JTA.

10 DOWNING STREET

THE PRIME MINISTER

29 May 1986

Dear Mrs. Schmidt.

Thank you so much for your letter and for sending me the review of Gerhard's work. I shall read this as soon as I get time and know that it will be fascinating and rewarding.

I am sorry that there was no opportunity to meet during my visit to the Weizmann Institute. I cannot tell you how much I enjoyed it, and look forward to an opportunity to return and spend more time there.

Yours sincerely

Margaret Thatcher

Mrs. Esther Schmidt.

Mrs. Esther Schmidt
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Rehovot, 26th May, 1986

Dear Mrs. Thatcher,

Jack Dunitz, who was here a few weeks ago, told me that you had asked him for a copy of a biographical sketch of Gerhard's which he had written.

May I round off the picture by presenting you with a copy of a recently published review in Endeavour about Gerhard's work. Knowing how much he valued your friendship, I feel that he would have wanted you to know that the little time he had was well spent.

Respectfully yours,

Esther Schmidt.

Carrying out organic chemistry within crystalline solids

Gautam R. Desiraju

Since organic solid state reactions must take place within the organised medium of the crystal lattice, their course and outcome can often be controlled and exploited. Although their major application is not in the area of organic synthesis, they are far from being academic curiosities. They have been involved in situations as diverse as observing the approach of reacting molecules, determining the absolute configurations of chiral molecules, and establishing crystallisation patterns for organic solids.

Friedrich Wöhler's conversion of ammonium cyanate to urea in 1848, signalling as it did the collapse of the vital force theory for organic compounds, is widely considered to mark the beginning of organic chemistry as a separate subject. However, it is not so well-known that this particular transformation occurs in the solid state. Organic reactions in crystals are, therefore, certainly not new and the early literature is varied and interesting. However, there was for many years no systematic development of this subject and these reactions remained isolated curiosities.

In retrospect, it is really not surprising that this was so and that organic chemists preferred to work with solutions. The ready solubility of organic substances in common solvents and the controlled conditions possible in solution enable the chemist to carry out reactions in an easy and reproducible manner. In contrast, solids are low-melting, volatile, and difficult to handle. Many organic reactions require activation energies that would be possible only at temperatures much above the melting point. Concepts such as electronic effects and kinetics which are simple enough to understand for solution reactions become all but intractable when applied to solid-state processes.

The difficulties associated with completely understanding solid state reactions arise mostly from the fact that while solution reactivity is largely a molecular property, solid state reactivity is a characteristic of an entire assembly of molecules. Indeed, organic solid state chemists are usually concerned with the most perfect molecular assembly of all, that is, a single crystal.

Gautam R. Desiraju, B.Sc., Ph.D.

Was born in Madras in 1952 and graduated from the University of Bombay in 1972. He subsequently gained a Ph.D. degree at the University of Illinois, Urbana, and then worked in the Research Laboratories of Eastman Kodak in Rochester, New York, and at the Indian Institute of Science, Bangalore. Since 1979 he has been at the Central University of Hyderabad, India, where he is now a Reader in Chemistry

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(see p. ii)

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Gerhardt Schmidt and the early developments

It was not possible to establish this crucial link between the structure of the assembly and solid state chemical reactivity, until the technique of X-ray crystallography was developed. So, while solution chemistry progressed through F. A. Kekulé, Emil Fischer, Christopher Ingold and R. B. Woodward, solid state organic chemistry waited for Gerhardt Schmidt, who probably did more than any other to develop this crystal structure-molecular reactivity link. The work carried out by his group at the Weizmann Institute in Israel in the 1950s and 1960s laid the foundations of this subject [1].

Schmidt found that for a series of photodimerisable olefins, the crystalline matrix provides an extraordinary spatial control on the initiation and progress of the solid state reaction. Such reactions were termed 'topochemical' since they were considered to occur with a minimum of atomic or molecular movement. If the geometry of the molecules in the reactant crystal structure favoured a chemical reaction, then it occurred; if not, nothing happened. In other words, any molecular diffusion of the type conventionally understood as taking place prior to a chemical process is unnecessary for a topochemical reaction. Conversely, the topochemical principle, as stated above, also implies that the structure of a product of such a solid state reaction bears a close relationship to the crystal symmetry of the reactant. Because of this fact, there are a very small number of products in the typical topochemical reaction. In contrast, there may be several products in the corresponding solution reaction while in many cases it is impossible to carry out a particular solid state conversion through any solution process (figure 1).

