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Polymorphic behavior of a yellow isoxazolone dye

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Abstract

The crystal growth of a monotropic polymorphic system of a yellow isoxazolone dye has been studied. One of the two metastable polymorphs grows into a needle-shaped morphology; the stable form is rhombic. The metastable third polymorph grows only from the melt and has a solid–solid phase transition to the needle-shaped form within hours at any temperature below the melting point. The polymorphic phase diagram has been determined for a wide range of concentrations in three solvents.

Keywords: Polymorphism; Morphology; Phase diagram; Isoxazolone dye

1. Introduction

A substance showing polymorphism is capable of crystallizing into different crystalline forms, resulting in different arrangements of the molecules in the solid state. Although each polymorph contains the same compound, the physical properties can differ significantly. The difference in crystal structure, in principle, leads to a difference in density, melting point, stability, solubility, morphology, optical properties, etc. Even if only one of these properties is critical, it is essential to selectively nucleate and grow the desired polymorph and to avoid possible transitions to another form. For example, in the photographic industry single crystalline compounds instead of amorphous powders are used because of their anisotropic optical properties, which can be used advantageously. To produce high quality products in a well-controlled way, a good knowledge of the polymorphic system is a must. Because the crystallization of one specific polymorph is controlled by a combination of thermodynamic and kinetic factors, it is necessary to determine the difference in Gibbs free energy as well as the difference in nucleation rate between the polymorphic forms.

In this work different polymorphic forms of an isoxazolone dye, that is used as a filter dye in photographic films, and the polymorphic phase diagram are studied to address the needs mentioned above for producing crystals in a well-controlled way. Differential scanning calorimetry (DSC) is used to study the phase transitions between the polymorphs. To determine the dissolution enthalpy and the dissolution entropy, solubility curves are measured for solvents such as methanol, ethanol and 2-propanol. Also the metastable zone width at well-defined cooling rates is measured for each polymorph in these solvents as a function of temperature, both for filtered and unfiltered solutions. The relevance of the measured polymorphic phase diagram in industrial applications is discussed.

2. Polymorphism

2.1. Thermodynamics

The polymorph that nucleates first is not necessarily the stable form. Ostwald already formulated this in 1897 in his rule of stages [1], to explain the appearance of metastable polymorphs. Nowadays, it is generally accepted that any compound can have different polymorphs, although they

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are not always observed. Based on the mutual stability of the polymorphs as a function of the temperature different polymorphic systems can be distinguished, which are described by Burger and Ramberger [2]. There are two main types of polymorphism, enantiotropic and monotropic. For a monotropic system one of the polymorphs is in the stable form at all temperatures. Only in that case an exothermal solid–solid phase transition of a metastable to the stable form can occur spontaneously. In case of enantiotropic polymorphism the solid–solid phase transition is reversible and there is a phase transition temperature that separates a low temperature stable form and a high temperature stable form. The phase transition is endothermic on heating. Because of the corresponding crossing of the free energy curves below the melting temperature also the solubility curves show this intersection point. At the transition temperature T_{tr} both forms are equally stable and may co-exist. The transition temperature is determined by thermodynamics, so independent of the solvent used [3].

A quick and easy method to obtain an insight of the polymorphic phase diagram is DSC. In general, polymorphs have different melting points and will also have different melting enthalpies. So, by recording DSC traces, the transition temperatures and corresponding enthalpies can be determined and thus information on the polymorphic phase diagram can be obtained. Starting from the melt, upon cooling, the kinetically most favorable polymorph will crystallize first and might subsequently transform into the thermodynamically most stable one. Though not frequently observed, this transition might be intermediated by other metastable phases.

