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'Tailormade' auxiliaries for nucleation, growth and dissolution of organic crystals

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Abstract – A new stereochemical approach for the controlled nucleation, growth and dissolution of organic crystals with well designed auxiliaries is described. The method is comprised of the use of appropriate stereospecific inhibitors of growth and dissolution of one or more preselected faces of the crystal. This approach has been successfully exploited for the engineering of organic crystals with desired morphologies, for the kinetic resolution of conglomerates by the process of crystallization, and for inducing etch-pits at preselected faces of crystals. A correlation has been established between crystal morphology and crystal purity. Oriented growth of organic and inorganic crystals at interfaces has been accomplished with the assistance of designed Langmuir and Langmuir Blodgett films. The approach has recently been extended to the study of solvent effects on the morphology of crystals in general, and of polar crystals in particular.

INTRODUCTION

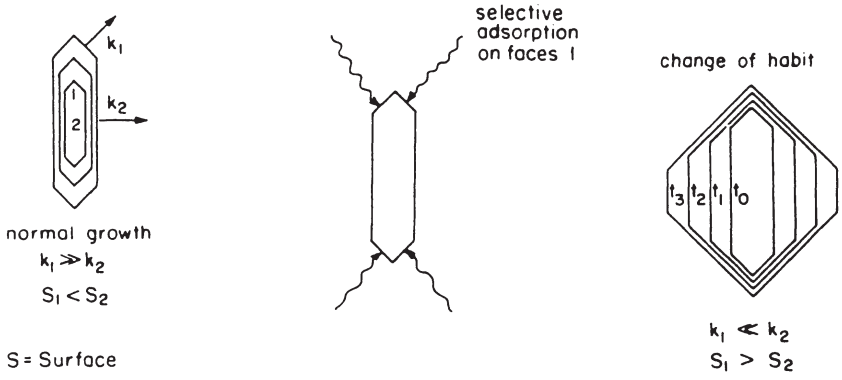
Crystallization of organic and inorganic crystals is a common process most frequently used for the purification of materials in the laboratory and in industrial plants; nevertheless, the selection of conditions, such as temperature, solvent and degree of supersaturation, for a particular system, is generally done, by and large, through experience and intuition. Of the many immensely important technological processes for producing crystals, we mention a few for illustrative purposes. Filtration which in industrial process is often the rate determining step in the plant cycle time, depends, in part, upon the habit and polymorphic structures of the crystalline solid. Many commercial products (for pharmaceuticals, pesticides, etc.), are crystalline solids which may be used as such or in dispersion. The crystal habit and surface structures of polymorphic forms can be important in achieving products of desired properties. Thus, for example, the rate of uptake of drugs by the body depends on the solubility of the drug crystals, which is governed by these factors. Single crystals play an important role of the fabrication of electro-optical devices. The most common example is that of the use of large transparent single crystals of sodium chloride, in infrared and Raman spectrophotometers. Scientists from the Kodak Co. reported recently (ref. 1) the preparation of photographic films of ultra-high sensitivity which was made possible by the ability to crystallise uniform tabular crystals of silver halides with a large surface to volume ratio. Nowadays polar organic single crystals are finding important applications in devices for non-linear optics, pyroelectricity and piezoelectricity.

In the course of our studies on the packing modes and crystal growth of organic molecular crystals we initiated a program to study of the interactions of growing crystals with their environment in general, and with "tailor-made" crystal growth inhibitors (ref.2) and Langmuir-Blodgett film nucleation promotors in particular (ref.3). With the assistance of these auxiliaries we are now in a position to engineer crystals with desired morphologies (ref.4), to decrease the quantity of impurities in growing crystals, to resolve enantiomers by crystallization (ref. 5), to etch molecular crystals at desired faces (ref.6), and to construct surfaces for oriented and epitaxial growth (ref.3).

MORPHOLOGICAL CRYSTAL ENGINEERING

The habit of a crystal is defined by the relative rates of growth of the crystal in different directions. The faster the growth in a given direction the smaller the face developed perpendicular to that direction and vice-versa (Scheme 1). The dramatic morphological changes associated with the growth of organic crystals in the presence of additives reveal the high degree of specificity in the interaction of the foreign material with the different structured surfaces of the crystalline matrix. Therefore, the morphological changes have a direct bearing on the mechanisms of the adsorption-inhibition process on a molecular level.

