

Exploitation of the hydrogen bond: recent developments in the context of crystal engineering

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(Received 10 December 1993; accepted 23 February 1994)

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ABSTRACT

The desire to design rationally technologically useful solid-state materials has coupled with our ever growing understanding of the nature of non-covalent intermolecular interactions and molecular

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recognition processes (i.e. supramolecular chemistry) to provide impetus for the emergence of crystal engineering. The "golden rule" of crystal engineering is that one has to assume that the architecture within crystals, and therefore the space group in which a given compound crystallizes, is determined solely by the strength and directionality of intermolecular or interionic interactions. In other words, most crystal structures can be regarded as *de facto* manifestations of self-assembly. The objective of this review is to provide chemists from all disciplines with an overview of recent developments in the field with particular emphasis on how symmetry and function at the molecular level can be used to control solid-state architecture. Hydrogen bonding represents perhaps the best understood non-covalent force and is one of the primary tools available to crystal engineers so it is also a focus of the review. Developments in all areas of chemistry subsequent to 1988 are highlighted, but we also cite earlier literature that deals specifically with hydrogen bonding in the context of long-range ordering of molecules or ions.

1. INTRODUCTION

The desire to design rationally technologically useful solid-state materials has led to a recent surge of interest in the concept of crystal engineering [1–3], a cross-disciplinary area that necessarily involves chemists (synthetic, physical, computational, theoretical and analytical), crystallographers and physicists and is of particular relevance to materials scientists. *Ab initio* prediction of crystal structures on purely theoretical grounds is not yet feasible [4], however, our ever growing understanding of the nature of intermolecular interactions and molecular recognition processes is providing the background knowledge that makes crystal engineering both a realistic and ultimately an achievable goal.

In order to practice, the crystal engineer has to have an understanding of the following: (i) intermolecular/interionic forces and how they influence self-assembly processes (i.e. how asymmetric aggregates form); (ii) the relationship between self-assembly and spatial arrangements of molecules or ions within a crystal (i.e. how asymmetric aggregates link or pack with one another, the topology of a solid); (iii) the relationship between space group symmetry and bulk physical properties.

Whereas the importance of the last aspect has been relatively well understood for several decades [5,6] areas (i) and (ii), in which chemists can and are playing very active roles, are still under active development. Given the above, it should be clear that the "golden rule" of crystal engineering is that one has to assume that the tertiary structure within crystals, and therefore the space group in which a given compound crystallizes, is determined solely by the strength and directionality of intermolecular or interionic interactions. In other words, most crystal structures can be regarded as *de facto* manifestations of self-assembly. This is a reasonable assertion when conventional hydrogen bonding is the prime driving force for self-assembly. However, this is not necessarily the case in the absence of strong or moderate intermolecular non-covalent forces. In such instances observed crystal packing can be regarded as optimization of two factors that often compete with one another: avoidance of vacuum and maximization of weak attractive non-covalent interactions. Recent attempts have been made to predict crystal structures based on the assump-

tion that attractive intermolecular forces can be effectively ignored [7–9]. This is indeed sometimes a valid assumption but even the weakest of non-covalent forces, which had in general tended to be neglected by chemists until very recent times, have now become the subject of systematic initiatives to recognize their importance in the context of both crystal structures and host–guest complexes.

From the aforementioned it should be clear that the term crystal engineering has now taken on a much wider meaning than that originally suggested by Schmidt [1], whose focus was rational assembly of reactant molecules in crystals in order to mimic transition states for photochemical reactions. The term crystal engineering has been adopted as a key word in the subject indexes of many journals, representing a general term for describing the nature and exploitation of intermolecular forces in the construction of long-range ordered solids [10–12] rather than the limited sense for which it was originally coined. The objective of this review is to provide chemists from all disciplines with a review of recent developments in the field with particular emphasis on exploitation of the hydrogen bond. Particular emphasis has been placed on developments subsequent to 1988, but we also cite some earlier literature that deals specifically with hydrogen bonding in the context of long-range ordering of molecules or ions. Earlier reviews on the subject of molecular recognition [13], self-assembly [14,15] and supramolecular chemistry [16–19] are also relevant. This review complements a recent review by Aakeroy and Seddon [3] which focussed more on the theory of hydrogen bonding and general strategies for crystal engineering rather than specific examples from the recent literature.

2. THE HYDROGEN BOND

2.1. History

The first proposal of bonding that we now recognize as hydrogen bonding was made by Moore and Winmill [20]. However, it was not until Latimer and Rhodebush postulated hydrogen bonding in 1920 [21] that the concept gained widespread recognition and attention. Subsequently, its existence in nature and importance in the function of chemical and biological processes have been well recognized. Several books have been devoted to the subject of hydrogen bonding [22–29] and its relevance to biological systems [30]. The concept of hydrogen bonding was originally used to explain physical properties of organic compounds (e.g. solubility of alcohol in water) and chemical reactivities (e.g. the unreactivity of the aldehyde group in salicylaldehyde), invoking intermolecular and intramolecular hydrogen bonding respectively [29]. In this regard, one of the most important aspects of hydrogen bonding is the formation of molecular aggregates through intermolecular hydrogen bonding. For example, the formation and existence of dimeric structures in carboxylic acids has been known for decades [22–29].

During more recent years this simple idea of intermolecular interactions has

been viewed somewhat differently: as “built-in information” for molecular recognition [17] or as a “synthetic vector for granting topological control over crystalline form” [3]. Hydrogen bonding is one of the better understood types of non-covalent bonding that have been invoked by chemists who generate supramolecular structures via self-assembly. The relative uniqueness of the “built-in information” inherent to a particular molecule or ion determines its ability to recognize selectively another molecule or ion [16,31,32]. Ironically, this means that chemically similar molecules can be dramatically different in the context of crystal engineering, whereas molecules that can appear at first sight to be unrelated can serve similar crystal engineering functions. It can even be said that when suitably positioned, the number and orientation of hydrogen bond donor and acceptor sites can be used to impart “intelligence” in molecules for the selective formation of supramolecular structures. In such a context there have been several aesthetically pleasing, if not spectacular, examples of molecules that self assemble to form predictable infinite supramolecular structures through hydrogen bonding [32–34]. This is not meant to imply that hydrogen bonding in solids had not been extensively investigated until recently, rather that the focus has changed. These recent successes can be attributed to this change of focus and several other factors.

(i) Recognition of hydrogen bonding patterns that generate reproducible motifs, and understanding and delineation of principles that govern such intermolecular hydrogen bonding [35].

(ii) Routine and ready availability of single-crystal X-ray and even neutron diffraction to provide quick and reliable feedback and make wide-ranging systematic studies possible.

(iii) Hydrogen bonding is just one example of non-covalent bonding but it can be relatively strong thermodynamically [3,36] and is relatively well understood compared with other non-covalent interactions [37,38].

2.2. *Hydrogen bond types*

The general prerequisites for the formation of a hydrogen bond are the presence of a relatively polarized X–H (X=O, N, F, or even C) bond, the H-bond donor, and a suitable H-bond acceptor Y. Y is normally a basic lone pair but could in principle be another electron-rich moiety such as an aromatic system. There are excellent reviews available on the subject of hydrogen bonds [3,39] and their thermodynamic [36], theoretical [37,38] and spectroscopic aspects [40–42]. Recent theoretical studies indicate that the hydrogen bond might best be described as electrostatic in origin [43,44], although very strong hydrogen bonds can be regarded as having some covalent character [45]. Hydrogen bonds are strong enough to form species that are identifiable in gas [36], solution and solid phases [46] but at the same time are typically weak enough to dissociate and reform by simple processes such as heating, dissolution and, in particular from the point of view of this article,

recrystallization. The relatively wide bond energy range (less than 1 to more than 8 kcal mol⁻¹ for hydrogen bonds between neutral molecules, as high as 50 kcal mol⁻¹ for hydrogen bonds between ionic components [3,37,41]) and their inherent directionality makes them exploitable, controllable and versatile. However, their relatively weak strength compared with covalent bonds means that steric [47] and other weak non-covalent bonding forces [48] have to be accommodated and external factors such as temperature [49,50] and pressure [51,52] can be important.

Observations that have taken place in recent years indicate that weak hydrogen bond interactions, such as C-H...O, C-H...Cl, C-H... π -bond (edge-to-face π -stacking), C-H... triple bond, even X-H... arene (π hydrogen bonds), can be characterized and play important roles in crystal engineering. In several instances such interactions have been shown to play a significant role in influencing solid-state structure, particularly for organic molecules [53,54]. These forces are normally secondary to strong hydrogen bonds when it comes to determining crystal structure, but there are a few recent examples in which they actually dominate [55-57]. The possible modes of hydrogen bonding are illustrated in Fig. 1.

2.3. Directionality and asymmetry

Hydrogen bonds are capable of displaying a sense of directionality and chemical specificity that is comparable with that of covalent bonds. From a statistical analysis of structures of acids, ketones, and ethers, probable spatial orientations of hydrogen

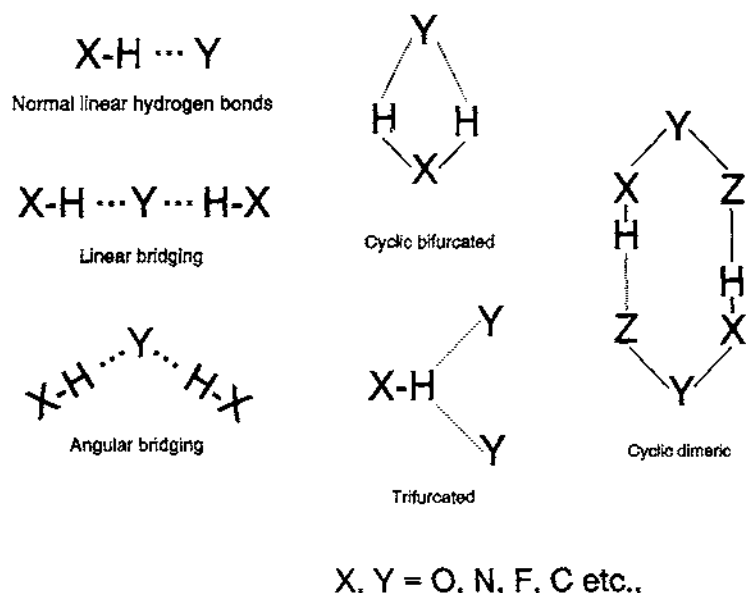


Fig. 1. Possible hydrogen bonding modes involving electronegative atoms.

bonds have been mapped out [58] and, with these data, the hydrogen bonding direction in new structures can be predicted with reasonable accuracy (Fig. 2). Similar studies have been carried out for derivatives of urea [59].

An aspect of the hydrogen bond that has become particularly important for crystal engineers is its inherent asymmetry and therefore polarity. This asymmetry can be exploited to form polar structures from achiral molecular or ionic components [60]. Bulk polarity is a prerequisite for a number of important physical properties such as piezoelectricity, ferroelectricity, pyroelectricity and second-order non-linear optical activity [2,5,61]. Self-assembly of identical molecules or ions that have both hydrogen bond donors and acceptors tends to afford predominantly centrosymmetric (i.e. non-polar) dimers and oligomers [62–64]. However, if polymeric motifs are formed and hydrogen bonds are aligned, then the center of symmetry is lost and the resulting polymeric strand is polar. As long as adjacent polymers are not antiparallel, the crystal itself will exist in a polar space group and bulk polarity will be present. Such is the case for one of the prototypal non-linear optic materials KH_2PO_4 . KH_2PO_4 forms an infinite three-dimensional (3D) network that is based on self-assembly of H_2PO_4 anions (Fig. 3) [51]. At room temperature the hydrogen bonds are randomly disordered, therefore generating a center of inversion. However, a phase change occurs at 122 K which results in ordering and alignment of the hydrogen bonds, a consequence of which is that the crystal becomes polar at this temperature. It should therefore not be surprising that a current trend is to recognize, understand and exploit molecular features that would predispose compounds to crystallize in polar space groups [60,65–67]. It is surprising, however, that until recently rational synthetic approaches to achieve bulk polarity in the solid state were essentially limited to pure enantiomorphs [2,67].

2.4. Functional groups

Several simple functional groups have the inherent capability to self assemble since they contain both hydrogen bond donor and hydrogen bond acceptor moieties. The complementary hydrogen bonding characteristics of these moieties can be ex-

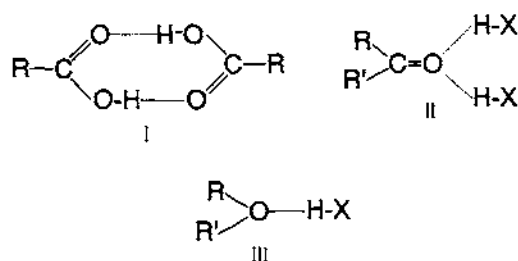


Fig. 2. Probable spatial orientations of hydrogen bonds around carbonyls and ethers.

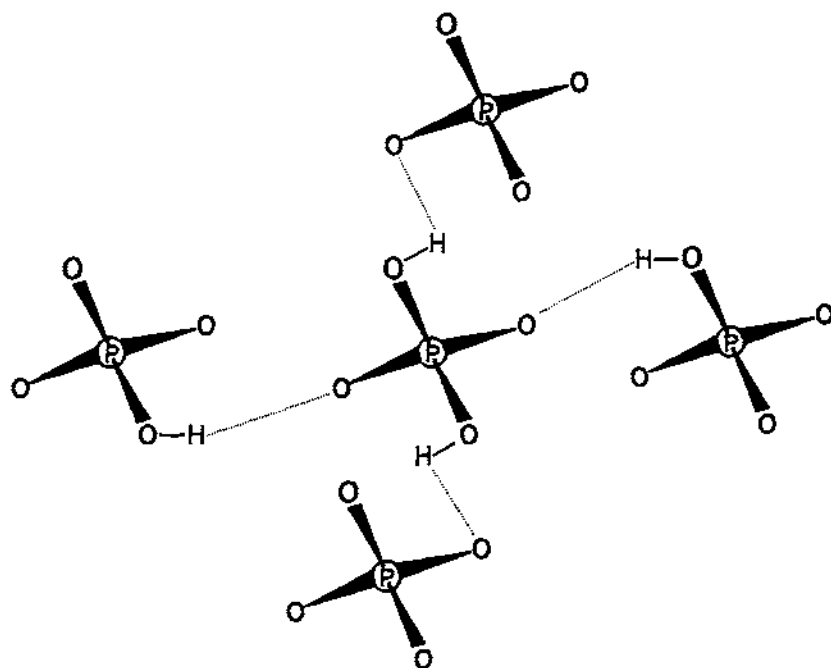


Fig. 3. The hydrogen bonding motif exhibited by dihydrogenphosphate anions.

ploited for long-range ordering in solids and they are therefore good design elements. The following paragraphs describe several of the more commonly encountered functional groups, the motifs they generate, and their utility in the context of crystal engineering. The motifs provide information only about the mode of intermolecular hydrogen bonding that would describe a possible asymmetric unit but, depending on the symmetry characteristics of the molecule to which they belong, they can form discrete supramolecular assemblies or 1D, 2D or 3D polymeric structures. Drawing an analogy with the primary, secondary and tertiary structures of proteins, we are in this section only concerning ourselves with primary structure. The secondary and tertiary structures that may result from such intermolecular hydrogen bonding depend on the number and spatial orientation of motifs in a molecule and these are described in Section 3.

