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Assignment of Absolute Structure of Polar Crystals Using Tailor-Made Additives. Solvent Surface Interactions on the Polar Crystals of α-Resorcinol, (R, S) Alanine and Y-Glycine

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ASSIGNMENT OF ABSOLUTE STRUCTURE OF POLAR CRYSTALS USING TAILOR-MADE ADDITIVES. SOLVENT-SURFACE INTERACTIONS ON THE POLAR CRYSTALS OF α-RESORCINOL, (R,S) ALANINE AND γ-GLYCINE.

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Abstract Various properties of polar crystals, in particular the effect of solvent on their growth, are directly related to the absolute structure of the crystal. The absolute structures of polar crystals composed of achiral molecules or racemic mixtures were assigned by three independent methods involving growth and dissolution in the presence of tailor made additives: Inhibition of crystal growth, anisotropic distribution of the occluded additive, and formation of etch pits on partial dissolution of the crystal. The method has been applied to crystals of α-resorcinol, (R,S) alanine and γ-glycine, each of which exhibits oxygen-rich and hydrogen-rich faces at the opposite ends of polar axes. All three crystals were found to grow almost unidirectionally from water at the oxygen-rich end of the crystal. The results are analysed in terms of solvent-surface interactions.

Effect of Solvent on Growth of Polar Crystals and their Absolute Crystal Structure

Crystals with polar axes display many physical and chemical properties which can only be fully understood in terms of the absolute structure of the specimen crystals. These properties include macroscopic phenomena such as pyroelectricity, piezoelectricity, second harmonic generation, optical activity, and anisotropy in growth or chemical reactivity along the polar axis.[1-3] The assignment of absolute structure is straightforward if both the crystal and its constituent molecules are chiral, in which case the known absolute

configuration of the molecule fixes the absolute structure of the specimen crystal. If the absolute configuration of such chiral molecules is unknown, if the molecules are nonchiral or if the polar crystal is racemic, then the determination of the absolute structure is generally performed by the Bijvoet method of anomalous dispersion of X-rays. Such determinations may be difficult and even untrustworthy, depending upon the types of constituent atoms of the molecule[4,5] and, in fact, is impossible if the molecule is a nonchiral hydrocarbon. Moreover, the Bijvoet analysis must be applied to each specimen crystal individually[4] unless the information on absolute structure is transferable from crystal to crystal by correlation to some property such as asymmetric morphology (i.e. hemihedral faces) or if the constituent molecules are chiral. Indeed the difficulties which surround the determination of absolute crystal structure may be responsible for the relative dearth of studies on the growth of polar crystals from solvent.

The role played by solvent in affecting crystal shape has long been and continues to be a matter of debate, in particular it is not clear whether strong solvent-surface interactions inhibit or accelerate growth.[6,7] A major obstacle in assessing the role played by the solvent remains the unscrambling of the contributions played by internal structure and the various solvent-surface interactions. One way to do so is by comparison of the habits of crystals grown from various solvents with those obtained by sublimation or with the theoretical form;[8,9] the habit obtained from sublimation is dependent primarily upon internal crystal structure while the theoretical form is derived from internal structure only. Another simpler way is by focusing on polar crystals since it is generally accepted that the difference in the rate of growth of opposite crystal faces (hkl) and ($\bar{h}\bar{k}\bar{l}$) along a polar direction must arise primarily from differences in their solvent-surface interactions,[10,11] neglecting such effects as atom polarizability[10] at the crystal surfaces and entropy factors (which might be important for molecules with rigid and flexible moieties).

Thus, an understanding of the effect of the solvent is reduced to a study of the differences in growth of the opposite hemihedral faces; however, such a use of polar crystals requires a knowledge of the absolute structure and one is again confronted with the difficulties outlined previously.

Our method for assignment of absolute structure of crystals utilizing stereoselective additives[12] is ideally suited for the

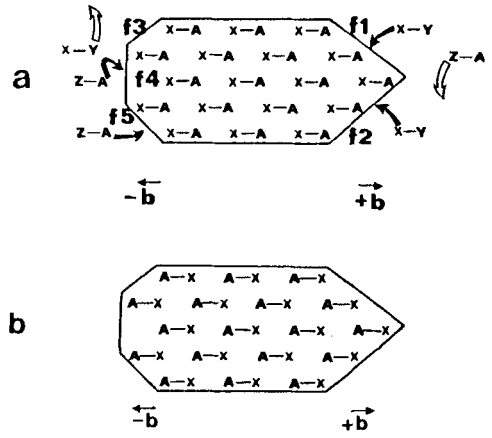
solution of such a problem. Here we shall demonstrate this approach for the assignment of absolute structure in the systems α-resorcinol, (R,S) alanine and γ-glycine whose polar crystal structures are suitable for the study of solvent-surface interactions.

