JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Perspective

pubs.acs.org/JACS

Crystal Engineering: From Molecule to Crystal

Gautam R. Desiraju*

Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560 012, India

ABSTRACT: How do molecules aggregate in solution, and how do these aggregates consolidate themselves in crystals? What is the relationship between the structure of a molecule and the structure of the crystal it forms? Why do some molecules adopt more than one crystal structure? Why do some crystal structures contain solvent? How does one design a crystal structure with a specified topology of molecules, or a specified coordination of molecules and/or ions, or with a specified property? What are the relationships between crystal structures and properties for molecular crystals? These are some of the questions that are being addressed today by the crystal engineering community, a group that draws from the larger communities of organic, inorganic, and physical chemists, crystallographers, and solid state scientists. This Perspective provides a brief historical introduction to crystal engineering itself and an assessment of the importance and utility of the supramolecular synthon, which is one of the most important concepts in the practical use and implementation of crystal design. It also provides a look to the future from the viewpoint of the author, and indicates some directions in which this field might be moving.

INTRODUCTION

Crystal engineering is the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in design of new solids with desired physical and chemical properties.[1] Crystal engineering has grown and developed over the past 50 years as a natural outcome of the interplay between crystallography and chemistry.[2] Chemistry has to do with molecules while crystallography has to do with crystals, which are extended, ordered assemblies of molecules. The interplay between chemistry and crystallography is therefore the interplay between the structure and properties of molecules on one hand and those of extended assemblies of molecules on the other.[3] The inter-relationship between molecules and crystals was first addressed by W. H. Bragg, who, in 1921, recognized that certain structural units like a benzene ring have a definite size and form that might be retained with hardly any change on going from one crystal structure to another (Figure 1).[4]

Bragg compared the unit cell parameters of naphthalene and anthracene and noted that these cell parameters were related: two axial lengths were nearly the same while the third was 8.66 Å in naphthalene and 11.66 Å in anthracene. With no further information, he concluded (correctly) that the long direction of the molecule(s) coincides with this third non-equal axis and that the width of a benzene ring is approximately 2.5 Å. This

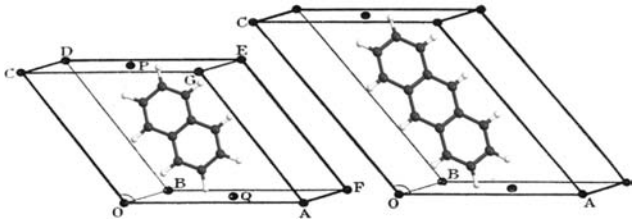

Figure 1. The relationship between the crystal unit cells of naphthalene and anthracene may be used to estimate the size of a benzene ring. Adapted from ref 4.

was perhaps the earliest correlation between a crystal property and a molecular property. Fifteen years later, J. D. Bernal (who had previously been Bragg's student), while studying the unit cell parameters of a number of aromatic hydrocarbons related to phenanthrene, was able to correct formulas for steroids and bile acids that had been earlier proposed by eminent chemists such as Wieland, Windaus, and Ruzicka.[5] This was a good example of how one might obtain structural information about a molecule from structural information about a crystal.

In the context of crystal engineering, however, it is the reverse question that is the more meaningful. *Given the molecular structure of a compound, what is its crystal structure?* The aims and goals of crystal engineering, which can also be called crystal synthesis, are well summarized in this question because one attempts in this subject to design crystal structures by using the molecule as a building block. It was J. M. Robertson who, at the University of Glasgow, first tried to provide an answer to this question in the context of a limited group of compounds, namely the polynuclear aromatic hydrocarbons.[6] Robertson (who incidentally was also a former student of Bragg) stated that these compounds could be classified into two groups. The first group consists of molecules in which the molecular area is small in comparison to the molecular thickness. This group is populated by hydrogen-rich molecules like naphthalene and anthracene, and crystal structures in this group are characterized by a short (monoclinic) axis of around 5.4−8.0 Å. The second group, in which the molecular area is large in comparison with the molecular thickness, is represented by carbon-rich molecules like coronene and ovalene that yield graphitic crystal structures. The short monoclinic axis in these cases lies in the range 4.6−5.4 Å or so. Robertson was able to successfully derive a crystal property from a molecular property and therefore deserves the credit for first raising and then answering the question, among chemical crystallographers, as to how crystal structure is related to molecular structure.

Received: April 2, 2013
Published: June 10, 2013

   dx.doi.org/10.1021/ja403264c | *J. Am. Chem. Soc.* 2013, 135, 9952−9967

WHAT IS CRYSTAL ENGINEERING?

The term *crystal engineering* was first introduced to the literature in 1955 by R. Pepinsky[7] in a meeting abstract of the American Physical Society, but it is more generally associated with G. M. J. Schmidt (a student of Dorothy Crowfoot Hodgkin, herself the student of Bernal, who coauthored the paper on fused phenanthrenes with him), who correlated the solid-state reactivity of a large number of photodimerizable compounds, notably *trans*-cinnamic acids, with their crystal structures on the basis of the topochemical principle (Figure 2).[8]

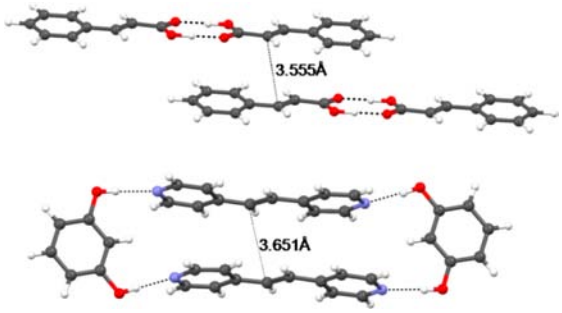

Figure 2. Solid-state topochemical 2+2 photodimerization of alkenes. Top: *α-trans*-cinnamic acid as studied by Schmidt (ref 8). Bottom: Resorcinol–dipyridylethylene cocrystal as studied by MacGillivray (ref 66).

This principle postulates minimum molecular movement in solid-state reactions. Schmidt, working in the then newly established Weizmann Institute, was actually harking back to the question first posed by Bragg and Bernal, namely how to extract a molecular property (reactivity of monomer and regiochemistry of dimer) from a crystal property (short crystal axis) of the monomer. However, he realized toward the end of his unfortunately short research career that real progress could not be made until such a time when the central issue, namely a fully predictable protocol to obtain the crystal structure of a molecular solid from the structure of the molecule itself, had become a reality. He termed this futuristic period as "the phase of crystal engineering".[8b]

Over the following years, there were a number of developments which brought to bear upon the central question of molecule → crystal. During the 1970s and 1980s, several solid-state reactions were investigated, and the course and outcome of these reactions were correlated on the basis of the topochemical principle.[9] In parallel to these developments, which are of a chemical nature, a distinctly different thought stream that addressed the molecule → crystal question was invoked by A. I. Kitaigorodskii, who stated that the packing of molecular solids was largely governed by considerations of size and shape, the so-called principle of close-packing.[10] The 1980s–1990s was also a period during which there was increasing appreciation of the role of intermolecular interactions in crystal engineering. In 1986, J. A. R. P. Sarma and I attempted to rationalize Schmidt's observations on the unit cell parameters of chloroaromatic compounds on the basis of short Cl···Cl interactions, in an early study of what would today be called a halogen bond.[11] M. C. Etter in 1990 identified the hydrogen bond as being both directional and strong and, in this respect, important as a determinant of crystal structures.[12] My 1989 book[1] attempted to bring together the chemical viewpoint of interactions with Kitaigorodskii's physical viewpoint based on close-packing. It described organic crystal structures as being predominantly governed by Kitaigorodskii's close-packing principles, which invoke geometrical arguments, but stated that the minor deviations from close-packing, which owe to chemical factors, are of the greatest importance because they lead to the formation of crystal structures that can be *engineered* in a systematic manner. Interaction directionality, such as it exists in organic crystals, is the handle that permits crystal design.

Entirely different types of molecular crystals, metal–organic coordination compounds, were described by R. Robson in the early 1990s, and early attempts at design of such substances were published.[13] It is interesting that the first detailed descriptions of a molecular crystal as a network pertained to organic crystals—hydroquinone by H. M. Powell[14] in 1948 and adamantane-1,3,5,7-tetracarboxylic acid by O. Ermer[15] in 1989—but the association of a molecular crystal structure as a network is most closely associated with coordination polymers and metal–organic framework (MOF) compounds today.[16] At the present time, the design of both pure organic and metal–organic solids properly belongs to the subject of crystal engineering, at least if the definition provided in my 1989 book is accepted. In both cases, one attempts to understand crystal structure in terms of intermolecular interactions; one attempts to define a reliable design strategy using these interactions; and finally one attempts to direct such a crystal design exercise toward a property that may be needed.

Crystal engineering is an evolving subject, and in any such subject there is a good likelihood of discussions and debates pertaining to nomenclature. A number of these terms (polymorph,[17] pseudopolymorph,[18] cocrystal,[19] coordination polymer,[20] metal–organic framework,[20] hydrogen bond,[21] halogen bond[22]) have seen lively discussions during the past decade or more. While it is the aim of every scientist to use terms that are both generally applicable and scientifically accurate, these two attributes sometimes come into conflict. The present Perspective contains several of the above terms, used in a manner that the author generally believes is in accordance with the consensus view today.

THE BIG QUESTIONS

When one seeks the crystal structure of an organic compound from its molecular structure, one is really asking how molecules recognize one another from the earliest stages of association, toward nucleation and finally crystallization. One starts with molecules in organic-based crystal engineering or in MOF chemistry because chemists have been trained to make molecules and molecules are, in this context, the building blocks for crystals. A core problem of crystal engineering is that crystal structures cannot be predicted easily from molecular structures, at least not with a modular approach such as is possible with functional groups. The behavior of a functional group in a molecule during crystallization depends on the nature and positioning of all the other functional groups in the molecule. The crystal structure of, say, 3-iodonitrobenzene[23] need not be closely related to that of either iodobenzene or nitrobenzene. In the limit, it need not even be related closely to that of 4-iodonitrobenzene.[24] Therefore, crystal structures are not related to molecular structures (functional groups) in simple ways: the crystal structure is an emergent property.[25] A further complication, and a serious one at that, is that the hydrocarbon portion of a molecule, be it aliphatic or aromatic, is a very effective supramolecular functional group. We found,

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952–9967

for example, several years ago that even in simple aminophenols, N−H···π interactions can compete effectively with the expected N−H···O hydrogen bonds (Figure 3).[26]

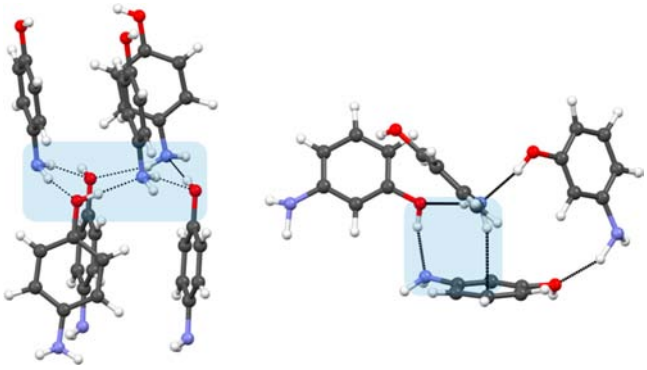

Figure 3. Crystal packing in the aminophenols. Left: N−H···O and O−H···N hydrogen bonds in 4-aminophenol. Right: N−H···O, O−H···N, and N−H···π hydrogen bonds in 3-aminophenol. See ref 26.

Another distinct problem is that the building up of a crystal needs to be considered in a stepwise manner, and these steps may be quite discrete:

One → Few → Many → Nucleus → Crystal

This building up Aufbau process[27] need not be a simple continuous one. A midsize cluster may be formed and then be unable to grow further so that it redissolves and an alternate pathway for nucleation needs to be found. A classical example is provided by acetic acid, in which nearly 90% of the liquid consists of the dimer but wherein the only known experimental crystal structure contains the infinite catemer.[28] The rationalization of such an observation is that dimer is formed very easily but is unable to grow further because very weak methyl···methyl interactions are the main cohesive interactions in the further assembly of dimers. The catemer is preferred because its formation provides a pathway for crystal growth quite readily in at least one dimension. We do not know how molecular crystals are built up, in a general sense: Are small clusters formed which increase in an orderly way to give larger clusters? Or are the events more irregular? Answers to such questions will almost undoubtedly come from spectroscopy[29] and computation[30] rather than from crystallography, as it is now practiced. When the Aufbau process is regular, however, the situation is a favorable one for crystal engineers. In such cases, the structure of the final crystals can be related more accurately to the structure of smaller and smaller modules until in the end even a basic recognition unit such as the carboxylic acid dimer or a phenol···phenol catemer is a good enough approximation to parts of the final structure. Such structural modularity is desirable, but it is a casualty when the Aufbau events are irregular.

Both these difficulties, namely the failure of the functional group approach and the stability and the variable interplay of kinetics and thermodynamics in the process of nucleation, together constitute a formidable challenge in the prediction or anticipation of crystal structures from molecular structures. A simplification is therefore required, and such a simplification has been provided by the definition of representative kinetic units called *supramolecular synthons*.[31] Supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthon operations involving intermolecular interactions (Figure 4).

