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A Kinetic Study on Crystallization of an Amorphous Lubricant

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Purpose. The purpose of the work was to study the crystallization kinetics of amorphous sterotex K at different temperatures and with different methods, and to compare the obtained kinetic and thermodynamic results.

Methods. Isothermal microcalorimetry was the principal technique to determine the crystallization behavior of sterotex K. X-ray powder diffraction and differential scanning calorimetry were employed to interpret the microcalorimetric heat flow curves and compare the kinetics and the calculated value for the transition enthalpy.

Results. The best way to analyze the x-ray diffractograms was the statistic Wakelin's correlation method. The method gave consistent quantitative results with microcalorimetry and both methods showed crystallization to consist of two partially parallel part-processes, which attached probably to the different growing rates of the forms consisting of different lattice planes having the same spacing. The quantitative analysis of differential scanning calorimetry scans was troublesome to perform but the obtained average value of −51 J/g for the enthalpy of the crystallization was in good agreement with the values obtained with the other methods, the average being −52 J/g. Calculating heat flow versus released energy plots from the microcalorimetric data the crystallization mechanism was observed to change as a function of temperature.

Conclusions. A sensitive isothermal microcalorimeter can give precise and fast knowledge about possible solid state transition mechanism, but the source of the heat flow signal must be verified with other analytical methods to avoid incorrect conclusions. Due to the sensitivity and the real-time data the microcalorimetry can show up the mechanism of the transition for varying as a function of temperature and reveal the uselessness of the conventional Arrhenius relationship for extrapolations.

KEY WORDS: amorphous material; crystallization; solid state reaction kinetics; XRPD; DSC; microcalorimetry.

INTRODUCTION

The lubricants used in the production of compressed dosage forms play an important role in the tableting process. In a wide sense lubricants are used to promote granule flow, prevent powder adhesion to punch faces, and to minimize die-wall friction (1). As crystal structure has an influence on the mechanical properties of the material, it can also affect the compression behavior and lubricant properties besides moisture content as has happened with magnesium stearate (2). The other factors affecting tableting have been reported to be particle size and surface area (3). The lubricant properties have been found to be better in the amorphous form as compared to crystalline forms (4,5) but the opposite conclusion, where the lubrication was found to depend mostly on water of crystallization, has been reported (6). As the amorphous form is always the metastable form, it transforms the stable modification spontaneously. However, metastable forms are used in the pharmaceutical industry because they have superior properties when compared to stable forms in some cases (4). As changes in the crystalline nature of a solid result in different physical properties, the sluggish transformation during storage can cause unexpected problems in processability of the powder. Furthermore, mechanical treatments, like compression and milling, can cause transformation processes and adversely change the properties of the powder (7). The transformation kinetics depend strongly on the temperature and thus momentary rising of the temperature during processing can affect the behavior of the powder. Therefore, the kinetics of the possible polymorphic transition or crystallization of the amorphous material should be known.

Determination of the stability of pharmaceuticals via chemical assays, e.g., chromatography, provides for possible changes in concentrations of a few percents. As degradation reactions in solid state may be slow and as rates of 0.5%/year at 25°C may have an impact upon the development of the drug, the time needed to complete the stability study may take up to several months. Therefore, the conventional technique typically consists of storing the sample at several elevated temperatures (and humidities) and determining the disappearance of the drug or the appearance of the degradation product. However, the analysis is still time-consuming and costly, and difficulties and inaccuracies in the extrapolation of the results are apt to arise. It is also noteworthy that the chemical assays are useless when the instability of the drug originates in changes in physical properties, e.g., transformations of the amorphous and polymorphic forms.

As the degradation reactions or crystallographic transformations usually obey some kind of exponential decay law (except autocatalytic-like reactions), the rate of heat production is the greatest at early stages of the reaction and therefore the calorimetric measurement produces the best data near the start of the reaction (heat is a by-product of nearly all reactions). Thus, a drug's stability could be determined in a short period. Due to its high sensitivity, isothermal microcalorimetry has been calculated to detect reactions with a rate of 0.01%/year (8). However, there have been few articles published in the field of material science concerning the slow solid state transformations of pharmaceuticals where no water is employed (9–13). The reports on the use of microcalorimetry in the studies of crystallographic transformations are almost totally nonexistent.

