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Epitaxial 2D nucleation of the stable polymorphic form of the steroid 7αMNa on the metastable form: Implications for Ostwald's rule of stages

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Abstract

This paper presents in situ observations of the epitaxial nucleation and growth of the stable polymorph of a steroid, 7αMna, on a specific face of the metastable form at low supersaturation, using optical microscopy and in situ Raman spectroscopy. The presence of the metastable polymorph is essential for the nucleation and growth of the stable one. The order of the metastable zones of the stable and metastable polymorphs is reversed for the epitaxial growth process as compared to the case of 3D nucleation. The rate of transformation of the metastable polymorph to the stable one can be controlled by the supersaturation.

Keywords: Polymorphism; Epitaxial nucleation; Metastable zone

1. Introduction

Polymorphism is a common phenomenon, frequently encountered in crystallization processes in the pharmaceutical, dyes and food industries. It is defined as the ability of a substance to crystallize in more than one crystal structure (Verma and Krishna, 1966). All the polymorphs of a substance have the same chemical composition but different physico-chemical properties due to the differences in the crystal structures. Owing to the differences in properties, a proper understanding of the polymorphic phase behavior is very important, especially for the pharmaceutical industry (Bernstein, 2002; Brittain, 1999). According to Ostwald's rule of stages, compounds that exhibit polymorphism crystallize first in their metastable forms (Ostwald, 1897). The metastable zone width (that is the supersaturation needed for crystals to be detected in a given time) of the stable form, thus, is larger than that of the metastable form. After crystallizing, the metastable form will undergo a transformation to the most stable polymorph, possibly via intermediate forms. This transformation is often solution-mediated (Boistelle and Rinaudo, 1981; Davey et al., 2002). The metastable zone width depends on many parameters like the time allowed for the system to nucleate, the temperature but also on the nucleation mechanism. Generally, the metastable zone width is smaller for heterogeneous nucleation as compared to homogeneous nucleation. For heterogeneous nucleation the metastable zone width depends on the properties of the nucleation surface, being either the crystallization vessel wall, dust particles or other foreign entities.

A special kind of heterogeneous nucleation, for which the metastable form nucleates epitaxially on the surface of the stable one beyond a threshold supersaturation, was first observed and discussed for the two modifications of uric acid crystals (Boistelle and Rinaudo, 1981) and recently for a steroid (Boerrigter et al., 2002a; Stoica et al., 2005). Epitaxial polymorphic growth is due to the resemblance of the two polymorphic crystal structures along certain orientations (Boerrigter et al., 2002b; Courvoisier et al., 2003). Epitaxial nucleation should not be confused with ordinary heterogeneous nucleation of polymorphs on top of each other (Ferrari and Davey, 2004; Cashell et al., 2003). Epitaxial nucleation of the metastable polymorph can be considered as a 2D version of Ostwald's rule of stages. Also, the transformation of the metastable form to the stable one

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has been observed both for the uric acid (Boistelle and Rinaudo, 1981) and for the present steroid (Boerrigter et al., 2002a; Stoica et al., 2005). It is generally believed that Ostwald's rule of stages is a rule of thumb and not a law. Although many authors mention this, it is hard to find genuine experimental exceptions to the rule. We found no example in the literature, for which the metastable form is found for high supersaturations, while the stable polymorph is formed at low supersaturations. Here we report on epitaxial 2D nucleation and growth of the stable form on specific faces of the metastable one, for relatively low supersaturations for the same steroid mentioned above. This is the reverse process of the one reported before (Boerrigter et al., 2002a; Stoica et al., 2005). We will show that, for the present case, the 2D version of Ostwald's rule of stages does not apply for low supersaturation.

2. The steroid

The steroid, to be abbreviated as 7αMNa (in full (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one) (Fig. 1), is used as an active ingredient in drugs for hormone replacement therapy. Two polymorphs are known: a monoclinic $P2_1$ structure (reference code ciyril00 in the Cambridge Structural Database) and a triclinic $P1$ structure (reference code ciyril01) (Fig. 2) (Declercq and Meerssche, 1984; Schouten and Kanters, 1991). At room temperature, the monoclinic structure is the stable polymorph. It has 4 molecules in the unit cell arranged in a XYXY sequence, where X and Y are the two conformers of the molecule. The triclinic structure contains one X molecule in the unit cell. Along the *b*-axis, the monoclinic structure can be considered as being built-up of layers of the triclinic conformer X intercalated by comparable layers of the other conformer Y. The metastable polymorph always nucleates first. The $P2_1$ form is obtained from polar solvents like acetone and acetonitrile resulting in a plate-like habit, after the metastable polymorph has been either transformed or

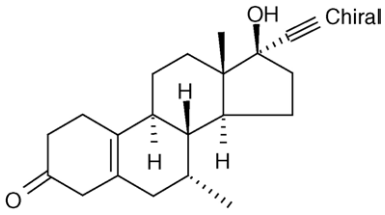

Fig. 1. The (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one steroid.