Scheme 1



In view of the above generalization concerning rate of growth and surface area, when growth is inhibited in a direction perpendicular to a given face the area of this face is expected to increase relative to those of other faces of the same crystal (Scheme 1). Differences in the relative surface areas of the various faces can therefore be directly correlated to the relative inhibition in the different growth directions. This type of morphological analysis was carried out on a variety of organic compounds crystallized in the presence of additives of molecular structure similar to those of the corresponding substrate molecules. A stereochemical correlation between the structures of the affected crystal surfaces and the molecular structure of the inhibitor could be deduced in each system (ref.7). We could infer that the additive is adsorbed on the growing crystals, but only at certain faces, and then with the part of the adsorbate that differs from that of the substrate emerging from the crystal. Once adsorbed, the additive inhibits the regular deposition of oncoming layers of substrate molecules, and this generally leads to a relative increase in the area of the face involved. Once this mechanism was established, it became possible to exploit it in order to systematically modify the morphology of crystals by tailoring additives which bind at a preselected face and thus inhibit growth in a predictable manner (refs.4,8).

This approach is illustrated here for the crystal of glycine grown in the presence of other α-amino acids (ref.9). Glycine crystallizes from water in space group $P2_1/n$, in the α-polymorphic form, assuming a bipyramidal morphology with the b-axis perpendicular to the base of the pyramid (Fig.1).

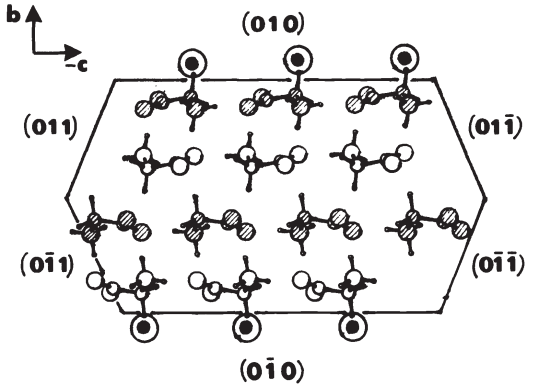


Fig. 1

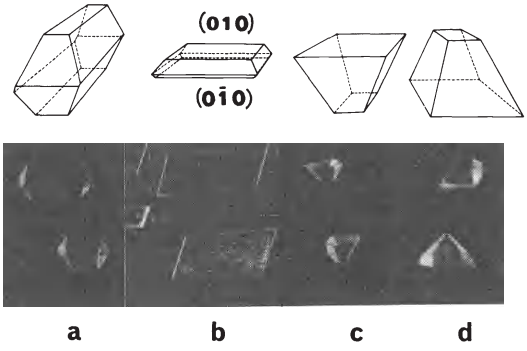


Fig. 2

Fig. 1 Packing arrangement of α-glycine delineated by its crystal faces; the large circles indicate the positions of the emerging side chains of (R)- or (S)-α-amino acid additives adsorbed at the (010) or (0$\bar{1}$0) faces, respectively.

Fig.2 Morphology of crystals of α-glycine grown in the presence of:
(a) no additives; (b) (R,S)-α-amino acids. (c) (S)-α-amino acids; (d) (R)-α-amino acids;

A racemic additive causes crystallization of {010} platelets (Fig.2b). We predicted from the crystal structure analysis and morphology of this crystal that all natural (S)-α-amino acid additives (but for proline) will, on growth, be selectively adsorbed and occluded at the -b end of the crystal; by symmetry the (R)-amino acid additives will be occluded at the +b end. As predicted, (S)-α-amino acids induce formation of pyramids (Fig.2c) with large (0$\bar{1}$0) faces, and (R)-α-amino acids that of pyramids with large (010) faces (Fig.2d).

This approach has been successfully applied for the selection of crystal growth inhibitors for a large variety of organic crystals, such as steroids, sugars, amides, acids, phenols, etc. (ref.10) and should, in principle, be generally applicable.

MORPHOLOGY AND CRYSTAL PURITY

During the crystallization of a substrate in the presence of an additive, a small amount of the latter (0.02-1%) is occluded into the bulk of the growing crystal. We suggested, and subsequently confirmed experimentally, that this occlusion occurs only through the face at which the additive molecule is initially stereoselectively adsorbed. Thus, for example, when {010} platelike crystals of glycine were analysed by HPLC for occluded α-amino acids (Fig.3); total enantioselective segregation along the b-axis was found; the (R)-amino acid predominate in the +b half of the crystal and the (S)-amino acid in the -b half.

