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Review

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A Practical Guide to the Design of Molecular Crystals

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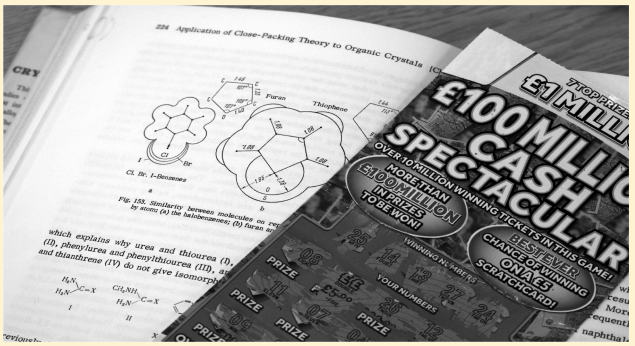
ABSTRACT: This Tutorial Review, aimed at both the novice and the seasoned solid-state chemist, provides a succinct overview of key findings that have, over the last half century, advanced our ability to make molecular crystals with targeted structures and desired properties. The article critically evaluates the efficiency and reliability of the well-established guidelines used by experimentalists in crystal engineering and highlights statistical and computational tools that are both advantageous to crystal design and accessible to experimental solid-state chemists.



The systematic development of our subject will be difficult if not impossible until we understand the intermolecular forces responsible for the stability of the crystalline lattice of organic compounds; a theory of the organic solid state is a requirement for the eventual control of molecular packing arrangement. Once such a theory exists we shall, in the present context of synthetic and mechanistic photochemistry, be able to 'engineer' crystal structures having intermolecular contact geometry appropriate for chemical reaction, much as, in other contexts, we shall construct organic conductors, catalysts, etc. In short, any rational development of the physics and chemistry of the solid state must be based upon a theory of molecular packing; since the molecules studied are complex, the theory will most likely be empirical for some time yet. Rules are now becoming available in what I regard as phase three, the phase of crystal engineering.

G. M. J. Schmidt[1]

1. INTRODUCTION

For centuries, molecular solids have been used as key components in medicines,[2] fertilizers,[3] pesticides,[4] inks and paints.[5] Their potential to perform as highly functional electronic and optical materials has recently also inspired the development of crystalline molecular semiconductors[6] and optoelectronics.[7] The transformation of specialty chemicals into fit-for-purpose crystalline solids is a lengthy and expensive process, one which, unfortunately, often fails to generate a marketable product due to a multitude of unfulfilled performance and safety requirements (many of which are associated with the solid-state properties of the target compound). The risky nature of such endeavors is best appreciated by considering the drug attrition rates in the pharmaceutical industry,[8] where the placement of an FDA-approved drug onto the market requires an average investment exceeding 2.6 billion USD over more than a decade.[9] The intensive investment demanded by research and development (R&D) activities, and the need to rapidly respond to societal needs in an efficient and environmentally friendly manner, drive current efforts to minimize the cost, time, and risk associated with such R&D projects. With this in mind, computational methods have been introduced into R&D to guide the fine-tuning of specialty chemicals.[10]

The last three decades have also witnessed remarkable advances in computational solid-state chemistry, advances underpinned by continuously increasing computational processing power and expanded funding for accessible supercomputers. These advances have enabled the use of materials modeling and crystal structure prediction of inorganic materials such as metal oxides[11] and zeolites.[12] Substantial progress has also been made when it comes to the modeling of organic solids: for instance, recent reports describe the use of crystal structure prediction and property calculations to accurately describe a range of feasible crystal structures and the accompanying electronic[13,14] or host−guest[15,16] properties of a molecular compound in the solid state. This was accomplished within a time frame that is appreciably shorter than that needed to synthesize, characterize and test the solid-state properties of the very same molecule.[16] Given such achievements, as well as the predictive accuracy and speed of the computational methods which are beginning to shape our pursuit of functional materials, it is reasonable to expect that such predictive methods will soon become a cornerstone of materials science.

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This is particularly true of crystal engineering,[1,17−23] a field that deals with the design, synthesis, and use of molecular and metal−organic crystals.[24] This branch of solid-state chemistry is primarily concerned with the synthesis of targeted solid-state structures that have desired properties, through an understanding and control of intermolecular interactions in the crystal.[19] Surprisingly, crystal engineering endeavors (at least those pursued in academic circles) rarely involve the manipulation of particle properties such as morphology, particle size, and particle-size distribution, although such approaches meaningfully alter physicochemical solid-state properties of organic molecules.[25−28] The crystal engineer's aspiration to design materials with absolute meticulousness is challenged by the fact that trivial changes to the molecular structures (e.g., a H/F atom exchange) regularly result in significantly and unpredictably altered crystal packing,[29,30] while more profound changes (e.g., addition of hydrogen-bonding groups) might even affect the dimensionality and topology of supramolecular solid-state structures.[31,32] It is therefore important that crystal engineers and solid-state chemists develop design guidelines that are as practical and reliable as the synthetic blueprints that organic synthetic chemists developed throughout the last century.[33]

The crystal engineer and experimental organic solid-state chemist generally resort to "predictive" guidelines that are mainly derived from crystallographic studies, extensive surveys of databases (such as the Cambridge Structural Database;[34,35] CSD), and other empirical data. While such guidelines are useful when making alterations of the supramolecular patterns in a molecular crystal, their use does not permit the preparation of solids with targeted crystal structures, particularly when molecules with a diverse range of functional groups are involved. Nevertheless, such controlled changes to crystal structures based on these guidelines have been used to modulate (and often improve) the properties of a wide range of specialty chemicals that are central to modern living (e.g., drug molecules,[36] nutraceuticals,[37] semiconductors,[38] energetic compounds[39]). There are thus numerous real-world examples that demonstrate the utility of crystal engineering in transforming a promising material into a fully functional product.

Such encouraging examples, though, must be considered alongside studies which show how unmanageable crystal design still is without the use of contemporary computational methods. These studies emphasize the fact that, except for a very small minority of cases, the structures of bespoke molecular crystals are still impossible to predict solely on the basis of previous crystallographic knowledge and intuition.[40] A brief survey of the relevant literature from the last two decades reveals that the crystal engineering community has primarily focused on crystal form design for individual compounds (mostly drug compounds), rather than on developing design strategies applicable to whole classes of molecules. So, there is clearly a pressing need to better understand the physical processes that control the assembly of molecules into crystals, in order to formulate more precise, reliable, and generally applicable predictive guidelines for crystal design.

In this Tutorial Review, we critically interrogate the utility and consistency of commonly used and well-established guidelines for the design of molecular crystals, with a view to stimulate a community-wide discussion of the current state of the art. While we also aim to provide novice crystal engineers with an introduction to the canonical literature of their field, we hope seasoned practitioners will critically evaluate the concepts, theories, and ideas discussed herein and feel encouraged to further develop the same. Although the field has advanced significantly in the last two decades, the initial goal of crystal engineers—namely, the development of a full understanding of the intermolecular interactions that control the structure and function of molecular crystals[18]—is still unfulfilled. Considering that the focus in crystal engineering has progressively shifted from structure to function,[41,42] it is vital to reiterate Schmidt's message from the epigraph to this review: "the systematic development of our subject will be difficult if not impossible until we understand the intermolecular forces responsible for the stability of the crystalline lattice of organic compounds".[1] Such systematic advancement of crystal engineering can only be achieved through the continuous refinement of extant models, the construction of entirely new models as necessary, and, crucially, rigorous testing of these models via well-crafted experiments. We therefore hope that this review will prompt the practicing solid-state chemist to rethink current crystal engineering practices and to consider the implementation of emerging predictive methods[43] into their research programs to develop and test new theories. With this Tutorial Review, we also intend to complement other recent works along similar lines,[44,45] by providing a more holistic view of the topic at hand (rather than focusing on particular aspects, such as the synthon approach) and by emphasizing promising statistical and computational tools for the design of molecular crystals that are easily accessible to experimental solid-state chemists.[24]

The reader should keep in mind that the scope of this review is limited to the design of crystals exclusively comprised of molecular entities (i.e., metal−organic crystals are excluded) and that the design principles and guidelines featured here are those that the authors regard as most relevant, established, and reliable. The nonspecialist is also referred to articles by Aitipamula et al.[46] and Lusi[47] for definitions of various types of multicomponent molecular crystals that will be discussed herein.

2. THE NATURE OF THE MOLECULAR CRYSTAL

To begin with, it would be useful to summarize the key characteristics of the molecular crystal, as these are the major design considerations for any crystal synthesis.

2.1. Crystal Packing. The long-range order in molecular crystals is governed by the shape of the assembling molecules, as well as by an array of weak, short- and long-range interactions that holds them together. At the beginning of the 20th century, Barlow and Pope proposed that atoms must pack closely in crystals,[48] and early studies by Kitaigorodskii showed that the close-packing principles postulated even earlier by Aristotle[49] also apply to molecules in organic crystals.[50] The extent of close-packing is described using the coefficient of molecular packing (more commonly referred to as the *packing coefficient*):

$$k = Z\frac{V_0}{V}$$

where k refers to the packing coefficient, V_0 to the molecular volume, V to the unit cell volume, and Z to the number of molecules in the unit cell. While Z and V are determined crystallographically, the value of V_0 can be estimated using calculated volume increments for atoms and functional groups, which are based on atomic van der Waals radii.[51,52] The values of calculated volume increments were initially determined and

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tabulated by Kitaigorodskii,[53] and were later more accurately calculated using methods developed by Gavezzotti,[54] Katser,[55] and Abraham.[56] Molecular volumes are nowadays rapidly computed using fairly accessible software such as *Gaussian*.[57] The packing coefficients can be easily determined with the *PLATON*[58] program, using the VOID command.

Kitaigorodskii's analysis of known molecular crystal structures revealed that most aromatic molecules exhibit a packing coefficient between 0.6 and 0.8, a range that was later corroborated using database analyses and statistical methods.[59] Orelkin (*c.* 1930) proposed that densely packed molecular crystals are obtained when the "bumps" of one molecule are inserted in the "hollows" of the neighboring molecule,[50] whereby intermolecular contacts are maximized and void spaces are minimized. The importance of complementary molecular surfaces was also emphasized in 1940 by Pauling and Delbrück.[60] In the 1940s, Kitaigorodskii adopted the "bump and hollow" principle to develop his *dense-packing theory*, which he utilized to predict the packing arrangements of organic molecules within crystal lattices. To develop his theories, Kitaigorodskii designed a mechanical device, the so-called "structure seeker" (Figure. 1), to model the packing of organic molecules.[61,62]

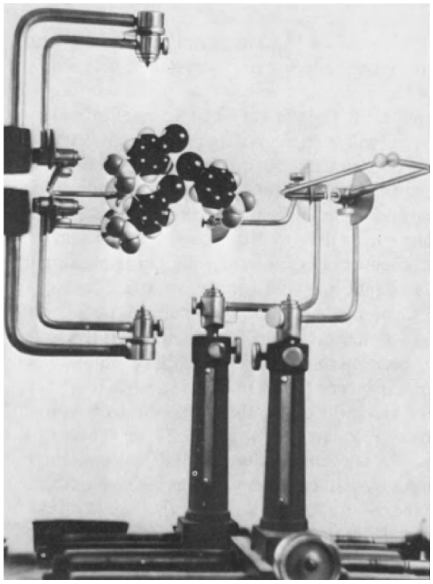

Figure 1. Kitaigorodskii's structure seeker, devised to explore molecular packing in the crystalline state. Reproduced with permission from ref 61. Copyright 1973 Elsevier.

The structure seeker was employed to deduce how molecules first form chains and layers by densely fitting molecular "bumps" into "hollows". These layers were then stacked following the same packing rules so that each molecule displays the highest possible coordination number,[63] which finally led to the deduction of the most likely crystal symmetry and structure (a principle later referred to as Kitaigorodskii's Aufbau Principle[64]). Kitaigorodskii realized that the habitually irregular shape of organic molecules poses limitations to the way these molecules can pack into a crystal lattice, and that out of the 230 mathematically possible space groups (first catalogued by Fedorov[65]), only a few would be chemically likely.

Using his dense-packing theory, Kitaigorodskii finally managed to predict that organic molecules are most likely to crystallize in the $P\bar{1}$, $P2_1$, $P2_1/c$, *Pca*, *Pna*, and $P2_12_12_1$ space groups.[50] Similar findings were reported by Nowacki, who studied nearly 1000 organic crystal structures to conclude that 44% of these crystallize in the $P2_1$, $P2_1/c$, and $P2_12_12_1$ space groups ($P\bar{1}$ was underrepresented at the time, as the crystallographic calculations for such structures were too challenging to be accomplished without the use of computers).[66,67] Remarkably, the findings of Kitaigorodskii and Nowacki were much later verified by Rodgers et al., who conducted an analysis of approximately 30 000 organic crystal structures to identify $P2_1/c$, $P\bar{1}$, $P2_12_12_1$, $P2_1$, and $C2/c$ as the most common space groups.[68] For more details on space-group frequencies, the reader is referred to an outstanding account of this topic by Dunitz et al.[69]

The geometrical approach to crystal packing played an important role in the early days of organic crystal chemistry, as it accounted for the minimization of the crystal free energy and the potential energy of intermolecular interactions between the molecules in the lattice. Computational and experimental studies demonstrated that packing coefficients and crystal lattice energies correlate well.[70] But the predictive power of the close-packing theory has its limits when it comes to the understanding of polymorphism and to crystal design, because "chemistry is not geometry".[21] A thorough understanding of molecular crystals can only be attained by considering and understanding the interplay of the full range of intermolecular interactions (and associated energies) that sustain molecules in their crystal lattices.

2.2. Intermolecular Interactions. In crystal chemistry, intermolecular interactions are the attractive and repulsive interactions that a stable molecule undergoes when surrounded by other molecules.[21] Intermolecular interactions can be categorized as short-range and long-range interactions. In long-range interactions (such as electrostatic, induction, and dispersion forces), energy decreases in inverse proportion to the distance between interacting molecules ($E \propto r^{-n}$, where r represents intermolecular separation), while in short-range interactions (e.g., repulsion, exchange, and charge transfer), energy decreases exponentially with increasing distance ($E \propto e^{-r}$). Supramolecular assembly and crystallization are controlled by an array of short- and long-range intermolecular interactions, a complex interplay that is tremendously difficult to understand and predict. The intricacies of these interactions, their mathematical descriptions, and ways in which these are modeled are beyond the scope of this Tutorial Review, and the reader is thus referred to an introductory text by Dunitz & Gavezzotti,[71] as well as to authoritative texts by Stone[72] and Gavezzotti.[73] We will, however, focus on two types of (mostly) electrostatic interactions, namely, the hydrogen bond and the halogen bond, as both types are fairly predictable in the context of supramolecular assembly owing to their strength and directionality. It is their ability to steer the formation of targeted, robust structures that make them an indispensable tool for crystal engineers. An overview of their energetic and geometric properties is given in the following sections.

