Effects of Isomorphic Compounds on the Purity and Morphology of L-Isoleucine Crystals

Hannia Canossa Koolman and Ronald W. Rousseau
School of Chemical Engineering, Georgia Institute of Technology, Atlanta, GA 30332

L-Isoleucine and the isomorphic amino acids L-leucine and L-valine serve as a model system in the examination of the effects of impurities on the purity and morphology of crystals recovered from batch crystallizations. Factors are determined that influence crystal purity and, concomitantly, crystal size and shape. Characteristics of the L-isoleucine crystal are determined by X-ray analysis and compare favorably with the literature. These and literature characteristics of L-leucine and L-valine are used in simulations to evaluate possible mechanisms by which lattice substitutions with impurities lead to size and morphological changes.

Introduction

The morphology of a crystalline product is acknowledged as a factor of great importance in determining product properties and several of the operations associated with crystal recovery by filtration or centrifugation and subsequent handling. Although the primary function of crystallization may be separation and/or purification, the relationship between purity and morphology is poorly explored. When the solution from which the primary solute is being recovered also contains compounds having a molecular structure similar to that of the primary product, the relationship can be unavoidable.

Morphological characteristics associated with crystal shape (habit) are determined by relative growth rates of the crystal faces; the slower the growth rate, the more pronounced the face. An important phenomenon associated with crystal growth is the capacity of some impurities to affect the growth rate and, thereby, to modify the shape of a crystal. Although the work of many researchers in this field could be cited, that of Lahav and coworkers (Addadi et al., 1982, 1983; Berkovitch-Yellin et al., 1985; Lahav and Leiserowitz, 1990) is especially significant with respect to the present study. They developed a general method for the controlled modification of the morphology of organic crystals through the use of "tailor-made" additives. These substances consist of two parts, one that is similar to the crystallizing species and fits into the primary crystal lattice and another that emerges from the crystal surface to interfere with the regular deposition of oncoming crystal layers. The result is retardation of growth of the affected face.

Batch crystallization of L-isoleucine (L-Ile) in the presence of small amounts of L-leucine (L-Leu) and L-valine (L-Val) was chosen as a model system in the present study. The common groups at one end of the molecules, coupled with differences in the hydrocarbon chains of the amino acids at the other end, make this system ideal for the study of the role of isomorphous impurities in determining structure and morphology of organic crystals. The system is also important from an industrial point of view; L-isoleucine is an essential amino acid widely used as a food additive and as an active ingredient in medicinal preparations. It is synthesized by fermentation and separated and purified by crystallization from solutions containing L-Leu and L-Val, which are also formed in the fermentation.

Earlier research (Zumstein et al., 1990) showed the influence of solution composition and mixing on crystal purity. In the present work, the direct relationship between solution and crystal impurity was observed again; as the concentration of L-Leu and/or L-Val in the initial solution increased, so did the presence of these impurities in recovered L-Ile crystals. Furthermore, L-Leu was incorporated by a factor of 3 or 4 times the incorporation of L-Val. The present work uses these results as a point of departure and addresses the size and shape of recovered L-Ile crystals. The study is composed of (a) experiments performed in a batch crystallizer in a manner consistent with the industrial processing of L-Ile; (b) supporting experiments geared to isolate specific phenomena; and (c) calculations intended to rationalize the experimental ob-

---

Correspondence concerning this article should be addressed to R. W. Rousseau.
Present address of H. C. Koolman: Ciba Geigy Corporation, P.O. Box 113, McIntosh, AL 36553.

servations. It will be shown that the impurities behave like tailor-made additives, and conclusions drawn rely on theories developed for such species.

Equipment and Procedures

Batch crystallizations performed in this study were conducted in 600-mL, jacketed, glass vessels equipped with covers to minimize evaporation and contamination from the environment. Calibrated stirrer plates along with a magnetic bar were used to provide mixing. A water bath was used to control the temperature of the crystallizer within ±0.1°C of the set point, and a constant cooling rate of 1.0°C/min was used in all experiments.

Predetermined amounts of L-Val and/or L-Leu were added to the crystallizing system of L-Ile in water. The amino acids were obtained from a commercial source and were used without further purification. Two sets of experiments at impurity levels ranging between 0.01 and 0.1 mol of L-Leu/mol L-Ile were conducted at stirrer speeds of 470 rpm and 160 rpm.

The initial mixture containing 4.29 g L-Ile/100 g H_2O was heated to 70°C and kept at this temperature until the solution was completely clear. After dissolution, the stirrer speed was set at the desired value and the temperature reduced to 30°C. The solubility of L-Ile in water at this temperature is 3.6 g L-Ile/100 g H_2O (Zumstein and Rousseau, 1989). As the initial charge contained 350 g H_2O, approximately 2.45 g of the initial L-Ile was expected to crystallize. The system was maintained at 30°C for 15 to 20 hours, the agitators were stopped, and a 2-qualitative-Whatman filter with a particle retention of 8 μm and smooth surface was used to separate the crystals from the mother liquor.

After filtration, the wet crystals were washed six times with a saturated solution of L-Ile in water. The washing time was 1 min and the ratio of wet crystals to solution was about 0.02 g of crystal/g of solution.

