Nucleation Control in Solution Mediated Polymorphic Phase Transformations: The Case of 2,6-Dihydroxybenzoic Acid

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This contribution describes the kinetics of the solution mediated phase transformation between forms 1 and 2 of dihydroxybenzoic acid. It is shown how a combination of kinetic, morphological, and modeling data can be used to give a full description of the rate-determining process in such a transformation. Surprisingly, secondary nucleation is found to dominate the kinetic processes. Such a phenomenon is well-known in continuous crystallization but is reported here for the first time in a polymorphic phase transformation. This observation has significant consequences for process and product control in the pharmaceutical and specialty chemicals industries.

Introduction

The importance of polymorphism as it occurs in molecular crystals is now well appreciated both in the context of fundamental issues of solid-state chemistry[1] and in terms of its impact on the preparation and formulation of specialty chemicals and pharmaceuticals.[2]

In many cases of practical importance, crystallization of active materials takes place from solution[3] and the occurrence of polymorphic modifications often follows Ostwald's Rule of Stages.[4] In such cases the initial appearance of the *most* metastable crystal form is expected followed by its transformation to the stable form via whatever intermediate structures may be accessible. Thus, for example, sulfathiazole crystallizes from hot aqueous solutions as the metastable form I which then transforms via forms II and III to yield crystals of the stable form IV.[5] In such situations the fact that the crystals are in contact with their saturated mother liquors offers a low activation energy pathway for the necessary molecular rearrangement to take place by dissolution of the metastable form and concomitant crystallization of the next most stable form.[3] This process has been frequently observed by direct microscopic observation[6,7] and was first given a quantitative treatment in 1983 by Cardew and Davey.[8] In their analysis it was clearly demonstrated that the kinetics of such a process are dominated by the relative growth and dissolution rate constants for the transforming polymorphs. For this reason, mechanistic information may only be derived through measurement of the solution composition with time and not[9] by assessing the evolution of the polymorph purity of the solid phases. Since 1983 a number of kinetic studies have been reported[10−12] and the utility of this kinetic formalism has been demonstrated.

The work reported here extends such kinetic studies to explore the role that some important processing parameters such as starting composition, temperature, hydrodynamics, solvent, and purity may have on such a kinetic process. 2,6-Dihydroxybenzoic acid (DHB) has been used as a material for this study. As reported previously[13] it is soluble in chloroform and toluene, and it has two polymorphs, 1 and 2, of known crystal structure and morphology. When crystallized from quiescent chloroform solutions at low supersaturations the most stable form, 2, may be crystallized directly, while crystallization from toluene always yields the metastable form 1. In stirred solutions such as are used in this study the system always follows Ostwald's Rule with form 1 appearing first followed by form 2. It is this spontaneous crystallization of form 1 followed by its transformation to form 2 which is the subject of this paper.

Kinetic Relations. Figure 1a shows a schematic solubility curve for a dimorphic, monotropic system such as DHB with the metastable form having the higher solubility. Consider a solution of composition x_i at a temperature T_i: this solution is supersaturated with respect to both polymorphs and hence will nucleate and crystallize. For systems which obey Ostwald's Rule the nucleation and growth of the metastable phase,1, will predominate but it is to be expected that even in such cases nuclei of the stable form, 2, will appear and that these will form the substrate for the subsequent growth of form 2 and dissolution of form 1.

From the starting point of a supersaturated homogeneous solution the nucleation process will be accompanied by a fall in concentration: if only form 1 nucleates then this decrease will be limited by the solubility, x_1, of form 1 while if form 2 also nucleates the concentration may fall below the form 1 solubility to approach the form 2 solubility, x_2. In the latter case subsequent dissolution of form 1 will cause a rise toward the form 1 solubility and the solution mediated process will start from this point. It seems reasonable to suppose that the higher the initial supersaturation (defined as $\sigma_i = (x_i - x_2)/x_2$) the more likely the nucleation of form 2 will be. Thus, Figure 1b shows the schematic form of the concentration versus time plot for nucleation followed by transformation at high and low values of σ_i. This plot shows the steady-state plateau region identified by Cardew and Davey[8] during which the growth and dissolution processes are balanced. If the growth and dissolution processes are both linear with respect to super (under) saturation the plateau supersaturation, σ_p is given by[8]