More detailed thermodynamic information is obtained by measuring solubility curves. For a regular solution the relation between the dissolution Gibbs free energy (ΔG^{diss}) and the solubility x as a mole fraction is:

$$\ln x = \frac{-\Delta G^{diss}}{RT} = \frac{-\Delta H^{diss}}{RT} + \frac{\Delta S^{diss}}{R} \quad (1)$$

from a Van't Hoff plot, i.e. the logarithm of the solubility versus the reciprocal of the absolute temperature, it is possible to determine the dissolution enthalpy ΔH^{diss} and entropy ΔS^{diss} directly. The restriction is that this equation is based on the assumption of regular solutions, i.e. a nonzero enthalpy of mixing and an ideal mixing entropy. This limits its use in most cases to highly diluted solutions.

2.2. Kinetics

According to Bernstein et al. [4] the most important kinetic factor in a polymorphic system is the nucleation rate. This rate will be different for each polymorph, and is not determined by the thermodynamic stability alone. The competition between the gain of bulk energy and the cost of surface energy plays the key role in the process of nucleation. For a spherical nucleus the corresponding Gibbs free energy is:

$$\Delta G(r) = -\left(4\pi r^3/3\Omega\right)\Delta\mu + 4\pi r^2\gamma \quad (2)$$

where r is the radius of the nucleus, Ω is the molecular volume, $\Delta\mu$ the driving force for crystallization and γ the surface free energy. So, the surface-to-volume ratio determines when a nucleus has the critical size ($r = r_c$) and becomes stable. In general, the nucleation barrier, $\Delta G(r_c)$, also determines the size of the metastable zone, which is the supersaturation needed to observe crystals in a given time. The nucleation rate (J) of each polymorph is related to the Gibbs free energy of this critical nucleus according to the equation:

$$J = A\exp(-\Delta G(r_c)/k_B T) \quad (3)$$

where A is a kinetic constant depending on the substance used. Also the nucleation mechanism, either homogeneous or heterogeneous, is important in order to determine which polymorph will nucleate first. The presence of foreign particles may not affect the nucleation rate of each polymorph equally but has its influence on the metastable zones. The result is that often the stable form will not be formed first, but rather the nearest metastable one, which has a lower nucleation Gibbs free energy ($\Delta G(r_c)$). There is a certain amount of activation energy necessary to transform from a metastable structure to a thermodynamically more stable polymorph, though this will eventually occur in time. This explains the coexistence of different polymorphic forms, often called concomitant polymorphism [4].

3. Materials and methods

The pure isoxazolone dye was provided by Agfa-Gevaert N.V. and used as received. The molecular structure is shown in Fig. 1, the bulk crystal structures of the rhombic and needle-shaped polymorphs at room temperature were determined based on single crystal XRD data (see Table 1) [5]. The unit cells show clearly a different arrangement of the molecules (Fig. 2). In the rhombic shaped polymorph two molecules stack to form centrosymmetrically-arranged dimers in an alternating open structure. The needle-shaped form consists of

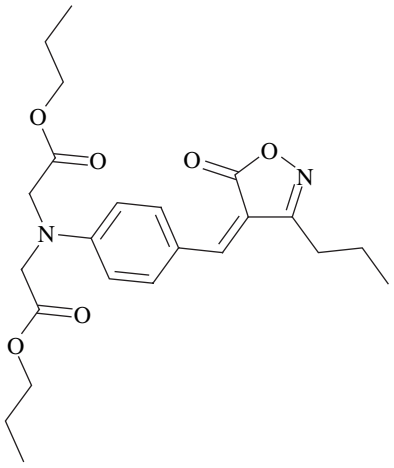

Fig. 1. Molecular structure of the isoxazolone dye.

Table 1
Unit cell parameters of two polymorphic forms of the isoxazolone dye

	Rhombic shaped polymorph	Needle-shaped polymorph
	Monoclinic	Orthorhombic
	$P2_1/n$ (no. 14)	$Cmc2_1$ (no. 36)
a (Å)	10.801(4)	33.667
b (Å)	13.229(4)	13.705
c (Å)	17.310(6)	9.650
α (°)	90	90
β (°)	102.28(2)	90
γ (°)	90	90
Z	4	8
V (Å^3)	2416.8(14)	4453.9

a herringbone like structure where all molecules stack along the direction of the needle.

