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Supramolecular Chemistry

Crystal Engineering: A Holistic View

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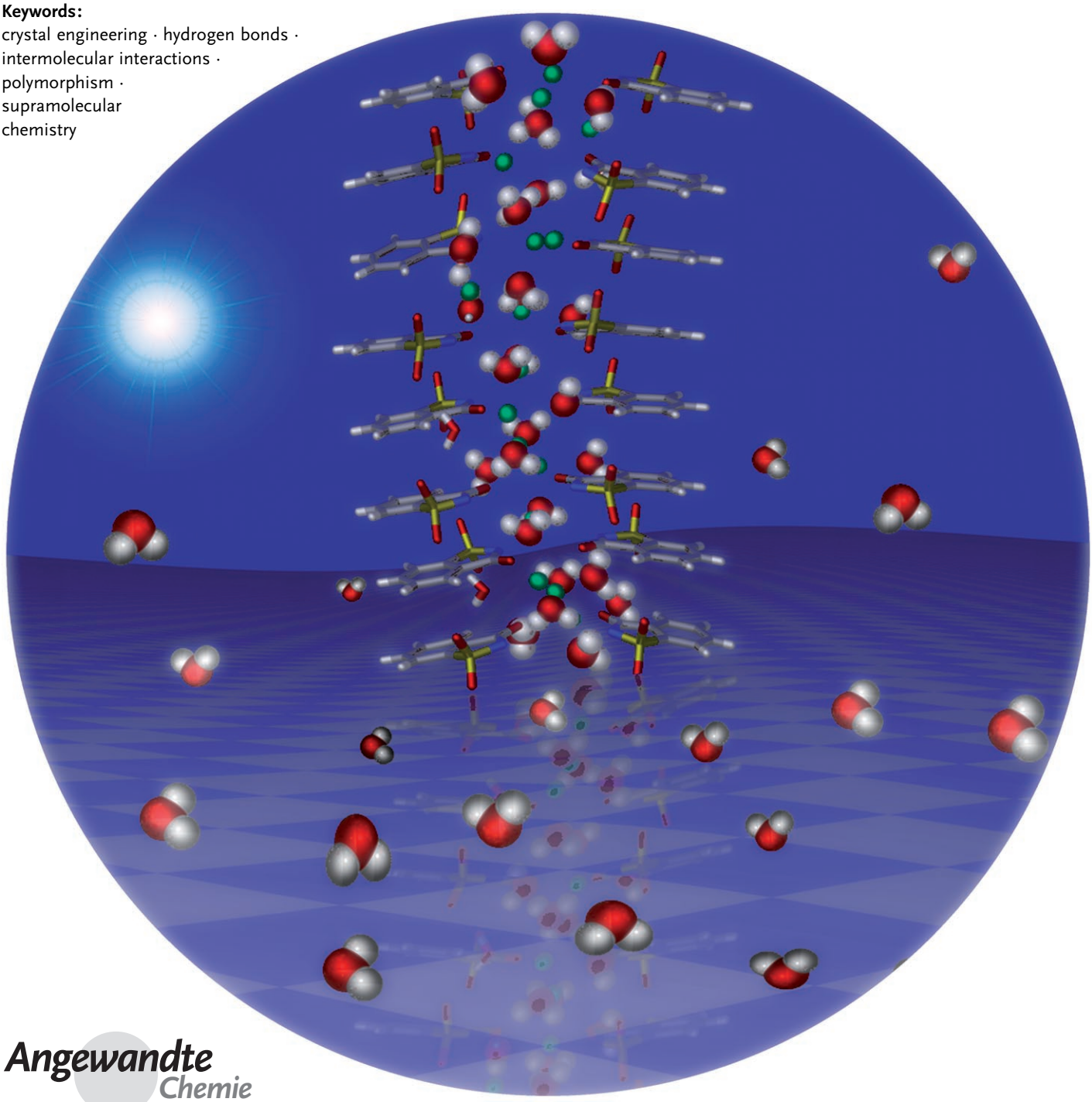

Crystal engineering, the design of molecular solids, is the synthesis of functional solid-state structures from neutral or ionic building blocks, using intermolecular interactions in the design strategy. Hydrogen bonds, coordination bonds, and other less directed interactions define substructural patterns, referred to in the literature as supramolecular synthons and secondary building units. Crystal engineering has considerable overlap with supramolecular chemistry, X-ray crystallography, materials science, and solid-state chemistry and yet it is a distinct discipline in itself. The subject goes beyond the traditional divisions of organic, inorganic, and physical chemistry, and this makes for a very eclectic blend of ideas and techniques. The purpose of this Review is to highlight some current challenges in this rapidly evolving subject. Among the topics discussed are the nature of intermolecular interactions and their role in crystal design, the sometimes diverging perceptions of the geometrical and chemical models for a molecular crystal, the relationship of these models to polymorphism, knowledge-based computational prediction of crystal structures, and efforts at mapping the pathway of the crystallization reaction.

From the Contents

1. Introduction

Crystal engineering is the rational design of functional molecular solids.[1] This subject is of both fundamental and practical interest to solid-state and structural chemists, and also important to those who attempt to design other kinds of organized phases and assemblies. In a broader sense, the concepts of crystal engineering are applicable to any kind of intermolecular assembly, for example, protein-ligand recognition. Crystal engineering is therefore of very wide scope and accordingly, it has brought together investigators from a variety of disciplines. The field has its origins in organic chemistry, more specifically organic solid-state photochemistry,[2] and in physical chemistry, notably studies on the packing of molecular crystals,[3] exemplified respectively by the contributions of G. M. J. Schmidt (1950–1970) and A. I. Kitaigorodskii (1940–1980). It gained an identity of sorts by the 1980s, attracting crystallographers, solid-state chemists, theoreticians, and inorganic chemists to its ranks.[4–6] Today, the subject covers a community of at least 150 independent research groups, with two specialist journals—*Crystal Growth and Design* from the ACS and *CrystEngComm* from the RSC—and even a dedicated webpage and a Wikipedia site maintained by the latter society. A working definition of crystal engineering, which I supplied in my 1989 book,[1] namely that it is "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", seems to have stood the test of time, and the subject today includes three distinct activities, which form a continuous sequence: 1) the study of intermolecular interactions; 2) the study of packing modes, in the context of these interactions and with the aim of defining a design strategy; and 3) the study of crystal properties and their fine-tuning with deliberate variations in the packing. In effect, these three stages represent the "what", "how", and "why" of crystal engineering.

With so many researchers approaching the subject from various independent and attractive viewpoints, individual opinions on what crystal engineering is and what it can do are bound to differ.[7–26] Arguably, these differences have to do with style and taste. Fundamentally, however, there are two aspects of crystal engineering which are above debate—that it is a type of synthesis, and that a molecular crystal lends itself to the supramolecular paradigm. These ideas took root in the 1990s and need to be placed in the context of broader trends in the chemical sciences that occurred during that time.

1.1. Supramolecular Synthesis

That a crystal can be viewed as a supramolecular entity follows from Lehn's argument that a supermolecule is to the molecule as an intermolecular interaction is to the covalent bond,[27] and it was Dunitz who first expressed this notion explicitly—the crystal is a supermolecule par excellence, and knowledge and control of intermolecular interactions is as vital to crystal synthesis as is control of the covalent bond is to molecular synthesis.[28] The meaning and execution of synthesis in the supramolecular context were a parallel development in the mid-1990s, and three reviews are notable in this context. The first of these by Whitesides and co-workers appeared in early 1995 and explained the difference between

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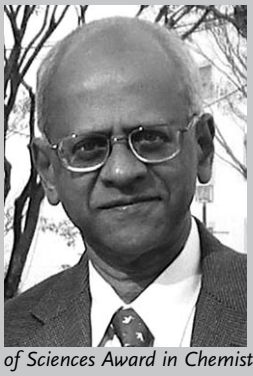
covalent and supramolecular synthesis.[29] The former is enthalpically controlled and products are often kinetic, while in the latter, the energies involved are much smaller and therefore the products reflect a balance between enthalpy and entropy. Implicit in this discussion is that the products are formed in solution in both processes. This is not the case in crystallization, a largely kinetic process, and in the second of these reviews, which appeared in late 1995, I put forward the concept of supramolecular synthons, kinetically defined structural units that ideally express the core features or kernel of a crystal structure, and which encapsulate the essence of the crystal in terms of molecular recognition.[30] The synthon consists of molecular fragments and the supramolecular associations between them, and these associations need not be just hydrogen bonds and other directional interactions. An important, indeed critical, assumption is that the supramolecular synthon is a reasonable approximation to the entire crystal despite the simplification that is inherent in its definition.[31] The third of these reviews, which followed in 1997, is aptly titled "Synthetic Supramolecular Chemistry" and in it, the authors Fyfe and Stoddart discuss processes both in solution and involving crystallization.[32] While Whitesides and Stoddart generally considered zero-dimensional supramolecular objects as synthetic targets, my review focused exclusively on the crystal, which is a three-dimensional object. Attacking either of these types of target (zero-dimensional or higher-dimensional) has its own attractions and difficulties. Since the rest of this review will deal with crystals, it is not out of place to mention now the elegant strategies proposed for zero-dimensional supramolecular targets by Fujita,[33,34] Stang,[35] Raymond,[36] Mirkin,[37] and Stoddart,[38] to name a few. In these cases, entropic considerations are of the greatest importance, and the supermolecule exists in solution before it gives a crystal, a necessary prerequisite perhaps for structural characterization, but crystallization is not implicated as a synthetic step.

