Growth and Morphology of L-Alanine Crystals: Influence of Additive Adsorption

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The effect of L-amino acids, as additives, on the crystal growth and morphology of L-alanine crystals has been studied. The crystal growth of L-alanine is described by the spiral growth mechanism. From examining the growth rate dependence on supersaturation at constant additive concentration, it is concluded that there is no change in the growth mechanism due to the presence of the different additives. L-Alanine crystals were grown both in the absence and in the presence of additives. The crystal morphology was characterized by optical goniometry assigning the different Miller indices to the well-developed crystal faces. The addition of L-amino acids selectively inhibits the development of certain L-alanine crystal faces. L-Alanine crystals grown in the presence of nonpolar amino acids, such as L-leucine, L-phenylalanine, and L-valine, at concentrations as low as 0.20 *m* (0.3%, w/w) develop the {120} faces, whereas the {010}, {110}, and {210} faces are not developed. The effect of these additives on the morphology of L-alanine is explained at the molecular level based on crystallographic considerations. The molecular structure of a face will determine the availability of sites that favor the adsorption of the additives. The availability of sites and their energy, on a particular crystal face, will determine the extent of adsorption. The growth rate of a crystal face is decreased by the adsorption of the additive. The inhibitory effect of these additives can be explained by a Langmuir isotherm, assuming that the inhibition of the growth rate is proportional to the degree of surface coverage and that the crystal surface is homogeneous with respect to the energy of adsorption sites.

KEY WORDS: L-alanine; crystal growth mechanism; crystal morphology; effect of additives; adsorption of additives; amino acids.

INTRODUCTION

The presence of additives in small amounts may greatly influence the crystallization kinetics of organic compounds from solution. An additive may affect the activity of the crystallizing solute in solution and interfere with the crystal growth process through adsorption onto the growing surface. Of particular importance is the study of the effect of additives that closely resemble the chemical structure of the crystallizing solute, such additives, referred to as "tailor-made additives" (1), offer a means of selectively modifying the crystal habit, either through adsorption onto the growing-crystal surface or through incorporation into the crystal lattice on specific sites. This kind of studies emphasizes the effect of additives on crystal morphology and lattice or surface energies.

A detailed study of the crystallization kinetics and host/additive structural properties has, however, been performed in very few systems (2–5). The objective of the present investigation is to study the effect of additives on the crystallization of organic compounds that can be used as models so that their kinetic and structural behavior can be applied to understand more complex systems. In the pharmaceutics field there has been a lack of systematic studies regarding the crystallization of drugs and drug-related compounds, even though both the physical and the chemical properties are affected by this process. An important, direct application of these concepts, that explain the effect of additives on crystal growth, can be used to aid in the design of crystalline drugs with the desired physicochemical properties. These properties include crystal morphology, size, lattice energy, solubility, and rate of dissolution.

We have studied the crystal growth mechanism of L-alanine from aqueous solutions as well as the effect of some L-amino acids and other organic compounds on crystal growth kinetics and morphology. Adsorption energies of the additives onto L-alanine crystals were evaluated by assuming that the inhibition of growth rate is proportional to the degree of surface coverage and that the crystal surface is homogeneous with respect to the energy of the adsorption sites.

EXPERIMENTAL

L-Alanine and all other chemicals used in these experiments 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.

Solubility and Concentration Measurements

The solubility of L-alanine in aqueous $(NH_4)_2SO_4$ solutions in the presence and absence of additives was determined. L-Alanine concentrations were measured by reversed-phase HPLC (System Gold, Beckman Instruments, Inc., San Ramon, CA) using a C_{18} column (Astec C_{18}, 5-μm spherical) at room temperature. The mobile phase was phosphate buffer (0.01 *M*, pH 6.0); the flow rate used was 1.75 mL/min. The L-alanine peak was detected at 2.0 min by means of a UV detector set at 200 nm. The presence of either L-leucine or L-phenylalanine did not affect the analysis of L-alanine. The L-leucine peak was detected at 3.7 min and the L-phenylalanine peak at 8.0 min.

