

How Specific Interactions between Acetaminophen and Its Additive 4-Methylacetanilide Affect Growth Morphology: Elucidation Using Etching Patterns

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ABSTRACT: The growth of acetaminophen single crystals in the presence of the structurally similar or “tailor-made” additive, 4-methylacetanilide, showed elongation along the *c* axis and reduction along the *a* axis when the additive’s concentration was increased from 1 to 6 mM. This may indicate preferred binding between the host and additive molecules along the *a* axis, but along the *c* axis there is little effect on the growth. In addition, at higher concentrations of 4-methylacetanilide (3 and 6 mM), new faces, $\{401\}$, appeared while the $\{201\}$ were absent. The alignment of host molecules on the growth front is likely to be a coordinated result of the adsorption of additive molecules and the adsorption-induced relaxation of the host molecule conformation. Earlier etching studies provide support for this argument. The additive was chosen as a “surrogate” for a solvent with similar molecular structural properties as part of the ongoing effort to investigate the effect of solvent on crystal morphology.

1. Introduction

Using a structurally similar or “tailor-made” additive to control or modify crystal morphology has been developed and applied in various areas.^{1–3} It is argued that because of the similarity to the host molecules, additive molecules may be able to incorporate into the crystal lattice (or block growth directions) and, because of the designed dissimilarities, they may affect or change the original growth rate of selected faces. As a result, growth morphology can be varied significantly. For instance, various additives have been tested to show the influence on the growth morphology of acetaminophen.⁴ Acetaminophen, paracetamol or 4-hydroxyacetanilide, is one of the most commonly used over-the-counter drugs for antipyretic and analgesic indications.⁵

Etching studies have been carried out in our laboratory to investigate how solvent molecules interact with acetaminophen single crystals. It was observed that different solvents produce different but regular etching patterns on the (010) face, i.e., parallelograms resulted from etching with water and acetic anhydride, slits with dichloroethane, hexagons with pyridine, squares with acetone, and rectangles with ethyl acetate.⁶ On the (010) face, hydrogen bonding forms a 2D network with one direction along the *a* (i.e., crystallographic [100]) axis and another along [102] as shown in Figure 1a. The (010) face is the major cleavage plane, and the acetaminophen single crystal can be viewed as these 2D layers stacked along the *b* axis. There is no hydrogen-bond interaction along either the *b* or *c* axis. Monte Carlo (MC) simulation was carried out to investigate the solvent effect on the formation of etch pits.⁶ It was concluded, based on the simulation and experiments conducted, that solvent molecules might be able to adsorb on the crystal surface, take part in the interac-

tion network, and change the energetic state of the host molecules. To further test the theory, dilute aqueous solutions of two structurally similar additives, acetanilide and 4-methylacetanilide, were used to etch the (010) face of acetaminophen.⁷ Changes in the etching patterns support the argument that some solvents or structurally similar additives can interact with host molecules on the surface and terminate or interfere with the 1D hydrogen bonding along the *a* axis. Because there is no hydrogen bonding interaction along the *c* axis, the original interaction may not be as significantly disturbed as that along the *a* axis upon adsorption of solvent or additive. It was further hypothesized that host molecules on the surface might take a different conformation relaxing the methyl group position that is energetically unfavorable in the bulk due to steric effects. The additive molecules adsorbed may take specific alignments to reinforce the relaxed conformation of the host molecules forming the etch patterns (such as [101] and [302] but not [102]).⁸ Single-crystal pulsed neutron diffraction studies of acetaminophen have been reported that hydrogen atoms of the methyl group show unusual libration or disorder that is not observed in other atoms of the acetaminophen molecule.^{9,10} Alignment along the [102] direction of adsorbed additive molecules on the (010) face may not leave host molecules enough space to relax and make it a less probable event. This was proposed as necessary to explain the angles of the etch pits formed on surfaces that were etched by dilute aqueous solutions of the two additives, acetone or ethyl acetate. Alignment of adsorbed additive molecules is most likely along the [101], [302], and [201] directions.