Tailor-Made Additives for Assignment of Absolute Crystal Structure

The absolute structure is determined independently by three different yet complementary methods which involve the growth and dissolution of organic crystals in the presence of tailor-made additives: (1) Morphological changes induced by the additive as inhibitor of growth at specific faces of the substrate crystal; (2) Selective occlusion of the additive through specific crystallographic sites on those faces at which the additive is adsorbed leading to anisotropic distribution within the crystal; (3) Analysis of etch pits formed during partial dissolution in the presence of additive, selectively on those faces at which the additive is stereospecifically adsorbed.

Studies on growth and dissolution of organic crystals in the presence of tailor-made additives[12] led to the establishment of a general stereochemical correlation between the crystal structure of the substrate, the molecular structure of the additive and the affected crystal faces. The additives chosen are, for the most part, slightly modified substrate molecules, which may bind stereospecifically to the affected face under the condition that the modified moiety emerges from the crystal surface. During the crystal's growth, this adsorption leads to retardation of growth by disruption of the regular deposition of the oncoming crystal layers, generally leading to a change in crystal morphology. The strong stereoselective adsorption of the additive on such faces during partial dissolution causes a disturbance of the normal dissolution in different directions and leads to the formation of etch pits.[13]

These stereochemical observations were exploited for the assignment of absolute structure of polar crystals.[14] An X-ray diffraction analysis of polar crystals assuming Friedel's law, would not allow assignment of the absolute atomic arrangement. Therefore, it would not be possible to distinguish between the polar structure of Scheme 1a and the enantiomeric structure of Scheme 1b, in which the orientation of the molecule X-A is reversed with respect to the polar b axis.



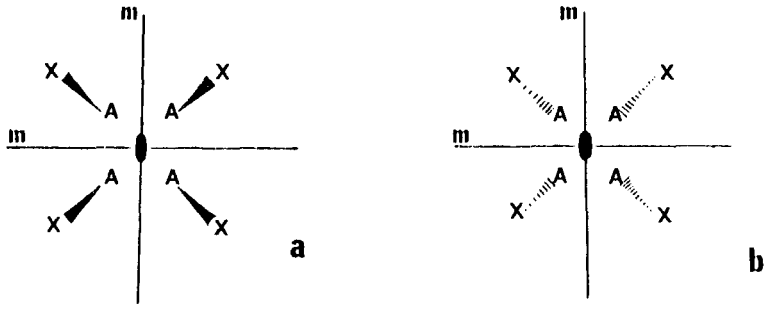
Scheme 1

In Scheme 1a (which depicts a polar crystal of point symmetry 2) the unique axis of the crystal is parallel to the X-A direction. Faces f1 and f2 delineate the crystal in the +b direction and f3, f4, f5 in the -b direction. Since the crystal is polar, the structure of the faces at the +b and -b ends are different. We have shown that in the crystal of Scheme 1a an inhibitor X-Y binds selectively at faces f1 and f2, and once bound, retards growth along +b (and possibly other directions) but not along -b. Analogously an inhibitor Z-A hinders the growth of faces f3, f4 and f5 but not of f1 and f2. The reverse situation would occur in the structure of Scheme 1b. Such retardation is associated with a relative increase in the areas of the inhibited faces or with the appearance of new faces on the affected end of the crystal. The observed morphological differences between crystals grown in the presence and in the absence of the additive allows us to establish the direction of substrate molecule X-A with respect to the polar axis and consequently derive the absolute structure of the crystal.

The principles described here apply to crystals exhibiting polar axes (i.e. for the point groups 1,2, m, mm2, 3, 3m 4mm, 6, 6m) as well as to polar crystals which do not contain polar axes such as point group 222.

In the past, we have applied this principle to chiral crystals composed of chiral molecules[14] Here we shall deal with polar crystals composed of nonchiral or racemic molecules. We shall elaborate on the specific example of point group mm2 since two of the three polar crystal structures described herein, α-resorcinol and (R,S) alanine, belong to this point group. The third example, belonging to point group 3, is easily understood in terms of the above analysis.

In the orthorhombic point group mm2 there is an ambiguity in the sense of the polar axis c. Conventional X-ray diffraction does not allow one to differentiate, with respect to a chosen coordinate system, between the two orientations of the mm2 structure depicted in Scheme 2a,b. Nevertheless, by determining which polar end of a given crystal is affected by the additive, (e.g. face (hkl) or $(h\bar{k}\bar{l})$, above and below the plane in Scheme 2b) it is possible to fix the absolute sense of the polar c axis; i.e. whether X-A points up or down.



