

Controlling and Predicting Crystal Shapes: The Case of Urea**

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Understanding crystal growth from solution is crucial to control the evolution of crystal morphologies. Since the interaction of crystals with their environment occurs through their surface, their shape controls a wide variety of properties.^[1–3] This is particularly important not only in nanotechnology, where shape–function relations play a key role, but also in medicine where changing the morphology of particles allows for instance for a better targeting of cancer cells.^[4] In this work we combine experiments, molecular simulations, and theory to examine the morphology of urea crystals grown in different solutions. To obtain a rational representation of all the possible habits we introduce a shape diagram in which the habit dependence on the relative growth rates is illustrated. A wide portion of the habit space can be experimentally explored by varying the composition of the mother solution. By doing so in the case of urea we obtain morphologies ranging from the paradigmatic needle-like habit in water to regular tetrahedra in acetonitrile/biuret mixtures. By combining advanced molecular simulation techniques and theory we can predict urea steady-state crystal habits and their dependence on additive concentration and/or supersaturation, thus paving the way towards a rational control of the habit of crystals grown from solution.

The calculation of equilibrium crystal shapes has been first addressed by Gibbs and made practical by the Wulff construction.^[5] However in real life crystal growth rarely leads to equilibrium morphologies. In particular crystal growth from solution is usually dominated by kinetics. This leads to what is commonly known as growth morphology. In this case

the distance $h_{\{hkl\}}$ of the $\{hkl\}$ face from the center of the steady-state shape of a crystal is proportional to its growth velocity $v_{\{hkl\}}$, that is, $h_{\{hkl\}}/v_{\{hkl\}} = \text{constant}$.^[6]

Here we examine urea crystallization from solutions of different composition. Urea is a paradigmatic case in which the steady state habit exhibits a clear dependence on both the nature of the solvent^[7,8] and the presence of additives.^[9–11] The urea crystal structure belongs to the $P\bar{4}2_1m$ space group ($Z = 2$) and develops steady state shapes dominated by only three crystal faces: $\{001\}$, $\{110\}$, and $\{111\}$.^[12] To rationally display the space of all possible habits, we use the construction of Ref. [6] to build the shape diagram (SD, Figure 1 A), where we represent the regions in the space of the relative growth rates in which specific crystal habits exist. Different crystal habits are classified on the basis of the crystal faces exposed as reported in Table 1 and discussed in detail in the Supporting Information. Continuous lines in the SD represent the boundaries through which specific faces appear or disappear (Figure 1 A). In the more complex cases, in which more than three faces play a role in the growth process the dimensionality of the SD should be increased.

The SD habit space can be accessed experimentally by tuning the composition of the liquid phase, that is, by choosing the solvent and/or the additive. In Figure 1 B representative SEM pictures of urea crystals obtained from different solutions are shown, which clearly exhibit habits belonging to well-defined regions of the SD. Urea crystals grown from water present the well-known prismatic needle shape belonging to the α region of the SD;^[7,8] this morphology exposes the $\{001\}$ and $\{110\}$ faces. The crystals grown in methanol exhibit the $\{110\}$ and $\{111\}$ faces, causing the crystals to have sharp instead of flat tips. In the SD they consequently belong to the γ region. In ethanol the crystals are slightly more compact, showing the morphology of the β region in which all three faces are exposed. In acetonitrile the crystals still belong to the β region of the SD but are more compact. Adding a shape-affecting additive such as biuret, that is, a foreign molecule that selectively binds to the fast growing face of the urea crystal in water,^[9] the range of accessible habits broadens even more. In fact in water biuret leads to a drift in the α region towards cuboid crystals as discussed at length in Ref. [9]. Here we show that adding biuret to acetonitrile leads to tetrahedral habits, characteristic of the ϵ region. Upon the addition of biuret to methanol, crystals with sharp tips that still belong to the γ region in the SD are obtained. Compared to pure methanol however, much reduced aspect ratios are obtained in this case.

