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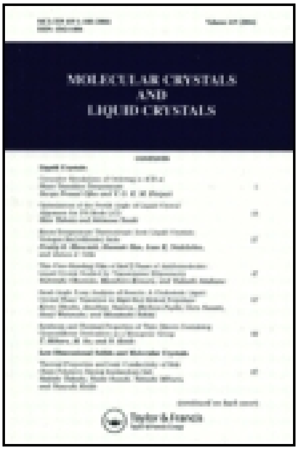

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MORPHOLOGY ENGINEERING OF ORGANIC CRYSTALS WITH THE ASSISTANCE OF “TAILOR-MADE” GROWTH INHIBITORS

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MORPHOLOGY ENGINEERING OF ORGANIC CRYSTALS WITH THE ASSISTANCE OF "TAILOR-MADE" GROWTH INHIBITORS

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Abstract Retardation of growth of organic crystals in the presence of additives in solution has been investigated in terms of their crystal structures and the stereochemistry of the additives. A simple correlation has been established between affected directions of growth and structure of the additive. This mecnanism has been successfully applied for monitoring, in a controlled manner, the morphology of organic crystals; this is illustrated for benzamides and benzoic acids. Furthermore, the absolute configuration of polar crystals and chiral molecules has been directly assigned. This is illustrated for the polar crystal of tr-cinnamoyl alanine, and for the molecule of threonine, through morphological changes this molecule induces in the centrosymmetric crystal of serine.

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INTRODUCTION

Impurities present even in minute amounts in systems undergoing crystallisation frequently cause pronounced retardation in the growth of the crystals. Furthermore, the overall morphology of crystals grown in the presence of impurity may differ dramatically from that of the pure material.

Recently, we systematically analysed the stereochemical correlation between the crystal structure, including morphology, of the compound undergoing crystallisation, and the stereochemistry of the added impurities. As a result of the understanding developed, we were able to induce controlled changes of the morphologies of a large variety of crystals of different molecular structures.[4-8] It was further possible to improve processes such as resolution of enantiomers by crystallisation[9], and to control systematically the rate and mode of dissolution of organic crystals.[10] In addition, the absolute configuration of chiral molecules was directly derived from controlled morphological changes.[6,11,12] Some of these principles are discussed in the present lecture.

DESIGN OF CRYSTALS WITH DESIRED MORPHOLOGIES

The stereochemical correlation which has been established between the molecular structure of the impurity, the crystal structure of the substrate and the affected growth directions led to the formulation of a two-step mechanism of stereospecific binding of the impurity at the growing crystal faces with a subsequent retardation of growth.[5,6,7] Slightly modified substrate molecules were found to be particularly effective in inducing morphological changes.

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By virtue of attractive interactions (e.g. ionic and/or hydrogen bonds), the unmodified moiety (with respect to the substrate) of the impurity is bound at the site of a substrate molecule on appropriate growing surfaces of the crystal such that the modified part of the impurity molecule is mainly directed away from the crystal surfaces. The modified side chain then perturbs the regular deposition of additional layers, decreasing the rate of growth of the crystal in these directions, relative to the rates in other directions which are unaffected. This modification of relative growth rates eventually results in changes in crystal morphology. Applying these principles it became possible to grow crystals with desired morphologies by "tailoring" retarders which bind at a preselected face and thus inhibit growth in a predictable manner. The effect of other factors such as temperature, solvent and supersaturation, which influence crystal growth and morphology, is kept constant by performing all the crystallisation experiments under standard conditions, but for the nature and concentration of impurity. We shall illustrate this approach for benzamides and benzoic acids.[7,8]

Benzamide crystallises from ethanol in the form of plate-like crystals elongated along *b*, displaying dominant faces {001} {011} and $\{10\bar{1}\}$ (Fig.1,2a). In the crystal of benzamide hydrogen bonded cyclic dimers are interlinked via NH...O bonds along a 5Å *b* axis to form the commonly observed ribbon motif. The ribbons are stacked along the 5.6Å *a* axis to yield {011} layers stabilised by attractive Coulomb interactions. In the third direction {001} layers juxtapose *via* weak van der Waals contacts between phenyl groups, thus accounting for the {001} plate-like nature