Optical microscopy was used to determine crystal size and morphology. The microscope was equipped with a calibrated scale in one of the occulars facilitating such measurements. A high-performance liquid chromatograph (HPLC) was used for amino acid analyses. The column used was a C_{18} Partisphere from Whatman. An orthophthaldehyde (OPA) precolumn derivatization technique was used with L-serine as an internal standard. Further details of the optical microscopy, X-ray, and HPLC instrumentation and procedures are given by Canossa Koolman (1992).

Crystal Size and Shape from Batch Crystallization

Crystal size depends upon a number of factors, all related to the relative rates of nucleation and growth. In industrial crystallizers, however, the key to controlling size is affecting those variables that influence nucleation, and, if significant, crystal breakage. Visual inspection of the product crystals showed that breakage was not significant in the present work.

Agitation and impurity concentration were projected to be important factors in determining crystal size, and a two-factor factorial design was used to evaluate the effect of these variables. All other variables in the batch crystallization operations were held constant. Two sets of 30 crystals each were examined for each batch experiment. The sets were selected randomly from areas of a microscope slide containing approximately 30 crystals. As mentioned earlier, the optical microscope allowed measurement of crystal dimensions. Length, *L*, corresponded to the largest side of the crystal and was parallel to the *b* axis; width, *W*, corresponded to the shortest side and to the edge parallel to the *a* axis. Average lengths and average width-to-length ratios were used to characterize the crystals.

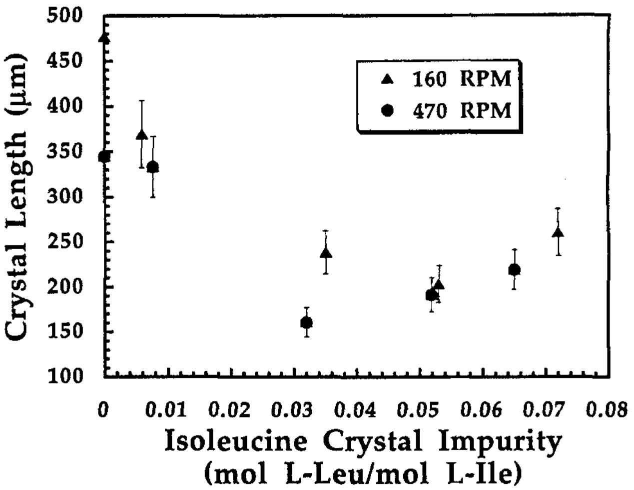


Figure 1. Effect of L-Leu and stirrer speed on L-Ile crystal size.

Samples from two replicates of experiments conducted at three impurity (L-Leu) levels and two stirrer speeds showed that both variables affect crystal size, but there was no interaction between these variables. Figure 1 shows these and additional data, which show qualitatively that the mean crystal length decreased as the impurity concentration within the crystal increased. The crystals had been washed as described earlier, so the impurity content was not associated with the crystal surface only. The major impact on size occurred in an impurity range of about 0.01–0.03 mol L-Leu per mol L-Ile; further increases in impurity had little effect on size. Stirrer speed had, at most, a modest influence on crystal size.

The width-to-length ratio was used as a measured of crystal morphology. Examination of crystals recovered from several experiments showed that agitation had no influence on crystal shape but, as shown in Figure 2, the L-Leu content did. Straight lines fit through the data indicate proportionality between the width-to-length ratio and the impurity content of the crystals; the ratio increased by a factor of about 3 as the impurity content increased ranged from 0 to about 0.07 mol L-Leu per mol L-Ile.

Experiments similar to those just described were performed to determine the effect of valine on crystal size and shape. Results from two replicates of experiments conducted at three impurity levels and two stirring speeds showed that L-Val had no effect on either crystal size or shape. However, L-Val concentrations in the solutions from which L-Ile crystals were recovered corresponded to those found in commercial processes. At these levels, the uptake of L-Val in the L-Ile crystals is minimal (Zumstein et al., 1990) and should not be expected to have significant impact on crystal growth rates.

The effects of the crystallizer were eliminated by performing a series of experiments in which drops of solution, either

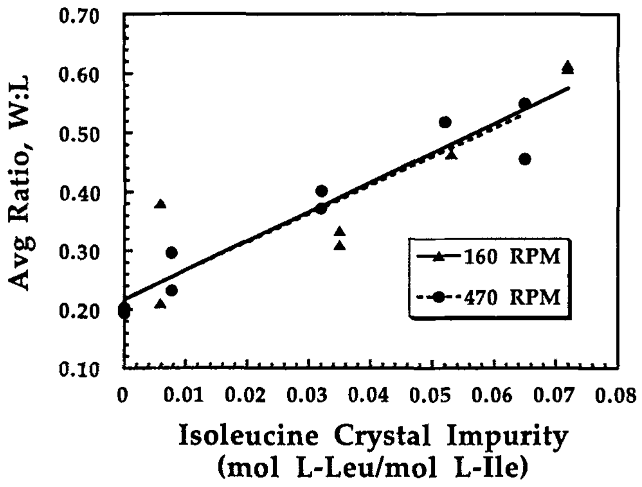


Figure 2. Effect of L-Leu content on the shape of L-Ile crytals.

