Influence of Tailor-Made Additives on Etching Patterns of Acetaminophen Single Crystals

Tonglei Li,[1] Kenneth R. Morris,[1] and Kinam Park[1,2]

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INTRODUCTION

The evolution of surface morphology and texture during crystallization and dissolution processes has received much attention for many years (1). Understanding of the formation of surface morphology and texture sheds light on the mechanism of crystal growth and dissolution, especially the interaction between solid and solvent molecules. Inspired by one study showing etching patterns of acetaminophen with an optical microscope (2), we have reported a study in which (010) faces of acetaminophen (APAP) single crystals (3,4) were examined with an atomic force microscope (AFM) after etching with several different solvents (5). It was found that etching patterns were regular and the shape was related to the solvent used for the etching. The etching patterns observed in that study were parallelograms (by water and acetic anhydride), slits (by dichloroethane), hexagonal (by pyridine), squares (by acetone), or rectangular (by ethyl acetate). Computer simulations showed that surface diffusion of APAP molecules played a key role in forming the etching pattern. The diffusion was confined by the underlying interaction network or so-called periodic bound chains (6) on the (010) face. For etching patterns formed by water, acetic anhydride and pyridine, ledges of etch pit were either parallel to the a axis or the c axis. The first and second strongest interaction networks are along the a axis and the c axis, respectively. Computer simulations, however, were not able to explain etching patterns formed by acetone, dichloroethane and ethyl acetate. It was hypothesized that the discrepancy between the simulation and the experiment was due to the fact that no adsorption of solvent molecules was considered in simulations. It was likely that acetone or ethyl acetate molecules adsorbed on the (010) face of acetaminophen, interrupted the original interaction network on the surface, and caused the mutation of etching patterns.

To test the hypothesis, the study was continued by using aqueous solutions containing "tailor-made" additives for etching the (010) face of acetaminophen single crystals. Use of tailor-made additives to control the nucleation and crystallization processes has been well demonstrated (7). The morphological changes of acetaminophen growth by additives have also been reported (8). In this study, acetanilide and 4-methyl acetanilide were used as additives. Acetanilide lacks APAP's hydroxyl group, and 4-methyl acetanilide replaces the hydroxyl group with a methyl group. They have similar molecular shape and similar volumes to acetaminophen. If molecules of these two additives are able to adsorb on the (010) face of acetaminophen, each molecule must occupy one lattice point and assume a similar conformation and the same orientation as the host. As a result, the two original hydrogen bonds shared by the hydroxyl group will be lost and the original supramolecular interaction network will be interrupted at the adsorption sites. The new etching pattern, based on our hypothesis, will be changed from parallelogram to square or rectangular. In this report, we report observations of AFM measurement of etched (010) faces of acetaminophen single crystals by aqueous solutions of tailor-made additives. Our results showed that the adsorption of additive or solvent molecules may affect the dissolution mechanism and thus, change the surface morphology.

MATERIALS AND METHODS

Acetaminophen raw materials (USP/BP) were gifts from Hoechst Celanese (Bishop, TX). 4-Methyl acetanilide (99%) and acetanilide (99.9+%, sublimed) were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI). Deionized distilled water was used.

Conditions and procedures of crystal growth, cleavage of the (010) face and etching of single crystals of acetaminophen were reported in details in (5). Crystals were grown in water at 25°C with a super-saturation ratio of 1.5. Regular, clear single crystals were collected and cleaved to expose the (010) face. Cleaved crystals were then glued on metal disks for etching and AFM observations. 1, 5, 10, 20 and 40 mM aqueous solutions of acetanilide, and 1, 3 and 6 mM aqueous solutions of 4-methyl acetanilide were used to etch (010) faces of acetaminophen crystals for 10~30 seconds at room temperature. (010) faces of etched crystals were observed with an atomic force (NanoScope Multi-Mode AFM, Digital Instruments, Inc., Santa Barbara, CA). Images shown in this report were generated by the AFM software in the deflection mode.

