Reviews

Molecular Recognition in the Solid State: Hydrogen-Bonding Control of Molecular Aggregation

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The design of molecular subunits that self-assemble into well-defined structures in the solid state is an area of intense current interest. A key to controlling the packing arrangement lies in manipulating the type and orientation of the non-covalent interactions between the subunits. The strong and directional nature of hydrogen bonds has led to their widespread use in self-assembling systems. In the solid state, rules have been delineated to allow the reasonable prediction of hydrogen-bonding packing patterns in crystals. This had led to a search for molecular components that because of their hydrogen-bonding characteristics will form persistent packing motifs in well-defined shapes or patterns. We have recently discovered that a strong bidentate hydrogen bonding interaction is formed between 2-amino-6-methylpyridine and carboxylic acids. Bis(2-amino-6-methylpyridine) derivatives and dicarboxylic acids will self-assemble into alternating cocrystal structures. The packing of the two components can be controlled in a rational way by changing the nature, size, and orientation of the spacer groups that link the hydrogen-bonding subunits.

Introduction and Background

The use of crystalline materials in modern science and technology is widespread. There is currently an intensive search for crystals that have superconducting properties that are noncentrosymmetric so that they can be used to change the frequency of incident light, and that can facilitate certain chemical reactions which are not possible in solution. A key goal in materials science is to first understand how the structure of an individual molecule might influence the structures of the resulting crystal and then use this knowledge to construct solids that have desired properties. This type of crystal engineering[1,2] has become increasingly attractive in the past two decades because modern synthetic methodology allows molecular structure and interactions to be manipulated in many different ways.

Since the crystal structures of organic solids are the result of the balance among different intermolecular interactions, one can view the process of crystal formation as a molecular recognition process at the surface of a crystal. Thus, the success of crystal engineering lies in understanding the crystal packing forces—electrostatic, hydrogen bonding, van der Waals and $\pi-\pi$ stacking interactions. The strength, directionality and selectivity of the hydrogen bond places it at the center of many research efforts aimed at controlling solid state structures. Detailed studies of existing crystal structures led to the delineation of various

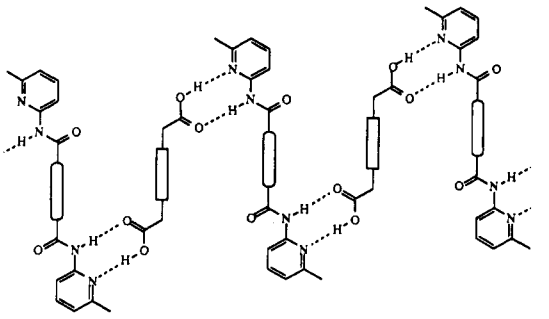

Figure 1. Packing pattern between bis(acylaminopyridines) and diacids.

rules to predict the hydrogen-bonding arrangements in single- and two-component crystals, as demonstrated by the groups of Leiserowitz[3,4] and Etter.[5,6] However, there remains a strong need for hydrogen-bonding motifs that can direct the formation of predictable and ordered solid-state structures despite changes in the shape and size of the spacer groups. The discovery of such persistent hydrogen-bonding motifs would allow not only the more reliable prediction of solid structures but also the construction of materials with a controlled positioning of key functional groups.

Etter et al. have reported on the crystal-packing patterns of diaryl ureas. One general arrangement[6] involved the

* Abstract published in *Advance ACS Abstracts*, August 15,1994.

