Journal of Thermal Analysis and Calorimetry, Vol. 77 (2004) 607–623

DSC AND ADIABATIC CALORIMETRY STUDY OF THE POLYMORPHS OF PARACETAMOL
An old problem revisited

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Abstract

Monoclinic (I) and orthorhombic (II) polymorphs of paracetamol were studied by DSC and adiabatic calorimetry in the temperature range 5 – 450 K. At all the stages of the study, the samples (single crystals and powders) were characterized using X-ray diffraction. A single crystal →polycrystal II→ I transformation was observed on heating polymorph II, after which polymorph I melted at 442 K. The previously reported fact that the two polymorphs melt at different temperatures could not be confirmed. The temperature of the II→I transformation varied from crystal to crystal. On cooling the crystals of paracetamol II from ambient temperature to 5 K, a II→ I transformation was also observed, if the 'cooling-heating' cycles were repeated several times. Inclusions of solvent (water) into the starting crystals were shown to be important for this transformation. The values of the low-temperature heat-capacity of the I and II polymorphs of paracetamol were compared, and the thermodynamic functions calculated for the two polymorphs.

Keywords: adiabatic calorimetry, DSC, polymorphs of paracetamol

Introduction

Paracetamol is an important analgesic and antipyretic drug that is used worldwide in the manufacture of many millions of tablets and other dosage forms every year. Three polymorphs were described for paracetamol [1], for two of them – the monoclinic (I) and the orthorhombic (II) ones – crystal structures were first solved by Haisa *et al.* [2, 3], and later repeatedly refined by several authors under various conditions [4–8]. There is enormous interest in the polymorphs of paracetamol in the literature. This interest can be ex-

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1388–6150/2004/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

plained by practical needs – in contrast to the stable polymorph I, the metastable polymorph II can be used for direct compression into tablets [4, 9, 10], and was also reported to dissolve faster in water [9, 10]. On the other hand, a comparison of the polymorphs of paracetamol is also of general interest. They can be considered as examples of molecular crystals, in which topologically identical H-bonded chains of molecules are linked differently into two-dimensional layers, and this results in the differences in the stability, various physical properties, dissolution behavior [11].

Although thermal properties of the polymorphs of paracetamol were repeatedly studied by many authors using several techniques (DSC [1, 4, 9, 10, 12–15], X-ray diffraction [4, 10, 12, 13, 15], hot-stage microscopy [4, 10, 12, 13], IR [12] and Raman [13] spectroscopy), many questions remain open. The experimental observations reported by different authors, and the interpretation of these observations are not always in a good agreement with each other. In particular, there is no agreement in the literature on the following questions:

- Can polymorph II transform directly into the polymorph I in the crystalline state, or is this transformation preceeded by melting of form II?
- Can polymorph II melt without being first transformed into polymorph I? If yes, are the melting temperatures of the two polymorphs different?
- Do the samples of paracetamol II obtained *i)* from solutions, *ii)* from the melt under different conditions behave differently on heating? If yes, then why?

It is also not known, what is the quantitative difference in the stability of the polymorphs I and II, in the values of their heat capacity, and other thermodynamic functions.

The polycrystalline samples that were used for the studies of thermal properties of paracetamol polymorphs may have contained impurities of another polymorph. The data on the thermal transformations obtained (even by the same authors) in the DSC, X-ray diffraction, or hot-stage microscopy experiments referred to different samples, and this could lead to the misinterpretation of the experimental observations. It is worth noting, that conclusions based on the X-ray diffraction and on the DSC measurements often contradicted each other [4, 10, 12, 15]. At the same time, a combination of several techniques, such as thermal analysis, calorimetry, X-ray diffraction and optical microscopy can be very helpful for careful studies of the relations between the polymorphs of molecular crystals in general, and drugs – in particular [16]. In our previous publications on glycine [17, 18] and sulfathiazole [19] we have shown that this combination of methods is especially successful, if applied to the same sample.

The aim of the present study was to carry out a comparative study of the polymorphs I and II of paracetamol in a wide temperature range (5–450 K) using DSC and adiabatic calorimetry and carefully controlling the phase composition of the samples at all the stages of the experiments by single crystal and powder X-ray diffraction.

Experimental

The samples of the paracetamol I and II were grown and kindly provided to us by Mikhailenko.