The aim of this work was to study the crystallization kinetics of an amorphous lubricant, sterotex K, with isothermal microcalorimetry and to compare the obtained kinetic and thermodynamic results with the results obtained via differential scanning calorimetry and x-ray powder diffraction. Sterotex K was chosen as the sample material because it was used in previous studies as an alternative to magnesium stearate, exhibiting negative interaction with other ingredients in a tablet formulation.

MATERIALS AND METHODS

Materials

Sterotex K is hydrogenated cottonseed oil (glyseryl-tris-12-hydroxy stearate, $C_{57}O_9H_{110}$) used as a stiffening agent, a

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sustained-release coating material, and a hardening agent (14) as well as a lubricant having mass portions of 0.1%–2% (1). The material was purchased from Orion Corporation, Turku, Finland. As the material exhibited similar crystallographic behavior as a function of temperature as did both triglycerides (15) and triglycerides-based suppositories, the unstable amorphous form was denoted as form A and the stable crystalline form as form B (16).

As the purchased sterotex K was not totally amorphous form A, the amorphism of the material was certified as follows. Sterotex K was melted at 80°C for at least three hours. The molten agent was solidified rapidly or quenched between two −18°C metal blocks so that the thickness of the solidified material was 0.5 mm. All the solidified and quenched samples were stored at least 24 hours at room temperature before starting any analysis. This storage was done to reduce the relaxation of the strains and the energy that were brought into the sample during quenching. The relaxation was observed as affecting the microcalorimetric measurements but the effect was undetectable with the other methods. The samples for all analysis were handled identically.

X-Ray Powder Diffraction (XRPD)

X-ray diffraction measurements were made with a Philips PW1050 angle dispersive powder diffractometer equipped with a hot stage. The temperature accuracy was in the range of ±1°C. The samples of the pure form A of sterotex K were placed in the hot stage, previously heated to measurement temperature. Because the measurement was prolonged for several hours the samples were stored in a temperature controlled oven between the diffraction scans. The diffractograms for form B were measured with individual samples heated for several days at 55°C until there were no detectable changes in the diffractograms.

The diffractograms were obtained with Ni-filtered CuK$_\alpha$-radiation (λ = 0.15418 nm, voltage 45 kV, current 35 mA) and with a 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 0.02° steps using 1.5 s averaging time.

The quantitative analysis could be performed in many ways. In this work the results with the highest precision and the best consistency were found to be obtained by Wakelin's statistical method (17,18). This method is suitable for polymorphic forms with the same mass absorption coefficients. There were some reductions and normalizations to be made in the measured diffractograms but the effects were minor. The data collected with Philips PC-APD program was totally uncorrected and the mathematical handling was done with ASCII form converted files in Origin. The determination of transformation degree α was based on the equation

$$\alpha = \frac{Y(\theta)}{X(\theta)} = \frac{I_c(\theta) - I_{sA}(\theta)}{I_{sB}(\theta) - I_{sA}(\theta)} \tag{1}$$

where $I_c(\theta)$, $I_{sA}(\theta)$ and $I_{sB}(\theta)$ are the intensity values as a function of reflection angle for the sample under study, for the sample of pure form A (A-standard) and for the sample of pure form B (B-standard), respectively.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry measurements were made with a Perkin-Elmer DSC7 instrument. The heating rate was 10°C/min and nitrogen (50 ml/min) was used as gas flow. The calibration was done with indium. The masses of the sample were about 3 mg. The analyses were performed in Origin with files imported as ASCII form.

Isothermal Microcalorimetry (IMC)

Isothermal microcalorimetry measurements were made with a Thermal Activity Monitor (TAM) (Thermometric AB) consisting of four independent isothermal heat-conduction microcalorimeters (19). The measuring technique and the calibration procedure were performed as described in the user manuals.

The quenched sterotex K was weighted (≤0.3 g) into calorimetric ampoules and the ampoules were inserted into the pre-equilibrium position within the TAM for 20 minutes. This time was referred to as t = 0 s. There were no differences found between using glass and stainless steel vials. Due to minor difference between the heat capacities of the reference and the sample, the empty ampoules were used as references. The baselines were recorded with empty measuring cylinders before and after the actual measurement and were used to correct the baseline drift during measurement. The baseline was assumed to be linear. All the measurements were made in duplicate at the least.