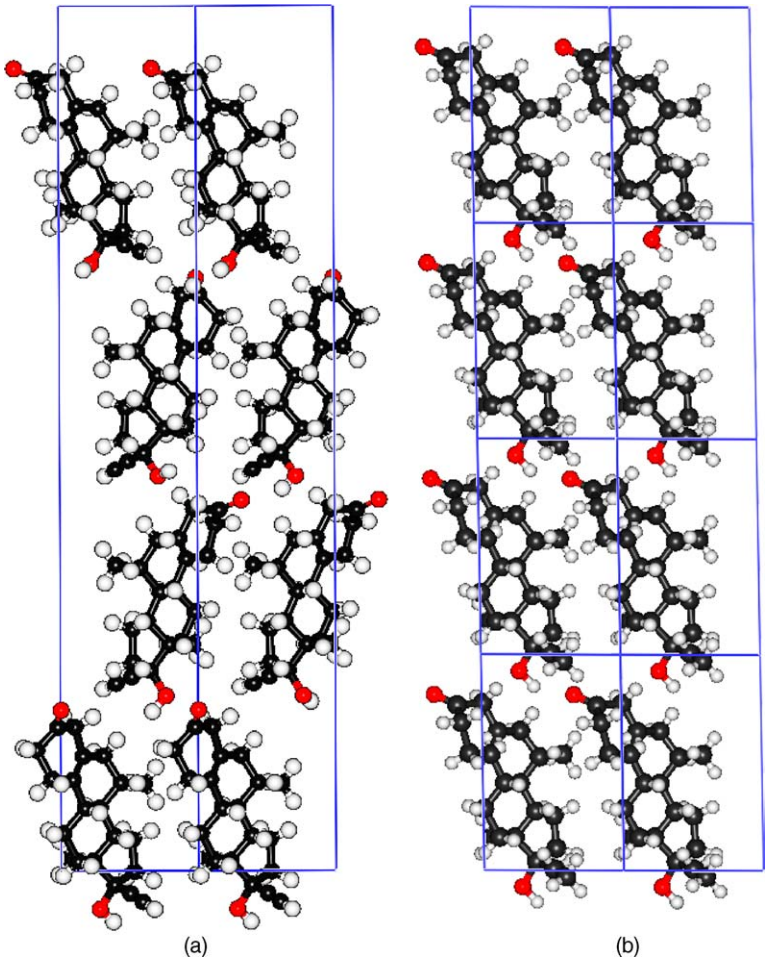

Fig. 2. The two polymorphs of 7αMNa. (a) Form I: the $P2_1$ monoclinic structure has four molecules in the unit cell. (b) Form II: the P_1 triclinic structure has one molecule in the unit cell.

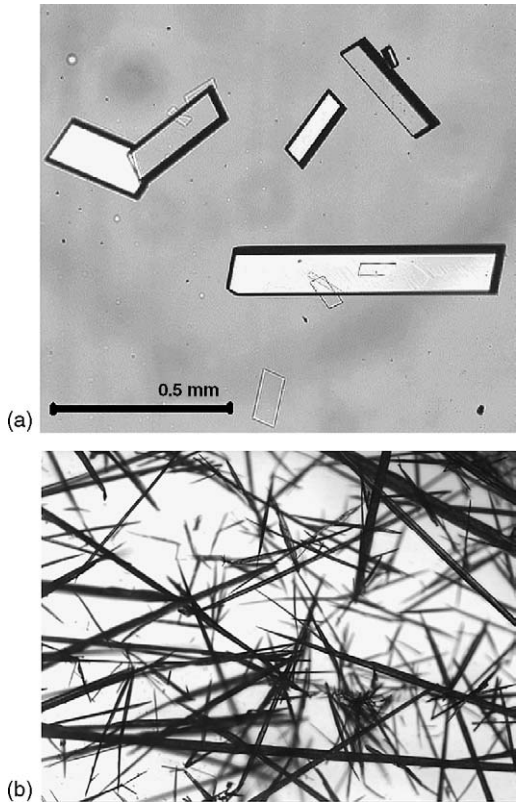

Fig. 3. Typical crystal habits of 7αMNa. (a) The stable polymorph I in acetone; it always grows with an {0 1 0} face on the bottom of the growth cell. (b) The metastable polymorph II in hexane.

dissolved (Fig. 3a). The *P*1 polymorph is stable for a very long time in apolar solvents like benzene and hexane, resulting in a needle habit (Fig. 3b), but also in an isometric habit from toluene. The two polymorphs are monotropically related within the practical temperature range (Stoica et al., 2005).

3. Experimental

3.1. Materials

N.V. Organon supplied the steroid. The starting material had a monoclinic $P2_1$ structure corresponding to the stable polymorph. As solvent ethanol of p.a. purity was used. The solutions were filtered with Rezist 30/0.2 PTFE syringe filters of 0.2 μm pore size, in order to reduce heterogeneous nucleation on foreign particles. The concentrations used ranged from 70 to 100 mg/ml.

3.2. Experimental set-up

The experimental set-up is an "in situ" growth cell composed of a 7 ml closed cell that is temperature controlled using a water bath. The cell was silanized using dimethyldichlorosilane to reduce the interaction of the polar {0 1 0} steroid crystal faces with the glass cell (Stoica et al., 2004). In this way the epitaxial nucleation and growth could also take place on the bottom face of the crystal. From the solubility data of both polymorphs in ethanol (Stoica et al., 2005) the supersaturation σ can be specified for each polymorph. A Zeiss Axioplan 2 polarization microscope was used to observe in situ the growth of the crystals as well as the polymorphic behavior.

The polymorphic modifications and the transformation of the metastable polymorph were determined with Raman spectroscopy. The Raman set-up (Renishaw System 1000) consisted of a micro-Raman spectroscope using an Ar-ion laser (514.5 nm) with an output power of 50 mW, a focused laser beam diameter of a few micrometers and alternatively an excitation wavelength of 785 nm. The in situ Raman measurements were done using a special open cell connected to a temperature-controlled water bath and an immersion objective to lower the background signal of the solution. Three regions are relevant for the distinction between the two polymorphs of 7αMNa: 1600–1800 cm^{-1}, 2100 cm^{-1} and 2900 cm^{-1}.

