A kinetic study of polymorphic transition of anhydrous caffeine with microcalorimeter

Vesa-Pekka Lehto, Ensio Laine[*]

University of Turku, Department of Physics, Laboratory of Industrial Physics, FIN-20014 Turku, Finland

Abstract

The phase transition of anhydrous caffeine form I → form II was investigated using isothermal microcalorimetry (IMC) and the kinetic results were compared with X-ray diffraction (XRD) studies. As the Arrhenius relationship was assumed to be valid in this study, the comparison was made by defining typical concentration vs. time curves and by generating Arrhenius plots based on times for different degrees of the transformation. The reverse transition was investigated with a differential scanning calorimeter (DSC) to estimate the value of the transition enthalpy ΔH_{trs} of the polymorphic transformation in question. The selected kinetic equations fitted in IMC data gave great variation in the values of ΔH_{trs} though the curves correlated usually quite well with the measured data points. Changes in the transition mechanism as the transition progresses were verified from IMC data via the technique, where the calorimetric heat flow signal dq/dt is plotted as a function of released energy Q for different measuring temperatures. The activation energies at specific degrees of the transformation were calculated from the plots of $\ln(dq/dt)$ vs. $1/T$ at corresponding energies. The values for activation energies increased as the transition progressed indicating changes in the transition mechanism. The tendency was obvious according to the XRD measurements, too. However, the kinetics obtained with IMC and XRD differed from each other remarkably, which is due to the differences in the detection principle and provides further information on the transition mechanism itself. The nonlinear correlation between IMC and XRD quantitative results showed the transformation to begin at regions with high stored energy. © 1998 Elsevier Science B.V.

1. Introduction

Most processes, whether chemical or physical, are accompanied by a heat change. As isothermal calorimeter, where the process progresses under highly isothermal conditions, can monitor these heats with great sensitivity, this kind of apparatus can obviously give advantages to investigations of, e.g. kinetics of phase transition. It has been estimated [1] that a change that would take more than 200 years to run to completion could easily be detected with this technique. Under these circumstances it is surprising that few articles are published in the field of material science concerning very slow solid state transformations where no water is employed (e.g. [2–7]). This could have been influenced by the nonspecific nature of microcalorimetry, since very small disturbances during the measurements, an unfamiliar transformation progressing in the sample or too short measuring

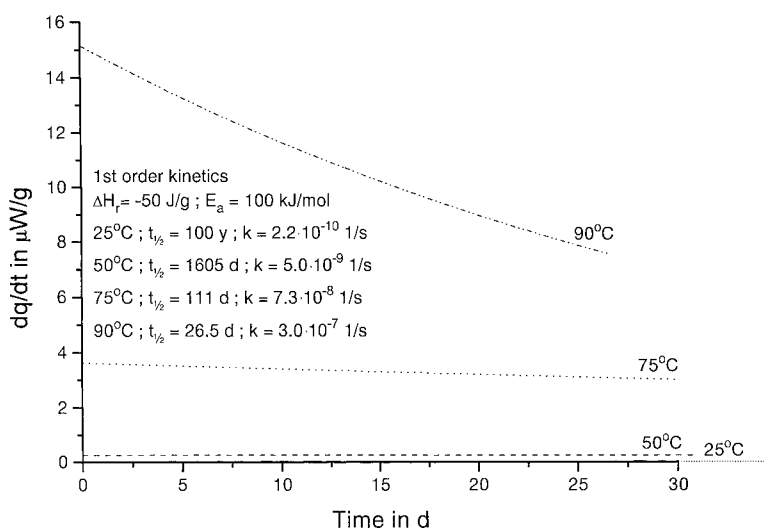*Corresponding author. Fax: +356 2 3335993; e-mail: enla@utu.fi

Fig. 1. Simulated heat flow curves for the first-order transition with the transition enthalpy of −50 J/g and the activation energy of 100 kJ/mol at different temperatures.

times can affect the analysis of a low and slowly varying heat flow signal dramatically, especially when the precise transition mechanism is unknown as is normally the case in the solid state.

Theoretically calculated limits for degradation rates, which are detectable with a highly sensitive isothermal heat flow microcalorimeter give usually optimistic results about the ability of the instrument. These represent simulated heat flow signals at different temperatures for a transition with a transition enthalpy of −50 J/g and an activation energy of 100 kJ/mol in Fig. 1. The transition is assumed to obey the first-order transition kinetics although those are rare among the transitions in solid state, but the chosen values are quite realistic. The signals in Fig. 1 are obtained with samples of 1 g. The degradation rate is about 0.7%/a at 25°C, which is not detectable according to this example. When the temperature of the measurements is risen to 50°C and above, the transition creates a heat output greater than the noise level 0.1 µW of the instrument and the signal is significant.