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of the crystal. In the light of the above correlation between the crystal structure and morphology of benzamide, it was possible to choose impurities which specifically modify the relative rates of growth along the three principal directions: retardation of growth primarily along the *b*-axis was achieved by crystallising in presence of benzoic acid as impurity. Substitution of a benzamide molecule by one of benzoic acid (which adopts the commonly observed *syn* planar O=C-OH conformation) results in replacement of an N-H bond of the amide by "lone pair" electrons of the hydroxyl oxygen atom of the acid, and thus replacement of an attractive NH...O bond by a repulsive O...O interaction. This induces the crystals to grow as bars extended along *a*. (Fig. 2b). Further support for this mechanism was obtained by atom-atom potential energy calculations.[8]

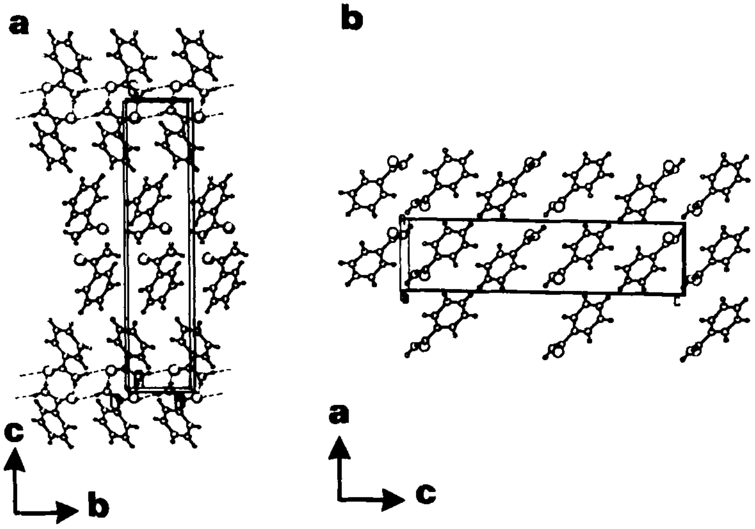

FIGURE 1. Packing arrangement of benzamide viewed: a) along the *a* axis; b) along the *b* axis.

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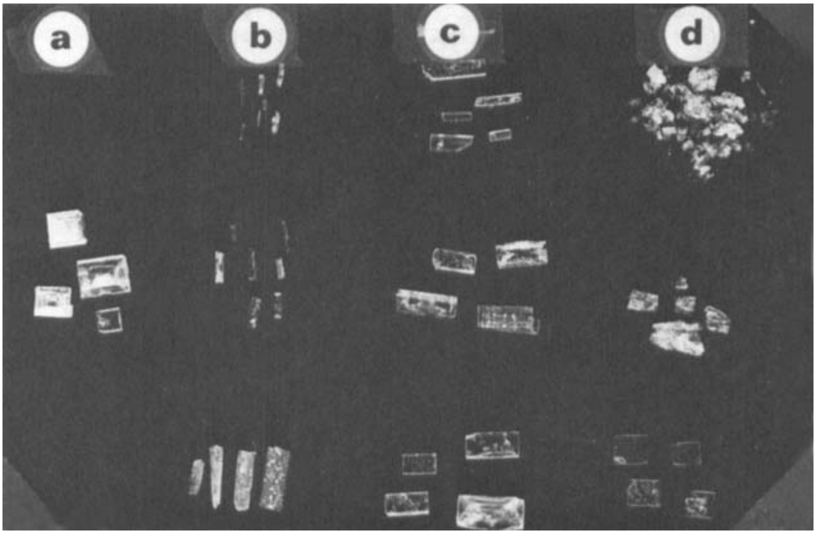

FIGURE 2. Crystals of benzamide: a) pure; b) crystallised in the presence of increasing amounts (from bottom to top) of benzoic acid; c) of o-toluamide; d) of p-toluamide.

