Molecular Recognition at the Solid-Solution Interface: A "Relay" Mechanism for the Effect of Solvent on Crystal Growth and Dissolution

L. J. W. Shimon, M. Vaida, L. Addadi,* M. Lahav,* and L. Leiserowitz*

Contribution from the Department of Structural Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel. *Received December 15, 1989*

Abstract: The effect of solvent on crystal growth and dissolution studied by two stereochemical strategies is described. The first approach involved the growth of two crystalline hydrates (asparagine monohydrate and rhamnose monohydrate) in the presence of primary alcohols as "tailor-made" solvents. It was demonstrated that stereospecific adsorption of the tailor-made solvent at a particular face inhibits its growth. The second approach, concerned the growth and dissolution of hemihedral faces at the opposite ends of the polar axes of (*R,S*)-alanine and γ-glycine in water, one pole exposing carboxylate groups and the other amino groups. Relatively fast growth and dissolution at the carboxylate end in water are explained in terms of strong solvent binding at a subset of surface sites and solvent repulsion at the remaining sites, so allowing for easy access of solute at the latter unhydrated surface sites followed by expulsion of water at the former. The repetitive succession of these steps results in a "relay"-type mechanism of crystal growth.

Introduction

Solvent has a strong influence on the structure and habit of crystalline materials; however, the role played by the solvent-surface interactions in enhancing or inhibiting crystal growth is still not well understood. To date there have been two distinctly different approaches to clarify this point. Calculations based on "surface-roughening" considerations predict that favorable interactions between solute and solvent on specific faces will lead to reduced interfacial tension, causing a transition from a smooth to a rough interface, and a concomitant faster surface growth.[1,2] Alternatively, it has been proposed that the preferential adsorption of solvent molecules at specific faces will inhibit growth of those faces as removal of a bound solvent molecule poses an additional energy barrier for continued growth.[3-6] In some of these studies, the binding of polar solvents was estimated by calculations of the electrostatic potential at the crystal surface and interpreted in terms of crystal surface hydrophobicity and philicity.[4,5]

We have previously reported that stereospecific adsorption of "tailor-made" additives affects both the growth and dissolution of the crystal surfaces to which the additive can bind, the absorbate being a substrate molecule with an altered moiety.[7,8] This adsorption was manifested by changes in crystal morphology with the rule that binding of the additive to a specific face causes an inhibition of growth perpendicular to that face generally resulting in an increase of its surface area relative to that of unaffected faces. Here we shall probe the assumption that tight binding of solvent will be analogous to the binding of additives. Two possible strategies to pin-point solvent-surface interactions and thereby clarify the solvent effect have been adopted. The first involves the growth of crystalline solvates in the presence of tailor-made solvents which have been targeted for stereospecific interactions at particular crystal surfaces. The selective adsorption of these modified solvents during crystal growth provides a means for isolating solvent-surface interactions. The second method involves the use of materials with polar axes for a study of relative rates of growth of hemihedral crystal faces in a variety of solvents. In such polar materials we exploit the fact that differences in the growth rates at the opposite ends of the polar axis arise primarily from differences in solvent-surface interactions.

Results and Discussion

(I) Crystal Growth of Hydrates. (a) (*S*)-Asparagine Monohydrate. To facilitate the transition from additive-surface to solvent-surface interactions, crystalline hydrates were chosen so that added solvents, such as methanol and higher alcohols, may be considered as both "tailor-made additive" and "tailor-made solvent". A systematic solvent-dependent change in morphology has been carried out using as substrate the resolved conglomerate (*R*)- or (*S*)-asparagine monohydrate: $NH_2COCH_2CH(NH_2)COOH \cdot H_2O$; $a = 5.584$, $b = 9.735$, $c = 11.701$ Å; space group $P2_12_12_1$; $Z = 4$.[9] This crystal grown in aqueous solution exhibits as many as 18 faces (Figure 1a) of the families {011}, {010}, {101}, {012}, and {111}.[10] We expected linear alcohols, (e.g., methanol) to behave as a tailor-made additive and be adsorbed primarily on the {010} or the {011} faces replacing H_2O with a hydroxyl hydrogen bond and oriented so that its alkyl group emerges from these faces (Figure 1c). When the water in the aqueous solution is gradually replaced by either methanol or ethanol, there is a marked increase in the relative surface area of the {010} crystal faces with respect to the original morphology (Figure 1b), the crystal eventually becoming platelike. This increase in size of the {010} face is indicative of an inhibition of growth perpendicular to it and is akin to the changes in morphology of asparagine which have been effected by "tailor-made" additives.[11,12] The arrangement of the hydrate molecules is such that one of the two O-H bonds of each water molecule emerge from the {010} faces

(1) (a) Bennema, P.; Gilmer, G. In *Crystal Growth: An Introduction*; Hartman, P., Ed.; North Holland: Amsterdam, 1973; p 274. (b) Elwenspoek, M.; Bennema, P.; van der Eerden, J. P. *J. Cryst. Growth* **1987**, *83*, 297. (c) Bennema, P.; van der Eerden, J. P. In *Morphology of Crystals*; Terra Scientific Publishing Co.: Tokyo, 1987; pp 1-75.

(2) Bourne, J. R.; Davey, R. J. *J. Cryst. Growth* **1976**, *36*, 278, 287.

(3) Wells, A. F. *Phil. Mag.* **1946**, *37*, 184. Wells, A. F. *Discuss Faraday Soc.* **1949**, *5*, 197.

(4) Wireko, F. C.; Shimon, L. J. W.; Berkovitch-Yellin, Z.; Lahav, M.; Leiserowitz, L. *J. Phys. Chem.* **1987**, *91*, 471.

(5) Berkovitch-Yellin, Z. *J. Am. Chem. Soc.* **1985**, *107*, 8239.

(6) Davey, R. J. *J. Cryst. Growth* **1986**, *76*, 637. Davey, R. J.; Milisavljevic, B.; Bourne, J. R. *J. Phys. Chem.* **1988**, *92*, 2032.

(7) Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; van Mil, J.; Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 466.

(8) Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. In *Topics in Stereochemistry*; Wiley: New York, 1986; Vol. 16, pp 1-85.