2.4.1. Carboxylic acids

The carboxyl group ($-\text{COOH}$) in carboxylic acids has the potential to self assemble and form either discrete dimeric or linear polymeric structures (Fig. 4). The polymeric strands formed by carboxylic acids are inherently polar and are therefore predisposed to crystallize in polar space groups. This was confirmed when Frankenbach and Etter [66] conducted a systematic analysis of crystal structures of substituted benzoic acids from the perspective of formation of polar solids. Using a

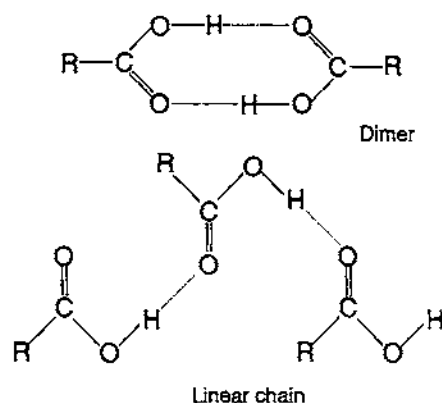


Fig. 4. Dimeric and linear hydrogen bonding motifs in carboxylic acids.

data set of 139 benzoic acids, a direct relationship was found to exist between the presence of an inversion center in hydrogen-bonded aggregates of benzoic acid derivatives and centrosymmetry in their crystal structures. Of the 139 structures analyzed, 118 exist as centrosymmetric dimers whereas 21 are linear polymeric chains or strands. Of the 21 linear chain polymers, 52% crystallize in polar space groups and 90% of them are ortho-substituted benzoic acids. Conversely, of the 118 acids that exist in dimeric form in the solid state, and therefore possess an inherent center of inversion, only 2% crystallize in non-polar space groups. Surprisingly, there appear to be no reports prior to that of Frankenbach and Etter that clearly demonstrate how asymmetry in hydrogen bonding can influence crystal polarity. Unfortunately, since most monocarboxylic acids form discrete dimers they are not of much use to crystal engineers because intermolecular interactions other than $C(O)=O \cdots H-O$ play the important role of determining long-range ordering in the solid state and their centrosymmetric nature means that their crystals are typically non-polar. However, when more than one carboxyl group is present, depending on their spatial orientation, the dimeric structure itself can play a decisive role in the formation of 1D, 2D or 3D polymeric structures. Notable examples include dicarboxylic acids [68], trimesic acid (benzene-1,3,5-tricarboxylic acid) [69] and adamantane-1,3,5,7-tetracarboxylic acid [34] respectively. These structures are discussed in more detail in Section 3.

2.4.2. Hydrogenbis(carboxylates)

Even though hydrogenbis(carboxylate) anions self assemble via a very strong hydrogen bond [70] and have been recognized as a distinctive species by both spectroscopic [41] and structural studies [71,72], they have not been given much attention as a structural motif for the engineering of solids. The possible conformations of a hydrogenbis(carboxylate) anion are shown in Fig. 5 and only type A has an inherent center of inversion. Hydrogenbis(carboxylates) of monocarboxylic acids

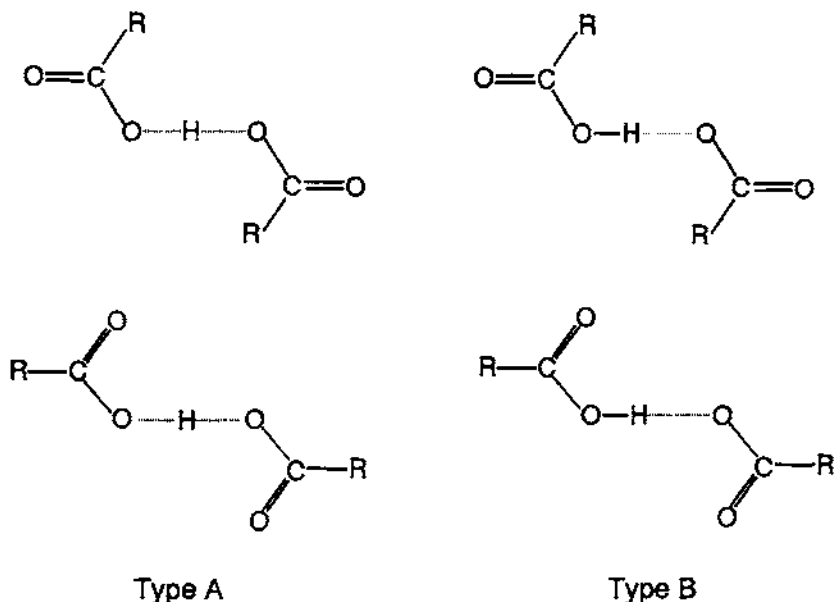


Fig. 5. Possible conformations of the hydrogenbis(carboxylate) anion.

do not have the potential to generate long-range ordering in solids through strong hydrogen bonding. However, if the secondary intermolecular/interionic interactions (e.g. π stacking and $C-H\cdots X$ hydrogen bonding) are directional then long-range ordering will occur. The inherent asymmetry of the hydrogen bond in the $O-H\cdots O=C$ motif in hydrogenbis(carboxylates) can be preserved and theoretical studies indicate that very little energy is required to maintain this asymmetry [73]. Hence, these species are potentially useful for the construction of polar solids. It should also be noted that the strength of the hydrogen bond of a hydrogenbis(carboxylate) is stronger than that in a carboxylic acid linear chain owing to an enhanced contribution from electrostatics [74]. Very little is presently known about hydrogenbis(carboxylates) of dicarboxylic acids even though they clearly offer possibilities for generating polymeric motifs.

2.4.3. Inorganic anions

Many inorganic anions can self assemble via hydrogen bonding. Pathaneni and Desiraju [75] recently summarized the various modes of hydrogen bonding that can occur between halides and water. Fluoride [76,77], chloride [78–80], sulphate [78,81] and diphosphate ($P_2O_7^{2-}$) [82] can bridge multi-protonated organic polyamines. Anions of partly neutralized multi-basic acids such as hydrogensulfate (Fig. 6) [83], dihydrogenarsenate [83], dihydrogenphosphate (Fig. 3) [84] and hydrogenselenate [85] are both hydrogen bond acceptors and donors. They can therefore be considered to be inorganic analogs of the various carboxylic acid

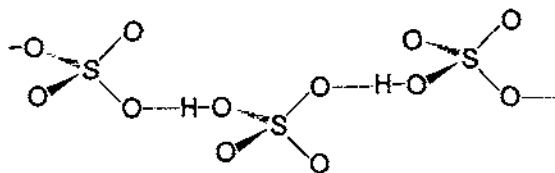


Fig. 6. The linear chain hydrogen bond motif generated by hydrosulfate anions.

moieties described earlier since, depending on the geometric features of the anions, 1D, 2D or 3D architectures can be sustained. Octahedral anionic complexes such as hexafluorophosphate [86], $[\text{Co}(\text{CN})_6]^{3-}$ [87], $[\text{Fe}(\text{CN})_6]^{4-}$ [88], $[\text{Fe}(\text{OH}_2)\text{Cl}_5]^{2-}$ [89–91] and dichromate ($\text{Cr}_2\text{O}_7^{2-}$) [92] have also been found to be involved in network hydrogen bonding.

2.4.4. Organic cation salts

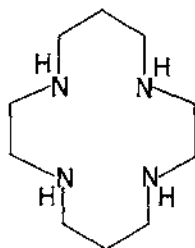
Organic cations, particularly primary and secondary ammonium salts, have the potential to form long-range hydrogen-bonded solids. Since inorganic and organic anions of the types described in Sections 2.4.2 and 2.4.3 can also contribute to network hydrogen bonding, complementary ions can be expected to determine the crystal structure in predictable ways. This can be stated because the structures of such salts are typically determined by the same kinds of forces that determine the structures of molecular solids rather than the types of electrostatic forces that determine the structures of more classical inorganic salts such as NaCl. There are several possible advantages in using organic salts for the construction of polar solids.

(i) When homochiral amines and/or acids are used, the resulting salts can be expected invariably to crystallize in acentric space groups.

(ii) Such salts can be potentially useful in non-linear optics since certain types of organic compound have high molecular second-order hyperpolarizabilities.

(iii) There are two components to manipulate and therefore two ways to fine tune the solid. This is particularly useful when the molecular second-order hyperpolarizabilities of organic cations and anions can be modified at will by appropriate substituents that do not influence the architecture within the crystal.

Polyamine (open chain and macrocyclic) cations are also capable of forming 1D, 2D or 3D hydrogen-bonded networks since they tend to adopt exodentate conformations. Quite a few examples of such salts [78–80, 87,91] have been studied, but not systematically. Recently, we investigated the structure of several salts of the tetraprotonated macrocycle, 1,4,8,11-tetraazacyclotetradecane or cyclam 1 [80,91,93]. The conformation of this cation, $[\text{H}_4(1)]^{4+}$, and the resulting orientation of the NH_2^+ moieties clearly facilitates networking, even to the extent of forming 3D networks with an appropriate counterion.



1

2.4.5. Amides, lactams and pyridones

All these compounds contain the common motif $R_C\text{CONHR}_N$. Amides are important not only because of their existence as peptide bonds in biologically important molecules, but also because they represent a motif that has been subjected to systematic study by crystal engineers [94,95]. Amide groups generally adopt the stereoelectronically favoured trans configuration (Fig. 7). In this configuration, the relative orientation of the hydrogen bonding sites facilitates 1D linear chain networks.

There is also stereochemical flexibility which can be controlled by the bulkiness of the substituents at the acyl carbon atom (R_C) and the nitrogen atom (R_N). Many of the molecular components recently investigated by Hamilton and co-workers [31], Lehn et al. [17,32] and Whitesides and co-workers [14,64] involve cyclic amides/lactams or derivatives of nucleotide bases. Some of these motifs are shown in Fig. 8. Wuest and co-workers studied the aggregation of derivatives of pyridones in both solution and the solid state [33,96]. Pyridones self assemble to form centrosymmetric dimers in a manner similar to that of carboxylic acids (Fig. 9) and therefore require more than one pyridone group to ensure formation of polymeric structures.

2.4.6. Urea and its derivatives

Urea has long been known as a compound that can act as a supramolecular host matrix for guest molecules, and it therefore represents a motif that has been particularly well studied [97]. Both lone pairs on the carbonyl oxygen atom of ureas act as hydrogen bond acceptors and, depending on the number of substituents on the nitrogen atoms, zero to four hydrogen atoms are available as hydrogen bond

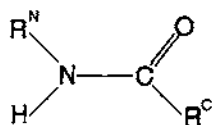


Fig. 7. Trans configuration of an amide group.

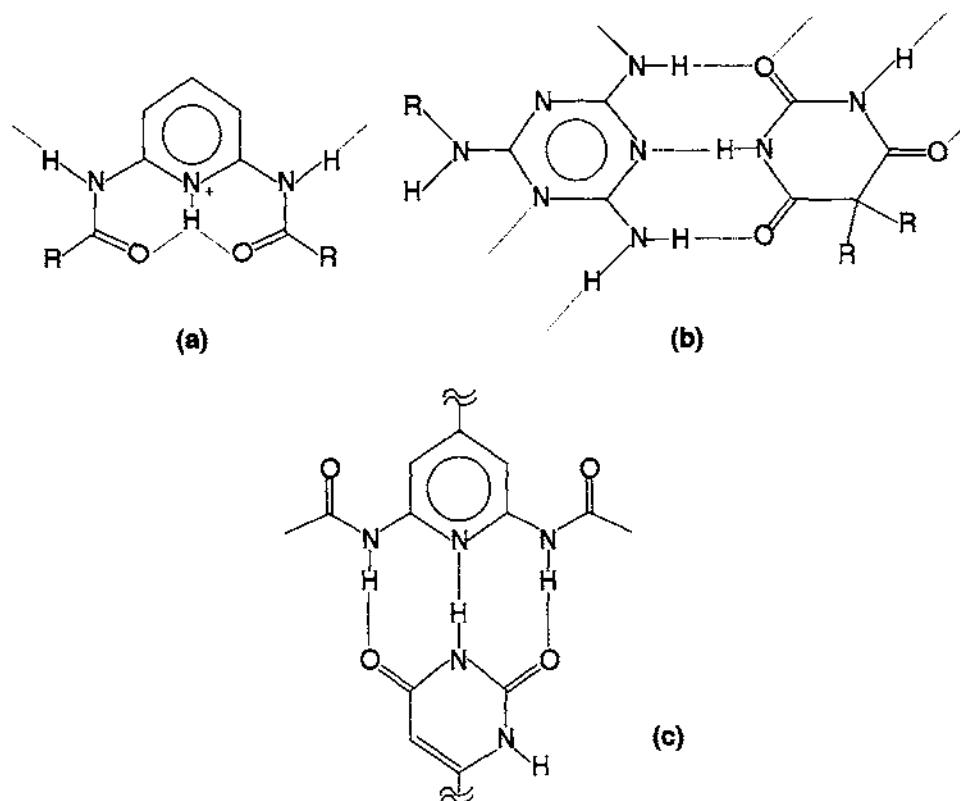


Fig. 8. Hydrogen bond motifs as investigated by (a) Hamilton and co-workers [31], (b) Whitesides and co-workers [14,64], and (c) Lehn et al. [17,32].

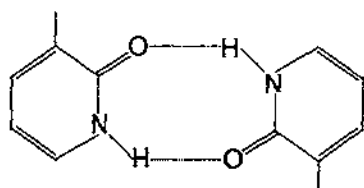


Fig. 9. Hydrogen bonding motif in pyridones.

donors. The general modes of hydrogen bonding in urea and substituted ureas are shown in Fig. 10.

