

Organic solid state chemistry—Some perspectives

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Abstract. Several strategies towards an understanding of the crystal chemistry of organic solids have been reviewed. The crystal structures of most organic compounds are the result of optimisation of rather weak intermolecular forces and this is illustrated for some alkoxy and chloro-aromatic compounds. Co-crystallisation of different organic molecules is the logical outcome of such methods of 'crystal engineering'. In the resulting complexes, the forces between the component molecules can vary in magnitude and directionality and three distinct situations are described. The role of packing calculations as an alternative method for the structure determination of a reactive organic solid is described. Thermal reactions are exemplified by a case of solid state co-operative tautomerism and one of a base-catalysed inter-lamellar dehydration in a layered structure.

Keywords. Organic solid state; topochemistry; crystal engineering; x-ray crystallography; molecular complexes; photochemistry; atom-atom potentials; solid state tautomerism; intercalation.

1. Introduction

How do organic molecules organise themselves in crystals? Can one predict the crystal structure of an organic solid? Comprehensive answers to such questions are still not available but attempts to obtain them have resulted in a spate of research activity during the last three decades. This activity delineates an area that has been somewhat loosely referred to as organic solid state chemistry.

There are several examples in the pre-1950 literature on solid state re-arrangements, decompositions, electrocyclic reactions, phase transitions and polymorphism. However, much of this data is empirical and since there had been no attempt at systematising it, initial activity in the field of organic solid state chemistry (1950-1970) was largely concerned with chemical reactivity in organic crystals. The first major contribution in this respect came from the work of Gerhardt Schmidt and his co-workers at the Weizmann Institute in Israel (Schmidt 1969). Their experiments on the photodimerisation of substituted cinnamic acids led to the confirmation of the topochemical principle that 'reaction in the solid state occurs with a minimum of atomic or molecular movement'. Although this early work was concerned mainly with the 2 + 2 solid state photodimerisation of olefins, organic solid state chemistry today encompasses rather more than the photochemistry of crystalline organic compounds.

The major reason for this change in awareness and activity in the field has been the progress in instrumentation and electronics technology. Advanced digital computers and diffractometers have converted small molecule x-ray crystallography into an automated procedure and this has in turn resulted in the setting up of crystallographic database facilities where it is possible to compare the features of not merely a handful but literally hundreds of structures in a few minutes. This has revealed an entirely new dimension in organic solid state chemistry, a dimension which has important

implications for even solution reactivity. The application of techniques such as high resolution electron microscopy (HREM) and solid state magic angle spinning nuclear magnetic resonance spectroscopy (MASNMR) has opened up absolutely new vistas of research in areas of both fundamental and commercial importance (Fyfe *et al* 1983).

Because of these several factors, phenomena as diverse as molecular recognition in crystals, structural mimicry, crystal engineering, asymmetric solid state synthesis, clathration and intercalation, thermal and photochemical topochemical and non-topochemical reactivity, assignment of absolute configuration from crystal morphology, and various means of designing molecules for specific purposes and applications (molecular architecture) are being pursued vigorously by organic solid state chemists all over the world today. It is not the purpose of this article to provide a comprehensive review or one that is encyclopaedic in its survey; judging from the range of subjects mentioned above, such a task would scarcely be possible here. However, it is sought to highlight a few areas of activity in this interdisciplinary field that lies at the crossroads of organic chemistry, solid state science, structural chemistry and x-ray crystallography.

2. Crystal engineering

Although Schmidt correlated the structural and photochemical data on *trans*-cinnamic acids, he was one of the first to realise that organic solid state reactions would be academic curiosities and have limited application unless it was somehow possible to predict crystal structures. It must be realised that an *ab initio* prediction of an organic crystal structure is still a formidable task. Being low symmetry molecular solids with all possible variations in conformation and stereochemistry, their crystal structures, unlike those of inorganic compounds are not expected to be governed by simple unifying principles such as the close packing of spheres. Realising such facts, it has been the usual practice to study a series of closely related compounds, so that a common structural principle can be deduced. Such activity has been termed crystal engineering and a particularly good example is furnished by dichlorosubstitution in aromatic compounds. For instance, while *trans*-cinnamic acid crystallises in the α (inversion-symmetry) and β (translation-symmetry) forms, the dichlorocinnamic acids crystallise exclusively in the β -form which is identified by a 4 Å unit cell axis (figure 1). Such crystallisation behaviour is characteristic of planar polychloro-aromatics and there are at least a hundred known cases (forty, unpublished from the Israeli group and about

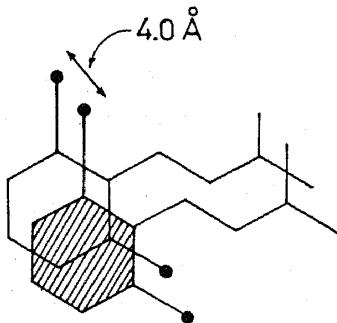


Figure 1. β -Packing and a 4 Å cell axis as exemplified by 2,6-dichlorocinnamic acid.

sixty from the 1982 version of the Cambridge Crystallography Database). This set includes not only non-polar hydrocarbons but also some of their more polar amino and hydroxyl derivatives.