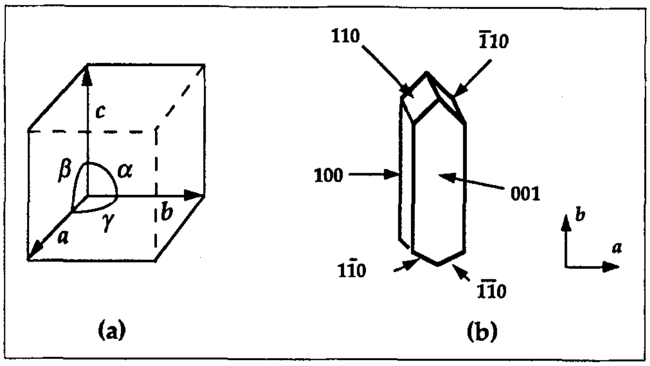


Figure 3. (a) Unit cell definition; (b) L-Ile shape.

free of L-Leu and L-Val or containing a given concentration of these species, were placed on a slide and water allowed to evaporate at room temperature. Photomicrographs of crystals obtained from solutions contaminated with L-Leu showed significant habit modification; there was a transformation from needlelike to hexagonal-blade crystals as the L-Leu content of the solution increased. A mixture of crystals with hexagonal and needlelike habits was observed in crystallization from solutions containing 5 and 10 mol L-Leu/100 mol L-Ile. Furthermore, the fraction of crystals having hexagonal shape increased as the concentration of L-Leu increased.

Photomicrographs of crystals obtained from solutions contaminated with L-Val showed small particles collected around well-formed needlelike crystals. These agglomerates may correspond to individual precipitates of L-Val formed as a consequence of the total evaporation of water from the drops. It is important to note that the presence of pure L-Val crystals was not detected on samples obtained from batch crystallizations.

The following can be concluded from the drop evaporation results: (a) L-Leu significantly modifies the habit of L-Ile from needlelike to hexagonal blade crystals; and (b) L-Val is not incorporated within the bulk of the crystal and, consequently, does not modify the L-Ile crystal habit.

Properties of Pure and Impure Crystals

The influence of impurities on the properties of crystalline products depends on the mechanism of contamination. Of the many possibilities, three means of contamination were dealt with in the present work: (1) If the initial impurity concentration in solution is sufficiently high, pure crystals of the impurities may form and be mixed physically with L-Ile crystals. For example, results from the drop-evaporation experiments in which L-Val was an impurity showed agglomerates believed to be comprised of separate crystals of both species. (2) At all impurity concentrations, the mother liquor can adhere to the crystal surface and contaminate the crystals. Washing of the kind to which the crystals in the present work were subjected is intended to minimize contamination by this mechanism. (3) Similarities between the crystal structures of the solutes (primary species and impurities) can lead to the formation of a mixed crystal. In such instances, the impurity is substituted for the primary species in the crystal lattice. The last mechanism was considered to be most probable and the experiments to be described confirmed its prominence.

Two substances that have similar molecular and crystal structures may form a mixed crystal. Table 1 shows literature values for the lattice constants of the amino acids under study, where a, b, c, α, β, and γ are as shown in Figure 3. The unit cells of the three substances are monoclinic and show corresponding a and b values within ±0.07 and ±0.03, respectively. The unit cell of L-Val is smaller than that of L-Ile, especially along the c axis, and the unit cell of L-Leu has a β angle notably smaller than that of L-Ile. Except for these minor differences, the lattice constants of L-Leu and L-Val closely resemble those of L-Ile, and the formation of mixed crystals is a possibility.

A redetermination of the crystal structure was undertaken in the present research to check the parameters given by Torii and Iitaka (1971). Well-formed L-Ile crystals, $1.09 \times 0.17 \times 0.07$ mm^3, were found of satisfactory quality for intensity measurements. The unit cell was found to be monoclinic with lattice parameters as shown in Table 2. An improved R value of 0.057, as compared to the Torii and Iitaka value of 0.117, was obtained.

As noted by Torii and Iitaka, the L-Ile crystal was found to contain two crystallographically independent molecules, A

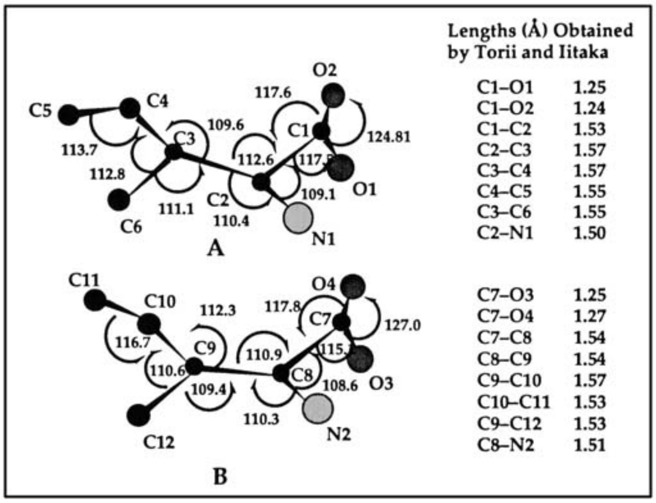
Table 1. Lattice Constants

	a	b	c	α(°)	β(°)	γ(°)
L-Ile	9.75	5.32	14.12	90	95.8	90
L-Leu	9.61	5.31	14.72	90	86.2	90
L-Val	9.71	5.27	12.06	90	90.8	90

Source: Torii and Iitaka (1971).