These features are well-exemplified by the *trans*-cinnamic acids, first studied systematically by Schmidt, and illustrated schematically in figure 2. Schmidt found that substituted cinnamic acids crystallise in one of three

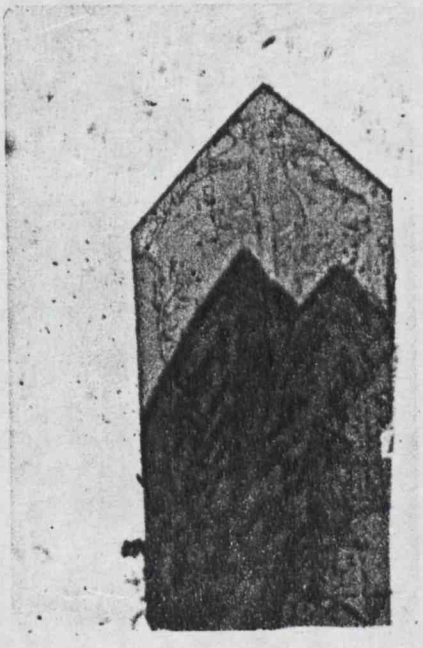


Figure 1 A single crystal of the yellow form of *p*-anisylbenzoquinone transforming thermally to the red form which has a different crystal structure [2]. Notice the reaction front which is parallel to some of the crystal faces. In this and many other solid state reactions studied in the early phase of the subject, the accent was on correlating chemical reactivity with crystal structure and crystallographic orientation. (Reprinted in part from the Journal of the American Chemical Society, *99*, 1594, (1977). Copyright (1977). American Chemical Society)

tructural types α, β, and γ, and that hile the $\alpha-$ and $\beta-$ forms react in a 2+2 fashion to give cyclobutane dimers when irradiated in the solid state, crystals of the γ-form are photostable. Recognising the reality of the topochemical principle, the formation of mirror symmetry products from the β-acids and inversion symmetry products from the α-acids becomes intuitively obvious. In both the α- and β- forms, potentially reactive double bonds in the monomer crystal are closer than a 'threshold' value of *ca.*4.2 Å. However, in the γ-crystals, double bond separations are around 4.9 Å and, therefore, presumably too far for photoreaction [3].

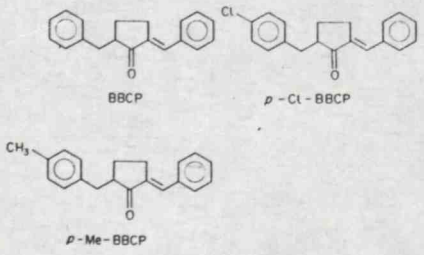
Crystal engineering

Because this 'on-off' model for a potentially reactive crystal has been very successful in predicting and understanding the course of many solid state reactions, attention shifted naturally to the control of the crystal structures themselves. This has proved to be more difficult, because an organic crystal structure is the result of a balance of many minor yet subtle intermolecular forces. Molecular variations that are seemingly trivial from the solution viewpoint; may alter the crystal structure drastically. Schmidt realised that 'simple' substitutent changes such as methyl → ethyl or chloro → bromo were not quite so innocuous when it came to crystal structures and a new branch of the subject, crystal engineering, came into being [4].

Crystal engineering is concerned with securing topochemical control in systematic ways and, more generally, with predicting, controlling, and exploiting crystallisation patterns in organic solids [5, 6, 7,]. By suitably engineering a family of structures, one may achieve very specific reaction pathways and products repeatedly and reproducibly. This strategy therefore involves choosing molecules according to their size, shape, stereochemistry, or topological structure and then inducing them to crystallise into certain predesignated crystallographic space groups. It has been observed by crystallographers and structural chemists that certain types of intermolecular interactions are associated with only certain geometrical arrangements of patterns or structural motifs. The key to crystal engineering therefore lies in being able to understand the nature of delicate yet non-trivial intermolecular forces.