Crystallization Experiments

The dependence of growth rate on supersaturation was studied at a constant agitation rate of 460 rpm and a 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 is the concentration at equilibrium. The supersaturation range studied was 0.015 to 0.15. The supersaturated solutions of L-alanine were prepared by dissolving a given amount of the amino acid in a known amount of solvent. The solution was warmed to approximately 40°C, filtered, and transferred into a jack-

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eted beaker with a rounded bottom, connected to a circulating water bath (Model RTE-210, Neslab Instruments, Inc. Newington, NH) set at 25 ± 1°C. Once the temperature of the metastable solution reached 25°C, the jacketed beaker was placed in the Coulter Multisizer sample stand and stirred at a constant angular velocity with a glass paddle. The crystal size distribution (CSD) of the crystals larger than 10 μm was monitored as a function of time using a 280-μm-orifice tube. During the course of an experiment the concentration was monitored. Filtered samples of about 1.5 mL were accurately weighed and analyzed as described above.

Effect of Additives on Crystal Growth

The effect of L-phenylalanine and L-leucine on the growth rate of L-alanine was studied at various levels of additive, with a constant supersaturation value of 0.025, at 25°C and at an agitation rate of 460 rpm. The additive was dissolved in the solvent prior to the addition of L-alanine. The range of concentrations of additives studied was between 0.0015 and 0.3% (w/w) for L-phenylalanine and between 0.025 and 0.5% (w/w) for L-leucine (concentrations are expressed for 100 g of solution).

The effect of L-phenylalanine and L-leucine on the growth mechanism was investigated by measuring the growth rate of L-alanine crystals as a function of the degree of supersaturation, at 25°C and an agitation rate of 460 rpm. The additive concentrations were 0.01% (w/w) for L-phenylalanine and 0.125% (w/w) for L-leucine.

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 and a flow rate of 5 mL/hr using 1/16-in tubing (Tygon). The additive was dissolved in the solvent prior to the addition of L-alanine. The concentration of additive studied was between 0.15 and 0.60% (w/w) (0.01 to 0.08 *m*). Additives selected can be grouped as follows: (i) those being structurally related, such as hydrophobic L-amino acids (Group B, Table I) and hydrophilic L-amino acids (Group A, Table I); (ii) those structurally related but having a different chirality (D-leucine); and (iii) those in neither of the above categories (benzoic acid).

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 (6).

Table I. List of Additives Studied to Determine Their Effect on the Morphology of L-Alanine Crystals

A	B
L-Asparagine	L-Cysteine
Benzoic acid	L-Histidine
D-Leucine	L-Leucine
L-Serine	L-Phenylalanine
	L-Tyrosine
	L-Valine

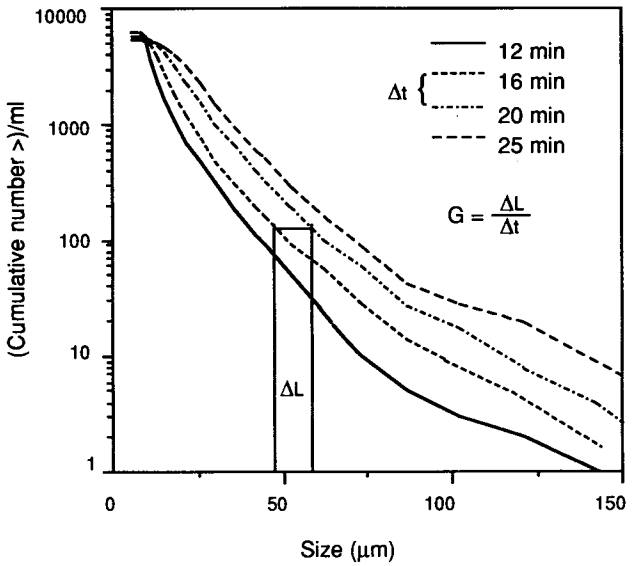

Fig. 1. Evolution of the crystal size distribution of L-alanine crystals from a batch experiment. ΔL is the average shift in size between CSD at t_i and CSD at t_{i+1}.