It is consistent from the etching studies that the solvent or additive needs to take a complimentary position when adsorbed on the crystal surface to keep host molecules in a more energetically stable conformation. If the same argument holds during crystallization of acetaminophen in the presence of structurally similar

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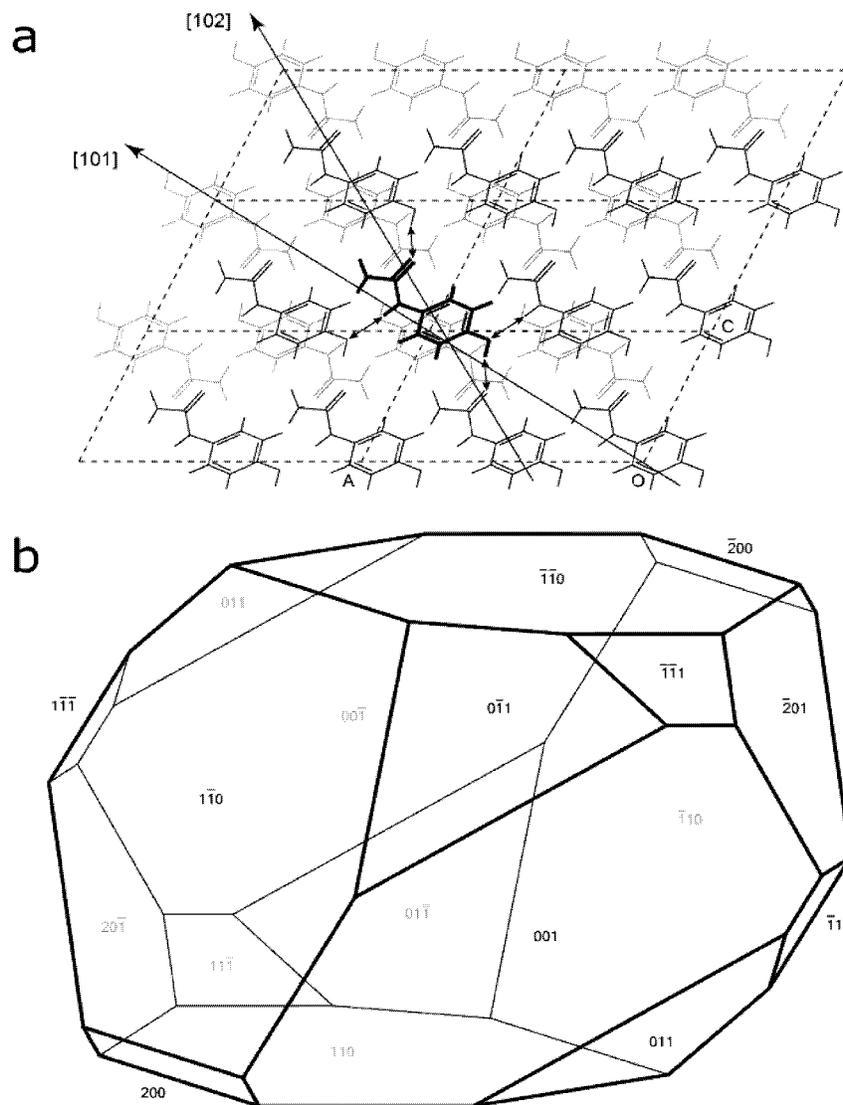


Figure 1. (a) Crystal structure of the (010) face of acetaminophen ($P2_1/a$; $a = 12.93 \text{ \AA}$; $b = 9.40 \text{ \AA}$; $c = 7.10 \text{ \AA}$; $\beta = 115.9^\circ$). Molecules in the second layer behind are shown in gray. For each molecule, there are four hydrogen bonds formed with its neighboring molecules, as marked with double-head arrows between the highlighted molecule and four molecules around. (b) Growth morphology of acetaminophen calculated by the Hartman-Perdok method. Major faces include $\{110\}$, $\{001\}$, and $\{201\}$.

additives such as 4-methylacetanilide, not only the relative sizes of the crystals but also the morphology may be changed. It has been noticed during the etching study that additive molecules affect the interaction network (i.e., periodic bond chain or PBC¹¹) along the a axis more significantly than other directions. Therefore, it is the purpose of the study reported here to examine the commonality of the mechanism where the crystal growth of acetaminophen was carried out in aqueous solutions of 4-methylacetanilide. The crystal morphology was analyzed by optical microscopy, and all faces were indexed with X-ray powder diffraction. The results show that the additive had a significant impact on the crystal morphology even at a concentration as low as 1 mM. In addition, new growth faces, $\{401\}$, appeared compared with crystals grown from pure water. This may only occur when the additive molecules adsorb onto the surface and arrange themselves in a specific pattern, which is similar to what was proposed during the etching studies in the presence of additive. Such an arrangement of additive molecules may be necessary for host molecules on the surface to relax or take a different

but a more energetically favorite conformation/orientation from those in the crystal bulk. This study supports the surface relaxation model as being effectual during both growth and dissolution of acetaminophen crystals.