(9) Verbist, J. J.; Lehman, M. S.; Koetzle, T. F.; Hamilton, W. C. *Acta Crystallogr.* **1972**, *B28*, 3006.

(10) Addadi, L.; Berkovitch-Yellin, Z.; Domb, N.; Gati, E.; Lahav, M.; Leiserowitz, L. *Nature* **1982**, *296*, 21.

(11) Indeed asparagine monohydrate when grown in the presence of aspartic acid crystallizes as {010} plates. Low-temperature neutron diffraction studies of the mixed crystal of asn/asp demonstrated the aspartic acid is preferentially absorbed on the {010} face, inhibiting growth along the *b* axis.[12]

(12) Wang, J. L.; Berkovitch-Yellin, Z.; Leiserowitz, L. *Acta Crystallogr.* **1985**, *B41*, 341. Weisinger-Lewin, Y.; Frolow, F.; McMullan, R. K.; Koetzle, T. F.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1989**, *111*, 1035.

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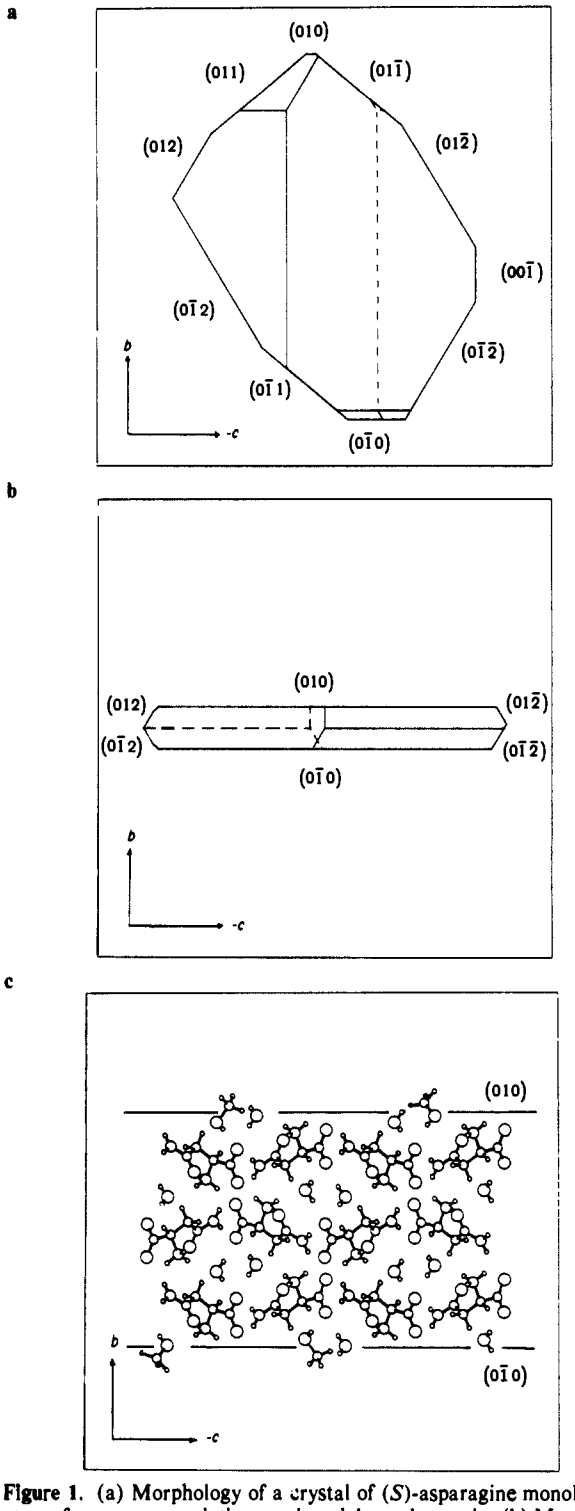

Figure 1. (a) Morphology of a crystal of (*S*)-asparagine monohydrate grown from aqueous solution, as viewed down the *a* axis. (b) Morphology of a crystal of (*S*)-asparagine monohydrate grown from 30:70 methanol–water solution, as viewed down the *a* axis. Note the inhibition of growth along the *b* axis. (c) Packing arrangement of (*S*)-asparagine monohydrate viewed down the *a* axis. The hydrate waters are oriented with one of their two OH bonds emerging from the {010} faces. Replacement of these water molecules by methanol is depicted.

and the other points into the crystal bulk, which means that in principle all four symmetry-related hydrate water molecules can be replaced by alcohol. On the {011} faces only two of the four symmetry-related water molecules can be substituted by methanol, and inhibition is less dramatic. That methanol can indeed be selectively absorbed on both the {010} and {011} faces was further demonstrated by experiments involving initial dissolution of asparagine·H_2O crystals in methanol solution, revealing etchpits on only these faces, although poorly developed.

(b) Rhamnose Monohydrate. In rhamnose monohydrate ($C_6H_{12}O_5$: $a = 7.901$, $b = 7.922$, $c = 6.670$ Å; $\beta = 95.52°$; space group $P2_1$; $Z = 2$)[13] advantage was taken of the existence of the polar *b* axis which allows for a direct comparison of affected and unaffected faces on the same crystal. The hydrating water molecules are oriented with their O–H bonds pointing in the $+b$, but not $-b$, direction (Figure 2a). Thus in the presence of alcohols we expected changes from the regular crystal morphology at the $+b$ side of the crystal, but not at the $-b$ side. Upon addition of CH_3OH in the solution, we observed a decrease in the relative rate of crystal growth in the $+b$ as against $-b$ direction vis-à-vis that of the crystal grown in aqueous solution, indicating a relative inhibition of growth at the $+b$ end. Furthermore, there is a pronounced increase in the size of {100} faces as well as that of the {110} faces relative to that of {$\bar{1}\bar{1}$0}[14] faces (Figure 2, b and c). This inhibition can be understood in terms of the relative ease of binding alcohol to these faces. According to Figure 2d, methanol can be easily adsorbed at the two different water sites on the {110} face, each hydroxyl group participating in three hydrogen bonds and the side chain being forced to emerge from the {110} face. On the opposite hemihedral {$\bar{1}\bar{1}$0} faces, only one of the two different water sites can be replaced by alcohol with the hydroxyl group bound by only one hydrogen bond (Figure 2d). The pronounced increase in the area of the {100} faces is compatible with the observation that on this face both water sites can be replaced by alcohol with the side chain emerging from the surface.