Large (up to 1x0.3x0.3 cm) single crystals of orthorhombic paracetamol II were grown by slow cooling of hot aqueous solutions as described in [20]. For the low-temperature adiabatic calorimetry studies, freshly prepared single crystals without visible imperfections were taken. The mass of the sample put into the low-temperature calorimeter was 1.07293(1) g. The crystals contained inclusions of water used as solvent during crystal growth. This was in an agreement with the observations previously described in [4]. Average water content in a sample was about 0.69±0.02%. For the DSC experiments at temperatures above the ambient one, the large single crystals of paracetamol II were cut into fragments using a perfect cleavage of this polymorph along the molecular layers (Fig. 1). A single fragment (with the mass in the range between 2.05 and 4.26 mg) was used in a DSC experiment. Using the fragments of the same large crystal in the comparative DSC-runs we aimed to improve the reproducibility of results, since the fragments of the same crystal can be expected to differ less in their properties, than different crystals even from the same batch.

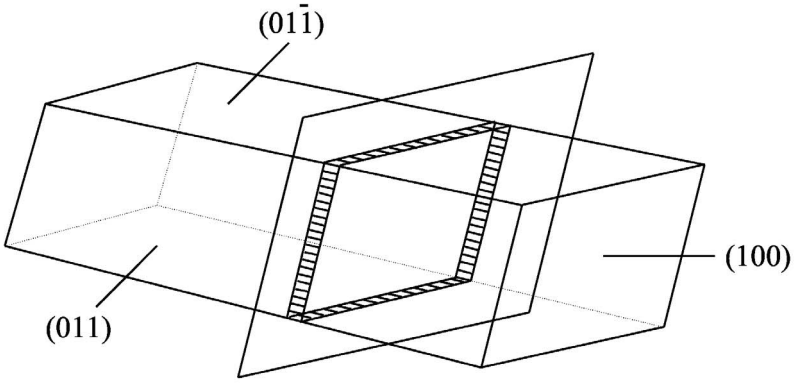

Fig. 1 The shape of a typical paracetamol II crystal and a schematic representation of cutting it into fragments for DSC measurements

The crystals of paracetamol II were slightly red. This indicated that they contained some impurities (possibly oxidation products) inevitably formed during the crystallization of this metastable polymorph. In order to make a comparison of the thermal properties of paracetamol I and paracetamol II more reliable, we have decided to produce paracetamol I by the transformation of paracetamol II, instead of growing the crystals of paracetamol I from ethanol solutions following a standard procedure [3]. The samples of monoclinic paracetamol for low-temperature adiabatic calorimetry were obtained from the orthorhombic form directly in the calorimeter (see more details in the section: 'Results and discussion. Low-temperature transformation'). On storage, large single crystals of paracetamol II recrystallized gradually into fine powder of paracetamol I. The water content in the partly recrystallized sam-

ple was about 0.09±0.01% and after a complete II to I conversion no water was left in the sample. The mass of the sample put into the calorimeter was 0.99423(1) g.

The phase composition of all the samples was controlled by single-crystal and powder X-ray diffraction. A four-circle STADI-4 (STOE, Darmstadt) and a Bruker GADDS (Karlsruhe) diffractometers were used for the measurements.

An important problem to solve was to estimate correctly the water content in the samples. The number and the size of the mother liquor inclusions in the crystals varied stochastically. It was difficult to find accurately the content of water in a sample, consisting of several crystals using standard analytical techniques. It was not possible to eliminate water by heating (TG), since heating would induce a II→I polymorphic transformation. As a possible solution, we could analyze the water content in a portion of the sample, assuming that it is representative enough and the sample taken for calorimetry has the same water content. However, this method would be very inaccurate, and we did not use it. Instead, the water content in the samples of orthorhombic and monoclinic paracetamol used for low-temperature calorimetry studies was calculated on the basis of measuring the heat of fusion of ice in the inclusions (see more details in Section 'Results and discussion. Low-temperature heat capacity').

An automatic adiabatic calorimeter used for low-temperature heat capacity measurements was described in the previous publications [21, 22]. After a sample was loaded into the calorimeter, the air from the calorimeter was evacuated and a small amount of helium was injected, to enable the heat exchange at extremely low temperatures. Low-temperature heat capacity of the monoclinic paracetamol was measured at 104 points and that of the orthorhombic polymorph at 59 points. The measurements of the orthorhombic polymorph were carried out from 5 to 300 K during subsequent runs with incresing temperature only, without repetitive series after decreasing temperature, to avoid the freezing and melting of ice inside the inclusions (see Section 'Results and discussion. Low-temperature transformation').

A DSC-204-Netzsch calorimeter was used for calorimetry measurements at temperatures above ambient. The samples were put into a standard aluminium crucible and studied in a dry argon flux (25 mL min^{-1}). Heating rate varied in the range from 10 to 0.5 K min^{-1}.

