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Supramolecular Structures – Reason and Imagination

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The one is the το ποιειν*, or the principle of synthesis, and has for its objects those forms which are common to universal nature and existence itself; the other is the* το λογιζειν *or principle of analysis, and its action regards the relations of things, simply as relations; .... Reason respects the differences, and imagination the similitudes of things. Reason is to the imagination as the instrument to the agent, as the body to the spirit, as the shadow to the substance.*

Shelley, 'A Defence of Poetry', 1821

Abstract

Supramolecular chemistry is the chemistry of the intermolecular bond and is based on the theme of mutual recognition. Such recognition is characterized by chemical and geometrical complementarity between interacting molecules. With the awareness that an organic crystal may be treated as a supermolecule, crystal engineering, the design of crystal structures, may be considered as a supramolecular equivalent of organic synthesis. Crystal engineering has been developed by structural chemists and crystallographers to better understand noncovalent interactions for the design of novel materials and solid-state reactions. The subject consists of two main components, analysis and synthesis, and because of this its resemblance to classical organic chemistry is marked. The concepts and principles of recognition and the nature of the interactions that mediate supramolecular construction in the solid state constitute the analytical component while the synthetic component consists of the strategies employed in the design of solids with particular topological and functional properties. Reason and imagination therefore come into play simultaneously in the quest for new functionalized solids.

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1. Introduction: crystals as supermolecules

The crystal structure is the ideal paradigm of a supermolecule, a supermolecule *par excellence* (Dunitz, 1995). The organic crystal is an example of a nearly perfect periodic selfassemblage of millions of molecules, held together by medium- and long-range noncovalent interactions, to produce matter of macroscopic dimensions. Crystals are ordered supramolecular systems at an amazing level of precision. The high degree of order in a crystal structure is the result of complementary dispositions of shape features and functional groups in the interacting near-neighbour molecules. From the early work of Kitaigorodskii (1973) on crystal packing, ideas of shape-induced recognition between molecules became firmly established (Gavezzotti, 1994). Accordingly, even for recognition between identical molecules as is the case in most crystal structures, it is the dissimilar parts that come into close contact and not the similar surfaces – bumps fit into hollows just as key fits into lock. Conversely, identical parts of neighbouring molecules tend to avoid one another and space groups containing rotation axes and mirror planes are found much less frequently when compared with those containing inversion centres, screw axes and glide planes. Centrosymmetric close packing is preferred even for those molecules that do not possess an inversion centre, and

the four space groups $P\bar{1}$, $P2_1/c$, $C2/c$ and $Pbca$ account for 56% of all organic crystal structures (Brock & Dunitz, 1994) in the Cambridge Structural Database (Allen, 1998). These close-packing arguments, based on the complementary recognition between molecules, are of an all-pervasive character and packing coefficients in most single-component organic crystal structures lie in the range 0.65 to 0.77 (Kitaigorodskii, 1973).

The space-group preferences of many heteroatom crystals parallel those derived on the basis of the Kitaigorodskii model because the directional requirements of several common heteroatom contacts such as O—H···O, N—H···O, C—H···O, Cl···Cl and S···halogen are in accord with the geometrical dictates of the same three symmetry elements that govern close packing: the inversion centre, the screw axis and the glide plane. This is generally not so well appreciated (Desiraju, 1989; see chs. 5 and 6). Indeed, specific intermolecular interactions tend to be associated with specific symmetry elements. For instance, carboxylic acids hydrogen bond across centres of inversion, phenols around 2_1 screw axes and the '*L*-shaped' geometry of Cl···Cl interactions are optimized when the contacting molecules are related by glide planes or screw axes. These geometrical preferences of the common heteroatom interactions reinforce the close-packing tendencies with the result that there is a dominance of a very small number of space groups; these mostly contain translational symmetry elements and are invariably distributed among the lower-symmetry crystal systems.

The crystal structure of a molecule is a free-energy minimum resulting from the optimization of attractive and repulsive intermolecular interactions with varying strengths, directional preferences and distance-dependence properties. Therefore, understanding the nature, strength and directionalities of intermolecular interactions is of fundamental importance in crystal engineering. Intermolecular interactions in organic compounds are of two types: isotropic medium-range forces that define the shape, size and close packing; anisotropic long-range forces which are electrostatic and include hydrogen bonds and heteroatom interactions. The observed three-dimensional architecture in the crystal is the result then of the interplay between the demands of the isotropic van der Waals forces whose magnitude is proportional to the size of the molecule and the anisotropic hydrogen-bond interactions whose strengths are related to donor-atom acidities and acceptor group basicities (Desiraju & Sharma, 1995; Desiraju, 1996*a*). These demands act sometimes in concert and at others in conflict; in the latter event, crystal structures are difficult to predict and the likelihood of polymorphism could increase. However, it is through the similar preferences of isotropic and anisotropic interactions for inversion and screw/glide symmetries that most organic crystal structures achieve efficient close packing. So, hydrogen-bonded solids are not as a rule less densely packed than, say, hydrocarbons. In this respect, organic crystals differ from inorganic ones where packing efficiency is obtained at the expense of coordination directionality or *vice versa* (Wells, 1975).