(II) A "Relay" Mechanism for the Crystal Growth in (*R*,*S*)-Alanine and γ-Glycine. The two hydrate systems discussed above demonstrate that the extension from tailor-made additives to tailor-made solvents is valid. We now examine systems without solvent of crystallization where it is generally difficult to determine at which surface site preferential binding of solvent occurs. We have selected the two polar crystal systems of γ-glycine (space group $P3_2$, or $P3_1$; $a = b = 6.975$, $c = 5.473$ Å; $Z = 3$)[15] and (*R*,*S*)-alanine (space group $Pna2_1$; $a = 12.06$, $b = 6.05$, $c = 5.82$ Å; $Z = 4$)[16] for their molecular simplicity, ability to form strong hydrogen bonds with water, as well as the fact that they expose NH_3^+ proton donors at one end of the polar *c* axis of the crystal and CO_2^- proton acceptors at the opposite end. These two structures have remarkably similar packing and morphological features (Figure 3, a–d), with an (00$\bar{1}$) face perpendicular to the polar *c* axis at one end of the crystal and capped faces at the opposite end. According to crystal growth and etching experiments on these two crystal systems[17a,b] as well as Bijvoet X-ray structure analysis on γ-glycine,[17b] the CO_2^- groups are exposed at the (00$\bar{1}$) face, the "flat $-c$ end", while the NH_3^+ amino groups are exposed at the $+c$ capped end.[17c] The crystal growth and dissolution experiments also indicated that in aqueous solution the $-c$ carboxylate end of crystals of γ-glycine and (*R*,*S*)-alanine grow and dissolve faster than the $+c$ amino end (Figure 4, a–c). The question remains as to which end of the crystal, water may bind more tightly, and to correlate the macroscopic phenomena with the binding and recognition of the solvent at a molecular level.

Inspection of the packing arrangement of both crystal structures (Figure 3) reveals that the (00$\bar{1}$) carboxylate faces comprise regular pockets on a molecular level and can be regarded as corrugated in two dimensions. This surface arrangement is generated by the screw axis perpendicular to the (00$\bar{1}$) face, which relates nearest neighbor amino acid molecules and is enhanced

(13) Takagi, S.; Jeffrey, G. A. *Acta Crystallogr.* **1978**, *B34*, 2551.
(14) The symbol {*hkl*} designates all the symmetry related faces; (*hkl*) designates the face specified. Thus for space group $P12_11$, with *b* the polar axis, {*hkl*} specifies to (*hkl*) and (*hkl*).
(15) Iitaka, Y. *Acta Crystallogr.* **1961**, *14*, 1. Kvick, A.; Canning, W. M.; Koetzle, T. F.; Williams, G. J. B. *Acta Crystallogr.* **1980**, *B36*, 115.
(16) Donohue, J. *J. Am. Chem. Soc.* **1950**, *72*, 949.
(17) (a) Shimon, L. J. W.; Wireko, F. C.; Wolf, J.; Weissbuch, I.; Addadi, L.; Berkovich-Yellin, Z.; Lahav, M.; Leiserowitz, L. *Mol. Cryst. Liq. Cryst.* **1986**, *137*, 67. (b) Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1985**, *107*, 3375. (c) The crystals of (*R*,*S*)-alanine and γ-glycine exhibit polar axes, and so the absolute arrangement of the molecules with respect to the polar *c* axis had to be determined.[17a,b]