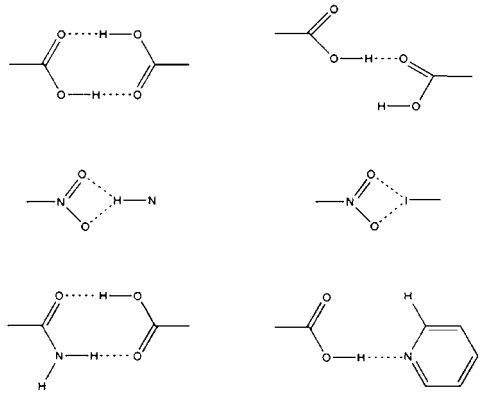

Figure 4. Representative supramolecular synthons. Dimer and catemer forms illustrate crystal packing in acids. The nitro···amino and nitro···iodo synthons show the similarity between hydrogen bonding and halogen bonding. Amide···acid and acid···pyridine heterosynthons are of relevance in the formation of pharmaceutical cocrystals.

Synthons are kinetically defined structural units that convey the essential features of a crystal structure, and a critical assumption is that the synthon is a reasonable approximation to the whole crystal. The closer the structure of a small synthon is to the actual crystal, the more useful is this entire concept. In such cases, the building up process of a crystal from molecules takes its place in a well-organized and regular way, and crystal engineering becomes viable. Smaller clusters are good approximations for larger clusters[32] so that the final crystal can be analyzed easily as a collection of robust synthons that were formed from the earlier stages of molecular association. The crystal structure in these cases may be viewed as a sequence of kinetically controlled events. Robust synthons are formed with strong and directional interactions. Once they are formed, they tend not to dissolve. New synthons are next formed that involve slightly weaker and slightly less directional interactions. In this way the building up of a crystal can be rationalized as a series of chemical reasonable and logical steps. The synthon is a practical concept aimed at the understanding and design of molecular crystal structures. A synthon is a probabilistic event.[33] The more often it is seen, the more likely it will be seen in the crystal structures of new molecules that contain the requisite functional groups. Good correspondences between molecular and crystal structures are seen in these optimal cases, and a number of robust synthons are observed. However, such occurrences are by no means universal. Discontinuities in the building up process lead to lack of easily observed correspondences between molecular and crystal structures, and crystal engineering is correspondingly difficult to carry out. In a general sense, molecular and crystal structures are not related in easily perceived ways. Competition between synthons becomes a complication, sometimes even with just a small increase in molecular functionality, leading to polymorphism.

Given all these considerations and concerns, this Perspective is written to draw the readers' attention to three distinct issues in contemporary crystal engineering that, to the mind of this author, constitute important and attractive challenges for the researcher: (i) intermolecular interactions, (ii) supramolecular

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952−9967

synthons and crystal design strategies, and (iii) a look to the future.

INTERMOLECULAR INTERACTIONS

A synthon is the outcome of early recognition events between molecules. But in order to appreciate which synthon might or might not form, one needs to understand the properties of the intermolecular interactions that are the primary reasons for specific recognition. Much has been written and spoken about specific interactions in the crystal engineering context; these include the hydrogen bond, including its weakest variant, the C−H···π interaction,[34] van der Waals interactions,[35] dipole−dipole interactions,[36] and more recently the halogen bond.[37] Mention has also been made of interactions such as aurophilic[38] and argentophilic[39] forces and the cation···π interaction.[40] However, the idea that a set of specific interactions, each between two nonbonded atoms, is a full descriptor of a subsequent supramolecular recognition event may be too simplistic—associations between two molecules may be modeled more accurately in terms of three-body interactions and in the limit an *n*-body interaction, in which case specific interactions gradually merge into the domain of what may loosely be termed close-packing.[41] These issues are important to crystal engineering: highly directional and atom-specific interactions that are also strong are kinetically favored. Close-packed structures, on the other hand, are thermodynamically favored.[42] So the interpretation of recognition as mediated by specific interactions (chemical recognition that could lead to hierarchic pairing of atoms) or by close-packing (geometrical recognition that leads to the most stable structures) is more than mere semantics, at least in polymorphic systems. There is a real conundrum in strongly hydrogen-bonded structures: there may be thermodynamic structures that can be dissected in terms of specific and strong hydrogen bonds that may be clearly considered as two-body interactions. Complications can arise in structures that have multiple molecules in the crystal asymmetric unit (Z′).[43] Sometimes, higher Z′ structures have higher energies, imputing perhaps that they are nucleus fossils.[43d] In other cases, a high Z′ structure is of a lower energy than a lower Z′ polymorph.[43c] What is the physical significance of such an observation?

Let us consider the case of synthon polymorphism[44] in the 1:2 cocrystals of 4,4′-bipyridine and 4-hydroxybenzoic acid (Figure 5).[45]

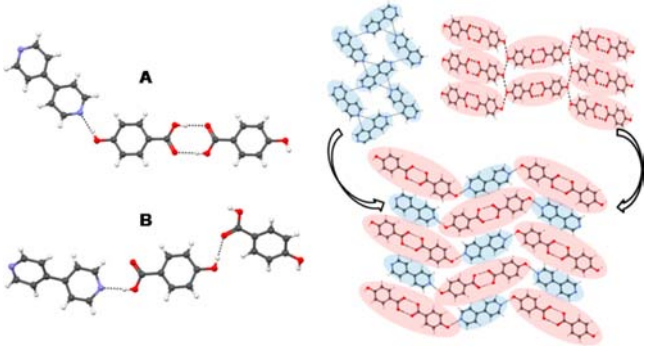

Figure 5. Synthon polymorphism in the 2:1 4-hydroxybenzoic acid−4,4′-bipyridine system. Notice the interleaving of the two species in the thermodynamic form, **A**. Such mutual interleaving is absent in the kinetic form, **B**.

There are two polymorphs, form **A** and form **B**, whose structures are illustrated. Both forms contain strong and directed hydrogen bonds. Form **A** is the thermodynamic form and, in packing terms, it can be described as an insertion of the bipyridine molecules in between the acid molecules as they occur in one of the native forms of the acid itself or, just as equally, as an incorporation of the acid molecules into the native bipyridine structure. This is shown in Figure 5. This mutual relationship could reflect the overall influence of close-packing (even) in a structure that had several strong and directed hydrogen bonds. In the kinetic form, this mutual topological relationship is only partial. While the bipyridine can be inserted into the other native structure of the acid (it is dimorphic) to give the cocrystal structure, the converse is not true. The acid cannot be inserted into the bipyridine native packing to give form **B**. Given also that interaction hierarchy (strongest donor to strongest acceptor; next strongest donor to next strongest acceptor) is seen in form **B** but not in form **A**, there is a hint that even in these hydrogen-bonded structures, close-packing is more important in the thermodynamic form **A**, while hydrogen bond interactions are more important in the kinetic form **B**. While all interactions (chemical or geometrical) arise from electrostatics at a primary level, these results raise questions as to whether the chemical and geometrical models are related to one another and, indeed, if the basis for the chemical model actually arises from the geometrical model. Kitaigorodskii was very succinct about this matter. In one of his textbooks he writes that "so far only one significant conclusion suggests itself; the formation of hydrogen bonds does not handicap the layout of molecules in conformity with the general (close packing) rules of the packing of crystals." [10]

It is with respect to contacts formed by covalently bonded or "organic" fluorine (C−F)[46] that issues pertaining to geometrical versus chemical recognition become very contentious. Several years ago, R. Boese and I analyzed the crystal structure of fluorobenzene in terms of a specific C−H···F−C hydrogen bond with an analogy argument.[47] This crystal packs in the (not so common) tetragonal space group $P4_12_12$ and is isomorphous to benzonitrile, pyridine hydrofluoride ($C_6H_5N{\cdot}HF$), and pyridine-*N*-oxide (Figure 6).

Our argument stated that in the three latter structures, C−H···N, C−H···$F^{\delta-}$, and C−H···O interactions are the respective equivalents of the C−H···F−C interactions in the fluorobenzene crystal structure. Since the latter three interactions are generally recognized as hydrogen bonds, the former, namely the C−H···F−C bond in fluorobenzene, must also be a hydrogen bond. This interpretation was questioned by J. D. Dunitz and W. B. Schweizer, who noted that similarity in crystal structures need not arise from electronic similarity among the equivalent interactions in the various structures.[48] They stated that one of the hypothetical computed high-pressure forms of benzene adopts the same tetragonal packing referred to above and that the H···H interaction in that structure is the counterpart of the C−H···F−C interaction in fluorobenzene. The implication here was that close-packing rather than anisotropic interactions are important in fluorobenzene. We argued against this contention of Dunitz and Schweizer in the following manner: the $P4_12_12$ structure of fluorobenzene is also adopted by alloxan and a few other compounds, all of which have a 1,2,3,5-tetrasubstituted benzene ring. If close-packing and molecular shape and size determine crystal packing exclusively, then 1,2,3,5-tetrafluorobenzene would also adopt the above-mentioned tetragonal packing.[49] However, it does

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952−9967

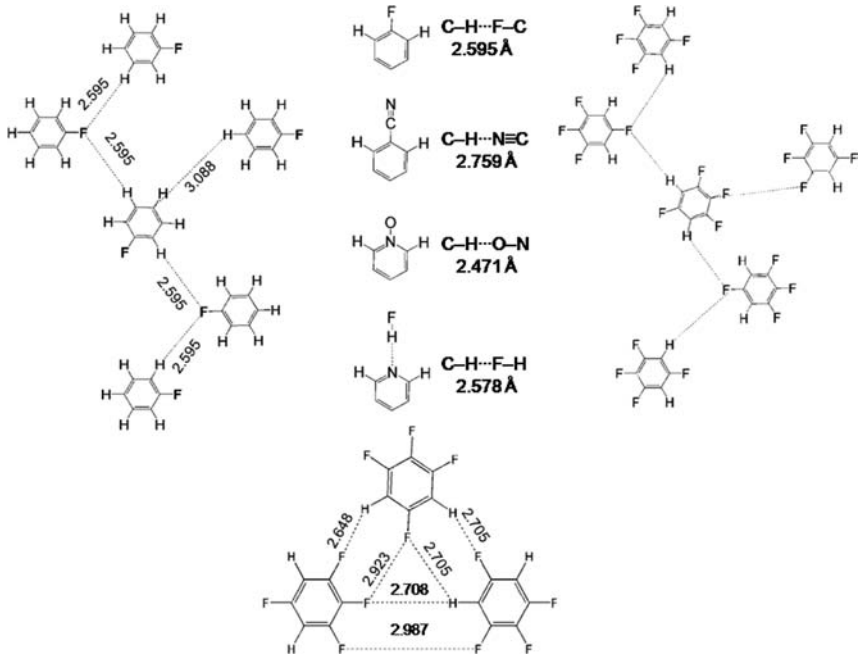

Figure 6. Equivalence of crystal structures of fluorobenzene with those of cyanobenzene, pyridine-*N*-oxide, and pyridine·HF based on C−H···F−C, C−H···N≡C, C−H···O, and C−H···F$^-$ equivalence. A similar packing is not possible for 1,2,3,5-tetrafluorobenzene because a C−F$^{\delta+}$···π interaction with an electron-deficient ring would be involved. The experimental crystal structure of 1,2,3,5-tetrafluorobenzene (bottom) is layered and has a C−H···F−C interaction. See ref 49.

not; the probable reason is that the formation of the $P4_12_12$ structure for 1,2,3,5-tetrafluorobenzene would necessitate C−F···phenyl interactions with a highly electron-deficient phenyl ring (Figure 6). The experimental crystal structure of 1,2,3,5-tetrafluorobenzene is layered with a profusion of lateral C−H···F−C hydrogen bonds and no chemically unfavorable contact such as would arise from a structure that is deduced from a purely geometrical viewpoint. So the dichotomy between chemical interactions and geometrical close-packing continues. It is hard to say when each of these factors will dominate in an unknown crystal structure. While all structures are nearly close-packed, it is the small deviations from close-packing that are of the greatest importance, because these small deviations from close-packing owe to chemical factors and in turn lead to the formation of crystal structures that can be engineered in a systematic manner. Directionality as it exists in organic crystals is *the* handle that permits crystal design, and pattern recognition is one of the first steps in crystal engineering strategy.

