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Effects of molecular structure and growth kinetics on the morphology of L-alanine crystals

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Abstract

The crystal morphology of L-alanine crystals was characterized by optical goniometry, the different Miller indices being assigned to the well developed crystal faces. L-Alanine crystals grown from water in the absence of additives are prismatic, and are elongated along the crystallographic *c*-axis bounded by the {120}, {010}, {110}, {210} and {011} faces. The growth rate of L-alanine crystals was measured by monitoring the change of size of individual crytals as a function of time. Examination of both the growth rate dependence on supersaturation and the structure of the crystal surface, reveals that the {120}, {010}, and {011} crystal faces of L-alanine grow following the spiral growth mechanism, in both the presence and absence of additives. The growth rate of L-alanine crystals in the presence of hydrophobic L-amino acids at concentrations as low as 0.02 *m* (i.e., 0.3 g additive/100 g solvent or 0.18 g additive/100 g L-alanine) is drastically reduced and the crystals are bounded by the {120} and {011} faces. The morphology of L-alanine crystals depends on the relative growth rate of the faces and the growth rate of a crystal face is decreased by the adsorption of the additive. The molecular structure of a face determines the availability of sites that favor the adsorption of the additives. The available sites and their energy, on a given crystal face, determine the extent of adsorption.

Keywords: L-Alanine; Crystal morphology; Additive effect; Additive adsorption; Amino acid

1. Introduction

Crystal morphology can influence properties such as the flowability of a powder, filtration time of a precipitate and dissolution characteristics of a suspension. The habit of a crystal is determined by the relative growth rates of the various crystal faces bounding the crystal. The crystal habit is therefore dependent on several factors such as those associated to the crystal itself, namely crystal structure and dislocations, and those determined by external factors imposed on the crystal by the crystallization conditions such as temperature, pressure, supersaturation, the presence of additives or influence of the solvent and the flow convection pattern.

Control of crystal morphology may be accomplished by identifying the factors that influence

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the relative growth rate of the crystal faces. Since these factors are related either to the internal structure or to some variables that affect the crystal growth process, in the present case the presence of additives in the crystallizing medium, a complete protocol should be aimed at the identification of the different crystal faces, determination of their molecular structure and assessment of their relative growth rate in order to characterize crystal morphology. In previous work (Lechuga-Ballesteros and Rodríguez-Hornedo, 1993a,b) we presented the morphology of L-alanine crystals grown in the absence and presence of additives and explained the morphology changes induced by the presence of the additive based on kinetic and structural considerations. In the present manuscript the molecular structure of the crystal faces is discussed in greater detail.

Additives, whose molecular structure is related to that of L-alanine, have a great effect on the crystal growth kinetics. Low concentrations of hydrophobic L-amino acids are enough to inhibit the growth rate of the {120} faces of the L-alanine crystals. The reduction of the growth rate due to the presence of hydrophobic L-amino acids is associated with a change in crystal morphology induced by a change in the relative growth rate of the different faces of L-alanine crystals. These results are interpreted on the basis of the molecular structure of both the additive species and the crystal structure.

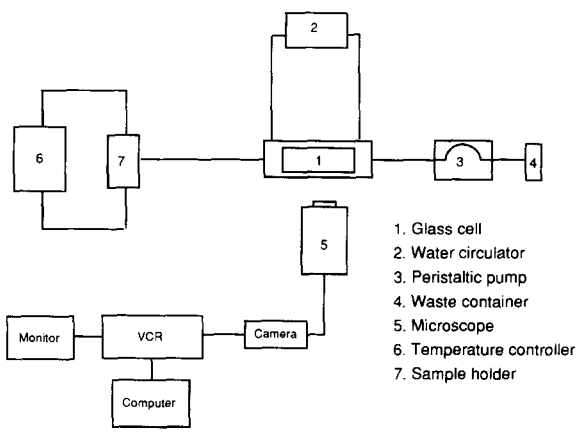

Fig. 1. Schematic representation of the flow cell experimental configuration.