2.2.1. The Hydrogen Bond. While the hydrogen bond is a canonical concept in modern chemistry, it is worth acknowledging the considerable and prolonged debate that preceded its widespread acceptance. Much insightful information on hydrogen bonding can be found in classic monographs, reviews, and essays by Desiraju,[74−76] Steiner,[77] Desiraju &

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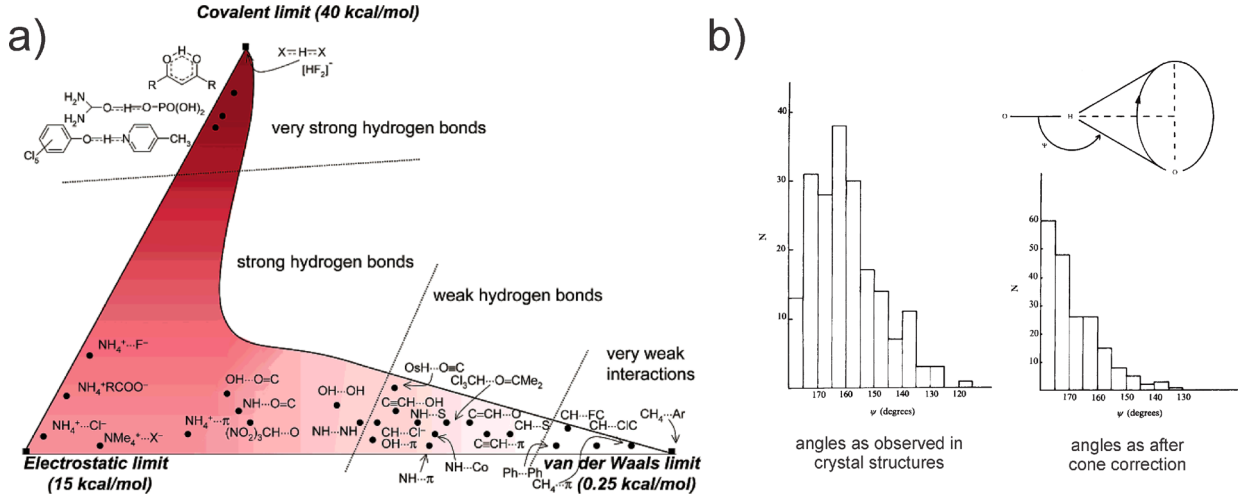

Figure 2. (a) Energies of a wide range of chemically diverse hydrogen bonds (darker colored areas indicate higher bond energies); (b) histograms of O−H···O bond angles as observed in 196 crystal structures (left) compared to the histogram of O−H···O bond angles in a sample of 60 crystal structures after the cone correction was applied. Panels (a) and (b) are adapted with permission from refs 75 and 82. Copyright 2002 American Chemical Society and 1974 Springer Nature.

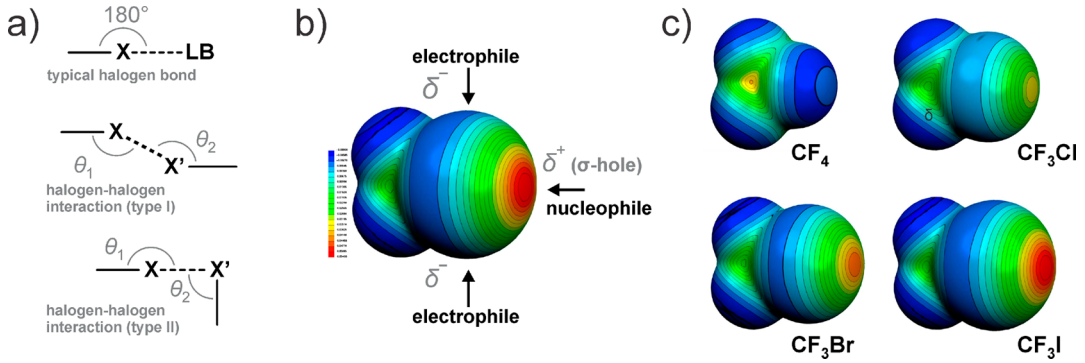

Figure 3. (a) Diagrams representing the typical halogen bond involving Lewis bases (LB) and the two known types of halogen−halogen interactions; (b) electrostatic potential map of CF_3I highlighting positive and negative regions on iodine that are usually participating in halogen bonding; (c) electrostatic potential maps of CF_4, CF_3Cl, CF_3Br, and CF_3I emphasizing how the σ-hole is shaped by the polarizability of the halogen-bond donor. Adapted with permission from ref 106. Copyright 2007 Springer.

Steiner,[78] and Gilli & Gilli.[79] The existence of hydrogen bonding was possibly first proposed by Werner in 1902: he suggested that physical properties of ammonia salts can be best rationalized by structural models wherein hydrogen atoms are located between ammonia molecules, resulting in a bonding interaction that he described as *Nebenvalenz* (loosely translated from the German as para-valence, subvalence, or secondary valence).[79] Since then, the concept of hydrogen bonding has significantly evolved through numerous discussions, throughout which several definitions have been proposed.[79] A definitive description of the hydrogen bond was finally put forth by the IUPAC in 2011: "...an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X−H [the hydrogen-bond donor] in which X is more electronegative than H, and an atom or a group of atoms [the hydrogen-bond acceptor] in the same or a different molecule, in which there is evidence of bond formation".[80] The classic hydrogen bond is denoted as X−H···Y−Z, where X−H and Y−Z describe the hydrogen-bond donor and acceptor, respectively, and the dots symbolize the attractive nature of the interaction. The energy of hydrogen bonds ranges from 0.2 to 40 kcal mol^{-1}, with the exact energy being determined by electrostatic, polarization, charge transfer, dispersion, and exchange-repulsion forces. According to Jeffrey,[81] hydrogen bonds can be classified based on their bond energies as weak, moderate, and strong. A weak hydrogen bond is dominated by electrostatic and dispersive forces, and is associated with energies <4 kcal mol^{-1}, moderate hydrogen bonds are electrostatic in nature and display energies in the range of 4−15 kcal mol^{-1}, while strong hydrogen bonds are strongly covalent in nature and display energies in the range of 15−40 kcal mol^{-1}. A slightly different classification of hydrogen bonds based on their strength was provided by Desiraju[75] and is shown in Figure 2a.

Although hydrogen bonds have a clear preference for linear geometries, their bond distances and angles depend on their strength and the polarity of the hydrogen-bond donor.[77] The preference for linearity was revealed through careful analyses of O−H···O hydrogen bond geometries and by the application of the so-called "cone correction" (Figure 2b).[82] However, due to the range of various effects, hydrogen bonds often deviate from linearity. Moderate hydrogen bonds, such as those observed among water molecules or carbohydrates where oxygen and nitrogen atoms act as donors and acceptors, exhibit X···Y bond distances in the range of 2.5−3.2 Å and X−H···Y bond angles larger than 130°.[77,81] From a crystal engineering point of view,

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moderate hydrogen bonds (with X, Y = N, O)—both neutral (X−H···Y−Z) and charge-assisted (X^-···H−Y^+−Z)—are sufficiently strong and directional to warrant their use as a tool for the design of molecular crystals, unlike weaker hydrogen bonds (X−H···Y−Z, where X = C, S, P, Si, and Y = halogens, S, Se, P, C).

2.2.2. The Halogen Bond. The historical origins of the halogen bond date back more than 200 years, when the first halogen-bonded material was synthesized.[83] But it is only since the 1950s, with Mulliken's[84] and Hassel's[85,86] landmark studies of charge-transfer interactions of halogens, that we have begun to understand the workings of this type of interaction. Extensive computational, spectroscopic, and crystallographic studies have since enabled the establishment of the halogen bond as a well understood phenomenon that fascinates materials scientists, biologists, and synthetic and computational chemists. The reader is encouraged to explore the current state of the art in halogen-bond research using recent comprehensive reviews by Gilday et al.[87] and Cavallo et al.[88]

The IUPAC recently published a recommendation to define the halogen bond as an interaction that "occurs when there is evidence of a net attractive interaction between an electrophilic region [the σ-hole] associated with a halogen atom [the halogen-bond donor] in a molecular entity and a nucleophilic region in another, or the same, molecular entity [the halogen bond acceptor]" (Figure 3a,b).[89] The halogen bond is denoted as R−X···Y, where R−X represents either a dihalogen molecule (e.g., Br_2), a haloalkane (e.g., CH_3I), a haloarene (e.g., iodobenzene), a 1-haloalkyne (e.g., diiodoacetylene), a halonium ion (e.g., bromonium derivatives), or a haloimide (e.g., N-bromosuccinimide), while Y signifies a Lewis base in the form of an atom featuring one lone electron pair (e.g., N-heterocycles), a π-system (e.g., arene moieties), an anion, or a halogen atom.[89]

The halogen bond is primarily an electrostatic interaction, but is also significantly affected by polarization, charge-transfer, and dispersion forces.[90] The energies of halogen bonds are comparable to those hydrogen bonds with values of up to around 40 kcal mol^{-1},[1,87,91−93] as determined using spectrometric,[94−96] calorimetric,[93,97] and computational[93,98,99] methods. The lowest energies correspond to Cl···Cl interactions in chlorocarbons,[100,101] while the highest were found for the X^-···X_2 interaction in the X_3^- species (where X = F, Cl, Br, I).[102] PIXEL calculations were employed to show that R−X···N (where X = Br, I) interactions exhibit energies of about 2−8 kcal mol^{-1}.[103,104] The energy of the halogen bond is related to the size and depth of the σ-hole[105,106] (Figure 3c) and decreases in the order: I > Br > Cl ≫ F. The strength of the halogen bond can be adjusted by varying the electronic properties of the molecular moiety (R) to which the halogen atom (X) is covalently bound. It is recognized that electron-withdrawing functional groups (such as fluorine atoms) lead to an increase in the region of positive electrostatic potential on the halogen atom (the σ-hole), and thus to an increase in the halogen-bond strength.

The extent of orbital hybridization of the *ipso*-C atom also has a significant effect on the halogen bond strength, and it is understood that the halogen bond strength decreases in the following order: C(sp)−X > C(sp^2)−X > C(sp^3)−X. Such behavior is rationalized by induction of a more pronounced σ-hole on the halogen-bond donor owing to the greater electronegativity of hybridized C atoms with greater s- and lower p-character.[88,107]

The halogen bond is highly directional, and most interactions deviate only marginally from linearity with respect to the R−X···Y angle.[90] Halogen···halogen interactions (e.g., R−X···X−R), on the other hand, are a subset of the halogen bonds that exhibit two types of geometries, named type I and II (Figure 3a).[108−110] Symmetric ($\theta_1 \approx \theta_2$) type I halogen bonds form when two halogen atoms interact through the neutral regions of their respective electrostatic potential surfaces to minimize repulsive forces between them. Asymmetric ($\theta_1 \approx 180°$, $\theta_2 \approx 90°$) type II halogen bonds are established through an interaction of the nucleophilic region of one halogen atom with the electrophilic region of another (Figure 3a,b).[108]

2.3. The (un)Predictability of Molecular Crystal Structures. The formation of molecular crystals is guided by the avoidance of a vacuum, the lessening of repulsive intermolecular interactions, as well as the boosting of attractive molecular forces. It is well-known that molecules can assemble in numerous ways to avoid the generation of void spaces,[50] and that these differently arranged crystal forms can be very similar in energy. The existence of a multitude of crystals of the same compound, of different spatial arrangements and similar energies is referred to as *polymorphism*.[111,112] A fine illustration of the ease with which molecules exhibit polymorphic crystal forms was provided in a recent review by Cruz-Cabeza et al.[113] This insightful account reports the results of a statistical analysis of crystallographic data from the CSD, and from solid-form screens performed at Hoffmann-La Roche and Eli Lilly and Company, and is complemented by calculations of crystal lattice energies. This was the first systematic study of polymorphism using large data sets, and revealed important and (some) unexpected facts about molecular crystals: for example, at least every other molecule exhibits polymorphism,[114] if sufficiently screened for it. In addition, crystal lattice energies of the polymorphs of a particular molecule differ in energy only marginally (by <1 kcal mol^{-1}). Polymorphism is also unrelated to most molecular features, including conformational molecular flexibility or size (viz. number of atoms). Molecules with hydrogen-bonding functional groups are slightly more prone to exhibit polymorphism, while chiral molecules are less disposed to polymorphism. Interestingly, different polymorphs are often found to materialize under the same experimental conditions (a phenomenon referred to as *concomitant polymorphism*[115]).

