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The Relation between Adsorption of Additives and Crystal Growth Rate of L-Alanine

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The growth kinetics of L-alanine from solution in the presence and absence of L-phenylalanine and L-leucine has been studied. L-Alanine crystal growth, from crystal size distribution measurements, is independent of the agitation rate suggesting that the growth mechanism is surface controlled. The dependence of growth rate on supersaturation at constant additive concentration suggests that there is no change in the growth mechanism of L-alanine due to the presence of additive. The growth rate of L-alanine is reduced by 50% with a mol fraction of 5×10^{-5} of L-phenylalanine and 2×10^{-4} of L-leucine. The solubility of L-alanine is not significantly affected by the presence of these additives in solution. The effect of these additives on the growth kinetics is due to their adsorption onto the growing L-alanine crystals. The extent of this effect is satisfactorily explained assuming both that (i) the inhibition of the growth rate is proportional to the degree of surface coverage and that (ii) the crystal surface is homogeneous with respect to the energy of adsorption sites.

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.

It has been observed that considerable effects on growth behavior occur with very small concentrations of additive (1). Additives such as surfactants or colloidal materials can usually affect the growth kinetics at concentrations as small as 10–100 ppm, whereas larger concentrations, such as 1.0%, of inorganic ions are often required (2). Usually the effect of large molecules is not specific; a given molecule may be effective in modifying the growth of many different crystals while a similar effect on the growth may be produced by several, very different, large molecules. The lack of specificity may result from the fact that large molecules can be adsorbed at various sites on a crystal by dispersion forces as a result of the surface excess at the solid/liquid interface.

Specificity of some additives to interact with certain crystal faces may be due to the interaction of the additive at the crystal/liquid interface. Anionic and cationic surfactants adsorb onto different faces of adipic acid and L-isoleucine crystals (3, 4). Enhancement of the dissolution rate of poorly water-soluble compounds crystallized in the presence of surfactants has also been observed (5, 6) and attributed to incorporation of the additive into the crystal lattice. Additive incorporation depends on the concentration of the additive in solution (7, 8), as well as on the capacity and affinity for its adsorption onto the crystal surface. Incorporation of the additive has been shown to inhibit secondary nucleation and to induce habit changes (9).

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" (13), 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. Most studies emphasize the effect of additives on crystal morphology and crystal energies.

Detailed studies of the crystallization kinetics and host/additive structural properties have however been performed on very few systems (10–14). 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 understanding 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 chemical properties of solid drugs are affected by this process. An important contribution of this work is the application of concepts that explain the effect of additives on crystal growth to the design of crystalline drugs with the desired physicochemical properties. These include crystal morphology, size, lattice energy, solubility, and rate of dissolution.

We have studied the crystal growth mechanism of L-alanine from aqueous solutions and the effect of L-phenylalanine and L-leucine on crystal growth kinetics. Crystal morphologies and size distributions were examined during growth.

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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 adsorption sites. Amino acids have been selected as model compounds since they comprise a series of compounds whose physical properties, including their crystallography, are well defined; moreover, they are structurally related to pharmaceutical compounds such as β-lactam antibiotics, peptides, and proteins.

EXPERIMENTAL

Crystallization experiments were performed in a batch crystallizer. During the experiments the crystal size distribution (CSD) was measured *in situ* by means of a Coulter Multisizer (Coulter Electronics, Inc., Hialeah, FL). This instrument is designed to measure changes in the resistivity of the medium, as the suspended particles pass through an orifice of known diameter. Such changes in resistivity are proportional to the size of the suspended particles and are converted to a volume equivalent diameter. The use of this instrument requires the use of an electrolyte solution. Even though amino acids are electrolytes in solution, they exist as the zwitterion at the pH of a neutral solution, and thus they are not good conductors. Different solvents were tested to provide conductivity to the system. The crystallization solvent chosen was 2.5 M ammonium sulfate ($(NH_4)_2SO_4$, since in addition to meeting the conductivity requirement it decreased the degree of aggregation of L-alanine crystals.

L-Alanine, L-leucine, L-phenylalanine, and $(NH_4)_2SO_4$ 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

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.