2. Experimental

2.1. Materials

L-Alanine, L-leucine, L-phenylalanine, L-serine, L-asparagine, L-cysteine, L-tyrosine, L-histidine, L-valine and benzoic acid were purchased from Sigma Chemical Co. (St. Louis, MO), and were used without further purification. Distilled water purified with a Milli-Q water system (Millipore, Bedford, MA) was used.

2.2. Crystal growth from single crystal measurements

The dependence of growth rate on supersaturation was studied at a constant flow rate and constant temperature of 25°C. The supersaturation is defined as $\sigma = \ln(C/C_s)$, where C is the instantaneous concentration of the supersaturated solution in the crystallizer and C_s denotes the concentration at equilibrium. L-Alanine crystals were grown at 25°C at various levels of supersaturation in the flow cell system depicted in Fig. 1. The supersaturation range studied was 0.01–0.10. Supersaturated solutions were prepared by dissolving appropriate amounts of L-alanine and additives in water at $T < 60$°C. The hot solution was filtered through a 0.22 μm membrane and then transferred into small glass vials which were placed into the heating block set at 30°C. The temperature in the crystallization cell was 25°C. The solution was circulated through the crystallization cell with a peristaltic pump (Whiz, ISCO®) at a constant linear velocity of 0.07 cm s^{-1} (flow rate of 5 ml h^{-1} using 1/16 inch i.d. tubing, Tygon®). L-Alanine crystals were allowed to nucleate into the crystallization cell from a 5.0% supersaturated solution. A solution with the desired composition, supersaturation and additive concentration, was circulated through the crystallization cell. The crystallization cell is made up of glass (0.2 × 0.4 × 3.0 cm) and is mounted in a jacketed holder and placed onto an inverted microscope stage (Nikon Diaphot) for microscopic observation. The size of crystals was measured using a 40 × long-working-distance objective.

Crystals are observed through a microscope as they grow and their image is projected on a TV monitor. The growth rate of the different faces is calculated from the change of the outline of the crystal as a function of time. Alternatively, the crystal picture can be recorded and the image can be digitized to be analyzed with the aid of a computer.

2.3. Effect of additives on crystal morphology

In order to study the effect of various additives on the morphology of L-alanine crystals, flow cell experiments were conducted. L-Alanine crystals were grown in the presence of the additive at different concentrations. These experiments were performed at a constant supersaturation value of 0.05, at 25°C at a flow rate of 5 ml/h using 1/16 inch tubing (Tygon®). The additive was dissolved in the solvent prior to the addition of L-alanine. The concentrations of additive studied were between 0.15 and 0.60 g additive/100 g solvent (i.e., 0.09–0.36 g additive/100 g solute or 0.01–0.08 *m*). Morphology changes of L-alanine crystals were documented photographically.

The additives studied are presented in Fig. 2. These additives can be classified according to their molecular characteristics, as follows:

(i) Those whose molecular structure resembles that of L-alanine and have the same chirality such as hydrophobic (group B, Fig. 2) and hydrophilic L-amino acids (L-asparagine and L-serine in group A, Fig. 2);
(ii) Those structurally related but having different chirality (D-leucine in group A, Fig. 2) and
(iii) Those whose molecular structure does not resemble that of L-alanine but possess functional groups present in the L-alanine molecule (benzoic acid in group A, Fig. 2).

