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Understanding the Formation of Etching Patterns Using a Refined Monte Carlo Simulation Model

Tonglei Li, Kinam Park, and Kenneth R. Morris*

Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana 47907-1336

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ABSTRACT: Tailor-made additives of acetaminophen were shown to be very effective in changing the etching patterns on the cleaved surface of the single crystal (i.e., the (010) face in an aqueous environment). The shape of the etch pits was "mutated" from a parallelogram to a square shape when the concentration of additives was increased. Monte Carlo simulation was carried out to study the formation mechanism of the square-shaped etch pit. When the intermolecular interactions between acetaminophen on the surface were treated the same as in the bulk, including the adsorption of additive molecules alone failed to align the additive-terminated kink sites perpendicular to the *c* axis. Therefore, it has been hypothesized that an additive molecule can stabilize a "relaxed" state of molecules on the surface of the crystal that may form stronger interactions with its neighboring molecules along the [102] axis. Such a relaxed state is possible only if the two neighboring sites along the [102] direction are unoccupied by host molecules because of the extra space that would be required for the methyl group's motion. Supporting evidence for the concept was found in the literature.

1. Introduction

Understanding the mechanism of the formation of various crystal forms and habits is crucial for the manufacture of pharmaceutical active ingredients and their bioavailability.[1] After a stable crystal form is identified, controlling the habit becomes vital as the crystal shape may influence physicochemical, mechanical, and biological properties greatly.[2] It has been shown that the solvent and impurities play a key role in affecting polymorphism and crystal habit.[3,4] With structurally similar guest molecules, or so-called tailor-made additives, crystal morphologies can be significantly changed and may often be controlled.[5]

Studying etching may provide equally important information about the interaction between drug crystal molecules and solvent molecules, as crystal growth and dissolution share similar underlying molecular mechanisms. The formation of etching pits has been investigated for many years.[6] The study has been pushed forwarded by the maturing of atomic force microscopy (AFM).[7−9] AFM can achieve the nanoscale resolution, and the observation can be carried out in situ under ambient environmental conditions or in liquid with little sample preparation.[10,11]

We have studied the etching patterns with AFM of acetaminophen (or paracetamol). Acetaminophen, 4-hydroxyacetanilide, is one of the most commonly used drugs for antipyretic (fever suppressant) and analgesic (pain killer).[12] Acetaminophen forms a molecular crystal with a large number of weak, nonbonding intermolecular interactions (especially hydrogen bonding) that maintain the supramolecular motifs. The acetaminophen crystal can be described as stacked 2D (010) layers through van der Waals and Coulombic interactions with stronger intermolecular interactions (i.e., hydrogen bonding) within the layer (Figure 1). On the (010) face, we have examined the etching patterns with AFM following exposure to several different solvents.[13] It was found that etching patterns were regular, and the shape was related to the solvent used for the etching and the underlying crystal-packing motif. The etching patterns observed were parallelograms (by water shown in Figure 2a, and acetic anhydride), slits (by dichloroethane), hexagonal (by pyridine), squares (by acetone shown in Figure 2b), or rectangular (by ethyl acetate). Monte Carlo simulation showed that the surface diffusion of acetaminophen molecules played a key role in forming the etching pattern.[13] The surface diffusion was confined by the underlying interaction network or so-called periodic bond chains on the (010) face. Ledges of etch pits formed by water, acetic anhydride, and pyridine were either parallel to the *a* axis or the *c* axis. The first and second strongest interaction networks are along the *a* and the *c* axes, respectively. The simulations, however, were not able to explain etching patterns formed by acetone, dichloroethane, and ethyl acetate. It was hypothesized that the discrepancy between simulation and experiment was because no adsorption of solvent molecules was considered in simulations. It was likely that acetone, dichloroethane, or ethyl acetate molecules adsorb on the (010) face of acetaminophen, interrupt the original interaction network on the surface, and cause the mutation of etching patterns.

To test the hypothesis, studies were conducted using aqueous solutions of "tailor-made" additives, acetanilide and 4-methylacetanilide, as solvent "surrogates" in a neutral solvent (one that behaved as expected in our earlier model, in this case water), for etching the (010) face of acetaminophen single crystals.[14] In terms of chemical structure, acetanilide lacks the hydroxyl group of acetaminophen, and 4-methylacetanilide replaces the hydroxyl group with a methyl group. It was observed when the concentration of acetanilide was 1 mM, the

* To whom correspondence should be addressed at Kenneth R. Morris, Ph.D., Purdue University, School of Pharmacy, West Lafayette, IN 47907-1336, Tel: 765/496−3387, Fax: 765/494−6545, E-mail: morriskr@purdue.edu.