Remarkably all this bewildering variety of shapes can be theoretically predicted. However to do so new computational tools need to be developed. In fact, all the molecular details of the system need to be taken into account and this still constitutes a challenge especially if one considers that

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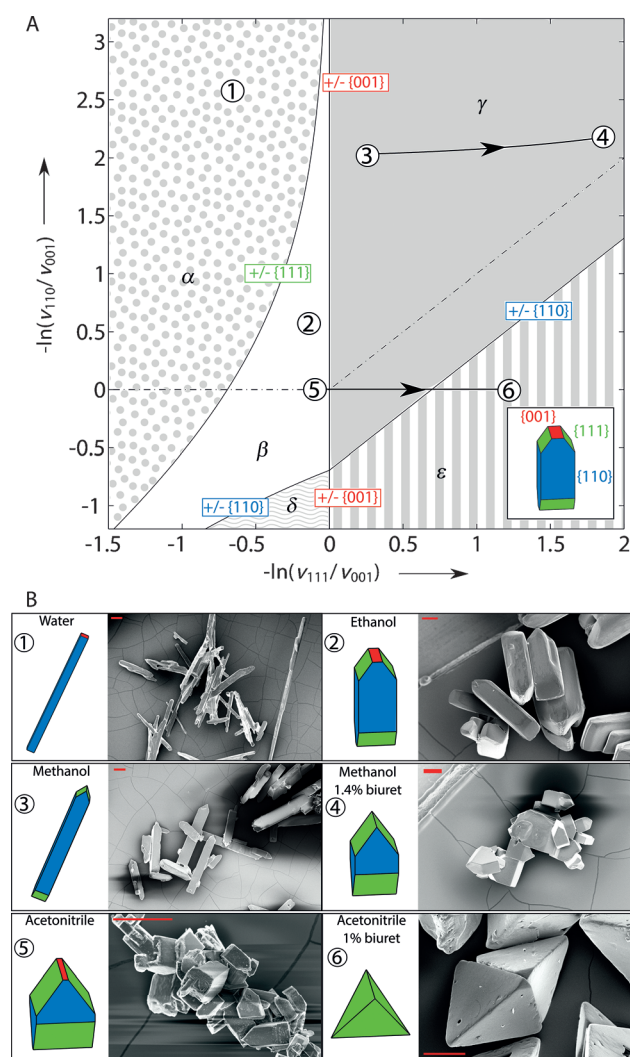


Figure 1. Shape diagram of urea. A) The accessible habit space of urea crystals as a function of the relative growth rates of three relevant crystal faces, {001}, {110}, and {111}, is displayed. The solid black lines indicate loci where faces dis- or re-appear, yielding five morphology regions (α – ϵ). The morphologies are predicted for different solvents (1–3,5). The transition from (3) to (4) and from (5) to (6) is realized by increasing the biuret concentration. The general morphology depicting all crystal faces is reported in the inset. B) Comparison of calculated to experimental morphologies for different solvent/additive combinations. The scale bar in the SEM pictures represents 100 μm .

Table 1: Crystal habit classification on the urea shape diagram, as a function of the faces exposed with an indication of the experimental conditions in which the habit is observed.

Name	Faces	Exp. Conditions
α	{001}, {110}	water, water/biuret
β	{001}, {110}, {111}	ethanol, acetonitrile
γ	{110}, {111}	methanol
δ	{001}, {111}	–
ϵ	{111}	acetonitrile/biuret

a multitude of parameters like temperature, degree of supersaturation, and composition need to be explored.^[13]

Simplified approaches, based on the calculation of the attachment energy^[14–16] are often used although their ability to predict crystal habits is extremely dependent on the system and its application to the case of crystal growth from solution is questionable.^[1] As shown by Boek et al.^[17] it is crucial to account for the solute dynamics at the solid–liquid interface to define the crystal growth units at the molecular level. The analysis of the liquid–crystal interface dynamics allowed capturing the effect of the solution on the growth rates of urea in water.^[7] Recently Piana et al.,^[8] with a combination of molecular dynamics (MD) and kinetic Monte Carlo techniques, demonstrated that accounting for molecular kinetics is indeed crucial to correctly represent the growth morphology of urea crystals. However, their approach requires the enumeration and calculation of all the relevant microscopic rates from MD simulations, which is a rather labor-intensive and delicate process. This renders this approach impractical for an extensive exploration of the habit space.