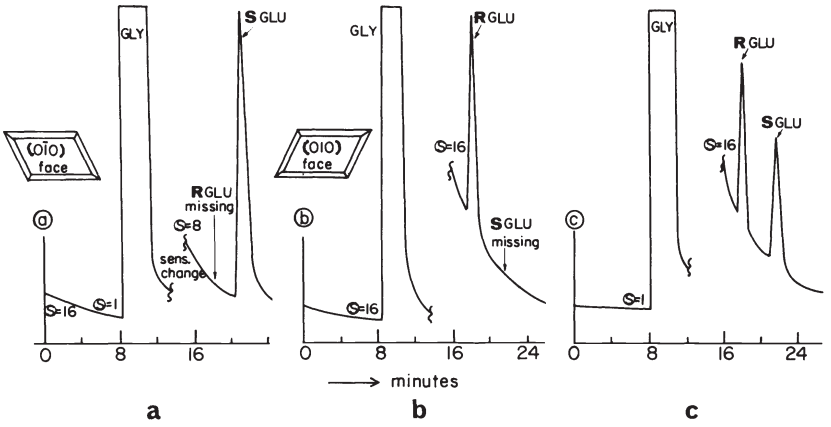


Fig. 3 Enantiomeric distribution of (R,S)-glutamic acid inside the crystals of α-glycine; (a) material taken from the (0$\bar{1}$0) face; (b) material taken from the (010) face; (c) whole crystal. S = detector sensitivity.

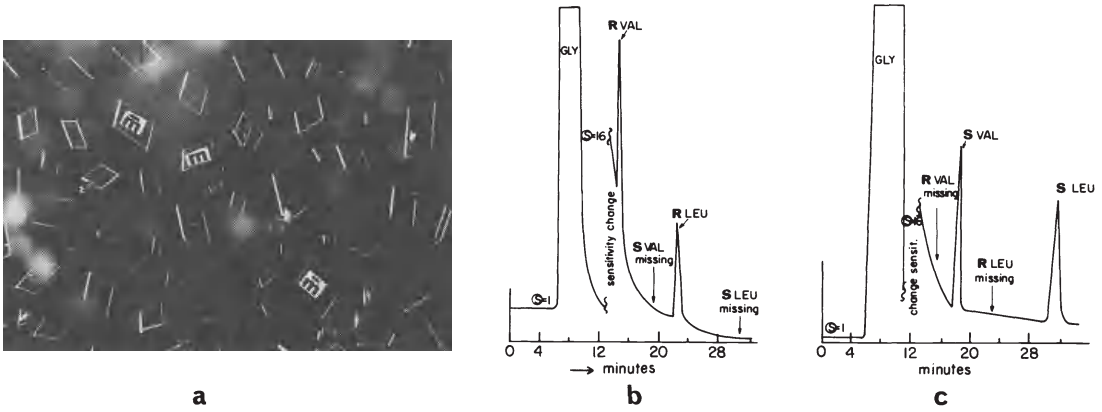


Fig. 4 (a) Crystals of α-glycine grown at the air/solution interface in the presence of (R,S)-leucine and (R,S)-valine; m and $\bar{m}$ designate crystals exposing their (010) and (0$\bar{1}$0) faces to solution respectively. (b) HPLC analysis of crystals m; (c) HPLC analysis of crystals $\bar{m}$.

When crystals of glycine were grown in the presence of small amounts of a hydrophobic α-amino acid, such as valine or leucine, the growing crystals exhibited a tendency to float at the air-water interface with their {010} faces exposed towards the air. If the glycine solution contains a mixture of (R,S)-α-amino acid additives, the floating crystals of glycine, exposing their (010) faces to the solution, will occlude only the (R)-α-amino acids; by symmetry the (S)-α-amino acids will be occluded into those crystals exposing their (0$\bar{1}$0) faces to the solution (ref. 11). HPLC analysis of the enantiomeric content of the occluded amino acids indeed confirmed these expectations. Such resolutions of (R,S)-leucine and (R,S)-valine are shown in Fig.4.

When such an experiment was performed in the presence of resolved, say (R)-α-amino acid, both pyramids and plates were found at the glass/water interface. At the glass walls of the vessel, all plates were oriented with their (010) faces towards the water solution and thus occluded upon growth the α-amino acids. The pyramids always exposed their (010) basal faces to the glass and were free from the (R)-α-amino acid, since these additives cannot be occluded from the -b side of the crystal.