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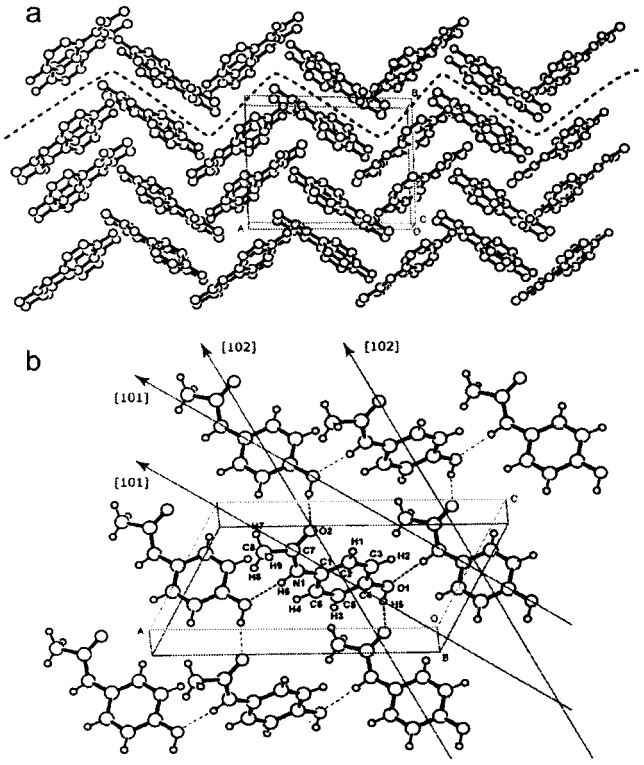

Figure 1. Crystal structure of acetaminophen ($P2_1/a$; a = 12.93 Å; b = 9.40 Å; c = 7.10 Å; β = 115.9°). It can be seen as a layering structure (as indicated by the dash line between two layers) where 2D layers stack along the b axis (a). On each layer (b), or the (010) face, there is a 2D hydrogen-bonding network along the a and [102] axes, respectively. Of the center molecule, each atom is indexed. The lattice lines, [102] and [101], are marked. (Note that the *ac* plane is a little tilted away from the paper).

etching pattern was close to a parallelogram as observed on the surface etched by water, and most of ledges were parallel to either the a axis or the c axis. When the concentration of the additive reached 20 mM, the etching patterns, which were close to rectangular, were very different from those created by pure water. The etching patterns created by 4-methylacetanilide aqueous solutions exhibited a more dramatic effect of increasing additive concentration. At 1 mM, the shape of etch pits closely resembled parallelogram. Ledges were parallel to either the a or the c axis (a few ledges were aligned with neither axis). At 3 mM, the etching patterns changed again, with a few large ledges that were parallel to the a axis and the etch pits were close to square or rectangular. At 6 mM, the etching pattern became much closer to square or rectangular as shown in Figure 2c.

The etching patterns strongly suggest that acetanilide and 4-methylacetanilide are able to adsorb on the (010) face of acetaminophen. Because additive molecules have similar molecular shape and similar volumes to the host molecule, when incorporated into the surface, each additive molecule should occupy one lattice point with a similar conformation and/or orientation as the host. As a result, the two original hydrogen bonds shared by the hydroxyl group disappear, and the original supramolecular interaction network may be interrupted at the adsorption sites. The new etching pattern may change from a parallelogram in absence of additives to