The solvents used were methanol, ethanol and 2-propanol, all of p.a. quality (Merck). Solutions with a known concentration were filtered over a 0.22 μm Millipore filter and put in a closed glass vessel which was placed in a temperature controlled cell connected to a Julabo F25 waterbath ($\Delta T = 0.01$ °C) (see Fig. 3). The temperature in this cell was measured using a PT 100 resistance thermometer ($\Delta T = 0.01$ °C). The temperature was lowered (10–0.1 °C/h) and the crystallization process was monitored with an optical microscope. To determine the equilibrium temperature of a polymorph, the temperature of the vessel with crystals of that polymorph in solution was varied carefully. The average of the temperatures for which the crystals just started to grow and just dissolved, respectively, was chosen as the equilibrium temperature. The DSC diagrams were measured using a Mettler Toledo DSC822 with the following conditions: aluminum pierced pan, temperature changes of 10 °C/min and a nitrogen atmosphere (40.0 ml/min). To characterize the products a powder XRD diagram was measured using a Philips PW1820 diffractometer with a Cu target ($\lambda = 1.5406$ Å) at room temperature. Powder XRD measurements of all products formed were compared with calculated spectra of the two known structures (Fig. 4). Since the polymorphs as well as the molecules have very characteristic optical absorption spectra, the concentration and the occurrence of degradation products were monitored using a Perkin Elmer Lambda 35 UV–vis spectrophotometer with a PTP-1 temperature controller.

4. Results and discussion

4.1. Nucleation

It was already known that the isoxazolone dye could crystallize from methanol into two possible morphologies, a rhombic form and as needles (see Fig. 5). Both polymorphs can be nucleated from all solvents used and at all concentrations studied, depending on the cooling rate. Slow cooling rates, 0.1 °C/h, give the rhombic form while more rapid cooling always results in needles. When nucleated, one to 10 nuclei per cm^3 of the rhombic polymorph grow out to separate mm-sized single crystals in a few hours. The needles always nucleate on the glass or on foreign particles as clusters or spherulites. Thousands of needle crystals per cm^3 grow out in a few seconds. The kinetics of the system is clearly in favor of the needle-shaped polymorph. When the solution is not filtered, i.e., when more foreign particles like dust or other impurities are present, nucleation of these needles always occurs first, in that case independent of the cooling rate. Conversion of the needle-shaped polymorph to the rhombic one always occurs via the solvent; solid–solid phase transitions are never observed, neither dry for all temperatures up to the melting point nor in solution. Looking at the crystal packing in Fig. 2, the large differences between the structures explain the large kinetic barrier for such a transition.

4.2. DSC

A different shape alone is not a proof for polymorphism, as a change in supersaturation can influence the morphology of a crystal dramatically. Therefore, DSC measurements on both products were performed. Figs. 6 and 7 present DSC heating runs starting from room temperature for the two habits. The rhombic shaped crystals have a melting peak at 94.4 ± 0.2 °C, with an onset at 88.5 ± 0.1 °C and an enthalpy of melting of $\Delta_{fus}H = -32.4 \pm 0.9$ kJ/mol (Fig. 6). The needle-shaped crystals have a melting peak at 90.0 ± 0.2 °C, an onset at 86.4 ± 1.4 °C and $\Delta_{fus}H = -27.3 \pm 0.9$ kJ/mol (Fig. 7). Neither a solid–solid phase transition is observed nor crystallization of the rhombic shaped crystals from the melt. These runs show a clear difference in melting point and enthalpy, for high temperatures the rhombic habit crystals are the stable