Another example relating crystal morphology and purity is provided by the crystallization of the polar crystal of resolved lysine.HCl.$2H_2O$ (refs. 2, 12). This compound crystallizes from water as a dihydrate in a polar monoclinic structure of space group $P2_1$. Fig.5 depicts the packing arrangement delineated by the observed crystal faces.

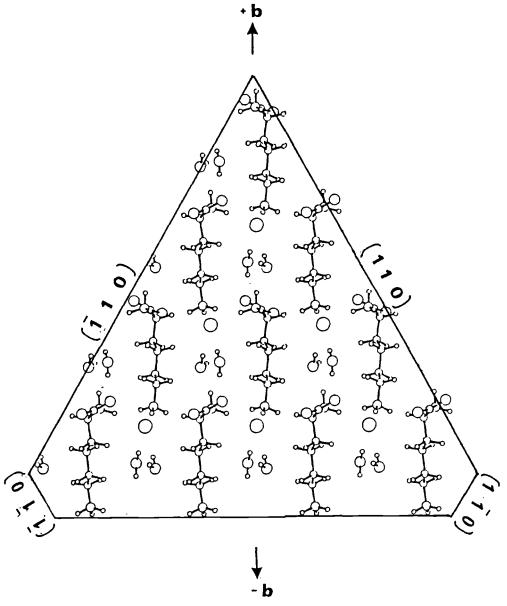


Fig. 5 Packing arrangement of (S)-lysine.HCl.$2H_2O$ viewed along the c axis and delineated by its crystal faces.

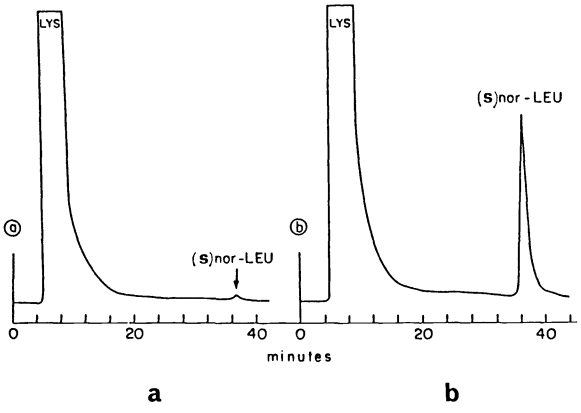
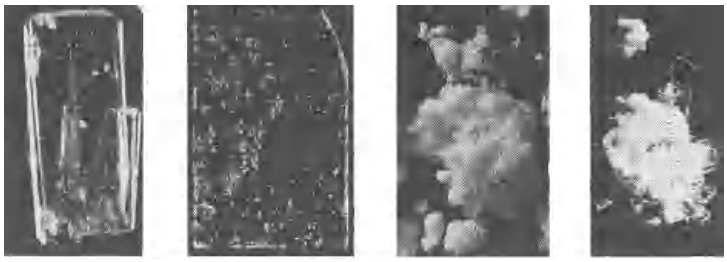


Fig. 6 HPLC analysis of (S)-norleucine occluded inside crystals of (S)-lysine.HCl.$2H_2O$; (a) material taken from the +b pole of the crystal; (b) Same amount as in (a), taken from the -b pole.

The constituent lysine molecules are aligned parallel to the b-axis with the amino acid head moiety emerging from the +b end of the crystal and the side chain emerging from the -b end. Crystallization of lysine in the presence of additives which bear modified side chains, like norleucine or norvaline, will yield crystals modified at the -b pole. The additive will be also occluded preferentially at that side of the crystal. This expectation was experimentally confirmed for the crystals of (S)-lysine.HCl grown in the presence of (S)-norleucine. According to a chromatographic analysis of the material taken from the +b and -b ends of the crystal, the additives were occluded preferentially at the -b end (Fig.6). These results exemplify that the purity of the crystal depends upon the crystal structure, the molecular structure of the impurity, the face exposed to the solution and the growth directions.