When dealing with polymorphic forms of the same solid substance, X-ray diffraction offers often an exact and practical technique to determine the relative amounts of the phases. Concentration as low as 2% is estimated to be detected acceptably [8] and the

accuracy of the quantitative analysis to be ca. 10% at higher concentrations. Consequently, the crystallization consisting of the nucleation and the crystal growth, the initial parts in the recrystallization of the new polymorphic grains may be undetectable with X-ray diffraction. However, the benefit of this technique in contrast to microcalorimetry is the exact origin of the recorded signal. All confusing factors can be eliminated or taken into account in the analysis, so that there is no obscurity about the calculated concentration–time curve. However, it is noteworthy that the spatial distribution of the crystalline regions in the sample may affect the diffraction results, since, e.g. if the crystalline fraction forms just a thin layer at the surface of the amorphous particles, the diffractograms may still indicate the sample to be totally amorphous.

The aim of this work was to study the kinetics of the polymorphic phase transition of anhydrous caffeine metastable form I to stable form II and interpret the transition mechanism based on the measurements made with isothermal microcalorimeter (IMC). The kinetic results obtained with IMC and the quantitative X-ray diffraction (XRD) analysis were compared. As the basis of these techniques are quite different it is not obvious that the results are consistent. As the differential scanning calorimeter (DSC) was not sensitive

enough to detect the transition form I → form II, it was used to measure the transition enthalpy ΔH_{trs} for the reverse transition. With the help of obtained value, the microcalorimetry heat flow curves were manipulated to get quantitative results. Microcalorimeter was also used to find out the actual temperature range for the transition form II → form I.

2. Theory

There are numerous kinetic equations derived to explain different kinds of phase transitions in solid state. Prout and Tompkins [9] made the assumption that a certain amount of nuclei is located at lattice imperfections that also includes the surface of the crystal. The difference in lattice constants between the new nuclei and the master crystals causes lateral strains, which is relieved by the formation of cracks. The process can spreads into the crystal along these crevices. The process will penetrate linearly still further into the crystal and the phenomenon is repeated until the chains of branches collimate and process ceases. The differentiated form for the Prout–Tompkins equation as a function of time can be written as

$$\frac{d\alpha}{dt} = \frac{kCe^{kt}}{(1 + Ce^{kt})^2} \tag{1}$$

where α is the progress parameter relating to the fraction of the transition that has occurred at time t, k is the rate constant and C is the fitting parameter. Eq. (1) is in the form suitable for fitting in IMC data. The Prout–Tompkins equation is also known as Boltzmann equation. Logistic equation can be obtained by modifying the Prout–Tompkins equation assuming the time dependence of transition to be logarithmic. The formula obtained for the IMC data is of the form of

$$\frac{d\alpha}{dt} = \frac{pt^{p-1}}{k^p(k^{-p} + t^p)^2} \tag{2}$$

where p is the shape parameter. The results of Eqs. (1) and (2) are sigmoidal α–t curves if $p>1$.

If the transforming particles are assumed to be spherical and the transition is assumed to start at the surface advancing linearly from the outside of the crystal inward as a circular phase boundary [10],

the obtained differential kinetic equation as a function of time is

$$\frac{d\alpha}{dt} = 3k(1 - kt)^2 \tag{3}$$

As the crystallization is generally accepted to consist of two constituent processes, nucleation and crystal growth, the Avrami equation was derived covering the possibility for different nucleation and growth mechanism where nucleation sites are assumed to be randomly distributed (e.g. [11–13]). The differential Avrami equation can be written as

$$\frac{d\alpha}{dt} = nk^n t^{n-1} e^{-(kt)^n} \tag{4}$$

Different possibilities for the values of exponent n are summarized in Table 1. All the presented kinetic equations are covered by the Ng equation [14]

$$\frac{d\alpha}{dt} = k\alpha^{1-p}(1 - \alpha)^{1-q} \tag{5}$$

The transition enthalpy is obtained by integration of the calorimetric heat flow signal dq/dt from the beginning to the completion of the transition, and the total integrated area of the heat flow curves can readily be derived since

$$\int_{-\infty}^{\infty} \frac{d\alpha}{dt} dt = 1 \tag{6}$$

As the heat flow signal is a product of transition rate and transition enthalpy, i.e.

$$\frac{dq}{dt} = \Delta H_{trs} \frac{d\alpha}{dt} \tag{7}$$

the transition enthalpy is obtained and the results are

Table 1
Values of the Avrami exponent n derived for different nucleation and growth mechanism

Growth geometry	Site saturated[a] Constant[b]	Constant[a] Constant[b]	Site saturated[a] Parabolic[b]	Constant[a] Parabolic[b]
One dimension	1	2	1/2	3/2
Two dimension	2	3	1	2
Three dimension	3	4	3/2	5/2

[a] Nucleation rate.
[b] Linear growth rate.

Table 2
Kinetic equations for fitting in microcalorimetric heat flow signal, obtained transition enthalpy and half times

Equation	dq/dt	$-\Delta H_{trs}$	$t_{1/2}$
Avrami	$Ct^{n-1}e^{-(kt)^n}$	C/nk^n	$(\ln 2)^{1/n}/k$
Prout–Tompkins (Boltzmann)	$\dfrac{C'e^{kt}}{(1+Ce^{kt})^2}$	C'/kC	$\ln C/k$
Mod. Prout–Tompkins (Logistic)	$\dfrac{Ct^{p-1}}{(k^{-p}+t^p)^2}$	Ck^p/p	$1/k$
Contracting volume	$C(1-kt)^2$	$C/3k$	$1/k$

listed in Table 2 as well as the half times $t_{1/2}$ for the kinetic equations.