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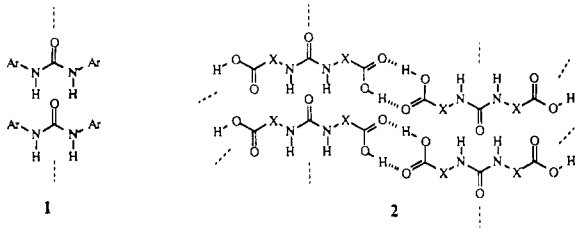
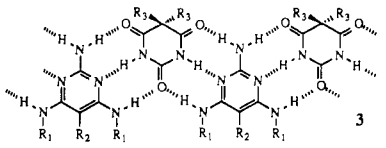
linear aggregation of urea, as in 1. Combining this crystal packing motif with that of dicarboxylic acids, Lauher and co-workers demonstrated the design of predictable two dimensional hydrogen bonding structures. The resulting ureylenedicarboxylic acids generally have the structure shown in 2.[7]



1 2

The groups of Lehn[8] and Whitesides[9] have used the association of melamine and barbituric acid derivatives to control the formation of hydrogen bonded molecular tapes, which maintain their basic structural features with different substituents on the two binding components. This general pattern is shown in 3.



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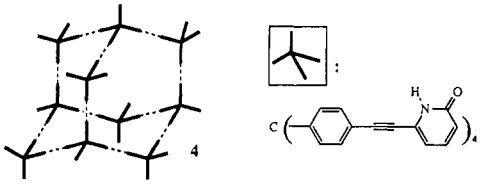
Wuest and co-workers have extensively studied the hydrogen bonding patterns of pyridone derivatives.[10-12] The dimerization of pyridone via hydrogen bonding allows the formation of well-defined aggregates in the solid state. A recent report from Wuest's group demonstrated the formation of rigid three-dimensional networks with large chambers (4).[12] The cavity of the chamber can accommodate a variety of molecules. Inclusion of butyric acid or valeric acid and related compounds has been observed.



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Hydrogen-Bonded Sheets Based on "Para-Linked" Bis(acylaminopyridines)

The common translational H-bonded packing of diamides[1,2] can be induced to interpose a second component by incorporating strong and complementary bidentate interactions between the crystal partners. We have

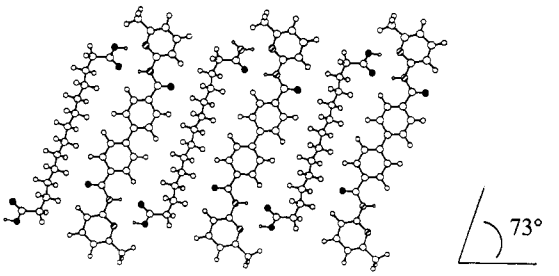


Figure 2. Crystal structure of 1,12-dodecanedicarboxylic acid and *N,N'*-bis[2-(6-methyl)pyridyl]-4,4'-biphenyldicarboxamide (5).

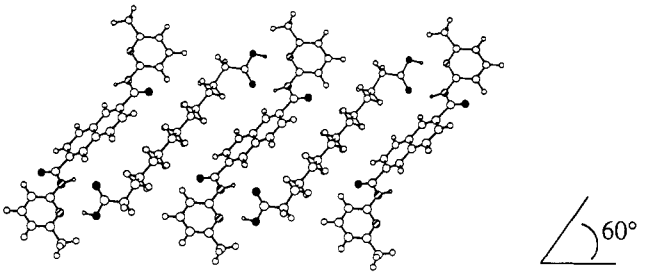
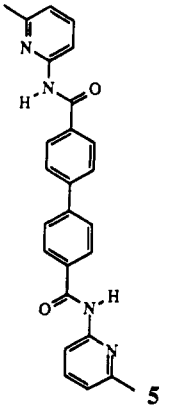


Figure 3. Crystal structure of 1,12-dodecanedicarboxylic acid and *N,N'*-bis[2-(6-methyl)pyridyl]-2,7-naphthyldicarboxamide.

shown[13] that the 2-acylaminopyridine/carboxylic acid pair provides a stronger interaction than the single hydrogen bond between simple diamides and can lead to polymeric aggregates as in Figure 1. These represent elongated molecular sheets whose dimensions are imposed by the hydrogen-bonding network and the relative size match of the alternating components. An important factor in this motif is expected to be the orientation of the two acylaminopyridine subunits. In Figure 1 these are shown separated on opposite sides of a rigid spacer (or "para-linked" as in, for example, 5) with a 180° relationship