Accordingly, studies of the hydrogen bond (and more recently the halogen bond) continue to be of the greatest importance.[50] In 2011, a new official definition of the hydrogen bond appeared as the outcome of an IUPAC project, as follows:[50b,c] *The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment, X−H···A in which X is more electronegative than H, and an atom or a group of atoms in the same or different molecule, in which there is evidence of bond formation.* It may be noted that this definition readily permits the inclusion of interactions C−H···O, C−H···N, and C−H···π as hydrogen bonds.[51]

In the crystal engineering context, there are two aspects of the new definition that are of interest.[52] The first pertains to the geometrical criteria used to characterize an X−H···A interaction as a hydrogen bond. In the new IUPAC definition, it it stated, "Historically, the X to A distance was found to be less than the sum of the van der Waals radii of X and A, and this shortening of the distance was taken as an infallible indicator of hydrogen bonding. However, this empirical observation is true only for strong hydrogen bonds. This criterion is not recommended." Unfortunately the van der Waals distance criterion still seems to be applied to the heavy-atom distance X···A in the assessment of a contact as a potential hydrogen bond. This does not cause serious problems for strong hydrogen bonds, but it may result in certain weak hydrogen bonds being overlooked. The use of the van der Waals criterion is always problematic for the weakest of hydrogen bonds, such as the C−H···π interactions. The second aspect of the definition that is of relevance to crystal engineering pertains to the directionality of hydrogen bonds and the ways in which they influence crystal structures. In the new definition, it is stated that "Hydrogen bonds are directional and influence crystal packing modes in chemically understandable ways. The crystal packing of a non-hydrogen-bonded solid (e.g., naphthalene) is often determined by the principle of close-packing, and each molecule is surrounded by a maximum number of other molecules. In hydrogen bonded solids, there are deviations from this principle to a greater or lesser extent depending upon the strengths of the hydrogen bonds that are involved. Correspondingly, the hydrogen-bond geometries are conserved with fidelities that depend on their strengths." It has always been well known that hydrogen bonds are directional, and the present definition seems to restate the obvious, but this aspect of hydrogen bonding, which is so important in crystal engineering, has generally not been mentioned in previous formal definitions of the interaction. As far back as 1953, J. M. Robertson wrote that "The hydrogen bond is something much more specific than merely a stronger type of attraction between molecules. It is effective only in certain definite directions, and this directive power is sometimes capable of maintaining an unusually open structure, where ordinary packing considerations would

indicate the possibility of alternative structures of higher density." [53] Robertson takes the opposite view from Kitaigorodskii when he continues: "Another generalization derived from a study these various crystal structures is what may be termed the principle of maximum hydrogen bonding. All the available hydrogen atoms attached to the electronegative groups are generally employed in hydrogen bond formation. Some of the bonds formed may be weaker than others, but the molecular packing is generally capable of adjustment in such a way as to fulfill this condition. Sometimes the resulting structures may not be the most compact that might be devised, but this condition and the steric requirements are nevertheless generally obeyed." According to Robertson, it is the close-packing that adjusts itself to the directionality requirements of the interactions! The dichotomy between interactions and close-packing continues, and it is the view of this author that a resolution, if at all, of this dichotomy will still take a while, during which time many interesting and new crystal structures will be uncovered.

The halogen bond has also been the subject of recent research and discussion.[37,54] In a provisional recommendation to the IUPAC the halogen bond has been defined as follows: *A halogen bond R−X···Y−Z occurs when there is evidence of a net attractive interaction between an electrophilic region on a halogen atom X belonging to a molecule or a molecular fragment R−X (where R can be another atom, including X, or a group of atoms) and a nucleophilic region of a molecule, or molecular fragment,Y−Z.* Key to this definition is that the halogen atom should be electrophilic in the contact. Accordingly, halogen bonds and hydrogen bonds can have similar effects on crystal packing. The equivalence of the halogen bond and the hydrogen bond in crystal engineering has long been known, in for example the equivalence of the crystal structures of 1,4-dichlorobenzene, γ-hydroquinone, and 1,4-diethynylbenzene (Figure 7).

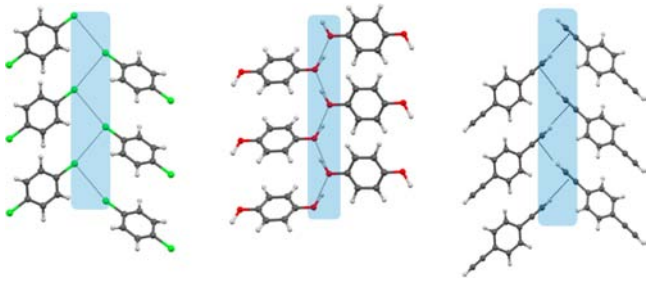

Figure 7. Equivalent crystal structures of monoclinic 1,4-dichlorobenzene, γ-hydroquinone, and 1,4-diethynylbenzene. Note that the respective halogen bond, hydrogen bond, and C−H···π interaction in these three structures are chemically and crystallographically equivalent.

The recent literature contains a large number of publications on the role of halogen bonding in crystal engineering[55] and in medicinal chemistry,[56] with implications in solution.[57] The contributions of the group of G. Resnati and P. Metrangolo are noteworthy.[58] The significance of the halogen bond in crystal engineering is that it is of a strength that is intermediate between the strong (O−H···O) and weak (C−H···O) hydrogen bonds. Therefore, one may use hydrogen bonds and halogen bonds together to obtain degrees of modular behavior that are not possible with just strong and weak hydrogen bonds.

SUPRAMOLECULAR SYNTHONS AND CRYSTAL DESIGN STRATEGIES

Since crystallization is a kinetic phenomenon, there is a tendency for the most directional interactions to form first in solution (because they are the most long-range) and to remain locked in, even if subsequent associations are more isotropic. The idea of a persistent pattern that is conserved in solution and carries through in the several stages of crystallization leads to its definition as a *supramolecular synthon*. The synthon represents directionality, and the concept of the synthon and how it may be used as a module in retrosynthetic analysis is now deeply embedded into the theory and practice of crystal engineering.[59] Many synthons are known that are mediated by specific anisotropic interactions or by shape filling factors. In the former category are the carboxylic acid and carboxamide dimers, and in the latter are the tetraphenyl and hexaphenyl embraces.[60]

The idea that a crystal structure is built with strong and/or directionally specific interactions leads naturally to the strategy of describing a crystal structure as a network where the molecules are the nodes and the interactions are the node connections. The crystal engineer may now break apart a target crystal structure at the node connections, and what is left are the molecules that will assemble to yield the desired target. This is very similar to the disconnection approach in which an organic chemist breaks critical covalent bonds in a proposed synthesis of a complex target molecule.[61] Retrosynthesis works well in both organic synthesis and crystal engineering because the making and breaking of both covalent bonds and intermolecular interactions are kinetically governed processes. Retrosynthesis is practically intuitive in the design of crystal structures of MOFs and coordination polymers because the linker interactions are very strong.[62] Exceptions to well-formulated strategies therefore need to be carefully examined.

I have already referred to the crucial problem in crystal engineering, namely that a smaller cluster need not be the best model for a larger cluster. The application of synthon theory to crystal engineering works well when smaller supramolecular clusters *are* good approximations to larger clusters. Good—that is, robust—synthons represent well the core features of a crystal structure and encapsulate the essence of crystals in terms of molecular recognition. Thus, it was not difficult to anticipate the crystal structure of 4-ethynylbenzonitrile from the known structures of HCN, cyanoacetylene, and 4-ethynyl-4′-cyanobiphenyl because it was correctly assumed that −C≡C−H···N≡C− is the operational synthon in all cases. The crystal probably grows by an extension of this linear pattern in all cases; the growth unit and the synthon are probably very similar.

The general idea is that a good or robust synthon is one which appears in a large number of cases wherein a particular set of molecular functionalities is present. Suppose functionalities M_1 and M_2 are present in many molecules. Then synthon $M_1\cdots M_2$ (S_1) is robust if it appears in all the molecules, irrespective of other functional groups that are present in these molecules. To paraphrase, the mere presence of M_1 and M_2 ensures the appearance of S_1. Accordingly, the synthon is the device through which information content passes from molecular structure to crystal structure. It is a means of simplifying a crystal structure. The synthon is a model for the entire crystal structure, and it is one which is hopefully representative of the complete crystal. In the most ideal cases, the smallest possible synthons encapsulate the largest amount

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952−9967

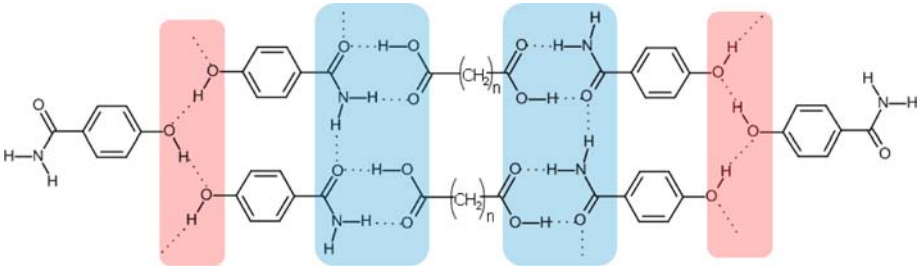

Figure 8. Synthon insulation in cocrystals of 4-hydroxybenzamide and dicarboxylic acids. See ref 64.

of determinative structural information. The entire arena is an energy and structural space of great complexity with local energy minima connected by several intersecting and nonintersecting paths. Good synthons help one to traverse this landscape with maximum efficiency.

Insulation of molecular functionality is a key element in the use of synthon theory to design increasingly complex structures.[63] Suppose other functionalities like M_3 and M_4 are present along with M_1 and M_2 in the above example, and suppose further that other synthons like S_2 ($M_1\cdots M_3$), S_3 ($M_2\cdots M_4$), and S_4 ($M_3\cdots M_4$) are also chemically reasonable. One would like ideally to obtain S_1 without *interference* from S_2 and S_3. When such interference is absent, one can say that the building up process is *modular*; S_1 may further be accompanied by S_4, and indeed the insulated combination of S_1 and S_4 may define new and more complex crystal structures. A good example is provided by the cocrystals of 4-hydroxybenzamide and aliphatic dicarboxylic acids (oxalic through sebacic) (Figure 8).[64]

There is a drive toward cocrystallization in these systems because the acid···amide synthon is more favored than the acid···acid and amide···amide synthons that would have been seen if the compounds crystallized separately. The design strategy assumes an insulation of the resultant acid···amide (S_1) and phenol···phenol (S_4 with $M_3 = M_4$) synthons and follows from a knowledge of crystal structures of γ-quinol, 4,4′-biphenol, and 4-hydroxybenzoic acid. These monocomponent structures contain infinite O−H···O−H···O−H··· cooperative synthons linked with molecular connectors such as phenyl and biphenyl, and supramolecular connectors such as the acid dimer in 4-hydroxybenzoic acid. In the present example, the cocrystal design was based on the anticipation that dicarboxylic acids would form supramolecular connectors with 4-hydroxybenzamide mediated by acid···amide synthons, leaving the O−H···O−H···O−H··· infinite synthons free to form. The short axis of such a structure will be around 5.12 Å, and this is borne out in 2:1 cocrystals of 4-hydroxybenzamide with oxalic, succinic, fumaric, glutaric, and pimelic acids. Hydrated variations of this structure type are seen in the cocrystals obtained with adipic and sebacic acids.

In more difficult cases, complexity of molecular structure may hinder a routine application of synthon theory. Many years ago, we showed that the expected β-As structure (two-dimensional chickenwire) of 4-aminophenol based on networked N−H···O−H recognition is not observed in the isomeric 2- and 3-aminophenols.[26b] However, and as always, an emergent property such as crystal structure becomes nonemergent as the number of examples increases, and in the end we were able to routinely design the N−H···π-based 3-aminophenol structure in a large number of compounds by the expedient of making many compounds wherein the approximate angle between the amino and hydroxyl substituents in the molecular skeleton is 120° (as in 3-aminophenol) rather than 180° (as in 4-aminophenol) and building up a sufficiently large database of crystal structures.[65] Polymorphism, especially synthon polymorphism wherein there are deep-seated structural differences among the polymorphs, poses an obvious problem to the easy application of synthon theory. Finally, when the interactions are weak, the synthons are not so robust and fidelity of crystal structures within the same (molecular) family is poor.

When the hydrogen bonding is strong and predictable, considerable control is possible in the design strategy. Based on Schmidt's topochemical principle for alkene photodimerization, L. R. MacGillivray and co-workers have developed cocrystals of 1,3-dihydroxybenzenes with various dipyridylethylenes in which potentially reactive double bonds are brought to within "photoreacting" distances using the known distance and angle properties of O−H···N hydrogen bonds (Figure 2).[66] A number of diverse examples that illustrate this design strategy have been elaborated.[67] The resorcinol, in effect, provides a template for crystallization and can be removed after the photoreaction. A very similar templating strategy has been used by V. Ramamurthy and co-workers with thiourea as an agent that directs the crystallization of azastilbenes toward a crystal structure that permits 2+2 photoreactivity in the solid state, with N−H···N hydrogen bonds.[68]

The study of cocrystals, or multicomponent molecular crystals, has now seized the imagination of a large number of workers in the crystal engineering field.[69] Considering that crystallization has been a technique for purification for millennia, the question arises as to why cocrystallization of more than one compound even takes place. Enthalpy-driven cocrystallization is characterized by distinctive intermolecular interactions A···B that are more favorable than interactions of the types A···A and B···B in the individual components. Cocrystals have been known to chemists ever since Wöhler crystallized quinhydrone from 1,4-benzoquinone and hydroquinone in 1844,[70a] and a book published in the late 1960s was particularly influential,[70b] but their significance in crystal engineering might have been triggered by the name "cocrystal" that was given to these compounds in the early 1990s.[70c] A seminal contribution by F. H. Herbstein is noteworthy.[70d] In any event, the formation of a cocrystal and the design of a cocrystal structure are strongly influenced by the identification of certain preferred supramolecular synthons. Synthon theory and cocrystallization go hand in hand, and the literature today is full of many diverse examples of crystal engineering of these compounds. Recently, there have been some attempts at the design of ternary cocrystals: the presence of three distinct organic molecules in the same crystal (excluding organic solvent molecules) seems to be counterintuitive.[71] However, the design of a family of ternary cocrystals by C. B. Aakeröy and

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952−9967

co-workers, using the principle of differential donor and acceptor capabilities of various hydrogen-bonded groups, is a noteworthy advance.[72]

A major development in crystal engineering, and one that has considerable practical implications in the pharmaceutical industry, required synthon theory and cocrystals for its development and was put forward by M. J. Zaworotko and Ö. Almarsson in 2004.[2i] It was proposed that an active pharmaceutical ingredient (API), or in simple terms a drug molecule, may be induced to form a binary cocrystal (*pharmaceutical cocrystal*) by suitable complexation with another molecule known as a coformer, which is selected on the basis of complementarity of molecular recognition sites with the API (Figure 9).[73]

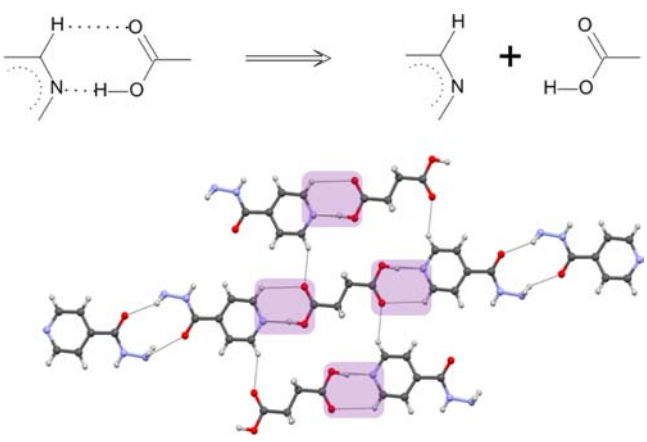

Figure 9. Retrosynthetic scheme for acid−pyridine cocrystal formation. See ref 80i.