RESOLUTION OF CONGLOMERATES

A natural application of the present two-step mechanism of stereoselective adsorption-inhibition is for the kinetic resolution of enantiomers crystallizing in the form of conglomerates with the assistance of "tailor-made" growth inhibitors. Louis Pasteur separated manually the two enantiomorphs of sodium ammonium tartarate tetrahydrate using the non-superposable morphologies of the two forms of the crystals (ref. 13). The stereochemical mechanism described above implies that presence of resolved "tailor-made" inhibitors in the solution of a racemic mixture crystallising in the form of conglomerate will impede selectively the growth of one of the enantiomorphs. The interaction of the chiral inhibitors with one of the growing enantiomorphs will also change the morphology of that crystal only. The other enantiomorph will grow unaffected. This phenomenon offers the possibility of modifying Pasteur's classical method and of extending it to any system which undergoes spontaneous resolution. A number of examples have been studied (ref.7). Here we illustrate with two systems, threonine and glutamic acid.



a b c d

Fig. 7 Crystals of (S)-Glu.HCl grown in the presence of increasing amounts of (S)-lysine: (a) none; (b) +2 mg/ml Lys; (c) +50 mg/ml Lys; (d) Crystals of (R,S)-Glu.HCl grown in the presence of (S)-Lys. The plates are the (R)-enantiomer while the powder is the (S)-enantiomer.

Crystallization of (R,S)-threonine in water yields elongated bars of resolved crystals of (R)- and (S)-threonine. When grown in the presence of (S)-glutamic acid, first there precipitate crystals of (R)-threonine with unchanged morphology, followed by (S)-threonine in powder form. Consistently, (R)-threonine grown in the presence of (S)-glutamic acid yields unaffected bars whereas (S)-threonine grown in the presence of (S)-glutamic acid yields a fine powder. Similar results were observed for (R,S)-glutamic acid.HCl, grown in the presence of (S)-lysine.HCl. In the absence of lysine, (R,S)-glutamic acid precipitates in the form of a conglomerate, the chiral crystal assuming a plate-like morphology. When-(S)-lysine.HCl is added, the (R)-glutamic crystals remain with the same morphology whereas the (S)-crystal precipitates as a white powder. The morphology of the affected crystal is concentration-dependent (Fig.7).

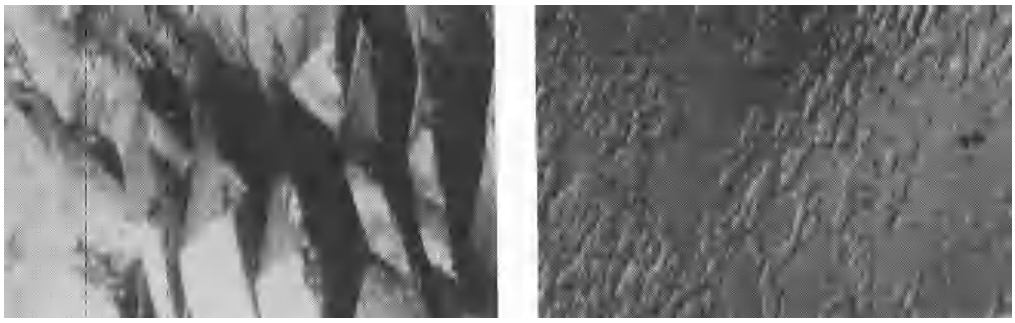
A morphological analysis akin to that for glycine demonstrated that the (S)-molecules of the additive interact enantioselectively with the (S)-crystals of threonine or glutamic acid.HCl, resulting in the kinetic resolution of the enantiomers (ref. 5). In keeping with this mechanism, we found that the additives were occluded enantioselectively inside the slow growing affected (S)-crystals; the fast-growing unaffected (R)-crystals were free from additive. This effect was also illustrated visually by using coloured additives; thus crystals of (R)- and (S)-glutamic acid.HCl grown in the presence of the yellow N^{ε}-(2,4-dinitrophenyl)-(S)-lysine as additive first yielded colourless plates of (R)-glutamic acid.HCl, followed by the yellow powder of the (S)-enantiomer (ref.2).

More efficient resolutions can be accomplished with soluble "tailor-made" polymers (ref.14). The latter comprise a polymeric backbone on which the inhibitor, which may be the substrate molecule, is grafted. Owing to cooperative effects, these polymers affect not only growth but delay enantioselectively the nucleation of the corresponding enantiomer. The potentiality of the method has been recently enlarged to encompass systems which pack in the form of racemic compounds and would not be naturally amenable to such a resolution.