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between the direction of the hydrogen bonding groups. Figure 2 shows the complex formed between biphenyldiamide 5 and 1,12-dodecanedicarboxylic acid (space group $P\bar{1}$). An almost flat sheet structure is taken up with a 73° slip or tilt angle between the polymethylene chains and the horizontal (defined by a line drawn through the pyridine-N atoms). This H-bonding motif is dominant and is retained despite changes in the size of the molecular components. Indeed, the extent of the slip angle can be varied in a systematic and predictable way by changing the size matching of the diamide and diacid. Shortening

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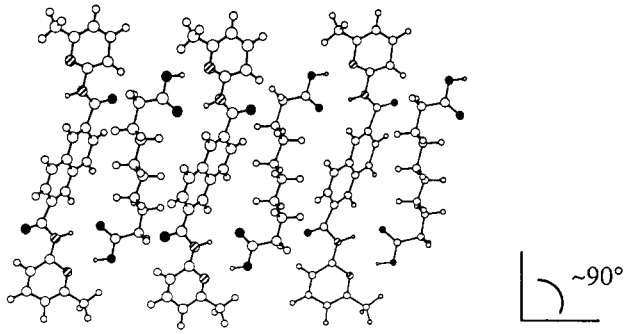


Figure 4. Crystal structure of 1,8-octanedicarboxylic acid and *N,N'*-bis[2-(6-methyl)pyridyl]-2,7-naphthyldicarboxamide.

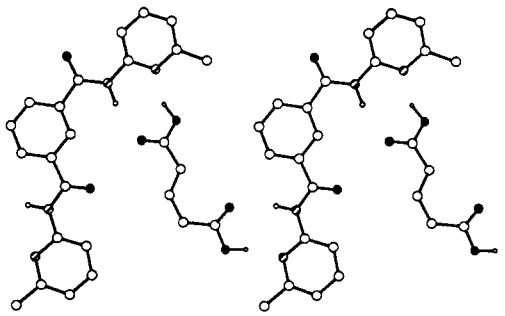


Figure 5. Crystal structure of 7 with glutaric acid.

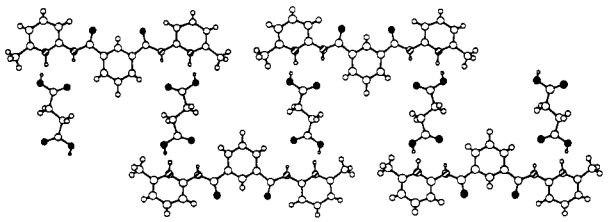
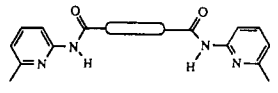


Figure 6. Crystal structure of 7 with succinic acid.

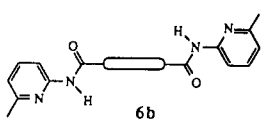
the diamide spacer from biphenyl to naphthyl (~2.2 Å shorter) leads to a decrease in the slip angle to 60° (Figure 3, space group $P\bar{1}$). A subsequent shortening of the diacid to 1,8-octanedicarboxylic acid increases the slip angle to the point where the two subunits are well-matched in length and the angle is ~90° (Figure 4, space group $P1$).

Hydrogen-Bonding Patterns of "Meta-Linked" Bis(acylaminopyridines)

In the bis(acylaminopyridines) described above (e.g., **5**), there are two low-energy conformations, **6a** and **6b**. When these receptors crystallize with a dicarboxylic acid that has a comparable $(CH_2)_n$ chain length, **6a** will lead to a 1:1 complex and **6b** will result in a polymeric aggregate. Both forms (**6a** and **6b**) of crystals have been observed,[13,14] while form **6b** appears to be more common due to the formation of extended hydrogen bonded ribbons.