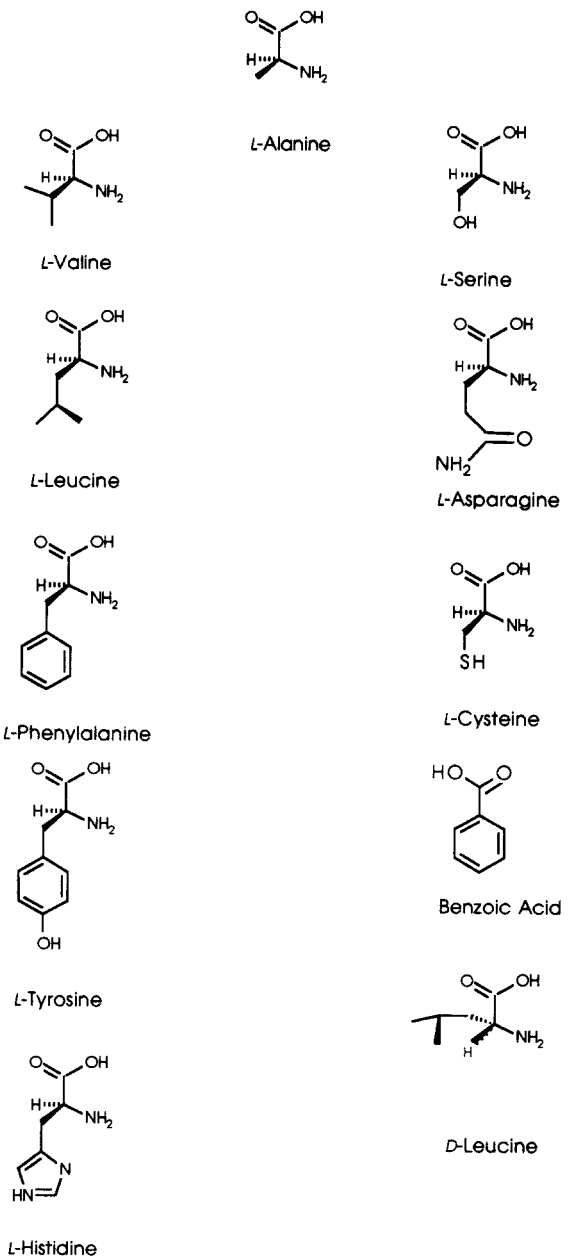

Fig. 2. Molecular structure of L-amino acids used as additives.

2.4. Determination of Miller indices

The Miller indices of the faces of L-alanine crystals grown in the presence and absence of additives were determined by measuring the interfacial angles using a two-circle optical goniometer. These values were then compared to the theoretical values calculated based on the knowledge of the unit cell parameters of L-alanine crystals (Simpson and Marsh, 1966).

Fig. 3. L-Alanine crystals grown in the flow cell from water at constant supersaturation (0.05) and temperature 25°C (a) in the absence of additives and in the presence of (b) L-serine (0.02 *m*), representative of the crystals grown in the presence of L-asparagine, D-leucine and benzoic acid and (c) L-leucine (0.02 *m*), representative of crystals grown in the presence of hydrophobic L-amino acids (Fig. 2, group B). Photograph was taken using an inverted optical microscope with a long-working distance objective 40×.

3. Results and discussion

3.1. Crystals grown in the absence and presence of additives

L-Alanine crystals grown from its aqueous solution in the absence of additives are elongated along its crystallographic *c*-axis, exhibiting a very well formed face zone around it, with up to eight faces and an additional face zone develops about the *a*- and *b*-axes (Fig. 3a). The morphology of the crystals grown in the absence of additives is shown in Fig. 4. The largest face zone is about the crystallographic *c*-axis where as many as eight well-developed faces can be identified, namely {010}, {110}, {210} and {120}.

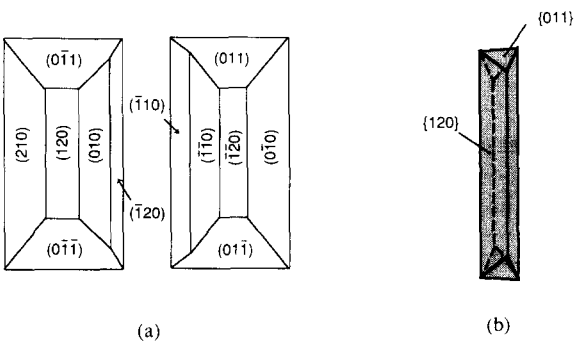

Fig. 4. Morphology of L-alanine crystals grown from aqueous solution (a) in both the absence and presence of L-serine, L-asparagine, D-leucine, and benzoic acids and (b) in the presence of hydrophobic L-amino acids. View (i) along and (ii) down the crystallographic *c*-axis.