$$\sigma_p = \sigma_{12}/(1 + \lambda)$$

with

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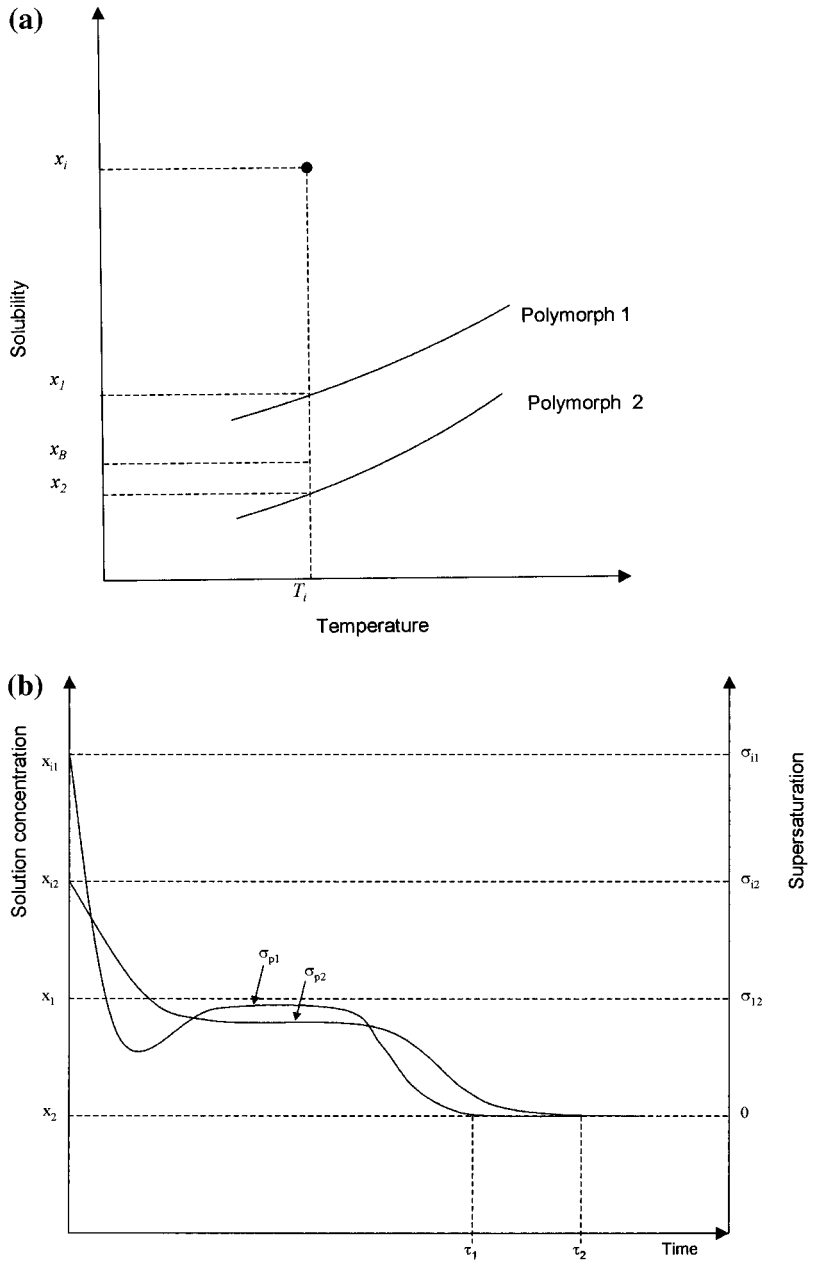

Figure 1. Thermodynamic and kinetic features of a solution mediated phase transformation. (a) solubility curves of monotropically related forms 1 and 2, (b) the time dependence of concentration and supersaturation in a solution mediated transformation from form 1 to form 2.

$$\sigma_{12} = (x_1 - x_2)/x_2$$

and

$$\lambda = \frac{k_G A_2(\rho_2 \alpha_2/\beta_2)}{k_D A_1(\rho_1 \alpha_1/\beta_1)}$$

in which k_G and k_D are the rate constants for growth and dissolution, A_1 and A_2 are the surface areas of the two forms, ρ_1 and ρ_2 their densities, and α and β their volume and surface area shape factors.