A common feature in the crystal structures of these planar chloro-aromatics is the occurrence of a large number of short Cl-Cl non-bonded contacts in the 3.2 to 3.6 Å region. These contacts are generally along directions which are parallel to or close to the planes of the aromatic rings, so that molecules which are related by them can be arranged in planar or corrugated sheets. In order then that C-C contacts can be optimised, these sheets can be stacked with an inter-sheet perpendicular distance of about 3.4 Å (van der Waals separation), that is with a crystallographic repeat of *ca* 4 Å. This kind of structure is illustrated by a compound such as hexachlorobenzene (figure 2a). Compare this structure with the herringbone structure of benzene which is shown in figure 2b. The reason that benzene cannot adopt the sheet structure is that, in that case, objectionably large H-H repulsions would be created. In the herringbone structure, on the other hand, the characteristic 'crossed' motif optimises C-H and C-C attractive interactions while minimising the bad H-H contacts. A consideration of H-H repulsions is important in that there is a greater tendency for molecules having a lesser number of H atoms per C atom to adopt sheet structures. For instance, many more substituted anthracenes adopt this structure than do substituted naphthalenes and benzenes which seem to prefer the herringbone structure.

It is therefore possible to summarise the reasons why planar polychloro organics tend to crystallise with a 4 Å repeat sheet structure:

- (i) Cl-Cl short contacts between laterally adjacent molecules stabilise the sheet. These interactions could be of the dispersive type.
- (ii) The number of H atoms per C atom is necessarily smaller than for the corresponding non-chloro analogue and there are consequently less H-H repulsive contacts which would tend to destabilise the sheet structure with respect to the herringbone structure.

One can now understand why a compound such as 3,4-methylenedioxycinnamic acid 1, crystallises in the 4 Å repeat β -structure (Desiraju *et al* 1984). A projection of the structure down the 4 Å (short) axis is given in figure 3. Note that this projection is in the form of a molecular sheet in which acid molecules form hydrogen bonded dimers. In addition, the layers are stabilised by O . . . H-C short contacts. Such contacts have also been referred to as 'hydrogen bonds' and have been reported in the literature regularly. But it is only recently that their importance in organic crystal structures has been appreciated and that their terminology as 'hydrogen bonds' been received without

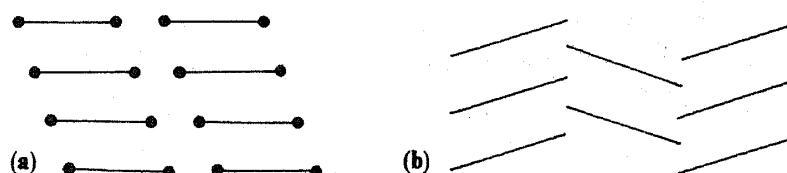


Figure 2. (a) Sheet (β , 4 Å) structure of hexachlorobenzene. Chlorine atoms are indicated by dark circles. Notice the Cl-Cl interactions. (b) Herringbone structure of benzene. The extremities of molecules (hydrogen atoms) point towards the carbon atoms of others to generate the 'crossed' motif.