2. Discussion

2.1. *Supramolecular synthons and retrosynthesis*

The synthesis of complex natural products is a cornerstone of organic chemistry. Corey (1967) introduced a formalism in organic synthesis to logically trace the chemical thought process from starting material to the target substance, defining *synthons* as 'structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operations'. A synthon is usually smaller and less complex than the target molecule and yet contains most of the vital bond connectivity and stereochemical information required to synthesize the goal substance. The analysis of a complex target molecule into simpler synthons is performed then through a series of rational bond disconnections, this exercise being termed *retrosynthesis* (Corey & Cheng, 1989). Recognizing that crystal engineering is the solid-state supramolecular equivalent of organic synthesis, *supramolecular synthons* are 'structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions' (Desiraju, 1995). By analogy

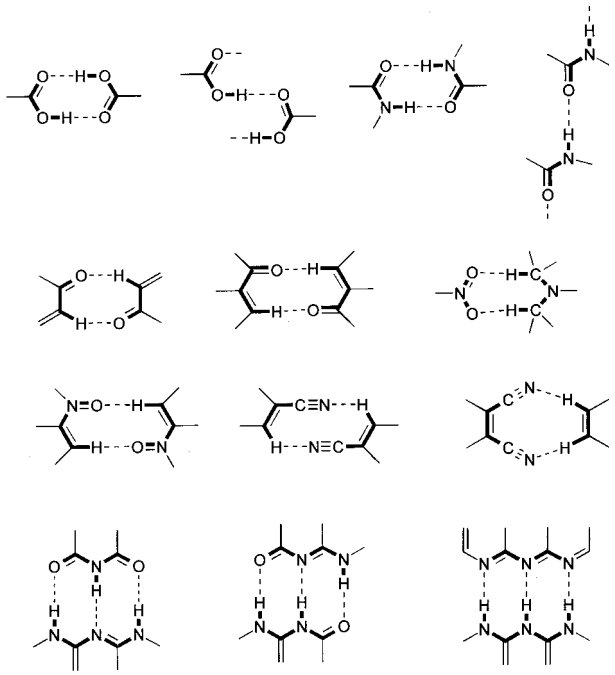


Fig. 1. Some representative supramolecular synthons. Notice the one-, two- and three-point recognition between molecular fragments.

again with organic synthesis, the analysis of the complex interplay of close packing, hydrogen bonding and other interactions in a crystal structure (and by implication during crystallization) may be termed *supramolecular retrosynthesis*. In that analysis and synthesis are carried out in opposite senses, the term 'retrosynthesis' aptly describes the procedure for the logical analysis of a structure, be it molecular or supramolecular.

Supramolecular synthons (Fig. 1) are spatial arrangements of intermolecular interactions between complementary functional groups and constitute the core of the retrosynthetic strategy for supramolecular structures. In this regard, they may be said to play the same focusing role in supramolecular synthesis (Fyfe & Stoddart, 1997) that conventional synthons do in molecular synthesis (Nicolaou & Sorensen, 1995). The synthon approach is advantageous in that it offers a considerable simplification in the understanding of crystal structures. The identification of useful synthons is also easier when crystal structures are defined as networks (Desiraju, 1997*a*) and much assistance may be obtained from inorganic structures that have been traditionally depicted in this manner (Wells, 1975; Dance, 1995). The emphasis in crystal engineering may therefore be increasingly diverted from the constituent molecules to the topological features and geometrical connectivities of nonbonded interactions between molecules. Networks constituted with node and node connections may be thus defined (Reddy, Craig & Desiraju, 1995; Thaimattam *et al.*, 1998). Retrosynthesis may be performed accordingly on the network structure to yield the node structure (molecules) and the node connectivity (supramolecular synthons). The advantage of such an approach in crystal engineering is that: (i) supermolecule $\Rightarrow$ molecule connections are easily established; (ii) comparisons between seemingly different crystal structures are facilitated; (iii) the

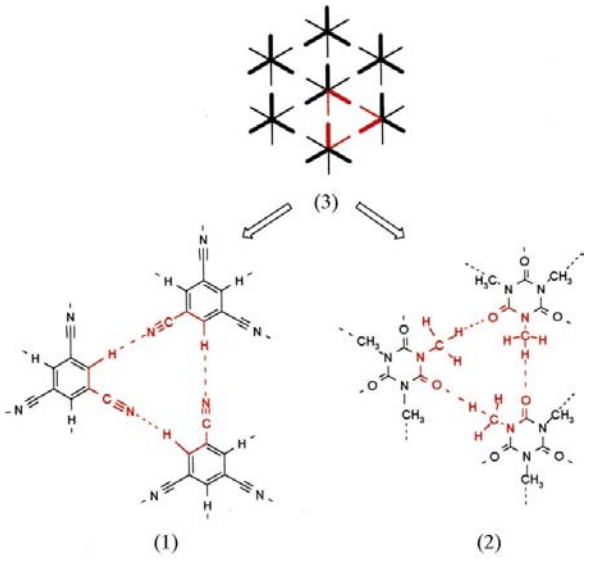


Fig. 2. Retrosynthesis of network (3) leads to trigonal layers of 1,3,5-tricyanobenzene and trimethyl isocyanurate in complexes (1) and (2). The supramolecular synthons are highlighted in red.