If crystal growth of form 2 is rate determining ($k_G \ll k_D$) then λ is less than unity and the plateau concentration lies close to the solubility of the metastable form while if the dissolution of form 1 is rate determining ($k_G \gg k_D$) the plateau concentration lies close to the solubility of form 2. The latter situation gives rise to a lower supersaturation for the growth for the stable form and hence often leads to slower transformation kinetics than in the growth controlled situation.[10] The overall driving force for the transformation is, of course fixed by the free energy difference ($\ln(x_1/x_2)$) between the polymorphic crystal forms and unaffected by the choice of solvent. However, if the growth of the stable phase is rate controlling then solvent may influence the transformation rate through its impact on the surface integration processes.[14,15] To have a convenient measure of the transformation kinetics, the transformation time, τ, may be used being the total time for the disappearance of form 1 and the growth of form 2 to its final size.[8] This time together with the magnitude of the plateau concentration defines the kinetics and rate-determining step in the transformation process. The overall transformation time,τ, may be expected to decrease as the initial supersaturation is raised due to the increase in surface area of stable form 2 nuclei.

In the experimental study reported here, the dependence of transformation rate on initial concentration, temperature, solvent, scale of operation, and solution purity has been assessed by

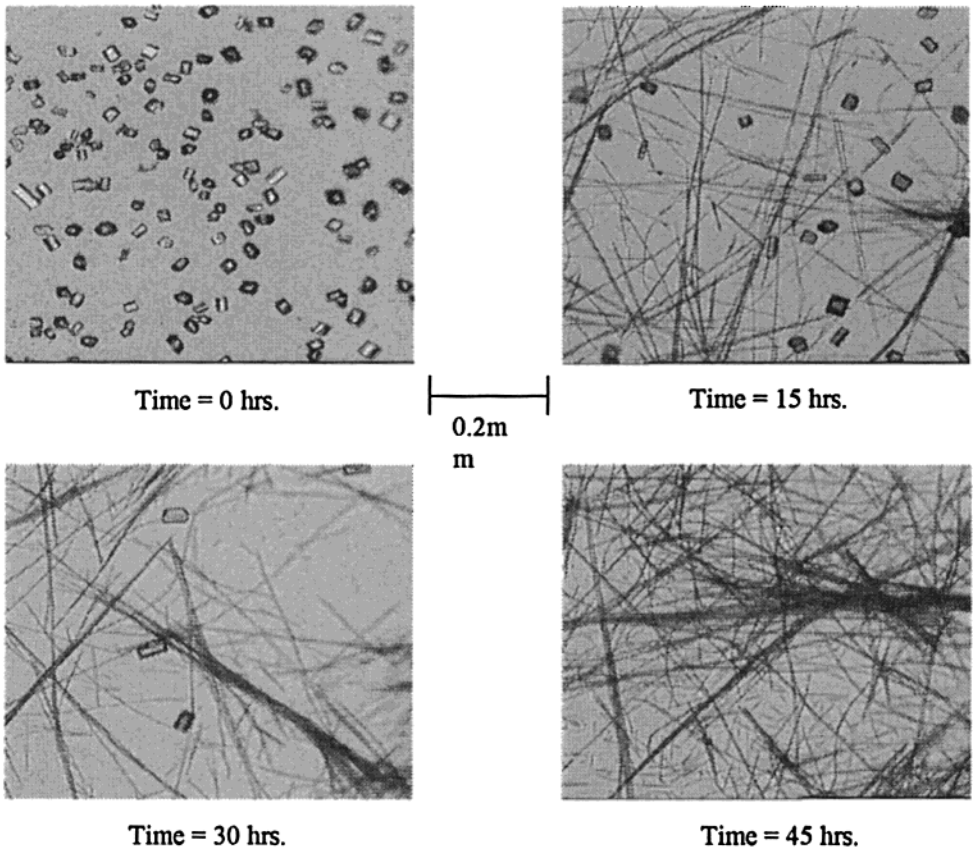

Figure 2. A time lapse sequence of optical micrographs showing the transformation between forms 1 and 2 of DHB in toluene.