The solubility of acetaminophen in water and in saturated 4-methyl acetanilide aqueous solution was measured after equilibration with an Agilent 1100 Series HPLC (Agilent Technologies, Palo Alto, CA) at 25°C, respectively. The mobile phase contained aqueous phosphate buffer, pH 4.5 and 30% v/v methanol. A Symmetry C18 column (Waters Corp., Miford, MA) was used and its temperature was maintained at 25°C. The flow rate was 1 ml/min. The solubilities of acetaminophen in the absence and presence of saturated 4-methyl acetanilide were 14.1 mg/ml and 15.2 mg/ml, respectively. Since the solubility increase in the presence of saturated additives is relatively small, 14.1 mg/ml was used to calculate the molar ratios between acetaminophen and additives at different concentrations.

RESULTS AND DISCUSSION

Etching patterns of acetaminophen crystals created by pure water are shown in Fig. 1. The shape of the etch pits is close to parallelogram and ledges are parallel to either the a axis or the c axis. Our earlier study showed that such forma-

[1] Departments of Pharmaceutics and Biomedical Engineering, Purdue University, West Lafayette, Indiana 47907-1336.

[2] To whom correspondence should be addressed. (e-mail: kpark@purdue.edu)

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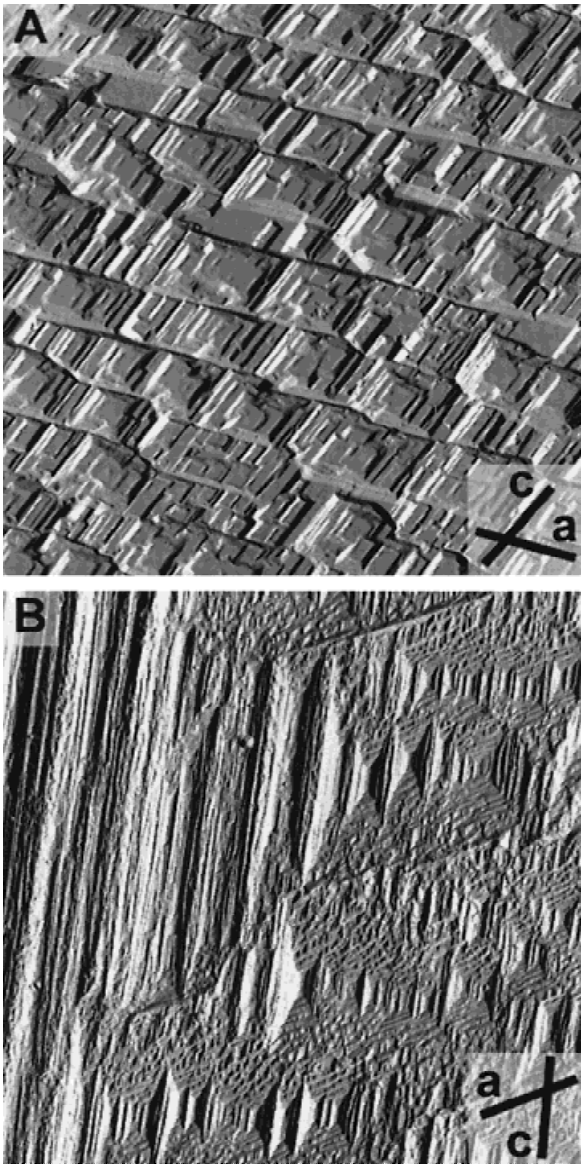

Fig. 1. AFM images of (010) faces of two acetaminophen single crystals etched in water. (A) a 60 × 60 μm^2 scan of a crystal dissolved for 120 seconds at 30°C. (B) a 60 × 60 μm^2 scan of a crystal dissolved for 600 seconds at 40°C. The a and c axes are marked on each image.

tion was due to the distribution of interaction network on the (010) face of crystals (5). The strength of interaction network decreases in the order of the a direction, c direction, and the direction in between a and c axes. Because of surface diffusion, the dissolved solid molecules may diffuse and form ledges to gain more favorable binding energies along the interaction directions. As the result, etch pits have a parallelogram shape. Based on our simulation, adsorption of water molecules may have little affect on the surface structure and interaction network, and water molecules may only act as dissolving agents.