4. Results

4.1. 3D nucleation and growth of the metastable form

Following Ostwald's rule, for a solution that is supersaturated with respect to both polymorphs the metastable form is expected to nucleate first. In situ Raman measurements on the first crystals nucleated at large undercooling confirmed this for the present system. Optical polarization microscopy showed that these crystals exhibit twinning (see Fig. 4a). The X-ray structure determination that was performed on one of the individuals after cutting the twin along the twin plane confirmed that the analyzed crystal was a single crystal of the metastable form. The twin plane and the face indices of the twinned crystal were determined using an optical goniometer mounted on the single crystal X-ray diffractometer. In order to be able to compare both polymorphic forms more easily an alternative setting for

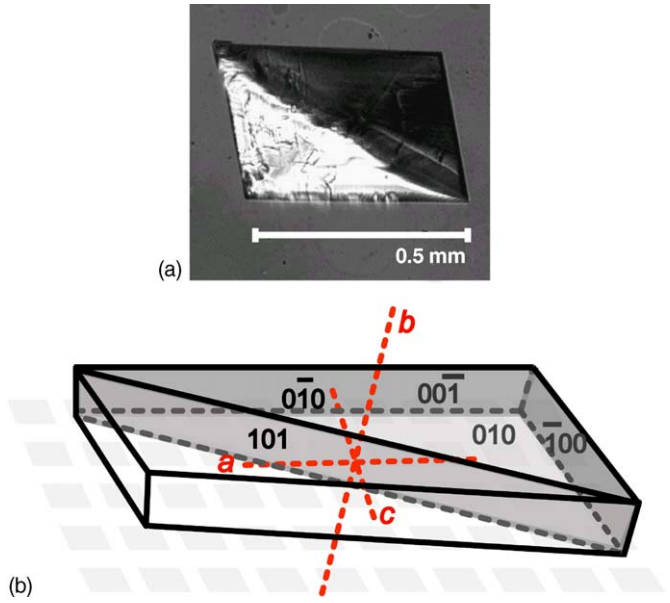

Fig. 4. (a) Twinned crystal of the metastable form observed in situ in polarized light; one individual of the twin is in the extinction orientation. (b) Indexed twin; the indices of the twinned crystal were determined with the aid of an optical goniometer on the single crystal X-ray diffractometer.

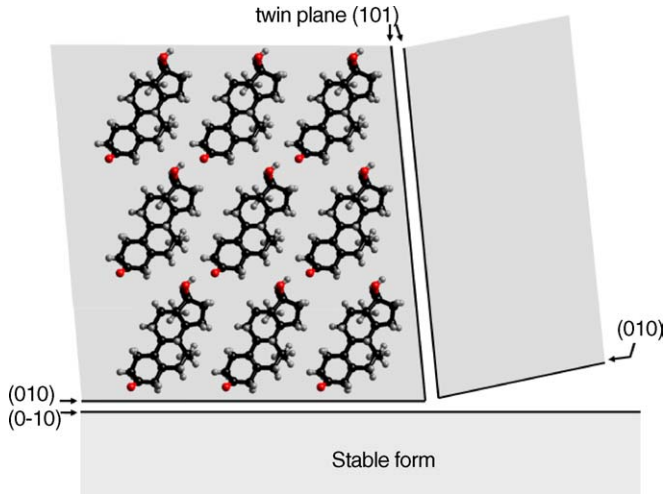

Fig. 5. The orientation of the molecules with respect to the twin plane; the stable $P2_1$ form nucleates on the (0 1 0) carbonyl terminated face of the metastable $P1$ form.

the metastable form structure was chosen according to $a' = a$, $b' = (-c)$ and $c' = b$ (Boerrigter et al., 2002b). Fig. 4b shows an indexed twin. Twinning occurs about a 180° rotation axis with $\{h\,0\,l\}$ as the composition plane. A further search for the most favorable position of the steroid molecules using the Cerius[2] program led to $\{1\,0\,1\}$ as the most probable indices for that plane (Fig. 5). The calculated reentrant angle between the twins is about 18°.

4.2. 2D epitaxial growth of the stable form

After raising the temperature, resulting in a low supersaturation with respect to the metastable polymorph ($\sigma(P1) < 0.5$, $\sigma(P2_1) < 1.57$), the stable form immediately nucleates epitaxially on the bottom face of the crystal half that lies on the glass cell, i.e., nucleation and growth occurs between the glass and the crystal. Note that the supersaturation will be even lower at this position because of the limited mass transport. Because the supersaturation of the stable form is still relatively high as compared to the metastable form, its crystals grow faster than the crystals of the metastable one at this temperature. The stable form crystals thus become bigger than the metastable ones on top. This shows that the mass transport to the bottom face is large enough to allow for a supersaturation larger than zero. The two forms can be distinguished in situ during growth and dissolution using polarization microscopy as can be seen in Fig. 6a. Fig. 6b shows the situation schematically. Increasing the temperature just above the equilibrium temperature of the metastable form will result in the dissolution and disappearance of the twins, while the stable form still grows, as can be seen from the time lapse micrographs in Fig. 7.