Retardation of growth along the a axis was achieved by adding small amounts of the heavily twisted molecule of o-toluamide to the mother solution. This induces crystallisation in the form of bars extended along the b axis (Fig.2c). Finally, as expected, thinner and thinner plates were obtained by adding increasing amounts of p-toluamide whose methyl substituent perturbs the regular deposition of {001} along the c-direction (Fig.2d).

In the benzamide/benzoic acid system we have considered the effect of impurity in which an hydrogen atom is replaced by the lone pair of oxygen. The inverse effect was studied in crystallisation of benzoic acid in the presence of benzamide as impurity. Benzoic acid crystallises from ethanol in the form of plates elongated in the b-direction (Fig.4a). The general features of the crystal habit may be

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understood in terms of molecular packing; the molecules form almost coplanar hydrogen-bonded dimers which are stacked along the 5.1 Å b-axis. These dimers,in turn, form an almost coplanar ribbon motif along this axis (Fig.3). The combined ribbon and stack motif generate {001} layers which are juxtaposed by weak van der Waals forces leading to plate-like crystals.

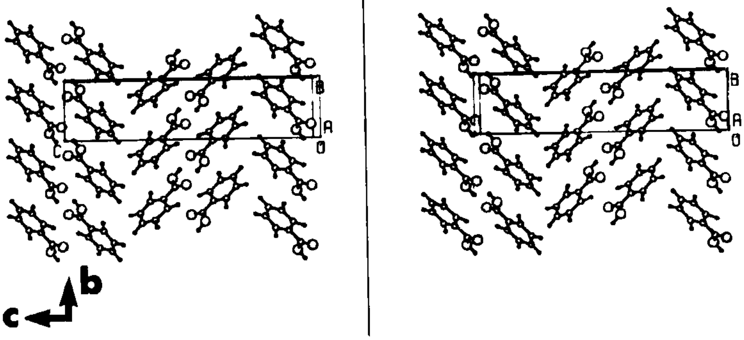

FIGURE 3. Stereoscopic view of the packing arrangement of benzoic acid along the a axis.

Introducing benzamide as impurity affected the crystals as shown in Fig. 4b inhibiting growth along the stack axis. The effect is explained in terms of the twist of 14° between the phenyl and amide moiety in the benzamide molecule, owing to the repulsion between the ortho and amide hydrogen atoms. Substitution of a planar benzoic acid, with twisted benzamide disturbs the deposition of benzoic acid dimers along the stack axis. This is supported by the observation that the planar picolineamide (**o**-pyridine benzamide) (Fig.4c) does inhibit growth along the **b**-axis.

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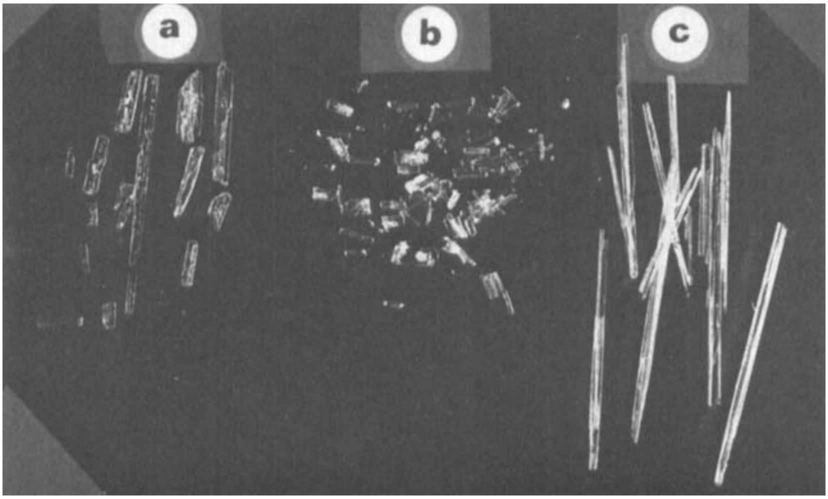

