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POLYMORPHISM OF PARACETAMOL
Relative stability of the monoclinic and orthorhombic phase revisited by sublimation and solution calorimetry

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The thermodynamic relationship between crystal modifications of paracetamol was studied by alternative methods. Temperature dependence of saturated vapor pressure for polymorphic modifications of the drug paracetamol (acetaminophen) was measured and thermodynamic functions of the sublimation process calculated. Solution calorimetry was carried out for the two modifications in the same solvent. Thermodynamic parameters for sublimation for form I (monoclinic) were found: ΔG_{sub}^{298}=60.0 kJ mol^{-1}; ΔH_{sub}^{298}=117.9±0.7 kJ mol^{-1}; ΔS_{sub}^{298}=190±2 J mol^{-1} K^{-1}. For the orthorhombic modification (form II), the saturated vapor pressure could only be studied at 391 K. Phase transition enthalpy at 298 K, ΔH_{tr}^{298} (I→II)=2.0±0.4 kJ mol^{-1}, was derived as the difference between the solution enthalpies of the noted polymorphs in the same solution (methanol). Based on ΔH_{tr}^{298} (I→II), differences between temperature dependencies of heat capacities of both modifications and the vapor pressure value of form II at 391 K, the temperature dependence of saturated vapor pressure and thermodynamic sublimation parameters for modification II were also estimated (ΔG_{sub}^{298}=56.1 kJ mol^{-1}; ΔH_{sub}^{298}=115.9±0.9 kJ mol^{-1}; ΔS_{sub}^{298}=200±3 J mol^{-1} K^{-1}). The results indicate that the modifications are monotropically related, which is in contrast to findings recently reported found by classical thermochemical methods.

Keywords: *paracetamol, phase transition, polymorphism, solution calorimetry, sublimation thermodynamics*

Introduction

Paracetamol (acetaminophen, Fig. 1) is one of the most frequently used antipyretic and analgesic drugs, available both as solid dosage forms (tablets, capsules, suppositories) and as liquids (solutions, suspensions). Therefore, a lot of attention has been paid to the properties of the solid phases. Three crystal modifications have been described in the literature: a monoclinic (form I) [1], an orthorhombic (form II) [2], and an unstable phase (form III), which can only be stabilized under certain conditions (for example between microscopy slide and cover glass) [3–5]. Numerous articles have been published dealing with the determination and refinement of crystal structures of modifications I and II using X-ray [6, 7] and neutron diffraction [8–10], including different temperatures and pressures [11]. It is also worth to mention several studies dedicated to 'in-situ' characterization of the polymorphs by Raman spectroscopy [12], a FT-IR/DSC method [13], and X-ray powder diffraction [14, 15].

The packing architectures of the two considered modifications are essentially different (Fig. 2). In both phases, the molecules in the crystal lattice are packed as sheets, which interact only by Van der Waals forces: the sheets of modification I have a zigzag pattern, whereas for modification II they are much more planar. Within the sheets, the molecules create hydrogen bond networks of approximately analogous topology, which can be described by the following graph set assignments [16]: infinite chains with six involved atoms – C(6). Although being structurally very close to each other, a number of physical properties (e.g. compression behavior, intrinsic dissolution rate) of the modifications are essentially different, which may explain the ongoing interest in this subject.

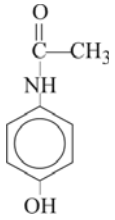

Fig. 1 Structure formula of paracetamol

However, the difference between the crystal lattice energies of the noted modifications is in the same order of magnitude as the experimental errors (i. e. 'isoenergetic' polymorphic modifications), the enthalpy of transition, ΔH_{tr}(II→I), is delicate to estimate, and the experimental values reported in different studies may even differ by the sign (exothermal/endothermal). Examples of such reported values are:

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$\Delta H_{tr}(II \rightarrow I) = 0.6$ kJ mol^{-1} at $T_m(I)$ [5] and $\Delta H_{tr}(II \rightarrow I) = -0.6$ kJ mol^{-1} at $T_m(II)$ [14]. Analysis of literature data reveals that the stability relationship of the considered phases would essentially depend on the ratio between the enthalpic and entropic terms of the Gibbs energy. Moreover, considering that the less stable modification II has the lowest crystal lattice energy (estimation from the thermodynamic cycle of the fusion process Solid(I)→Liquid(I) and Solid(II)→ Liquid(II)), but the higher density in comparison to modification I (see summary of literature data in [14]), the question about the nature of this phase transition remains open. Burger [5], Yu [17], and Sacchetti [18] consider the phases as enantiotropically related, with a phase transition temperature below 263 K. It is still unclear which role defects in the crystal lattices play for the experimental results of nucleation and growth of the new phase. It may be suspected that particularly equilibrium and non-equilibrium defects are among several factors that induce the formation of 'isoenergetic' polymorphic modifications. Moreover, the work of Di Martino *et al.* [19] demonstrates clearly that defects (free volume) in the amorphous state, and the temperature and time interval for their relaxation (ageing process before crystallization) play a very important role in the process of creating the paracetamol modifications. It should be noted that there is a set of calculation studies devoted to prediction of morphology and mechanical properties of the two modifications of paracetamol [20–22], and to the structure solution of the unstable modification III by means of X-ray diffraction experiments from polycrystals in combination with ab initio calculations [23].