An early example of a chemical substituent group yielding a group of related crystal structures is furnished by the behaviour of planar chloroaromatic compounds [4]. Many of these crystallise with unit cells having a short edge of *ca.* 4.0 Å, which is characteristic of a structure containing highly overlapped molecules stacked with a plane-to-plane separation of around 3.4 Å (van der Waals separation). At least a hundred such chlorocompounds are known. While the reason for this specificity is still largely unexplained, chloro-substitution remains a powerful method for engineering a crystal structure so as to obtain a 4 Å short axis [8]. This structure is a particularly useful one, because it can lead to topochemical 2+2 photoreactively (in the manner of β-crystals of cinnamic acid, figure 2) if the molecule in question has a potentially dimerisable olefinic double bond (figure 3).

A unique and dramatic application of crystal engineering is the use of the 2-benzyl-5-benzylidenecyclopentanone (BBCP) carbon framework, by J. M. Thomas, W. Jones and their coworkers in Cambridge, to obtain a new class of 'diffusionless', topochemical and topotactic photodimerisation reactions [9–12]. Reference has already been made to the lack of necessity of



molecular diffusion in topochemical processes. In keeping with this theme, the constant structural motif in all the reactive members of the BBCP family is a centrosymmetric pair of molecules where 'potentially dimerisable' double bonds are situated within the critical reaction distance of 4Å. Yet these reactions are not only topochemical but also topotactic; that is, single crystals of monomer give single crystals of dimer in quantitative yields. The secret here lies in the choice of the carbon framework—large non-polar molecules with conformational flexibility are

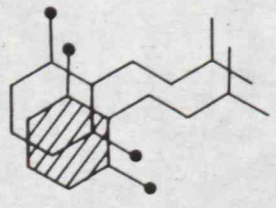


Figure 3 Schematic view of two molecules of 2,6-dichlorocinnamic acid ($C1_2-C_6H_3-CH=CH-CO_2H$) to show the β-structure. This molecule will dimerise on solid state photoirradiation to yield a mirror symmetry product.

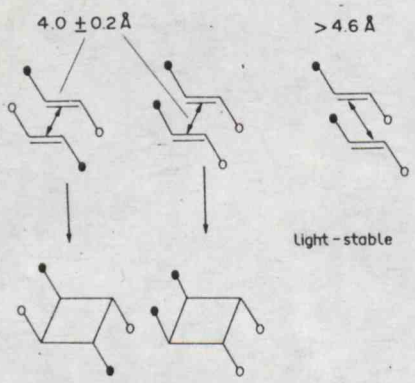


Figure 2 Photoactive (α, β) and photostable (γ) forms of *trans*-cinnamic acid. After Schmidt [1,3,4].

more likely to adjust their sizes and shapes with the progress of the reaction, so that single crystallinity is never lost, even though some of the atoms in the crystal change their position by more than 1.0 Å during the reaction [11, 12]

Monitoring the course of an organic solid state reaction

Reference has already been made to the ability of chloro groups to steer crystal structures into 4 A unit cells. This is strictly true only for planar molecules. When chloro-groups are pendant on large, bulky, irregular shaped and, typically, non-polar molecules like BBCP, such steering effects are not so obvious. In these cases, close-packing, as first described by A. I. Kitaigorodskii (of the Academy of Sciences, Moscow) is of paramount importance and molecules pack in such a way that the 'voids' in one are locked into the 'protrusions' of the other [13]. Volume and shape considerations hold sway rather than electronic factors, and it is no surprise that compounds like methyl BBCP (*p*-MeBBCP) and chloro BBCP (*p*-ClBBCP) are isomorphous (volumes, methyl 24 $Å^3$; chloro 19 $Å^3$) nor even that these molecules form true solid solutions in the entire composition range [14].