Recognition between API and coformer results in the formation of a synthon which is called a *heterosynthon*, because the two components that constitute this synthon arise from quite different molecules and are therefore different. The pharmaceutical cocrystal is designed to optimize a property of interest. If the API is too soluble or too insoluble, a suitable cocrystal is designed so that the solubility is decreased or increased. Other properties that have been optimized by cocrystal formation include shelf life,[74] stability to moisture loss,[75] hardness and brittleness,[76] and bioavailability.[77] It is no exaggeration to say that cocrystal screening has become a very important part of drug development in recent years. This topic has also become a major activity in academic laboratories that specialize in crystal engineering.[78] If crystal engineering required the synthon concept for its development, the use of cocrystals in the pharmaceutical industry needed the concept of the heterosynthon. Identifying the heterosynthon as a particular type of synthon was important because it has helped to focus design strategies for pharmaceutical cocrystals. In the sense that every new field in chemistry needs a link to an application of commercial and practical interest to sustain interest, crystal engineering has truly benefited from the idea of the pharmaceutical cocrystal. Each new field generates a whole new set of ideas, paradigms, and models, which need to be tested in a wide variety of forums, such as industry, to prove their generality. The subject of crystal engineering appeared in its modern manifestation in the late 1980s and the early 1990s, and two main branches of this subject emerged. The field of coordination polymers quickly found its practical application in the gas absorption properties of MOFs.[79] The field of organic crystal engineering found it, a little later in 2004, in the area of pharmaceutical cocrystals and salts.[80]

A major reason for the development of pharmaceutical cocrystals in industry is that they lend themselves well to patent protection.[81] They satisfy well the patentability criteria of novelty, non-obviousness, and utility. A cocrystal almost always satisfies the novelty criterion because it is a new composition of matter substance. Non-obviousness is provided by the fact that the identification of the coformer is based on retrosynthesis and is generally therefore not routine, unlike salt formation wherein an acid is obviously required to make a salt from a base. Utility is generally the only criterion that must be established but it is often easy to demonstrate—usually it is the lack of a particular attribute (solubility, bioavailability, dissolution profile, good shelf life) that has led to the development of a particular pharmaceutical cocrystal. With respect to patentability, cocrystals expand the pharmaceutical space around any given API and consequently the types of advantageous properties that may be accessed.

The issue of non-obviousness is particularly attractive: the design of a cocrystal using synthon theory has all the elements of design and strategy. The choice of a coformer is in this sense understandable, but not completely predictable, in that there is no guarantee that every cocrystal that is designed retrosynthentically will actually be obtained in practice. Cocrystal formation is often truly non-obvious (it cannot be undertaken by a "skilled artisan"), and in such a situation, high-throughput methods are also of relevance. We studied the cocrystal formation of the anti-HIV drug lamivudine, where it was noted that cocrystals were formed either with a logic-driven, synthon-based approach or with high-throughput crystallization.[82] Possibly, a combination of these two entirely different methods may be required to obtain a fully representative set of cocrystals for each API of interest. A number of recent works attest to these broad generalizations.[80c]

High-throughput methods of crystallization have acquired importance in crystal engineering.[83] A large number of factors influence crystallization outcome, and thus the theoretical basis for predicting such outcomes is poorly developed. Accordingly, there is a need for high-throughput crystallization methods that sample variables such as temperature, solvent, concentration, additives, vessel design, time, heating and cooling rates, pH, and mixing rates. This is important in a general sense. A nagging worry in any experimental study is that all possible crystal forms of a single- or a multi-component system have not been isolated. Some of the conclusions we draw about structures and structure design could be biased by the fact that we are not dealing with a statistically significant number of examples. This is of even greater concern today, with our newly emerging ideas about crystal energy landscapes[84] and structural landscapes,[85] and the notion that *a* crystal structure of a compound is just that, a data point. It is not *the* crystal structure of that compound. High-throughput crystallization, accompanied by the related technique of high-throughput crystallography, will go a long way in reducing these concerns.[86] The repetition of a synthon even with high-throughput methods of obtaining crystals will reinforce the confidence of the crystal engineer that these structural units are of the greatest importance in defining and designing crystal structures.

It is now nearly 20 years since the supramolecular synthon concept was introduced into the subject of crystal engineering. It was clear from the earliest days of the subject that crystal structures were difficult to understand in terms of molecular

structures and that some form of simplification is required so that crystal structures may be described in more modular terms. One may well ask why the supramolecular synthon approach has remained in vogue all these years, even as other methods of structure simplification and description have faded in importance and yet other approaches continue to be proposed. One may also ask if it is likely that the synthon approach will continue to be used in the future.

The synthon approach continues to be employed because it is easy to grasp and use. It is sufficiently qualitative in its outlook and incorporates chemical principles, mostly the importance of kinetic factors in crystallization. Because the synthon is a probabilistic descriptor, it does not depend on precise numerical and topological parameters, although recent work shows that many synthons that were proposed on the basis of qualitative chemical arguments are also justified in a computational treatment. The synthon approach needs no crystallographic jargon. It is a practical method of describing molecular crystals, and one that permits a ready identification of molecules that will crystallize to yield a desired network structure. The subjectivity that is inherent in its qualitative nature permits the chemist to use his/her creativity and intuition. It permits a comparison of strong and weak interactions that give topologically and chemically similar synthons (consider the example of fluorobenzene given earlier in this Perspective). The most significant aspect of synthon theory is that rather than viewing a crystal as a molecule → crystal building up process, which would entail the use of accurate atom potentials and force fields, or in other words a computational chemistry approach, it takes an organic synthesis approach and views a crystal as a network, in other words as a retrosynthetic target, to derive the structure of the molecule from that of the crystal, that is crystal ⇒ molecule. Unlike other methods of structure description that are peculiar to either pure organics or coordination polymers, the synthon approach is valid for both classes of compound. Because it is based on chemistry rather than on geometry or topology, the synthon approach is more than just a way of describing crystals. A synthon is not just a static motif. Synthon theory is a way of designing crystals. The prevalence of the supramolecular synthon is not confined to crystals but also to the solution from which the crystal is obtained. For all these reasons, it is likely that the supramolecular synthon will continue to be used in operational crystal engineering for some time to come.

■ TO THE FUTURE

Modern chemistry may be described as the interplay between structure, synthesis, and dynamics, and the future of crystal engineering will most likely look at the molecule → crystal progression in terms of these three themes, and will address related questions that pertain to (i) the robustness and viability of supramolecular synthons and (ii) the fundamental nature of intermolecular interactions. We know about molecular structure, and we can determine a large number of crystal structures, but we still do not know much about how molecules assemble into crystals. The mechanism of crystallization of a molecular solid is one of the Holy Grails of chemistry, and many experiments are being carried out today to elucidate this mechanism.[29d,37,87] There is some consensus that crystallization follows a two-step or a multi-step mechanism rather than the classical one-step mechanism. The intermediacy of those synthons, which occur in high-energy metastable species early in the nucleation and/or crystallization event, is accordingly crucial. Crystallization may be likened in this respect to protein folding and the supramolecular synthon likened to the semicompact random globules in protein folding, with the equivalent in MOF crystallization being the zero charge intermediate proposed by A. Ramanan and M. S. Whittingham.[88] To study the molecule → crystal progression, one may employ crystallography, computation,[89] and spectroscopy.[90] Let us examine each of these techniques.

The use of crystallography as a tool to investigate the course of crystallization is limited to the late stages of this supramolecular reaction. This technique can be employed only for species that have three-dimensional long-range order. The most complex among these are the ones that occur earlier in the reaction coordinate; they may contain much solvent,[91] or they may have multiple molecules in the asymmetric unit,[43a,b] and they are of higher energy. They are formed according to Ostwald's Rule of Stages and, when isolated, constitute a number of polymorphs and pseudopolymorphs.[83a,92] Crystal growth under nonambient conditions—high pressure,[93] low temperature,[94] vacuum sublimation,[95] supercritical liquid as a solvent, shock cooling—may produce crystals that lie in this high-energy region. The numbers of crystals that may be obtained in these more extreme regions of the crystal landscape[96] depend on the imagination of the experimentalist[97] and the techniques that are available and used. Polymorphs of phenylacetylene and 2-, 3-, and 4-fluorophenylacetylene contain robust synthons in their multiple Z′ crystals (Figure 10).[98]

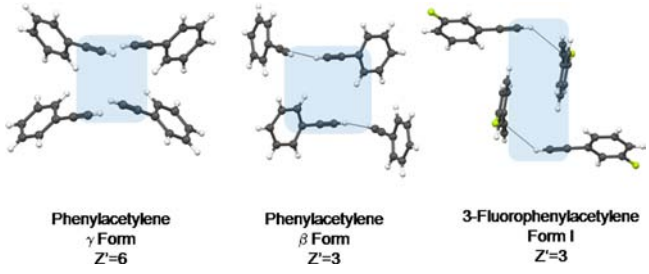

Figure 10. Synthon evolution in high Z′ crystals of substituted phenylacetylenes. See ref 98.

This observation indicates that these synthons could be mediated in nucleation and early stages of crystallization. Sodium saccharin dihydrate is a heavily hydrated multiple Z′ crystal that shows evidence of ordered and disordered domains in the asymmetric unit.[99] It has been suggested that this crystal is a model for a crystal nucleus. It is of sufficient instability (it loses and gains water equally easily)[100] to hint that it is a highly metastable species. Cryocrystallography is expected to become an important technique in crystal engineering because it can be used with compounds (liquids) in which the intermolecular interactions are not so strong.[101] Therefore, there is a greater likelihood of polymorphism and accordingly a better chance of sampling many regions of the crystal landscape. Crystallography does not end with X-ray diffraction of 3D crystals, and it might become possible to trap more exotic species in 2D crystals[102] or with other techniques such as electron diffraction[103] that is now being used in MOF chemistry. The examination of such samples extends the range of structures that can be examined with crystallographic, that is, diffraction-based techniques.

Occasionally, intriguing results provide hints about the crystallization mechanism. We have noted that the crystal structure of 3,4,5-trichlorophenol contains hydrogen-bonded

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952−9967

domains that occur respectively in the structures of 4-chlorophenol and 3,5-dichlorophenol.[104] The former structure seems to be like an amalgam of the two latter structures (Figure 11).

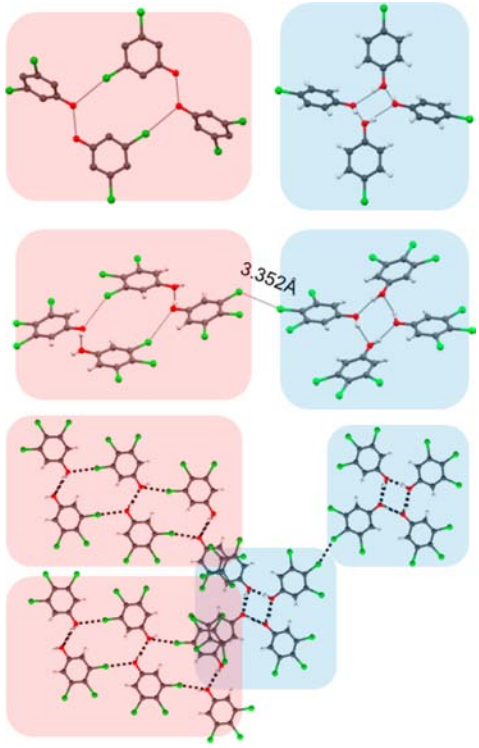

Figure 11. Synthon modularity. Synthons in the native structures of 3,5-dichlorophenol (pink top) and 4-chlorophenol (blue top) are reproduced in 3,4,5-trichlorophenol (middle), and connected with a halogen bond of 3.352 Å. The extended packing of the trichlorophenol (bottom) shows that the construction of the pink and blue modules is largely "blind" to each other.