Results and discussion

High-temperature transformation

A typical DSC-curve measured when heating a single crystal of paracetamol II is shown in Fig. 2. Two endothermic events were observed. A small peak was observed at different temperatures T_{tr} for different crystals in a rather wide range (about 20°C) around 120°C. The shape of this peak was asymmetric and 'inverted' as compared with the shape of a typical DSC-peak corresponding to melting. This can be an evidence of an 'overheated transformation', like an exothermic peak of crystallization of metals on cooling: a rapid signal growth at the left slope of the peak results from a fast heat absorption, after which a slow relaxation of the temperature of the sample to

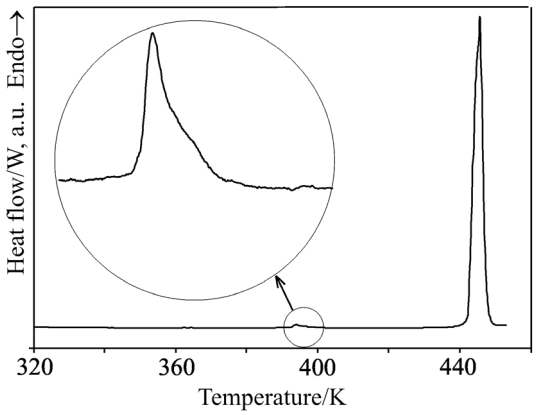

Fig. 2 DSC curve of paracetamol II above ambient temperature

Table 1 Parameters of the runs and the duration of the heat absorption by a sample during the II→I polymorphic transition in paracetamol

Heating rate/K min^{-1}	Sample mass/mg	Duration/s
0.5	2.61	13
1	2.05	9
2	2.55	16
3	4.26	13
5	2.64	18
10	2.79	10

the temperature of the crucible takes place. The rate of the signal increase at the start of the peak did not depend on the heating rate, i.e. on the difference between the temperature onset and the crucible temperature. The values of the heating rate, of the sample mass, and the time of the increase of the DSC signal up to the maximum are summarized in Table 1.

For several samples, heating was stopped immediately after this small endothermic peak was observed. After cooling a sample back to ambient temperature, no changes in the habit of the crystal were observed. The angles between the edges were sharp and there was no evidence that fusion could have taken place (Fig. 3a). The crystal became opaque. X-ray diffraction showed that the sample was not a single crystal of the paracetamol II any longer, but a polycrystalline pseudomorph of paracetamol I (Fig. 3b). Even a slight mechanical action at the pseudomorph was enough to destroy the pseudomorph – the shape of the starting single crystal of paracetamol II was preserved only because of the adhesion of small crystallites of paracetamol I.

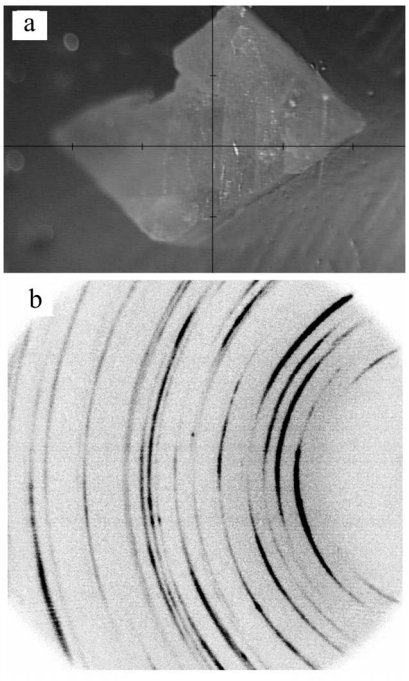

Fig. 3 a – a paracetamol crystal (initially – orthorhombic) after its transformation into the monoclinic pseudomorph; b – its powder diffraction pattern

Thus, the endothermic event at about 120° (no exact temperature can be given, since it essentially differed from sample to sample) was proved to be a single-crystal -to-polycrystal polymorphic transformation of paracetamol II to paracetamol I. The transition is overheated, and the temperature limit of the stability of the orthorhombic polymorph is below 100°C. Further heating resulted in the melting of the monoclinic paracetamol I (the second, larger endothermic peak at 169°C, Fig. 2).

The enthalpy of II→I polymorphic transition near 100°C ranges from 3.3 to 3.8 J g^{-1} (540 J mol^{-1}). For comparison, the enthalpy of melting of polymorph I is 50 times greater (176–182 J g^{-1} = 27 kJ mol^{-1}).

Our results can be compared with those published in the literature. During this comparison it is important to distinguish between the observations and their interpretations. For example, in many papers claiming that a direct melting of paracetamol II was observed, there were actually no proofs that the 'melting' crystals were really orthorhombic, but, as was written, e.g. in [14], 'form II was identified from its known melting temperature of 156°C–157°C'.