use of solution composition measurements combined with time lapse optical micrography. In this way, the factors governing the kinetics of the solution mediated transformation between forms 1 and 2 of DHB have been defined and the rate-determining process identified.

Experimental

The preparation and characterization of forms 1 and 2 of DHB as well as their solubilities and solution chemistry in toluene and chloroform have been reported previously.[13] In the work described here these solubility data are used to define the initial supersaturation (with respect to form 2, $(x_i - x_2)/x_2$) for crystallization from toluene and chloroform and the UV/vis absorption at 327 nm has been used to follow the solution composition during the transformation from form 1 to 2. The quoted values of supersaturation have a reproducibility of ± 0.02 while the curves drawn through the supersaturation time data are intended only to aid the eye. The transformation times themselves were estimated from the trend of the data points and carry a maximum uncertainty of 10% depending on the exact number of experimental points available.

Crystallization and subsequent transformation experiments were carried out at three scales: the first using a 100 mL glass reactor with (constant) magnetic stirring, the second a baffled 500 mL glass reactor with a propeller agitator operating at 550 rpm and the third a glass 2-L baffled reactor with a 6 bladed stainless steel Rushton turbine running at 125−250 rpm. Solutions were prepared by dissolving the required amounts of DHB in the reactors under reflux and then cooling to the required crystallization temperature. Liquid-phase samples were removed through a 0.2 μm syringe filter at known time intervals, diluted 60-fold, and subjected to UV analysis. Suspension samples were also taken at known times and imaged in the polarizing microscope. The effects of supersaturation, solvent, purity, and temperature were investigated at the 100 mL scale and a limited number of experiments were repeated at 25 °C in the 500 mL and 2-L reactors for comparison. Crystals from these experiments were also subject to SEM analysis. Chemicals were purchased from Aldrich, DHB was recrystallized before use, and solvents were distilled and dehydrated with phosphorus pentoxide.

The molecular modeling software Cerius^{2} [16] was used for both selection of additives to inhibit the nucleation of form 2 and energy calculations aimed at assessing the potential for mutual epitaxy of forms 1 and 2. While the former was achieved through simple visualization the latter utilized the "interface builder module", within which appropriate surfaces of the two forms could be constructed and attachment energies of one surface on the other calculated. The Dreiding II force field was employed and atomic charges determined using the AM1 method in MOPAC 6. Different relative orientations of the surfaces were examined and the most favorable (i.e., negative) interaction energies recorded. Interfacial distances were set at 2−2.5 Å to avoid close contacts.

Results

In our previous report of this system[13] we defined the morphologies of each form and noted the solvent-induced appearance of the {310} faces from chloroform. Figure 2 shows a time lapse sequence of micrographs taken during a crystallization and subsequent transformation in toluene for an unstirred experiment at 30 °C with an initial supersaturation of 1.25. In line with expectations form 1 crystallizes initially as *b*-axis prisms followed by the appearance of form 2 as *c*-axis needles.

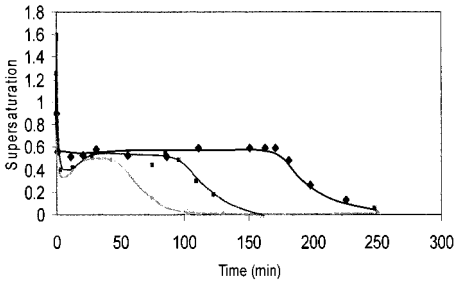

Figure 3. The kinetics of transformation from form 1 to form 2 of DHB at 25 °C in toluene at initial supersaturations: ◆ = 0.9, ■ = 1.25, and ▲ = 1.6.