RESULTS AND DISCUSSION

XRPD

The diffractograms for crystallization of amorphous sterotex K at 50°C are shown in Figure 1. The increase in the sample temperature has an instant effect on the diffractogram, moving it to smaller 2θ values. This is a normal consequence of the temperature vibrations of molecules that cause the reduction in the intensity, the broadening of Bragg reflection, and the angular dependence of the reflection on temperature. This is the reason that the first measured diffractogram at t = 0 s for pure form A cannot be used in Wackelin's method since it leads to negative slopes for the regression line or negative values for the transformation degree α at the beginning of the crystalliza-

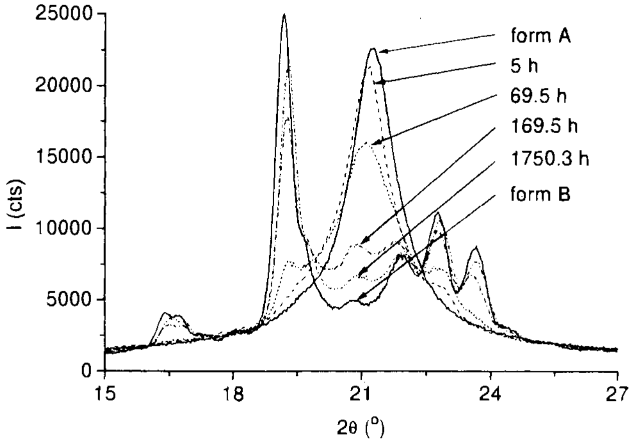

Fig. 1. The conversion of diffractograms in the range of 15° < 2θ < 27° during the crystallization of the amorphous sterotex K form A to the crystalline form B at 50°C.

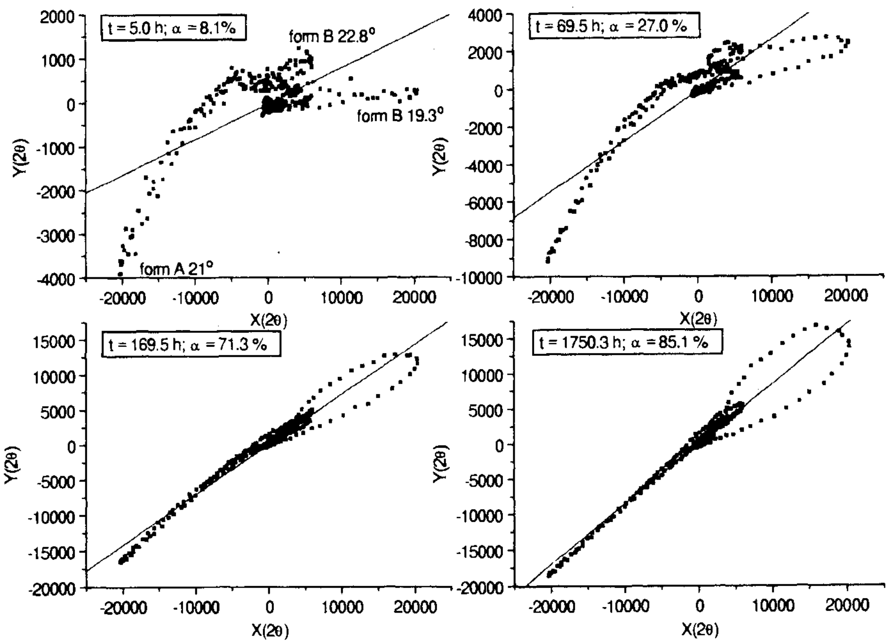

Fig. 2. The graphs for Wakelin's correlation method at different transformation degrees of sterotex K form A at 50°C.

tion. So, the first diffractogram recorded at the measurement temperature (t < 0.5 h) was regarded as the A-standard in Wakelin's correlation method. The effect on results was found to be less than 2 percent. The graphs for Wakelin's correlation method at different degrees of crystallization are represented in Figure 2. The slopes of the regression line directly give the relative amount of the form B for transformation degree α. In the first graph of Figure 2 there are marks to indicate the reflections at 22.8° and 19.3° for form B and at 21° for form A. It is noteworthy that the reflections do not convert with the same rate and thus the slope of the regression line gives just an average of the transformation degree. The correlation coefficient is higher the farther the crystallization has progressed.

