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Perspective

A Stereochemical Approach that Demonstrates the Effect of Solvent on the Growth of Polar Crystals: A Perspective

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A basic question in crystal growth concerns the role played by solvent on the kinetics of growth of the different faces. To clarify this issue, focus was placed by researchers on surface−solvent interactions via two apparently contradictory approaches: according to the one model the interactions promote crystal growth but, in the alternative model, delay the growth. Numerous studies over the past 25 years have shown the latter to be the more operative.

To help unravel the role played by internal crystal structure and solvent−surface interactions determining the kinetics of growth, extensive use has been made of crystals with polar axes delineated by hemihedral faces (*hkl*) and (−*h*−*k*−*l*) at their opposite poles, given that their hemihedral surfaces are different in structure. Applying the concept of the crystal (*hkl*) layer attachment energy E_{att}, which is defined as the energy per molecule released when a new (*hkl*) layer is attached to the crystal face, the principle was invoked that, in polar crystals containing an ordered arrangement of molecules, the layer attachment energy E_{att} at the opposite and hemihedral faces (*hkl*) and (−*h*−*k*−*l*) are the same. This principle neglects effects such as differences in conformation or charge density of the molecules in the bulk and the to-be-attached solute molecules at the opposite faces, which, being difficult to quantify,[1] are assumed to be minor compared with that of solvent. Consequently, a *pronounced* difference in growth rate at the opposite faces implies differences in their interactions with the solvent environment.

In 1949, Wells reported a benchmark study on the growth kinetics of the polar crystal of α-resorcinol (space group $Pna2_1$).[2−4] He noticed preferential growth at one pole of the crystal along the polar *c*-axis in aqueous solution. However, since the absolute sense of crystal polarity could not be fixed at the time, Wells was not able to resolve the structural ambiguity as to the preferred direction of growth. The absolute molecular arrangement vis-à-vis the bounding {011} and $\{0\bar{1}\bar{1}\}$ polar faces of specimen crystals of α-resorcinol was assigned only in the mid 1980s by Wireko et al.,[5] applying both the Bijvoet method and the use of "tailor-made" inhibitors[6−9] of crystal growth. Results reported by Davey et al., who grew the crystals on silica, were in accord with the above assignment.[10] Studies involving monitoring the growth kinetics of pertinent faces of specimen crystals led both groups to the same conclusion: strong solvent (i.e., water, dimethyl sulfoxide, ether)−surface interactions delayed growth of the hemihedral highly corrugated "hydrogen-rich" {011} faces along the +*c* direction as opposed to the faster-growing smooth "oxygen-rich" $\{0\bar{1}\bar{1}\}$ faces along −*c*. These experimental results were supported by complementary surface binding energy computations by Wireko et al.[5] and by detailed molecular dynamics MD simulations by Hussain and Anwar,[11] which indicated a stronger binding of water to the slower growing {011} face.

In a recent manuscript, Srinivasan and Sherwood (S&S) reported crystal growth experiments of α-resorcinol from the vapor phase and in aqueous solution.[12] They found that α-resorcinol in the vapor phase grew unidirectionally at the $\{0\bar{1}\bar{1}\}$ faces along −*c*. Regarding solution studies, S&S report that growth along +*c* is zero or immeasurably small. Indeed, they write, "The previously observed growth of α-resorcinol in this direction is shown to be a consequence of facetting around a nucleus or damaged seed and not a rational growth process as assumed previously". Most important, S&S came to the following conclusion: "Anisotropic growth is a fundamental property of acentric materials, and its cause needs to be addressed from this viewpoint. There may well be a solvent inhibition effect superimposed on this intrinsic difference but if we are correct, it should act on all polar faces and not solely on those that develop in one polar direction. This question will be addressed in a forthcoming paper".