The findings of the Cruz-Cabeza review raise interesting and important questions for crystal engineers. There are numerous examples of nearly isoenergetic polymorphs exhibiting distinct supramolecular patterns based on different types of hydrogen bonds. Given this, it is clear that it will be profoundly difficult to predict crystal structures empirically and thus to design a bespoke crystal structure without the guidance of contemporary structure prediction methods, as demonstrated by a test wherein crystallographers were tasked to visually identify the correct crystal structure from a list of computationally predicted structures.[40] On the other hand, the literature suggests that it is much more feasible to design supramolecular assemblies within a crystal lattice, albeit without fine control of the crystal packing of such assemblies. This is particularly true if molecules with very few functional groups are involved and is demonstrated by a plethora of crystal engineering studies over the last two decades.[42,116,117]

Interestingly, many members of the crystal engineering community appear to have little confidence about their

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collective predictive capabilities. In this context, an opinion poll was carried out by one of the authors of this review, at the 23rd International Conference on the Chemistry of the Organic Solid State (Stellenbosch, 2017). Participants with more than 10 years of experience in dealing with molecular crystals were asked to rate their ability to *empirically* predict the supramolecular structure of a putative 1:1 cocrystal comprised of the drug molecule veliparib and niacin (Figure 4) on a 1−10

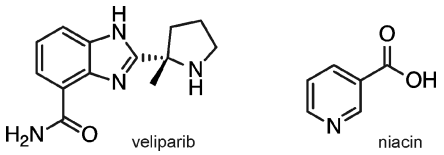

Figure 4. Chemical structures of veliparib and niacin.

scale (where 1 = cannot predict, 10 = can predict 100% accurately). Intriguingly, the average self-rating for this group was very low (~2 on the above scale), and only 38% of these experienced solid-state chemists believed that crystallographic studies alone will ever enable the empirical prediction of supramolecular structures in molecular crystals.[118]

3. SUPRAMOLECULAR SYNTHONS AND TECTONS AS TOOLS FOR CRYSTAL DESIGN

Of the three aforementioned factors that guide the formation of molecular crystals (viz. evasion of a vacuum, lessening of repulsive interactions, boosting attractive forces), the boosting of attractive molecular forces is a popular option when designing molecular crystals, as it is driven by seemingly predictable molecular recognition events. Numerous studies in the late 1980s and early 1990s by Etter,[119−122] Desiraju[18,123] and others recognized that hydrogen and halogen bonds engage molecular functional groups in the formation of foreseeable and well-defined structural units connecting molecules in a crystal structure (Figure 5). Desiraju termed

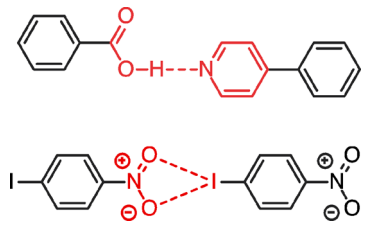

Figure 5. Supramolecular synthons (colored red) formed by two compatible molecular functional groups belonging to two distinct interacting molecules (colored black). The dotted lines represent noncovalent forces bonding two functional groups.

such structural fragments *supramolecular synthons*[124] to underpin conceptual similarities between retrosynthetic analyses in conventional organic synthesis and supramolecular chemistry.[125,126]

A great leap forward in recognizing (and classifying) supramolecular synthons viable for crystal design applications was made in the late 1980s, when Etter used structural information deposited in the CSD to establish empirical hydrogen-bond rules (see Section 5). These considerably aided the prediction of interactions between hydrogen-bond donating and accepting functional groups, even if other functional groups capable of engaging in supramolecular interactions are present in a molecule.[122] The identification and classification of feasible supramolecular synthons were accomplished using a graph-set approach, whereby complex hydrogen-bond networks are represented by combinations of four types of simple patterns: chains, rings, intramolecular hydrogen-bonded structures, and discrete structures (designated as **C**, **R**, **S**, and **D**, respectively). The hydrogen-bond pattern is further detailed through the addition of the number of hydrogen-bond donors (**d**; as subscripts) and the number of acceptors (**a**; as superscripts) to the pattern designator, while the number of atoms involved in the hydrogen-bond pattern (**n**) is indicated in parentheses. The graphs descriptor is finally presented as $\mathbf{G}_{\mathbf{d}}^{\mathbf{a}}(\mathbf{n})$. The use of graph sets to describe hydrogen-bond patterns in molecular crystals is illustrated in Figure 6. The reader is also referred to a review by Bernstein et

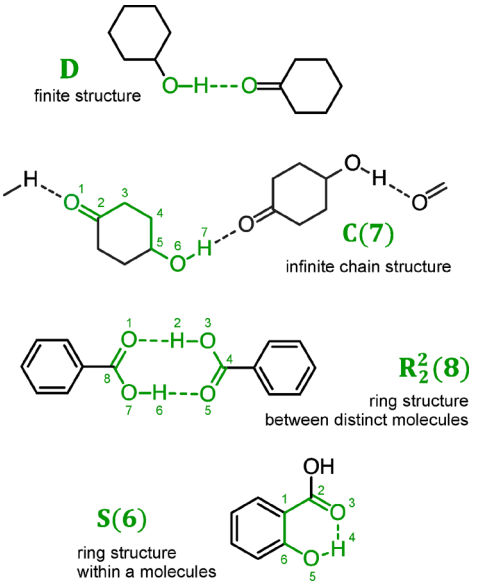

Figure 6. Supramolecular synthons (colored green) formed by two compatible functional groups belonging to two distinct molecules (colored black). The dotted lines represent supramolecular interactions bonding two functional groups. Note that the notation **C**(7) is preferred to $\mathbf{C}_1^1(7)$.

al. that elegantly describes how the graph-set formalism can be used to systematically interpret and describe hydrogen-bond patterns and supramolecular synthons in molecular crystals.[127] The assignment of graph sets is nowadays simply done through free and readily available CSD software.[35]

The last three decades witnessed the discovery of numerous robust synthons, comprised of either identical and complementary functional groups (*supramolecular homosynthons*[128,129]) or distinct yet complementary functional groups (*supramolecular heterosynthons*[128,129]) that reliably appear in a wide range of molecular crystals. The newly developed aptitude to engage molecules into crystal structures with anticipated supramolecular patterns soon established the synthon approach as the method of choice for adjusting solid-state properties of specialty chemicals (such as pharmaceuticals,[130] energetic materials,[39] colorants,[131] electronic materials[132]) through the formation of supramolecular assemblies that crystallize as multicomponent solids (e.g., cocrystals and salts).

Another concept closely related to supramolecular synthons, namely, molecular *tectons*,[133,134] was also developed in the late

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1980s by Wuest to facilitate the formation of molecular networks with predictable and controlled topologies and porosities.[134] Tectons are molecular building blocks that have peripheral functional groups, capable of hydrogen- or halogen-bonding, joined to a molecular core; their number and their arrangement dictate the topology of the network (Figure 7).[135] Wuest and others discovered and developed a wide

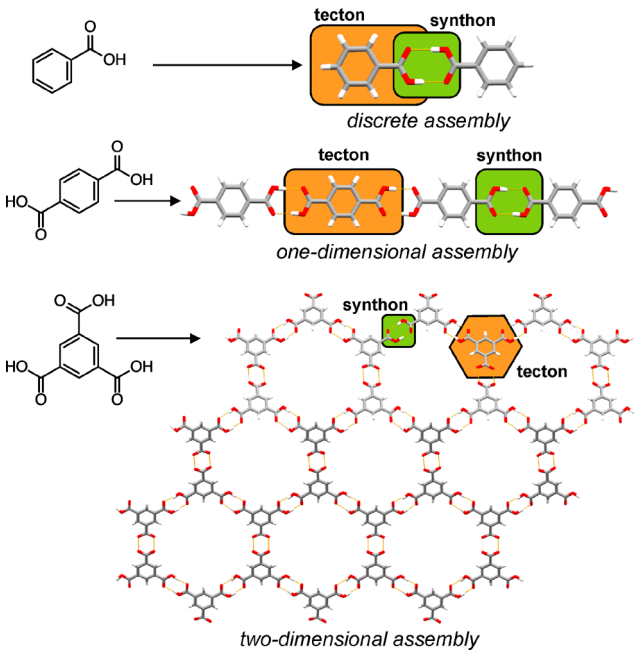

Figure 7. Supramolecular tectons based on benzene and carboxylic-acid functional groups give rise to discrete supramolecular assemblies, or infinite one- and two-dimensional assemblies, depending on the number and arrangement of the carboxylic acids on the benzene core. The rounded rectangles highlight the fundamental difference between synthons (green) and tectons (orange). CSD reference codes for the shown crystal structures (top to bottom): BENZAC01,[144] TEPHTH12,[145] and BTCOAC.[137]

range of tectons for discrete assemblies,[136] one-[136] and two-dimensional (2D)[137] arrays and diamondoid molecular arrays,[133,138−143] whereby carboxylic acids,[137,143] pyridinone,[133,136,139] boronic acid,[140] and aminotriazine[138,141,142] were used as handles that were attached onto molecular backbones consisting of acetylene,[136] benzene,[137] adamantane,[143] silicon,[139] tin,[139] tetraphenylmethane,[133,138−141] tetraphenylsilane,[140] and spirobifluorene.[142]

So far, the use of the synthon approach has been successful only when it comes to the design of supramolecular solid-state structures of molecular tectons with a single type of functional group.[134,135] The same success rates are unfortunately unattainable with molecules that involve a broad range of functional groups.[31,32] The difficulties involved in predicting supramolecular structures in such solids arise from the inevitable competition of halogen- and hydrogen-bond donating and accepting groups, which ultimately results in unwanted supramolecular crossover reactions.[146] The difficulty of predicting outcomes of complex supramolecular reactions has recently prompted a surge in studies of synthon hierarchies[147] in molecular crystals, with a particular focus on synthons based on stronger hydrogen- and halogen-bond donors and acceptors. Examples of supramolecular synthons that are commonly studied and utilized in the context of crystal design are shown in Figure 8 (the schemes are accompanied by references to relevant studies of the corresponding synthons), while a summary of established synthon hierarchies is given in Section 5.

The current need to understand molecular recognition events and synthon hierarchies, as well as the desire to predict self-assembly processes involving weaker interactions, also continues to fuel long-standing and intense arguments about C−H···*X* contacts in molecular crystals (where X = O, N, F, Cl), particularly those about C−H···O[148,149] and C−H···F[150,151] contacts. These debates mainly revolve around two questions: first, are C−H···X contacts indeed attractive, or are they only random contacts between peripheral atoms belonging to adjacent molecules in a crystal lattice?[71,152] And second, if attractive, can these interactions be employed to design molecular crystals?[148]

As far as the first question is concerned, the classification of C−H···O contacts as hydrogen bonds has been suggested[153] and argued against[154] since the 1960s.[152,155,156] Several comprehensive statistical and computational studies have since then established that such energetically weak interactions play a significant role in the stabilization of crystal structures.[149,157−159] Taylor recently conducted a statistical analysis of intermolecular contacts of structures deposited in the CSD to establish the significance of various types of close atom−atom contacts in the context of crystal packing, whereby a scale was devised by comparing the ratio (R_F) of observed frequencies of occurrence of a specific atom···atom contact to its frequency expected at random.[157,158] These studies clearly established that molecular crystals exhibit significantly more C−H···X contacts than one would expect to observe if such contacts occurred randomly. Although computational studies of a smaller set of C−H···X interactions suggest that C−H···O and C−H···N interaction in structures of small molecules can be relevant in the stabilization of crystal lattices,[159] it is now accepted that such interactions are of "secondary importance in directing the supramolecular assembly"[155] in molecular crystals, and these were previously described as structure-directing only in the absence of stronger hydrogen and halogen bonds that are regularly used in crystal engineering exercises.[152,155] As to the second question, a related CSD study by Taylor demonstrated that O−H···F and N−H···F hydrogen bonds are indeed favorable interactions, but lack the strength to be competitive in the presence of other hydrogen-bond donors and acceptors.[160]

Despite a large number of reports of successfully designed molecular crystals, the difficulty associated with creating bespoke crystal structures while solely relying on the synthon approach cannot be denied.[29,161] The associated challenges are exemplified by the ability of molecular compounds to exhibit *synthon polymorphism*,[162] whereby the crystal constituents engage in distinct supramolecular interactions. Bearing in mind that polymorphism is triggered by thermodynamic and kinetic influences that often go beyond the chemical and supramolecular features of the crystallizing molecule, it is not surprising that polymorphism was declared as the nemesis of crystal engineering and synthon-based crystal design in their early days.[163] Examples of such influences are solvent choice, reaction times, or, surprisingly, environmental impurities that can act as heteronuclear seeds. For example, Robertson et al. reported that the choice of solvents dictates the self-assembly of cocrystal components either through hydrogen or halogen bonding, depending on the polarity of the solvent.[164] Kulla et

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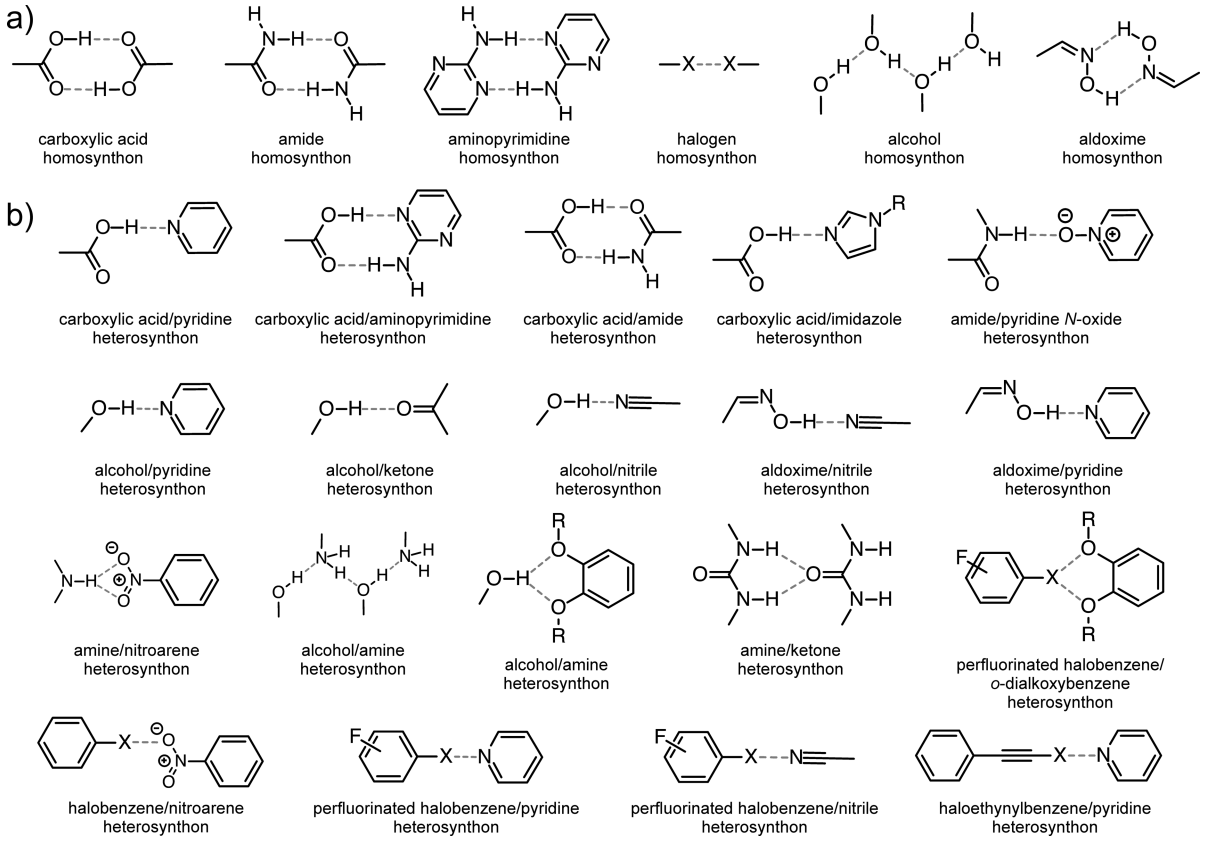

Figure 8. Supramolecular homo- and heterosynthons commonly studied and utilized in crystal design: (a) homosynthons based on carboxylic acids,[169] amides,[170] aminopyrimidines,[171] halogen atoms,[172,173] and aldoximes;[174] (b) heterosynthons involving carboxylic acids and pyridines,[128] carboxylic acids and aminopyrimidines,[175] carboxylic acids and amides,[176] carboxylic acids and imidazoles,[177] amides and pyridine *N*-oxides,[178] alcohols and pyridines,[179] alcohols and carbonyl groups,[31] alcohols and nitriles,[180] aldoximes and nitriles,[181] aldoximes and pyridines,[182] amines and nitroarenes,[119] alcohols and amines,[183] alcohols and *o*-dialkoxybenzenes,[184] amines and carbonyl groups in urea derivatives,[121] halobenzenes and nitroarenes,[185] perfluorinated halobenzenes and *o*-dialkoxybenzenes,[186] perfluorinated halobenzenes and pyridines,[187] perfluorinated halobenzenes and nitriles,[188] haloethynylbenzenes and pyridines[189] (where R = H, alkyl; X = Br, I).