Table 2. Measured vs. Literature Lattice Parameters for L-Ile

Parameter	This Study	Torii & Iitaka (1971)
a	9.709	9.75±0.02
b	5.2910	5.32±0.02
c	14.018	14.12±0.02
β	95.84°	95.8±0.2°
Volume	716.37 Å^3	723 Å^3
Space group	P21	P21



Lengths (Å) Obtained by Torii and Iitaka

C1–O1	1.25
C1–O2	1.24
C1–C2	1.53
C2–C3	1.57
C3–C4	1.57
C4–C5	1.55
C3–C6	1.55
C2–N1	1.50
C7–O3	1.25
C7–O4	1.27
C7–C8	1.54
C8–C9	1.54
C9–C10	1.57
C10–C11	1.53
C9–C12	1.53
C8–N2	1.51

Figure 4. A and B molecules of L-isoleucine.

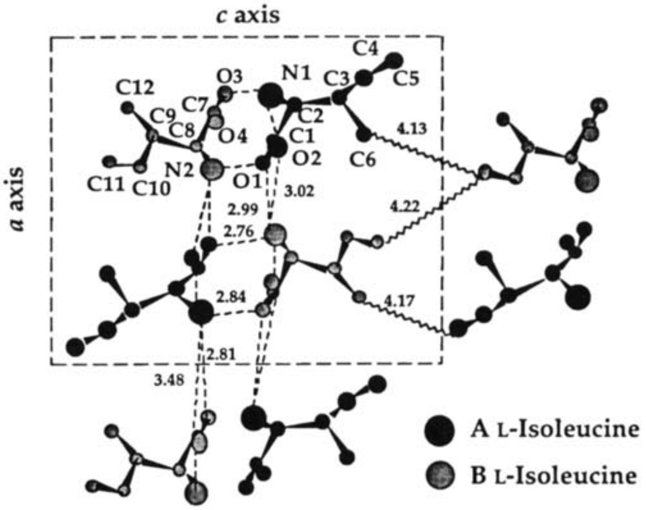


Figure 5. View of the L-Ile structure along the *b* axis.

and B, shown in Figure 4. The unit cell contains 2 A and 2 B molecules, both of which are present in the zwitterionic form and whose main differences are the torsion angles. Molecule A shows a gauche configuration around C_α-C_β, while molecule B shows a *trans* arrangement. Figures 5 and 6 show views of the crystal structure of L-Ile along the *b* and *c* axes, respectively. The A and B molecules are interlinked by N···H···O hydrogen bonds along the *a* axis, which give rise to double layers of molecules. The layers are joined along the *c* axis by weak van der Waals forces. The hydrogen-bond distances range between 2.76 Å and 2.99 Å while the contacts along *c* range between 4.13 Å and 4.22 Å.

According to Figure 6, the linking between two unit cells along the *b* axis is characterized by four strong hydrogen bonds (less than 2.99 Å separation) while only two strong hydrogen bonds are found to link the unit cells along the *a* axis. The primary direction of growth is therefore along the *b* axis, where hydrogen bonds result in the strongest intermolecular forces and most efficient packing. Since the hydrogen bonds present along the *a* axis are stronger than the van der Waals forces found along the *c* axis, growth along *a* should be more rapid than growth along *c*. The crystal is then expected to show a large (001) face with some elongation along *a*. Since the faster growing faces are the smaller ones, the crystal should grow as a needle along *b*.

The morphology of an L-Ile crystal was determined on an X-ray diffractometer by matching the position of a crystal face with a previously determined Miller index. The crystal used to determine the structure was also used in this study. The experimental morphology is shown in Figure 3b. The crystal was formed by the (001), (100), (110), $(1\bar{1}0)$, $(\bar{1}10)$, and $(\bar{1}\bar{1}0)$ faces with the (001) face being the most prominent.

A qualitative powder X-ray diffraction analysis of the structures of pure and contaminated crystals was performed and used to check for two possible mechanisms of impurity contamination: (a) formation of mixed crystals (crystals that contain both L-Ile and L-Leu in their lattices); and (b) precipitation of impurities as separate, individual crystals. Mechanism (b) was not expected since the amounts of impurities present in the solutions were considerably below solubility limits.

High-intensity reflections in the X-ray diffraction spectra (given by Canossa Koolman, 1992) of samples containing 0, 3.5, and 7.2 mol L-Leu/100 mol L-Ile shifted to lower angles as the impurity concentration in the crystals increased. Such behavior indicates an alteration of the crystal lattice, presumably caused by introduction of foreign molecules within the crystal lattice. As the reflections are shifted with increasing L-Leu content, as opposed to the appearance of multiple peaks, it is clear that the impure system corresponds to a modified crystal containing both L-Ile and L-Leu molecules.