How diffusionless these reactions really are is demonstrated by crystallographic experiments involving partially reacted single crystals of the *p*-MeBBCP—*p*-ClBBCP solid solution compound described above. Since the crystallographic unit cells of the reactant and product are virtually identical, collection of three-dimensional X-ray intensities on partially reacted methyl-chloro mixed crystals is possible. These X-ray measurements reveal the presence of (unreacted) monomer and (reacted) dimer molecules in the same crystal with partial positional occupancy parameters and thus vividly show

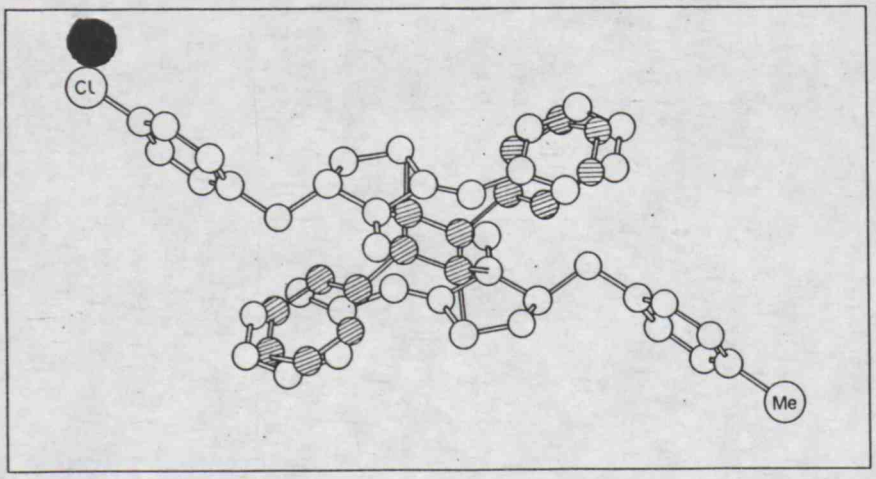
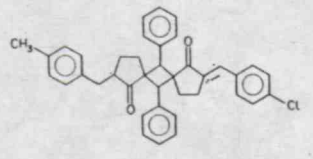


Figure 4 Positions of the monomer (○) and dimer (⊜) molecules during photoirradiation of *p*-ClBBCP—*p*-MeBBCP mixed crystals as determined by *in-situ* X-ray diffractometry on partially reacted single crystals. Notice the formation of the cyclobutane ring and the puckering of the two cyclopentanone residues as the reaction progresses. The atomic positions of the Cl-benzyl and Me-benzyl rings do not change appreciably during the reaction. This 'anchoring' effect is, in large measure, responsible for the single crystal → single crystal nature of the reaction [14, 15].

the starting and final positions of molecules on the reaction coordinate from a single physical measurement [15]. By implication, the direction of movement of molecules towards the transition state is revealed, and this experiment represents one of the few cases where it is possible actually to 'see' the direction of close approach of two reacting molecules; in other words, to view simultaneously reactant and product molecules as a chemical reaction is taking place (figure 4).

Asymmetric syntheses and topochemistry

It may be noted that one of the products of the solid state reaction in mixed crystals of *p*-MeBBCP and *p*-ClBBCP is an unsymmetrical (actually, pseudo-symmetrical) cyclobutane. Such a product molecule is dissymmetric and, in this particular reaction, is formed as a racemate because the space group in which the monomer starting material crystallises happens to be centrosymmetric. However, if a dissymetric product is obtained through a



topochemical solid state reaction from a reactant which crystallises in a enantiomorphous space group, only a single enantiomer will be produced and will show measurable solution optical activity. Such asymmetric syntheses using crystal lattice chirality (right- or left-handedness; *cheir*=hand, Greek) as the only source of molecular dissymmetry have been an attractive challenge to organic solid state chemists ever since Schmidt and B. S. Green showed that they were possible [16]. A compelling reason for this interest stems from the fact that crystal lattice controlled asymmetric syntheses might well have been involved in the generation of, or at least in the amplification of, optical activity in prebiotic conditions in the history of our planet. Further work on this subject at the Weizmann Institute has culminated in the contributions of M. Lahav and his collaborators who have devised a route for an absolute asymmetric synthesis with close to quantitative enantiomeric yields.