FIGURE 4. Crystals of benzoic acid; a) pure;
b) crystallised in the presence of benzamide;
c) crystallised in the presence of picolineamide

Modelling Impurity Effects in the Growth of Polar Crystals

Further insight into the mechanism of adsorption of the impurity and retardation of growth may be obtained by the study of the effect of "tailor-made" growth inhibitors on chiral crystals possessing a polar axis.[6,13]

Scheme 1 describes the structure of such a crystal, belonging to space group $P2_1$. The unique axis of the crystal is parallel to the axis of the molecule X-A. Faces f1 and f2 delineate the crystal in the polar $+\underline{b}$ direction, and f3, f4, f5 in the $-\underline{b}$ direction. The faces within each pair (f1, f2 and f3,f5) are homotopic since they are related by 2-fold symmetry. The polarity of the crystal precludes a symmetry relationship between the $+\underline{b}$ and $-\underline{b}$ directions.

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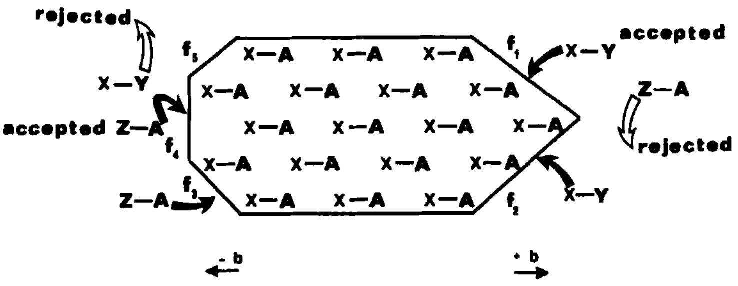

SCHEME 1.

By application of the two-step mechanism of adsorption-inhibition described above, an impurity X-Y will bind selectively at faces f1 and f2, and once bound will retard growth along +*b* and possibly other directions, but not along -*b*, in the crystal of Scheme 1. The same logic applies to an impurity Z-A, which will hinder the growth of faces f3, f4 and f5 but not of f1 and f2. Such retardation will be associated either with an increase in the areas of the inhibited faces with respect to the unaffected ones or with the appearance of new faces on the affected side of the crystal. It should consequently be possible to determine on which of the polar faces the impurity has been adsorbed, and thus to assign directly the absolute configuration of the crystal. These requirements are met by a number of polar crystals, among which are those of sucrose, which have drawn an increasing amount of attention of the sugar technologists.[15,16]

A number of systems have been studied by our group. We shall illustrate the method here for the case of *tr*-cinnamoyl alanine. Enantiomerically pure *tr*-cinnamoyl-

(S)-alanine crystallises in polar crystals (Space group $P2_1$). According to the packing arrangement of the crystal all OH groups of the acid form H bonds with a major component along -b whereas the C(chiral)-H bond is directed along the +b direction. The orientation of the molecules with respect to the crystal faces in the pure crystal are depicted in Fig. 5. We expect, according to the above

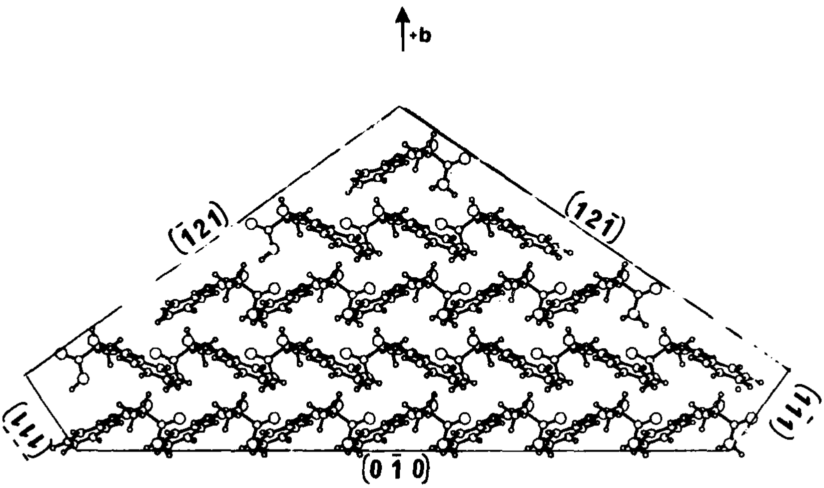

FIGURE 5. Packing arrangement of tr-cinnamoyl-(S)-alanine viewed along the a axis, as delineated by the faces of pure crystals grown from ethanol.