A well-formed contaminated crystal having a size of 0.25 mm × 0.25 mm × 0.034 mm was selected for X-ray analysis. Although the quality of the crystal was insufficient to determine the atomic positions from intensity measurements, it was possible to determine the lattice constants with good accuracy. The unit cell was found to be monoclinic and showed the following parameters: $a = 9.70$ Å, $b = 5.37$ Å, and $c = 14.46$ Å, $\beta = 103.11°$. The volume of the unit cell was calculated from the parameters to be 733.58 Å^3. According to these values, the *b* axis of the affected crystal is 0.079 Å longer than that of the pure L-Ile crystal, while the *c* axis of the contaminated crystal is 0.44 Å longer than that of an L-Ile crystal. Significant differences between the unit cell parame-

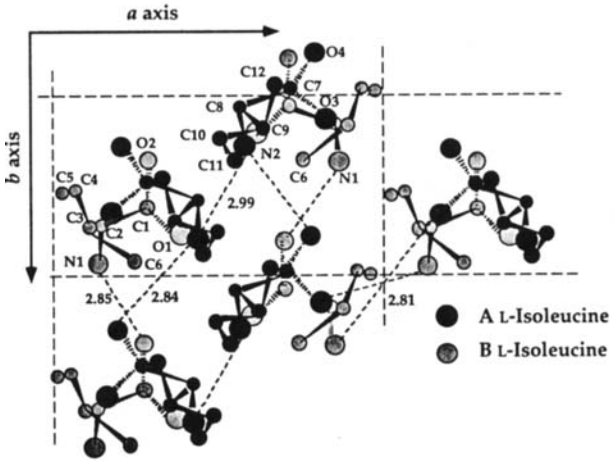


Figure 6. View of the L-Ile structure along the *c* axis.

ters of pure and contaminated crystals are consistent with the powder x-ray diffraction indication of a mixed crystal. As would be expected, the increase of the axes lengths with contamination suggests that the use of space is more efficient in a pure crystal than in a contaminated one.

An estimate of the L-Leu content of the crystal described earlier was determined by selecting between 5 and 10 contaminated crystals with the assistance of a microscope and analyzing them by HPLC. An average impurity mole ratio of 0.13 ±0.01 mol L-Leu/mol L-Ile was obtained from the analysis of six sets of affected crystals; on average, these crystals contain 1 molecule of L-Leu for every 8 molecules of L-Ile.

Simulation of Lattice Substitution by Impurities

Computer simulations were used to examine the molecular orientation of molecules in the impure crystals of L-Ile through the substitution of impurities for L-Ile in the crystal structure. It was shown that L-Leu was attracted selectively toward the surface of the L-Ile crystals, in much the same way an L-Ile molecule would be attracted. Once included in the crystal, however, the L-Leu molecule projects from the surface and sterically hinders further attachment of the more plentiful L-Ile molecules. The resulting decrease in the growth rate of the impure face explains the observed increase in the area of the face and concomitant modification of crystal shape.

As defined by Hartman and Bennema (1980), flat (F) faces that grow layer by layer determine crystal shape. The mechanism by which F faces grow is therefore an important factor affecting crystal morphology. Davey et al. (1986) applied the dislocation theory of growth developed by Burton et al. (1951)—the BCF surface diffusion model—to analyze the kinetics of crystal growth in the presence of tailor-made additives. According to Black et al. (1986), the adsorption of tailor-made additives on crystal surfaces generally occurs on step sites as viewed by the Albon and Dunning (1962) model. In that model, spontaneous fluctuations produce kinks along the entire length of the step. Adsorption of impurities at the step reduces the area for kink formation and provides steric barriers for the entry of new units. If the molecular structures of the substrate and the impurity are similar, the impurity could act as a "pseudokink" by attracting new building units toward the surface.

The Albon and Dunning (1962) model was based on their observations of the growth of sucrose in the presence of raffinose, which may be considered a substituted sucrose molecule. Their experimental data indicated that raffinose acted as a pseudokink with a potential to reduce the step distances and increase the kink sites for adsorption. However, it was shown that the raffinose molecule also provided steric hindrance to sucrose molecules entering the step and, thus, reduced step velocity. Even though L-Ile and L-Leu have similar molecular structures, L-Leu may act as a pseudokink, causing the rates of growth of the affected L-Ile faces to decrease. This indicates that, as for the growth of sucrose in the presence of raffinose, L-Leu molecules cause steric hindrance and affect the regular deposition of oncoming L-Ile layers.

The possibility of steric hindrance as the main factor affecting the growth of L-Ile crystals was examined by using the principles introduced by Berkovitch-Yellin et al. (1985). In the case of crystals of L-Ile, the strong interactions between the group $NH_3^+COO^-$ of the substrate and the molecules at the growing site are expected to lead to the binding of an L-Leu molecule at the surface of a growing crystal, the same way as an L-Ile molecule is attracted. Once the impurity molecule is attached to the crystal surface, it may affect the regular deposition of oncoming L-Ile molecules and, eventually, it becomes a part of the crystal structure. Observation of the modeled structure of a contaminated crystal is then a tool to predict the earlier interactions between L-Leu and L-Ile at the crystal surface.

