provided in Table 1.

Table 1 Heat of fusion and melting point for acetaminophen Forms I and II. Errors represent 95% confidence intervals (n=4)

Form	T_m/°C[a]	ΔH_f/kJ mol^{-1}
I	168.6±0.2	28.1±2.2
II	156.4±0.2	27.6±1.2

[a]Extrapolated onset temperature

The average molar heat capacity for Forms I, II and liquid are plotted in Fig. 2. Form I has a lower heat capacity than Form II over the measured range down to –30°C.

Figure 3 shows the thermodynamic functions for acetaminophen as calculated from heat capacity data. The free energy of Form II is higher than that of Form I, as anticipated. The free energy difference between the two polymorphs was extrapolated to provide an estimate of the transition temperature at approximately –165°C. The lower 95% confidence interval curve indicates that the transition temperature may be as high as –120°C, considering error in the measurements.

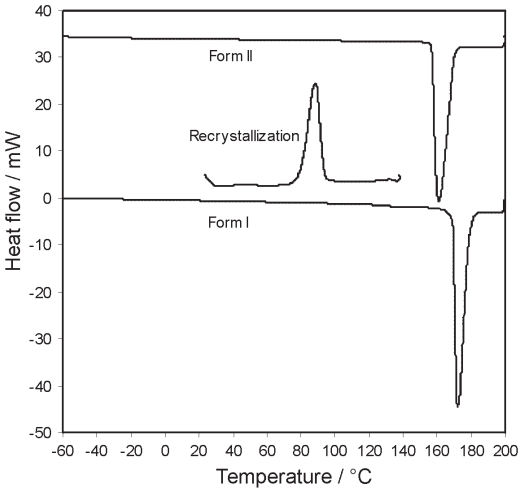

Fig. 1 Raw DSC data (heat flow) for acetaminophen Form I (bottom), annealing of glass to Form II (middle) and Form II (top) scans

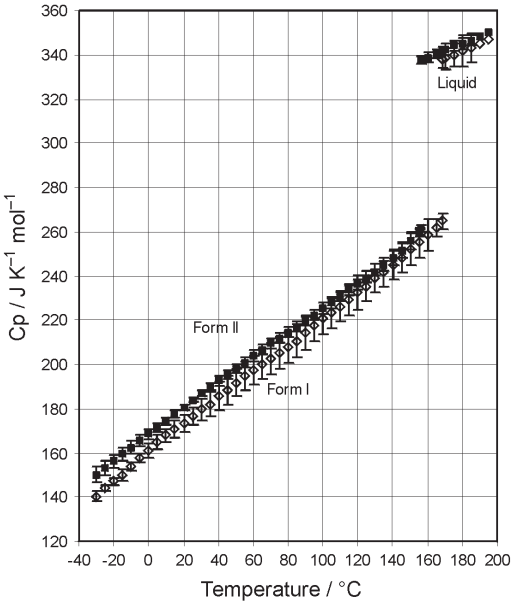

Fig. 2 Average molar heat capacity for acetaminophen Forms I, II and liquid. Error bars represent 95% confidence intervals (n=4)

Figure 3 also provides the enthalpic and entropic breakdown of the free energy. Form II is of lower enthalpy and entropy than Form I. As the temperature is lowered, the enthalpic and entropic differences become more pronounced, which is due to the fact that the heat capacity of Form II remains above that of Form I over the temperature range examined (Fig. 2).

Discussion

The higher heat of fusion of Form I compared to Form II (Table 1) is reflected in its lower heat capacity at temperatures near melting (Fig. 2). This study has determined that Form I's heat capacity is below that of Form II over the entire temperature range covered (Fig. 3).

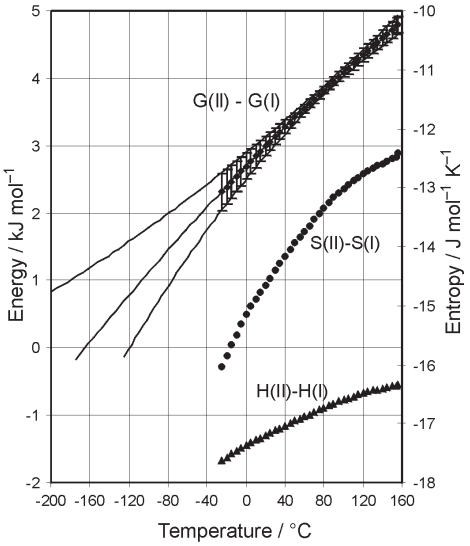

Fig. 3 Molar free energy (top), enthalpy (bottom) and entropy (middle) differences for acetaminophen polymorphs. Error bars for free energy represent 95% confidence intervals (n=4). Average, upper and lower confidence interval curves are extrapolated using second order polynomials

The free energy of Form II is higher than that of Form I down to the lowest temperature examined (–30°C). A solubility estimate from dissolution experiments at 37°C determined that Form II is the more soluble polymorph with a solubility ratio of 1.3 [8], which, neglecting activity corrections, translates to 0.7 kJ mol^{-1} difference in free energy. By comparison to Fig. 3, the free energy difference at 37°C is determined to be 3.2 kJ mol^{-1}. The large discrepancy is not readily explained and would clearly require further experimental work on true equilibrium solubility measurements in a solvent in which no transformation of the solids transpired. It can be stated that if the free energy curve in Fig. 3 were shifted down to 0.7 kJ mol^{-1} at 37°C, the transition point would be estimated as –10°C, which is far above the –70°C value for which Form II spontaneously converted to Form I [4]. Thus, it is believed that the magnitudes of the free energy differences measured in this article are more accurate.

The differences in free energy between the polymorphs diminish with lowering temperature, and are extrapolated to reach zero at –165°C or less than –120°C accounting for error in the measurements of heat capacity, heat of fusion and melting point. Although the data are not sufficiently reproducible to provide a more accurate

estimate of the transition temperature, the results have improved upon a previous estimate of –30°C [6]. Indeed, the results in this report are consistent with the observation that Form II spontaneously converted to Form I at –70°C [4], and suggest that the transition is significantly lower than previously thought.

The enthalpic and entropic contributions to the free energy (Fig. 3) illustrate that the greater stability of Form I is not driven by a lower energy packing arrangement but by higher entropy. The statistical mechanical interpretation is that the packing arrangement in Form I allows for greater degrees of freedom (more eigenstates) in the vibrational motions (intramolecular, intermolecular and lattice). Acetaminophen affords an excellent example of the importance of crystal entropy, which is rarely investigated for pharmaceuticals in comparison to enthalpy.

Conclusions

In general, this work has demonstrated how DSC data can be used to determine relative stability of polymorphs. Specifically, it was found that acetaminophen Form II is of higher free energy than Form I down to at least –30°C. The transition temperature between the two polymorphs is estimated to be less than –120°C. The greater physical stability of Form I is due to its higher entropy, since the enthalpy of its packing arrangement is larger than that of Form II.

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