In order to find answers to these questions, the present work tries to estimate the nature of the phase transition by alternatives to the classical experimental methods that involve fusion of the crystals: In the present study, the thermodynamics of the sublimation process is studied by the transpiration method at lower temperatures and used as a direct measure of the crystal lattice energy. Enthalpies of dissolution of the respective modifications studied by solution calorimetry are also used for the same purpose.

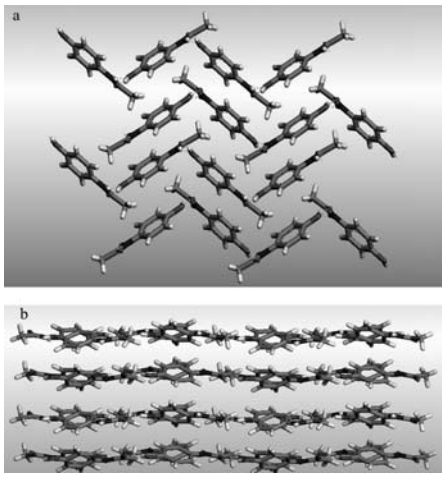

Fig. 2 Packing architectures of paracetamol based on the X-ray data from Nichols *et al.* [6] at 123 K: a – Form I and b – Form II

Experimental

Materials

Paracetamol (Acetaminophen, $C_8H_9NO_2$, FW 151.16, Lot A 7085) was purchased from Sigma Aldrich Inc. (www. sigmaaldrich.com). Methanol (MeOH, CH_3OH, FW 32.04) HPLC grade, lot K27636907 was from Merck (Darmstadt, Germany).

Preparation of modification I

The monoclinic phase was obtained as follows: a saturated aqueous solution was prepared at boiling temperature and left at 313 K for 24 h. For identification of the dried crystals, two independent methods were used, namely DSC and single crystal X-ray diffraction experiments. Parameters of the unit cell derived by X-ray diffraction (single crystals) agreed with the values of the monoclinic modification [1]. For further experiments, the crystals were carefully powdered (using mortar and pestle). Temperatures and enthalpies of fusion obtained by DSC correspond to the monoclinic form. DSC measurements were carried out up to the melting point with open crucibles in order to check for traces of remaining original solution – which may be incorporated into the crystals during crystal growth as mentioned in [6, 28]). Mass loss was not observed, confirming dry and pure samples.

Preparation of modification II

In order to prepare homogenous polycrystals of polymorph II for the solution calorimetry experiments, the following procedure was used: 1) The crystals of modification I were put into a DSC sample pan and heated in the DSC in an inert gas atmosphere with a heating rate of 10 K min^{-1} up to 5 K above the temperature at which the heat effect of fusion ended; 2) Thereafter, the melt was cooled at a cooling rate of 80 K min^{-1} down to 258 K, and the amorphous material yielded was equilibrated for 5 min; 3) As a next step, the sample was re-heated with a heating rate of 10 K min^{-1} to a temperature of 5 K above the temperature of the end of the exothermic peak connected with crystallization of phase II from the amorphous state (353–358 K); 4) The freshly prepared phase II was cooled down at 40 K min^{-1} to room temperature, powdered carefully (using a spatula,

in order to avoid phase transition, which was observed in cases where mortar and pestle were used) and immediately transferred to the ampoule for the solution calorimetry experiment. It should be mentioned that during handling phase II, the material was carefully protected from moisture in order to prevent phase transition II→I [6]. The preparation scheme described leads to nucleation and growth of phase II from the amorphous phase. In order ensure purity of form II, we used a DSC method to verify the melting point, which completely coincided with literature data.

Methods

Sublimation experiments were carried out by the transpiration method as described previously [24]. In brief: a stream of an inert gas passes above the sample at a given constant temperature and at a known slow constant flow rate in order to achieve saturation of the carrier gas with the vapor of the substance under investigation. The vapor is condensed at some point downstream, and the mass of sublimate and its purity are determined. The vapor pressure over the sample at this temperature can be calculated from the amount of sublimated material and the volume of the inert gas used.