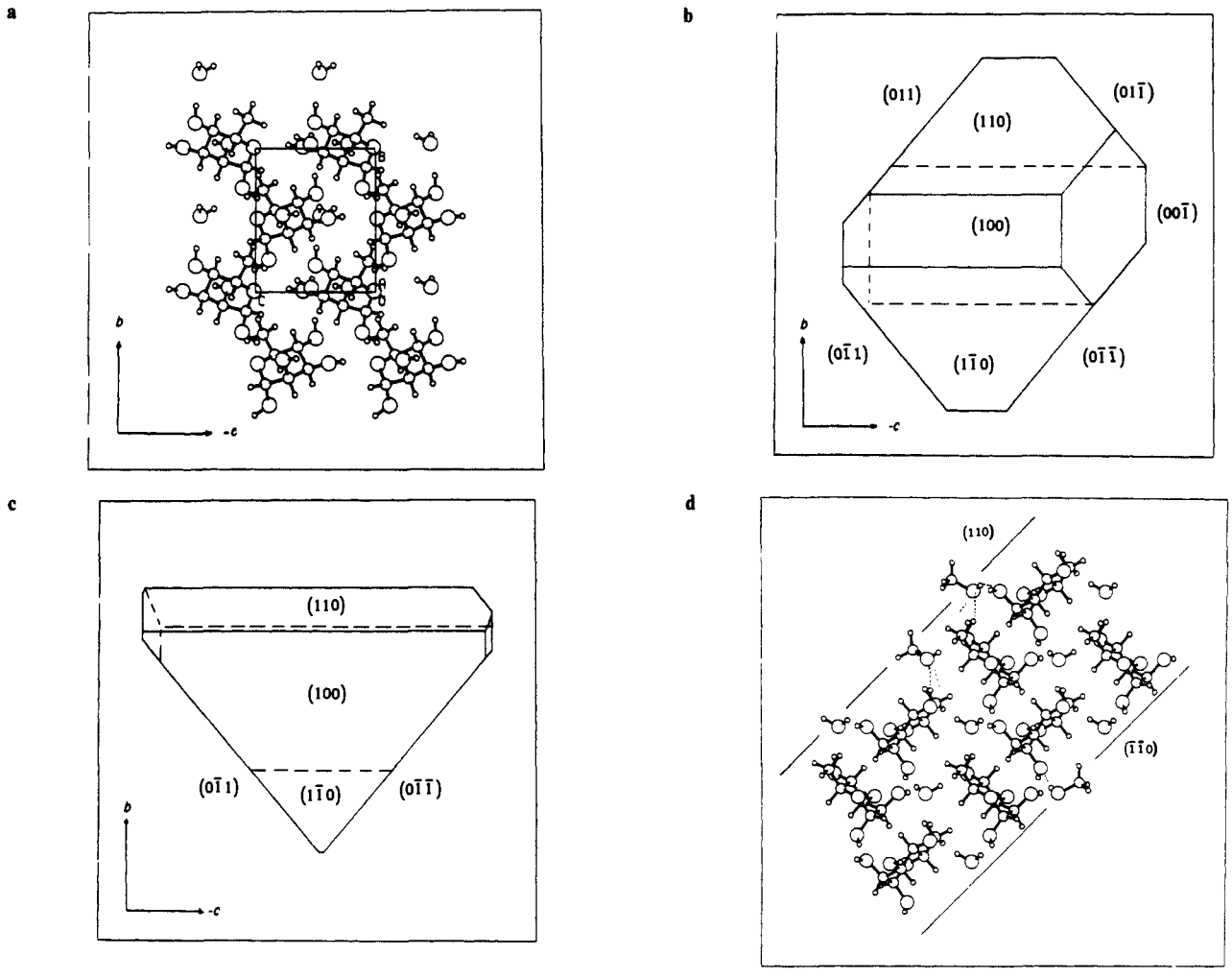

Figure 2. (a) Packing arrangement of α-rhamnose monohydrate viewed down the *a* axis. The OH bonds of the hydrate waters point toward the $+b$, but not the $-b$, direction. (b) Morphology of a crystal of α-rhamnose monohydrate grown form aqueous solution, viewed down the *a* axis. (c) Morphology of α-rhamnose grown from 90:10 methanol–water solution, viewed down the *a* axis. Note the marked change in the morphology at the $+b$, but not the $-b$, end of the crystal and the increase in size of the {100} faces. (d) Packing arrangement of α-rhamnose monohydrate viewed down the *a* axis. The two different hydrate waters oriented with their OH bonds emerging from the (110) face are shown replaced by methanol. On this surface both water molecules may be replaced by methanol, which are each tightly bound via three hydrogen bonds (because of the projection only two hydrogen bonds are visible). On the ($\bar{1}\bar{1}$0) face methanol can replace only one of the two water molecules and which may be loosely bound by only one hydrogen bond.

by the fact that the molecules are aligned with their long axis parallel to the polar screw axis. (*R,S*)-Alanine, because of the 2_1 axis, has only two levels of molecules on the (00$\bar{1}$) face, each lying $c/2 = 2.9$ Å above or below its neighbor so fixing the depth of the pocket; in γ-glycine the pocket is deeper because of the 3_2 axis leading to a difference in level of $2c/3 = 3.6$ Å. The faces which cut the amino end of (*R,S*)-alanine or γ-glycine, {201}, {011} and {10$\bar{1}$3}, respectively, are comparatively smooth.

We may explain the binding of water qualitatively as follows. The pockets at the (00$\bar{1}$) face expose primarily oxygen atoms, acting as proton acceptors for the NH_3^+ proton donor groups of the solute molecules and so fit to and bind the NH_3^+ moiety of the amino acid (Figure 5, a–d). It has been previously established in numerous primary amide/carboxylic acid systems that when the N–H group of an N–H···O(carbonyl) hydrogen bond is replaced by a hydroxyl oxygen, the resulting (hydroxyl)O···O(carbonyl) lone-pair interaction will be repulsive.[18] More specifically, it was found that the molecules prefer to position themselves so that the O···O distance will be minimally 3.5 Å, instead of 2.8 to 2.9 Å for the N-H···O(carbonyl) distance.

Replacement of the NH_3^+ by water within the pockets of (*R,S*)-alanine and γ-glycine is possible in essentially two different orientations; one orientation comprises one O–H···O hydrogen bond and two O···O lone-pair repulsions and the other two O–H···O bonds and one O···O lone-pair–lone-pair repulsion. Consequently introduction of water yields repulsive or at best weakly attractive interactions. The pocket will therefore be unhydrated or only slightly hydrated and relatively easily accessible to approaching solute molecules. In contrast, the water molecule may be strongly bound to the outermost layer of CO_2^- groups via O-H···O (carboxylate) hydrogen bonds.[23] As glycine or alanine molecules are incorporated into adjoining pockets, the CO_2^- groups of the newly added substrate molecules are within 3 Å of the water bound on the outermost surface and expel the water, thereby generating a new unsolvated pocket on the crystal surface. This relay process of solvent water binding and expulsion helps growth and dissolution by both desolvating the surface and perpetuating the natural

(18) This was made manifest by distorted hydrogen bond geometry in crystal structures,[20,21] by crystal growth[22] and etching experiments,[19] from selective occlusion of "tailor-made" acid additives in host amide crystals[12,21] and by atom–atom potential energy calculations.[22]

(19) Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *Nouv. J. Chim.* **1986**, *10*, 723.

(20) Huang, C.; Leiserowitz, L.; Schmidt, G. M. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 503.

(21) Vaida, M.; Shimon, L. J. W.; van Mil, J.; Ernst-Cabrera, K.; Addadi, L.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **1989**, *111*, 1029.

(22) Berkovitch-Yellin, Z.; van Mil, J.; Addadi, L.; Idelson, M.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1985**, *107*, 3111.

(23) The water molecules bound to the outermost layer of CO_2^- groups via O–H–O hydrogen bonds provides additional stabilization energy to the (00$\bar{1}$) surface layer which has a low molecular density with all molecular dipoles pointing approximately in the same direction.