As well as urea itself, Etter et al. studied hydrogen bonding patterns in diaryl ureas [59] and the concept of urea-based architectures has been extended to ureylene-dicarboxylic acids **2** by Lauher and coworkers [98]. In the latter the known hydrogen bonding patterns of ureas and carboxylic acids were utilized cooperatively to form 2D solids.

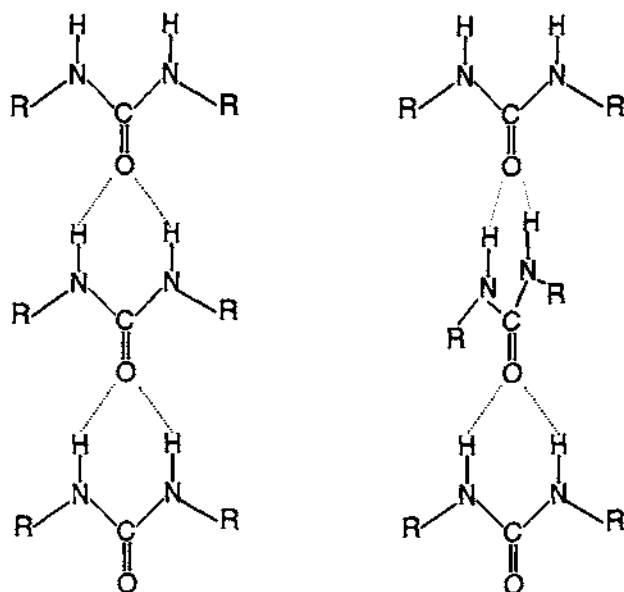
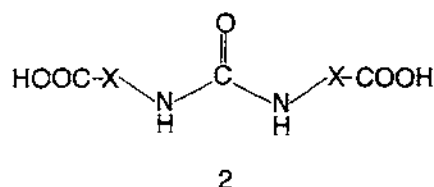
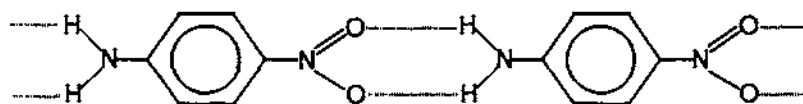


Fig. 10. Hydrogen bonding motif in urea.



2.4.7. Nitroanilines

Nitroanilines inherently possess high molecular polarizability and have found widespread use as a motif to introduce non-linear optical properties in crystals [61,99,100]. The successful use of this motif depends on the formation of strong asymmetric hydrogen bonds between the nitro (acceptor) and amino (donor) groups on adjacent molecules. Such a head-to-tail (Fig. 11) disposition in *p*-nitroanilines can afford an infinite chain that is inherently polar. Curtin and Paul [67] analyzed crystal structures of aromatic compounds and found that meta substituted compounds in general prefer to crystallize in polar space groups. Furthermore, Etter and

Fig. 11. Linear head to tail hydrogen bonding in *p*-nitroaniline.

Huang recently noted that compounds containing nitroaniline motifs have a higher than normal probability of crystallizing in polar space groups [65].

2.5. Cocrystals

Cocrystals of complementary molecules or ions can offer greater versatility than individual molecules or ions, yet they have not received much attention. Indeed, the process of self-assembly can be promoted by mixing molecules that would not normally self assemble by themselves. This, of course, is what typically happens in nature and the term “strict self-assembly” has been applied to such systems [15]. A recent trend is to form supramolecular assemblies involving two or more (Fig. 12) structurally different molecules that bear complementary hydrogen bonding motifs [32,101–107]. Etter and Baures [104] demonstrated that cocrystallization of potential organic hydrogen donors with triphenyl phosphine oxide, a strong hydrogen bond acceptor, produces good quality and large crystals, which otherwise were not always attainable. Cocrystals also offer the distinct advantage of a modular approach to generating a wide range of related materials and one does not have to resort to covalent synthesis of new compounds [101–107]. Isomorphic substitution, systematic replacement of molecules from a crystal lattice with suitable molecules of comparable size and shape [108], is closely related and relevant to the field of inclusion chemistry. Finally, one cannot ignore the role of solvents [109,110] which may act as competitive hydrogen bond donors and/or acceptors or be enclathrated as guest molecules [48].

3. CRYSTAL ENGINEERING VIA SELF-ASSEMBLY OF MOLECULES OR COMPLEMENTARY MOLECULES OR IONS

In this section we deal with specific polymeric motifs and how they can be generated in a generic fashion. Specific compounds are used to illustrate patterns

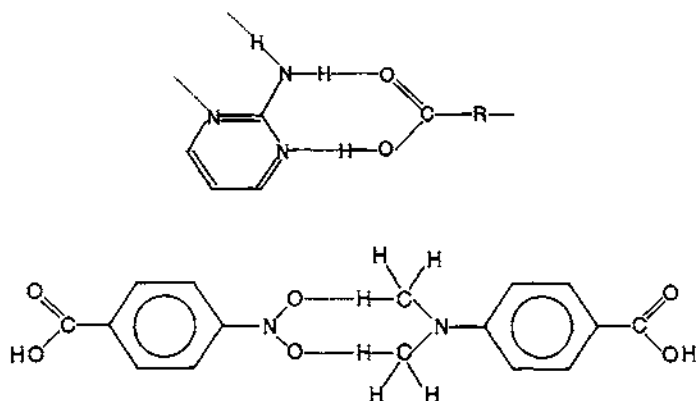


Fig. 12. Hydrogen bonding motifs in cocrystals of aminopyrimidine with carboxylic acids and *p*-nitrobenzoic acid with *p*-*N,N*-dimethylbenzoic acid.

but it should be stressed that the chemical nature of the species is not as important as the inherent symmetry and functionality, and that in principle the functional groups that link molecules are interchangeable.

3.1. *Molecular symmetry and crystal structure*

That there can be a direct relationship between molecular symmetry (or lack thereof) and space group symmetry should be apparent. However, chemists have only just started to give rigorous consideration to this concept and rationalization of crystal structure hydrogen bonding parameters for the purpose of crystal engineering is still in its infancy [2]. In recent years, analysis of solid-state structures of known compounds has afforded predictable hydrogen bonding patterns and preliminary rules have been proposed [35,39]. Unfortunately, the precise solid-state tertiary structure that will result from a given motif remains quite unpredictable [2,4]. The primary reason for this situation is that although the most thermodynamically stable hydrogen bonding interactions between molecules can be predicted reliably, the effect of other non-covalent interactions or crystal packing is not yet predictable with any certainty. Also, the roles of solvent molecules, particularly of polar protic and aprotic solvents that could compete as hydrogen bond donors and acceptors, and polymorphism [2,3] are hard to predict. Fortunately, these are problems that can ultimately be overcome using experimental and computational techniques. For example, in recent years, analytical techniques such as electrospray mass spectroscopy and vapor phase osmometry have been used to identify hydrogen-bonded aggregates in solution [62-64]. Computational chemists are also beginning to address the issue of weak non-covalent forces and arene-arene and water-arene interactions have been particularly well studied [111-116].

The ability to predict asymmetric aggregates in a facile manner is clearly a critical first step to calculating a crystal structure. Application of symmetry principles to such asymmetric units should in principle greatly enhance the predictability of solid-state structures. Organics have been subjected to detailed analysis [2], however, inorganics and organometallics remain less well studied [117-119]. The first classes of compounds studied systematically were carboxylic acids [68] and amides [94,95]. More recently, Etter developed the concept of graph sets to classify hydrogen-bonding patterns in various types of compounds and delineated definite rules [35]. Some of these rules are given in Table 1. Rules 1-3 are general for most of the motifs discussed in Section 2 whereas others are specific to certain motifs.

Statistical analysis of substitution patterns and space group symmetry in which aromatics crystallize has been conducted by Curtin and Paul [67], by Frankenbach and Etter for carboxylic acids [66], and by Etter and Huang for nitroanilines [65].

In Section 2 various types of structural motifs and the modes of hydrogen bonding between such motifs were presented. We paid no attention to how such interactions could be exploited to generate infinite architectures. The number and

TABLE 1

Some hydrogen bond rules for organic compounds

(A) General rules for all classes of compounds

- (1) Preferentially all strong hydrogen bond donors and acceptors are utilized in hydrogen bonding.
- (2) Six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds (see Fig. 8(a)).
- (3) The best proton donors and acceptors remaining after the formation of intramolecular hydrogen bonds form intermolecular hydrogen bonds to one another.

*(B) Additional rules for specific classes of functional groups**Nitroanilines*

- (4) Amino protons will hydrogen bond to nitro groups (see Fig. 11).
- (5) One or more intermolecular amino-nitro hydrogen bonds will form.
- (6) The aggregate patterns formed from intermolecular hydrogen bonds between substituents in meta and para positions will be acentric (see ref. 65).
- (7) The amino-nitro interaction is usually a three-center hydrogen bond (graph set $R_1^2(4)$).
- (8) Ortho-substituted primary nitroanilines usually form two-center intermolecular hydrogen bonds, rather than three-center bonds (graph set $R_2^2(6)$).

Diaryl ureas

- (4) The N–H hydrogens prefer to adopt an anti relationship to the carbonyl group and to form three-center bonds to urea carbonyl groups (see Fig. 10, graph set $C(4)[R_1^2(6)]$).
- (5) Cocrystals form in $R_2^2(6)$ patterns when there are strong meta-substituted electron-withdrawing substituents, like NO_2 groups, on the aryl rings, and when the guest molecules have acceptor groups that are stronger than the internally hydrogen bonded urea carbonyl oxygen.
- (6) When cocrystals form, the N–H protons form three-center bonds to acceptor groups (graph set $R_2^2(6)$).
- (7) Nitro groups of meta nitro substituted diarylureas are not usually used as hydrogen-bond acceptors for urea N–H hydrogens in the presence of guest molecules with good hydrogen-bond acceptors (see ref. 59).

Carboxylic acid cocrystals with 2-aminopyrimidine

- (4) Both N–H protons and both ring nitrogens are used in hydrogen bonds (see Fig. 12).
- (5) 2-Aminopyrimidine prefers to form hydrogen bonds to acids rather than to itself.
- (6) 2-Aminopyrimidine forms cyclic patterns (graph set $R_2^2(8)$) with acids and with itself.
- (7) The two N–H protons need not form hydrogen bonds to identical groups, likewise for the ring nitrogens. (For a ranking of proton accepting ability and proton donor ability of 2-aminopyrimidine see ref. 32.)

Nucleotide base cocrystals

- (4) Adenine and cytosine form cocrystals with many acidic organic compounds, but thymine and uracil do not.
- (5) Cocrystals of adenine and cytosine with carboxylic acids give patterns with $R_2^2(8)$ or $R_2^2(9)$ graph sets.
- (6) Neutral *N*-acylamino acids complex with adenine or cytosine in $R_2^2(8)$ patterns.
- (7) Cyclic alternant $-\text{C}(\text{O})-\text{NH}-$ groups complex with adenine and cytosine with preferred graph set $R_2^2(9)R_2^2(9)$.
- (8) Three-centered hydrogen bond contacts are frequently found with $N_1 = R_2^2(8)$ and $N_2 = R_2^2(12)$ (N_1 and N_2 denote the number of types of hydrogen bonds one and two respectively).
- (9) A common motif for nucleotide base complexes involves two primary amines and two carbonyl groups in an $R_2^2(8)$ or $C_1^1(4)$ pattern (for similar examples see Figs. 8(b) and 8(c)).

The motifs described by graph set notations are interpreted as follows: C chain, R ring; the subscripts and superscripts represent the number of donors and acceptors respectively. The number in parentheses indicates the degree or size of the motifs, i.e. the number of atoms involved in a motif. See ref. 35 for further details.

orientation of the hydrogen bond donor/acceptor moieties will obviously influence critically the type of array that is generated. Molecules which have the capability to be exploited in such a manner have been termed “tectons” [33] or “exo-receptors” [17]. In this section we consider how polyfunctional molecules or ions can be exploited in the self-assembly process to form infinite 1D, 2D or 3D arrays and subdivide accordingly.

3.2. One-dimensional networks

Molecules with motifs poised for 1D self-assembly have been shown to form strands, helices or tapes. The requirement is that there be two points of contact between component molecules irrespective of the number of hydrogen bonds per contact. The number of hydrogen bond contact sites at each functional group can influence both the selectivity and the strength of the network but not the overall architecture.

3.2.1. Molecular tapes and strands

An excellent and simple example is that of terephthalic acid **3** [120]. The rigid para disposition of the two carboxylic acid groups ensures that a 1D polymeric strand will occur (Fig. 13). Derivatives of barbituric acid **4** and pyrimidine **5** also have complementary hydrogen bonding sites that sustain formation of 1D solids. Kondo et al. [121] used 4'-acetamidobenzal-1,3-dimethyl barbituric acid **6** to construct polar strands. Molecules of **6** are disposed in a zigzag fashion along the *c* axis and held together by a head-to-tail intermolecular hydrogen bonding between the acetamide N–H moiety and the C=O group at the 2-position of the barbituric acid (Fig. 14). **6** represents a good example where the inherent asymmetry of the hydrogen bond can be preserved unambiguously for the selective construction of polar structures suitable for use in non-linear optics. Recently, Lehn et al. [32] studied self-complementary systems such as 4,6-diamino-5-octylpyrimidin-2(H)-one **7** and 2-amino-5,5-dibutylpyrimidine-4,6(1H)-dione **8**. Even though these two compounds are complementary to each other they are designed to form preferentially self-assembled molecular sheets. Another system described in the same report is that of 5-(1-naphthyl)methylpyrimidine-2,4,6-triamine **9** which forms molecular tapes. In **9** steric factors direct the self-assembly of hydrogen-bonded motifs. Dipyridones linked by acetylenic bridges such as **10** and **11** have been studied by Wuest and co-workers [33,122]. Once again, the relative orientation of the hydrogen bond motif and the inherent symmetry of the molecule plays a significant role in determining the type

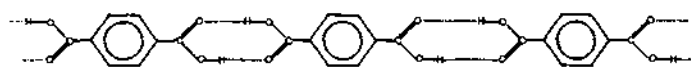
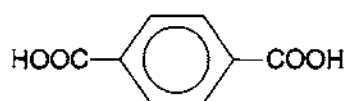
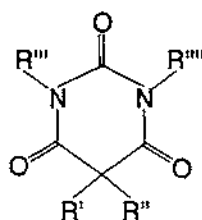


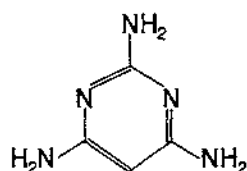
Fig. 13. Linear chain formation through carboxylic acid dimer motifs in terephthalic acid.