analysis, that the methyl ester of the acid will decrease the growth rate in the -b direction. By the same reasoning growth should be inhibited along the opposite direction, +b, using tr-cinnamoyl-(R)-alanine or tr-cinnamoyl-(R)-serine as the impurity. As expected, the most pronounced change induced by the methyl ester of tr-cinnamoyl-(S)-

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alanine is the large increase in the areas of the symmetry related ($1\bar{1}1$) and ($\bar{1}\bar{1}\bar{1}$) faces, since the (carboxyl) O-H...O (amide) H-bonds are almost perpendicular to these faces. Conversely, the impurity *tr*-cinnamoyl-(R)-alanine induces formation of the (010) face as shown in fig. 6 as a result of inhibition of growth along +*b*.

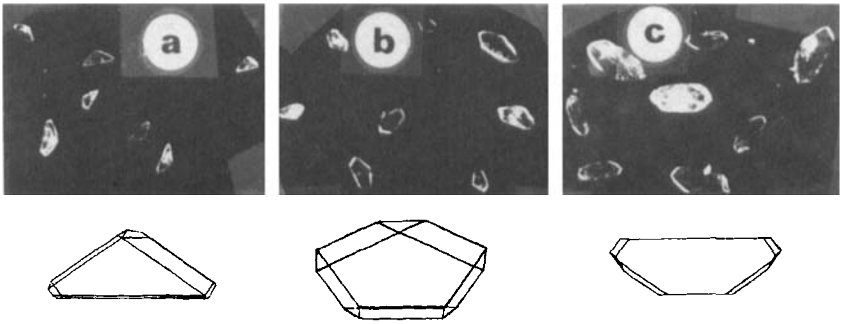

FIGURE 6. Cinnamoyl-(S)-alanine crystals. (I) Photographs (II) Computer drawn pictures
a) pure; b) grown in the presence of the methyl ester, c) grown in the presence of cinnamoyl-(R)-alanine.

From these changes the orientation of the *tr*-cinnamoyl alanine molecule with respect to the *b* axis is assigned, thus fixing unambiguously the absolute configuration of the molecule. This information cannot be obtained by X-ray diffraction, unless the Bijvoet method of anomalous dispersion is applied.

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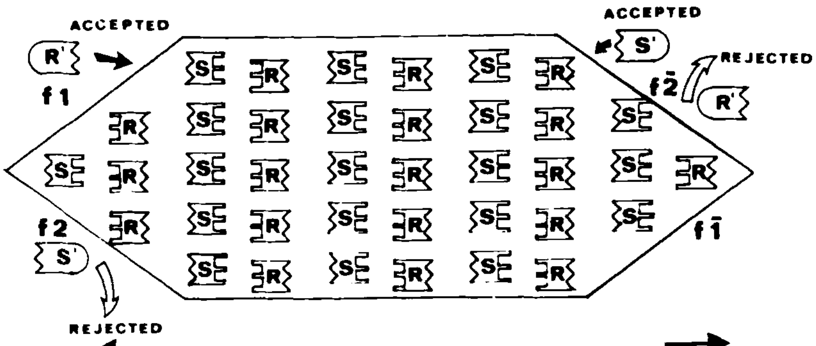
Assignment of the Absolute Configuration of Chiral Molecules

The above method of determining absolute configuration is not limited to polar crystals but is applicable as well to chiral molecules, which induce morphological changes in achiral crystals composed of racemic mixtures or meso compounds.[11] The method is based on the fact that, in contradistinction to chiral crystals, in centrosymmetric ones the orientations of the constituent molecules with respect to the crystal axes are unambiguously assigned. This known orientation of the enantiomers in such crystals can be directly exploited for the assignment of the absolute configuration of chiral resolved molecules provided the structural information is transferred to a chiral resolved impurity molecule. The absolute configura*tion of such resolved impurities is determined through the* morphological changes the impurity molecules induce selectively on the enantiotopic faces of appropriately selected crystals. *A prerequisite for application of this* method is that within the centro-symmetric racemic crystal *a specific functional group attached to an R molecule will point towards the face f1 but not towards f$\bar{1}$* (Scheme 2).