With increasing time the prisms disappear to be replaced by form 2. The time scale for the transformation in this unstirred situation is of the order of 50 h at 30 °C.

Figure 3 shows kinetic data measured at 25 °C in toluene at the 100 mL scale with magnetic stirring and 3 different starting supersaturations. The time scale of the transformation is of the order of 100 minutes in this experimental configuration. The data follow the trends described above. All show the existence of a plateau supersaturation and allow the transformation time τ to be estimated (to include the final growth of form 2 since for these experiments this time is significant compared to plateau time[8]). At the higher supersaturations the initial dip in supersaturation is consistent with increasing nucleation of form 2 as seen schematically in Figure 1b. Decreasing the initial supersaturation not only extends τ from approximately 130 to 250 min but also eliminates the initial dip in supersaturation. Both these effects presumably arise from the reduction in the number of available form 2 nuclei suggesting that nucleation of form 2 may be rate determining. This view is supported by the observation that the plateau supersaturations lie very close to σ_{12}, (i.e., the solution composition is close to that of a saturated solution of form 1) confirming that the crystallization of form 2 is the rate-controlling factor. For example, in toluene σ_i = 1.61, σ_{12} = 0.63, σ_p = 0.55, and λ = 0.145. Assuming then that form 1 and 2 crystals have dimensions 30 × 10 × 1 and 300 × 1 μm, respectively, allows k_G/k_D to be estimated as 0.12 implying that $k_D \approx 10k_G$.

Figure 4 shows kinetic data measured at 25, 30, and 35 °C in both toluene (Figure 4a) and chloroform (Figure 4b) at an initial supersaturation of 0.9 using the 100 mL reactor. As expected the transformation times decrease with increasing temperature and it is also clear that chloroform facilitates the transformation more effectively than toluene giving values of τ that are significantly smaller. This result is consistent with previous observations[13,17,18] that chloroform favors form 2 while toluene favors form 1. Using the measured values of τ^{-1} as a measure of the transformation *rate* and plotting ln τ^{-1} versus T^{-1} it is possible to estimate (graph not shown) the activation energy for the transformation as 22.0 and 32.0 (±2.0) kJ mol^{-1} from toluene and chloroform, respectively. It is important to note that at all temperatures the solution compositions at the plateaus lie at or just below the composition of a saturated solution of form 1 indicating that the crystallization of form 2 is the rate-determining step at all the temperatures measured. It follows therefore that the activation energies can be associated with this crystallization process. Given that the actual transformation times are a factor of 4 longer in toluene than chloroform these energies must be offset by other kinetic factors which favor chloroform. For example it is to be expected, given our previous work,[13] that form 2 will nucleate more rapidly from chloroform hence providing a greater surface area for subsequent crystallization; this together with the higher prevailing values of the plateau supersaturation and solubility in chloroform then gives a shorter transformation time. Unfortunately, the fragile needle-like morphology of the stable phase made it impossible to verify this conclusion with consistent measurement of either crystal numbers or size to estimate the nucleation rate of this form. The absolute values of the activation energies are half those typically associated with crystallization processes[3] from aqueous solutions which may reflect the relative ease of DHB desolvation in these nonsolvating organic solvents.