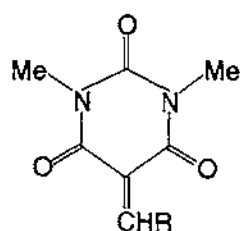
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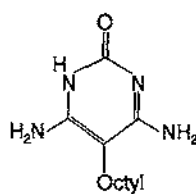
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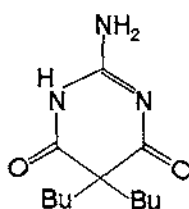
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6, R = 4-acetamidophenyl



7



8

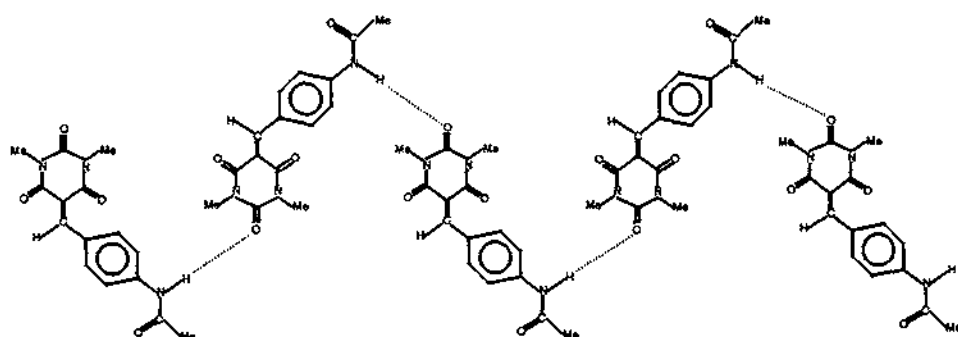
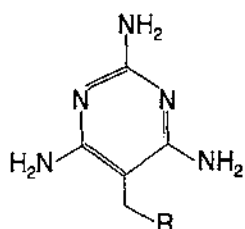


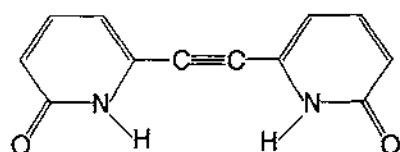
Fig. 14. The polar chain formed by 4'-acetamidobenzal-1,3-dimethylbarbituric acid.

of solid state structure that results. The asymmetric dipyrindone **10** forms a discrete dimeric structure whereas the symmetrical dipyrindone **11** forms a linear zigzag array that is sustained by intermolecular hydrogen bonding.

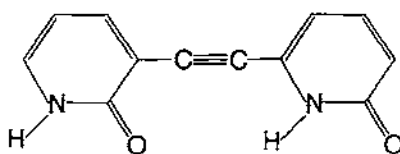
Geib et al. [123] exploited the conformational change induced in the proton-



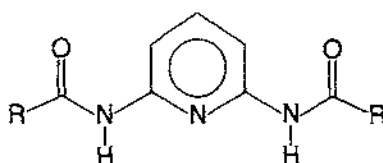
9, R = 1-naphthyl



11



10



12

ated form (Fig. 8(a)) of 2,6-diamidopyridine **12** with diarylphosphate counter ions to form one 1D solids. Intramolecular hydrogen bonding facilitates the formation of an alternating arrangement of anions and cations (Fig. 15) through intermolecular hydrogen bonding.

Using the hydrogen bonding motif present in the 1:1 complex of cyanuric acid–melamine system (Fig. 16) as a model, Zerkowski et al. have constructed self-assembling structures that form “linear” [124], “crinkled” or cyclic “rosette” type

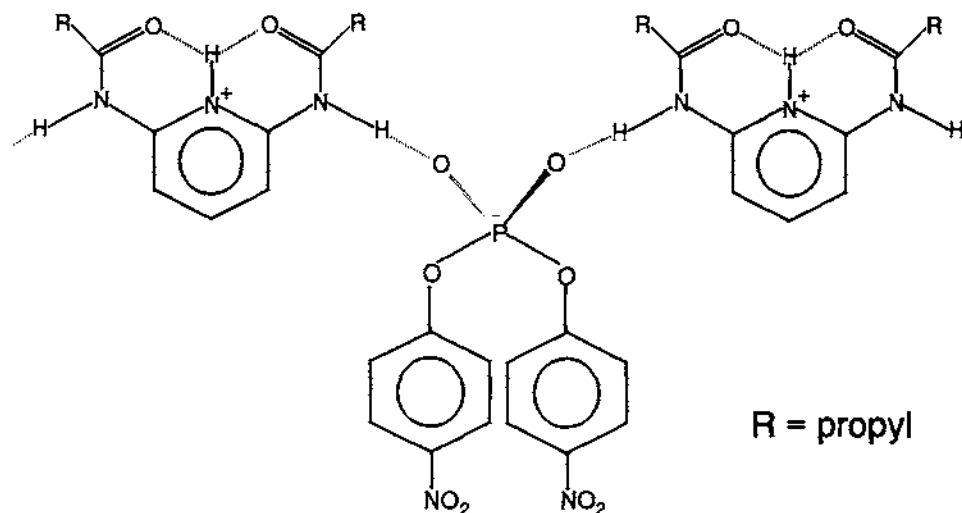


Fig. 15. The linear chain formed by interionic hydrogen bonding between $[H(12)]^+$ and a diarylphosphate anion.

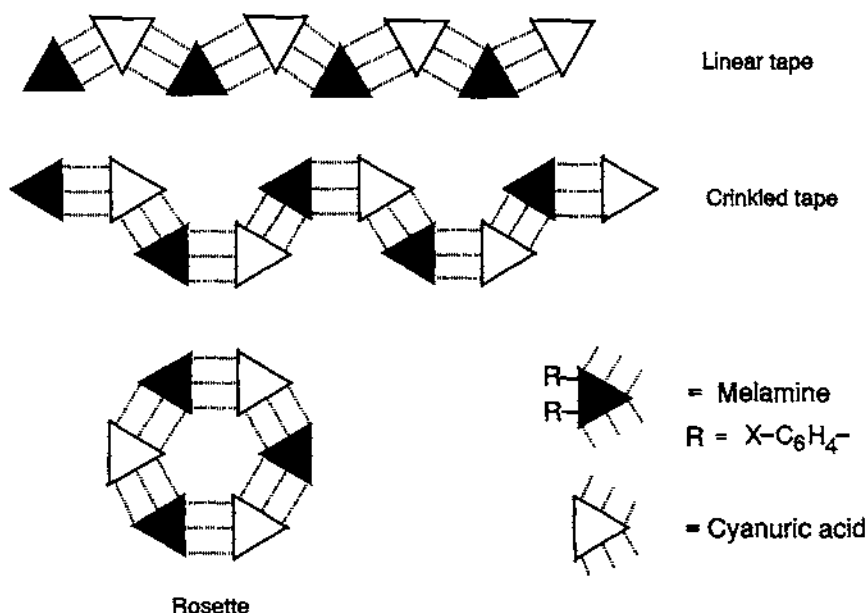


Fig. 16. Various types of hydrogen bonding patterns involving derivatives of melamine and cyanuric acid.

structures [125]. 1:1 cocrystals of suitably functionalized melamine and barbituric acid derivatives were shown to form linear tape structures rather than the sheet structures that normally result from simple melamine and barbituric acid. Crinkled tape or rosette type structures were found to result from 1:1 cocrystals of *N,N'*-bis(*p*-substituted phenyl)melamine and 5,5-diethylbarbituric acid (Fig. 8(c)). The type of structure, i.e. the crinkled tape or rosette, was shown to be a function of the competition between non-bonded steric interactions between the para-substituents and the tendency for a high packing coefficient [126]. It was demonstrated that linear tape structures result if the para-substituent is a small group such as F, Cl, Br, I or CH_3 . However, increasing the size of this substituent beyond that of CF_3 or I affords a crinkled tape structure with inclusion of a solvent molecule (ethanol). With even bulkier substituents such as *t*-butyl groups a "rosette" structure was observed.

An unusual 1D anionic porphyrin system was described by Scheidt et al. [77]. Difluoro(*meso*-tetraphenylporphinato)iron(III) anions are bridged into a linear chain by an intervening imidazolium cation (Fig. 17). The $\text{F} \cdots \text{N}$ (2.622(7)) distance is consistent with hydrogen bond distances typically observed for these atoms [22–29].

The hydrogensulfate anion also has a propensity to form polar strand structures and therefore polar crystals. RbHSO_4 [127] and $[\text{NH}_4][\text{HSO}_4]$ [128] are known ferroelectrics but until recently organic cation hydrogensulfates had not been investigated. We have studied the structures of a number of flat organic cation salts of hydrogensulfate and observed that they tend to exhibit structures that are dominated

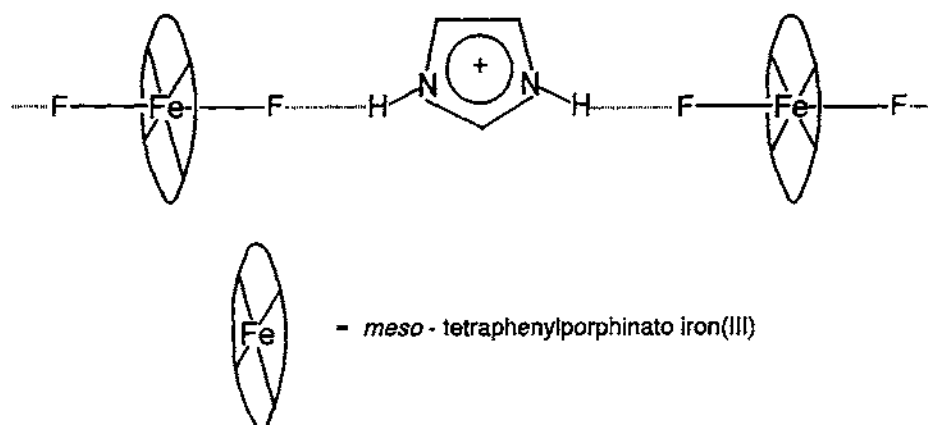


Fig. 17. The aggregate formed by imidazolium cation and *trans*-difluoro-*meso*-tetraphenylporphinatoiron(III) anions.

by the formation of polar anionic $[\text{HSO}_4]^-$ strands [129]. The structure of [isoquinolinium][HSO_4], [13][HSO_4], shown in Fig. 18, illustrates how the anions align themselves by forming strong $\text{OH}\cdots\text{O}$ hydrogen bonds ($\text{O}\cdots\text{O}=2.505(7)\text{ \AA}$). This particular compound crystallizes in the polar space group $P2_1$ even though adjacent strands are aligned anti-parallel. Hydrogensulfate and dihydrogenarsenate salts were also investigated by Pecaut et al. [83]. The structures of 2-amino-5-nitropyridinium hydrogensulfate, [14][HSO_4], and dihydrogen arsenate, [14][H_2AsO_4], were investigated as candidates for non-linear optics. In the case of the hydrogensulfate salt, anti-parallel but polar chains of $[\text{HSO}_4]^-$ anions ($\text{O}\cdots\text{O}$, 2.573(3) and 2.577(3) \AA ; $\text{O}-\text{H}\cdots\text{O}$, 177(3)° and 173(4)°) were observed and the cations are hydrogen bonded

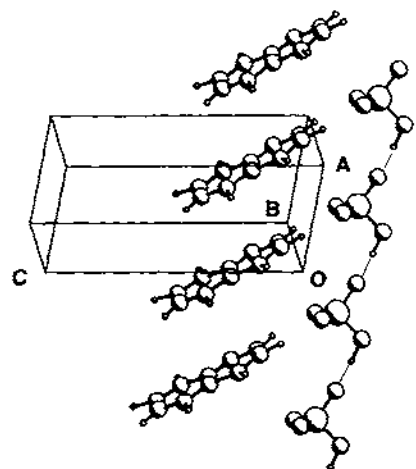
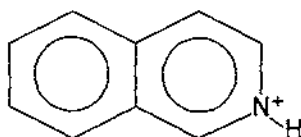
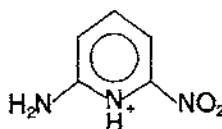


Fig. 18. PLUTO plot of isoquinolinium hydrogensulfate showing the linear chain of hydrogensulfate anions.

to the chain. The -NH_2 hydrogen atoms bridge adjacent $[\text{HSO}_4]^-$ anions and the cations are anchored further to the anionic chain through $(\text{Py})\text{NH}\cdots\text{O}$ bonds. Two independent cations with a pseudo inversion center occur in the crystal structure. The orientation of cations in alternate layers is such that there is anti-parallel ordering and loss of bulk polarity. However, in the dihydrogenarsenate salt, the anion forms a double strand which sandwiches the cations. The cations are hydrogen bonded to the anionic layer and are ordered in a herring-bone fashion that maintains the polarity of the chain. The salt therefore crystallizes in a polar ($Pna2_1$) space group.



13



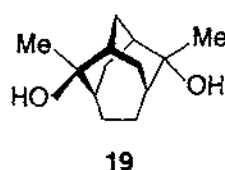
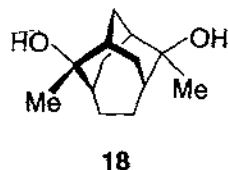
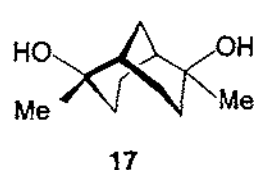
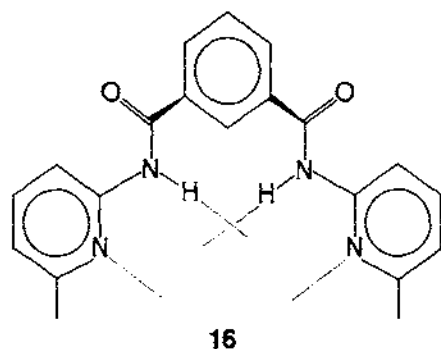
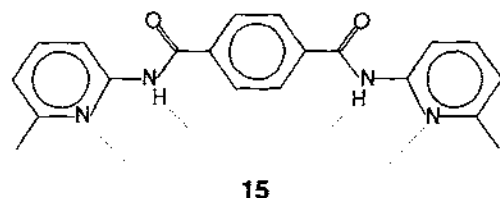
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Pecaut and Masse [92] also investigated the crystal structure of [14] $[\text{Cr}_2\text{O}_7]$. In this compound the dichromate anions are arranged in a polar chain parallel to the b -axis and the cations are hydrogen bonded to this chain. The two crystallographically independent cations are related through a pseudo inversion center. The two -NH_2 protons bridge adjacent anions within a chain and a strong hydrogen bond occurs between $\text{Py}(\text{N})\text{-H}$ and the anion. The compound crystallizes in a polar space group ($P2_1nb$), however, the pseudo inversion center around is manifested by low SHG efficiency. It should be clear from the above that the herring-bone arrangement of cations and polar ordering of anions is a common feature of salts of 14. An advantage of such salts is that the polar ordering of anions and cations is efficient and predictable as the strong electrostatic interactions are complemented by strong hydrogen bonding interactions. This is not often the case for molecular solids where weaker van der Waals type interactions tend to prevail.