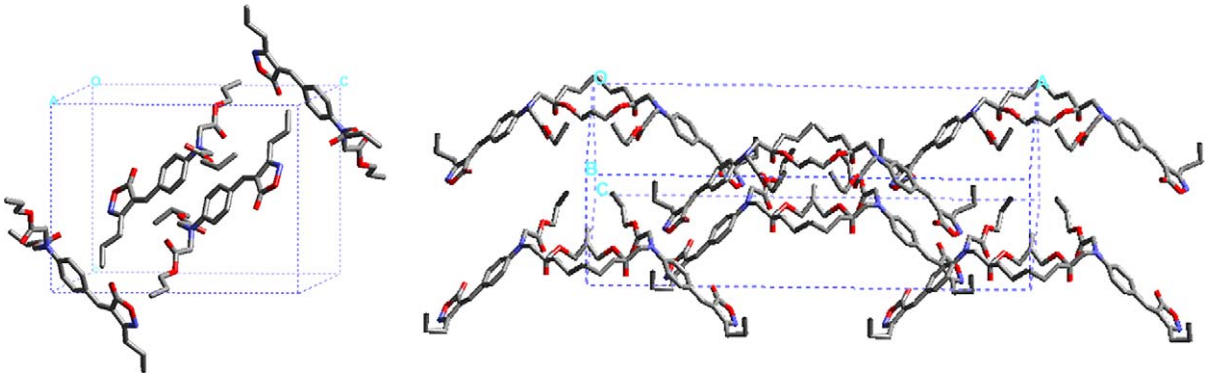

Fig. 2. Unit cells of the rhombic polymorph (left) and the needle-shaped polymorph (right).

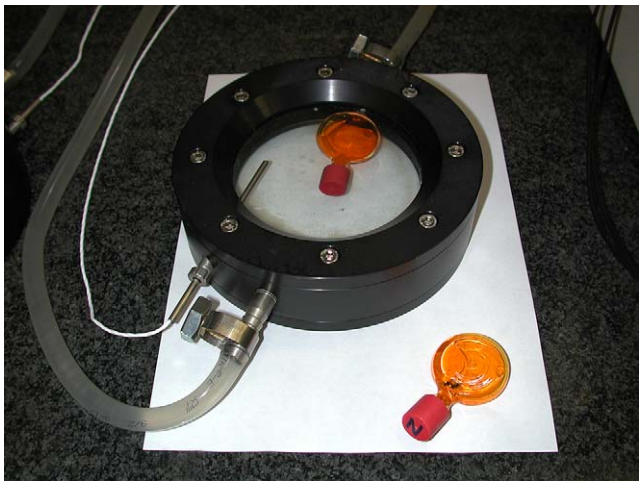

Fig. 3. Temperature controlled cell containing a closed glass vessel with the dye solution, for in situ observation of crystal growth.

polymorph because of the higher melting temperature. Both these samples were subsequently cooled down until −60 °C but no phase transitions were observed, not at a cooling rate of 10 °C/min or for 1 °C/min. When the temperature was subsequently raised for a second heating run, again by 10 °C/min, the results for both samples were identical. In Fig. 8 the corresponding DSC trace is given, showing a small endothermic peak at −6 °C, a broad exothermic peak around 55 °C and one sharp endothermic peak at 90.0 °C, the latter corresponding to the melting peak of the needle-shaped form. Quick cooling of a melt often leads to an amorphous product that on heating undergoes a glass transition followed by crystallization [6], which explains the other two peaks. To monitor the crystallization and melting processes visually a hot stage microscope was used. Single crystals of the polymorphs were heated up to 120 °C, approximately 10 °C/min. For the rhombic shaped polymorph a melting point of around 94 °C was observed and for the needle-shaped crystals around 90 °C, and no other transitions. From this melt, upon cooling, again no transition was observed. A second heating run showed crystallization around 60 °C and melting at 90 °C. These observations are consistent with the DSC measurements.