The polymorphic form that nucleates epitaxially on the twins was identified as the stable form using in situ time lapse Raman spectroscopy. These measurements were performed at a temperature above the equilibrium temperature of the metastable form showing very clearly the difference between the stable and the metastable form during the growth of the former and dissolution

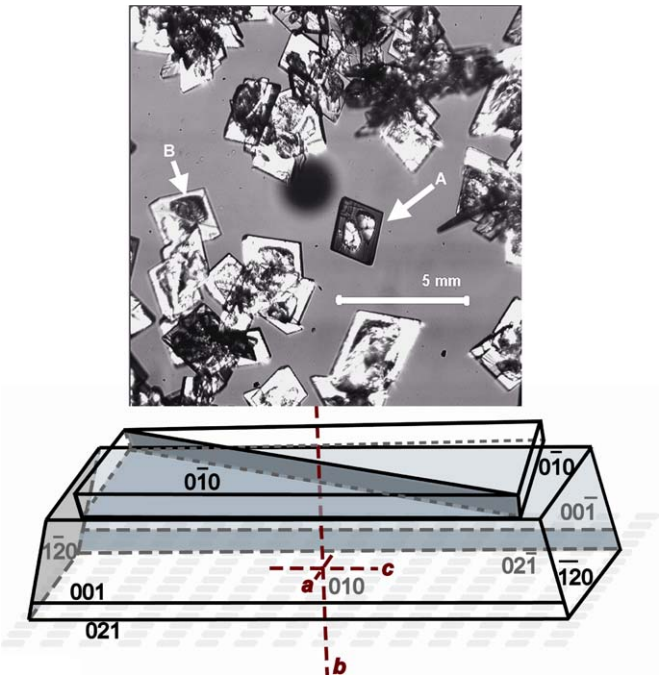

Fig. 6. (a) In situ micrograph of the two forms during growth of the stable form and dissolution of the metastable one using polarized light. The two forms have different extinction directions being alternatively light or dark. The arrow labeled A indicates a dark crystal of the stable form that lies under the remains of the twins of the metastable form that are light. The B-arrow points to such crystals for which one of the metastable individuals is dark. (b) Schematic drawing of the epitaxial growth of the stable form on the bottom of the metastable individual that lies on the glass cell. The indices of the stable form crystal were determined ex situ using an optical goniometer.

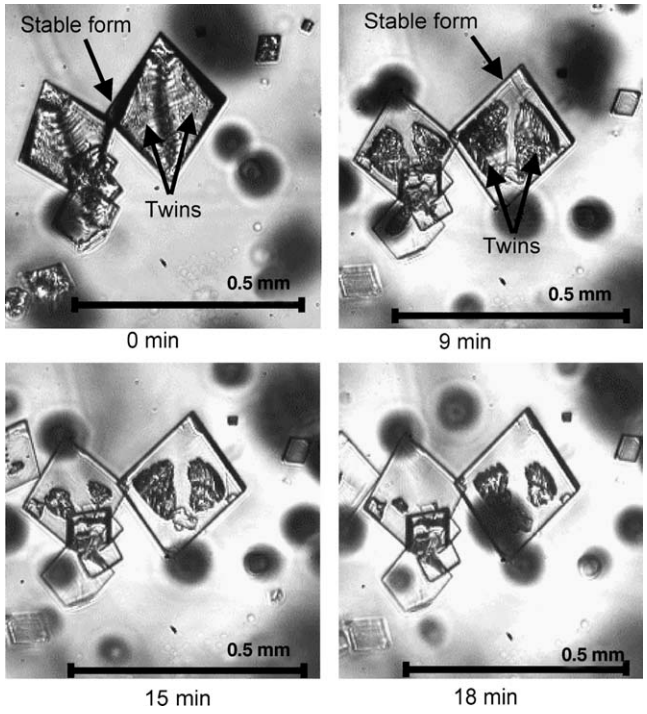

Fig. 7. Time lapse in situ optical micrographs that show epitaxial growth of the stable form under the metastable form while the metastable form dissolves ($\sigma P2_1 = 0.5$). The stable form nucleated between the glass cell and one of the twins of the metastable form.

of the latter (Fig. 8). Care was taken to measure the spectra while focusing just below the crystal surface. The traces are numbered in chronological order, starting with measurement number one that was taken while the metastable form was still present and ending with measurement number five that shows the presence of the stable form only. In the figure, the arrows marked "a" and "d" indicate the regions where the difference between the metastable form that dissolves and the stable one that grows epitaxially is most obvious. Measurement number two, that was taken at the very end of the dissolution of the metastable form, shows an unusual peak indicated by the "b" arrow. This is probably due to the solution; cf. reference peak "c". One can see that also the peaks of either polymorph are very weak or even absent in this measurement. In measurement number three, the metastable form appeared completely dissolved visually, but one can see that the peaks are not completely resolved yet. This might be due to some remaining layers of the metastable form. The last two traces only show the presence of the stable form.

For a better understanding of the 2D nucleation mechanism of the stable form on the metastable one it is necessary to determine on which crystal faces of the metastable form the nucleation takes place. Previous experiments showed that the crystals of both forms prefer to orient themselves with the (0 1 0) surface on the glass cell (Stoica et al., 2004). Moreover, the epitaxial nucleation of the metastable form turned out to occur with its (0 $\bar{1}$ 0) face on the (0 1 0) face of the stable form (Stoica et al., 2005). Considering these observations and the similarities between the layered structures, we conclude that the stable form nucleates on the carbonyl (0 1 0) surface of the metastable form, with its (0 1 0) surface pointing to the glass cell.

Using scanning electron microscopy, X-ray powder diffraction and in situ observations, we found that 2D epitaxial nucleation and growth of the stable form on the metastable one also takes place in other solutions like ethanol/acetone (80%/20% and 50%/50%), acetone and 2-propanol, or when using an antisolvent (like water in ethanol/water 80%/20% solutions) in precipitation experiments.