DISSOLUTION OF CRYSTALS WITH 'TAILORMADE' INHIBITORS

Growth and dissolution under conditions close to equilibrium are considered as converse processes, that can be interchanged by altering the degree of saturation of the solution. Consequently an inhibitor of growth of a given crystal face must in principle affect the rate of dissolution of that same face. This reciprocity was tested in a number of systems. The plate-like crystals of glycine with well-developed {010} faces were submitted to partial dissolution in an undersaturated solution of glycine containing variable amounts of other α-amino acids (ref.6b). When resolved (R)-alanine was present in the solution, well developed etch-pits were formed only at the (010) face. These pits exhibit twofold morphological symmetry with surface edges parallel to the a and c axes of the crystal. The enantiotopic ($0\bar{1}0$) face dissolved smoothly in the same way as it does when the crystal is dissolved in an undersaturated solution of pure glycine without additive. As expected, (S)-alanine induces etch-pits on the ($0\bar{1}0$) face. Racemic alanine etches both {010} faces (Fig.8).

Kinetic studies on the dissolution of the opposite {010} faces of plate-like crystals of glycine in undersaturated glycine solutions revealed indeed, that the {010} face which interacts with the additive, dissolves more slowly than the opposite {010} face. On the other hand, when one continues to dissolve partially etched glycine crystals in undersaturated solutions of the pure substrate, in the absence of additive, the rate of dissolution of the etched faces is enhanced with respect to that of the non-etched ones, due to the larger surface areas of the former. Such a process should find important applications in the pharmaceutical industry, where there is great interest in controlling the dissolution properties of solid crystalline drugs.



a b

Fig. 8 Optical microscope pictures (x50) of the {010} faces of an α-glycine crystal after partial dissolution in the presence of (R)-ala. (a) (010) face; (b) ($0\bar{1}0$) face.

EFFECT OF SOLVENT ON CRYSTAL GROWTH

So far we have used for convenience well designed inhibitors for both growth and dissolution of crystals. As a matter of fact, any solvent present during crystallization is an "additive". We have extended our approach on 'tailor-made' additives towards understanding of the morphology of crystals grown in different solvents, by formulating the hypothesis that the crystal face which interacts most firmly with a given solvent tends to grow slower than faces which interact weakly. Crystals with polar axes, for example lysine.HCl described earlier, are ideal systems for such studies because the difference in growth rate of the opposite faces at the two poles should originate primarily from the differences in their solvent-surface interactions. A number of such polar crystals have been studied; these include α-resorcinol (ref. 15), (R,S)-alanine (ref. 16), resolved valine and γ-glycine (ref. 6b). We shall illustrate our approach for the growth of crystals of γ-glycine and (R,S)-alanine.

γ-Glycine crystallizes from 0.6M sulfuric acid in the trigonal space group $P\bar{3}_1$. The molecules are hydrogen bonded along the polar c-axis and oriented so that the carboxylate CO_2^- groups are exposed at one end of the polar axis and the amino NH_3^+ groups at the opposite end (Fig.9). The crystals exhibit a trigonal prismatic morphology elongated in c and grow preferentially at the CO_2^- side of the crystal but not at the NH_3^+ side. (The absolute structure of the crystal was assigned by using the etching method described above and by independent Bijvoet measurements).

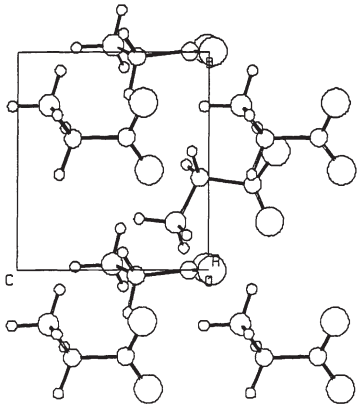


Fig. 9 Packing arrangement of γ-glycine viewed along the b axis.

One way of rationalizing the role of the solvent in the kinetic of growth at the opposite poles of the γ-glycine crystal is to assume a strong interaction between the NH_3^+ groups of the crystal surface and the divalent sulfate anions which block the surface and inhibit the deposition of additional layers of the glycine molecules at that face. The existence of strong attractive interactions between sulfate ions and those faces at which NH_3^+ emerge is supported by the observation that sulfuric acid etches stereospecifically only these faces but not the opposite face at which the CO_2^- groups emerge.