Nevertheless, when the sample is not immediately heated for the second heating run but brought to room temperature, another product starts to crystallize after approximately 2 h. DSC measurements on this product (Fig. 9) show a melting peak at 86.1 ± 0.4 °C and a second one at 90.0 ± 0.2 °C, the latter again corresponding to the melting peak of the needle-shaped form. No transition or crystallization peaks were found as presented in Fig. 8. We were not able to isolate the product that melts at 86 °C for identification because this form and the needle-shaped polymorph always co-existed. Nevertheless, the combined product always fully transformed into the needle-shaped polymorph within 12 h at room temperature: powder XRD measurements of a fresh sample show reflections of the needle-shaped polymorph, some amorphous product as well as extra peaks, of which the latter disappear with time. The amorphous background did not disappear. This unidentified crystalline form was never observed to grow from solution.

4.3. Solubility curves

For the solubility curves various known concentrations in the closed glass cell were used. To be certain that no degradation products were formed or other reactions took place the concentration was determined after the growth experiments with the use of UV−vis spectroscopy. When the concentration measured afterwards differed from the original one, e.g. because the solution was degraded as a result of heating or light, the measurement was rejected. This is visible by the presence of another optical absorption peak at 325 nm. At high concentrations a blue shift of the maximum was observed, showing that a strong interaction between the dye molecules occurs, resulting in a more ordered solution. As a result the solution does not have an ideal character and Eq. (1) is no longer valid. This is clearly visible in Fig. 10 where the solubility curves are shown for methanol; the equilibrium temperature at high concentration is lower than expected. For all the three solvents

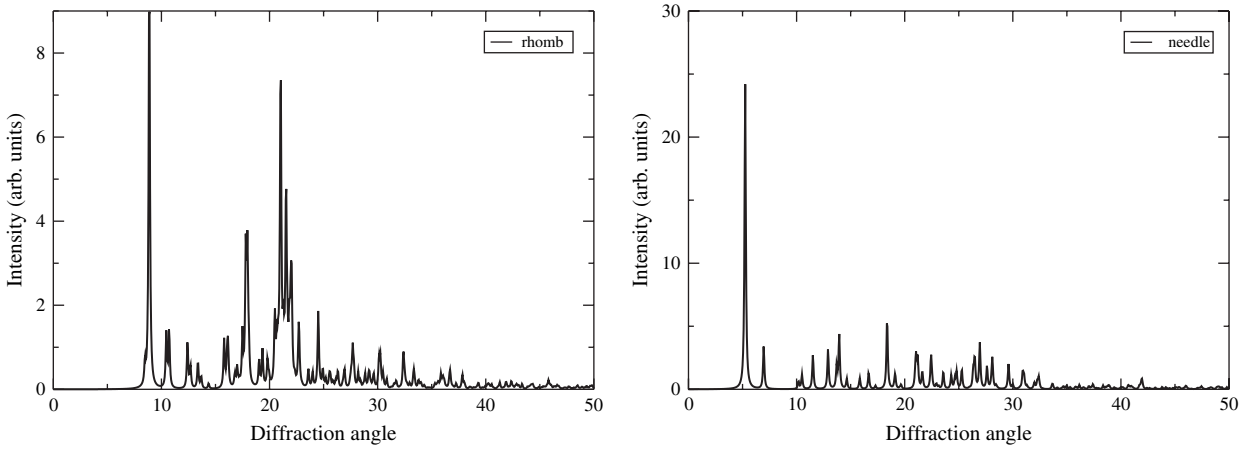

Fig. 4. Simulated powder XRD spectra of the rhombic polymorph (left) and the needle-shaped form (right). The clear differences allow unambiguous assignment of the measured powder XRD spectra to either of these forms.

