Engineering layers in molecular solids with the cyclic dipeptide of (*S*)-aspartic acid

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Hydrogen-bonded tapes formed by the cyclic dipeptide of (*S*)-aspartic acid 1 are used as a scaffold on which to build two-dimensonal layers that vary in size, shape and chemical composition.

Numerous research groups have demonstrated considerable success at using non-covalent interactions to build supramolecular structures in crystalline solids.[1] The most common interaction in these structures is the hydrogen bond, which occurs between functional groups strategically located on the constituent molecules.[2–5] Several molecules have been investigated, including a few that form robust supramolecular structures that can be modified in terms of their size and shape (*i.e.* modular). The advantage of a supramolecular structure that is both robust and modular is that it provides a scaffold with which to engineer the structure (and possibly the function) of molecular solids.

We have initiated a program of research aimed at understanding the influence of molecular structure on the kinetics of crystal growth using atomic force microscopy. To simplify these studies, we require molecular solids with a common supramolecular structure whose dimensions can be modified systematically. Our approach to preparing a series of related solids is to use the strength and directional character of hydrogen bonds to build the supramolecular structure, and exploit the selectivity of hydrogen bonds for different hydrogen-bond donors and acceptors to modify the supramolecular structure. We have focused our efforts on the cyclic dipeptide of (*S*)-aspartic acid **1** based on the following rationale.[6] First, **1** is representative of a family of molecules known to form hydrogen-bonded tapes in their crystalline solids [Fig. 1(*a*)].[1,7] Tapes are one-dimensional aggregates that typically pack with their long axes parallel. Second, **1** contains two types of functional groups (*cis*-amide and carboxylic acid) that contain both a hydrogen bond donor and a hydrogen bond acceptor.

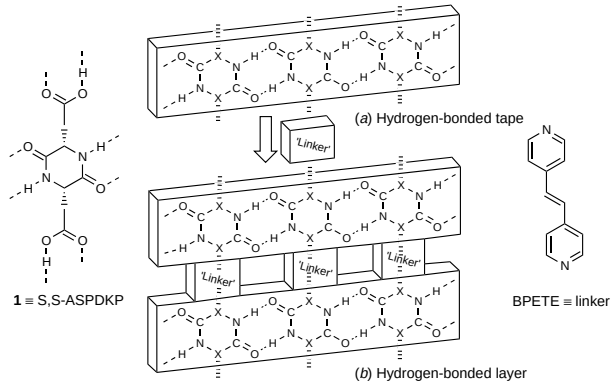

Fig. 1 (*a*) Tape that results when the *cis*-amides of (*S,S*)-ASPDKP (**1**) form a pair of hydrogen bonds (dashed lines) with the *cis*-amides of two adjacent molecules. X represents a substituted carbon atom. (*b*) Layer that forms when parallel tapes are cross-linked either directly through functional groups on X or indirectly through cocrystallization with 'linker' molecules (*e.g.* BPETE).

Functional groups such as *cis*-amides and carboxylic acids are known to form an $R_2^2(8)$ pattern of hydrogen bonds—a two-point interaction that is stronger and orientationally more restrictive than chains of hydrogen bonds.[8–10] Third, the hydrogen-bonding functional groups in **1** are positioned to preorganize the direction of their hydrogen bonds mutually orthogonal, which will promote the formation of hydrogen-bonded layers through the cross-linking of tapes [Fig. 1(*b*)]. Layers are two-dimensional aggregates that should pack with their planes parallel. Fourth, *cis*-amides and carboxylic acids have different selectivities for hydrogen-bond donors and acceptors.[10] With cocrystallization techniques, this difference in selectivity can be exploited to modify the interdigitation of tapes or the shape of the hydrogen-bonded layers.