RESULTS

The solubility of L-alanine in 2.5 *M* $(NH_4)_2SO_4$ at 25°C was determined to be 0.1110 g of L-alanine/g of solvent. The presence of different amounts of L-leucine and L-phenylalanine had no significant effect ($p < 0.05$) on the solubility of L-alanine in 2.5 *M* $(NH_4)_2SO_4$. The evolution of the CSD during batch crystallization experiments is shown in Fig. 1. Each curve represents the cumulative number of crystals larger than the given size for each crystal population measured at different time intervals, as obtained from the Coulter Multisizer. The average shift between adjacent lines represents the increase in size of the CSD (ΔL), which, divided by the time interval (Δt), is defined as the crystal growth rate ($G = \Delta L/\Delta t$). The dependence of crystal growth rate on initial supersaturation is presented in Fig. 2. Each value represents the average growth rate from an experiment; the variation coefficient associated with these measurements is ≈30%. In Fig. 3 the growth rate of L-alanine crystals measured in the presence of additive is presented as a function of supersaturation. The effect of additives on the growth rate of L-alanine is shown in Fig. 4, where η is the ratio of growth rate observed in the presence of additive, at a given mole fraction χ, to the growth rate measured in the absence of additive at the same supersaturation and temperature ($\sigma = 0.025$, $G = 0.47$ μm/min). Although the growth rate of L-alanine crystals was reduced when grown in the presence of any of the additives studied, the morphology was not affected in the same way. Figure 5 is a drawing of the L-alanine crystals grown in the presence and absence of additives; the Miller indices, determined from the measure-

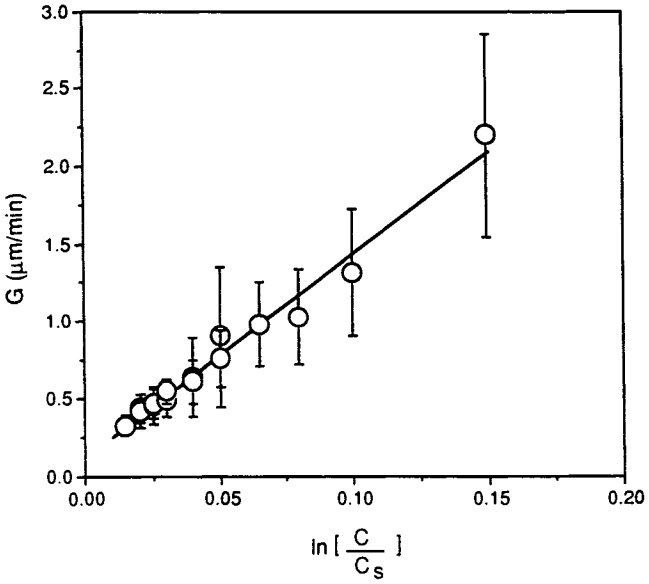

Fig. 2. Growth rate (G) dependence on supersaturation [$\sigma = \ln(C/C_s)$]. The error bars represent the standard deviation for the growth rate calculated from CSD measurements.

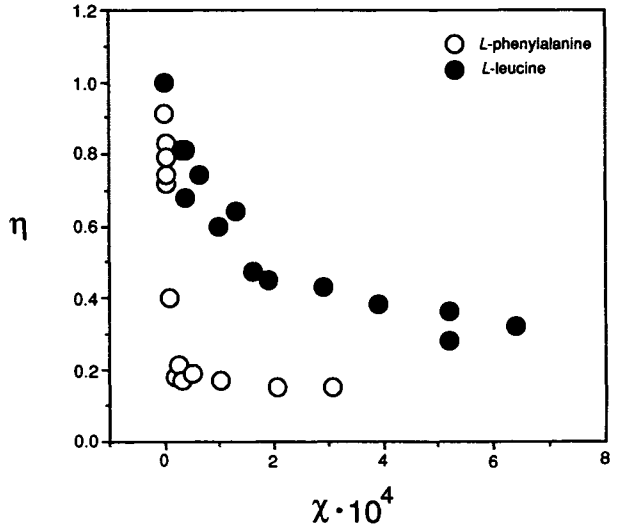

Fig. 4. Effect of the presence additives at different concentration levels (χ is the mole fraction of additive in solution) on the growth rate ($\eta = G_a/G_{max}$) of L-alanine crystals.