When L-alanine crystals were grown in the presence of additives, two different effects were observed: (i) hydrophilic L-amino acids, benzoic acid and D-leucine in concentrations as high as 0.2 *m* (3% w/w) did not induce appreciable changes in the morphology (Fig. 3b), the Miller indices of the different faces being the same as shown in Fig. 4a; and (ii) the addition of hydrophobic L-amino acids selectively inhibited the development of specific L-alanine crystal faces, at concentrations as low as 0.02 *m* (0.3% w/w) (Fig. 3c). Crystals affected by the presence of hydrophobic L-amino acids are much more elongated along the *c*-axis and their width is very different from that of the prismatic L-alanine crystals grown in the absence of additives. The Miller indices of these crystals (Fig. 4b) clearly show that the {120} and {011} faces are developed whereas the {010}, {110} and {210} faces are not.

3.2. Kinetic considerations to explain the morphology changes induced by the presence of some additives

The morphology of a crystal is determined by the slowest growing faces. This is illustrated in Fig. 5. Consider the initial shape of a crystal at time t_0 (Fig. 5a), which is comprised of two sets of faces with different growth rates, and let $R_1 \gg R_2$. At time t_1 (Fig. 5b), the displacement of those faces that grow at a rate R_1 is larger than the ones growing at a rate R_2. This process is continued as shown in Fig. 5c and d. Eventually, the slow growing faces will exhibit a much larger surface area and will determine the morphology of the growing crystal. Often the slow growing faces are referred to as morphologically important faces.

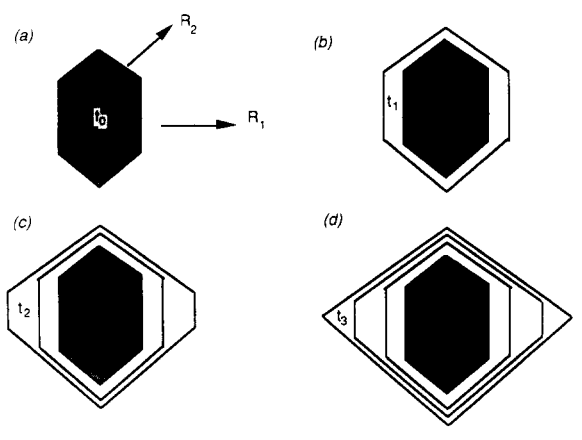

Fig. 5. Changes in morphology due to different face growth rates.

Table 1
Growth rate (R) of L-alanine crystals from flow cell experiments

Additive	R (μm/min)	
	a-axis	*c*-axis
None	0.12 (0.07) [a]	0.43 (0.16)
D-Leucine	0.10 (0.05)	0.32 (0.11)
L-Leucine	0.01 (0.00)	0.41 (0.16)
L-Serine	0.13 (0.06)	0.36 (0.12)

Supersaturated solution was circulated at a linear velocity of 0.070 cm s^{-1} (5 ml h^{-1} using 1/16 inch tubing) $\sigma = 0.05$ and $T = 25$°C, along both *a* and *c* crystallographic axes in the presence and absence of additives.

Because the morphology of the growing crystals is determined by the relative growth of the faces, any change in morphology must be accompanied by a change in the relative growth rates. The growth rates of L-alanine crystals along both the *a* and *c* crystallographic axes in the absence and presence of some additives are shown for comparison in Table 1. Because the growth rate of a given face is that one perpendicular to it, the growth rate of the faces that lie parallel to the *c*-axis (i.e., {210}, {120}, {010} and {110}) is associated with the growth rate observed along the *a*-axis and the growth rate of the faces that lie parallel to the *a*-axis (i.e., {011}) is associated with the growth rate observed along the *c*-axis.

The presence of D-leucine or L-serine does not significantly change the growth rate along either the *a*- or *c*-axis whereas the presence of L-leucine significantly reduced the growth rate along the *a*-axis, however, the growth rate along the *c*-axis remained unchanged. Therefore, in the case of L-alanine crystals grown in the presence of hydrophobic L-amino acids, we can postulate that the reduction of the growth rate along the *a*-axis is a result of selective adsorption of additive molecules onto specific faces about the *c*-axis of L-alanine crystals. Since the {120} faces are the