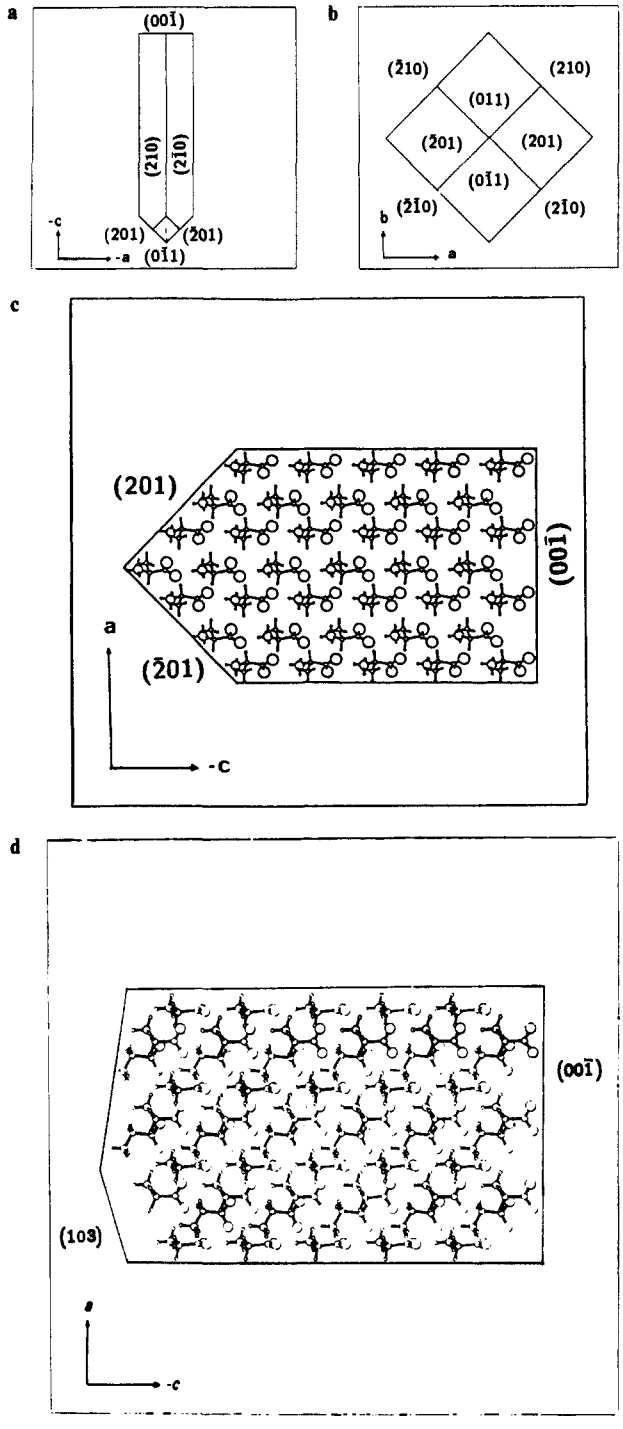

Figure 3. (a) Crystal morphology of (*R*,*S*)-alanine viewed down the *b* axis. The crystal exhibits nine faces of the type {201}, {011}, {210}, and (00$\bar{1}$). (b) Crystal morphology of (*R*,*S*)-alanine viewed down the $-c$ axis. (c) Packing arrangement of (*R*,*S*)-alanine delineated by crystal faces viewed down the *b* axis. The capped faces, {201} and {011} at the $+c$ end of the polar axis, expose NH_3^+ and CH_3 groups at their surfaces; the opposite (00$\bar{1}$) face exposes carboxylate CO_2^- groups. The two horizontal lines parallel to *c* do not represent faces seen edge on, but rather the intersections of the (210) and (2$\bar{1}$0) faces and the (2$\bar{1}$0) and (2$\bar{1}$0) faces. (d) Packing arrangement of γ-glycine delineated by crystal faces viewed down the *b* axis. The capped faces {10$\bar{1}$3} which cut the $+c$ axis exhibit different surface structures from that of the (00$\bar{1}$) carboxylate face. At the $+c$ end is shown the (10$\bar{1}$3) face and the edge $2a + b + {}^1/_3c$ which delineates the intersection between the ($\bar{1}$103) and (0$\bar{1}$13) faces.

corrugation of the surface, on a molecular level (see Figure 6, a and b). Conversely, the {011} and {201} faces of (*R*,*S*)-alanine which expose NH_3^+ and CH_3 groups at the $+c$ end of the crystal are relatively smooth and comprise molecules which are equally accessible for water binding. The corresponding three {10$\bar{1}$3} faces of γ-glycine have a similar surface structure exposing NH_3^+ and