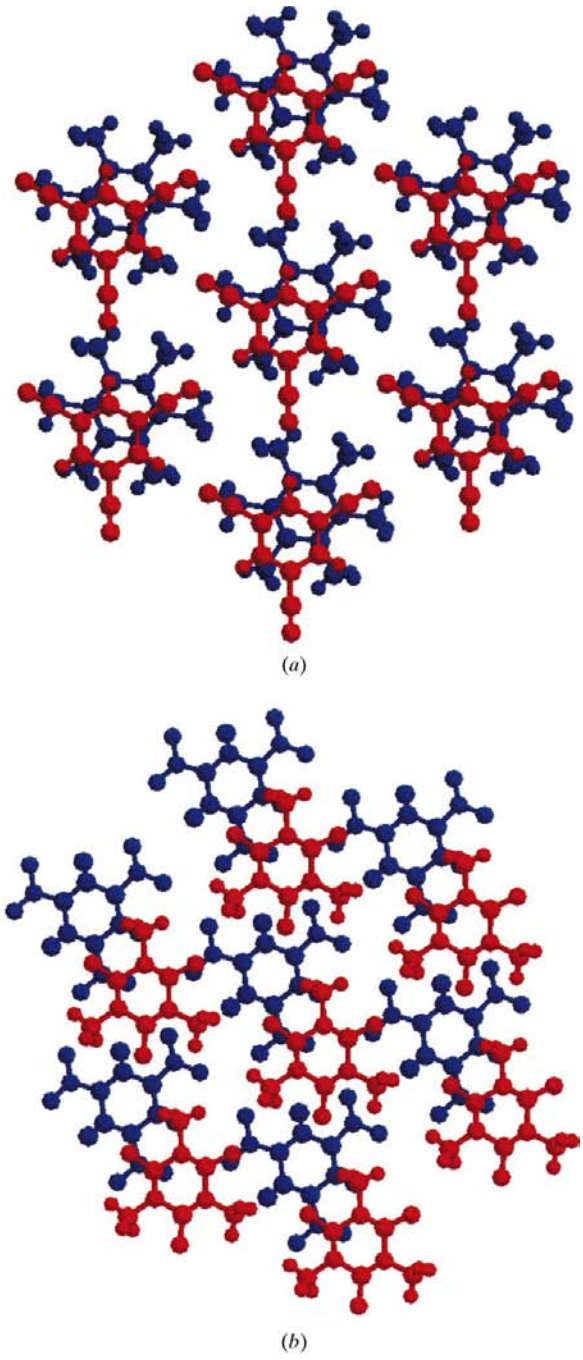


Fig. 3. Crystal structures of complexes (1) and (2). (*a*) Layers of 1,3,5-tricyanobenzene (red) are offset from layers of hexamethylbenzene (blue) because of optimal π–π overlap, leading to loss of global threefold symmetry in complex (1); (*b*) Layers of trimethyl isocyanurate (red) and 1,3,5-trinitrobenzene (blue) alternate without loss of threefold symmetry in complex (2).

interference between supramolecular synthons can be strategically minimized; and (iv) more than one combination of molecular and supramolecular synthons are seen to lead to similar crystal structures. Operationally, such supramolecular retrosynthesis is carried out most conveniently with the Cambridge Structural Database (Allen, 1998), a facility that has established itself as an indispensible tool in crystal engineering.

As an illustration of these ideas, the crystal structures of the 1:1 complexes 1,3,5-tricyanobenzene : hexamethylbenzene, (1), and 1,3,5-trinitrobenzene : trimethylisocyanurate, (2), may be considered (Reddy *et al.*, 1993; Thalladi *et al.*, 1995). Both structures are layered, with alternating donor and acceptor molecules. The structures of the tricyanobenzene layers in (1) and the trimethylisocyanurate layers in (2) are of particular interest because both may be derived retrosynthetically from the trigonal network (3) using weak C—H···N and C—H···O hydrogen bonds, respectively (Fig. 2). Both distinct layers in both complexes have threefold symmetry but a translational offset of layers in (1) leads to a loss of global threefold symmetry and the space group is $C2/c$ (Fig. 3*a*). In (2), on the other hand, the symmetry axes of adjacent layers coincide, the alternating layers are rotated by exactly 60° and threefold symmetry is fully retained, the space group being $P\bar{6}$ (Fig. 3*b*). It is of further interest to note that a quasi-trigonal networking of C—H···N hydrogen bonds is also found in pure 1,3,5-tricyanobenzene (Reddy, Panneerselvam *et al.*, 1995), but that it occurs here in a helical modification rather than as the closed loop seen in (1). Such behaviour is a manifestation of a more general trend wherein a crystal structure strives to increase its dimensionality but this is only a restatement of Kitaigorodskii's close-packing principle. A structure for pure 1,3,5-tricyanobenzene consisting of parallel