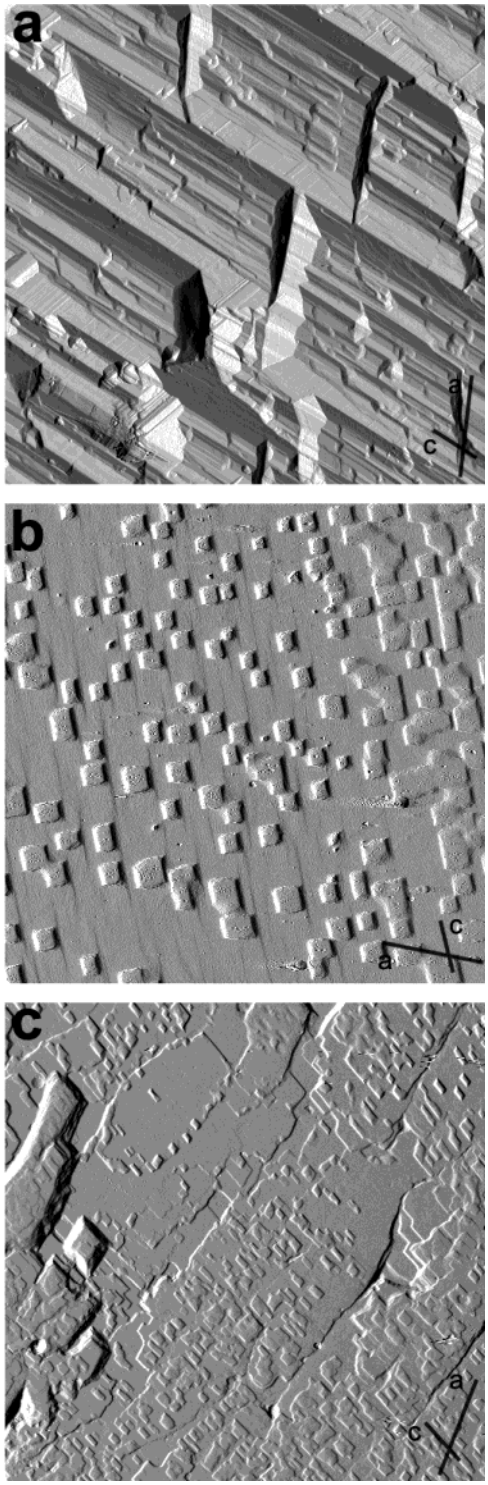

Figure 2. AFM images (deflection mode) of etching patterns on the (010) faces of acetaminophen single crystals. (a) A 30 × 30 μm^2 scan of a crystal etched by water for 30 s. (b) A 30 × 30 μm^2 scan etched by acetone/CCl_4 (1:1 v/v) for 10 s, and (c) a 20 × 20 μm^2 scan etched by 6 mM aqueous solution of 4-methylacetanilide for 30 s. The Z ranges of corresponding height images are 3 μm, 250 and 800 nm, respectively. All dissolution tests were done at the room temperature. Axes are marked for each image.

a square or rectangular shape. In addition, 4-methylacetanilide may disrupt the original interaction network more efficiently after incorporation in the crystal lattice due to the molecular shape and volume being closest to the host molecule. Consequently, it is concluded that

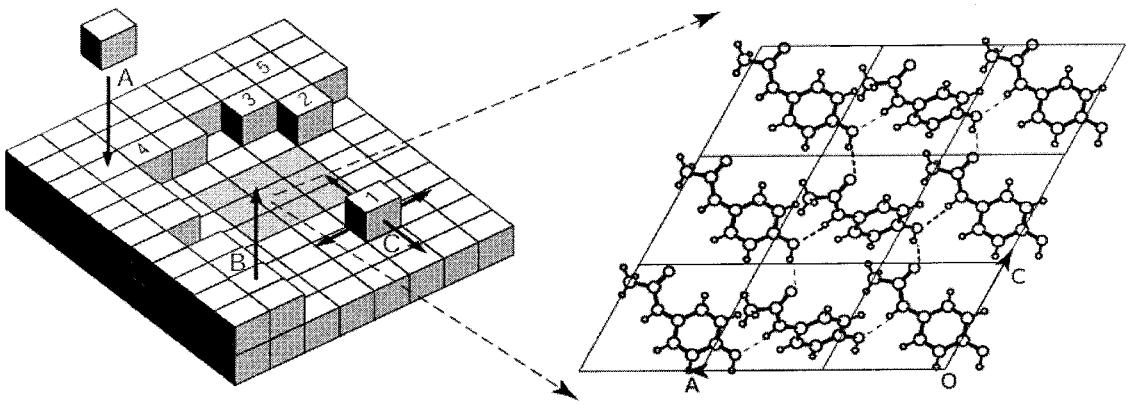

Figure 3. The lattice model used in the simulation. Each lattice represents a molecule. There are three elementary mechanisms to be considered: adsorption (A), detachment (B), and surface diffusion (C). According to the number of nearest neighbors, the surface molecules can be labeled as adatom (#1), ledge (#2), kink (#3), step (#4), and terrace (#5).

the formation of etching patterns on a crystal surface is not only determined by the average interaction between the solid and the solvent molecules, but also influenced by the adsorption of solvent, impurity, or additive molecules on the crystal surface. Similar observations have been reported by others.[5,15]

The simulation reported earlier[13] did not consider the specific adsorption of solvent or additive molecules, only the detachment and surface diffusion (Figure 3). Simulated etching patterns, from parallelogram to hexagon, were the result of increasing solvent quality (from a poor to a good solvent). To further elucidate the observed etching patterns in the presence of additive molecules, the earlier computer model has been refined to consider adsorption of additive molecules. Here we report the simulation studies of the etching mechanism in the presence of additive molecules and present arguments for the formation of the square or rectangular shape pits. The simulation results indicate that solvent or additive molecules may play a key role in not only controlling the etching pattern but also stabilize possible different energy-favorable conformation and/or orientation of host molecules on the surface.

2. Computer Model

The computer model reported earlier[13] has been expanded to include consideration of adsorption of solvent or additive molecules. The model is a 3D-lattice abstraction of the crystal structure of acetaminophen.[13] Shown in Figure 3, each lattice point (or equivalently, a lattice box) represents an acetaminophen molecule. The model surface is aligned with the (010) crystal face, and all layers are treated as being stacked evenly. A molecule is "dissolved" when the corresponding lattice box is updated as "empty". The early model ignored the conformation and the orientation of each individual molecule. Nevertheless, the interaction energies were calculated based on the actual crystal structure[16] with Cerius[2] 3.5 (Molecular Simulation Inc., San Diego, CA). The force field used was Dreiding 2.21, and partial atomic charges were computed with charge equilibrium method, Gasteiger-Quanta 1.0. The interactions calculated include van der Waals interaction (with Ewald summation), Coulombic force (with Ewald summation), and hydrogen bonding. Only adjacent molecules were considered when calculating interaction energies of a molecule. Therefore, for a given molecule, the intermolecular interactions with all its neighbors in the model make up a $3 \times 3 \times 3$ matrix called a "force matrix". During the simulation, the energy evaluation of a molecule is done by screening the force matrix in accordance to the existing status of its neighbor molecules.