The solubility of L-alanine in aqueous $(NH_4)_2SO_4$ solutions in the presence and absence of additives was determined. An amount of solid, exceeding the solubility value, was added to the vials containing the liquid solvent. The vials were sealed, immersed in a shaking water bath at 25°C and agitated for at least 24 h to allow equilibration of the system. Aliquots were withdrawn and filtered using a 0.22-μm filter (Acrodisc-LC13 PVDF, Gelman Sciences Inc., Ann Arbor, MI). The effect of L-phenylalanine as well as that of L-leucine on the solubility of L-alanine in 2.5 M $(NH_4)_2SO_4$ was determined by adding L-phenylalanine at 0.1, 0.2, and 0.3% (w/w) and L-leucine at 0.2, 0.4, and 0.55% (w/w) to the solvent before dissolving L-alanine. In batch crystallization experiments aliquots were filtered through 0.22-μm filters, weighed, suitably diluted with water and analyzed as described above.

Crystallization Experiments

Supersaturated solutions of L-alanine were prepared by dissolving a given amount of the amino acid in a known amount of solvent to yield about 120 g of solution. The solution was warmed to approximately 40°C with constant agitation until all the solid was dissolved, filtered through a 0.44-μm filter, and transferred into a jacketed beaker with a rounded bottom connected to a circulating water bath (Model RTE-210, Neslab Instruments, Inc., Newington, NH) set at 25 ± 0.1°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 stirrer paddle. The angular velocity was measured with an optical tachometer (model 8211, Cole-Parmer Instrument Co., Chicago, IL). The size distribution 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.

The dependence of growth rate on supersaturation was studied at a constant agitation rate of 460 rpm 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 is the concentration at equilibrium. The supersaturation range studied was 0.015 to 0.10. The effect of the agitation rate on the growth rate was studied at a constant supersaturation value of 0.025, at 25°C, and at various angular velocity values (135, 260, 460, and 900 rpm).

Effect of Additives on Growth Kinetics

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).

In order to obtain information about the effect of L-phenylalanine and L-leucine on the growth mechanism, 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, was measured. The additive concentrations were 0.01% (w/w) for L-phenylalanine and 0.125% (w/w) for L-leucine.

RESULTS

The solubility of L-alanine in 2.5 M $(NH_4)_2SO_4$ at 25°C is 0.1110 g of L-alanine per gram 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. As shown in Fig. 2, during the initial 20 min of batch crystallization the decrease of L-alanine concentration is very small. The cumulative-number distributions, Fig. 1, show a constant shift in size during the same period of time. Thus, the initial growth rate was evaluated as the average displacement in the cumulative distributions measured during the time for which the supersaturation change was negligible. More specifically, 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. 3. Each value represents the average growth rate from an experiment. Figure 4 shows that the growth rate of L-alanine is independent of the rate of agitation. The effect of additives on the growth rate of L-alanine is shown in Figs. 5 and 6, for L-phenylalanine and L-leucine, respectively. Where η is the ratio of the growth rate observed in the presence of the additive at a given molar fraction χ, to the growth rate measured in the absence of additive at the same conditions ($\sigma = 0.025$, $G = 0.47$ μm/min). In Fig. 7 the growth rate of alanine crystals is presented as a function of supersaturation at constant concentration of the two additives.

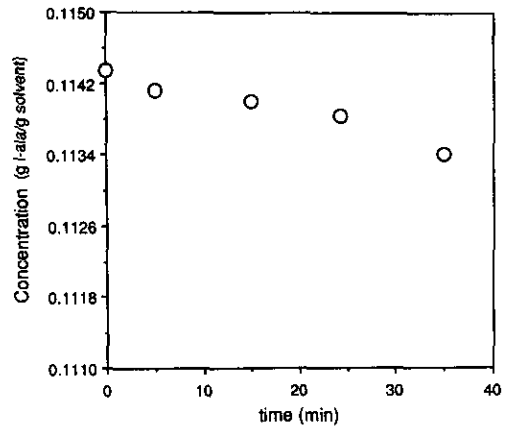

FIG. 2. Concentration of L-alanine in solution during batch crystallization from 2.5 M $(NH_4)_2SO_4$ in water, $\sigma = 0.030$, 460 rpm, 25°C.