al. demonstrated that cocrystal polymorphs based on different supramolecular synthons may be obtained mechanochemically by simply varying the reaction time.[165] Corpinot et al. described how two cocrystal formers yield synthon polymorphs under apparently identical experimental conditions but at different locations,[29] which was attributed to undetectable and uncontrollable laboratory contaminants that "seeded" the formation of a structure based on distinct synthons.[166] The formation of synthon polymorphs can also be achieved deliberately and in a controlled fashion using polymers as heteronuclear seeds.[167]

Another situation that exemplifies the limitations of the synthon approach is the unexpected incorporation of solvent molecules into a crystal lattice, which occurs either to minimize void space in the crystal lattice or to compensate for an imbalance of hydrogen-bond donors and acceptors in the crystallizing molecule.[168] This was effectively shown in a study by Sander et al. wherein, despite the sound use of the synthon strategies, attempts to prepare nonsolvated cocrystals of paracetamol and *trans*-1,2-*bis*(4-pyridyl)ethylene yielded several cocrystal hydrates, wherein all hydrogen-bond donors and acceptors were separated by water molecules (Figure 9), thus leading to the formation of so-called "masked synthons".[190] The unwelcome incorporation of solvent molecules has serious implications for the properties of a material. In another study, the Zaworotko group described the non-selective and

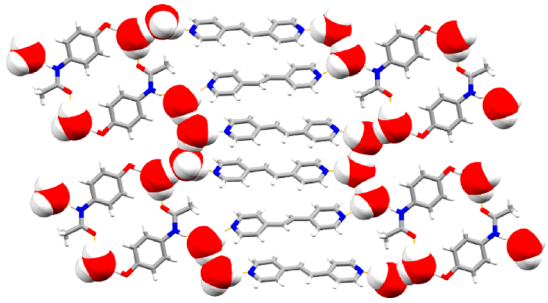

Figure 9. Supramolecular structure of a paracetamol: *trans*-1,2-bis(4-pyridyl)ethylene cocrystal hydrate wherein all hydrogen-bond donors and acceptors of the cocrystal formers are separated by water molecules (CSD reference code KETZIU[190]).

unpredictable incorporation of water molecules in crystal lattices of pharmaceutical cocrystals, which resulted in the observation of unforeseeable thermal properties of the prepared materials. The authors rightly declared that water is essentially another nemesis of crystal engineering.[191] The cause of hydrate and solvate formation is currently being investigated using experimental,[192] statistical,[192,193] and computational methods.[194−196]

The aforementioned challenges to control and foresee crystal structures led in recent years to the development of a range of statistical and computational tools to facilitate crystal

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design. The following section will outline effective and prominent predictive and analytical methods that are readily accessible to experimental organic solid-state chemists and whose use does not require extensive training.

4. COMPUTATIONAL AND STATISTICAL TOOLS FOR THE DESIGN OF MOLECULAR CRYSTALS

4.1. The Cambridge Structural Database Toolbox. In August 2018, the CSD contained records for more than 960 000 organic and metal−organic small-molecule crystal structures, whereof 43% (more than 416 000 structures) were typed as organic.[197] The Cambridge Crystallographic Data Centre (CCDC) has developed several tools that allow effortless surveys of the CSD. *Conquest* is the main program that enables the search and retrieval of structural data (e.g., molecular fragments, intermolecular close contacts, unit cell parameters) and provides bibliographic information and links to related literature sources.[198] The program *Mogul* supports statistical analyses of geometric features (e.g., bond lengths, valence angles, torsion angles, etc.) of molecules found in the CSD and consequently allows the prediction of molecular conformations in the solid state.[199] *Isostar* is another useful CSD tool that facilitates the estimation of the likelihood of the occurrence of intermolecular interactions and provides spatial characteristics (in form of 3D scatterplots, Figure 10) of such interactions using CSD data.[200,201] Lastly, *Mercury* is a crystal-structure visualization tool that enables graph-set analyses of hydrogen-bond patterns, calculates diffractograms using the atomic coordinates of the visualized crystal structure (these calculated patterns are regularly used in analyses of experimentally obtained powder patterns), and supports the calculations of intermolecular potentials using force fields. The program also includes the *CSD-Materials* module with features aimed at assisting the search for packing patterns and the calculation of similarities between crystal structures. It enables the prediction of crystal morphologies, the discovery of preferred intermolecular interactions, the assessment of hydrated crystal structures, and the identification of molecules that are likely to form a cocrystal with a target molecule. The relevance of the CSD tools to crystal engineering has recently been excellently described by Bond.[202] Several other case studies that demonstrate the same are described below.

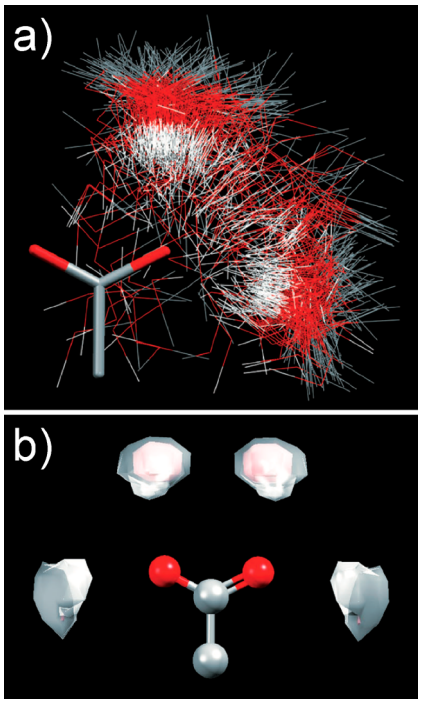

Figure 10. A 3D scatterplot of the distribution of O−H hydrogen-bond donor in crystal structures of molecules containing a charged carboxylate group (a) and a derived contour plot of the distribution around the carboxylate (b). The plots were adapted from with permission from ref 35. Copyright 2014 Wiley.

4.1.1. Polymorph Assessment. Galek et al. demonstrated how CSD tools can be applied to estimate which donors and acceptors in a given molecule are likely to engage in hydrogen bonding in a crystal structure, using results of statistical analyses of hydrogen bonds in the CSD. Hydrogen-bond patterns that were based on improbable interactions were deemed a sign of a less stable crystal structure and implied the existence of a more stable polymorph of the molecule in question.[203] The subject of their study was ritonavir, the active ingredient in a medication that was infamously subjected to market withdrawal owing to the unforeseen appearance of a poorly performing (e.g., less soluble) polymorph.[166] Using statistical analyses of CSD data, the authors assigned propensities[203] to the experimentally observed hydrogen bonds based their donor and acceptor types, as well as molecular environments. The authors found that the initially discovered and marketed ritonavir crystal form displayed a set of unlikely hydrogen bonds and, notably, that these interactions formed despite the presence of alternative functional groups able to engage in more probable, high-propensity hydrogen bonding. The authors stressed that the calculated propensities strongly suggested the existence of a polymorph with more likely hydrogen-bond patterns.[204] Considering that such an alternative crystal form indeed materialized very unexpectedly after ritonavir was marketed, and that this new form precluded the subsequent production of the commercial form, thus leading to the temporary withdrawal of the drug from the market, it is evident that hydrogen-bond propensity studies are critical to the engineering of stable functional solids. Propensity studies have also been used by others to estimate the risk of polymorphism with various degrees of success.[205]

The *CSD-Materials* module was recently enhanced through the addition of a feature that aids the understanding of relative crystal structure stabilities. The so-called full-interaction map (Figure 11) enables the identification, quantification, and visualization of interaction preferences of a molecule in a specific conformation.[206]

4.1.2. Knowledge-Based Design of Salts and Cocrystals. Hydrogen-bond propensity calculations[203] have recently also been applied to the design of multicomponent crystals,[207] namely, salts and cocrystals. Using pyrimethamine as model compound, Delori et al.[208] conducted a cocrystal and salt screen using a series of 10 carboxylic acids as coformers, whereby seven multicomponent solids were discovered. The salt/cocrystal formation was unsuccessful in only three cases. The crystal screen was followed up by propensity calculations to predict the success rates of a supramolecular syntheses using data derived from the CSD and by considering molecular structure and ΔpK_a values of acidic and basic functional groups. The results of the crystal form screen were in complete agreement with the outcome of propensity calculations, thus

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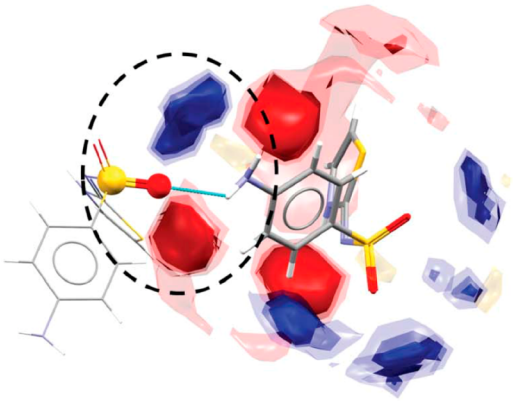

Figure 11. Full-interaction map of sulfathiazole form **I**. The map highlights sites from which hydrogen-bond donors (blue) and acceptors (red) are expected to interact with a functional group. The dashed ellipse highlights the lack of a donor (dark blue) engaging with the primary amine, as well as an acceptor well outside the suggested red area indicating a poor hydrogen bond geometry. The map was adapted with permission from ref 206. Copyright 2013 Royal Society of Chemistry.

demonstrating the utility and reliability of this design approach.

To further scrutinize the predictive power of propensity calculations, the authors conducted salt/cocrystal screens involving pyrimethamine and a selection of chemically complex coformers.[209] Although similar success rates were attained, and despite the wider range of plausible intermolecular hydrogen bonds, the main feature of this study was the revelation that propensity calculations could account for the formation of solvates of salts and cocrystal.

4.1.3. Cocrystal Design Based on Molecular Complementarity. Fábián devised a semiquantitative predictive model for cocrystal formation based on statistical analyses of known cocrystals in the CSD.[210] The identification of molecular properties that govern cocrystal formation was accomplished by quantifying a wide range of molecular attributes (131 in total) of each cocrystal component, whereby several descriptors refer to one physical property. For example, log*P* and several surface descriptors refer to molecular polarity. The working hypothesis was that sets of descriptors referring to a property that governs cocrystal formation will assume favorable combinations of values more often than unfavorable combinations, and that molecular complementarity (in terms of cocrystal formation) is indicated when the descriptors of two distinct cocrystal formers correlate. The data survey and the statistical analyses revealed molecular properties that influence cocrystal formation. Molecular size and polarity strongly affect cocrystallization, whereas the balance of hydrogen-bond donors and acceptors of two molecules is not indicative of the tendency of two molecules to cocrystallize.

The utility of this predictive method was demonstrated in a crystal engineering exercise involving the antimalarial drug artemisinin.[211] Artemisinin is a challenging compound from a crystal engineering point of view, as it has no "good" hydrogen-bonding functional groups. A mechanochemical cocrystal screen involving 75 coformers resulted in the discovery of only two cocrystals. However, a virtual screen using Fábián's predictive method identified 42 coformers (out of the 75 studied ones) that were likely to form cocrystals. Despite the 40 false-positive results obtained from the virtual cocrystal screen, it was concluded that semiquantitative evaluations of molecular complementarity are a viable way to meaningfully cut down cocrystal screening times, by eliminating unlikely coformers from the experimental procedures. Fábián's method was recently implemented in the CSD-Materials module of *Mercury*.

4.2. Prediction of Synthon Hierarchies Using Electrostatic Potential Maps. The fine-tuning of solid-state properties of specialty chemicals (e.g., pharmaceuticals) is commonly achieved through the formation of multicomponent solid forms. Since most of these specialty compounds are structurally very complex and display a range of functional groups, it is crucial to understand the hierarchy of plausible supramolecular interactions between the constituents of an envisioned multicomponent solid. While Etter established that the best hydrogen-bond donor and acceptor are likely to engage in hydrogen bonding with one another (see Section 5),[122] it remains challenging to estimate empirically what the best donors and acceptors are in molecules that contain a wide range of hydrogen-bonding functional groups. A solution was offered by Hunter, who proposed that molecular electrostatic potential surfaces (MEPS) may be used to identify plausible hydrogen-bonding functional groups, and to rank the strength of donors and acceptors.[212] MEPS visualize local maxima and minima in charge distributions on the van der Waals surface, which correspond to hydrogen-bond donor and acceptor sites, respectively (Figure 12). The maps are easily generated using commercially accessible software packages (e.g., Gaussian).

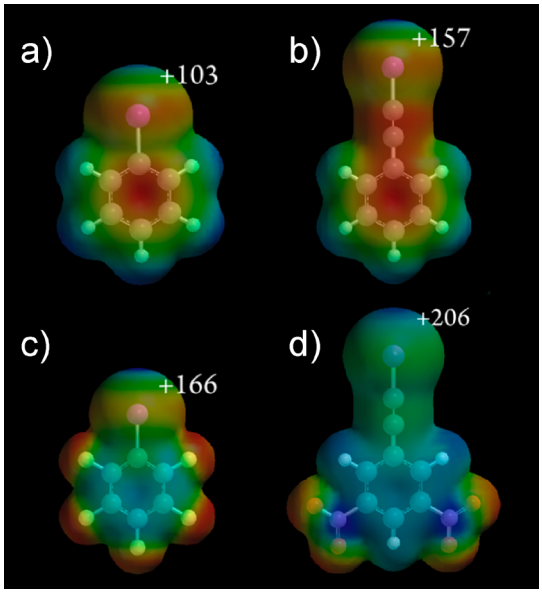

Figure 12. Molecular electrostatic potential surfaces (MEPS) of (a) iodobenzene, (b) iodoethynylbenzene, (c) pentafluoroiodobenzene, and (d) 1-(iodoethynyl)-3,5-dinitrobenzene. The MEPS were used to evaluate relative strengths of the halogen-bond donors. Adapted with permission from ref 189. Copyright 2015 American Chemical Society.

The usefulness of MEPS in the context of crystal design was highlighted by the Aakeröy group in a series of studies that aimed to establish synthon hierarchies in solid-state structures (Figure 12).[189,213−216] Section 5 of this Tutorial Review features additional examples of how MEPS were used to rank relative strengths of halogen and hydrogen bonds.