The force matrix indicates that on the (010) face the interaction along the *a* axis is the strongest and the interaction along the *c* axis is the second strongest. The hydrogen-bonding network on the (010) face is made up of two routes (or PBCs), one along the *a* axis and another stronger along the [102] direction. Because of a very large repulsive van der Waals force opposing the largest hydrogen-bonding interaction, the total interaction along the [102] route is smaller than that along the *c* axis where no hydrogen bonding exists. The repulsive van der Waals interaction is caused by the unfavorable distance between a hydrogen atom of the methyl group (i.e., one of H7, H8, or H9) of one molecule and a hydrogen atom (i.e., H3) of the phenyl ring of the neighboring molecule on the (010) face (about 2.4 Å).

The Monte Carlo simulation reported earlier[13] considered only two molecular events, detachment and surface diffusion. When a surface molecule is randomly chosen to be detached, the energy change of the molecule is computed. The Metropolis rule[17] is then applied to decide whether this site is removed from the surface. After the surface molecule is detached, a number of surface diffusion events are carried out around the detached site. Three types of surface diffusion are defined, strong, medium, and weak diffusion. In the strong diffusion mode, a diffusing molecule searches and moves to the most stable unoccupied site within a predefined range even if there are blocking molecules in the diffusion path. Blocking molecules are considered in the medium diffusion mode. In the weak diffusion mode, the diffusing molecule only searches for a better place among its nearest neighbor sites. The effect of these diffusion modes was shown to have a significant impact on the shape of the etching patterns.[13]

To simulate the adsorption of solvent or additive molecules, the computer model has been expanded to include the adsorption event. Each lattice includes a representation of the additive in its data structure besides the original solid or solvent status. For an

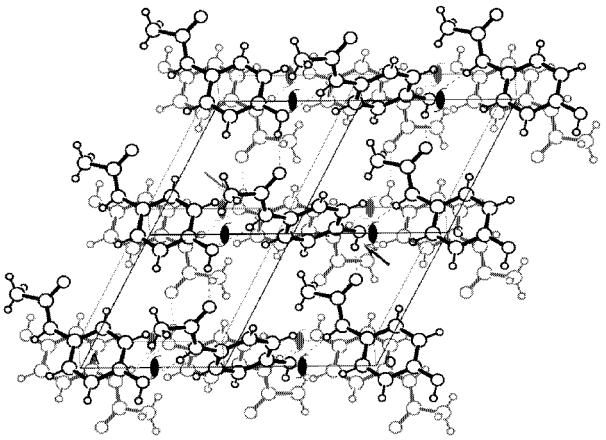

Figure 4. Illustration of the 2-fold screw axis along the *b* axis. Two adjacent layers are shown. The top one is in the dark color and the bottom in gray. The arrows point to the hydroxyl groups of the center molecules, respectively. (Note that the *ac* plane is a little tilted away from the paper).

additive molecule, because of the lack of the hydroxyl group, it can only form two hydrogen bonds at one end with host acetaminophen molecules. Between additive molecules, no hydrogen bonds are assumed to exist. In addition, because of the 2-fold screw axis perpendicular to the (010) face, the binding between an additive molecule and a host molecule is mirrored at 180 degrees between adjacent layers in Figure 4. That is, if an additive binds to the left via hydrogen bonds, on the layer below, an additive can only bind to the right with host molecules via hydrogen bonds. Therefore, it is necessary to identify two layer types. A variable in the lattice data structure is added to indicate the layer bonding type.

Furthermore, more force matrixes have been used to evaluate the interaction energies. Between the additive and acetaminophen host molecules, two force matrixes are used in accordance with the two types of model layers. Because it is difficult to obtain the exact positions of additive molecules that are incorporated inside the host crystal, the new force matrixes are created based on the original force matrix that is used to calculate the interaction energies among host molecules. The new energy values are modified relatively based on host−host interactions along corresponding directions. Of the crystal-additive force matrixes, the values with its nearest neighbors on the top and bottom layers are kept the same as those of the crystal−crystal force matrix. Interaction values on the middle layer are adjusted given the missing hydrogen bonds along the *a* axis and the [102] direction between crystal and additive molecules. Moreover, a force matrix is used to evaluate interactions among additive molecules. It is assumed that additive molecules take similar conformations to the host molecules and no hydrogen bond between additive molecules exists. Consequently, this matrix shares the same energy values as the original force matrix but all hydrogen bond terms are removed. It is worthwhile to point out that the interaction terms in these new force matrixes are not always satisfactory in matching the simulated pattern with the observed experimental pattern. By adjusting the interaction values relative to the matching host−host interactions, especially those along the *a* axis and the [102] direction, simulated patterns can be affected and may start to match the observed shape. This iterative process has been used to refine the energy terms and, hence, the model. With the refined model, it is possible to further hypothesize on how the additive molecules interact with the host lattice.