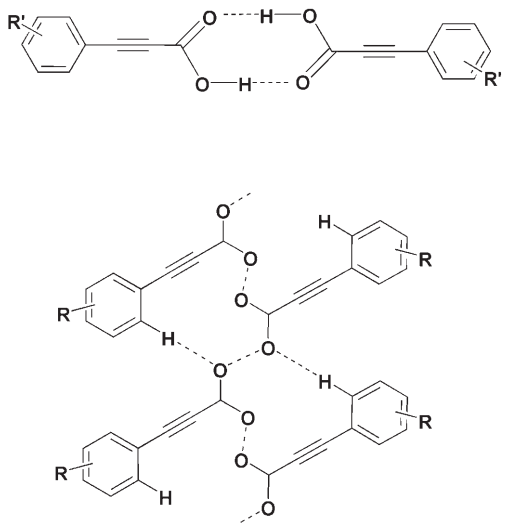
1.2. Simplifying the Problem

But what of the crystal? When one claims that a crystal is a supramolecular entity, one is admitting ipso facto that it is not possible to predict or directly anticipate the structure of a crystal from the structure of the constituent isolated molecule. The essence of supramolecular chemistry is that the structure and properties of the higher-level entities (supermolecules, crystals) cannot be predicted directly or immediately from those of the lower-level entities (molecules). Crystals represent a higher level of complexity than molecules, and crystal structure is accordingly an emergent property with crystallization being a supramolecular reaction.[39] The main aim of crystal engineering is to construct crystal structures from molecular structures. This is the synthetic step, and it is not straightforward because of the emergent nature of the crystal structure. To develop a synthetic strategy, a retrosynthetic step is invoked which effectively simplifies the crystal structure to a smaller unit called the synthon. Let us consider a molecule to consist of several functionalities or functional groups (F_1, F_2, … F_n) and during crystallization, these functionalities come together through a process of molecular recognition utilizing weak interactions to generate supramolecular synthons (S_1, S_2, … S_n). The conjunction of particular supramolecular synthons uniquely defines any crystal structure. If the kinetic factors are sufficiently dominant, some synthons (say, S_1, S_3) may invariably occur when the molecules contain some specific functionalities (say, M_2, M_3, M_5), whatever be the nature of the other molecular functionalities present. It is precisely this situation that the crystal engineer seeks, for then one can identify a series of related molecules which (through some conserved synthons) will give a series of related crystals. However, this is an ideal situation, and serious problems often arise in that no correspondence between molecular and crystal structure is easily perceived. This happens for several reasons: 1) the number of possible and competing supramolecular synthons can quickly become very large for a small increase in molecular functionality because all the intermolecular interactions are weak; 2) structural interference from remote molecular functionalities may be fickle and unpredictable; 3) the hydrocarbon core of an organic molecule, which is not generally considered to be a functional group in molecular chemistry, is very much a supramolecular functionality and will interfere regularly with other putative interactions from more polar residues. This final issue is perhaps the most difficult to handle.

The crystal structures of the substituted phenylpropiolic acids illustrate the interference offered by remote functionalities. Carboxylic acids show either the common dimer or the rare catemer patterns in their crystals (Scheme 1). However, both catemers and dimers have two O–H···O hydrogen bonds for each carboxyl group, and so the reasons for the rarity of the catemer must lie elsewhere. A recent study from our group shows that the formation of the catemer is only possible if there is a supporting hydrogen bond (say, C–H···O) from another location on the molecule.[40] This condition prevails in the family of substituted phenylpropiolic acids. When, why, and how this supporting interaction manifests itself is not easy to establish. We examined at least 30 to 40 crystal structures over a decade[41] before we were able to draw some conclusions. In the end, however, understanding crystal structures is like pattern recognition. The larger the sampling of crystal structures examined, the greater the likelihood that



Gautam R. Desiraju (born 1952, Madras, India; PhD, University of Illinois, 1976) has been associated, for over two decades, with the subject of crystal engineering and structural aspects of the hydrogen bond and other intermolecular interactions. He has authored two definitive books (Crystal Engineering: The Design of Organic Solids and The Weak Hydrogen Bond in Structural Chemistry and Biology) and is the recipient of several awards and recognitions including the Alexander von Humboldt Forschungspreis (2000) and the Third World Academy of Sciences Award in Chemistry (2000). He is a member of the editorial advisory boards of Chemistry – An Asian Journal, Crystal Growth & Design, and CrystEngComm.



Scheme 1. Dimer (top) and catemer (bottom) structures in phenylpropiolic acids. Unlike other carboxylic acids, the catemer dominates in this family.

increasingly complex molecule→crystal algorithms will be decoded. It would seem that brute-force methods will eventually win.

1.3. Scope of this Review

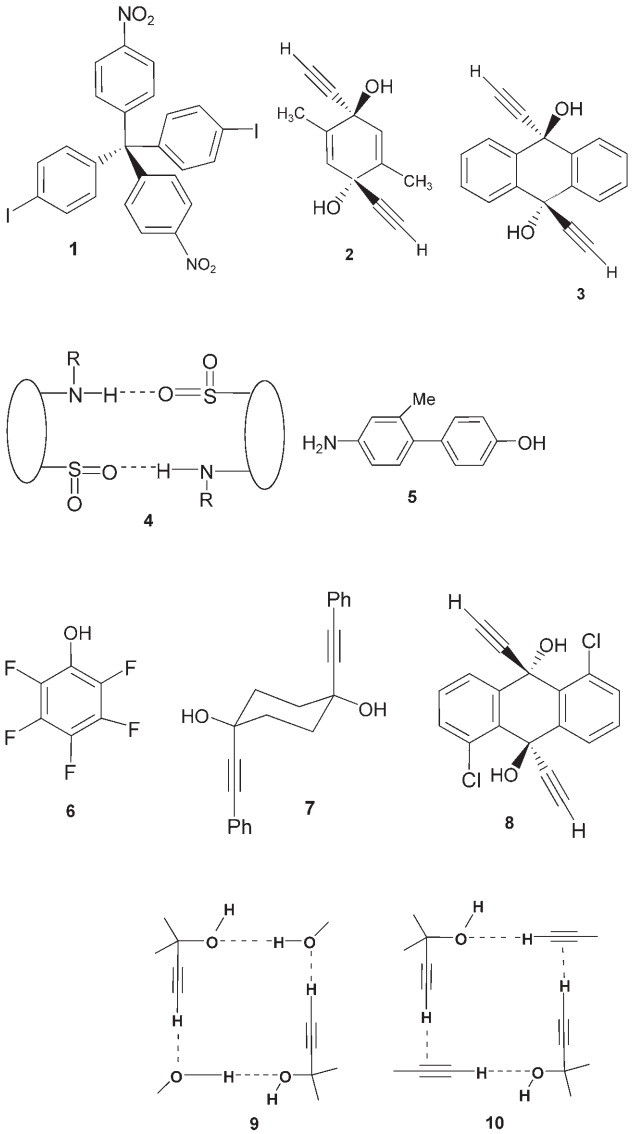
With this background, I would like to enumerate and briefly discuss some of the outstanding problems and challenges in crystal engineering today. This view is a subjective one, and a survey of all interesting and useful ongoing studies is neither practical nor possible in a subject that is currently undergoing a phase of explosive growth. Notably, much work is being undertaken in industry and academia on polymorphism,[42,43] or the existence of multiple crystal forms of drugs and active pharmaceutical ingredients (APIs), especially with regard to the legal implications of such work, but the reader of this article will not find here a discussion of API polymorphism[44] and the extension of pharmaceutical space through, say, the device of the so-called cocrystal formation.[45] Undoubtedly, drug polymorphism has highlighted the importance of crystal engineering to a larger scientific audience, but there are more basic aspects to the study of polymorphism. This subject goes far beyond legal issues: It might offer the key to unlocking the mystery of crystallization.