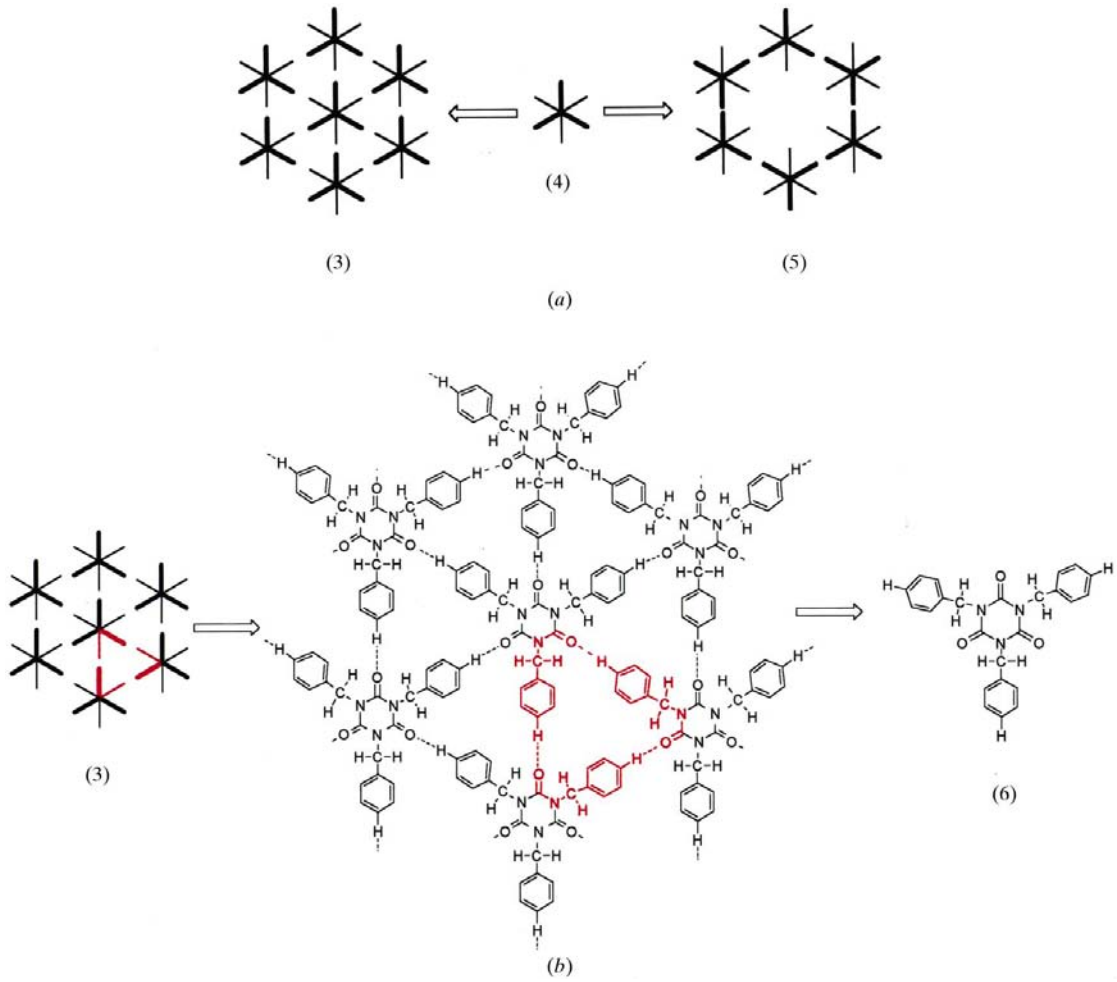


Fig. 4. (*a*) A trigonal molecule, (4), arranged with interactions between unlike and like groups to give, respectively, a noncentrosymmetric trigonal network (3) and a centrosymmetric hexagonal network (5). (*b*) Retrosynthesis of network (3) identifies tribenzyl isocyanurate, (6), as a possible candidate for octupolar NLO applications. The C–H···O-based supramolecular synthon is shown in red.

stacked trigonal layers containing closed loops of C—H···N hydrogen bonding is certainly plausible and such a structure would have the same number of hydrogen bonds as the observed helical structure. That it is not obtained is indicative of the subtle factors that seem to operate in crystal packing or perhaps crystal growth. To rephrase this issue, if all other factors are the same, three-dimensional close packing is more favourable than a stacking of two-dimensionally close-packed layers, which is in turn more favourable than an alignment of one-dimensionally close-packed ribbons into a two- and finally three-dimensional crystal. The networking of trimethylisocyanurate molecules in (2) may similarly be contrasted with pure trimethylisocyanurate, which does not contain a trigonal network in its crystal structure but, rather, a higher-dimensional low-symmetry packing (Thalladi *et al.*, 1998). In the case of both complexes (1) and (2), it would seem therefore that a lowering of dimensionality by the device of molecular complex formation (interaction insulation) is required in order that a global [in (2)] or local [in (1)] high-symmetry structure is obtained. In summary, if a supramolecular structure is defined as a network and analysed retrosynthetically, general connectivity strategies can be systematically derived.

The essential difference between organic synthesis and crystal engineering is that the stepwise and sequential covalent bond formation in the former is replaced by an organized selfassembly of molecules, containing orthogonal recognition sites ideally, in a single step in the latter (Philp & Stoddart, 1996). During crystallization, all the functional groups present in the molecule compete for the numerous possible combinations of intermolecular interactions even while it is understood that only some of these recognition events are eventually fruitful. Thus, if a molecule M containing functional groups F_1, F_2, F_3, ..., F_n approaches another molecule of M, then a matrix of intermolecular interactions, F_i–F_j is theoretically possible. Two or more molecules of M may now come together to form, in principle, several supramolecular synthons S_1, S_2, S_3, ..., S_n, some of which may be very close in energy. However, there is a simplifying feature here. Some combinations of F_i–F_j inherent in S_1, S_2, S_3, ... may exclude others with the result that the complex matrix of intermolecular interactions and supramolecular synthons converges rapidly to a free-energy minimum (the crystal structure) without really sampling all the recognition patterns. The absence of rampant polymorphism in molecular crystals suggests that crystallization is an inherently very efficient process that cascades into stable crystal structures.

2.2. *Engineering of structures and properties*

Crystal engineering today is properly concerned not only with the design of specific structures but also with the design of specific properties (Bryce, 1997; Desiraju, 1997*b*). Very recently, a new class of second-harmonic generation (SHG)-active substances, namely octupolar molecules, have been proposed and been shown to display significant nonlinear optical (NLO) behaviour at the molecular level (Ledoux & Zyss, 1997). At the crystalline or supramolecular level, it has been shown that octupolar SHG is characteristic of trigonal networks. Inasmuch as two-dimensional systems are concerned, the crystal-engineering problem amounts to steering the structure of an appropriately substituted trigonal molecule (4) towards the trigonal noncentrosymmetric network structure (3) characterized by specific interactions between unlike groups in the molecular skeleton rather than towards the hexagonal centrosymmetric network (5) characterized by close approaches between like groups (Fig. 4*a*). Of course, the majority of trigonal molecules (4) adopt neither structure (3) nor (5) but some trivial close-packed arrangement and this renders the engineering problem even more challenging.