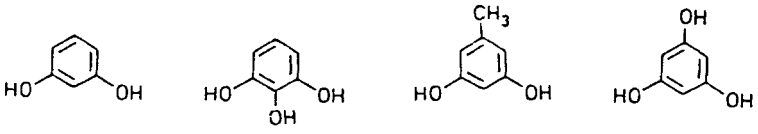
Scheme 2

α-Resorcinol

In 1949, Wells found that in an aqueous solution the α-form of resorcinol (space group $Pna2_1$, point group mm2) grows unidirectionally along the polar c axis.[15] The crystal (Fig.1a) exhibits hydrogen-rich (011) and $(0\bar{1}1)$ faces at one end of the c axis and oxygen-rich $(01\bar{1})$ and $(0\bar{1}\bar{1})$ faces at the other end (Fig.1b). The absolute direction of growth along the polar axis with respect to the crystal structure could not be fixed at that time. Therefore Wells did not know which end of a given crystal was "phenyl"-rich (hydrogen-rich in our approach) and which end "hydroxyl"-rich (oxygen-rich in our approach). Wells interpreted this unidirectional growth along c to take place at the "phenyl"-rich faces as a result of stronger adsorption of water to the "hydroxyl"-rich faces, so inhibiting their growth.

Later, Davey proposed that strong surface-water interactions should enhance crystal growth.[7] By use of oriented growth on silica surfaces, Davey, Bourne, and Milisavljevic deduced that the oxygen-rich $\{0\bar{1}\bar{1}\}$ [i.e. $(0\bar{1}\bar{1})$ and $(01\bar{1})$][16] faces are those that grow quicker in aqueous solution.

We unambiguously assigned the absolute direction of growth of resorcinol crystals in aqueous solution by employing additives pyrogallol, orcinol and phloroglucinol, and independently by the Bijvoet method.[17]



resorcinol pyrogallol orcinol phloroglucinol

The additive pyragallol should inhibit the growth of α-resorcinol at the oxygen-rich faces whereas orcinol should affect growth at the hydrogen-rich faces.

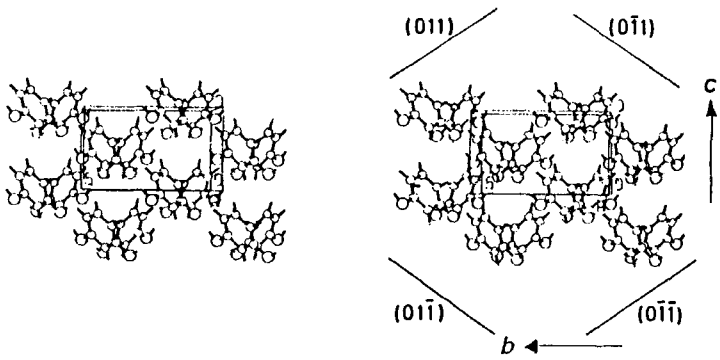


Fig.1 (a) Typical crystal of α-resorcinol grown from water. The faces (011), (0$\bar{1}$1), (01$\bar{1}$) and (0$\bar{1}\bar{1}$) are marked;

(b) Stereoscopic view of the packing arrangement of α-resorcinol along the a axis. The planes parallel to the hydrogen-rich {$\bar{1}$11} and oxygen-rich {0$\bar{1}\bar{1}$} faces are denoted.

Resorcinol grown from aqueous solution typically exhibits growth defects (in the form of occlusions) at the fast growing end of the crystal (see Fig.1a). In other systems such defects have been attributed to the local undersaturation of the solute molecules at the fast growing end of the crystal.[18]

Crystals of α-resorcinol grown in the presence of pyragallol exhibited the same faces as pure resorcinol but they were shorter in length in the c direction and developed no observable defects during growth (Fig.2).

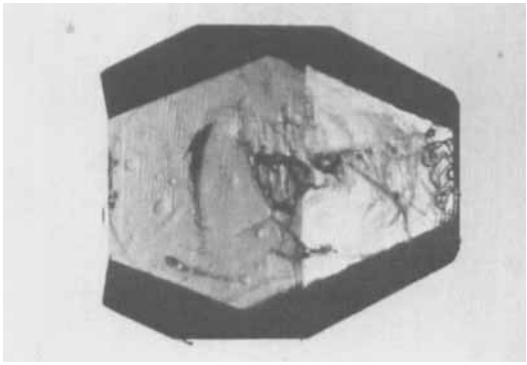


Fig.2: Crystal of resorcinol grown in the presence of pyragallol (x10).