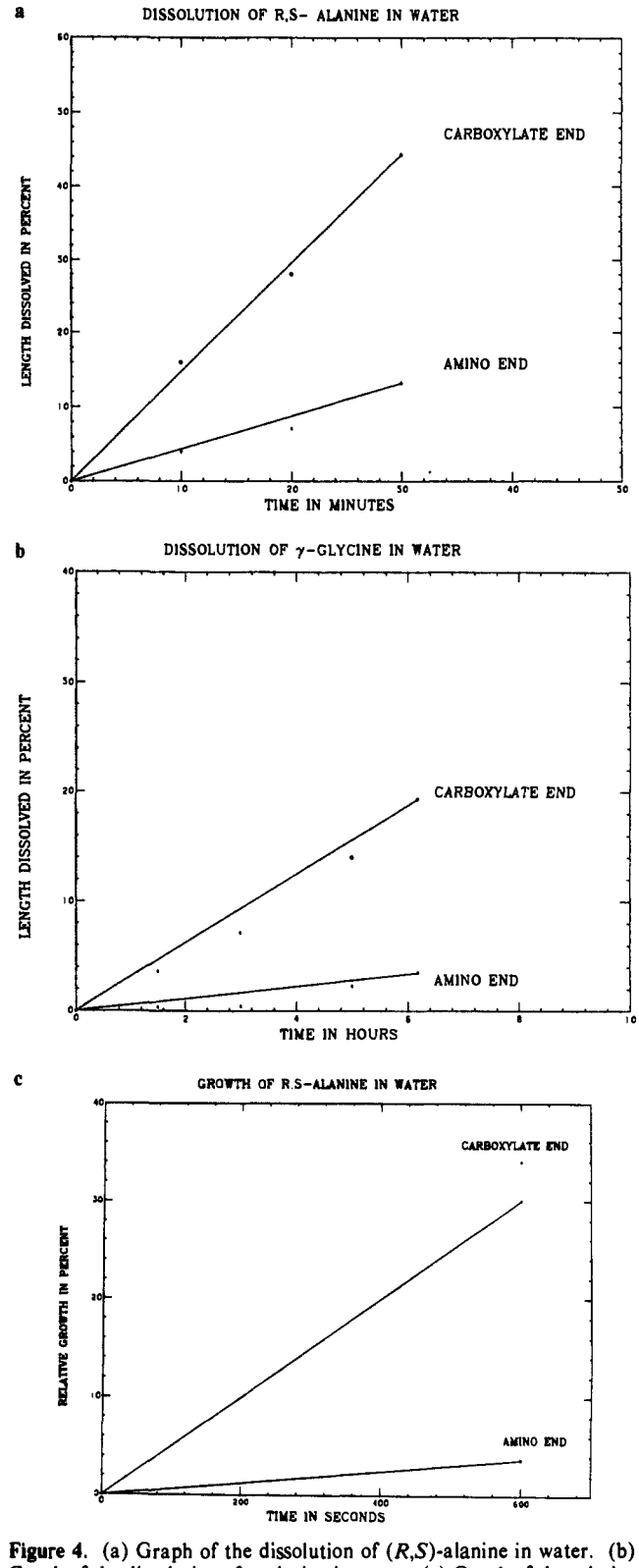

Figure 4. (a) Graph of the dissolution of (*R*,*S*)-alanine in water. (b) Graph of the dissolution of γ-glycine in water. (c) Graph of the relative growth at the opposite poles of the polar axis of (*R*,*S*)-alanine in water.

CH_2 groups, and their molecular surfaces should be equally accessible to water.

To further elucidate this proposed binding of water, we next chose a solvent which should be able to bind tightly to all sites on the NH_3^+ face almost as effectively as water but will be able to bind to all sites on the pocketed CO_2^- face as well; this solvent was methanol. The binding of methanol to the NH_3^+ groups at the capped crystal end may take place via its oxygen atom, but, unlike water, methanol can bind within the pocket via a strong O–H···O (carboxylate) bond and three, albeit weak, CH···O

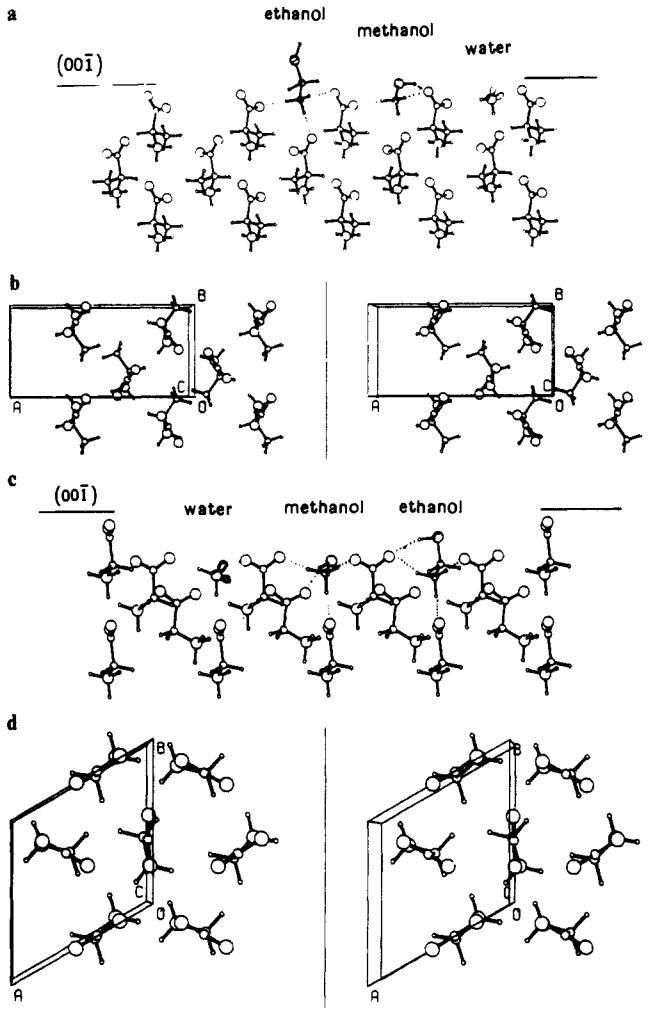

Figure 5. (a) Packing arrangement of (*R,S*)-alanine viewed along *b* showing part of the exposed structure at the (00$\bar{1}$) face and molecules of H_2O, CH_3OH, and CH_3CH_2OH adsorbed in the pockets. Note the lone pair–lone pair repulsion, between the water oxygen and the neighboring oxygens on the periphery of the pocket. Methanol makes CH···O contacts and an OH···O hydrogen bond in the pocket. Ethanol, although it makes CH···O contacts, cannot form an OH···O bond with the surface. (b) Stereoscopic view of the pocket on to the (00$\bar{1}$) face. (c) Packing of γ-glycine viewed along *b* showing part of the exposed structure at the (00$\bar{1}$) face and molecules of H_2O, CH_3OH, and CH_3CH_2OH adsorbed in the pockets. Note the lone pair–lone pair repulsion between the water oxygen and the neighboring oxygens at the periphery of the pocket. Methanol makes CH···O contacts and an OH···O hydrogen bond in the pocket. Ethanol is bound within the pocket by both CH···O contacts and also an OH···O hydrogen bond, which presence is possible because the pocket in γ-glycine is about 0.6 Å deeper than in (*R,S*)-alanine. (d) Stereoscopic view of the pocket on to the (00$\bar{1}$) face.

(carboxylate)[24] interactions, with length 3.1–3.3 Å, as depicted in Figure 5, a and b.