A simulation program, Plot 3D (Bertrand, 1985), was used to analyze molecular orientations and to calculate distances between immediately adjacent molecules. The flexibility of this program allowed the substitution of impurities within the L-Ile structure and facilitated the present study. The L-Ile crystal structure data from Torii and Iitaka (1969) and the molecular parameters for L-Leu presented by Coll and Font-Altaba (1986) were used to perform the calculations.

As with L-Ile, molecules of L-Leu and L-Val in crystals are usually in two conformations, A and B (Torii and Iitaka, 1971; Coll and Font-Altaba, 1986). While A molecules present a gauche conformation, B molecules show a *trans* conformation about C_α-C_β. The substitution of L-Ile by any of these conformers should be possible, but in this study only the substitution of a B L-Ile molecule by a B L-Leu or a B L-Val molecule was considered.

When an impurity molecule is substituted into a crystal lattice, it disrupts bonds that exist between the lattice units of the pure substance. The greater the bond disruption required, the less likely the substitution becomes. In the present system, the well-formed impure hexagonal crystals consisted of more than 10% L-Leu. When compared to other systems where habit modification is observed at impurity levels of 0.5% (Berkovitch-Yellin, 1985), this percentage is high and indicates that L-Leu exerts only relatively weak interactions. This observation supports the assumption that an L-Leu molecule is included in the crystal lattice in nearly the same manner as L-Ile. The low degree of incorporation observed for L-Val could be the result of strong bond disruption or external effects.

Figure 7 shows the affected crystal structure viewed along the b axis. The L-Leu molecule is positioned so that hydrogen bond distances are unchanged from the pure L-Ile crystal. Under these conditions, the C11 carbon of L-Leu is only

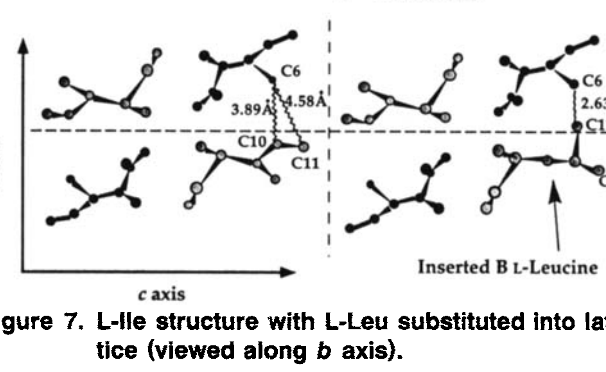


Figure 7. L-Ile structure with L-Leu substituted into lattice (viewed along *b* axis).

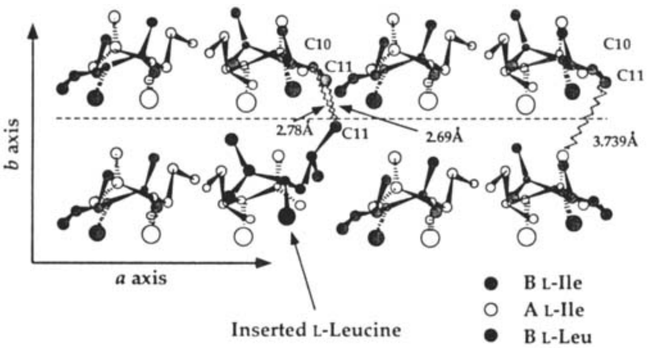


Figure 8. L-Ile structure with L-Leu substituted into lattice (viewed along *c* axis).

2.63 Å along the *a* axis from the C6 carbon of the closest L-Ile molecule. In contrast, the distances between C6 of an A L-Ile molecule and C10 and C11 of a B L-Ile molecule are 3.89 Å and 4.58 Å, respectively. From Kitaigorodsky (1973), the minimum distance between nonbonded carbon atoms is 3.0 Å under normal conditions and 2.9 Å at extreme conditions. When the atoms are closer than this minimum distance, the electron shells begin to overlap, giving rise to strong repulsions that may disrupt the molecular conformations or the crystal structure. The observed carbon–carbon distance of 2.63 Å between L-Leu and L-Ile may, therefore, affect the regular bonding of L-Ile to the crystal surfaces growing perpendicular to the *a* axis.

According to the observations presented previously, crystal growth along the *a* axis should be affected by a decrease in the bonding forces at the crystal surface. However, the experimental observation of affected crystals is not in agreement with this prediction: the growth rate along *a* is hardly affected by the presence of L-Leu. In an amino acid crystal, growth in the *a* and *b* directions is related to the electrostatic forces exerted by the ionic groups on the surrounding building units. A greater attractive force toward the faces growing perpendicular to the *b* axis is observed, as L-Ile crystals grow 5 times faster in the *b* direction than along the *a* axis. A foreign amino acid molecule is expected to behave as an L-Ile molecule and, therefore, should be selectively attracted toward the *b* faces. This observation is in agreement with the fact that the *b* faces are the ones most affected by the impurity.