Our first objective was to demonstrate that the two *cis*-amide functional groups in **1** form a symmetric $R_2^2(8)$ pattern of hydrogen bonds with adjacent molecules to generate the tape motif in the solid state. Based on Etter's rules for hydrogen-bonds, where the strongest hydrogen bond donor (acid hydroxy) preferentially interacts with the strongest hydrogen bond acceptor (amide carbonyl), carboxylic acids crystallized in the presence of amides should form an asymmetric $R_2^2(8)$ pattern of hydrogen bonds.[10,11] Further evidence that supports the preferential formation of an asymmetric $R_2^2(8)$ pattern of hydrogen bonds is the packing modes of monocarboxamide derivatives of dicarboxylic acids.[8] Due in part to restrictions in the conformation of **1** imposed by its stereochemistry, the crystalline solid of **1** contains the tape motif generated from a *symmetric* $R_2^2(8)$ pattern of hydrogen bonds between the *cis*-amide functional groups. The asymmetric unit cell contains two crystallographically distinct molecules of **1** that generate two distinct tapes, labelled A and B (Fig. 2).† Tapes pack with their long axes parallel. The hydrogen bond distances and angles between the *cis*-amides depend on the tape to which **1** belongs: N–H···O = 2.860 Å, 166° and 2.868 Å, 167° for tape A; 2.864 Å, 163° and 2.871 Å, 163° for tape B. Although a C_2-axis of symmetry is present in a two-dimensional drawing of **1**, this symmetry element is absent in the solid state due to the different conformations adopted by the two side-chains. Consequently, a

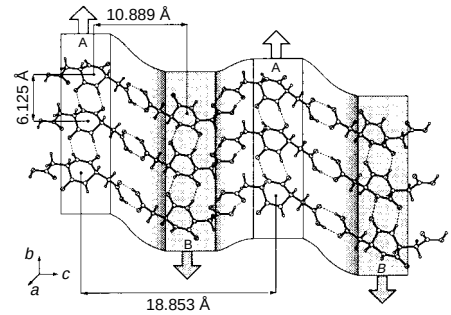

Fig. 2. Layer in crystal structure of **1**. The asymmetric unit cell contains two molecules of **1**, each of which generate a distinct tape (A and B), which alternate in their direction of propagation (arrows). Each tape is cross-linked to adjacent tapes through an $R_2^2(8)$ pattern of hydrogen bonds between the carboxylic acid groups to form a *non-planar* layer.

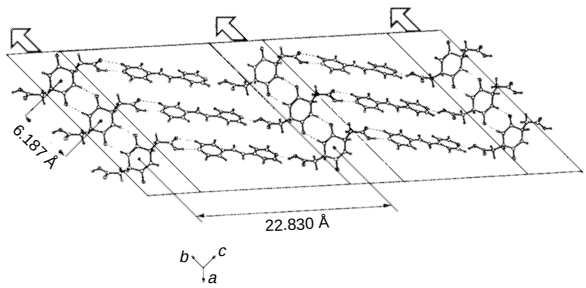

Fig. 3 Layer in crystal structure of **1**–**BPETE**. A symmetric $R_2^2(8)$ pattern of hydrogen bonds between the *cis*-amides of **1** form tapes, which are cross-linked into planar layers through an $R_2^2(7)$ pattern of hydrogen bonds between the carboxylic acid functional groups on **1** and the nitrogen atom and *ortho* carbon atom on BPETE. All tapes propagate in the same direction relative to tapes in the same layer and in adjacent layers (arrows).

non-planar layer results when each tape is cross-linked to adjacent tapes through a symmetric $R_2^2(8)$ pattern of hydrogen bonds between carboxylic acid functional groups (O–H···O interactions: 2.665 Å, 176°; 2.633 Å, 161°; 2.753 Å, 174°; and 2.740 Å, 175°). Layers pack with a slippage of 3.737 Å along the *c* axis while maintaining a periodicity of 4.985 Å between layers. Close contacts between layers include: O9–H16···O4, 2.886 Å and C15–H15···O2, 3.088 Å.