DISCUSSION

Growth Kinetics

In order to characterize the crystallization kinetics 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. 3, which clearly suggests a linear dependence of crystal growth on supersaturation. Crystallization is a phase transformation process that can be limited either by the diffusion of the molecules through the bulk of the solution to get to the surface of the solid phase or by the integration of molecules into the crystal lattice. It is possible to draw conclusions on

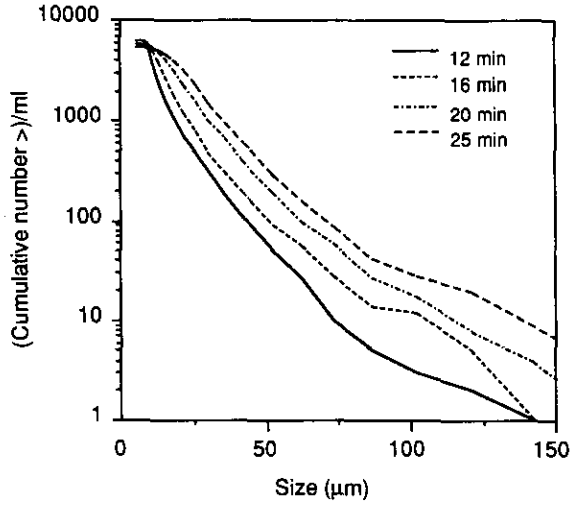

FIG. 1. Cumulative number density size distribution. L-alanine batch crystallization in 2.5 M $(NH_4)_2SO_4$, $\sigma = 0.030$, 460 rpm, 25°C.

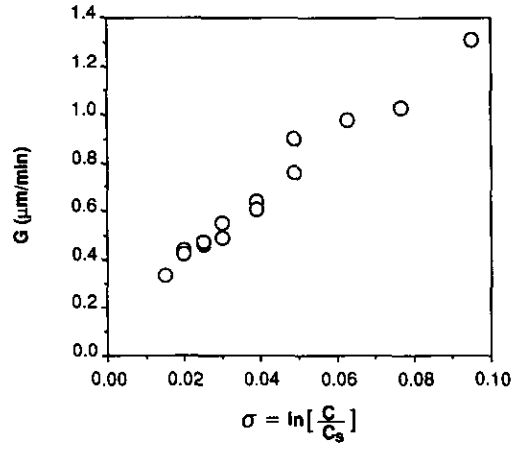

FIG. 3. Dependence of growth rate on supersaturation. Growth rates of L-alanine crystals in 2.5 M $(NH_4)_2SO_4$ at 25°C and 460 rpm.

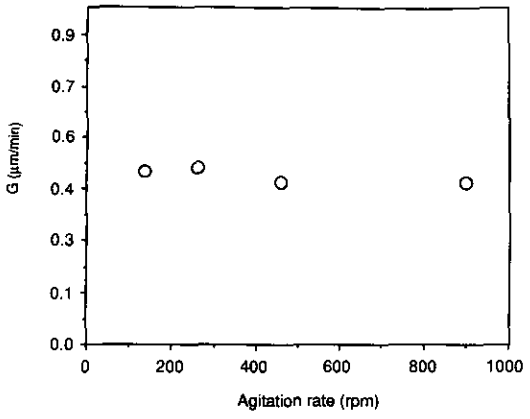

FIG. 4. Effect of agitation rate on the growth rate of L-alanine crystals in 2.5 M $(NH_4)_2SO_4$ at 25°C.

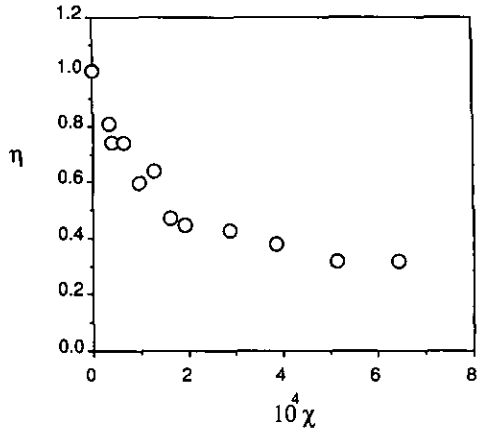

FIG. 6. Effect of L-leucine on the growth rates of L-alanine crystals from batch crystallization in 2.5 M $(NH_4)_2SO_4$ at σ = 0.025, 25°C, 460 rpm.

the growth mechanism from the growth rate dependence on supersaturation. However, since the growth mechanism is surface specific, i.e., the growth of different faces in the same crystal may be governed by a different mechanism, only general conclusions can be inferred from average growth rates obtained from CSD measurements. Based on the models described in the literature (15, 16) the linear behavior of $G(\sigma)$ can be explained as follows.