The chief problem here is, of course, to identify molecules, achiral in solution, which will crystallise in enantiomorphous space groups. Although such molecules are known and some are included in the early compilation by P. Groth [17], the phenomenon, in general, is uncommon. Identification of such molecules is still a 'hit-and-miss' affair, because it is still largely unknown why some molecules which do not show solution optical activity should pack in an enantiomorphous space group. This difficulty has been ingeniously circumvented by Lahav, who has shown that the 1:1 solid solution of *iso*propyl and 3-pentyl derivatives of an aromatic photodimerisable diolefin (both derivatives achiral and adopting racemic space groups when taken separately) crystallises isomorphously with the corresponding resolved *sec*-butyl derivative, which being chiral, must crystallise in an enantiomorphous space group. The effective volumes and non-bonded interactions in the solid solutions closely approximate the situation in the chiral compound so that the same space group is adopted. This solid solution and other related ones yield chiral products on solid-state irradiation [18].

Crystalmorphology and the absolute configurations of molecules

The solid state reactions described above show how crystal dissymmetry can result in molecular chirality. There are cases, however, when these roles are reversed; in other words, where a 'feedback' mechanism exists so that chiral molecules in solution can crystallise with morphologies that are characteristic of their 'handedness'. The most famous example of this phenomenon is surely the resolution of racemic sodium ammonium tartrate by Louis Pasteur in 1848. His observation of hemihedrism for this compound underscored the relationship between optical activity and molecular structure and marks the very beginning of stereochemistry.

Ever since, chemists have recognised the existence of enantiomeric molecules; that is, molecules whose spatial bond connectivity is related as object and non-superimposable mirror image. But for a century it was not possible to assign absolute configurations to molecules. 'Which is the right hand and which one the left?' remained an unanswered question until, in 1951, J. M. Bijvoet showed that for a non-centrosymmetric crystal an X-ray beam of appropriate wavelength would give a diffraction pattern where violations of Friedel's Law could be observed ($I_{hkl} \neq I_{\bar{h}\bar{k}\bar{l}}$). Using this 'anomalous' dispersion of X-rays, the assignment of absolute configurations was possible [19].

In recent years there have been two sets of experiments by organic solid-state chemists to determine absolute configurations without recourse to the method of Bijvoet. Both D. Y. Curtin and I. C. Paul of the University of Illinois and Lahav and L. Leiserowitz of the Weizmann Institute and their collaborators use the feedback mechanism relating crystal morphology to molecular dissymmetry. The fundamental concept, recognised by both sets of workers, is that any method which fixes the orientation of any functional group of the chiral molecule with respect to the crystallographic axes establishes the absolute configuration of the molecule. Both the Illinois and Israeli groups have done exactly that, and in doing so have greatly extended the scope of Pasteur's original experiment [20, 21]. This experiment incidentally seems to have influenced both