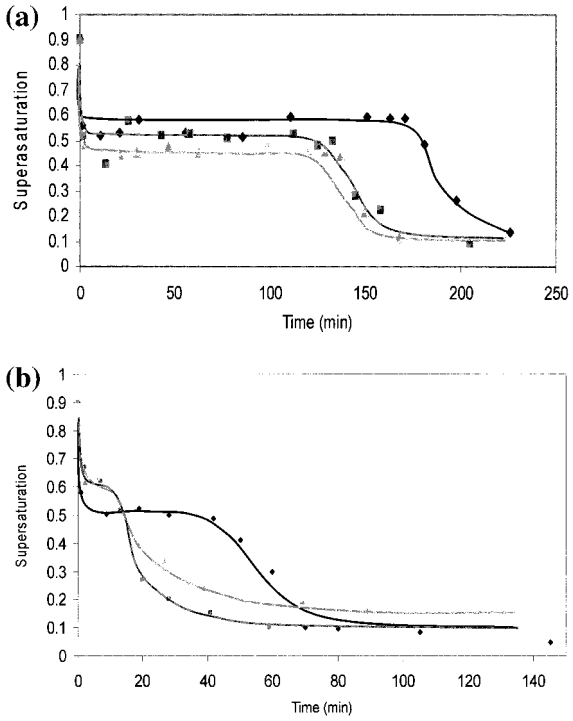

Figure 4. The dependence of the transformation kinetics on temperature for an initial supersaturation of 0.9 in (a) toluene (◆ = 25, ■ = 30, and ▲ = 35 °C) and (b) chloroform (◆ = 25, ▲ = 30 and ■ = 35 °C).

Equivalent experiments carried out on the 500 mL and 2-L scale showed surprising results. On the 500 mL scale, at 25 °C with a supersaturation of 0.9 and stirring speed of 550 rpm, the overall time taken for the transformation increased by orders of magnitude to approximately 24 h in both solvents. At the larger 2-L scale with the turbine running at 250 rpm, the time increased still further to about 60 h. As at the smaller scale the plateaux again lie close to the saturation of form 1 in each solvent indicating that the crystallization of form 2 remains the rate-controlling step. This large increase in time strongly suggests that it is the nucleation of form 2 and hence its available surface area which limits the overall transition time. Further experiments shed more light on this. Substituting the propeller at the 500 mL scale with a magnetic stirrer reduced the transformation time in toluene to 3 h. At the 2-L scale in toluene, reducing the stirrer speed to 125 rpm resulted in an increase in transformation time to 96 h while no stirring required in excess of 20 days. Seeding with 2 wt % of form 2 seeds at the 500 mL scale reduced the time from 24 to 2 h. Taken together these data confirm that nucleation of form 2 limits the transformation at these larger scales and also suggests that the nucleation of form 2 is induced by mechanical contact between the crystals and the agitator itself. Thus, in a large vessel such contacts are rare (unless seeds are added) and the energy imparted small. In a small crystallizer agitated by a magnetic stirrer which revolves

