

Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis

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Dedicated to Professor David Y. Curtin and Professor Iain C. Paul

A crystal of an organic compound is the ultimate supermolecule, and its assembly, governed by chemical and geometrical factors, from individual molecules is the perfect example of solid-state molecular recognition. Implicit in the supramolecular description of a crystal structure is the fact that molecules in a crystal are held together by noncovalent interactions. The need for rational approaches towards solid-state structures of fundamental and practical importance has led to the emergence of crystal engineering, which seeks to understand intermolecular interactions and recognition phenomena in the context of crystal

packing. The aim of crystal engineering is to establish reliable connections between molecular and supramolecular structure on the basis of intermolecular interactions. Ideally one would like to identify substructural units in a target supermolecule that can be assembled from logically chosen precursor molecules. Indeed, crystal engineering is a new organic synthesis, and the aim of this article is to show that rather than being only nominally relevant to organic chemistry, this subject is well within the mainstream, being surprisingly similar to traditional organic synthesis in concept. The details vary because one is

dealing here with intermolecular interactions rather than with covalent bonds; so this article is divided into two parts. The first is concerned with strategy, highlighting the conceptual relationship between crystal engineering and organic synthesis and introduces the term *supramolecular synthon*. The second part emphasizes methodology, that is, the chemical and geometrical properties of specific intermolecular interactions.

Keywords: crystal engineering · hydrogen bonding · molecular recognition · organic synthesis · supramolecular chemistry

*Par ma foi! il y a plus de quarante ans
que je dis de la prose sans que j'en susses rien.*^[**]
Molière

1. Introduction

Chemistry constantly seeks analogies and connections and supramolecular chemistry has grown into a distinct field around Lehn's analogy that "supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond".^[1] This analogy represents a departure from classical chemical thought in that it discards the notion that the molecular structure of an organic substance embodies all of its chemical and physical properties.^[2–4] Supermolecules are not just collections of molecules; their structure and characteristic properties are distinct from the aggregate properties of the constituent

molecular species.^[5] Of course, the hydrogen bond has always been recognized by organic chemists as being significant, especially in biomolecular structures,^[6] and it is known that the strongest intermolecular interactions are stronger than the weakest of covalent bonds.^[7] However, in general it has been felt that the aims of supramolecular chemistry fall somewhat outside the mainstream of organic chemistry.^[8]

Structural chemists and crystallographers have, however, been quick to realise that a crystal of an organic compound is the perfect supermolecule,^[9,10] according to Dunitz "a supermolecule par excellence", an assembly of literally millions of molecules self-crafted by mutual recognition at an "amazing level of precision".^[11] If molecules are built by connecting atoms with covalent bonds, solid-state supermolecules (crystals) are built by connecting molecules with intermolecular interactions. So, the supramolecular equivalents of structural isomers are crystalline polymorphs, and the solid-state topochemical photodimerization of cinnamic acids a very good example that relates polymorphism (in the reactant) with structural isomerism (in the product).^[12] Continuing the analogy further, a molecular isomerization may be compared with a phase transition and stereoisomers with enantiomorphous crystals. Again, disorder in a topochemically reactive crystal finds a molecular parallel in alternative reaction pathways.^[13] Homology is not a

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[**] With regard to organic synthesis, the practitioner of crystal engineering today seems to be in the position of M. Jourdain in "Le Bourgeois Gentilhomme" when he exclaims, "I've been talking prose for the last forty years and have never known it!"

property restricted to molecules alone, and crystalline homologous series have been identified in which patterns of intermolecular interactions (rather than patterns of covalent bonds) are systematically graded; typical examples are benzene, naphthalene and anthracene, or alternatively, benzene, biphenyl, terphenyl.^[14]

Given this background, it is instructive to consider the subject of crystal engineering, which has been defined as “the understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solids with desired physical and chemical properties”.^[15] Crystal engineering is concerned with the systematic architecture of crystal structures.^[16] This architecture is governed by the rules of supramolecular valence, that is, by the chemistry and geometry of the intermolecular interactions, which are, in effect, the supramolecular cement.^[17] Therefore, if crystals are the supramolecular equivalents of molecules, crystal engineering is the supramolecular equivalent of organic synthesis.

2. General Principles and Strategies

*... structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operations.**

Corey's definition of a synthon

Targets in organic synthesis are defined in terms of the connectivity of covalent bonds (that is, a molecular structural formula). At a supramolecular level, it should be recognized that targets in crystal engineering are defined in terms of interaction connectivity, that is, in geometrical and topological terms. One aims, for example, at particular patterns such as ribbons, sheets, layers, channels, tubes, and cavities, which may be appropriately functionalized to yield materials that act as templates for subsequent chemical transformations (catalysts, nanostructures, organic zeolites). Alternatively, the desired geometrical pattern may itself be of inherent significance, because it defines a useful physical property (electronic or proton conductivity, ferromagnetism, nonlinear optics).

[*] This and succeeding quotations are taken from Refs. [18, 19].

All crystal structures of organic compounds may be formally depicted as networks with the molecules being the nodes and the intermolecular interactions representing node connections.^[5] Therefore, the predictable self-organization of molecules into one-, two-, or three-dimensional networks is of the utmost importance in crystal engineering. For such rational design, hydrogen bonding of the conventional OH...O and NH...O variety has been the most commonly used supramolecular cement, yet weaker forces such as CH...O, CH...N, I...I, O...I, N...Cl, or even C...H and C...C can be used. All these interactions, be they strong or not so strong, are directional—anyway directional enough in combination that the orientation of molecules in the solid can be predicted with a reasonable degree of accuracy. These interactions can be combined by a designed placement of functional groups in the molecular skeleton to generate *supramolecular synthons*, examples of which are shown in Scheme 1.

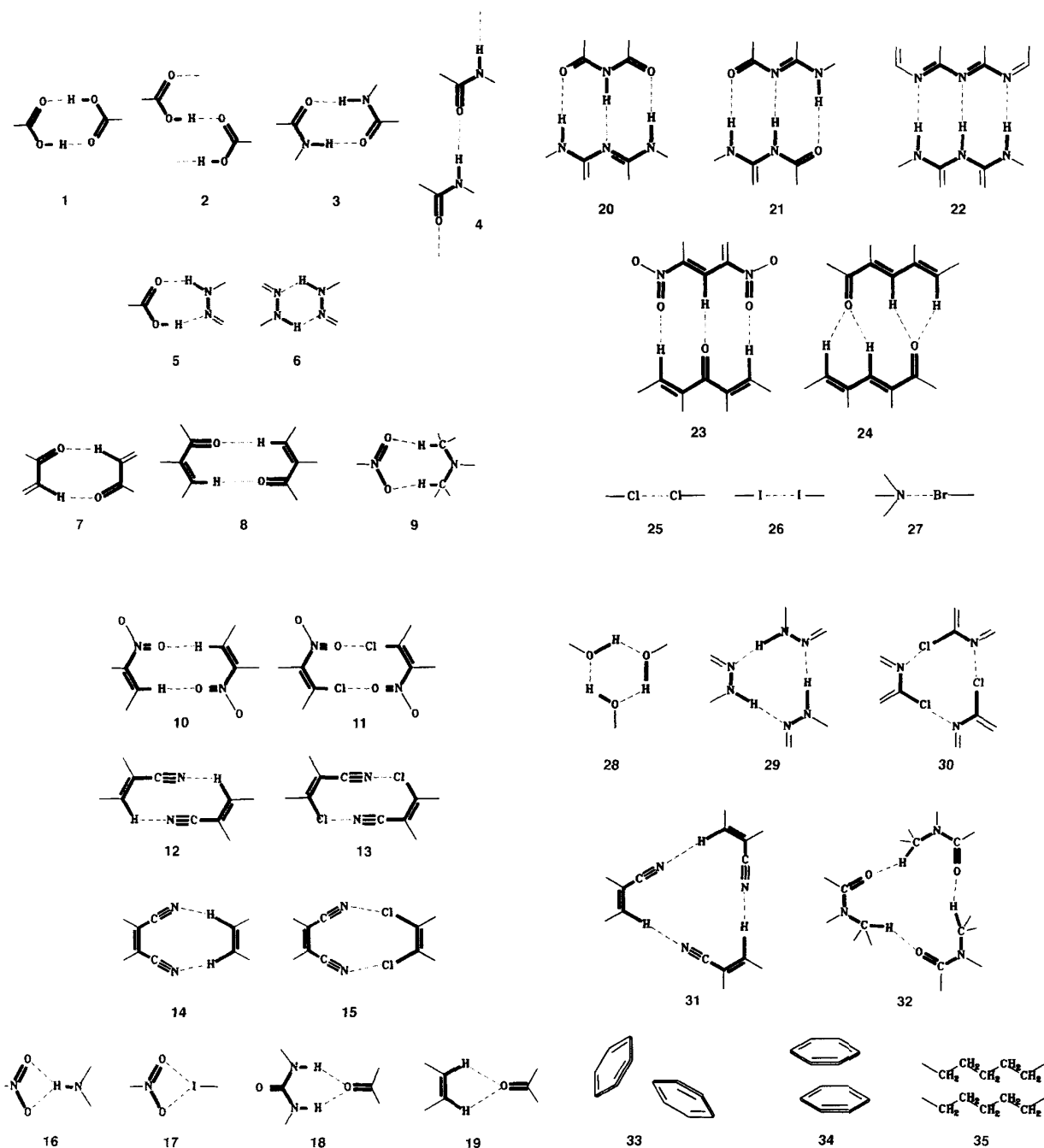
The term “synthon” was introduced by Corey in 1967 in an article entitled “General Methods for the Construction of Complex Molecules”.^[18] This article was of extraordinary importance in shaping the course of organic synthesis. Corey's definition of a synthon is stated above, and the term was traditionally used to represent key structural features in a target molecule in organic synthesis. In later years the term fell into disuse as explained by Corey himself in 1988^[19] and Seebach in 1990,^[20] because it degenerated into a descriptor of synthetic intermediates. However, since crystal engineering and an appreciation of the properties of intermolecular interactions are probably today at that stage of sophistication that organic synthesis and an appreciation of the properties of covalent bonds were in the fifties and sixties, and also because the term synthon is so useful in the context of retrosynthetic analysis,^[20] the supramolecular counterpart of which is crystallographic database analysis, the term “synthon” has been retained here and used in the manner originally intended. In keeping with modern organic synthetic parlance the term “retron” might have been more appropriate^[21] but this is a subjective matter. Corey's definition of a synthon is so general and flexible that more than twenty-five years later it can be used with almost the same connotations but in a supramolecular sense. Thus *supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions*, and crystal engineering is the new