Activation energy for the process is defined through the Arrhenius equation

$$k = Ae^{-E/RT} \qquad (8)$$

which defines the temperature dependence of the rate constant k. As the heat flow signal is a measure to the transition rate, which is different from the rate constant, the isothermal calorimetric signal cannot be used as such. One way to overcome this complication is to compare plots of heat flow vs. evolved energy for different measuring temperatures. If the transition mechanism does not differ at different temperatures, the heat flow curves are to be of similar shape. If it is also assumed that the degree of the progressing of the transition is directly proportional to the energy evolved in the transition, the activation energy for specific degrees of progressing (α values) can be calculated from the graphs of $\ln(dq/dt)$ vs. $1/T$ at corresponding energies since now α can be treated as a constant in Eq. (5). This implies that the transition rate and the rate constant are proportional quantities.

By comparison of activation energies calculated at different energies, it is possible to check the similarity of the transition mechanism at different degrees of the transition. Of course, it is an essential condition when applying the values of the activation energy to consider the transition mechanism, that the rate constants obey the Arrhenius law in the range of the whole temperature range in interest, which is not always the case, e.g. when the crystal growth is controlled by nucleation. The deviation in the E_a values as a function of transformation degree can be caused by the incorrect assumptions in derivation of the Arrhenius equa-

tion, e.g. it is observed in some occasions that the released energy is not proportional to the fraction crystallized [15]. This was found to be caused by the beginning of recrystallization in regions of high energy in deformed material. When comparing the IMC and XRD results, it is noteworthy that the crystallization can begin as formation of little nuclei that are not detectable with XRD but give remarkable heat flow signal in IMC [16].

3. Experimental

3.1. Material

Commercially obtained caffeine (Sigma Chemical) was recrystallized twice from distilled water to get the material used in the studies, i.e. form II of caffeine. The crystals were dried for 8 days at 30°C and then an additional 4 h at 80°C using silica gel. Form I of caffeine was prepared by heating the sample at 180°C for 16 h in a separate closed vessel. As form II was used in the measurements, the sample was treated at 128°C for 16 h. After the heat treatment the samples for instruments were prepared in room air or under nitrogen flush and the measurements were started immediately.

3.2. Isothermal Microcalorimetry (IMC)

A 2277 Thermal Activity Monitor (TAM), Thermometric AB, Sweden, heat-conduction isothermal microcalorimeter [17] was used to measure heat flow dq/dt (μW) vs. time signals. The samples (ca. 1.0 g) of caffeine form I were prepared immediately after the heat treatment in the 4 ml stainless-steel ampoules and were closed hermetically. The weighting was performed after the measurement. The samples were placed in the pre-equilibrium state of microcalorimeter for 20–25 min while the signals reached baseline levels. After this, the samples were lowered very gently into the measurement position and collection of the data points were started when the signal had become steady again. The starting point of the measurements was considered as the time when the samples were lowered in the pre-equilibrium state. Measurements were done at three temperatures: 45°C, 60°C and 70°C. The use of empty stainless-

steel ampoules as a reference vessel was suitable because of the minor mass of the sample comparing with the mass of vessels (ca. 14 g). The calibration of the instrument was carried out beforehand electrically with an inbuilt calibration resistor using empty measuring cylinders. The measurements in duplicate were done with the samples prepared under nitrogen flush, so that the portion of the oxidation or hydration for the heat flow signal could be eliminated. The duplicated measurements also ensured that there have been made no faults in sample handling, e.g. fingerprints on the measuring vessels can affect the measured signal dramatically.

Before and after collecting the actual data points for the transition, the baseline was always measured. The baseline, assuming to be linear, was used to eliminate the baseline drift during the measurement. All the microcalorimetric data were exported as an ASCII file and the calculations were done in Origin™, a graphic curve-fitting package. Calculations consisted of baseline correction, scaling the mass to 1 g, judging the starting point of the measurement as $t=0$ s, fitting the kinetic functions, or integration of the measured curve and extrapolation the initial and final part of the transition.

3.3. X-ray diffraction (XRD)

X-ray diffraction measurements were made with Philips PW 1050-type angle dispersive powder diffractometers. The diffractograms were obtained with Ni-filtered Cu K$_\alpha$ radiation (λ=0.15418 nm, voltage 45 kV, current 35 mA) and with fixed 1° divergence slit, 0.2 mm receiving slit and 1° scatter slit. The 2θ-angle was calibrated with copper. The scanning was performed in 0.025° or 0.02° steps using 4 or 7 s averaging time. The measurements for kinetic studies at 60°C and 80°C were made with a goniometer, equipped with a hot stage assembly. For kinetic studies at room temperature and at 45°C the measurements were made with a normal goniometer and the sample at 45°C was stored in a precision oven between the scans. Data were collected and analyzed using Philips PC-APD diffraction software. The background-corrected integrated intensities of characteristic reflections were determined from diffractograms with the PW1877 profile fitting program. The quantitative analysis was based on the assumption that the relative changes in the integrated intensities of the characteristic reflections give directly the change in the concentration of the form in question. This is well grounded as the mass absorption coefficients for different polymorphic forms coincide.