Figure 8 shows the crystal structure of L-Ile viewed along the *c* axis, and with a B L-Leu molecule inserted for a B L-Ile molecule. The distances between C11 of the L-Leu molecule and C10 and C11 of an adjacent L-Ile molecule are 2.78 Å and 2.69 Å. Again, these distances are less than the minimum C···C spacing (3.0 Å), and strong repulsions may result in a decrease in the growth rates of faces growing perpendicular to the *b* axis.

Introduction of an L-Leu molecule on the (110) surface of an L-Ile crystal results, as shown in Figure 8, in an L-Leu segment containing C11 that is directed out from the crystal surface and blocking an incoming L-Ile molecule, thereby retarding growth of the (110) face. Examination of pure and contaminated crystals shows that the relative areas of the (110) faces are greater for impure crystals, which is consistent with a reduction in growth rates of those faces.

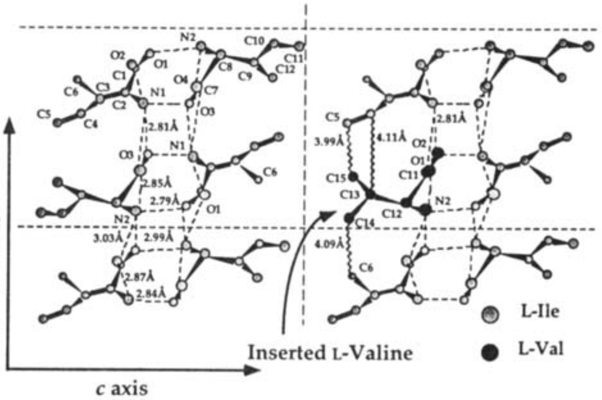


Figure 9. L-Ile structure with L-Val substituted into lattice (viewed along *b* axis).

As determined from the drop-evaporation tests and from the analysis of crystals obtained from batch crystallizers, L-Val does not modify the habit L-Ile crystals. This may be due to the degree of incorporation of L-Val being rather low, especially in comparison to that of L-Leu. However, depending on the effect of the impurity molecule on the crystal structure, even small amounts of an impurity could give rise to significant habit modifications. The potential role played by an L-Val molecule in the crystal structure of L-Ile was examined using the same methods used for L-Leu.

Figure 9 shows the structure of a crystal contaminated with L-Val as viewed along the *b* axis. As described for L-Leu, the molecule was substituted so that the hydrogen bonding was consistent with the unit cell and the modified distances were calculated. The shortest carbon–carbon spacings between the tail carbons of L-Val and those of adjacent L-Ile molecules, 3.99 Å and 4.09 Å, are greater than the minimum spacing (3 Å), which eliminates the possibility of repulsion forces along the *a* axis.

Figure 10 illustrates the crystal structure along *a*. The distance between C15 of L-Val and C11 of the immediate

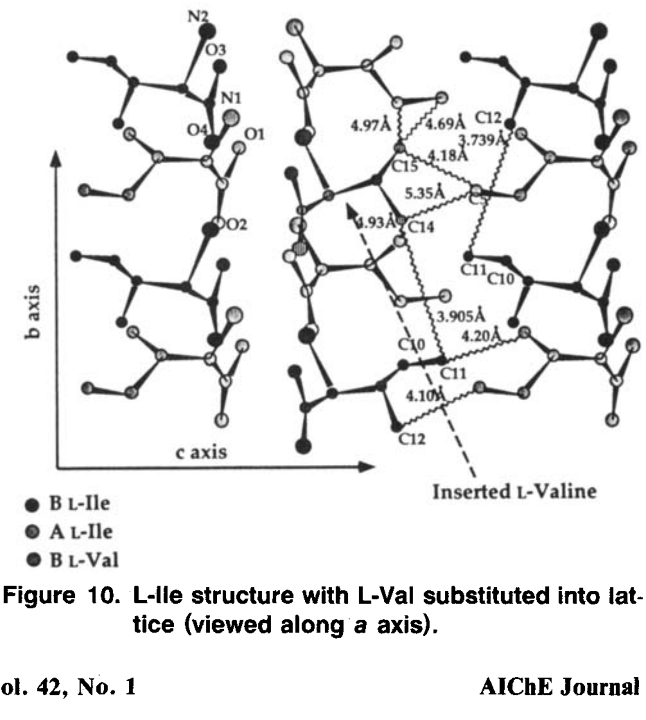


Figure 10. L-Ile structure with L-Val substituted into lattice (viewed along *a* axis).

molecule along *b* is 3.91 Å, whereas the distance between the C12 carbon of an unsubstituted L-Ile molecule and C11 of the closest B L-Ile molecule is 3.74 Å. The increase in the bond distances upon substitution eliminates the probability of steric hindrance along the *b* axis. Also, the carbon–carbon distances along the *c* axis vary from 4.1 Å before substitution to 4.18 Å after substitution. This fact clearly shows that L-Val has a minimum effect on the crystal structure of L-Ile.