2. Materials and Methods

Acetaminophen raw materials (USP/BP) were gifts from Hoechst Celanese (Bishop, TX). 4-Methylacetanilide (99%) was purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI). Ultrapure deionized distilled water was produced by NANOpure Infinity UV deionization system (Barnstead, Dubuque, IA) at resistivity of 18 megohm-cm and was used for the crystallization.

For crystal growth, first a 6 mM 4-methylacetanilide solution was prepared and filtered. Then, 3 and 1 mM solutions were prepared by dilution of the 6 mM solution. Acetaminophen was weighed and dissolved into 600 mL of 1, 3, and 6 mM 4-methylacetanilide aqueous solutions, respectively, as well as water to obtain a supersaturation ratio of 1.25 at room temperature (based on a solubility of 14 mg/mL of acetaminophen in water¹²). Solutions were warmed and stirred until all acetaminophen was dissolved. Then, the beakers were sealed with Parafilm and kept at ambient condition. Crystals were harvested after one month.

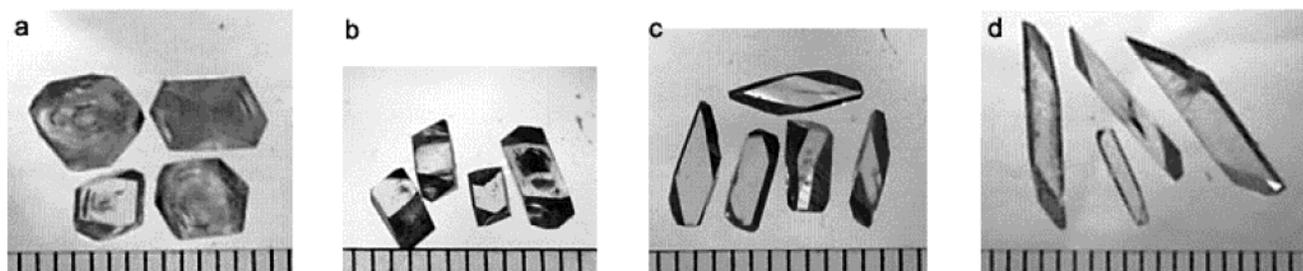


Figure 2. Acetaminophen single crystals as grown in water (a), 1 mM (b), 3 mM (c), and 6 mM 4-methyl acetanilide aqueous solutions (d), respectively. Each unit of scale bars is 1 mm.

Well-formed single crystals were chosen and examined under an optical microscope. Pictures were taken with a digital camera, and a few representative single crystals harvested from each solution were used to carry out X-ray powder diffraction indexing (XRD-6000, Shimadzu, Japan). The voltage and current of the X-ray diffractometer were set at 40.0 kV and 40.0 mA, respectively. A typical scan range was from 10° to 30° with step size of 0.02° . A copper source was used with wavelength of 1.5406 \AA . For smaller faces, rotation of the sample holder was employed with 60 rpm to intensify signals.

Crystal structure examination and morphology calculations were performed with Cerius² 4.6 (Accelrys, San Diego, CA). The force field used was Dreiding 2.21, and partial atomic charges were computed with the charge equilibrium method, Gasteiger-Quanta 1.0. The morphology figures were reproduced with Illustrator 9.0 (Adobe, San Jose, CA). The single-crystal structure of acetaminophen, HXACAN01, was retrieved from the Cambridge Structural Database (Cambridge, UK) for the morphology study.

3. Results and Discussion

The acetaminophen single crystals harvested ranged from millimeters to over one centimeter. The quality was affected significantly by the concentration of 4-methylacetanilide used. In pure water, crystals are chunky, and defects can be seen inside crystal with the naked eye. When the additive concentration increased, the quality was improved considerably. Most of the crystals grown from 6 mM 4-methylacetanilide aqueous solution are free of obvious defects and are transparent. It was observed during the crystallization process that the induction time (when the smallest crystals could first be identified with the naked eye) increased dramatically as more additive was used. The quality of the resulting crystals is possibly the result of slow growth as opposed to other specific effects of the additive (although this will be examined).