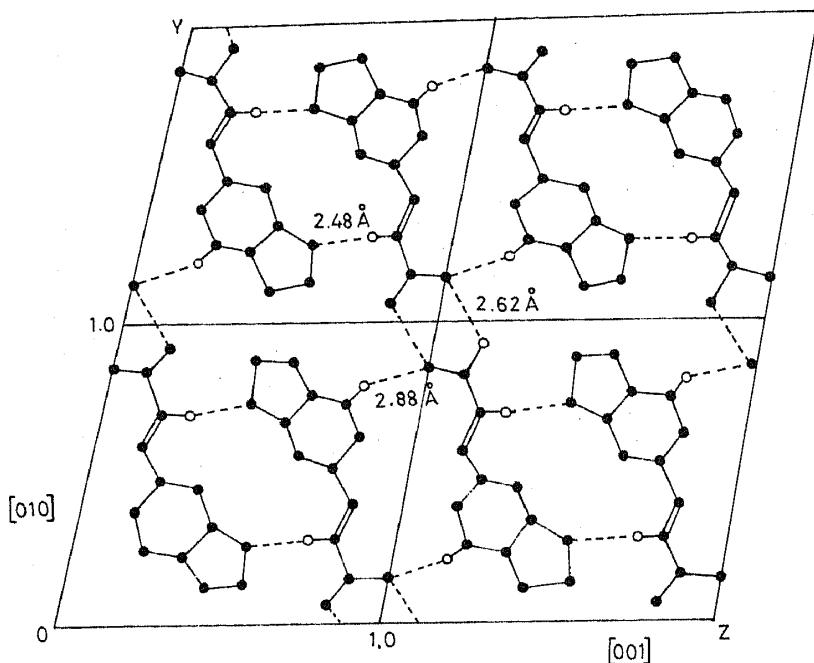


Figure 3. Projection of the crystal structure of 3,4-methylenedioxycinnamic acid, **1**, down the 4 Å axis to show the sheet structure (adapted from Desiraju *et al* 1984).

scepticism by the crystallographic community. Figure 3 shows that since the aromatic hydrogens can participate in O...H-C contacts, H-H repulsion is not a major problem and that therefore, the molecular sheet is stabilised. The sheets are stacked with a 3.4 Å crystallographic repeat to generate the observed β -structure. One should note, however, that on account of the stacking, the methylene hydrogen atoms which are located above and below the planes of the molecular sheets will be involved in bad contacts. In fact, the nearest non-bonded distance between such methylene hydrogen atoms in the crystal structure of acid **1** is only 2.16 Å and this tendency is expected to be even greater for 3,4-dimethoxycinnamic acid, **2**.

In the case of acid **2**, although the sheet structure is stabilised because of O...H-C contacts (figure 4), the repulsive inter-sheet H-H interactions would become prohibitively large if the sheets were to be stacked with a 4 Å repeat axis. This is because of the larger number of hydrogen atoms in the methoxyl groups (six) as compared to those in the methylenedioxy group (two) in acid **1**. Therefore the β -structure is not possible for acid **2**.

Other methylenedioxy compounds that can adopt the 4 Å β -structure include the chloro and nitro acids **3** and **4** and the coumarin, **5**, ayapin, which is a natural product. Note that in all these cases, the molecules are planar and the number of hydrogen atoms is fairly small (Desiraju *et al* 1984).

3. Molecule-molecule interactions

The principles of crystal engineering are concerned with the manipulation of delicate but non-trivial intermolecular forces. A proper choice of molecules A and B can therefore optimise non-bonded interactions such as A...B with respect to interac-

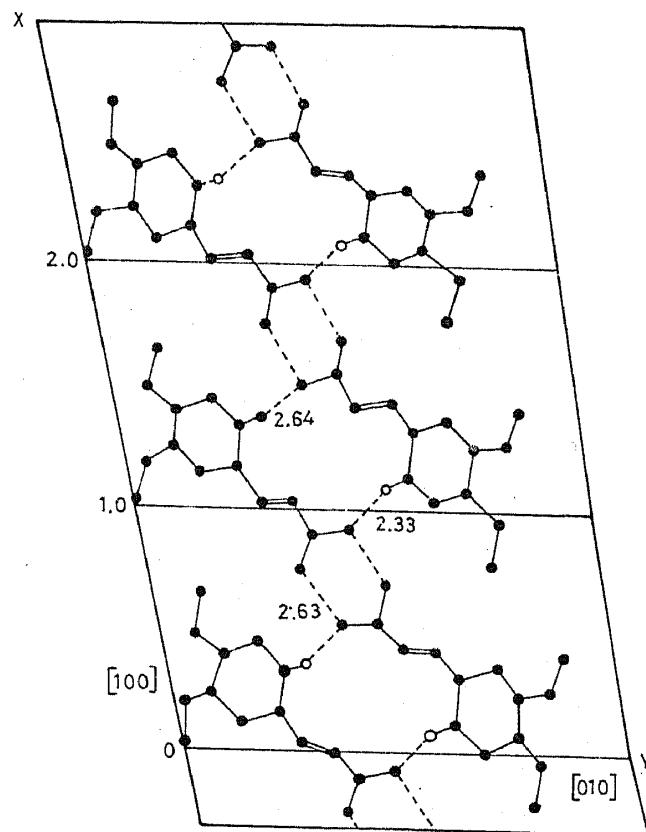
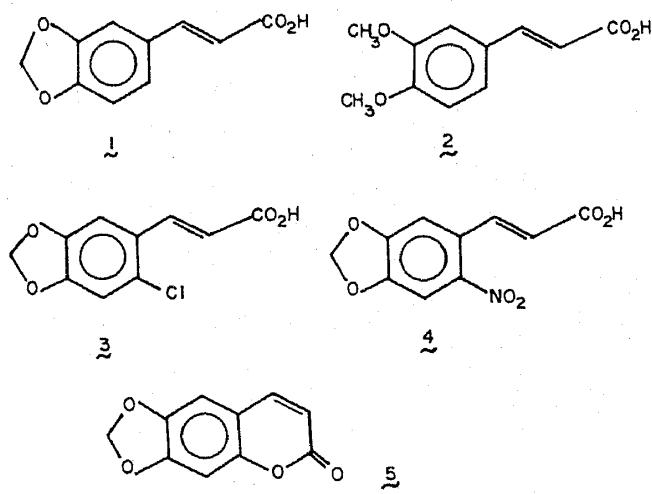