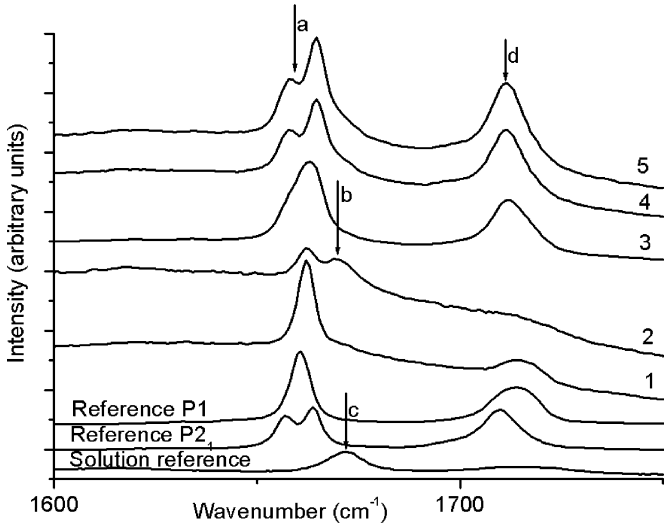

Fig. 8. In situ time lapse Raman measurements in ethanol solution ($\sigma(P2_1) \approx 0.2$). The numbers represent the order of the measurements and the time interval at which they were made is 200 s. The reference spectra were taken ex situ for both polymorphs. The arrows marked a–d are discussed in the text.

4.3. 3D nucleation and growth of the stable form

The stable form does not immediately nucleate from a fresh solution. However, for supersaturations higher than the supersaturation at which 2D epitaxial nucleation and growth of the stable form on the metastable form takes place, and in the case that crystals of the stable form prepared as described in Section 4.2 are already present in solution, then the stable form nucleates also non-epitaxially after some 24 h. As a result of the corresponding relatively low supersaturation with respect to the stable form, the newly nucleated crystals have a polar shape (Stoica et al., 2004). These crystals were identified to be of the stable form using polarization microscopy. Under these conditions, no 3D metastable crystals are nucleated anymore. If the temperature is raised above the equilibrium temperature of the metastable form, the polar crystals will slightly dissolve on the sharp top, which is the carbonyl (0 1 0) side (Stoica et al., 2004), indicating that epitaxial layers of the metastable form were present on this rough face.

The 3D nucleation and growth of the stable form for conditions where the stable form crystals are already present is not understood and might be due to attrition or other kinds of secondary nucleation, although the solution was stagnant.

4.4. Lifetime of metastable form

In ethanol solutions the metastable form has a much longer lifetime than in acetone solutions. In order to study the lifetime of the metastable form in ethanol solutions we performed several crystallization experiments in which the temperature was varied differently, as is shown schematically in Fig. 9. In this section we indicate the supersaturation in terms of the undercooling instead of supersaturation as the large number of crystals present in the solution makes the concentration of the steroid in the solution less reliable. In all cases first 3D nuclei of the metastable polymorph were formed and then crystals of the stable polymorph were nucleated epitaxially on the crystals of the metastable form as described in Section 4.2. For both, curves A and B, in Fig. 9, the temperature was then raised above the equilibrium temperature of the metastable form ($\Delta T(P1) > 2\,^{\circ}\mathrm{C}$) to dissolve the majority of the crystals of the metastable form, followed by a decrease in temperature to preserve a few remaining crystals of that form. The remaining crystals then consist of stable and metastable form crystals in contact, similar to Fig. 6a. For curve A, the system was then kept for 24 h at high supersaturation with respect to both forms ($\Delta T(P1) \approx 20\,^{\circ}\mathrm{C}$, $\Delta T(P2_1) \approx 28\,^{\circ}\mathrm{C}$), far below the equilibrium temperature of the metastable form. After 24 h, we took the crystals out of the solution and found from Raman spectroscopy that the crystals of the stable form still had patches of the initial metastable crystals left on the surface (Fig. 10). However, no patches of the

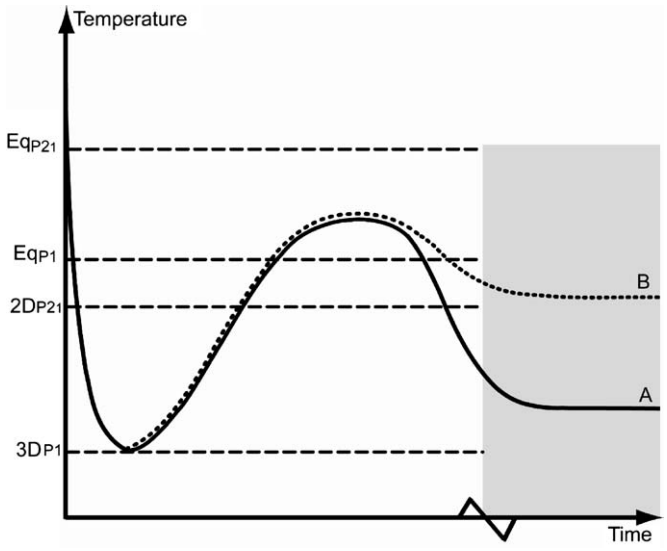

Fig. 9. Curves A and B represent different experiments discussed in the text to study the lifetime of the metastable polymorph: $3D_{P1}$ is the nucleation temperature of the metastable form, $2D_{P2_1}$ the temperature were the stable form nucleates epitaxially on the metastable form and Eq_x indicates the equilibrium saturation solubility temperature of form x. The grey area represents the 24 h waiting time.

initial metastable crystals were observed anymore after 30 h. We repeated the experiment but keeping this time the system at room temperature ($\Delta T(P1) \approx 10\,^{\circ}C$, $\Delta T(P2_1) \approx 18\,^{\circ}C$), that is, closer to the equilibrium temperature of the metastable form although still well below it (Fig. 9, curve B). The Raman analysis showed that in this case the metastable form was completely transformed into the stable one in a time between 10 and 24 h.