SCHEME 2

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By symmetry, the same functional group attached to an (S) molecule will emerge at the enantiotopic face $(\bar{h}\bar{k}\bar{l})$, but not at (hkl). It is useful here to regard centrosymmetric crystals containing chiral molecules as enantiopolar, namely comprising two enantiomeric sets of intermeshed polar crystal structures related to each other by a centre of inversion. Crystallisation of such a compound in the presence of a chiral additive (R'), appropriately designed so that it will fit in the site of an (R) molecule on the growing crystal faces f1 or f2, but not on the enantiotopic faces $f\bar{1}$ or $f\bar{2}$, will hinder growth along the +*b* direction but not along -*b*. By virtue of symmetry, the enantiomeric additive (S') will inhibit growth of faces $f\bar{1}$ and $f\bar{2}$, while racemic (R')(S') will inhibit growth along both directions +*b* and -*b*.

Using this principle we succeeded in determining the absolute configurations of all the α-amino-acids through morphological changes they induce on a growing single crystal of α-glycine.[12] Here we shall rather illustrate its application to the system threonine/serine. Racemic serine crystallises in an appropriate molecular packing, space group $P2_1/a$ (Fig. 7). Both C-H bond vectors of the rigid methylene group of serine have major components along the unique *b*-axis. Thus replacement of one of them by a methyl (as in threonine) will inhibit growth along the *b*-direction. In an (R)-Thr molecule [with the side-chain β carbon of chirality (S)], the methyl group will replace the pro-(S) hydrogen atom of (R)-Ser so as to inhibit growth along +*b*. By symmetry the $-CH_3$ group of (S) Thr will replace the pro-(R) hydrogen of (S) Ser and hence inhibit growth along -*b*.

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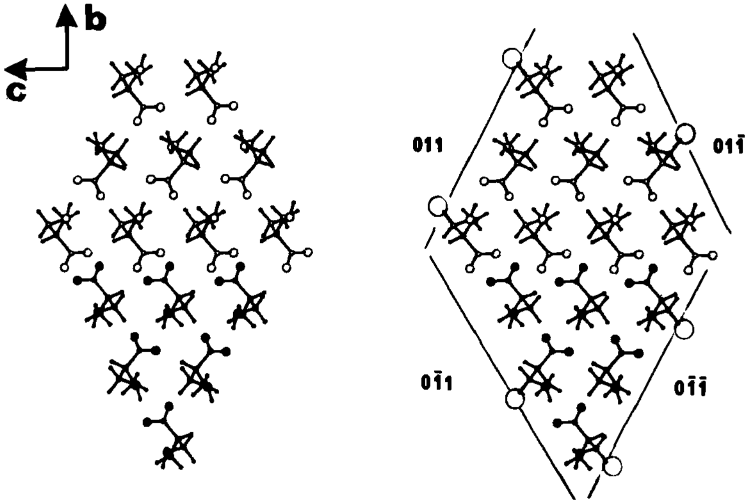

FIGURE 7. Stereoscopic view of the packing of (R)(S) serine along the a axis. Molecules are packed in b,c layers which are homochiral. For clarity only half of each (R) (open circles) and(S) (full circles) layer is shown, delineated by the four $\{011\}$ crystal faces. Threonine impurity molecules (with the $-CH_3$ group indicated by large circles), are inserted stereospecifically.

