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USE OF "TAILOR-MADE" ADDITIVES FOR THE STUDY OF DISORDER IN CRYSTALS. APPLICATION TO THE RACEMIC COMPOUND OF VALINE.

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We dedicate this article to the memory of Prof. Mendel D. Cohen, our mentor, colleague and friend.

Abstract The packing disorder in racemic valine is characterized by techniques previously used to control nucleation, growth, and dissolution of crystals. *R,S*-valine crystals were grown and dissolved in the presence of other racemic α-amino acid additives. We inferred the presence of disorder in *R,S*-valine crystals from the lack of enantiomeric segregation of the additives occluded inside growing crystals, and from the non-specific etch-pit formation on the faces of dissolving crystals. Subsequent X-ray diffraction studies showed the disorder to arise from "flipping" of hydrogen-bonded bilayers across interfaces which are linked by relatively weak hydrophobic interactions. Possible mechanisms for the disorder are discussed.

1. INTRODUCTION.

Recent studies from our laboratory have demonstrated that it is possible to control nucleation, growth and dissolution of crystals with the assistance of "tailor-made" auxiliary molecules[1]. This methodology has led to the design of surfaces for oriented crystallization of both organic[2] and inorganic[3] materials at interfaces, to the ability to monitor crystal morphology[4], crystal polymorphism[5], and to the design of etchants for a given face of a crystal[6]. We wish to demonstrate here that this method is also applicable for the study of disorder in crystals. We illustrate this approach with racemic valine.

1.1 Packing arrangements of the racemic α-amino acids.

Many racemic α-amino acids such as valine[7], leucine[8], and isoleucine[9] have common structural features with the α-form of glycine[10]. These molecules crystallize in triclinic or monoclinic centrosymmetric space groups which incorporate bilayer-stacked structures (Fig. 1). Within each single layer

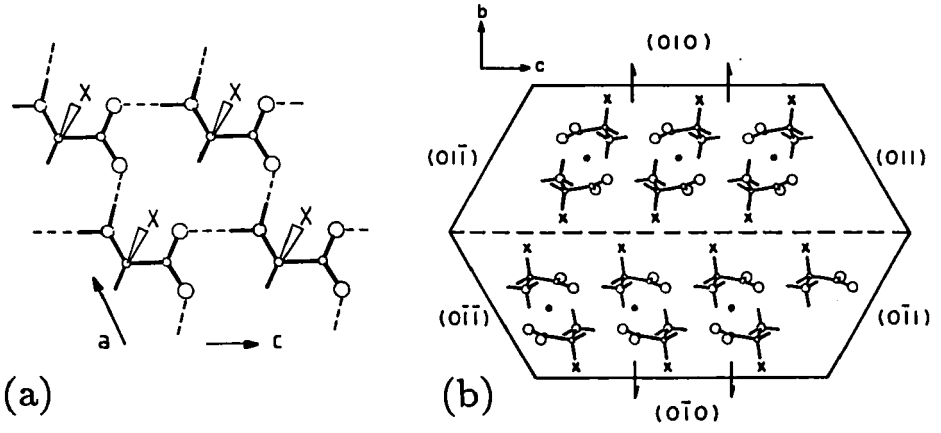

FIGURE 1. Packing arrangement of hydrophobic α-amino acids. X = hydrocarbon chain for valine[7], leucine[8], etc. X = H for glycine[10]. (a) An *ac* layer of hydrogen-bonded molecules viewed along the *b*-axis. The molecules are related by translation. (b) A view along the *a*-axis shows the hydrogen-bonded bilayers edge-on. The layers are related by center-of-inversion symmetry, and the bilayers are stacked by glide symmetry. The crystal faces of α-glycine are delineated. Symmetry elements are shown.

molecules are related by translation, forming homochiral layers. Each such layer interacts with another of opposite chirality via strong electrostatic hydrogen-bonding interactions. In some crystal systems the bilayers are related by translation and in others, by glide symmetry. Adjoining bilayers are related to one another by weak hydrophobic interactions. These crystals generally express faces parallel to the bilayer. Their surfaces are chiral so that the two opposite faces are related by a center-of-inversion and are thus enantiotopic[11] (see Fig. 1b).