3.2.2. Helices

The double helical structure of DNA is stabilized by both hydrogen bonding and π -stacking [30] yet synthetic analogs of such structures are relatively rare. Bishop and Dance [130] summarized the symmetry requirements for helix formation and described several systems that form helical structures through intermolecular hydrogen bonding. Appropriate orientation of hydrogen bonding sites precludes chains, meaning that helical structures become favored. Such an approach has also been elegantly demonstrated by Hamilton and co-workers [131]. The diamide derived from 2-amino-6-methyl pyridine and terephthaloyl chloride 15 forms discrete 1:1 adducts with dicarboxylic acids. However, the diamide derived with isophthaloyl chloride 16 forms helical structures with dicarboxylic acids. The selective formation of helical structures results from inability of 16 to form 1:1 complexes with dicarbox-

ylic acids. In the 1:2 complex the pendant pyridine groups are projected above and below the plane of the isophthaloyl ring, thereby resulting in the formation of a twisted U-shaped motif that facilitates the formation of helices



Ung et al. [108] described helical tubuland diols cocrystallized with *p*-chlorophenol and hydroquinone. The diols **17**, **18** and **19** are known to form isostructural helicates (Fig. 19(a)) through a trigonal hydrogen bonded spine-motif. Replacement of a diol by *p*-chlorophenol maintains the same trigonal spine motif, but the 3D structure changes to a 2D layered structure. Replacement by hydroquinone changes the 2D layered structure back into a 3D helicate (Fig. 19(b)) structure while maintaining the same space group symmetry ($P2_1/c$). These changes are readily explainable in terms of well understood [2] non-covalent interactions. In the case of the *p*-chlorophenol structure, strong $\text{Cl}\cdots\text{Cl}$ interactions stabilize the adjacent phenol molecules, whereas in the case of hydroquinone both the phenolic ($-\text{OH}$) groups are involved in the trigonal spine motif and bridge adjacent layers.

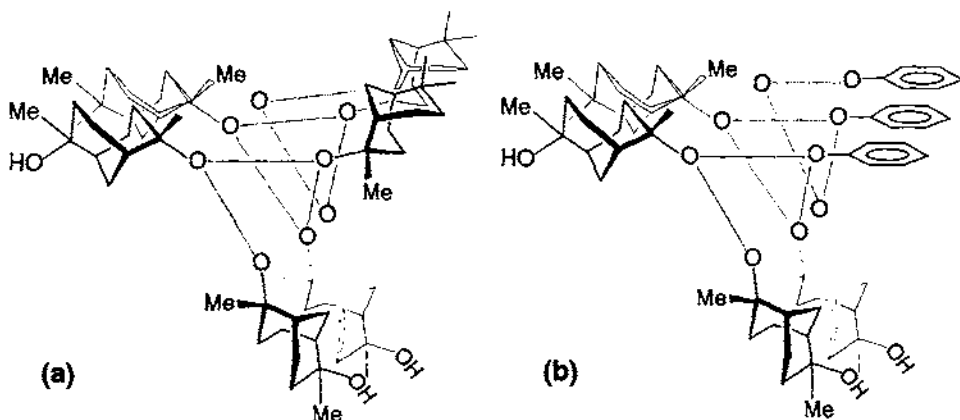
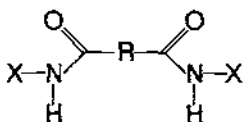


Fig. 19. Helical strands formed by (a) intermolecular hydrogen bonding between diol 17 and (b) isostructural helicates formed by isomorphous substitution of 17 by hydroquinone.

3.3. Two-dimensional structures

In the past, only strong hydrogen bonding interactions ($X-H\cdots X$, where X is an electronegative atom such as O or N) tended to be recognized by chemists whereas weak hydrogen bonding interactions such as $C-H\cdots X$ and $\pi\cdots H$ were not considered to be major contributing factors to crystal packing. However, in the absence of insufficiently strong hydrogen bond donors and acceptors such weak interactions play a decisive role and many of the 1D structures already known can be reanalyzed as 2D layered or even 3D structures.

As mentioned earlier, amides, ureas and their cyclic analogs have been studied in detail and are potentially good candidates for the construction of 2D layered structures. In the early 1980s Lieserowitz and Hagler [132] conducted a detailed analysis of amide structures and found distinct patterns of hydrogen bonding in these compounds. In particular, N-substituted amides were found to exhibit intermolecular hydrogen bonding that affords linear chains. However, in amides of dicarboxylic acids such as 20, the hydrogen-bonded chains were observed to be cross-linked via the covalent carbon chain and hence a 2D solid was formed (Fig. 20). This is



20

the basic structural type found in the technologically important fibre material "Kevlar" (Fig. 21) which is a linear chain covalent polymer of terephthalic acid and 1,4-phenylenediamine that is cross-linked by hydrogen bonds [133].

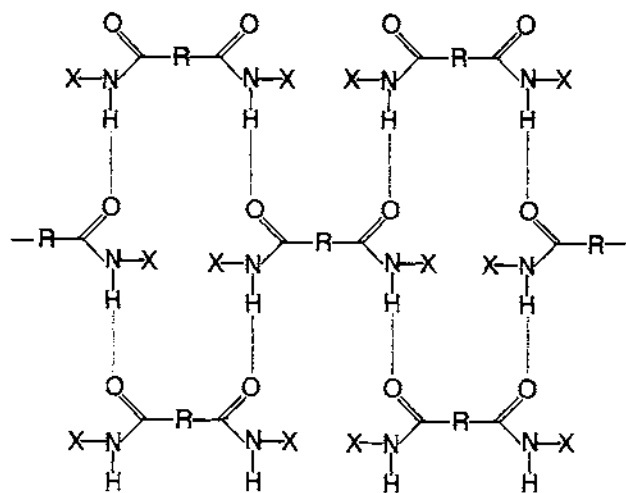


Fig. 20. The hydrogen bonding pattern exhibited by diamides of dicarboxylic acid.

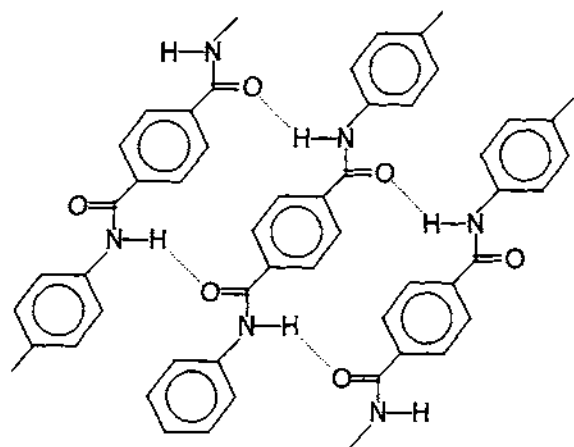


Fig. 21. The hydrogen bonding pattern in Kevlar (polymer of *p*-phenylene diamine with terephthalic acid).

Hydrogen bonding in aryl ureas has been investigated by Etter et al. [59]. Their studies established the unique "urea hydrogen bonding motif" (Fig. 10). This motif was exploited in a recent publication that focussed on dicarboxylic acid derivatives of urea. Chang et al. [134] detailed the construction of 2D layered structures. The ketonic oxygen atom in the diamide or urea structure is a double hydrogen bond acceptor in many diamide structures and is therefore predisposed to form linear polymeric chains. Such a 1D structure can in principle be readily transformed into a 2D motif with judicious choice of ancillary groups. In this particular case the carboxylic acid group, which is known to form centrosymmetric dimeric structures, was used. A combination of these two motifs forms the basis for

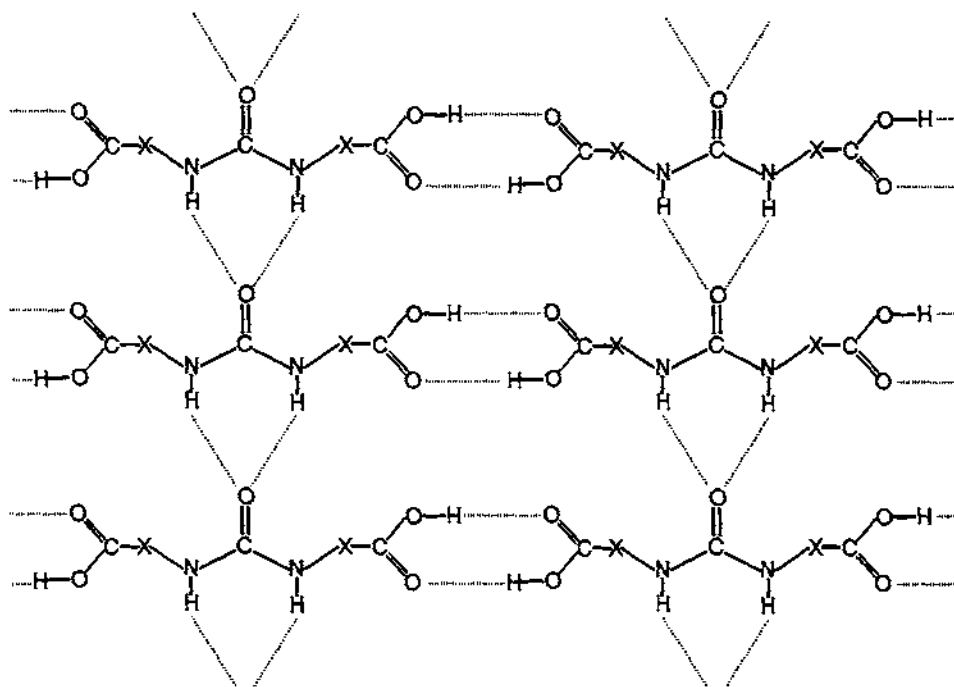


Fig. 22. The hydrogen bonding pattern in ureylenedicarboxylic acids.

the layered structures in ureylenedicarboxylic acids (Fig. 22). The success of such a strategy results from non-interference between the separate motifs.

Trimesic acid **21** represents another classic example of 2D networking in which the network is open enough to necessitate interweaving in order to fill space within the crystal lattice [135–137]. Compounds which are interwoven are often capable of forming clathrates selectively with guest molecules and trimesic acid has been extensively studied in this context. Figure 23 illustrates how **21** self assembles through all three carboxylic acid sites, generating large cavities. These cavities either hold guest molecules [138–140] or concatenate with two other networks [141–143]. Seddon and co-workers [84] characterized a series of organic cation salts of the dihydrogenphosphate anion in order to study their SHG activities. Unlike KH_2PO_4 which forms a diamondoid array [51], monofunctional organic cations cannot act as linear hydrogen bond donors and are too large to sit in cavities, precluding a 3D network. However, the cations are capable of cross-linking and they play an essential and necessary role in aligning the molecular dipoles and therefore enhancing the SHG activity. For example, the crystal structures of piperidinium **22** and benzylammonium **23** dihydrogenphosphate illustrate the concept quite well [84]. In $[\mathbf{22}][\text{H}_2\text{PO}_4]$ the anions form infinite chains ($\text{O}\cdots\text{O}$, 2.568(4) and 2.630(4) Å; $\text{O}\cdots\text{H}-\text{O}$, 153(5)° and 151(6)°) which are cross linked by the cations. In $[\mathbf{23}][\text{H}_2\text{PO}_4]$ the ammonium centers and dihydrogenphosphate anions are hy-

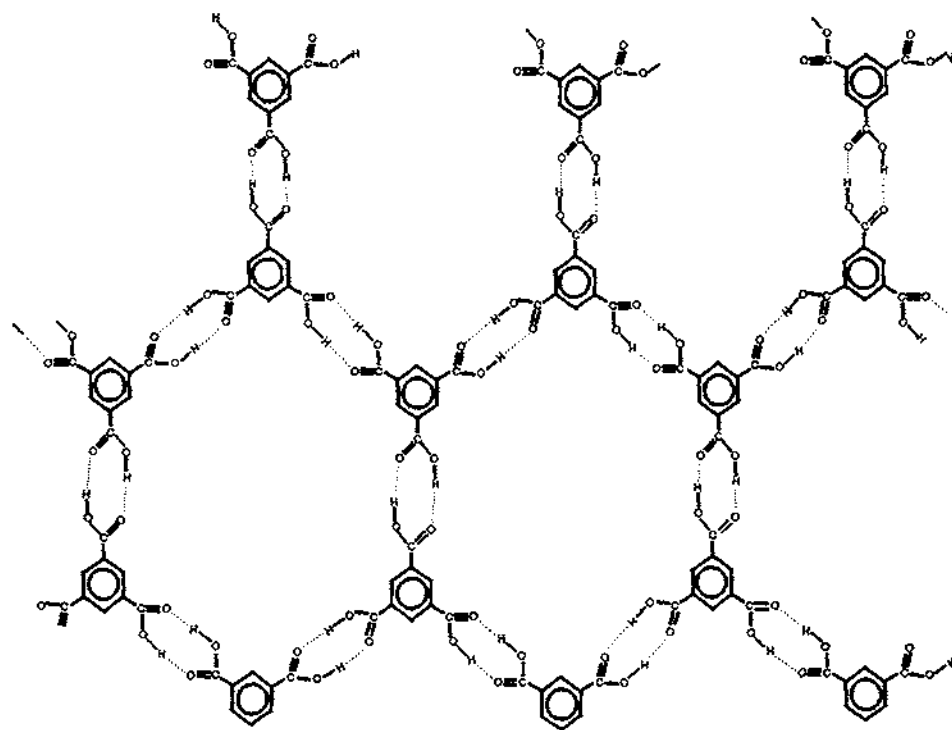
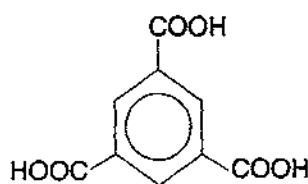
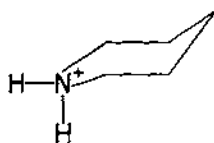


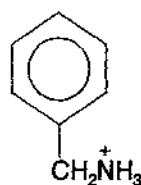
Fig. 23. Network hydrogen bonding in trimesic acid.