6a



6b

With these results in hand, we sought to investigate a bis(acylaminopyridine) with a different spacer as a way of studying the dependence of crystal packing on the

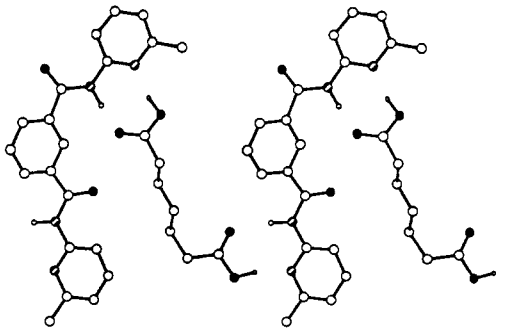
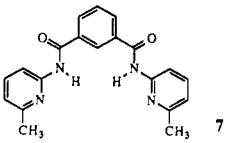


Figure 7. Crystal structure of 7 with pimelic acid (plate type).

conformational characteristics of the spacer. Compound **7** was chosen and synthesized from 2-amino-6-picoline and isophthaloyl dichloride.[15] The isophthaloyl group was used as the spacer in order to eliminate the possibility of forming a 1:1 complex between the receptor and a dicarboxylic acid. As a consequence only polymeric cocrystals would be expected.



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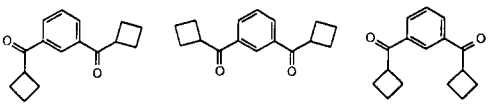
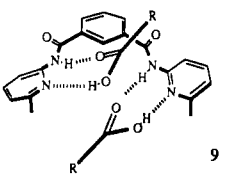
Diamide **7** has three major conformations, **8a–c**. Of these **8a** and **8b** are expected to form polymeric aggregates with dicarboxylic acids of the types similar to those seen in Figure 1. However, when **7** takes a convergent



8a 8b 8c



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conformation of the two aminopicolines, as in **8c**, two carboxylic acids can bind only in a nonplanar fashion with one acid group above the plane of the receptor and the other below, as shown in **9**. Propagation of this arrangement in the crystal would lead to an extended, helical structure.

Crystal structures of **7** that adopt conformations **8a** and **8b** are seen in the polymeric sheet cocrystals with glutaric acid and succinic acid, respectively. These two structures are shown in Figures 5 and 6.[15,16]

A key to the formation of these two structures appears to be a complementarity between the conformations of the dicarboxylic acid substrates and those of receptor **7**. In Figure 5, the aminopicoline hydrogen-bonding sites of **7** are directed ~120° away from each other (as in **8a**). The substrate glutaric acid has adopted one gauche conformation so that the two carboxylic acid groups have a ~120° relationship to each other. This results in a complementarity of the curvature present in both the receptor and

(14) Garcia-Tellado, F.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265–9269.

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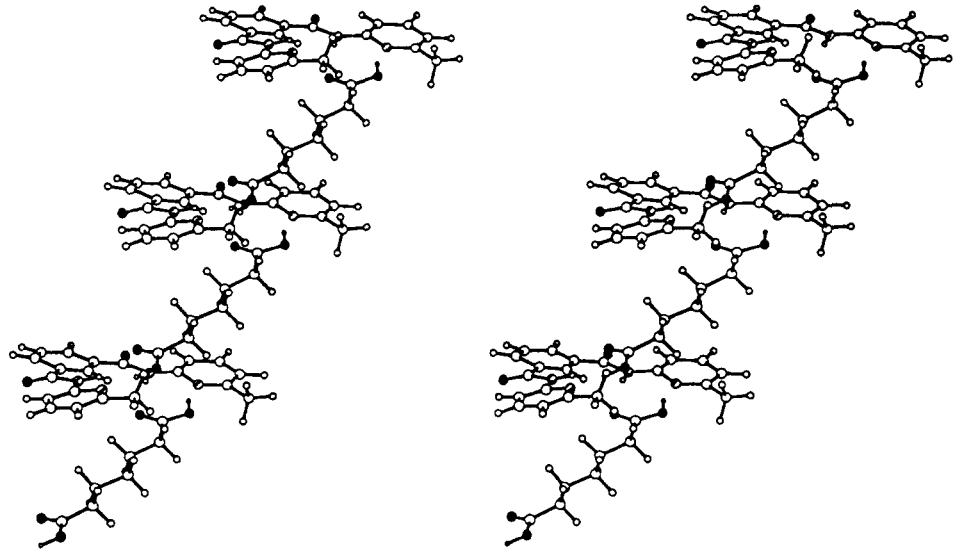