2. Crystal Design and Function

Predictability of crystal structure is the first step towards fine-tuning of properties. It is of little use if a given crystal structure is very sensitive to minor molecular changes because such changes would be required anyway in the optimization of the crystal properties. In an ideal situation, a crystal structure is held by sets of robust intermolecular interactions in roughly orthogonal directions, and the crystal engineer should be able to manipulate each set independently. Crystal design seems to have developed in two distinct ways, and these are best exemplified by the organics and the metal–organics; these categories differ in terms of one's ability to thus manipulate the structure.

The main design problem with a pure organic crystal is that for a three-dimensional structure with comparable (and strong) interactions in the three directions, the molecular structure itself should be three-dimensional. This would tend to suggest aliphatic molecules, but not so much work has been done with this category of substance. The noteworthy exceptions are the organic diamondoid solids, the structures of which are inspired by Ermer's prototype, adamantane-1,3,5,7-tetracarboxylic acid with its fivefold interpenetration of open hydrogen-bonded networks.[46] Open frameworks are advantageous in achieving microporous structures, and if they can be designed so as not to interpenetrate, then this property could become a reality. However, avoidance of interpenetration is difficult.[47] Another disadvantage of these tetrahedral molecules is that they are functionally similar in all directions, and so independent and modular manipulation of functionality is a distant dream. We attempted some work in this direction. The tetraphenylmethane derivative **1** (Scheme 2) was made to ascertain if the $NO_2\cdots I$ synthon is robust enough that it can act as a connector in the generation of a diamondoid structure. If this were the case, the unsymmetrical substitution pattern in the molecule would introduce polarity in the crystal.[48] The structure fulfilled our prediction (space group *Fdd*2) , but it is still interpenetrated, and the yields of the molecular precursor (in a six-step synthesis) were so low that this is a hardly a practicable method for general crystal engineering (Figure 1).

Aromatic molecules have been studied extensively, but by their very nature, some intermolecular interactions ($\pi\cdots\pi$, C–H···O) in the crystal structure will be much weaker than others (for example, O–H···O and N–H···O hydrogen bonding) in different directions. Accordingly, two-dimensional structural control is easily achieved in the planes of the aromatic rings, but control in the third dimension is mostly elusive. The challenge here is to avoid structural interference from competing interactions. We examined a family of geminal alkynols, a group of compounds wherein the structural fidelity between related molecules is particularly poor because the two hydrogen bond donors (O–H, C–H) and two acceptors (O–H, C≡C) are all in close proximity in the molecule and therefore sterically hindered.[49] The resulting modifications in hydrogen bond donor and acceptor strengths make all the four possible hydrogen bonds (O–H···O, C–H···O, O–H···π, C–H···π) of comparable importance, leading to structural unpredictability. However, even in a fickle set of compounds such as this, we observed some structural consistency. For example, the crystal structures of the dimethyl derivative **2** (Scheme 2) and the anthracene derivative **3** are the same down to the level of fine details of hydrogen bonding (Figure 2). The methyl groups in **2** are surrogates of the annelated benzo residues in **3**; indeed one may view them as vestigial benzene rings, and the characteristic cooperative chain of hydrogen bridges (O–H···O–H···C≡C–H···C≡C–H···O–H···) which forms an infinite pattern is



Scheme 2. Molecules and synthons discussed in this review.

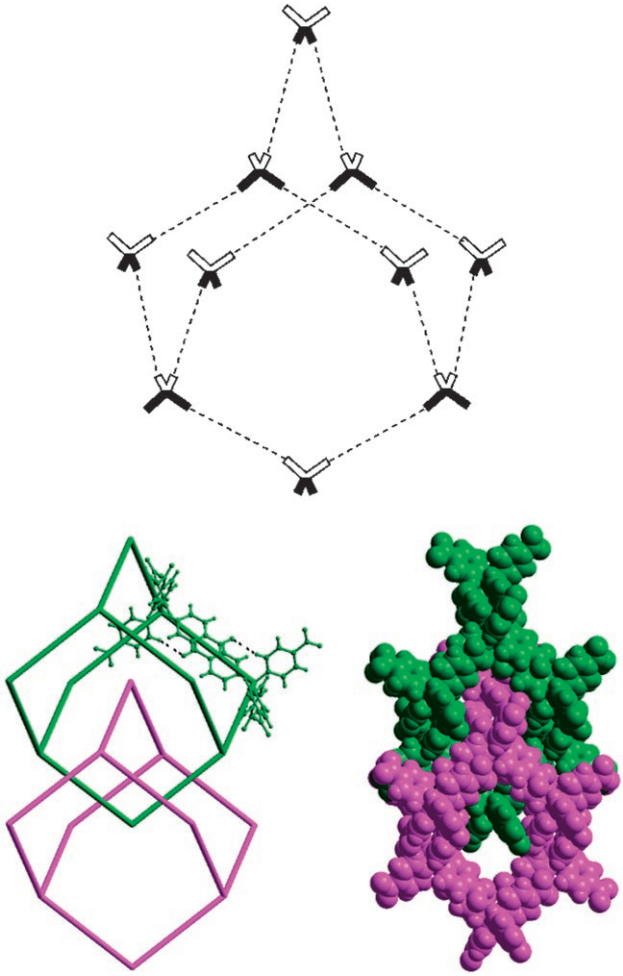


Figure 1. Crystal engineering of a polar network. An unsymmetrically substituted tetraphenylmethane (in this case, a dinitro diiodo derivative) with a sufficiently robust heteroatom interaction (in this case, NO_2···I) will generate a polar crystal.

conserved in both structures. These geminal alkynols show an unexpected level of three dimensionality in their crystal packing. The hydrogen bonds are arranged in a sheet while the aryl residues interdigitate in a perpendicular direction, and the isostructurality between the dimethyl and anthracene derivative is a consequence of interaction insulation between the hydrogen-bonded layers and the hydrocarbon residues. Interestingly, though, the crux of this structure is constituted with the tetrahedral C atom and the various interactions formed by the substituents at this position—and the C atom is aliphatic.

All this is still quite far from functional crystals. The greatest opportunities in this direction possibly lie within the metal–organic framework (MOF) structures which are in themselves a part of a larger group of structures known as coordination polymers.[10,50–53] A polyvalent (transition-)metal ion acts as an effective multidimensional hub, from which emerge organic spokes that connect the hubs forming the three-dimensional structure. The distinction between coordination chemistry in general and coordination polymers in the context of crystal design and engineering was first made by Robson, who showed that because of the strength of the interactions, metal–organic compounds show a degree of structural modularity that is unknown in the pure organics.[54] Rather quickly, strategies to avoid interpenetration were in place, and large framework structures were obtained. These large spatial voids could be used to contain guest molecules of various types. The so-called first-generation coordination polymers in which the host frameworks collapsed upon guest removal gave way to more sturdy second-generation compounds wherein the host framework is stable when evacuated. The work of Yaghi, in particular, on MOFs that can include large volumes of hydrogen is noteworthy.[55] The challenge now is to make a MOF with a property (for example, hydrogen storage) which is industrially competitive and can lead to large-scale production.[56] Third-generation compounds also have the aspect of function which is related to a flexible host framework. The work of Kitagawa and coworkers wherein a metal–organic solid is able to discriminate between acetylene and CO_2, two molecules with nearly the