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organic synthesis. To summarize, supramolecular synthons are spatial arrangements of intermolecular interactions and play the same focusing role in supramolecular synthesis that conventional synthons do in molecular synthesis. In effect, the goal of crystal engineering is to recognize and design synthons that are robust enough to be exchanged from one network structure to another, which ensures generality and predictability. Such structural predictability leads, in turn, to the anticipation of one-, two-,

and three-dimensional patterns formed with intermolecular interactions. There is a particular relevance of the solid state to this kind of supramolecular chemistry, because many of the weaker interactions are probably deformed if not destroyed in solution. However, the persistent recurrence of patterns mediated by weak forces in crystals indicates that such interactions might still be important in solution for transient processes such as those associated with biomolecular structure and conformation.



Scheme 1. Representative supramolecular synthons.

2.1. Solid-State Architecture with Supramolecular Synthons

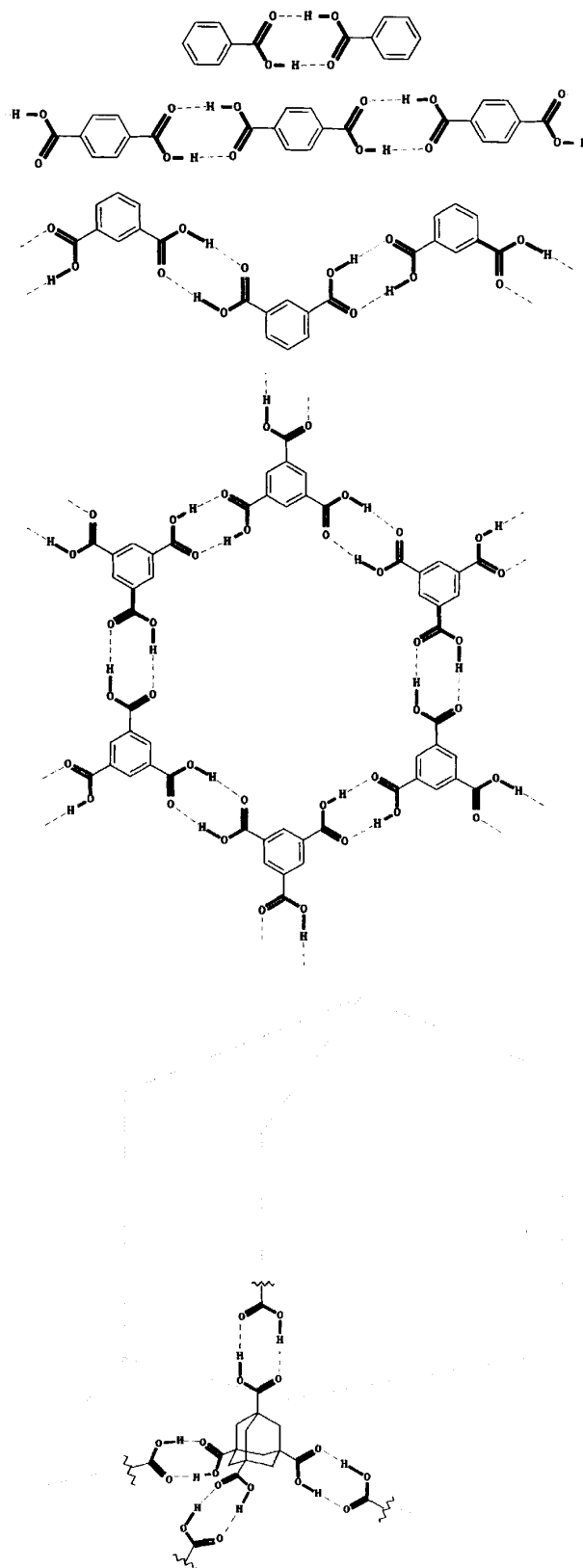
*...recognition of some synthons
(usually the larger or major synthons)
normally is more useful in analysis than that of others.*

Scheme 1 shows a variety of supramolecular synthons **1–35**, culled from the recent literature. A supramolecular synthon is an identifiable design element and should be, strictly speaking, distinguished from an intermolecular interaction. It must be emphasized that synthons are *derived* from designed combinations of interactions and are *not identical* to the interactions. For example, the carboxyl dimer synthon **1** is assembled with two centrosymmetrically related $C=O \cdots HO$ hydrogen bonds. In still other synthons, for example **33–35**, the involvement of the interactions is implicit. Though subtle, this distinction between an interaction and a synthon is real, because supramolecular synthons incorporate *both* chemical and geometrical recognition features of molecular fragments, in other words both explicit and implicit involvement of intermolecular interactions. On occasion, however, when chemistry and geometry are inextricably linked, a single interaction may be regarded as a synthon, for instance $Cl \cdots Cl$, **25** or $N \cdots Br$, **27**.

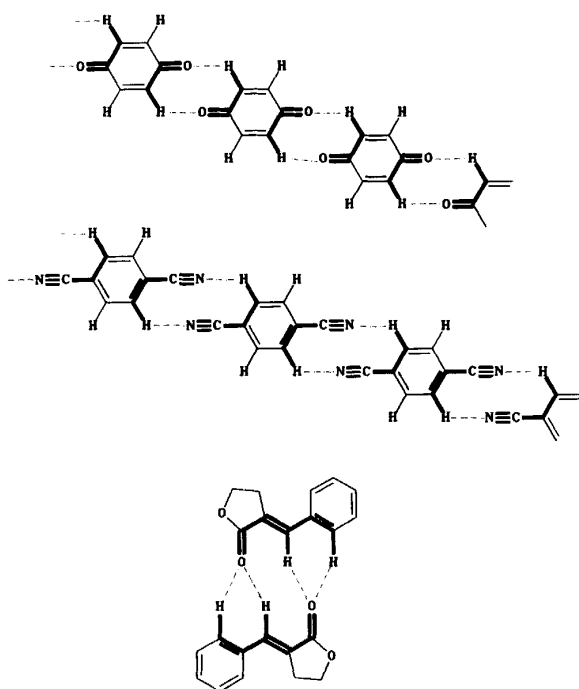
The supramolecular synthon concept is conveniently illustrated in the crystal structures of some aromatic carboxylic acids. Scheme 2 shows how the structures of benzoic, terephthalic, isophthalic, trimesic, and adamantane-1,3,5,7-tetracarboxylic acids (**36**) are built with phenyl rings and dimer synthons **1** in a logical progression. The benzoic acid dimer is zero-dimensional, the linear or crinkled ribbons in the dibasic acid structures are one-dimensional patterns, while the sheet structure in trimesic acid is two-dimensional.^[2,21] The three-dimensional extension of these structures is the diamondoid structure of acid **36**, where synthons **1** are disposed tetrahedrally about the adamantyl nucleus to yield a network that is topologically similar to diamond, in which **1** replaces C–C bonds, and the adamantyl nucleus becomes a super-C atom.^[2,3]

Weaker hydrogen bonding of the $CH \cdots X$ variety may now be considered. Although these bonds have energies only in the $2\text{--}20\text{ kJ mol}^{-1}$ range, their effects on crystal structure and packing are just about as predictable as the effects of conventional hydrogen bonding.^[2,4] Scheme 1 includes several $CH \cdots X$ -mediated synthons, and Scheme 3 shows some typical crystal structures based on these synthons. In crystalline 1,4-benzoquinone, the symmetrical disposition of functional groups results in a linear ribbon pattern linked by synthon **7**. This pattern is carried over largely unscathed into the crystal structure of 2-methoxy-1,4-benzoquinone, while the $CH \cdots N \equiv C$ analogue **12** is observed in 1,4-dicyanobenzene.^[2,5] Another common $CH \cdots O$ synthon **24** is seen in the crystal structure of α -benzylidene- γ -butyrolactone.^[2,6]

A comparison of the crystal structures of solid chlorine and the monoclinic form of 1,4-dichlorobenzene (Fig. 1) is revealing and shows how the supramolecular synthon concept may be extended to lesser known intermolecular interactions.^[1,5] The contacts between the halogen atoms define the $Cl \cdots Cl$ synthon **25** and are virtually identical in the two structures. The aromatic rings in 1,4-dichlorobenzene fulfill a spacer function.



Scheme 2. Construction of aromatic carboxylic acid crystal structures with synthon **1**.



Scheme 3. Construction of crystal packing patterns with $\text{CH}\cdots\text{X}$ synthons **7**, **12**, and **24**.

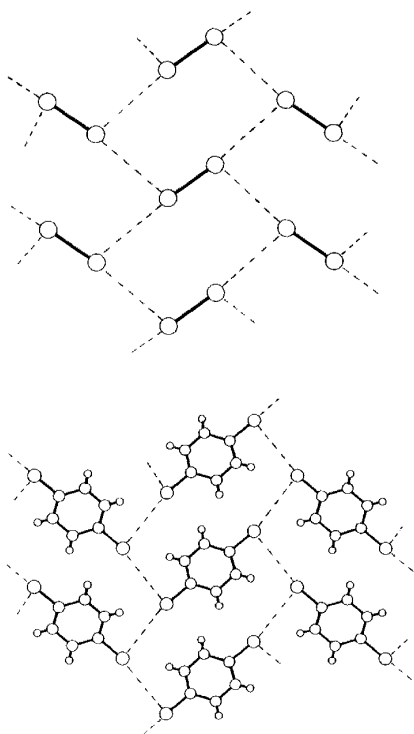


Fig. 1. Similarity between the crystal structures of chlorine (top) and 1,4-dichlorobenzene (bottom). Note the identical disposition of the $\text{Cl}\cdots\text{Cl}$ synthons **25** in the two cases.