Upon crystal growth in 20% methanol in water, (*R,S*)-alanine still grew faster at the carboxylate end than at the amino end, but at a smaller speed of growth relative to pure water. Indeed with 80% methanol in water mixtures, the needlelike crystals grew slightly faster at the +*c* amino end than at the −*c* carboxylate end (Figure 7, a and b). Analogously, when crystals of γ-glycine or (*R,S*)-alanine were dissolved in methanol, their dissolution took place primarily from the +*c* amino end of the crystal, the dissolution from the −*c* carboxylate end having been inhibited by the binding of the methanol (Figures 8a and 9a). These results are a clear indication that methanol is more strongly adsorbed at the (00$\bar{1}$) face than water. (*R,S*)-Alanine grows as very thin [001] whiskers from sublimation; thus it is evident that both water and

(24) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063. Berkovitch-Yellin, Z.; Leiserowitz, L. *Acta Crystallogr.* **1984**, *B40*, 159.

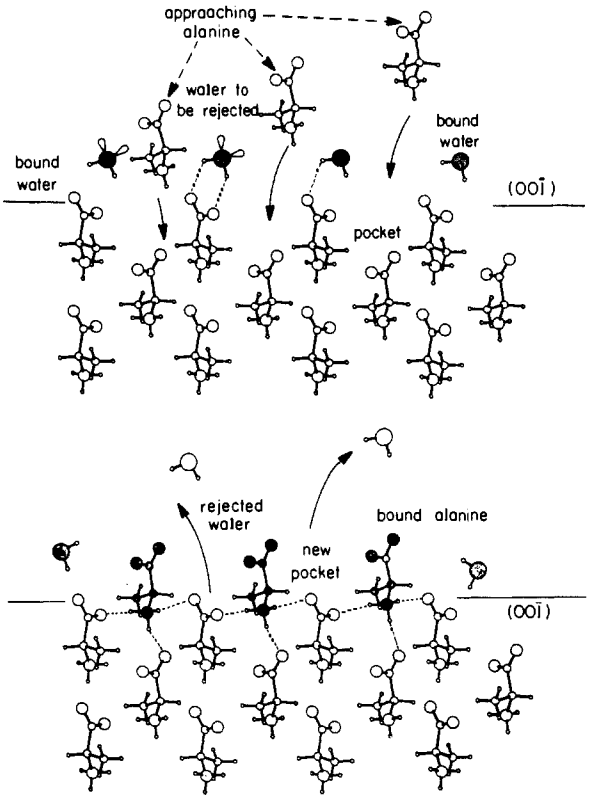

Figure 6. Schematic representation of the (00$\bar{1}$) face of (*R,S*)-alanine during the crystal growth process. (a) In this first view approaching solute alanine molecules are depicted about to be bound within the pockets of this face. Also shown are water molecules bound to the outermost layer of this face. The pockets remain primarily unsolvated because lone-pair-lone-pair oxygen–oxygen repulsion inhibits the binding of water within them. (b) In this second view, at the (00$\bar{1}$) surface alanine molecules are bound via three NH···O hydrogen bonds. The previously bound water molecules are shown being rejected by O(water)···O(carboxylate) lone-pair–lone-pair repulsions. Note the formation of new unsolvated pockets.

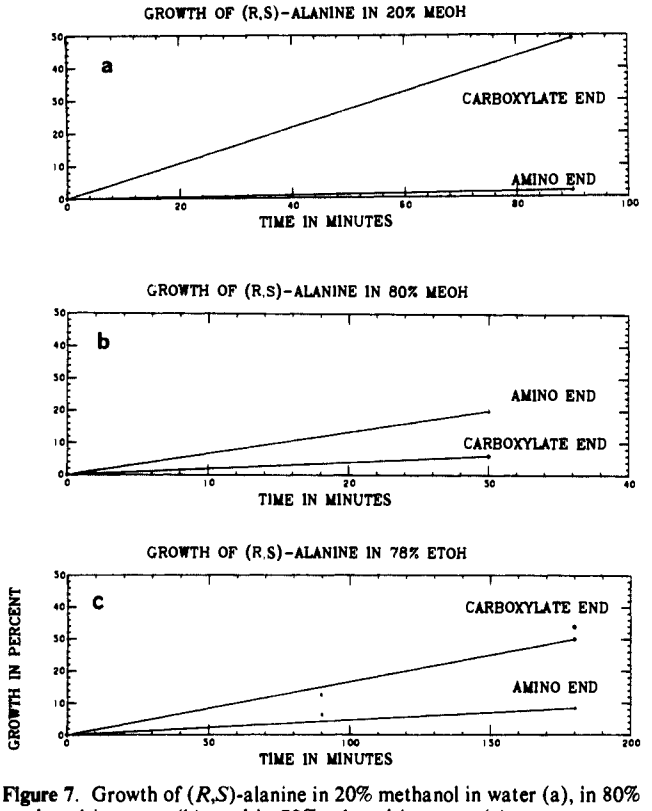

Figure 7. Growth of (*R,S*)-alanine in 20% methanol in water (a), in 80% methanol in water (b), and in 78% ethanol in water (c).

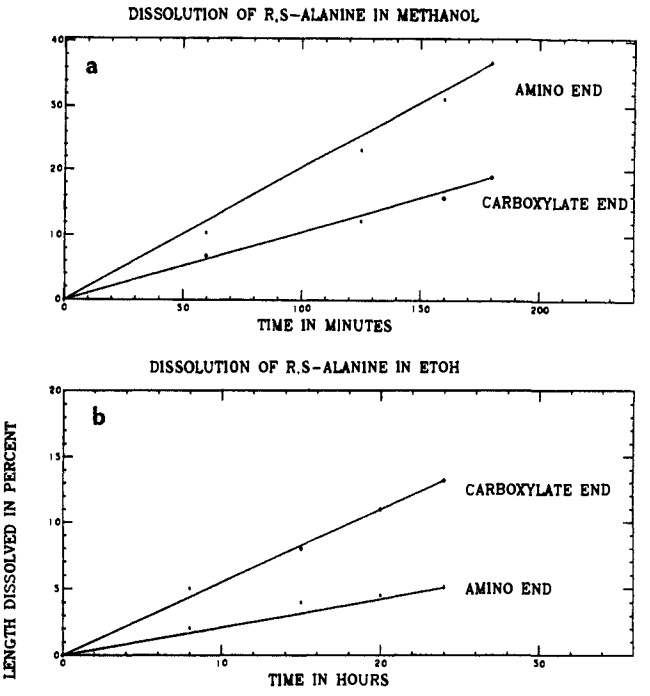

Figure 8. Dissolution of (*R,S*)-alanine in presence of methanol (a) and ethanol (b).

methanol inhibit growth along the *c* axis, in view of the dramatic relative increase in the ratio of the cross-sectional crystal area to its length.[25] The observation that the needlelike crystals of (*R,S*)-alanine grown in methanol/water mixtures are decidedly thinner than those grown in water suggests that methanol binds stronger than water to the {210} side faces. These faces appear to have more hydrophobic character than the (00$\bar{1}$) carboxylate and {201} and {011} amino faces as they expose C–CH_3 methyl groups,[26] and it appears as if such molecules can be replaced by methanol where its OH group binds to a neighboring alanine molecule.