The results of the DSC experiments reported by different authors are summarized in Table 2. Nichols and Frampton [4] have reported that they have observed three endothermic events in the DSC curves (using powder samples of paracetamol II crystallized from solution). The first event was broad and weak, in the temperature

Table 2 A summary of the results obtained in various DSC experiments on heating paracetamol II

Peaks observed	Heat effects	Interpretation (in the original publication)	Reference, source of the sample
1) about 100°C (different from sample to sample) 2) 169°C	1) 0.54 kJ mol^{-1} 2) 27 kJ mol^{-1}	1) II to I polymorphous transition 2) melting of paracetamol I	this study, from aqueous solution
1) 87°C 2) 155°C 3) 168°C	1) +0.4 kJ mol^{-1} 2) 26.9 kJ mol^{-1} 3) 28.1 kJ mol^{-1}	1) II to I transformation 2) melting of II 3) melting of I	[23], from the melt, as purchased
1) 157°C 2) 169°C	1) 26.5 kJ mol^{-1} 2) 28.0 kJ mol^{-1}	1) melting of II 2) melting of I	[13], from the melt, as purchased
1) 156°C 2) 169°C	1) 27 kJ mol^{-1} (177 J g^{-1}) 2) 28 kJ mol^{-1} (184 J g^{-1})	1) melting of II 2) melting of I	[1], from the melt, as purchased
1) 115–128°C (centered at about 122°C) 2) 157°C 3) 171°C	1) 2 J g^{-1} 2) 1 J g^{-1} 3) 185 J g^{-1}	1) no interpretation 2) melting of II 3) melting of I	[4], (crystallized from EtOH solution)
157°C	no exact value reported ('a single strong endothermic event')	melting of II	[4], (melt crystallized)
about 170°C	no exact value reported ('a single strong endothermic event')	melting of I	[15], from solution
157°C (heating rate 10°C min^{-1}) or 169°C (heating rate 0.1°C min^{-1})	no exact value reported ('a single strong endothermic event')	melting of II	[12], from the melt
1) a set of small exotherms in the region of 122°C 2) 155°C 3) 167°C	1) no exact values given ('small') 2) no exact value given (a sharp endo-peak, the largest in the DSC curve) 3) no exact value given (a sharp endo-peak, smaller than 2)	1) no interpretation 2) melting of II 3) melting of I	[10] from the melt from solution

range 115 to 128°C, centered at about 122°C (enthalpy 2 J g^{-1}). The second event was a weak and sharp peak at about 157°C (enthalpy 1 J g^{-1}). The third endotherm was a strong sharp peak at about 171°C (enthalpy 185 J g^{-1}). The authors of the publication have interpreted these events as (in order of increasing temperature) a solid-state conversion of form II to form I (event 1), followed by the melting of non-converted form II (second event), and finally, the melting of form I (third event). They have also noticed that thermal behavior of paracetamol II that has been crystallized from solution was different from that of form II crystallized from the melt. Melt-crystallized paracetamol had a single strong endothermic event at about 157°C, which was ascribed to melting. Thermomicroscopy has shown that individual crystals of paracetamol II converted in the solid state to form I from about 60°C. Melting of the individual paracetamol crystals was observed in the range 157 and 170°C. Based on the results of our experiments, we can now suppose, that Nichols and Frampton have observed a solid-state paracetamol II→I transformation at about 122°C, but that the event at 157°C was not the melting of the orthorhombic paracetamol II. It is worth noting, that the heat effect reported for this peak by Nichols and Frampton [4] is too small for melting (compare with the heat of fusion of paracetamol I measured in the same experiment). In our experiments, we did not observe the endothermic peak at 157°C that was mentioned in several publications before [4, 10, 12, 13, 23]. The possible origin of this peak is now under a special study and will be a subject of another publication.

De Wet *et al.* have studied melt-crystallized powder samples of paracetamol II using DSC and have observed 'a set of very small exotherms in the region of 120°C' (which they failed to interpret) and two endotherms: at 155°C (the largest one) and at 167°C (somewhat smaller), which they have interpreted as melting of paracetamol II and paracetamol I, correspondingly [10]. They have assumed that they saw direct melting of paracetamol II.

Conflant and Guyot-Hermann [15] have also observed a solid-state transition from melt-grown powder samples of paracetamol II to form I on heating with subsequent melting of form I using X-ray powder diffraction. These results are also in good agreement with our observations. At the same time, the same authors could not detect the polymorphic transition using DSC. We can assume that the equipment used in their experiment was not sensitive enough. No II to I transformation could be registered in [9, 12–14] either, presumably due to the same reason. It is very remarkable, that DiMartino *et al.* [12] have actually observed the transition II→I at nearly 156°C with a subsequent melting of the monoclinic paracetamol I at about 169°C, when they carried out an X-ray diffraction experiment *vs*. temperature using a Guinier-Lenne camera. However, despite these X-ray diffraction data, they have interpreted their DSC data (an endothermic peak at about 157°C, if the heating rate was equal to 10°C min^{-1}, and at about 169°C, if the heating rate was 0.1°C min^{-1}) as an evidence of the melting of the orthorhombic form II.