We first review published results on the growth of α-resorcinol in the light of the first-mentioned claim by S&S. Applying a stereochemical approach of controlling crystal growth with tailor-made auxiliaries,[6−9] Wireko et al.[5] demonstrated that crystals of α-resorcinol grown in aqueous solution in the presence of 20% pyrogallol, which retarded development of the fast-growing "oxygen-rich" $\{0\bar{1}\bar{1}\}$ faces, but left the opposite corrugated "hydrogen-rich" {011} faces to grow unimpeded, resulted in approximately equal rates of growth at the opposite polar ends (Figure 1), instead of an 8:1 ratio measured in pure

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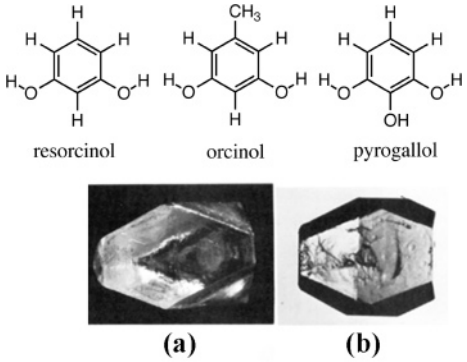


Figure 1. α-Resorcinol crystals grown in aqueous solution containing 20% pyragallol additive, viewed along the *a*-axis. The top and bottom pair of slanted faces are {011} and {01$\bar{1}$} respectively. Crystal grown: (a) without seed; (b) from seed whose outline is evident.

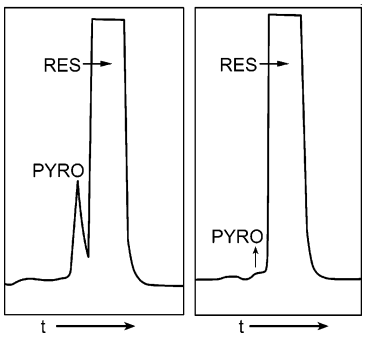


Figure 2. HPLC analysis of material taken from (left) the normally fast growing $-c$ end and (right) the normally slow growing $+c$ end of α-resorcinol grown in the presence of 20% pyragallol additive.

aqueous solution. Naturally, when the crystals were grown in the presence of 8% orcinol, an additive that inhibits extension of the slow-growing "hydrogen-rich" {011} faces, the crystals grew unidirectionally. The stereospecific growth of the two opposite poles of the crystals was confirmed by the presence of occluded additive via chromatographic analysis (Figure 2). These results, which are consistent with experiments reported by Davey et al.,[10] who found that both surfaces grew but at different rates depending upon the state of supersaturation of the solution, indicate that α-resorcinol crystals grow in aqueous solution at the highly corrugated "hydrogen-rich" {011} faces along the $-c$ direction by a rational process, albeit at a slow rate.

We now examine, in the light of published reports, the general conclusion by Srinivasan and Sherwood on anisotropic growth of polar crystals in solution (vide supra). We shall present evidence that the extent of such anisotropic growth and the polar hemihedral faces formed may depend on the type of solvent used and can be rationalized, by and large, in terms of solvent binding to the pertinent crystal faces: in general, the stronger the solvent binding, the slower the growth.

First, we note there are polar crystals that grow at both poles; for example, those of rhamnose monohydrate (space group $P2_1$), when grown from aqueous solution, exhibit the morphology shown in Figure 3b. Advantage had been taken of this crystalline solvate by choosing a cosolvent of crystallization that plays the dual role of solvent and "tailor-made" auxiliary: addition of methanol inhibited the growth of rhamnose monohydrate at only one end of its polar axis (Figure 3c), which was predicted from the known orientation of the water molecules in the crystal (Figure 3a).[13] A similar inhibiting effect was observed for

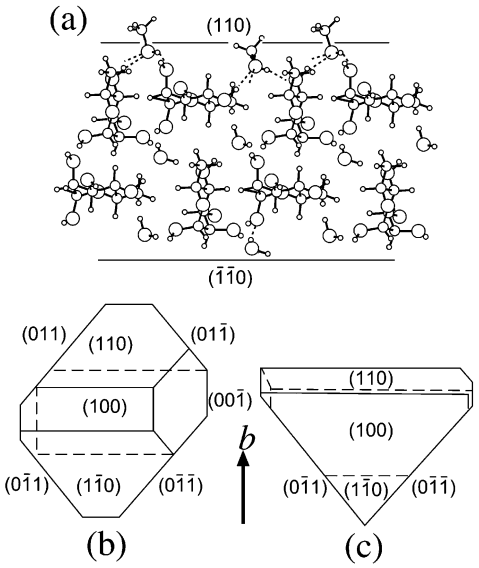


Figure 3. (a) Packing arrangement of α-rhamnose monohydrate crystal viewed along the *a* axis; the OH bonds of the hydrate water molecules point toward the $+b$, but not the $-b$ direction; replacement of water by methanol on the {110} faces is depicted. (b, c) Crystal morphologies of α-rhamnose monohydrate grown from: (b) aqueous solution; (c) 9:1 methanol/water solution.