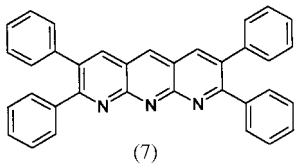
The crystal structure of complex (2) therefore appeared to be a suitable starting point in the crystal engineering of an octupolar nonlinear optical crystal. However, (2) is a molecular complex and, in general, single-component crystals are preferred to molecular complexes for NLO applications because of issues connected with material purification, crystal growth and optical characterization in both solution and the solid state. Therefore, we turned our attention to the symmetrical isocyanurates, all of which have alternating C—H···O donors and acceptors in the molecular structure. Such an alternation is an essential prerequisite for the formation of network (3).

Keeping such considerations in mind, tribenzyl isocyanurate, (6), with its C(sp^2)—H groups was next examined. The crystal structure of (6), derived retrosynthetically from network (3) (Fig. 4*b*), shows that the desired noncentrosymmetric trigonal structure has been obtained (Thalladi *et al.*, 1997). The molecules are far from planar. With respect to the central heterocyclic ring, two benzyl groups point in one direction whilst the third points in the other leading to an overall 'chair' shape (Fig. 5). The layer structure in (6) is therefore corrugated and this increase in dimensionality could well assist in the C—H···π stacking of layers that results in overall three-dimensional noncentrosymmetry, confirmed by a visible SHG powder signal of 0.1 × urea at 1.064 μm.

2.3. *Analysis of intermolecular interactions and weak hydrogen bonds*

Molecular recognition is conventionally considered to be mediated by chemical and geometrical factors (Gavezzotti, 1991). This is a useful distinction though, from the viewpoint of the purist, an arbitrary one; after

all, the origin of all these factors is ultimately the same. While strong hydrogen bonds predominate in current supramolecular synthetic strategies (Lehn, 1990; Whitesides *et al.*, 1995; Hamilton, 1996; Aakeröy, 1997), there is increasing awareness in weak or nonconventional hydrogen bonds (Desiraju, 1996*b*; Steiner, 1997). The nature of the weak C—H···π interaction is particularly interesting (Weiss *et al.*, 1997). We have found recently that 2,3,7,8-tetraphenyl-1,9,10-anthyridine, (7),



(7)

forms 1:1 solvates with toluene and chlorobenzene (Madhavi *et al.*, 1997). The packing of the heterocyclic host molecules is virtually identical in the two structures (Figs. 6*a* and *b*). The minor differences in the arrangement of the guests provide convincing evidence for the hydrogen-bond nature of the C—H···π interaction. The orientation of the methyl group in the toluene molecule and the chloro group in the chlorobenzene molecule is 'switched' with respect to the anthyridine cavity. This hints that chemical rather than geometrical factors operate here. Not only are the C—H···π lengths shorter in the toluene solvate, they are also more numerous and are assisted by cooperative effects. All this means that even moderately activated systems such as tolyl rings participate in interactions that may be considered to be weak hydrogen bonds formed by soft acids and soft bases. It is important to state here, incidentally, that these weak hydrogen bonds encompass a wide scale of strengths just as do carbon acidities. It is therefore misleading to consider all kinds of weak hydrogen bonds as being exactly alike, even as it is misleading to assign hydrogen-bond character only to a certain class of C—H···X (X = O, N) contacts and to consider the rest as nothing more than classical van der Waals interactions (Cotton *et al.*, 1997). A C—H···X hydrogen bond does not become a van der Waals contact just because the H···X distance crosses an arbitrary threshold, though in a number of C—H···N geometries the H···N distance is shorter than the van der Waals value (Mascal, 1998). Rather, the distinction between hydrogen bonds and van der Waals interactions lies in their orientational and angular attributes (Steiner & Desiraju, 1998).

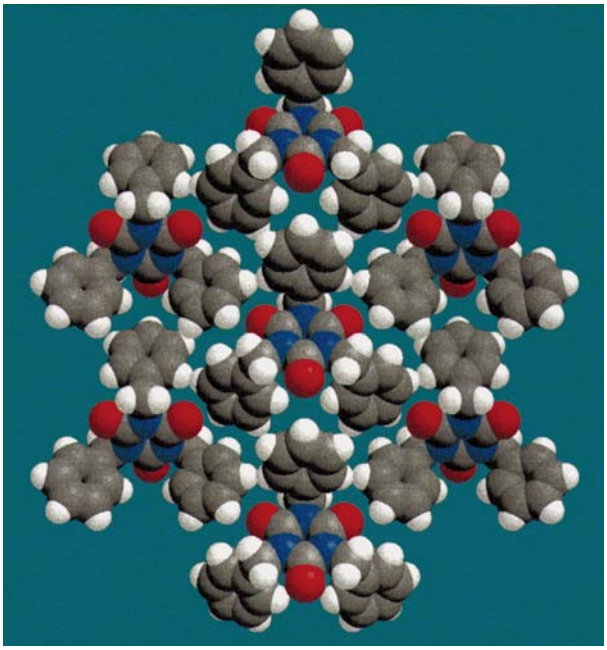


Fig. 5. Crystal structure of tribenzyl isocyanurate, (6), showing the corrugated trigonal layer structure. Notice that the layer is noncentrosymmetric.