Summing up our experimental results and a careful analysis of the literature data, we can make a conclusion, that the II→I polymorphic transformation of paracetamol does take place in the solid state, in accordance with the prediction [1, 16], that

paracetamol forms I and II are monotropically related, and only solid–solid transitions from modification II into I are thermodynamically allowed at ambient pressure. Since the transition was more often observed in the sample crystalized from solution, water traces can be supposed to catalyze this transformation.

Ambient-temperature transformation

De Wet *et al.* [10] have observed a solid-state transformation of the individual crystals of paracetamol II into paracetamol I upon storage at ambient temperature. At the same time, Di Martino *et al.* have claimed paracetamol II to be stable at ambient temperature even after 11 months [9]. According to our own observations, this discrepancy may be due to different humidity: traces of water facilitate the II to I transformation. In our experiments, the large single crystals of orthorhombic paracetamol II that were stored at ambient temperature in a closed glass vessel during a long time (at least 6 months), recrystallized partly into a fine powder of monoclinic paracetamol I. Inclusions of mother liquor (water) into the crystals played an important role in this process. In the previous publications [4, 20] it was also mentioned that water traces in a sample of paracetamol II provoke the transformation of this form to paracetamol I at ambient temperature.

Low-temperature transformation

Low-temperature properties of the polymorphs of paracetamol were not described in the literature. Burger and Ramberger [23] have estimated the thermodynamic transition point between the polymorphs to be below 283 K, but no experimental data supported this hypothesis.

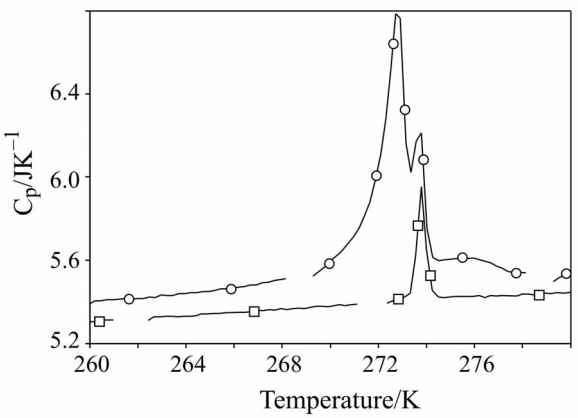

Fig. 4 Raw data on the low-temperature heat capacity (sample + calorimeter) near the ice melting point. Freshly prepared crystals of orthorhombic paracetamol (circles) and those stored at ambient conditions more than 6 months (squares)

The changes of the heat capacity of a paracetamol II sample on cooling (raw data, sample + calorimeter) are plotted in Fig. 4. At temperatures below 273 K, near the ice melting point, we could measure pronounced peaks. They could be interpreted as crystallization – melting of ice in the mother liquor inclusions in the crystals of paracetamol II. The very presence of the DSC peaks at this temperature, and their shapes, show clearly, that water was included into the crystals as liquid bubbles, and not as individual molecules participating in the crystal structure formation.

In our DSC experiments, during cyclic cooling/heating of very small crystals of paracetamol II, of the same size as were used for studying heat of transformation of form II into form I (see a previous Section), ice in the inclusions could be repeatedly reversibly crystallized (frozen) and melted without fragmentation of crystals. When large crystals of paracetamol II were used (for adiabatic calorimetry), some of the inclusions were also large. When freezing, the ice crystals destroyed the envelopes of the inclusions. In this case, during cyclic heating and cooling, a part of water present as ice crystals in the sample still melted within the envelopes of the inclusions, but another part (from those inclusion whose envelopes were already destroyed) formed a saturated solution with paracetamol, that froze and melted at a lower temperature. Only one peak of ice melting was observed at 273.15 K in the first cycle of cooling/heating of the sample stored for 6 months. During subsequent runs, the peak gradually decreased along with the drift in the heat capacity and ceased when the heat capacity became reproducible (see below). Freshly prepared orthorhombic paracetamol exhibited a more complicated picture of ice melting. Besides the peak at 273 K, there was also an additional lengthy and more intensive peak at temperature below 273 K. This was probably the melting of solvent inside inclusions. Comparing properties of freshly prepared sample and one stored for 6 months, we may conclude that the saturated solvent inside inclusions disappears during a partial transformation of the orthorhombic paracetamol into the monoclinic form. Similarly, when a sample was measured by low-temperature calorimetry, freezing and melting of water inclusions was accompanied by a polymorphic transformation of paracetamol II to paracetamol I.