The above examples cannot be exhaustive, but they illustrate the importance of being able to identify structurally significant synthons in a supermolecule. Such identification helps in the analysis of more complex crystal packings and the design of new target structures. These examples also highlight two other important features that should be noted in systematic crystal engineering. These are the following:

1) Consideration of a crystal structure in terms of supramolecular synthons can effect a simplification, which facilitates comparison with other seemingly different crystal structures. Accordingly, different molecular functionalities can result in similar crystal structures provided synthons in the various crystal structures possess shape or topological similarity.

2) The interference between the significant supramolecular synthons should be a minimum. Alternatively, the nature of such interference should be understood so that it may be exploited in the engineering strategy. These features will now be discussed in greater detail.

2.2. Simplification of Crystal Structures

... even in the earliest stages of the process of simplification of a synthetic problem, the chemist must make use of a particular form of analysis which depends on the interplay between structural features that exist in the target molecule...

Kitaigorodskii's close-packing principle implies that molecules undergo a shape simplification as they progress towards dimers, higher aggregates, and ultimately crystals.^[27] Shape is a very powerful agent of molecular recognition that in crystals generally proceeds in a way such that supramolecular fragments of a crystal structure have simpler shapes than the constituent molecular species. Accordingly their packing patterns may be easier to predict (see Section 2.8). Molecules in organic crystals are surrounded typically by twelve to fourteen near-neighbors to define quasi-spherical clusters.^[28] Similar shape-simplifying effects are seen in Rebek's "tennis ball" dimer,^[29] and the tertiary structural features in globular proteins are responsible for converting an exceedingly complicated molecular structure into a nearly spherical unit.^[30]

These geometrical consequences of shape recognition can be employed in crystal engineering. A comparison of the crystal structures of benzoic acid and *p*-terphenyl (Fig. 2) is pertinent. Because of the parallel hydrogen bonds in synthon **1**, the shape and size of the benzoic acid dimer mimics that of *p*-terphenyl. The two crystal structures are not identical but reasonably similar with the same space group $P2_1/n$, comparable cell dimensions and volumes, and most importantly, the benzoic acid dimers are packed together using the same herringbone $\text{C}\cdots\text{H}$ interactions that exist in *p*-terphenyl.^[31] To be sure, there are differences in the two structures but these can be understood and rationalized. For example, *p*-terphenyl molecules are tilted along their molecular lengths to optimize herringbone interactions and form slabs that are themselves aligned parallel to optimize other herringbone interactions. In benzoic acid, the dimers are stacked rather than tilted to form slabs, which are then inclined in a herringbone fashion. Stacking rather than

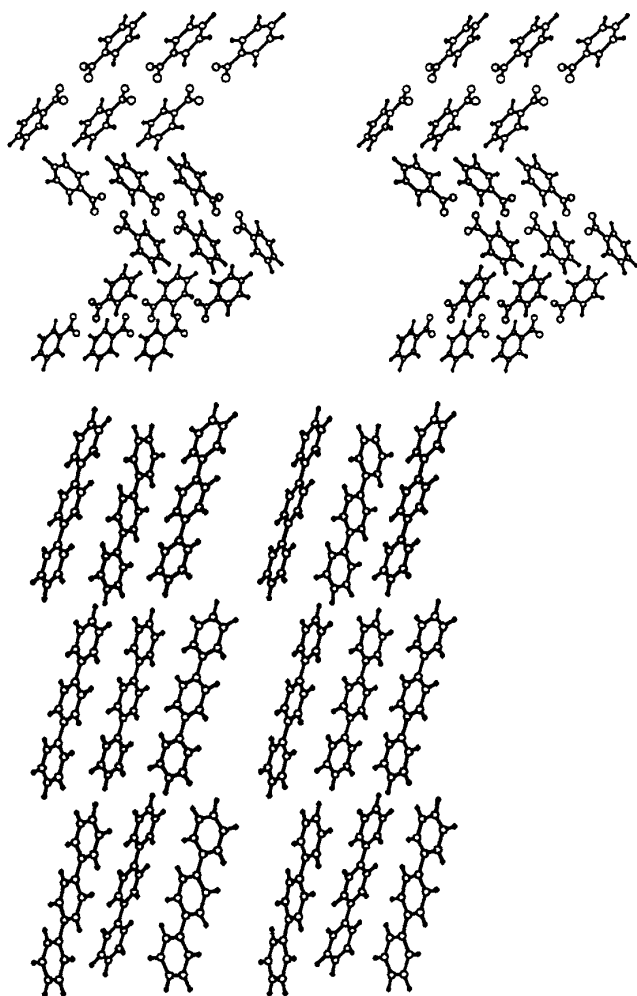
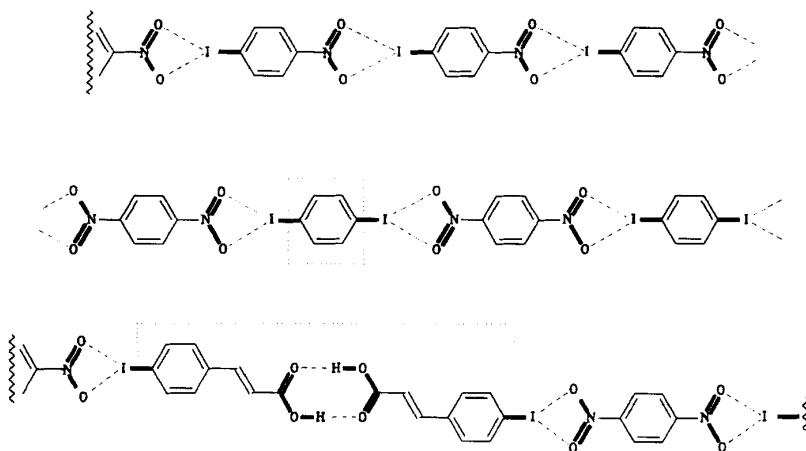


Fig. 2. Stereoviews of the crystal structures of benzoic acid (top) and *p*-terphenyl (bottom), each showing three slab sections. Notice that the benzoic acid dimer mimics the shape of the terphenyl molecule and also the similar herringbone dovetailing between slabs in the two structures.



Scheme 4. Use of the iodo...nitro synthon 17 in crystal engineering. Note how the 1,4-disubstituted phenyl ring and the extended carboxylic dimer are similarly employed.

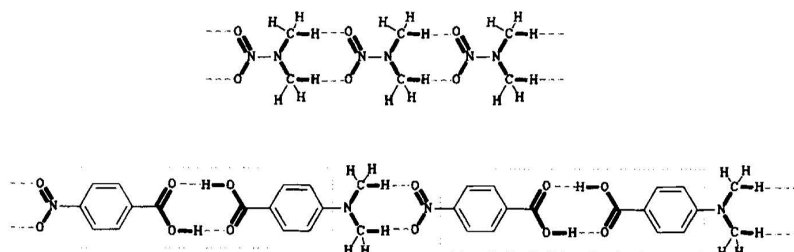
tilting occurs within the benzoic acid slabs because of the tendency of a phenyl ring to be overlaid on a carboxyl dimer ring.^[32] However, the main message is clear—the carboxyl dimer synthon **1** can be used as a surrogate for a 1,4-disubstituted phenyl ring, and it is pertinent to compare this dissection of the benzoic acid dimer supramolecular skeleton with that of the squalene molecular skeleton by Corey.^[18]

This strategy can now be used in the design of crystal structures. We found that halogen atoms, especially iodine, tend to form short polarization-induced contacts with nitro groups (synthon **17**) where the oxygen atoms of the nitro group grip the iodine atom in a two-pronged fashion.^[33] This synthon was initially introduced in the crystal structure of 4-iodonitrobenzene, where it alternates with the phenyl rings to give a ribbon as expected (Scheme 4).^[34] In fact, this molecule has few other crystallization options. The strategy was then extended to the crystal structure of the 1:1 complex of 1,4-dinitrobenzene and 1,4-diiodobenzene where again **17** alternates, but in opposite senses with phenyl rings.^[35] At this stage the hydrocarbon spacer between the **17** synthons was extended by crystallizing a 2:1 complex of 4-iodocinnamic acid with 1,4-dinitrobenzene.^[34] The carboxyl synthon **1** elongates the (now supramolecular) diiodo moiety, which is then able to link with the nitro moiety through synthon **17**. These results are surprising—acids are known to complex with bases or with other acids but not with neutral compounds; however, in this case the acid dimer behaves effectively like a neutral diiodohydrocarbon because the hydrogen bonding requirements of the monomers are completely satisfied by dimer formation.

A very similar exercise may be carried out with $\text{CH}\cdots\text{O}$ hydrogen bonds. Nitro and dimethylamino groups form a $\text{CH}\cdots\text{O}$ -mediated synthon **9**, and the crystal structure of *N,N*-dimethylnitramine is unique in that it consists exclusively of infinite ribbons of this synthon (Scheme 5).^[36] The crystal structure of the 1:1 complex of 4-nitrobenzoic acid and 4-(*N,N*-dimethylamino)benzoic acid may now be anticipated as a ribbon consisting of synthon **9** alternating with an extended terphenyl surrogate formed by a linking of acid molecules with synthon **1**.^[37] To summarize, the crystal packing properties of

an aromatic carboxylic acid dimer are distinct from those of the monomer and are more reminiscent of an aromatic hydrocarbon.