Figure 4. Molecular sheets in the crystal structure of 3,4-dimethoxycinnamic acid 2. These sheets cannot be stacked like in acid **1** with a repeat axis of 4 Å.



tions such as A . . . A or B . . . B. In other words, under certain conditions, it is more likely that two compounds in solution will co-crystallise rather than crystallise separately. Mixed crystals and molecular complexes of organic compounds are especially interesting because if two reactants can be induced to co-crystallise, it is possible to study solid state reactions of the type A + B → Products. This offers much

more scope when compared to reactions such as $A \rightarrow \text{Products}$ or $A + A \rightarrow \text{Products}$ or $A + A + \dots \rightarrow \text{Polymer}$ which are the only types possible from crystals of a pure compound. Mixed crystals can be true solid solutions or they can show varying degrees of order. Three different degrees of intermolecular interaction will be described here.

3.1 Disordered structures with variable stoichiometries; Non-directional forces

Although the chloro group can stabilise stack structures of planar aromatics by the formation of molecular sheets, this is not possible for molecules that contain aliphatic fragments of more than about two carbon atoms. If this is the case, the molecules generally adopt non-planar conformations and their shape can be quite arbitrary. In these cases, the crystal structures are governed by close-packing principles as described by Kitaigorodskii. Each non-polar substituent group of a certain volume can be exchanged for another non-polar group of a similar volume without a change in the crystal structure. Chloro-methyl interchange (volumes Cl , 19 \AA^3 , CH_3 , 24 \AA^3) is in fact, well known and for example, a pair of compounds like **6** and **7** is isostructural. These two form solid solutions in all proportions. As it turns out, each of the individual compounds is photoactive in the solid state and the mixed crystals also react to form pseudo-inversion symmetry cyclobutanes.

However, volume effects may be used to force the conformations and crystal structures of such compounds into non-native ones. For example, compounds **8** and **9** crystallise in photoactive and photostable forms respectively. The main difference between the forms lies in the molecular conformation (figure 5). Yet, these two compounds will form mixed crystals, isostructural to **8**, primarily as a result of forced changes imposed upon the molecular geometry of the minor component **9** by the dominating major component **8**. In the mixed crystals, the 'photostable' chloro derivative **9** is forced to adopt the molecular conformation, crystal structure and solid

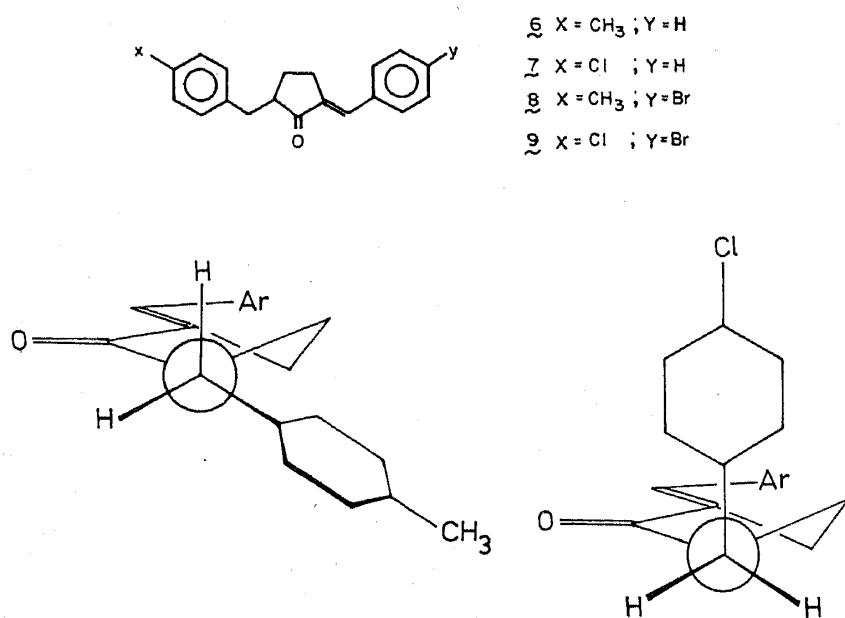


Figure 5. Conformations exhibited by cyclopentanones **8** and **9** in the pure crystal (from Jones *et al* 1983a).

state reactivity of the 'photoactive' methyl derivative **8** (Jones *et al* 1983b; Theocharis *et al* 1984).