Etching patterns of acetaminophen crystals created by acetanilide aqueous solutions are shown in Fig. 2. When the concentration of the tailor-made additive was 1mM, the etching pattern was close to a parallelogram and most of ledges were parallel to either the a axis or the c axis, as shown in Figs. 2-A and 2-B. The figures, however, showed that a few ledges are "derailed" from the a axis. When the concentration of the additive reached 20 mM, the etching patterns, shown in Figs. 2-C and 2-D, were very different from those created by pure water. The shape of etch pits were close to rectangular. Ledges were much straighter along the c axis, and there were at least two other directions for ledges, the a axis and the one roughly perpendicular to the c axis. More interestingly, on another area of the same crystal, shown in Fig. 2-E, the etching pattern became circular. This circular pattern was also observed on another crystal shown in Fig. 2-F. This pattern means that the interaction network on the surface is likely to have been distributed evenly at this observation scale. There was no dominant interaction direction. One reason for the difference between the rectangular shape and the circular shape of etch pits on the same crystal surface might be the difference of local concentration of the additive. In Figs. 2-E and 2-F, it is hard to find any trace of an etching pattern similar to those created by water. However, in other four figures, they seemed to be created by a joint effect of water and additive molecules.

Etching patterns of acetaminophen crystals created by 4-methyl acetanilide aqueous solutions are shown in Fig. 3. The effect of concentration of the tailor-made additive is obvious. When the concentration was 1 mM, as shown in Figs. 3-A and 3-B, the shape of etch pits closely resembled parallelogram. Ledges were parallel to either the a axis or the c axis. There were a few ledges not following either axis. When the concentration was 3 mM, as shown in Figs. 3-C and 3-D, the etching patterns changed. There were a few large ledges in Fig. 3-C that were parallel to the a axis. Etch pits were close to square or rectangle. When the concentration was increased to 6 mM, the etching pattern, shown in Figs. 3-E and 3-F, became much sharper and close to square or rectangle. It was difficult to find any ledge that is parallel to the a axis. The angle between the two ledge directions of ledges was close to 90 degrees. Compared three small-scale scans as in Figs. 3-B, 3-D and 3-F, the effect of 4-methyl acetanilide became apparent.

The two additives, acetanilide and 4-methyl acetanilide, are able to fit into the crystal lattice of acetaminophen because of their shape and volume similarity to the host molecule. After additive molecules are adsorbed on the (010) face of acetaminophen, they should be able to diffuse and occupy surface sites. However, unlike the host molecules that can form four hydrogen bonds with two at each end, the additive molecule can only form two hydrogen bonds at one end. Consequently, the interaction network along the a axis is terminated at the adsorption site. Based on the hypothesis presented in our previous publication (5), one can see that the etching pattern was changed from a parallelogram to a square or rectangular shape. This is demonstrated in Figs. 2 and 3. In addition, the shape of the pits is apparently more sensitive to 4-methyl acetanilide. This may be attributed to the shape and volume being closest to the host molecule. After taking part in the crystal lattice, molecules of 4-methyl acetanilide may disrupt the original interaction network significantly.

The circular etching patterns shown in Figs. 2-E and 2-F may be explained by both a heterogeneous distribution of acetanilide molecules on the (010) face as well as by the disruption of the original interaction network. Because of steric repulsion between neighbor acetaminophen molecules on the