The equipment was calibrated using benzoic acid. The standard value of sublimation enthalpy obtained was ΔH^0_{sub}=90.5±0.3 kJ mol^{-1}. This is in good agreement with the value recommended by IUPAC of ΔH^0_{sub}=89.7±0.5 kJ mol^{-1} [25]. The saturated vapor pressure values were measured at least 5 times at each given temperature, with the standard deviation between samples being within 3–5%. The experimentally determined vapor pressure data were described in (ln$P$; 1/T) co-ordinates by Eq. (1):

$$\ln P = A + B/T \quad (1)$$

The value of the enthalpy of sublimation is calculated by the Clausius-Clapeyron equation:

$$\Delta H^T_{sub} = -R\partial(\ln P)/\partial(1/T) \quad (2)$$

The entropy of sublimation at a given temperature T was calculated from the following relationship:

$$\Delta S^T_{sub} = (\Delta H^T_{sub} - \Delta G^T_{sub})/T \quad (3)$$

where $\Delta G^T_{sub} = -RT\ln(P/P_0)$ and P_0=1.013·10^5 Pa.

The absence of chemical degradation of the investigated paracetamol was proven by the absorption spectrum of the sublimate and the substances in the cell (after each cycle of the heating-cooling procedure). No traces of degradation were found (no additional peaks, and no change in extinction coefficients).

Differential scanning calorimetry (DSC) was carried out using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin Elmer Analytical Instruments, Norwalk, Connecticut, USA) and Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing (20 mL min^{-1}) dry nitrogen gas of high purity 99.990% using standard closed aluminum sample pans. The DSC was calibrated with indium from Perkin-Elmer (*P*/*N* 0319–0033). The value of the determined enthalpy of fusion corresponded to 28.48 J g^{-1} (reference value 28.45 J g^{-1}). The melting point was 429.7±0.1 K (n=10). All the DSC-experiments were carried out at a heating rate of 10 K min^{-1}. The accuracy of mass measurements was ±0.005 mg.

Solution calorimetry

Enthalpies of solution at a concentration m(ΔH^m_{sol}) were measured using a Precision Solution Calorimeter in the 2277 Thermal Activity Monitor Thermostat (both from Thermometric AB, Järfälla, Sweden). The software SolCal Version 1.2 (Thermometric) was applied to all calculations. The temperature of the measurements was 298±10^{-4} K, volume of the vessel 100 mL, stirrer speed 500 rpm and the mass of the respective samples approximately 40 mg each. To prepare this amount of phase II, large DSC pans (50 μL volume) were used, and material collected from several repeated DSC cycles as described above. The time consumed by one complete procedure from filling the ampoule until the end of the experiment was approximately 2 h. The accuracy of mass measurements corresponded to ±0.005 mg. Seven consecutive runs were carried out for each crystal modification. The calorimeter was calibrated using KCl (analytical grade >99.5%, from Merck) in water in a wide concentration interval with more than 10 measurements. The standard value of solution enthalpy obtained was ΔH^0_{sol}=17225±50 J mol^{-1}. This is in good agreement with the value recommended by IUPAC of ΔH^0_{sol}=17217±33 J mol^{-1} [25].

Results and discussion

Sublimation experiments

The temperature dependency of the saturation vapor pressure of modification I is presented in Table 1. Some thermodynamic characteristics of sublimation, fusion and vaporization processes of this polymorphic phase are summarized in Table 2.

Due to instability of modification II, the measurement of vapor pressure *vs.* temperature could not be carried out in the same way as for modification I, but was studied by an alternative method. In order to estimate the sublimation characteristics of modification II, a temperature of 391 K was chosen because a measurement at this temperature takes approximately

20 min, which is optimum with respect to representative sampling, minimum experimental error and reasonable throughput.

A typical experiment was carried out as follows: Modification I was loaded into the measurement cell, and during the entire experiment maintained in an inert atmosphere (nitrogen gas of high purity 99.990%). This was controlled very carefully to protect the material against degradation. Thereafter, the cell was heated to 453 K, equilibrated for 5 min until all material was molten (where the construction of the equipment enables one to check this). Then the cell was cooled down to room temperature and left until modification II crystallized (where during crystallization the clear amorphous substance blinded which was observed visually). When the crystallization was finished, the sublimation experiment was started at 391 K. The reproducibility of the vapor pressure values at the beginning of each of the sublimation experiments confirmed that any possible leftovers of the amorphous state in modification II transformed quickly to phase II during the heating up to 391 K; moreover, no glass transition was observed during additional DSC experiments of part of the substance in the sublimation cell (after cooling down from the melting temperature). After finished sublimation experiment, the cell was cooled to room temperature and the same measurement repeated after 12 h using the very same material. At least 8 independent experiments were carried out. Results of the experiments are presented in Fig. 3.