Inherent in structural simplification is a reduction of a crystal structure to its interaction network information. The crystal structure of tetraacid **36** has been described in Section 2.1 in terms of a diamond network with synthons **1** tetrahedrally disposed about the adamantyl skeleton.^[23] It is therefore possible to substitute other synthons for **1** on adamantyl or other tetrahedral templates and generate similar diamondoid structures (Fig. 3). Typical examples of such alternative synthons are metal...NC,^[38] $\text{I}\cdots\text{I}$ **26**,^[39, 40] $\text{O}-\text{H}\cdots\text{N}$,^[41] and the *cis*-amide dimer synthon **3**.^[42] We have



Scheme 5. Use of the dimethylamino...nitro synthon **9**. The strategy for the design of these structures is similar to that employed for the design of the structures in Scheme 4.

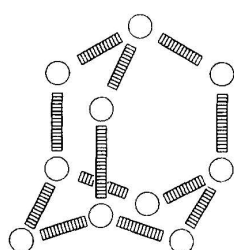


Fig. 3. Archetypal diamondoid network structure. $\circ$ represents a tetrahedral molecular template (for example, adamantyl) and $\blacksquare$ an appropriate supramolecular synthon.

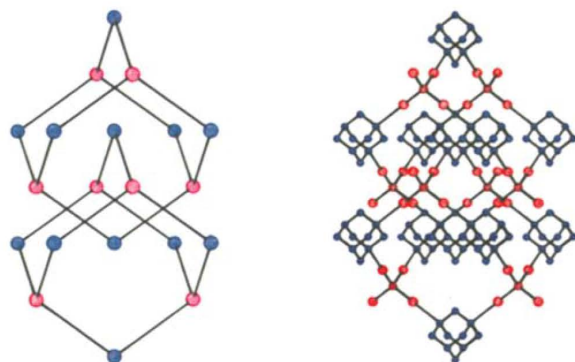


Fig. 4. Schematic (left) and complete (right) representations of the diamondoid network structure of the 1:1 complex hexamethylenetetramine (**42**, blue) and CBr_4 (red). Both intra- and intermolecular bonds are shown as solid lines. The $\text{N} \cdots \text{Br}$ synthon **27** connects molecules. Notice the catenation of networks and the similarity to Fig. 3.

A recurring theme in crystal engineering is that quite different covalent bond frameworks and chemical functionalities in the monomer building blocks can still result in similar supramolecular (crystal) structures. It has long been known that molecules with similar sizes, shapes, and functionalities have similar crystal structures; this principle of structural mimicry explains, for instance, phenomena such as solid-solution formation.^[46] However, a more powerful generalization in the crystal engineering context is that *supramolecular fragments with similar sizes, shapes, and topologies have similar crystal structures*. Such a generalization is more useful, because it recognizes the interchangeability of supramolecular synthons within a particular family of crystal structures.

2.3. Synthon Interference and Structural Robustness

Proximity of reactive functional groups is of major importance in synthesis.

The examples discussed above might imply that supramolecular synthons are completely modular, capable of being introduced, removed, or replaced at will to generate new crystal structures. This would be an ideal, indeed a Utopian situation.

However, chemistry is not geometry, and the major challenge in the practice of crystal engineering is that a crystal structure is a compromise, at times quite uneasy, between interactions of varying strengths, directionalities, and distance-dependence properties (see Section 2.9). Indeed, interference between synthons is the critical problem in crystal engineering, and structural robustness or the ability to use the same supramolecular synthon in a variety of situations is the key to a successful practice of the subject. A thorough understanding of the several ways in which intermolecular interactions interfere with one another is essential for a predictive control over crystal packing. Interactions in an organic crystal are numerous and weak. At a basic level, one attempts to insulate various types of interactions from one another so that their individual (geometrical) features are manifested more effectively. At a higher level, one can exploit the interfering effects of one interaction type on another to realize a supramolecular target structure very much as a synthetic chemist would use a neighboring or proximal group effect.

A discussion of structural robustness begins again with the carboxyl dimer synthon **1**. Generally, aliphatic and aromatic carboxylic acids RCO_2H adopt this dimer pattern in crystals, because its stability and packing efficiency are largely unaffected by the nature of the R group.^[32] The robustness of **1** is revealed by considering the packing preferences of the patterns in Scheme 2. In benzoic, isophthalic, and terephthalic acids, the dimers and ribbons can close-pack without complications. In trimesic acid, however, the "holes" in the hexagonal hydrogen-bonded patterns pose a packing problem, which is solved by inclusion of a second molecular species (a guest).^[22] This problem of voids is seemingly worse in acid **36**, but Nature solves it in a fascinating way by the catenation of as many as five distinct diamondoid networks.^[23] Significantly, the close-packing problems caused by awkwardly shaped networks do not perturb the **1** synthons. However, even such a seemingly robust supramolecular synthon has limits on its use, and we have, in recent years, described four anomalous situations (Fig. 5) in which the centrosymmetric dimer synthon **1**, though expected, is not observed: 1) 4-Chloro- and 4-bromophenylpropionic acids adopt a variation of the carboxyl catemer synthon **2** (actually 50:50 *syn:anti* $\text{O}=\text{C}-\text{OH}$ conformations), while the corresponding cinnamic and benzoic acids adopt synthon **1**. This occurs because the phenylpropionic acids cannot form $\text{CH} \cdots \text{O}$ hydrogen bonds.^[47] 2) 3,5-Dinitrocinnamic acid forms a carboxylic dimer, but this pattern has two-fold rather than inversion symmetry. This occurs because of the dominance of $\text{CH} \cdots \text{O}$ bonding.^[48] 3) In the 1:1 complex between

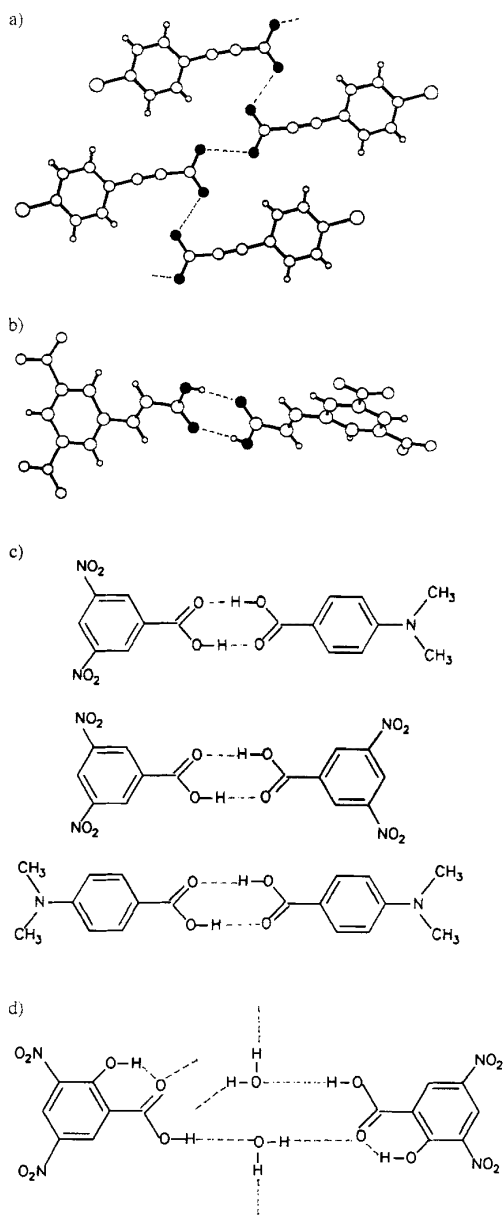


Fig. 5. Anomalous hydrogen-bonded carboxylic acid structures: a) modified catemer synthon **2** in 4-chlorophenylpropionic acid; b) dimer located on a twofold axis in 3,5-dinitrocinamic acid; c) observed homodimers (bottom) and unobserved, though expected, heterodimer (top) in the 1:1 complex 3,5-dinitrobenzoic acid and 4-(*N,N*-dimethylamino)benzoic acid; d) 3,5-dinitrosalicylic acid monohydrate with interrupting water molecules. In all cases, OH...O hydrogen bonds are shown as dashed lines.

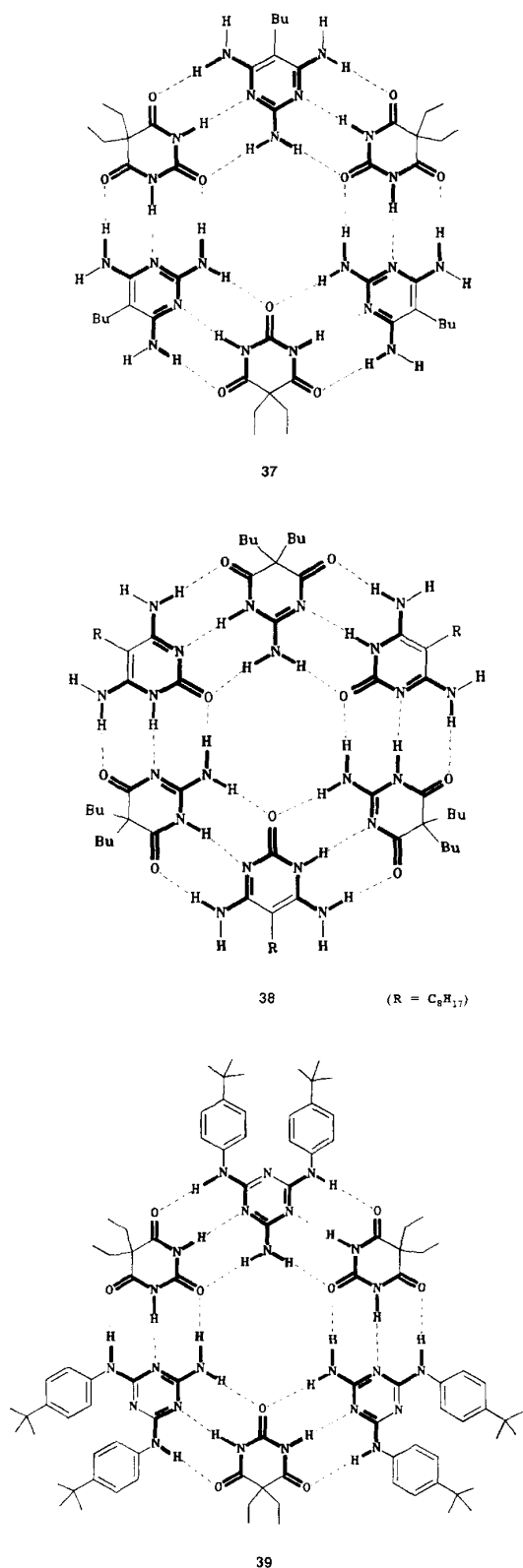
3,5-dinitrobenzoic acid and 4-(*N,N*-dimethylamino)benzoic acid, homodimers are formed between like acids rather than the expected heterodimers between unlike acid monomers. This occurs because of the importance of $\pi \cdots \pi$ interactions.^[49] 4) Unlike other salicylic acids, which adopt the dimer pattern, 3,5-dinitrosalicylic acid crystallizes as a hydrate in which hydrogen-bonded water molecules interrupt the dimer network.^[50]