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4.3. Analyzing and Understanding Intermolecular Interactions and Packing in Molecular Crystals. Since structures of molecular crystals (and crystals in general) are incredibly difficult to predict empirically, it is not surprising that the design of molecular crystals is usually approached through reverse engineering, that is, the extraction of design principles from similar and related crystal structures. To derive such needed guidelines from known crystal structures, the crystal engineer regularly resorts to crystal packing diagrams and to the measurement of bond distances and angles. These analyses, however, do not enable an evaluation of all close contacts that a molecule engages in, nor do they yield much-needed insights into how particular contacts contribute to the crystal lattice energy. The need to identify and to estimate energetic contributions of close contacts to lattice energies has led to the development of numerous computational methods, among which Hirshfeld surface analyses and PIXEL calculations are the most prominent ones.

4.3.1. Hirshfeld Surface analysis. Important interactions in crystal structures are commonly described with pairs of atoms that exhibit distances that are closer than the sum of their van der Waals radii. Unfortunately, such close-packing analyses that rely on surveys of geometrical features (e.g., atom−atom distances) are not suitable to fully describe the entire surroundings of a molecule within a crystal. This knowledge is, however, essential to understand the complex interplay of close packing and intermolecular interactions. With this in mind, Spackman and co-workers developed a method that defines the shape of a molecule within a crystal lattice.[217] This method also enables the mapping of the entire surroundings of this molecule onto an isosurface, the so-called Hirshfeld surface.

The Hirshfeld surface is constructed using electron distributions as shape-defining criteria and the weight function $w(r)$ to describe the proportion of electron density at point r that belongs to a molecule in a crystal lattice:

$$w(r) = \frac{\rho_{\text{promolecule}}(r)}{\rho_{\text{procrystal}}(r)} = \frac{\sum_{A\in\text{molecule}} \rho_A(r)}{\sum_{A\in\text{crystal}} \rho_A(r)} \simeq \frac{\rho_{\text{molecule}}(r)}{\rho_{\text{crystal}}(r)}$$

(where $\rho_A(r)$ represents the spherically averaged atomic electron density centered on nucleus A, while "promolecules" and the "procrystal" are defined as sums over spherical atoms belonging to the molecules and the crystal, respectively).

The Hirshfeld surface is an isosurface defined by $w(r) = 0.5$ and encloses a volume of the crystal lattice wherein the electron density of the "promolecule" exceeds that from all surrounding molecules (Figure 13). The ratio between electron densities of the "promolecules" and the "procrystal" is viewed as a reasonable approximation to the ratio between electron densities of "true molecules" and the "true crystal". Hirshfeld surfaces and volumes are significantly larger than conventional ones (e.g., those based on van der Waals radii) and fill the crystal space more efficiently (>95%) than conventionally calculated molecular volumes (60−80%, see Section 2.1).

Hirshfeld surface analyses provides the opportunity to map calculated structural (e.g., shape index, curvedness,[218] or normalized contact distances between molecules[219]) and electronic features (e.g., electrostatic potentials[220]) of a molecule onto its Hirshfeld surface. Normalized contact distances (d_{norm}) and d_{norm} surfaces were reported to be particularly valuable for the identification of *all* intermolecular

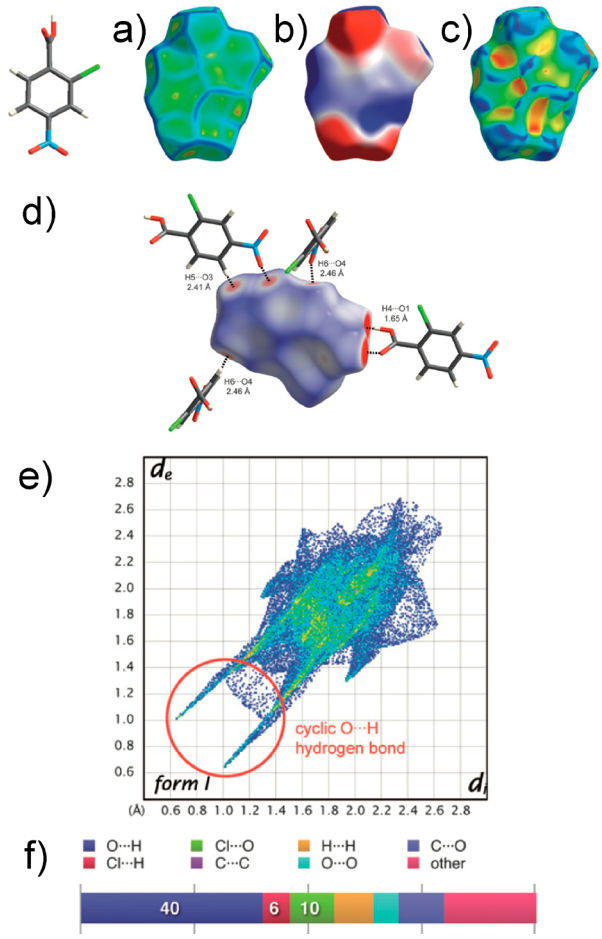

Figure 13. Hirshfeld surfaces of 2-chloro-4-nitrobenzoic acid (form I) mapped with (a) curvedness, (b) electrostatic potentials, (c) shape index, and (d) d_{norm} over a −0.4 to 1.4 Å range. The 2D finger plot of form I is shown in (e), while (f) features the percentage contributions to the Hirshfeld surface area for different intermolecular contacts. Adapted with permission from ref 218. Copyright 2009 Royal Society of Chemistry.

contacts in a crystal structure,[219] while other mapped features (e.g., shape index and curvedness) are useful in studies of molecular packing modes (Figure 13).[218] Hirshfeld surfaces are therefore ideal tools to study the role of molecular shape and electrostatic complementarity in crystal packing.

Since Hirshfeld surfaces are three-dimensional, their features can only be effectively explored using computational visualization tools. The need to highlight and report complete sets of intermolecular interactions at once in 2D media led to the development of 2D fingerprint plots that qualitatively and quantitatively describe intermolecular interactions that a molecule experiences in a crystal lattice (Figure 13e).[221] The fingerprint plots are constructed using calculated distances from the surface to the nearest atom interior to the surface (d_i) and distance from the surface to the nearest atom exterior to the surface (d_e) for each point on the Hirshfeld surface. The d_i and d_e values of each surface point are binned in intervals of 0.01 Å to form a pixel on the 2D plot. Each pixel is then colored based on the fraction of surface points in it, whereby a blue signifies a pixel with a low fraction, green indicated moderate fractions, while red indicates high fractions.

The 2D fingerprint plots are now well-established tools for crystals structure analyses and are commonly used to compare

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crystal structures of structurally related molecules[222] and polymorphs.[222,223] Hirshfeld surfaces and the corresponding fingerprint plots are straightforwardly and quickly calculated using the *CrystalExplorer* software package.[224]

4.3.2. PIXEL Calculations. Recognizing the need to reliably and quickly quantify intermolecular interactions in organic crystals, Gavezzotti developed a method for the computation of intermolecular potentials from molecular properties only. The so-called PIXEL method[225,226] is based on the numerical integration of classical formulas over quantum chemical electron densities and allows the partition of the cohesive energy between two molecules into Coulombic, polarization, dispersion, and repulsion terms, thus revealing the inherent character of an intermolecular interaction.[71] PIXEL calculations are based on molecular electron densities, which are calculated by a quantum-chemical program, such as *Gaussian*.[57] The obtained number of electron pixels (several millions) is reduced by identifying insignificant points on the electron-density grid and condensing the remaining pixels into superpixels (up to 20 000). Each superpixel is assigned a charge that corresponds to the sum of all the charges of their original pixels, as well as the atomic polarizability of its nearest atom. The molecule and its superpixels are then replicated using symmetry operations defined by the crystal symmetry of the studied system to obtain a molecular cluster. The Coulombic energy of the system is then obtained by direct summation over pixel−pixel, pixel−nucleus, and nucleus−nucleus Coulomb interactions in the molecular cluster. Unlike the Coulombic term that is derived from ab initio calculations, the polarization, dispersion, and repulsion terms are determined using parameters that are derived from physically consistent data. The PIXEL method enables calculations of the sublimation enthalpies of molecular crystals and intermolecular interaction energies, providing results that are comparable to those obtained using high-order ab initio calculations,[227−229] but also with a remarkable 100-fold reduction in computational cost. The computation of crystal lattice energies of large organic molecules takes only few minutes on a modern desktop computer.[71]

The PIXEL method is an extremely useful tool to explore the nature and strengths of supramolecular interactions that crystal engineers regularly employ to design molecular crystals. In a recent study,[230] Dunitz and Gavezzotti demonstrated that PIXEL calculations can be used not only to rank synthons by strength (Table 1), but also to identify intermolecular interactions that are perceived as binding, but are in fact associated with repulsion ("antagonist synthons"), or interactions that are characterized by insignificant attractive or repulsive forces ("neutral synthons"). The study revealed that the strongest supramolecular synthons are sustained by O−H···O, N−H···O, and N−H···N hydrogen bonds, which display binding energies of −35 kJ mol^{-1}, −30 kJ mol^{-1}, and −25 kJ mol^{-1}, respectively. Synthons based on weaker interactions (e.g., C−H···O, Cl···Cl) were shown to be exhibit very modest binding energies (less than −10 kJ mol^{-1}). Furthermore, several trends have been identified. For example, the binding energy of centrosymmetric homosynthons is usually doubled, while the energy in heterosynthons amounts to the sum of the all hydrogen bond energies involved. The synthon strength was also found to be significantly affected by the electronic properties of substituents (e.g., electron withdrawing substituents weaken the synthon strength). The authors concluded their study with the acknowledgment that most investigated synthons appear to be stable crystal building blocks. In a related study by Moggach et al., the authors showed how PIXEL calculations can be employed to identify destabilizing hydrogen bonds that would be otherwise very likely presumed as strongly stabilising interactions based on their bond distances and angles.[231]

Table 1. Binding Energies of Supramolecular Synthons Calculated Using the PIXEL Approach, As Reported in Ref 230

synthon	E/kJ mol^{-1}
acetic acid double O−H···O	−72
trifluoroacetic acid double O−H···O	−67
acetic acid single O−H···O	−32
acetic acid O−H···O (plus C−H···O)	−38
acetamide double N−H···O	−60
acetamide single N−H···O	−28
acetic acid/trifluoroacetamide	−64
pyrazole double bent N−H···N	−58
pyrazole single linear N−H···N	−39
phenol O−H···O	−25
urea/acetone bifurcated N−H···O	−37
urea/hexafluoroacetone bifurcated N−H···O	−17
trans-but-1-en-3-one, double C−H···O	−14
1-chloro-2-nitropropene double N−O···Cl	−9
benzene offset $\pi\cdots\pi$ stacking	−6
benzene/hexafluorobenzene offset stacking	−17
benzene T-shaped C−H···π interaction	−11
linear Cl···Cl	−2

The PIXEL method has been utilized in various aspects of crystal chemistry in recent years. For example, PIXEL calculations were employed to understand crystal packing,[232−234] solid-state reactions,[235] polymorphism,[236−238] and high-pressure structures,[239,240] and they have also been used in the context of crystal structure prediction (to analyze structural motifs and calculate interaction energies between pairs of molecules in predicted structures).[241,242]

The popularity and efficacy of such fast and fairly accurate calculations led recently to the incorporation of a method analogous to the PIXEL approach into *CrystalExplorer*, thus enabling Hirshfeld surface analyses along with the calculation of intermolecular interaction energies.[243,244] The analysis of intermolecular interactions is also greatly enhanced by the recent development of *processPIXEL*,[245] a program that visualizes the output of PIXEL calculations by generating energy vectors that represent individual interactions. We expect that these recent developments will further ease the crystal engineer's efforts to understand intermolecular interactions in molecular crystals.

5. EMPIRICALLY DERIVED GUIDELINES FOR THE DESIGN OF MOLECULAR CRYSTALS

The fine-tuning of properties of specialty chemicals is nowadays habitually approached through the formation of multicomponent solids, particularly salts, cocrystals, and solid solutions. The growing interest in cocrystals[246] (and other multicomponent solids) in recent years prompted numerous investigations that focused on the understanding of self-assembly processes in the organic solid state, with the ultimate goal of developing guidelines that would allow one to design and predict supramolecular structures in solids.

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This section highlights design principles that were derived from crystallographic studies and statistical analyses of databases that were occasionally supported by computational studies. The collection of guidelines in this section is limited to those that may be generally applicable (i.e., to whole compound classes), rather than applicable to particular compounds.

5.1. Solid Solutions and Isostructurality. Molecular solid solutions (also commonly referred to as mixed crystals) were extensively studied by Kitaigorodskii in the 1950s. His pioneering work and established guidelines for their preparation are still regarded as authoritative in the field. According to Kitaigorodskii, molecular and crystal isomorphism, as well as isoelectronicity, are conditions for the formation of continuous solid solutions (viz. the components of the solid solution exhibit unlimited solubility in the solid state).

To replace one molecule with another in a crystal lattice without significant disruptions to the ordered structure, the molecules need to be similar in size and shape. Kitaigorodskii proposed the coefficient of geometrical similarity (ε) as a measure of molecular isomorphism:

$$\varepsilon = 1 - \frac{\Delta}{\tau}$$

where Δ refers to the minimal non-overlapping volume of the two molecules, while τ refers to the maximal overlapping volume of both molecules.[62] Consequently, the closer ε is to 1, the more similar two molecules are in size and shape.