The growth morphology of acetaminophen, calculated with the Hartman-Perdok method,^{11,13} is shown in Figure 1b. The major faces are $\{110\}$ parallel to the c axis and $\{001\}$ perpendicular to the c axis. However, crystals grown in water and the 4-methylacetanilide aqueous solutions have consistently different habits, as shown in Figure 2. The trend, when the additive concentration increased, is that the crystal becomes relatively longer in a direction closer to alignment with the c crystallographic axis than the a or b axis, i.e., the ratio between the longest and shortest dimensions increases. Upon indexing, it can be seen that crystals grown in water have $\{110\}$ as the major faces and that at either end of each crystal, the $\{201\}$ and $\{001\}$ are present (Figure 3a). On a few crystals, the $\{011\}$ faces were also identified. Compared with the morphology

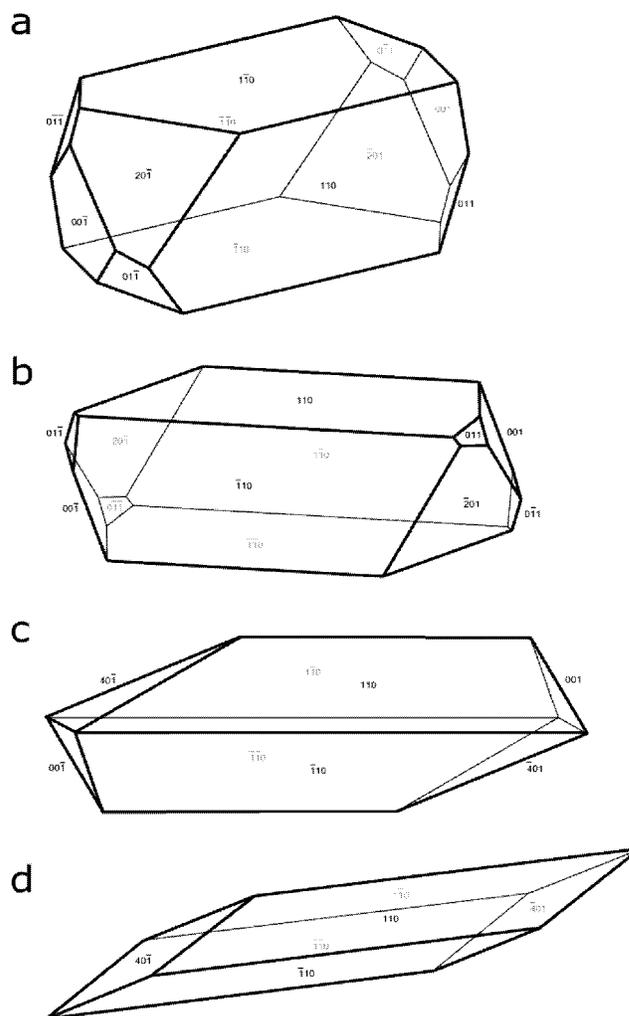


Figure 3. Representative growth morphologies of acetaminophen crystals grown in water (a), 1 mM (b), 3 mM (c), and 6 mM 4-methyl acetanilide aqueous solutions (d), respectively.

predicted by the Hartman-Perdok method (Figure 1b), the crystals grown in water are much longer along the c axis. As the additive concentration increased, the crystals became even longer, and the $\{110\}$ faces are dominant. For those grown in the 1 mM 4-methylacetanilide solution, compared with crystals harvested from pure water, the aspect ratio increases while it is visually determined that the $\{201\}$ faces are relatively enlarged and $\{001\}$ reduced (Figure 3b). On some crystals, the $\{011\}$ were observed. When the concentration increased to 3 mM, the $\{110\}$ are still the major faces; however, $\{401\}$ faces appear and the $\{201\}$ are absent (Figure 3c). The $\{001\}$ remain on both ends of

the crystal. The $\{401\}$ faces become more important on crystals grown from the 6 mM additive solution at the expense of the $\{001\}$ faces (Figure 3d). The $\{110\}$ remain the major faces.

The effect of 4-methylacetanilide on the growth morphology is obvious even at concentrations as low as 1 mM. When the additive concentration increased, the growth morphology shows the trend that the growth along the c axis is enhanced. In fact, it was observed that the overall growth rate was decreased (as expected) as the additive concentration was increased from 0 mM (i.e., pure water) to 6 mM. The crystal quality observed supports this as it is commonly accepted that crystals may become more nearly perfect when the growth rate is slower. Therefore, it is not the growth along the c axis that was enhanced during the crystallization, but rather, it is the growth along other directions that was reduced. From etching studies,⁶⁻⁸ additive molecules can adsorb on the crystal surface and terminate the hydrogen bonding network along the a axis, but the adsorption may not significantly disturb the interaction network along the c axis. The similar interaction mechanism between the host and additive molecules may be confirmed by the growth morphology of acetaminophen in the presence of the additive. Since the additive molecules affect the growth along the a axis much more significantly than other directions, the crystals show the elongation along the c axis that becomes the dominant dimension when there are more additive molecules in the solution.