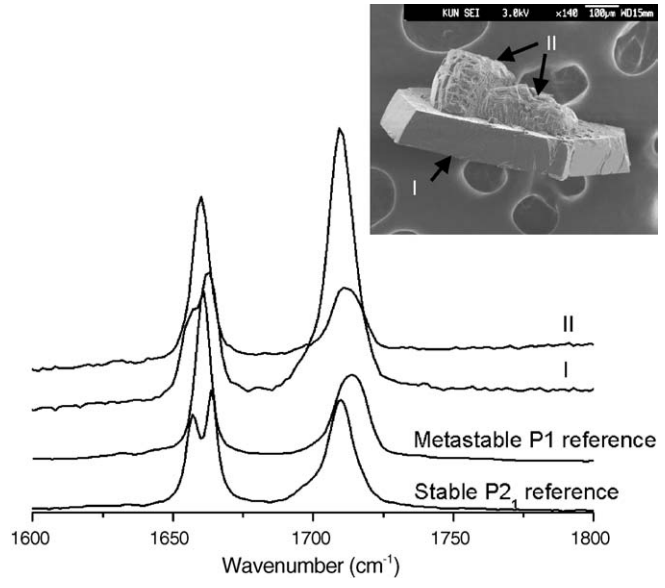

Fig. 10. Ex situ Raman measurements on crystals harvested at the end of curve A in Fig. 9; the arrows in the SEM image of the inset show indicate the stable form I and two patches left from the metastable form II on which Raman spectra were taken.

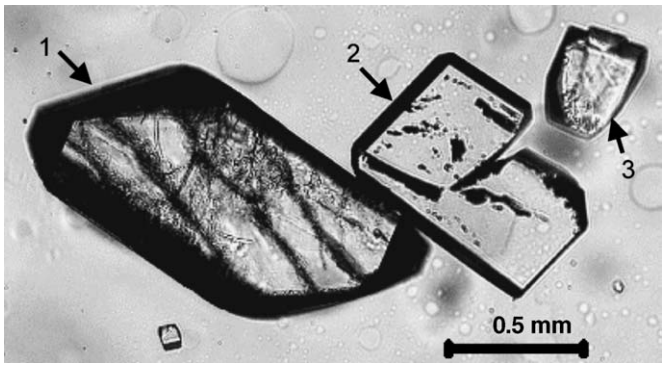

Fig. 11. In situ micrographs of crystals of the stable form after 24–48 h obtained in a solution in which the concentration decreases gradually; crystal 1 has an external shape that resembles that of the metastable one as a result of the phase transformation to the stable form; crystal 2 has the shape of the stable form; crystal 3 has a polar shape; another even smaller polar crystal is present at the bottom of the image.

4.5. Effect of supersaturation on final growth morphologies of the stable crystals

If, after the initial nucleation of the metastable form, the solution is kept at a low temperature ($\Delta T(P1) \approx 20\,^{\circ}C$, $\Delta T(P2_1) \approx 28\,^{\circ}C$), the supersaturation will initially be high but decreases due to the large number of growing crystals. Raman analysis showed that all crystals were transformed to the stable form after 40–48 h. There are, however, roughly three types of crystals present in the final batch as is shown in Fig. 11. Crystal 1 has the external shape of the metastable form but the structure of the stable one. This phenomenon was reported earlier for crystals grown from the vapor (Boerrigter et al., 2002b). Crystal 2, simultaneously present, is smaller and has the external shape of the stable polymorph. This crystal was nucleated epitaxially on a metastable crystal at a later stage for which the supersaturation had decreased considerably. The metastable crystal on top of it has dissolved completely, as a result of the low supersaturation. The same figure also shows a relatively small polar crystal 3, which must have been nucleated even later, at the smallest supersaturation. We reported on polar crystals of 7αMNa for low supersaturation in a previous paper (Stoica et al., 2004).

5. Discussion

5.1. Polymorphic phase diagram

Although metastable zone widths depend on many parameters like the time the system is allowed to nucleate, we will use the term mainly in a comparative fashion. That is, the polymorphic form that nucleates first, for a given supersaturation, will have the lowest metastable zone width.

The metastable zone width for 2D epitaxial nucleation is clearly smaller than that for 3D nucleation for both polymorphs. For the metastable polymorph this was shown before (Boerrigter et al., 2002a; Stoica et al., 2005). In Fig. 12, the situation is drawn schematically. In this figure, the metastable zone widths for 2D