Alternatively, crystals grown in the presence of orcinol contained defects, indicative of a fast growing end, and exhibited a habit identical to pure resorcinol. These results suggested that growth of resorcinol in pure aqueous solution along the polar axis takes place preferentially at the oxygen-rich $(01\bar{1})$ and $(0\bar{1}\bar{1})$ faces, those faces which were inhibited by pyragallol. To further verify this point, we made use of the anisotropic distribution of occluded additive during crystal growth [method (2), vide supra]. α-Resorcinol was grown from a pure seed in the presence of pyragallol and orcinol. The growth defects in the seed crystal provided a marker as to its original fast and slow growing ends. HPLC analysis of additive within the resulting crystal, not completely defect-free at the original fast growing end, showed the following: only orcinol was embedded at the completely smooth end (i.e. the original slow-growing end of the seed crystal) and at the opposite slightly rough end, pyragallol with traces of orcinol (Fig.3).

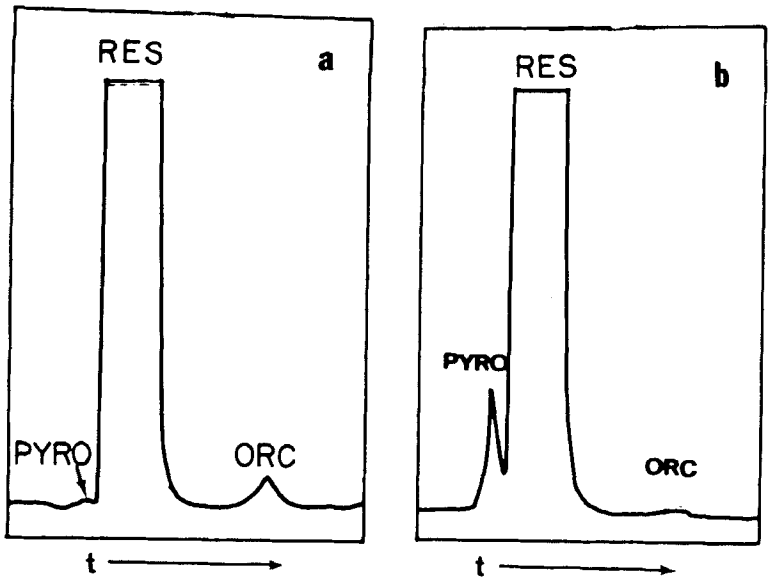


Fig.3: HPLC analysis of a crystal of α-resorcinol grown in the presence of pyrogallol and orcinol. (a) Material removed from the smooth end; (b) Material removed from the rough end.

We may conclude that pyragallol is stereospecifically occluded through the original fast growing $(01\bar{1})$ and $(0\bar{1}\bar{1})$ faces and orcinol through the original slow-growing (011) and $(0\bar{1}1)$ faces; the traces of orcinol found at the slightly rough end are probably due to mechanical trapping.

We also carried out dissolution experiments of α-resorcinol in the presence of phloroglucinol and pyragallol. We found that etch pits were formed on the slow-growing end faces only in the presence of phloroglucinol (Fig.4) which is once again completely compatible with our assignment of the structure of the growing faces at the polar ends. Oriented asymmetric pits on the four {110} side faces of the crystal were obtained by partial dissolution in a solution of m-cresol. The polar shape of the etch pits provides a further means of relative assignment of crystal polarity.

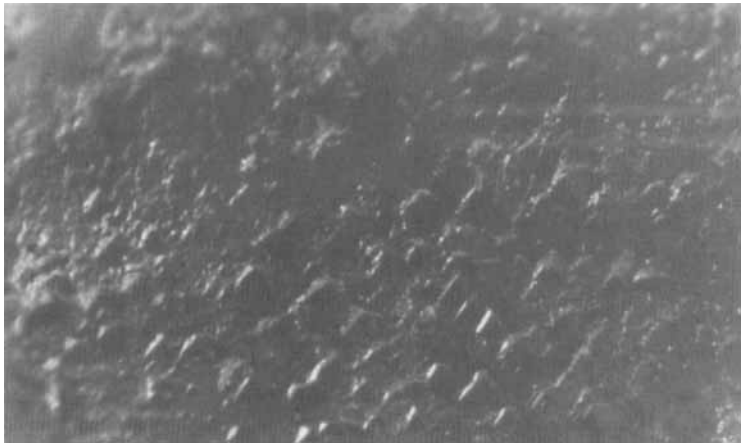


Fig.4: Optical microscope photograph of an {011} face of resorcinol etched by phloroglucinol (x80).