Furthermore, it is very likely to be the incorporation of additive molecules that results in the appearance of the $\{401\}$ faces and disappearance of the $\{201\}$ faces of acetaminophen crystals grown in the 3 and 6 mM additive solutions. For those crystals grown in the 1 mM additive solution, the relative surface area of the $\{201\}$ faces is enlarged compared with those grown in the pure water solution. The slowed growth rate of $\{201\}$ faces is possibly due to the adsorption and incorporation of 4-methylacetanilide molecules along the faces. As the additive concentration was increased to 3 and 6 mM, enough additive molecules might adsorb along the growth front to force the host molecules along the $[104]$ axis, as shown in Figure 4. Nevertheless, it is intriguing that the $\{201\}$ faces did not become even larger as the additive concentration increased but instead disappeared, and the $\{401\}$ became visible and more dominant. It might be expected that at a higher concentration additive molecules terminate every ledge along the a axis and align themselves along the $[102]$ or $[101]$ crystallographic axis. Thus, the $\{201\}$ faces could grow larger and the $\{101\}$ faces could appear. In reality, however, these are not the case.

From etching studies,⁶⁻⁸ it was observed during the formation of etch pits on the (010) face that 4-methylacetanilide molecules seemed to align on the $[101]$ and/or the $[302]$ direction but not the $[102]$ direction, as shown in Figure 5. It was hypothesized that such alignments were needed to allow the host molecules on the surface to relax the position of the stressed methyl group. The possible conformations, which host molecules surrounding additive molecules on the surface take, may reduce the repulsive van der Waals force along the $[102]$ direction existing between acetaminophen molecules in

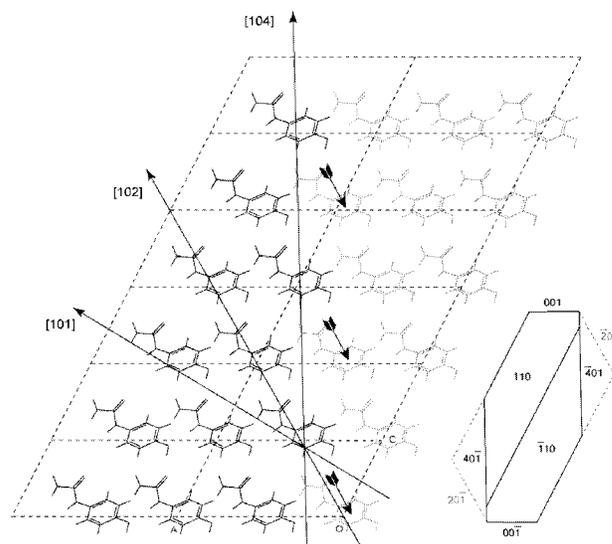


Figure 4. The growth frontline of the (401) face as seen along the (010) face. The corresponding morphology as appearing from crystals grown in 3 or 6 mM additive solution is superimposed with the crystal structure. Unoccupied positions are marked with molecules in gray. Possible adsorption sites by additive molecules are indicated with arrows. All host molecules next to adsorbed additive molecules may take different conformations from that in the bulk to relax the stressed van der Waals force along the $[102]$ axis.

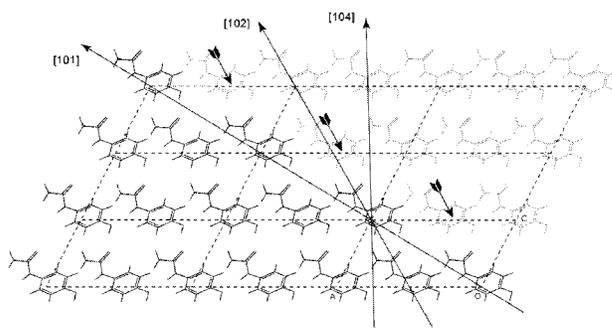


Figure 5. The adsorption scheme of additive molecules on the (010) face during dissolution. Dissolved sites are marked with molecules in gray. Adsorption sites by additive are marked with arrows. Host molecules next to additive may take relaxed conformations.

the bulk of the crystal. As a result, the overall attraction force increases due to the existence of the strongest hydrogen-bonding interaction existing along the $[102]$ direction. It can be seen in Figure 5 that each bound additive molecule terminates the two hydrogen-bonding networks along the a axis and the $[102]$ direction. However, the additive molecule does not form hydrogen bonds with the host molecule along the $[102]$ direction since the hydroxyl group of acetaminophen is replaced with the methyl group of the additive.