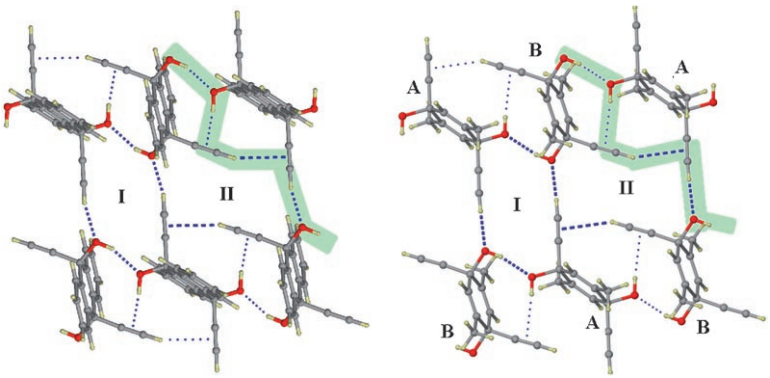


Figure 2. Isostructurality in dimethyl and anthracene geminal alkynols. The anthracene derivative **3** (left) forms a hydrogen-bonded sheet in the plane of the paper with the benzo rings pointing in and out of the plane. The same sheet is conserved in the dimethyl derivative **2** (right), and the methyl groups point up and down (A and B refer to symmetry-independent molecules). In both cases, these 2D patterns interdigitate with their orthogonally located hydrocarbon substituents. The cooperative hydrogen-bonded network is highlighted green in both parts. Synthons **I** and **II** are identical to **9** and **10** in Scheme 2. Note that **I** and **II** are conjoined in the same way in the two structures.

same shape and size, is of seminal importance.[57,58] The host, which is originally collapsed, expands in contact with acetylene, which is absorbed rapidly. There is no similar affinity with CO_2. Why do these two gases behave differently? It is seen that the acetylene guest binds to the host with C–H···O hydrogen bonds by the end of the process; clearly these interactions are specific enough to bring about an expansion of the host framework and concomitant entry of the guest. In general, the role of C–H···O contacts in crystals has been debated.[59–61] Do they fulfill specific structure-directing roles, or are they merely innocuous bystanders in the general packing panorama? The above-mentioned example of Kitagawa shows that C–H···O interactions are specific and attractive; they literally "suck" the acetylene molecules into the host framework.

3. Intermolecular Interactions

After metal-coordination bonds and ionic interactions, the strongest interactions in crystal engineering are hydrogen bonds. They are also directionally specific, and this is distinctly advantageous in crystal design, wherein they are widely used. Robertson's criterion of maximum hydrogen bonding[62] seems to be followed almost invariably with multifurcation and hydration being employed to fulfill the hydrogen bond capabilities of all donors and acceptors. In small organic molecules the acceptors are generally in excess of the donors, and so "free" X–H groups are extremely rare. The converse is true incidentally in macromolecular structures in which the donors (if C–H groups are included) outnumber the acceptors; as a result, any available acceptor is used, including π rings, accounting for a higher incidence of, for example, X–H···π interactions.[63] Hydrogen bonding is by now so well understood that there seems to be little to learn that is startlingly new about the interaction itself.[59,60,64] What is largely unexplored is the use of some of the more exotic varieties (organometallic,[65,66] charge-assisted,[67] blue-shifted[68]) in routine crystal engineering. Molecular inorganic systems have also been studied;[69] the well-known aurophilic Au···Au interaction is described in a crystal engineering context.[70] The uranyl group has also been mentioned.[71] There is even an in silico design of a molecular quasicrystal.[72]

As far as intermolecular interactions are concerned, the last frontier in terms of grappling with them lies indubitably in understanding the supramolecular chemistry of the C–F group, the so-called "organic" fluorine. Fluorine is so electronegative and nonpolarizable that it forms nonbonding contacts only with great reluctance. Dunitz has pointed out that the C–F···H–O hydrogen bond is extremely rare.[73] The C–F group is not a good hydrogen bond acceptor like the C–NH_2 and the C–OH groups, although F is more electronegative than O and N. C–F···H–C contacts are very weak and seem to have hydrogen bond like characteristics only in compounds such as polyfluorinated benzenes wherein the acidity of the C–H groups is enhanced to levels which permit hydrogen bonding,[74] and there seems to be an adequate theoretical basis for their viability.[75] We do not know the nature of the putative F···F interaction because fluorine is a very complex element in supramolecular terms. If one takes a hydrocarbon and successively replaces the H atoms by F atoms, the boiling point rises (as it is expected to) initially but then falls. For example, the boiling point of methane and its fluorinated derivatives are as follows: CH_4 (−161.5 °C), CH_3F (−78.4 °C), CH_2F_2 (−51.7 °C), CHF_3 (−82.2 °C), CF_4 (−128.0 °C). Such behavior is not exhibited by the other halogens. For example, the boiling points of the corresponding chloromethanes are: CH_3Cl (−24.2 °C), CH_2Cl_2 (39.5 °C), $CHCl_3$ (61.2 °C), CCl_4 (76.0 °C). No one has been able to explain this anomaly properly. Does this arise from some kind of F···F repulsion? Fluorine effectively "repels" itself in crystals, and the work of Hulliger[76] and Fourmigué[77] reveals this effect adequately. The element is also unusual in that the so-called "fluorous" compounds with many C–F bonds (for example, teflon) are neither hydrophilic or hydrophobic.[78] In the end, I am not sure what a van der Waals radius of (organic) fluorine signifies,[79] considering that the element does not form any intermolecular contacts of note with any other element. The understanding of "organic" fluorine is one of the big challenges in crystal engineering. Success in this area might well lead to industrial spin-offs,[80] and there are biological implications as well in the drug design area, as noted by Diederich.[81]

4. Crystal Packing and Polymorphism. The Holistic Crystal

The packing of organic molecular crystals will now be considered from two different viewpoints. The original approach is based on geometry and goes back to Kitaigor-

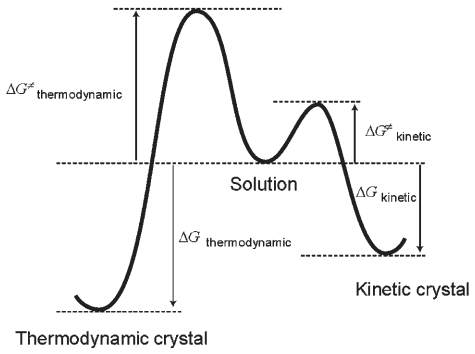


Figure 3. Thermodynamic and kinetic outcomes of crystallization (reproduced with permission from reference [95]).

odskii.[3] Interactions between molecules are assumed to be weak and lacking in directionality; it is further assumed that all interactions taper off at longer distances in roughly the same way. In this isotropic model, crystal structures are governed by close packing. The structure that makes the most economical use of space is the best one, and molecules crystallize so that the bumps in the surface of one molecule fit into the hollows in the surface of the other. The 6-exp potential (or its variants), which is commonly used to describe such a situation, implies long-range attractions and short-range repulsions, which effectively determine molecular shape.[82] This model generally does not assign any significant role to directional intermolecular interactions, and has been advocated in recent times by Dunitz and Gavezzotti, who have presented a number of crystal structures wherein overall close packing rather than specific interactions seems to be the critical determinant.[83–85] Kitaigorodskii himself was guarded on the role of hydrogen bonding and donor–acceptor interactions in crystal structures.[86] In reality, however, hydrogen bonding is quite important in crystals; molecules that have functional groups which can form hydrogen bonds almost always prefer to use these groups in such interactions.[62] As hydrogen bonds become weaker, the anisotropic component in the packing decreases, but it never goes away entirely.[87] One can model these interactions with electrostatic terms within a standard set of empirical isotropic potentials, but this will only provide an approximate description of a molecular crystal. Kitaigorodskii was not ashamed about this. He said that it is better to have a rough theory for all crystals rather than a fine theory that would be applicable only to benzene and urotropin.[3] He added (in a later work)[88] that atom potentials were not even required to describe crystal packing. But many decades have elapsed since he wrote this. Can we do better today?