The intermolecular forces involved in the formation of these solid solutions are the weakest possible and are not very directional. This type of behaviour can be considered to be a 'volume effect' and consequently solid solutions can be formed throughout the composition range.

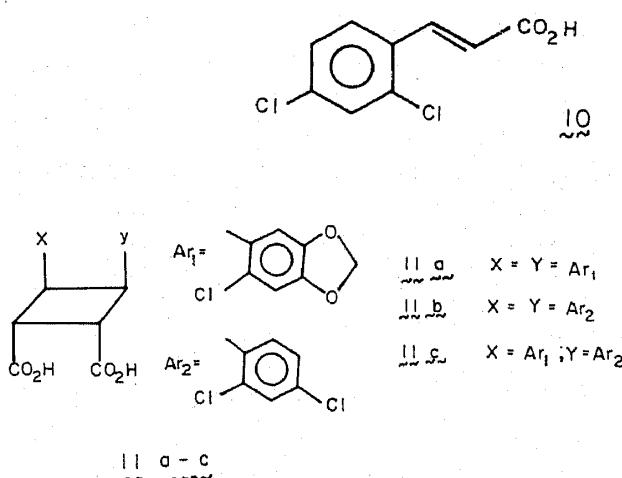
3.2 Disordered structures with fixed stoichiometries; Directional forces

When the pair of chloro-substituted acids **3** and **10** is allowed to co-crystallise, crystals of the 2:1 complex are obtained even though the two acids are taken in 1:1 ratio in solution. Both acids crystallise individually with the 4 Å β -structure since the sheet structure can be stabilised in either case. In the complex also, it seems likely that the sheets can be stabilised and that each sheet has a fixed stoichiometry of 2:1, because the number of Cl atoms in the individual molecules are one and two respectively. Yet the sheets themselves are disordered in the 4 Å stack direction, since all the three cyclobutanes **11a**, **11b** and **11c** are formed in the solid state photoreaction of the 2:1 complex. If the sheets were to be completely ordered in the stack direction, only the two symmetrical products **11a** and **11b** would have been produced. Another possibility for an ordered structure is when a molecule of acid **10** is sandwiched regularly between two molecules of **3**. In this case, only the unsymmetrical product **11c** and perhaps **11a** might have been formed, but not **11b**. Further confirmation for a disordered structure is furnished by the fact that the final product distribution of the cyclobutanes **11a**, **11b** and **11c** is in the ratio 4:1:4. This is the ratio expected from an ideally disordered arrangement of a 2:1 distribution of monomers in the stack (figure 6).

Although one is dealing with directional forces here, the ordering extends only to the two-dimensional structure, *i.e.*, the molecular sheets. This leads to an overall fixed stoichiometry but the structure is disordered in the third dimension which corresponds to the 4 Å stack direction (Sarma and Desiraju 1984).

3.3 Ordered structures with fixed stoichiometries; Directional forces

The example above clearly shows that for chloro-substituted planar aromatics, the intra-sheet forces are more specific than the inter-sheet ones and further, that the latter



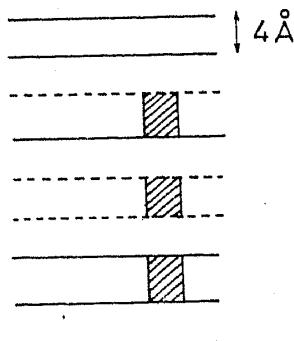
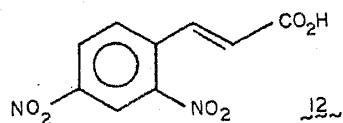


Figure 6. Disordered stack structure in the 2:1 complex between acids **3** and **10**. Each of the three contacts leading to **11a**, **11b** and **11c** are shown. Note that the number of molecules shown is too small to depict the 4:1:4 distribution of dimers actually observed. (from Sarma and Desiraju 1984).



need not be specific enough to order the structure. If the intermolecular forces A . . . B are much stronger and/or distinctly more directional than the A . . . A and B . . . B forces, a fully ordered molecular complex may be produced. It has been shown that when acids **2** and **12** are taken in arbitrary quantities in solution, the 1:1 molecular complex is the exclusive product (Desiraju and Sarma 1983). The crystal structure of the complex shows that it is of the orthodox Mulliken or donor-acceptor type. A consequence of optimal π - π overlap is that the olefinic double bonds of molecules adjacent in the stack are close enough to allow a topochemical dimerisation which is expected to yield exclusively an unsymmetrical cyclobutane. Such product molecules are dissymmetric and if the space group of the starting material were noncentrosymmetric, the product, if obtained normally, should show measurable solution optical activity.