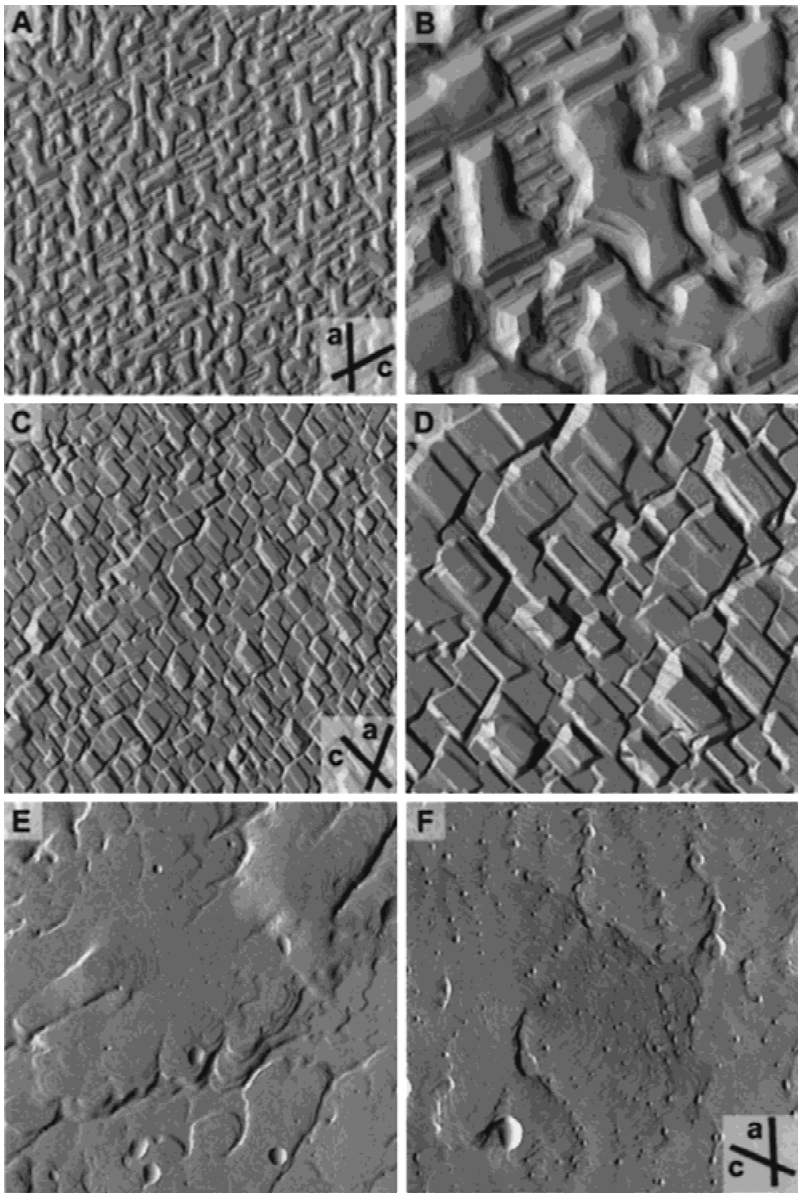

Fig. 2. AFM images of (010) faces of three acetaminophen single crystals etched in acetanilide aqueous solutions for 30 seconds. (A) and (B) are a 25 × 25 μm^2 and a zoomed-in 7 × 7 μm^2 scan, respectively, from the center of a crystal in 1 mM solution. (C), (D), and (E) are a 25 × 25 μm^2, a zoomed-in 10 × 10 μm^2 from the center of (C), and a 10 × 10 μm^2 scan of a different area, respectively, of a crystal etched in 20 mM solution. (F) is a 8 × 8 μm^2 scan of another crystal etched in 20 mM solution. The a and c axes are marked on (A), (C), and (F), respectively.

(010) face along the direction between the a and c axes (Table 3 in (5)), the strongest hydrogen bonding may be cancelled out along that direction. However, the steric repulsion may disappear due to the adsorption of acetanilide, which has a smaller molecular volume than acetaminophen and 4-methyl acetanilide and thus more flexible inside the host lattice. It is likely that the interaction is near equal in the different directions at adsorption sites. It is intriguing that on the same crystal surface, one area has etch pits of rectangular shape while another area has circular shape (Figs. 2-D and 2-E).

The effect of the additives on changing the etching pattern is tremendous, given the very small concentrations of additives used in etching solutions. At 25°C, the saturated solubility of acetaminophen in water is 14.1 mg/ml (or 0.093 M). If the concentration of acetaminophen near the crystal surface is assumed to reach the solubility limit, the molar ratios near acetaminophen (010) surfaces between aqueous acetanilide and acetaminophen in the experiments ranged from 0.011 to 0.215. The molar ratios between 4-methyl acetanilide and acetaminophen ranged from 0.011 to 0.064. It is apparent that adsorption of additive molecules causes significant changes of etching patterns despite their relatively minute amounts in solutions, especially the case by 4-methyl acetanilide. This is most likely due to modification of the crystal surface interaction network.