The cycles of experiments showed that after 60 h, the saturated vapor had decreased by a factor of four, and this particular value coincides (within experimental error) with the vapor pressure of modification I at the same temperature (Table 1). The next step was to heat the cell again to 453 K, melt the remaining material and prepare phase II similarly to the procedure used in the beginning of the experiment. The saturated vapor pressure value of the newly prepared phase was the same (within experimental error) as obtained the first time (Fig. 3).

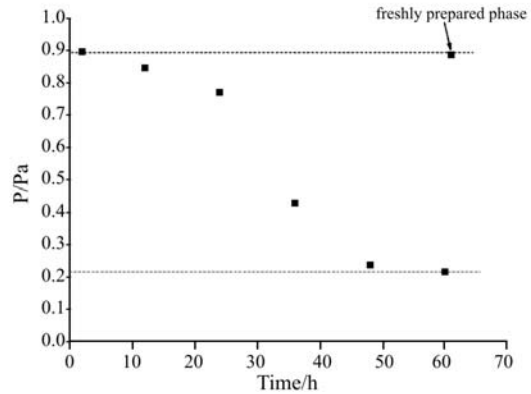

Fig. 3 Vapor pressure *vs.* time of the polymorphic Form II of paracetamol (for experimental details see text)

Table 1 Temperature dependencies of saturation vapor pressure of paracetamol (Form I)

Paracetamol I	
T/K	*P*/Pa
355.2	$6.10 \cdot 10^{-3}$
359.2	$9.28 \cdot 10^{-3}$
367.7	$2.13 \cdot 10^{-2}$
370.7	$3.02 \cdot 10^{-2}$
377.2	$5.78 \cdot 10^{-2}$
379.2	$7.07 \cdot 10^{-2}$
386.7	$1.50 \cdot 10^{-1}$
389.7	$1.92 \cdot 10^{-1}$
392.2	$2.42 \cdot 10^{-1}$
394.2	$3.01 \cdot 10^{-1}$
396.7	$3.64 \cdot 10^{-1}$

$\ln(P[\text{Pa}])=(34.3\pm0.2)-14010\pm86)/T$
$\sigma=2.76 \cdot 10^{-2}$; $r=0.9998$, $F=26517$; $n=11$

The data presented in Fig. 3 indicate that modification II is not stable but consecutively transfers to modification I. Upon melting and recrystallization, modification II is yielded again. This indicates that there are no problems regarding chemical stability of the studied material during the entire experiment. The difference of Gibbs energies of the phases can be directly calculated from the differences in vapor pressure at the given temperature:

$$\Delta G_{\text{sub}}^{391}(\text{I}\rightarrow\text{II}) = RT\ln(P^{\text{II}}/P^{\text{I}}) = 4600\pm300 \text{ J mol}^{-1} \quad (4)$$

However, if the Gibbs energy of transition is estimated using fusion characteristics taken from the literature (as presented in Table 2) and Eq. (5):

$$\Delta G^{\text{i}} = \Delta H_{\text{fus}}^{\text{i}}(T_{\text{m}}^{\text{i}} - T)T_{\text{m}}^{\text{i}} \quad (5)$$

where *i*=I, II, the Gibbs energy of transition at the same temperature calculates to $\Delta G^{391}(\text{I}\rightarrow\text{II})=$ 830 J mol^{-1}. The two values differ essentially from each other by approximately a factor of 5. The classical method is the fusion method, which may be regarded experimentally easier, but it may also be regarded less accurate since the actual measurement takes place at higher temperatures and the calculation is an extrapolation to another temperature (where probably the association states of the molecules in the melt are slight different at various temperatures).

Solution calorimetry experiments

For the calorimetric experiments, a sample mass (approx. 40 mg, accurately weighed) was used to make a concentration of approx. $3 \cdot 10^{-3}$ mol kg^{-1}.

Table 2 Thermodynamic characteristics of sublimation, fusion and vaporization processes of the two forms of paracetamol

	ΔG_{sub}^{298}[a]/ kJ mol^{-1}	ΔH_{sub}^{T}/ kJ mol^{-1}	ΔH_{sub}^{298}/ kJ mol^{-1}	$C_{p_c}^{298}$/ J mol^{-1} K^{-1}	ΔS_{sub}^{298} J mol^{-1} K^{-1}	T_m/ °C	ΔH_{fus}/ kJ mol^{-1}	ΔH_{fus}^{298}[i]/ kJ mol^{-1}	ΔS_{fus}[e]/ J mol^{-1} K^{-1}	ΔH_{vap}^{298}[f]/ kJ mol^{-1}
Paracetamol I	60.0	116.5±0.7[b]	117.9±0.7[c]	163±1	190±2	169.0±0.2[d]	28.0±0.2[d]	18.9	63.3±0.6	99.0
Paracetamol II	56.1[j]		115.9±0.9[h]		200±3	157.0±0.2[d]	26.5±0.2[d]	18.4	61.6±0.6	97.5