There are two synthons, I and II, that are connected to each other by a Cl···Cl halogen bond of 3.352 Å. Synthon I is a cooperative hydrogen-bonded finite tetramer, similar to the tetramer in 4-chlorophenol. Synthon II is a Cl···Cl ladder pattern made up of tetramers formed with O−H···O and O···Cl interactions, similar to that seen in 3,5-dichlorophenol. It is almost as if the packing of the synthon I module is "blind" to the 3- and 5-chloro substituents, and that the packing of the synthon II segments is "blind" to the 4-chloro substituent. Such functional group modularity that is accompanied by an equivalent crystal packing modularity is very rare in molecular crystals, but it can, in principle, be useful as far as transferability of motifs is concerned in general terms. In the sense that a synthon is a crystallization precursor, we may speculate that both synthon I and synthon II have some independent existence in solution (as they must in the crystallization of 4-chlorophenol and 3,5-dichlorophenol, respectively). The later stages of nucleation perhaps involve a coming together of these synthons via Cl···Cl halogen bonding. Such a model would imply that O−H···O and O···Cl interactions are stronger than Cl···Cl interactions—a conclusion that is hardly disputable.

One of the consequences of the polymorph screens that are being conducted in the pharmaceutical industry and which have become almost de rigueur in academic crystal engineering groups is that a large numbers of crystal structures may be now available for any given compound. These include the structures obtained by crystallization in nonambient conditions, say, at low and high temperatures, high pressure, and metastable conditions.[105] With all these structures, one can chart out a crystal energy landscape that depicts the later stages of crystallization. This landscape is characterized by hills and valleys, and one may move through the valleys as one transforms one crystal form into another either according to Ostwald's rule or because of thermal transformations. The crystal energy landscape is a profile of the energy changes that take place during the late stages of crystallization of an organic compound, and it consists of the polymorphs of the compound.[84] One might also define, in a corresponding way, a structural landscape that includes, in addition to polymorphs, pseudopolymorphs (solvates), cocrystals, and other chemical entities that are related to the compound in question. In these cases, structural profiling of the crystallization event is possible.[83a,85,92] Solvates often contain synthons "on the way", and they could represent incomplete crystallization situations.[106] The term "masked synthon" has been used for some hydrates by MacGillivray, and this term might be quite appropriate.[107]

Any given compound can be associated with a number of putative crystal structures (say, 100−200) that lie in a small low-energy window (say, 1−2 kcal mol^{-1}) from the global minimum. Most of these structures cannot be accessed experimentally for reasons that are not fully clear (say, a dimer structure for acetic acid). These structures are generally of slightly higher energy (a few may be of lower energy) than the experimental structure. These structures can be, however, captured computationally through the technique of crystal structure prediction (CSP) that is based on force fields and needs a space group as input. CSP is one of the best computational tools to map the various structural possibilities that are available to the molecule.[108] It has been used in the blind tests that have been conducted from time to time. In these tests, there has been an emphasis on obtaining the experimental crystal structure from nothing more than the structural formula of a test molecule. Such a method assumes that the lowest energy structure obtained computationally is the experimental structure. The better the choice of the force field, the more "correct" the final answer is supposed to be. "Wrong" answers are usually ascribed to inappropriate force fields. There is some question as to whether CSP and crystal engineering are one and the same, or CSP is a subset of crystal engineering, or the two are entirely distinct, even mutually exclusive?[16b] To the mind of this author, these endeavors are parallel approaches to a larger question, if crystal engineering is taken as an experimental route, aided maybe with database research, toward obtaining functional crystals. If, however, *crystal engineering* is the larger theme in itself, then there is little doubt that CSP is a subset of crystal engineering. This is because CSP is an energy probing of the landscape, which can lead to the elucidation of crystallization pathways, which in turn approaches the Holy Grail of crystal engineering. In any event, it is the opinion of this author that CSP is rapidly becoming a part of the toolkit of the experimental crystal engineer. Still, it is clear that in CSP, as currently practiced, the higher energy structures with poorer ranks are largely ignored.

By altering the chemical substitution in certain (minor) ways or at certain (innocuous) positions, it is possible that some of these hitherto inaccessible structures can be experimentally captured.[109,110] The F-atom is just a little larger than the H-

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952−9967

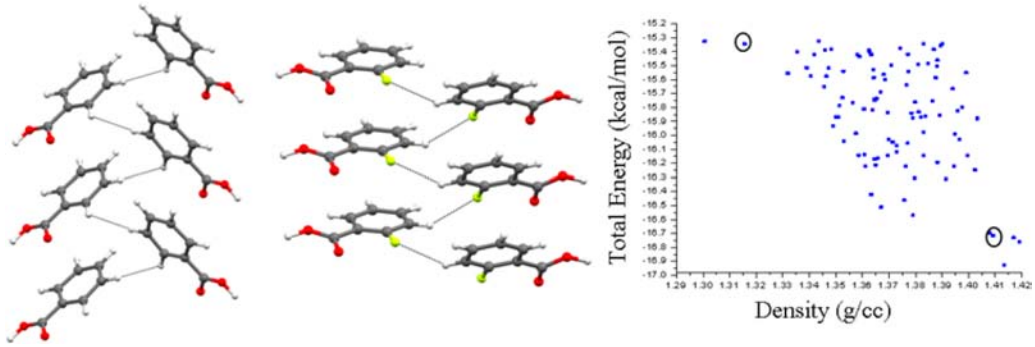

Figure 12. Structural landscape of benzoic acid. The experimental structure is located in the bottom right-hand corner of the CSP energy density plot and is ranked 5th lowest in energy. If the experimental structure of 2-fluorobenzoic acid is altered such that an H-atom replaces the F-atom, a structure is obtained that approximates the 99th ranked structure in the plot in the top left corner. A collection of such computationally simulated structures with an experimental counterpart among the substituted fluorobenzoic acids constitutes the landscape. See ref 110.

atom. However, its electronic effects on the crystal structure are quite different from those of the latter. We showed that F-substitution in benzoic acid reveals crystal structures that are high-energy data points in the structural landscape of benzoic acid itself. For example, 2- and 3-fluorobenzoic acids have experimental crystal structures in which the carboxyl dimers are held in helical patterns with C−H···F hydrogen bonds (Figure 12).

We found that these crystal structures occur in the CSP results of benzoic acid itself: they appear in the 99th position. Similarly, the crystal packing in 4-fluorobenzoic acid corresponds to the 55th position for benzoic acid. For comparison, the experimental crystal structure of benzoic acid occurs in the 5th position in the CSP. A collection of experimental crystal structures of derivatives that are closely related to, for example, benzoic acid constitutes a structural landscape of benzoic acid. The merit of this method is that it can access structures of interest without particularly accurate force fields. There is much overlap between the CSP results of benzoic acid and of its monofluorinated derivatives. A chemical substitution is a kind of force field change; all that changes is the energy ordering of the structures. What is more significant is that all the compounds that lie in a given landscape constitute a closed group. Their crystal structures may be permuted among themselves and any of these structures is, in principle, reasonable for any of these compounds. Structure permutability is the criterion for inclusion of a compound in the landscape.

The very final stages of crystallization involve the fine-tuning of the supramolecular assembly of smaller clusters which are themselves organized with the basic and modular synthons. In this regard, a synthon is typically taken to be a zero- or one-dimensional module of short-range character. The design of a 3D crystal structure begins with locating the short-range synthon elements from different molecules and then letting these supramolecular elements organize themselves into a long-range geometry characteristic of the molecules themselves. This directs the assembly of the final crystal structure. In the synthon approach, as used today, not much attention is paid to the way the synthon, which is driven by 1D interactions, is assembled into the final 3D crystal structure. In the final stages of crystal assembly, the interactions defining the structure are very weak and could often have little resemblance to their nature in their original milieu. At this stage, packing considerations could become important.

With this background, P. Ganguly and I attempted a synthesis of the geometrical and chemical models for crystal assembly, in which we defined the Long-range Synthon Aufbau Modules (LSAMs) by which short-range synthons are assembled to form long-range Aufbau modules which are then further structured to form the 3D crystal structure.[27] In this approach, the last stages of the all-important space-group-defining assembly of the crystal involve weak packing interactions. In this regard, there are similarities to the approach of A. Gavezzotti, who defined structure-defining clusters with some appropriate translational symmetry.[111] The LSAMs are late synthons (Figure 13).

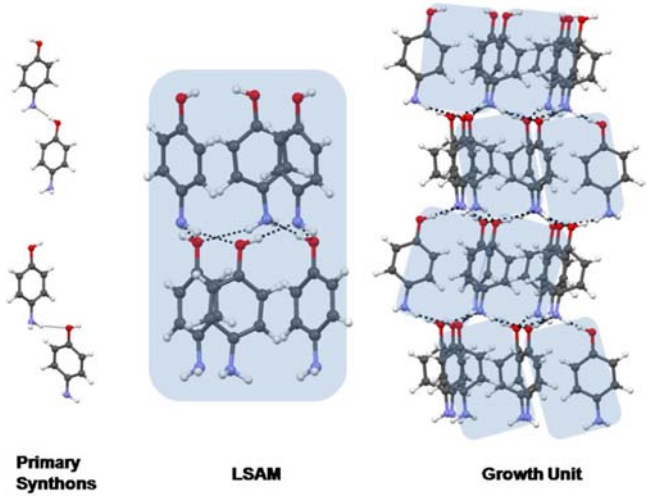

Figure 13. Long-range Synthon Aufbau Modules (LSAMs) in 4-aminophenol could be the link between primary synthons and growth units. See ref 26a for a basic description of the crystal structure.

They may have little relationship with or influence from the strong interactions that lead to the early synthons that dominate short-range packing. The LSAM concept was illustrated with the family of fluorobenzenes $C_6H_nF_{6-n}$ ($6 \geq n \geq 0$). Crystal assembly is initiated by forming LSAMs that carry the imprint of the synthons. The early synthons are formed with C−H···F interactions. These synthons do not, in themselves, yield a 3D structure. They have to be assembled into a 3D crystal following Aufbau principles. Figure 13 shows a typical assembly through an LSAM.

The LSAM model is general and is aimed at highlighting the symbiotic manner in which shape and chemical factors manifest themselves in the recognition involved for an ordered

dx.doi.org/10.1021/ja403264c | J. Am. Chem. Soc. 2013, 135, 9952−9967

organization of matter. The phenyl rings in these fluorobenzenes can represent any complex molecule, including the so-called secondary building units (SBUs) or point zero charge molecules (PZCs) that are used for the discussion of open framework structures. As with SBUs or PZCs, the LSAMs are transient species en route to crystallization. Examination of crystal structures may not be sufficient to identify the fundamental LSAMs since they may undergo reconstruction in the final crystal; this point has been made by K. Biradha.[112] However, because of the long-range nature of the LSAMs, the dynamics of their reorientation or inherent conformational changes are likely to be slow as they become integrated into the crystalline framework; therefore, the character of the LSAMs may well be maintained in the final crystal structure. As such, the LSAMs may provide the much sought after link between supramolecular synthons and R. J. Davey's crystal growth units.

Would experimental verification of LSAMs be possible? As one moves higher along the reaction coordinate, one moves out of the crystallographic domain and into that of spectroscopy. Do small early synthons persist in the final crystal? This question was raised earlier in this Perspective. Davey has commented that if there is such a connection, then stable clusters in the intermediate stages should also have the same structure and the one-step classical nucleation theory (CNT) applies. If such a connection does not hold, then a two-step mechanism for crystallization may need to be invoked. There is some evidence for this latter situation: Small clusters of phenylacetylene as examined by IR spectroscopy in the gas phase do not have a counterpart in the crystal structures of polymorphs of this compound. Small, stable synthons are always formed early in the molecular assembly process. It should be possible, in principle, to detect their presence in solution in favorable cases, when the CNT mechanism operates. IR studies by Davey show precursor dimer and catemer synthons in solutions of tetrolic acid that lead to the respective polymorphs.[113] NMR studies of *p*-acetanisidide in chloroform solution show N−H···O═C hydrogen bonds that are seen in the crystal structure.[114] Unpublished NMR work by our group shows that 1,2,3-trichlorobenzene molecules are stacked in $CDCl_3$ solution in an antiparallel fashion, as in the crystal. Davey has used crystallography and spectroscopy to show a similarity in the local environment of trimesic acid in solution and in crystals of its metastable trisolvate with DMSO.[115] The connection between heavily solvated crystals and the structures of prenucleation aggregates in solution has been discussed. We have described the crystal structure of sodium saccharin dihydrate as a model for a crystal nucleus. Davey has criticized this interpretation on the grounds that no stable crystal structure can be a model for a nucleus. However, we maintain that if the structure is sufficiently disordered, or solvated, or has a very large unit cell (all these conditions apply for sodium saccharin dihydrate), then the crystal structure represents a metastable high-energy intermediate that is close enough to the nucleus. Of course, no one is ever going to observe a crystal nucleus in the same way, as no one can ever observe a transition state directly. But spectroscopy offers a good preview of crystallization in that small synthons and LSAMs may be observed in special instances.