If the growth kinetics is limited by diffusion it follows that

$$G = DV_mC_s\sigma/\delta, \qquad [1]$$

where G is the growth rate, V_m is the molar volume, D is the diffusion coefficient, σ is the supersaturation, C_s is the solubility, and δ is the diffusion layer thickness. A reasonable value for δ is between 10–100 μm (17). To test the validity of Eq. [1] in our system, δ was calculated using the value of the slope of $G(\sigma)$, 1.87×10^{-5} cm/s, obtained from linear regression (slope = 2.02, intercept = 0.18, r^2 = 0.97), the experimentally determined solubility value, and the values found in the literature for V_m and D.

The L-alanine solubility in the crystallization solvent was determined to be 0.0014 mol/cm^3 at 25°C, the molar volume is 60.5 cm^3/mol (18), and the diffusion coefficient for L-alanine in a 0.036 M solution in water at 25°C is 9.1×10^{-6} cm^2/s (19). A value of δ of 412 μm is found, which is four times greater than the largest δ expected. This discrepancy can hardly be attributed to a change in D due to the concentration of L-alanine (1.4 M) and the viscosity of the system that we studied. This suggests that the crystal growth of L-alanine is not diffusion controlled. In addition, from the results presented in Fig. 4 it can be concluded that crystallization experiments described above were conducted in the kinetic regime of growth, where the diffusive resistance of the boundary layer to the supply of crystallizing matter to the surface was much lower than the resistance to integration

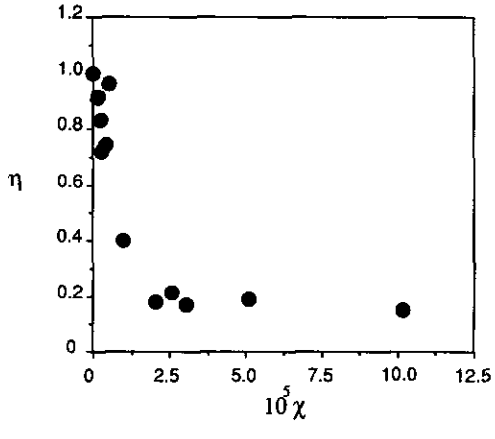

FIG. 5. Effect of L-phenylalanine on the growth rates of L-alanine crystals from batch crystallization in 2.5 M $(NH_4)_2SO_4$ at σ = 0.025, 25°C, 460 rpm.

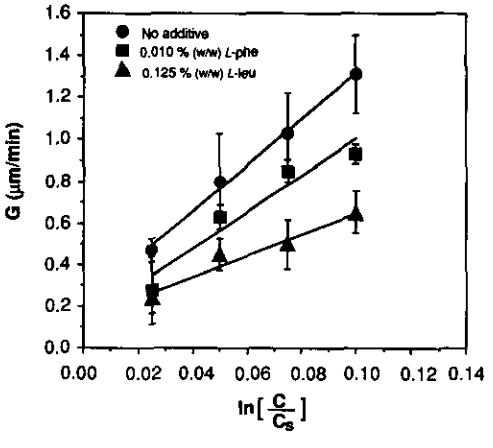

FIG. 7. Dependence of growth rate on supersaturation at constant additive concentration. Growth rates of L-alanine crystals in 2.5 M $(NH_4)_2SO_4$ at 25°C, 460 rpm.

of the growth unit to the surface. Thus, the diffusion controlled mechanism can be disregarded and it can be concluded that the growth of L-alanine is governed by surface integration. In such a case two mechanisms can be considered (15, 16): (a) rough surface and (b) step formation, where the source of steps is spiral growth (20) or surface nucleation. Additional experiments on L-alanine single crystals are currently being conducted in order to determine the growth mechanism that describes the growth of L-alanine crystals.

Effect of Additives on the Growth Kinetics

The influence of additives on L-alanine growth rate is presented in Figs. 5 and 6. Addition of 0.01% (w/w) of 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 ($\eta = 0.17$), Fig. 5. A drastic change in L-alanine's habit is observed in the presence of L-phenylalanine which causes L-alanine crystals to become plate-like. Nucleation is also affected by the presence of the additive. An increase in additive concentration decreases the total number of crystals obtained.