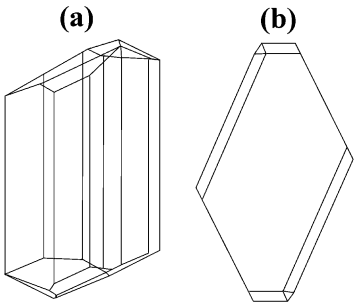


Figure 4. Crystals of *S*-asparagine·H_2O, grown from (a) water; (b) methanol/water solutions.

asparagine monohydrate grown in water−methanol mixtures (Figure 4) the structure of which does not have polar axes (space group $P2_12_12_1$). It is noteworthy that a similar change in morphology due to crystal growth inhibition was obtained when asparagine monohydrate was grown in the presence of aspartic acid.[14,15] We may predict that changes in morphology for crystalline solvates grown in the presence of alcohol cosolvents, which act as tailor-made inhibitors, to be a general phenomenon, be the crystal polar or not.

The principle that a pronounced difference in growth rate at opposite hemihedral faces of polar crystals is associated with differences in their solvent−surface interactions was firmly established in the crystal family of enantiomeric alkylgluconamides, $C_nH_{2n+1}NHCO(CHOH)_4CHOH$, $n = 7-10$. In the two crystal structures of $n = 7, 8$ the molecules stack in layers, head to tail (Figure 5) so that the polar plate-like faces are hydrophobic at one side and hydrophilic at the opposite side.[16] A measure of the relative binding strengths of the polar solvents to these hemihedral faces was gleaned from their macroscopic wetting properties determined by contact angle measurements.[17] As expected, methanol wets the hydrophilic face more strongly than the hydrophobic face. This observation was directly correlated with the relative rates of growth of the two crystal faces in methanol; the crystals of the octyl derivative ($n = 8$) grew almost four times faster at the hydrophobic side than at

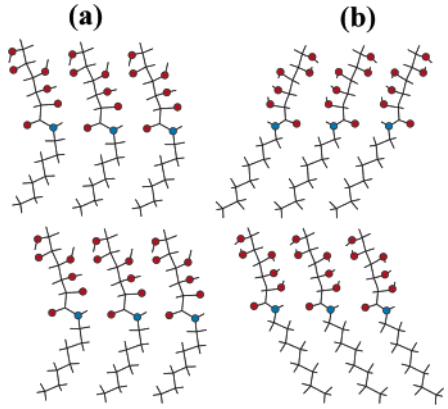


Figure 5. Head-to-tail packing arrangement of (a) *N*-(*n*-heptyl)-D-gluconamide in space group *P*1; (b) *N*-(*n*-octyl)-D-gluconamide in space group $P2_1$.

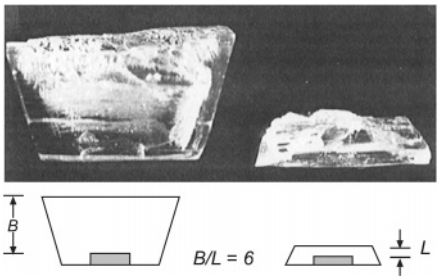


Figure 6. Morphology of octylgluconamide crystal grown from methanol. The seeds are seen as opaque shadows at the bottom of the crystals. Thickness of added material on the hydrophobic surface (left) is denoted as *B* and that added on the hydrophilic surface (right) as *L*.

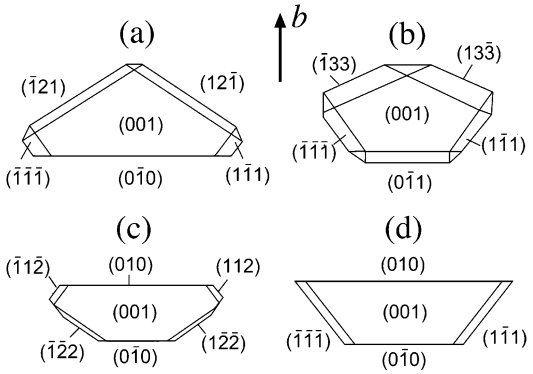


Figure 7. Morphologies of cinnamoyl-*S*-alanine **1a** crystals. (a−c) Crystals grown from methanol: (a) pure crystal; (b) grown in the presence of the methyl ester **1b**; (c) grown in the presence of cinnamoyl-*R*-alanine **1c**. (d) Pure crystal grown from acetic acid.

the hydrophilic side (Figure 6).[18] Computations by Khoshkoo and Anwar[19] of the average solvent binding energy to the different crystal faces are in full agreement with observation.