Computer simulations in which the adsorption of solvent

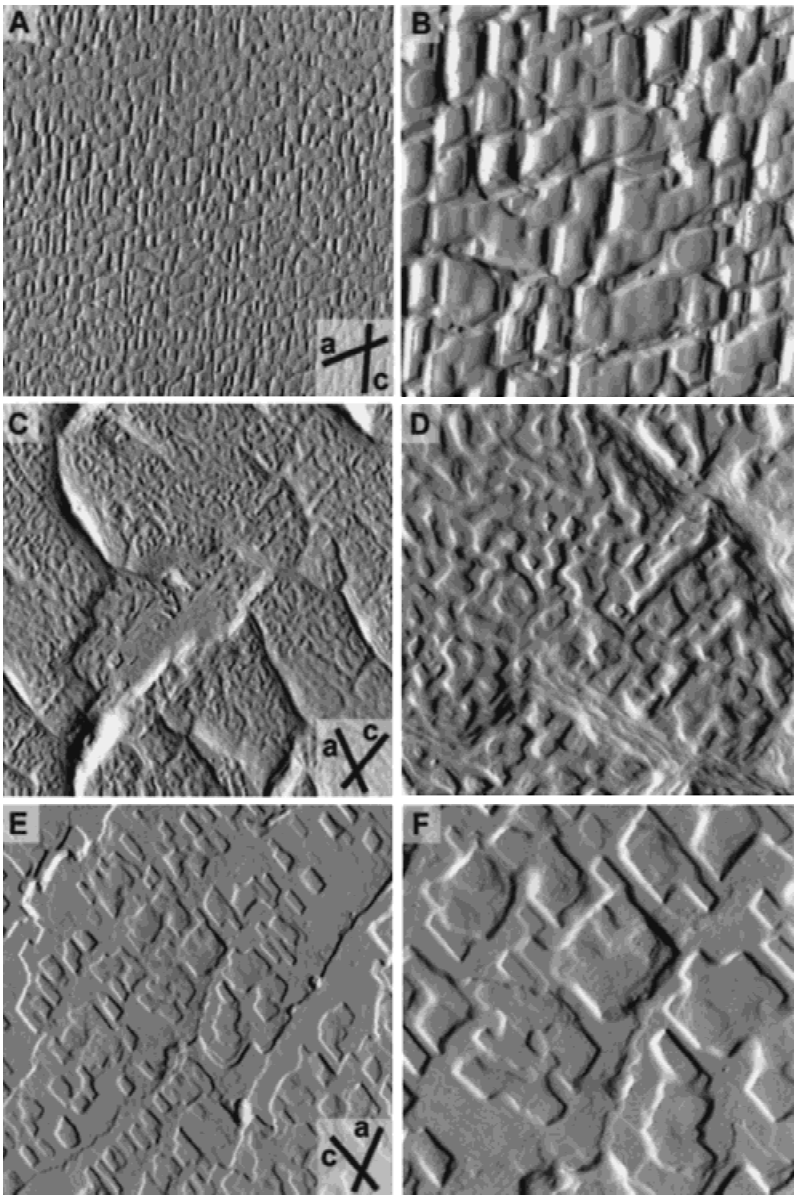

Fig. 3. AFM images of (010) faces of three acetaminophen single crystals etched in 4-methyl acetanilide aqueous solutions. (A) and (B) are a 40 × 40 μm^2 and a zoomed-in 10 × 10 μm^2 scan close the center, respectively, of a crystal in 1 mM solution for 10 seconds. (C) and (D) are a 15 × 15 μm^2 and a zoomed-in 5 × 5 μm^2 scan close to the center, respectively, of a crystal in 3 mM solution for 30 seconds. (E) and (F) are a 10 × 10 μm^2 and a zoomed-in 4 × 4 μm^2 scan of the center, respectively, of a crystal in 6 mM solution for 30 seconds. The a and c axes are marked on (A), (C), and (E), respectively.

and/or additive is considered are under way. It is expected that additive molecules (which have anisotropic interactions with host molecules) can selectively adsorb on the surface and affect the formation of etch pit by differentially intervening with growth along periodic bound chains.

CONCLUSIONS

Etching patterns of (010) face of acetaminophen single crystals created by aqueous solutions of tailor-made additives, acetanilide and 4-methyl acetanilide, were examined by AFM. The data support the hypothesis that additive molecules were able to adsorb on the crystal surface, diffuse and occupy crystal lattices, disrupt the original supramolecular interaction network and thus, change the shape of etch pits from parallelogram to rectangular, square, or circular. Because tailor-made additives were used, the changes of etching patterns are very likely to be a result of the adsorption of additive molecules.

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