In the presence of 0.15% (w/w) of L-leucine ($\chi_{leu} = 2 \times 10^{-4}$) the growth rate is reduced to a limiting value of 0.13 μm/min ($\eta = 0.28$), equivalent to 40% of the growth rate of the reference system, Fig. 6. A further decrease is not expected since the crystallization solvent is almost saturated with L-leucine, whose solubility in the crystallization solvent is 0.55% by weight. A change in habit is also promoted by the presence of L-leucine, albeit not as pronounced as that promoted by L-phenylalanine. L-alanine crystals grown in the presence of these additives are elongated plates.

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 merely physical since no covalent bonding is expected to occur in this system. The kind of interactions expected to occur are hydrogen bonding, van der Waals, and dispersion.

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 additive adsorption onto the crystal faces.

Since the growth rate from CSD measurements represents an overall value and the growth mechanism is related to a given crystal face, identification of the mechanism has not been done. However, the fact that the shape of the different $G(\sigma)$ remains linear in the presence of a constant amount of additive in solution, as shown in Fig. 7, suggests that the growth mechanism is not being altered by the presence of the additive. The growth rate mechanism of the L-alanine crystal faces to determine the additive/host interaction on the various crystal faces is currently under investigation.

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 (23). 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 on any type of adsorption site of the surface has been used to determine the adsorption sites. 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 (24),

$$V_a = V_{max} - (V_{max} - V_{min})\theta, \qquad [2]$$

where V_a is the velocity of advance of the step in the presence of additive, V_{max} the velocity in the absence of the additive, V_{min} the limiting velocity in the presence of additive, and θ the degree of coverage given by the adsorption isotherm between the additive and the solute as the substrate. Equation [2] can be rearranged as

$$(1 - \eta)/(1 - \eta^0) = \theta, \qquad [3]$$

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 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. [3] can be rewritten as

$$(1 - \eta)/(1 - \eta^0) = b\chi/(1 + b\chi) \qquad [4a]$$

$$(1 - \eta^0)/(1 - \eta) = 1 + 1/(b\chi) = 1/\theta, \qquad [4b]$$

and a plot of $(1 - \eta^0)/(1 - \eta)$ vs $1/\chi$ should render a straight line, Figs. 8a and 8b. The value of b, the Langmuir constant, is the reciprocal value of the slope. 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. Table 1 shows the values for ΔG_{ads}. The intercept value obtained from the fit of this model to explain the inhibitory effect of both L-leucine and L-phenylalanine is not significantly ($p < 0.05$) different from 1, as predicted by the Bliznakov–Langmuir model, Eq. [4b]. The values obtained for the total energy of adsorption are in the order of magnitude expected for the interactions that occur at the crystal/liquid interface (25). It is important to note that Eq. [4b] is just one of various forms in which Eq. [4a] can be written to yield a linear function. In addition to [4b] we have tested three alternative forms of Eq. [4a] to determine ΔG_{ads}. The values of ΔG_{ads} determined were in agreement to the ones obtained from Eq. [4b].