Figure 8. Section of the X-ray structure of the needle type crystal of 1:1 **7** and pimelic acid (stereoview).

the diacid that can lead to the tightly packed polymeric complex seen in Figure 5. A gauche conformation in succinic acid would introduce much more steric hindrance than in glutaric acid due to the close positioning of the acid groups. Thus, the two acid groups take up a 180° arrangement in an extended conformation of succinic acid. This is matched by the receptor which takes up conformation **8b** in which the two hydrogen-bonding sites are parallel and pointing in the same direction. The resultant polymeric complex (Figure 6) shows a ladderlike structure with the diacid forming the rungs and the receptor the sides.

Crystallization of a 1:1 mixture of **7** and pimelic acid gave very interesting results. Slow diffusion of hexane into a $CHCl_3$ solution containing the 1:1 mixture produced two different types of crystals in the same container. A colorless triclinic needle type of crystal (≈70% of total) formed initially at the top of the solution. Later, a plate type of crystal (≈30% of total) formed at the bottom of the solution. X-ray analysis revealed that the two crystals have different structures. However, both contain a 1:1 mixture of **7** and pimelic acid linked by a ribbon network of hydrogen bonds.

The crystal formed at the bottom of the solution (plate type) showed a structure that is very similar to the one from the 1:1 mixture of **7** and glutaric acid. As seen in Figure 7, this structure is almost identical to the one shown in Figure 5. Again the presence of a single gauche conformation in the diacid leads to a curved shape complementarity to the receptor which is in conformation **8a**. The average hydrogen-bond lengths in this type of crystal are 1.7 Å for OH···N and 1.9 Å for NH···O.

The needle type crystal formed at the top of the solution gave a completely different structure.[15] In this case, **7** has adopted a conformation similar to **8c**. However, **7** is not strictly planar in the crystal structure; one acylaminopyridine ring is 20.5° above and the other 9.4° below the plane of the isophthalate spacer. Each pimelic acid molecule remains in its preferred all-trans conformation and forms two pairs of bidentate hydrogen bonds to different receptors (average hydrogen bond lengths: 2.1 Å for NH···O and 1.8 Å for OH···N). Due to the U-turn nature of **7** in this conformation, the overall shape of the

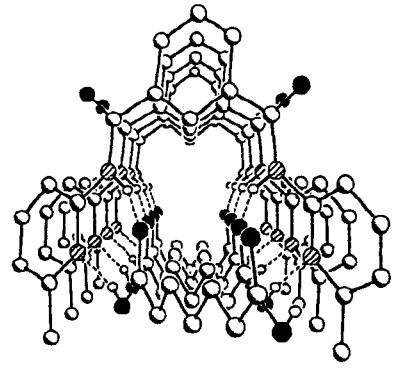

Figure 9. Top view of the crystal structure of 1:1 **7** and pimelic acid (needle type, hydrogens on carbons are deleted for simplicity).

structure is a self-assembling, hydrogen-bonded helix.[17-19] Figure 8 shows one strand of the helical structure in stereoview. A top view of the structure (Figure 9) shows a perfect alignment of the individual subunits with a spacing of 7.04 Å between each isophthalate ring on neighboring molecules of **7**.