Multipoint recognition of functional groups is expected to improve synthon robustness as in the triply hydrogen-bonded synthon **20**, which has been used by Lehn, Whitesides, Kunitake, Ringsdorf, and others.^[51] The relationship of **20** to recognition patterns between nucleotide bases in DNA is unmistakable. The existence of three hydrogen bonds in **20** (rather than two bonds in, say, synthon **1**) means that it can be used to construct more intricate supramolecular structures. For example, **20** is a constituent of the rosette structures **37–39** in Scheme 6. Such rosettes themselves occur within the proposed infinite network structure of the 1:1 complex of cyanuric acid and melamine.^[52] Rosettes **37–39** are supermolecules of intermediate hierarchy (see Section 4) in that they consist of a finite number of molecules and have become attractive goals in what is perhaps one of the first examples of a target-oriented supramolecular synthesis. While synthon **20** is quite robust, it can align with itself through further hydrogen bonding in at least three distinct ways to yield, in Whitesides's terminology, a linear tape, a crinkled tape, and the desired rosette.^[53] Two possible approaches to the rosette have been described. Lehn et al. found that the molecular complex of 5,5-diethylbarbituric acid and 5-*n*-butylpyrimidine-2,4,6-triamine contains a linear tape pattern rather than **37**. Cocrystallization of unsymmetrical precursors was expected to yield rosette **38**, but the compounds crystallized separately instead.^[54] Whitesides and co-workers, on the other hand, employed bulky *tert*-butyl substituents on the amine component. The buttressing effects of these groups disfavor linear and crinkled patterns for steric reasons, leading successfully to rosette **39**.^[55] Further attempts to synthesize similar rosette structures based on hydrogen bonding^[56] and other types of interactions are anticipated, but already a certain sophistication in the manipulation of supramolecular synthons is apparent, and the resemblance to logic-directed organic synthesis is clearly discernible.^[57] As our knowledge about intermolecular forces increases, there can be no doubt that complex supramolecular structures will be synthesized with increasing reliability and regularity.

2.4. Subjectivity in Synthon Choice

The recognition of synthons within molecules is purely a utilitarian device; the derivation of all possible synthons in a molecule may never be required.

The dissection of a crystal structure and the identification of particular supramolecular synthons within it is entirely subjective. A variety of patterns may be derived from any given structure and none of these are fundamentally more significant than the others. Rather, all of them assist in what is hopefully a better comprehension of the crystal structure and better methods for the systematic design of related structures. The same intermolecular interaction may be a constituent of several overlapping supramolecular synthons. Assessments of the "significance" of a particular supramolecular synthon are related to the question of structure simplification and could be quite arbitrary. For instance, in the iodo-nitro structures discussed in Section 2.2, it is arguable whether synthon **1** or **17** is the more significant.



Scheme 6. Target rosette structures: 37, 38 (not observed); 39 (observed). The synthons are highlighted. Notice the slightly different synthon structure in 38.

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It is particularly appropriate here to discuss the aryl...aryl synthons **33** and **34**, which are based, respectively, on herringbone and stacking modes of association of aromatic rings,^[58] and the hydrophobic synthon **35**. The geometries of **33** and **34** are well-defined and occur in thousands of structures. If one were to assign significance to supramolecular synthons on the basis of specific interaction strengths, these synthons might not rank very high. However, it is known that they play an important role in determining stable crystal packing arrangements characterized by sparing solubility and high crystallinity.^[59] Figure 6 shows the crystal structures of benzene and 2-amino-

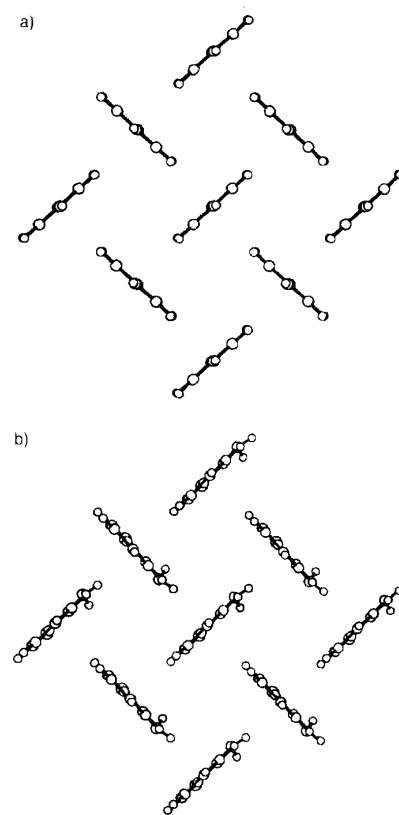


Fig. 6. Comparison of the crystal structures of benzene (top) and 2-aminophenol (bottom). Note the almost identical arrangement of phenyl rings (synthon **33**) in the two structures.

phenol. The latter structure contains alternating polar and apolar bilayers. The structure of the apolar layer is almost identical to the benzene structure with aromatic rings mutually perpendicular. The identification of synthon **33** in both these structures confirms their close relationship.^[60] The nature of aryl...aryl stacking interactions, as manifested in synthon **34**, has also been the subject of intensive studies, and their utilization in crystal engineering depends on the well-known proclivity of planar π donors and acceptors to form overlapped layered structures.^[61] Hydrophobic effects are revealed by the appearance of synthons such as **35** and have been exploited in the design of monolayer structures.

2.5. Conventional and Exotic Interactions

...it may be desirable to attempt a synthesis by the use of new reactions if a great simplification can result or if there is simply no alternative.

Reactions are used in organic synthesis to make covalent bonds, and if structural transformations are to be reliable and efficient, such reactions should evidently be of known mechanism and scope. In the supramolecular context, one would like to use interactions of known directionalities, which can be combined to give structurally robust synthons. Not surprisingly, many current studies in crystal engineering are centered around conventional hydrogen bonding of the OH...O or the NH...O type. But just as organic synthesis progressed by the study of new and (at the time) exotic reaction types, crystal engineering is also amenable to the use of lesser known or weaker and possibly less directional interactions. Gratifyingly, it appears that these weaker interactions are just as effective, especially if they are used in multipoint recognition.

A recent example of the use of CH...O interactions in supramolecular design is provided by the complexation of 1,3,5-trinitrobenzene with dibenzylidene ketones.^[62] The target synthon **23** is obtained by replacing the conventional hydrogen bonds in **20** with CH...O hydrogen bonds. The precursor molecular components suggest themselves naturally, and **23** is obtained in the crystal structures of the molecular complexes formed by either 1,3,5-trinitrobenzene or picryl chloride with either dibenzylideneacetone or 2,5-dibenzylidenecyclopentanone (Fig. 7). Reference has already been made to diamon-

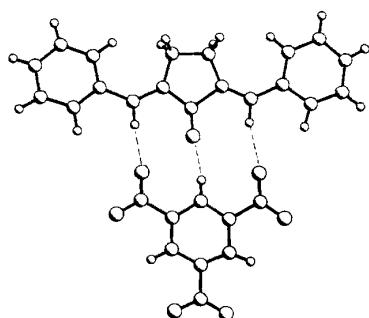


Fig. 7. CH...O-mediated recognition (synthon **23**) in the 1:2 molecular complex formed between 2,5-dibenzylidenecyclopentanone and 1,3,5-trinitrobenzene. Only one of the two symmetry-independent trinitrobenzene molecules is shown.

doid structures assembled with I...I synthons (**26**) and N...Br synthons (**27**, Section 2.2, Fig. 4).^[39, 40, 43] The scope of ionic interactions in crystal engineering studies is only just beginning to be realized. The structures of organic malates and tartrates, for example, contain strongly hydrogen-bonded networks that are robust in two dimensions, permitting other structural variations in the third dimension.^[63]

Conventional hydrogen bonding continues to be used in new and ingenious ways.^[64] Two recent reports are based on the complementarity of the hydrogen-bonding capabilities of the OH and NH₂ groups. Ermer and Eling have pointed out that

while an OH group has one hydrogen bond donor and two acceptors, an NH₂ group has two donors and one acceptor.^[65] Accordingly, compounds or complexes that contain equal stoichiometric amounts of these groups are likely to have highly organized hydrogen-bonded networks with a tetrahedral environment about the O and N atoms. Ermer and Eling have utilized this fact in the design of several diphenol–diamine complexes. Hanessian et al. have discussed the crystal structure of the 1:1 complex between *trans*-1,2-cyclohexanediol and *trans*-1,2-diaminocyclohexane while recognizing again that half of the heteroatoms are fully tetracoordinated.^[66]

In general, one may expect to witness several new and exciting developments in the systematic engineering of crystal structures based on interactions with boron, sulfur, and halogen atoms,^[67, 68] on hydrogen bonding of the CH...X^[24] and XH...π^[69] type (in which X can also perhaps be C), and metal–atom interactions, the latter being, of course, exclusive to organometallic clusters and complexes.^[70] These constitute the supramolecular reaction methodologies of the future.