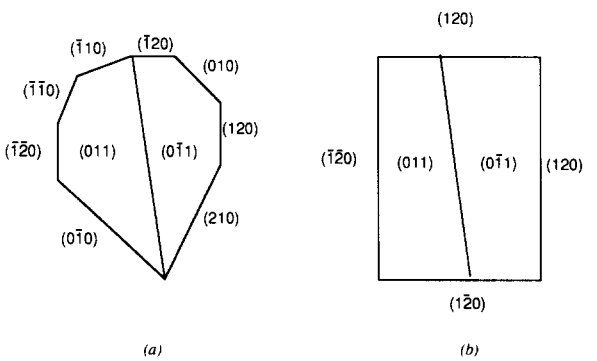

Fig. 6. Comparison of the crystal morphology of L-alanine crystals grown in the absence and presence of hydrophobic L-amino acids. View down the crystallographic *c*-axis. In the absence and presence of additives listed in group A of Fig. 2, the {110}, {010} and {210} faces are developed whereas in the presence of hydrophobic L-amino acids only the {120} faces are developed. The {011} set of faces develop in both cases.

only morphologically important ones lying parallel to the *c*-axis for the crystals grown in the presence of L-leucine, additive molecules can be thought of as selectively adsorbing onto these faces, therefore reducing their relative growth rate. This growth rate reduction induces an increase in the surface areas of the {120} faces. Eventually, the slow growing faces will bound the crystal about the crystallographic *c*-axis as schematically shown in Fig. 6.

Because the morphology of L-alanine crystals grown from aqueous solution in the presence of L-asparagine, L-serine, D-leucine and benzoic acid is not affected, two hypotheses can be put forward: (i) the relative growth rate of the different faces is not affected because there is a nonspecific interaction between the additive and the different crystal faces; or (ii) the growth rate is not changed due to the presence of these additives. Since a significant change in the growth rate of L-alanine crystals is not observed in the presence of either D-leucine or L-serine (Table 1), the reason for not observing a morphology change is explained by the latter hypothesis.

3.3. Relation between L-alanine crystal morphology and crystal structure

So far, we have shown how the crystal morphology is determined by the relative growth rate of the dfifferent crystal faces. We have been able to relate the changes in the relative growth rate of a particular crystal face to the presence of additives in the supersaturated aqueous solution via an interaction of the additive molecule with the crystal surface. The following observations suggest certain structural requirements for the interaction between the additive molecule (Fig. 2) and the crystal surface to result in morphology changes:

(i) The presence of benzoic acid does not affect the crystal morphology of L-alanine crystals even though two of its functional groups are common to the L-phenylalanine molecule whose presence does induce a morphology change, i.e., the phenyl ring and carboxylic group;

(ii) The presence of neither L-asparagine nor L-serine induces a change in the morphology

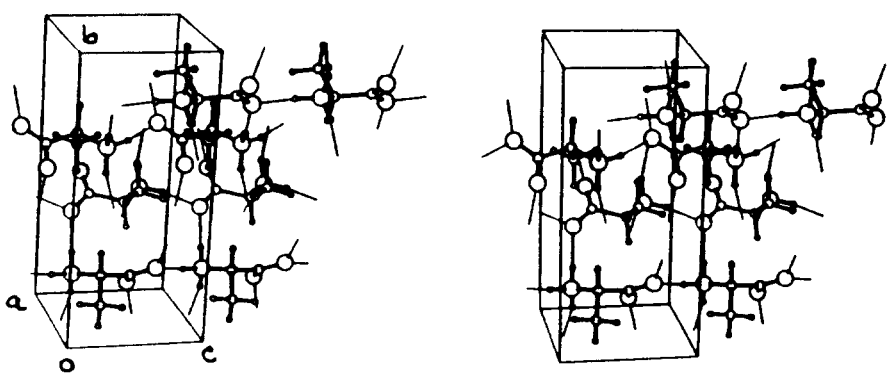

Fig. 7. Stereo view of the L-alanine unit cell.

of L-alanine crystals, thus, it can be inferred that besides the structural requirement an increased molecular affinity is needed;

(iii) The interaction between the additive molecule and the crystal surface must be stereospecific as is demonstrated by the fact that L-leucine promotes a morphology change whereas D-leucine does not.

To answer the question of what structural requirements are necessary to induce the morphology changes observed it is necessary to consider the L-alanine crystal structure, as obtained from X-ray diffraction studies, to infer the structure of the different crystal planes.