2.4. *Polymorphism*

Polymorphism is defined as the phenomenon wherein the same chemical substance exists in different crystalline forms (Threlfall, 1995). With the current intense levels of activity in crystal engineering, there is much interest in this well known though little understood phenomenon (Leusen, 1996; Desiraju, 1997*c*). While there is as yet no clear consensus even on the exact definition of polymorphism, it may be understood in the present context as supramolecular isomerism (Dunitz, 1995). Polymorphism is a very complex issue and this complexity relates not only to causes of its occurrence but also to criteria that can judge as to whether it is present at all. The propensity of polymorphism in a family of crystals can be a considerable nuisance as far as crystal engineering is concerned. The best laid of synthetic plans can become more or less useless if a polymorphic structure is obtained. A positive approach to this phenomenon is to view it as a good opportunity to study the same chemical substance in different crystalline environments. Generally, it might be said that the occurrence of polymorphic forms under widely different crystallization conditions is not exceptional. When the phenomenon occurs under similar conditions, or in the same crystallization batch (for some selected examples, see Ciechanowicz *et al.*, 1976; Desiraju *et al.*, 1977; Anthony *et al.*, 1998; Ojala *et al.*, 1998), it is worthy of more detailed study. In such cases, the free energies of crystallization of the various forms are surely evenly matched and consequently one or more forms are likely to be kinetically favoured.

The degrees of differences between polymorphs may also vary. While there are polymorphs that contain completely different supramolecular synthons, there are others that contain the same synthon occurring in slightly different ways (Sarma & Desiraju, 1998). Three distinct situations are possible: (i) the same synthons are formed by the same functional groups but the differ-

ences in overall packing are caused by variations in the rest of the structure; (ii) the same synthons are formed by the same functional groups but there are multiple occurrences of these groups in distinctive molecular locations leading to different packing arrangements; (iii) different synthons are formed leading to radically different packings. These three situations are illustrated in Figs. 7(*a*)–(*f*).

2.5. *Differences and similitudes between crystal structures*

It is well known that similar molecules can have dissimilar crystal structures and that dissimilar molecules can have similar crystal structures (Allen *et al.*, 1997; Kálmán & Párkányi, 1997). This is because the core constituents of a crystal, the synthons, result from complementary approaches of molecular functional groups. So the exact patterns formed depend not just on the functional groups present in the molecules but also on their relative juxtapositioning. The ramifications of this issue will be appreciated when it is realised that *all* portions of a molecule are supramolecular functionalities (Desiraju, 1997*c*). Therefore, a detailed understanding of crystal packing and crystal design depends very substantially on viewing the molecule as an organic whole. Indeed, the supramolecular paradigm is parti-

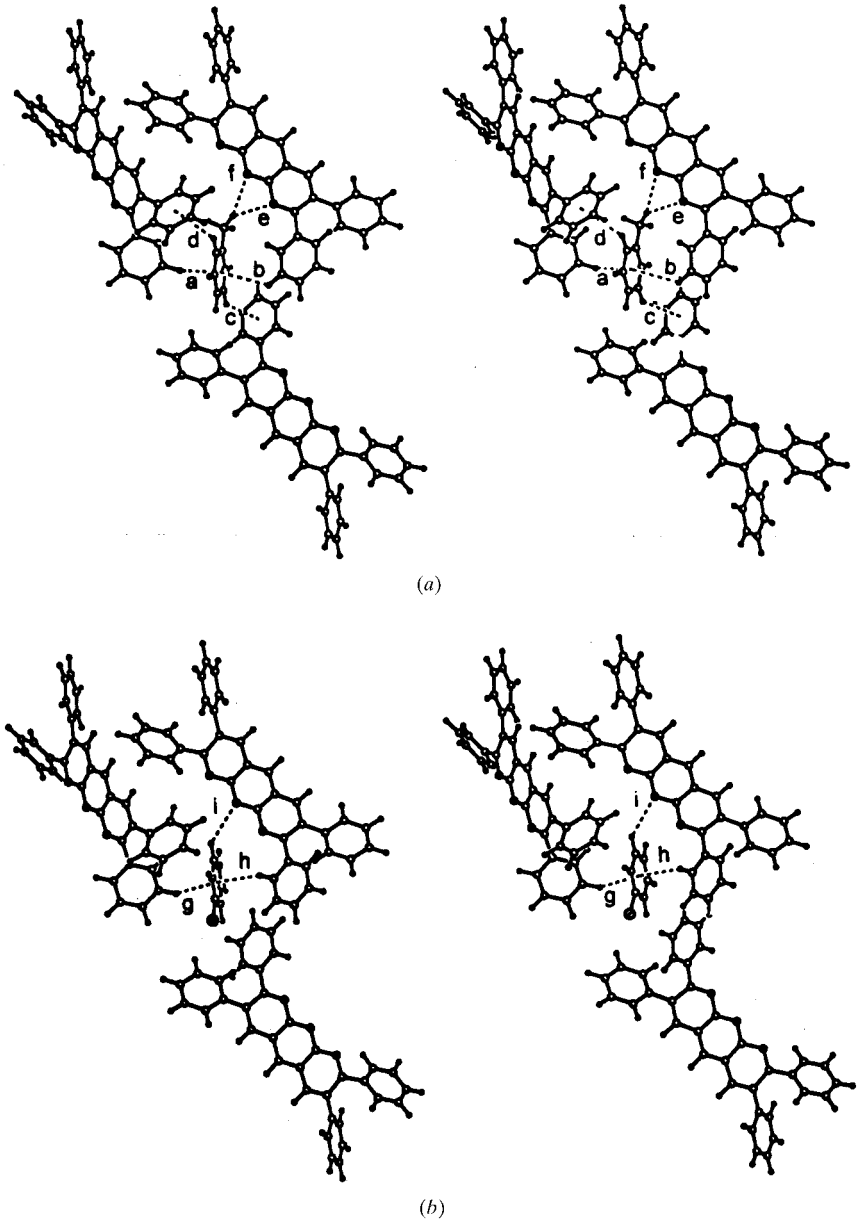


Fig. 6. Crystal structures of the (*a*) toluene and (*b*) chlorobenzene solvates of 2,3,7,8-tetraphenyl-1,9,10-anthyridine, (7). Notice that there are more weak hydrogen bonds in the former structure.

cularly appropriate in the crystalline world because the essential structural attributes of a crystal are supramolecular rather than molecular in nature.