ment of the interfacial angles with the two-circle optical goniometer, are indicated. The morphology of L-alanine crystals grown in the presence of hydrophilic L-amino acids, D-leucine, and benzoic acid (Group A, Table I) was the same as that observed for L-alanine crystals grown in the absence of additives (Fig. 5a). In contrast, the morphology of L-alanine crystals grown in the presence of hydrophobic L-amino acids (Group B, Table I) was drastically changed (Fig. 5b).

DISCUSSION

Growth Mechanism

In order to characterize the crystallization mechanism of L-alanine in the absence of additives it is necessary to find a model that can explain the $G(\sigma)$ plot shown in Fig. 2, which clearly suggests a linear dependence of crystal growth on the supersaturation range studied. Growth mechanisms are specific for each crystal face, however, useful information can be still obtained from CSD measurements. The mechanistic information so obtained will be global, and care should be exercised in its interpretation.

Crystallization is indeed a phase transformation process that can be controlled either by the diffusion of the molecules through the bulk of the solution to the crystal surface of the solid phase or by the integration of molecules into the crystal lattice. Based on the models described in the literature (7,8) the behavior of $G(\sigma)$ for L-alanine has been determined to be best explained by a surface-controlled growth mechanism (9). Further analysis reveals that, in this case, the overall growth of L-alanine crystals is best explained by the screw dislocation mechanism (10) and it follows a complex dependence on supersaturation, given by

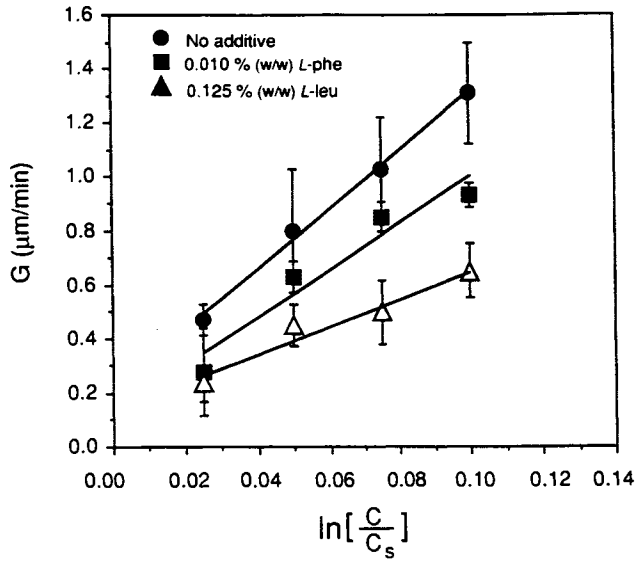

Fig. 3. Effect of the presence of additive on the growth rate (G) dependence on supersaturation [$\sigma = \ln(C/C_s)$]. The error bars represent the standard deviation for the growth rate calculated from CSD measurements.

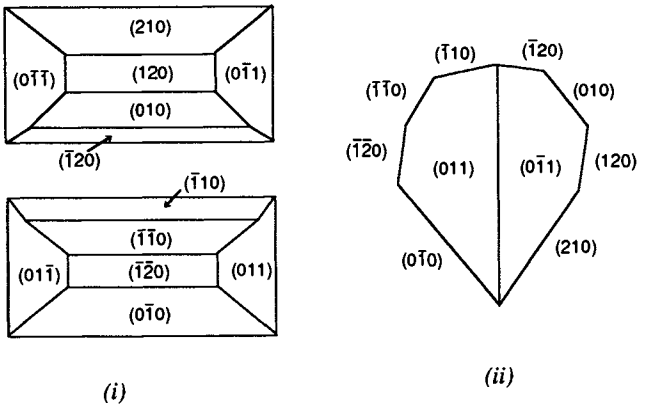

Fig. 5a. Morphology of L-alanine crystals grown from aqueous solution both in the absence of additives and in the presence of those additives listed in Group A in Table I. (i) View along the crystallographic c-axis; (ii) view down the crystallographic c-axis.