Early studies of solid solutions based on naphthalene and some of its β-substituted derivatives showed that solubility is observed in cases where two molecules exhibit ε values larger than 0.85.[247] On the other hand, it was also found that the α-substituted naphthalene derivatives with virtually identical ε values cannot be dissolved in naphthalene. This observation suggested that molecular shape alone is not a decisive condition for solid-state solubility, and also led to the speculation that solubility may depend on whether a molecular substitution leads to the disruption of molecular assemblies in the crystal lattice through unfavorable interactions of the protruding part of the solute with the host lattice. This also implies that small molecules dissolve more readily into crystal lattices of larger molecules than larger molecules into structures of smaller compounds. These considerations led to the formulation of the *basic rule of solubility* that states that a "molecule A dissolves in the crystal B only if the coefficient of the geometrical similarity of the molecules ε exceeds 0.8, and if a replacement of the molecule A by the molecule B does not disturb significantly the molecular packing".[247] It was also proposed that a disruption of molecular packing should not occur if intermolecular distances in the crystal lattice do not change by more than 0.4−0.5 Å.[62]

Such minimal disturbances are likely to occur if solutes with geometrically similar structural moieties (i.e., functional groups) are used. Early work of Kitaigorodskii suggested that approximate isomorphous solutes may be prepared through substitutions of the following atoms: (1) a halogen atom with another one (Cl, Br, and I are particularly interchangeable), (2) O with S, and (3) C with Si, Ge, Sn, and Pb (Figure 14).[62,248] It was further claimed that azo (R−N═N−R), ethylene (R−CH═CH−R), and ethyl (R−CH_2═CH_2−R) moieties can be also be considered isomorphous.[62] The structural equivalence of chlorine and methyl groups[249,250] was next proposed based on Kitaigorodskii's studies[61] of molecular

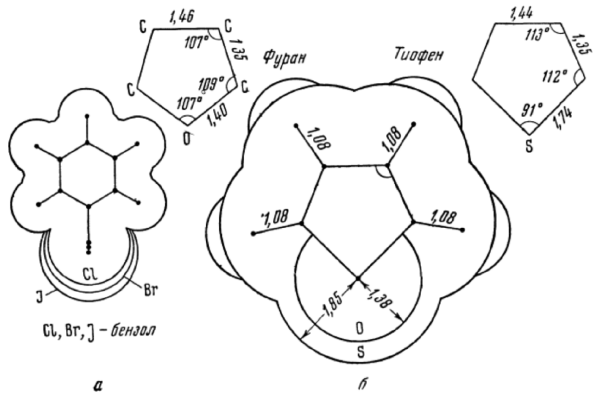

Figure 14. Geometrical similarities between halobenzenes (left), furan and thiophen (right), as illustrated by Kitaigorodskii. Reproduced with permission from ref 248. The halobenzenes are labeled as *Cl, Br, I - Benzol*, while furan and thiophene are labeled as *Furan* and *Tiofen*, respectively, in Russian (Cyrillic script). Copyright 1955 Russian Academy of Sciences.

volumes in crystals. Ensuing studies by other groups corroborated that the halogen,[251,252] the Cl/CH_3,[251−253] ethylene/ethyl[254] and O/S[255] interchangeabilities support the formation of solid solutions. More recent investigations reported the preparation of solid solutions based on pairs of molecules wherein other molecular moieties were exchanged, such as S and Se,[256,257] or H and F.[258,259]

Kitaigorodskii also recognized that geometrical relationships alone are not always critical to the formation of solid solutions, and established two additional rules of solubility. The first one states that "solubility is impossible if the impurity molecule would break the intermolecular hydrogen bonding network".[247] The second exception refers to dipole moments and the change in the energy of dipolar interactions: "dipole moments are not affecting solubility provided that the molecules in the crystals are oriented so that two (or more) molecules form an island with no net dipole".[247]

Kitaigorodskii acknowledged in his early studies that *molecular* isomorphism and the occurrence of minimal disruptions during the molecular replacement alone are not sufficient conditions for the formation of continuous solid solutions, and that *crystal* isomorphism is required to accomplish continuous solubility in the solid state.[247] More recent studies have, however, demonstrated that crystal isomorphism is not an essential condition. Specifically, Schur et al. showed that phenazine and acridine display continuous solubility over a wide composition range in spite of not exhibiting any isomorphous nor isostructural polymorphs, as demonstrated by limited crystal structure predictions.[260] In a related study, Lusi et al. showed that immiscible isomorphous molecules, such as anthracene and phenazine, can be prompted to form a solid solution when a third isomorphous molecule (such as acridine) is introduced.[261]

Although crystal isostructurality and isomorphism are not a crucial condition for solid-state solubility, they are regularly used as probes to estimate the solid-state miscibility of two molecular compounds.[254] Crystal isostructurality has also become an attractive materials feature, because it holds appealing prospects for the development of materials with tunable properties, yet common structural motifs.[262] In this context, numerous studies investigated isostructurality in single- and multicomponent molecular crystals by interchang-

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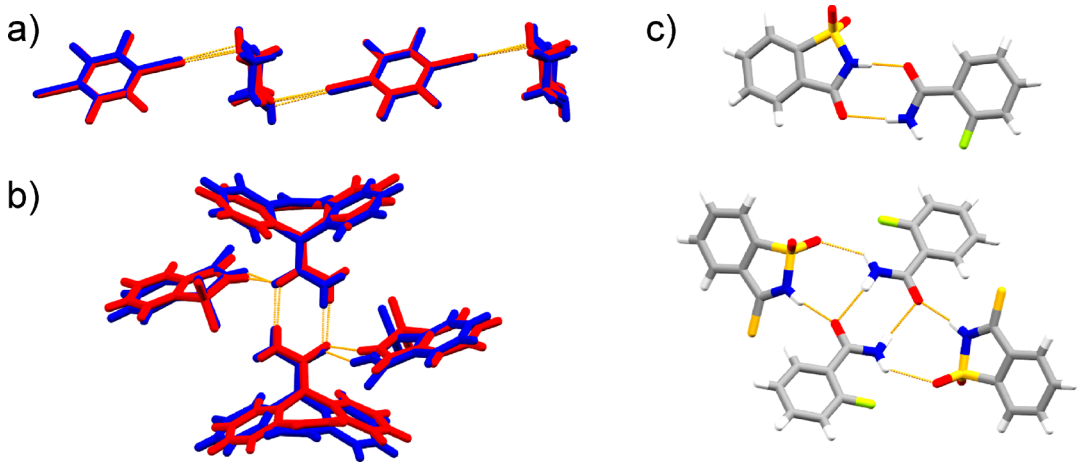

Figure 15. Crystal structures: (a) the halogen-bonded cocrystals of 1,4-diiodotetrafluorobenzene with morpholine (red) and thiomorpholine (blue)[262] (b) carbamazepine with saccharin (red) and thiosaccharin (blue),[270] and (c) 2-fluorobenzamide with thiosaccharin and thiosaccharin.[270] Isomorphous solids were obtained upon O/S exchanges in cases where an exchanged O atom was involved in halogen bonding (a) or was not engaged in hydrogen bonding (b). Distinct cocrystals formed if the exchanged O atom is involved in hydrogen bonding (c). (CSD reference codes for the depicted crystal structures: (a) DIVCOB and DIVCER,[262] (b) UNEZAO,[286] and YAJGEY,[270] and (c) YAJFIB and YAJGOI[270]).

ing atoms and functional groups that were deemed as approximately isomorphous by Kitaigorodskii. Although these studies (mainly focused on Cl/CH_3,[249,263−265] Cl/Br,[266,267] Br/I,[262,268,269] O/S,[262,270] and azo/ethylene[271] substitutions) were pleasingly consistent with Kitaigorodskii's proposed exchange principles, it was found that interchanges of functional groups are, in some cases, only achieved if the exchanged atom is not involved in any directional or electrostatic interaction. For example, CH_3/Cl exchanges are only permitted if the Cl atoms are not involved in directional and/or electrostatic interactions.[265,272]

The substitution of a carbonyl O atom with a S atom leads to the formation of isostructural (or isomorphous) crystals only if the O atom does not participate in hydrogen bonding (Figure 15b).[270] An O/S exchange does, however, support isostructurality if the substituted atoms participate in halogen bonding with I- or Br-based donors (Figure 15a).[262] The same applies to I/Br exchanges in cases where the halogen interacts with N-based acceptors.[262,268,269] These findings demonstrate that Kitaigorodskii's exchange principles apply under specific conditions, which depend on the environment of the exchanged functional group, as well as the types of intermolecular interactions this group is engaged in. The interested reader may find Lusi's recent review on the design, synthesis, and characterization of organic and metal−organic solid solutions useful in this context.[273]

5.2. Proton Transfers and the ΔpK_a Rule. An essential step in the design of molecular salts and cocrystals is the selection of appropriate counterions or coformers. This choice is regularly based on the pK_a rule of thumb, which states that if a ΔpK_a value:

$$\Delta pK_a = pK_a\,(\text{base}) - pK_a\,(\text{acid})$$

of an acid−base pair is greater than 3, a salt is expected to form. The origin of this rule is not perfectly clear, but was likely formulated based on accumulated experience within the pharmaceutical industry.[274] The literature entails only a very limited number of spectroscopic and crystallographic studies that investigated the dependence of ΔpK_a on salt formation and validated this rule. Johnson et al. used IR spectroscopy to study proton transfers in a series of solids composed of benzoic acid and 18 pyridine derivatives, and observed that salt formation occurs at $\Delta pK_a > 3.75$.[275] The same observations were made in a crystallographic investigation of pyridine:carboxylic acid complexes by Bhogala et al.[276] Their analyses revealed that salt formation occurs at $\Delta pK_a > 3.75$, while a $\Delta pK_a < 0$ leads to cocrystal formation. Notably, complexes with components in the ΔpK_a range of 0−3 display hydrogen bonds with a partial ionic character, which renders the prediction of salt (or cocrystal) formation in this ΔpK_a range virtually impossible.

With this in mind, Cruz-Cabeza attempted a verification of the ΔpK_a rule using a large CSD data set of chemically diverse acid−base complexes, along with pK_a calculators.[274] The analyses revealed that ionized acid−base complexes (i.e., salts) observed $\Delta pK_a > 4$, while neutral complexes (i.e., cocrystals) are obtained at $\Delta pK_a < -1$. Acid−base pairs with ΔpK_a values that lie in-between −1 and 4 exhibit a linear relationship between the probability of salt formation and their ΔpK_a value (Figure 16). Considering the size of the data set (nearly 6500 crystal structures) and the chemical diversity of the studies solids, it is fully justified to use these revised ΔpK_a ranges as useful guide in the design of multicomponent molecular crystals. The reader must be aware, however, that this empirical rule is based on pK_a values, which are a quantitative measure of the strength of acids in *solution*, rather than the solid state. Because of this critical limitation, the ΔpK_a rule should be used only as a *guide* in the design of a molecular crystal, and it should be expected that the rule will not always guide such efforts accurately.

5.3. Experimentally Derived Guiding Principles for the Design of Molecular Crystals. The design of targeted crystal structures based on molecules that display a large number and variety of functional groups is regularly associated with modest success rates, as shown by Bučar et al.,[32] Corpinot et al.[29] and many others. To gain a better understanding of such hard-to-predict self-assembly processes, the crystallographic community has engaged in numerous crystallographic analyses of supramolecular structures in molecular crystals. A large proportion of these investigations was focused on particular "iconic" compounds (e.g., carbamazepine) or classes of compounds (e.g., xanthines), and any understanding of the

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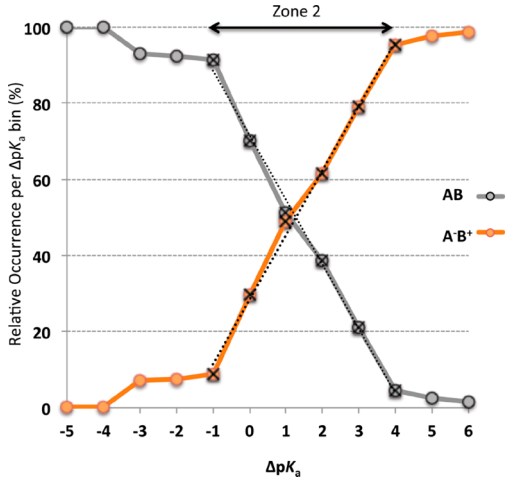

Figure 16. Relative occurrences of neutral acid−base complexes (**AB**, gray) and ionic complexes ($\mathbf{A^-B^+}$, orange) shown as a function of the calculated ΔpK_a values. Adapted with permission from ref 274. Copyright 2012 Royal Society of Chemistry.

supramolecular solid-state chemistry of these compounds is not likely to aid the design of crystal forms of any given molecule. With this in mind, numerous groups engaged in systematic and carefully designed crystallographic studies of halogen- and hydrogen-bonded structures of reasonably simple model compounds, to establish their hierarchy in supramolecular reactions.

In this section, we highlight a selection of model studies that have shaped our current understanding of supramolecular structures in the solid state. The design principles and synthon hierarchies described here should be used as guidelines, rather than strict rules, considering that they are in some cases derived from a very limited number of crystal structures. It also may be that the derived guidelines apply to certain classes of compounds and are not universally applicable. We expect that further studies of these and other supramolecular systems will transform our current understanding of some synthon hierarchies that are described hereafter.

5.3.1. General Rules for Hydrogen Bonding. In the late 1980s, Etter recognized the need to identify general phenomena that guide hydrogen-bond-driven self-assembly of organic compounds into crystals. She reported three general rules[122] (the first of which is based on Donohue's observations[120,277]) in her seminal paper on the encoding and decoding of hydrogen-bond patterns in molecular solids:

(1) "All good proton donors and acceptors are used in hydrogen bonding."
(2) "Six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds."
(3) "The best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds to one another."

These three rules (and the third one in particular) are nowadays regularly applied in the design or multicomponent cocrystals[175−178] and have proved particularly useful in the development of ternary cocrystals[278−280] (Figure 17).

5.3.2. Synthon Hierarchies in Molecular Crystals. 5.3.2.1. Homosynthons or Heterosynthons? A consequence of Etter's hierarchy principle (best donors interact with best acceptors) is that the formation of heteromeric synthons is preferred to the formation of homomeric interactions. The

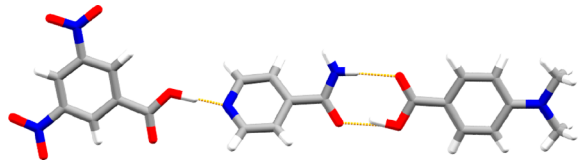

Figure 17. X-ray crystal structure of a ternary supermolecule that was designed using Etter's general rules for hydrogen bonding (CSD reference code BUFBIP[278]).

formation of homosynthons in the presence of functional groups that can engage in the formation of heteromeric interactions is, however, not unprecedented. For example, Basavoju et al.[281] reported a indomethacine/saccharin cocrystal that is based on indomethacine carboxylic-acid homodimers and saccharin amide homodimers (Figure 18,

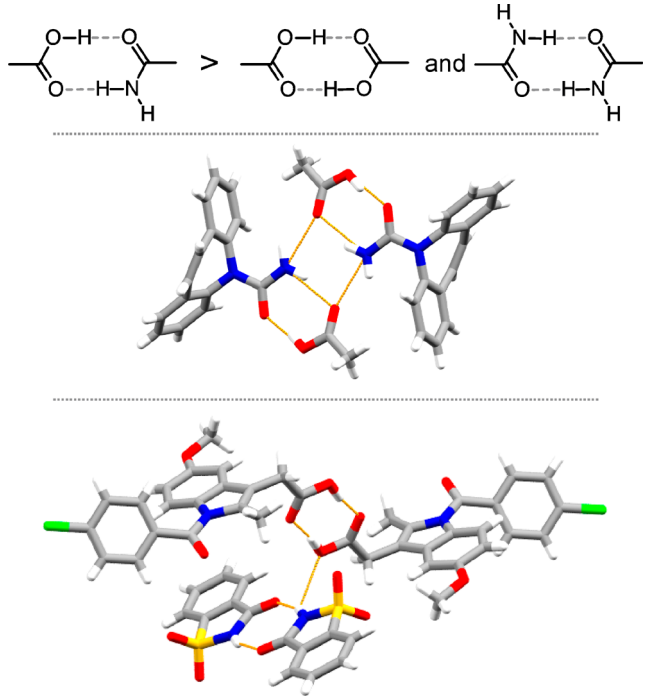

Figure 18. Synthon hierarchies in cocrystals composed of carboxylic acids and amides (top) and the crystal structures of supermolecules that do (middle, CSD reference code UNEZIW[286]) and do not conform (bottom, CSD reference code UFERED[281]) to this hierarchy.

bottom). Similar observations were made in the case of cocrystals composed of imidazole and carboxylic acids. Specifically, Bučar et al. showed that caffeine and 6-hydroxynaphthoic acid cocrystallize to form four-component assemblies based on carboxylic acid homodimers and heteromeric O−H(hydroxyl)···O(carbonyl) interactions, while the strong imidazole hydrogen-bond acceptor is not involved in any noticeable supramolecular interaction.[282] Such an observation was certainly unexpected, considering that all caffeine/carboxylic acid cocrystals known at the time invariably formed structures based on a heterosynthon involving the acid and imidazole functional groups. A more recent study by Diez et al., however, reported that caffeine and 6-hydroxynaphthoic acid can indeed engage the formation of crystal forms based on the anticipated carboxylic-acid/imidazole heterosynthon.[283]

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That the formation of heterosynthons is favored over the formation of homosynthons was revealed by several crystallographic studies. For example, Desiraju showed in the 1990s that only 10% of cocrystals composed of two distinct carboxylic acids (**A** and **B**) form cocrystals composed of **AA** and **BB** homodimers.[284] Similar observations were made later by Aakeröy et al.[285] who observed that the formation of heterodimers is favored over the formation of homodimers in cocrystals composed of benzoic acids with amides, nicotinamide, and pyrazinecarboxamide (Figure 18, top). The unexpected observation of homomeric interactions, as opposed to the expected formation of heteromeric synthons, was observed in only 16% of the investigated cocrystals. Similar results were reported by the Zaworotko group in a related study of carbamazepine/carboxylic acid cocrystals, which established that the formation of cyclic amide/acid heterosynthons (Figure 18, middle) is clearly favored over the generation of the cyclic amide- and carboxylic-acid homodimers[286] (Figure 18, bottom).