Here we take a more coarse-grained view and rather than focusing on individual molecular processes we consider the collective process of formation of a new crystal layer. In general, the growth of a crystal face is the result of two parallel mechanisms: the direct formation of crystalline structures on the surface due to the inclusion of solute molecules in the crystal lattice (rough growth, 2D nucleation); and the growth due to the propagation of defects (spiral growth). For low free-energy barriers ($1\text{--}4k_bT$) the first mechanism dominates, while for barriers higher than $10k_bT$ spiral growth becomes relevant.^[18,19] As shown in our previous work^[9] and experimentally observed,^[8] urea crystal growth from solution proceeds through 2D nucleation or rough growth depending on the crystal face considered. While we are here in this regime, as shown by the results of our free-energy calculations discussed in the Supporting Information, several aspects of our analysis would apply also to regimes in which spiral growth comes into play. However, the proposed approach remains valid only when the growth events at the liquid–crystal interface dominate crystal growth and is not directly applicable when mass transfer is the rate-determining step of the growth process. Inspired by transition state theory we write the growth rate of the {*hkl*} face as Equation (1).

$$v_{\{hkl\}} = v_0 \exp\left(-\frac{\Delta G_{\{hkl\}}^*}{k_b T}\right) \quad (1)$$

In this expression, the preexponential factor v_0 can be interpreted as the rate of an ideal barrierless growth process in which all the molecules that arrive in contact with the surface are included in the crystal lattice. It is therefore reasonable to assume that v_0 depends only on the properties of the liquid phase, but not on the crystal face. Since a given steady-state crystal habit depends only on the relative growth rate between different faces, the quantity v_0 drops out of the calculation. We highlight that this approach does not allow computing absolute growth rates and therefore does not allow the estimation of the size of crystals at the steady state. Moreover the growth rate reported in Equation (1) refers to the collective process of crystal growth; because of finite size effects, the evaluation of an absolute rate for such a trans-

formation from the unbiased dynamics is far from being trivial, as discussed in detail in Ref. [9]. A detailed discussion of Equation (1) is reported in the Supporting Information.

In Equation (1) $\Delta G_{\{hkl\}}^*$ is the free-energy barrier associated with the collective process of crystal growth. In this free-energy barrier the dependence of the growth rate on the solvent and the crystal face is lumped together. Therefore $\Delta G_{\{hkl\}}^*$ establishes a link between the molecular scale and the mesoscopic scale of the crystal. Its intrinsic collective character allows to avoid an a priori formulation of the growth mechanism. However, its calculation requires an extensive sampling of the growth events, leading to computational costs that typically exceed that of MD simulations aimed at studying the structure of the liquid-crystal interface, focusing on single-molecule configurations and dynamics.^[8,17]

In order to calculate $\Delta G_{\{hkl\}}^*$ we simulate the growth processes of the different faces in a variety of solvents. To this end, enhanced sampling methods are used to explore the rare surface nucleation events that lead to the growth of crystal faces. Here we use well-tempered (WT) metadynamics^[20] to enhance sampling and to obtain the free-energy surfaces (FES) associated with the growth of crystalline layers in the finite sized molecular models employed to represent the relevant urea crystal faces.

The number of crystal-like urea molecules N_u^c in the system is the variable naturally associated to layer growth; thus we shall compute $F(N_u^c)$, the free-energy as a function of N_u^c , using the well-tempered ensemble^[20] and the reweighting procedure explained in detail in Ref. [21] (see the Supporting Information for the mathematical definition of N_u^c).