Given such realities, an immediate need in the analysis of crystal structures is to be able to compare crystal structures (Nangia & Desiraju, 1998). Many will appreciate that the structure of say naphthalene resembles that of anthracene more than it resembles benzene. Is it possible to quantify such comparisons? If so, such quantification would amount to pattern matching and becomes important because crystals that are structurally similar are also likely to have similar properties. Ideally, one would like to arrive at an index of similarity between two crystal structures. In order that two or more structures are deemed to be similar or dissimilar, two steps are involved: (i) identification of the core structural features; (ii) evaluation of the extent of their likeness.

Such an exercise can be carried out at varying levels of scrutiny. The traditional approach is to manually analyse several crystal structures and decide whether they are similar or not. The problem with such analyses is that there are always minor differences between any two structures and the decision as to what is important and what is not is, in the end, quite subjective, except say in an area like structure correlation described elsewhere in this Special Issue (Bürgi, 1998). Inspection of the unit-cell parameters, a procedure resorted to in earlier times (Schmidt, 1964; Leiserowitz & Schmidt, 1969; Desiraju & Gavezzotti, 1989), can obscure the focus and need not always be helpful because crystals with different crystal symmetries, space groups and unit-cell parameters may be structurally quite similar. For these and related reasons, manual comparison of complete crystal structures is neither practical nor reliable in a general context. Some simplification is necessary.

A graph set notation for comparing crystal structures has been suggested (Etter, 1990; Etter *et al.*, 1990) and several clarifications of earlier ambiguities have since appeared (Bernstein *et al.*, 1995). This method recognizes that crystal structures need to be simplified before they can be compared. Accordingly, the essential hydrogen-bond connectivity information is retained while the covalent framework on which the functional groups are mounted is neglected. The graph set representation offers an exact network depiction of hydrogen-bonded patterns but the rules for its application are difficult to implement. It has been noted that while the rigour in the graph set definition provides a precise topological description, the same rigour can also obscure general similarities in hydrogen-bonding patterns that would need to be revealed during a comparison of crystal structures (Kubicki *et al.*, 1996; Subramanian *et al.*, 1996). Among other problems with the graph set notation are the definition of acceptors as single atoms and the inapplicability of the method to the many interactions that cannot be considered as being of the donor–acceptor type.

The concept of the supramolecular synthon also recognizes the need to be able to simplify a three-dimensional crystal structure into modular units prior to structural comparison. Again, the emphasis is on the hydrogen bonds and intermolecular interactions between functional groups, neglecting the molecular skeleton that is deemed to be passive. However, the definition of a supramolecular synthon is deliberately left unconstrained and nonquantitative. Synthons range from a single interaction to multipoint recognition patterns that contain hydrogen bonds and nondirectional interactions; the term encompasses both chemical and geometrical recognition and implies structural robustness. Such flexibility is advantageous and allows the chemist to select crystal patterns *not only on the basis of topological attributes but also through chemical intuition and utility*. This in-built subjectivity in defining the term 'synthon' and a certain flexibility in its definition and usage are necessary because the property being described, that is crystal packing, is not rigorously quantifiable. In this respect, the usage of the synthon concept in crystal engineering (Desiraju, 1995) and supramolecular chemistry (Fyfe & Stoddart, 1997) follows very closely its usage in classical organic synthesis (Corey, 1967; Corey & Cheng, 1989). In both these usages, simplification is combined with chemical focus. Given that crystal structures need to be simplified before they can be compared and analysed, the graph set notation doubtless offers an accurate topological description of hydrogen-bonded patterns. However, the simplification is drastic and is achieved at the cost of obscuring the chemical nature of the recognition events that are the primary causes of crystallization. In balance, synthons occupy a middle ground between the full crystal structure and its graph set notation. Implicit in their usage is a simplification that is obtained without compromising the chemical information contained in the supramolecular system (Nangia & Desiraju, 1998).

Graph sets and supramolecular synthons gather together molecular entities so as to produce a supramolecular pattern that is meaningful and useful. Related ideas are employed in models for crystal growth. In the Hartman–Perdok theory, the relative growth of a face depends on the attachment energy, the energy required to remove a growth unit from the particular surface. Crystals are bounded by the slowest-growing faces and, in the context of the Hartman–Perdok theory, these are the ones with the lowest attachment energies (Bennema, 1996). Implicit in this argument is that molecules in a crystal may be grouped in certain ways that depend on the specific intermolecular interactions. All these approaches to understanding crystals underscore the fact that crystals are supermolecules and this attribute pertains not only to structure but also to properties.