The differentiated transformation degree curves versus time are shown in Figure 3. The curves suggest the crystallization process consists of two partially overlapping processes, at least at temperatures of 55°C and 50°C. Thus, the use of one kinetic fitting function in transformation degree curves is not accountable.

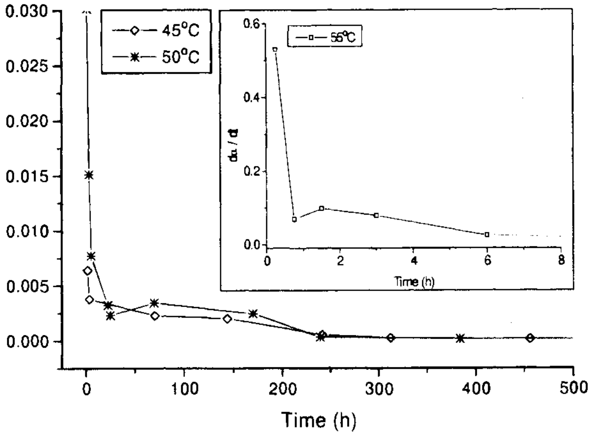

Fig. 3. Differentiated curves for the transformation degree versus time curves obtained with Wakelin's correlation method.

DSC

The heating rate in DSC measurements was kept quite high so that the transformation would proceed as little as possible during the measurement itself. At the heating rate of 10°C/min there was no exothermic peak in the thermogram, although the crystallization should produce one. The exothermic peak was observed with the heating rate of 1°C/min after an endothermic peak but it was tiny and was not suitable for quantitative analysis. The melting endotherm (~30 J/g) was situated at about 87°C.

Changes in the thermograms for the crystallization of sterotex K at 50°C are shown in Figure 4. The thermogram for form B was measured with a sample stored at 55°C for several days. At the very beginning of the transformation the thermograms change remarkably as the first endotherm at 63°C disappears and the peak at 75°C starts to grow. The analyzed endotherm is illustrated with arrows in Figure 4. Multiple Gaussian curve fitting was employed in the analysis to determine the relative change in the area of the endotherm at 75°C. Due mainly to the interpolation of the nonlinear baseline over the temperature range 50°C–90°C the precision of the results was quite poor.

An estimate for the enthalpy of the crystallization process could be made on the basis of the thermograms of the pure form A and form B in accordance with the scheme in Figure 5. The total area of the thermogram between 48°C–92°C for the melting of form A was obtained as 123 J/g as an average of five measurements. The corresponding value for form B was determined to be 174 J/g. As a substraction −51 J/g is obtained for the transformation of form A to form B.

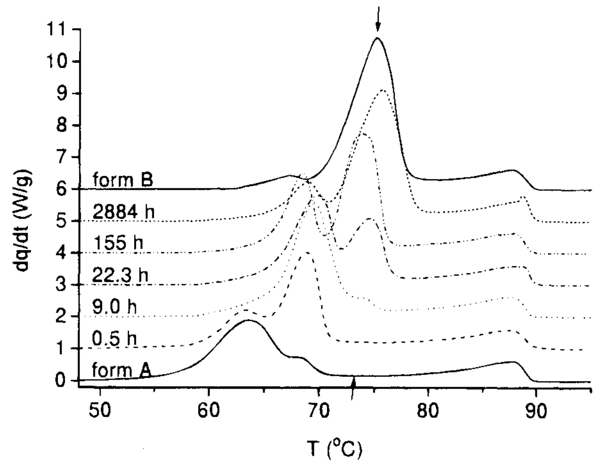

Fig. 4. The heat flow curves of DSC as a function of temperature for the samples of amorphous sterotex K form A stored different times at 50°C. The endotherm used in quantitative analysis is pointed out with arrows.

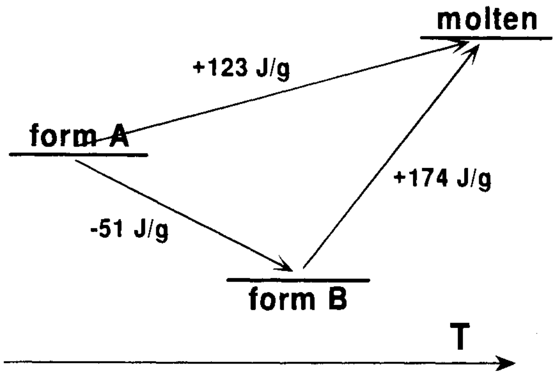

Fig. 5. The scheme for phase transitions of sterotex K and the corresponding values for enthalpies determined with DSC.