The adsorption of additive molecules is considered in the refined model in addition to detachment and surface diffusion. An input parameter is used to define the ratio between the numbers of total adsorption and detachment events. After each successful movement, adsorption or detachment, a number of surface diffusion events are performed. The area from which to select host molecules for surface diffusion, the number of molecules to be considered in the surface diffusion, and the diffusion length are defined in the input file. The system energy is evaluated before and after the move (sorption or surface diffusion) is made. The Metropolis rule is then used to judge whether the move is accepted. Furthermore, all the molecules in the solvent are considered to be in the "bulk" state and are treated the same. The solvated additive molecules are not explicitly included in the model. Their existence in the bulk is represented by predefined energy parameters that are used to calculate the interaction energy before adsorption onto or after detachment from the surface.

3. Results and Discussion

In this section, it will be discussed first how the discrepancy between the shapes simulated from our program and experimentally observed patterns led to the modification of force matrixes and improvement to the simulation model. It will be then shown how the enhancement of the program has been used to develop the argument that the host molecules on the surface may take a more relaxed conformation than molecules in the bulk of the crystal and the adsorption of additive molecules may stabilize the relaxed host molecules and take a different conformation and/or orientation.

Figure 5 shows a simulated surface when the adsorption is considered. The force matrixes of the crystal-additive interaction used in the simulation are summarized in Table 1 along with the crystal−crystal force matrix. The middle layers of force matrixes are listed as they contain the only differences from the original force matrix.[13] The model size was $6 \times 80 \times 80$, and the number of sorption moves including adsorption and detachment was 5000 while the adsorption ratio was 0.7. Unlike the earlier simulation results that showed a parallelogram-shape etching pattern (without the consideration of adsorption of additive molecules), the pattern in Figure 5 illustrates that the ledges along the *a* axis are terminated by adsorbed additive molecules either on the right or on the left. As expected, the 2-fold screw axis along the *b* axis dictates that host molecules on the even number indexed layers and the odd number indexed layers bind oppositely with additive molecules (Figure 5b). It is shown on one layer, the terminated kink sites form a zigzag ledge away from *a* axis. The zigzag ledge formed on the layer below is parallel with the ledge above. Those ledges not terminated by additive molecules dissolve regularly along the *a* and *c* axes,

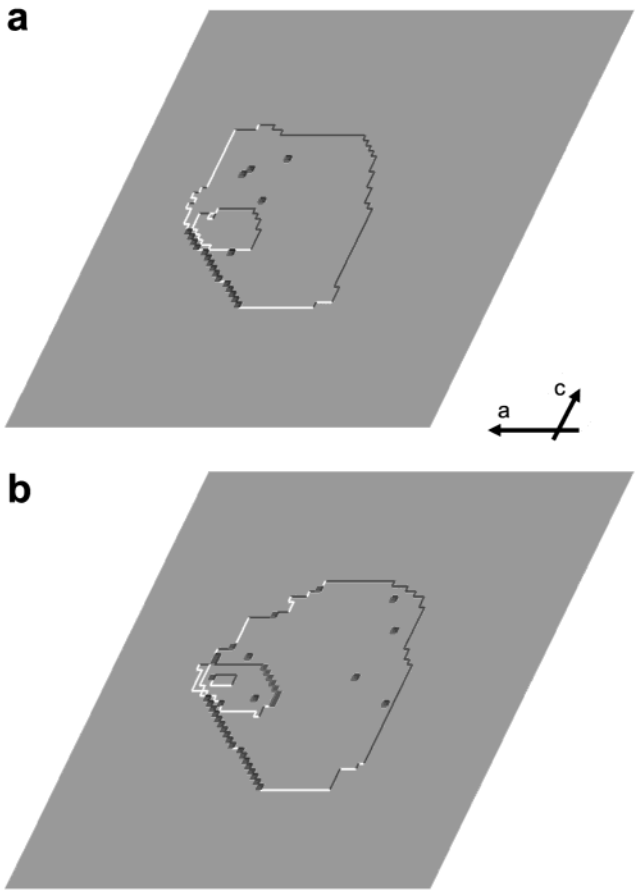

Figure 5. Simulated patterns with the consideration of adsorption of additive molecules that are drawn in the dark color. The model size was 6 × 80 × 80. The first one was simulated after 250 sorption moves (a), and the second one was simulated after 4000 moves (b).

Table 1. Interaction Energies (kcal/mol) of a Molecule with Its nearest Neighbors on the (010) Face[a]

		c axis	
	−0.6037	−1.1578	0.0890
a axis	−5.8889	n/a	−5.8889
	0.0890	−1.1578	−0.6037
	−0.5	−1.0	0.1
a axis	−5.0 or −1.0	n/a	−1.0 or −5.0
	0.1	−1.0	−0.5
	−4.5 or −1.0	−1.1578	0.0890
a axis	−5.8889 or −2.0	n/a	−2.0 or −5.8889
	0.0890	−1.1578	−1.0 or −4.5

[a] Calculated with Cerius[2] 3.5. The first three numerical rows were used for the original simulation where no adsorption was considered. The second three rows were used for crystal-additive interactions when the adsorption of additive molecules was considered. There are two values along the *a* axis due to the 2-fold screw axis. The third three rows were used for the relaxed crystal-additive interactions in the refined simulation model.

respectively. Nevertheless, the etch pit simulated in Figure 5 does not match the experimentally observed pits.