21



22



23

drogen bonded and lie towards the center of a bilayer with the phenyl groups projecting outside and arranged in a herring-bone structure. The bilayers are arranged parallel to the *bc* plane. All three ammonium protons are involved in hydrogen bonding. Two of these protons are bonded to two dihydrogenphosphate oxygens within one half of the bilayer and the third to the dihydrogenphosphate across the layer. Similarly, the dihydrogenphosphate anions form two sets of hydrogen bonds. One set forms hydrogen bonds within one half of the bilayer to form a chain ($\text{O} \cdots \text{O}$, 2.553(6) and 2.571(6) Å) structure parallel to the *c*-axis which is further cross linked by hydrogen bonds to the anions in the other half of the bilayer. These two structures

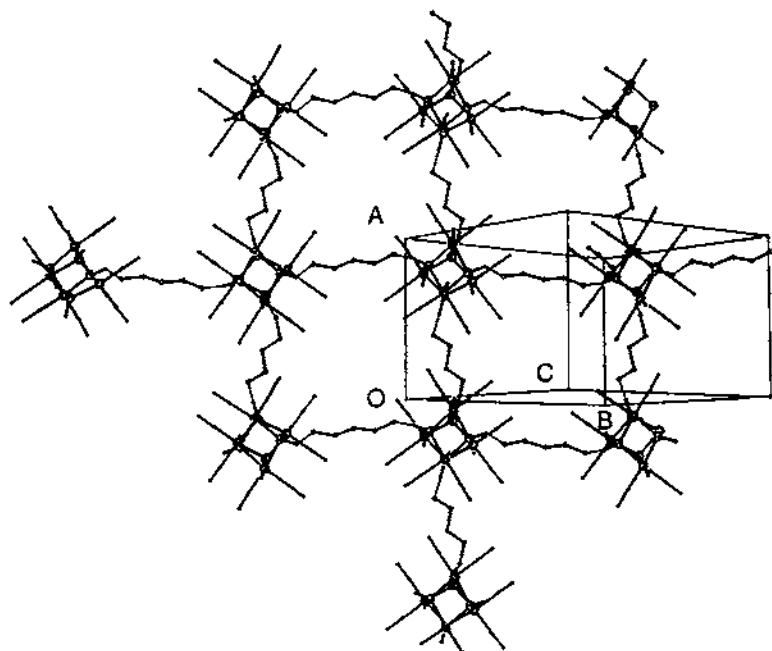


Fig. 24. ORTEP view of the 2D grid formed by $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4$ and propylene diamine.

demonstrate how the nature of the substituent and the number of hydrogen donors on the nitrogen atom can influence network hydrogen bonding between dihydrogen-phosphate anions and, ultimately, the tertiary structure. Seddon's group [144] also presented a study involving organic cation salts of L-tartaric acid, which are necessarily polar because of the L-tartarate anion. Once again, organic cations which cannot bridge in a linear fashion manifest themselves by cross-linking to form 2D sheets.

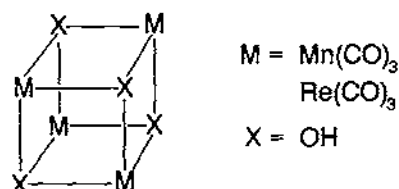
We have recently investigated 2D frameworks formed from self-assembly of two or more neutral molecules [102]. The cubane-like clusters $[\text{M}(\text{CO})_3(\mu_3\text{-OH})]_4$ ($\text{M} = \text{Mn, Re}$) **24** have T_d symmetry and four rigid H-bond donor moieties (i.e. the $\mu_3\text{-OH}$ groups). When **24** is cocrystallized with angular bifunctional H-bond acceptor molecules, it manifests its symmetry by facilitating the formation of infinite 2D square grid frameworks. The grid formed from **24** and two molecules of 1,3-diaminopropane is illustrated in Fig. 24. If **24** is linked via longer spacer moieties such as 4,4'-dipyridyl...ROH then concatenation of networks occurs in order to fill the cavities within the square grid framework. One of the independent networks so formed is illustrated in Fig. 25.

3.4. Three-dimensional structures

Obviously, to form 3D hydrogen-bonded structures, both the number and orientation of the complementary hydrogen bonding motifs are critically important.



Fig. 25. ORTEP view of the 2D network formed by hydrogen bonding between $[\text{Re}(\text{CO})_3(\mu_3\text{-OH})]_4$, 4,4'-dipyridyl and methanol.

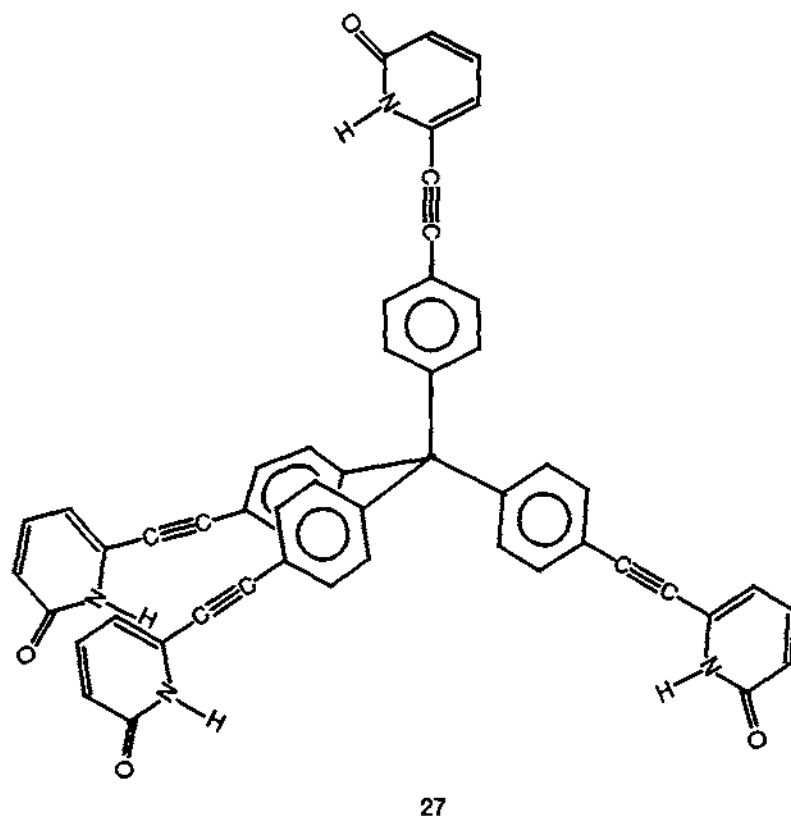
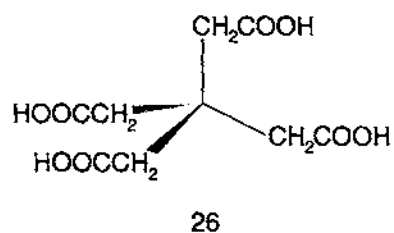
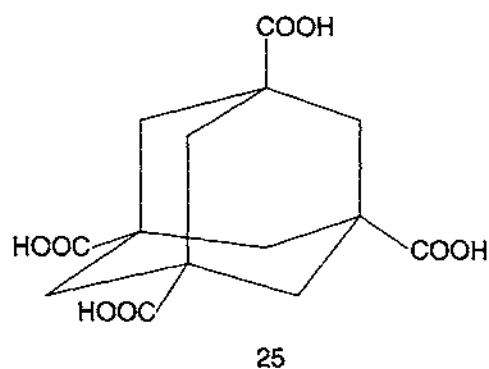


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In this section we discuss how symmetry and functionality at the molecular level can afford several classes of 3D network, many of which are capable of exhibiting microchannels and/or microcavities that are capable of enclathrating guest molecules.

3.4.1. Diamondoid structures

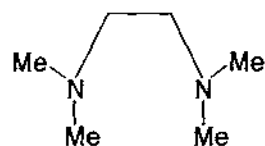
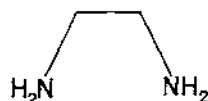
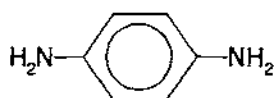
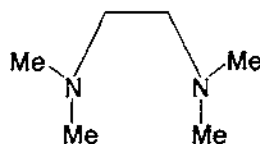
Molecules in which the motifs are related by T_d or even S_4 symmetry are strong potential candidates for the engineering of 3D diamondoid structures. Diamond itself, two forms of ice and KH_2PO_4 are just three examples of 3D arrays that are structurally related to one another (i.e. diamondoid) and have been known for decades [29,145]. Furthermore, the T_d point group does not contain an inversion center and one would therefore assume that molecules which possess T_d symmetry are more predisposed to crystallize in polar space groups than, say, octahedral complexes. It is therefore somewhat surprising that it was not until 1988 that organic diamondoid structures based on hydrogen bonding were realized. In a series of elegant papers Ermer and co-workers [34,146,147] demonstrated how tetracarboxylic acids with S_4 symmetry form superdiamondoid arrays in the solid state. The prototypal molecule studied by Ermer [34] was adamantane-1,3,5,7-tetracarboxylic acid **25**. The carboxylic acid moieties are necessarily rigidly directed towards the vertices of a tetrahedron and the intermolecular interactions are defined by centrosymmetric carboxylic acid dimer motifs. The resulting superdiamondoid structure is five-fold, i.e. there are five independent diamondoid networks which are interwoven but independent of one another. Ermer and Lindenberg [147] demonstrated subsequently that by manipulating steric factors in related compounds the level of interpenetration and inclusion of guest molecules can be controlled rationally.



Tetra-substituted derivatives of methane that have linear orientation of hydrogen bond donor/acceptor moieties also possess the right symmetry and functionality to self assemble into 3D diamondoid arrays. This was first demonstrated by Ermer and Eling [146] in the case of methanetetraacetic acid **26** which forms a three-fold network. Wuest and co-workers [33] took matters further by exploiting the ability of pyridones to self assemble. The tetrakis(pyridone) derivative of methane **27** was shown indeed to be capable of self-assembly but, unlike **26**, it does not interweave. Remarkably, a one-fold open network with enough space to enclathrate two molecules of butyric acid per molecule of **27** exists.

Another group of compounds with T_d symmetry and rigidly directed hydrogen bond donors is M_4X_4 pseudocubanes such as **24**. **24** are readily accessible [148,149] and they are excellent candidates for construction of 3D superdiamondoid networks since μ_3 -OH moieties are particularly good H-bond donors. We have utilized the cubanes **24** (both Mn and Re) to form 3D architectures by cocrystallizing them with linear difunctional hydrogen bond acceptors [101,103]. The linear difunctional acceptors exploited in our studies cover diverse organic functional groups and hence a variety of hydrogen-bonding modes. The level of concatenation or interpenetration of the diamondoid networks is logical based on the length and volume of the linear spacer with two-fold ($NNN'N'$ -tetramethylethylenediamine **28**, 1,4-diaminobenzene **29**), three-fold (ethylenediamine **30**) or four-fold networks (4,4'-dipyridyl **31**) observed depending on the linear spacer used. All structures retain at least the S_4 symmetry of the cubane in the crystal and two of the networks also exhibit microchannels that run parallel to the c -axis in tetragonal space groups. These microchannels contain two (**29**) or four (**31**) molecules of acetonitrile per molecule of **24**.

In principle, the strict-assembly [15] approach is modular and therefore more generic than the self-assembly approach since one does not have to resort to covalent

**28****30****29****31**

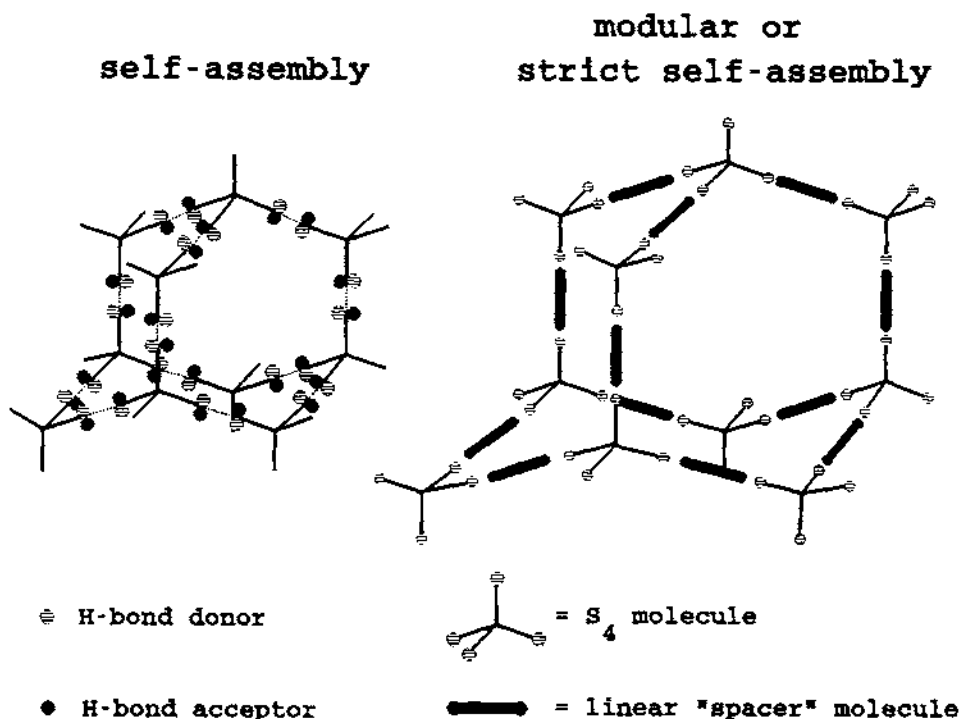


Fig. 26. Self-assembly vs. strict self-assembly of diamondoid networks.

bond breakage or assembly in order to "fine-tune" the components. The difference between the self-assembly and strict self-assembly processes is illustrated schematically in Fig. 26.

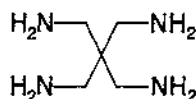
3.4.2. Other three-dimensional arrays

Several open chain and macrocyclic polyammonium cation salts have been characterized structurally with a variety of counter ions. In these polyammonium cations, owing to electrostatic repulsion, the carbon chain linking the nitrogen atoms tends to adopt a conformation such that the ammonium centers are disposed as far away as possible from one another. For example, in the tetraprotonated spermidine **32** [82] and cyclam **1** [91] cations, the ammonium groups are oriented towards the periphery of the cation. Such an orientation of the hydrogen bond donor moieties facilitates strong intermolecular interactions between cations, anions and solvent molecules since the cation is in effect an exo-receptor. The symmetry of these components and the intermolecular interactions between these components determines the topology of resulting hydrogen-bonded networks.