L-Alanine exists as the zwitterion in the solid state. A stereo view of the L-alanine molecule arrangement in the unit cell is shown in Fig. 7. The L-alanine crystal lattice is orthorhombic, belongs to the space group $P2_12_12_1$ with unit cell parameters $a = 6.023$; $b = 12.343$ and $c = 5.784$ Å, $Z = 4$, as has been determined from X-ray diffraction and neutron diffraction data (Simpson and Marsh, 1966; Lehmann et al., 1972).

The crystal is held together by a network of hydrogen bonds that involves the use of all available N–H $\cdots$ O bonds. All protons in the amino group are used to form these hydrogen bonds, two to O^2 and one to an O^1 atom, which results in a small but significant lengthening of the C–O^2 in comparison to C–O^1. One of the N–H $\cdots$ O^2 hydrogen bonds links the L-alanine molecules together to form a chain along the *c*-axis of the crystal, the other two hydrogen bonds binding these chains together in a three-dimensional network. The channels formed by this network are occupied by the methyl groups. The L-alanine molecule in the bulk of the crystal forms six hydrogen bonds with its neighbors. The hydrogen bond distances are nearly identical as shown in Table 2.

The total energy of formation of the hydrogen bond includes contributions from various energy terms involving the N, O and H atoms as well as electrostatic energy terms arising from the partial charges on the N, O and H atoms and neighboring atoms. Energy calculations from crystal packing studies, assuming a 10–12 Lennard-Jones potential, have been performed to determine the energy contribution of the O $\cdots$ H (1.11 kcal mol^{-1} at an average bond distance of 1.9 Å) (Némethy et al., 1983). It was found that the energy contribution is strongly dependent on the bond distance. In the case of L-alanine all six hydrogen bonds present should be energetically equivalent with a bond energy of approx. 6–7 kcal mol^{-1}.

Table 2
Distances (Å) and angles (°) in the hydrogen bonds of L-alanine crystals (after Lehmann et al., 1972)

Bond distances		Bond angles	
$O^1 \cdots H^1$	1.861 (3)	$O^1 \cdots H^1$–N	160.9 (2)
$O^1 \cdots N$	2.853 (1)		
$O^2 \cdots H^2$	1.780 (2)	$O^2 \cdots H^2$–N	168.1 (2)
$O^2 \cdots N$	2.813 (1)		
$O^3 \cdots H^3$	1.828 (3)	$O^3 \cdots H^3$–N	163.7 (2)
$O^3 \cdots N$	2.832 (2)		

3.4. Molecular arrangement in different crystal planes and possible interaction with molecules of additive

In order to understand the role of crystal structure in the crystal growth process and determine how it will be influenced by the presence of an additive in the crystallizing medium the 'periodic bond chain' (PBC) theory can be invoked (Hartman and Perdok, 1955a–c; Hartman, 1973, 1987). The basic assumption of this theory rests in the fact that crystal growth can be considered as the formation of bonds between crystallizing particles (growth units) such as atoms, ions or molecules. In order to form a crystal, these growth units have to come close together, thus only strong bonds are considered, defined as 'bonds in the first coordination sphere'. The PBC approach is therefore a geometrical one rather than one based on bond energies and only recently has it been used to relate crystal morphology to crystal structure of drug compounds (Hartman and Chan, 1993; Zipp and Rodríguez-Hornedo, 1993).

In the case of L-alanine, these bonds should be mainly hydrogen bonds and van der Waals contacts between the atoms of the methyl groups of neighboring molecules. According to the PBC theory a crystal layer will be determined by two

uninterrupted chains of strong bonds in different directions. Different crystal faces can be classified accordingly to the number of PBCs found in a slice of thickness d_{hkl} as follows:

F faces: a slice d_{hkl} contains two or more PBCs

S faces: a slice d_{hkl} contains only one PBC

K faces: a slice d_{hkl} contains no PBCs at all

The slice thickness d_{hkl} is the interplanar distance of the plane (*hkl*). The surface structure of a crystal face is defined by the minimum of the specific surface energy, thus d_{hkl} represents the distance of this energy. Therefore, the presence of a symmetry element such as a screw axes or glide planes perpendicular to the face (*hkl*) and a submultiple of d_{hkl} should be used. Thus, the same extinction rules used in X-ray diffraction are valid.