The crystal structures of such racemic centrosymmetric systems may be regarded as enantiopolar, namely the crystal consists of two enantiomeric sets of intermeshed polar arrangements related to each other by a center-of-inversion. For an enantiomeric set composed of, say, *R* molecules, a functional group attached to the molecule which points toward the face fl (for instance, group W in Fig. 2) does not point toward the opposite face f$\bar{1}$. By symmetry, the same group attached to an *S* molecule in the other

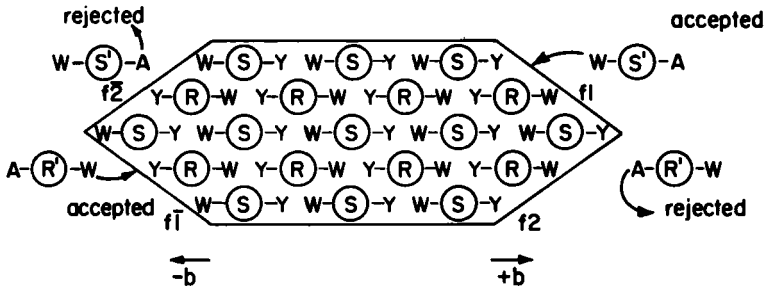

FIGURE 2. Schematic drawing of an enantiotopic crystal. Additive *R'* may be occluded only at face f1 where the modified moiety (A) points away from the crystal surface, and rejected from the enantiotopic face f1 where the moiety A points towards the crystal bulk.

enantiomeric set will emerge at the enantiotopic face f1, but not at f1. In *R,S*-valine, the C_α-C_β bond of all *R*-valine molecules point to the $+b$ direction, whereas the same bond for *S*-valine molecules point to the $-b$ direction of the crystal. The concept of enantiopolarity is not confined to racemic systems. For instance, the molecules of α-glycine assume a chiral conformation in the crystal (centrosymmetric monoclinic, $P2_1/n$) whose packing is shown in Fig. 1, and so we may regard all molecules related by translation or 2_1 axes as forming an enantiomeric set. For further discussion of enantiopolarity, see reference 1(b).

In previous studies on α-glycine crystals we have shown that such an enantiopolar system displays the following phenomena:

(a) Oriented stereospecific growth at the air-solution interface in the presence of soluble or insoluble amphiphilic α-amino acid monolayers[2].

(b) When dissolved in the presence of enantiomerically pure α-amino acids, these crystals display enantioselective etching on specific faces[6].

(c) The enantiomers of soluble *R,S*-α-amino acids, which are present as additives in the crystallizing solution, are segregated upon occlusion through the opposite enantiotopic faces of the growing crystals of α-glycine[12].

We extended these studies to *R,S*-valine, whose crystal structure is similar to that of α-glycine[10]. The crystals are well-formed thick hexagonal platelets. Growth and dissolution experiments, as well as additional X-ray diffraction results, proved the *R,S*-valine crystals to be disordered. From the results we were able to identify and characterize the type of disorder found in these crystals.

2. TAILOR-MADE ADDITIVES USED TO CHARACTERIZE PACKING DISORDER.

2.1 Valine growth under Langmuir films of chiral resolved α-amino acids.

Recent work from this laboratory has shown that floating Langmuir monolayers of enantiomerically pure α-amino acid amphiphilic molecules such as palmitoyl lysine (PL), can induce enantiospecific epitaxial growth of α-glycine crystals, provided that the packing arrangement of the amphiphile head groups is similar to that of the *ac* layer structure of α-glycine[2,13]. For instance (see Fig. 3), if the monolayer spread over a supersaturated aqueous solution of glycine comprises molecules of *S*-configuration, then the growing α-