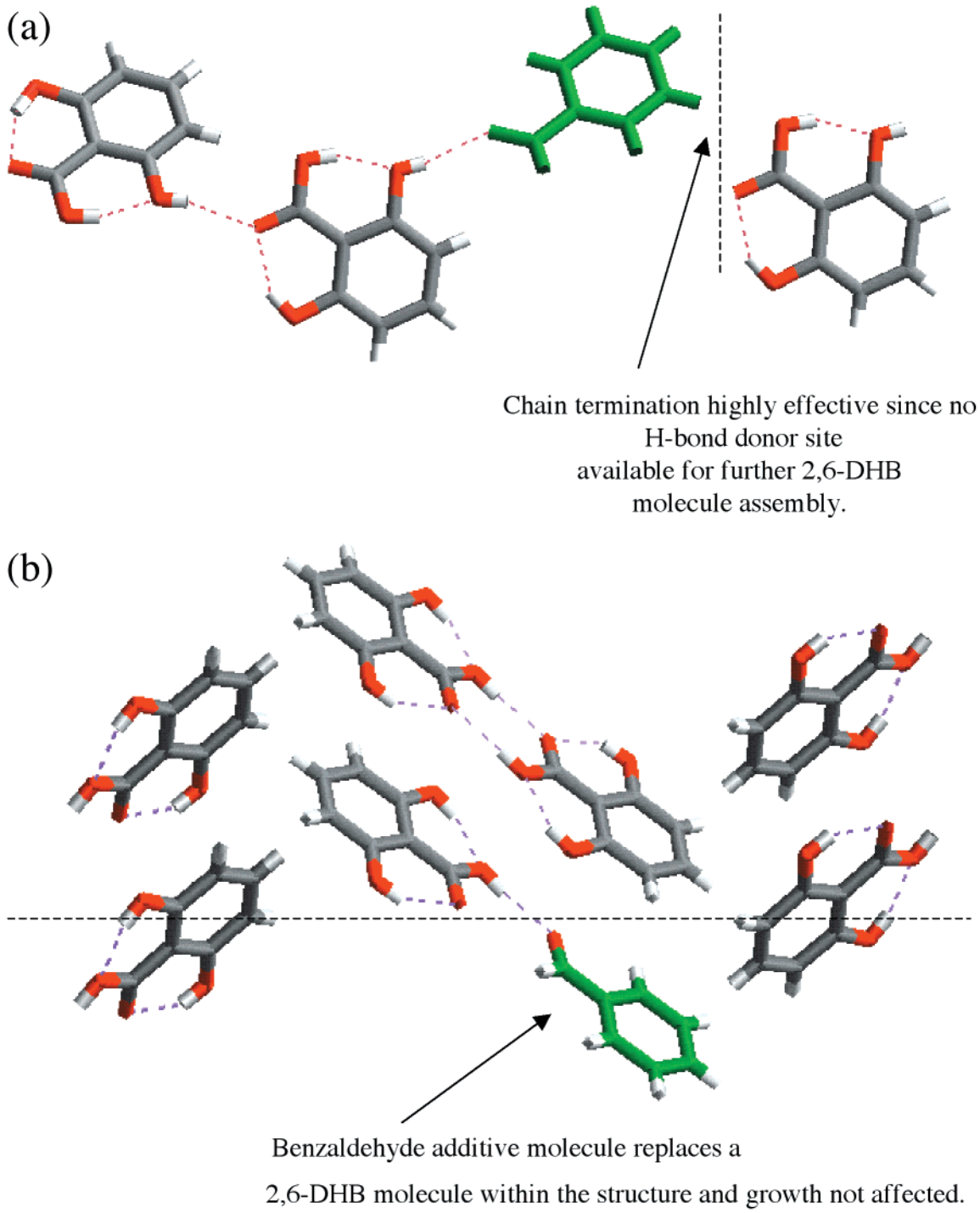

Figure 5. The interaction of benzaldehyde with the form 1 and 2 structures of DHB showing (a) termination of the form 2 chain, (b) incorporation in a form 1 dimer.

on the vessel base the situation mirrors a mill and the extent of crystal attrition is likely to be great. Such a process of secondary nucleation is known to dominate the behavior of large scale batch and continuous crystallizers[3] but has not previously been identified as a factor in polymorphic transformations.

This conclusion was further tested in two ways. First, attempts were made to mimic the action of the magnetic stirrer by adding 100 PTFE 3 mm beads to the 500 mL reactor and agitating at 550 rpm. Consistent with the concept of a secondary nucleation mechanism this reduced the transformation time from 24 to 15 h substantiating the importance of attrition. Second the effect of an additive molecule designed to selectively disrupt the nucleation of form 2 was examined. The chosen additive was benzaldehyde since as shown in Figure 5 it is able to disrupt the chains of the form 2 structure (Figure 5a) without interfering with the form 1 dimers (Figure 5b). Additions of this molecule would thus be expected to inhibit nucleation of form 2 while not affecting form 1 and hence to extend the measured transformation time. At the level of 2 mol % on the mass of DHB this additive increased the transformation time in the magnetically stirred vessel to 150 h in toluene and to greater than 30 days in chloroform. This results is again consistent with a transformation process controlled by nucleation of the more stable form 2.