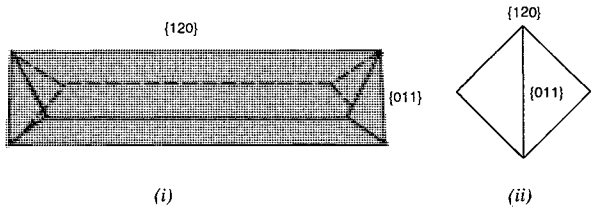

Fig. 5b. Morphology of L-alanine crystals grown from aqueous solution in the presence of those additives listed in Group B in Table I. (i) View along the crystallographic c-axis; (ii) view down the crystallographic c-axis.

$$G = k_1 T\sigma^2 \tanh\left(\frac{k_2}{T\sigma}\right) \quad (1)$$

where k_1 and k_2 are constants. Simplification of this equation can be made considering two limiting cases depending on the magnitude of the supersaturation. At low supersaturation the term $\tanh(k_2/T\sigma)$ approaches unity and the growth rate is proportional to the square of the driving force, $\ln^2(c/c_s)$. Also, as σ increases, $\tanh(k_2/T\sigma)$ approaches $k_2/T\sigma$ and the growth rate is proportional to $\ln(C/C_s)$. An empirical relation widely used, known as the power law, to determine the supersaturation dependence is

$$G = k_g \sigma^n \quad (2)$$

where k_g is a proportionality constant and n is the order of growth. Depending on the value of n, conclusions about the mechanism are often made (7).

This model was fitted by linear regression to the experimental results, the solid line shown in Fig. 2, and a growth order of 0.7 was determined. This implies that the crystallization of L-alanine occurs by the screw dislocation model and that the system is already close to the high-supersaturation limiting case. This is in agreement with the situation at high supersaturation when surface diffusion becomes less important, since there are so many kink sites available that integration is much faster than surface diffusion. Current research on single crystals of L-alanine is being conducted in our laboratory to confirm these results.

Effect of Additives on the Growth Kinetics and Mechanism

The influence of additives on L-alanine growth rate is presented in Fig. 4. The addition of 0.01% (w/w) L-phenylalanine ($\chi_{phe} = 1 \times 10^{-5}$) decreases the growth rate to less than half its value in the absence of additive, and 0.05% (w/w) ($\chi_{phe} = 5 \times 10^{-5}$) suppresses the growth rate to a limiting value of 0.08 μm/min ($\eta^0 = 0.17$). In the presence of 0.15% (w/w) L-leucine ($\chi_{leu} = 2 \times 10^{-4}$), the growth rate is reduced to a limiting value of 0.13 μm/min ($\eta_0 = 0.28$), equivalent to 40% of the growth rate of the reference system. A further decrease in this system is not expected since the crystallization solvent is almost saturated with L-leucine, whose solubility in the crystallization solvent is 0.55% by weight. Inhibition of the growth rate and crystal morphology changes are evidence of additive adsorption onto the L-alanine crystal surface. The nature of this adsorption must be physical, because no covalent bonding is expected to occur in this system. The kind of interactions expected to occur are hydrogen bonding, dipole–dipole, induced dipole–induced dipole, or van der Waals. Since the solubility, i.e., the activity of L-alanine, is not affected by the presence of the additives, it can be concluded that the observed growth rate behavior is most likely a consequence of the interaction of the additive with the crystal.

The growth mechanism is not being altered by the adsorption of either L-phenylalanine or L-leucine onto the crystal surface of L-alanine, since the functionality of the different $G(\sigma)$ remains linear in the presence of a constant amount of additive in solution, as shown in Fig. 3. This also implies that the inhibition of the growth rate of L-alanine should be the same regardless of the degree of supersaturation, in the supersaturation range studied.