The example now presented involves a comparison of the morphology of cinnamoyl-*S*-alanine **1a** (space group $P2_1$) grown in methanol in the absence and presence of tailor-made additives **1b,c** and also in pure glacial acetic acid, the latter having induced a morphological change akin to that of the tailor-made auxiliaries in methanol.[9] As expected, additive **1b** induced large $\{1\bar{1}1\}$ faces (cf. Figure 7, panels a and b) since the O−CH_3 group replaces an O−H group emerging from such faces according to the crystal structure (Figure 8). The additive cinnamoyl-*R*-alanine **1c**, of configuration opposite to that of the host, induced formation of an (010) face because the C(*S*)−H bond of the

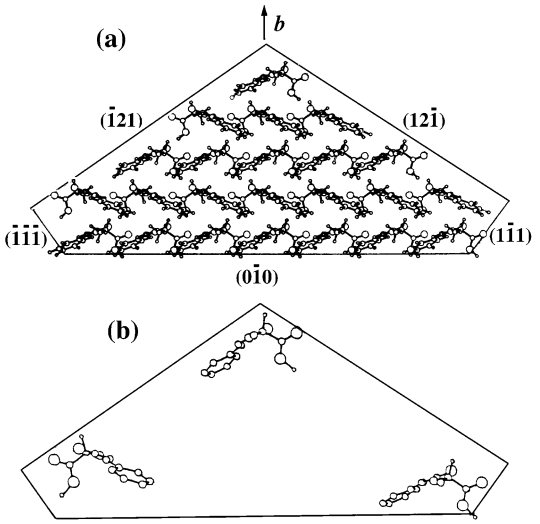
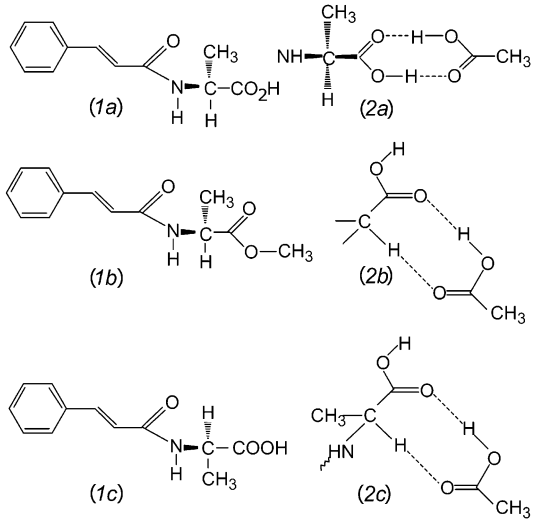


Figure 8. (a) Packing arrangement of cinnamoyl-*S*-alanine delineated by the faces of the pure crystal grown from methanol. (b) Orientations of only three host molecules vis-à-vis the crystal faces to envisage the effect thereon by the additives **1b** and **1c** and acetic acid solvent.

host, directed along the +*b* axis, is replaced by the C(*R*)−CH_3 bond of the guest. The change in morphology induced by acetic acid (cf. Figure 7, panels a and d) may be explained in terms of binding to the $\{1\bar{1}1\}$ and (010) faces and growth inhibition thereof: the acid can form cylic hydrogen-bonded dimers **2a** with the exposed carboxylic acid groups at the $\{1\bar{1}1\}$ faces and can also bind to the $CHCO_2H$ moiety of cinnamoyl-*S*-alanine forming a cyclic hydrogen-bonded dimer **2c** on the (010) face, where **2c** is akin to the motif **2b** adopted by acetic acid in its own crystal structure. With respect to the existence of dimers **2a** at the crystal surface, it is relevant that acetamide as cosolvent in an alcohol solution of benzamide retards its crystalline growth, inducing formation of very thin benzamide plates. This behavior was explained by the presence of ordered cyclic hydrogen-bonded benzamide−acetamide dimers at the plate surface, verified by crystal surface structure determination using grazing incidence synchrotron X-ray diffraction measurements.[20]



The growth behavior of the *β*-form of glycine (space group $P2_1$) along its polar *b*-axis in water−methanol solutions is also in accordance with the principle that the stronger the solvent−surface interaction, the more pronounced is the growth inhibition.[21] The [010] needlelike crystals of *β*-glycine extend faster

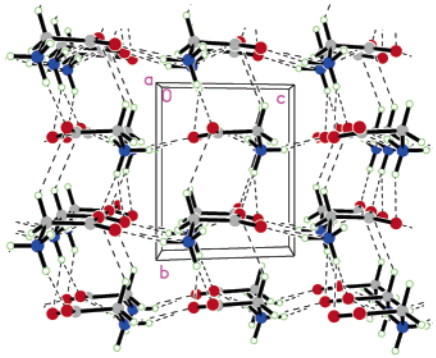


Figure 9. Packing arrangement of β-glycine.