The most obvious discrepancy between the simulated and observed patterns is the angle between the ledges around etch pits. AFM images of the etched (010) face of acetaminophen single crystals show an approximately 90-degree angle. The angle shown in Figure 5, however, is far from 90 degrees. This zigzag ledge made up of the terminated chains (PBCs) is the result of the

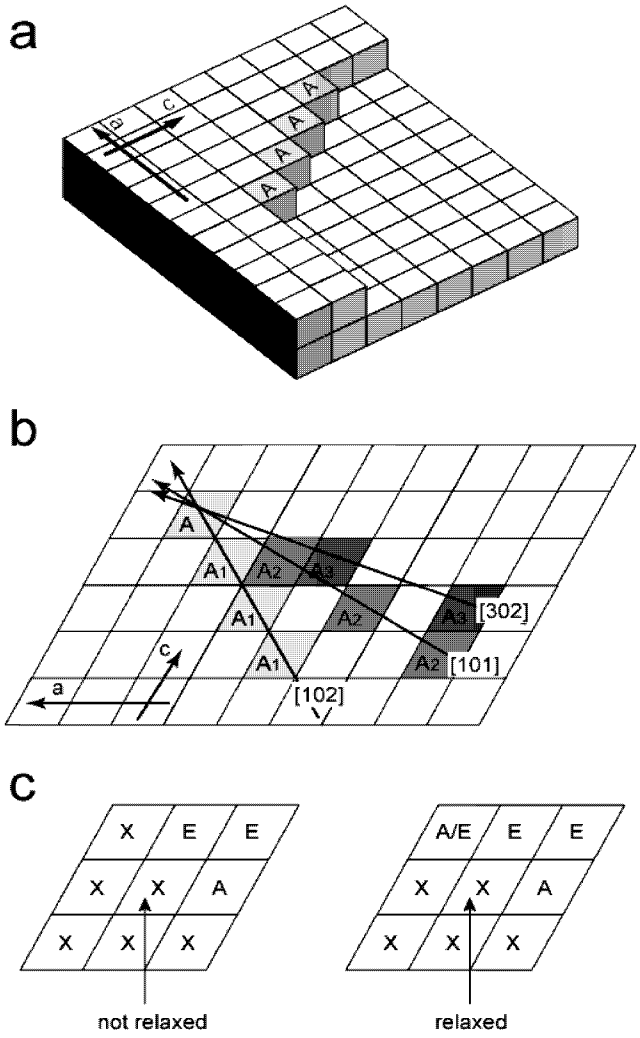

Figure 6. Refinement of the simulation model to consider the adsorption of additive molecules. (a) A simplified simulated model where adsorbed additive molecules are marked with "*A*". The alignment of additive molecules, marked with "*A*" and "*A1*", is along the [102] direction as shown in (b). Additives can be aligned along the [101] direction, as marked with "*A*" and "*A2*". They can also be aligned along the [302] direction, as marked with "*A*" and "*A3*". (c) Definition of the relaxed state of crystal molecules on the surface. Lattices marked with "*X*", "*E*" and "*A*" are crystal molecules, empty sites and additive molecules, respectively.

alignment of additive molecules along the [102] direction (Figure 6a). There are several possible alignment schemes of adsorbed additive molecules as shown in Figure 6b. If all additive molecules are aligned along the *c* axis, the etch pits have the same parallelogram shape as simulated without consideration of adsorption of the solvent or additive molecules (the angle between the *a* and *c* axes is 115.9 degrees). If additive molecules are aligned along the [102] direction, the angle between the terminated ledges along the *a* axis and the *c* axis is 53.7 degrees. Aligned along the [101] and [302] directions, the angles are 82.9 and 94.5 degrees, respectively. The angle becomes 100.2 degrees when additive molecules align the [201] direction. On the basis of the experimental results, therefore, it has been assumed that the additive molecules have to bind to the host molecules by hydrogen bonding and align along the [101] and [302] directions to produce the observed angles.