2.6. Knowledge of Other Crystal Structures

Knowledge or enlightened speculation as to the way in which a molecule to be synthesized has previously been brought into existence can be extremely helpful in simplifying a synthetic problem.

As far back as 1961 Hassel commented on the hexagonal, layered network of weak N...Cl interactions (synthon **30**) in the crystal structure of cyanuric chloride.^[71] which had been previously reported by Hoppe, Lenné, and Morandi in 1957.^[72] More recently we noted that synthons such as **12** are common in cyanoaromatic compounds.^[73] These ideas and the knowledge of the linearity of CH...N hydrogen bonds led to the identification of 1,3,5-tricyanobenzene as a potential candidate for the formation of similar hexagonal networks. Cocrystallization with hexamethylbenzene proved serendipitous, for the 1:1 complex of these two compounds contains the desired hexagonal network (synthon **31**; Fig. 8).^[74] A comparison of **30** and **31** shows that they are interchangeable with a substitution of the N...Cl interaction by the CH...N interaction.

A knowledge of the 1,3,5-tricyanobenzene–hexamethylbenzene crystal structure leads to the possibility of obtaining similar hexagonal networks with related molecules. Trimethylisocyanurate (**40**) was identified, because it contains only CH...O donor and acceptor groups in its symmetrical framework, and the crystal structure of its 1:1 complex with 1,3,5-trinitrobenzene con-

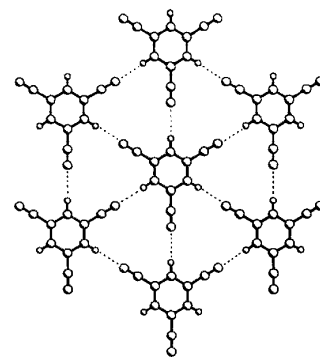


Fig. 8. CH...N network of 1,3,5-tricyanobenzene molecules (synthon **31**) in the crystal structure of the 1:1 complex formed by this substance with hexamethylbenzene. The interleaving hexamethylbenzene network is not shown.

sists of discrete molecular layers.^[75] The layers of **40** are networked into a hexagonal pattern (synthon **32**), while the trinitrobenzene molecules are close-packed in two dimensions to yield another hexagonal pattern (Fig. 9).^[76] Most interestingly,

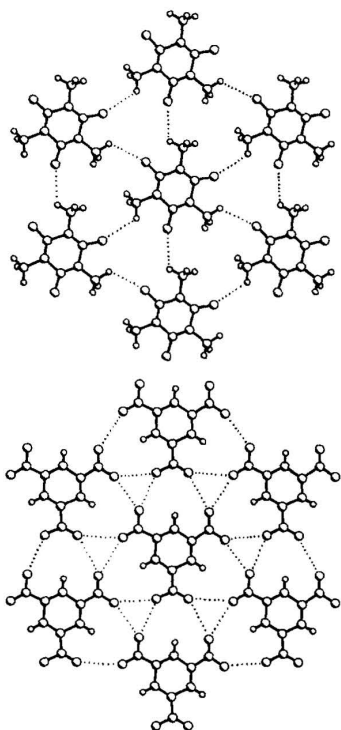


Fig. 9. Hexagonal CH $\cdots$ O network of trimethylisocyanurate (**40**, synthon **32**) (top) and O $\cdots$ O-mediated network of 1,3,5-trinitrobenzene (bottom) in the layered structure of the 1:1 complex formed by these substances.

and unlike the 1,3,5-tricyanobenzene–hexamethylbenzene complex, which is monoclinic, this complex crystallizes in the hexagonal space group P6 $\bar{3}$; in other words the molecular symmetries have been fully retained in the crystal, a rare and exceptional event (see also Section 2.8). Why this happens is not clear—perhaps it has to do with a certain amount of structural insulation of the layers of **40** and trinitrobenzene, thereby reducing three-dimensional interference.

We have observed recently that tetrabromoadamantane (**41**) and hexamethylenetetramine (**42**) form a 1:2 complex in which the molecules of **41** and half those of **42** form a CH $\cdots$ N-mediated diamondoid network related topologically to that in tetraacid **36** (Fig. 10).^[77] Instead of catenation as in acid **36**,^[23] the other half of the molecules of **42** are clathrated within the

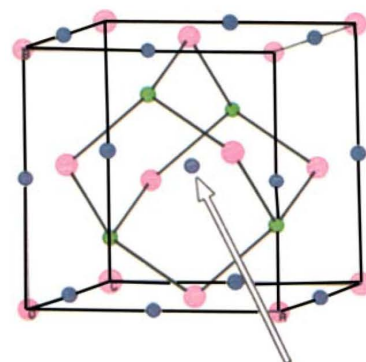
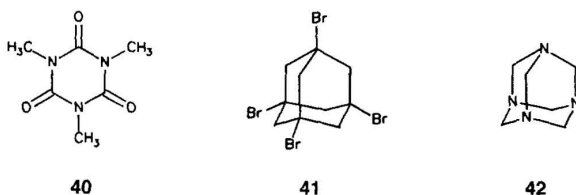


Fig. 10. Organic alloys; a molecule of hexamethylenetetramine (**42**, blue) may be replaced (arrow) by a CBr $_4$ molecule, leaving the diamondoid CH $\cdots$ N network of **42** (green) and 1,3,5,7-tetrabromoadamantane (**41**, pink) intact.

diamondoid cavities and are disordered. We therefore felt that these clathrated molecules of **42** could be replaced by another molecule of similar shape and size. Accordingly we cocrystallized a 1:1:1 complex of **41**, **42**, and CBr $_4$. The structure of this ternary complex was exactly as expected. The diamondoid network is retained and the CBr $_4$ molecules enter the cavities formerly occupied by the disordered molecules of **42**. Interestingly, the CBr $_4$ molecules are ordered, because they participate in auxiliary Br $\cdots$ Br interactions with the molecules of **41**.

2.7. Supramolecular Retrosynthesis— The Cambridge Structural Database

*This is the oldest and most traditional
of all synthetic strategies . . .*

Retrosynthetic analysis in organic synthesis associates synthons, the substructural units in the target structure, with precursor structures in a sequential pathway. This process eventually leads to an identification of one or more potential starting materials.^[19, 21] In crystal engineering, target structures are geometrically and topologically defined, and so the equivalent thought process should associate these target networks with precursor molecules that when crystallized will yield appropriate supramolecular synthons that are compatible with the target network structure. Retrosynthetic analysis is at the heart of organic synthesis, because it uses what is known (target structure) to heuristically derive what is unknown (precursor structure). Supramolecular retrosynthesis is of equal importance in crystal engineering and for the same reason. It uses a particular target network and works backwards to identify molecules that by using their intermolecular interactions will crystallize in the target structure.

Traditional retrosynthetic analysis is based on the bedrock of knowledge of the various reactions (covalent bond-making processes) available to the synthetic chemist. This knowledge has been built up through the endeavors of generations of organic chemists.^[20] The practice of supramolecular retrosynthesis must analogously depend on an intimate knowledge of the myriad ways in which intermolecular interactions are manifested in crystals. This knowledge has come to us through the endeavors

of generations of crystallographers who have bequeathed to us around 125 000 accurate crystal structures of organic and organometallic small-molecules. To a large extent, the assimilation and digestion of the organic synthetic repertoire is still a manual, individual effort.^[78] However, because of the peculiarly geometrical nature of intermolecular forces, supramolecular synthetic methodology is suited to computer storage and retrieval techniques, and the essential tool for retrosynthetic analysis in crystal engineering already exists in the form of the Cambridge Structural Database (CSD).^[79]

The CSD is now more than ever suited to the purpose of supramolecular retrosynthesis, because it may be searched for patterns of intermolecular forces. Till very recently, the search protocols in the CSD were molecular in their bias; only questions based on covalent bond connectivity could be posed. In studies of interaction geometry, the hits that were thus obtained through molecular-type searches were manipulated with geometrical calculation programs. Today it is possible to code the supramolecular synthon structure directly (as shown in Scheme 1) *inclusive of geometrical attributes* in the search question and obtain all crystal structures that contain the chosen synthon. As a typical example, in attempting to extract all structures that contain dimer synthon **1**, one might typically, in former times, have retrieved all carboxylic acid structures using in the search question a molecular fragment such as CO₂H. This search would have yielded not only compounds that contain the desired **1**, but also acids that adopt the alternative catemer **2**. Yet, structurally related synthons like **3** would not have been obtained. In contrast, the distinctly supramolecular bias of the latest versions of the CSD surely takes into account its ever-increasing relevance in systematic crystal engineering.

The CSD is extremely useful in the study of intermolecular forces weaker than conventional hydrogen bonding. For any given interaction there is an ideal intermolecular orientation. However, this ideal geometry is deformed to a greater or lesser extent in crystals, because the crystal geometry is the result of interaction interference (see Section 2.3). Therefore a statistical analysis of crystal structures is mandatory when studying weak interactions. These statistical techniques minimize the crystallographic noise, that is, the effects of the various deformations, which are inevitable when the interactions are weak. The greater the sampling of crystal structures, the weaker the interaction that may be analyzed. It is reasonable to expect that the present size of the CSD is sufficient to permit an analysis of most types of intermolecular interactions that have been used in crystal engineering or are likely to be used in the foreseeable future.

2.8. Supramolecular Symmetry

...any synthetic scheme which does not take full cognizance of stereochemical possibilities or problems will have a correspondingly low expectation of success.