Overall the data lead to a consistent view of this crystallization process in which the relative nucleation rates of the forms

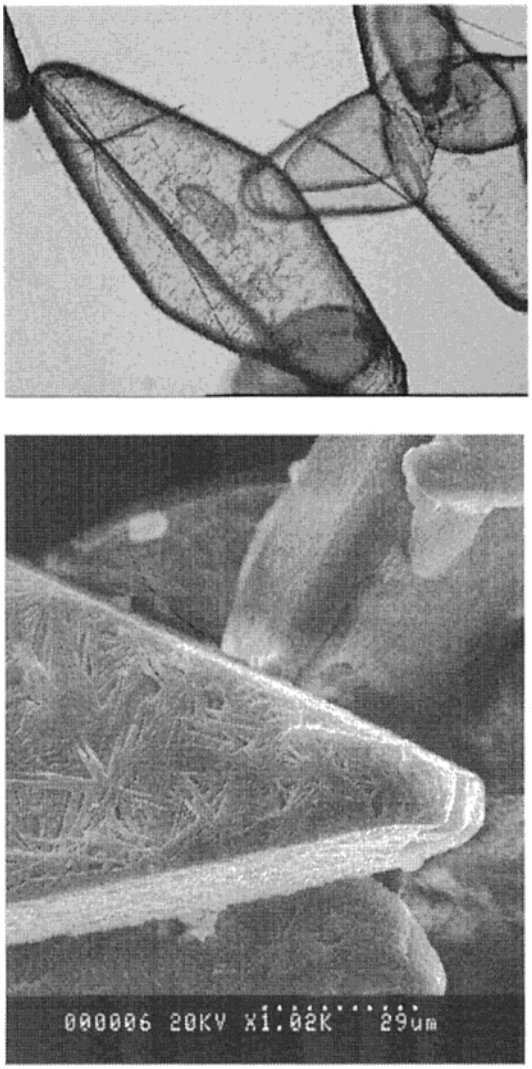

Figure 6. The crystallization of form 2 on the {002} surfaces of form 1. (a) Optical micrograph (the crystal shown is 1.5 mm in length), (b) SEM image, scale as shown.

control the time evolution of the polymorphs. In particular it has highlighted the role played by secondary nucleation in this process. The question of why mechanical damage of form 1 crystals should lead to enhanced nucleation of form 2 remains to be resolved. Examination of optical micrographs (Figure 6a) showed that form 2 needles often appear close to or attached to form 1 surfaces while SEM examination of a sample (Figure 6b) taken from the 2-L experiment in chloroform showed the {002} surfaces of form 1 to be covered in an array of needles. Assuming these to be the usual form 2, *c*-axis needles the surfaces in contact are most likely to be {002} of form 1 and {200} or {110} of form 2. Table 1 summarizes the calculated attachment energies for this combination of forms. It is clear from these calculations that none of the potential epitaxial matches between the forms are favorable compared to the growth of the pure form indicating that the topotactic nucleation of one form on the other seems unlikely. It seems more plausible to assume therefore that the surface nucleation of form 2 is driven by the higher supersaturation at the dissolving interface and that mechanical action is an effective way of removing these surface nuclei, hence optimizing their available surface area for driving the transformation process. Thus the more mechanical energy utilized the higher the surface area of free growing form 2 crystals and the faster the transformation.

TABLE 1: Calculated Attachment Energies for the Interactions of Polymorphs 1 and 2 of DHB

interface	attachment energy (kcal/mol)
form 1 {002}−form 1 {002}	−2.570
form 2 {200}−form 2 {200}	−2.701
form 2 {110}−form 2 {110}	−1.267
form 1 {002}−form 2 {200}	−0.675
form 1 {002}−form 2 {110}	+ 0.291

Conclusions

This kinetic study of the solution mediated phase transformation between polymorphs 1 and 2 of dihydroxybenzoic acid has revealed that in both toluene and chloroform the process is controlled by the crystallization rate of form 2. A study of the influences of supersaturation, temperature, and scale of operation indicates that it is the nucleation rate of the stable form 2 that is the rate-determining step in the overall kinetic sequence. This has been confirmed by the use of a form 2 selective additive and by the observation that mechanical impact appears to play a key role in the nucleation process. This secondary nucleation mechanism, well-known in the operation of continuous crystallizers, has not previously been identified in phase transitions of the type reported here. It is noted finally that this result has significant implication for process operation in the specialty and pharmaceutical industry where nucleation and isolation of the appropriate polymorph can be of vital commercial benefit.

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