3.4. Differential scanning calorimetry (DSC)

A Perkin Elmer DSC model 7 with Thermal Analysis System software was used. The scanning experiment was run with the heating rate of 10°C/min using nitrogen flow and ca. 3 mg samples with empty aluminum pans as references. The melting endotherm of indium was used for the calibration of the instrument.

3.5. Solution calorimetry

A 2225 Precision Solution Calorimeter, Thermometric AB, Sweden, was used to measure the heat of solution for both forms of caffeine at four temperatures: 25°C, 45°C, 60°C and 70°C. The samples of 0.2 g and water of highest purity were employed. The reaction was over in 5–10 min, and two separate experiments were done at each temperature and form.

4. Results and discussion

4.1. Transition form II → form I

The transition temperature for the enantiotropic transition of anhydrous caffeine low-temperature form II to the high-temperature form I was measured with DSC to be about 143°C as an onset temperature of the endothermic peak (Fig. 2). As the onset depends on the heating rate, the onset temperature is probably less than 140°C with the heating rate of 0°C/min. When calculating the transition enthalpy for the transformation from DSC measurements, the baseline was assumed to be sigmoidal during the transformation since the two polymorphic forms have different specific heat capacities. According to DSC curves, the difference in heat capacities was estimated to be −0.3 J/g°C and the transition enthalpy to be 16.4 J/g.

The transition temperature for the transition form II → form I was investigated also with microcalorimeter. The samples were treated as described earlier, but the
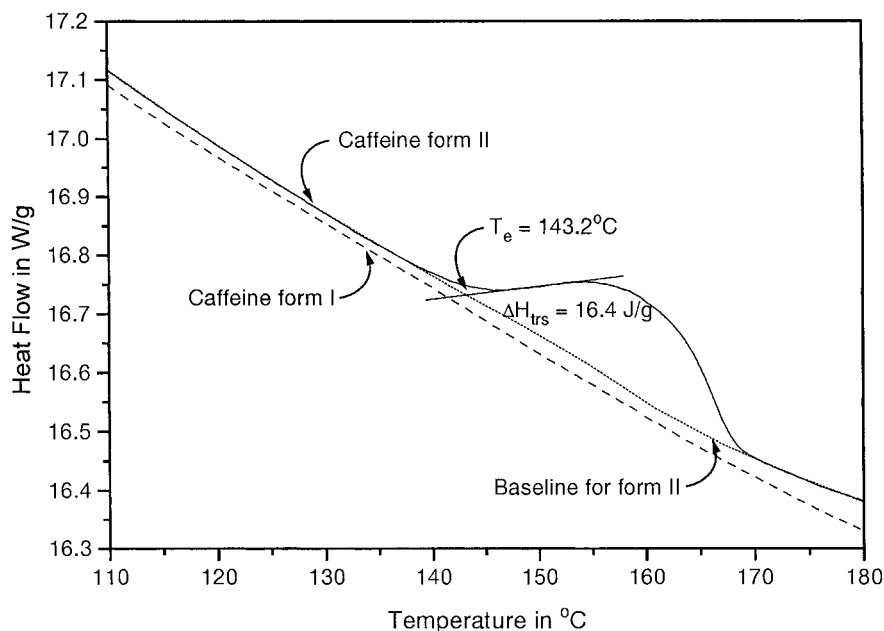
Fig. 2. The DSC curves of the anhydrous caffeine form I and form II at the heating rate of 10°C/min. The transition enthalpy and the onset temperature for the transition form II → form I have been enclosed.

storage temperature for 16 h was changed for different samples to be 120°C, 130°C, 135°C or 180°C accuracy being ±1°C. The measuring temperatures for these samples were 30°C, 30°C, 25°C and 25°C, respectively, and the measurements were started immedi-

ately after the heat treatment. As shown in Fig. 3, the heat flow curves differ from each other remarkably when the samples were treated at 130°C or 135°C. During the storage at 130°C the process was toward the form II that is the stable form at room temperature
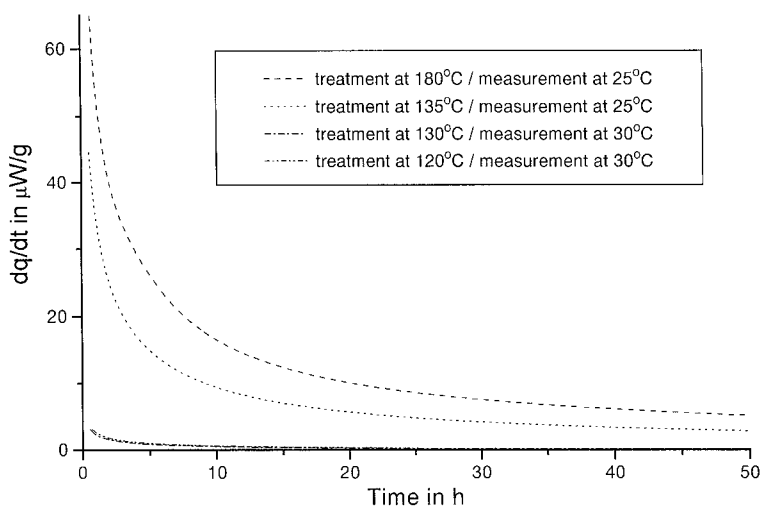