(R,S)-Ser forms tabular crystals, with point symmetry 2/m (Fig.8a); the crystals affected by either (R)-Thr or (S)-Thr exhibit reduced morphological symmetry 2 (the mirror plane is lost) and are enantiomorphous (Fig.8b,c). (R)(S)-Thr as impurity leaves the morphological symmetry unchanged at 2/m, as a result of a combination of the effects induced by each impurity separately, turning

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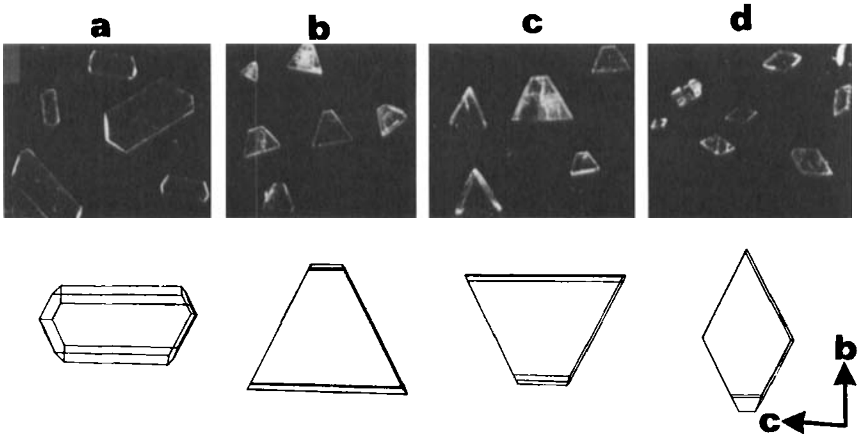

FIGURE 8. Crystals of (R,S) serine, (I) photographs (II) computer drawn picture; a) pure and grown in the presence of: b) (R) threonine; c)(S) threonine; d) (R),(S) threonine.

the crystals into rhombs (Fig.8d). The morphological changes, and our interpretation thereof, imply that in this last experiment (R),(S)-Thr must segregate along the b-axis during crystal growth; occluded (R)-Thr will prevail at the +b half of the crystal, whereas (S)-Thr will prevail at the -b half of the crystal. This expectation was confirmed experimentally by HPLC analyses of tips of serine crystals which were taken from the two ends of the polar b-axis (Fig.9).

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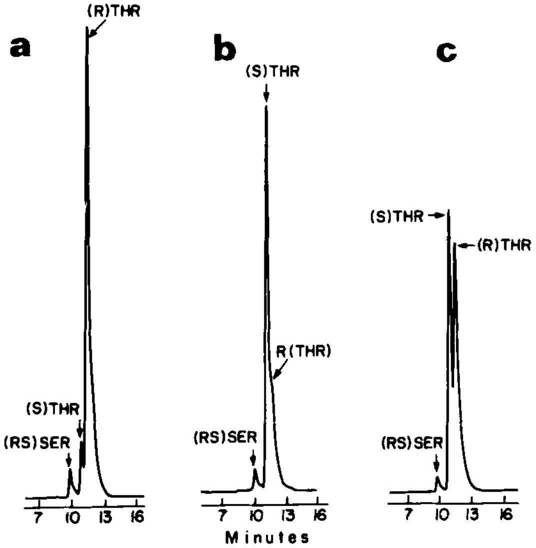

FIGURE 9. Chromatographic analysis of (R) and (S) threonine occluded in the rhomb-like crystals of (R),(S) serine: a) tip of the crystal from the +<u>b</u> direction; b) tip of the same crystal from the -<u>b</u> direction; c) whole crystal. The small amounts of (R),(S) serine are residual from the previous separation of serine from threonine.

Concluding Remarks

A simple correlation between crystal structure, crystal morphology and impurities present during the crystallisation of organic compounds has been established. We described here some applications of this mechanism such as the design of crystals with desired morphologies, and a new method for the direct assignment of the absolute configuration of chiral crystals and molecules. In addition we have successfully applied the method to the kinetic resolution of enantiomers by crystallisation and for the controlled dissolution of organic crystals; these applications are discussed elsewhere[4,10].

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