Empirical relations have been proposed to relate the crystal growth kinetics to the degree of coverage of the additive onto the surface of the growing crystal (11). The degree of coverage can be related to the adsorption isotherm of the additive onto the crystal surface. The free energy of adsorption can then be estimated from growth kinetics experiments. A general, but quantitative description of the effect of adsorption on the step velocity, which considers that adsorption may occur onto any type of adsorption site of the surface, has been used to determine the extent of surface coverage from crystal growth measurements. If the step velocity is proportional to the extent of surface coverage, then the total growth rate of the face can be expressed by the model proposed by Bliznakov and Kirkova (12):

$$V_a = V_{max} - (V_{max} - V_{min})\theta \quad (3)$$

where V_a is the velocity at which a step on the crystal surfaces advances in the presence of additive, V_{max} is the step velocity in the absence of the additive, V_{min} is the limiting step velocity in the presence of additive, and θ is the degree of coverage given by the absorption isotherm between the additive and the solute as the substrate. Equation (3) can be rearranged as

$$\frac{1 - \eta}{1 - \eta^0} = \theta \quad (4)$$

where η is the dimensionless growth velocity V_a/V_{max} and η^0 is the limiting value when $V_a = V_{min}$. The fact that V is proportional to the experimentally measured growth rate G, which is the growth rate perpendicular to a given face, allows the use of this model. This model does not assume that the crystal growth follows any given mechanism.

If the adsorption of the additive onto the crystal surface is described by the Langmuir isotherm, Eq. (4) can be rewritten as

$$\frac{1 - \eta}{1 - \eta^0} = \frac{b\chi}{1 + b\chi} \quad (5)$$

The value of b, the Langmuir constant, was estimated from a nonlinear regression fit of Eq. (5) to the experimental values (Fig. 6). The total free energy for adsorption is $\Delta G_{ads} = -RT\ln b$, which includes the adsorption of all the species affecting the growth rate. The values for ΔG_{ads} obtained are presented in Table II. The values obtained for the total en-

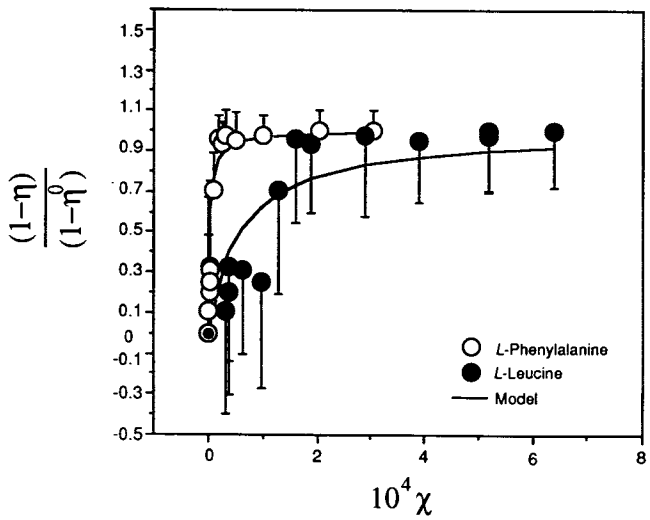

Fig. 6. Effect of additives on the degree of coverage [$\theta = (1 - \eta)/(1 - \eta^0)$] calculated from the experimental growth rate of L-alanine crystals as a function of the concentration of additive in solution (χ is the mole fraction), according to the Bliznakov–Langmuir model, Eq. (5). The error bars represent the standard deviation for the degree of coverage calculated from the error propagation of the measured growth rate.

ergy of adsorption are of the order of magnitude expected for the interactions that occur at the crystal/liquid interface (13).