[a]$\Delta G_{sub}^{298} = -298.15\ RT \ln(P^{298}/P_0)$, where P_0=101300 Pa;

[b]without correction;

[c]with correction on ΔC_p [29]: $\Delta H_{cor}=(C_{p_c}-C_{p_g})(T-298)=(0.75+0.15\ C_{p_c}^{298})(T-298)$, where C_{p_c} and C_{p_g} are heat capacities crystal and gas phase, correspondingly; $\Delta H_{sub}^{298}=\Delta H_{sub}^{T}+\Delta H_{cor}$;

[d]Ref. [12] (obtained by us data correspond within the experimental errors with Ref. [12] data);

[e]$\Delta S_{fus}=\Delta H_{fus}/T_m$;

[f]$\Delta H_{vap}^{298}=\Delta H_{sub}^{298}-\Delta H_{fus}^{298}$;

[h]$\Delta H_{sub}^{298}(II)=\Delta H_{sub}^{298}(I)-\Delta H_{tr}^{298}(II\rightarrow I)$, where ΔH_{tr}^{298} (II→I) obtained by the solution calorimetry (see text);

[i]$\Delta H_{fus}^{298}=\Delta H_{fus}-\Delta S_{fus}(T_m-298)$;

[j]estimated from $\ln P^{II}=34.9-(13714\pm109)/T$

The energy difference of the crystal lattices was estimated from the difference in solution enthalpies obtained by dissolution in the same solvent (in this case MeOH). We have used this approach earlier for measuring differences of modifications of respectively cimetidine and glycine [26, 27]. Methanol as a solvent was chosen in the present study, because the drug under investigation dissolves well with a large endothermic heat effect. The results of the calorimetric experiments are presented in Table 3.

Table 3 The solution enthalpies, ΔH^{m}_{sol}, of the different polymorphic forms of paracetamol at 298 K

	Form I		Form II	
Run	g/ mg	ΔH^{m}_{sol}/ kJ mol^{-1}	g/ mg	ΔH^{m}_{sol}/ kJ mol^{-1}
1	42.401	13.9	41.245	11.9
2	43.445	13.6	42.567	11.7
3	41.482	13.9	43.026	12.2
4	42.034	13.9	42.875	12.1
5	43.423	13.8	40.365	11.7
6	43.211	14.0	43.896	11.9
7	42.537	14.2	42.478	12.1
	ΔH^{m}_{sol}	13.9±0.2	ΔH^{m}_{sol}	11.9±0.2

From the data in Table 3 follows, that the crystal lattice energy at 298 K for modification I is higher by 2000±400 J mol^{-1} than for modification II.

Using the above mentioned enthalpy values and the Gibbs energy values, the change in entropy during phase transition (I→II) at 391 K can be estimated:

$$\Delta G^{391}_{tr}(\text{I}\rightarrow\text{II}) = \Delta H^{391}_{tr}(\text{I}\rightarrow\text{II}) - T\Delta S^{391}_{tr}(\text{I}\rightarrow\text{II}) \quad (6)$$

In order to correct the ΔH^{298}_{tr}-value for T=391 K, Sacchetti's data on heat capacity were used [18]: $\Delta C_p = C_p(\text{II}) - C_p(\text{I})$=5 J mol^{-1} K^{-1}. The ΔH^{298}_{tr}-value of 2000 J mol^{-1} is thereby corrected to ΔH^{391}_{tr}= 2465±400 J mol^{-1}, and $\Delta S^{391}_{tr}(\text{I}\rightarrow\text{II})$= –5.5 J mol^{-1} K^{-1}. Thus, the entropy decreases at phase transition I→II, which is in a good agreement with X-ray and densimetric data (for a summary of the data see reference [14]). Moreover, the ratio $\Delta S^{391}_{tr}(\text{I}\rightarrow\text{II})/\Delta S_{sub}(\text{I})$ is approximately 3%, and this value is in a good agreement with the density values [6]: $(d(\text{II})-d(\text{I}))/d(\text{I})\cdot 100\%$=3.4%).

Comparison of sublimation and solution calorimetry experiments with fusion methods

In order to better understand the thermodynamic relationship between the phases under study, the vapor pressure – temperature dependency of modification I (Table 1, Eq. (7)), the vapor pressure value of modification II at 391 K, and the ΔH^{298}_{tr}-value inferred from solution calorimetry experiments and corrected for heat capacity (Table 3) were used to calculate the vapor pressure dependency on temperature for modification II (Eq. (8)):

$$\ln P^{\text{I}} = (34.3\pm0.2) - (14010\pm86)/T \quad (7)$$

$$\ln P^{\text{II}} = 34.9 - (13714\pm109)/T \quad (8)$$

From the two equations (Eqs (7) and (8)), the phase transition temperature can be calculated and the result is a virtual temperature below 0 K (under the assumption that the difference in heat capacity $\Delta C_p = C_p(\text{solid}) - C_p(\text{gas})$ is temperature-independent). As the vapor pressure is a direct measure of the Gibbs energy of the phases at a given temperature, the value found would indicate that the polymorphic modifications I and II are monotropically related. This is in good agreement with the thermodynamic rules of polymorphic transition according to Burger and Ramberger [4].