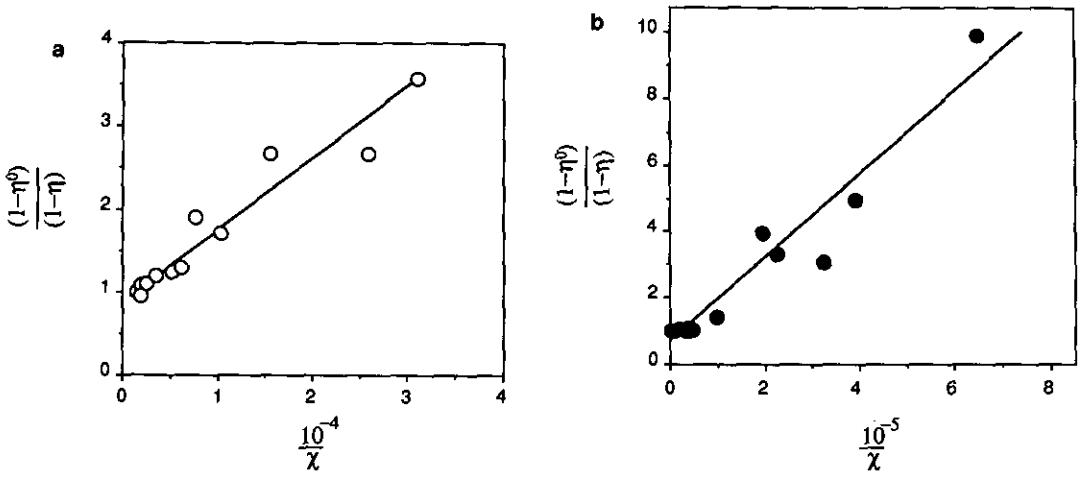

FIG. 8. Effect of (a) L-leucine and (b) L-phenylalanine on the growth rates of L-alanine crystals from batch crystallization in 2.5 M $(NH_4)_2SO_4$ at σ = 0.025, 25°C, 460 rpm. Values are according to Bliznakov's model assuming a Langmuir isotherm (Eq. [4b]).

Growth rates and surface coverage of L-alanine in the presence of both L-leucine and L-phenylalanine have been calculated, using the parameter values of the Langmuir model, Eq. [4a], Fig. 9. The fit is good; however, in both cases the surface coverage is underestimated, i.e., the growth rates are overestimated, in the shoulder portion for L-alanine in the presence of L-phenylalanine and in the final portion for L-alanine in the presence of L-leucine. This lack of fit is implicit in the choice of the Langmuir model, since it assumes a homogeneous surface which may not be the case for the growing crystal. The heterogeneous character of a growing surface has been recognized earlier (26). There are three different types of sites available for adsorption of the additive onto the growing surface: kink, step, and terrace. Attachment of the additive to any of these sites will result in a different adsorption energy, depending on the number of bonds that can be formed between the additive molecule and the crystal surface. Therefore, when using the Langmuir isotherm, in the case of L-phenylalanine the population of sites of higher energy is underestimated. In the case of L-leucine the distribution of sites of lower energy is underestimated.

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 (21, 22). 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 and by the presence of hydrophobic groups and it is decreased by the presence of hydrophilic groups in the amino acid molecule.

SUMMARY

Even though the activity of the host molecule is not appreciably changed, the presence of additives, whose structure is similar to that of the host molecule, greatly affects its growth rate. The extent of the inhibitory effect can be related to the adsorption capacity of the given additive onto the surface of the growing solute. The effect of additive adsorption on the

TABLE 1
Linear Regression Parameters Obtained for the Growth Rate Dependence on the Additive Concentration According to the Bliznakov–Langmuir Model, Eq. [8b]

System	Slope	Intercept	r^2	b	ΔG_{ads} (kcal mol^{-1})
L-ala/L-leu	8.28×10^{-5}	0.91	0.93	1.2×10^4	−5.6
L-ala/L-phe	1.06×10^{-5}	0.69	0.93	9.4×10^4	−6.8

Note. 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.

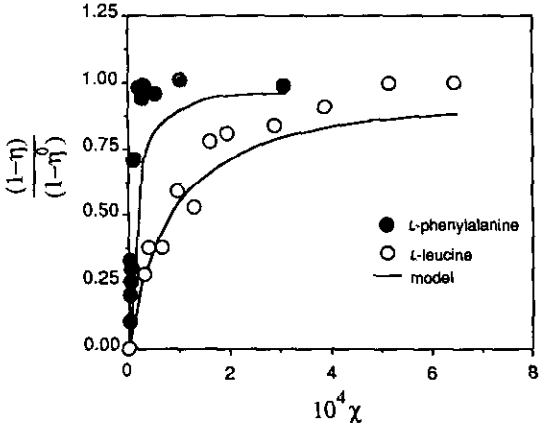

FIG. 9. Effect of L-leucine and L-phenylalanine on the growth rates of L-alanine crystals from batch crystallization in 2.5 M $(NH_4)_2SO_4$ at σ = 0.025, 25°C, 460 rpm. Values according to the Bliznakov's model assuming a Langmuir isotherm (Eq. [4a]).

crystallization kinetics is explained by a Langmuir isotherm. The difference in the extent of the inhibitory effect observed for the two additives studied is explained by considering different adsorption capacities due to the functional groups present.

ACKNOWLEDGMENTS

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