The differences observed in the extent of the inhibitory effect between L-phenylalanine and L-leucine can be explained by the equilibrium adsorption isotherms of each additive with L-alanine, i.e., different adsorption capacities. This hypothesis is supported by the fact that the differences in adsorption capacity observed for the additives studied are consistent with the results obtained from studies of the adsorption isotherms of amino acids onto activated carbon in aqueous solutions (14,15). It was found that about 96% of L-phenylalanine in aqueous solution was adsorbed onto activated carbon, at equilibrium, compared to 47% of the L-leucine initially in solution. The difference in the adsorption capacities observed is explained by the presence of the π-electron system in the L-phenylalanine molecule. In general, adsorption 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.

Table II. Parameters Obtained from Nonlinear Regression for the Growth Rate Dependence on the Additive Concentration According to the Bliznakov–Langmuir Model, Eq. (5)[a]

System	r^2	$b \times 10^{-4}$	ΔG_{ads} (kcal mol^{-1})
L-Ala/L-Leu	0.96	1.8 (0.3)[b]	−5.8
L-Ala/L-Phe	0.98	34 (6.6)[b]	−7.6

[a] r^2 = determination coefficient; b = Langmuir constant. Free energy of adsorption: $\Delta G_{ads} = -RT\ln b$; $R = 1.987 \times 10^{-3}$ kcal mol^{-1} K^{-1}; $T = 298$ K.

[b] Standard deviation in parentheses.

Effect of Additives on Crystal Morphology

L-Alanine crystals were grown in both the absence and the presence of additives in a flow cell at a constant supersaturation and temperature. The morphology of L-alanine crystals was characterized assigning Miller indices to the crystal faces. These Miller indices were calculated based on the interfacial angles, measured by optical goniometry, and on the geometry of the unit cell of L-alanine crystals, determined from single crystal x-ray diffraction measurements (6). The morphology of the crystals grown from aqueous solution in the absence of additives is shown in Fig. 5a. 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}. The addition of hydrophilic L-amino acids, D-leucine, and benzoic acid (Group A, Table I) reduced the growth rate of L-alanine crystals, but the morphology was not changed, suggesting that there is no preferential adsorption of these additives onto the L-alanine crystal faces. Conversely, the addition of hydrophobic L-amino acids (Group B, Table I) selectively inhibited the development of specific L-alanine crystal faces.

Different crystal faces have different surface energies as a result of the different functional groups that comprise a given face. In addition, the molecular structure of a face will determine the availability of sites that favor the adsorption of the additives. The availability of sites and their energy on a particular crystal face will determine the adsorption of the additive. Adsorption of the additive onto a crystal face frequently decreases the growth rate perpendicular to it. The presence of the hydrophobic L-amino acids, at concentrations as low as 0.02 m (0.3%, w/w), promotes the development of the {120} faces, whereas the {010}, {110}, and {210} faces are not developed (Fig. 5b). In this case, selective adsorption of hydrophobic L-amino acids onto the {120} faces increases their surface area and reduces the growth rate perpendicular to the face. Eventually, the slow growing faces will bound the final crystal habit as is schematically shown in Fig. 7. The effect of hydrophobic L-amino acids on the morphology of L-alanine can be explained at the molecular level based on crystallographic considerations. Figure 8 shows the

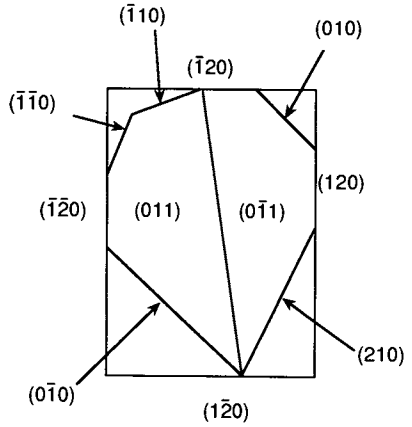

Fig. 7. L-Alanine crystal morphology along the crystallographic c-axis. In the presence of additive the {120} faces are developed, whereas in the absence of additive, the {110}, {010}, and {210} faces are developed.