However, as has been shown by Sacchetti [18], the difference between the heat capacity values of the two forms $\Delta C_p = C_p(\text{II}) - C_p(\text{I})$ in the temperature interval from 233 K up to the melting point is in the range between 5 and 10 J mol^{-1} K^{-1} (taking experimental errors into account). Based on the thermodynamic functions of the polymorphic modifications obtained in the present study and using Sacchetti's data [18], it is possible to estimate the relative stability of the polymorphic forms in a wide temperature interval. The results of the calculations are presented in Fig. 4, where filled symbols indicate the thermodynamic functions $\Delta Y_{tr}(\text{I}\rightarrow\text{II})$ for ΔC_p=5 J mol^{-1} K^{-1}, and hollow symbols the same for ΔC_p=10 J mol^{-1} K^{-1}, as the two extreme cases.

As follows from Fig. 4, ΔH_{tr} and ΔG_{tr} values are positive for ΔC_p=5 J mol^{-1} K^{-1} in the entire temperature range, whereas the entropic term, $T\Delta S_{tr}$, is negative. This fact confirms once more that the outlined polymorphic modifications are connected monotropically. Only if the largest ΔC_p-value is used as the extreme case (ΔC_p=10 J mol^{-1} K^{-1}), this relationship would change. For example, at ΔC_p=10 J mol^{-1} K^{-1}, the ΔH_{tr}-function changes the sign from a negative to a positive value at T≈105 K, whereas at T≈24 K the entropic term is equal to the enthalpic one (in absolute scale), the ΔG_{tr} function passes through zero, and enantiotropic phase transition would be the consequence. Therefore, the analysis and conclusion connected with the nature of the phase transition is very sensitive to the accuracy of the heat capacity experiments. It is important to note that it is difficult to experimentally measure equilibrium C_p-values for the two forms, which is due to several reasons: a) it is delicate to prepare single crystals of form II without any

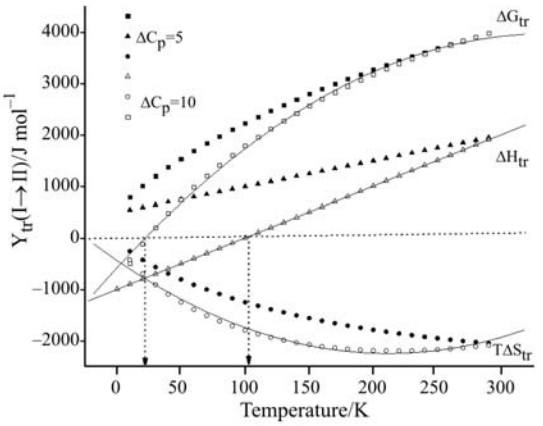

Fig. 4 Temperature dependencies of the thermodynamic functions of I→II polymorphic form transition, ΔY_{tr}(I→II), based on our and on Sacchetti's data. The solid symbols correspond to the thermodynamic functions ΔY_{tr}(I→II) for ΔC_p=5 J mol^{-1} K^{-1}, and hollow symbols are for ΔC_p=10 J mol^{-1} K^{-1}

defects and imperfections, e.g. inclusions of solvent molecules [28]; b) it is not easy to exclude poor contact between the single crystal and crucibles in the DSC experiment; c) it is difficult to achieve a thermodynamic equilibrium of defects of the crystals at low temperatures (in this case the interpretation of the results is disturbed by kinetic artifacts).

Despite of the modifications most probably being related monotropically, phase transition II→I has actually been observed in some cases (e.g. [28]). These are not necessarily connected to enantiotropy: as the phases are not always in their thermodynamically ideal equilibrium state and other factors (e.g. presence of moisture, impurities, water inclusions in the crystal of phase II during crystallization) [6, 28] may activate the materials and thereby enable a phase transition below the (ideal) temperature of fusion. Taking this into account, assumptions made by other authors about phase transition taking place at temperatures around 200 K [17], lower than 263 K [5], or lower than 150 K [18], may nevertheless be connected to monotropic relationship. Moreover, in other cases, no phase transition at low temperatures, neither by X-ray [6, 7] nor by neutron diffraction [8–10] was observed.