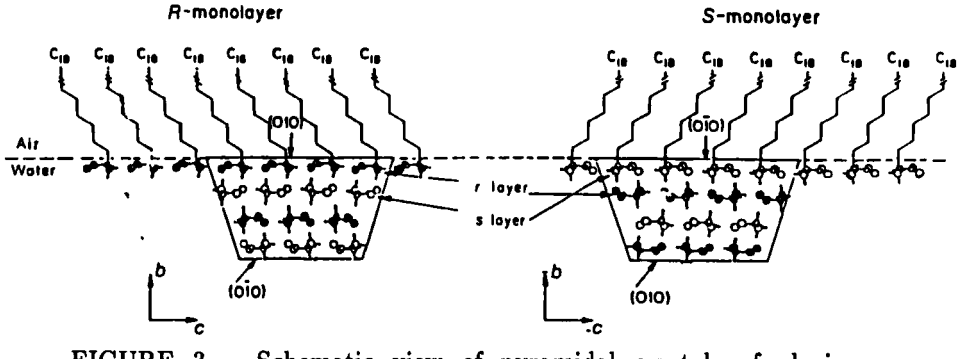

FIGURE 3. Schematic view of pyramidal crystals of glycine grown under compressed *R*- or *S*- α-amino acid monolayers. The (010) face is attached to the *R*-monolayer and the (0$\bar{1}$0) face to the *S*-monolayer.

glycine crystals are attached to the surface only by their (0$\bar{1}$0) faces. By symmetry, when the spread monolayer is composed of molecules of *R*-configuration, then crystals are attached to the surface only by their (010) faces. This can be understood from the packing arrangement of crystalline α-

glycine (see Fig. 1). Glycine molecules are attached to the Langmuir monolayer via pseudo center-of-inversion symmetry, forming the first hydrogen-bonded bilayer of the growing crystal. This provides the observed stereospecificity of the epitaxially grown crystals. Indeed, it has been shown by grazing angle X-ray diffraction that the structure of the polar head groups in a chiral resolved PL monolayer at the air-water interface is very similar to the layer structure of α-glycine at the (010) face[13].

$CO_2^-CH_2(NH_2)(CH_2)_4NHCO(CH_2)_{14}CH_3$	PL
$CO_2^-CH_2(NH_2)(CH_2)_nCOO(CH_2)_{17}CH_3$	SAA n=1 SGA n=2

For *R,S*-valine crystals, in spite of the fact that the Langmuir α-amino acid monolayers induced nucleation of the crystals attached at the platelet {010} faces, any enantiospecific preference for either the (010) or ($0\bar{1}0$) faces could not visually be discerned.

The crystal structures of chiral resolved valine[14], leucine[15], isoleucine[16] and other hydrophobic α-amino acids consist of hydrogen-bonded layers similar to those found in α-glycine and their racemic counterparts. These layers form hydrogen-bonded bilayers by a (pseudo) twofold axis. Therefore we were interested to see whether the crystallization of an *S*-α-amino acid under an *S*-α-amino acid surfactant Langmuir monolayer would be different from the crystallization of the same compound underneath a monolayer of *R*-configuration. Deposition and compression of monolayers of chiral resolved *S*-PL or *S*-stearoyl glutamic acid (SGA) over supersaturated solutions of chiral resolved *S*-valine caused immediate nucleation and growth of the crystals attached by the {001} faces, which are parallel to the hydrogen-bonded bilayers. Similar results were achieved with *S*-valine grown under the same kind of monolayers but of *R*-configuration. These observations indicate that the resolved valine crystals can epitaxially attach to α-amino acid monolayers

via either pseudo center of symmetry (*S*-valine under *R*-monolayers) or by pseudo twofold symmetry operations (*S*-valine under *S*-monolayers).

2.2 Etching Experiments

Growth and dissolution of enantiopolar crystals in the presence of tailor-made chiral resolved additive can result in the enantioselective binding of the additive at certain crystal faces[6,12]. The additive, which must be similar in molecular structure to the substrate molecule, may bind stereoselectively to a specific crystal face, as if it were a substrate molecule, on the condition that its modified moiety emerges from the crystal surface (see Fig. 2). During the crystal's growth, adsorbed additives hinder growth by disturbing the deposition of oncoming layers at specific faces on which the adsorption occurs[12]. Similarly, during dissolution, the additive molecules adsorb only at those faces at which the molecules are properly oriented to accommodate the additive with minimal disturbance[6]. The adsorbed additive then acts as an etchant of the face during partial dissolution. In fact, it was found[6] that when {010} plate-like crystals of α-glycine are partially dissolved in the presence of a resolved α-amino acid, like *R*-alanine, only the (010) face of glycine is etched. By symmetry, when dissolved in the presence of *S*-alanine, only the $(0\bar{1}0)$ face of α-glycine is etched.