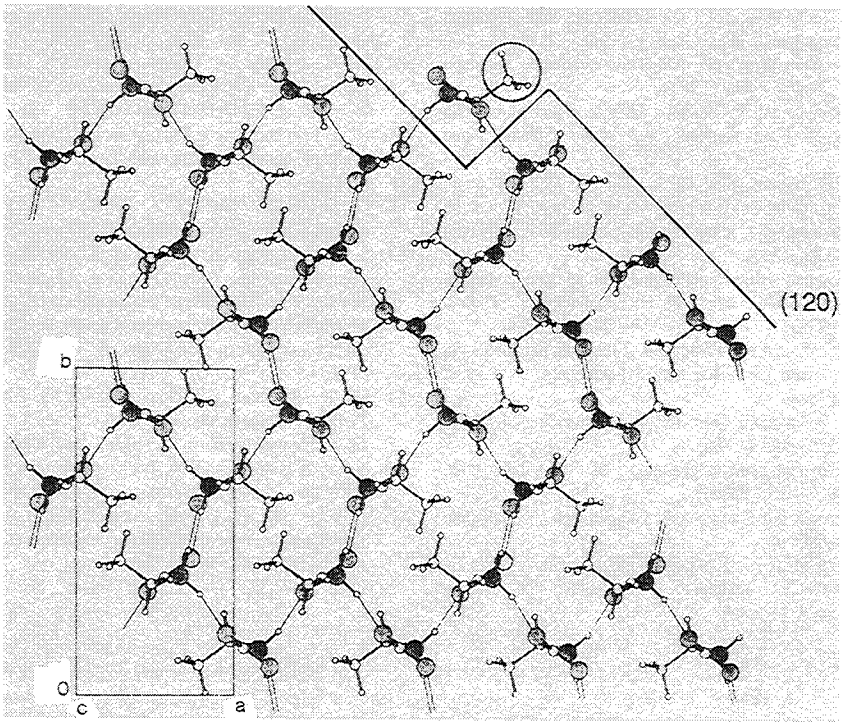

Fig. 8. Molecular structure of the (001) plane of L-alanine crystals showing hydrogen bounding network. White, carbon and hydrogen (smaller) atoms; gray, oxygen atoms; black, nitrogen atoms. The position of the circled functional group will be occupied by the dissimilar portion of the additive molecule.

molecular structure of the (001) plane, along which the major crystallographic zone develops. In the original L-alanine crystal grown from water, the morphology is characterized by the crystallographic planes that cut through the network of hydrogen bonds.

In the presence of hydrophobic L-amino acids, only the {120} faces 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 one of four molecular sites can be occupied by an additive molecule having the dissimilar portion of the molecule perpendicular to the plane. This will disrupt the formation of the next layer on this plane, inhibiting the growth rate perpendicular to it. The fact that D-leucine does not selectively adsorb onto L-alanine crystal faces demonstrates that stereoselectivity plays an important role. Furthermore, the nonpreferential interaction between hydrophilic L-amino acids as well as benzoic acid and the {120} planes is explained by the fact that these are more hydrophobic than the other crystal faces, as they exhibit a greater number of methyl groups per unit area.

In summary, L-alanine growth, in both the presence and the absence of additives, is described by the spiral growth mechanism. The effect of hydrophobic L-amino acids can be explained by assuming that the growth rate decreases proportionally to the degree of coverage and that their adsorption onto L-alanine crystal faces follows a Langmuir isotherm. The adsorption of these additives is limited by the adsorption capacity and the stereoselectivity of adsorption sites at the growing crystal surface.

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NOMENCLATURE

b	Langmuir constant
ΔG_{ads}	Free energy of adsorption
G	Growth rate
k_1	Constant
k_2	Constant
k_g	Constant
n	Growth order
R	Universal constant of gases
T	Temperature
V_a	Advance step rate in the presence of additive
V_{max}	Maximum step velocity in the presence of additive
V_{min}	Minimum step velocity in the presence of additive

Greek

η	Dimensionless growth rate: V_a/V_{max}
η^0	Minimum dimensionless growth rate: V_{min}/V_{max}
θ	Degree of surface coverage
χ	Mole fraction of additive
σ	Supersaturation

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