Our findings demonstrated that the unidirectional growth in water takes place primarily at the oxygen-rich faces in accordance with the findings of Davey, Bourne, and Milisavlijevic.[16] We tend to the paradoxical view, however, that the unidirectional growth at the oxygen-rich faces is due to inhibition of growth at the hydrogen-rich faces because of a higher affinity of water for the latter. We base our arguments on the relative structures and on the van der Waals and Coulomb energy potentials of these surfaces, described elsewhere.[17]

(R,S) alanine

This compound crystallizes in the orthorhombic polar space group $Pna2_1$ (point group mm2). 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 amino NH_3^+ groups at the opposite end[19] (Fig.5a).

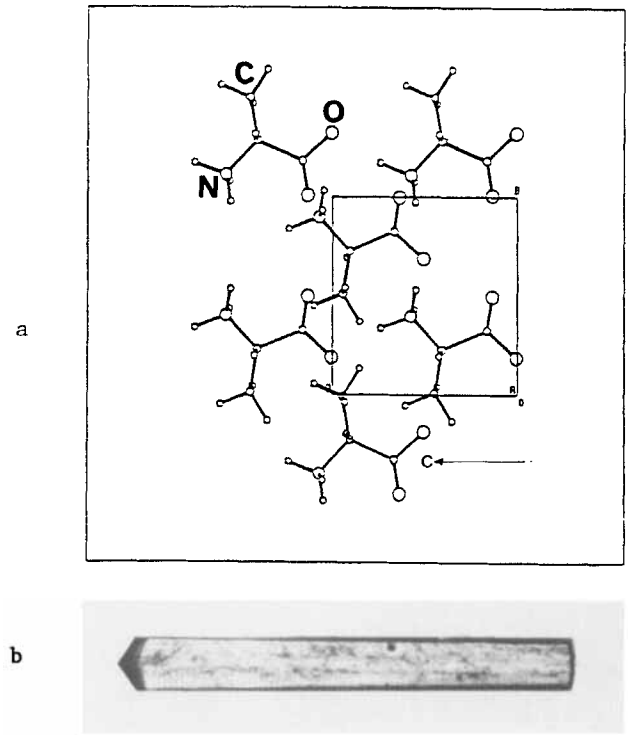


Fig.5: (a) Packing arrangement of (R,S) alanine viewed along the a axis; (b) Crystal of (R,S) alanine pure. Note flat and capped ends of crystal (x20).

(R,S) alanine crystallizes from water as needles elongated in c (Fig.5b). Crystallization of alanine followed under an optical microscope revealed a pronounced tendency for unidirectional growth along the polar axis (Fig.6). The absolute polarity of such crystals was determined by growth of alanine in the presence of N-methyl alanine and methyl alaninate. N-methyl alanine should hinder growth in the c direction from which the amino moiety emerges whereas methyl alaninate (with a synplanar $O{=}C{-}O{-}CH_3$ conformation)[20] should affect at the opposite carboxylate end of the crystal. Growth in the presence of N-methyl alanine yielded long needles growing unidirectionally at one end of the polar axis, akin to growth of the unaffected

crystal. On the other hand, growth in the presence of methyl alaninate yielded stubby crystals. These experiments demonstrate without doubt the preferential growth of (R,S) alanine at the carboxylate pole of the c axis.