5.3.2.2. Formation of Carboxylic-Acid/Pyridine Synthons in the Presence of Amide Functional Groups. Aakeröy et al. reported a series of cocrystals based on isonicotinamide and various carboxylic acids. The study showed that cocrystal formation occurred according to Etter's hierarchy rules. In particular, the reported cocrystals invariably exhibited supramolecular structures wherein the best donor (the carboxyl group) and best acceptor (the pyridyl moiety) interact with each other, while the second-best donors and acceptors (the amide moiety) were left to interact with each other.[287]

In a related study of carboxylic-acid/isonicotinamide cocrystals, Vishweshwar et al. showed that only about 70% of the prepared cocrystals formed structures based on carboxylic-acid/pyridine heterosynthons and amide/amide homosynthons, while 30% of structures displayed carboxylic-acid/amide synthons. The carboxylic-acid/amide synthons were observed only in cases were weaker carboxylic acids were used as coformers.[288] Despite the lower observed supramolecular yield, it is still reasonable to expect the formation of acid-pyridine heterosynthons in cases where amide moieties are available to participate in a supramolecular interaction (Figure 19).

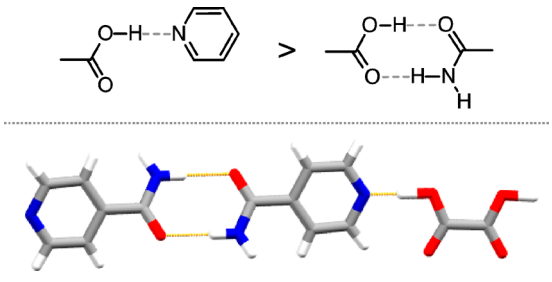

Figure 19. Synthon hierarchies in cocrystals composed of carboxylic acids and isonicotinamide (top), as seen in the X-ray crystal structure of the (isonicotinamide)·(oxalic acid) cocrystal (bottom, CSD reference code ULAWAF[288]).

These observations are also corroborated by a CSD survey of carboxylic-acid/(iso)nicotinamide cocrystals that was conducted as a part of this literature review.[197] The search revealed that 204 carboxylic-acid/(iso)nicotinamide cocrystals were reported to date, whereof 84 contain nicotinamide and 120 isonicotinamide as cocrystal former. It was found that 89% of these cocrystals entail carboxylic-acid/pyridine synthons and only 26% featured carboxylic-acid/amide synthons.

Of the 84 nicotinamide cocrystal structures, 82% were based on carboxylic-acid/pyridine interactions, an amide/amide homosynthon or, as in an insignificant number of cases, an interaction of the amide with a third functional group. Only 33% of the cocrystal structures entailed carboxylic-acid/amide interactions. A survey of these cocrystals revealed that *all* carboxylic-acid/amide interactions are enabled by the presence of more than one carboxyl group in the coformer (the carboxyl groups of the coformer can therefore interact with both the pyridyl and the amide group); or by the presence of additional hydrogen-bond donors that are stronger than the carboxyl donor (e.g., hydroxyl groups) and are thus the preferred donor to the hydrogen-bonding pyridyl group. Only less than 4% of the analyzed cocrystals feature structures wherein the carboxylic group interacts with the amide, while the pyridyl group is not engaged in any kind of hydrogen bond. Of the 120 isonicotinamide cocrystals, nearly 94% displayed the carboxylic-acid/pyridine synthon, whereas only 23% displayed carboxylic-acid/amide interactions. As in the case of the nicotinamide cocrystals, the majority of structures that display a carboxylic-acid/pyridine synthon also feature amide/amide interactions. Also, structures that feature carboxylic-acid/amide synthons are mainly based on coformers that contain more than one carboxyl group or an additional hydrogen-bond donor that is stronger than its carboxyl group. Only less than 6% of the isonicotinamide cocrystal structures did not display a carboxylic-acid/pyridine synthon.

5.3.2.3. Amide/Pyridine-N-Oxide versus Amide/Amide Synthons. About 10 years ago, the Nangia group engaged in the study of a previously recognized heterosynthon comprised of amide and pyridine *N*-oxide groups.[178,289] Two combined crystallographic and CSD analyses demonstrated that the amide-*N*-oxide heterosynthon prevails over the formation of amide/amide homosynthons in structures where both types of interactions can occur. Specifically, it was shown that 70% of the studied structures exhibited amide/pyridine-*N*-oxide heterosynthons (Figure 20), while only 30% of structures exhibited amide/amide homosynthons. The formation of structures that favor amide homosynthons, and lack the amide/pyridine-*N*-oxide heterosynthons, was attributed to steric factors.

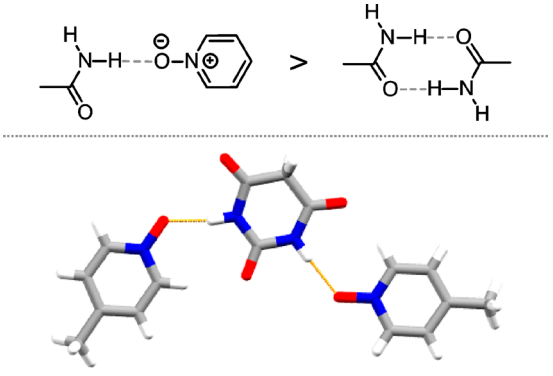

Figure 20. Synthon hierarchies in cocrystals composed of pyridine-*N*-oxides *and* amides (top), as seen in the X-ray crystal structure of the (barbituric acid)·(picoline-*N*-oxide) cocrystal (bottom, CSD reference code VIGFEX[289]).

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Another CSD survey conducted in conjunction with this literature review[197] identified 72 relevant single- or multi-component crystal structures built from molecules that involve: (1) a primary or secondary amide and (2) a pyridyl-*N*-oxide or the structurally related pyrazyl-*N*,*N*′-dioxide or pyridazyl-*N*,*N*′-dioxide moiety. Further analyses showed that 72% of these structures display an interaction involving the amide group and an *N*-oxide moiety. Of 66 crystal structures involving molecules with amide and pyridyl-*N*-oxide groups, 46 featured an inter- or intramolecular interaction involving the amide/pyridyl-*N*-oxide synthon shown in Figure 20. The main reason for the lack of amide/pyridyl-*N*-oxide synthon in the remaining 20 structures is the involvement of pyridyl-*N*-oxide in an interaction with a stronger hydrogen-bond donor. The CSD survey revealed six cocrystal structures involving an amide and a coformer based on a pyrazyl-*N*,*N*′-dioxide group. All structures exhibit an amide/pyrazyl-*N*-oxide interaction. No CSD entries were found for structures containing amide and pyridazyl-*N*,*N*′-dioxide functional groups.

5.3.2.4. Hydroxyl/Pyridyl Hydrogen Bonds in the Presence of Cyano Functional Groups. The Zaworotko group established the hierarchy of supramolecular synthons in structures composed of molecules entailing pyridyl, cyano and hydroxyl groups.[180] While CSD analyses revealed that hydroxyl/pyridyl and hydroxyl/cyano hydrogen bonds form reliably in the absence of any third competing functional group, a crystallographic study of a novel set of cocrystals (comprised of coformers containing pyridyl, cyano and hydroxyl groups) showed that the hydroxyl/pyridyl interactions persisted in all structures wherein alcohol/nitrile heterosynthons and alcohol/alcohol homosynthons could form (Figure 21).

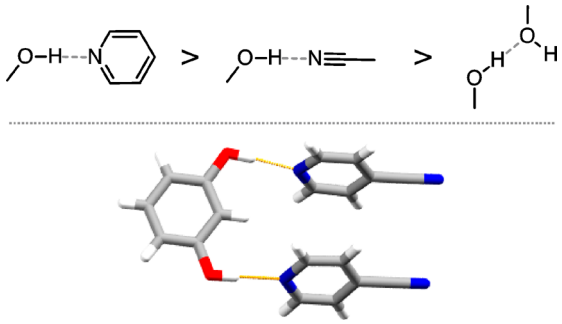

Figure 21. Synthon hierarchies in cocrystals based on molecules that contain pyridyl, hydroxyl, and cyano functional groups, as seen in the crystal structure of the (resorcinol)·(4-cyanopyridine)$_2$ cocrystal (bottom, CSD reference code KIHZAD[180]).

5.3.2.5. Relative Strength of Carboxyl and Hydroxyl Groups As Hydrogen-Bond Donors and Synthon Hierarchies of Interactions Involving Pyridyl Groups. Another study of synthon hierarchies by the Zaworotko group focused on supramolecular interactions in structures based on molecules entailing pyridyl, hydroxyl, and carboxylic-acid groups.[290] A CSD analysis revealed that the carboxylic-acid/pyridine and the alcohol/pyridine heterosynthons are strongly favored over the formation of carboxylic-acid and alcohol homosynthons in cases where no third competing functional group is present (Figure 22). To establish a relative ranking of the carboxylic-acid/pyridine, alcohol/pyridine, and alcohol/alcohol synthons, a series of new cocrystals was prepared and structurally

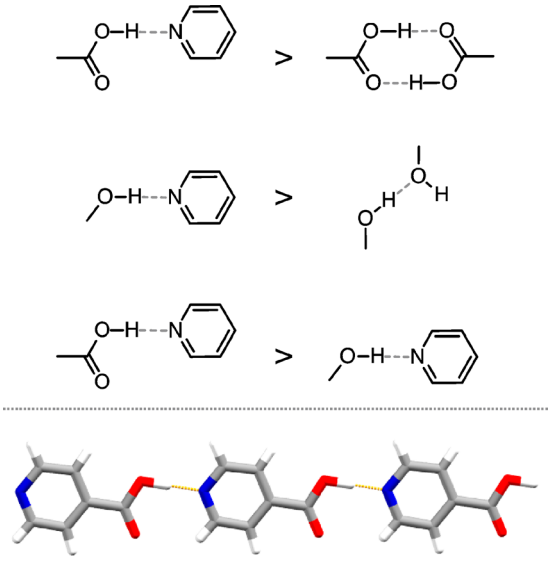

Figure 22. Synthon hierarchies in crystals based on molecules that contain carboxyl, hydroxyl and pyridyl functional groups (top), and persisting carboxylic-acid/pyridine heterosynthons in the crystal structure of isonicotinic acid (bottom, CSD reference code ISNICA[294]).

analyzed. The cocrystals (based on molecules with the same three functional groups) revealed supramolecular structures that are dominated by carboxylic-acid/pyridine and alcohol/pyridine heterosynthons. Failed cocrystallization experiments, carried out using highly effective mechanochemical cocrystallization reactions involving nicotinic and isonicotinic acids, suggested that the carboxlic-acid/pyridine heterosynthons in the crystal structures of both acids (Figure 22) are favored over the formation of a hydroxyl/pyridyl interaction in the putative cocrystals.[291−293]

The results described above may be interpreted to conclude that carboxylic acid groups are stronger hydrogen-bond donor than hydroxyl groups. However, such an interpretation may not be justified. A recent study by Aakeröy et al. demonstrated that, contrary to general belief, (phenolic) hydroxyl groups are superior hydrogen-bond donors to carboxyl groups.[211] Although pK_a values suggest that carboxylic acid groups are better hydrogen-bond donors, molecular electrostatic potentials suggest otherwise. To determine the relative strength of the two donors, two hydroxybenzoic acids were cocrystallized with ditopic molecules that exhibit distinct hydrogen-bond acceptor strengths. A crystallographic analysis of the resultant solids showed that the hydroxyl group invariably bonded with the better acceptor of the ditopic coformer (following Etter's hierarchy principle), while the carboxylic-acid group interacted with the second-best acceptor (Figure 23).