A crystal may alternatively be considered on the basis of chemical factors, in other words on the basis of directional interactions formed by the heteroatoms. In a major simplification, one might assume that it is sufficient to look just at strong hydrogen bonds like N–H···O and O–H···O. Indeed, one could simplify this even further and state that the hydrogen bond between the best hydrogen bond donor and the best acceptor is the most significant interaction in the crystal, and that it will form typically. This model was originally proposed by Etter and calls for a hierarchy of hydrogen bonds: The donors and acceptors pair off in order of strength, and crystal structures can hopefully be understood on this basis.[89] Empirical "rules" for hydrogen bonding in crystals were proposed, which included specific "rules" for specific functional groups, and examples that satisfied such "rules" were reported.[90] However, exceptions are common, and other examples which do not follow the hierarchic model have also been published.[91–93] In retrospect, much of this should be taken as guidelines rather than as formal rules, and today's exceptions become tomorrow's rules as the number and variety of crystal structure determinations increase. Indeed, this was acknowledged by Etter, who noted that "the rules should evolve as new structures become available". Notably, in the context of polymorphic compounds, there are lesser chances of adherence to interaction hierarchy in some of the polymorphs. To summarize, one notes that as the subject of crystal engineering has grown in breadth and scope, a very large number of crystal structures have been designed using the principles of hydrogen bonding.

The geometrical approach (lack of structural directionality)[94] relies on energy-landscape scenarios in discriminating between potential structures while the chemical approach (structural directionality brought about by chemical factors) requires a real-space examination of molecular features to select a packing direction. The supramolecular synthon concept provides a middle ground between these approaches because a synthon includes elements of both geometrical and chemical recognition. In this sense, the synthon concept is a more holistic approach to understanding molecular crystals. An oblate molecule packs with shape (geometrical recognition) as a structure director while an interaction direction (chemical recognition) leads eventually to close packing. Consider the prototype structure, benzene. Does one term it a close-packed structure based on the herringbone geometry, or is the herringbone geometry derived from a directional C–H···π hydrogen bond? To conclude, the reader should note that the geometrical and chemical approaches do not necessarily negate each other.

4.1. Thermodynamic and Kinetic Crystallization

At their idealized extremes, the geometrical and chemical models seem to be contradictory. In the former, the system has every chance to sample all possible multimolecular clusters in solution before selecting the one lowest in energy. These clusters would then aggregate to form larger clusters, but at each stage, the system is able to select that path which will minimize the energy. If some of these events lead to a local minimum, the system is able to correct itself and eventually find the global minimum. To paraphrase, we are speaking here of the thermodynamic crystal. In the chemical model, the individual interactions are all-important. Once a hydrogen bond forms between the strongest donor and acceptor, it cannot be "undone", and the formation of the next hydrogen bond between the second donor and acceptor is inevitable. This is the kinetic crystal, or at least one of the

kinetic possibilities of crystallization. If crystallization is viewed as a supramolecular reaction, polymorphs are alternative reaction products (Figure 3).

Two possibilities need to be considered during crystallization. In the first, the thermodynamic and kinetic outcomes of crystallization are identical; in other words, the crystal that is formed the fastest is always the most stable. In this case, it would normally not be possible to observe ambient-pressure polymorphism, however exhaustive the performed experimentation is. I have pointed out often in talks that compounds like benzoic acid, naphthalene, and D-glucose almost surely belong to this monomorphic category. In the second case, the kinetic form(s) is (are) different from the thermodynamic crystal, and polymorphs may, in principle, be observed with a greater or lesser degree of ease, provided adequate experimentation is carried out.[95,96] This dichotomy can lead to some ambiguity. The crystal structures of decidedly monomorphic substances (such as the above-mentioned compounds) would seem to obey the geometrical or chemical models equally well. Polymorphic substances, on the other hand, would seem to follow either one or the other model, depending on which polymorph is selected. In effect, either or both models seem to be valid in different situations, leading to contradictions and statements to the effect that this or that model may or may not be correct.[82–85,90–93] Only through a systematic study of polymorphic systems would it be possible to distinguish between kinetic and thermodynamic pathways during crystallization, and in effect to evaluate the chemical and geometrical models for a molecular crystal.

Such studies are only just beginning to appear. In recent, important work Roy and Nangia have found that the hydrazone $RSO_2NHN{=}CR_2$ (R = *p*-tolyl) exists as three polymorphs and one pseudopolymorph.[97] The most stable form, as determined by differential scanning calorimetry (DSC) and calculations, has the highest melting point (160°) but does not contain the best hydrogen bond, namely N–H···O=S. Indeed, the N–H group is not hydrogen-bonded at all, not even to the weak π-ring acceptor in the molecule. Yet this form is more stable by 2.5 kcal mol^{-1} than the polymorph nearest in energy, a kinetic form with the "expected" N–H···O=S hydrogen bond (synthon **4** in Scheme 2), and which converts to the stable thermodynamic form at about 140°. So, the best crystal packing does not always go with the best interactions. In another similar result, we found that the biphenyl aminophenol **5** (Scheme 2) exists as two conformational polymorphs.[98] The kinetic form has the better interactions in terms of an infinite N–H···O–H···N–H···O–H chain stabilized by cooperative effects. It is known that this infinite hydrogen-bonded chain is the most favored synthon for aminophenols.[99] The more stable form has the better packing (by 1.5 kcal mol^{-1}) but has to make do with the less favorable O–H···O and N–H···N interactions.

Alloxan is a more enigmatic case. No polymorphism has been reported for this compound, but the stable crystal structure is unusual in that a molecule which is very rich in NH donors and C=O acceptors does not form good N–H···O bonds in the solid state. The reason for this seems to be that a high-density, low-energy structure is possible with dipolar C···O interactions[100] such that strong hydrogen bonds may be evaded. Commenting on this structure, I noted a few years ago that "any way of minimizing the free energy is a respectable way."[101] Dunitz and Schweizer have provided a quantitative rationalization of this structure in a recent publication, and they echo similar thoughts when they say that "it is held together by whatever factors contribute to the cohesive energies".[85] Alloxan also teaches us about the trade-off between close packing and directionality requirements of interactions. Dunitz and Schweizer note that "although it has no 'conventional length' hydrogen bonds—*perhaps even because of this?*—it has a higher density than any of the hypothetical structures with conventional hydrogen bonds", implying that such a trade-off between good interactions and good packing is important at least in some crystals. But in the end, one is tempted to suggest that the similarities between the geometrical and chemical models are more significant than the differences. To paraphrase informally, one joins closest-neighboring atoms in a crystal with dotted lines in the chemical model. But if one relaxes the criterion for "joining the dots" and draws a sufficiently large number of these dotted lines, one is back to the shape argument of the geometrical model. Reality probably lies somewhere in between, or maybe there is even no contradiction between these schools of thought.[100]

A major challenge is to establish general experimental protocols to obtain the thermodynamic crystal in any polymorphic system. This would mean finding methods to slow down nucleation, whether it be through high-temperature and hydrothermal experiments, gel growth, crystallization from supercritical fluids, or other methods still untried and unexplored. Obtaining the thermodynamic polymorph by brute-force methods could be difficult because crystallization is a kinetic phenomenon, and a kinetic polymorph could be locked in for years before one is even aware that there exists a more stable crystal form. This lesson came to us when we realized that the only form of 1,3,5-trinitrobenzene known for 125 years is a kinetic polymorph enabled through C–H···O interactions.[102] This form is as much as 5.80 kcal mol^{-1} less stable than the elusive thermodynamic form, which is three-dimensionally close-packed and which was obtained only from ethyl acetate, and not even consistently at that. Being sure that a certain polymorph is the thermodynamic crystal is in itself a major breakthrough. In effect, it would mean proving that this particular crystal form has the lowest possible free energy in the structural landscape—and this would imply a very high degree of confidence in the various experimental and computational techniques that would be required.