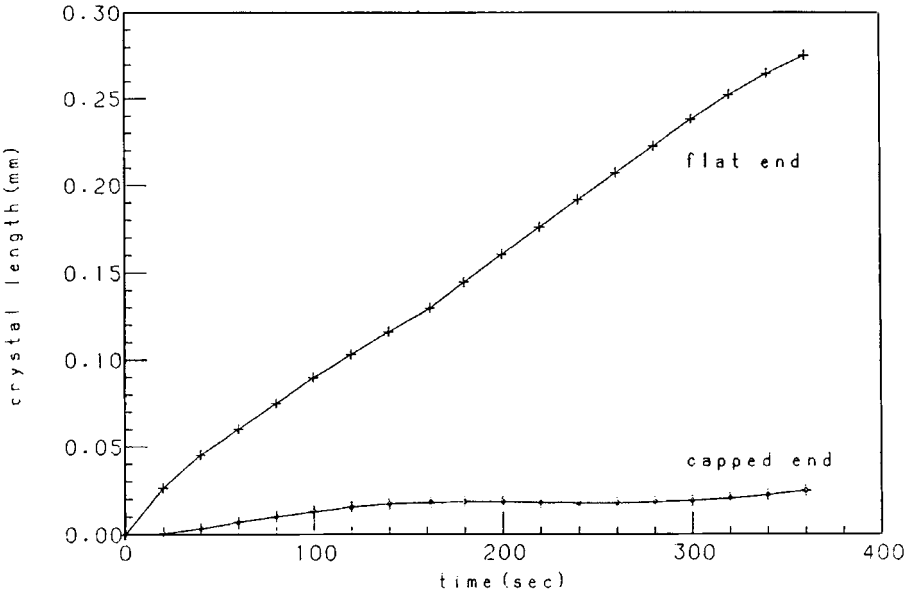
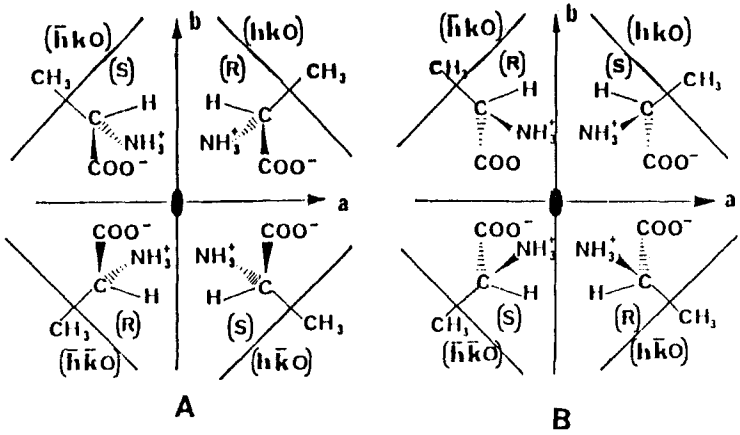


Fig.6: Increase in length of a crystal of (R,S) alanine at its opposite ends as a function of time.

It is also possible in principle, to establish the absolute structure of the growing crystal by partial dissolution in the presence of the same additives to yield etch figures at the appropriate end faces of the crystal. These etch figures have as yet not been seen as the surface area of the end faces is limited by the extreme thinness of the crystals. One may circumvent this drawback by inducing etch figures on the side {hk0} faces with an appropriate chiral resolved amino acid of known absolute configuration. Consider for example the arrangement of (R,S) alanine in Scheme 3 (which is equivalent to Scheme 2 in the case of a racemic mixture) bounded by the four symmetry-related {hk0} faces. Growth, or partial dissolution, of the crystal in the presence of chiral amino acid additives

with a modified side chain of (S) configuration will affect the $(\bar{h}k0)$ and $(h\bar{k}0)$ faces in Scheme 3a but would affect the (hk0) and $(\bar{h}\bar{k}0)$ pair in the opposite orientation of Scheme 3b. As expected, etch pits were formed on one pair of side faces of (R,S) alanine by (S) threonine (Fig.7), so fixing the absolute structure of the crystal. Analogously (R,S) alanine crystallized in the presence of (S) threonine exhibited two affected and two unaffected side faces.[2]



Scheme 3

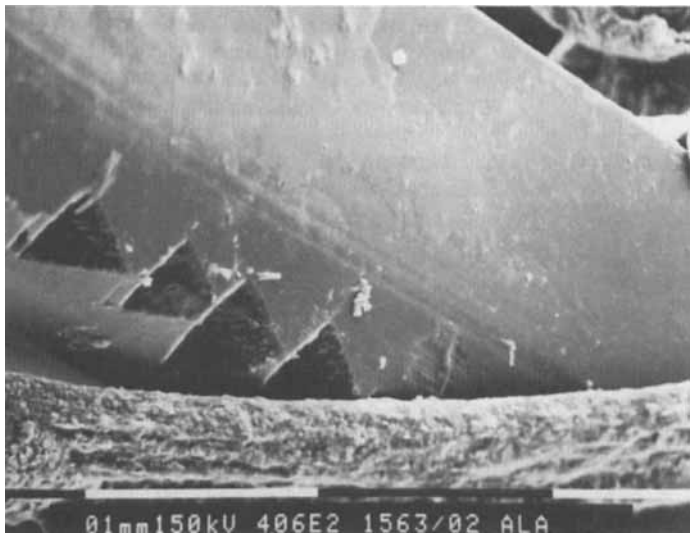


Fig.7: Scanning electron micrograph of (hk0) side faces of (R,S) alanine etched by (S) threonine (x400).

γ-Glycine

Glycine crystallizes from 0.6 M. sulphuric acid in the trigonal polar space group $P3_1$ (or $P3_2$). The molecules are hydrogen-bonded along the polar c axis in an arrangement 2_1 very similar to that in (R,S) alanine. Thus the molecules are oriented with respect to the c axis so as to expose carboxylate CO_2^- groups at one end of the polar axis and amino NH_3^+ groups at the opposite end (Fig.8a). The crystals exhibit a trigonal prismatic morphology elongated in c as in Fig.8b and grow preferentially at one end of the polar axis.