The crystal structures of $[\text{H}_4(\mathbf{33})]\text{Cl}_4$ and $[\text{H}_4(\mathbf{33})](\text{SO}_4)_2$ were reported by Cameron et al. [78]. In the chloride salt, the anions and cations were found to be



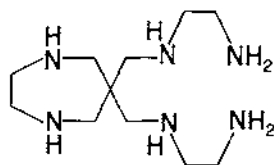
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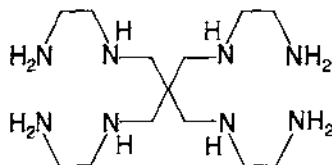
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arranged in slabs parallel to the 001 plane and supported by extensive short (N)H...Cl hydrogen bonding (2.15 Å, N—H...Cl 180°). The adjacent slabs were found to be further interlinked by long (N)H...Cl hydrogen bonds (2.80 Å, N—H...Cl 100°). The resulting 3D network can be considered to be composed of tetragonally compressed Cl₁₂ cubo-octahedra packed in such a way that each chloride ion is shared by three adjacent cubooctahedra. The corresponding sulfate salt [H₄(33)](SO₄)₂ crystallizes in a polar space group (*P*2₁2₁2₁) and the cations and anions were found to be interconnected by an exhaustive 3D network of hydrogen bonding. The overall structure was described as a very distorted fluorite structure.

McAuley et al. [79] studied the crystal structures of polyammonium cations closely related to 33, [H₆(34)]Cl₆·4H₂O and [H₈(35)]Cl₈·2H₂O. In the latter the



34



35

cation essentially adopts a planar conformation as in [H₄(33)]⁴⁺ salts and is arranged in slabs. The water and chloride ions occupy the interstitial space between these slabs of cations. The cations are linked together through hydrogen bonding between the chloride anions and nitrogen atoms (N...Cl: 3.10 Å). Surprisingly, the water molecules are not involved in hydrogen bonding with either the cation or the chloride. The closest interionic contact observed was between water and a chloride ion, 3.31(2) Å, just over the sum of the van der Waal's radii for chlorine and oxygen. The structure of [H₆(34)]Cl₆·4H₂O is quite different. The cations, anions and the water molecules are all involved in network hydrogen bonding. The cations are arranged in a head to tail fashion, i.e. the open chains face the 1,4-diazacycloheptane ring. The anions and water molecules lie within the plane of cations and there are no distinct planes of cations or anions. The crystal structure can be described as planes of hydrogen-bonded cations, anions and water molecules with no interplanar hydrogen bonds.

Subramanian and Zaworotko [80,91,93] recently studied the crystal structures of several salts of the cyclam tetracation [H₄(1)]⁴⁺ ([H₄(1)]⁴⁺X₄ where X = Cl[−], CNS[−], HSO₄[−], TsO[−], Br[−], [Fe(OH₂)Cl₅]^{2−}, 2Cl[−], all with water of crystallization; X = CF₃COO[−], [Fe(OH₂)Cl₅]^{2−}, 2Cl[−], with no water of crystallization). The cation

$[\text{H}_4(1)]^{4+}$ adopts the same exodentate conformation in all salts, all eight N–H hydrogen atoms poised for network hydrogen bonding. However, the type of network varies from 1D to 3D depending on the nature of the anion and the role of the water molecules.

The structure of the tetrachloride salt [80] is perhaps the most interesting because it forms a 3D array which contains microchannels that contain water molecules. The cations are stacked over one another as a result of intervening chloride ions that form $\text{NH}^+ \cdots \text{Cl} \cdots \text{HN}^+$ bridging units. The $\text{N} \cdots \text{Cl}$ distances vary between 3.065(3) and 3.242(3) Å and the $\text{N}-\text{H} \cdots \text{Cl}$ angle is 137° . The obtuse hydrogen bond angle is the key to making the resulting array 3D. Each of the two microchannels illustrated in Fig. 27 contains two molecules of water per cation. In channel i the water molecules are disordered but channel ii has the right prerequisites (size and disposition of hydrogen bond acceptors) to sustain a symmetrical 1D water polymer. To our knowledge this represents the first example of such a situation.

In network hydrogen bonding the inherent asymmetry of complex anions such as $[\text{Fe}(\text{OH}_2)\text{Cl}_5]^{2-}$ can manifest itself in the formation of asymmetric hydrogen

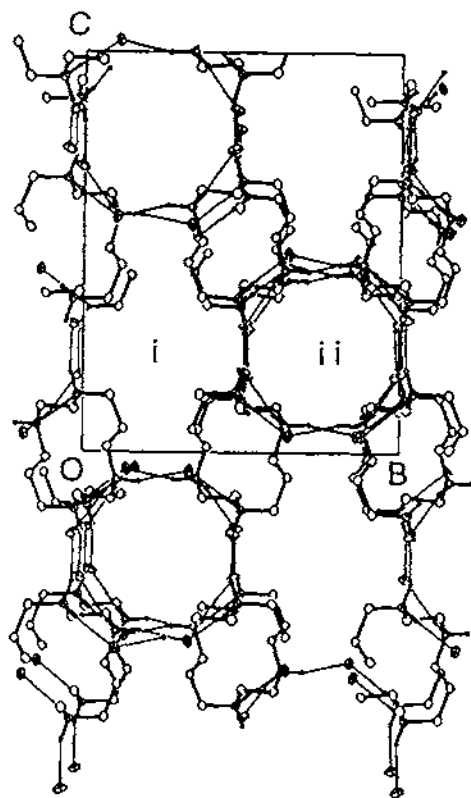


Fig. 27. ORTEP plot showing the microchannels that contain the 1D water polymer in $[\text{H}_4(1)]\text{Cl}_4 \cdot 2\text{H}_2\text{O}$.

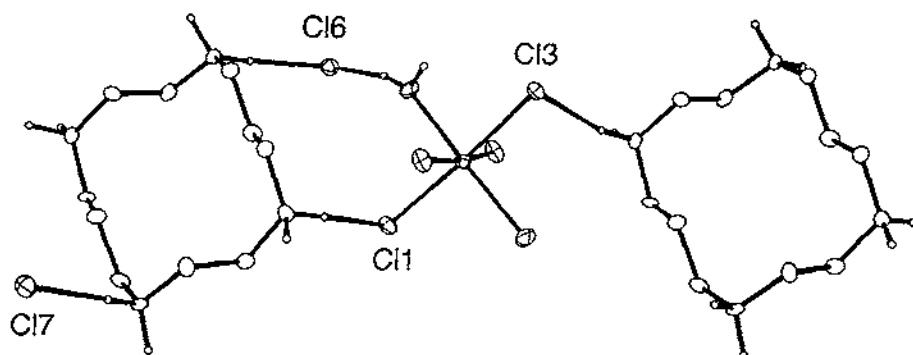
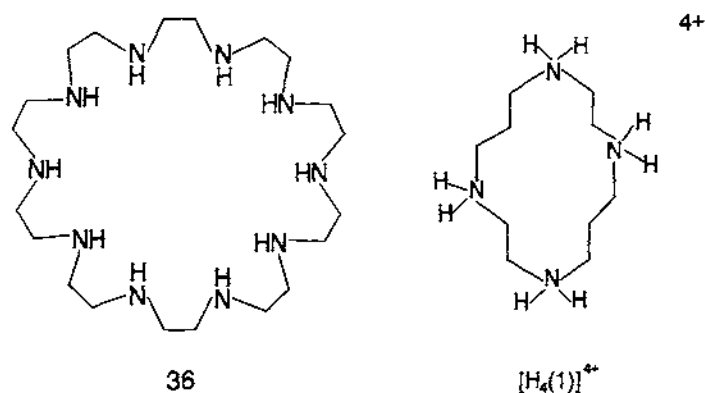


Fig. 28. ORTEP plot showing the polar strand formed by hydrogen bonding between the $[H_4(1)]^{4+}$ cation, $[Fe(OH_2)Cl_5]^{2-}$ and Cl^- anions.

bonds and compounds such as $[NH_4]_2[Fe(OH_2)Cl_5]$ [89] and $[OH_3]_2[Fe(OH_2)Cl_5]$ [90] crystallize in polar space groups. Zaworotko and Subramanian [91] exploited this aspect in the formation of a polar solid using $1^{4+} = [H_4(1)]^{4+}$. Figure 28 shows how $[Fe(OH_2)Cl_5]^{2-}$ and chloride anions are involved in bridging adjacent cations. The involvement of the water molecule in the complex anion in the networking makes the two directional senses of the hydrogen bonding physically and geometrically different and hence causes the compound to crystallize in a polar space group. This would not be expected to occur in more symmetrical anions such as $[Fe(CN)_6]^{3-}$.

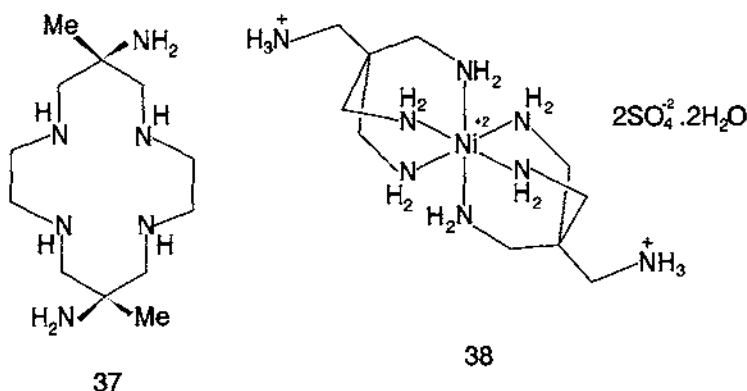
Early literature on anion complexation studies led to the structural characterization of a number of macrocyclic polyammonium salts of complex anions and these structures invariably exhibit extensive hydrogen bonding networks. Bencini et al. [87] studied the crystal structure of $[H_8L_1][Co(CN)_6]_2Cl_2 \cdot 10H_2O$ where $L_1 = 1,4,7,10,13,16,19,22,25,28$ -decaazacyclotriacontane **36**. The crystal packing can



be described in terms of parallel chains of anions and cations. Owing to electrostatic repulsion between the protonated amines, the macrocyclic moiety is stretched out

with the unprotonated secondary amines apart. This leads to an exodentate orientation of the nitrogen atoms such that the ammonium hydrogen atoms are easily accessible for hydrogen bonding, affording a 2D layered structure.

In a similar study, Bernhardt et al. [88] described the crystal structure of $[\text{H}_4\text{L}_2]_{1.5}[\text{Fe}(\text{CN})_6]_2 \cdot 3\text{H}_2\text{O} \cdot 3/4\text{HCN}$ ($\text{L}_2 = 6,13\text{-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine } \mathbf{37}$). There are two independent cations, one lying around a crystallographic inversion center, the other around a quasi inversion center, with extensive and strong hydrogen bonding interactions between cations, anions and water molecules. However, no detailed analysis of the network was attempted.



In more recent years several examples of coordination compounds stabilized by 3D hydrogen bonding interactions have been studied. The crystal structure of an octahedral nickel(II) complex **38** that exhibits extensive 3D hydrogen bonding was described by McAuley et al. [81]. In this complex, there are 13 sterically accessible hydrogen bond donors (from the —NH_3^+ , coordinated —NH_2 groups and two water molecules of crystallization) and 12 acceptors (from the sulfate anion and the two water molecules of crystallization). They are all involved in hydrogen bonding. The sulfate and water molecules are hydrogen bonded in such a way that the water molecules link symmetry-related sulfate groups. The sulfate and water molecules also show strong hydrogen bonding interactions with the —NH_2 and —NH_3^+ groups. The sulfate anions sit over the faces of the octahedron around the Ni(II) complex and link the adjacent cations through $\text{N—H}\cdots\text{O}$ bonds.

A 3D coordination polymer $[(\text{Me}_3\text{Sn})_4\text{Fe}(\text{CN})_6 \cdot 2\text{H}_2\text{O} \cdot \text{C}_4\text{H}_8\text{O}_2]_\infty$ stabilized by intermolecular hydrogen bonding interactions was described by Adam et al. [150]. The polymeric structure is stabilized by two types of non-linear chain that connect the octahedral iron centers. In one of these chains, $\text{Sn(1)—O(water)}\cdots\text{O(1,4-dioxane)O}\cdots\text{O(water)—Sn(2)}$ linkages exist. The $\text{O}\cdots\text{O}$ distances are relatively long (2.779 Å) but closely match with those found in liquid water [151] and water clathrates [152]. The dioxane component in this polymer can be replaced by two molecules of water to obtain $[(\text{Me}_3\text{Sn})_4\text{Fe}(\text{CN})_6 \cdot 4\text{H}_2\text{O}]$

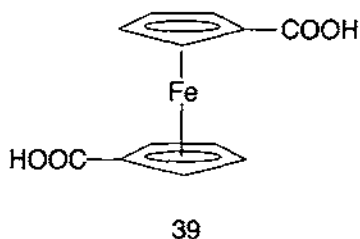
[153]. Two types of chain stabilize the structure. $\text{H}_2\text{O}\cdots\text{H}_2\text{O}-\text{Sn}-\text{NC}-\text{Fe}-\text{CN}-\text{Sn}-\text{OH}_2\cdots\text{H}_2\text{O}$ chains have hydrogen bond distances of 2.628(11) Å. This compound represents a good example of how solvent molecules can play a decisive role in determining the asymmetric unit that forms the basic building block of the crystal.

4. THE ROLE OF WEAK HYDROGEN BONDS

As mentioned earlier it is beyond the scope of this review to provide detailed coverage of weaker classes of hydrogen bond. This does not, however, mean that they are beyond the scope of the crystal engineer. Recent advances in our understanding of weaker non-covalent forces have brought them into the realm of crystal engineering. A couple of important classes are discussed below.