Fig. 3. Microcalorimetric heat flow curves for anhydrous caffeine treated at different temperatures.

and does not give a signal. The signal at the very beginning of the measurement is caused mainly by the thermal relaxation of the sample and the disturbances due to lowering of the vessels into the measuring positions. When storing at 135°C, the sample undergoes the conversion toward the unstable form I, and the calorimeter is recording the process form I → form II at 25°C. As the storage time of 16 h at 135°C has not been long enough to transform the entire sample to form I, the signal for the sample prepared at 180°C is still higher.

4.2. Transition form I → form II; XRD

XRD measurements were performed at 45°C, 60°C and 80°C as well as with the sample stored at room temperature for verifying the predicted kinetics. The quantitative analysis based on the reflection at $2\theta = 28.4°$ that is characteristic for form II and does not overlap with any other reflection. The diffractograms in the range $25° < 2\theta < 29°$ of the transition at 60°C are shown in Fig. 4. The degree of transforma-

tion or α was determined by comparing the background corrected integrated intensities with the corresponding reflection of pure form II. The sample of the pure form II was prepared by heating the individual sample at 128°C for 16 h.

The quantitative results at different temperatures are shown in Fig. 5. The kinetic equations presented above were fitted in every set of data the correlation being excellent with the Avrami equation. The values for exponent n were 0.40, 0.37 and 0.47 at 45°C, 60°C and 80°C, respectively, the average being 0.4. The corresponding values for rate parameters k were 1.40×10^{-8} 1/s, 1.78×10^{-7} 1/s and 1.45×10^{-6} 1/s. Using the Arrhenius relationship Eq. (8) the rate parameter k was calculated to be 5.14×10^{-10} 1/s at 23°C the activation energy E_a being 123 kJ/mol. To compare the kinetic results with corresponding IMC results the values of $t_{0.05}$, $t_{0.2}$ and $t_{0.3}$ (the times needed to reach the transformation degree of 0.05, 0.2 and 0.3) were determined and the inverses were used in Arrhenius plots (Fig. 10). The activation energies were 93.9, 101 and 113 kJ/mol, correspondingly.
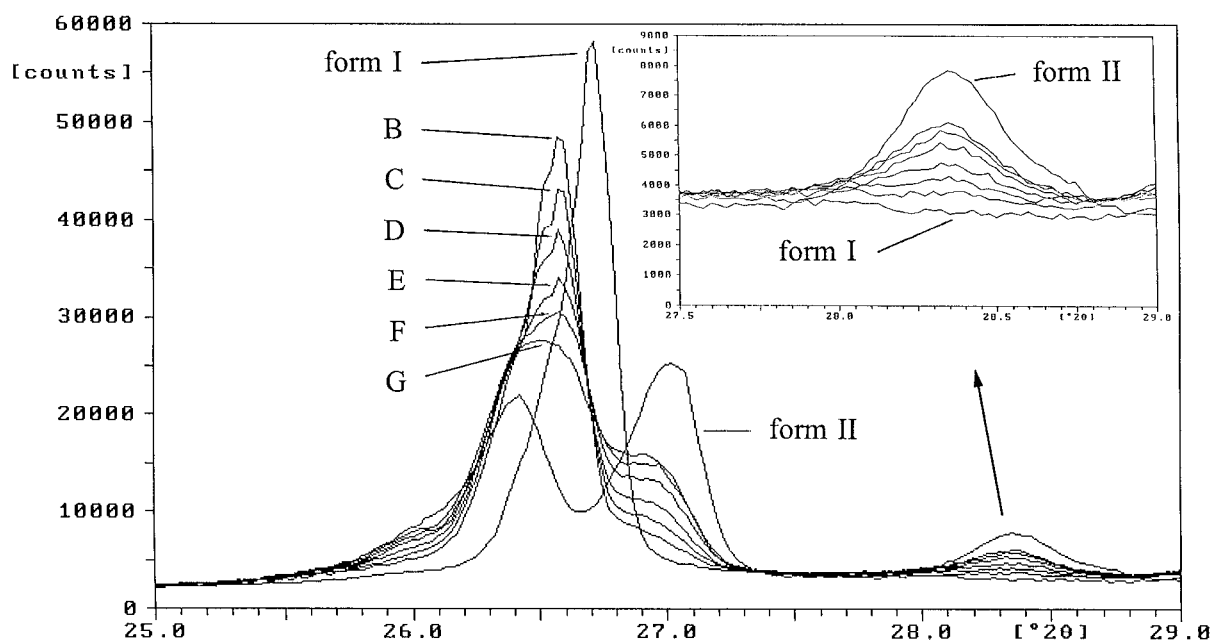