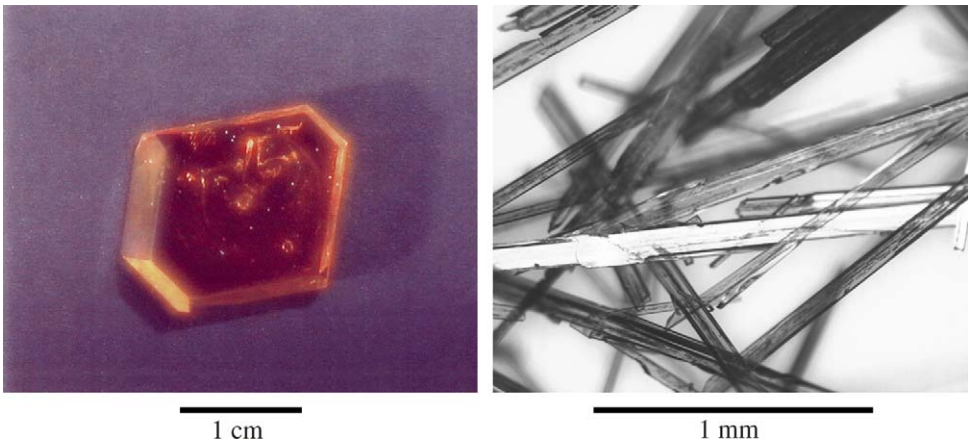

Fig. 5. Two polymorphic forms of the isoxazolone dye, to the left a rhombic shaped crystal and to the right needle crystals.

used we find a regular character of the solution at low concentration, and a clear deviation from this at higher concentration.

To get an impression of the metastable zone width of both polymorphs the nucleation was studied in more detail. In general, when continuously cooling down, first the metastable needles nucleate followed by a transition to the stable rhombic phase in time. Only at a small cooling rate of 0.1 °C/h separate nucleation temperatures for both polymorphs are clearly observed: nucleation of a few rhombic crystals, followed by nucleation and quick growth of clusters of needles. But at concentrations where the solubility curves deviate from the regular solution behavior the rhombic polymorph nucleates selectively. The metastable phase is formed at these high concentrations only by precipitation, resulting in many well-separated very fine needles. In Fig. 11 the equilibrium and nucleation temperatures are plotted in relation to the mole fraction for a filtered solution. Similar results were found for ethanol and 2-propanol. This nucleation behavior is only partly in accordance with Ostwald's rule of stages, which states that the metastable polymorph nucleates first, followed by a transition to the stable phase. For higher concentrations, in the non-linear part of the solubility curves, the stable polymorph nucleates. This might be a result of some ordering in the solution, like the formation of dimers, which are favorable precursors for the structure of the stable phase (Fig. 2). This would also explain the blue shift of the optical absorbance spectrum as observed. A similar reasoning can explain the nucleation at lower cooling rates; for such rates the solute apparently has enough time to form precursing dimers which favor the formation of the stable polymorph.

The results of the fit of the solubility measurements to Eq. (1) are summarized in Table 2. The difference in enthalpy

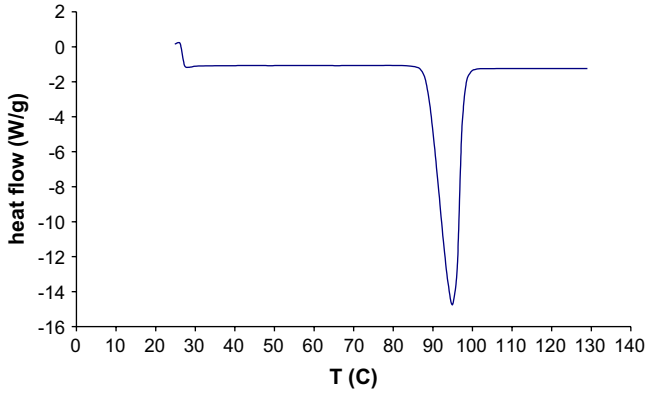

Fig. 6. DSC heating run for the rhombic habit crystals, the melting peak is at 94.4 °C.