4.1. $\text{C}-\text{H}\cdots\text{X}$ hydrogen bonds

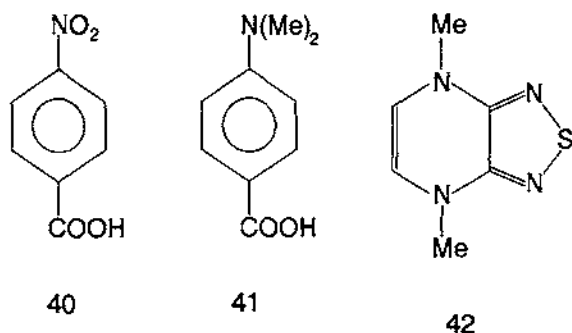
Though $\text{C}-\text{H}\cdots\text{X}$ ($\text{X}=\text{O}, \text{N}, \text{Cl}, \text{S}$) hydrogen bonds were the subject of debate for over two decades [154], a statistical analysis [155] of all available crystal structures with short $\text{C}-\text{H}\cdots\text{X}$ contact distances ($\text{C}-\text{H}\cdots\text{X}$ distances shorter than the sum of the van der Waal's radii of C and X) validated their existence. Their relatively long bonding distances and definite orientation, directed by electrostatic interactions, can make them important in crystal engineering when stronger hydrogen bonding is not able to dominate. $\text{C}-\text{H}\cdots\text{X}$ hydrogen bonds can be particularly relevant when acidic $\text{C}-\text{H}$ hydrogens are involved.



An example of $\text{C}-\text{H}\cdots\text{O}$ hydrogen bonding (see Fig. 12) is found in 1,1'-ferrocenedicarboxylic acid **39** [156]. **39** crystallizes in monoclinic and triclinic forms and the crystal structure of the triclinic modification has been determined by both X-ray and neutron diffraction studies. In the triclinic form, owing to the eclipsed conformation adopted by **39**, two molecules form a discrete hydrogen-bonded centrosymmetric dimer. Two types of dimer occur in the crystal structure and the corresponding neighboring dimers are joined by weak $\text{C}-\text{H}\cdots\text{O}$ type interactions. No interaction between dimers of different types was observed. The $\text{C}-\text{H}$ hydrogens (from C(2) and C(5)) involved were those adjacent to the carbon atom bearing the $-\text{COOH}$ groups. These are more acidic owing to the inductive effect and are

hydrogen bonded only to the carbonyl oxygen of the —COOH group. In the monoclinic form discrete centrosymmetric dimers are also formed and these dimers also exhibit $\text{C—H}\cdots\text{O}$ interactions. However, in contrast to the triclinic form, both the carbonyl and hydroxylic oxygen atoms of the —COOH groups are involved. In both cases the $\text{C—H}\cdots\text{O}$ distances are in the range 2.25 to 2.61 Å. An important difference between these forms lies in the dimensions of the —COOH groups. In the triclinic form the —COOH groups are ordered and hence the C—O(H) and C=O distances are distinct, but this is not so in the monoclinic form because of crystallographic site symmetry.

There are quite a few recent publications that identify $\text{C—H}\cdots\text{X}$ type interactions. A $\text{C—H}\cdots\text{O}$ (see Fig. 12) interaction has been described in the crystal structure of a 1:1 complex of 4-nitrobenzoic acid **40** and 4-(*N,N*-dimethylaminobenzoic acid [106] **41**. These acids form a discrete 1:1 centrosymmetric dimer through hydrogen bonding between the acid groups. These units are further linked by $\text{C—H}\cdots\text{O}$ bonds ($\text{C}\cdots\text{O}$ distances 3.658(4) and 3.725(4) Å) between the C—H hydrogen atoms of the *N*-methyl groups and the oxygen atoms of the nitro group. As a result, a linear chain structure with alternating units of **40** and **41** is observed. In the crystal structure of 4,7-dimethyl-4,7-dihydro[1,2,5]thiadiazolo-[3,4-*b*]pyrazine [157] **42**, $\text{C—H}\cdots\text{N}$ interactions (2.5 Å) that stabilize a sheet-like structure were



observed. This is further supported by $\text{S}\cdots\text{N}$ and $\pi\text{—}\pi$ type interactions. Very recently, $\text{C—H}\cdots\text{N}$ interactions were described in the 1:1 cocrystals of 1,3,5-tricyanobenzene and hexamethylbenzene [107]. The formation of this complex was premeditated on the fact that $\text{C—H}\cdots\text{N}$ interactions can lead to hexagonal layered structures. The crystal structure (Fig. 29) features alternate layers of 1,3,5-tricyanobenzene and hexamethylbenzene. The aromatic rings are stacked over one another at a centroid to centroid distance of 3.855 Å to optimize $\pi\text{—}\pi$ interactions. In the 1,3,5-tricyanobenzene layers $\text{C—H}\cdots\text{N}$ interactions are observed between the —CN groups and C—H hydrogens. Site symmetry requires four of the six $\text{C—H}\cdots\text{N}$ bonds (3.471(4) Å, $172(2)^\circ$) to be equal while the other two must be perfectly linear (3.516(6) Å, 180°).

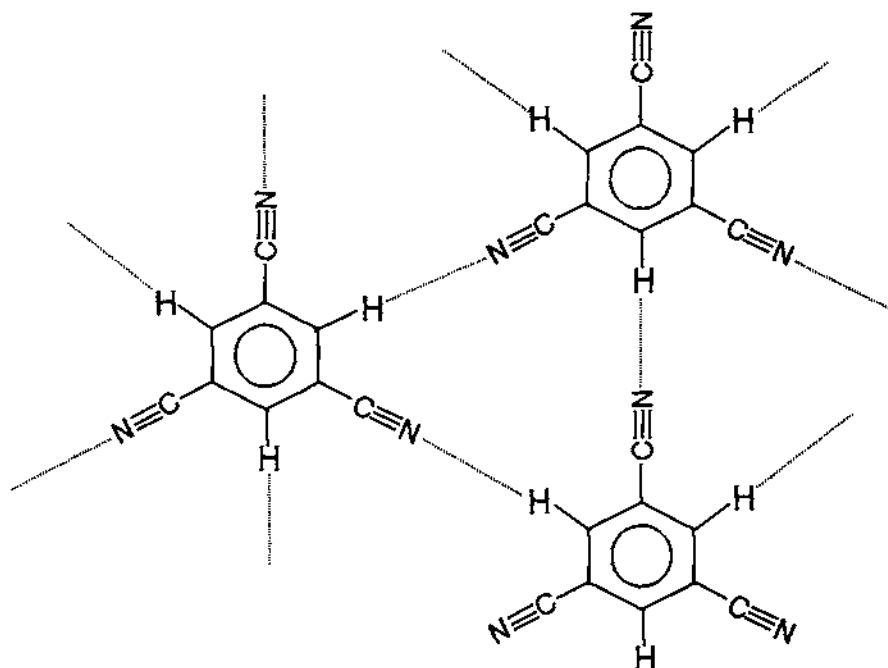


Fig. 29. Hydrogen bonding pattern between the 1,3,5-tricyanobenzene molecules in the cocrystals of hexamethyl benzene and 1,3,5-tricyanobenzene.

4.2. π -Hydrogen bonds

Aromatic π -electrons are potential hydrogen bond acceptors and the existence of π -hydrogen bonds was known prior to the 1960s [22]. Both early [47,158] and recent literature [159–161] indicates that π -hydrogen bonds can be more than a curiosity. Recent spectroscopic [114] and crystallographic evidence [56,57,115,116] is available to support this view and such interactions have even been used as a design element in host–guest chemistry for molecular recognition of aromatics [53]. The prevalent view amongst theoretical chemists is that $\pi \cdots \text{H}-\text{X}$ ($\text{X}=\text{C}, \text{N}, \text{O}$, halogens) interactions are essentially electrostatic in nature [114]. However, whereas recognition and understanding of π -hydrogen bonding are now quite advanced, the same cannot be said about direct application or exploitation.

The various modes in which π -hydrogen bonds can occur are shown in Fig. 30. According to the rules (see Table 1) delineated by Etter [35], the molecules will pack so that all strong hydrogen bond donors and acceptors are paired up before weaker hydrogen bonding interactions take precedence. Under such circumstances, in the absence of strong hydrogen bond acceptors, hydrogen bonding to the π -system of aromatic rings can occur and will therefore be expected to play a dominant role in the packing of crystals. This aspect has been demonstrated in a molecular assembly

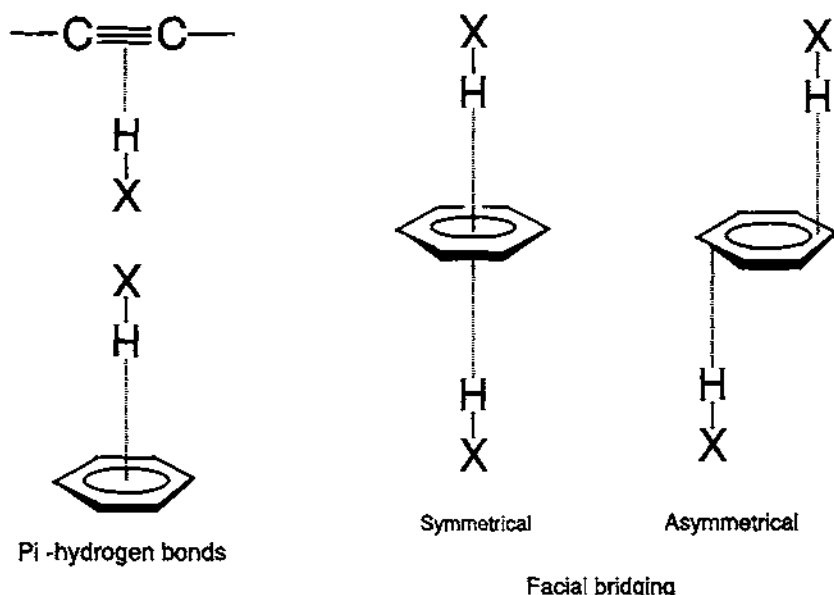


Fig. 30. Possible modes of π -hydrogen bonding.

that is deficient in hydrogen bond acceptors [54]. Of the various modes of π -hydrogen bonding, the bifacial bridging mode is rather uncommon, but highly relevant to crystal engineering since it is directional. A benzene molecule in a symmetrical bifacial bridging mode was proposed by Horn et al. [55] in $[(\text{Mn}(\text{CO})_3)_4(\mu_3\text{-OH})_2(\mu_3\text{-F})_2] \cdot 2\text{C}_6\text{H}_6$. In a more recent investigation of the crystallization of **24** with various aromatic compounds [57], asymmetric bifacial bridging π -hydrogen bonding played a significant role in the formation of superdiamondoid structures. The compounds studied include benzene, toluene, *p*-xylene, *p*-fluorotoluene, 1,4-difluorobenzene, naphthalene, 1-methylnaphthalene, mesitylene and 1,2,3,4-tetramethylbenzene. Mesitylene and 1,2,3,4-tetramethylbenzene exist as 4:1 discrete adducts (i.e. a type A π -hydrogen bond). Mesitylene and 1,2,3,4-tetramethylbenzene are presumably more sterically demanding, thereby precluding diamondoid networking. IR spectra of these compounds show a shift towards lower wave numbers for O–H frequencies compared with free $[(\text{Mn}(\text{CO})_3(\mu_3\text{-OH}))_4]$. An ORTEP view of an adamantoid portion of these networks is illustrated in Fig. 31.

5. CONCLUSION AND FUTURE DIRECTIONS

The salient feature of the results that we have collated herein is that it should be clear that patterns of predictability of crystal structures based on directed hydrogen bonding are beginning to be recognized, understood and exploited. Crystal engineering has indeed become an appropriate term for several classes of compound

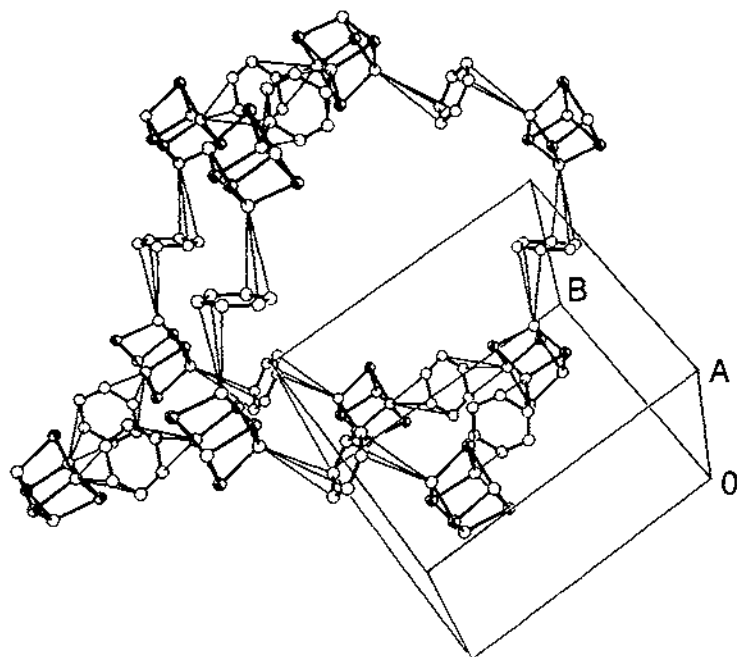


Fig. 31. ORTEP plot showing one adamantoid portion of the diamondoid network formed between benzene and $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4$.

since crystal structures were obtained by rational design rather than empirical observation. The provocative statement “*One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical compositions*” [162] is therefore no longer necessarily true in the case of structures which are defined by moderate to strong hydrogen bonding. We feel particularly hopeful about prospects for multi-component systems (i.e. salts or cocrystals) which are in effect generic and modular since in principle at least one component can be changed without destroying the architecture within the solid. This implies that crystal engineering is ready to enter a new and potentially significant phase, fine control of structure/function relationships in the context of inclusion chemistry and materials science. Indeed, many of the 2D and 3D structures described herein have bulk polarity or zeolitic inclusion capabilities yet are chemically different from prototypal solids with these functions. However, successes have only come in very limited situations and chemists have still taken only a small step towards accumulating enough knowledge to engage successfully in routine *ab initio* calculation of long-range crystal packing and space group symmetry. This is particularly the case for organic compounds with few, many or flexible H-bonding sites. In such molecules, which represent the majority of organics and organometallics, intermolecular forces are typically weak enough to afford several global minima, a consequence of which is likely to be polymorphism.

Ironically, a molecule which we used as an example of predictability, terephthalic acid [119], also serves as an example of the difficulties one can face. Terephthalic acid can easily be predicted to exist as 1D strands. However, adjacent strands are able to pack with one another in several ways, and several polymorphs have been observed of terephthalic acid and its hexadeuterio analog [163,164]. The key to future advances in such situations and in general therefore rests as much in the hands of theoretical and computational chemists as crystallographers and synthetic chemists. However, given the obvious practical relevance of crystal engineering, the next decade is likely to see the field moving forward at a fast pace.

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