Fig. 4. X-ray diffractograms for transformation of caffeine form I to form II during storage at 60°C. The shift in the peak positions to smaller 2θ values after the first diffractogram is caused by the increase in the thermal vibrations as the diffractogram for form I is measured at room temperature and the others at 60°C. The labels are B: 2 h, C: 9 h, D: 30 h, E: 120 h, F: 297.5 h and G: 624 h.
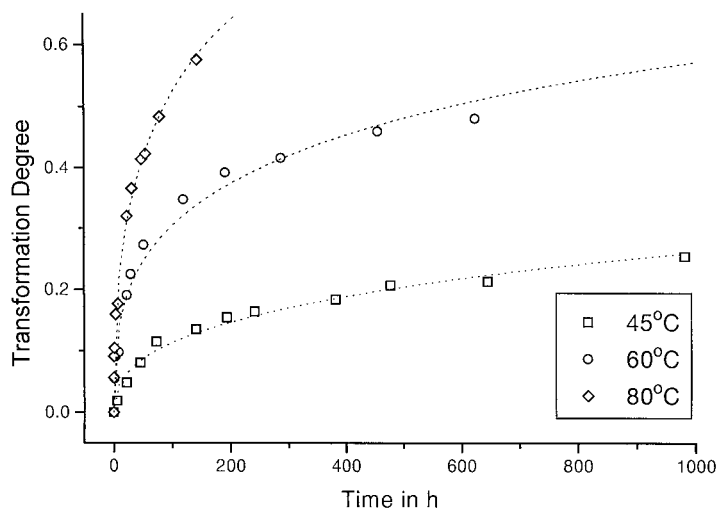
Fig. 5. Transformation degree for caffeine form II as a function of storage time at different temperatures obtained with XRD. The dotted lines present the fittings of the Avrami equation.

4.3. Transition form I → form II; IMC

The microcalorimetric measurements were performed at 45°C, 60°C and 70°C (Fig. 6). The differentiated kinetic equations (Table 2) were fitted in the calorimetric data and the best results were obtained with the Avrami equation. Usually the defects related to the great variations in the values of the transition enthalpy achieved from the fitting parameters. Avrami equation gave good correlation the squared deviation being less than unity and the ΔH_{trs} values were -17.9, -14.6 and -15.4 J/g at 45°C, 60°C and 70°C, respec-
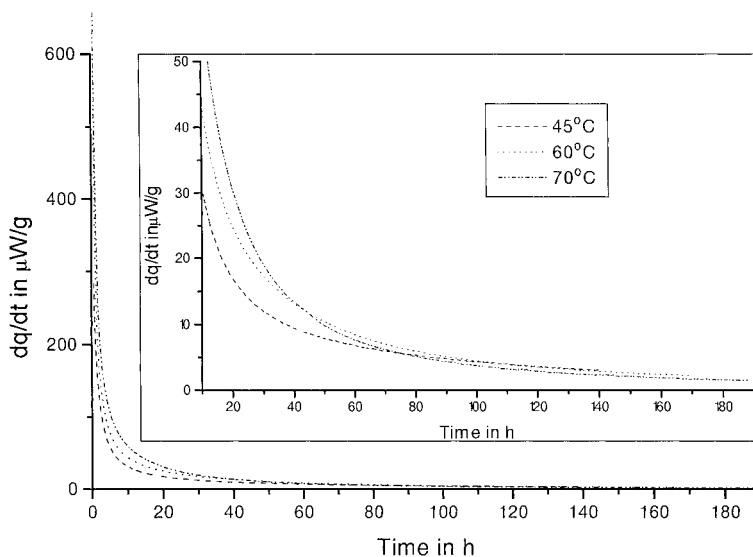

Fig. 6. Microcalorimetric heat flow signals at different temperatures for the phase transition form I → form II of anhydrous caffeine samples prepared in room air. In the smaller figure the time axis is scaled to 10 h–190 h.

tively, for the samples prepared in room air, the average of five measurements being −16.5 J/g. The corresponding values for exponent n were 0.24, 0.33 and 0.37. The values for rate parameter k were 5.86×10^{-7} 1/s, 8.08×10^{-6} 1/s and 2.16×10^{-5} 1/s yielding the activation energy of 134 kJ/mol.

To achieve the transformation degree as a function of time, the total energy evolved in the transition must be known. As the transition enthalpy for the reverse transformation was determined with DSC to be 16.4 J/g the enthalpy at any temperature for the transition form I → form II could be calculated using Kirchhoff's equation. This provides the knowledge of the difference in the heat capacities between the polymorphic forms over the whole temperature range. Unfortunately, this is impossible to measure with DSC because of the high tendency of sublimation of caffeine molecules and the transition process progressing in the sample of form I.

The value of the transition enthalpy was also defined with solution calorimetry at the specific temperatures of interest. The heat of solution values for both of the forms were measured at 25°C, 45°C, 60°C and 70°C, and applying the Hess's law the heat for the transition form I → form II was obtained as a function of temperature. As the heat of solution values was corrected for buoyancy of air, heat of evaporation and temperature but not corrected for the conversion of the

form I during temperature equilibration (ca. 1 h) the equation for the transition enthalpy was $\Delta H_{\text{trs}} = (0.0721T - 14.1)$J/g, where T is in °C. The correlation to temperature seems evident but after the correction due to conversion during equilibration according to IMC measurements, the value for transition enthalpy is not depending on the temperature the average being −14.7 J/g. However, in this work, the transition enthalpy was considered to be −16.53 J/g based on the consistency of IMC and DSC results.