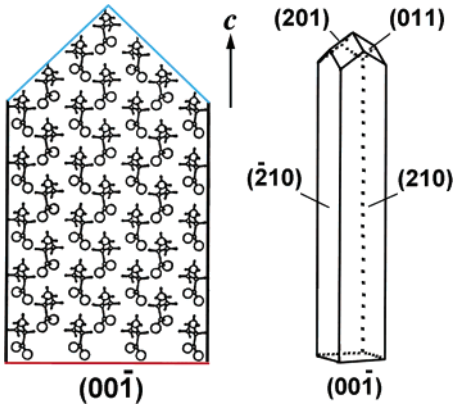


Figure 10. Packing arrangement of *R,S*-alanine delineated by crystal faces, viewed down the *b*-axis. The "blue" capped faces at the $+c$ end of the polar axis expose NH_3^+ and $-CH_3$ groups at their surfaces, the opposite (00$\bar{1}$) "red" face exposes carboxylate CO_2^- groups.

at the top end, which exposes C−H groups as opposed to the opposite bottom end, which exposes N−H groups (Figure 9). We rationalize this behavior in terms of a (glycine)C−H···O(solvent) bond, which is weaker than a (glycine)N−H···O(solvent) hydrogen bond. It is noteworthy that the strongest solvent−surface interactions do not occur at the ends of the polar axis but rather at the {*h*0*l*} side faces of the needle. This deduction is based on a comparison of the theoretical growth form of β-glycine, which is almost isometric in habit,[21] with the needle habit obtained from solution. This difference is consistent with hindrance of growth normal to the needle side faces as a result of strong solvent (i.e., H_2O, CH_3OH) attachment thereto via O−H···O and N−H···O hydrogen bonds.

The role played by solvent−surface interactions is also exemplified by the polar crystals of *R,S* alanine and γ-glycine, which have similar packing arrangements and morphologies, despite having different space groups ($Pna2_1$ and $P3_1$ respectively). The zwitterionic molecules expose COO− groups at the corrugated (00$\bar{1}$) face and the NH_3^+ groups at the opposite capped faces (Figure 10). In aqueous solution, the crystals of *R,S* alanine along its polar axis grow much faster at at the corrugated end than at the opposite capped face end (Figure 11a).[13] The fast growth of the (00$\bar{1}$) face was explained in terms of poor hydration within its cavities, due to strong repulsion that would occur between the electron lone pairs of the water molecules and of the carboxylate O atoms in the interior of the pockets. By such means oncoming alanine molecules can easily dock into the cavities at the surface sites at the (00$\bar{1}$) face. This model is supported by experiments involving addition of methanol to the aqueous solution. The cosolvent CH_3OH can dock into a surface cavity of the (00$\bar{1}$) face, by virtue of

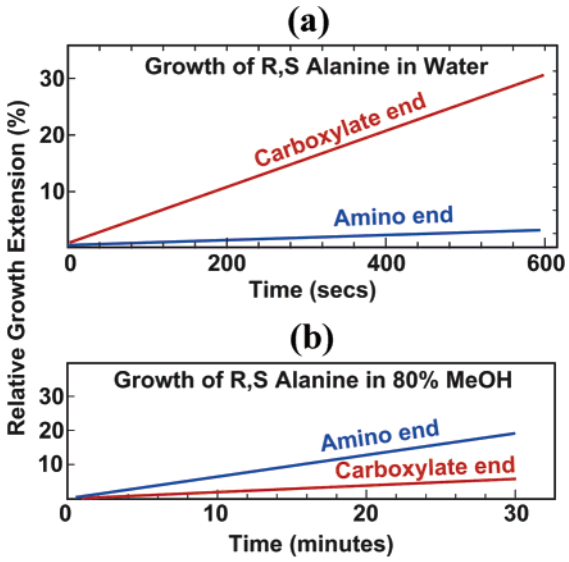


Figure 11. Graph of the relative growth at the opposite ends of the polar axis of *R,S*-alanine crystals: (a) in water; (b) in 4:1 methanol/water mixture.