It is reasonable to argue that adsorbed additive molecules may not only terminate ledges along the *a* axis but may also make them dissolve more slowly than those ledges without bound additive molecules. The experimentally observed etching patterns show that etch pits may be confined by additive terminated ledges and ledges along the *c* axis. However, additive molecules can only bind and terminate ledges along the *a* axis on one side on each layer. So the opposite side of the etch pit is confined not by the additive-terminated ledge on this layer but by the ledge on the adjacent layer. This can be true only if the host surface molecules that are associated with additive molecules dissolve more slowly than those without any additive interaction. This may be due to the kinetic effect. Additive molecules adsorbed on the surface may have a lower free energy than those in the solvent bulk because of the negative concentration gradient from the bulk to the surface. In other words, additive molecules prefer adsorption to desorption. Adsorbed additive molecules may, therefore, be less readily dissolved (or desorbed) into the solvent and associated host molecules detachment may also be retarded relative to host molecules that are not bound by additive. Furthermore, it is possible that the surface host molecules associated with additive molecules via hydrogen bonds could be locally stabilized into an otherwise nonequilibrium orientation and/or conformation. If such a relaxed conformation is taken, "stabilized" host molecules may be less likely to be lost (i.e., dissolved) than nonadditive associated host molecules. Therefore, it may be concluded that by aligning in the [101] and [302] directions, additive molecules may make host molecules harder to detach from the surface than unassociated host molecules.

To test this hypothesis, a new variable has been introduced to the data structure of the lattice model. It is used to depict a host molecule that is switched to a "relaxed" status (Figure 6c). The relaxed status is turned on if (i) an additive molecule is bound by a hydrogen bond along the *a* axis, and if (ii) there is no more than one adjacent host molecule along the [102] axis. The second condition is required since there is a repulsive van der Waals interaction between two hosts molecules along the [102] direction. If a host molecule has two other host molecules as its nearest neighbors along this direction, it is thought that the space is insufficient to allow the necessary motion to adopt alternate conformation/orientations. As a result, the repulsive van der Waals interaction dominates so the molecule could not relax. Three more forces matrixes are needed to evaluate the interaction energies (i) between a relaxed host molecule and a normal host molecule, (ii) between a relaxed host molecule and an additive molecule, and (iii) between two relaxed host molecules. It is assumed that between two relaxed or between a relaxed and a normal host molecule along the [102] direction, the repulsive van der Waals interaction energy vanishes and the overall interaction becomes more favorable (Table 1). The new simulated etch pit is shown in Figure 7 (The model size was 6 × 50 × 50, the number of sorption moves including adsorption, and detachment was 2500 and the adsorption ratio was 0.4.). It shows that the adsorbed additive molecules have a different alignment from the pattern in Figure 5. The alignment is along the [101] direction, and the angle is close to the experimental value. In addition, the alignment shows the expected occurrence in the opposite direction on the adjacent layers (due to the 2-fold screw axis along the *b* axis).

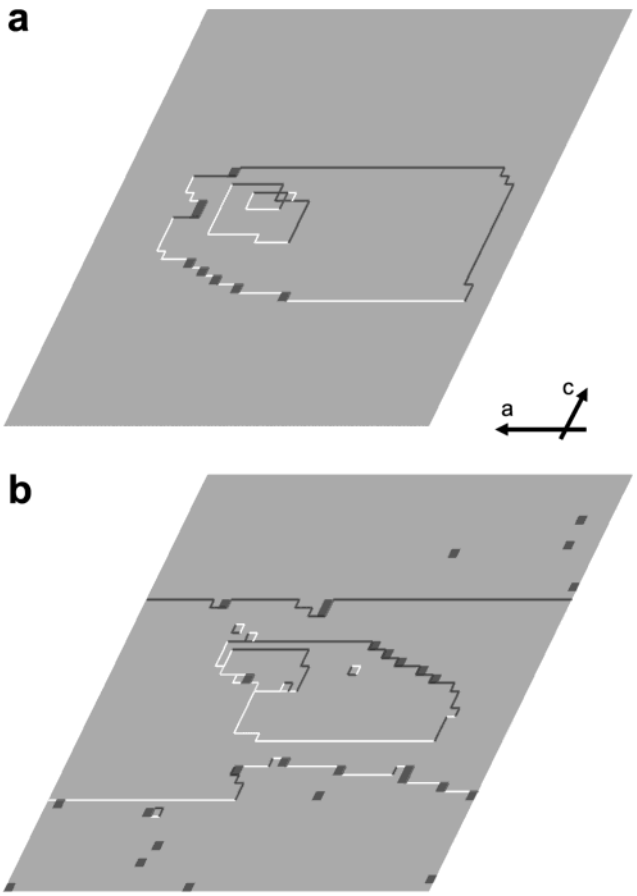

Figure 7. Simulated patterns with the refined model where surface crystal molecules were allowed to be relaxed. Additive molecules are drawn in the dark color. The model size was 6 × 50 × 50. The first one was simulated after 1000 sorption moves (a), and the second one was simulated after 2500 moves (b).