The heat flow signal caused by the thermally active transformation progressing in the measurement ampoule can be recorded just after the thermal excursions due to lowering of the sample in the measurement position have dissipated. The time was determined to be the point where the differentiated dq/dt-curve started to increase monotonically. The portion of the unrecorded data to the total energy was extrapolated by using the Avrami relationship. The estimation of the real heat flow curve, at the very beginning of the measurement was troublesome as the heat conduction in the sample was unknown. The error made was about 5 percent at maximum. The quantitative results are represented in Fig. 7 together with XRD results from Fig. 5. As the evolved energy Q of the transition obtained from IMC data is plotted as a function of XRD quantitative results (Fig. 8), the nonlinear correlation indicates the
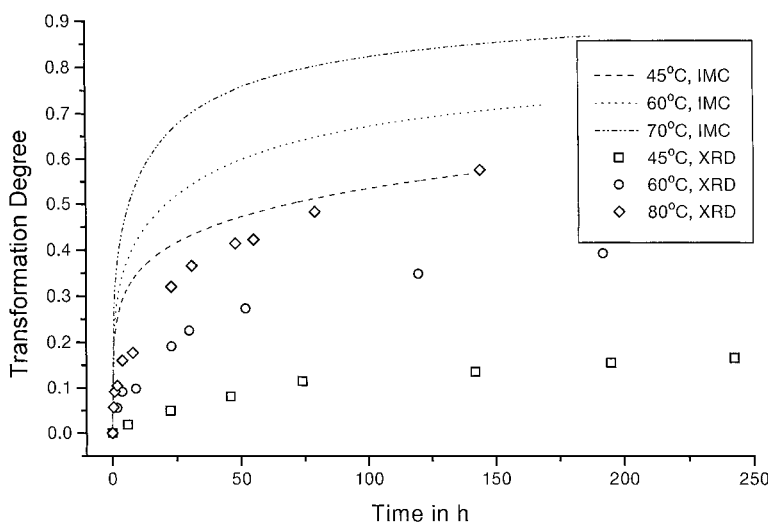

Fig. 7. The quantitative results of IMC and XRD as a function of time for the transition of anhydrous caffeine form I → form II.
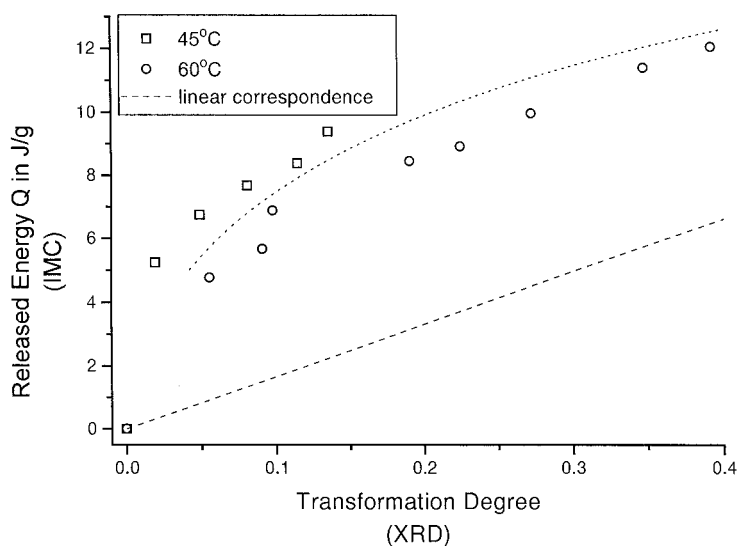
Fig. 8. Correlation of the evolved energy (quantitative results of IMC) and the transformation degree (quantitative results of XRD) for the transition of caffeine form I → form II at 45°C and 60°C. The dotted line stands for both of the symbols and crosses the point (0, 16.5).

transformation to begin at regions with high stored energy.

Though the total energy change in the transformation is not known, the similarity of the transition mechanism through the transition could be checked. Defining the heat flow as a function of released energy (Fig. 9) and determining Arrhenius plots at different degrees of transition (Fig. 10), the corresponding activation energies can be calculated. The energy values of 6.0, 7.6 and 10.3 J/g in Fig. 10 equal to the transformation degree of 0.05, 0.2 and 0.3, respectively, according to the dotted line in Fig. 8. The total transition enthalpy was considered here as −16.53 J/g. The corresponding activation energies were 79.3, 90.8
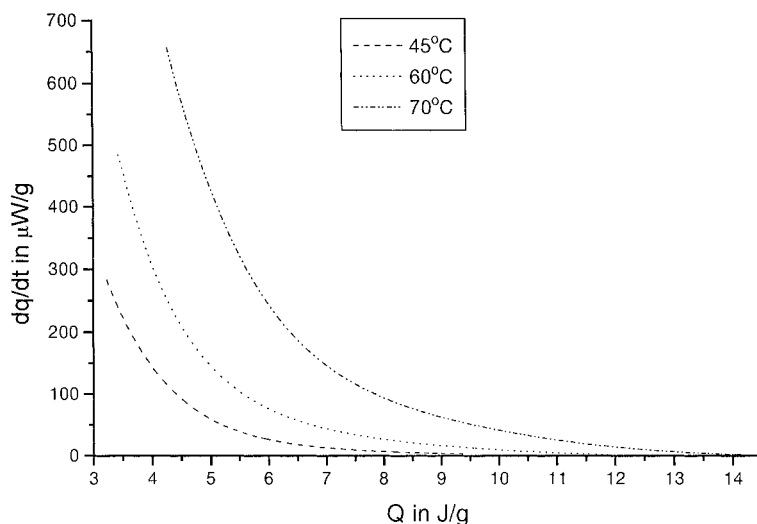