We conducted similar etching experiments on the plate-like faces of valine crystals grown both under a monolayer and in solution. Resolved *S*-valine crystals, in which the platelike (001) and the $(00\bar{1})$ faces are congruent (being related by (pseudo) twofold symmetry), exhibited etching results as expected; etch pits were observed on both faces when dissolved in the presence of *S*-Glu (2%) while neither face exhibited etch pits when dissolved in the presence of *R*-Glu. However, the experiments with *R,S*-valine did not display consistent stereospecific etching. Dozens of individual crystals were dissolved in the presence of *R*- or *S*-Glu. Some crystals, dissolved in the presence of *S*-Glu, for instance, exhibited etch pits on both the (010) and the

(0$\bar{1}$0) faces[17]. Examples of partially dissolved *R,S*-valine crystal faces

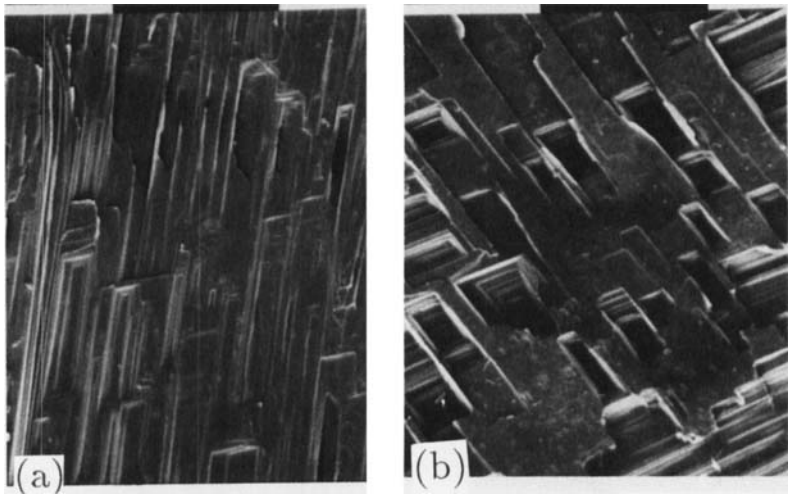

FIGURE 4. *R,S*-valine crystals partially dissolved. (a) Without additive, the face exhibits simple dissolution. (b) Dissolved in the presence of *S*-glutamic acid, etch pits are formed. Magnification X 300. Black bar on top = 0.1 mm

exhibiting etch pits are shown in Fig. 4. In the case of crystals grown under the *S*-monolayer, it was found that *S*-Glu produces etch pits on both platelet faces of *R,S*-valine; the monolayer faces (those which grow attached to the monolayer), and the opposite ones. However, even when etching with *R,S*-glutamic acid, the monolayer face exhibited far fewer etch pits than did the opposite faces. It might be that the monolayer material sticks to the surface and protects it from etching. The etching results suggested that orientational disorder exists in the *R,S*-valine crystals.

2.3 Occlusion of Additives into Growing Crystals

A more quantitative measure of the packing disorder in *R,S*-valine crystals was provided by growing them in the presence of tailor-made additives. It has been shown[12] that when crystals of α-glycine are grown in the presence of minute quantities of α-amino acid additives, the additive molecules are occluded enantiospecifically in the crystal through the growing crystal faces. *R*-α-amino acid additives were designed so that they will be able to adsorb on

the growing (010) face of α-glycine, in a surface site where a pro-*R* hydrogen of glycine emerges from the face, but will not fit on the enantiotopic ($0\bar{1}0$) face. Consequently, the adsorbed additive hinders growth in the $+b$ direction but not in the $-b$ direction. By virtue of symmetry, the enantiomeric *S*-additive will inhibit growth of the ($0\bar{1}0$) face while the racemic mixture of *R,S*-additives will inhibit growth in both the $+b$ and $-b$ directions. Consequently, the *R*-additive may be occluded into the crystal only from the $+b$ side and the *S*-additive only from the $-b$ side. Moreover, in α-glycine crystals grown under a compressed Langmuir monolayer of an α-amino surfactant, such as *S*-palmitoyl lysine, from a supersaturated solution containing a minute quantity of *R,S*-glutamic acid, only the *R*-glutamic acid was occluded[2]. This enantioselectivity arises because in this case growing α-glycine crystals are attached to the monolayer by their ($0\bar{1}0$) faces, and consequently, only the (010) faces of attached α-glycine crystals are exposed to the aqueous solution. Thus only *R*-glutamic acid may be occluded into the crystals.