Donor-acceptor forces are so strong and directionally specific that the molecular complex of acids **2** and **12** has an ordered structure (figure 7). This is a clear example as to how a structure may be deliberately engineered to a packing mode that will permit only a certain type of solid state reaction, and one which, in this case, offers a convenient route to chiral materials from achiral precursors through topochemistry.

The three cases described above show that a certain gradation may be obtained in molecule-molecule forces. Each case also illustrates a different type of solid state reactivity. It is always of interest if a structure can be linked to solid state reactivity but the principles of crystal engineering, from which the crystal structures of the complexes described here were derived, are perfectly general and are expected to apply in a wide variety of solids whether or not they exhibit solid state reactivity.

4. Topochemistry and crystal structure analysis. Criteria for **2 + 2** solid state cycloaddition

The formulation of the topochemical principle follows from the crystal structure of a reactive organic solid. The detailed correlations made by Schmidt and his co-workers

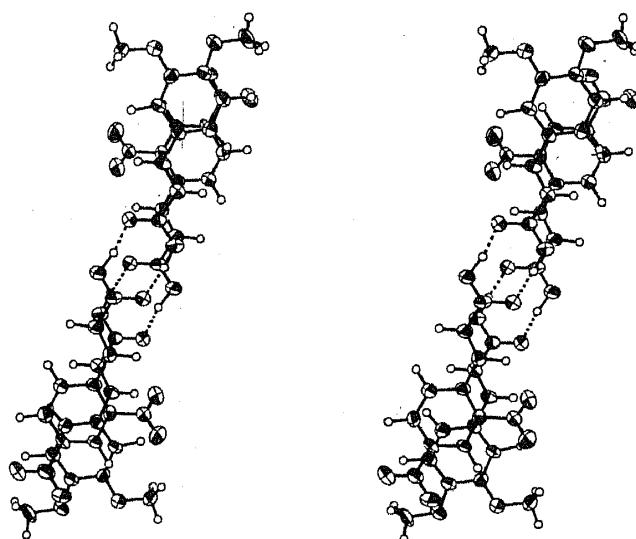
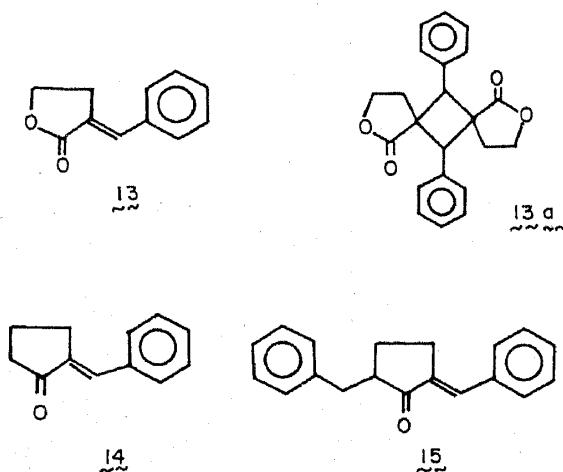


Figure 7. Stereoscopic view of the crystal structure of the 1:1 complex between acids **2** and **12** showing hydrogen bonding and π -complexing (from Desiraju and Sarma 1983).



on the topochemistry of the *trans*-cinnamic acids trace the relationship between two experimental facts: the crystal structure of the reactant and the molecular structure of the product. Generally, knowledge of the former furnishes information about the latter.

However, in some cases, it is possible to carry out this procedure in reverse, in other words, to arrive at the crystal structure of a reactive solid from the structure of the solid state reaction product while recognising the reality of the topochemical principle. Such a case is furnished by the photoreactive olefin, α -benzylidene- γ -butyrolactone, **13** which yields the inversion symmetry *anti*-dimer **13a** on solid state irradiation. On the other hand, the isoelectronic 2-benzylidene-cyclopentanone, **14**, is photostable in the solid state.

In view of the close analogy between **13** and the photoreactive derivatives of 2-benzyl-5-benzylidene-cyclopentanone, **15**, the starting point in the structure analysis of **13** was not the monomer lactone but an 'incipient' dimer pair, the centroid of which was constrained to lie at the origin of the centrosymmetric space group (figure 8). The

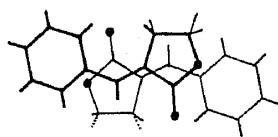


Figure 8. Construction of the 'incipient dimer' pair, the starting point in the crystal structure analysis of 13.