C−H···O(alanine) bonds, albeit weak, and a O−H O(alanine) hydrogen bond, hence cooperative and specific to the layer (as opposed to the molecule in solution), leading to growth inhibition at the (00$\bar{1}$) end and a concomitant preferential growth at the opposite pole of the crystal. (Figure 11b). The γ-glycine polymorph displays a related behavior on dissolution and, as recently reported, also on growth.[21]

The study on *R,S* alanine implies that it may be necessary to assess the ease of replacement of solvent by solute at the different surface sites, as well as the different modes of docking the solute molecules at the surface. For example, Boek et al.[22] calculated the theoretical growth form of tetragonal urea and found that it is almost cube-like so that it compares well with those of urea crystals from ethanol or benzene. But the theoretical form is very different in shape from the [001] needles obtained from aqueous solution. Boek and Briels[23] performed MD simulations of interfaces between water and crystalline urea. They argued that the observed needle habit cannot be explained using a simple layer model because of strong adsorption of water to the relevant faces. By examining the interface between a saturated aqueous urea solution and crystalline urea via MD simulations, Liu et al.[24] explained the [001] needle habit in terms of wrongly and randomly absorbed urea molecules to the {110} side faces, so providing an increased interfacial entropy.

Surface−solvent interactions have been recently invoked by Hong et al.[25] to explain the unidirectional crystal growth of 3-methyl-4-methoxy-4′-nitrostilbene. In another study, Swift and co-workers demonstrated that the polar crystals of 4-iodo-4′-nitrobiphenyl grew at either end, depending upon the structure of the self-assembled monolayer that nucleates 4-iodo-4′-nitrobiphenyl by virtue of chemical epitaxy.[26]

We now examine the unusual unidirectional growth of α-resorcinol in the vapor phase. At a recent scientific meeting in Glasgow,[27] a suggestion by Lahav that the cause may be due the presence of residual water in the vapor growth is considered unlikely by S&S in view of scrupulous drying of the material prior to the experiments.[12] However, no direct evidence was presented that may exclude the presence of minute quantities of water as a result of strong binding to the resorcinol OH groups in the vapor phase.[28]

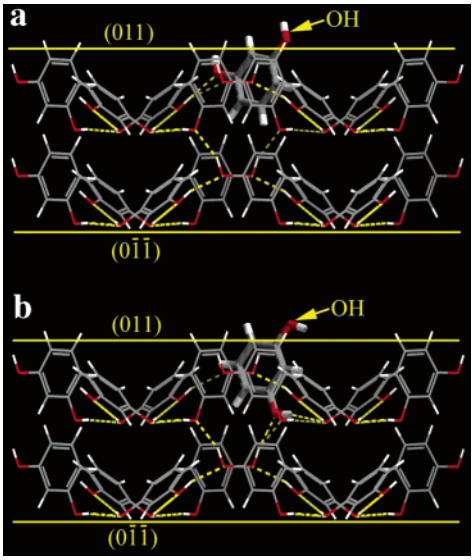


Figure 12. Misdocking at the (011) face of the resorcinol molecules at site type **1** in orientations (a) I and (b) II, viewed along the direction $-b + c$. For clarity, the atom−atom bonds of the misoriented molecules are drawn as "cylinders" unlike the other molecules.

Lahav and Bennema suggested self-poisoning as an alternative cause to explain the observation. S&S alluded to this possibility, expressing the view that experimental proof for this alternative would be difficult to devise.[12] To examine the feasibility of self-poisoning in α-resorcinol, we performed molecular modeling computations, described in the following article in this issue.[29] Here we outline the basic findings.