(R,S) alanine, which crystallizes in the orthorhombic polar space group $Pna2_1$, was found to grow unidirectionally along its polar axis in aqueous solution. As in the crystal structure of γ-glycine, the molecules of (R,S)-alanine are oriented with respect to the polar c-axis so that the carboxylate CO_2^- groups are exposed at one end of the polar axis and the NH_3^+ groups at the opposite

end. When grown from water the crystal has needle-like morphology and is elongated in c. Crystallization of alanine followed under an optical microscope revealed a pronounced tendency for unidirectional growth along the polar axis. Here again, we observed that the crystal of (R,S)-alanine grows faster at the CO_2^- side of the crystal. If our explanation for the influence of "tailor-made" additives and solvent sulfuric acid above is also applicable for (R,S)-alanine, this implies that water interacts more firmly with the surface of the emerging NH_3^+ groups than with the opposite face where the CO_2^- groups emerge. Other systems such as resolved methionine or valine, which crystallize in structures akin to that of (R,S)-alanine, display similar growth behaviours. Atom-atom potential calculations should throw light on the solvent-surface interactions (ref.17).

ORIENTED GROWTH WITH 'TAILORMADE' SURFACES

Another way to control crystal growth is by use of designed structured surfaces which may act as appropriate sites for primary nucleation of a given crystal (refs.3,18). The structure of the synthetic surface should be almost identical or complementary to one of the molecular layers of the to-be-grown single crystal. For that purpose a joint program has been initiated with Prof. J. Sagiv from this Institute, on the crystallization of organic crystls at air/water interfaces with the assistance of Langmuir monolayers.

A densely packed Langmuir monolayer of amphiphilic homochiral α-amino acid molecules would exhibit in the aqueous subphase a hydrogen-bonded layer arrangement very similar to that in α-glycine, provided the hydrophobic moieties of the monolayer allow the neighbouring α-amino acid head groups to be interlinked by N-H...O bonds. Consequently, a monolayer of, say, resolved (R)-α-amino acids packed as tightly as in an ac layer of α-glycine, should simulate an r layer (as shown in Fig.10) of glycine molecules exposed at the (010) face of the crystal and thus might induce nucleation of a glycine crystal with this face attached to the monolayer. By symmetry, the corresponding monolayer of (S)-amino acids should, under identical conditions, simulate an s layer of glycine and induce nucleation of a glycine crystal with its $(0\bar{1}0)$ face attached to the monolayer.

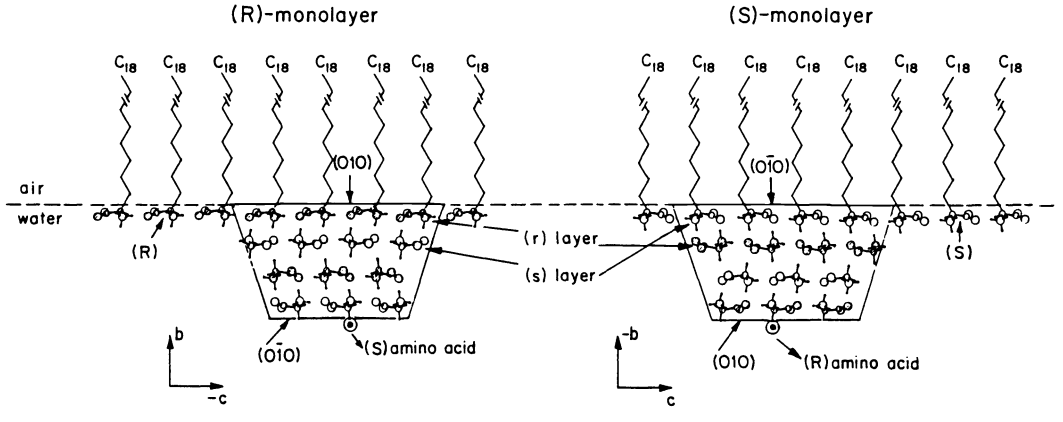


Fig. 10 Schematic representation of α-glycine crystals grown under compressed (R)-and (S)-α-amino acid monolayers.

A number of amphiphilic molecules bearing an α-amino acid as the hydrophilic head groups have been synthesized. Thus, for example, a monolayer of resolved or racemic stearyl-α-glutamate promoted immediate nucleation (within seconds after formation of the film) of pyramidal glycine crystals with their basal ac faces attached to the monolayer. When a monolayer of the R-α-amino acids was used, most pyramids were attached through their basal (010) faces to the monolayer and, by symmetry, when (S)-α-amino acids were used, enantiomorphous pyramids were formed with their basal $(0\bar{1}0)$ faces attached to the monolayer. Monolayers of racemic composition yielded attached pyramidal crystals of both orientations. When a cholestanoyl moiety was attached to the α-amino acid head group the limiting area per molecule in the monolayer is determined by the bulky steroid skeleton. This was found to be 38$Å^2$, a value distinctly larger than that of the glycyl head group, thus precluding hydrogen bonding between the latter groups. Indeed, crystallization of glycine under such a monolayer was observed to occur at a much slower rate than with monolayers of the previous compound (hours as opposed to seconds) and mostly in the bulk subphase rather than at the monolayer. In the few cases in which glycine also crystallized at the interface, these crystals exhibited both pyramidal and bipyramidal morphologies with no preferential orientation.