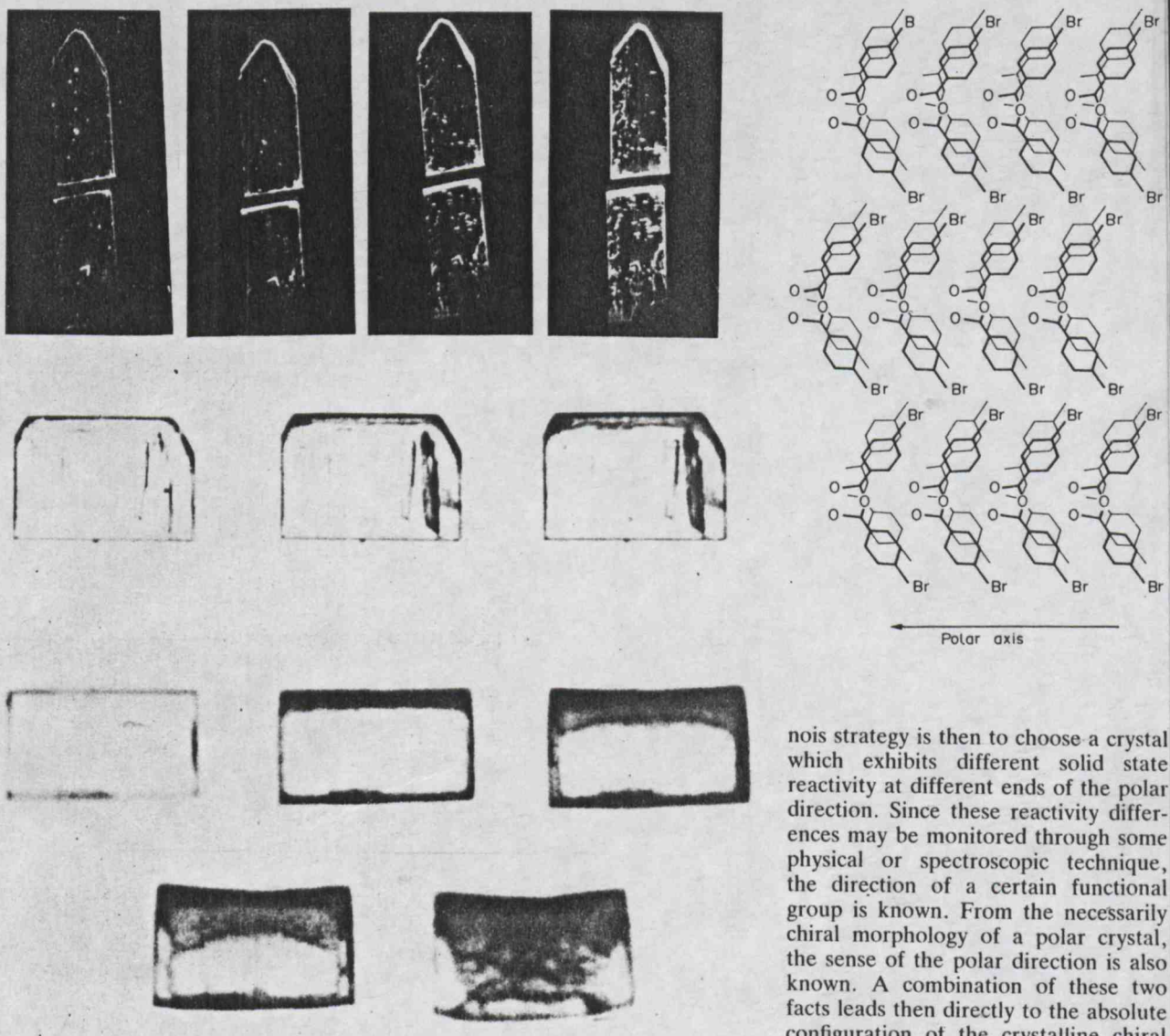


Figure 5 Reaction of polar crystals of *p*-bromobenzoic anhydride (Br-C_6H_4-CO-O-CO-C_6H_4Br) with ammonia gas [20, 22]. The crystals in the top, middle and bottom series have different morphologies but, in all cases, the polar axis is vertical in the plane of the paper. Chirality in this molecule is due to restricted rotation in the solid state. The schematic diagram shows the internal structure of a crystal of the S-anhydride. The carbonyl groups point in the + polar direction while the bromo groups point in the – direction. The photographs show the preferential reaction of ammonia along the + direction, that is at those crystal faces where the carbonyl groups emerge. In the R-crystal, preferential reaction will still be at those faces where carbonyl groups emerge, but these will be towards the – polar direction. (Copyright 1975. American Association for the Advancement of Science.)

groups considerably, and the almost freakish nature of Pasteur's 1848 result is commented upon by both. Lahav and Leiserowitz [21] write: 'This (Pasteur's) experiment is remarkable because combination of such spontaneous resolution with visual distinguishability is rare, with less than a dozen examples being recorded'. More explicitly, Curtin and Paul [22] state that: 'Pasteur's success in achieving the first resolution of a chiral compound depended not only on his keen powers of observation but also on an enormous amount of luck'.

These latest extensions to Pasteur's work using the methods of organic solid-state chemistry rest on the existence of the polar axis in crystals of chiral molecules. All such molecules must crystallise in enantiomorphous space groups and these have associated with them one or more polar directions. The polar axis is, therefore, a uniquely solid state phenomenon and at a molecular level, its structural implications are that when one views a crystal from the opposite ends of such an axis, chemically distinct parts of molecules are revealed [22]. The Illinois strategy is then to choose a crystal which exhibits different solid state reactivity at different ends of the polar direction. Since these reactivity differences may be monitored through some physical or spectroscopic technique, the direction of a certain functional group is known. From the necessarily chiral morphology of a polar crystal, the sense of the polar direction is also known. A combination of these two facts leads then directly to the absolute configuration of the crystalline chiral molecule (figure 5) [20].