The absolute arrangement of the molecules in such a crystal was assigned by etching its top and bottom faces with additives N-methyl glycine and ethyl glycinate.

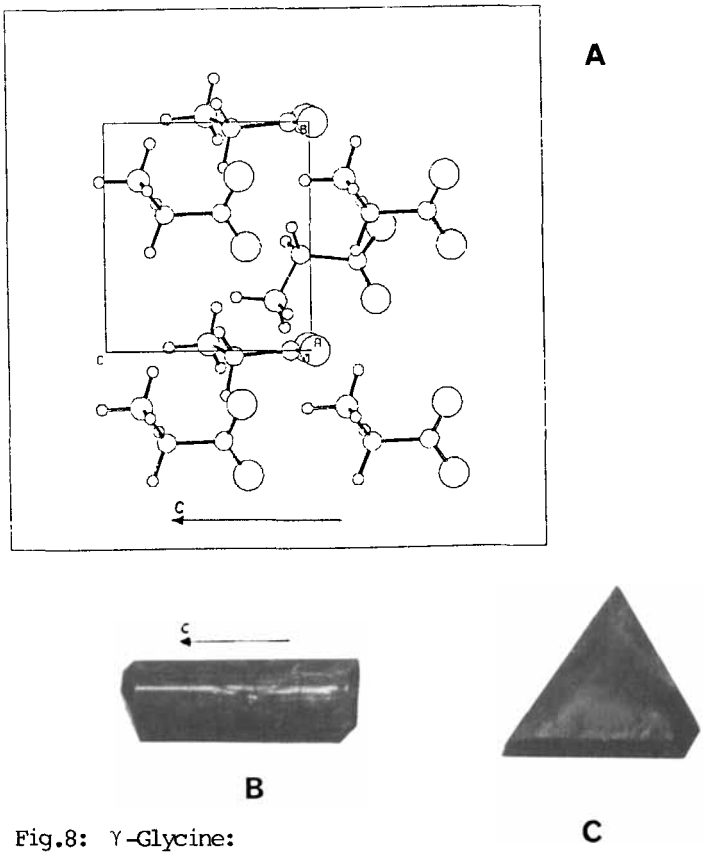


Fig.8: γ-Glycine:
(a) Packing arrangement viewed along the a axis;
(b) Morphology of pure crystal viewed perpendicular to the c axis;
(c) Morphology of crystal grown in the presence of ethyl glycinate viewed down the -c axis.

The three well-formed trigonal end faces {103} were etched during partial dissolution in the presence of N-methyl glycine indicating that this was the end of the emerging amino groups (Fig.9a). Similarly the ethyl ester of glycine etched the opposite (00$\bar{1}$) face (Fig.9b) independently revealing that the CO_2 groups are exposed at that pole of the crystal.

Growth experiments with these same additives yielded truncated capped crystals when the fast-growing CO_2^- end was inhibited by glycine ethyl ester (Fig.8c) and unaffected prisms when N-methyl glycine was used. Both dissolution and growth experiments unequivocally demonstrate a tendency for unidirectional growth at the CO_2^- end. The absolute structure was then confirmed by the Bijvoet method on a specimen crystal exhibiting the hemihedral faces {103} and $(00\bar{1})$.