The free-energy profiles obtained as a function of N_u^c are well-described by an analytical model based on the classical 2D nucleation theory.^[18] Such a model allows us to describe crystal growth in a MD simulation box with constant number of molecules and in the presence of periodic boundary conditions, hence to extract the values of $\Delta G_{\{hkl\}}^*$. Because of the finite size and periodic boundary conditions, that tend to over stabilize bidimensional nuclei, such free-energy barriers represent lower bound estimations of the actual barriers associated to growth in a nonperiodic system. Nevertheless this approach leads in the case of urea to a reasonable estimate of the relative growth rates of the different faces considered. In this framework, a systematic investigation of the scaling of $\Delta G_{\{hkl\}}^*$ with the size of the model surface could constitute an area of significant improvement for the estimation of the relative growth rates.

The values of the free-energy barriers associated with the growth of the {001}, {111}, and {110} faces in water, methanol, ethanol, and acetonitrile are reported in the Supporting Information. The crystal habits predicted can be seen in Figure 1B, where the excellent agreement between the predicted morphologies and the experimental SEM images is clearly evident. The predicted crystal morphologies have also been placed in their exact locations in the SD (numbered circles Figure 1A).

This analytical model can be used to describe the dependence of the crystal habits on the supersaturation in the liquid phase (Supporting Information). As expected increasing the supersaturation decreases the free-energy barriers until they

vanish. Under these conditions the crystal reaches a limiting shape independent of the solvent, which is represented by the origin of the SD. The trajectories in the SD that describe the change in habit as function of the solute concentration are discussed in the Supporting Information.

Previous results^[9] have shown that additive molecules interact with the growing crystal face competing with the solute for the occupation of surface-lattice sites. Here we provide a quantitative estimation of the growth inhibition because of their preferential interaction with specific crystal faces. In order to compute the effect of additive on the growth rates one could have repeated the free-energy calculations for different additive concentrations and solvents. However because of the low experimental concentrations of the additive this brute force approach would have required impractically large simulation boxes. To overcome this issue, we derive an analytical correction to Equation (1) based on the use of a Langmuir isotherm to describe the additive adsorption (refer to the Supporting Information for details) that leads to the following expression for the {hkl} face in the presence of an additive [Eq. (2)].

$$v_{\{hkl\}} = v_0 \frac{1}{1 + x_A \exp\left(-\frac{\Delta G_{\text{ads},\{hkl\}}}{k_B T}\right)} \exp\left(-\frac{\Delta G_{\{hkl\}}^*}{k_B T}\right) \quad (2)$$

x_A is the additive molar fraction in solution, and $\Delta G_{\text{ads},\{hkl\}}$ is the free-energy of adsorption of the additive on the crystal face. This expression allows to calculate trajectories in the SD representing the expected steady-state habit as a function of the additive concentration. We consider here the effect of biuret on crystal growth in acetonitrile and methanol only and recall that the effect of biuret on crystals grown from water has been discussed at length in Ref. [9]. In agreement with experiments Equation (2) predicts that the addition of biuret to urea/acetonitrile solutions changes the crystal habit from the faceted prisms of the region β to the perfect tetrahedral pyramids of the ε region. In urea/methanol solutions it predicts a reduction in aspect ratio, whereas the basic morphology still belongs to the γ region of the SD.

In conclusion, foreign molecules such as solvents and additives affect the shape of growing crystals because of their markedly face-dependent interaction with the solid. From our findings it clearly emerges that the role of the liquid phase in inducing steady-state crystal habits can be computed from molecular simulations in which the solvent, solute, and additives, when present, are explicitly taken into account. In this work we demonstrate that from the free-energy profiles associated with the growth of successive crystal layers one can quantitatively estimate the ratio between growth rates and thus predict the crystal morphology. This finding allows for a better understanding of the molecular determinants of different macroscopic crystal habits in different solution environments. Moreover the use of the SD to represent the results provides an extremely useful tool to rationalize the appearance of the different crystal habits. We show that the combination of theory, molecular modeling, and experimental results allows to broaden our current understanding of crystal

habits from solution, indicating a route for the development of rational, model-based shape control strategies.

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