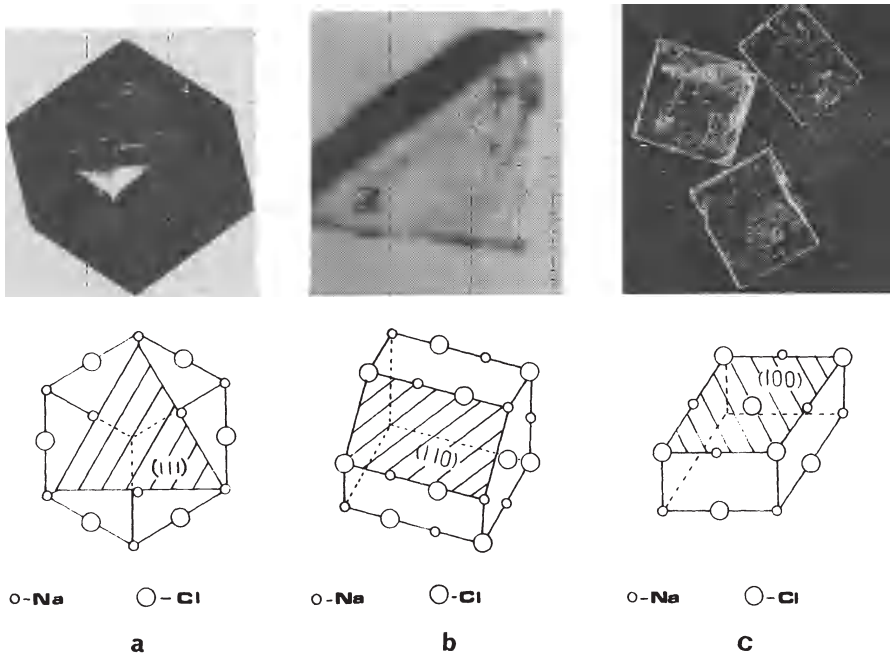


Fig. 11 Crystals of NaCl grown under monolayer of (a) stearic acid; (b) stearyl-(R)-glutamate; (c) stearylamine.

Recently, similar studies were performed on the crystallization of NaCl (ref.18). Thus, for example, when NaCl is crystallized underneath a monolayer of stearic acid, most of the crystals attached at the monolayer develop the (111) face, which is composed of alternate layers of Na^+ and of Cl^- ions (Fig.11a). When monolayers of α-amino acids are spread on top of the supersaturated solution of the sodium chloride, the crystals which nucleate at the interface develop the {110} face, a face which contains rows of Na^+ and rows of Cl^- separated from one another by 2.8Å (Fig.11b). If stearylamine is used as nucleating matrix the crystals develop the (100) face. This face contains layers composed of ions of Na^+ and ions of Cl^- separated by 2.5Å (Fig.11c). These preliminary results clearly indicate that the structured films can control the orientation of a variety of nucleating crystals, both inorganic and organic. In fact, these studies are currently being extended to the construction of desired surfaces for epitaxial growth of other crystals. We are also studying mixed monolayers with the purpose of obtaining information regarding the size and dimension of the nucleating centres.

CONCLUDING REMARKS

Preliminary studies have been reported on utilization of "tailor-made" auxiliaries in the form of molecular additives, polymers and two-dimensional surfaces for controlled crystal nucleation, growth and dissolution. Although the principles have been applied only to a limited number of systems, we are of the opinion that they are of a general value and should be applicable to a large variety of crystallizing systems in the laboratory and in pilot plants.

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CORRIGENDUM

The list of references had inadvertently not been supplied by the authors (I. Weissbuch et al.) for the manuscript published in Pure & Appl. Chem., Vol. 58, No. 6 (June 1986), pp. 947-954. The missing References are printed on this sheet which may please be inserted after page 954.

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