Similar experiments were performed under chiral resolved Langmuir monolayers and growing crystals of *R,S*-valine. A small amount (4%) of *R,S*-aspartic acid was added to a supersaturated solution of *R,S*-valine and *S*-SGA was deposited and compressed over the solution. The crystals of *R,S*-valine which grew attached to the monolayer were analyzed by HPLC for their additive content. It was found that every *R,S*-valine crystal included additives of both enantiomers. The results for six representative examples are given in the experimental section, showing molar ratios of occluded S/R additive ranging from 0.4 to 3. To check the distribution of the additive within the bulk of *R,S*-valine crystals grown under an *S*-monolayer in the presence of *R,S*-asp, we removed sequential layers by partially dissolving the crystals for several seconds in different drops of water. Both enantiomers were found in each drop analyzed for additive content. Crystals were also cut in half, normal to the *b*-axis, and analyzed separately, with similar results.

3. CONFIRMATION OF DISORDER BY X-RAY CRYSTALLOGRAPHY.

As stated previously, the packing arrangement of *R,S*-valine is similar to that of α-glycine. The structural literature on this compound revealed three separate reports[7] in which the following space groups were assigned; $P2_1/c$ in 1969, $P\bar{1}$ or $P1$ in 1951, and $P2_1$ in 1943. The most recent study[7a] reports the X-ray crystal structure, refined to R=0.1. Space group $P2_1/c$ with cell constants of a=5.21, b=22.10, c=5.41 Å, and β=109.2 °. In the structure, which is similar to that of α-glycine, the layers are stacked normal to the b axis. The reported $P2_1$ and $P1$ space groups are improbable, since the crystal is racemic. In the following paragraphs we try to resolve the question of why such space groups were proposed.

We collected X-ray diffraction data with a Weissenberg camera from fifteen *R,S*-valine crystals, some of which were grown under the monolayer, while others were grown in aqueous solution. Large differences in diffraction results from crystal to crystal were observed, but with no correlation to whether the crystals were grown from solution or under the monolayer. Three distinctly different kinds of *[010]* oscillation X-ray photographs were found: (1) Those showing a b axis of 11 Å; (2) those showing a b axis of 22 Å; (3) those with a b axis of 22 Å, but with strong *hkl* reflections for which k = 2n and weak reflections for which k = 2n + 1. The last category suggests crystal domains with a major fraction containing the 11 Å axis and a minor fraction with the 22 Å axis. If there were crystals with both types of domains but with a majority containing the 22 Å axis, it could not be easily discerned from the X-ray diffraction photographs.

Several *h0l* Weissenberg pictures showed twinning about the reciprocal vector $a^* \pm c^*$, yielding apparent *mm* Laue symmetry. However, several other photographs displayed doubled reflections, indicating imperfect twinning. The reported[7c] crystal symmetry of $P2_1$ with a b-axis of 22 Å can be understood in light of these results. The $P2_1$ structure has the systematic absences *0k0*

with $k = 2n + 1$. The *h0l* diffraction patterns, which we found with apparent *mm* Laue symmetry, would mask the required reflections for the identification of the glide in the $P2_1/c$ space group (*h0l* with $l=2n+1$ are absent) and might thus erroneously be assigned the space group of $P2_1$. This diffraction result can be explained by a stacking disorder of the *ac* bilayers along the *b* axis. It may be envisaged by considering the effect of starting with the ordered $P2_1/c$ crystal structure of *R,S*-valine and rotating (010) domain slices about the $a \pm c$ axis by 180 ° in random locations within the crystal. This disorder appears to be possible due to the fact that the *a* and *c* axes are almost equal in length (5.21 and 5.41 Å respectively) in the refined $P2_1/c$ crystal structure. We cannot say, however, that the crystal will be commensurate at the twinned interface, since we did several times observe double reflections.