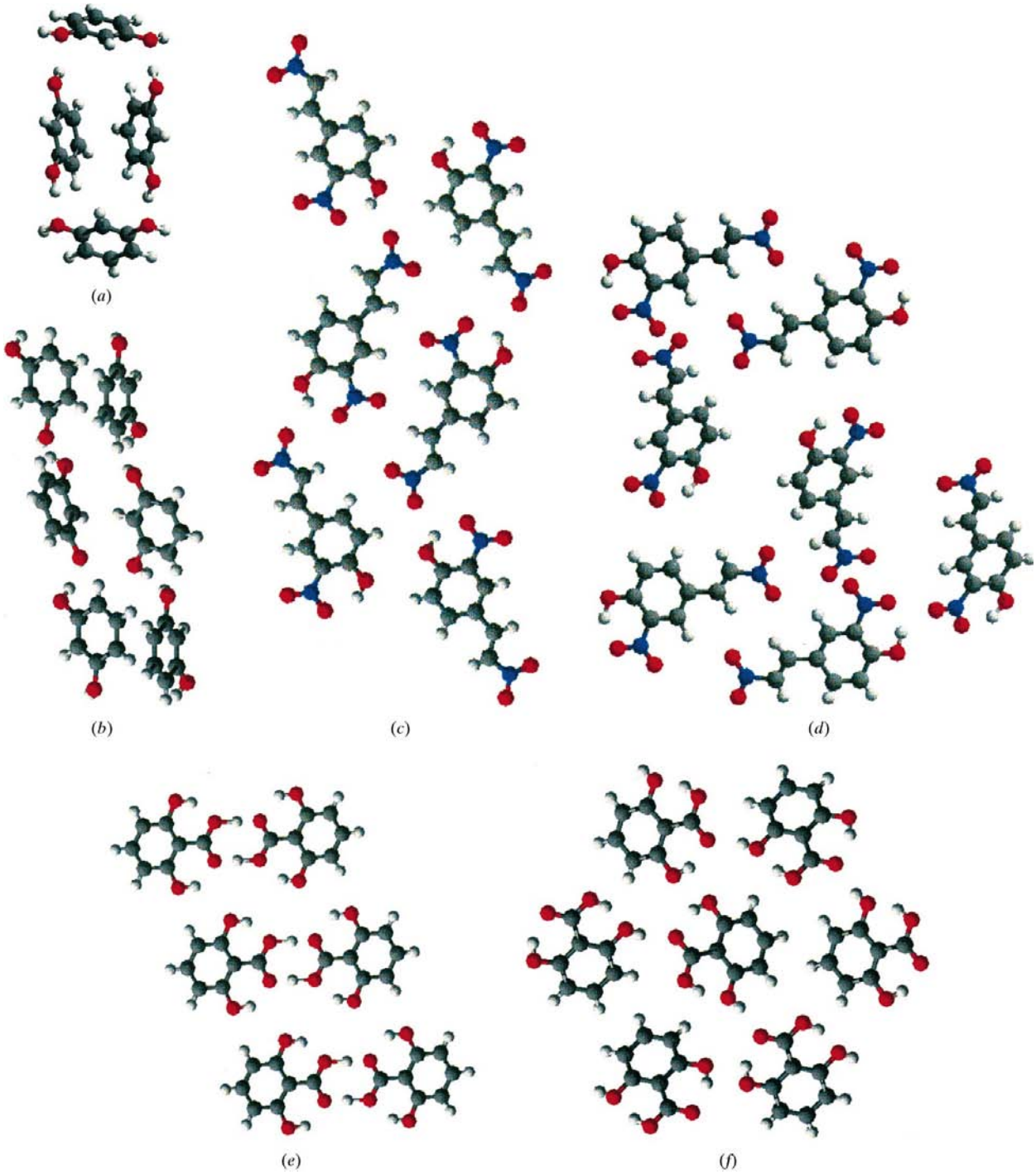


Fig. 7. Three variations of polymorphism based on the supramolecular synthon concept. (*a*), (*b*) The same O—H···O synthons are formed by the same phenolic groups in the dimorphs of resorcinol but the differences in overall packing are caused by the manner in which these synthons are linked topologically. (*c*), (*d*) The same multipoint C—H···O synthon is formed by the same functional groups, $-NO_2$ and $C(sp^2)-H$ in 4-hydroxy-3-nitro-β-nitrostyrene but this synthon can be constituted in two distinct ways because of the occurrences of the $-NO_2$ group in two chemically distinctive molecular locations. (*e*), (*f*) Different O—H···O-based synthons are formed in the dimorphs of 2,6-dihydroxybenzoic acid leading to radically different packing arrangements. Note that the carboxylic and phenolic —OH groups are hydrogen bonded either intramolecularly or intermolecularly in the two forms and that the carbonyl and phenol O atoms act as competing acceptors for these bonds.

3. Conclusions: analysis and synthesis

Crystal engineering has grown and developed from the region of intersection of X-ray crystallography and organic chemistry. In the context of this Special Issue of *Acta Crystallographica* that commemorates the 50th anniversary of the journal, it is appropriate to very briefly trace the progress that has occurred in these two major disciplines during this half-century. During the early days of crystallography, structure determination was too difficult for meaningful comparisons to be made between different crystal structures. Even so, it is inspiring to note that the design principle is already latent in some of the earliest crystal structure determinations. The early papers (also 50 years old!) on the crystal structures of some dicarboxylic acid dihydrates [Dunitz & Robertson (1947); for a contemporary view of the same work, see Dunitz (1998)] contain much that is relevant to the modern subject of crystal engineering. With the extraordinary progress that has been made in methods for the collection and handling of diffraction data of small molecules (Hall, 1998), chemical crystallographers have been gradually transformed into structural chemists and as chemists they have become increasingly concerned with the subject of crystal synthesis. In turn, the development of organic chemistry during the last several decades shows that synthesis can be taken to a higher plane only if it is accompanied by analysis. We are now at the threshold of similar developments in crystal engineering, where imagination will be fuelled by reason to yield supramolecular structures, the variety and utility of which will only be limited by the ingenuity of the practitioner.

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