Because *F* faces are formed by at least two PBCs they must be stepped faces which are able to grow according to a layer mechanism, so that their growth rate is rather small. Therefore, they determine the theoretical habit, although this does not imply that *F* faces should be present on the observed habit. The growth of *K* and *S* faces is greater and they do not occur on the crystal. *F* faces must be determined from the crystal structure as they may not be observed during growth.

PBCs not only define a face (*hkl*) as an *F* face but they also define at the same time the molecular configuration at the surface. This is consistent with the fact that for L-alanine all well formed faces are formed along the hydrogen bonding network (Fig. 8 and 9).

The molecular structure of the (001) and the (100) planes, along which the major crystallographic zones develop is demonstrated in Fig. 8 and 9. When the concepts of the PBC theory are applied to examine the nature of the crystal faces of L-alanine, we have found that the only *F* faces are the {120} and the {011}. Interestingly, these are the only faces observed in the crystals grown in the presence of additives.

Regarding the molecular composition of these faces the following can be said. From Fig. 8 we can see that the {120} faces run along the tunnels formed by hydrogen bonding where the methyl

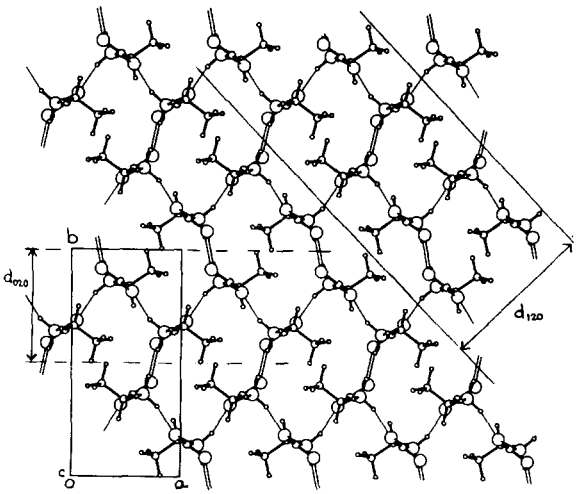

Fig. 8. Molecular structure of the (001) crystallographic plane of L-alanine crystals showing the hydrogen bonding network. A PBC is a zigzag chain. Neighboring PBCs are bonded only in d_{120} so {120} is an *F* face and {010} as well as {210} are *S* faces.

groups are accommodated; these planes are therefore hydrophobic in nature. In contrast, the {210} faces are comprised mainly by amine and carboxylic groups and therefore present a more hydrophilic nature. The character of the {010} faces should be somewhat in between as they exhibit both hydrophilic and hydrophobic groups. In Fig. 9 the molecular composition of the {011} faces is indicated and it can be considered hydrophilic since it is comprised of carboxylic and amino groups.

The molecular structure of a crystal face will determine its surface energy and the availability of sites for adsorption of the additive molecules. Although the chemical composition of all faces in a crystal is the same, the surface energies they exhibit may be very different because of the type of functional groups in a particular face. It was shown above that adsorption of the hydrophobic L-amino acids onto specific crystal faces decreased their growth rate, inducing morphology changes.

The morphology of L-alanine crystals grown in the absence of additives is characterized by the crystallographic planes that cut through the network of hydrogen bonds. In the presence of hy-