Incorporating both kinetic and thermodynamic possibilities, the supramolecular synthon concept provides a working blueprint for crystal design. I would like to reemphasize that synthons encapsulate features of both geometrical and chemical recognition. There is no stipulation that supramolecular synthons must contain hydrogen bonds or other directed interactions.[103] They could just as well contain information of the mutual recognition of hydrocarbon fragments, such as rings and chains.[30] Of course, the most optimal (that is, useful) synthon is a structural unit which condenses the maximum amount of information regarding molecular

recognition into an entity of the minimum size.[31] All models for the visualization of crystal structures use some method of simplification to generate smaller units which are hopefully representative of the complete crystal. The real question is, how much simplification is optimal, how much is insufficient, and how much is excessive? The geometrical model of Gavezzotti uses space group information to simplify the structure and generate smaller clusters of molecules; the purely chemical model of Etter uses only strong hydrogen bonds to reduce the crystal structure to its bare bones. The synthon model is another form of structural simplification, but it demands neither a scale of interaction energies, as does the chemical model, nor a scale of crystal packing energies, as does the geometrical model. It is purely probabilistic and is concerned only with the frequencies of occurrence of subjectively chosen but hopefully representative patterns in crystal structures. If a pattern is seen often enough, it is assumed to be (kinetically) favored and likely to recur in other crystal structures of related molecules. If a sufficiently large number of crystal structures are examined, any kind of molecule→crystal relationship may be predicted even if it is not understood entirely. Identifying a robust, or recurring, synthon does not presuppose any direct knowledge of the crystallization event, although indirect inferences may be drawn as discussed later in this review. The kinetic nature of crystallization, which arises from the high degrees of supersaturation that are generally involved, is the underlying reason and has so many conceptual similarities with covalent-bond-making processes, which proceed often under kinetic control. The striking parallels that I drew between molecular and supramolecular synthons in my 1995 review[30] are accordingly no surprise. They arise from the fact that one is comparing two kinetically controlled phenomena. Crystallization, then, is fundamentally different from the kinds of thermodynamically controlled supramolecular situations described by Whitesides in his 1995 review.[29]

5. Crystal Structure Prediction (CSP)

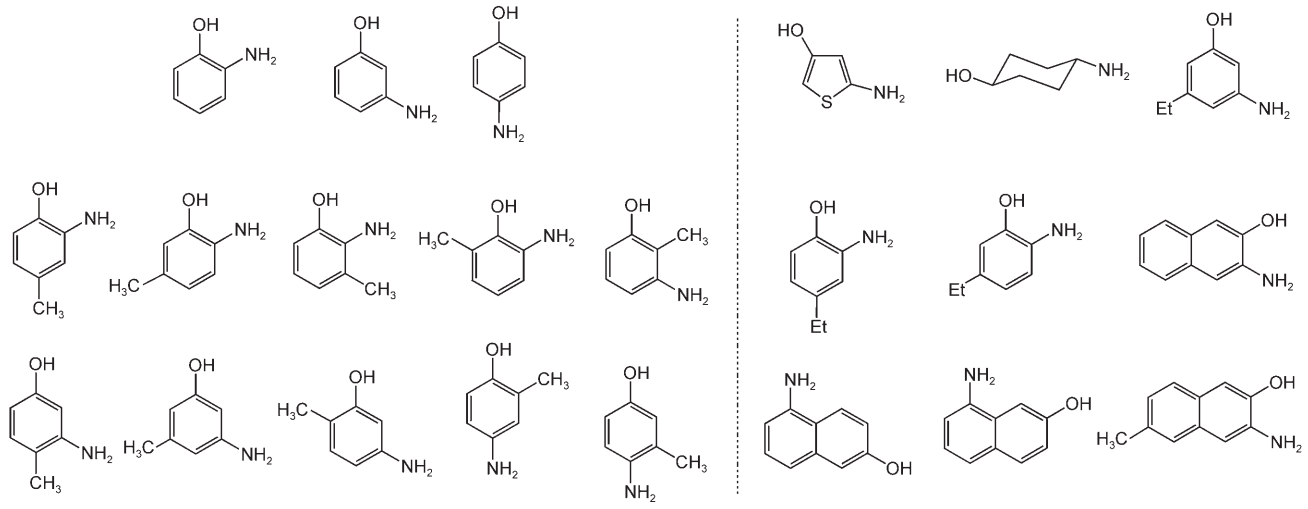
Crystal structure prediction (CSP) is the computational prediction, from the molecular structure, of the space group and the positional parameters of the atoms in the crystal structure.[95,104] It is the most quantitative type of crystal engineering and is recognized to be a major scientific problem of great difficulty.[105,106] A number of crystal structures are obtained computationally by using a selected force field, and the experimental structure is hidden generally amongst the 100 or so lowest-energy structures. When the experimental structure is also the thermodynamic structure, accurate force fields may reveal this structure as the global minimum. When the experimental structure is a higher-energy kinetic structure, a purely computational technique is often inadequate. CSP has been highlighted in a series of blind tests organized regularly since 2000 by the Cambridge Crystallographic Data Centre (CCDC) in which the participants are given a few (three and most recently four) molecular structures for each of which three solutions have to be deposited after a time period of around six months.[107] The results have been mixed. For rigid molecules containing only C, H, N, and O atoms (less than 20 non-H atoms) and with the number of symmetry-independent molecules in the crystal (Z') is 1, CSP generally gives the correct solution if the most stable form is the one which is also experimentally observed. With any relaxation of these conditions (flexible molecule, other elements present, greater than 20 non-H atoms, $Z' > 1$, most stable form not observed experimentally), the problem quickly becomes extremely difficult to intractable.

5.1. Synthon-Based CSP

When the kinetic form is the one obtained experimentally, we have suggested a knowledge-based alternative, the supramolecular synthon approach to CSP.[99,108] In this methodology the computational results are biased manually with synthon information from a database of known crystal structures to incorporate the kinetic factors. Synthons in this database are loosely classified as "small" and "large" based on their complexity. The absence of a small synthon in a predicted structure is a negative factor and is justification for its down-ranking or elimination. The presence of a large synthon in a predicted structure is a positive factor and is grounds for its up-ranking. The highest ranked structures in this reranked list are taken as the predictions.

We have shown that such synthon-based CSP (with the COM force field) works well for rigid aminophenols and related compounds. In this work, CSP was performed for nine amino–hydroxy compounds (mostly substituted benzenes and naphthalenes; Scheme 3, right) with unknown crystal structures, using a training database of the 10 isomeric methylaminophenols and the three simple unsubstituted aminophenols (Scheme 3, left). Subsequent experimental verification of four of these predictions showed that two predictions were accurate (8-amino-2-naphthol, 4-aminocyclohexanol), one was somewhat acceptable in that the predicted synthons were found in the experimental packing (3-amino-2-naphthol), and one was incorrect (2-amino-4-ethylphenol).[109] We assess these results as acceptable given the current scenario.

Among all the problems associated with CSP, the most serious one seems to relate to molecular flexibility. The issue of conformational polymorphism has long been known.[42] It is always difficult to anticipate the packing of a molecule when the molecular structure and the crystal structure influence one another implicitly. In the context of a computational exercise, how does one fix the molecular conformation before beginning a search of crystal space? Clearly molecular conformation and crystal packing cannot be varied simultaneously in the CSP protocol; the problem would quickly rise to unmanageable proportions. Some assumption is required regarding the molecular structure. Whether or not it is a correct assumption is not known before the CSP. In a recent study, Price and co-workers correctly predicted a second (and at that time unknown) form of aspirin.[110] The assumption they made is that the unknown conformation is similar to the one in the known polymorph. This turns out to be a correct assumption, and all went well. However, if this were not the case, then the entire effort might well have been a failure. A



Scheme 3. 13 training-set compounds (left) are used for the crystal structure prediction of nine aminophenols and related derivatives (right).

general strategy for the CSP of flexible molecules (say, two or three rotatable bonds) is a major challenge, and if successful would lead to considerable progress in crystal engineering in silico.

6. Crystallization Mechanisms

At the heart of crystal engineering is the process of crystallization. As this process becomes better understood, crystal structure prediction will become more reliable, and in turn more effective control will be obtained over the design of both structure and function. Determining the mechanism of crystallization is the ultimate goal of crystal engineering and one of the outstanding problems in supramolecular sciences because the crystal is an emergent property of molecules. Crystallization is a supramolecular reaction. On the one side, there is the solution, which is an entropy-dominated situation. On the other, there is the crystal, which is the largely enthalpically determined outcome of the reaction. Between these must lie the crystal nucleus, which is possibly the highest energy point in the reaction coordinate. The path from solution to the nucleus represents an ever-changing balance between entropy and enthalpy, in favor of the latter. While very little is known about the actual course of events during crystallization, a plausible scenario may be sketched assuming that the nucleus lies somewhere along a smooth pathway from solution to crystal. As the elements of short-range order enter the immediate vicinity of the solute molecules, the solution "rigidifies", gradually becoming a solute–solvent cluster. The point of nucleation may be likened to the transition state in a covalent-bond-making process, and is followed immediately by the exit of solvent into the bulk with the simultaneous formation of the crystal, a species which is characterized by long-range order. Just as it is nearly impossible to "see" a transition state directly, it will be correspondingly difficult to "catch" a crystal nucleus. It will not be easy to study crystal nucleation because crystallization is a non-equilibrium process which occurs under conditions of supersaturation (of solutions) or supercooling (of liquids). But the energies involved in a supramolecular reaction like crystallization are much smaller than those involved in typical covalent-bond-making processes. Accordingly, it might be possible to draw some inferences about the crystallization mechanism from experiment. How this could be done is still an open question. Spectroscopy and crystallography, both of the normal and the time-resolved type, are possibilities.