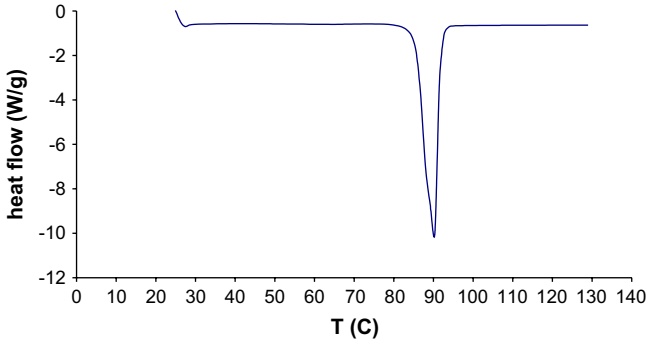

Fig. 7. DSC heating run for the needle habit crystals, the melting peak is at 90.0 °C.

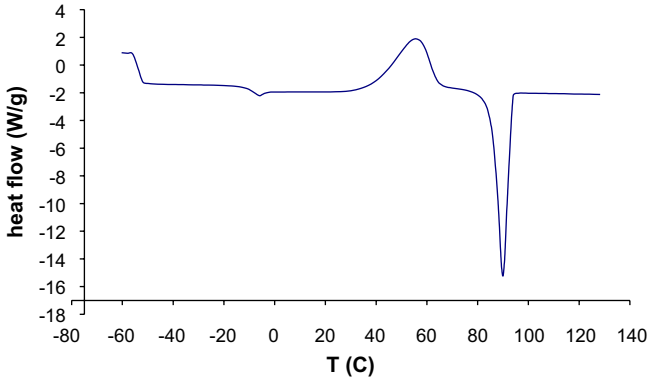

Fig. 8. Second DSC heating run, starting from an undercooled melt, peaks at −6.0 °C, 55 °C and 90.0 °C.

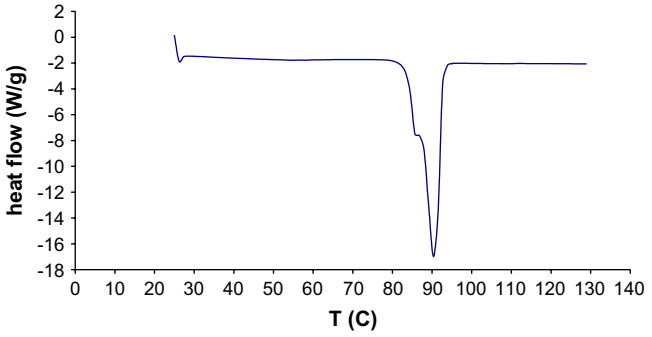

Fig. 9. Third DSC heating run, the starting material had been crystallized from the melt that was cooled down to −60 °C and subsequently kept at room temperature for at least 2 h, peaks at 86 °C and 90.0 °C.

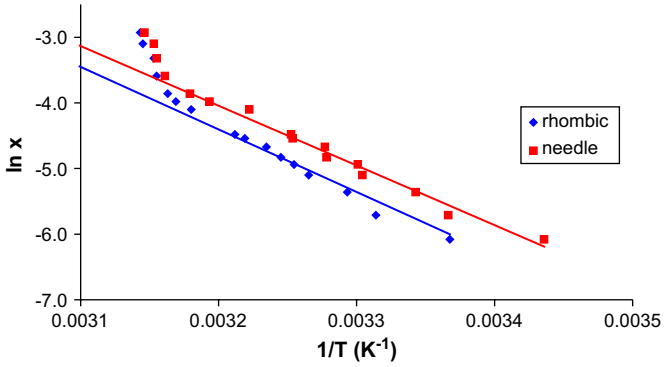

Fig. 10. Measured equilibrium concentrations in methanol for the two polymorphic forms as a function of the temperature. The solid lines are based on Eq. (1), a deviation at high concentrations is clearly visible for both forms. This is due to some structural ordering of the dye molecules in solution. The rhombic polymorph is always the thermodynamically stable form; therefore this is a monotropic polymorphic system.