Crystals with a *b* axis of 11 Å can belong only to the $P\bar{1}$ space group since the stacking distance between the hydrogen-bonded bilayers is 11 Å and we can safely assume that the hydrogen-bonded (*010*) bilayer is centrosymmetric.

4. DISCUSSION AND CONCLUSIONS

The same techniques used to characterize the stereospecificity of epitaxially grown well-ordered crystals such as α-glycine, were also useful in the discovery and identification of the character of disorder in the *R,S*-valine crystals. The diffraction results showed the crystal to be twinned and the *a* and *c* axes to be equivalent in the extremely disordered crystals. The HPLC results show that this disorder prevails throughout the crystal along the *b* axis. Since the *a* and *c* axes are almost equal in length, the degree to which stacking between domains will be incommensurate is reduced. We note that the bilayer stacking in resolved valine and the other resolved hydrophobic α-amino acids is propagated by pseudo or real twofold axes. The disordered *R,S*-valine

probably adopts similar bilayer contacts. The bilayer rotation, or "flipping", in *R,S*-valine would most likely occur between the hydrophobic residue contacts, as the hydrogen-bonded bilayers in which the molecules are related by inversion centers would be energetically much more difficult to disrupt.

An analogous kind of disorder has been shown to occur with structures consisting of heterochiral monolayers where the molecules within the monolayer are related by glide symmetry. There are two different well-ordered *R,S*-methionine crystal structures[18], $P2_1/a$ and $I2/a$. Both forms consist of hydrogen-bonded bilayers, with the differences lying in the stacking of the bilayers. Neighboring bilayers in the $P2_1/a$ structure are stacked by twofold screw and center-of-inversion symmetries. The major contact across the bilayers is between molecules of the same chiral configuration across 2_1 axes, with the minor contacts are across inversion centers. In the $I2/a$ structure there is a shift of the bilayer unit relative to the former by $1/2(a+b)$ so that the major contact is between molecules of opposite configuration across inversion centers and the minor contact across twofold axes. It was deduced from x-ray diffraction photographs of disordered *R,S*-norleucine[19] that a superlattice is being formed by various sequential arrangements of these structures in the same crystal. It was also reported that *R,S*-α-amino-N-butyric acid crystallizes in four different structures, differing only by the stacking displacement of the hydrogen-bonded bilayers[20] in the same manner as in *R,S*-methionine. Examination of Weissenberg photographs of racemic octanoic α-amino acid indicates a similar kind of disorder.

An interesting observation is that stacking disorder cannot occur with the corresponding crystals of the chiral resolved compounds mentioned above. Such crystals give diffraction patterns with no evidence of packing disorder. It may be concluded that the disorder in *R,S*-valine is generated in the following way: During the growth of the crystal, hydrogen-bonded bilayers assemble quickly (formed either by center of symmetry, for racemic crystals,

or by two-fold symmetry for resolved crystals), as the hydrogen-bonding energy is very favorable (calculated to be 5 kcal/mole per dimer[21]). The resulting hydrophobic surfaces, consisting of the hydrocarbon residues pointing towards the solution, seem to be enantiotopically non-specific. This implies a very small (if any) energetic difference between contacts generated by glide symmetry or by rotational symmetry: i.e., no difference between further deposition of *R* or *S*-valine molecules. This causes occational flipping of the newly grown bilayer relative to the existing ones. The disorder in the crystal originates, then, from the kinetics of interaction between the hydrophobic surface of the growing crystal and the hydrophobic chains of the racemic species deposited from solution onto the crystal face.

5. EXPERIMENTAL

R,S-valine, analytical grade, purchased from Fluka. All monolayer materials were synthesized in our laboratory[2(b)]. Crystals which were not grown under the monolayer were grown by slow evaporation from aqueous solutions. The monolayer solutions were prepared by taking approximately 3 mg of material and dissolving it in 10 ml of 96% spectroscopic grade chloroform and 4% distilled trifluoroacetic acid.