The dissolution of these two remarkably similar systems proceeds differently in ethanol, giving further evidence that the structure of the surface plays a key role in the binding ability of the solvent. When (*R,S*)-alanine was dissolved in ethanol, the crystals dissolved more rapidly from the carboxylate end (Figure 8b). Growth of (*R,S*)-alanine from 78% ethanol in water showed analogously faster growth at the CO_2^- end relative to the NH_3^+ end (Figure 7c). These results are understandable since the (00$\bar{1}$) face of (*R,S*)-alanine cannot bind ethanol as it is unable to form both C–H···O interactions and an O–H···O hydrogen bond within the pockets of (*R,S*)-alanine, leaving the (00$\bar{1}$) face free for growth or dissolution as in aqueous solution (Figure 5a). On the other hand, the γ-glycine pocket is sufficiently deep as to follow ethanol binding via three methyl CH···O interactions as well as an O–H···O hydrogen bond (Figure 5b). As expected, therefore, the dissolution of γ-glycine is inhibited from this direction (Figure 9b). Finally, if CF_3CH_2OH is used as a solvent, it can no longer bind within the CO_2^- pockets via C–F···O contacts; the solvent may in fact be even repelled from the CO_2^- crystal surface owing to the net electronegative charge on the fluorine atoms. Indeed, no inhibition

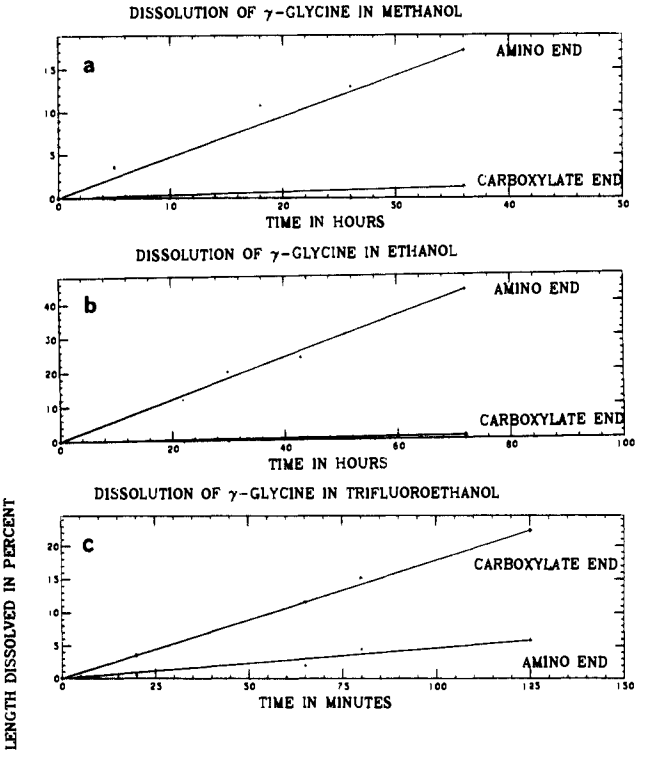

Figure 9. Dissolution of γ-glycine in presence of (a) methanol, (b) ethanol (note the reversal of the direction of fastest dissolution compared to (*R,S*)-alanine), and (c) trifluoroethanol.

of the dissolution of γ-glycine from the −*c* end of the crystal is observed (Figure 9c).

Conclusions

We have studied the effect of solvent on crystal growth on a molecular level and explained the phenomena in terms of molecular recognition at crystal surfaces.

Crystal growth experiments of asparagine monohydrate and rhamnose monohydrate demonstrate that an extension from "tailor-made" additives to solvents can be made. Namely, the "tailor-made" solvent will inhibit the growth of the face to which it is strongly adsorbed. Therefore, it appears that the desolvation of the crystal surface is the rate-determining step for the speed of growth of the face. It is important to note that the "tailor-made" solvent occupies a natural surface site; its binding is not weakened by completion of the surface layer structure. We may extend this argument to "normal" solvents which are strongly bound to the surface. But if the solvent is strongly bound at a subset of sites and repelled (or very weakly adsorbed) at the remaining surface sites (pockets, for example), a different set of rules may apply according to the results on γ-glycine and (*R,S*)-alanine;[1,2] the surface may be exposed to a cycle of solvent binding at a subset of surface sites, solute adsorption at the "free sites", followed by solvent expulsion, leading to relative fast growth of this face by a kind of "relay" mechanism. This "relay" mechanism is not confined to crystals with polar axes but should be general. Perhaps we may also conclude that, in general, the inhibiting properties of the solvent cannot be estimated by simply evaluating the average binding energy of solvent to a specific face, but one must take into account its relative binding properties at the different surface sites. Moreover, we are of the opinion that the fast growth arising from strong adsorption of solvent on a subset of sites and repulsion on the others might be the connecting link to surface roughening arising from strong solvent–surface interactions.

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(25) Similar evidence for inhibition at both ends of the polar crystals is provided by preliminary crystal growth experiments of γ-glycine in the presence of ionic species such as $Ca(OH)_2$, NH_4Cl, LiCl, NaCl, KCl, RbCl, and CsCl, which indicate inhibition at both ends of the polar axis, restricting growth to within the *ab* crystal plane.

(26) Butbul, O. M.Sc. Thesis, Weizmann Institute of Science, Rehovot, Israel, 1986.