For the purpose of engineering related solids, the formation of a symmetric $R_2^2(8)$ pattern of hydrogen bonds in the crystalline solid of **1** is significant in that it suggests the tape motif can be used as a scaffold on which to build layers with different repeat distances between tapes. For example, a guest molecule can be inserted within the layer of **1** by cocrystallization techniques, which allows for systematic modification of the periodicity of tapes within the layer. We illustrate this point in Fig. 3, which shows the crystal structure of **1** cocrystallized with (*E*)-1,2-bis(4-pyridyl)ethene (BPETE).‡ In this example, parallel tapes are cross-linked into a planar layer through hydrogen bonding interactions between the carboxylic acid functional groups on **1** and the nitrogen and *ortho* carbon atoms of BPETE (O–H··N = 2.893 Å, 162°; and 2.633 Å, 143°; C–H··O = 3.103 Å, 126°; and 3.511 Å, 116°). The carboxylic acid functional groups do not form an $R_2^2(8)$ pattern of hydrogen bonds in the presence of BPETE because the pyridyl nitrogen atom is a stronger hydrogen-bond acceptor than the carbonyl oxygen atom of carboxylic acids.§ Moreover, the interaction is not ionic; proton transfer from the carboxylic acid to BPETE does not occur. We base this assertion on the similar C–N–C bond angles of BPETE in the presence (115.8°) or absence (115.4°) of **1**.[12] In a manner similar to the crystalline solid of **1**, the crystalline solid of **1**–**BPETE** contains an $R_2^2(8)$ pattern of hydrogen bonds between *cis*-amides of adjacent molecules to give tapes (N1–H1··O2 = 2.857 Å, 166°, N2–H2··O1 = 2.829 Å, 167°). Tapes lie with their long axes parallel. Layers pack with slippage of 4.511 Å along the *c*-axis and a periodicity of 4.211 Å between adjacent layers. The closest contact between layers is 3.203 Å (C20–H20··O5).

Several research groups have demonstrated that hydrogen-bonded layers can be assembled in crystalline solids from molecules that are designed to form hydrogen bonds in two directions. Compound **1** is a new addition to this type of molecule. An important feature of **1** is that the presence of competing hydrogen-bonding functional groups, either as part of (carboxylic acid) or external (pyridyl) to the molecular structure of **1**, does not preclude the formation of tapes defined by an $R_2^2(8)$ pattern of hydrogen bonds between *cis*-amide functional groups. Consequently, these tapes can be modified in terms of their interdigitation or used as scaffolds on which to build layers (or three-dimensional structures) that systematically differ in their size, shape and chemical composition. We demonstrate the use of tapes as scaffolds with the two examples shown, which are representative of the tremendous potential that molecules such as **1** have in engineering layers in the solid state. Studies of other layered solids built with **1** are currently in progress and will be the subject of future reports.

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Footnotes and References

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†All data were collected at 130 K on a Siemens P4/RA diffractometer with graphite-monochromated Cu-Kα radiation (λ = 1.541 78 Å) using 2θ scans over the range 2–57°. Lattice parameters were determined from least-squares analysis of 30–35 reflections. Two standard reflections were measured every 198 reflections. Structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXTL, Version 5.03. All non-hydrogen atoms were refined anisotropically. All hydrogen-bonded hydrogen atoms were refined after location on a difference map with isotropic temperature factors. Other hydrogen atoms were placed in idealized positions with assigned isotropic thermal parameters. *Crystal data* for **1**: $C_8H_{10}N_2O_6$, M = 230.18 g mol^{-1}, triclinic $P\bar{1}$, colorless needle measuring 0.18 × 0.06 × 0.04 mm, a = 4.985(1), b = 5.039(1), c = 18.853(4) Å, α = 82.50(3), β = 88.47(3), γ = 75.33(3)°, V = 454.2(2) Å^3, Z = 2, D_c = 1.683 Mg m^{-3}, μ = 1.275 mm^{-1}; T_{max} = 0.96, T_{min} = 0.93, GOF on F^2 = 1.083; R_1 = 0.0344, R_{all} = 0.0346 for 1215 independent observed reflections, based on $I > 2.0\sigma(I)$.

‡ Cocrystals of **1** and BPETE were obtained by slow evaporation from a methanol solution containing an equimolar mixture of **1** and BPETE. *Crystal data* for cocrystal of **1**–**BPETE**: $C_{20}H_{20}N_4O_6$; M = 412.40 g mol^{-1}, triclinic $P\bar{1}$, yellow needles measuring 0.52 × 0.14 × 0.08 mm, a = 6.1779(13), b = 6.187(2), c = 13.404(3) Å, α = 82.63(2), β = 83.92(2), γ = 68.23(2)°, V = 471.0(2) Å^3, Z = 1, D_c = 1.454 Mg m^{-3}, μ = 0.919 mm^{-1}; T_{max} = 0.94, T_{min} = 0.89, GOF on F^2 = 1.043; R_1 = 0.0860, R_{all} = 0.0982 for 1240 independent observed reflections, based on $I > 2.0\sigma(I)$.

§ Based on β-values for pyridine (0.64) and ethyl acetate (0.41).

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