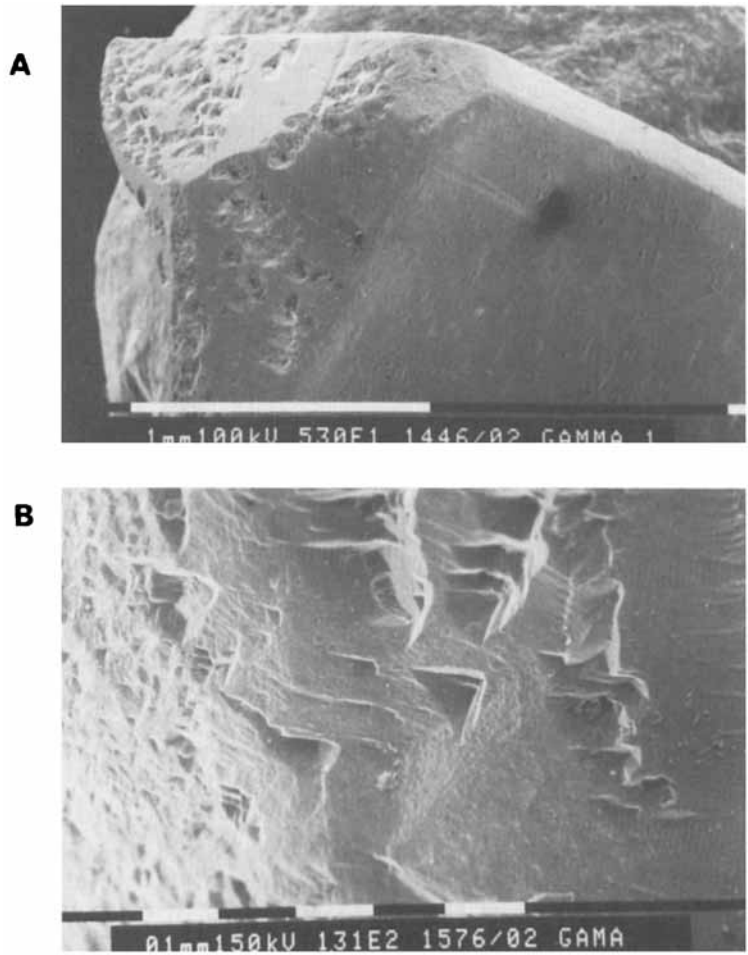


Fig.9: (a) Crystal faces {103} of γ-glycine etched by N-methyl glycine.
(b) Crystal face $(00\bar{1})$ etched by ethyl glycinate.

DISCUSSION

Absolute Crystal Structure

The absolute structure of crystals with polar axes and composed of nonchiral molecules or racemic mixtures has been determined by growth and dissolution experiments in the presence of tailor-made additives.

This same method has already been applied on several systems for the assignment of absolute configuration of chiral molecules in crystals which exhibit either polar axes[14] or polar directions[2] and, with variations, on the assignment of the absolute configuration of additives by their effect on centrosymmetric crystals.[12] It is further possible to extend this approach to chiral crystals which are composed of nonchiral molecules and which do not contain polar axes (e.g. point group 222) provided the additives are chiral. The method has several advantages: It is simple, and reliable in so far as it encompasses several related, yet independent experimental approaches. Its reliability is based on our knowledge of how the additive molecules are adsorbed with respect to the crystal structure and faces and has been cross-checked on many systems.

We have demonstrated in this paper how one may assign the absolute structure of crystals with orthorhombic mm2 and trigonal 3 point groups. In the case of the latter the assignment of absolute structure vis-a-vis the polar axis did not entail determination of the chirality of the crystal i.e., $P3_1$ or $P3_2$. Having established the absolute polaritry of the crystal it is moreover straightforward to assign its chirality by conventional diffraction.*

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* Here it is noteworthy that the intensities of the X-ray diffraction patterns of $P3_1$ and $P3_2$ superimpose only upon rotation of 60° about the c-axis of one of the patterns. Thus if the crystal develops trigonal morphological point symmetry of the type 3, 3/m or 3m, but not morphological sixfold symmetry, one may perform a Pasteurian separation of the $P3_1$ from the $P3_2$ crystals by conventional diffraction. One cannot however decide which is which without resorting to assignment of absolute structure.

Effect of Solvent on Crystal Growth

In this study, we have applied the above method for the determination of absolute structure of three systems α-resorcinol, (R,S) alanine and γ-glycine. The experiments showed that the slow-growing end in each crystal system was that which exposed (either N-H, O-H or C-H) hydrogen atoms and the opposite fast growing end exposed (carboxylate or hydroxyl) oxygen atoms. Preliminary experiments have been performed on other resolved amino acids whose chiral crystals contain polar axes, such as valine and methionine. The results indicate that in these systems as well there is preferential growth which takes place at that end of the polar axis where the carboxylate oxygens emerge. If we assume that strong solvent-surface interactions are the cause of inhibition of growth at the slow-growing end of the polar axis (akin to the effect of tailor-made additives) then this indicates that water is more strongly bound to the hydrogen-rich faces. One may however have to take into account the effects of crystal surface-roughening,[5] and solvent-solute interactions both of which act in the same way and opposite to that of inhibition. It has been in fact proposed that strong solvent-surface interactions cause surface roughening which in turn may result in enhanced growth rate. The problem may be resolved by performing experiments on polar crystals composed of molecules with hydrophobic and hydrophilic groups at opposite ends, so that the solvent (hydrophilic or hydrophobic) is preferentially solvating one end of the solute molecule and one polar end of the crystal. Under these circumstances one should be able to differentiate between inhibition of growth due to solvent-surface interactions and the effects of solvent-solute and crystal surface roughening. An ideal system for such an experiment would be a β-tetrolic acid.[22]

We hope that these types of experiments coupled with atom-atom potential energy calculations will provide information on solvent-surface interactions and their influence on crystal growth.

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