The binding scheme between additive and host molecules during crystal growth (Figure 4) is similar to the pattern during etching (Figure 5). Each additive molecule terminates two hydrogen-bonding networks. The only difference, however, is how the additive molecule terminates the hydrogen-bonding network along the $[102]$ direction. Unlike adsorbed additive molecules during etching, the additive molecules during growth form the hydrogen bond with the host along the $[102]$ direction after adsorption on the growth front.

Although patterns of acetaminophen molecules surrounding additive molecules seem different between dissolution and growth (Figures 4 and 5), adsorbed additive molecules may have similar binding energies to host molecules. During dissolution of the (010) face, the additive molecules will try to bind to every freshly exposed host molecule and terminate all ledges along the a axis. Since there is always a layer, which has not been dissolved underneath the dissolving layer, to "support" the additive molecule, the van der Waals force along the b axis may partially compensate for the lack of hydrogen bonding along the [102] direction between the additive and host molecules. During growth, assuming each time a single molecule is attached to the growth front, however, there may not be any underlying layer to sandwich or "support" the additive molecule. Thus, considering the existence of the supportive van der Waals force in etching and the hydrogen bonding along the [102] direction in growth, adsorbed additive molecules may be in similar energy environments in both cases.

Therefore, it is likely that the difference of binding patterns is due to differences in magnitude (kinetic variation) of the two mechanistically identical processes, dissolution of the {010} faces, and the growth of the {401} faces. In etching, additive molecules try to bind to all possible host molecules on the surface so that every ledge along the a axis is truncated by the additive (Figure 5). In growth, additive molecules need to compete with the host when incorporated into the growth front so that they will use the same features of the molecule structure as the host (i.e., acetanilide) when they dock on the surface but leave the dissimilar functional group (i.e., the methyl group) outward (Figure 4). They cannot truncate every ledge along the a axis if they align themselves along the [102] direction since not all host molecules are relaxed. Neither can they align themselves along the [101] or [302] direction as they could during etching. This may be due to a kinetic factor. During dissolution, dissolution of host molecules is not the rate-limiting step when compared with adsorption of additive molecules. During slow growth, however, adsorption and incorporation on the growth front can have similar rates for both host and additive molecules depending upon activity. Consequently, adsorbed additive molecules stabilize the {401} faces, and they become one of the families of growth faces (again, due to the surface relaxation of host molecules). Incoming molecules may continue to add to the {401} faces since those ledges with the additive bound will grow more slowly and retard the appearance of those directions without the additive. Regardless of how the additive molecules adsorb on the crystal surface, the energy states of acetaminophen molecules that surround adsorbed additive molecules are similar in both etching and growth. The two binding schemes may allow nearby acetaminophen molecules around additive molecules on surface to relax and bind more strongly with other host mol-

ecules. This should be especially true of the interaction along the [102] direction. The adsorption and incorporation of the structurally related additive into the host crystal affects the conformation of surrounding host molecules and, in turn, changes the result of dissolution and growth. Whether and how additive molecules will be "expelled" from the crystal lattice after integrated during crystal growth remain a challenge, and further experiments need to be done. Refinement of the MC simulations are underway to include the "unsupported" growth feature leading to the {401} faces, thus allowing the more accurate prediction of growth faces from etching simulations.

4. Conclusions

The growth morphology of acetaminophen crystals grown in water is much different from what is predicted by current methods, which are unable to integrate the solvent effect. In addition, structurally similar additives such as 4-methylacetanilide have a significant impact on the growth morphology. Not only do crystals grow longer along the c axis, but new faces also appear.

Early etching studies from this laboratory explain the increase of aspect ratio observed in the growth morphology. This is because of the ability of the additive to terminate the hydrogen-bonding network along the a axis with limited disruption of the interaction along the c axis (along which no hydrogen bonding exists). Furthermore, the appearance of the {401} may be a result of preferred adsorption of 4-methylacetanilide and the consequent relaxation of host molecule conformation in the growth front, as hypothesized in the etching studies. The differences will be used to refine the MC model to predict faces expected during growth from different solvents.

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