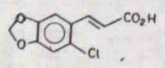
The Israeli approach is to monitor changes in the morphology of crystals of pure enatiomer upon the addition of carefully selected impurities. Since crystal morphology depends on the directions of weak intermolecular forces, the presence of a small amount of a rogue molecule can result in its selective adsorption on certain faces only, thereby inhibiting further growth on these faces and so effecting gross morphology changes. Since, by definition, different functional groups emerge at opposite ends of the polar direction, it is possible to design impurities that will be adsorbed selectively at one end only. Observation of the resulting morphology changes establishes a method of fixing the orientation of a certain functional group with respect to the polar axis and therefore of fixing the absolute configuration (figure 6) [21].

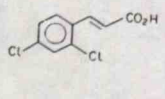
While it is still early to comment on all the implications of the Illinois and Israeli results, it seems clear that they will be studied in detail as they involve fundamental questions, as did the

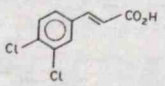
earlier experiments of Pasteur and Bijvoet.

Structural mimicry

The work of Lahav and Leiserowitz and their collaborators on absolute configurations [21] and asymmetric syntheses [18] exploits the idea that the crystal lattice of a compound can incorporate into it variable amounts of a chemically or structurally related impurity. Structural mimicry has become a field of increasing importance in organic solid state chemistry today [14]. Notwithstanding solid solution behaviour of the type *p*-ClBBCP-*p*MeBBCP, there are many instances in the organic crystallographic literature where two compounds having completely different crystal structures form 'mixed crystals' primarily as a result of forced changes imposed upon the molecular geometry of the minor component by the dominant major component. Co-crystallisation of two organic compounds is a delicate exercise and may be considered as an extension of the crystal engineering concept. The great advantage in obtaining these mixed crystals is that the chemist may then study reactions of the type A + B → Product rather than the more restrictive types A → Product or A + A → Product or A + A + . . . → Polymer which would be the only options open to reactive crystals of a simple molecular solid. However, since the intermolecular forces associated with the crystallisation of organic solids are very weak, a great variety of mixed crystals may be expected [23]. Recently, it has been found that acids such as 2, 4 and 3, 4-dichlorocinnamic acid co-crystallise with 6-chloro-3, 4-methylenedioxycinnamic acid, with







which they are not isomorphous, to give crystalline compounds with fixed stoichiometry [8]. The fact that the 3,4-dichloro acid gives a 1:1 complex, whereas the seemingly closely related 2,4 acid gives a 1:2 complex only emphasises that the intermolecular forces in these and many other mixed crystals must be much more specific and directional than the forces in solid solutions of the BBCP type, and that there is a great deal to be learned about such forces by studying systems like these in more detail.

The field of structural mimicry is a rich one since there are many circumstances in which it is important to be able to co-crystallise molecules in very specific ways. In the case of organic metals, for instance, it is extremely critical to know why compounds like tetracyanoquinodimethane, TCNQ (A) and tetrahiafulvalene, TTF(D) form segregated stack complexes, AAAA . . . . . DDDD . . . . . while TCNQ and say, anthracene (D) form mixed stack DADADA . . . . . complexes. Although there have been several explanations, no unifying picture has emerged, and the application of crystal engineering and related methods to such problems has hardly even begun.