The longer range structure of the **7**:pimelic acid complex reveals some interesting features of helix–helix packing interactions in the crystal lattice. Figure 10 shows that each hydrogen-bonded helix is interlocked with a second helix of opposite handedness. The critical interaction involves the isophthalate groups of one helix in a face-to-face stacking arrangement[20] (ring–ring distance: 3.44 Å) with the corresponding groups of the second helix. On each strand the isophthalate groups take up a parallel arrangement linked by hydrogen-bonded pimelic acid units which lie at an angle to the plane (as seen in Figure 8). Efficient interdigitation of the isophthalate groups is only possible between two strands of opposite handedness. Helixes of the same handedness would take up an

(17) The formation of helical structures in solid-state inclusion complexes has been reviewed: Bishop, R.; Dance, I. G. *Top. Curr. Chem.* **1988**, *149*, 137–188.

(18) Several self-assembling helices based on metal template effects have been reported. For a recent example, see: Constable, E. C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1450–1451.

(19) For a recent example of covalently linked molecules that take up a helical structure, see: Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 6787–6795.

(20) Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561–6562.

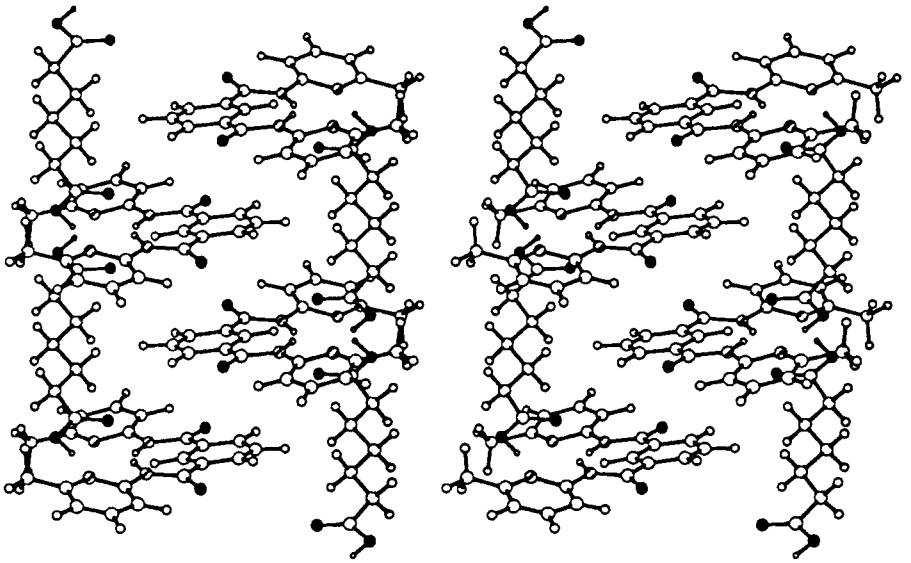

Figure 10. Side view of a section of the helical crystal structure showing intercalation (stereoview).

X-structure with only one point of contact. It is likely that $\pi-\pi$ stacking is a key stabilizing factor for this type of crystal structure. This can also explain why the helix formation is seen with pimelic acid but not with glutaric acid. It appears that the length of glutaric acid is insufficient to provide a ring-ring distance of ~3.4 Å, while maintaining hydrogen-bonding interactions and without introducing steric hindrance.

In this review we have shown that different cocrystal structures can be induced by controlling the direction and positioning of hydrogen-bonding sites in the two components. In particular the bidentate interaction between 2-acylaminopyridine and carboxylic acid is a strong and general one that can survive in the solid state despite substantial changes in the structure of the subunits. By changing the length, shape, and orientation of the spacer groups, we have demonstrated that either subtle changes in the alignment of the molecules or large changes in their packing arrangements can be controlled in a well-defined and predictable manner.

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