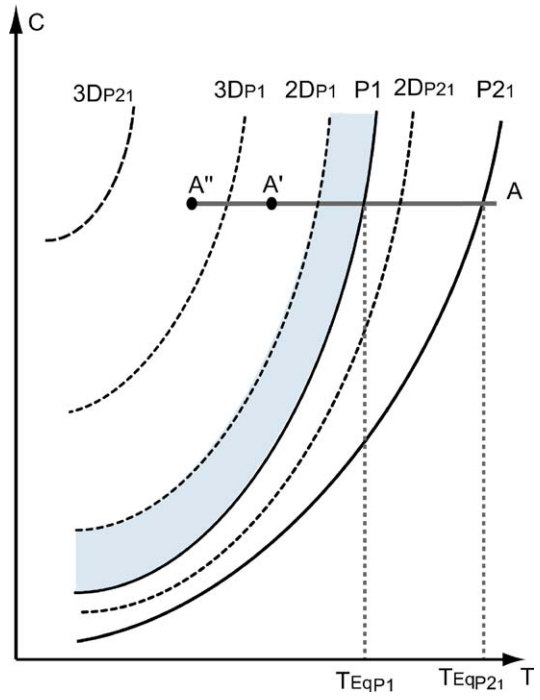

Fig. 12. Schematic representation of the nucleation and growth conditions of both forms in terms of solution concentration c. With full lines the solubility curves are indicated and with dashed lines the metastable zone widths for 3D and 2D epitaxial nucleation of the stable $P2_1$ polymorph and the metastable $P1$ form (after Threlfall, 2000). The metastable zone widths for 2D nucleation refer to nucleation and growth on the (0 1 0) face of the metastable form only. The labels A–A″ are discussed in the text. For 3D nucleation of the stable $P2_1$ form the metastable zone width was not determined. The grey area indicates the conditions for which the 2D version of Ostwald's rule of stages does not hold.

nucleation refer to nucleation and growth on the (0 1 0) face of the metastable form only. The metastable zones for 2D (epitaxial) nucleation and growth of the metastable form ($2D_{P1}$) on the metastable and stable form almost coincide (Stoica et al., 2005).

Concerning 3D nucleation the steroid follows Ostwald's rule of stages. The stable $P2_1$ polymorph does not nucleate for temperatures just above the metastable zone of the metastable $P1$ form (A′ in Fig. 12) even if one waits for two days. For lower temperatures (A″ in Fig. 12) the metastable form nucleates. Therefore, we conclude that the metastable zone of the stable form is beyond that of the metastable polymorph. Moreover, we never observed 3D nucleation and growth of the stable polymorph for any supersaturation in a fresh solution. As the metastable zone width of the stable polymorph could not be determined, its position in Fig. 12 is merely speculative.

For 2D nucleation and growth on the (0 1 0) face of the metastable crystals the metastable zone lines for the metastable and stable forms have the opposite order as compared to the zones for 3D nucleation. We observe 2D nucleation and growth of the metastable form for supersaturations beyond the metastable zone indicated as $2D_{P1}$. There the usual growth kinetics favor the metastable polymorph in accordance with a 2D version of Ostwald's rule of stages. For supersaturations between the zones indicated by $2D_{P2_1}$ and $2D_{P1}$, however, the stable form nucleates on the metastable form. For supersaturations below the metastable zone of $2D_{P1}$ but still above the solubility line of the metastable form, this behavior is contradictory to the 2D version of Ostwald's rule of stages. This area is indicated in grey in Fig. 12. A tempting picture is that each growth layer has initially a $P1$ structure but that this will transform to the stable $P2_1$ structure if enough time is provided. The transition to 2D nucleation and growth of the $P1$ polymorph then corresponds to conditions for which this transformation rate cannot keep up with the growth rate.

5.2. Transformation kinetics

A convenient measure for the transformation kinetics is the total time for the disappearance of the metastable form, which was determined for curves A and B of Fig. 9. These experiments differ in the supersaturation at the starting point for the transformation, as indicated by the grey area in Fig. 9. In case of curve A, the experiment starts at a concentration far beyond the $2D_{P2_1}$ metastable zone. Under these conditions, the growth of the metastable patches remaining on the stable form (cf. the inset to Fig. 10) is relatively fast. For curve B, on the other hand, the starting supersaturation is much lower and the metastable form grows slower. For 7αMNa the transition from the metastable to the stable form is solution mediated, in the sense that the crystal has to be in contact with the solution for it to transform (Boerrigter et al., 2002a). As a rule of thumb the transformation rate is higher when the solubility of a compound in a certain solvent is higher (Stoica et al., 2005; Gu et al., 2001) because of the higher exchange rate of the solute, even in thermodynamic equilibrium. At a finite supersaturation, obtained by decreasing the temperature, the flux of solute from the crystal to the solution is suppressed due to the lower solubility. As a consequence the rate of transformation is lower for the conditions of curve A as compared to curve B in Fig. 9.

5.3. (0 1 0) versus (0 $\bar{1}$ 0)

Previous experiments showed that in polar solvents the carbonyl terminated (0 1 0) surface is a faster growing face than the hydroxyl (0 $\bar{1}$ 0) surface (Stoica et al., 2004). In a forthcoming paper we will show that for the stable form the (0 1 0) surface grows via a 2D nucleation mechanism, while the slow growing (0 $\bar{1}$ 0) face grows unexpectedly via a spiral growth mechanism (Stoica et al., in preparation). Assuming the same mechanisms for the polar metastable crystals, it is likely that the 2D epitaxial nucleation and growth of the stable polymorph takes place preferentially on the (0 1 0) surface as the permanent steps provided by the spirals on the (0 $\bar{1}$ 0) face favor the growth of the metastable form. As a result of the layered structure, 2D nuclei are less sensitive to the structure of the underlying polymorph. This is not only in agreement with the observations presented here, but also with the reverse process; the epitaxial growth of the metastable form on the stable one starts always on the (0 1 0) face, while on the (0 $\bar{1}$ 0) surface the epitaxial nucleation and growth takes place only at higher supersaturations (Stoica et al., 2005) where 2D nuclei are formed on the terraces of spi-