The inconsistency mentioned above, however, may be the consequence of experimental errors. Therefore, the effect of experimental errors in the data for enthalpy of fusion ΔH_{fus} and for the melting temperatures T_m on the calculation of the temperature of phase transition was estimated, using the well-known and often used Eq. (9):

$$T_{tr} = (\Delta H^{I}_{fus} - \Delta H^{II}_{fus})/(\Delta H^{I}_{fus}/T^{I}_{m} - \Delta H^{II}_{fus}/T^{II}_{m}) \quad (9)$$

Experimental errors for the fusion enthalpies of ±0.2 kJ mol^{-1}, and ±0.2 K for the melting points were added to the respective values from the literature [12]. The results of calculation are presented in Fig. 5.

The results indicate in all cases, irrespective of the experimental error, a monotropic relationship. For the actual value of the temperature of the virtual transition calculated, the accuracy of the melting point temperatures for both phases have comparably little influence (as seen from the tilting of the layers in the graphs in Fig. 5), whereas enthalpies of fusion both of phase I (difference between the three graphs in Fig. 5) and of phase II (difference between three layers in each

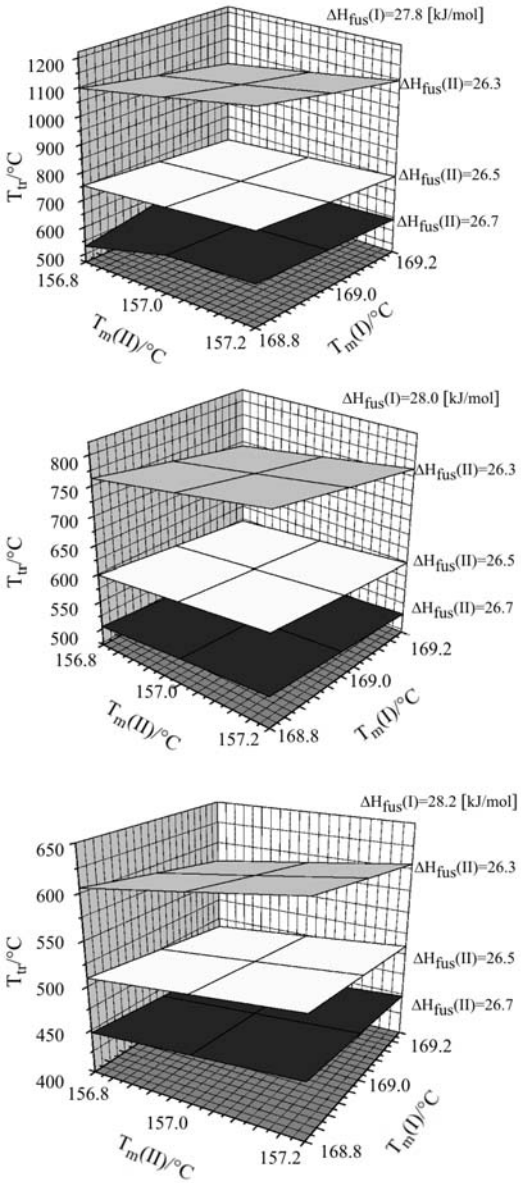

Fig. 5 Calculation results of influence of the experimental errors of ΔH_{fus} and T_m-values on the calculated phase transition temperature, T_{tr} (a – ΔH^{I}_{fus}=27.8; b – ΔH^{I}_{fus}=28.0; c – ΔH^{I}_{fus}=28.2 kJ mol^{-1})

graph) are much more important. With regard to the experimental difficulties one faces when measuring the enthalpy of fusion in the DSC caused by particle sizes, packing properties of powder samples in the sample pans, contact area between sample and pan etc., the calculated T_{tr}-values are even less reliable. Particularly, the closer the values for two modifications are to each other ('isoenergetic' polymorphs), the less accurate the calculation is. In the present case, the calculated transition temperature T_{tr} varies by more than 500 K (from 833 to 1423 K) if ΔH^{II}_{fus} is changed from 26.3 to 26.7 kJ mol^{-1} (while keeping ΔH^{I}_{fus}= 27.8 kJ mol^{-1} constant). This provides good arguments for giving preference to estimate phase transition enthalpy by solution calorimetry rather than by DSC.

Conclusions

For the monoclinic polymorphic modification (form I) of paracetamol (acetaminophen) temperature dependence of saturated vapor pressure can be measured in a wide temperature interval and allows us to calculate thermodynamic functions of the sublimation process. However, for the orthorhombic modification (form II), this can only be studied at one single temperature (391 K). Phase transition enthalpy at 298 K, ΔH^{298}_{tr}(I→II)=2.0±0.4 kJ mol^{-1}, was derived as a difference between the solution enthalpies of the polymorphs in the same solution (methanol). Based on ΔH^{298}_{tr}(I→II), differences between temperature dependencies of heat capacities of both the modification and the vapor pressure value of form I at 391 K, the temperature dependence of saturated vapor pressure and thermodynamic sublimation parameters for modification II were also estimated (ΔG^{298}_{sub}=56.1 kJ mol^{-1}; ΔH^{298}_{sub}=115.9±0.9 kJ mol^{-1}; ΔS^{298}_{sub}=200±3 J mol^{-1} K^{-1}). The results indicate a monotropic relationship, as do previously reported fusion experiments, although the latter are much more sensitive to experimental errors.