Crystal engineering attempts to design new solids with desired physical and chemical properties. This Perspective is written from the viewpoint of synthon theory and is not directly aimed at property engineering. Any property that is a function of crystal structure can be engineered using the principles of crystal engineering. A number of papers[116] have elaborated on the engineering of crystals that are able to undergo the 2+2 photodimerization reaction of olefins, pioneered by Schmidt. Elaborate molecular syntheses, such as of ladderane compounds, have been engineered by MacGillivray using synthon-based retrosynthesis.[117] The design of crystal structures that display conductivity,[118] second harmonic generation,[119] luminescence,[120] ionic liquid behavior,[121] ferroelectricity,[122] and elasticity,[123] and of crystals that can be used in separation technologies,[124] has been described and more work is surely expected in the future. Discussions of porosity are usually centered around MOFs, COFs, and coordination polymers, but there is a surely growing body of work on organic molecular crystals that show significant guest adsorption and release properties. Characterization techniques such as nanoindentation have been recently applied to molecular crystals and can probe the nature and strength of intermolecular interactions and differences between polymorphs.[125] The recently discovered elusive second polymorph of aspirin is much softer than the more common crystal form of the compound that has been known for more than a century. Nanoindentation explains this softness in terms of easy slippage of layer planes.[126] Nanoindentation and nanoscratching techniques have given experimental results that question the basic assumptions of Schmidt's topochemical principle. G. Kaupp has proposed that organic solid-state reactions take place with a considerable amount of molecular movement. A reconciliation of the viewpoints of Schmidt and Kaupp is still awaited because there is experimental evidence for both viewpoints.[127] The entire matter of mechanochemistry has been important in recent years, and developments not only reach back to history but also can speak to the issue of understanding mechanisms of crystallization (albeit without aid of solvent). There is also recent work in the field of induced morphological changes to single crystals, for example, crystal bending.[128] Plastic and elastic deformation of molecular crystals,[123,129] and some of their mechanical properties such as their explosive character, very much capture the imagination of chemists and interested laypersons because these phenomena emphasize not only that chemistry is a subject where the researcher can make the object of his/her research but also that chemistry is all about seeing, touching, smelling, and hearing. The subject of crystal engineering is like the rest of chemistry—an assault on the senses—and it allows for the limitless possibilities of property design based on crystal structure design.

■ CONCLUSIONS

Crystal engineering has grown and developed into a major activity within structural chemistry. The creative and intellectual challenge in designing and constructing a new crystal structure is similar to that in organic synthesis. The understanding of new intermolecular interactions is a fundamental problem that needs to be handled with crystallography, spectroscopy, and computation. The engineering of properties is still a largely uncharted territory. This Perspective concentrates on the design of organic molecular crystals and the application of synthon theory to study the building up of crystals from molecules. However, enough is already known that reveals that the principles of organic crystal engineering may be profitably employed in the design of coordination polymers and metal−organic frameworks.

AUTHOR INFORMATION

Corresponding Author

desiraju@sscu.iisc.ernet.in

Notes

The author declares no competing financial interest.

ACKNOWLEDGMENTS

I thank Arijit Mukherjee, Srinu Tothadi, and Ritesh Dubey for their assistance in the preparation of this manuscript. I acknowledge financial support from the DST (New Delhi) in the form of a J. C. Bose fellowship.

REFERENCES

(1) Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: Amsterdam, 1989.

(2) (a) Schmidt, G. M. J.; et al. In *Solid State Photochemistry*; Ginsburg, D., Ed.; Verlag Chemie: New York, 1976. (b) Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1978**, *100*, 2838−2844. (c) Thomas, J. M. *Nature* **1981**, *289*, 633−634. (d) Copp, S. B.; Subramanian, S.; Zaworotko, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 8719. (e) Aakeröy, C. B.; Seddon, K. R. *Chem. Soc. Rev.* **1993**, *22*, 397−407. (f) Bishop, R. *Chem. Soc. Rev.* **1996**, *25*, 311−319. (g) Nassimbeni, L. R. *Acc. Chem. Res.* **2003**, *36*, 631−637. (h) Braga, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2−11. (i) Almarsson, Ö.; Zaworotko, M. J. *Chem. Commun.* **2004**, 1889−1896. (j) Hosseini, M. W. *Acc. Chem. Res.* **2005**, *38*, 313−323. (k) Desiraju, G. R.; Vittal, J. J.; Ramanan, A. *Crystal Engineering: A Text Book*; World Scientific: Singapore, 2011. (l) Bond, A. D. *CrystEngComm* **2012**, *14*, 2363−2366. (m) Cooper, A. I. *Angew. Chem., Int. Ed.* **2012**, *51*, 7892−7894.

(3) Dunitz, J. D. *X-Ray Analysis and the Structure of Organic Molecules*; Cornell University Press: Ithaca, NY, 1979.

(4) Bragg, W. H. *Proc. Phys. Soc. London* **1921**, *34*, 33−50.

(5) Bernal, J. D.; Crowfoot, D. *J. Chem. Soc.* **1935**, 93−100.

(6) (a) Robertson, J. M.; White, J. G. *J. Chem. Soc.* **1945**, 607−617. (b) Robertson, J. M.; White, J. G. *J. Chem. Soc.* **1947**, 358−368. (c) Robertson, J. M. *Proc. R. Soc. London* **1951**, *A207*, 101−110.

(7) Pepinsky, R. *Phys. Rev.* **1955**, *100*, 971.

(8) (a) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 1996−2000 and the succeeding papers. (b) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647−678.

(9) (a) Cohen, M. D.; Ludmer, Z.; Thomas, J. M.; Williams, J. O. *Proc. R. Soc. London A* **1971**, *324*, 459−468. (b) Thomas, J. M. *Philos. Trans. R. Soc. London, Ser. A* **1974**, *277*, 251.

(10) Kitaigorodskii, A. I. *Molecular Crystals and Molecules*; Academic Press: New York, 1973.

(11) Sarma, J. A. R. P.; Desiraju, G. R. *Acc. Chem. Res.* **1986**, *19*, 222−228.

(12) (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120−126. (b) Ward, M. D.; Hollingsworth, M. D. *Chem. Mater.* **1994**, *6*, 1093.

(13) (a) Hoskins, B. F.; Robson, R. *J. Am. Chem. Soc.* **1989**, *111*, 5962−5964. (b) Hoskins, B. F.; Robson, R. *J. Am. Chem. Soc.* **1990**, *112*, 1546−1554. (c) Robson, R. *Dalton Trans.* **2008**, *38*, 5113−5131.

(14) Powell, H. M. *J. Chem. Soc.* **1948**, 61−73.

(15) Ermer, O. *J. Am. Chem. Soc.* **1988**, *110*, 3141−3154.

(16) (a) Eddaoudi, M.; Moler, D. B.; Li, H. L.; Chen, B. L.; Reinecke, T. M.; O'Keeffe, M.; Yaghi, O. M. *Acc. Chem. Res.* **2001**, *34*, 319−330. (b) Moulton, B.; Zaworotko, M. J. *Chem. Rev.* **2001**, *101*, 1629−1658. (c) Biradha, K.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3392−3395. (d) Kitagawa, S.; Kitaura, R.; Noro, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2334. (e) Vittal, J. J. *Coord. Chem. Rev.* **2007**, *251*, 1781−1795.

(17) (a) Haleblian, J.; McCrone, W. *J. Pharm. Sci.* **1969**, *58*, 911−929. (b) Bilton, C.; Howard, J. A. K.; Madhavi, N. N. L.; Nangia, A.; Desiraju, G. R.; Allen, F. H.; Wilson, C. C. *Chem. Commun.* **1999**, 1675−1676. (c) Bernstein, J.; Davey, R. J.; Henck, J.-O. *Angew. Chem., Int. Ed.* **1999**, *38*, 3440−3461.

(18) Nangia, A. *Cryst. Growth. Des.* **2006**, *6*, 2−4.

(19) (a) Desiraju, G. R. *CrystEngComm* **2003**, *5*, 466−467. (b) Dunitz, J. D. *CrystEngComm* **2003**, *5*, 506. (c) Aitipamula, S.; Banerjee, R.; Bansal, A. K.; Biradha, K.; Cheney, M. L.; Choudhury, A. R.; Desiraju, G. R.; Dikundwar, A. G.; Dubey, R.; Duggirala, N.; Ghogale, P. P.; Ghosh, S.; Goswami, P. K.; Goud, N. R.; Jetti, K. R. K.; Karpinski, P.; Kaushik, P.; Kumar, D.; Kumar, V.; Moulton, B.; Mukherjee, A.; Mukherjee, G.; Myerson, A. S.; Puri, V.; Ramanan, A.; Rajamannar, T.; Reddy, C. M.; Rodriguez-Hornedo, N.; Rogers, R. D.; Row, T. N. G.; Sanphui, P.; Shan, N.; Shete, G.; Singh, A.; Sun, C. C.; Swift, J. A.; Thaimattam, R.; Thakur, T. S.; Thaper, R. K.; Thomas, S. P.; Tothadi, S.; Vangala, V. R.; Variankaval, N.; Vishweshwar, P.; Weyna, D. R.; Zaworotko, M. J. *Cryst. Growth Des.* **2012**, *12*, 2147−2152.

(20) (a) Biradha, K.; Ramanan, A.; Vittal, J. J. *Cryst. Growth Des.* **2009**, *9*, 2969−2970. (b) Batten, S. R.; Champness, N. R.; Chen, X.-M.; Garcia-Martinez, J.; Kitagawa, S.; Öhrström, L.; O'Keeffe, M.; Suh, M. P.; Reedijk, J. *CrystEngComm* **2012**, *14*, 3001−3004.

(21) Desiraju, G. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 52−59.

(22) Metrangolo, P.; Resnati, G. *Cryst. Growth Des.* **2012**, *12*, 5835−5838.

(23) Merz, K. *Acta Crystallogr.* **2003**, *C59*, o65.

(24) Thalladi, V. R.; Goud, B. S.; Hoy, V. J.; Allen, F. H.; Howard, J. A. K.; Desiraju, G. R. *Chem. Commun.* **1996**, 401−402.

(25) Desiraju, G. R. *Curr. Sci.* **2005**, *88*, 374−380.

(26) (a) Ermer, O.; Eling, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 925−944. (b) Allen, F. H.; Hoy, V. J.; Howard, J. A. K.; Thalladi, V. R.; Desiraju, G. R.; Wilson, C. C.; McIntyre, G. J. *J. Am. Chem. Soc.* **1997**, *119*, 3477−3480.

(27) Ganguly, P.; Desiraju, G. R. *CrystEngComm* **2010**, *12*, 817−833.

(28) (a) Waldstein, P.; Blatz, L. A. *J. Phys. Chem.* **1967**, *71*, 2271−2276. (b) Mooij, W. T. M.; van Eijck, B. P.; Price, S. L.; Verwer, P.; Kroon, J. *J. Comput. Chem.* **1998**, *19*, 459−474.

(29) (a) Davey, R. J.; Dent, G.; Mughal, R. K.; Parveen, S. *Cryst. Growth Des.* **2006**, *6*, 1788−1796. (b) Kulkarni, S. A.; McGarrity, E. S.; Meekes, H.; ter Horst, J. H. *Chem. Commun.* **2012**, *48*, 4983−4985. (c) Hunter, C. A.; McCabe, J. F.; Spitaleri, A. *CrystEngComm* **2012**, *14*, 7115−7117. (d) Davey, R. J.; Schroeder, S. L. M.; ter Horst, J. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 2166−2179.

(30) (a) Williams-Seton, L.; Davey, R. J.; Lieberman, H. F. *J. Am. Chem. Soc.* **2004**, *126*, 13347−13353. (b) Crespo-Otero, R.; Sanchez-Garcia, E.; Suardiaz, R.; Montero, L. A.; Sander, W. *Chem. Phys.* **2008**, *353*, 193−201. (c) Sander, W.; Roy, S.; Polyak, I.; Ramirez-Anguita, J. M.; Sanchez-Garcia, E. *J. Am. Chem. Soc.* **2012**, *134*, 8222−8230. (d) Desiraju, G. R.; Johnson, M.; Sander, W. *ChemPhysChem* **2013**, *14*, 1−4.

(31) Desiraju, G. R. *Angew. Chem., Int. Ed.* **1995**, *34*, 2311−2327.

(32) Chakraborty, D.; Patey, G. N. *J. Phys. Chem. Lett.* **2013**, *4*, 573−578.

(33) Allen, F. H.; Motherwell, W. D. S.; Raithby, P. R.; Shields, G. P.; Taylor, R. *New J. Chem.* **1999**, *23*, 25−34.

(34) Nishio, M. *CrystEngComm* **2004**, *6*, 130−158.

(35) Paulini, R.; Muller, K.; Diederich, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1788−1805.

(36) (a) Gavezzotti, A.; Simonetta, M. *Acta Crystallogr.* **1976**, *A32*, 997−1001. (b) Whitesell, J. K.; Davis, R. E.; Saunders, L. L.; Wilson, R. J.; Feagins, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 3267−3270.

(37) Metrangolo, P.; Neukirch, H.; Pillati, T.; Resnati, G. *Acc. Chem. Res.* **2005**, *38*, 386−395.

(38) (a) Katz, M. J.; Sakai, K.; Leznoff, D. B. *Chem. Soc. Rev.* **2008**, *37*, 1884−1895. (b) Ovens, J. S.; Truong, K. N.; Leznoff, D. B. *Dalton Trans.* **2012**, *41*, 1345−1351.

(39) (a) Omary, M. A.; Webb, T. R.; Assefa, Z.; Shankle, G. E.; Patterson, H. H. *Inorg. Chem.* **1998**, *37*, 1380−1386. (b) Che, C. M.; Tse, M. C.; Chan, M. C. W.; Cheung, K. K.; Phillips, D. L.; Leung, K. H. *J. Am. Chem. Soc.* **2000**, *122*, 2464−2468.

(40) Dougherty, D. A. *Science* **1996**, *271*, 163−168.