When the adiabatic calorimeter was loaded with freshly prepared crystals of paracetamol II, the sample mass was stable. After the sample was cooled down to 5 K, all the measurements completed, and the sample re-heated back to ambient temperature, the calorimeter with the sample was open. After that the sample mass started to decrease, presumably due to the evaporation of water from the inclusions destroyed during the cooling-heating cycle. Visual inspection of the sample revealed fragmentation of large single crystals of paracetamol II; small powder particles appeared in the sample. X-ray diffraction has shown the large crystals to be still paracetamol II, and the small powder particles – already paracetamol I.

Multiple repeated cooling of a sample containing large single crystals of paracetamol II down to 77 K / heating back to ambient temperature was carried out. Heat capacity was measured during this cycling. At first, the values of heat capacity changed after each cycle, but after several cycles they became reproducible. After the calorimeter was open and the sample visually inspected, all the large crystals were found to be destroyed, and the sample consisted of small powder particles only. Mass

of the sample decreased after the calorimeter was open, similarly to what was observed when studying the samples of the orthorhombic polymorph on cooling down to 5 K (see previous paragraph). X-ray analysis has shown the sample to contain pure monoclinic paracetamol I only. The results of the measurements of that sample after the stabilization of heat capacity were considered as the low-temperature heat capacity of the monoclinic paracetamol and used for the evaluation of its thermodynamic functions in the temperature range 5–300 K (see the next Section).

Thus, also at temperatures below 273 K, orthorhombic paracetamol II is unstable with respect to the monoclinic polymorph I and transforms into it. The crystals of the orthorhombic paracetamol II can be stable with respect to one cycle 'cooling down to liquid nitrogen (or lower) temperatures – re-heating back to ambient temperature', but are eventually transformed into the monoclinic polymorph I if such 'cooling-heating' cycles are repeated. This effect was observed also during a recent single-crystal variable-temperature X-ray diffraction study of paracetamol II crystals [8]. The transformation is facilitated by a small amount of water present as inclusions in the parent crystals. Experiments on cyclic 'cooling-heating' of paracetamol II fragments without water inclusions are needed, to show if the transformation is possible also without the presence of water. This work is now in progress.

Low-temperature heat capacity

The measurements of low temperature heat capacity are essential for comparing the thermodynamic functions of the two polymorphs. Only low-temperature heat capacity makes it possible to calculate the absolute value of entropy as a function of temperature. It is impossible to define relative thermodynamic stability of polymorphs without entropy [24]. Experimental values of the heat capacity are listed in Tables 3 and 4 for monoclinic and orthorhombic polymorphs, respectively.

Water content in a sample was estimated after the enthalpy of ice melting was measured, following the procedure as described below.

Heat capacity measured is the average value:

$$C_P(T_{avg}) = \Delta H/\Delta T = \Delta H/(T_2 - T_1)$$

where ΔH is the enthalpy increment during the run at heating from starting temperature T_1 to final one T_2, and $T_{avg} = (T_1+T_2)/2$ is the mean temperature of the run. At the first melting after the first freezing, ice melts at 273.15 K (Fig. 4). Thus, only one run, say, number n, with $T_1 < 273.15 < T_2$ contains the enthalpy of ice melting. Fitting three points $C_p(T)$ before the melting (n–3, n–2, n–1) to a linear polynomial $C_p = a + bT$, we can calculate the value of the n-th run with the melting by extrapolation. Similarly, the same point is calculated after fitting and extrapolation of runs n+1, n+2, n+3. These two calculated values of $C_p(T_n)$ are less than the experimental value by $q\Delta m/(T_2–T_1)$, where q = 333.6 kJ mol^{-1} is the specific enthalpy of melting and Δm is the water mass in a sample. Difference between two extrapolated values of $C_p(T_n)$ allows us to estimate the accuracy of the water content calculation.

Table 3 Experimental heat capacity of monoclinic paracetamol (I) (formula mass 151.1658)