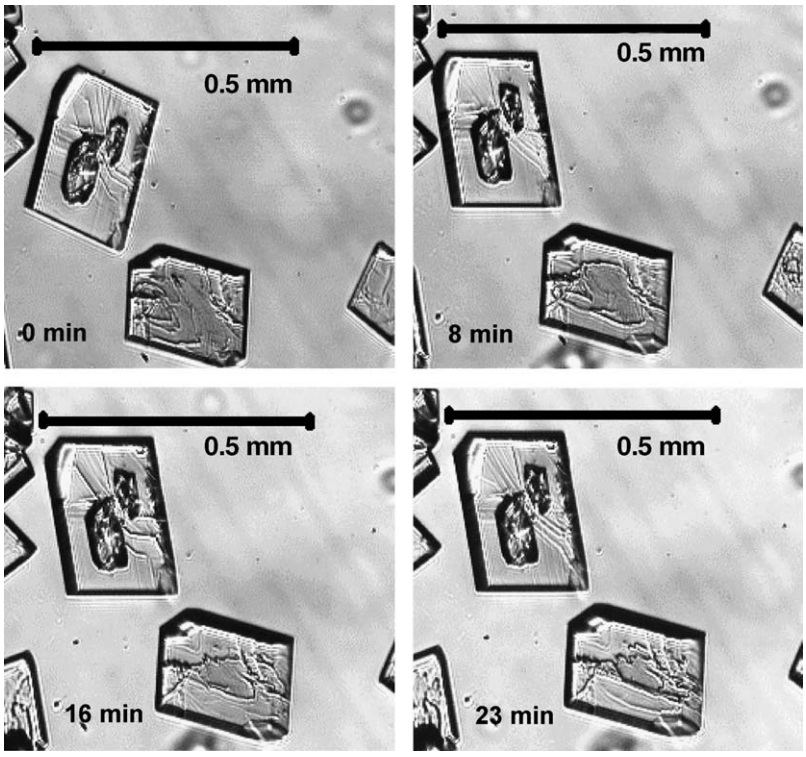

Fig. 13. Time lapse in situ optical microscopy showing the growth of both forms ($\sigma P2_1 = 0.71$, $\sigma P1 = 0.2$). The two patches on the upper crystal are of the metastable form and the big crystals have the stable form structure.

rals. These nuclei, again, are less sensitive to the structure of the underlying polymorph.

5.4. Concomitantly growing polymorphs

The 2D epitaxial growth of the stable form on surfaces of the metastable crystals takes place in a supersaturation region ($\sigma(P1) < 0.5$) where the metastable form grows rather slowly. The supersaturation of the stable form is still high ($\sigma(P2_1) < 1.57$), meaning that the stable crystals grow slightly faster (Fig. 13). Davey and Cardew studied the transformation of metastable crystals to the stable form under conditions of a constant solution composition (Davey et al., 2002; Davey and Cardew, 1986). Their observations lead to a theoretical description of the dissolution–recrystallization process for supersaturations between the solubility curves of the two polymorphs. Similar experimental observations, where the appearance and growth of the stable form occurred concomitantly with the dissolution of the metastable one, were done for other compounds (Boistelle and Rinaudo, 1981; Courvoisier et al., 2003). The metastable form of the 7αMNa steroid is quite stable in ethanol solutions (see Section 4.2), and thus we were able to observe the crystals of the two forms growing simultaneously for low supersaturations (Fig. 13). As the solution concentration gives rise to different relative supersaturations for each polymorph, the crystals of the stable form can grow faster exceeding the sides of the metastable form crystals. Yu reported a comparable observation for D-sorbitol and D-mannitol (Yu, 2003).

5.5. Practical applications of heterogeneous epitaxial polymorphic nucleation

As a consequence of the heterogeneous polymorphic epitaxial nucleation and growth, the number and size of the stable crystals is easy to control, because one can control the number of the initial metastable form crystals by varying the experimental conditions. The basic idea is that if one waits longer in a high supersaturation region where the metastable polymorph grows faster than the stable one, the stable form crystals that result after decreasing the supersaturation will be bigger (curve A in Fig. 9). If the supersaturation is smaller after the initial nucleation of metastable crystals (curve B), the stable crystals that grow epitaxially will have a bulky and well-defined size distribution as in Fig. 7. The size of the stable crystals can be tuned using the supersaturation to determine the relative growth rates of the two polymorphs.

6. Conclusions

This paper treats in detail the complex phenomenon of concomitant polymorphism occurring for heterogeneous epitaxial polymorphic nucleation and growth. Using as a model compound a steroid that has two polymorphs, we show that the earlier proposed 2D-version of Ostwald's rule of stages only holds at high enough supersaturations.

For 3D nucleation the system follows Ostwald's rule of stages; the metastable polymorph is always formed first.

This implies that the metastable zone for 3D nucleation of the stable polymorph is beyond that of the metastable form.

For 2D nucleation and growth the stable polymorph nucleates at low supersaturations only when the metastable one is already present; the stable polymorph instantaneously grows epitaxially on the (0 1 0) face of the metastable one. Therefore, in contrast to the 3D case, the metastable zone for 2D nucleation of the metastable polymorph lies beyond the corresponding zone for the stable polymorph.

We were able to observe both polymorphs growing for temperatures just below the equilibrium saturation solubility of the metastable form, that is, under conditions where the supersaturation is positive for both polymorphs.

The rate for the transformation from the metastable form to the stable one was found to be lower for higher supersaturations. This is explained by the decrease of the flux of solute from the crystal to the solution for higher supersaturations.

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