Fig. 9. Heat flow curves for the phase transition of anhydrous caffeine as a function of the released energy.
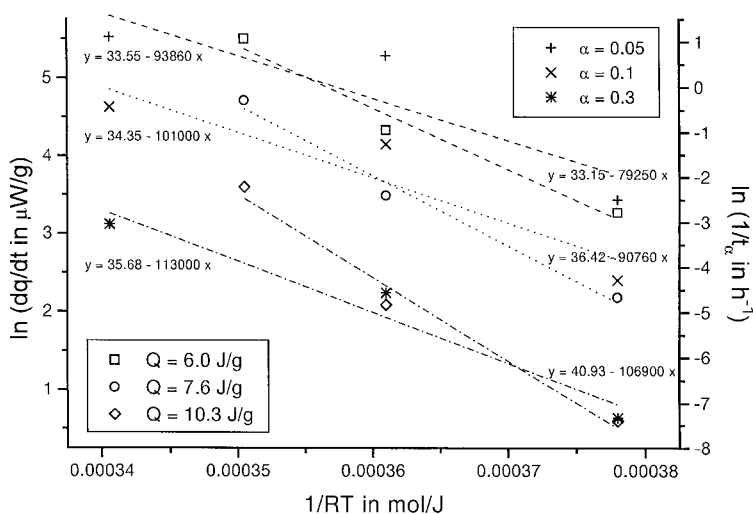
Fig. 10. Logarithmic heat flow values (left axis) and logarithmic $1/t_\alpha$ values (right axis) as a function of reverse temperature at different degrees of transformation. The slopes equal to the activation energies.

and 107 kJ/mol. Since, the activation energy increases as the transition proceeds, the transition mechanism is likely to change if the Arrhenius law is assumed to be valid.

5. Conclusions

The sensitivity of DSC was not good enough to detect the solid state crystallographic phase transformation of anhydrous caffeine form I to form II, but for the reverse transition the enthalpy value of 16.4 J/g was obtained. The actual transition temperature for the transition form II → form I was estimated to be less than 140°C, which was certified with IMC measurements with the samples prepared at different temperatures to be between 130°C and 135°C. For the transition form I → form II, IMC gave the enthalpy value of −16.5 J/g, which was well consistent with the result of DSC.

The values for the Avrami exponent n derived via both IMC and XRD data were abnormal low. If the transition would be diffusion controlled and one dimension growth from heterogeneous nucleation, the exponent n would be 0.5 at minimum. On the other hand, the low value for n could be attributable to the inhomogeneity of the microstructure. This would lead to nonrandom distribution of nucleation sites and

stored energy and to a growth rate which decreases with time. In both the cases, the Arrhenius relationship is valid, but in the latter the activation energy is depending on the transformation degree. The latter explanation is apparent in this study, since although the results obtained with IMC and XRD were not consistent, the transition mechanism of the transition of anhydrous caffeine form I → form II could be considered to change as the transformation progressed. This was obvious from XRD and IMC results as the activation energy increased as a function of transformation degree. Besides, when combining the quantitative results of IMC and XRD, the phase transition was observed to begin at the regions with high stored energy, i.e. high driving force to the transformation. This leads to the situation where a certain fraction of the transformation is associated with a greater energy evolution during the early stages of the transformation than during the later stages.

As the transition mechanism changes during the transformation process, it is understandable that for XRD measurements using the Avrami parameters to extrapolate the kinetics at room temperature gave erroneous results. The extrapolated value for the Avrami rate parameter k at 23°C was about 5×10^{-10} 1/s ($t_{1/2}$=9000 d if n=0.4) the measured value being about 7×10^{-9} 1/s ($t_{1/2}$=800 d as

n=0.5). Still, if the Avrami equation is wanted to be applied the activation energies derived at different transformation degrees should be employed.

As the transformations in solid state could be complex, the far advanced conclusions based on IMC measurements alone should be avoided. The microcalorimeter gives exact real time information on the structural changes progressing in a measurement vessel. Hence, can IMC give instant knowledge about the thermal activity and stability of the sample, especially, when the transformation starts with a highly energetic process, e.g. nucleation. However, the predictions could fail due to insufficient knowledge of the transition mechanism. To avoid mistakes, the results should be verified with other analytical methods.

Acknowledgements

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