The behavior observed for the system L-Ile/L-Val is not completely explained by using the present method of analysis. The small effect of L-Val on crystal habit is rationalized, but the method does not explain why L-Val is so moderately incorporated in the crystal structure. It would seem that since L-Val does not affect the crystal packing to a significant extent, a high degree of contamination would occur.

Conclusions

The present work shows that the size and morphology of recovered L-Ile crystals depend upon their purity, which in turn depends on solution composition and crystallization kinetics. Once incorporated onto the surface of a growing L-Ile crystal, both L-Val and L-Leu molecules have the potential of altering crystal morphology. However, experimental results showed that L-Leu exhibited such behavior but L-Val had little impact. Modeling the crystal growth showed that the steric hindrance associated with substituting an L-Leu molecule into the L-Ile lattice brings carbon atoms in adjacent layers along the *b* axis into very close proximity, causing repulsion of an oncoming crystal layer. The L-Val structure does not introduce such problems. The generated conditions cause a reduction of growth in the *b* direction and lead to modification in crystal shape. Such behavior is directly analogous to that expected in the presence of tailor-made additives.

Acknowledgments

Financial support of the National Science Foundation through award number 8722281 is acknowledged gratefully. Amino acids were provided graciously by Ajinomoto USA. J. Aaron Bertrand of the School of Chemistry at Georgia Tech was especially helpful with his advice and assistance with the program Plot 3D.

Literature Cited

Addadi, L., Z. Berkovitch-Yellin, N. Domb, E. Gati, M. Lahav, and L. Leiserowitz, "Resolution of Conglomerates by Stereoselective Habit Modifications," *Nature*, **296**, 21 (1982).

Addadi, L., Z. Berkovitch-Yellin, I. Weissbuch, M. Lahav, and L. Leiserowitz, "Morphology Engineering of Organic Crystals with the Assistance of 'Tailor-Made' Additives," *Mol. Cryst. Liq. Cryst.*, **96**, 1 (1983).

Albon, N., and Dunning, W. J., "Growth of Sucrose Crystals: Determination of Edge Energy from the Effect of Added Impurities on Rate of Step Advance," *Acta Crystallog.*, **15**, 474 (1962).

Berkovitch-Yellin, Z., "Toward an ab Initio Derivation of Crystal Morphology," *J. Amer. Chem. Soc.*, **107**, 8239 (1985).

Berkovitch-Yellin, Z., J. van Mil, L. Addadi, M. Idelson, M. Lahav, and L. Leiserowitz, "Crystal Morphology Engineering by Tailor-Made Inhibitors: A New Probe to Fine Intermolecular Interactions," *J. Amer. Chem. Soc.*, **107**, 3111 (1985).

Bertrand, J. A., "Plot 3D: Three Dimensional Modeling of Crystal and Molecular Structures," School of Chemistry, Georgia Institute of Technology, Atlanta (1985).

Black, S. N., R. J. Davey, and M. Halcrow, "The Kinetics of Growth in the Presence of Tailor Made Additives," *J. Cryst. Growth*, **79**, 765 (1986).

Burton, W. K., N. Cabrera, and F. C. Frank, "The Growth of Crystals and the Equilibrium Structure of Their Surfaces," *Phil. Trans.*, **A243**, 299 (1951).

Coll, M., and Font-Altaba "Structure of L-Leucine: A Redetermination," *Acta Crystallog.*, **C42**, 599 (1986).

Canossa Koolman, H., "Effect of Impurities and Agitation on Purity, Size, and Morphology of L-Isoleucine Crystals Obtained from Batch Crystallizers," MS Thesis, Georgia Inst. of Technol., Atlanta (1992).

Davey, R., W. Fila, and J. Garside, "The Influence of Biuret on the Growth Kinetics of Urea Crystals from Aqueous Solutions," *J. Cryst. Growth*, **79**, 607 (1986).

Hartman, P., and P. Bennema, "The Attachment Energy as a Habit Controlling Factor: III," *J. Cryst. Growth*, **49**, 145 (1980).

Kitaigorodsky, A. I., *Molecular Crystals and Molecules*, Academic Press, New York (1973).

Lahav, M., and L. Leiserowitz, "Tailor-Made Auxiliaries for the Control of Nucleation, Growth and Dissolution of Crystals," *Proc. Symp. on Industrial Crystallization*, A. Mersmann, ed., Garmish-Partinkirchen, Germany (1990).

Torii, K., and Y. Iitaka, "The Crystal Structure of L-Isoleucine," *Acta Crystallogr.*, **B27**, 2237 (1971).

Zumstein, R. C., and R. W. Rousseau, "The Influence of Surfactants on the Crystallization of L-Isoleucine," *Ind. Eng. Chem. Res.*, **28**, 334 (1989).

Zumstein, R. C., T. Gambrel, and R. W. Rousseau, "Factors Affecting the Purity of L-Isoleucine Recovered by Batch Crystallization," *Crystallization as a Separations Process, ACS Symp. Ser., 438*, A. S. Myerson and K. Toyokura, eds., p. 85 (1990).

Manuscript received July 21, 1994, and revision received Feb. 8, 1995.