IMC

The samples for IMC measurements were prepared in the same way as the other methods in this paper. After the rapid cooling of the melted sterotex K, the solidified matter was annealed at room temperature for two days in order for the energy and strains stored in the sample during quenching to relax and not give any signal in IMC, which would hinder the comparison of the results.

In Figure 6 is shown the heat flow curves for the transition form A → form B of sterotex K at three temperatures. At first the signals rise to milliwatts per gram at higher temperatures, which then fall rapidly at a moderate level of heat flow. The signals are clearly observable even after hundreds of hours.

As represented in Figure 6, there is a shoulder in the heat flow curves at 55°C and 50°C. This suggests that the crystallization process consists of at least two statistically overlapping part-processes as was found with XRPD studies. As there was no shoulder observed in the heat flow curves at 45°C the part-processes are either likely to progress inseparably and parallel or the transition mechanism changes as a function of temperature.

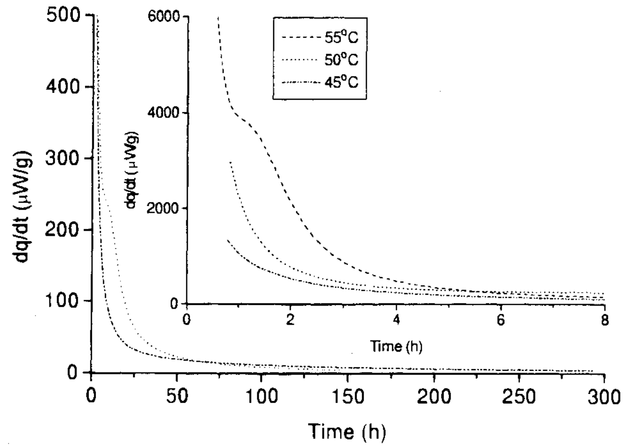

Fig. 6. The heat flow curves of IMC for the crystallization of sterotex K form A at 45°C, 50°C and 55°C.

To calculate the transformation degree curve from IMC data, the total heat exchange of the transition or the transition enthalpy ΔH_{tr} should be known. To get a reliable value for ΔH_{tr} from the heat flow curve of IMC the measurement had to cover a large part of the reaction. Otherwise, the extrapolations needed to estimate the trace of the signal before and after the measured data points might fail. Of course, the reaction enthalpy could be obtained with other methods, e.g., DSC. One possibility is as follows. First, the heat flow curve was integrated and the unmeasured part at the beginning of the transformation was estimated. The estimation was critical since it contributed several percents to the total evolved energy. With sterotex K, the estimation was difficult to perform reliably due to high initial heat flow values. As the conduction of the heat through the sample was unknown and the exact calorimetric trace during the first half hour was impossible to approximate, the initial unmeasured portion was estimated according to the first data point of the integrated curve as a triangle, which equals the use of a rectangle in the calorimetric data. The portion obtained was about the same magnitude when compared with quantitative diffraction results. The estimated portion was added to the integrated data points and the transformation degree of the transition at the end of the measurement was estimated with the help of the quantitative XRPD results. The value for the total heat exchange could thus be calculated and using the value as a divisor the integrated heat flow curve could be turned into the transformation degree curve versus time. In Table 1 values for transition enthalpy of the crystallization process of sterotex K obtained with different analyzing methods and

Table 1. Comparisons of Values for the Transition Enthalpy of Amorphous Sterotex K Obtained with Different Techniques

Technique	T (°C)	ΔH_{tr} (J/g)
DSC	—	−51
IMC + XRPD	45	−55.5
IMC + XRPD	50	−47.7
IMC (Avrami)	55	−52.2
IMC (mod. Prout-Tompkins)	55	−53.5