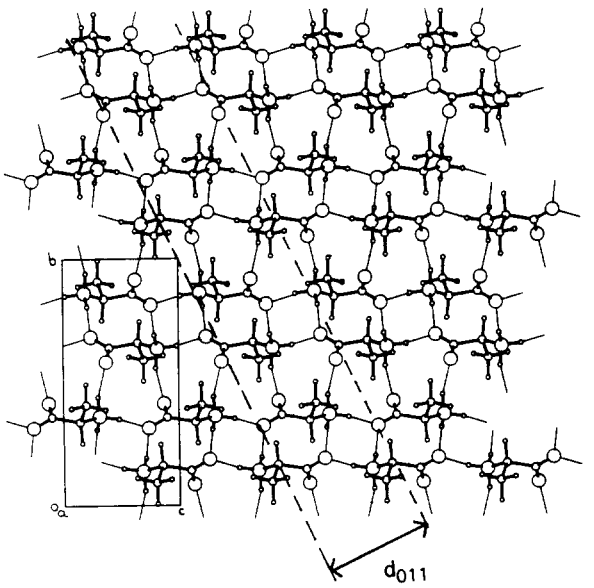

Fig. 9. Molecular structure of the (100) crystallographic plane of L-alanine crystals showing the hydrogen bonding network. A PBC is a zigzag chain. Neighboring PBCs are bonded only in d_{011} so {011} is an F face.

drophobic L-amino acids only the {120} develop, suggesting that adsorption on these planes is favored. Structurally, tailor-made additives have a functional group that differs from the host molecule. Upon examination of the structure of the {120} planes it is found that of every four molecular sites one can be occupied by an additive molecule having the dissimilar portion of the molecule perpendicular to the plane as graphically demonstrated in Fig. 8. The inclusion of an additive molecule in the crystal sturucture will disrupt the formation of the next layer on the {120} plane inhibiting its growth. The fact that D-leucine does not selectively adsorb onto L-alanine crystal faces whereas L-leucine does demonstrates that stereoselectivity plays an important role to occupy these sites.

An important structural feature of the {120} planes is that they possess a more hydrophobic character than the other crystal faces since they exhibit a greater number of methyl groups per unit area (Fig. 10). The increased hydrophobicity may be the factor that determines the lack of interaction of both hydrophilic L-amino acids and benzoic acid with the {120} planes.

In contrast, morphologically important faces in crystals grown in the absence of hydrophobic L-amino acids such as the {210} (Fig. 10) have a much more hydrophilic character as they are comprised of amino and carboxylic groups and therefore do not interact as strongly with the hydrophobic L-amino acids. The {011} planes are developed in the L-alanine crystals and their development is not affected by the presence of the additives. The {011} planes, whose molecular structure is depicted in Fig. 9, are expected to be hydrophilic in nature as they are mainly comprised of carboxylic and amino groups. This behavior is similar to that observed in the case of glycine crystals, whose {011} planes are similar to those of L-alanine (Li and Rodríguez-Hornedo, 1992).

The differences observed in the extent of the inhibitory effect between the hydrophobic and hydrophilic L-amino acids can be explained by the potential for adsorption of each additive onto L-alanine crystal faces. This hypothesis is consistent with the results obtained from studies of the adsorption isotherms of amino acids onto activated carbon in aqueous solutions (Rosene et al., 1976; Piperaki et al., 1978). In general, adsorp-

Fig. 10. Molecular structure of the {120} planes showing the molecular conformation of L-alanine molecule in the solid state as obtained from X-ray crystallographic data.

tion of amino acids onto activated carbon is favored by the presence of sulfur atoms or hydrophobic groups and is decreased by the presence of hydrophilic groups in the amino acid molecule.

4. Conclusions

In summary, from the kinetic, mechanistic and structural considerations we have found that the ability of the hydrophobic L-amino acids to modify the crystal morphology of L-alanine crystals is explained by considering the relation between the structure of both the additive molecules and the L-alanine crystallographic planes. We have found that the sites available for adsorption at the crystal surface are highly specific as is demonstrated by the fact the presence of benzoic acid does not affect the crystal morphology of L-alanine crystals even though two of its functional groups are common to the L-phenylalanine molecule (i.e., phenyl ring and carboxylic group) whose presence does induce a morphology change. Moreover, the interaction between the additive molecule and the crystal surface must be stereospecific as it is demonstrated by the fact that L-leucine promotes a morphology change whereas D-leucine does not. Finally, besides the structural requirements, an increased molecular affinity is needed as is demonstrated by the fact that the presence of neither L-asparagine nor L-serine induces a change in the morphology of L-alanine crystals. Thus, the growth rate of the different crystal faces and, therefore the crystal morphology, can be controlled by choosing the additives with the appropriate molecular characteristics

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