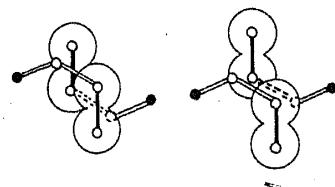


Figure 9. Orbital overlap between C=C double bonds in lactone 13 and ketone 14 viewed perpendicular to the molecular planes.

crystal structure solution of lactone 13 was not carried out with programmes such as MULTAN or SHELX (in fact these approaches proved unfruitful) but with the aid of atom pairwise evaluation procedures (Kearsley and Desiraju 1984).

The topochemically derived starting point greatly simplified the packing analysis. The optimisation of two features: (a) the plane-to-plane interaction within the incipient dimer and (b) the orientation of the incipient dimer with respect to the cell axes, allowed the structure to lock into the global minimum, in other words into the correct solution.

The pair of compounds 13 and 14 are also interesting from the point of view of crystal structure–solid state reactivity correlations. In both crystal structures, nearest neighbour molecules are related across an inversion centre. However, the increased lateral displacement of nearest neighbour double bonds in the structure of 14 (contrast the situation for 13), means that orbital overlap is reduced to a point where solid state photoreactivity is no longer permitted (figure 9). This observation must be viewed in the light of the fact that the distance between neighbouring parallel double bonds in the structure of 14 is only 4.14 Å and that it has been common practice to predict solid state photoreactivity in all cases where the double bond centre-to-centre separation is less than *ca* 4.2 Å. It is felt that the extent of orbital overlap, rather than arbitrary geometrical criteria (such as the double bonds being parallel and the distance between the double bond centres) must be considered when analysing the solid state 2 + 2 photoreactivity of olefins.

5. Thermal reactions

Many interesting organic solid state reactions can be initiated thermally and one category of reactions that is important both from practical considerations as well as from an academic viewpoint concerns rearrangements of labile protons (Curtin and Paul 1981). In these hydrogen atom rearrangements, the positions of the heavy atoms in the crystal remain practically unchanged. The thermochromism and photochromism reactions of anils are in this category. Another example which has been studied recently is concerned with co-operative intermolecular proton shifts between the azo and hydrazone tautomers of the dye 2-amino-3-hydroxy-6-phenylazopyridine. It has been found that this dye crystallises in two modifications; the solution of the crystal structures show that these correspond respectively to the azo and hydrazone tautomers 15a and 15b. Form 15a is converted to 15b on heating. In the crystal structure of 15a, the hydroxy group is close to an azo group of an adjacent molecule and the solid state tautomerisation can be accounted for by an intermolecular co-operative shift of protons across the various hydrogen bonds in the crystal structure of 15a (figure 10) (Desiraju 1983).

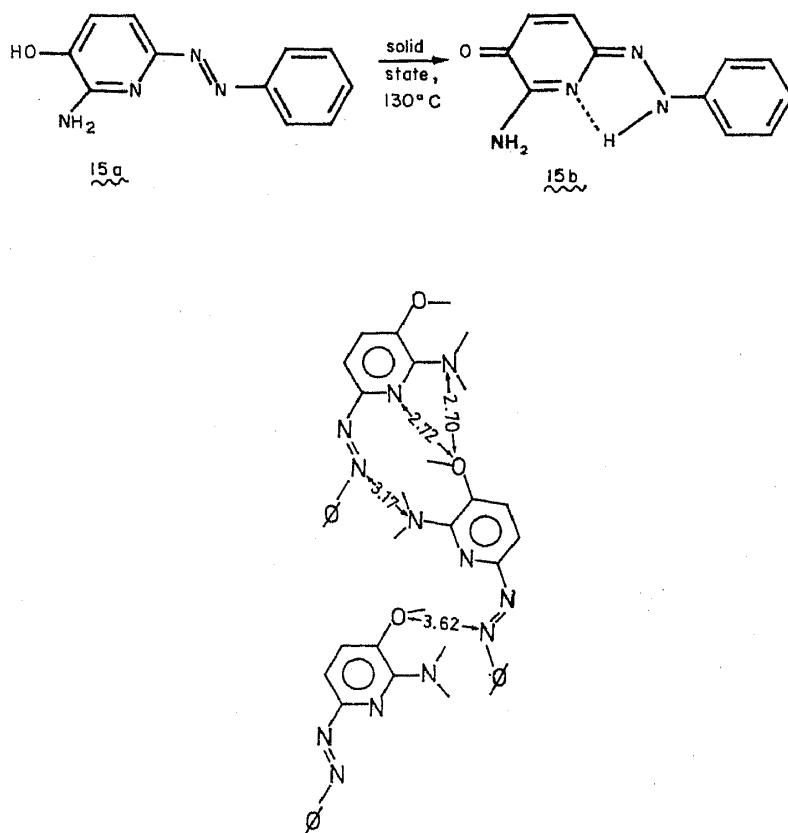
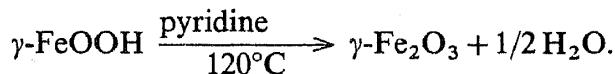


Figure 10. Hydrogen bonding arrangement in the hydroxyazo dye **15a** (adapted from Desiraju 1983).