(41) (a) Dunitz, J. D.; Gavezzotti, A. *Cryst. Growth Des.* **2005**, *5*, 2180−2189. (b) Dunitz, J. D.; Gavezzotti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1766−1787. (c) Dunitz, J. D.; Gavezzotti, A. *Cryst. Growth*

Des. **2012**, *12*, 5873−5877. (d) Shishkin, O. V.; Medvediev, V. V.; Zubatyuk, R. I. *CrystEngComm* **2013**, *15*, 160−167.
(42) (a) Roy, S.; Banerjee, R.; Nangia, A.; Kruger, G. J. *Chem. Eur. J.* **2006**, *12*, 3777−3788. (b) Desiraju, G. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 8342−8356.
(43) (a) Desiraju, G. R. *CrystEngComm* **2007**, *9*, 91−92. (b) Steed, J. W. *CrystEngComm* **2007**, *5*, 328−330. (c) Nangia, A. *Acc. Chem. Res.* **2008**, *41*, 595−604. (d) Sathishkumar, R.; Mahapatra, S.; Thakur, T. S.; Desiraju, G. R. *Curr. Sci.* **2010**, *99*, 1807−1811.
(44) Sreekanth, B. R.; Vishweshwar, P.; Vyas, K. *Chem. Commun.* **2007**, *23*, 2375−2377.
(45) Mukherjee, A.; Desiraju, G. R. *Chem. Commun.* **2011**, *47*, 4090−4092.
(46) Reichenbächer, K.; Süss, H. I.; Hulliger, J. *Chem. Soc. Rev.* **2005**, *34*, 22−30.
(47) Thalladi, V. R.; Weiss, H.-C.; Bläser, D.; Boese, R.; Nangia, A.; Desiraju, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 8702−8710.
(48) Dunitz, J. D.; Schweizer, W. B. *Chem. Eur. J.* **2006**, *12*, 6804−6815.
(49) Thakur, T. S.; Kirchner, M. T.; Bläser, D.; Boese, R.; Desiraju, G. R. *CrystEngComm* **2010**, *12*, 2079−2085.
(50) (a) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76. (b) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. *Pure Appl. Chem.* **2011**, *83*, 1637−1641. (c) Desiraju, G. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 52−59.
(51) (a) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441−449. (b) Bernstein, J. *Cryst. Growth Des.* **2013**, *13*, 961−964.
(52) Desiraju, G. R. *Cryst. Growth Des.* **2011**, *11*, 896−898.
(53) Robertson, J. M. *Organic Crystals and Molecules*; Cornell University Press: Ithaca, NY, 1953; pp 224−239.
(54) (a) Brammer, L.; Bruton, E. A.; Sherwood, P. *Cryst. Growth Des.* **2001**, *1*, 277−290. (b) Raatikainen, K.; Rissanen, K. *CrystEngComm* **2009**, *11*, 750−752. (c) Legon, A. C. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7736−7747.
(55) (a) Saha, B. K.; Nangia, A.; Jaskólski, M. *CrystEngComm* **2005**, *7*, 355−358. (b) Aakeröy, C. B.; Fasulo, M.; Schultheiss, N.; Desper, J.; Moore, C. *J. Am. Chem. Soc.* **2007**, *129*, 13772−13773. (c) Clarke, S. M.; Friščić, T.; Jones, W.; Mandal, A.; Sun, C.; Parker, J. E. *Chem. Commun.* **2011**, *47*, 2526−2528.
(56) (a) Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16789−167894. (b) Jentzsch, A. V.; Emery, D.; Mareda, J.; Nayak, S. K.; Metrangolo, P.; Resnati, G.; Sakai, N.; Matile, S. *Nat. Commun.* **2012**, *3*, 905−913.
(57) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. *Chem. Soc. Rev.* **2013**, *42*, 1667−1680.
(58) (a) Metrangolo, P.; Resnati, G. *Chem. Eur. J.* **2001**, *7*, 2511−2519. (b) Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6114−6127. (c) Metrangolo, P.; Resnati, G. *Science* **2008**, *321*, 918−919.
(59) (a) Bishop, R. *Chem. Soc. Rev.* **1996**, *25*, 311−319. (b) Marjo, C. E.; Scudder, M. L.; Craig, D. C.; Bishop, R. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2099−2104. (c) Desiraju, G .R. In *Stimulating concepts in chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, S., Eds.; Wiley-VCH: Weinheim, 2000; pp293−306. (d) Angeloni, A.; Orpen, A. G. *Chem. Commun.* **2001**, 343−344. (e) Dolling, B.; Gillon, A. L.; Orpen, A. G.; Starbuck, J.; Wang, X.-M. *Chem. Commun.* **2001**, 567−568. (f) Collings, J. C.; Roscoe, K. P.; Thomas, R.L.; Batsanov, A. S.; Stimson, L. M.; Howard, J. A. K.; Marder, T. B. *New J. Chem.* **2001**, *25*, 1410−1417. (g) Anderson, K. M.; Goeta, A. E.; Steed, J. W. *Cryst. Growth Des.* **2008**, *8*, 2517−2524. (h) Mukherjee, A.; Tothadi, S.; Chakraborty, S.; Ganguly, S.; Desiraju, G. R. *CrystEngComm* **2013**, *15*, 4640−4654.
(60) (a) Scudder, M.; Dance, I. *CrystEngComm* **2001**, *12*, 1−4. (b) Dance, I.; Scudder, M. *CrystEngComm* **2009**, *11*, 2233−2247.
(61) Warren, S.; Wyatt, P. *Organic Synthesis: The Disconnection Approach*; John Wiley & Sons: Chichester, UK, 2008.
(62) (a) Delgado-Friedrichs, O.; O'Keeffe, M. *Acta Crystallogr.* **2009**, *A65*, 360−363. (b) O'Keeffe, M. *Chem. Soc. Rev.* **2009**, *38*, 1215−1217. (c) O'Keeffe, M.; Yaghi, O. M. *Chem. Rev.* **2012**, *112*, 675−702.
(63) Sharma, C. V. K.; Panneerselvam, K.; Pilati, T.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1992**, 832−833.
(64) Tothadi, S.; Desiraju, G. R. *Cryst. Growth Des.* **2012**, *12*, 6188−6198.
(65) (a) Vangala, V. R.; Bhogala, B. R.; Dey, A.; Desiraju, G. R.; Broder, C. K.; Smith, P. S.; Mondal, R.; Howard, J. A. K.; Wilson, C. C. *J. Am. Chem. Soc.* **2003**, *125*, 14495−14509. (b) Dey, A.; Desiraju, G. R.; Mondal, R.; Howard, J. A. K. *Chem. Commun.* **2004**, 2528−2529.
(66) MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 7817−7818.
(67) (a) MacGillivray, L. R.; Papaefstathiou, G. S.; Reid, J. L.; Ripmeester, J. A. *Cryst. Growth Des.* **2001**, *1*, 373−375. (b) Sokolov, A. N.; Friscic, T.; Blais, S.; Ripmeester, J. A.; MacGillivray, L. R. *Cryst. Growth Des.* **2006**, *6*, 2427−2428. (c) MacGillivray, L. R.; Papaefstathiou, G. S.; Friščić, T.; Hamilton, T. D.; Bučar, D.-K.; Chu, Q.; Varshney, D. B.; Georgiev, I. G. *Acc. Chem. Res.* **2008**, *41*, 280−291. (d) Friščić, T.; MacGillivray, L. R. *Chem. Commun.* **2009**, 773−775. (e) Lee, E.; Ju, H.; Lee, S. S.; Park, K.-M. *Cryst. Growth Des.* **2013**, *13*, 992−995.
(68) Bhogala, B. R.; Captain, B.; Parthasarathy, A.; Ramamurthy, V. *J. Am. Chem. Soc.* **2010**, *132*, 13434−13442.
(69) (a) Childs, S. L.; Chyall, L. J.; Dunlap, J. T.; Smolenskaya, V. N.; Stahly, B. C.; Stahly, G. P. *J. Am. Chem. Soc.* **2004**, *126*, 13335−13342. (b) Bučar, D.-K.; Henry, R. F.; Lou, X.; Duerst, R. W.; Borchardt, T. B.; MacGillivray, L. R.; Zhang, G. G. Z. *Mol. Pharmaceutics* **2007**, *4*, 339−346. (c) Sreekanth, B. R.; Vishweshwar, P.; Vyas, K. *Chem. Commun.* **2007**, 2375−2377. (d) Reddy, L. S.; Bhatt, P. M.; Banerjee, R.; Nangia, A.; Kruger, G. J. *Chem. Asian J.* **2007**, *2*, 505−513. (e) Santra, R.; Ghosh, N.; Biradha, K. *New J. Chem.* **2008**, *32*, 1673−1676. (f) Stahly, G. P. *Cryst. Growth Des.* **2009**, *9*, 4212−4229. (g) Bernstein, J.; Novoa, J. J.; Boese, R.; Cirkel, S. A. *Chem. Eur. J.* **2010**, *16*, 9047−9055. (h) Kirchner, M. T.; Bläser, D.; Boese, R. *Chem. Eur. J.* **2010**, *16*, 2131−2146. (i) Moorthy, J. N.; Natarajan, P.; Venugopalan, P. *Chem. Commun.* **2010**, *46*, 3574−3576. (j) Seaton, C. C. *CrystEngComm* **2011**, *13*, 6583−6592.
(70) (a) Wöhler, F. *Ann. Chem. Pharm.* **1844**, *51*, 145−163. (b) Foster, R. *Organic Charge-Transfer Complexes*; Academic: London, 1969. (c) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426. (d) Herbstein, F. H. *Crystalline Molecular Complexes and Compounds* (2 volumes); Oxford University Press: Oxford, 2005.
(71) Tothadi, S.; Mukherjee, A.; Desiraju, G. R. *Chem. Commun.* **2011**, *47*, 12080−12082.
(72) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3240−3242.
(73) Fleischman, S. G.; Kuduva, S. S.; McMahon, J. A.; Moulton, B.; Walsh, R. D. B.; Rodriguez-Hornedo, N.; Zaworotko, M. J. *Cryst. Growth Des.* **2003**, *3*, 909−919.
(74) Babu, N. J.; Sanphui, P.; Nangia, A. *Chem. Asian J.* **2012**, *7*, 2274−2285.
(75) (a) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Cryst. Growth Des.* **2005**, *5*, 1013−1021. (b) Cherukuvada, S.; Babu, N. J.; Nangia, A. *J. Pharm. Sci.* **2011**, *100*, 3233−3244.
(76) Karki, S.; Friščić, T.; Fábián, L.; Laity, P. R.; Day, G. M.; Jones, W. *Adv. Mater.* **2009**, *21*, 3905−3909.
(77) Smith, A. J.; Kavuru, P.; Wojtas, L.; Zawarotko, M. J.; Shytle, R. D. *Mol. Pharm.* **2011**, *8*, 1867−1876.
(78) (a) Price, C. P.; Grzesiak, A. L.; Matzger, A. J *J. Am. Chem. Soc.* **2005**, *127*, 5512−5517. (b) Caira, M. R. *Mol. Pharmacol.* **2007**, *4*, 310−316. (c) Babu, N. J.; Nangia, A. *Cryst. Growth Des.* **2011**, *11*, 2662−2679.
(79) (a) Li, J.-R.; Kuppler, R. J.; Zhou, H.-C. *Chem. Soc. Rev.* **2009**, *38*, 1477−1504. (b) D'Alessandro, D. M.; Smit, B.; Long, J. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6058−6082. (c) Panda, T.; Pachfule, P.; Chen, Y.; Jiang, J.; Banerjee, R. *Chem. Commun.* **2011**, *47*, 2011.

(80) (a) Wouters, J.; Quéré, L. *Pharmaceutical Salts and Cocrystals*; RSC Publishing: Cambridge, UK, 2012. (b) Rodríguez-Spong, B.; Price, C. P.; Jayasankar, A.; Matzger, A. J.; Rodríguez-Hornedo, N. *Adv. Drug Delivery Rev.* **2004**, *56*, 241−274. (c) Morissette, S. L.; Almarsson, Ö.; Peterson, M. L.; Remenar, J. F.; Read, M. J.; Lemmo, A. V.; Ellis, S.; Cima, M. J.; Gardner, C. R. *Adv. Drug Delivery Rev.* **2004**, *56*, 275−300. (d) Vishweshwar, P.; McMahon, J. A.; Peterson, M. L.; Hickey, M. B.; Shattock, T. R.; Zaworotko, M. J. *Chem. Commun.* **2005**, 4601−4603. (e) Babu, N. J.; Reddy, L. S; Nangia, A. *Mol. Pharmaceutics* **2007**, *4*, 417−434. (f) Porter, W. W., III; Elie, S. C.; Matzger, A. J. *Cryst. Growth Des.* **2008**, *8*, 14−16. (g) Báthori, N. B.; Lemmerer, A.; Venter, G. A.; Bourne, S. A.; Caira, M. R. *Cryst. Growth Des.* **2011**, *11*, 75−87. (h) Caira, M. R.; Bourne, S. A.; Samsodien, H.; Engel, E.; Liebenberg, W.; Stieger, N.; Aucamp, M. *CrystEngComm* **2012**, *14*, 2541−2551. (i) Cherukuvada, S.; Nangia, A. *CrystEngComm* **2012**, *14*, 2579−2588. (j) Goswami, P. K.; Thaimattam, R.; Ramanan, A. *Cryst. Growth Des.* **2013**, *13*, 360−366. (k) Steed, J. W. *Trends Pharmacol. Sci.* **2013**, *34*, 185−193.