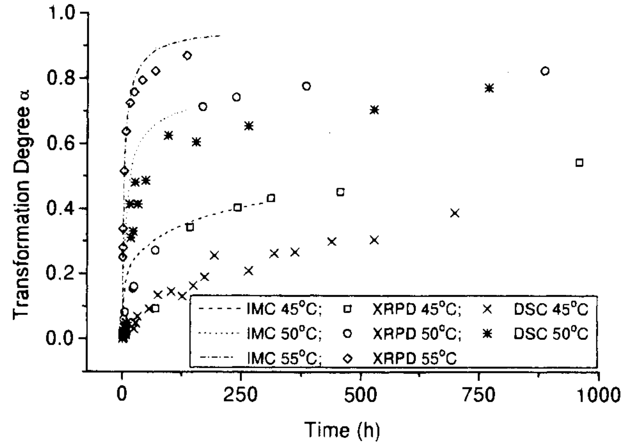

Fig. 7. Transformation degree obtained with DSC, XRD and IMC as a function of time for the transition form A → form B of sterotex K at 45°C, 50°C and 55°C.

calculating techniques are listed. The transition proceeds at 55°C so quickly that the IMC heat flow curve alone can be used to get ΔH_{tr} by fitting the kinetic Avrami or modified Prout-Tompkins equations to the last data points of the integrated heat flow curve (20). The transformation degree curves together with the quantitative results of XRPD and DSC have been summarized in Figure 7. The data points of IMC and XRPD meet well, especially at 45°C and 50°C, due the calculating technique of IMC data but, DSC systematically gives quantitative values too low for the degree of the crystallization.

The heat flow curves, as a function of released energy Q, are shown in Figure 8. The heat flow curves should be of similar shape if the transition mechanism does not differ at different temperatures. With sterotex K the inflection-points situate at different Q values due to the dissimilar shapes of the curves. Accordingly, the activation energy cannot be calculated through the Arrhenius relationship for the transition as a whole but the part-processes can be separated and manipulated as individuals.

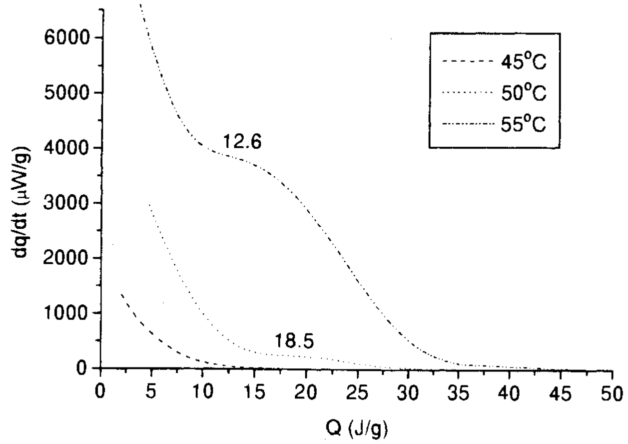

Fig. 8. The heat flow curves as a function of evolved energy indicating changes in the crystallization mechanism of amorphous sterotex K. The inflection-points are marked.

CONCLUSIONS

The consistent results obtained with XRPD and IMC for the transformation degree of the crystallization of the amorphous sterotex K form A to crystalline form B show that the transformation consists of two part-processes. In our previous study (7) the same kind of crystallization process of tripalmitin was observed as starting via the formation of nuclei which give an outstanding response in IMC measurements but the nuclei were found to be so small that no constructive interference was produced in X-ray scattering due to the nuclei size. In this study the situation was of another kind and the crystallization process could be detected with XRPD and IMC completely. In the graphs of heat flow versus released energy, the transition mechanism was observed to change as a function of the temperature. The conclusion was supported by the XRPD results as the differentiated transformation degree curve at 45°C indicated no part-processes, as was also the case with the IMC measurement. DSC was used to analyze the transition quantitatively, also, but the precision of the results was poor and the method was troublesome. However, DSC gave the average value of −51 J/g for the transition enthalpy that was in agreement with other values calculated, the average being −52 J/g.

The most difficult part of analyzing the IMC data was the estimation of the initial unmeasured part of the transition. To estimate the heat flow trace during the first ten minutes of the reaction reliably, knowledge of the heat conduction would be essential. The significance of the initial part is more important the higher the signal is at the beginning of the reaction. Thus, an autocatalytic-like reaction is the most convenient transition to investigate with IMC. However, IMC is a rapid, accurate, and easy method to apply, but due to its unspecific nature it needs complementary analysis by other methods to certify the exact source of the heat flow signal. The researcher should also bear in mind that the thermal history, e.g., the conditions of the quenching, can have an effect on the stored energy that is released during the phase transition.

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