6.1. Structures with Multiple Molecules in the Asymmetric Unit ($Z' > 1$)

An indirect way of observing the course of crystallization is offered by the study of crystal structures which contain multiple molecules in the crystallographic asymmetric unit ($Z' > 1$).[111] In the context of crystallization pathways, a crystal with $Z' > 1$ could be a kinetic form which has been trapped before the molecules have adjusted themselves in their final orientations, which would be seen in a more stable form with $Z' = 1$ (or a value less than in the kinetic form). This is an example of an interrupted crystallization, and the structure of this "reaction intermediate" could provide an approximation to the precursor crystal nucleus. Contributions in this regard have been made by Steed, who has referred to the high-Z' structure as a "fossil relic" of the more stable crystal,[112] and by Nangia, who has referred to these structures as "snapshots" of the crystallization reaction.[113] We have noted this situation in two crystals, **6** and **7** (see Scheme 2).[114] In pentafluorophenol (**6**) the more stable form with $Z' = 1$ contains an infinite O–H···O–H···O–H···O–H··· chain, the adjacent molecules being related by 2_1 symmetry. The $Z' = 3$ structure is more interesting, being obtained in an in situ cryocrystallography experiment when an additive, pentafluoroaniline, is added. This structure contains finite trimer O–H···O–H···O–H fragments, and we expect that it is an intermediate on the way to the infinite chain, with a concomitant synthon evolution towards the final structure (Figure 4).

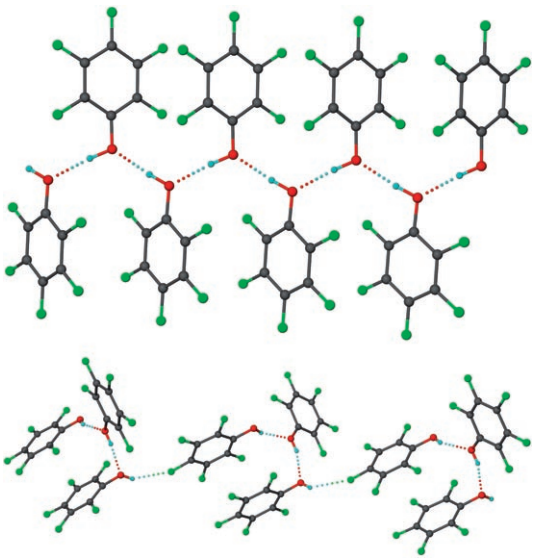


Figure 4. Orientation of pentafluorophenol (**6**) in the crystal (F green, C gray, O red, H blue). The structure with high Z' (bottom) contains a fragment of the eventual infinite O–H···O–H··· synthon seen in the structure above with $Z'=1$.

Similarly, the transformation of the higher-energy $Z'=8$ form of cyclohexane (**7**) into the more stable $Z'=3$ form was observed experimentally. Both forms have essentially the same packing, but there is a greater variation in conformations in the $Z'=8$ form. Accordingly, we have proposed that this is a case of *symmetry evolution* during crystallization.

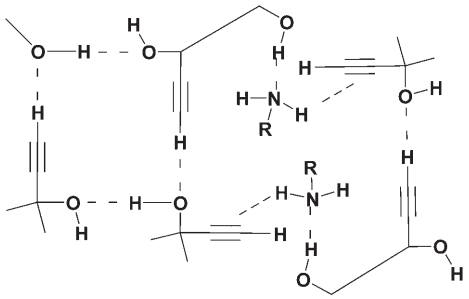
6.2. Early Stages of Crystallization

More direct glimpses of the events during crystallization are reported in recent studies from Davey,[115] Howard,[116] and ourselves.[117] Davey and co-workers showed that the application of FT-IR spectroscopy to concentrated solutions of tetrolic acid shows a direct relationship between molecular self-association in solution and H-bonded patterns in the subsequently crystallized solid phases. Davey's work sheds light on the early stages of crystallization, because it involves measurements in solution. Tetrolic acid is notable in that it takes both the zero-dimensional dimer and one-dimensional catemer in its dimorphs. As mentioned in Section 1.2, the dimer–catemer dichotomy is a classical problem in crystal engineering, and Davey's work is important in that it is the first evidence that the supramolecular synthons which are present in the final crystal have an existence in solution prior to crystallization. The metastable α form is obtained from $CHCl_3$ and contains the dimer. The stable β form is catemeric and is obtained from ethanol. Fortunately, some IR spectral features of the two forms are non-overlapping, and it is possible to unequivocally assign some peaks to just one or the other of the forms, leading to the above-mentioned result. This result is far-reaching and shows that the synthon is a structural unit of significance in all stages of crystallization, from solution, to aggregation, nucleation, and finally growth. The synthon is of mechanistic significance and not merely a structural descriptor of crystals. Accordingly, I do not use or advocate the use of terms like motif and pattern, which seem to be suggestive of the static crystal alone, as equivalents of synthon.

6.3. Late Stages of Crystallization

To the extent that the nucleus lies on a smooth path between the solution and the crystal, its structure could be approximated as a liquid-like cluster which contains solute and solvent with some elements of order. However, most crystals of non-ionic organic compounds do not contain solvent. Accordingly, a characteristic occurrence during or just after nucleation would be the expulsion of solvent from the nucleus to the bulk solvent; this removal of solvent from the crystal is entropically advantageous and is possibly facile. Conversely, the retention of (ordered) solvent molecules in the crystal is evidence of enthalpic factors, notably the formation of strong hydrogen bonds between solute and solvent.[118] According to such a model, the presence of solvent in a crystal could be taken as evidence of "interrupted" crystallization. The entropically facilitated expulsion of solvent from the crystal is countered by the enthalpic advantage that is gained from hydrogen bonding in retaining the solvent so that, in effect, the solvent is held by the crystal. If solvent expulsion is characteristic of "completed" crystallization, then solvent retention is evidence of "incomplete" or "interrupted" crystallization.

Howard et al. have obtained evidence of such interruption in solvates of the alkyne diol **8** (Scheme 2), and their work highlights the late stages of crystallization when solvent is being expelled from the nascent crystal.[116] Crystals were obtained both for the unsolvated diol and for the cyclooctylamine solvate. The compound belongs to the geminal alkynol family, for which synthons **9** and **10** (Scheme 2) are representative. The asymmetric unit of the solvate comprises two half molecules of the diol, each sitting on distinct inversion centers, together with one amine molecule (Scheme 4). The interaction hierarchies of the two diol molecules are distinctly different; while one of them is involved in forming synthon **9**, the hydroxyl group of the other forms a strong O–H···N hydrogen bond with the amine. In doing so, it comes in



Scheme 4. Interruption of synthon formation by solvent. Cyclooctylamine (RNH_2) forms a hydrogen bond with a hydroxy group in alkynol **8**, preventing the formation of synthon **10**. Synthon **9** is formed as usual. Without such interruption, synthons **9** and **10** would be formed in their usual fused manner as seen in Figure 2 for alkynols **2** and **3**.

between two ethynyl groups and intervenes in the formation of synthon **10**. As a result of this, the ethynyl H atom remains "free". However, the orientation of the ethynyl groups is closely reminiscent of both the cooperative synthons **9** and **10**, which are the hallmarks of the geminal alkynol family; only in the solvate these groups are obstructed and separated by the steric bulk of the cyclooctylamine. In other words, this is the closest example of what could be imagined as the interruption of a representative synthon (in this case, **10**) by the formation of a strong O–H···N bond from the solvent. The presence of two relatively weak N–H···π (2.96 Å, 3.15 Å) interactions could be rationalized as bringing the structure one step closer to the crystallization point, when solvent extrusion from the bulk occurs and a solute-rich structure results.