With the refined model, the simulated angle between the terminated ledges along the *a* axis and the *c* axis matches that observed. This supports the argument that the surface acetaminophen molecules may take a different conformation and/or orientation from the bulk. Such a conformation may allow the relaxation of additive-bound surface molecules. The role of adsorbed additive molecules may be able to kinetically stabilize the host molecules in the relaxed state. From the simulated and observed patterns, it is very possible that the repulsive van der Waals interaction along the [102] direction is relieved between relaxed surface molecules (which is necessary for the postulated packing motif). Single-crystal pulsed neutron diffraction studies of acetaminophen found in the literature seem to support the argument.[18,19] It was reported that hydrogen atoms of the methyl group show unusual libration or disorder that is not observed from other atoms of the acetaminophen molecule. This was detected between 20 and 300 K (the equivalent isotropic temperature factors from the literature are listed in Table 2).[19] From these data, it may be reasonable to argue that the large librational

Table 2. Equivalent Isotropic Temperature Factors (multiplied by 100) of Acetaminophen at 330 K from Single Crystal Neutron Diffraction[19]

C1	C2	C3	C4	C5	C6	C7	C8	N1	O1
2.45	3.19	3.47	3.17	3.68	3.85	3.08	4.69	3.19	4.36
O2	H1	H2	H3	H4	H5	H6	H7	H8	H9
5.12	6.61	6.72	8.28	7.20	4.78	5.27	14.83	20.93	17.15

movement of the methyl's hydrogen atoms may be due to a localized unfavorable energy environment. Any of the three hydrogen atoms (H7, H8, or H9) may approach the hydrogen atom (H3) of another acetaminophen molecule causing too much repulsion to remain stable. If one of these three hydrogen atoms moves away, due to the rigidity of the whole molecule or unfavorable contact with another atom, it may move back and approach H3 again. All three hydrogen atoms show large librational movements. Furthermore, the libration or disorder of the methyl group suggests that the evaluation of the interaction energy along the [102] direction between molecules may not be accurate (an error perpetuated in all the pure crystal force matrixes). This includes the strongest hydrogen bonding and the repulsive van der Waals interactions. It may be much stronger on the surface thanks to the adsorption of tailor-made additive (and/or solvent) molecules.

Although the refined model has been able to simulate the adsorption of additive molecules and match the angle between the alignment of adsorbed additive molecules and the *c* axis to the experimentally observed value, it cannot produce a "perfect" etch pit that looks like the inward pyramid as observed from AFM images that penetrates many layers. In Figure 5, the pit confined by the first layer is much larger than the one confined by the second layer. In Figure 7b, the top layer "dissolved" much faster than the second layer, and the pit is confined by only one additive-terminated kink sites. This may be because all the molecules of the surface model are treated the same in terms of interaction energy. The program randomly picks a surface site and runs the Metropolis scheme to calculate its probability of detachment from the surface. For any two molecules exposed on the surface, no matter which layer they are on, if their neighboring molecules are of the same type (number and layout), they have the same probability of being both picked up and detached. Because the program uses uniformly distributed random numbers to pick up surface molecules for the Monte Carlo simulation, every exposed host molecule has the same probability of being chosen. The dissolution rate of a layer is, therefore, proportional to the area exposed to the solvent. An exposed layer with a larger surface area dissolves faster. Upper layers around an etch pit dissolve faster, and the etch pit is thus made up of only a few layers in the simulation. Therefore, it is not possible with our current computational approaches for etch pits to grow deeper without spreading over the surface.

Nevertheless, it is the surface defects that not only initiate the etching but also control the size and shapes of the etch pits. At a defect site, molecules may have higher energies due to local strain than molecules within the bulk of the crystal lattice.[20] Molecules are dissolved more easily and faster within the strain field. Because the strain field is mostly caused by point defects, the distribution of the field is centered at the defect and extinguishes over a short distance. It is argued that the strain field may be attributed to the localization of etch pits. The current model is under refinement to include the strain field to simulate the etching behavior yet more accurately.

Finally, an extension to the surface relaxation postulate discussed above is under investigation. This extended hypothesis is being explored to determine an additional interaction motif between the additive and host molecules may accurately exhibit the observed behavior. On the (010) face, all of the acetaminophen molecules exhibit two different orientations and the hydroxyl group either point outward from the face or inward to the face (Figure 1b). If two orientations are denoted by *A* and *B*, surface molecules have an *ABAB* packing motif along the *a* axis, while along the *c* axis the motif is *AA* or *BB*. Along the [102] direction, the motif is *ABAB*, but along the [101], it is *AA* or *BB*. Due to the possible specific binding with host molecules, additive or solvent molecules may only be able to "dock" or adsorb at either *A* or *B* sites and as a result, the terminated kinks sites cannot align in the [102] but only the [101] direction. This argument is currently being tested in the laboratory.

4. Conclusions

The simulation work reported here illustrates the possible relaxation of acetaminophen molecules on the surface to a more locally favorable conformation and/or orientation due to the stabilization provided by the adsorption of tailor-made additive molecules. Should relaxation occur, the overall interaction energy along the [102] direction increases significantly. Nevertheless, attached additive molecules seem to better align along the [101] and/or [302] directions because the relaxation of acetaminophen molecules may require space along the [102] direction to accommodate the librational motion of the methyl group. This may be the explanation for the straight angle of etching patterns observed during experiments including adsorption of additive molecules.

The simulation has not yet been able to generate "perfect" etch pits as observed in the experiments. It is believe that defects and their associated strain fields may play a key role in the dissolution process. The simulation model to integrate the strain field is under development.

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