6. Intercalation compounds

Intercalation refers to the phenomenon when small molecules can be introduced into the interlamellar regions of an organic or (especially) inorganic layered structure. In these compounds, the interactions between the molecules of the (organic) guest and (inorganic) host are weak but directionally specific. Two notable examples in the recent literature are intercalates of sheet silicate minerals (Jones *et al* 1983) and of perovskites (Tieke and Wegner 1981). In both these cases, the organic guest molecules participate in unusual chemical reactions; in the case of the silicates, the host acts as a proton-donor catalyst while in the perovskites, the host is a container of a certain shape and size that will only permit a certain type of guest-guest interaction. This arrangement can then lead to very specific reactivity. Another very similar phenomenon is clathration and many examples of reactivity in clathrates are provided by the inclusion compounds of tri-ortho-thymotide, deoxycholeic acid and the cyclodextrins (Tsoucaris *et al* 1983).

It has been found that a hydrated iron oxide like γ -FeOOH which has a layered structure can form intercalates with organic bases like pyridine (Desiraju and Rao 1982). On heating, the interlamellar pyridine acts as a catalyst in the elimination of water to give a quantitative yield of the topotactically related γ -Fe₂O₃.



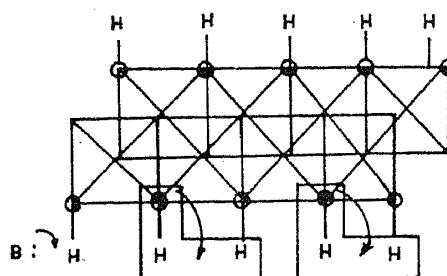


Figure 11. Schematic diagram showing the layered structure of γ -FeOOH and a possible mechanism for pyridine catalysed water removal under mild conditions (from Desiraju and Rao 1982).

The corresponding thermal reaction occurs at *ca* 350°C. The first step in this base-catalysed dehydration is an intercalation while the second and faster step could be a sequential elimination of water from the interlayer (figure 11). Although we are dealing here with a reaction of the host material, the principle is the same as in the reactions of intercalates of silicates and perovskites; the formation of the intercalate allows for unusual groupings of molecules in the solid state and this then leads to reaction. It is of interest to note that the related compound α -FeOOH cannot be converted to the topotactically related α -Fe₂O₃ by the action of pyridine because it does not have the layer-structure which is necessary for intercalate formation.

7. Overview

There is a considerable amount of work being carried out in organic solid state chemistry and the field today seems to be concerned with a large variety of phenomena and not merely with trying to find better ways of preparing organic compounds. Solution organic chemists have had a headstart of approximately a hundred years in such activities and one of the unfortunate features of the early years of organic solid state chemistry was the desire to establish credibility in the eyes of the solution chemist! Many areas of this subject such as the 'locking-in' of weak intermolecular forces, the relationship of crystal morphology and polarity to molecular dissymmetry, inclusion phenomena and proton exchange hardly have a 'solution' equivalent and yet research in these fields has the potential of having the widest possible applicability. At this point, it is also pertinent to comment on the role of small molecule x-ray crystallography in organic solid state chemistry. Generally, the technique has been used with some discrimination where and when necessary, but there is a real danger today that irrelevant structural analyses will obscure the essential chemical character of this subject.

It is hoped that this account has conveyed to the reader, the range of topics that are being investigated today and the merits of taking an interdisciplinary approach to this subject, which is a happy blend of so many attractive areas of chemistry.

Acknowledgements

This article reviews work that has been carried out in Hyderabad and Cambridge between 1981 and 1983. The contributions from the School of Chemistry, University of

Hyderabad deal with crystal engineering, cinnamic acid molecular complexes, proton migrations and intercalation and include work done by J A R P Sarma, R Kamala, B Hanuma Kumari and Madan Rao.

It is a pleasure to acknowledge a lively collaboration with Professor J M Thomas and his group at the Department of Physical Chemistry, University of Cambridge. The work on benzylcyclopentanone solid solutions and packing calculations was done with W Jones, C R Theocharis and S K Kearsley over two summers in Cambridge.

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