These observations are also in agreement with the findings of Bučar et al., who investigated synthon hierarchies in cocrystals composed of caffeine and hydroxybenzoic acids. Their study showed that all anhydrous cocrystals were based on hydroxyl/carbonyl heterosynthons (involving the best donor and acceptor) and carboxylic-acid/imidazole heterosynthons (linking the second-best donor and acceptor) (Figure 23).[31]

The complexity of synthon hierarchies in molecular crystals and the difficulty of designing them is further illustrated by Lemmerer et al. in a study that addresses the relative strength of carboxyl and hydroxyl groups as hydrogen-bond donors in

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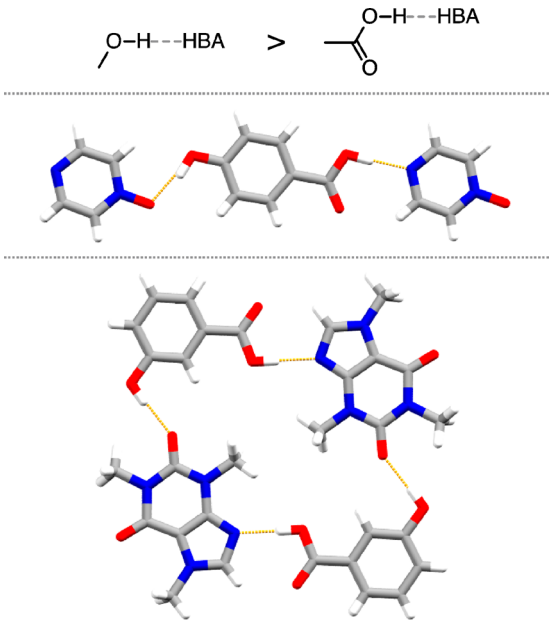

Figure 23. Relative strength of carboxyl and hydroxyl groups as hydrogen-bond donors (top). The crystal structures shown in the middle (CSD reference code CIRNIC[213]) and on the bottom (CSD reference code MOZCOU[31]) display supramolecular assemblies wherein the hydroxyl group interacts with the best hydrogen-bond acceptor and the carboxyl group with the second-best acceptor, thus indicating that the hydroxyl group is a more efficient hydrogen-bond donor than the carboxyl group (HBA = hydrogen-bond acceptor).

cocrystallization experiments involving pyridyl-based compounds. Using the (3-hydroxybenzoic acid)·(acridine) and (2,4-dihydroxybenzoic acid)·(nicotinamide) cocrystals as model compounds, it was shown that minor changes in experimental conditions (such as the crystallization solvent) yield cocrystal polymorphs with either carboxyl/pyridine or hydroxyl/pyridine interactions.[295]

5.3.2.6. Relative Strengths of Hydroxyl and Cyanooxime Groups As Hydrogen-Bond Donors. The oxime group is quite common in pharmaceuticals and agrochemicals and is, thus, of interest to supramolecular chemists and crystal engineers. The CSD and literature, however, lack any data that could shed light on its hydrogen-bonding capabilities. Accordingly, Aakeröy et al. conducted a crystallographic study of cocrystals of a compound that contains both hydroxyl and cyanooxime functional groups (namely, (*Z*)-*N*,4-dihydroxybenzimidoyl cyanide), to evaluate the relative strength of their hydrogen-bond donating properties. The study showed that when a ditopic molecule with varying acceptor strengths is cocrystallized with (*Z*)-*N*,4-dihydroxybenzimidoyl cyanide, the hydroxyl group interacts with the stronger hydrogen-bond acceptor, while the cyanooxime interacts with the second-best acceptor (Figure 24).[296]

5.3.2.7. Hierarchies of Halogen-Bond Donors and Acceptors. The increasing relevance of halogen bonding in crystal engineering, materials science, and supramolecular chemistry imposed the need to expand the limited selection of commercially available and useful halogen-bonding building blocks (e.g., diiodotetrafluorobenzene) and to fully understand the hierarchy of halogen-bond-donor strengths in the extended set of halogen-bond donors. A group of haloethynylbenzenes emerged from computational and crystallographic studies as particularly useful halogen-bond donors.[104,187,189] Their

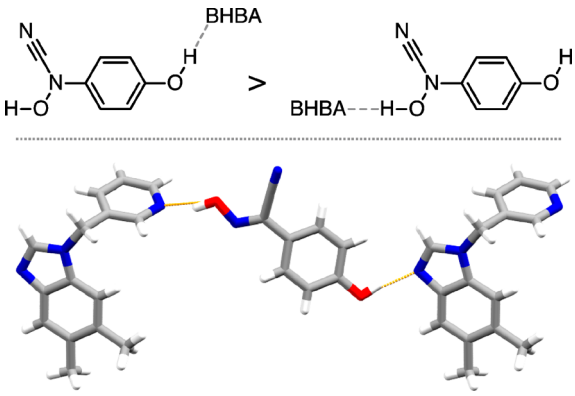

Figure 24. Synthon hierarchies in cocrystals based on molecules involving phenol and cyanooxime functional groups (top), as seen in the crystal structure of a cocrystal involving (*Z*)-*N*,4-dihydroxybenzimidoyl cyanide and a ditopic receptor (bottom, CSD reference code HIDQUI[296]) (BHBA = best hydrogen-bond acceptor).

efficiency was ascribed to their distinctly electrophilic halogen atoms, which are "doubly activated" through the imposition of strongly polarizing sp carbon atoms between the halogen atoms and the molecular backbone, and electron-withdrawing groups on the molecular backbone. The iodo- and bromo ethynylbenzenes were shown to be more effective than the commonly utilized iodo- and bromo-fluorobenzenes, particularly when substituted with strong electron-withdrawing groups (e.g., nitro groups) (Figure 25). Chloroethynylben-

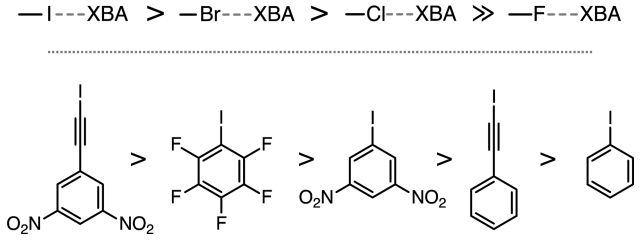

Figure 25. Hierarchies of commonly studied halogen-bond donors. (XBA = halogen-bond acceptor).

zenes, on the other hand, were unsurprisingly found to be insufficiently strong halogen-bond donors, even when functionalized with nitro groups (see Section 2.2.2).

A hierarchy of halogen-bond acceptors was proposed by Cinčić et al.,[262] who studied a series of isostructural halogen-bonded cocrystals composed of structurally equivalent donors and acceptors using bromo- and iodofluorobenzenes as donors, and morpholine, thiomorpholine, thioxane, and piperazine as acceptors. An assessment of the melting points of the resultant isomorphous cocrystals suggested that the O···I and S···I interactions are comparable in strength, while the N···I bond is significantly stronger, and consequently, that N is a better halogen-bond acceptor than O and S. A related assessment of relative strengths of halogen-bond acceptors was recently reported in a study by Zbačnik et al.[297] wherein the authors suggest that cyano groups act as preferred halogen-bond acceptors when in competition with *o*-dialkoxybenzene (Figure 26).

5.3.2.8. Hydrogen and Halogen Bonding in Competitive Supramolecular Systems. Aakeröy et al. assessed the relative importance of hydrogen and halogen bonds in the arrangement of supramolecular solid-state structures. For this purpose, a

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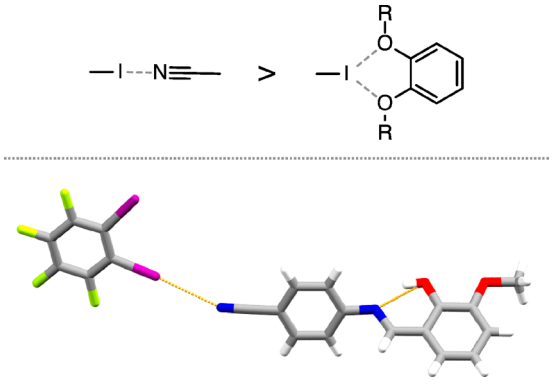

Figure 26. Synthon hierarchies in cocrystals based on fluoro-activated halogen-bond donors and molecules displaying *o*-dialkoxybenzene and nitrile acceptors (top), as seen in the crystal structure of a cocrystal involving 1,2-diiodotetrafluoro-benzene and (*E*)-4-((2-hydroxy-3-methoxybenzylidene)amino)benzonitrile (bottom, CSD reference code IWONAL[297]).

ditopic molecule with two potential hydrogen and halogen-bond donors (in the form of pyridyl and benzimidazole groups) was cocrystallized with a molecule that contains a weak (an imine C−H moiety) and a strong hydrogen-bond donor (an oxime O−H moiety), as well as a fluoro-activated halogen-bond donor (in form of a F, Br, or I atom). A structural study of three cocrystals so obtained revealed that the oxime hydrogen-bond donor invariably binds to the best acceptor, namely, the benzimidazole N atom. The second-best acceptor (the pyridyl N atom) was available to participate in hydrogen bonding with the C−H moiety or in halogen bonding with the variable halogen-bond donor. Notably, a halogen bond was only realized in the cocrystal that featured a fluoro-activated iodine as halogen-bond donor, whereas C−H···N(pyridyl) hydrogen bonds were formed in cocrystals including F and Br substituents as halogen-bond donors. These findings clearly suggest that the self-assembly process in these cases is dominated by hydrogen bonding.[298]

To further probe the dominance of hydrogen and halogen bonding in supramolecular assembly processes, Aakeröy et al. engaged in a more elaborate and systematic structural study of cocrystals based on molecules with both hydrogen- and halogen-bond capabilities.[182] For this purpose, 10 distinct molecules containing both halogen- and hydrogen-bond donors were cocrystallized with 20 acceptors. Ensuing structural analyses of 24 cocrystals so obtained revealed hydrogen bonding in each and every case (100%), while halogen bonding was observed in only 13 out of the 24 cocrystals (53%), thus corroborating the findings of the previously described study (Figure 27). The appearance of halogen- and hydrogen-bonding was dictated by the *Q* value, which reflects the difference of the interaction energy of the hydrogen-bond donor and a point charge and the interaction energy of the halogen-bond donor and a point charge. Structures that exhibited both hydrogen and halogen bonding featured a *Q* value of 142 kJ mol^{-1}, while cocrystals based on hydrogen bonding alone featured a *Q* value of 175 kJ mol^{-1}.

Another related study by the Aakeröy group highlights the challenges of supramolecular solid-state synthesis by reporting another extensive study focusing on the competitiveness of hydrogen bonds and halogen bonds. This time, in contrast, it was found that halogen-bond donors outpaced hydrogen-bond donors in the competition for the best acceptor site in di- or

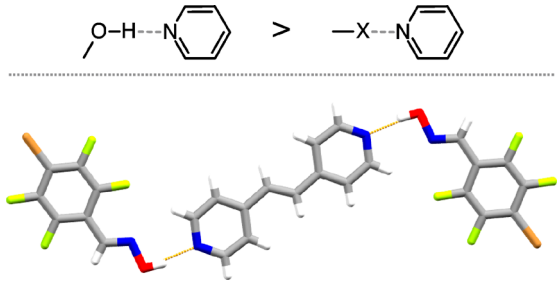

Figure 27. Synthon hierarchies in cocrystals based on molecules capable of hydrogen and halogen bonding (top, X = halogen atom), as observed in the crystal structure of a cocrystal involving 1,2-bis(4-pyridyl)ethylene and (*E*)-4-bromo-2,3,5,6-tetrafluoro-benzaldehyde oxime (bottom, CSD reference code BUNHID[182]).

tritopic probe molecules: 12 out of 15 crystal structures (80%) revealed that the halogen-bond interacts with the best acceptor (according to MEPS calculations), while the hydrogen-bond donor interacts with the best acceptor in only three cases (20%) (Figure 28).[299]

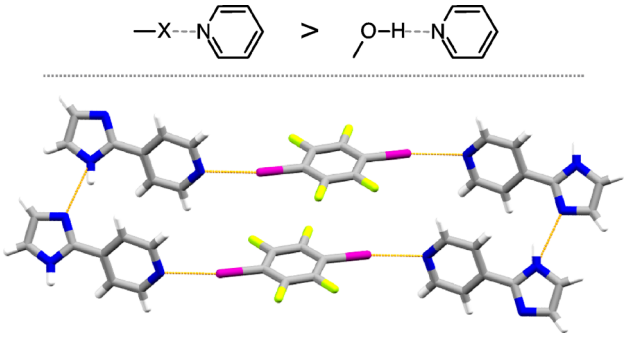

Figure 28. Synthon hierarchies in cocrystals based on molecules capable of hydrogen and halogen bonding (top, X = halogen atom), as observed in the crystal structure of a cocrystal involving 2-(4-pyridyl)-imidazole and 1,4-diiodotetraflouobenzene (bottom, CSD reference code ZOGSAR[299]).

Similar findings were reported in an earlier and significantly narrower study by Corradi et al.,[300] which also suggested that halogen bonding, rather than hydrogen bonding, drives and controls the supramolecular assembly process. Such a conclusion was derived from a cocrystallization experiment involving 1,2-bis(4-pyridyl)ethane (bpe), 1,4-diiodotetra-fluoro-benzene (ditfb), and hydroquinone (hq) where a solution of bpe, ditfb, and hq yielded a two-component (bpe)·(ditfb) cocrystal, while hq remained in solution. The reported conclusions were also substantiated by results of thermal analyses, including measurements of the enthalpies of fusion of the (bpe)·(ditfb) and the (bpe)·(hq) cocrystals, which suggested that structures sustained by halogen bonding are more stable than structures held together by hydrogen bonding.

The studies highlighted in this section underline the complexity of the interplay of halogen and halogen bonding and suggest that other factors (such as molecular geometries, number, and arrangement of donors and acceptors on a molecule) are capable of tipping the balance between halogen and hydrogen bonding in supramolecular reactions.

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6. CONCLUSION AND OUTLOOK

The literature contains numerous review articles that give accounts of recent advances in crystal engineering[116,117,301,302] (particularly in areas pertaining to the development of efficient preparative methods[303,304] and the discovery of new functional features of molecular crystals[36,38]), as well as several books that address design strategies for molecular crystals in great length.[44,305] We have found, however, that the field still lacks a concise yet comprehensive review that holistically addresses crystal design principles. In this review, we therefore summarized the main characteristics of molecular crystals that need to be taken into consideration in crystal design exercises, to highlight the simple yet effective computational and statistical tools that are accessible to experimental solid-state chemists and to summarize consistent design strategies that are derived from comprehensive and well-conceived crystallographic studies and CSD analyses.

Despite the tremendous advances in development of crystal design strategies, and the availability of the useful tools described herein, it is still impossible to predict the outcome of a crystallization experiment using empirically derived guidelines.[29,166,306] Computational crystal structure prediction methods[43,307] have become increasingly efficient in predicting sets of thermodynamically feasible crystal structures of organic molecules[43,308−311] and calculating their physicochemical properties.[13,14,16,312] Despite their success, we excluded them from this review because of their complexity and the required specialty knowledge that is needed to capably use them (and which is outside the area of expertise of most crystal engineers and experimental solid-state chemists). We anticipate that further development in this area, along with increasing computational power and the emergence of readily available and user-friendly software packages, will make high-level quantum mechanical calculations of molecular crystals in the near future an effective and reliable standard tool in crystal engineering. We believe that such calculations are vital to the elucidation of the principles that guide the formation of molecular crystal structures, and such methods must play a critical role in the evaluation of new, experimentally derived guidelines. However, until such methods are fully incorporated into materials research programs, experimental solid-state chemists will have to rely on strategies and methods described in this review.

Finally, we hope that our attempt to provide workable guidelines for the design of molecular crystals will prompt discussions and investigations that will add to existing strategies and improve our ability to devise molecular crystals with targeted structures and properties.

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