(81) (a) Trask, A. V. *Mol. Pharmaceutics* **2007**, *4*, 301−309. (b) Karki, S.; Friščič, T.; Fábián, L.; Jones, W. *CrystEngComm* **2010**, *12*, 4038−4041. (c) Connelly, P. R.; Vuong, T. M.; Murcko, M. A. *Nature Chem.* **2011**, *3*, 692−695.

(82) (a) Bhatt, P. M.; Azim, Y.; Thakur, T. S.; Desiraju, G. R. *Cryst. Growth Des.* **2009**, *9*, 951−957. (b) Ellena, J.; Bocelli, M. D.; Honorato, S. B.; Ayala, A. P.; Doriguetto, A. C.; Martins, F. T. *Cryst. Growth Des.* **2012**, *12*, 5138−5147.

(83) (a) Mukherjee, A.; Grobelny, P.; Thakur, T. S.; Desiraju, G. R. *Cryst. Growth Des.* **2011**, *11*, 2637−2653. (b) Sarma, D.; Ramanujachary, K. V.; Stock, N.; Natarajan, S. *Cryst. Growth Des.* **2011**, *11*, 1357−1369.

(84) (a) Gavezzotti, A. *CrystEngComm* **2003**, *5*, 439−446. (b) Blagden, N.; Davey, R. J. *Cryst. Growth Des.* **2003**, *3*, 873−885. (c) Price, S. L. *Acc. Chem. Res.* **2009**, *42*, 117−126.

(85) Tothadi, S.; Desiraju, G. R. *Philos. Trans. R. Soc., A* **2012**, *370*, 2900−2915.

(86) Chen, J.; Sarma, B.; Evans, J. M. B.; Myerson, A. S. *Cryst. Growth Des.* **2011**, *11*, 887−895.

(87) (a) Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Cryst. Growth Des.* **2003**, *3*, 125−150. (b) Vekilov, P. G. *Cryst. Growth Des.* **2010**, *10*, 5007−5019. (c) Erdemir, D.; Lee, A. Y.; Myerson, A. S. *Acc. Chem. Res.* **2009**, *42*, 621−629. (d) Derdour, L.; Skliar, D. *Cryst. Growth Des.* **2012**, *12*, 5180−5187.

(88) Ramanan, A.; Whittingham, M. S. *Crystal Growth Des.* **2006**, *6*, 2419−2421.

(89) (a) Gavezzotti, A. *CrystEngComm* **2008**, *10*, 367. (b) Gavezzotti, A. *CrystEngComm* **2011**, *13*, 3573−3579. (c) Gavezzotti, A. *Top. Curr. Chem.* **2012**, *315*, 1−32.

(90) (a) Ganguly, S.; Fernandes, J. R.; Bahadur, D.; Rao, C. N. R. *J. Chem. Soc., Faraday Trans. 2* **1979**, *75*, 923−928. (b) Ramírez, F. J.; Aranda, M. A. G.; Hernández, V.; Casado, J.; Hotta, S. *J. Chem. Phys.* **1998**, *109*, 1920−1929. (c) Heberle, J.; Gensch, T. *Nat. Struct. Biol.* **2001**, *8*, 195−197.

(91) Fucke, K.; Howard, J. A. K.; Steed, J. W. *Chem. Commun.* **2012**, *48*, 12065−12067.

(92) Braun, D. E.; Bhardwaj, R. M.; Florence, A. J.; Tocher, D. A.; Price, S. L. *Cryst. Growth Des.* **2013**, *13*, 19−23.

(93) (a) Fabbiani, F. P. A.; Allan, D. R.; David, W. I. F.; Moggach, S. A.; Parsons, S.; Pulham, C. R. *CrystEngComm* **2004**, *6*, 504−511. (b) Fabbiani, F. P. A.; Allan, D. R.; Parsons, S.; Pulham, C. R. *CrystEngComm* **2005**, *7*, 179−186. (c) Boldyreva, E. V. *Acta Crystallogr.* **2008**, *A64*, 218−231. (d) Katrusiak, A. *Acta Crystallogr.* **2008**, *A64*, 135−148. (e) Johnstone, R. D. L.; Ieva, M.; Lennie, A. R.; McNab, H.; Pidcock, E.; Warren, J. E.; Parsons, S. *CrystEngComm* **2010**, *12*, 2520−2523.

(94) (a) Dunitz, J. D. *Pure Appl. Chem.* **1991**, *63*, 177−185. (b) Schödel, H.; Näther, C.; Bock, H.; Butenschön, F. *Acta Crystallogr.* **1996**, *B52*, 842−853. (c) Takahashi, H.; Ito, Y. *CrystEngComm* **2010**, *12*, 1628−1634.

(95) Mahapatra, S.; Thakur, T. S.; Joseph, S.; Varughese, S.; Desiraju, G. R. *Cryst. Growth Des.* **2010**, *10*, 3191−3202.

(96) A representative selection of references that describe more than five polymorphs for a single compound: (a) Yu, L.; Stephenson, G. A.; Mitchell, C. A.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J. J.; Borchardt, T. B.; Stowell, J. G.; Byrn, S. R. *J. Am. Chem. Soc.* **2000**, *122*, 585−591. (b) Chen, S.; Guzei, I. A.; Yu, L. *J. Am. Chem. Soc.* **2005**, *127*, 9881−9885. (c) Chen, S. A.; Xi, H. M.; Yu, L. *J. Am. Chem. Soc.* **2005**, *127*, 17439−17444. (d) Lopez-Mejias, V.; Kampf, J. W.; Matzger, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 9872−9875.

(97) (a) Ouvrard, C.; Price, S. L. *Cryst. Growth Des.* **2004**, *4*, 1119−1127. (b) Vishweshwar, P.; McMahon, J. A.; Oliveira, M.; Peterson, M. L.; Zaworotko, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 16802−16803.

(98) (a) Thakur, T. S.; Sathishkumar, R.; Dikundwar, A.; Row, T. N. G.; Desiraju, G. R. *Cryst. Growth Des.* **2010**, *10*, 4246−4249. (b) Dikundwar, A. G.; Ranganathan, S.; Row, T. N. G.; Desiraju, G. R. *Cryst. Growth Des.* **2011**, *11*, 3954−3963.

(99) Banerjee, R.; Bhatt, P. M.; Kirchner, M. T.; Desiraju, G. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2515−2520.

(100) Kiran, M. S. R. N.; Varughese, S.; Ramamurty, U.; Desiraju, G. R. *CrystEngComm* **2012**, *14*, 2489−2493.

(101) (a) Wiechert, D.; Mootz, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1974−1976. (b) Bond, A. *Chem. Commun.* **2003**, 250−251. (c) Choudhury, A. R.; Islam, K.; Kirchner, M. T.; Mehta, G.; Guru Row, T. N. *J. Am. Chem. Soc.* **2004**, *126*, 12274−12275.

(102) (a) De Feyter, S.; De Schryver, F. C. *Chem. Soc. Rev.* **2003**, *32*, 139−150. (b) Slater, A. G.; Betonb, P. H.; Champness, N. R. *Chem. Sci.* **2011**, *2*, 1440−1448.

(103) (a) Chanzy, H.; Pérez, S.; Miller, D. P.; Paradossi, G.; Winter, W. T. *Macromolecules* **1987**, *20*, 2407−2413. (b) Firment, L. E.; Somorjai, G. A. *J. Chem. Phys.* **1975**, *63*, 1037−1038. (c) Kolb, U.; Gorelik, T.; Kübel, C.; Otten, M. T.; Hubert, D. *Ultramicroscopy* **2007**, *107*, 507−513. (d) Chow, E. H. H.; Bučar, D.-K.; Jones, W. *Chem. Commun.* **2012**, *48*, 9210−9226.

(104) Mukherjee, A.; Desiraju, G. R. *Cryst. Growth Des.* **2011**, *11*, 3735−3739.

(105) (a) Zakharov, B. A.; Losev, E. A.; Boldyreva, E. V. *CrystEngComm* **2013**, *15*, 1693−1697. (b) Ridout, J.; Probert, M. R. *Cryst. Growth Des.* **2013**, *13*, 1943−1948.

(106) Mondal, R.; Howard, J. A. K.; Banerjee, R.; Desiraju, G. R. *Cryst. Growth Des.* **2006**, *6*, 2507−2516.

(107) Sander, J. R. G.; Bučar, D.-K.; Henry, R. F.; Giangiorgi, B. N.; Zhang, G. G. Z.; MacGillivray, L. R. *CrystEngComm* **2013**, *15*, 4816−4822.

(108) (a) Lommerse, J. P. M.; Motherwell, W. D. S.; Ammon, H. L.; Dunitz, J. D.; Gavezzotti, A.; Hofmann, D. W. M.; Leusen, F. J. J.; Mooij, W. T. M.; Price, S. L.; Schweizer, B.; Schmidt, M. U.; van Eijck, B. P.; Verwerj, P.; Williamsk, D. E. *Acta Crystallogr.* **2000**, *B56*, 697−714. (b) Sarma, J. A. R. P.; Desiraju, G. R. *Cryst. Growth Des.* **2002**, *2*, 93−100. (c) Neumann, M. A.; Leusen, F. J. J.; Kendrick, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2427−2430.

(109) Kirchner, M. T.; Reddy, L. S.; Desiraju, G. R.; Jetti, R. K. R.; Boese, R. *Cryst. Growth Des.* **2004**, *4*, 701−709.

(110) Dubey, R.; Pavan, M. S.; Desiraju, G. R. *Chem. Commun.* **2012**, *48*, 9020−9022.

(111) Gavezzotti, A. *Acc. Chem. Res.* **1994**, *27*, 309−314.

(112) Biradha, K. *Curr. Sci.* **2007**, *92*, 584−585.

(113) Parveen, S.; Davey, R. J.; Dent, G.; Pritchard, R. G. *Chem. Commun.* **2005**, 1531−1533.

(114) Saito, A.; Igarashi, K.; Azuma, M.; Ooshima, H. *J. Chem. Eng. Jpn.* **2002**, *35*, 1133−1139.

(115) Davey, R. J.; Brychczynska, M.; Sadiq, G.; Dent, G.; Pritchard, R. G. *CrystEngComm* **2013**, *15*, 856−859.

(116) For a typical example from the earlier literature, see: Kane, J. J.; Liao, R.-F.; Lauher, J. W.; Fowler, F. W. *J. Am. Chem. Soc.* **1995**, *117*, 12003−12004.

(117) (a) Gao, X.; Friscic, T.; MacGillivray, L. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 232−236. (b) Atkinson, M. B. J.; Mariappan, S. V. S.;

Bučar, D.-K.; Baltrusaitis, J.; Friščić, T.; Sinada, N. G.; MacGillivray, L. R. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 10974−10979.
(118) Yoon, M.; Suh, K.; Kim, H.; Kim, Y.; Selvapalam, N.; Kim, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 7870−7873.
(119) Thomas, S. P.; Nagarajan, K.; Guru Row, T. N. *Chem. Commun.* **2012**, *48*, 10559−10561.
(120) (a) Bolton, O.; Lee, K.; Kim, H.-J.; Lin, K. Y.; Kim, J. *Nature Chem.* **2011**, *3*, 205−210. (b) Roy, S.; Mondal, S. P.; Ray, S. K.; Biradha, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12012−12015.
(121) (a) Bica, K.; Rijksen, C.; Nieuwenhuyzen, M.; Rogers, R. D. *Phys. Chem. Chem. Phys.* **2010**, *12*, 2011−2017. (b) Bica, K.; Shamshina, J.; Hough, W. L.; MacFarlaned, D. R; Rogers, R. D. *Chem. Commun.* **2011**, *47*, 2267−2269. (c) Kelley, S. P.; Narita, A.; Holbrey, J. D.; Green, K. D.; Reichert, W. M.; Rogers, R. D. *Cryst. Growth Des.* **2013**, *13*, 965−975.
(122) Horiuchi, S.; Tokura, Y. *Nat. Mater.* **2008**, *7*, 357−366.
(123) Ghosh, S.; Reddy, C. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 10319−10323.
(124) Lee, T.; Chen, H. R.; Lin, H. Y.; Lee, H. L. *Cryst. Growth Des.* **2012**, *12*, 5897−5907.
(125) Varughese, S.; Kiran, M. S. R. N.; Ramamurty, U.; Desiraju, G. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 2701−2712.
(126) Varughese, S.; Kiran, M. S. R. N.; Solanko, K. A.; Bond, A. D.; Ramamurty, U.; Desiraju, G. R. *Chem. Sci.* **2011**, *2*, 2236−2242.
(127) (a) Cohen, M. D.; Schmidt, G. M. J.; Sonntag, F. I. *J. Chem. Soc.* **1964**, 2000−2013. (b) Kaupp, G. *Angew. Chem., Int. Ed.* **1992**, *31*, 592−595.
(128) Reddy, C. M.; Kirchner, M. T.; Gundakaram, R. C.; Padmanabhan, K. A.; Desiraju, G. R. *Chem. Eur. J.* **2006**, *12*, 2222−2234.
(129) Mishra, M. K.; Varughese, S.; Ramamurty, U.; Desiraju, G. R. *J. Am. Chem. Soc.* **2013**, *135*, 8121−8124.