Stereochemistry is an expression of molecular topology, and its supramolecular equivalent is expressed in terms of the spatial and geometrical relationships between supramolecular fragments in the crystal. For instance, how does one obtain particular dispositions and arrangements *between* ribbons, layers and

networks within a crystal structure? This is a matter of considerable importance in crystal engineering, because it results in the manifestation or disappearance of physical effects such as Second Harmonic Generation (SHG) or chemical effects such as host-guest complexation. For instance, crystallization in an enantiomorphous space group of an SHG-active material may be likened to a supramolecular asymmetric synthesis. Such considerations are closely linked to questions concerning symmetry. In general, three sorts of symmetry need to be considered: molecular symmetry, the symmetry of supramolecular fragments (tapes, helices, knots, sheets, channels, voids), and crystal symmetry. The first and the third kinds of symmetry are matters of fact, while the second is subject to individual interpretation.

The carry-over of molecular symmetry into the crystal is not a trivial matter, and in no aspect of crystal engineering is the practitioner of the subject quite so helpless today as in establishing connections between molecular and crystal symmetry. Indeed, Kitaigorodskii's laws of close-packing almost dictate that molecular symmetry is a very poor guide to the molecular site-symmetry in the crystal. The inversion center is the only molecular symmetry element that is routinely carried over into the crystal, because it is the only crystal symmetry element that does not entail loss of packing efficiency by its presence.^[27, 80] In practice this means that higher symmetry molecules almost always do not adopt higher crystal symmetries. However, the shape factor is also important and when the molecular shape exceeds a certain awkwardness, which is still not really quantifiable, close-packing is problematic leading to the formation of open networks in which the full molecular symmetry is retained, and a second molecular species is included as a guest to improve packing efficiency. For example, 1,3,5-triphenylbenzene forms 1:3 host-guest complexes with benzene, whereas mesitylene, 1,3,5-trichlorobenzene, and 1,3,5-trinitrobenzene form single-component crystals.^[10] The presence of high molecular symmetry coupled with a symmetrical interaction pattern is a more powerful combination for the engineering of host networks. In such cases, there is a pronounced conflict between close-packing and directional factors. Such a situation often arises when groups capable of hydrogen bonding are symmetrically disposed in a symmetrical molecular framework. The rigid scaffolding of hydrogen bonds is also compelled to be symmetrical, because the directionality of the hydrogen bonds cannot be compromised. Gross violations of the close-packing principle may sometimes result leading to guest-molecule inclusion (hydroquinone-C₆₀), catenation of networks (acid **36**), or simultaneous inclusion and catenation (hydroquinone with small guests, trimesic acid).

Consideration of spatial relationships between supramolecular fragments in a crystal reveal the following alternatives: 1) Translation versus inversion stacking of two-dimensional fragments such as ribbons and sheets.^[81] 2) Packing of fragments of similar and opposite chiralities, for example helices.^[82] 3) Alternative topologies of catenation of two- and three-dimensional networks.^[83] 4) Segregated versus mixed stacks of planar donor and acceptor molecules in organic metal structures.^[84] Many of these possibilities are influenced by extremely weak interactions and are not only poorly understood at present, but also not very amenable to computational techniques. Since the final outcome of crystallization is often governed by a combination of kinetic

and thermodynamic factors, stereoselective supramolecular synthesis remains a difficult though achievable goal for the future.

2.9. Polymorphism

...the possibility of competing reaction paths should be minimized...

No discussion of crystal engineering can sidestep the problem of polymorphism. This phenomenon is as mysterious and vexing as when a wrong isomer is obtained in a reaction sequence in spite of the best planning and effort. As in traditional synthesis, our inability to grapple with such a problem stems from an incomplete or incorrect knowledge of the factors that affect structure. On occasion it also appears to arise because of outright bad luck, a commodity that is probably as prevalent in crystal engineering as in organic synthesis.

Much has been said about the frequency of occurrence of polymorphism among small-molecule substances, on whether the proportion of polymorphic structures in the CSD is representative of the global proportion of polymorphs in all possible crystal structures (if such details could be ascertained reliably), or even if the number of polymorphs of a given substance increases with the amount of time and effort spent on studying the compound.^[85] Many of these questions are rhetorical and quasi-philosophical and are not very helpful in solving the practical problems of crystal engineering. However, a few generalizations may be made: 1) The frequency of occurrence of polymorphic modifications is not uniform in all categories of substances. The phenomenon is probably more common among molecules that have flexible conformations or many different groups capable of hydrogen bonding. By the same token, rigid, flat molecules such as condensed aromatic hydrocarbons are unlikely to have many polymorphic modifications under normal conditions of temperature and pressure. Again, the likelihood of polymorphism may be greatest in an intermediate molecular weight range, approximately C_{10} to C_{20} . 2) Ingenious methods of crystal engineering that create several sites for (three-dimensional) multipoint recognition of molecules will probably decrease the likelihood of polymorphism. In such cases, the general strategy would be to ensure that there is a unique pattern of supramolecular synthons. 3) For the particular application under consideration, it may not really matter whether polymorphs exist, because the critical, property-defining supramolecular fragment (that is, the particular synthon) may be found intact in all the polymorphs. 4) Polymorphism is strongly solvent-dependent in some cases, and computer simulation of crystal structures with and without adhering solvent molecules may provide guidelines for the crystallization of a particular polymorph.

The study of polymorphism in organic crystals is still in a process of evolution, and much more data will be required before firm and general conclusions can be drawn. Recent computational approaches based on molecular dynamics calculations seem to show considerable promise. The Monte-Carlo-based Polymorph Predictor technique has been implemented in the Cerius² package from BIOSYM/Molecular Simulations to

obtain ab initio predictions of a number of polymorphs.^[85] Yet, crystallization almost certainly does not depend exclusively on energetics and may proceed through discrete stages with the result that multimolecular clusters are trapped in higher energy minima in the final crystal structure. A better understanding of polymorphism will depend on a better understanding of the crystallization process itself, and this in turn will rely on advances in spectroscopy (detection of crystal nuclei), physical chemistry (thermodynamics, chaos theory), and biophysics (protein folding). These are difficult issues, and only better experimental and theoretical insights will lead to any measure of control over the problem of polymorphism.

3. Methodology—Intermolecular Interactions

A number of intermolecular interactions, the nuts and bolts of crystal engineering, have been discussed implicitly in the preceding sections, and several detailed and definitive experimental CSD-based and theoretical studies of these interactions have been the subject of recent publications.^[6–10, 13, 15, 24, 40, 58, 59, 67–70, 85, 86] The purpose of this section is therefore only to enumerate these forces and to very briefly highlight some of our own results especially those pertaining to the weaker interactions.

The most meaningful criteria for the classification of intermolecular forces from the crystal engineering standpoint are distance-dependence and directionality. Typically, the medium-range forces are isotropic in character and define molecular shape, size, and close-packing (implicit involvement of interactions). Generally, these forces are limited to $C \cdots H$, $C \cdots C$ and $H \cdots H$ interactions. The long-range forces on the other hand are electrostatic and anisotropic and involve heteroatom interactions, that is, interactions among N, O, S, Cl, Br, I (rarely B, F, P, Se) or between any of these elements and C or H (explicit involvement of interactions). Ionic forces are extremely long-range in nature and are quite specific, directing supramolecular structure effectively.

3.1. Nondirectional Forces

Nondirectional forces ($2\text{--}10\text{ kJ mol}^{-1}$) traditionally, though not necessarily exclusively, include $C \cdots C$, $C \cdots H$ and $H \cdots H$ interactions.^[87] The relative importance of these interactions in any particular crystal depends on the C:H stoichiometry. Aromatic compounds (high C:H ratios) have a much stronger tendency to stack, since this would increase the number of $C \cdots C$ interactions. The coulombic character of the $C \cdots H$ interaction could account for its prevalence in a wide variety of aromatic and aliphatic compounds (Section 2.4). For planar aromatic compounds these interactions result in the characteristic T-shaped herringbone synthon **33**. Crystal structures are also known where an unusually acidic C–H group (alkyne) makes close contacts with conjugated π systems.^[88] Whether these contacts are to be termed $CH \cdots \pi$ hydrogen bonds, like the recently studied $OH \cdots \pi$ hydrogen bonds (see Section 3.2.1), or whether they are merely extreme manifestations of the $C \cdots H$ herringbone interaction is an open question.

3.2. Hydrogen Bonding

Hydrogen bonding, the master key for molecular recognition, is the most reliable directional interaction in supramolecular construction, and its significance in crystal engineering can scarcely be underestimated. As a vast amount of work has been carried out on the various aspects of hydrogen bonding, it would be futile to attempt even a brief review of these efforts here. Hydrogen bonds of the type $\text{OH}\cdots\text{O}$ and $\text{NH}\cdots\text{O}$ may be termed “strong” or “conventional” (energies 20–40 kJ mol^{-1})^[89] to distinguish them from the weaker $\text{CH}\cdots\text{O}$ and $\text{OH}\cdots\pi$ interactions (energies 2–20 kJ mol^{-1}), which share many of their characteristics and which are discussed in greater detail in Section 3.2.1.