T/K	C_p/J mol^{-1} K^{-1}	T/K	C_p/J mol^{-1} K^{-1}	T/K	C_p/J mol^{-1} K^{-1}
Series 1		Series 3		153.33	110.32
6.66	0.5807	43.69	40.33	160.29	113.81
7.80	0.9489	48.27	45.18	168.92	118.19
8.94	1.442	55.83	52.68	178.87	123.60
9.89	1.936	60.95	56.30	188.78	128.56
10.84	2.490	Series 4		198.74	133.55
11.96	3.266	83.01	72.76	208.73	139.19
13.05	4.079	90.06	76.37	218.67	144.18
Series 2		97.06	81.10	228.64	150.29
6.85	0.6327	104.04	84.99	238.62	156.11
8.03	1.034	Series 5		248.63	162.19
9.09	1.505	82.82	72.61	258.66	169.13
10.20	2.103	85.84	74.53	267.64	172.99
11.29	2.776	88.89	76.43	269.67	174.17
12.35	3.522	91.95	78.30	275.38	177.66
13.40	4.379	95.00	80.13	282.81	181.35
14.45	5.216	98.10	81.97	290.24	185.91
15.72	6.566	Series 6		251.74	163.78
17.05	7.891	158.43	112.97	254.74	165.67
18.57	9.589	165.43	116.53	257.74	167.83
20.32	11.50	172.40	120.19	260.77	170.09
22.08	13.55	Series 7		263.78	172.99
23.86	15.75	294.62	188.21	266.74	172.44
25.92	18.40	297.12	189.63	269.73	173.35
28.19	21.34	299.61	191.08	272.76	175.05
30.50	24.34	296.71	188.98	Series 9	
33.36	28.02	299.22	190.52	6.83	0.6397
36.60	32.00	Series 8		7.88	0.9828
39.86	35.89	88.33	75.92	8.97	1.444
43.09	40.07	93.36	79.08	10.04	2.023
51.51	48.56	98.40	82.07	11.22	2.725
56.68	53.19	104.51	85.35	12.35	3.522
61.79	57.47	111.50	89.02	13.38	4.364
67.35	61.83	118.55	92.61	14.69	5.523
73.38	65.53	125.54	96.16	16.25	7.117
79.40	70.41	132.50	99.78	17.67	8.573
85.43	74.19	139.44	103.34	19.07	10.15
91.44	77.84	146.39	106.79		

Table 4 Experimental heat capacity of orthorhombic paracetamol (II) (formula mass 151.1658)

T/K	C_p/J mol^{-1} K^{-1}	T/K	C_p/J mol^{-1} K^{-1}	T/K	C_p/J mol^{-1} K^{-1}
Series 1		45.30	41.77	124.78	96.21
6.40	0.5031	49.48	46.10	131.80	99.94
7.60	0.8658	53.62	50.11	138.76	103.60
8.69	1.311	58.21	54.50	149.87	108.15
9.82	1.874	63.29	58.49	157.81	113.29
10.88	2.484	68.70	62.82	167.78	118.38
11.95	3.225	73.74	66.46	177.81	123.68
13.14	4.109	78.77	69.84	187.81	129.02
14.39	5.193	83.78	73.04	197.80	134.17
15.66	6.449	Series 2		207.87	139.95
17.09	7.853	291.84	190.30	217.89	144.89
18.61	9.587	294.34	191.82	227.81	150.97
20.39	11.52	296.84	193.42	237.81	156.87
22.45	13.97	299.33	194.76	247.90	162.88
24.49	16.51	Series 3		255.46	167.54
26.52	19.07	89.56	77.05	263.02	174.83
29.12	22.47	94.62	80.09	273.06	214.78
32.28	26.54	99.69	82.98	283.09	185.09
35.46	30.48	104.71	85.75	291.55	190.65
38.60	34.25	110.76	88.97	296.63	193.12
41.69	37.75	117.79	92.60		

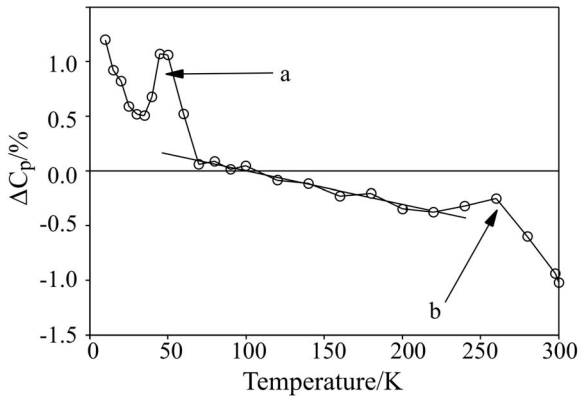

Fig. 5 The difference between the values of heat capacity C_P of the monoclinic (a) and the orthorhombic (b) forms of paracetamol: C_P(mon)–C_P(orth). The arrows indicate a peak in the heat capacity of the monoclinic polymorph and contribution from water after destruction of the inclusions in crystals. See further comments in the text

Table 5 Thermodynamic functions of monoclinic paracetamol (I) (formula mass 151.1658)