between both polymorphs, $\Delta\Delta H$, equals the difference in the dissolution enthalpies for any solvent and the difference in melting enthalpies. Using the solubility data for each solvent as well as the melting enthalpies found in the DSC measurements, we find an average difference of 5.0 ± 0.4 kJ/mol. The difference in dissolution entropy, $\Delta\Delta S$, is 12 ± 2 J/mol K.

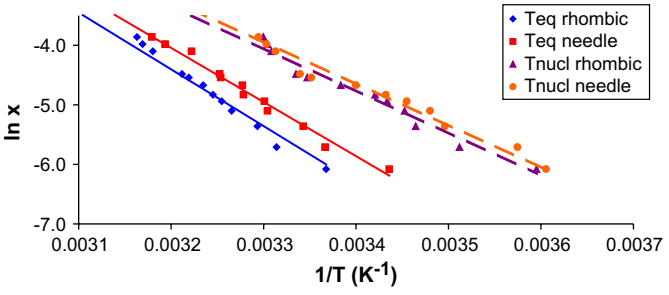

Fig. 11. Measured equilibrium temperatures and nucleation temperatures of the two polymorphic forms as a function of the mole fraction x in methanol. The nucleation temperatures were determined for a cooling rate of 0.1 °C/h. Only the low concentration data are used to fit the data to Eq. (1) (solid lines). The dashed lines are a guide to the eye.

Table 2
Results of a fit of Eq. (1) to the solubility curve data of two polymorphic forms of the isoxazolone dye at low concentrations in different solvents

	Rhombic		Needle	
	ΔH^{diss} (kJ/mol)	ΔS^{diss} (J/mol K)	ΔH^{diss} (kJ/mol)	ΔS^{diss} (J/mol K)
Methanol	79.2 ± 0.7	217 ± 4	75.0 ± 0.5	208 ± 4
Ethanol	89.0 ± 0.9	242 ± 5	83.5 ± 1.0	229 ± 4
2-Propanol	102 ± 1.2	279 ± 5	97.0 ± 1.0	266 ± 6

5. Conclusions

The polymorphic system of three forms of a yellow isoxazolone dye has been studied. One new polymorph was formed only from the melt, the two others grew from solution. Melting points as well as solubility curves in methanol, ethanol and 2-propanol have been measured for these two polymorphs. The system is monotropic; the metastable form has a needle-shaped morphology while the stable form grows as rhombic crystals. The third polymorph has a solid–solid phase transition to the needle-shaped form and only nucleates at room temperature from an undercooled melt. This indicates that this polymorph is not only kinetically the most favorable, but also that it is thermodynamically the least stable. The transition from the melt or from solution to the stable crystalline form occurs via intermediate metastable phases.

The solubility curves at relatively low concentrations follow the behavior of regular solutions. At high concentrations the solubility shows a deviation to lower equilibrium temperatures, indicative for ordering in the solution which was confirmed by the blue shift in optical absorption measurements. For these high concentrations, nucleation of the stable polymorph is preferred in contradiction with Ostwald's rule of stages. Only for very high cooling rates, the kinetics takes over again resulting in very thin needles of the metastable polymorph. The latter situation of high concentrations and very high cooling rates is relevant in industrial production where precipitation is used. Especially in this case where no solid–solid transition to the thermodynamically stable polymorph is observed the needle polymorph will be harvested unless the system is given enough time to undergo a solvent-mediated transformation at not too low temperature. Concentration and cooling rate are, however, not the only discriminating factors in this system, the presence of nucleation sources determines which polymorph will nucleate first. To obtain the stable polymorph the solution generally has to be as clean as possible.

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