The distinctive geometrical attributes of a hydrogen bond $\text{D}\cdots\text{H}\cdots\text{A}\cdots\text{X}$ (D = donor, A = acceptor) are the $\text{D}\cdots\text{A}$ and $\text{H}\cdots\text{A}$ lengths, the hydrogen bond angle $\text{D}\cdots\text{H}\cdots\text{A}$ or θ , the $\text{H}\cdots\text{A}\cdots\text{X}$ angle or ϕ and the planarity of the DHAX system. All these features have been discussed extensively.^[6, 15] Typical values for the $\text{H}\cdots\text{A}$ distance are 1.80 to 2.00 Å for $\text{NH}\cdots\text{O}$ bonds and 1.60 to 1.80 Å for $\text{OH}\cdots\text{O}$ bonds. More relaxed definitions of these distance criteria permit a consideration of the slightly longer three-centered and four-centered bonds, which seem to be very common in several hydrogen-bonded structures. Ranges for θ and ϕ occur around 150–160° and around 120–130°, respectively. This marked directionality of hydrogen bonds is well-established and is the basis for efficient and reliable supramolecular construction using supramolecular synthons that contain groups such as $-\text{OH}$, $-\text{CO}_2\text{H}$, $-\text{CONHR}$, and $-\text{CONH}_2$. Synthon **28**, for instance, occurs in several phenols and in the water trimer and is related to other synthons such as $(\text{OH})_4$ and $(\text{OH})_6$.^[90] We have found recently that many hydrogen-bonded synthons containing carboxyl and hydroxyl groups in organic crystals are retained largely intact in organometallic crystals.^[91]

3.2.1. $\text{CH}\cdots\text{O}$ and $\text{OH}\cdots\pi$ Hydrogen Bonds

This discussion is also valid for the related $\text{CH}\cdots\text{N}$ and $\text{NH}\cdots\pi$ ^[69, 92] interactions. Furthermore, while there is some question whether the $\text{CH}\cdots\text{Cl}$ interaction is a viable one, recent reports provide evidence for $\text{CH}\cdots\text{F}$ ^[94] and $\text{CH}\cdots\text{Se}$ ^[95] hydrogen bonds.

There is little doubt that $\text{CH}\cdots\text{O}$ hydrogen bonds are important, even if subtle, determinants of crystal packing, especially when strong $\text{OH}\cdots\text{O}$ and $\text{NH}\cdots\text{O}$ hydrogen bonds are absent.^[24, 96] As has been discussed in Section 2.3, $\text{CH}\cdots\text{O}$ hydrogen bonds may distort the geometry and topology of even the strong hydrogen-bond network in specific instances. Anomalies and puzzles in the strong hydrogen-bond patterns of certain crystal structures are explained on the basis of the interplay of strong and weak hydrogen bonds. In general, the strength and effectiveness of a $\text{CH}\cdots\text{O}$ hydrogen bond depends on C–H carbon acidity^[97] and on O-atom basicity,^[98] which is enhanced by cooperative effects. We have shown for instance that $\text{CH}\cdots\text{O}$ distances in crystals correlate so well with solution C–H group $\text{p}K_a$ values that it is even possible to define a crystallographic scale of carbon acidity.^[99]

The criteria for the significance of a particular $\text{CH}\cdots\text{O}$ geometry have also been the subject of some discussion. Recent

analysis has shown that the angular characteristics of many longer $\text{CH}\cdots\text{O}$ contacts ($\text{C}\cdots\text{O}$ 3.50–4.00 Å) and their effects on crystal structures resemble those of the shorter contacts (3.10–3.50 Å).^[24] It should be emphasized that the $\text{CH}\cdots\text{O}$ bond is not really a van der Waals contact but is primarily electrostatic; as its strength therefore falls off much more slowly with distance, it is viable at distances equal to or longer than the van der Waals limit. Therefore, even long $\text{C}\cdots\text{O}$ separations (about 4.00 Å) have to be considered seriously, and these weak hydrogen bonds are expected to have orienting effects on molecules prior to nucleation and crystallization. This underlines the important role of these bonds in crystal engineering especially in orchestration.

While $\text{CH}\cdots\text{O}$ hydrogen bonds are widespread, the complementary $\text{OH}\cdots\pi$ interactions are rare, because C is not as electronegative as O and also because unsaturated carbon atoms are not often situated in sterically unhindered positions, unlike carbonyl and ethereal O atoms, which permit easy access for C–H groups to form $\text{CH}\cdots\text{O}$ bonds. In spite of these limitations, a sufficiently electron-rich C atom (alkyne, alkene, aromatic) has a propensity to form a hydrogen-bond-like interaction with O–H groups thus contributing to crystal stability.^[100] We have studied these interactions systematically with the CSD: around 50 unambiguous cases of intermolecular $\text{OH}\cdots\pi$ and $\text{NH}\cdots\pi$ hydrogen bonding were found in the 1993 update.^[69]

3.3. Halogen Atom Interactions

It has long been known that the halogens Cl, Br, and I form short nonbonded contacts in crystals.^[15] Not only are these contacts (synthons **25**, **26**) clearly manifested in the crystal structures of the elements themselves; they are also of historical importance in crystal engineering, because they form the basis of the so-called “4 Å chloro rule” enunciated by Schmidt for planar dichloroaromatic compounds.^[101] The nature of these interactions is still somewhat obscure. Nyburg and Wong-Ng,^[102] and more recently, Price et al.,^[86] have held that these short contacts are the result of elliptically shaped atoms (anisotropy), while others including ourselves have maintained that there are specific attractive forces between halogen atoms in crystals.^[40, 103] Certainly atomic polarization is an important factor here, because there are clear distinctions between $\text{Cl}\cdots\text{Cl}$, $\text{Br}\cdots\text{Br}$ and $\text{I}\cdots\text{I}$ interactions and between these symmetrical interactions on the one hand and unsymmetrical interactions such as $\text{I}\cdots\text{Cl}$, $\text{Br}\cdots\text{F}$ and $\text{I}\cdots\text{F}$ on the other. Directional interactions formed by the halogens with O and N atoms are also polarization-induced and have been used by us and others in systematic crystal engineering (Section 2.1).^[33–35, 45]

3.4. Other Interactions: Hardness and Softness

As in the case of halogens, polarization effects are important for sulfur, which is known to form short directional contacts of the type $\text{S}\cdots\text{N}$, $\text{S}\cdots\text{S}$, and $\text{S}\cdots\text{Cl}$. These contacts have been thoroughly studied in the crystal chemistry of the TTF–TCNQ family of compounds.^[104] Intermolecular interactions that are

specific to organometallic compounds have only been the subject of very recent study.^[105] Our systematic survey of Au...Au interactions has shown that they affect molecular conformation and crystal packing.^[106] Hydrogen-bonding patterns in organometallic crystals are, in general, similar to those in simple organic compounds. However, the CO ligand is a base unique to organometallic compounds, and our results indicate that it is more important for CH...O bonding than for OH...O bonding.^[91, 107] A possible explanation for such an observation considers the hardness and softness of intermolecular interactions. It appears that the hard and soft acid and base (HSAB) principle may be profitably extended to supramolecular chemistry. For instance, NH...O and OH...O could be considered hard hydrogen bonds, CH...O and CH... π soft hydrogen bonds, and NH...N have perhaps intermediate character.^[107] Accordingly, it might be argued that the soft acceptor CO prefers to form a hydrogen bond with the soft donor C–H, or alternatively the hard donor O–H prefers to form bifurcated or solvated hydrogen bonds with hard acceptors rather than waste itself on the soft acceptor CO. Along these lines, the unexpected formation of the CH...Se may be understood in terms of the relative softness of both donor and acceptor species.^[95] Again, Scheme 3 shows how the hard synthon **1** and the soft synthon **17** operate independently, but equally effectively, in the crystal.

4. Summary and Outlook

...although chemistry is a science of vast scope and countless specialties, it has no real boundaries...

In writing this article and drawing an analogy between crystal engineering and organic synthesis, I have tried to address two groups of chemists whose concerns and goals might at the outset appear to be somewhat unrelated. Yet, crystal engineering today seems to be poised at the point where organic synthesis was in the fifties and sixties. Empirical, largely intuitive strategies or manipulations within narrowly defined structural families dominate the scene even as one already discerns glimmers of a more logic-driven approach. All these developments have generated a substantial body of data on intermolecular interactions and crystal packing. It is from this corpus that more systematic strategies of crystal engineering will appear. I have attempted to show that the kernel of such strategies already exists in synthetic organic chemistry, and that with this foreknowledge, solid-state supramolecular chemists might well be able to create patterns of extraordinary finesse in crystals. On the other hand, it is hoped that synthetic organic chemists will recognize in crystal engineering a natural extension of so many principles in their canon and realize that with an appreciation of the properties of intermolecular interactions, they may be equally well-equipped to undertake research in this challenging discipline. In either case, crystal engineering, which has been recognized as the central issue in organic materials chemistry, is well set to become the breakthrough technology for industrial research and development.

The term "supermolecule" has been used synonymously with "crystal" in this article, and as mentioned at the very outset, a crystal is the *ultimate* example of a supermolecule in that it

consists of an infinity of molecules divergently bound. Hierarchies of supramolecular species may accordingly be recognized, and the synthesis of lower hierarchy supermolecules consisting of two or more convergently bound molecular components has become an extremely attractive and competitive area of research combining molecular synthetic methodology with supramolecular ideas of molecular association.^[108] However, such efforts must logically progress towards crystal engineering in the quest for complex three-dimensional networks based on complex polyfunctional molecules.

At one level it is remarkable that concepts and models which were developed in the sixties for organic synthesis can be so readily reapplied today, and in such minute and faithful detail, to a research area which was barely conceived at that time. This parallelism has continued to unfold itself for me even during the writing of this article—I have little doubt that other structural and synthetic chemists will be able to uncover more relationships between these two fascinating areas of chemistry. Yet, at another level such a striking resemblance only reaffirms the oneness or nonduality in the chemical thought process. Though I have quoted only a few sentences from Corey's 1967 article here,^[18] almost the entire Part I can be reread and reassimilated in the context of crystal engineering and solid-state supramolecular chemistry, and perhaps even such an eventuality was foreseen, for it is stated while justifying the quest for a general strategy of synthesis that "such an effort surely is more than an intriguing theoretical exercise; it is a prerequisite to a deeper comprehension of Synthesis and the methodologies which are fundamental to it, and it is likely to be the keystone in the rational development of Synthesis to still higher forms."^[*]

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