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References

1 M. Haisa, S. Kashino, R. Kawai and H. Maeda, Acta Cryst. B., 32 (1976) 1283.
2 M. Haisa, S. Kashino and H. Maeda, Acta Cryst. B., 30 (1974) 2510.
3 P. Di Martino, P. Conflant, M. Drache, J. P. Huvenne and A. M. Guyot-Hermann, J. Therm. Anal. Cal., 48 (1997) 447.
4 A. Burger and R. Ramberger, Microchim. Acta, (Wien) II, (1979) 273.
5 A. Burger, Acta Pharm. Technol., 28 (1982) 1.
6 G. Nichols and C. S. Frampton, J. Pharm. Sci., 87 (1998) 684.
7 D. Y. Naumov, M. A. Vasilchenko and J. A. K. Howard, Acta Cryst., C 54 (1998) 663.
8 C. C. Wilson, Chem. Phys. Lett., 280 (1997) 531.
9 C. C. Wilson, N. Shankland, A. J. Florence and C. S. Frampton, Physica B, 234-236 (1997) 84.
10 C. C. Wilson, J. Mol. Struc., 405 (1997) 207.
11 E. V. Boldyreva, T. P. Shakhshneider, H. Ahsbahs, H. Sowa and H. Uchtmann. J. Therm. Anal. Cal., 68 (2002) 437.
12 M. Szwlagiewicz, C. Marcolli, S. Cianferani, A. P. Hard, A. Vit, A. Burkhard, M. von Raumer and U. C. Hofmeier, J. Therm. Anal. Cal., 57 (1999) 23.
13 S. Y. Lin, S. L. Wang and Y. D. Cheng, J. Phys. Chem. Solids, 61 (2000) 1889.
14 P. Espeau, R. Ceolin, J. L. Tamarit, M. A. Perrin, J. P. Gauchi and F. Leveiller, J. Pharm. Sci., 94 (2005) 524.
15 A. Rossi, A. Savioli, M. Bini, D. Capsoni, V. Massarotti, R. Bettini, A. Gazzaniga, M. E. Sangalli and F. Giordano, Thermochim. Acta, 406 (2003) 55.
16 M. C. Etter, Acc. Chem. Res., 23 (1990) 120.
17 L. Yu, J. Pharm. Sci., 84 (1995) 966.
18 M. Sacchetti, J. Therm. Anal. Cal., 63 (2001) 345.
19 P. Di Martino, G. F. Palmieri and S. Martelli, Chem. Pharm. Bull., 48 (2000) 1105.
20 T. Beyer, G. M. Day and S. L. Price, J. Am. Chem. Soc., 123 (2001) 5086.
21 S. L. Price, Advanced Drug Deliv. Rev., 56 (2004) 301.
22 B. A. Hendriksen, D. J. W. Grant, P. Meenan and D. A. Green, J. Cryst. Growth, 183 (1998) 629.
23 M. L. Peterson, S. L. Morissette, C. McNulty, A. Goldsweig, P. Shaw, M. LeQuesne, J. Monagle, N. Encina, J. Marchionna, A. Johnson, J. Gonzalez-Zugasti, A. V. Lemmo, S. J. Ellis, M. J. Cima and O. Almarsson, J. Am. Chem. Soc., 124 (2002) 10958.
24 W. Zielenkiewicz, G. Perlovich and M. Wszelaka-Rylik, J. Therm. Anal. Cal., 57 (1999) 225.
25 J. D. Cox and G. Pilcher, Thermochemistry of organic and organometallic compounds, Academic Press, London, 1970.
26 A. Bauer-Brandl, E. Marti, A. Geofrey, A. Poso, J. Suurkuusk, E. Wappler and K. H. Bauer, J. Therm. Anal. Cal., 57 (1999) 7.
27 G. L. Perlovich, L. K. Hansen and A. Bauer-Brandl, J. Therm. Anal. Cal., 66 (2001) 699.
28 E. V. Boldyreva, V. A. Drebushchak, I. E. Paukov, Y. A. Kovalevskaya and T. N. Drebushchak, J. Therm. Anal. Cal., 77 (2004) 607.
29 J. S. Chickos, S. Hosseini, D. G. Hesse and J. F. Liebman, Struct. Chem., 4 (1993) 271.

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