In the crystal structure, an {011} layer contains two pairs of differently oriented resorcinol molecules, labeled site types **1** and **2**, which are related by the *a*-glide (Figure 12). Within each pair, the two molecules are related by the *n*-glide. Of the four OH groups per two molecules related by the *a*-glide, three participate in intralayer O−H···O bonds, which are exposed at the smooth "oxygen-rich" {01$\bar{1}$} face and the fourth emerges along the +*c*-direction at the highly corrugated "hydrogen-rich" {011} face to link neighboring layers. It is possible at this {011} face to misdock resorcinol molecules at site-type **1** in two possible ways, I and II. In both orientations a "wrongly placed" OH group emerges from the {011} surface close to a groove (Figure 12), thus avoiding repulsive contacts. This OH group, which can bind to water molecules, will perturb, in its vicinity, the regular surface deposition of oncoming solute molecules. The misdocked molecules do not have the full complement of hydrogen bonds, which is compensated by molecular rearrangement according to atom−atom potential energy computations. Misdocking is not possible at the opposite {0$\bar{1}\bar{1}$} sites for it would incur repulsive intermolecular contacts. An experimental test of the self-poisoning model is proposed in the following article in this issue.[29]

The self-poisoning model invoked for α-resorcinol grown in the vapor phase may also operate in solution in tandem with the solvent. In general, we may surmise that self-poisoning of crystal surfaces leading to growth inhibition would depend on the molecular structure, packing arrangement, crystal morphology, and the nature of the solvent, if present, be the crystal polar or otherwise. Self-poisoning has been invoked by Visser and Bennema[30] in the crystallization of α-lactose, by Liu et al.[24] to account for the needlelike morphology of urea grown in aqueous solution, and more recently by Towler et al.[31] to understand the exclusive precipitation of γ-glycine in acidic or basic aqueous solutions. For lactose, the β-anomer formed in situ during the crystallization experiments, is the poisoning species and for glycine, the ionized molecule, each of which act like classic "tailor-made" inhibitors.

We may conclude that differences in solvent−surface interactions may account, in the main, for the anisotropic growth of polar crystals. For example, the results on the *R*,*S* alanine−water−methanol and rhamnose monohydrate−water−methanol systems show that along the polar axis the rates of growth can be modified, or direction of preferred growth reversed, with a change in solvent composition and solvent−surface interactions, almost in a manner akin to that demonstrated for α-resorcinol using pyragallol as growth inhibitor. Furthermore, changes in hemihedral faces formed, as in the case of cinnamoyl-alanine, were found to depend on solvent composition and related to growth inhibition, the effect of which is similar to that induced by tailor-made additives. Most importantly, the examples reviewed here provide ample evidence that differences in the binding of polar solvents at opposite hemihedral faces is a primary factor that leads to differences in their growth rates; in general, the stronger the solvent−surface interaction, the more pronounced the surface growth inhibition, irrespective of whether the crystal is polar or not.

According to McBride,[32] there can be two types of solvent inhibition: One in which the foreign (solvent) molecule is incorporated into the layer in a way that makes it complicated to remove because part of the layer must be unpacked as may be expected to occur in the *R*,*S* alanine-methanol−water system (vide supra); another, where it is only a question of removing that single solvent molecule, which may still be difficult.

On the basis of the self-poisoning model, and other possible approaches,[33] we see no reason as yet to invoke an "enigma" in the growth behavior of the hemihedral faces of α-resorcinol proposed by S&S. To date, application of molecular level mechanisms such as solvent-induced inhibition, the "relay" type of growth in the case of *R*,*S*-alanine[13] and γ-glycine[13,21] or self-poisoning, the asymmetric growth behavior of polar crystals in solution has been rationalized. Finally, the mechanisms of growth in the vapor phase and in solution are very different, in particular with regard to rate-determining steps controlling crystal face development. In solution, desolvation of the growing crystal surfaces as well as that of the solute molecules prior to their docking at the crystal surface sites clearly play significant roles, which are absent in the vapor phase.

Nevertheless, the studies of Srinivasan and Sherwood on α-resorcinol reveal that probing the growth of crystals in the absence of solvent may unveil the presence of unforeseen factors, which may be present, although masked, in the crystallization process in solution, be the crystal polar or otherwise.

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References

(1) Docherty, R.; Roberts, K. J.; Saunders, V.; Black, S.; Davey, R. J. *Faraday Discuss.* **1993**, *95*, 11.
(2) Wells, A. F. *Philos. Mag.* **1946**, *37*, 180.
(3) Wells, A. F. *Philos. Mag.* **1946**, *37*, 217.
(4) Wells, A. F. *Discuss. Faraday Soc.* **1949**, *5*, 197.
(5) Wireko, F. C.; Shimon, L. J. W.; Frolow, F.; Berkovitch-Yellin, Z.; Lahav, M.; Leiserowitz, L. *J. Phys. Chem.* **1987**, *91*, 472.
(6) Addadi, L.; Berkowitch-Yellin, Z.; Weissbuch, I.; van Mil, J.; Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 466.