6.4. Intermediate Stages of Crystallization. Catching the Nucleus

The early stage of crystallization involves the first synthon formation in solution while the late stage involves solvent expulsion. The intermediate stage of crystallization is in many ways the most fascinating because it may be that it is during this stage that nucleation occurs. We recently determined the crystal structure of sodium saccharin dihydrate, Na(sac)-$(H_2O)_{1.875}$ (**11**) and showed that this heavily hydrated structure is a very good model for the nucleus of the lower hydrate $Na_3(sac)_3(H_2O)_2$ (**12**).[117] Indeed this complex structure is akin to a metastable high-energy intermediate, and for a number of reasons, we have argued that it is as good a model for a crystal nucleus as can be obtained presently.

The structure of dihydrate **11** is shown in Figure 5 and has several unusual features. The first is the large unit cell (15614 Å^3, $P2_1/n$, $Z=4$). With 64 Na^+ ions, 64 sac^- ions, and 120 water molecules in the unit cell, this structure is one of the largest and most complex ever for ions/molecules that are as small and simple as these. The second feature is that a part of it, the regular region, resembles a conventional crystal, but an adjacent part, the irregular region, has "solution-like" characteristics. In the former domain, the saccharinate anions are nearly parallel and stacked, the Na^+ ions are hexacoordinated with water and sac^-, and the water molecules are efficiently hydrogen-bonded. In the irregular region, there is disorder of sac^-, Na^+ (some of which is not necessarily hexacoordinated), and water (some of which is ill-resolved). Notably, there is a variation in the occupancies of these species between crystal to crystal and possibly between one temperature and another. All in all, we carried out structure determinations of four crystals at four different temperatures (total of eight data sets). The overall conclusion is that there is appreciable mobility of the species in the irregular region, and it may be taken to be in a state of incipient crystallization. The third unusual feature is that dihydrate **11** can exist in equilibrium with water. When a crystal is placed in the proximity of a single drop of water in a closed environment, it absorbs water rapidly. Further exposure to the vapor results in dissolution, which is followed by rapid recrystallization if the water-saturated environment is removed. All of this, when taken with the presence of the irregular disordered domains, indicates a crystal that is very close to the dissolution point. We note further that the solubility of **11** at 27 °C is 120 g in 100 g water, which is equivalent to a water content just seven times less than the saturated solution. The fourth feature of note is that crystals of **11** also lose water readily. Remarkably, a solid that is deliquescent in a water-rich environment is efflorescent in a water-poor environment, and water loss occurs in two stages. The first stage begins as low as 35 °C and is essentially complete by 50 °C to yield the lower hydrate **12**, the structure of which is shown in Figure 6. The second stage occurs between 100 °C and 115 °C and leads to the anhydrate.

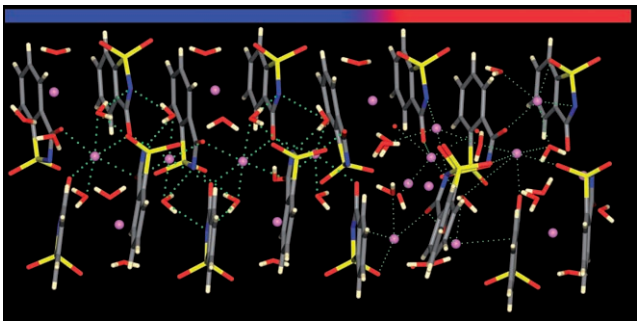


Figure 5. Crystal structure of the asymmetric unit of sodium saccharin dihydrate, Na(sac)$(H_2O)_{1.875}$ (**11**; Na purple, S yellow, O red, N blue, C gray, H beige). Notice the ordered (left) and disordered (right) regions of the crystal with five and three saccharin dimers, respectively. The latter region is in a state of "incipient crystallization".

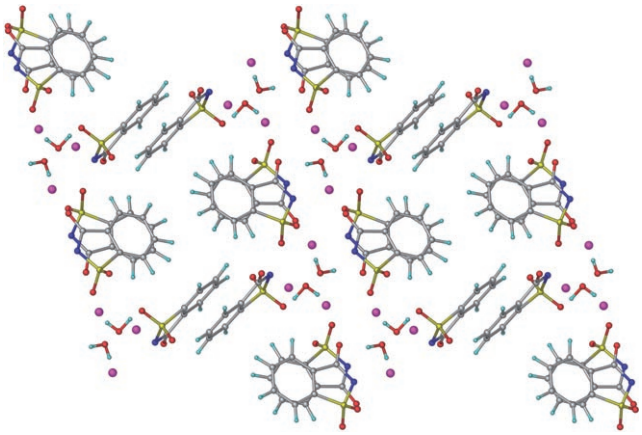


Figure 6. Crystal structure of the lower hydrate, $(Na)_3(sac)_3(H_2O)_2$ (**12**; Na purple, S yellow, O red, N blue, C gray, H light blue), obtained from dihydrate **11** by loss of water. Note that the residues stacked perpendicular to the plane of the page are related to the ordered regions in the dihydrate structure.

Inspection of the crystal structures of **11** and **12** shows that while the sac^- residues in **11** are all nearly parallel, those in **12** occur in two groups that are perpendicular to each another. The stacking of residues in the infinite stack down [001] bears a close resemblance to that in the regular domains of hydrate **11**. The residues that occur as discrete dimers in **12**, perpendicular to the infinite stack, are in a stoichiometry that is half that of the residues in the infinite stack. This 2:1 stoichiometry of residues in **12** is reminiscent of the 5:3 demarcation of sac^- residues in the regular and irregular

regions of dihydrate **11**, and is suggestive of a possible mechanism for the **11**→**12** conversion. While the regular domains are largely conserved, the residues in the irregular domains might move into the empty regions created by the loss of water, and also assume a perpendicular geometry. This mechanism is reasonable because maximum movement of residues occurs in those regions of **11** where the arrangement is the least regular and where molecular motion is already expected to be facile. Additionally, selected supramolecular synthons in dihydrate **11** are retained in hydrate **12**. The stacked synthons in the regular domains of **11** are preserved as mentioned above. Hydrogen-bonded synthons in the irregular domains of **11** are also conserved in **12**. The fact that these synthons are carried over into **12** even as there is much structural reorganization is in keeping with the idea of synthons as kinetically significant units that are preserved through all stages of crystallization.

The unusual features in the structure of **11** argue that it is a good model for nucleation in the crystallization of the hydrate **12** from water. A large unit cell, in itself, is not exceptional, but for crystals wherein the building blocks (molecules, ions, solvent) are so small, such a large unit cell is noteworthy. The combination of the large cell, with regular and irregular domains, and also the excessive amount of solvent in the crystal are very suggestive of a crystallization reaction still in progress. Indeed, dihydrate **11** seems to be evenly poised between solution and hydrate **12**. There is no other reported example of a substance that gains and loses solvent so easily, and there is not much difference in water content between crystalline **11** and the saturated solution. Amazingly, the same compound loses water at 35 °C, and the resulting hydrate **12** does not gain water when exposed to the vapor. Easy water gain or loss is, in itself, unexceptional. When it occurs for the same substance, it becomes significant and suggests that **11** is a high-energy intermediate which bridges the saturated solution and the stable hydrate **12**. In keeping with the idea of crystallization as a supramolecular reaction and the description of dihydrate **11** as a supramolecular transition state, one can apply the Hammond postulate and conclude that **11** is an example of a late transition state. Large regions of **11** resemble that of **12**, and there are no water···water interactions. The elements of order have well entered the crystal nucleus, the important supramolecular synthons are in place (if not exactly in the correct locations), and the product of crystallization (hydrate **12**) is a kinetic product. It is still a matter of conjecture that crystal nuclei which are early transition states will have solution-like character, and that they will lead to thermodynamic products (perhaps the anhydrate).

7. Summary and Outlook

I have tried to sketch some current themes in a discipline that has crossed the threshold between a developing and mainstream activity. Crystal engineering has much to offer the chemist because it is mechanistic, synthetic, and conceptual in its theme. As a mechanistic subject, there are considerable opportunities for the use of instrumental techniques. Indeed, some of the difficult questions posed in this review will yield their secrets only with the application of sophisticated experimental methods, which can make measurements in very small distances and time scales. As a type of synthetic activity it offers considerable scope for artistry and imagination, both of which are bounded only by human ingenuity. But above all, it is the conceptual challenges in understanding the crystal and crystallization that strain the limits of the chemical researcher because crystal engineering is a study of systems that are both diverse and complex.

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