All monolayer experiments were performed in ring-shaped Fromhertz troughs equipped with Wilhelmy balances. The valine saturated solutions were at room temperature when poured into the troughs. The surface was then cleaned by vacuum suction, and the monolayer material spread using an adjustable micropipette (between 15 to 30 μl). The mobile barrier was then compressed until the area between the barriers reached the limiting area (Fig. 5). The amphiphiles used in the Langmuir monolayer experiments were stearoyl glutamic acid (SGA), stearoyl aspartic acid (SAA) and palmitoyl lysine (PL). All exhibited π-A diagrams similar to that of *R*-PL, shown in Fig. 5.

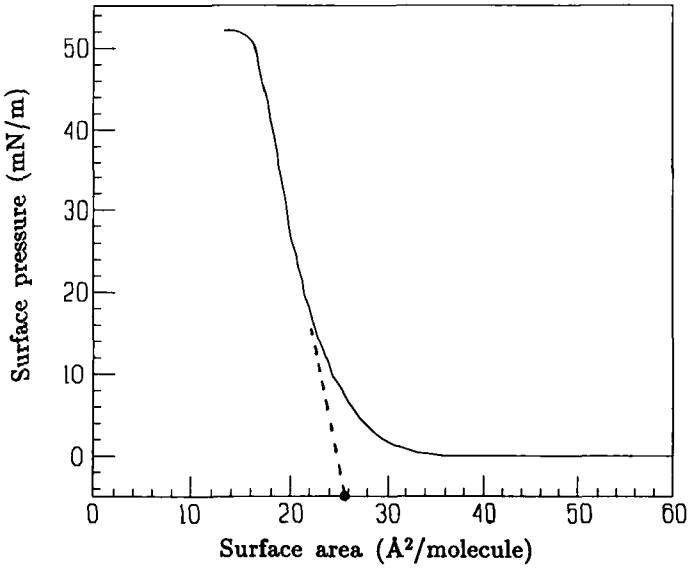

FIGURE 5. Isotherm of PL compressed over a water subphase at 20 °C. The limiting area of 25.8 Å²/molecule is marked.

Analysis of occluded additive in the crystals grown under the monolayer was performed by HPLC[22] using a column capable of separating amino acid enantiomers (Nucleopore, 5 μ mesh, and 25 cm long stainless steel). The chiral reagent, *S-NN'*-dipropyl alanine (DPA), was synthesized and added to a solution of copper acetate for a solution of 2 mM $Cu(Ac)_2$, 4 mM (S)DPA. The pH was adjusted with sodium acetate to 5.5. The column was placed in an ice bath during analysis. The fluorescence reagent (OPA) was prepared freshly when necessary. It was pumped in a 2:1 ratio with the chiral phase. The chiral phase rate was 0.2 ml/min. These conditions gave a ten minute separation between aspartic acid enantiomers. Results for six representative *R,S*-valine crystal samples are given. All crystals were grown under a compressed monolayer of *S*-SGA in the presence of 4% *R,S*-asp. Molar ratios of *S*-asp to *R*-asp are given below for the six crystals.

Fully dissolved crystals:

(1) S/R = 0.6

(2) S/R = 0.4

(3) S/R = 1.0

(4) Crystal cut in half perpendicular to the *b* axis. S/R = 0.5 for one half and 0.9 for the other.

Partially dissolved crystals:

(5) From the monolayer face, several sequential layers gave S/R = 0.7. From the opposite face; S/R = 1.

(6) From the monolayer face; S/R = 3. From the opposite face; S/R = 1.

Etching experiments were performed by placing individual crystals, or crusts of crystals grown under the Langmuir monolayer, in beakers containing a slightly undersaturated solution of *R,S*-valine with 4% *R,S*-glutamic acid for 2 minutes. Scanning electron microscope images were produced with a Philips Analytical SEM 505/515 microscope. All X-ray diffraction measurements on *R,S*-valine were done using a Weissenberg camera, with the crystal mounted along the *b* axis.

Acknowledgments

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17. We note that the (010) face of *R,S*-valine is enantiotopically equivalent to the {001} face of *R*-valine, while the (0$\bar{1}$0) face of *R,S*-valine is equivalent to the {001} face of *S*-valine.

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