(7) Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. In *Topics in Stereochemistry*; Eliel, E. L., Willen, S. H., Allinger, N. L., Eds.; John Wiley & Sons Inc.: New York, 1986; Vol. 16, p 1.
(8) Weissbuch, I.; Addadi, L.; Lahav, M.; Leiserowitz, L. *Science* **1991**, *253*, 637.
(9) Weissbuch, I.; Popovitz-Biro, R.; Lahav, M.; Leiserowitz, L. *Acta Crystallogr. Lead Article* **1994**, *B51*, 115.
(10) Davey, R. J.; Milisavljevic, B.; Bourne, J. R. *J. Phys. Chem.* **1988**, *92*, 2032.
(11) Hussain, M.; Anwar, J. J. *J. Am. Chem. Soc.* **1999**, *121*, 8583.
(12) Srinivasan, K.; Sherwood, J. N. *Cryst. Growth Des.* **2005**, *5*, 1359.
(13) Shimon, L. J. W.; Vaida, M.; Addadi, L.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1990**, *112*, 6215.
(14) Addadi, L.; Berkovitch-Yellin, Z.; Domb, N.; Gati, E.; Lahav, M.; Leiserowitz, L. *Nature* **1982**, *296*, 21.
(15) Weisinger-Lewin, Y.; Frolow, F.; McMullan, R. K.; Koetzle, T. F.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1989**, *111*, 1035.
(16) Zabel, V.; Müller-Fahrnow, A.; Hilgenfeld, R.; Saenger, W.; Pfannemüller, B.; Enkelmann, V.; Welte, W. *Chem. Phys. Lipids* **1986**, *39*, 313.
(17) Wang, J.-L.; Lahav, M.; Leiserowitz, L. *Angew. Chem., Int. Ed.* **1991**, *30*, 696.
(18) Wang, J.-L.; Leiserowitz, L.; Lahav, M. *J. Phys. Chem.* **1992**, *96*, 15.
(19) Kaoshkhoo, S.; Anwar, J. J. *Chem. Soc. Faraday Trans.* **1996**, *92*, 1023.
(20) Edgar, R.; Schultz, T. M.; Rasmussen, F. B.; Feidenhans'l, R.; Leiserowitz, L. *J. Am. Chem. Soc.* **1999**, *121*, 632.
(21) Weissbuch, I.; Torbeev, V. Y.; Leiserowitz, L.; Lahav, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3226.
(22) Boek, E. S.; Feil, D.; Briels, W. J.; Bennema, P. *J. Cryst. Growth* **1991**, *114*, 389.
(23) Boek, E. S.; Briels, W. J. *J. Chem. Phys.* **1992**, *96*, 7010.
(24) Liu, X. Y.; Boek, E. S.; Briels, W. J.; Bennema, P. *Nature* **1995**, *374*, 342.
(25) Hong, H.-K.; Park, J. W.; Lee, K.-S.; Yoon, C. S. *J. Cryst. Growth* **2005**, *277*, 509.
(26) Hiremath, R.; Varney, S. W.; Swift, J. A. *Chem. Mater.* **2004**, *16*, 4916.
(27) International Workshop on the Crystal Growth of Organic Materials, Glasgow, Scotland, UK, 2003.
(28) According to J. M. McBride, it is potentially relevant that thin surface water layers are almost ubiquitous in atomic force microscopy (AFM) studies of "dry" samples that are not held in high vacuum. The resulting meniscus forces are an important generality in AFM studies (private communication, 2005).
(29) Weissbuch, I.; Leiserowitz, L.; Lahav, M. *Cryst. Growth Des.* **2006**, *6*, 625.
(30) Visser, R. A.; Bennema, P. *Neth. Milk Dairy* **1983**, *37*, 109.
(31) Towler, C. S.; Davey, R. J.; Lancaster, R. W.; Price, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 13347.
(32) McBride, J. M. Private communication, Yale University, 2005.
(33) Another hypothesis currently being investigated theoretically by J. Anwar and J. Kendrick (Institute of Pharmaceutical Innovation, Bradford) is that involving surface reconstruction. The surfaces, being perpendicular to a polar axis, have a different charge distribution and are expected to undergo different degrees of reconstruction, giving rise to different kinetics of attachment. Private communication, 2005.

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