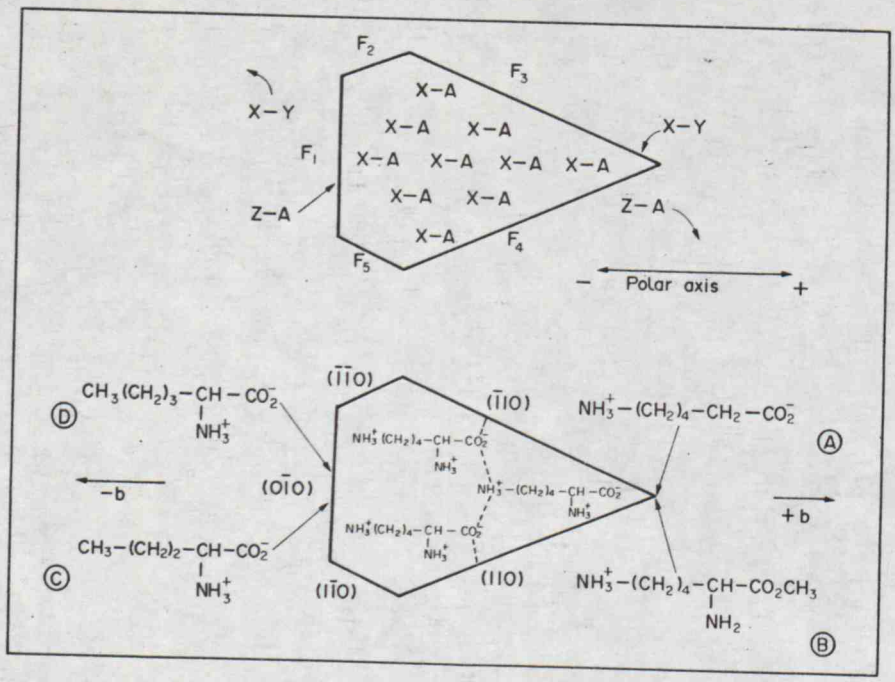


Figure 6 Adsorption of impurity X–Y is possible on faces F_3 and F_4 while Z–A may be adsorbed on F_1 in the hypothetical polar crystal X – A above. These effects may be seen below in single crystals in lysine hydrochloride hydrate which crystallises in the polar space group $P2_1$. Hydrogen bonds are shown as ------. Impurities such as ϵ-aminocaproic acid, A, and methyl lysinate, B, can be adsorbed on faces where carboxylate groups emerge while those like norvaline, C, and norleucine, D, may be adsorbed on faces where ϵ-ammonium groups emerge. The adsorption of such impurities leads to gross morphology changes, from which the absolute configuration of lysine can be determined [21].

Current status and future prospects

Organic solid state chemistry was originally linked closely to X-ray crystallography and to many organic chemists, especially to those working with solutions, appeared esoteric, even irrelevant. Now, however, it is clear that the various studies that are being conducted to carry out organic chemistry within crystals will have considerable impact on other apparently quite unrelated areas of chemical research. Not only may one monitor organic reactivity at a molecular level, but one might attempt to answer stereochemical questions of a fundamental nature. Yet another area where topochemical principles are likely to be important concerns organic reactions in other less perfect organised media such as liquid crystals, polymers, films, and micelles. At the same time, work in organic solid state chemistry has every possibility of leading to industrially important applications. Chemical memory devices and organic conductors and superconductors are not yet commercial products, but there is every chance that this situation may change in the future. With the ever-increasing cost of chemicals there will also be an incentive to use these reactions in industrial processes and achieve solventless conversions.

Ultimately, however, the subject rests on the crucial, all-encompassing question: Can one reliably predict the crystal structure of an organic solid? While there is as yet no definitive answer to this question, the typical approach today, mostly experimental, is to carry out as large a number of reactions on as large a number of solids and to solve as many crystal structures as possible, so that the existing data bank of relevant crystal structures becomes larger and the prediction of a new structure correspondingly easier.

Yet there is another approach, computational in nature which might in the long run be equally profitable. *Ab initio* predictions of organic crystal structures have hitherto confined themselves

largely to the simplest and most non-polar of molecules, namely hydrocarbons. However, with the appearance now of faster and more powerful computers one may expect that more polar molecules will be handled with increasing confidence. The use of even minimal crystallochemical information (unit cell parameters, topochemistry, etc) greatly enhances the power and extends the scope of these energy minimizing search programmes with the result that crystal structures may be reliably and accurately predicted in ever increasing numbers. In any case, the stage seems to be set for a period when laboratory and computer experiments will go hand-in-hand to obtain a fuller understanding of the fascinating behaviour of organic solids.

Acknowledgments

The author would like to express his thanks to Professor J. M. Thomas, FRS for helpful guidance in the preparation of this article, and for his enthusiasm and continued interest during visits to Cambridge in 1982 and 1983. The work on partially reacted BBCP mixed crystals was the outcome of a collaboration between Dr. W. Jones, Dr. C. R. Theocharis, and the author of that time. The assistance of Professors D. Y. Curtin and I. C. Paul (Urbana) in promptly providing a print of figure 5 is gratefully acknowledged.

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