T/K	C_p/J mol^{-1} K^{-1}	H/J mol^{-1}	S/J mol^{-1} K^{-1}
(5)	(0.250)	(0.312)	(0.083)
10	1.997	5.002	0.667
15	5.809	23.64	2.127
20	11.15	65.7	4.511
25	17.20	136.3	7.635
30	23.62	238.4	11.34
35	29.96	372.6	15.46
40	36.01	537.6	19.86
45	41.77	732.2	24.44
50	47.00	954	29.12
60	56.03	1471	38.51
70	63.61	2069	47.72
80	70.54	2741	56.67
90	76.88	3479	65.36
100	82.85	4278	73.78
120	93.31	6041	89.81
140	103.52	8009	105.0
160	113.63	10181	119.4
180	123.95	12557	133.4
200	134.28	15138	147.0
220	145.14	17931	160.3
240	156.76	20951	173.5
260	168.41	24204	186.5
280	179.47	27681	199.3
298.15	189.68	31032	210.9
300	190.64	31384	212.1

Heat capacity of the two polymorphs was corrected for the heat capacity of ice and water and then smoothed. At $T < 10$ K, the experimental values of heat capacity for both polymorphs fit the Debye model well. Low-temperature heat capacity of the orthorhombic paracetamol II can be fitted by equation $C_p = 0.00198 \cdot T^3$ ($s = 1.73\%$), that of the monoclinic polymorph I – with the equation $C_p = 0.00200 \cdot T^3$ ($s = 0.80\%$). Thermodynamic functions of both paracetamol polymorphs were calculated using the cubic polynomials below 10 K and after the smoothing procedure described

Table 6 Thermodynamic functions of orthorhombic paracetamol (II) (formula mass 151.1658)

T/K	C_p/J mol^{-1} K^{-1}	H/J mol^{-1}	S/J mol^{-1} K^{-1}
(5)	(0.248)	(0.308)	(0.082)
10	1.973	4.944	0.659
15	5.756	67.71	2.107
20	11.06	155.4	4.466
25	17.10	267.9	7.572
30	23.50	405.3	11.25
35	29.81	567.6	15.35
40	35.77	754.8	19.73
45	41.33	966.8	24.26
50	46.50	1204	28.89
60	55.74	1753	38.20
70	63.57	2401	47.40
80	70.48	3149	56.34
90	76.88	3997	65.02
100	82.81	4945	73.43
120	93.39	7140	89.47
140	103.64	9735	104.6
160	113.89	12730	119.1
180	124.21	16126	133.2
200	134.75	19921	146.8
220	145.68	24116	160.1
240	157.27	28710	173.3
260	168.8	33755	187.1
280	180.5	39155	200.1
298.15	191.5	44402	211.7
300	192.6	44955	212.9

above. The results of the calculations for monoclinic and orthorhombic polymorphs are summarized in Tables 5 and 6, respectively.

The difference in heat capacity between the monoclinic and the orthorhombic polymorphs is shown in Fig. 5. Two polymorphs of paracetamol differ in structure significantly, but their thermodynamic functions are very similar. The same was observed previously in our comparative studies of the polymorphs of glycine [17, 18, 24, 25].

The difference in heat capacity between the monoclinic and the orthorhombic polymorphs changes sign at about 100 K: heat capacity of paracetamol I becomes larger, than that of paracetamol II. Near 50 K there is a peak of C_p of the monoclinic form. This peak is very small, but the effect exists with certainty because the preparation of the samples for the calorimetric measurements excluded any contribution from impurities, and the experimental conditions during the measurements were identical for paracetamol II and I. The nature of this peak requires further studies. In the temperature range 70–230 K, the difference between heat capacities of the two polymorphs changes almost linearly with temperature with the standard deviation from the straight line by 0.06% (the straight line is shown in Fig. 5). The difference of 0.06% agrees well with the standard deviation of separate functions $C_P(T)$ for the both polymorphs (about 0.03% each). In the temperature range of 230–290 K, the difference C_P(mon) – C_P(orth) deflects from the straight line forming 'broad' peak (shown in Fig. 5 by the arrow). We think this is due to the contribution of the melting of water impurity in a form of a solution in the sample of monoclinic paracetamol. Both samples contained water from the very beginning. Heat capacity was measured after the destruction of initial crystals and inclusions in the monoclinic polymorph but before the destruction in the orthorhombic polymorph.

Conclusions

A careful comparative study of the well-characterized single-crystal and powder samples of paracetamol I and II combining thermal analysis, calorimetry, X-ray diffraction and optical microscopy proved to be very helpful for revealing the relations between the polymorphs of paracetamol. It gave reliable data on the transformation of paracetamol II to paracetamol I on heating and on cooling, on the values of heat capacity and of the thermodynamic parameters of the two polymorphs. Discrepancy in the previously published literature data on the thermal properties of paracetamol I and II could be interpreted.

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The study was supported by grants NO-008-X1 (from USA-Russia BRHE Program), (from Russian Ministry of Education), 02-03-33358 (from RFBR), and a grant from the Foundation of Support of National Science (Russia) for EVB.

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